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Efficient Dehydrogenation of Amines and Carbonyl Compounds Catalyzed by a Tetranuclear Ruthenium-μ-oxo-μ-hydroxo-hydride Complex

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Efficient Dehydrogenation of Amines and Carbonyl Compounds Catalyzed by a Tetranuclear Ruthenium-μ-Oxo-μ-Hydroxo-Hydride Complex

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Abstract: The tetranuclear ruthenium-μ-oxo–μ-hydroxo-hydride complex $\{[(PCy_3)(CO)RuH]_4(\mu_4\text{-}O)(\mu_3\text{-}OH)(\mu_2\text{-}OH)\}$ (**1**) was found to be a highly effective catalyst for the transfer dehydrogenation of amines and carbonyl compounds. For example, the initial turnover rate of the dehydrogenation of 2-methylindoline was measured to be 1.9 s^{-1} with the TON of 7950 after 1 h at 200 °C. The extensive H/D scrambling patterns observed from the dehydrogenation reaction of indoline-N-d_1 and indoline-α-d_2 suggest a monohydride mechanistic pathway with the C-H bond activation rate-limiting step.

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Catalytic dehydrogenation reaction is a highly desired functionalization method for unreactive sp^3 C–H bonds since the corresponding alkenes are valuable synthetic intermediates for a variety of industrially important processes.[1] Significant economic and environmental gains are anticipated from an efficient catalytic dehydrogenation process because the current dehydrogenation methods by stoichiometric oxidizing agents generate copious amount of toxic byproducts,[2] and heterogeneous catalytic dehydrogenation methods often suffer from poor product selectivity and incompatibility with functionalized substrates.[3] Considerable research has been devoted to develop homogeneous catalysts to selectively form α-olefin products and to gain mechanistic insights on the catalytic dehydrogenation reaction.[4] In a seminal work, Jensen and Kaska reported that the pincer-ligated (PCP)IrH_2 complex is a highly efficient homogeneous catalyst for the transfer dehydrogenation of alkanes, giving up to 1000 turnovers at 200 °C using *t*-butylethylene (TBE) as the sacrificial hydrogen acceptor (Figure 1).[5] Subsequent experimental and computational studies led to a detailed description on the reaction mechanism involving a highly unsaturated (PCP)Ir complex as the key intermediate species.[6] The phosphite-modified (PCP)IrH_2 catalysts, which were found to significantly increase the turnover rate,[7] have been successfully utilized in tandem dehydrogenation and metathesis reaction of *n*-alkanes.[8] However, these Ir-pincer catalysts are generally not suitable for the dehydrogenation of heteroatom-functionalized substrates because of their poor functional group tolerance and due to their extreme air and water sensitivity, though limited success has been reported on the dehydrogenation of amines and related compounds.[9]

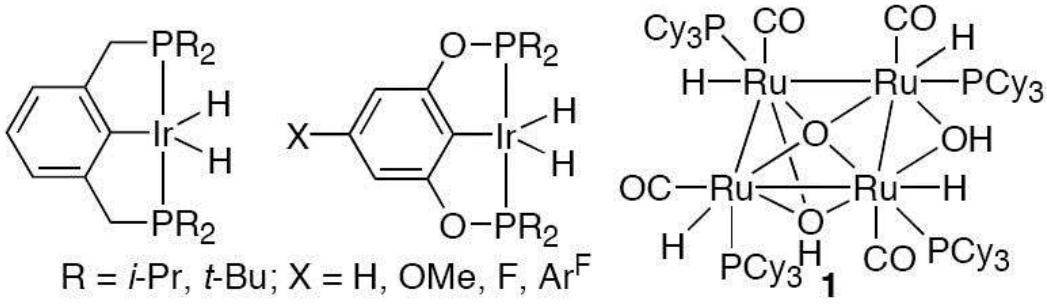
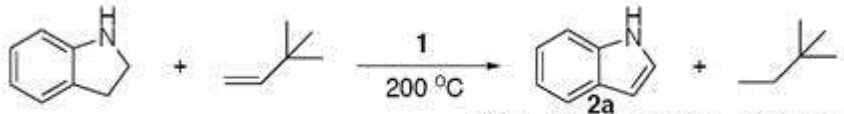


Figure 1

Organometallics, Vol 28, No. 4 (February 23, 2009): pg. 947-949. DOI.

In a conceptually related reaction, we previously discovered that the ruthenium-hydride complex $(PCy_3)_2(CO)RuHCl$ is an effective catalyst precursor for the dehydrogenative coupling reaction of cyclic amines and alkenes to give α-substituted cyclic imines, that featured both transfer dehydrogenation and α-C-H bond insertion steps.[10] We also reported the synthesis of the novel tetrametallic ruthenium-μ-oxo–μ-hydroxo-hydride complex $\{[(PCy_3)(CO)RuH]_4(\mu_4\text{-}O)(\mu_3\text{-}OH)(\mu_2\text{-}OH)\}$ (**1**) and its high cooperative activity for the alcohol dehydrogenation and nitrile hydration reactions.[11] Since the complex **1** showed high thermal stability and functional group tolerance in catalyzing these reactions, we thought that it might be suitable for the dehydrogenation reactions of unreactive C-H bonds. Here we report a highly efficient dehydrogenation reaction of amines and carbonyl compounds, which is catalyzed by the tetranuclear ruthenium complex **1**.

Initially, the dehydrogenation activity of **1** was tested by using cyclooctane. Thus, a 1:1 mixture of cyclooctane (3.0 mmol) and TBE (3.0 mmol) in the presence of **1** (3.0 μmol) was heated at 200 °C in a sealed Schlenk tube.[12] The initial turnover frequency (TOF) for the formation of cyclooctene product after 8 min was measured to be 7.8 min^{-1}, but the turnover number (TON) reached only 96 after 1 h. The direct dehydrogenation of cyclooctane under the "acceptorless" condition led to the TOF of 1.2 min^{-1}. The activity of other selected ruthenium complexes such as $(PCy_3)_2(CO)RuHCl$, $(PPh_3)_3(CO)RuH_2$, $(PPh_3)_3RuHCl$, $[(COD)RuCl_2]_x$ and $RuCl_3{\cdot}3H_2O$ was found to be very low (<0.05 min^{-1}), although the previously synthesized bimetallic ruthenium-μ-hydroxo-hydride complex $\{[(PCy_3)_2(CO)RuH](\mu\text{-}OH)(\mu\text{-}H)[(PCy_3)(CO)RuH]\}$ exhibited a significant activity under the similar conditions (TOF = 1.0 min^{-1}).[11]



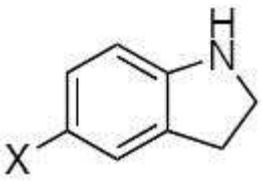
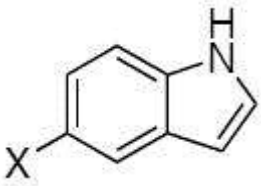
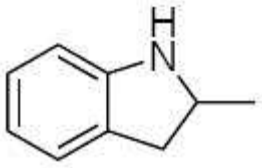
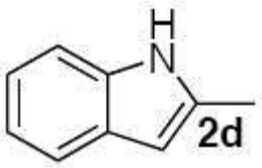
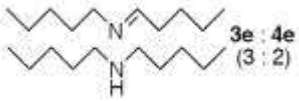
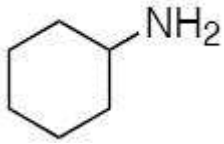
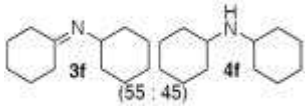
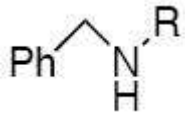
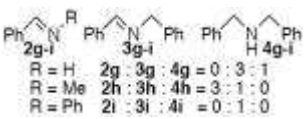
(1)

From a synthetic point of view, the ruthenium catalyst **1** has a number of salient features, in that it is air-and water-stable in solid state and is compatible with a variety of heteroatom functional groups.

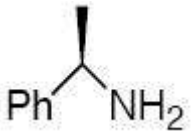
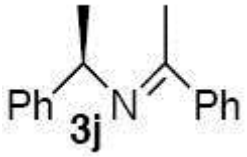
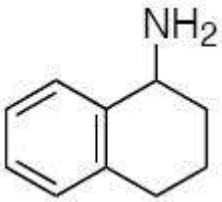
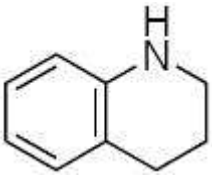
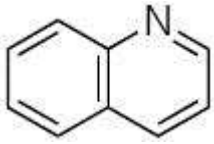
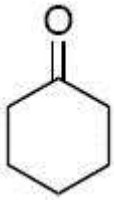
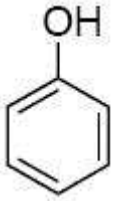
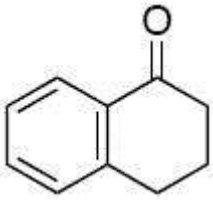
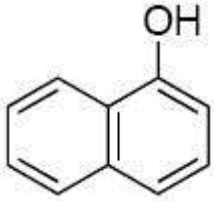
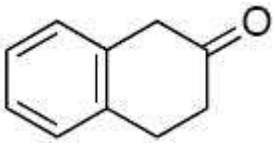
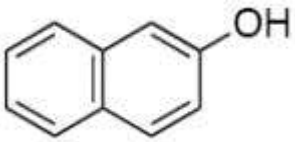
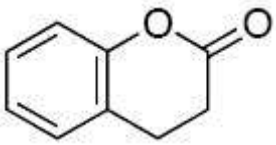
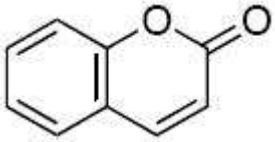
Organometallics, Vol 28, No. 4 (February 23, 2009): pg. 947-949. DOI.

Encouraged by the initial results, we next explored the catalytic activity of **1** for the dehydrogenation reaction of amines and carbonyl compounds. In a typical setting, an equimolar of indoline (6.0 mmol) and TBE (6.0 mmol) with **1** (3.0 μmol) was heated in a sealed Schlenk tube at 200 °C (eq 1). The initial TOF for the formation of indole product **2a** after 8 min was measured to be 73 min^{-1}, and moreover, TON of 1000 was reached within 1 h as determined by GC and GC-MS analyses (Table 1). Propene was found to be just as effective hydrogen acceptor as TBE. Remarkably, a nearly 8000 TON was achieved within 1 h for the dehydrogenation of 2-methylindoline under the acceptorless condition (entry 7). It should be mentioned that the reaction rate slowed considerably after ~50% conversion apparently due to the indole product inhibition, but a greater than 20000 TON can be easily achieved by running a longer reaction time (2-3 h) and the adding more indoline substrate to the reaction vessel.

Table 1. Dehydrogenation and Dehydrogenative Coupling Reactions of Amines and Carbonyl Compounds.[a]

entry	substrate	acceptor	Product(s)	TON[b]
1		TBE		1080
2		propene		1180
3		none		1577[c]
4		TBE		3180[d]
5		TBE		6840[d]
6		TBE		6750[d]
7		none		7950[c,d]
8		TBE		105
9		TBE		496
				
10		TBE		210[e]
11		TBE		126

Organometallics, Vol 28, No. 4 (February 23, 2009): pg. 947-949. DOI.

entry	substrate	acceptor	Product(s)	TON[b]
12		TBE		45
13		TBE	 **3j**	162
14		TBE	 **3k**	400
15		TBE		185
16		TBE		31
17		TBE		216
18		TBE		73
19		TBE		35

[a]Reaction conditions: substrate (6.0 mmol), alkene (6.0 mmol), **1** (5 mg, 3.0 μmol), 200 °C.
[b]TON = mol of product/mol of **1** after 1 h. The turnover rate was determined by GC and GC-MS.
[c]H_2 was removed periodically.
[d]Substrate:**1** = 15000:1.
[e]Trace amount of PhCN was formed in the product mixture.

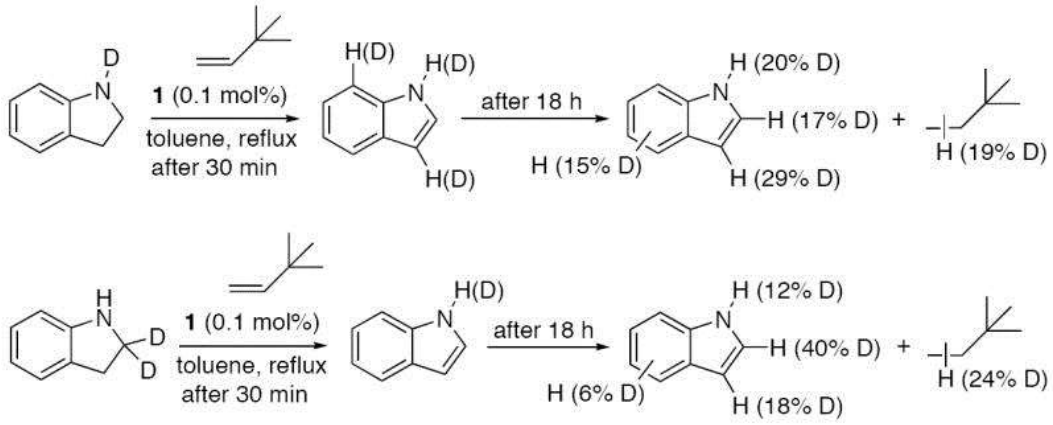
Organometallics, Vol 28, No. 4 (February 23, 2009): pg. 947-949. DOI.

The primary aliphatic amines gave a mixture of both imine and secondary amine products **3** and **4** (entries 8, 9). In contrast, the imine products **3i**-**3k** are exclusively produced from benzylic amines with sterically demanding groups (entries 12-14). Apparently, the initially formed imine further reacted with an unreacted amine to give the product **3** and NH_3 in these cases. In support of this notion, the formation of ammonia was detected by NMR in the crude reaction mixture for these cases. Cyclic ketones and lactones were also found to be suitable substrates under the transfer dehydrogenation conditions using TBE, albeit with a considerably lower turnover rate (entries 16-19). To the best of our knowledge, the dehydrogenation activity of **1** towards amines and carbonyl compounds is uniquely high, as very few homogeneous metal complexes have been able to mediate the dehydrogenation of both amine and carbonyl compounds.[9]

We performed the following preliminary experiments to gain mechanistic insights. First, the reaction rate was found to be strongly inhibited by phosphine ligand. For example, the addition of PCy_3 (6-30 μmol) to the reaction mixture of indoline under otherwise similar conditions led to a steady decrease on the turnover rate (TON = 546, 313 and 197 for 2, 5 and 10 equiv of PCy_3 after 20 min, respectively). This result is consistent with a dissociative activation of the Ru catalyst.

Next, the deuterium labeling studies were performed to examine the reversibility of the C-H and N-H bond activation steps. Thus, a mixture of indoline-N-d_1 (0.60 mmol) and TBE (0.60 mmol) with **1** (0.6 μmol) in toluene-d_8 (0.3 mL) was monitored by NMR (Scheme 1). After 30 min of heating under refluxing conditions, selective deuterium incorporation to both 7-position of the indoline and the vinyl positions of TBE substrates was observed prior to the product formation as detected by both ^{1}H and ^{2}H NMR. Eventually, an extensive H/D exchange to both indole and the ethyl group of *t*-butylethane products was observed after 18 h. A relatively rapid H/D exchange to the vinyl group of TBE indicates a reversible vinyl C-H activation of TBE. In a complementary experiment, the treatment of a 1:1 mixture of indoline-α-d_2 (0.60 mmol) with TBE (0.60 mmol) led to the extensive deuterium incorporation to both *t*-butylethane and indole products, where the formation of a mixture of *t*-butylethane-d_1, -d_2 and -d_3 was detected by GC-MS.[12,13]

Organometallics, Vol 28, No. 4 (February 23, 2009): pg. 947-949. DOI.



Scheme 1

While details of the dehydrogenation reaction remain unclear at this time, these results suggest of a mechanism involving rapid and reversible N-H and C–H bond activation steps via a ruthenium-monohydride species for the dehydrogenation reaction. Both the formation of a mixture of *t*-butylethane-d_1, -d_2 and -d_3 and a rapid H/D exchange to the vinyl positions of the indole product bear the hallmark features of a mechanistically similar "monohydride mechanism" commonly proposed for the ruthenium-catalyzed hydrogenation reactions.[14] Such monohydride mechanism would be complementary to a well-known "dihydride mechanism" of the Ir-pincer catalyzed dehydrogenation reaction, wherein the reductive elimination of TBE from (PCP)IrH_2 species has been found to be the rate-limiting step under the catalytic conditions.[1b,7] Further kinetic and mechanistic studies are warranted to establish the detailed reaction mechanism of the ruthenium-catalyzed dehydrogenation reaction.

In summary, the tetranuclear ruthenium complex **1** was found to exhibit exceptionally high catalytic activity for the dehydrogenation of amines and carbonyl compounds, giving up to 20000 TON within 2 h at 200 °C. Such high activity for the direct dehydrogenation of amines and carbonyl compounds has not been achieved by using homogeneous metal catalysts, although heterogeneous Pd and Pt catalysts are well-known to mediate the dehydrogenation reactions under oxidative conditions.[3a,15] Efforts to establish the scope and detailed mechanism of the dehydrogenation reaction are currently underway.

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Acknowledgments

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Supplementary Material

Supporting Information Available:

Experimental procedures and selected NMR spectra of the organic products (9 pages, print/PDF). This material is available free of charge via the Internet at http//:pubs.acs.org.

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Supporting Information

Efficient Dehydrogenation of Amines and Carbonyl Compounds Catalyzed by a Tetranuclear Ruthenium-μ-Oxo-μ-Hydroxo-Hydride Complex

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General Information. All operations were carried out in an inert-atmosphere glove box or by using standard high vacuum and Schlenk techniques unless otherwise noted. Tetrahydrofuran, benzene, hexanes and Et_2O were distilled from purple solutions of sodium and benzophenone immediately prior to use. The NMR solvents were dried from activated molecular sieves (4 Å). All organic substrates were received from commercial sources and used without further purification. The ^{1}H, ^{2}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian 300 or 400 MHz FT-NMR spectrometer. Mass spectra were recorded from a Agilent 6850 GC/MS spectrometer. The TON of the products was measured from a Hewlett-Packard HP 6890 GC spectrometer.

Representative Procedure of the Catalytic Reaction. In a N_2 filled glove box, complex **1** (5 mg, 2.9 μmol) was charged with indoline (0.71 g, 6.0 mol) and TBE (0.53 g, 6.0 mol; contained 5% TBA) in a 10 mol Schlock tube equipped with a Teflon stopcock and a stirring bar. The tube was closed and was brought out of the box. The reaction tube was fully immersed into a silicone oil bath, which was preset at 200 °C, and the reaction mixture was stirred for 1 h. The tube was cooled to room temperature, and was open to air. The crude product mixture was analyzed by GC and GC/MS. Analytically pure organic product **2a** was isolated after a simple column chromatography on silica gel (Et_2O/hexane).

For **Phosphate Inhibition Experiments**: PCy_3 (2-10 mg) was added to the reaction tube containing the same amount of substrates, and the reaction mixture was analyzed after 20 min of heating at 200 °C.

Deuterium Labeling Study. Indoline-N-d_1 (72 mg, 0.60 mol) and indoline-α-d_2 (73 mg, 0.60 mol) were added to a separate J-Young NMR tube containing TBE (53 mg, 0.60 mol) and **1** (1 mg, 0.60 μmol), and the mixture was dissolved in toluene (0.3 mol). The reaction tubes were brought out of the box, and were immersed in a silicone oil bath set at 200 °C. The deuterium content of the products was measured by both ^{1}H NMR (toluene-d_8) and ^{2}H NMR (toluene). The distribution of deuterium measured from the reaction of indoline-N-d_1 with TBE in toluene after

18 h: Ar (15%), N-D (20%), C_α (17%) and C_β (29%) of indole; methyl (12%) and methylene (7%) of *t*-butylethane. From the reaction of indoline-α-d_2 with TBE in toluene after 18 h: Ar (6%), N-D (12%), C_α (40%) and C_β (18%) of indole; methyl (15%) and methylene (9%) of *t*-butylethane.

Preparation of Labeled Indoline Compounds. Indoline-N-d_1 was prepared by following a reported procedure.[1] In a 25 mL Schlenk tube, indoline (5.0 g, 42 mmol) was added to a NaOD (40 wt% in D_2O, 1.0 g, 10 mmol) solution in D_2O (5 mL), and the reaction mixture was stirred at 110 °C for 16 h. The tube was cooled to room temperature, and 20 mL of CH_2Cl_2 was added to reaction tube. Organic layer was separated from the aqueous layer, and the solution was washed two times with brine solution. The extracted solution was dried in anhydrous $MgSO_4$, and was concentrated under vacuum. The product was isolated after distillation under high vacuum (4.7 g, 94% yield; 93% deuterium as determined by both ^1H and ^2H NMR).

N-Nitrosoindoline-α-d_2 was prepared by following a reported procedure.[1] In a 25 mL Schlenk tube containing NaOD (40 wt% in D_2O, 1.0 g, 10 mmol) in D_2O (5 mL), was added N-nitrosoindoline (3.0 g, 20 mmol),[2] and the reaction mixture was stirred at 110 °C for 16 h. The tube was cooled to room temperature, and 20 mL of CH_2Cl_2 was added to the reaction tube. Organic layer was separated from aqueous layer, and the solution was washed two times with brine solution. The solution was dried in anhydrous $MgSO_4$, and was concentrated under vacuum. The product (2.7 g, 90% yield), which was isolated after recrystallization in CH_2Cl_2 and hexanes, was found to contain 94% of deuterium as determined by both ^1H and ^2H NMR.

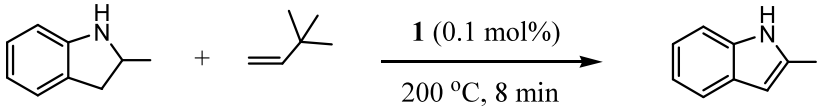
Indoline-α-d_2 was prepared by a modified reported method.[1] In a 100 mL Schlenk flask, N-nitrosoindoline-α-d_2 (2.7 g, 18 mmol) was added slowly to a diluted 6 N HCl (10.5 g, 54 mmol) in water solution (30 mL). After refluxing the reaction mixture for 3 h, the reaction flask was cooled to room temperature. The black precipitate was filtered through a fritted funnel, and

was washed 3 times with water. Saturated aqueous $NaHCO_3$ solution was slowly added to neutralize the solution. Ethyl ether (100 mL) was added to the reaction mixture, was extracted from the aqueous solution, and the ether solution was washed two times with brine solution. The solution was dried in anhydrous $MgSO_4$, and was concentrated under vacuum. The product was isolated after distillation under high vacuum (1.0 g, 46% yield; 94% deuterium as determined by both ^1H and ^2H NMR).

(1) Lautie, M. F. *J. of Labeled Compounds and Radiopharmaceuticals* **1979**, *16*, 735-744.

(2) Ohwada, T.; Miura, M.; Tanaka, H.; Sakamoto, S.; Yamaguchi, K.; Ikeda, H.; Inagaki, S. *J. Am. Chem. Soc*. **2001**, *123*, 10164-10172.

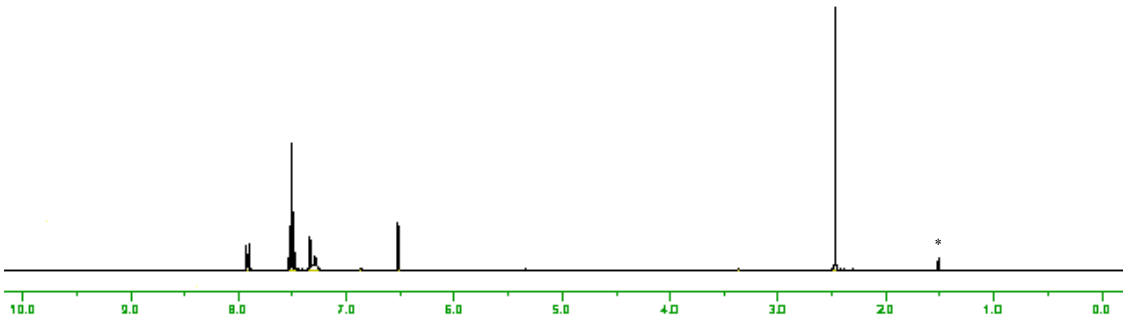
The ^{1}H and ^{13}C NMR Spectra of Selected Crude Product Mixture



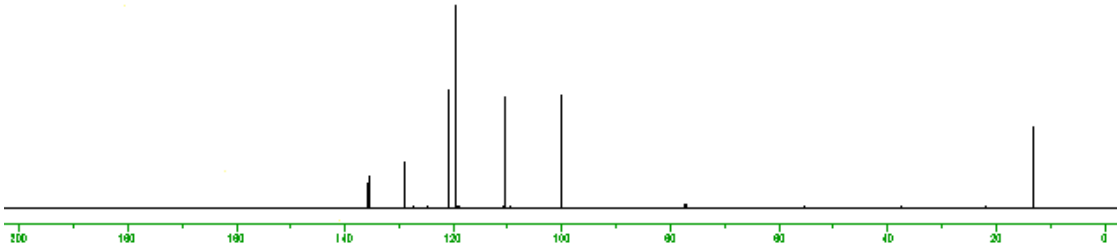
2d

90%

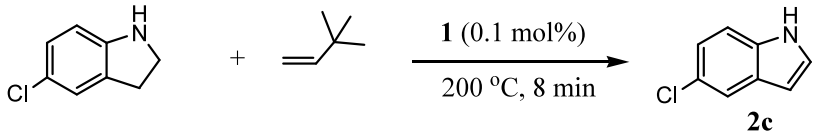
^{1}H NMR ($CDCl_3$, 400 MHz)



$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100.6 MHz)



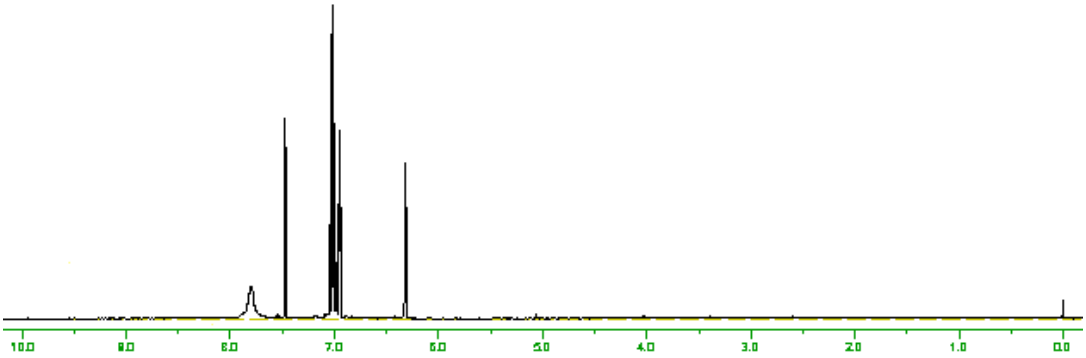
* denotes starting material.



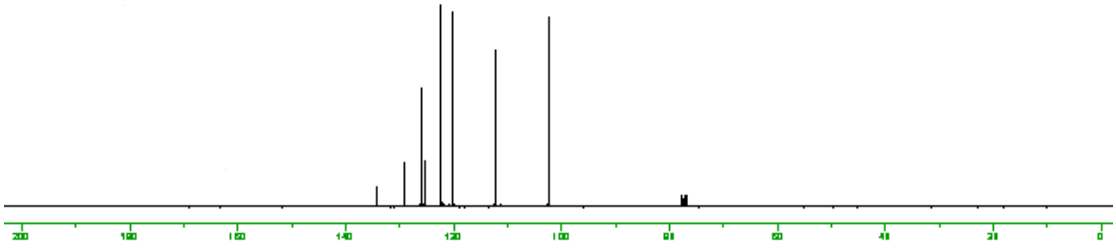
2c

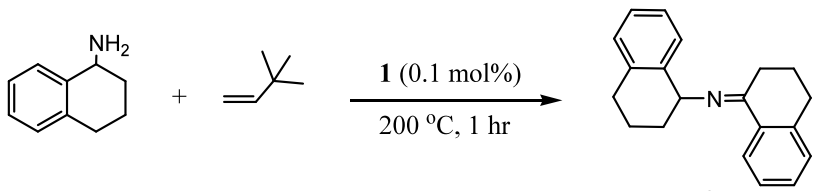
90%

^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz)

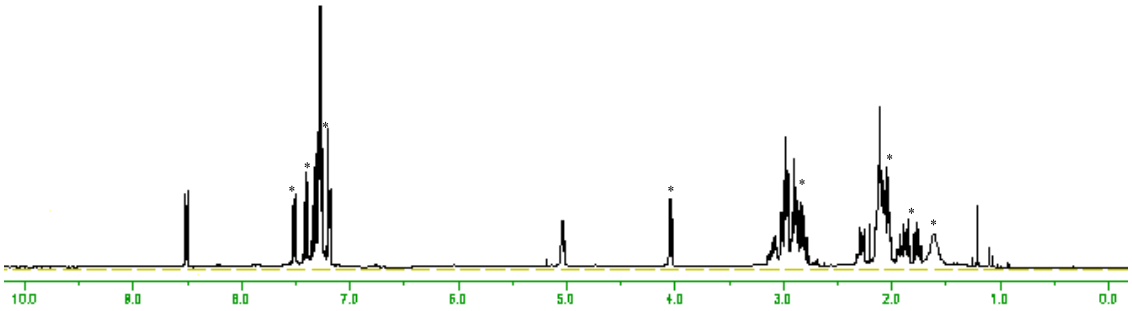




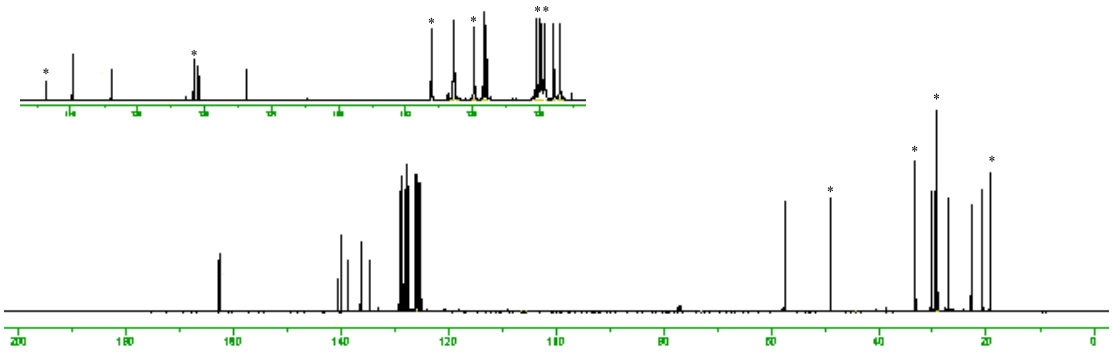
3k

40%

^{1}H NMR ($CDCl_3$, 400 MHz)

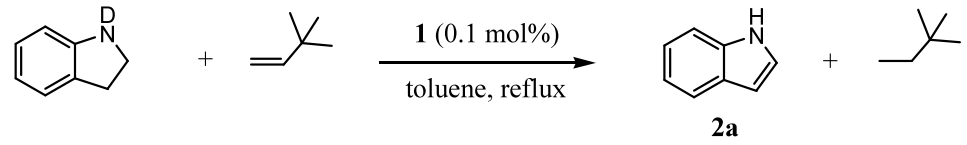


^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz)



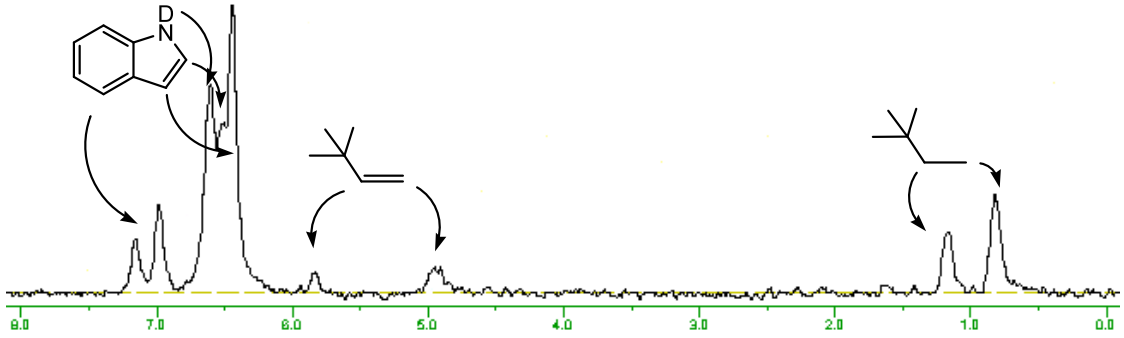
* denotes starting material.

^{2}H NMR (61.36 MHz) spectra in toluene



2a

t = 18 hr



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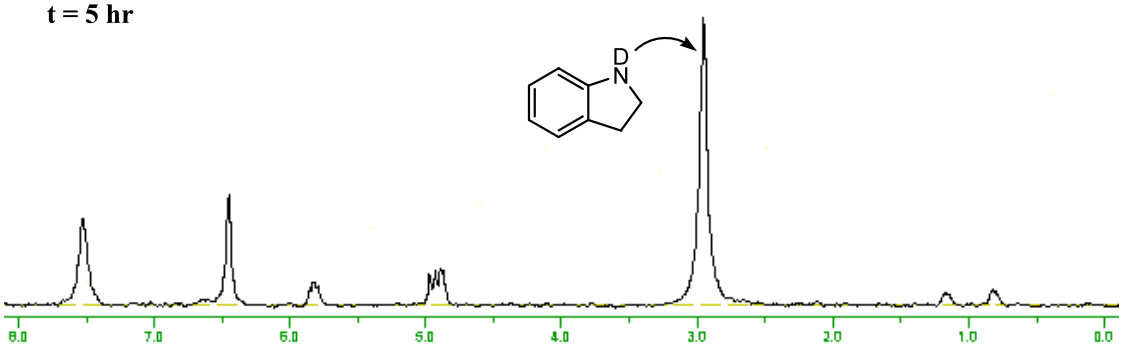

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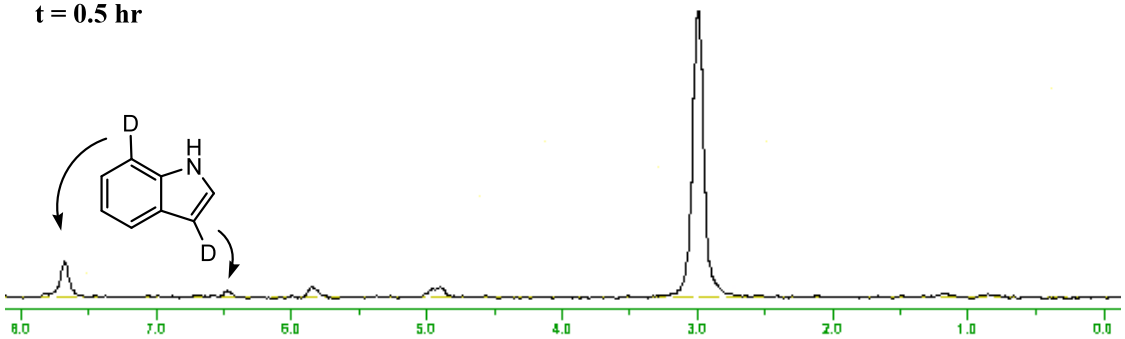
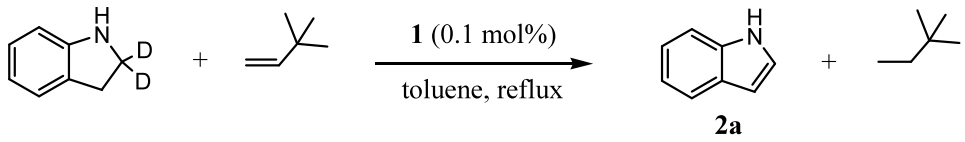


^{2}H NMR (61.36 MHz) spectra in toluene



2a

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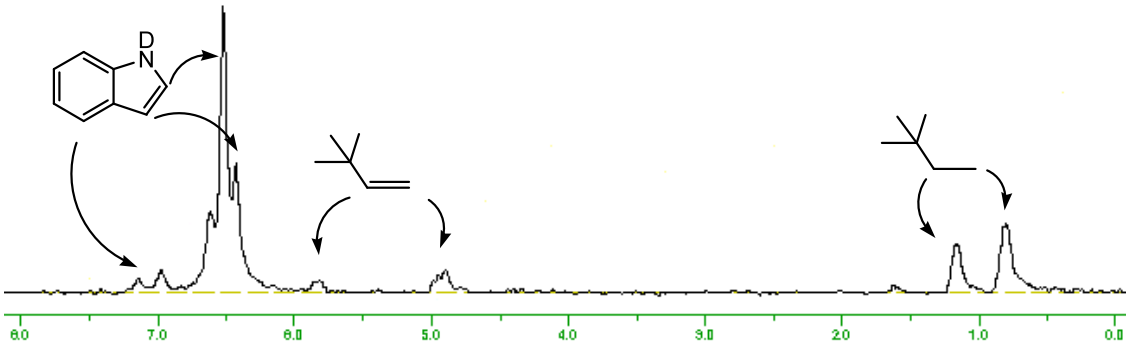

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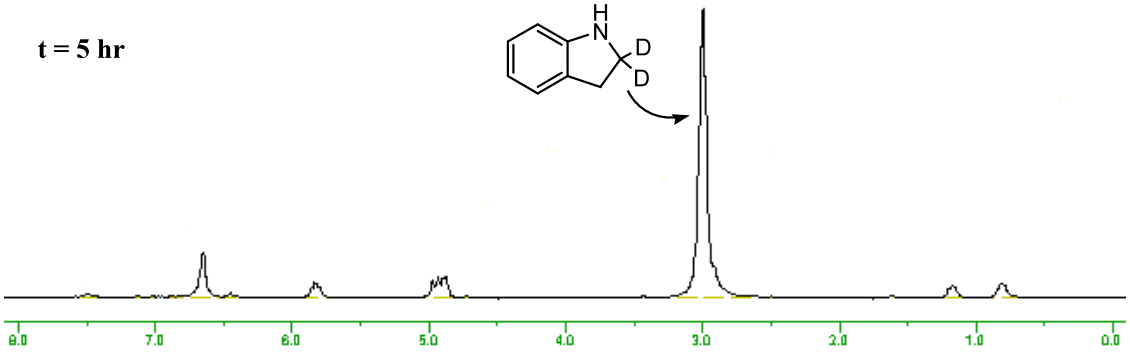

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