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Dehydrogenation of secondary amines to imines catalyzed by an iridium PCP pincer complex: initial aliphatic or direct amino dehydrogenation?

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Abstract

The PCP pincer complex, $IrH_2(C_6H_3\text{-}2,6\text{-}(CH_2PBut_2)_2)$ catalyzes the transfer dehydrogenation of secondary amines to imines. The catalytic system is highly sensitive to both steric and electronic factors and greater than 99% regioselectivity are observed in the dehydrogenation of the asymmetric substrates, cyclohexyethylamine and benzylpropyl amine. Good to excellent yields are obtained when the reactions are carried out in toluene solution. The dehydrogenation of 2,2,2′,2′-tetramethyldibutylamine leads exclusively to the production of the corresponding imine indicating that the catalytic reaction pathway involves direct amino rather than initial aliphatic dehydrogenation.

Keywords: Dehydrogenation; Catalysis; Secondary amines; Imines; Pincer complex

1. Introduction

Imines are one of the basic building blocks of modern synthetic organic chemistry. Although, simple aldimines can be conveniently prepared through the reaction of primary amines with aldehydes [1,2], the synthesis of many classes of imines is more problematic. For example, the preparation of ketimines (especially aryl ketimines) is difficult and often requires the use of metal chlorides as dehydrating agents to overcome the competing reverse reaction [3]. The HCl generated by the metal chlorides leads to unwanted side reactions in many systems even in the presence of excess amine. As a result, methods involving the transformation of primary amines to bis(trimethylsilyl) amines [4] and bis(dichloroaluminal)imides [5] prior to the reaction with ketones, as well as substitution of $Si(OEt)_4$ as a dehydrating agent [6] have been developed.

The dehydrogenation of secondary amines has been explored as an alternate route for the preparation of imines. Stoichiometric methods utilizing strong oxidants such as Swern oxidation have the disadvantage of forming major amounts of side products [7]. Catalytic systems utilizing oxidants under mild conditions have also been developed [8,9]. The most practical of these systems (TON $=\sim$ 50, 80–93% conversion) entails the oxidation of *tert*-butylhydroperoxide catalyzed by $RuCl_2(PPh_3)_3$ [8]. However, the requisite strong oxidant and high catalyst loadings render this system unattractive and it has not been widely employed. The recent discovery of a dinuclear copper(II) complex of 7-azaindole which catalyzes the oxidation of secondary imines by O_2 [10], is an important advance in the development of this methodology but

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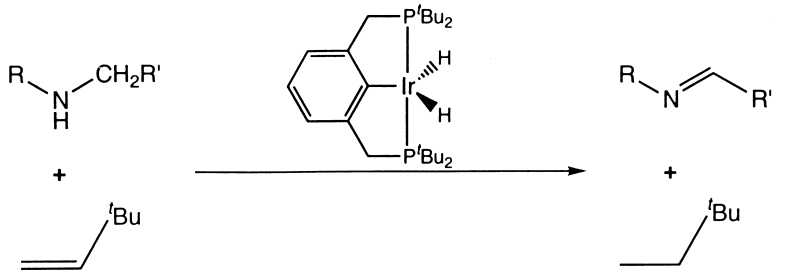
the dehydrogenation activity persists for only five catalytic turnovers.

The iridium PCP pincer complex, $IrH_2(C_6H_3$-2,6-$(CH_2PBut_2)_2)$ (**1**) has been found to be a high efficient and robust catalyst for the dehydrogenation of the aliphatic C–H bonds of cycloalkanes [11,12], linear alkanes [13], ethylbenzene, and tetrahydrofuran [14]. It was therefore, of interest to investigate whether this reactivity could be extended to amines. We have found that **1** is highly effective for the transfer dehydrogenation of saturated secondary amines. However, we found that hydrogen elimination occurs across C–N rather C–C bonds to give imines as seen in Eq. (1). We report here our studies of the scope, utility, and mechanism of this novel catalytic reaction.



(1)

2. Experimental

All manipulations were carried out using standard Schlenk and glovebox techniques under purified argon. Solvents were degassed and dried using standard procedures. The secondary amines were purchased from Aldrich Chemicals Co. and used without further purification. The complex (**1**) was synthesized by the literature method [12]. The ^{1}H NMR spectra were recorded on a Varian Unity Inova 300 spectrometer. Gas chromatographic analysis were performed with a Hewlett-Packard 5890 instrument with a HP 5980A flame ionization detector and HP-1 capillary column (25.0 m). Gas chromatographic–mass spectral (GC–MS) analysis were carried using a HP 5890 SERIES II instrument with an 5971A mass selective detector and HP-1 capillary column (25.0 m).

2.1. Catalytic reactions

Solutions of the secondary amines (1.3 mmol), *tert*-butylethylene (*t*be; 0.20 ml, 1.53 mmol) and 4 ml of toluene were charged with **1** (22 mg, 0.037 mmol) in sealed Schlenk tubes in a vacuum atmospheres glovebox under argon. The tubes were then fully immersed in a constant temperature bath at 200 °C for 72 h. After this time the tubes were allowed to cool to room temperature. All products were identified by GC–MS analysis upon comparison to authentic samples of the imines, that were prepared by the reaction of primary amines with aldehydes by the method of Campbell et al. [1]. Product yields were calculated from the ratio of the integrated intensities of signals produced by the products and those of the toluene solvent after weighting the data by a predetermined relative molar response factor. Mass spectrum of *N*-2,2-dimethylbutyl-2,2-dimethyl-3-butanalimine: (*m*/*e*): 183, $[M]^+$; 168, $[M–CH_3]^+$; 155, $[M–C_2H_4]^+$; 112, $[M–CMe_2C_2H_5]^+$; 98 $[N{=}CHCMe_2C_2H_5]^+$.

2.2. Synthesis of 2,2,2′,2′-tetramethyldibutylamine

A solution of 2,2-dimethylbutylamine (2.80 g, 0.028 mol) and triethylamine (7 ml, 0.050 mol) in dichloromethane (20 ml) was added to a stirred solution of 2,2-dimethylbutanoyl chloride (4.2 g, 0.031 mol) in dichloromethane (20 ml) at 0 °C. The resulting solution was stirred for 1 h at 0 °C and then overnight at 25 °C. The reaction mixture was then washed sequentially with water, 5% sodium bicarbonate, 2N hydrochloric acid, and brine. Removal of the solvent gave 4.90 g (88% yield) of *N*-2,2-dimethylbutyl-2,2-dimethylbutyramide which was used in the next step without further purification.

The intermediate amide (4.90 g, 20 mmol) was reduced to the amine product in anhydrous diethyl ether solution (100 ml) upon gentle reflux with $LiAlH_4$ (0.836 g, 22 mmol) for 48 h. The reaction mixture was cooled in an ice bath and then water was carefully

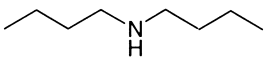
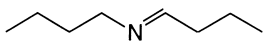
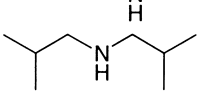
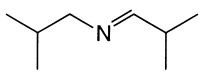
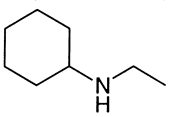
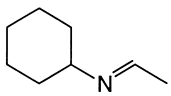
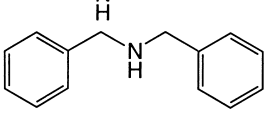
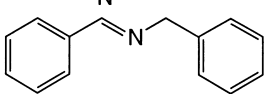
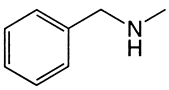
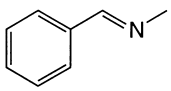
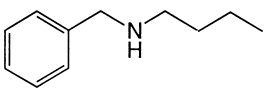
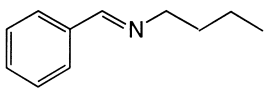
added to decompose any remaining hydride. The resulting sandy suspension was filtered and the solid was washed thoroughly with diethyl ether. The filtrate and washes were combined, dried over magnesium sulfate and distilled. The product, 1.52 g (41% yield), was collected at 194–198 °C as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 4H, HC-1,1′), 1.27 (q, $J = 7.6$ Hz, 4H, H_2C-3,3′), 0.85 (s, 12H, H_3C), 0.82 (t, $J = 7.6$ Hz, 6H, H_3C-4,4′). ^{13}C (^{1}H) NMR (75 MHz, $CDCl_3$): δ 61.30 (C-1,1′), 34.30 (C-2,2′), 32.42 (C-3,3′), 25.13 (C-4,4′), 8.30 (CH_3). MS (*m/e*): 185, $[M]^+$; 170, $[M–CH_3]^+$; 156, $[M–C_2H_5]^+$; 114, $[M–CMe_2C_2H_5]^+$; 85, $[CH_2CMe_2C_2H_5]^+$.

3. Results and discussion

The activity of **1** as a catalyst for the dehydrogenation of secondary amines was initially screened using solutions consisting of only amine, the hydrogen acceptor, *t*be and 0.01 mol% of **1**. The orange solutions were sealed in tubes under argon and fully immersed in an oil bath at 200 °C for 18 h. The solutions became red upon heating and gradually change color to yellow-orange during the reaction period. In all cases, only one dehydrogenated product was detected to the limits of GC analysis. The imine products were identified through GC–MS analysis upon comparison of their mass spectrum to that of authentic samples that were prepared through standard methods. A wide variety of secondary amines were found to undergo highly selective dehydrogenation to imines. Greater than 99% regioselectivity was observed in the dehydrogenation of the asymmetric substrates, cyclohexyethylamine and benzylpropyl amine, which underwent dehydrogenation to *N*-cyclohexylacealimine and *N*-propylbenzalimine, respectively. These results demonstrate the high sensitivity of the catalytic system to both steric and electronic factors.

Approximately 10% conversion to the imine products was achieved in our initial studies of the dehydrogenation of the neat amine. It was found that further catalytic activity could be obtained from **1** upon its isolation from the reaction mixture. Thus catalytic activity ceases after ∼1000 turnovers not as the result of complex degradation rather because an inhibiting concentration of the imine product is attained. This finding is consistent with the established pattern of product inhibition that has uniformly been found to limit dehydrogenation reactions catalyzed by **1** [15]. We previously found that in case of alcohol dehydrogenation, this problem was eliminated upon dilution

Table 1
Dehydrogenation of secondary amines using **1** as catalyst

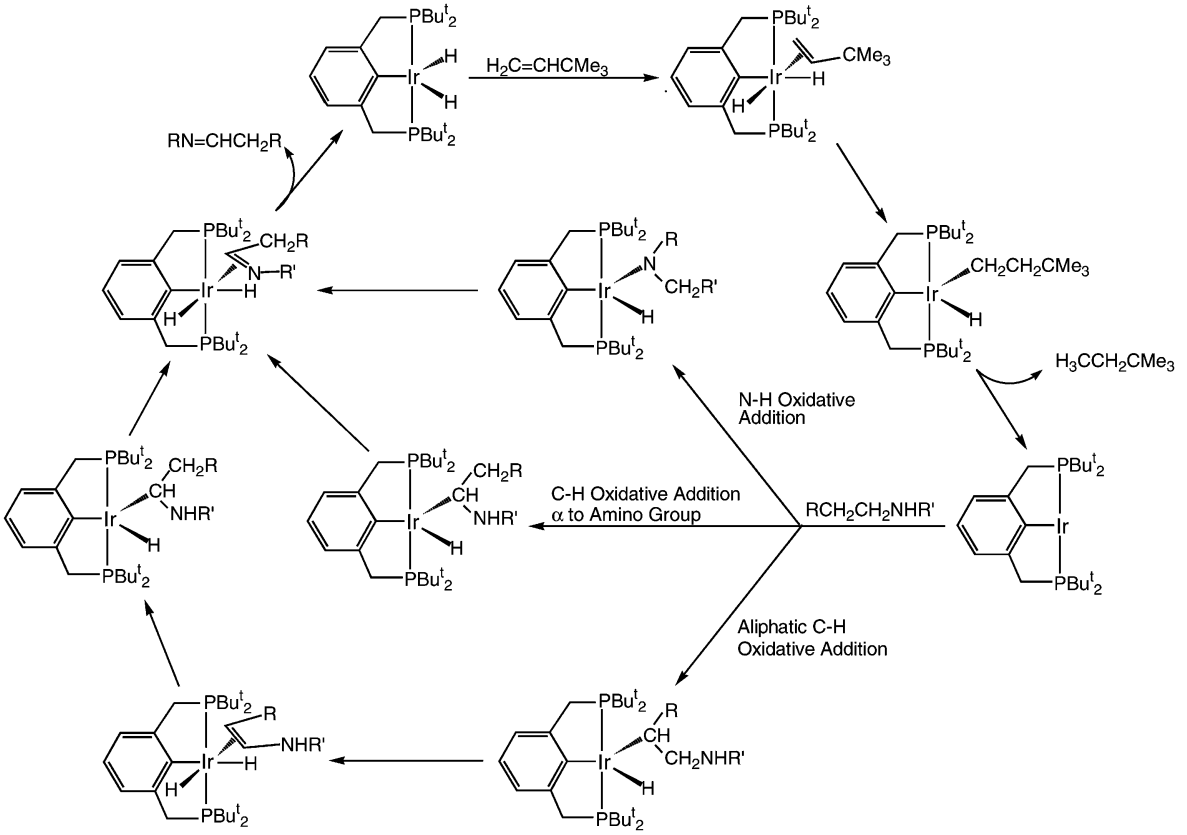
Subtrate	Product	Yield (%)
		72
		77
		94
		64
		53
		60

Reaction conditions: amine, 0.26 mmol; *t*be, 0.26 mmol; 4 ml of toluene and **1**, 22 mg, 0.037 mmol at 200 °C for 72 h.

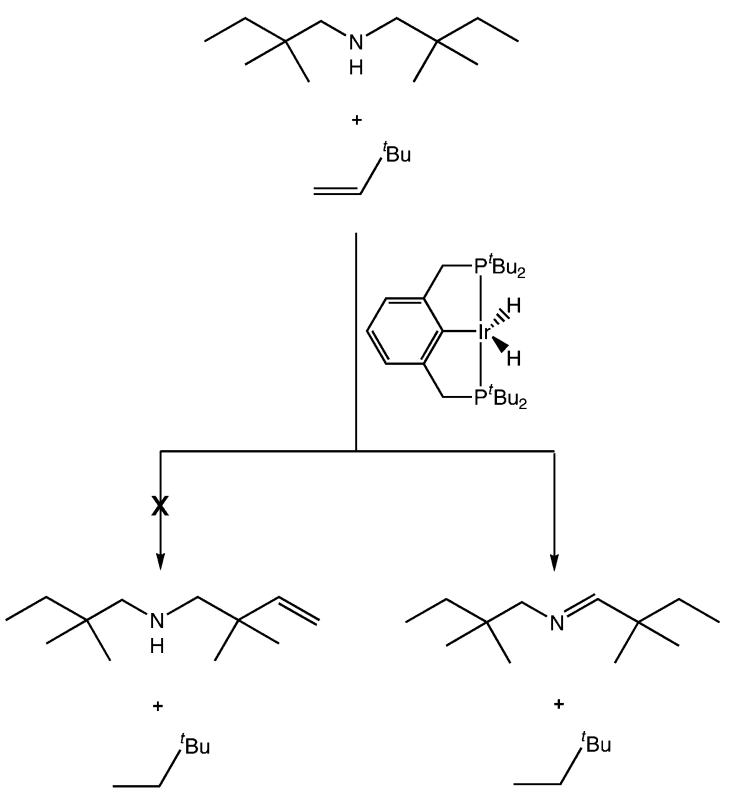
of the catalytic system with toluene [16]. This strategy was also found to be successful with secondary amines. As seen in Table 1, good to excellent yields were obtained in reactions carried out in diluted toluene solutions in the presence of very high catalyst loading. However, it should be noted that the catalytic efficiency is greatly diminished in these high yield reactions. Even at 200 °C, a reaction time of 3 days is required to reach the optimal yields and the turnover numbers are nearly two orders of magnitude lower than those obtained in the reactions with neat amines.

It is now generally accepted that the transfer dehydrogenation of linear alkanes by **1**, occurs predominantly through the initial oxidative addition of methyl C–H bonds to the intermediate 14-electron complex, Ir(C_6H_3-2,6-(CH_2PBut_2)$_2$), **2** which arises upon dehydrogenation of **1** by *t*be [15,17]. Previous studies of the catalytic dehydrogenation of linear alkanes revealed that while terminal alkenes are the kinetically preferred product of the reaction, they are subject to secondary catalytic isomerization by **1** and ultimately internal alkenes are obtained [13]. Additionally, mechanistic studies of the palladium black catalyzed hydrolysis of tertiary amines indicated that the reaction involves the initial aliphatic dehydrogenation of amines to enamines that are subsequently converted to imines [18]. Thus, a priori the "aliphatic C–H oxidative addition" pathway seen in Scheme 1 seem to be a viable mechanistic possibility. We also considered an alternative mechanism involving direct dehydrogenation across a C–N bond through an initial N–H or C–H oxidative addition to **2** followed by beta hydrogen elimination as per the "N–H oxidative addition" and "C–H oxidative addition to a amino group" pathways seen in Scheme 1.

In order to distinguish between the pathways involving initial alipathic versus direct amino dehydrogenation, we examined the dehydrogenation



Scheme 1.



Scheme 2.

of 2,2,2′,2′-tetramethyldibutylamine (**3**). If **3** underwent dehydrogenation across the terminal ethyl C–C bond to give the enamine product seen in Scheme 2, the presence of a quanternary carbon in the aliphatic chain would prevent secondary internalization of the unsaturation via sequential hydride migration and β-elimination. The transfer dehydrogenation of **3** was carried out under the standard conditions employed in this study. GC–MS analysis of the reaction mixture indicated that only one product was produced whose mass spectrum is identical to that of an authentic sample of *N*-2,2-dimethylbutyl-2,2-dimethyl-3-butanalimine that was prepared by the condensation of 2,2-dimethylbutylamine and 2,2-dimethylbutanal. The mass spectrum of the imine is distinct from that expected for the enamine as it contains a peak at *m/e* 98 corresponding to a $[N{=}CH_2CMe_2C_2H_5]^+$ fragment. The presence of an internal unsaturation is also indicated by the presence of *m/e* 155, $[M–C_2H_4]^+$ peak rather than a *m/e* 155 $[M–C_2H_5]^+$ peak. The *m/e* 112, $[M–CH_2CMe_2C_2H_5]^+$ peak is the most intense in the spectrum. Thus, the lack of a *m/e* 114, $[M–CH_2CMe_2CH{=}CH_2]^+$ peak clearly indicates the lack of a distal unsaturation. Additionally, the production of the imine was confirmed by NMR spectroscopy of the crude product that was obtained upon removal of the volatile components from the reaction mixture en vacuo. The ^{1}H NMR spectrum contained a distinctive signal at ∂ 7.47 ppm that can readily be assigned to the alpha hydrogen of a dialkyl imine and the ^{13}C NMR spectrum contained the expected resonance at 171.3 ppm for the imine carbon. Therefore, it appears that the reaction pathway involves direct amino rather than initial aliphatic dehydrogenation. This conclusion is consistent with the observation that the catalytic system to be completely ineffective with tertiary amines [19].

4. Conclusions

The PCP complex **1** catalyzes the dehydrogenation of secondary amines to imines. Good to excellent yields can be obtained upon dilution of the catalytic system with toluene but the practicality of the system for organic synthesis is questionable in view of the high catalyst loading that is required. The lack of reactivity with tertiary amines and the exclusive production of the corresponding imine in the dehydrogenation of 2,2,2′,2′-tetramethyldibutylamine indicate that the catalytic reaction pathway involves the direct amino rather than initial aliphatic dehydrogenation.

Acknowledgements

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