

# Novel synthesis of enamines by iridium-catalyzed dehydrogenation of tertiary amines†

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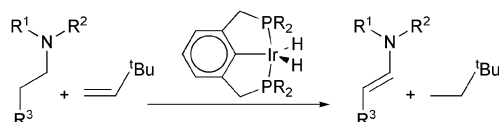
**A novel route to enamines is reported, the dehydrogenation of tertiary amines catalyzed by a “pincer-ligated” iridium catalyst.**

Enamines are of great importance as organic synthons. They are used extensively as nucleophiles for the selective formation of C–C bonds by Michael reactions, as Diels–Alder dienophiles, and in a wide range of other reactions.<sup>1</sup> Enamines are most commonly synthesized by the condensation reaction of secondary amines with carbonyl compounds.<sup>1</sup> This method has several limitations including harsh reaction conditions. Other routes that have been applied include dehydrocyanation of  $\alpha$ -aminonitriles,<sup>2</sup> dehydrohalogenation of haloethylamines,<sup>3</sup> addition of Grignard reagents to dialkylformamides,<sup>4</sup> and hydroamination of alkynes.<sup>5,6</sup> Barluenga has recently reported palladium-catalyzed cross-coupling between secondary amines and alkenyl bromides.<sup>7</sup> Cyclic tertiary amines have been reported to undergo oxidation by mercuric acetate, generally involving the removal of a tertiary hydrogen atom.<sup>1a</sup> All of these approaches have very significant limitations.<sup>1–7</sup>

In recent years “pincer”-ligated transition metal complexes such as  $(t\text{-BuPCP})\text{IrH}_2$  ( $t\text{-BuPCP} = \eta^3\text{-2,6-(}t\text{Bu}_2\text{PCH}_2)_2\text{C}_6\text{H}_3$ ) (**1**) have been found to be effective and robust catalysts for the dehydrogenation of alkanes<sup>8</sup> (also ethylbenzene and THF<sup>9</sup>) either with or without the use of a sacrificial hydrogen acceptor (an olefin, typically *tert*-butylethylene or norbornene). Recently, Jensen has reported that **1** catalyzes dehydrogenation of the H–N–C–H linkage of secondary amines to give imines.<sup>10</sup> We have initiated a program to explore the potential of pincer-ligated catalysts for the dehydrogenation of H–C–C–H linkages of functionalized organic molecules. Herein we report on the transfer-dehydrogenation of alkyl groups of tertiary amines to give enamines.

A wide variety of tertiary amines were found to undergo surprisingly facile dehydrogenation by **1** (Scheme 1). Reactions were typically conducted at 90 °C in *p*-xylene solution with *ca.* 100 mM amine, 10 mM **1** (10% catalyst load), and 200 mM *tert*-butylethylene (TBE) acceptor, until catalytic activity ceased, unless otherwise indicated.† Reaction yields are moderate to good. Results are summarized in Table 1.

Heating a solution of **1** (10 mM), triethylamine (100 mM) and TBE (100 mM) at 90 °C for 12 h yields vinyl(diethyl)amine as the only observable product in 65% yield‡ (further heating yields no additional product). However, when the TBE : triethylamine ratio is 3 : 1, a significant yield of di-dehydrogenated product, *N,N*-divinylethylamine (25%), is



**Scheme 1** Transfer-dehydrogenation of tertiary amines catalyzed by **1** (*tert*-butylethylene shown as hydrogen acceptor).

† Electronic supplementary information (ESI) available: detailed experimental procedures and spectroscopic information. See <http://www.rsc.org/suppdata/cc/b3/b304357f/>

obtained (in addition to 54% mono-dehydrogenated *N,N*-diethylvinylamine).

To preclude the complicating (though potentially useful) phenomenon of multiple dehydrogenations, *N,N*-di(isopropyl)ethylamine and *N,N*-dimethylethylamine were investigated as dehydrogenation substrates. The reaction with *N,N*-di(isopropyl)ethylamine was found to reproducibly give excellent dehydrogenation yields at 90 °C (*ca.* 100%). Even at ambient

**Table 1** Dehydrogenation of tertiary amines catalyzed by **1**

| Entry | Amine | Product | Ref. | Conditions <sup>a</sup>      | Yield (%) <sup>b</sup> |
|-------|-------|---------|------|------------------------------|------------------------|
| 1     |       |         | c    | 5 h<br>24 h<br>2 mM <b>1</b> | 98                     |
|       |       |         |      |                              | 65                     |
| 2     |       |         | 3    | a                            | 65                     |
| 3     |       |         | 3    | 12 h<br>0.1 M TBE            | 65                     |
| 4     |       |         | 3    | 0.3 M TBE<br>0.3 M NBE       | 64                     |
|       |       |         |      |                              | 25                     |
| 5     |       |         | c    | 0.3 M TBE<br>0.3 M NBE       | 25                     |
|       |       |         |      |                              | 75                     |
| 6     |       |         | 12   | a                            | 43                     |
|       |       |         |      |                              | 11                     |
| 7     |       |         | 13   | a                            | 10                     |
| 8     |       |         | 14   | a                            | 30                     |
| 9     |       |         | 15   | a                            | 35                     |
| 10    |       |         | 16   | 0.3 M TBE<br>0.2 M NBE       | 67                     |
|       |       |         |      |                              | 92                     |
| 11    |       |         |      | 110 °C                       | N.R.                   |

<sup>a</sup> Conditions unless otherwise specified: 90 °C, 10 mM **1**, 100 mM amine, 200 mM TBE, 24 h, *p*-xylene-*d*<sub>10</sub> solvent. <sup>b</sup> Yields determined by <sup>1</sup>H NMR. <sup>c</sup> Previously unreported compound.

temperature 60% yield was obtained after 24 h. *N,N*-Dimethylethylamine also gave clean dehydrogenation but the yield of the corresponding vinylamine was not as high (65% at 90 °C), and was lower still at lower temperatures.

In the dehydrogenation reactions of two amines containing *N*-bound *n*-propyl groups, *N,N*-di(isopropyl)-*n*-propylamine and tri-*n*-propylamine, (*E*)-1-propenylamines were formed (*ca.* 40% yield; Table 1, entries 5 and 6). Yields and rates were lower than those found for the aminoethyl groups in accord with the previously reported kinetic preference of **1** for the dehydrogenation of the terminal position of *n*-alkanes.<sup>8d</sup>

Using norbornene (NBE) instead of TBE as a hydrogen acceptor was found to give higher yields in some cases. For example, dehydrogenation of triethylamine gave *ca.* 100% conversion with 75% yield of di-dehydrogenated product, *N,N*-divinylethylamine.

It is noteworthy that *N,N*-di(isopropyl)vinylamine, *N,N*-divinylethylamine, *N,N*-diisopropyl-1-(*E*)-propenylamine, and *N,N*-di-(*E*)-1-propenylpropylamine are all previously unreported compounds.

All of the enamine products noted above degraded (usually within several hours) after being isolated from the catalyst (*via* vacuum transfer of enamine and solvent); this observation is consistent with the known instability of simple enamines.<sup>1,3</sup> Remarkably, however, we find that the products are stable for extended periods in the original catalyst-containing solutions. Presumably, the catalyst inhibits chain decomposition reactions. This property may substantially contribute to the utility of the present method for generating and exploiting enamines.

*N*-Methylpyrrolidine was dehydrogenated to *N*-methylpyrrole in modest yield. However *N*-methylpiperidine was surprisingly resistant to dehydrogenation. In accord with the lack of reactivity of the six-membered heterocycle, *N*-ethylpiperidine showed dehydrogenation exclusively at the ethyl group (see Table 1, entries 8–11).

The apparently high reactivity of the acyclic amine substrates, as indicated by the good product yields, was confirmed in a competition experiment between *N,N*-di(isopropyl)ethylamine (60 mM) and cyclooctane (600 mM).<sup>‡</sup> (Cyclooctane is a substrate frequently used in alkane dehydrogenation studies because of its anomalously low enthalpy of dehydrogenation.) The ratio of cyclooctene to vinylamine remained roughly constant (1 : 2.0), even from the earliest reaction times, indicating that the observed product ratio reflects reaction kinetics, not thermodynamics.<sup>¶</sup> Dehydrogenation of the aminoethyl group was thus found to be 20 times more rapid than dehydrogenation of cyclooctane on a per mol basis; on a per C–C bond basis the ratio is therefore 160.

Competition experiments between varying *N,N*-di(alkyl)ethylamines reveal that reactivity is dependent upon the ancillary *N*-alkyl group as follows: isopropyl > ethyl > methyl in the ratio 140 : 7 : 1. This seems in discord with expectations based on steric or electronic factors, at least if the reaction is assumed to proceed *via* an oxidative-addition/ $\beta$ -hydrogen elimination mechanism.<sup>11</sup> In particular, although oxidative addition is expected to be favored by a less electron-rich substrate, the more electron-rich, more highly substituted, *N,N*-di(alkyl)ethylamines apparently favor dehydrogenation. Very likely, this trend is closely tied to the high reactivity found for tertiary amines, in general, relative to alkanes.

We considered that the unusually high reactivity of the tertiary amines, and the more highly substituted amines in particular, might be attributed to a mechanism involving electron transfer (oxidation of the amine). In this context we conducted the following isotope-effect experiments. <sup>i</sup>Pr<sub>2</sub>N(C<sub>2</sub>D<sub>5</sub>) was synthesized (from the reaction of <sup>i</sup>Pr<sub>2</sub>NH and C<sub>2</sub>D<sub>5</sub>I<sup>17</sup>). In a competitive catalytic reaction **1** (10.2 mM), TBE (250 mM), *N,N*-di(isopropyl)ethylamine (30.7 mM) and *N,N*-di(isopropyl)(ethyl-d<sub>5</sub>)amine (61.4 mM), were reacted; *k<sub>H</sub>*/*k<sub>d</sub>* was found to be 7. A stoichiometric competition reaction gave the same value (within experimental error): (PCP)Ir(H)(Ph) (32.8 mM) was reacted with *N,N*-di(isopropyl)ethylamine (95

mM) and *N,N*-di(isopropyl)(ethyl-d<sub>5</sub>)amine (296 mM), and *k<sub>H</sub>*/*k<sub>d</sub>* was found to be 6. Thus electron transfer from the amine is apparently not rate-determining. Analogous isotope-effect studies are presently being conducted with alkanes which will be used for purposes of comparison.

In summary, we report the first catalytic synthesis of enamines from tertiary amines. The tertiary amines show surprisingly high reactivity and, fortuitously, the presence of the catalyst prevents decomposition of the enamine products. Studies regarding the scope of applicability of this reaction, as well as the mechanism and the origin of the surprisingly high reactivity, are presently underway.

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## Notes and references

‡ All reactions gave no spectroscopically observable materials other than the product noted. Products were characterized by <sup>1</sup>H NMR and, in some cases, GC-MS. All yields were determined by <sup>1</sup>H NMR. Removal of volatiles from the catalyst by vacuum transfer was conducted in some cases to facilitate characterization. Detailed experimental procedures and spectroscopic information are given as ESL.<sup>†</sup>

§ For example a solution of *N,N*-di(isopropyl)vinylamine was found to be stable for 2 months in the catalyst-containing solution (even after evacuating unreacted TBE, thus indicating that the presence of TBE is not responsible for the unusual stability of the enamines).

¶ Cyclooctane dehydrogenation is thermodynamically more favorable ( $\Delta H = 24 \text{ kcal mol}^{-1}$ )<sup>18</sup>) than dehydrogenation of an aminoethyl group (estimated  $\Delta H = 26.1 \text{ kcal mol}^{-1}$ ).<sup>1d</sup>

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