Reduction of Imines to Amines through Use of the Cp2MoH2 and Protonic Acid System

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Imines are conveniently reduced to the corresponding amines by molybdenum dihydride Cp_2MoH_2 under mild conditions in good yields. In the presence of a ketone only an imine was reduced and the ketone was recovered quantitatively.

Although much is known about the reduction of ketones and aldehydes by metal hydrides, the analogous reduction of imines has received much less attention. However, from the standing point of the field of alkaloid syntheses, a reduction of imino groups is particularly interesting.[1] In our continuing research for molybdenum polyhydride compounds,[2] we reported previously the unique ability of a system consisting of molybdenum dihydride Cp_2MoH_2[3] ($Cp = \eta\text{-}C_5H_5$) **I** and protonic acids such as RCOOH, HCl, and TsOH (*p*-toluenesulfonic acid) to effect reductions of aldehydes and ketones to the corresponding alcohols (eq. (1)).[4,5]

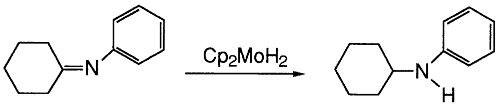
$$\underset{\mathbf{I}}{Cp_2MoH_2} + 2RCOR' \xrightarrow{2HA} \underset{\mathbf{II}}{Cp_2MoA_2} + 2RCHOHR' \qquad (1)$$

$$HA = HCl, AcOH, TsOH$$

With the system shown in eq. (1), reductions take place under mild conditions stereoselectively. For example, in the reduction of 4-*t*-butylcyclohexanone to *cis*-4-*t*-butylcyclohexanol, an extremely high diastereoselectivity was achieved. Furthermore it was found that the system was unreactive to esters. An important feature of this reducing system is that the diacetate **II** (A = AcO) formed can be reverted quantitatively to the starting **I** by treatment with $NaBH_4$ in propan-2-ol. Thus the dihydride complex **I** can be recycled. We now report that the use of this system for imines results in facile reductions to the corresponding amines.

At first we carried out the reduction of *N*-cyclohexylideneaniline (imine **1**) to *N*-cyclohexylaniline at room temperature under various conditions in order to obtain the optimum conditions. Three different types of solvents, namely methanol, THF, and toluene, were tested (Table 1).

The reductions were performed via a procedure similar to that employed for reduction of ketones. The typical one is as follows (Table 1, Run 1): to a solution of Cp_2MoH_2 (0.165 g, 0.725 mmol) and the imine **1** (0.255 g, 1.47 mmol) in toluene (10 ml) was added equimolar amount of AcOH (0.103 g, 1.71 mmol). The reaction mixture was stirred at ambient temperature for 34 h under argon. The resultant solution was concentrated to dryness under reduced pressure. To this residue was added a proper quantity of 5% sodium hydrogen carbonate solution and the mixture was extracted with ether in three portions. The extracts were combined and dried over $MgSO_4$. The product was purified by medium pressure column chromatography using hexane - ethyl acetate (9 : 1).



imine **1**

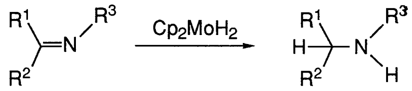
Table 1. Reduction of *N*-cyclohexylideneaniline **1** with Cp_2MoH_2 **I**

Run	Cp_2MoH_2 (mmol)	Imine (mmol)	Solvent	Yield %[a]
1	0.73	1.47	toluene	89[b]
2	0.77	0.77	toluene	0
3	0.81	1.69	THF	81[b]
4	0.81	1.69	THF	0
5	0.72	1.44	methanol	79

a) Isolated yield based on the Cp_2MoH_2 **I**.
b) Acetic acid (1.71 mmol) was added.

The reactions proceeded in satisfactory yields and all solvents tested were suited to this process. The reductions were completed within 70 h at room temperature in all cases. It was noted that in contrast to the reduction of ketones and aldehydes, the imine was reduced without protonic acid in methanol (Run 5). In toluene (Run 2) or in THF (Run 4), no product was obtained in the absence of protonic acid. Since the imines are known to be more susceptible to the nucleophilic attack than ketones or aldehydes, it is conceivable to consider that methanol played a role of protonic acid in this case.

Subsequently, we carried out the reduction of several imines and the results are shown in Table 2. The reductions proceeded smoothly in all cases.[6] In the case of imine **4** (Run 8), the reduction was slow in the absence of protonic acid.



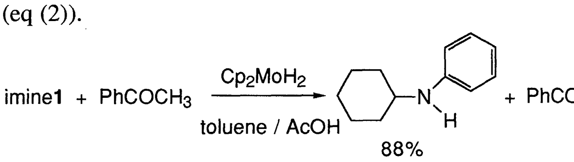
imine **2** $R^1 = R^2 = Et$, $R^3 = Ph$
imine **3** $R^1 = R^2 = {}^nPr$, $R^3 = Ph$
imine **4** $R^1 = Et$, $R^2 = Ph$, $R^3 = Ph$

Table 2. Reduction of imines with Cp_2MoH_2 **I**[a]

Run	Imine (mmol)	Cp_2MoH_2 (mmol)	Time (h)	Yield %[b]
6	**2** (3.10)	1.10	18	78
7	**3** (2.69)	1.05	72	48
8	**4** (1.48)	1.47	24	53[c]

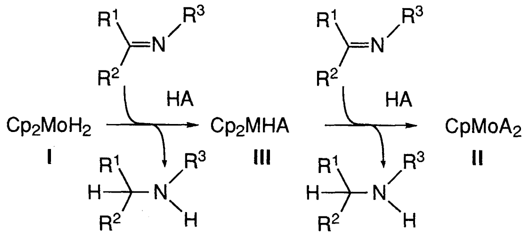
a) All reductions were carried out in methanol at room temperature under argon.
b) Based on the Cp_2MoH_2 used.
c) The reduction was carried out in the presence of TsOH.

As *N*-cyclohexylideneaniline **1** seems to be more reactive than ketones, we examined the reduction of imine **1** in the presence of acetophenone in our system and confirmed that imine **1** was reduced selectively and acetophenone was recovered unreacted (eq (2)).



(2)

Although the mechanism of this reduction is not known with certainty, it seems likely that it is basically a two-step process as shown in the following Scheme, which is similar to that of the reduction of ketones. Monohydride complex **III** has been observed in ^{1}H-NMR in the course of reduction process. In addition, monohydride complex **III** has been independently prepared[7] and was shown to give the amine when treated with imine **1**.



HA : AcOH, TsOH, CH_3OH

Further studies are in progress aimed at inducing asymmetry through the use of chiral acid.

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References and Notes

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6 We found that *N*-cyclohexylidenecyclohexylamine (R^3 = cyclohexyl) can not be reduced by the present system. However, in the presence of Lewis acids, that imine was found to be reduced to afford the corresponding aminne. A more detailed report of the reaction will be presented elsewhere.

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