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Titanium promoted reduction of imines with Grignards, silanes, and zinc: identification of a new mechanism with silanes

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ABSTRACT

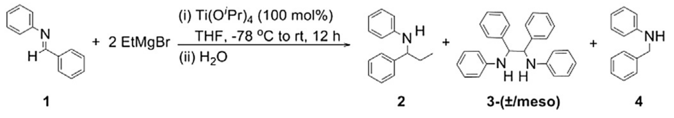
Aldimines react with reducing agents, such as Grignards, phenylsilane or zinc in the presence of titanium(IV) isopropoxide to form amines and reductively coupled imines (diamines). Using deuterium labeled reagents, the mechanism of reduction to form amines is described. Reducing agents, such as the Grignard and zinc result in the formation of low valent titanium (LVT), which in turn reduces the imine. On the other hand, phenylsilane reacts by a distinctly different mechanism and where a hydrogen atom from silicon is directly transferred to the titanium coordinated imine.

1. Introduction

Amines are key functional groups, extensively present in natural products, in catalysts, and in radiopharmaceuticals.[1] A convenient route to synthesize amines is through reduction of imines. Unfortunately, this reaction is often complicated by a reductive coupling reaction, leading to the formation of diamines. Thus, in the reduction of *N*-benzylideneaniline mediated by alkali metals, only minor amounts of the reduced product are observed, which is attributed to the dimetallation of the imine.[2] However, the major product is a diamine, which is reminiscent of the pinacol type coupling promoted by reduced titanium species.[3] The formation of dimetallated species in such reactions is confirmed by quenching the reaction with deuterium oxide, which results in the formation of *N*-(α-deuterobenzyl)aniline with >85% deuteration.[3d] Fujiwara and co-workers have reported that the reaction of ketimines with Yb metal in the presence of a catalytic amount of MeI gave reduced imines in good yield via hydrolysis of the Yb(II) *N*-diarylmethyleneaniline dianion.[4] In order to get a better understanding of the La promoted reactions, Nishiyama and co-workers have performed similar reactions and hydrolyzed the intermediate with D_2O instead of H_2O.[4c] About 79% deuterium incorporation was observed in the resulting reduced imine, suggesting the intermediacy of a dianion. The intermediacy of the dianion or a three membered azametallacycle is well established in the case of titanium.[3] In these reactions, Grignard reagents or alkyl lithium reagents are used to generate the low valent titanium(II) species.[3h,i]

In the case of titanium, a second path has also been established where the low valent titanium reagent generated from $TiCl_4$ transfers a single electron (SET) to the imine.[5] This generates a radical anion, which then abstracts a hydrogen from the solvent to give the reduced product. The facile delivery of a hydrogen radical by THF is said to be responsible for the formation of the amine.

We have recently reported[6] that the reaction of Grignard reagents with imines at low temperatures (−78 °C), in the presence of stoichiometric amounts of titanium isopropoxide ($Ti(O^iPr)_4$) is significantly different from that carried out at −40 °C.[3c] It leads to formation of the coupled imine **3** (major) rather than the reduced amine **4**, with minor amounts of the alkylation product **2** (Scheme 1). Deuterium labeled Grignard reagents were used to understand the mechanism of alkylation leading to **2** and the formation of the coupled imine.[6]



Scheme 1. Titanium isopropoxide mediated reaction of imine **1** with EtMgBr.

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In the present study we have investigated the mechanism of formation of amines from imines using titanium(IV) isopropoxide and three different reducing agents (Grignard reagents at −78 °C, phenylsilane, and zinc metal). Isotopic labeling studies and quenching experiments with deuterium oxide indicate that the mechanisms involved in these reactions are significantly different from one another and in the case of zinc, dependent on the solvent.

2. Results and discussion

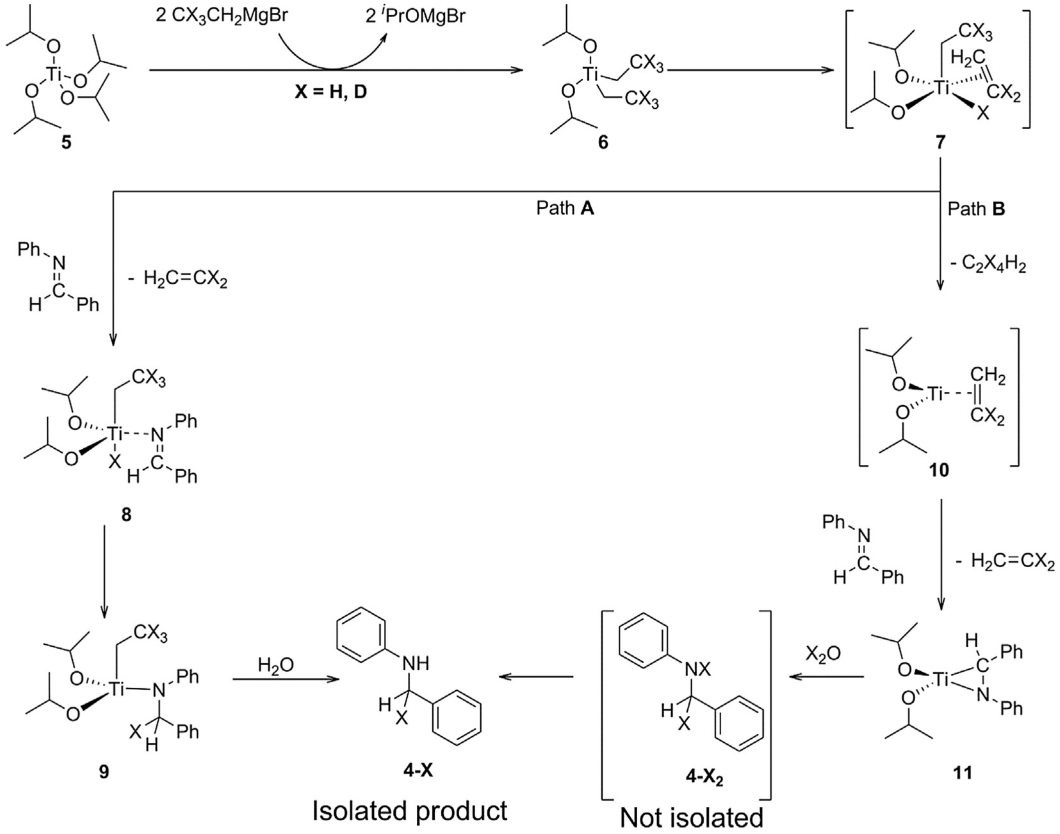
2.1. Reduction of *N*-benzylideneaniline with Grignards

The reduced product **4** occurs via a parallel reaction and can be formed either through path **A** or through path **B** (Scheme 2). Path **A** involves transfer of β hydrogen from the alkyl group to the aza carbonyl carbon of the imine via Ti. Hence if path **A** is involved in the reduction of imine, then on use of deuterium labeled substrate ethyl-2,2,2-d3-magnesium bromide (CD_3CH_2MgBr), which contains a β deuterium, one should observe deuterium incorporation in the reduced product **4**.

The reaction of imine **1** with 2 equiv of CD_3CH_2MgBr in the presence of 1 equiv of titanium isopropoxide was carried out. After completion of the reaction it was quenched with water. The reduced product formed was analyzed by ^2H and $^{13}C\{^1H\}$ NMR spectroscopy. The ^2H NMR spectrum showed a very small peak at δ 4.34 and the $^{13}C\{^1H\}$ NMR spectrum showed a small triplet centered at δ 47.95 and a more intense singlet at δ 48.28 in the ratio 0.14:1.00. The deuterium incorporation observed in the product was about 12% indicating that only a small amount of the product is formed through path **A**.

In order to address the possibility of intermediates like **11** shown in path **B** of Scheme 2, the reaction of imine **1** was carried out with 2 equiv of ethylmagnesium bromide (CH_3CH_2MgBr) in the presence of 1 equiv of titanium isopropoxide. The reaction mixture was quenched with deuterium oxide (D_2O). Not surprisingly ^2H and $^{13}C\{^1H\}$ NMR spectroscopy analysis of the reduced product formed showed significant amount of deuterium incorporation. The ratio of the triplet at δ 47.95 to the singlet at δ 48.28 was 3.11:1.00. The reduced product **4** formed was found to be about 76% deuterated. This clearly indicates that the three membered titanacycle intermediate **11**, which is responsible for the formation of the coupled product **3** as reported earlier,[3,6] is also responsible for the formation of the reduced product from a hydrolysis reaction. Although the product distribution is different from that reported by Sato from a reaction at −40 °C, the intermediate involved in the reaction appears to be the same. Sato and co-workers have previously reported 90–98% deuterium incorporation due to a three membered azatitanacycle in similar reactions.[3c]

A comparison of the peaks corresponding to reduced product **4** in $^{13}C\{^1H\}$ NMR for CD_3CH_2MgBr on hydrolysis and CH_3CH_2MgBr on deuterolysis is given in Fig. 1. Only a minor amount (12%) of reduced product is formed via path **A** due to the transfer of hydride to imine **1** from a Ti–H species **8** formed as a result of β hydride elimination.



Scheme 2. Plausible mechanism for the formation of reduced imine **4** in the titanium isopropoxide mediated reaction of imine **1** with CX_3CH_2MgBr through path **A** and through path **B** where X=H/D.

2.2. Reduction of *N*-benzylideneaniline with phenylsilane

It would be interesting to see if the same type of intermediate **11** is involved, when reducing agents other than Grignards are used. To probe this, we examined the reaction of phenylsilane with imine **1** mediated by titanium isopropoxide where minor amounts of