Pergamon

Tetrahedron Letters, Vol. 38, No. 43, pp. 7487-7490, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01797-8

Reduction of Imines via Titanium-Catalyzed Hydromagnesation

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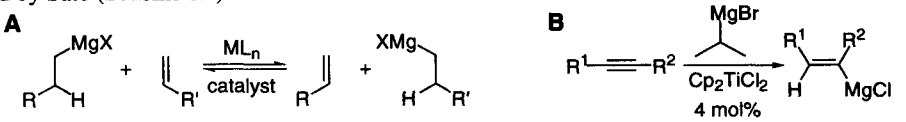
Abstract: We have recently discovered that imines can be reduced to amines via a titanium catalyzed hydromagnesation reaction. These reactions employ *n*-BuMgCl (1.2 eq) as the stoichiometric reducing agent and Cp_2TiCl_2 (3-5 mol%) as a catalyst. Reactions are run under nitrogen at ambient temperature and pressure. For most aldimine and cyclic ketimine substrates amine products are obtained in yields ranging from 69-94%. The reaction is not tolerant of bulky nitrogen substituents or primary enolizable protons on the imine substrate.

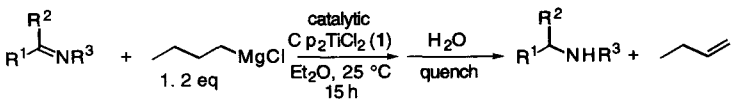
The catalytic reduction of imines[1-5] and hydrazones,[6] particularly the enantioselective reduction of prochiral substrates, has attracted considerable interest in recent years. Processes have been developed using titanium,[1,2] ruthenium,[3] iridium[4] and rhodium,[5,6] complexes as catalysts and hydrogen[1,3-6] or silanes[2] as stoichiometric reducing agents. We recently found that imines can be reduced to amines via titanium-catalyzed hydromagnesation. Herein we report our preliminary findings.

It has been known for some time that some transition metal compounds will catalyze the exchange of H-MgX between Grignard reagents possessing β-hydrogens and certain unsaturated hydrocarbons (Scheme 1A).[7,8] One of the most widely used variants of this reaction is the alkyne hydromagnesation protocol developed by Sato (Scheme 1B).[9]



Scheme 1

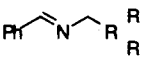
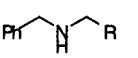
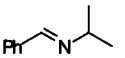
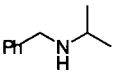
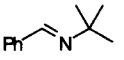
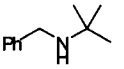
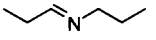
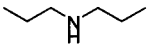
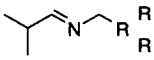
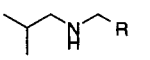
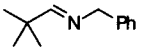
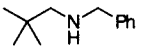
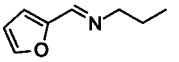
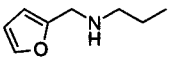
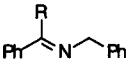
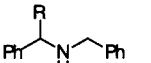
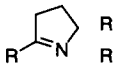
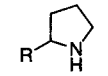
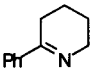
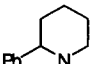
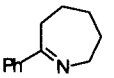
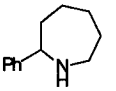
During the course of our studies of the titanium-mediated reductive cyclization of δ,ε-unsaturated imines,[10] we discovered that imines are readily reduced by *n*-BuMgCl in the presence of a catalytic quantity of Cp_2TiCl_2 (**1**, Eq 1). Excellent yields are obtained using slightly more than 1 equivalent *n*-BuMgCl and 3-5 mol % Cp_2TiCl_2.[11,12] Results are summarized in Table 1.



(1)

The imine hydromagnesation reaction that we have described above may proceed as described in Scheme 2 (catalytic cycle). Imine insertion into a Cp_2Ti-H species followed by transmetallation between the titanium amide intermediate and *n*-BuMgBr generates Cp_2Ti-*n*-Bu and magnesium amide product. The catalytic cycle

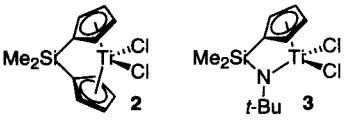
Table 1. Titanium-Catalyzed Reduction of Imines

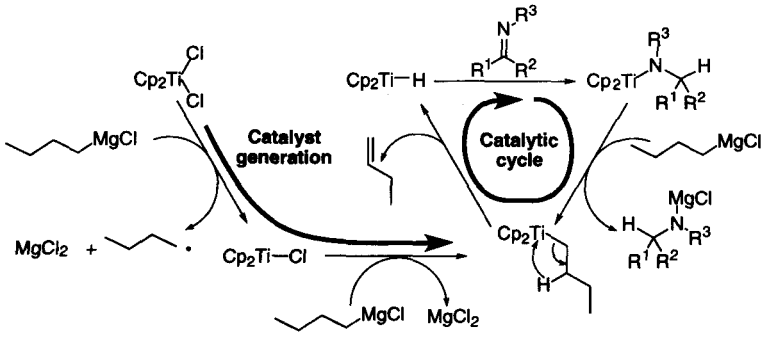
Entry	mol% 1	substrate	Unreacted[b]	product	Yield[a]
1	3	 R = Et	0		94
2		R = Ph	0		89
3	5		88		5
4	100		0		94
5	5		92		0
6	100		46		46
7	5		c		0[d]
8	5	 R = Et	0		93
9		R = Ph	0		92
10	5		23		71
11	10		0		83
12	3		40		48
13	10		11		69
14	5-20	 R = Me, Et, *i*-Pr	c	 R = Me, Et, *i*-Pr	0[d]
15	3	 R = Me	< 5		0[d]
16	3	R = Ph	6		85
17	3		10		83
18	3		10		89

(a) Reported yields (%) are for pure, isolated products. (b) Unreacted imine substrate estimated by NMR integration of crude product. (c) Not determined. (d) A complex mixture of products was obtained.

is completed by a β-hydride elimination converting Cp_2Ti-*n*-Bu to Cp_2Ti-H and 1-butene. Formation of the Ti(III) hydride species, Cp_2Ti-H, initially generated via reduction of Cp_2TiCl_2 to Cp_2Ti-*n*-Bu followed by β-hydride elimination is well precedented (Scheme 2, catalyst generation).[13,14]

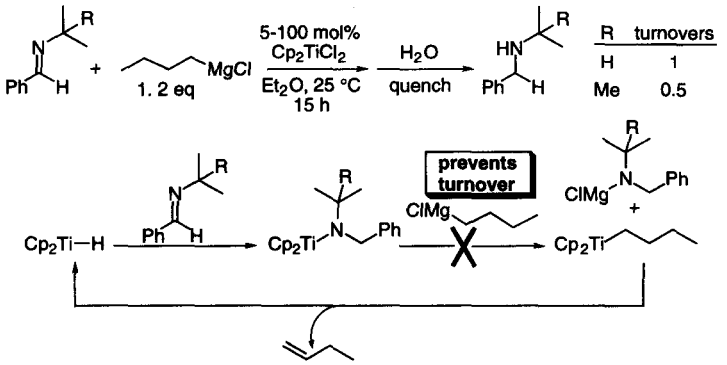
A variety of other transition metal complexes, including $Ti(O\text{-}i\text{-}Pr)_4$ and Cp_2ZrCl_2, failed to mediate the hydromagnesation reaction described above in either a catalytic or stoichiometric fashion. $NiCl_2$ was found to catalyze the transfer of H-MgX from n-BuMgCl to imines, albeit much less efficiently (30 mol%) than Cp_2TiCl_2. Linked cyclopentadienyl complexes **2** and **3** were also much less effective than Cp_2TiCl_2.[15]





Scheme 2

The reaction is not tolerant of primary or secondary enolizable protons on acyclic imine substrates (Table 1, entries 7, 14, 15). Tertiary enolizable protons or endocyclic enolizable protons on cyclic ketimine substrates are tolerated (entries 8, 9, 16-18). Secondary or tertiary nitrogen substituents are also problematic (entries 3-6). To see whether catalytic turnover for substrates bearing large nitrogen substituents is prevented by the failure of imine insertion into Cp_2TiH or amide displacement by *n*-BuMgCl, we examined the effect of catalyst stoichiometry on product yield (Scheme 3). For the N-isopropyl-substituted substrate, one turnover was observed for catalyst stoichiometries ranging from 5-100 mol%. For the N-*t*-butyl-substituted substrate, approximately 0.5 turnover was observed for the catalyst stoichiometries examined. These results indicate that it is failure of the amide displacement step that prevents turnover.



Scheme 3

Transition metal catalyzed imine hydromagnesation does not appear to have been studied prior to this report.[16] The reactivity of Grignard reagents as bases and nucleophiles poses some limitations to their use as reducing agents relative to less reactive, conventional reductants such as hydrogen. The Grignard-mediated hydromagnesation reaction, however, does possess the advantage of operational simplicity, particularly when compared to procedures which require elevated temperatures or pressures. Like previously reported hydrogenation and hydrosilylation reactions catalyzed by chiral titanium complexes,[1,2] titanium-catalyzed hydromagnesation should be well suited for asymmetric catalysis. Efforts to broaden the scope and to develop an asymmetric version of the titanium-catalyzed hydromagnesation reaction are currently underway.

Acknowledgment. Support of this work by the National Institutes of Health (GM 53172) is gratefully acknowledged.

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11. A representative procedure: To a mixture of 725 mg of benzylidene *n*-propylamine (5 mmol) and 37.5 mg of titanocene dichloride (0.15 mmol) in 75 mL of diethyl ether was added 3 mL (2 M soln in diethyl ether, 6 mmol) of *n*-BuMgCl dropwise at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 15 hrs, then quenched with 1 mL of H_2O. The mixture was filtered through a pad of celite then dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide 690 mg (94%) of benzyl-*n*-propylamine as a colorless liquid.
12. All compounds were characterized spectroscopically by ^1H NMR, ^{13}C NMR, and IR spectroscopy.
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14. Recent mechanistic studies on the alkyne hydromagnesation reaction have confirmed the original proposal that the reaction proceeds via alkyne insertion into a Cp_2Ti-H species followed by transmetallation between the alkenyltitanium intermediate and *i*-PrMgBr generating Cp_2Ti-*i*-Pr and the alkenylmagnesium product. Gao, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1995**, 659-660.
15. As previously noted for acetylene hydromagnesation,[9] our imine reductions are also highly dependent on Grignard reagents and solvent. Isobutyl magnesium chloride can be used in place of *n*-butylmagnesium chloride with no change in reaction efficiency, however ethylmagnesium bromide was not capable of inducing imine reduction. *n*-Butyllithium underwent butyl (rather than hydride) addition to the imine substrate (either in the presence or absence of Cp_2TiCl_2). Imine reduction does not occur in tetrahydrofuran.
16. Reduction of ketones via titanium-catalyzed hydromagnesation has previously been reported: Sato, F.; Jimbo, T.; Sato, M. *Tetrahedron Lett.* **1980**, *21*, 2171-2174. Interestingly, competitive alkyl (rather than hydride) addition to the ketone substrates is largely (although not completely) supressed. By comparison, competitive alkyl addition does not occur for imine substrates.

(*Received in USA* 13 *August* 1997; *accepted* 27 *August* 1997)