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Catalytic Reactions of Titanium Alkoxides with Grignard Reagents and Imines: A Mechanistic Study

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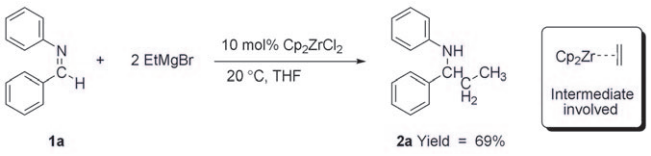
Abstract: The reactivity of Grignard reagents towards imines in the presence of catalytic and stoichiometric amounts of titanium alkoxides is reported. Alkylation, reduction, and coupling of imines take place. Whereas reductive coupling is the major reaction in stoichiometric reactions, alkylation is favored in catalytic reactions. Mechanistic studies clearly indicate that intermediates involved in the two reactions are different. Catalytic reactions involve a metal–alkyl complex. This has been confirmed by reactions of deuterium-labeled substrates and different alkylating agents. Under the stoichiometric conditions, however, titanium olefin complexes are formed through reductive elimination, probably through a multinuclear intermediate.

Keywords: alkylation · catalysis · Grignard reagents · isotopic labeling · titanium isopropoxide

Introduction

The alkylation of imines is one of the most promising routes to amines, which are important precursors to bioactive molecules.[1,2] Imines are less reactive than carbonyl compounds towards Grignard reagents. The reduced reactivity is attributed to the reduced electrophilicity of the imine carbon atom relative to a carbonyl carbon atom. Tomioka et al. were the first to report the stoichiometric addition of organolithium reagents to imines.[3] A combination of either indium–silver or zinc–silver is known to bring about the alkylation of imines in a one-pot three-component condensation of various aldehydes, amines, and unactivated alkyl iodides in aqueous media, which leads to a large library of amines.[4] Addition of dialkylzinc to aldimines promoted by Lewis acids such as zinc salts are well documented.[5,6] Copper complexes are known to catalyze the diorganozinc additions to activated imines.[7] There are also few reports of [Cu(salen)]-catalyzed (salen = *N*,*N*′-bis(salicylidene)ethylenediamine) imine alkylation carried out under phase-transfer conditions.[8] Many palladium complexes are widely used to catalyze the allylation of imines with allyl tributylstannane.[9] Cook and co-workers have extensively studied the catalytic enantioselective allylation of hydrazones and imines.[10]

Early transition metals like Ti^{IV}[11,12] and Zr^{IV}[13–15] are good Lewis acids and hence suitable for the catalytic alkylation of imines. However, in these reports, more than stoichiometric amounts of alkylating agents are used to ensure complete alkylation (Scheme 1). In some instances, the methoxy group that is *ortho* to N in the imine has been shown to be essential to achieve a good yield.[14] It has also been reported that Grignards are limited to EtMgBr because higher magnesium alkyls, namely, *n*PrMgBr and *n*BuMgBr, do not give alkylated products.[11,13]



Scheme 1. Ethylation of aldimine **1a** catalyzed by [Cp_2ZrCl_2] (Cp = cyclopentadienyl).[13b]

We report here a mechanistic investigation of the alkylation of imines with a variety of Grignard reagents promoted by Group IV metal alkoxide. The reactions carried out under catalytic and stoichiometric amounts of Ti^{IV} alkoxide are distinctly different. The catalytic conditions are suitable for synthetic purposes.

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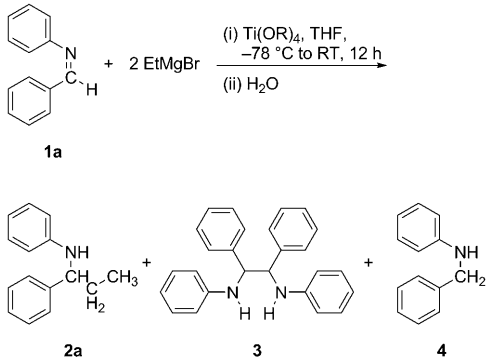
Results and Discussion

The primary aim of this study is to examine the utility of Group IV metal alkoxides, both chiral and achiral, in changing the reactivity of imines with Grignard reagents.

For this purpose, *N*-benzylidineaniline **1a** was used as a test imine and its reactivity towards ethylmagnesium bromide (EtMgBr) tested in the presence of stoichiometric and catalytic amounts of titanium isopropoxide ($Ti(OiPr)_4$). Equivalent amounts of imine **1a** and $Ti(OiPr)_4$ maintained at −78 °C in dry THF were reacted with two equivalents of EtMgBr in a dropwise fashion. Subsequent workup showed the presence of a mixture of products. The reaction (Table 1, entry 1) produces, in addition to the alkylated product **2a**, the reduced product **4** along with significant amounts of coupled product **3**. The formation of reduced imine **4** and the C–C coupled diamine **3** have been reported earlier by Eisch and Gitua, who have studied the stoichiometric reaction in great detail.[16]

Table 1. Reaction of ethylmagnesium bromide with *N*-benzylidineaniline **1a** mediated by titanium alkoxide.

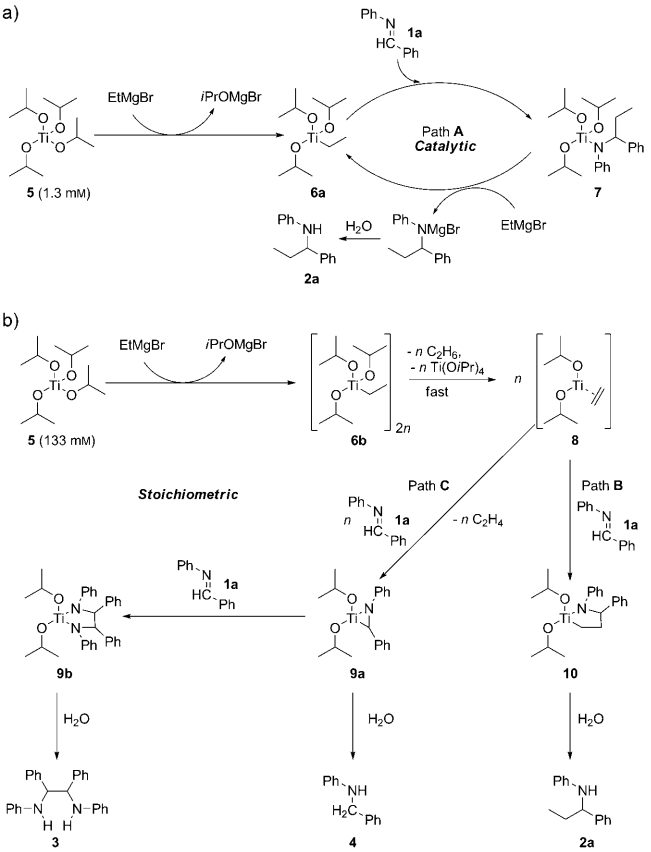


Entry	$Ti(OR)_4$	$Ti(OR)_4$ [mol %]	Yield of isolated product [%][a] 2a	3	4
1	$Ti(OiPr)_4$	100.0	20	48	22
2	$Ti(OiPr)_4$	10.0	42	33	15
3	$Ti(OiPr)_4$	1.0	74	8	9
4	$Ti(OiPr)_4$[b]	100.0	12	84	–
5	$Ti(OiPr)_4$[b]	1.0	79	6	10
6	$Ti(BINOL)_2$	1.0	94	–	–
7	$Ti(BINOL)_2$	0.1	96	–	–

[a] All yields of isolated product are wt % with respect to imine **1a** and are an average of two runs. [b] One equivalent of ethylmagnesium bromide was used.

Since the stoichiometric reaction gives a mixture of products, a catalytic reaction was attempted (Table 1, entry 2). Surprisingly, with a reduction of the amount of $Ti(OiPr)_4$, there was an increase in the yield of **2a** (Table 1, entry 3). Catalytic amounts of $Ti(OR)_4$, especially $Ti(BINOL)_2$ (BINOL = 1,1′-binaphthalene-2,2′-diol), were found to give the best yield of the addition product (Table 1, entries 6 and 7).

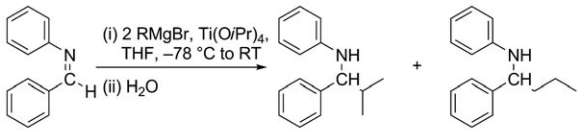
A mechanistic scheme was proposed to serve as a working hypothesis for the catalytic (Scheme 2a) and the stoichiometric (Scheme 2b) paths. In the absence of any catalyst, EtMgBr reacted with **1a** to give very low yields (16 %) of the ethylated product **2a**.[13b] A reaction with a catalytic amount of titanium isopropoxide (1 %) preferentially produced the alkylated product **2a** in excellent yields (74 %) along with small amounts of **3** and **4**. The reduction in the yield of **2a** with stoichiometric amounts of titanium isopropoxide can be attributed to the formation of polynuclear titanium species such as **6b**, which in turn led to low-valent Ti^{II} species **8**. The intermediate **8** gave rise to alkylation through path B and reduced products through path C, as suggested by Eisch et al.[16–18] To verify the hypothesis that alkylation proceeded along path B under stoichiometric conditions and predominantly along path A under catalytic conditions, a detailed study of the reaction mechanism was taken up.



Scheme 2. a) Plausible steps involved in the reaction of ethylmagnesium bromide with **1a** catalyzed by titanium isopropoxide. b) A mechanistic scheme to explain the reaction of ethylmagnesium bromide with **1a** mediated by stoichiometric amounts of titanium isopropoxide.

When isopropylmagnesium bromide (*i*PrMgBr) or *n*-propylmagnesium bromide (*n*PrMgBr) was used as the alkylating agent in the presence of stoichiometric amounts of titanium alkoxide, **12** was the exclusive product (Table 2, entries 1 and 2). On the other hand, in the presence of catalytic amounts of titanium alkoxide, *i*PrMgBr gave only **12** (Table 2, entry 3). The sole product obtained with *n*PrMgBr was **13** (Table 2, entry 4). If the reaction proceeds along path B during the catalytic reaction, both *i*PrMgBr and

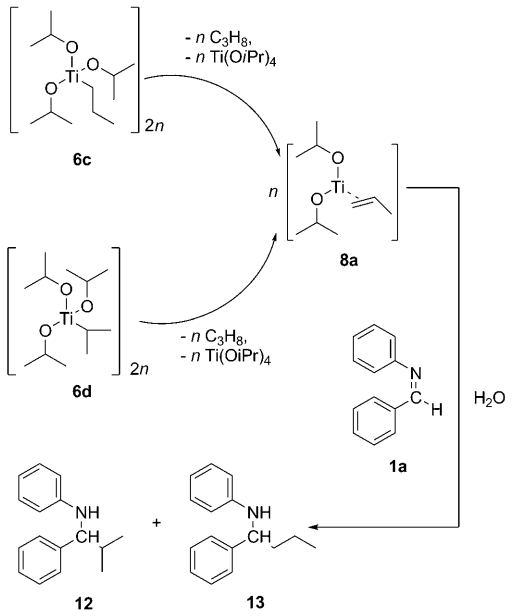
Table 2. Ratio of alkylated products formed in the reaction of isopropylmagnesium bromide and *n*-propylmagnesium bromide with *N*-benzylidineaniline **1a** in the presence of titanium isopropoxide.



Entry	*t* [h]	$Ti(OiPr)_4$ [mol%]	R	Yield of isolated product [%][a] **12**	**13**
1	15	100.0	*i*Pr	24	–
2	15	100.0	*n*Pr	22	–
3	18	1.0	*i*Pr	88	–
4	18	1.0	*n*Pr	–	74

[a] All yields of isolated product are wt% with respect to imine **1a** and are an average of two runs.

*n*PrMgBr should lead to the same intermediate **8a**. This should result in a mixture of **12** and **13** in the same ratio with either alkylating agent (Scheme 3). Clearly catalytic reactions are proceeding through path A without the intermediacy of an olefin complex.



Scheme 3. Formation of **8a**, which leads to **12** and **13**.

Deuterium-labeled alkylating agents CD_3CH_2MgBr and CH_3CD_2MgBr were utilized to confirm the reaction path. The imine **1a** was treated with CD_3CH_2MgBr in the presence of catalytic amounts of $Ti(OiPr)_4$, and the crude product obtained after workup was analyzed by ^1H, ^2H, and ^{13}C NMR spectroscopy. The ^1H NMR spectra of the crude product indicated that the ratio of $CH/CH_2/CH_3$ protons is 1.00:1.98:0.16, whereas one would have expected this ratio to be 1.00:2.00:3.00 for compound **2a** with no deuterium labeling. So it is likely that $\mathbf{2a_1}$ was the major product, which has three deuterium atoms on the methyl carbon. This assumption was further confirmed by ^{13}C NMR spectra of the crude product. A septet centered at $\delta = 10.38$ ppm was observed that corresponds to the trideuterated methyl carbon atom. The ^2H NMR spectra of the crude product was also recorded, and it indicates the presence of the trideuterated species $\mathbf{2a_1}$ and dideuterated species $\mathbf{2a_3}$ in the ratio 1:0.05. The major product formed in this reaction is $\mathbf{2a_1}$, and the relative ratios of products were determined from ^1H and ^2H NMR spectroscopy (Table 3, entry 5).

On the other hand, when **1a** was treated with CD_3CH_2MgBr in the presence of stoichiometric amounts of $Ti(OiPr)_4$, ^2H NMR spectroscopy revealed that two dideuterated species $\mathbf{2a_2}$ and $\mathbf{2a_3}$ were obtained in the ratio 1.44:1 (Table 3, entry 2). In this case, the ^1H NMR spectra of the crude product indicates that the ratios of the $CH/CH_2/CH_3$ protons are 1.00:1.02:1.89, which is consistent with the ratio obtained from ^2H NMR spectroscopy.

The ^2H NMR spectra for the stoichiometric and catalytic reactions are given in Figure 1. Three peaks were obtained in the ^2H NMR spectra at $\delta = 0.98$, 1.03, and 1.87 ppm, which correspond to $\mathbf{2a_1}$, $\mathbf{2a_2}$, and $\mathbf{2a_3}$, respectively. These peaks were assigned relative to the deuterium peak of $CDCl_3$ at $\delta = 7.26$ ppm. When CD_3CH_2MgBr was used as the alkylating agent, the trideuterated species $\mathbf{2a_1}$ arose from a direct addition of the alkyl group of metal alkyl complex **6e** (Scheme 4). The formation of the dideuterated species $\mathbf{2a_2}$ and $\mathbf{2a_3}$ is best explained by the formation of an intermediate metal olefin complex **8b**. If this hypothesis is true, then when one uses CH_3CD_2MgBr, one should obtain $\mathbf{2a_3}$ (which arises from a metal alkyl complex **6f**) as a major product with catalytic amounts of $Ti(OiPr)_4$ and a mixture of $\mathbf{2a_2}$ and $\mathbf{2a_3}$ (which arises from a metal olefin complex **8b**) when stoichiometric amounts of $Ti(OiPr)_4$ are used (Scheme 4).

When imine **1a** was treated with CH_3CD_2MgBr in the presence of catalytic amounts of $Ti(OiPr)_4$, $\mathbf{2a_3}$ was obtained as a major product. The ratios of $CH/CH_2/CH_3$ protons were found to be 1.00:0.00:3.00 from the ^1H NMR spectra of the crude product. The ^{13}C NMR spectra of the crude product have a quintet centered at $\delta = 31.46$ ppm that corresponds to the dideuterated methylene carbon atom. Further ^2H NMR spectroscopy of the crude product showed a major peak at $\delta = 1.87$ ppm. These data confirm the presence of a large excess amount of about 98% of $\mathbf{2a_3}$ in the crude product (Table 3, entry 6).

The product obtained in the reaction of **1a** with CH_3CD_2MgBr in the presence of stoichiometric amounts of $Ti(OiPr)_4$ was similar to that obtained with CD_3CH_2MgBr. However, this reaction gave a mixture of $\mathbf{2a_2}$ and $\mathbf{2a_3}$ in the ratio 1:1 (Table 3, entry 3). The ^1H NMR spectra of the crude product indicated the ratios of $CH/CH_2/CH_3$ protons to be 1.00:1.00:2.08. The ^{13}C NMR spectra of the crude product showed two quintets centered at $\delta = 31.42$ and 10.42 ppm that correspond to the dideuterated methylene carbon and the dideuterated methyl carbon atoms, respec-

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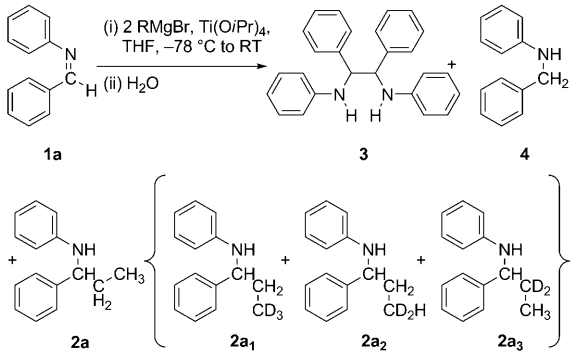
Table 3. Reaction of ethylmagnesium bromide with *N*-benzylidineaniline **1a** mediated by titanium isopropoxide.



Entry	RMgBr	$Ti(OiPr)_4$ [mol%]	Product ratio [%][a] **2a** (**2a**$_1$/**2a**$_2$/**2a**$_3$)[b]	**3**	**4**
1	CH_3CH_2MgBr	100.0	29	39	32
2	CD_3CH_2MgBr	100.0	42 (0.0:59.0:41.0)	41	17
3	CH_3CD_2MgBr	100.0	34 (0.0:50.0:50.0)	30	36
4	CH_3CH_2MgBr	1.0	73	11	16
5	CD_3CH_2MgBr	1.0	81 (95.0:0.0:5.0)	6	13
6	CH_3CD_2MgBr	1.0	91 (0.0:2.0:98.0)	4	5

[a] Ratios of products were determined by ^{1}H NMR spectroscopy of the crude product and are an average of two runs. [b] The ratios of **2a**$_1$/**2a**$_2$/**2a**$_3$ were determined by ^{2}H NMR spectroscopy of the crude product and are an average of two runs.

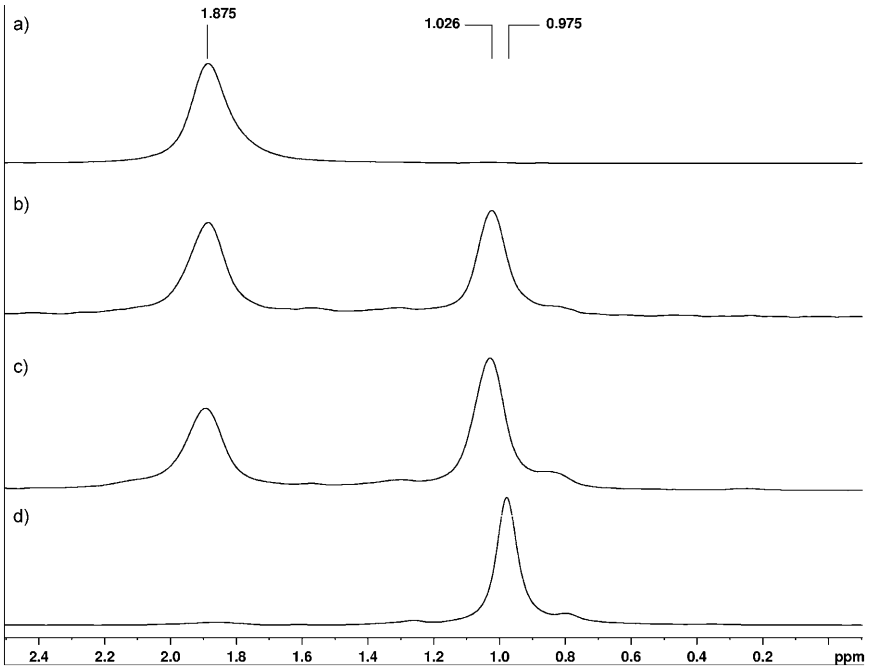


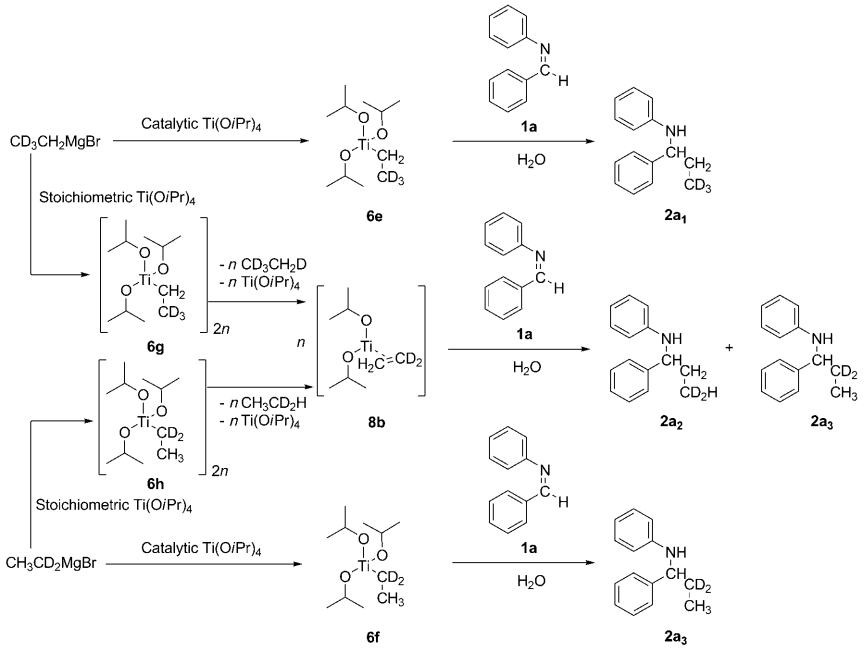
Figure 1. ^{2}H NMR spectra of the products that arise from the reaction of CH_3CD_2MgBr or CD_3CH_2MgBr with **1a** in the presence of catalytic amounts of titanium isopropoxide (a, d, respectively) and stoichiometric amounts of titanium isopropoxide (b, c, respectively).

tively. Only two peaks were observed in the ^{2}H NMR spectra at $\delta = 1.87$ and 1.03 ppm, which correspond to the deuterium atom on **2a**$_3$ and **2a**$_2$, respectively. A comparison of the ^{1}H NMR spectrum of the crude product obtained in the reaction of imine **1a** with CH_3CH_2MgBr, CD_3CH_2MgBr, and CH_3CD_2MgBr in the presence of stoichiometric and catalytic amounts of $Ti(OiPr)_4$ is given in Figures 2 and 3, respectively. All observations point to the formation of an olefin intermediate (path B) when stoichiometric amounts of $Ti(OiPr)_4$ are used.

The reaction of imines with a Grignard reagent in the presence of catalytic amounts of titanium(IV) alkoxides is very useful for synthetic applications because it leads to preferential formation of alkylated products. The best results were obtained when a modified procedure was followed with $Ti(BINOL)_2$ as a catalyst in the alkylation reaction in which only one equivalent of the Grignard is added to the imine at room temperature. The reactions give slightly better yields at room temperature and proceed smoothly for a variety of alkylating agents (Table 4). This suggests that the Ti–alkyl intermediate is stable enough at room temperature in the presence of imines, which capture them before they decompose.

Conclusion

Grignard reagents react rapidly with imines in the presence of catalytic amounts of titanium alkoxides. These reactions are different from the stoichiometric reactions reported by Eisch and Gitua.[16] The stoichiometric reactions permit intermolecular reactions of Ti species that lead to the reduction and coupling of imines in addition to alkylation. Under catalytic reaction conditions, the large ratio of the imine relative to Ti promotes alkylation rather than coupling reactions of Ti intermediates, with high turnover numbers under ambient conditions. Only one equivalent of the alkylating agent is required. The alternative procedure for the alkylation of imines with Grignard reagents, catalyzed by simple Group IV metal alkoxides is more useful



Scheme 4. Pathways that lead to the formation of **2a**$_1$, **2a**$_2$, and **2a**$_3$.

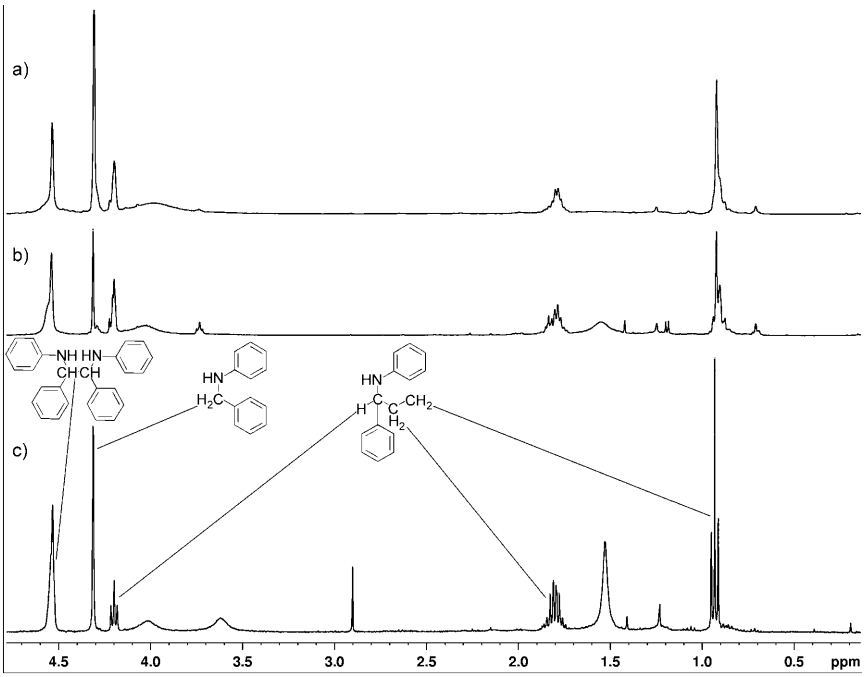


Figure 2. Comparison of the ^{1}H NMR spectra of the products that arise from the reaction of a) CH_3CD_2MgBr, b) CD_3CH_2MgBr, and c) CH_3CH_2MgBr with **1a** in the presence of stoichiometric amounts of titanium isopropoxide.

than the stoichiometric reaction. Deuterium labeling experiments conclusively reveal that the alkylation observed in stoichiometric reactions arises from the involvement of a metal–olefin complex, whereas the alkyl intermediate is the active species in catalytic reactions.

Experimental Section

General

All manipulations were carried out under an inert atmosphere of dry nitrogen with a standard double manifold. Tetrahydrofuran was freshly distilled from sodium/benzophenone prior to use. Grignard-grade magnesium turnings, 2,2,2-[D_3]ethyl bromide, 1,1-[D_2]ethyl bromide, and titanium(IV) isopropoxide were obtained from Aldrich USA. Ethyl bromide, *n*-propyl bromide, and isopropyl bromide were purchased from Spectrochem India. The imines[19] and Ti(BINOL)$_2$[11,20] were prepared by standard literature procedures.

Physical Measurements

^{1}H and ^{13}C{H} NMR spectra were recorded with a Bruker AMX 400 operating at 400 MHz for ^{1}H NMR spectroscopy and 100 MHz for ^{13}C NMR spectroscopy, with tetramethylsilane or $CDCl_3$ as internal reference. ^{2}H NMR spectroscopy was carried out with a Bruker DRX 500 operating at 76.7 MHz for ^{2}H NMR spectroscopy with $CDCl_3$ as internal reference. All spectra were recorded in $CDCl_3$. ESIMS measurements were done with an Esquire 3000 Plus ESI (Bruker Daltonics) or a Thermo Finnigan LCQ Deca Plus instrument. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 CHNS analyzer.

*Reaction of Ethylmagnesium Bromide with Imine **1a** in the Presence of Catalytic Amounts of Titanium Isopropoxide (1 mol%)*

Ethyl bromide (0.40 mL, 5.35 mmol) was dissolved in dry THF (5 mL) and a small portion was added to magnesium turnings (0.65 g, 26.8 mmol) diluted with dry THF (10 mL). The reaction was initiated with gentle warming. The remainder of the ethyl bromide/THF solution was added dropwise with constant stirring over a period of half an hour while cooling the reaction mixture to maintain the temperature around 50 °C. After the addition of ethyl bromide, the reaction mixture was heated at reflux for an additional hour to ensure completion of reaction. The above Grignard was added in drops to a solution of imine **1a** (0.49 g, 2.67 mmol) and Ti(O*i*Pr)$_4$ (0.008 g, 0.03 mmol) in dry THF (10 mL) maintained at −78 °C with a dry-ice–acetone slush bath. After addition, the reaction mixture was allowed to attain room temperature and stirred at room temperature over a period of 12 h. It was quenched by the addition of a saturated NH_4Cl solution and filtered through a Celite pad; the filtrate was extracted with diethyl ether. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was then removed under

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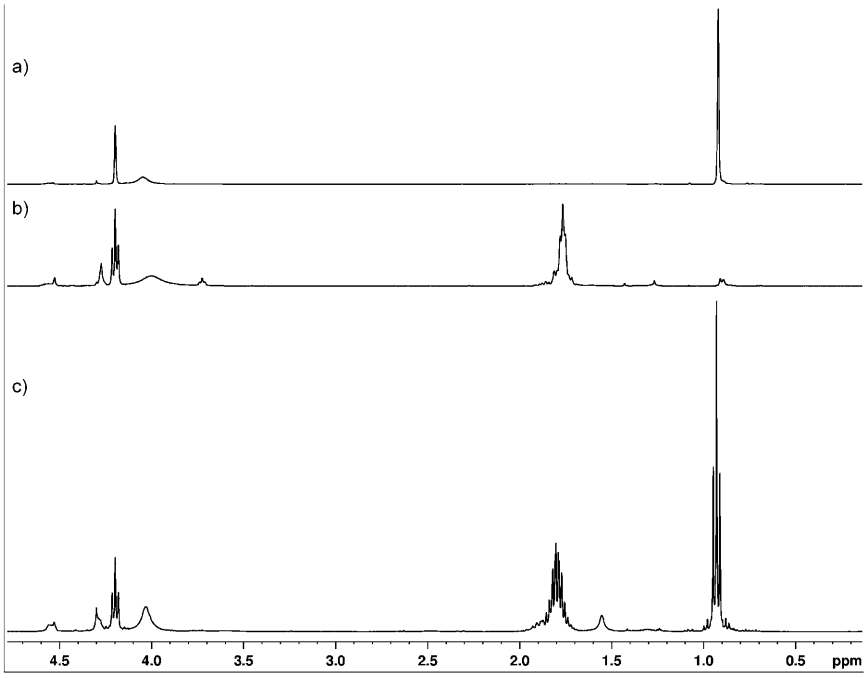
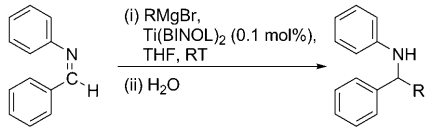


Figure 3. Comparison of the ^{1}H NMR spectra of the products that arise from the reaction of a) CH_3CD_2MgBr, b) CD_3CH_2MgBr, and c) CH_3CH_2MgBr with **1a** in the presence of catalytic amounts of titanium isopropoxide.

Table 4. Reaction of **1a** with various alkylating agents catalyzed by Ti(BINOL)$_2$ (0.1 mol%) at room temperature.



1a

R = Et, **2a**
R = *i*Pr, **12**
R = *n*Pr, **13**

Entry	R	*t* [h]	Product	Yield of isolated product [%][a]
1	Et	15	**2a**	97
2	*i*Pr	17	**12**	92
3	*n*Pr	18	**13**	80

[a] All yields of isolated product are wt% with respect to imine **1a** and are an average of two runs.

reduced pressure to yield a yellow oil. This yellow oil was treated with petroleum ether to precipitate the **3** present. Subsequently, it was passed through a silica gel column and eluted with petroleum ether, ethyl acetate, and triethylamine in the ratio 98:1:1. Compound **2a** was the first to elute and this was followed by compound **4**. Solvent was evacuated from the desired fraction to obtain **2a** as a pale yellow oil. Yields: **2a** = 0.42 g (74%), **3** = 0.04 g (8%), and **4** = 0.04 g (9%).

A similar experimental procedure was followed in the reaction of isopropylmagnesium bromide, *n*-propylmagnesium bromide, 2,2,2-[D_3]ethylmagnesium bromide, and 1,1-[D_2]ethylmagnesium bromide with imine **1a** in the presence of catalytic amounts of titanium isopropoxide (1 mol%).

*Reaction of Ethylmagnesium Bromide with Imine **1a** in the Presence of Stoichiometric Amounts of Titanium Isopropoxide (100 mol%)*

Ethyl bromide (0.40 mL, 5.35 mmol) was dissolved in dry THF (5 mL) and a small portion was added to magnesium turnings (0.65 g, 26.8 mmol) diluted with dry THF (10 mL). The reaction was initiated with gentle warming. The remainder of the ethyl bromide/THF solution was added dropwise with constant stirring over a period of half an hour while cooling the reaction mixture to maintain the temperature around 50 °C. After the addition of ethyl bromide, the reaction mixture was heated at reflux for an additional hour to ensure completion of the reaction. The above Grignard was added in drops to a solution of imine **1a** (0.49 g, 2.67 mmol) and Ti(O*i*Pr)$_4$ (0.76 g, 2.67 mmol) in dry THF (10 mL) maintained at −78 °C using an dry ice–acetone slush bath. After addition, the reaction mixture was allowed to attain room temperature and stirred at room temperature over a period of 12 h. It was quenched by the addition of saturated NH_4Cl solution and filtered through a Celite pad; the filtrate was extracted with diethyl ether. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to yield a yellow oil. This yellow oil was treated with petroleum ether to precipitate compound **3**. Subsequently, it was passed through a silica gel column and eluted with petroleum ether, ethyl acetate, and triethylamine in the ratio 98:1:1. Compound **2a** was the first to elute and this was followed by compound **4**. Solvent was evacuated from the desired fraction to obtain **2a** as a pale yellow oil. Yields: **2a** = 0.11 g (20%), **3** = 0.23 g (48%), and **4** = 0.11 g (22%).

A similar experimental procedure was followed in the reaction of isopropylmagnesium bromide, *n*-propylmagnesium bromide, 2,2,2-[D_3]ethylmagnesium bromide, and 1,1-[D_2]ethylmagnesium bromide with imine **1a** in the presence of stoichiometric amounts of titanium isopropoxide (100 mol%).

*Reaction of Ethylmagnesium Bromide with Imine **1a** in the Presence of Substoichiometric Amounts of Titanium Isopropoxide (10 mol%)*

Ethyl bromide (0.40 mL, 5.35 mmol) was dissolved in dry THF (5 mL) and a small portion was added to magnesium turnings (0.65 g, 26.8 mmol) diluted with dry THF (10 mL). The reaction was initiated with gentle warming. The remainder of the ethyl bromide/THF solution was added dropwise with constant stirring over a period of half an hour while cooling the reaction mixture to maintain the temperature around 50 °C. After the addition of ethyl bromide, the reaction mixture was heated at reflux for an additional hour to ensure completion of reaction. The above Grignard was added in drops to a solution of imine **1a** (0.48 g, 2.67 mmol) and Ti(O*i*Pr)$_4$ (0.08 g, 0.27 mmol) in dry THF (10 mL) maintained at −78 °C using an dry ice–acetone slush bath. After addition, the reaction mixture was warmed to room temperature and stirred at room temperature over a period of 12 h. It was quenched by the addition of saturated NH_4Cl solution and filtered through a Celite pad; the filtrate was extracted with diethyl ether. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to yield a yellow oil. This yellow oil was treated with petroleum ether to precipitate compound **3**. Subsequently, it was passed through a silica gel column and eluted with petroleum ether, ethyl acetate, and tri-

ethylamine in the ratio 98:1:1. Compound **2a** was the first to elute, and this was followed by compound **4**. The solvent was evacuated from the desired fraction to obtain **2a** as a pale yellow oil. Yields: **2a** = 0.24 g (42%), **3** = 0.16 g (33%), and **4** = 0.07 g (15%).

*Reaction of Ethylmagnesium Bromide with Imine **1a** in the Presence of Catalytic Amounts of Ti(BINOL)$_2$ (0.1 mol%) at Room Temperature*

Ethyl bromide (0.50 mL, 6.70 mmol) was dissolved in dry THF (5 mL) and a small portion was added to magnesium turnings (0.80 g, 33.50 mmol) diluted with dry THF (10 mL). The reaction was initiated with gentle warming. The remainder of the ethyl bromide/THF solution was added dropwise with constant stirring over a period of half an hour while cooling the reaction mixture to maintain the temperature around 50 °C. After the addition of ethyl bromide, the reaction mixture was heated at reflux for an additional hour to ensure completion of the reaction. The above Grignard was added in drops to a solution of imine **1a** (1.21 g, 6.70 mmol) and Ti(BINOL)$_2$ (0.004 g, 0.007 mmol) in dry THF (10 mL) maintained at room temperature. After addition, the reaction mixture was stirred at room temperature over a period of 15 h and quenched by addition of saturated NH_4Cl solution. It was filtered through a Celite pad and the filtrate was extracted with diethyl ether. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to yield a yellow oil. This yellow oil was passed through a silica gel plug and eluted with petroleum ether, ethyl acetate, and triethylamine in the ratio 98:1:1. The solvent was evacuated from this fraction to obtain **2a** as a pale yellow oil. Yield: **2a** = 1.370 g (97%).

A similar experimental procedure was followed in the reaction of isopropylmagnesium bromide and *n*-propylmagnesium bromide with imine **1a** in the presence of catalytic amounts of Ti(BINOL)$_2$ (0.1 mol%).

*Compound **2a***

Benzenemethanamine, α-ethyl-*N*-phenyl- ^{1}H NMR (400 MHz): δ = 7.34 (m, 4H), 7.23 (m, 1H), 7.09 (t, J = 8.0 Hz, 2H), 6.63 (t, J = 7.2 Hz, 1H), 6.51 (d, J = 8.0 Hz, 2H), 4.20 (t, 6.8 Hz, 1H), 4.1 (brs, 1NH), 1.84 (m, 2H), 0.96 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ = 10.86, 31.64, 59.78, 113.30, 117.18, 126.44, 126.77, 128.56, 129.15, 143.99, 147.59 ppm; MS (ESI): m/z: 212.1 $[M+H]^+$, m/z:240.1 $[M+K]^+$.

*Compound **3***

d,l,meso 1,2-Ethanediamine, *N,N′*,1,2-tetraphenyl- ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.5–7.5 (m, 40H), 4.98 (2H, *meso*-NCH, d, J = 8.0 Hz), 4.55 ppm (6H; brs, *d,l* and *meso* NH, *d,l* NCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 62.43, 64.50, 114.25, 114.60, 118.35, 118.61, 127.88, 128.06, 128.81, 128.95, 129.65, 129.96, 138.69, 140.43, 147.00, 147.56 ppm; MS (ESI): m/z: 365.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{26}H_{24}N_2$: C 85.68, H 6.64, N 7.69; found: C 84.74, H 5.58, N 7.56.

*Compound **4***

Benzenemethanamine, *N*-phenyl- ^{1}H NMR (400 MHz): δ = 7.37 (m, 4H), 7.18 (t, J = 8.0 Hz, 2H), 6.72 (t, J = 7.6 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 4.34 ppm (s, 2H); ^{13}C NMR (100 MHz): δ = 48.35, 112.87, 117.60, 127.27, 127.55, 128.68, 129.31, 139.45, 148.18 ppm.

*Compound **12**[6a]*

Benzenemethanamine, α-(1-methylethyl)-*N*-phenyl- ^{1}H NMR (400 MHz): δ = 7.29 (m, 4H), 7.2 (m, 1H), 7.05 (t, J = 6.0 Hz, 2H), 6.62 (t, J = 7.6 Hz, 1H), 6.49 (d, J = 5.6 Hz, 2H), 4.12 (d, J = 6.0 Hz, 1H), 2.03 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.93 ppm (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ = 18.71, 19.82, 34.79, 63.83, 113.29, 117.06, 126.85, 127.26, 128.28, 129.14, 142.66, 147.80 ppm.

*Compound **13**[6a]*

Benzenemethanamine, *N*-phenyl-α-propyl- ^{1}H NMR (400 MHz): δ = 7.29 (m, 4H), 7.20 (m, 1H), 7.08 (t, J = 8.4 Hz, 2H), 6.63 (t, J = 7.6 Hz, 1H), 6.52 (d, J = 8.4 Hz, 2H), 4.31 (t, J = 6.8 Hz, 1H), 1.79 (m, 2H), 1.45 (m, 2H) 0.97 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ = 14.01, 19.64, 41.22, 58.18, 113.32, 117.24, 126.92, 128.43, 129.16, 144.41, 147.60 ppm.

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