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Weinreb amides : novel titanium enolate reagents

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Weinreb Amides: Novel Titanium Enolate Reagents

By

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Abstract

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The amides of N-methoxy-N-methylamine or "Weinreb amide" have earned an important role in synthetic chemistry as both a protective group and as synthetic intermediates. We have discovered that the Weinreb amide of acetic acid, N-methoxy-N-methylacetamide adds to aldehydes to afford classic aldol products in good to excellent yields. The scope of this novel aldol reaction will be discussed.

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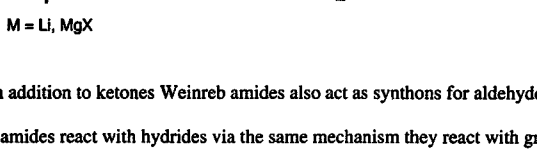
Introduction

Weinreb Amides

Weinreb amides (**1**) were nicknamed for Dr. Steven Weinreb, who's research group first discovered their unique reactivity. Weinreb and coworkers observed that N-methoxy-N-methyl amides selectively react with Grinard reagents and organolithium to yield ketones (Scheme1). Weinreb amides afford this unique activity because the metal ion chelates the carbonyl oxygen and the *N*-methoxy oxygen providing structure **2** (Figure 1). This chelated structure offers stability and does not collapse until acidic workup, thus preventing any over addition.[1]

Scheme 1



1

M = Li, MgX

2

In addition to ketones Weinreb amides also act as synthons for aldehydes. Weinreb amides react with hydrides via the same mechanism they react with grinard and organolithium reagents (Scheme 2).[1] The reduction of Weinreb amides to aldehydes has been shown to work very effectively even on large scale reactions[2]

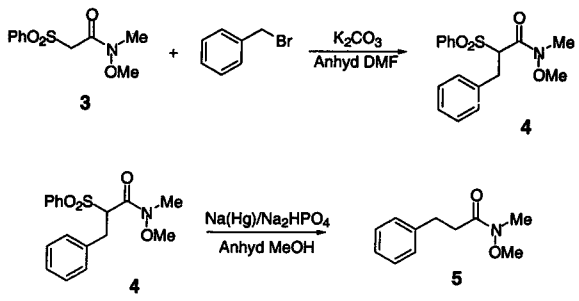
Scheme 2

1

The preparation of Weinreb amides in synthetic chemistry is usually accomplished from the conversion of acids and their derivatives to the Weinreb amide. A concept that could become quite useful for the employment of Weinreb amides in synthetic chemistry would be its incorporation into molecules via formation of an enolate nucleophile. Presently, examples using Weinreb amides as enolate nucleophiles are very rare.

Aidhen and coworkers have shown that a sulfonylated analog of Weinreb's amide (**3**) will form an enolate anion and will react with primary alkyl halides (Scheme 3).[3] Sulfonylation of the amide effectively increases the acidity of the α-protons. This increase in acidity is sufficient enough that a mild base, such as potassium carbonate can be used to efficiently to remove an α-proton and form the enolate anion. A drawback to this process is that it requires a desulfonylation using sodium-mercury amalgam (Scheme 3) that could affect other sensitive areas of the molecule.

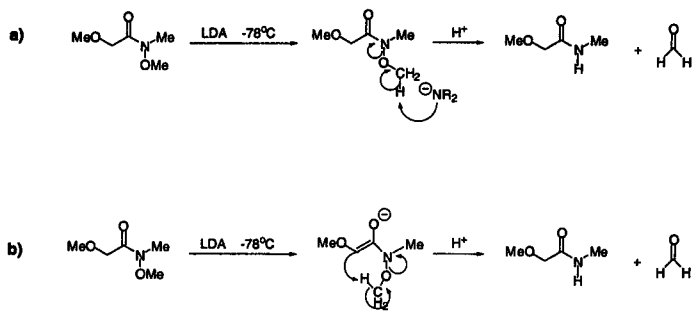
Scheme 3



Graham and Scholz observed an alternative mode of reactivity for Weinreb's amide in the presence of a sterically hindered strong base. They observed that Weinreb's

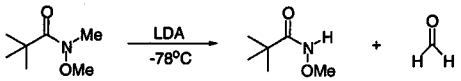
amide decomposes in the presence of lithium diisopropylamide (LDA) to liberate formaldehyde and produce the secondary amide. To explain this mode of reactivity they proposed two possible mechanistic pathways through which this decomposition occurs (Figure 1). The pathways of decomposition proposed by Graham and Scholz include an intermolecular and an intramolecular reaction. In the intermolecular reaction (Figure 1a) to liberate formaldehyde and methoxy-*N*-methylacetamide, an E2 elimination occurs when the strong base removes a methoxy proton. In the second possible pathway (Figure 1b), the enolate anion is formed, but it removes a methoxy proton and the molecule undergoes a subsequent rearrangement to liberate formaldehyde.[4]

Figure 1: a) Intermolecular *N*-methoxy Deprotonation **b)** Intramolecular Enolate Deprotonation



With the results of two experiments Graham and Scholz proved that the favored pathway for the decomposition of Weinreb's amide in the presence of a sterically hindered strong base is the intermolecular E2 elimination reaction. The first experiment performed that suggests the E2 pathway is preferred involves the Weinreb amide of pivalic acid (**6**). Weinreb amide **6** was exposed to LDA at –78°C and decomposition to liberate formaldehyde was still observed (Scheme 4). Since the absence of α protons eliminates the possibility of enolate formation in **6**, decomposition must occur via the E2 pathway. They also performed an experiment involving the Weinreb amide of d_3-acetic acid (**7**). In this experiment the deuterated amide **7** was exposed to LDA and a mixture of d_2 and d_3 species were obtained in a 65:35 ratio (Scheme 5). The results of this experiment indicate that the enolate formed, however it did not lead to the intramolecular decomposition.[4] Even though it has been shown that the E2 pathway is the mode of decomposition, it is possible that the intramolecular decomposition as a result of methoxy deprotonation by the enolate anion may cause problems in some cases. These experiments performed by Graham and Scholz demonstrate the need for a mild method to generate the enolates of Weinreb amides.

Scheme 4



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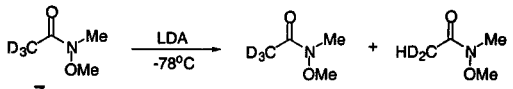
Scheme 5

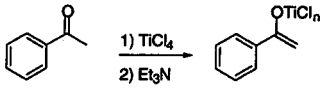


7

Chlorotitanium Enolates

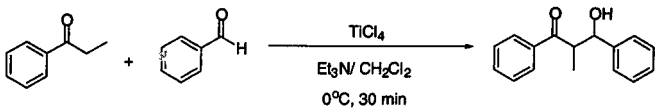
Chlorotitanium enolates offer a mild alternative to traditional aldol chemistry. These enolates employ the use of $TiCl_4$ and a tertiary base to perform nucleophilic addition. In the formation of a titanium enolate titanium acts as a lewis acid to an enolizable substrate and increases the acidity of the α-protons. This increase in acidity allows an α-proton to be removed with a tertiary amine, creating an enolate nucleophile (Scheme 6). The enolate nucleophile is then ready to react with an appropriate electrophile.

Scheme 6



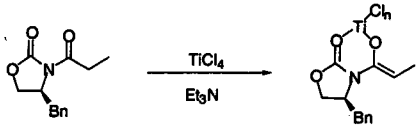
Although they were not specifically referred to Lehnert was the first to use chlorotitanium enolates in aldol chemistry.[6] Harrison greatly improved upon Lehnert's method with an *in situ* generation of a titanium enolate using titanium tetrachloride, an aryl ketone, and triethylamine. The enolate was then reacted with an aryl aldehyde (Scheme 7).[7]

Scheme 7



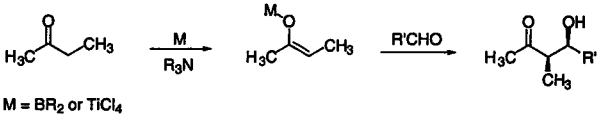
Evans and coworkers utilized the titanium tetrachloride/tertiary amine system to generate enolates in their study with the titanium enolates of *N*-propionyloxazolidone (scheme 8). Through these studies they expanded the electrophile pool to include alkyl halides, orthoesters, acetals, unsaturated nitriles, ketones, and esters.[5]

Scheme 8



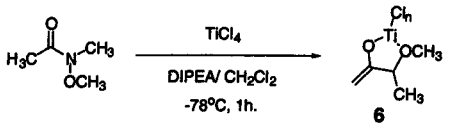
Evans and his group also showed that the sterioselectivity of aldol condensations performed with chlorotitanium enolates is comparable to those performed with boron enolates.[8]

Scheme 9



The mild conditions of aldol condensations performed with titanium enolates may offer a solution to the problems that limit the use of Weinreb's amide in traditional aldol chemistry. The method discussed in this thesis proposes the formation of titanium enolates with Weinreb amides followed by an aldol condensation (Scheme 10).

Scheme 10



Results & Discussion

In theory the proposed enolate formation with Weinreb amides using titanium tetrachloride and diisopropylethylamine should avoid the amide decomposition problems observed by Graham and Scholz.[4] Unlike traditional aldol chemistry in which it has become common practice to use a strong base, formation of the enolate anion of titanium enolates only requires a tertiary amine. By avoiding the use of strong bases, the intermolecular E2 pathway (Figure 1a) for the decomposition of the amide and liberation of formaldehyde is likely avoided.

The titanium enolate formed with Weinreb's amide should also avoid the possibility of deprotonation of the *N*-methoxy group by the enolate anion (figure 1b) because the titanium chelates the carbonyl oxygen and the *N*-methoxy oxygen. The chelation of both oxygens by the titanium effectively removes the methoxy protons from a position in which they would be susceptible to deprotonation by the enolate anion.

Evidence to support this theory is given by the absence of formaldehyde in the crude ^{1}H-NMR spectra of the products formed with this new method. The only species observed in the crude ^{1}H-NMR spectra are the expected product, starting aldehyde, the starting amide, and isopropoxide from the titanium isopropoxide.

Initial studies showed that a reaction time of 1h for the enolate formed with *N*-methoxy-*N*-methylacetamide (1.1 eq, 1.1 mmol) and an aryl aldehyde (*p*-chlorobenzaldehyde, 1.0 eq, 1.0 mmol), while holding the temperature constant at –78°C yielded a 67% conversion (Scheme 11). Conversion ratios in these experiments are determined by the^{1}H-NMR spectrum of the crude reaction mixture after workup. A ratio

of the integration of product proton peak "a" to aldehyde proton peak "b" gives the conversion ratio. Both peaks "a" and "b" represent one proton. Figure 3 shows a comparison of these two peaks.

Scheme 11

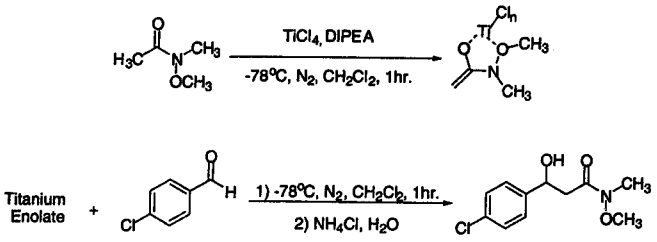
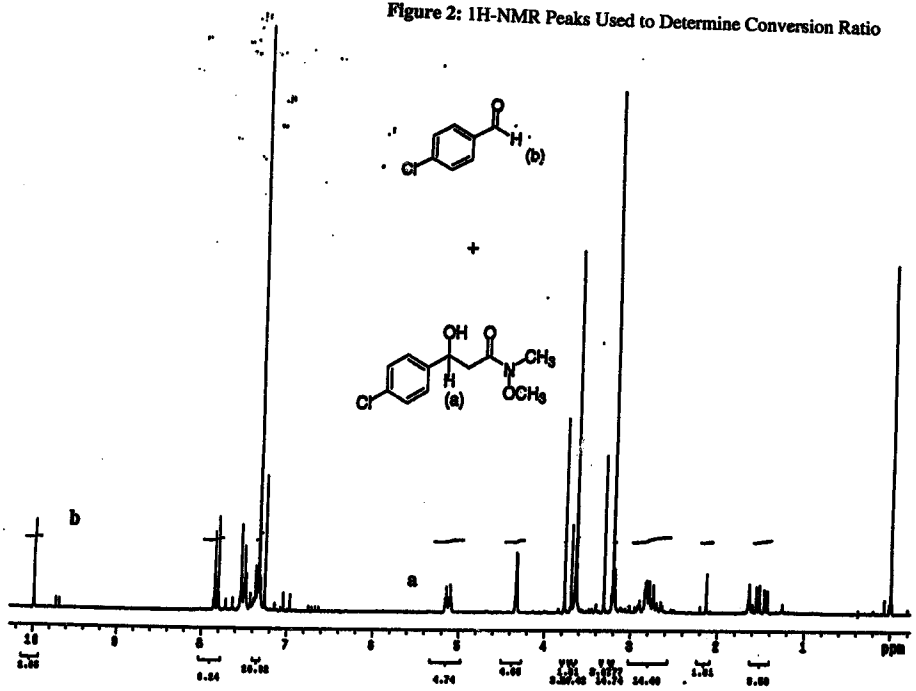


Figure 2: 1H-NMR Peaks Used to Determine Conversion Ratio



The first experimental variation made upon the reaction was to increase the length of reaction time. Increasing the reaction time of the aldehyde and enolate from 1h to 24h while maintaining constant temperature at –78°C showed no improvement in conversion ratio. Also important to note is that the increased reaction time resulted in no observable side reactions. The results of this time-varying experiment indicate that extended reaction time does not play a crucial role in these enolate reactions.

We next turned our attention to altering temperature conditions with time held constant (Table 1). We observed that when the temperature of reaction was allowed to increase from –78°C to 0°C while maintaining a constant reaction time of 1h, the conversion ratio increased to 75% (Table 1). This was followed by allowing the reaction to warm to room temperature. Under the conditions of this reaction the conversion ratio showed an increase to 87% (Table 1).

Table 1: Varying Temperature Data[a]

Temperature (°C)	% Conversion
-78	67
-78 → 0	75
-78 → R.T.	87

a) Reaction time: 1h

These temperature-varying experiments produced exciting results that indicate good conversion can be obtained by allowing the enolate-electrophile reaction mixture to warm from –78°C to room temperature while keeping the reaction time at 1h. Although increasing the temperature increases the rate of conversion, it is also detrimental to the stability of the enolate. Titanium enolates have been shown to slowly decompose at temperatures above –78°C. So while the conversion ratio increases with temperature, some of the possible product is lost due to decomposition of the enolate. This provides

supporting information as to why the conversion ratio for this temperature method never exceeded 86%.

Experiments were performed to determine if activating the aldehyde with a lewis acid would increase the conversion ratio. Several inorganic salts were tested at 1 eq and the results appear in Table 2. For these experiments temperature was held constant at –78°C and reaction times were in the range of 16-20h. The best percent conversion, 87%, was obtained with GeO_2. Interestingly, the copper lewis acids in some way interfered with the reaction and afforded lower conversion ratios than those obtained when no lewis acid was employed. $TiCl_4$ and $AlCl_3$ did not show an effect on the conversion ratio. $ZrCl_4$ activated the aldehyde and increased the conversion ratio to 75%, however this increase was not as large as the increase observed when GeO_2 was employed.

Table 2: Lewis Acid Data

Lewis Acid	% Conversion
$TiCl_4$	64
GeO_2	86
$ZrCl_4$	75
CuI	50
$AlCl_3$	67
$CuBr_2$	25
CuCl	50

Since GeO_2 appeared to be only sparingly soluble in CH_2Cl_2, it was tested using a catalytic amount (20 mol%, 0.2 eq) and showed about the same level of activity that it has when 1 eq is employed (Table 3). At 0.2 eq, some of the GeO_2 was still insoluble in CH_2Cl_2 suggesting that it takes less than 0.2 eq to efficiently activate the aldehyde. In addition to GeO_2, three isopropoxides were also tested using catalytic amounts (20 mol%, 0.2 eq). The data for the isopropoxides appears in Table 3. Out of the lewis acids tested

using catalytic amounts, titanium isopropoxide worked the best, yielding 100% conversion. The isopropoxides of germanium and zirconium showed little effect on the conversion ratio.

Titanium isopropoxide was tested at levels lower than 0.2 eq to determine the lowest amount needed to maintain full activity. The lowest amount of titanium isopropoxide added, while maintaining 100% conversion was determined to be 0.05 eq (0.05 mmol, this data appears in Table 3). Titanium isopropoxide was tested at 0.01 eq, however only an 86% conversion was obtained.

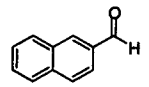
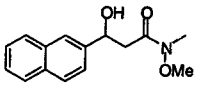
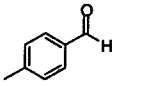
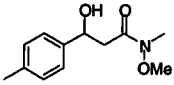
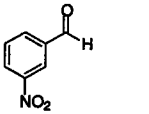
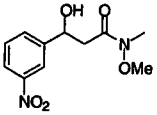
Table 3: Data for Lewis Acids Tested at Catalytic Amounts

Lewis Acid	Eq.	% Conversion
GeO_2	0.2	80
$Ge[OCH(CH_3)_2]_4$	0.2	63
$Zr[OCH(CH_3)_2]_4$	0.2	66
$Ti[OCH(CH_3)_2]_4$	0.2	100
$Ti[OCH(CH_3)_2]_4$	0.1	100
$Ti[OCH(CH_3)_2]_4$	0.05	100
$Ti[OCH(CH_3)_2]_4$	0.01	86

The experiments performed using lewis acids to activate the aldehyde show that GeO_2 at 0.2 eq will result in good conversion. However, GeO_2 has solubility issues in CH_2Cl_2 that make it difficult to determine the amount that is effectively activating the aldehyde. Furthermore, the low solubility of GeO_2 in CH_2Cl_2 limits the possibility of making more of the lewis acid available to the aldehyde. The metal isopropoxides did not have this solubility problem. Titanium isopropoxide proved to be the most effective lewis acid producing 100% conversion on a catalytic amount of 0.[illegible]eq. Reactions that employed metal isopropoxides showed isopropoxide in the crude ^{1}H-NMR spectra, however this remaining isopropoxide is easily removed by flash column chromatography.

Reactions with other aryl aldehydes obtained moderate success. Addition of the enolate to 2-naphthaldehyde, *p*-tolualdehyde, and 3-nitrobenzaldehyde did not result in 100% conversion (Table 4). Naphthaldehyde afforded the best result with a conversion ratio of 89%. 3-nitrobenzaldehyde and *p*-tolualdehyde showed lower conversion ratios with 65% and 53% respectively. However, these additions were only attempted once and we must reattempt them before solid conclusions are made.

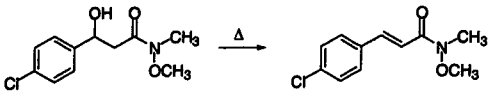
Table 4: Addition to Other Aldehydes

Aldehyde	Product	% Conversion
		89%
		53%
		65%

Initially, the crude yields obtained from these reactions were very poor. The poor yields were a result of quenching with 1 N HCl and applying heat while evaporating the solvent. Under these conditions, we believe the product dehydrated and formed the α, β-unsaturated product (Scheme 12). The solution for this problem came from quenching

with saturated $NH_4Cl_{(aq)}$ and avoiding heat while removing the solvent on a rotary evaporator. Under these conditions excellent crude yields were obtained.

Scheme 12



Conclusions

It has been shown that Weinreb amides can indeed form titanium enolate nucluophiles and add to aryl aldehydes. Good conversion can be obtained by allowing the enolate-electrophile reaction mixture to warm from –78°C to room temperature maintaining a reaction time of 1h, and also by using 0.2 eq GeO_2 as a lewis acid to activate the aldehyde while maintaining a temperature of –78°C for 20h. Excellent conversion is obtained using 0.05 eq titanium isopropoxide as a lewis acid to activate the aldehyde, while maintaining a temperature of –78°C for 20h.

Experimental

General Procedure

All reactions were performed using CH_2Cl_2 distilled from CaH_2. Thin Layer Chromatography (TLC) was performed on E. Merck silica gel 60 Å analytical glass plates. E. Merck silica gel 60 Å was used to perform flash column chromatography. Flash column chromatography was performed according to the method of Still.[9] Melting points were obtained using a Mel-Temp II® capillary melting apparatus. ^{1}H-NMR was performed in $CDCl_3$ at 200 MHz using a Varian Gemini 2200 spectrometer. The following conventions were used in interpreting the ^{1}H-NMR spectra: s=singlet, bs=broad singlet, d=doublet, dd=doublet of doublets, t=triplet, bt=broad triplet, td=triplet of doublets, and m=multiplet.

Enolate formation

A 25 mL 3-neck round bottom flask equipped with a stir bar and septa is purged under nitrogen for five minutes. *N*-methoxy-*N*-methylacetamide (1.1 eq, 113 μL) and 3 mL of methylene chloride are then added in that order via syringe. The flask is then cooled to -78°C in a dry ice-acetone bath. After cooling for a few minutes, 1 M titanium tetrachloride in methylene chloride (1.2 eq, 1.2 mL) is added via syringe. Upon addition of the titanium tetrachloride, the solution becomes bright pale yellow. After allowing the amide and the titanium to complex for a few minutes, diisopropylethylamine (1.25 eq, 218 μL) is added dropwise via syringe and the solution becomes dark purple. The enolate is allowed to stir at –78°C for one hour.

Aldehyde Preparation and Enolate Transfer

While the enolate is stirring, the aldehyde (1.0 eq) is weighed out and placed in a 25 mL round bottom flask that is equipped with stir bar and septum. The flask is then purged under nitrogen for five minutes. 3 mL of methylene chloride and titanium isopropoxide (0.05 eq, 15μL) are then added in that order via syringe. Upon addition of the titanium isopropoxide, the solution begins to show a very slight shade of yellow. This solution stirs at room temperature for twenty minutes before being cooled to –78°C, at which it stirs for an additional ten minutes.

After stirring for one hour at –78°C, the enolate is transferred to the flask containing the aldehyde via cannula. The reaction is then allowed to stir overnight (16-24hrs) at –78°C.

***N*-Methoxy-*N*-methyl-3-hydroxy-3-(4-chlorophenyl)propanamide**

The enolate was added to a stirred solution of *p*-chlorobenzaldehyde (140 mg, 1.0 mmol) and titanium isopropoxide (15 μL, 0.05 mmol) in 3 mL CH_2Cl_2 at –78°C. The resulting reaction mixture stirred at –78°C for 18h and was quenched with 1 mL NH_4Cl. Upon quenching the solution becomes yellow and a white solid precipitates (presumably titanium salts). This solid was removed by gravity filtration. The organic layer was separated, washed with saturated $NaHCO_3$ (10 mL) followed by brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow solid was purified by flash chromatography to afford 144 mg of a white solid (60% yield), mp=78-80°C. R_f=0.13 (SiO_2 2% MeOH/CH_2Cl_2). 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.34 (s, 4H), 5.12 (m, 1H), 4.32 (d, 1H), 3.64 (s, 3H), 3.21 (s, 3H), 2.78 (m, 2H). LRMS, calcd for $C_{11}H_{14}ClNO_3$ 243.69, found 243.1.

***N*-methoxy-*N*-methyl-3-hydroxy-3-naphthylpropanamide**

The enolate was added to a stirred solution of 2-napthaldehyde (1.0 mmol) and titanium isopropoxide (15μL, 0.05 mmol) in 3 mL CH2Cl2 at –78°C. The resulting reaction mixture stirred at –78°C for 23h and was quenched with 1 mL NH_4Cl. Upon quenching the solution becomes yellow and a white solid precipitates (presumably titanium salts). This solid was removed by gravity filtration. The organic layer was separated, washed with saturated $NaHCO_3$ (10 mL) followed by brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow oil was purified by flash column chromatography to afford 80 mg of a yellow oil (31 %). R_f=0.17 (SiO_2 2.5% MeOH/CH_2CH_2). 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.86 (m, 4H), 7.48 (m, 3H), 5.33 (m, 1H), 4.39 (d, 1H), 3.64 (s, 3H), 3.23 (s, 3H), 2.92 (m, 2H).

***N*-methoxy-*N*-methyl-3-hydroxy-3-(3-nitrophenyl)propanamide**

The enolate was added to a stirred solution of 3-nitrobenzaldehyde (1.0 mmol) and titanium isopropoxide (15μL, 0.05 mmol) in 3 mL CH_2Cl_2 at –78°C. The resulting reaction mixture stirred at –78^{0}C for 26h. and was quenched with 1 mL saturated NH_4Cl(aq). Upon quenching the solution becomes yellow and a white solid precipitates (presumably titanium salts). This solid was removed by gravity filtration. The organic layer was separated, washed with saturated $NaHCO_3$ (10 mL) followed by brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow/orange oil was purified by flash column chromatography to afford 117 mg of a yellow oil (46% yield) R_f=0.24 (SiO_2 2% MeOH/CH_2Cl_2). 200 MHz ^{1}H-NMR δ 8.28 (s, 1H), 8.13 (d,

1H), 7.76 (d, 1H), 7.54 (t, 1H), 5.24 (m, 1H), 4.52(s, 1H), 3.67 (s, 3H), 3.22 (s, 3H), 2.82 (m, 2H).

_N_-methoxy-_N_-methyl-3-hydroxy-3-(4-methylphenyl)propanamide

The enolate was added to a stirred solution of *p*-tolualdehyde (1.0 mmol) and titanium isopropoxide (15 μL, 0.05 mmol) in 3 mL CH_2Cl_2 at –78°C. The resulting reaction mixture stirred at –78°C for 29 h. and was quenched with 1 mL of saturated NH_4Cl(aq). Upon quenching the solution becomes yellow and a white solid precipitates (presumably titanium salts). This solid was removed by gravity filtration. The organic layer was separated, washed with saturated $NaHCO_3$ (10 mL) followed by brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow oil was purified by flash column chromatography to afford 32 mg of a yellow oil (14 % yield). R_f=0.13 (SiO_2 2% MeOH/CH_2Cl_2). 200 MHz ^{1}H-NMR δ 7.20 (dd, 4H), 5.11 (m, 1H), 4.15 (s, 1H), 3.61 (s, 3H), 3.20 (s, 1H), 2.80 (m, 2H).

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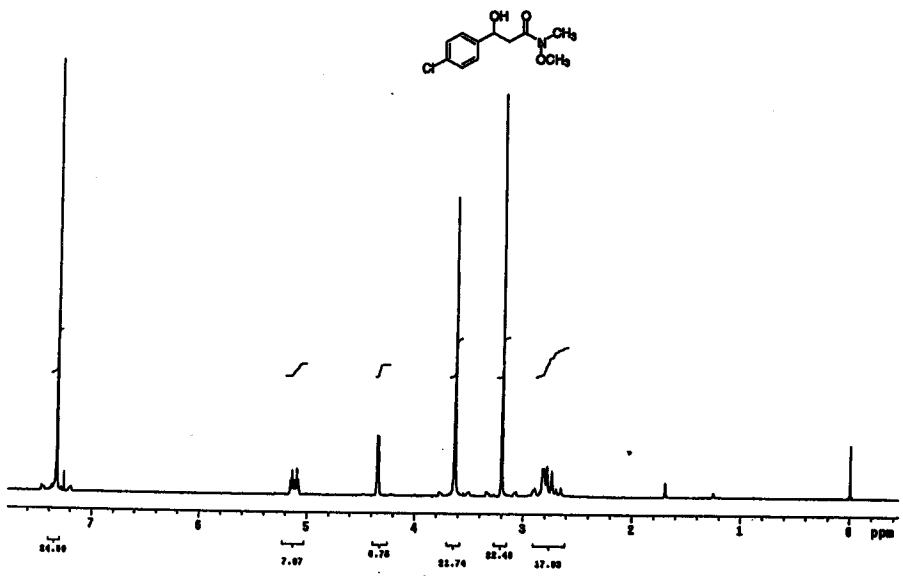
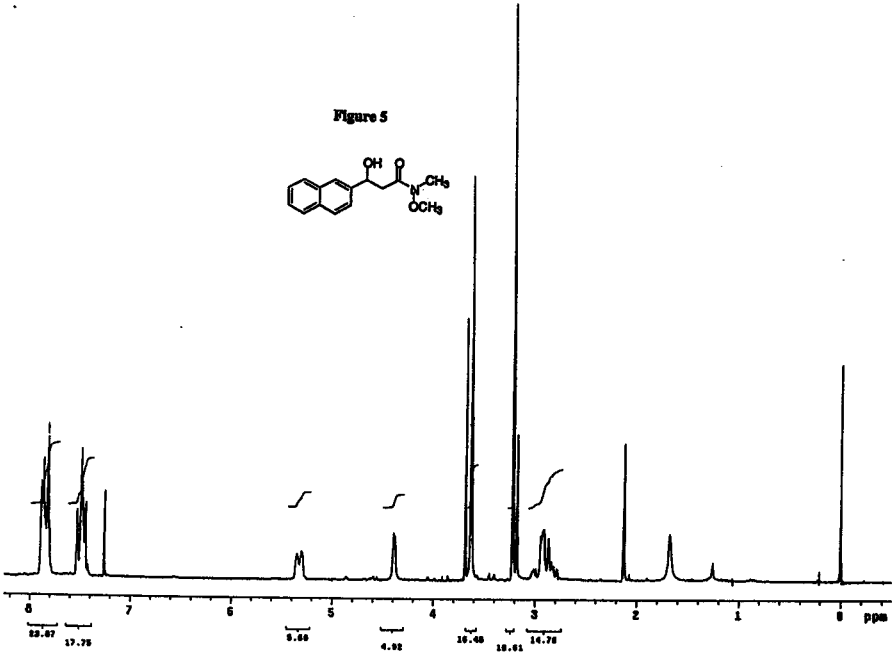
Figure 4



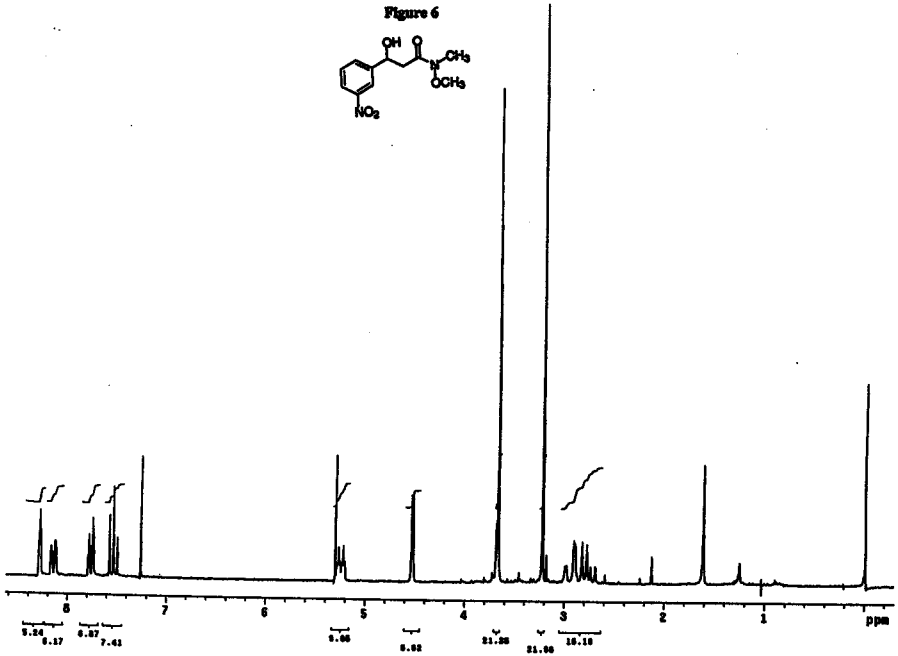
A1

Figure 5



A2

Figure 6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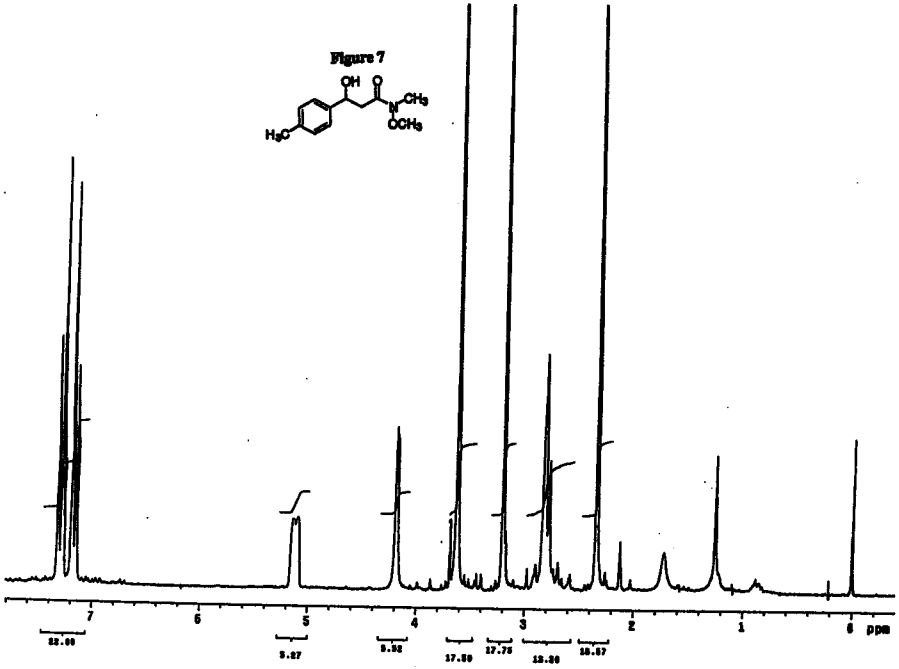
A3

Figure 7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A4