Facile Reduction of Aromatic Aldehydes, Ketones, Diketones and Oxo Aldehydes to Alcohols by an Aqueous $TiCl_3/NH_3$ System: Selectivity and Scope

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A simple and rapid procedure for the almost quantitative reduction of aromatic aldehydes, ketones, diketones and oxo aldehydes to alcohols by use of $TiCl_3/NH_3$ in aqueous methanol solution is reported. The reducing system distinguishes between different classes of aldehydes and/or ketones, and many functionalities that usually do not survive under reducing conditions are tolerated well. The concept of reversal of chemoselectivity has also been developed. A mechanism based on two sequential one-electron transfers from Ti^{III} to the carbonyl carbon atom is proposed, the second SET becoming operative only in the presence of ammonium ion (either added or formed in situ).

Introduction

The reduction of aldehydes and ketones to alcohols by use of a variety of metal hydrides, often in conjunction with titanium(IV) salts or other metals with Lewis acidity, has been widely studied.[1] However, many common functionalities do not survive exposure to metal hydrides,[1,2] and the development of reducing agents capable of discrimination between various classes of carbonyl and/or other groups continues to be a topic of great interest in synthetic organic chemistry.[3]

Methods based on electron transfer (SET), as opposed to hydrogen transfer, include the use of low-valent metal species, but most of these are primarily of interest as reagents for pinacol coupling reactions.[4] Of those reducing agents, low-valent titanium compounds have proved to be quite effective, and are being intensively studied by many research groups.[5]

In particular, we have established in the past decade that

a) an aqueous acidic $TiCl_3$ solution efficiently couples only carbonyl groups bearing powerful EWG substituents in their α positions[6] (EWG = COOMe, CN, COOH, 2-Py and 4-Py[7]),

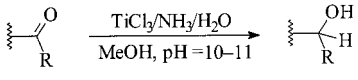
b) an aqueous methanol $TiCl_3$/NaOH solution, owing to the increased reducing power of Ti^{III} ion in basic medium, homocouples simple aromatic ketones[7] with moderate *dl* stereoselectivity, and

c) an anhydrous $TiCl_3/CH_2Cl_2$ solution stereo- and chemoselectively couples aromatic aldehydes, but not aromatic ketones, to afford *dl*-hydrobenzoins.[8]

To date, no report on the use of low-valent titanium salts in reductions to form alcohols from aldehydes and ketones has appeared. Only recently[9] have we first reported that an aqueous acidic $TiCl_3$ solution readily reduces cyclic aliphatic ketones to the corresponding thermodynamically less stable axial alcohols when aqueous NH_3 is used instead of NaOH as a coexisting base to obtain a pH of 10−11.

From these results, it was of interest to define the synthetic potential of this procedure further, in terms of the chemoselective reduction of carbonyl compounds to alcohols. In addition, this simple procedure is attractive both from economic and from environmental points of view: the aqueous acidic $TiCl_3$ solution is commercially available at low cost, safe and easy to handle. The use of aqueous solvents and the formation of non-toxic materials after workup (ultimately NH_4Cl and TiO_2) greatly reduce the environmental impact, contributing to the overall synthetic efficiency of the method.[10]

Here, we now report that aqueous $TiCl_3$ in combination with aqueous NH_3 in methanol at pH = 10−11 rapidly converts aromatic aldehydes and aromatic ketones[11] (Table 1), diketones and oxo aldehydes (Table 2) to the corresponding alcohols in good to excellent yields [Equation (1)], while many common functional groups, such as acids, esters, amides and cyano, bromo, chloro, methoxy, dimethyl acetal and α-cyclopropyl groups, are recovered unaffected. Bimolecular coupling does generally not occur, or else is a very minor pathway.



(1)

Competition experiments between different classes of aldehydes and/or ketones were performed to illustrate the chemoselectivity of the method, while the concept of in situ protection of the more reactive aldehyde revealed interesting opportunities for reversal of chemoselectivity [Equations (2) and (3)]. From the mechanistic point of view, the

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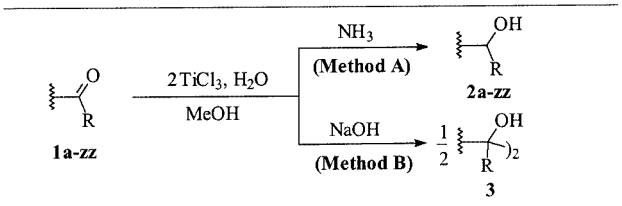
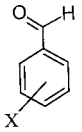
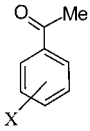
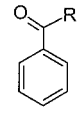
Table 1. Reduction of aromatic aldehydes and ketones by $TiCl_3/NH_3$ (Method A) and $TiCl_3$/NaOH (Method B), a comparison



Substrate 1		Method A[a] Products (% yield)[b] 2	3	Method B Products (% yield)[b] 2	3
	**a** X = H	quant.[c]		12	88[d]
	b X = 4-OMe	90	traces[e]	21	70[d]
	c X = 4-Br	80	15	22	76[d]
	d X = 3-Br	quant.			
	e X = 2-Br	quant.			
	f X = 4-CN	81	19		
	g X = 3-CN	quant.			
	h X = 4-COOMe	78	8		
	i X = 4-COOH	63			
	j X = 4-Cl	80	traces		
	k 3-Pyridine-carboxaldehyde	quant.		28	60[d]
	**l** X = H	quant.			83[f]
	m X = 4-OMe	quant.			83[f]
	n X = 4-CN	76	15		75[f]
	o X = 3-CN	quant.			
	p X = 4-Cl	quant.			
	q 3-Acetylpyridine	quant.			73[g]
	**r** R = Et	92			95[f]
	s R = *cy*-C_3H_5	quant.			
	t R = CH_2Ph	95			62[f]
	u R = *t*Bu	70		30	30[f]
	v R = Ph	74	17	quant.[d]	
	w Fluorenone	58	42	quant.[d]	
	x Indanone	quant.			
	y 3-Me-Indanone	quant. (*cis*/*trans* = 77:33)			
	z Tetralone	quant.			
	yy Chromanone	quant.			
	zz 3-Ph-Chromanone	quant. (*cis*/*trans* = 65:35)			

[a] The reaction was carried out under N_2 with 5 mmol of **1** and 10 mmol of $TiCl_3$: with aldehydes **1a**−**k**, the reducing solution was added to the MeOH/H_2O/NH_3 solution of **1**; with ketones **1l**−**zz**, the aqueous NH_3 solution was added to the MeOH/H_2O/$TiCl_3$ solution of **1**. [b] Product distribution was determined by ^1H NMR analysis, the difference to 100% was the unchanged substrate. [c] "quant." means: ^1H NMR purity of the crude alcohol > 95%; mass balance ≥ 95%. [d] This work: the reducing $TiCl_3$ solution was added to the MeOH/H_2O/NaOH solution of **1**. [e] traces means: ≤ 5% yield. [f] Data from ref.[7b]. [g] Data from ref.[7]

results reported here highlight the important role of ammonium ion in determining unimolecular reduction to the detriment of pinacolization (Scheme 1).

Results and Discussion

Reduction of Aromatic Aldehydes and Ketones by Aqueous $TiCl_3/NH_3$ (Method A) and by Aqueous $TiCl_3$/NaOH (Method B) (Table 1)

After a survey to optimize the reaction conditions, we found that on addition, under N_2, of 2 equimolar amounts of aqueous acidic 15% (w/v) $TiCl_3$ solution to an MeOH/H_2O/NH_3 solution of the aldehyde (**1a**−**k**, Table 1, Method A), a very fast reaction (like a titration) took place. The blue color of the reducing solution, added dropwise (1 min) in order to maintain the temperature below 20−25 °C, was immediately discharged to give a white suspension. The amount of aqueous 30% NH_3 solution used was such as to maintain the final reaction mixture at pH = 10−11. After workup, alcohols **2a**−**k** were recovered in good to excellent yields. It is worth noting that benzaldehydes **1c**, **1f**, and **1h**, each bearing an electron-withdrawing group (EWG) in the *para* position, were partially converted into the corresponding dimers **3**, whereas the *meta* isomers **1d** and **1g** did not give the dimer.

We next applied this procedure to aromatic ketones. Although selective unimolecular reduction occurred, the resulting alcohols were in some cases contaminated with condensation products that lowered the yields. By use of a "reverse order" of addition of the reagents (with respect to that adopted for the aldehydes), however, the reduction of the fifteen monoaromatic ketones **1l**−**u** and **1x**−**zz**) became straightforward (Table 1).

That is, on addition of aqueous NH_3 solution to an aqueous acidic solution of $TiCl_3$ and the ketone (molar ratio, 2:1) in methanol until pH = 10−11, the reduction proved to be so clean that, with a few exceptions, no chromatographic separation was required in order to obtain spectroscopically pure alcohols (^1H NMR purity > 95%). As already pointed out for *para*-EWG-substituted aldehydes, 4-acetylbenzonitrile (**1n**) also underwent partial dimerization (15%) while 3-acetylbenzonitrile (**1o**) did not give the reductive coupling product (vide infra).

With the goal of standardising the method for both aldehydes and ketones, we also tried this "reverse order" of addition with aldehydes. The reaction did not proceed to completion, however, since a considerable portion of the starting aldehyde was converted into its dimethyl acetal (50−60% yield), which was not reduced under these conditions.[12]

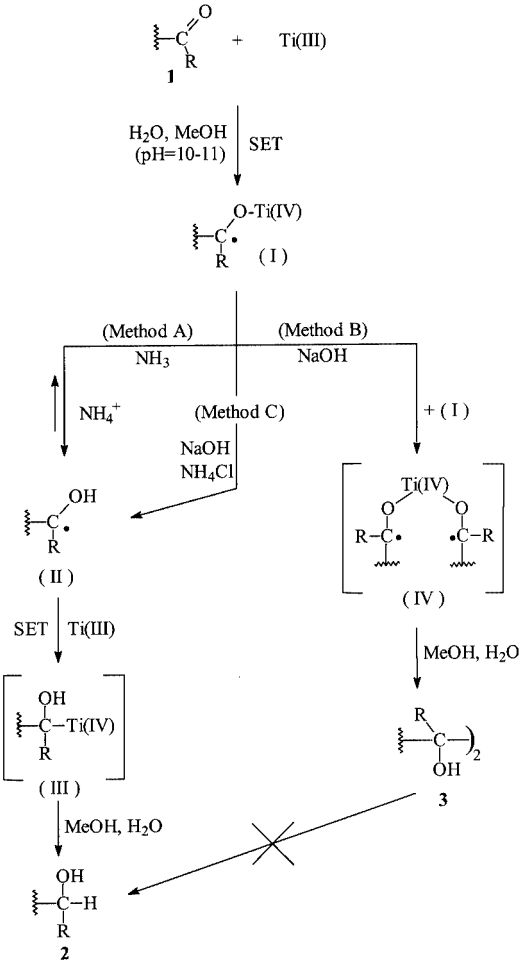
In our previous reports,[7] we had found that aromatic ketones **1l**−**n**, **1r**, **1t** and 3-acetylpyridine underwent exclusive pinacolization when NaOH was used in conjunction with $TiCl_3$ solution (Method B). In the current study we have shown that benzaldehydes **1a**−**c** and 3-pyridinecarboxaldehyde[13] **1k** also stereorandomly gave dimers **3** as major products under the conditions of Method B. These results, together with selected data from ref.[7], are shown in Table 1.

On comparison of data relating to methods A and B it clearly emerges that, simply on switching of the coexisting base from NaOH to NH_3, $TiCl_3$ promotes the monomolecular reduction instead of the dimerization.

Since it could be imagined that the alcohols might have been obtained by subsequent bond cleavage of the initially formed dimers, we established that pinacols produced from benzaldehyde and acetophenone were stable under the conditions of both Method A and Method B, whereas dimers produced from benzophenone and fluorenone, though inert

under the conditions of Method A, were quantitatively converted into the corresponding alcohols **2v**−**w** under the conditions of Method B after 30 min. This finding would explain the apparent anomaly found in the reduction of bis(aromatic) ketones **1v**−**w**, which, unlike the monoaromatic ones, were quantitatively reduced to alcohols by the $TiCl_3$/NaOH system but partially dimerized by the $TiCl_3/NH_3$ system (vide infra).

The mechanistic hypothesis put forward in ref.[9] and now outlined in Scheme 1 is undoubtedly strengthened by examination of the data reported in Table 1.



Scheme 1

Under the conditions of Method A, ammonium ion (pK_a = 9.24) is formed in situ and behaves as the strongest acid available in the basic aqueous methanol solution. Thus, it would render thermodynamically feasible the protonolysis of the intermediate metal-bonded ketyl **I**, formed by inner-sphere SET from Ti^{III} ion to the carbonyl carbon atom. The resulting α-hydroxy radical **II** (pK_a = 9−10)[14] would then be rapidly reduced under conditions in which the first electron transfer to the substrate takes place.[15]

The stereochemistry found in the reduction of aliphatic cyclic ketones[9] suggests the formation of a "transient" C−Ti bond during the second SET. Protonation of the organometallic (or anionic) intermediate **III** affords the observed final alcohols **2**.

When methanol (pK_a = 15.2) and water (pK_a = 15.74) are the only hydrogen ion sources (Method B), protonolysis of ketyl **I** becomes less favorable than bimolecular coupling, and a titanium-"bridged" intermediate **IV** or a dimeric ion pair[7b] affords the observed dimers **3**. Proton availability in aqueous MeOH/NaOH solution can, however, be increased by addition of ammonium chloride. Therefore, in two separate experiments, we observed that both benzaldehyde and acetophenone were quantitatively reduced to the corresponding alcohols by the $TiCl_3$/NaOH system, provided that the aqueous MeOH/NaOH solutions of the substrate were saturated with NH_4Cl prior to $TiCl_3$ addition (Method C, Scheme 1). Thus, the second SET becomes operative only in the presence of ammonium ion (added or formed in situ).

As mentioned previously, with bis(aromatic) ketones (**1v**−**w**) and those aldehydes and ketones (**1c**, **1f**, **1h** and **1n**) bearing a strong EWG in the *para* position, relatively large amounts of dimers were formed under the conditions of Method A. Since the acidity of the OH group in the free α-hydroxy radical **II** is no doubt increased by resonance stabilization of the corresponding radical anion (for instance, pK_a = 6.3 for fluorenone radical **II**),[14] ammonium ion could be too weak an acid to promote the critical proton transfer to ketyls **I** of the above substrates, and so partial dimerization would become competitive.

Actually, however, 3-cyanobenzaldehyde, 3-bromobenzaldehyde and 3-acetylbenzonitrile, deliberately selected[16] to test this working hypothesis, were quantitatively reduced to alcohol.

Reduction of Dicarbonyl Compounds by Aqueous $TiCl_3/NH_3$ (Table 2)

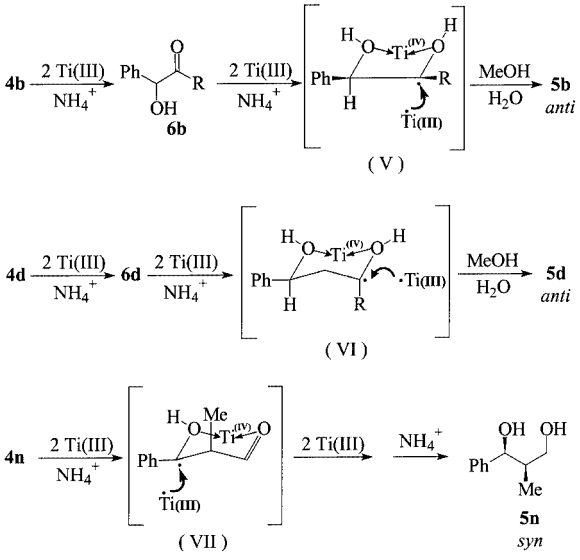
The results for the reduction of various classes of dicarbonyl compounds by the aqueous $TiCl_3/NH_3$ system to form alcohols highlight the usefulness of the procedure. Table 2 reports, together with isolated product yields and isomer ratios, the reaction conditions (e.g., reaction order and equiv. of $TiCl_3$) that suit a particular class of substrates in order to obtain higher yields of reduction products **5**.

In the reduction of symmetric aromatic diketones **4c**, **4e** and **4g**−**i** with four molar equivalents of $TiCl_3$, the corresponding diols **5** were invariably formed as the major products. However, higher yields were obtained by addition of the aqueous $TiCl_3$ solution to the aqueous $MeOH/NH_3$ solution of **4** under experimental conditions similar to those adopted for aromatic aldehydes (cf. Entries 9−12). The type of by-product **6** is strictly dependent on the separation of the two aromatic oxo groups. Whereas diols **5c** and **5i** were formed in quantitative yields (^1H NMR purity > 95%) from 1,2- and 1,6-diketones, respectively, competitive intramolecular reductive coupling of 1,4- and 1,5-diketones to the corresponding cyclic *cis*-diols **6g** and **6h** was observed (their amount being related to the sequence of reagents addition: cf. Entries 9−12). Partial dehydration, followed by successive reduction, could explain the formation of **6e** from 1,3-diketone.

Although due care was taken in carrying out the reactions, selective reduction of only one of the two aromatic oxo groups in **4c** or in **4g−i** was not achieved: mixtures of diols and oxo alcohol were invariably formed with different molar equivalents (two or less) of $TiCl_3$.

As regards aliphatic/aromatic diketones, chemoselective reduction of the more reactive aromatic oxo group[17] was observed only when the number of methylene groups between the two oxo functionalities was such as to prevent titanium chelation ($[CH_2]_n$, $n \geq 2$): the reduction of 1,4-diketone **4f** to oxo alcohol **6f** in 70% separated yield even when four molar equivalents of $TiCl_3$ were used (cf. Entries 7, 8) is in line with this reasoning. In contrast, 1,2- and 1,3-diketones **4b** and **4d** were reduced to mixtures of diol and oxo alcohol by 2 equiv. of the reducing agent (data for **4d**, Entry 5) and to the corresponding diols **5** (*anti*/*syn* ≥ 80:20) by 4 equiv.

Since we had established that, under the above experimental conditions, the β-oxo alcohol **6d** was quantitatively reduced to the diol **5d** (*anti*/*syn* = 85:15) whereas the γ-oxo alcohol **6f** remained unchanged, the sequence of reductions depicted in Scheme 2 for **4b** and **4d** (R = Me) to give the corresponding diols **5** seems very likely.[18]



Scheme 2

The reduction of an aliphatic oxo group occurs only because Ti^{III} chelation with the α- or β-hydroxy group becomes feasible, thereby facilitating what would now be an intramolecular SET to give five- or six-membered chelate radicals (**V** or **VI** of Scheme 2).

The preferential formation of the *anti*-diols **5b** and **5d** demands that the metal ion and its coordinated ligands (MeOH, H_2O etc.) exert a greater steric control than the methyl group during the second stereodetermining SET, which should then occur from the less hindered side, as indicated by the arrows in Scheme 2. Formation of a "transient" C−Ti bond[19] (*trans* to the phenyl group in **V** and in an equatorial position in **VI**) followed by very fast protonolysis would yield the *anti*-diol.

The formation of diols from α- and β-oxo aldehydes **4a** and **4k−m** could be explained as shown for diketones **4b** and **4d** (R = H, Scheme 2). The preferential formation of *syn*-**5n** (Table 2, Entry 18) is in line with intramolecular titanium chelation prior to or synchronous with the first SET to the aromatic oxo group (intermediate radical **VII**, Scheme 2). The second SET, occurring *trans* to the methyl group, would be responsible for the observed stereochemistry.

We next examined the reduction of aromatic ketones bearing an additional carbonyl function in the side chain: specifically the oxo ester **4o**, the oxo acids **4p−q** and the oxo amide **4r**. In all cases, only the aromatic oxo group was selectively and quantitatively reduced. The quantitative conversion of γ- and δ-oxo acids **4p−q** to the corresponding alcohols, followed by cyclization into butyrolactone **5p** and valerolactone **5q** upon aqueous acidic workup, should be underlined since many procedures[20] directed towards these syntheses have been devised under more drastic conditions and with lower yields.

Intermolecular Chemoselective Reductions of Aldehydes and/or Ketones and Reversal of Chemoselectivity

Reduction of aliphatic aldehydes and aliphatic acyclic ketones by $TiCl_3/NH_3$ system is without synthetic interest,[9] unless a proximal α- or β-hydroxy group activates the reagent, enabling reduction of the aliphatic moiety. This synthetic limitation, however, provides an effective and simple method for effecting the selective reduction of aromatic substrates in the presence of aliphatic ones. A number of competition experiments between aliphatic and aromatic aldehydes and/or ketones were carried out. By addition of 10 mmol of aqueous $TiCl_3$ solution to a 1:1 mixture of the two substrates (each 5 mmol in aqueous $MeOH/NH_3$ solution), clean reduction with excellent aromatic/aliphatic discrimination was achieved. For instance, benzaldehyde, in the presence of cyclohexanecarbaldehyde, 1-nonanal or even the more reactive cyclohexanone,[9] afforded benzyl alcohol in ≥ 95% yield with ≥ 97% selectivity, as revealed by GC analysis of the crude reaction mixture.

Similarly, acetophenone was reduced to the corresponding alcohol in ≥ 93% yield with ≥ 95% selectivity over either 1-hexanone or cyclohexanone. Predictably, the degree of discrimination between benzaldehyde and acetophenone was lower, but preferable formation of benzyl alcohol (80% yield) over α-methylbenzyl alcohol (15% yield) occurred (selectivity 84:16).

Finally, we report an interesting application of this titanium chemistry, new to the literature, involving reversal of chemoselectivity in a one-pot procedure:[21] the chemoselective reduction of an aromatic ketone in the presence of an aromatic aldehyde.

Table 2. Reduction of dicarbonyl compounds by the $TiCl_3/NH_3$ system

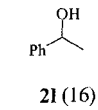
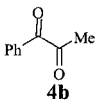
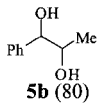
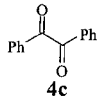
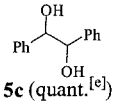
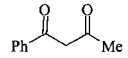
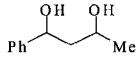
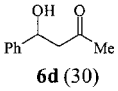
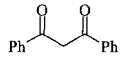
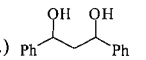
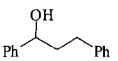
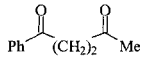
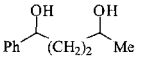
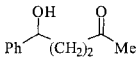
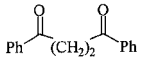
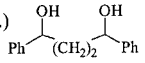
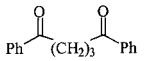
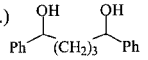
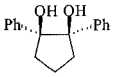
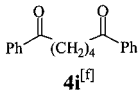
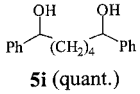
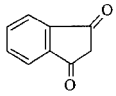
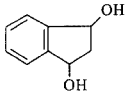
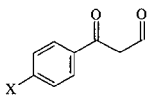
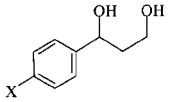
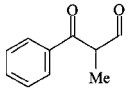
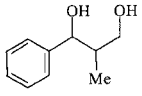
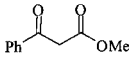
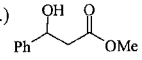
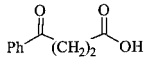
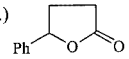
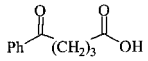
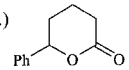
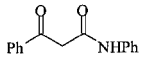
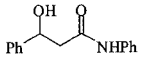
Entry	Dicarbonyl	Order of addition [a]	Products (yield % [b])	isomer ratio [c]
1	 **4a**	$TiCl_3$(4 equiv.) NH_3	 **5a** (80[d])	 **2l** (16)
2	 **4b**	$TiCl_3$(4 equiv.) NH_3	 **5b** (80)	*anti:syn* 82:18
3	 **4c**	$TiCl_3$(4 equiv.) NH_3	 **5c** (quant.[e])	*meso:dl* 85:15
4	 **4d**	NH_3 $TiCl_3$(4 equiv.)	 **5d** (85)	*anti:syn* 80:20
5	**4d**	NH_3 $TiCl_3$(2 equiv.)	**5d** (25)	 **6d** (30)
6	 **4e**	NH_3 $TiCl_3$(4 equiv.)	 **5e** (65)	 **6e** (12)
7	 **4f**	NH_3 $TiCl_3$(4 equiv.)	 **5f** (<5)	 **6f** (70)
8	**4f**	NH_3 $TiCl_3$(2 equiv.)	**5f** (<3)	**6f** (70)
9	 **4g**	$TiCl_3$(4 equiv.) NH_3	 **5g** (67)	 **6g** (18)
10	**4g**	NH_3 $TiCl_3$(4 equiv.)	**5g** (84)	**6g** (traces)
11	 **4h**	$TiCl_3$(4 equiv.) NH_3	 **5h** (46)	 **6h** (47)
12	**4h**	NH_3 $TiCl_3$(4 equiv.)	**5h** (63)	**6h** (31)

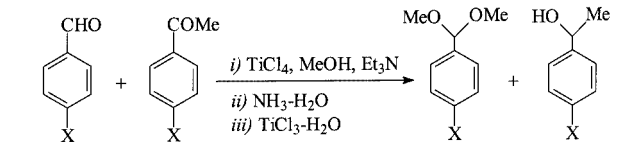
Table 2. *(continued)*

Entry	Dicarbonyl	Order of addition [a]	Products (yield % [b])	isomer ratio [c]
13	 **4i**[f]	NH_3 $TiCl_3$(4 equiv.)	 **5i** (quant.)	
14	 **4j**	$TiCl_3$(4 equiv.) NH_3	 **5j** (quant.)	*cis:trans* 60:40
15	 **4k** X=H	NH_3 $TiCl_3$(4 equiv.)	 **5k** (87)	
16	**4l** X=Cl	NH_3 $TiCl_3$(4 equiv.)	**5l** (85)	
17	**4m** X=OMe	NH_3 $TiCl_3$(4 equiv.)	**5m** (86)	
18	 **4n**	NH_3 $TiCl_3$(4 equiv.)	 **5n** (86)	*syn:anti* 70:30
19	 **4o**	$TiCl_3$(4 equiv.) NH_3	 **5o** (quant.)	
20	 **4p**	$TiCl_3$(4 equiv.) NH_3	 **5p** (quant.)	
21	 **4q**	$TiCl_3$(4 equiv.) NH_3	 **5q** (quant.)	
22	 **4r**	NH_3 $TiCl_3$(2 equiv.)	 **5r** (quant.)	
23	**4r**	$TiCl_3$(2 equiv.) NH_3	**5r** (66)	

[a] Order of addition of $TiCl_3$ (equiv. in brackets) and NH_3 to the mixture of **4** (5 mmol) in MeOH (20 mL) under N_2. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Recovered after continuous extraction by percolation. [e] "quant." means: ^1H NMR purity of the crude product > 95%, mass balance ≥ 95%. [f] Because of the low solubility of **4i** in MeOH, CH_3CN (20 mL) was used as co-solvent.

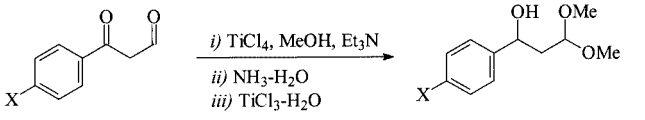
Our previous investigations[12,22] on the acetalization of various classes of aldehydes under catalysis by $TiCl_4/Et_3N$ (or NH_3) in MeOH revealed interesting opportunities for the chemoselective protection of the more reactive aromatic aldehydes in situ, while the $TiCl_3/NH_3$ system reduces the unprotected aromatic ketones to alcohol [Equation (2)].

In fact, when an equimolar mixture of an aromatic ketone and an aromatic aldehyde (5 mmol each) was allowed



(2)

to react with a catalytic amount of $TiCl_4$ (1 mol %) and Et_3N for 15 min in 20 mL of MeOH, and then treated with aqueous ammonia followed by $TiCl_3$ addition (10 mmol), a very selective reaction occurred. The aldehyde was recovered almost quantitatively in its protected form (dimethyl acetal **7a** or **7j**), whereas the secondary alcohol (**2l** or **2p**) was generated in high yield. The same reaction sequence, when applied to β-oxo aldehydes **4k−m** [Equation (3)], allowed selective intramolecular protection of the aldehyde function[22] and selective reduction of the oxo group, affording the protected β-hydroxy aldehydes **8k−m** in good isolated yield.



(3)

Conclusions

The synthetic significance of the aqueous $TiCl_3/NH_3$ system can be summarized by the following points:

1) it is easily accessible from cheap reagents, and is experimentally easy, safe and environmentally benign,

2) the yields of alcohols from aromatic aldehydes and ketones or of diols from aromatic diketones, α- and β-aromatic/aliphatic diketones or α- and β-oxo aldehydes are very high,

3) it behaves chemoselectively (i.e., it distinguishes between different classes of carbonyl groups, and many functionalities that usually do not survive under reducing conditions[1,2] are tolerated well), and

4) because of the basic reaction medium, acetals are among the groups tolerated, so that reversal of chemoselectivity is possible in a one-pot procedure that provides a useful alternative to the Luche reduction.[21a][21b]

In conclusion, this study greatly extends the chemistry of aqueous $TiCl_3$, since Ti^{III} salts have until now been considered of primary interest only for reductive coupling reactions, but of no utility in reduction to form alcohols.

Experimental Section

General Remarks: The substrates in Tables 1 and 2 were of commercial quality (Acros, Aldrich, Merck) except for the β-oxo aldehydes **4k−m**, which were prepared according to ref.[22] Et_3N and liquid aldehydes were distilled prior to use. The 30% aqueous NH_3 and the 15% aqueous (w/v) $TiCl_3$ solutions were purchased from C. Erba; $TiCl_4$ (0.1 M solution in CH_2Cl_2) was purchased from Aldrich. All reductions were performed under N_2 and, if not otherwise stated, 5 mmol of the substrate were used. Flash chromatography: Merck 60 silica gel (40−60 μm); thin layer chromatography: Merck 60 F_{254} silica gel. GC analyses of product mixture: 5% OV-17 on a chromosorb W-HP 80/100 column. ^1H and ^{13}C NMR analyses (in $CDCl_3$ when not otherwise stated): Bruker AC 250 MHz instrument; mass spectra: Finnigan MAT-TSQ70 spectrometer; melting points (uncorrected): Kofler apparatus; microanalyses: analytical section of REDOX Laboratories, Cologno Monzese (MI).

General Procedure for the Reduction of Aldehydes (1a−k) (Table 1, Method A): An aqueous acidic $TiCl_3$ solution (15%, 10 mmol, ca 10 mL) was added dropwise at 0 °C under N_2 (1 min, in order to keep the temperature in the range of 20−30 °C) to a well-stirred solution of the aldehyde (5 mmol) in MeOH (30 mL) and aqueous 30% NH_3 (10 mL). After additional stirring (5 min) at room temperature, the resulting suspension was diluted with water (10 mL) and then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water and dried with anhydrous Na_2SO_4, and the solvents were evaporated in vacuo (mass balance ≥ 95%). In most cases the crude reaction mixture revealed the presence only of the alcohol **2** (^1H NMR purity > 95%). When the dimer **3** was present, the product distribution was determined by ^1H NMR analysis.

General Procedure for the Reduction of Ketones (1l−zz) (Table 1, Method A): An aqueous NH_3 solution (30%, 10 mL), was added dropwise at 0 °C under N_2 (1 min) to a well-stirred solution of the ketone (5 mmol) in MeOH (30 mL) and of an aqueous acidic $TiCl_3$ solution (15%, 10 mmol, ca 10 mL). Workup was as in the above procedure.

General Procedure for the Reduction of Aldehydes and Ketones (Table 1, Method B): The reduction of aldehydes **1a−c** and **1k** and of bis(aromatic) ketones **1v−w** was performed under experimental conditions comparable to those of Method A for aldehydes and ketones, the only exception being that an aqueous NaOH solution (30%, 10 mL) was used instead of aqueous 30% NH_3 solution.

General Procedure for the Reduction of Dicarbonyl Compounds by the $TiCl_3/NH_3$ System (Table 2): a) When the first reagent reported in the third column of Table 2 is $TiCl_3$, the procedure adopted was that employed for the reduction of aldehydes **1a−k** (Table 1, Method A); b) when the first reagent reported in the third column of Table 2 is NH_3, the procedure adopted was that employed for the reduction of ketones **1l−zz** (Table 1, Method A). In both cases, the amount of $TiCl_3$ used is quoted in brackets in the third column of Table 2. When 4 equiv. of $TiCl_3$ were used (i.e., 20 mmol per 5 mmol of **4**), 20 mL of an aqueous 30% NH_3 solution was required to produce the final solution at pH = 10−11. After the usual workup, the crude residue was purified by flash column chromatography, unless the ^1H NMR spectrum of the crude product revealed a purity ≥ 95%.

Representative Procedure for the Chemoselective Reduction of an Aromatic vs. an Aliphatic Substrate: An aqueous acidic $TiCl_3$ solu-

tion (15%, 10 mmol, ca 10 mL) was added dropwise (1 min) at 0 °C under N_2 to a well-stirred solution of a 1:1 mixture of benzaldehyde and cyclohexanecarbaldehyde (5 mmol each) in MeOH (30 mL) and aqueous NH_3 (30%, 10 mL). The other experimental conditions and workup were the same as in the preceding procedures. GC analysis of the crude reaction mixture revealed a 97:3 ratio of benzyl alcohol/cyclohexylmethanol (conversion: 95%).

General Procedure for Reversal of Chemoselectivity by in situ Protection of the Aldehyde: The two carbonyl compounds [5 mmol each, Equation (2)] or the β-oxo aldehyde (5 mmol, Equation (3)], dissolved in MeOH (30 mL), were allowed to react, at 0 °C under N_2, with a catalytic amount of $TiCl_4$ (5×10^{-2} mmol of a 1.0 M solution in CH_2Cl_2, 50 μL). After 15 min, Et_3N was added (83 μL, 0.6 mmol) and stirring was continued for an additional 10 min. The aqueous NH_3 solution (30%, 10 mL) was then added to the reaction mixture in one portion, followed dropwise (1 min) by the aqueous $TiCl_3$ solution (15%, 10 mmol, ca 10 mL). After 5 min, the resulting suspension was diluted with water (10 mL) and extracted with EtOAc (3×50 mL). On the usual workup, GC and/or ^{1}H NMR analyses of the crude reaction mixture gave the yields stated in Equations (2) and (3).

Spectroscopic Data: All reduction products listed in Table 1 are known compounds and, for purposes of comparative identification, all but six were commercially purchased from Aldrich. Identification of the non-commercial products **2** and **3** was made by comparison with literature data obtained from the references quoted for each compound.[23] The reduction products of Table 2 and Equation (3), when known or commercially available, were characterized by direct comparison of their spectroscopic data with those of authentic commercial samples or with those reported in the literature.[24−39]

1-Phenyl-1,2-ethanediol (5a): The reaction mixture was continuously extracted by percolation with EtOAc for 4 h. Evaporation of the solvent left a solid residue that was purified by flash column chromatography (hexane/EtOAc, 3:1) to yield **2l** (100 mg, 16%) and **5a** (0.55 g, 80%) as colorless crystals melting at 66−68 °C. Both products were identified by comparison with authentic commercial samples.

1-Phenyl-1,2-propanediol (5b): After the usual workup, the crude residue was purified by flash column chromatography (hexane/EtOAc, 4:1), affording an inseparable mixture of stereoisomers (0.61 g, 80%). The *anti*[24]/*syn*[25] ratio (82:18) was determined by integration of the proton signals in the ^{1}H NMR spectrum of the crude mixture by comparison with the literature data.[24,25]

Hydrobenzoin (5c): After workup, **5c** was recovered in quantitative yield (1.05 g) as a mixture of stereoisomers. The *meso*/*dl* ratio (85:15) was determined by the ^{1}H NMR spectrum of the crude mixture, by comparison with authentic commercial samples.

1-Phenyl-1,3-butanediol (5d): After workup and purification by flash column chromatography (hexane/EtOAc, 4:1), **5d** was obtained (0.70 g, 85%) as a mixture of stereomers. The *anti*/*syn* ratio (80:20) was determined by integration of the proton signals in the ^{1}H NMR spectrum of the crude mixture by comparison with the literature data.[26]

4-Hydroxy-4-phenylbutan-2-one (6d): When the reduction of **4d** was performed with 2 molar equiv. of $TiCl_3$ (Table 2, Entry 5), a mixture of diol **5d** and oxo alcohol **6d** was obtained. After usual workup, flash chromatography (hexane/EtOAc, 7:3) afforded, in that order, unchanged **4d** (0.25 g, 30%), **6d**[27] (0.25 g, 30%) and **5d** (0.21 g, 25%).

1,3-Diphenyl-1,3-propanediol (5e) and 1,3-Diphenylpropan-1-ol (6e): After workup, the residue was purified by flash column chromatography (Et_2O/petroleum ether, 1:1) to give **6e**[28] (0.13 g, 12%) and **5e** (0.74 g, 65%) as a mixture of diastereomeric diols (*anti*[26]/*syn*,[26] 55:45) as shown by ^{1}H NMR analysis of the crude reaction mixture.

1-Phenyl-1,4-pentanediol (5f) and 5-Hydroxy-5-phenylpentan-2-one (6f): After workup, the residue, purified by flash column chromatography (hexane/EtOAc, 7:3), afforded **6f** as a yellow oil (0.62 g, 70%) and traces (30 mg, 3.2%) of **5f** as a 1:1 mixture of the two isomers.[29b] **6f:** ^{1}H NMR ($CDCl_3$): δ = 1.97 (q, *J* = 7.0 Hz, 2 H, CH_2), 2.13 (s, 3 H, CH_3CO), 2.54 (t, *J* = 7.0 Hz, 2 H, CH_2), 3.0 (s, br, 1 H, OH, D_2O exch.), 4.70 (t, *J* = 7.0 Hz, 1 H, CH), 7.3 (m, 5 H, Ph H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.9 (CH_3), 32.5 (CH_2), 39.7 (CH_2), 73.3 (C−OH), 125.6 (2 Ar-C), 127.4 (Ar-C), 128.4 (2 Ar−C), 144.8 (Ar-C_q), 208.8 (CO) ppm. IR (neat): $\tilde{\nu}$ = 3421, 2934, 1711, 1451, 1363, 1025, 702 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 178 (25) [M^+], 160 (23), 120 (100), 107 (35). $C_{11}H_{14}O_2$ (178.2): calcd. C 74.13, H 7.92; found C 74.25; H 7.95. **5f:** ^{1}H NMR ($CDCl_3$): δ = 1.15 (2 d, *J* = 6.2 Hz, 3 H, CH_3), 1.4−1.6 (m, 2 H, CH_2), 1.7−1.9 (m, 2 H, CH_2) 3.0 (s, br, 2 H, 2OH, D_2O exch.), 3.7−3.9 (m, 1 H, CH), 4.65 (dd, *J* = 7.3, 5.4 Hz, 1 H, CH, one isomer), 4.69 (t, *J* = 6.2 Hz, 1 H, CH, the other isomer).

1,4-Diphenyl-1,4-butanediol (5g) and *cis*-1,2-Diphenyl-1,2-cyclobutanediol (6g): After workup, flash column chromatography (hexane/EtOAc, 6:4) of the crude reaction mixture afforded **6g** as white crystals (0.22 g, 18%), m.p. 135−137 °C (ref. 138−140 °C).[30] ^{1}H NMR ($CDCl_3$): δ = 2.35 (m, 2 H, CH_2), 2.69 (m, 2 H, CH_2), 3.5 (s, 2 H, 2 OH, D_2O exch.), 7.0−7.2 (m, 10 H, Ph H) ppm. The second eluted fraction corresponded to **5g:** White needles (0.81 g, 67%), m.p. 90−91 °C (ref.[29b] 90−91 °C). ^{1}H NMR ($CDCl_3$): δ = 1.84 (m, 4 H, 2 CH_2), 2.50 (s, 2 H, 2 OH, D_2O exch.), 4.68 (m, 2 H, CH_2), 7.3 (m, 10 H, Ph H) ppm. By comparison of the melting point and the ^{1}H NMR of **5g** with those reported in the literature,[29] this diol ought to be the *syn* (≡ *dl*) isomer; according to ref.[31], however, the ^{13}C NMR spectrum of **5g** revealed the presence of both isomers (1:1). ^{13}C NMR ($CDCl_3$): δ = 144.3 (*syn*), 144.1 (*anti*), 128.2 (*syn* + *anti*), 127.2 (*syn* + *anti*), 125.5 (*syn* + *anti*), 74.2 (*syn*), 73.8 (*anti*), 35.86 (*syn*), 34.7 (*anti*) ppm. In ref.[32] all these ^{13}C NMR signals were interpreted as due solely to the *anti* isomer. After addition of $TiCl_3$ to the aqueous MeOH/NH_3 solution of **4g** (Table 2, Entry 10), **5g** was obtained in higher yield (1.02 g, 84%). The ^{13}C NMR spectrum still revealed the presence of both isomers (*anti*/*syn*, 60:40).

1,5-Diphenyl-1,5-butanediol (5h) and *cis*-1,2-Diphenyl-1,2-cyclopentanediol (6h): After workup, flash column chromatography (hexane/EtOAc, 1:1) of the crude residue gave **6h** (0.60 g, 47%) as first eluted fraction, colorless crystals, m.p. 103−104 °C (ref.[33] 104 °C). ^{1}H NMR ($CDCl_3$): δ = 1.9−2.4 (m, 4 H, CH_2 + 2 CH), 2.4−2.6 (m, 2 H, 2CH), 3.2 (s, 2 H, 2 OH, D_2O exch.), 6.9−7.2 (m, 10 H, Ph H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.9 (CH_2), 36.7 (2 CH_2), 85.5 (2 C−OH), 126.2 (4 Ar-C), 126.7 (2 Ar-C), 127.0 (4 Ar-C), 142.3 (2 Ar-C_q) ppm. IR (KBr): $\tilde{\nu}$ = 3469, 3300, 2970, 1446, 1071, 865, 758, 694 cm^{-1}. MS (CI): *m*/*z* (%) = 255 (20) [M^+ + H], 237 (100). The second eluted fraction gave a mixture of stereoisomeric diols **5h** (0.59 g, 46%), indistinguishable by ^{1}H NMR analysis. ^{1}H NMR ($CDCl_3$): δ = 1.20−1.80 (m, 6 H, 3 CH_2), 2.6 (s, 2 H, 2 OH, D_2O exch.), 4.57 (dd, *J* = 7.8, 5.2 Hz, 2 H, 2 CH), 7.25 (m, 10 H, Ph H) ppm. The ratio of diastereomeric diols (*syn*/*anti*, 55:45) was determined by integration of the carbon signals in the ^{13}C NMR spectrum after an analytical sample of *syn*-**5h** had been obtained by two recrystallizations from Et_2O/petroleum ether: m.p. 93−97

°C (ref.[29b] 94−95). ^{13}C NMR ($CDCl_3$): δ = 22.17 (CH_2), 38.67 (2 CH_2), 74.19 (2 C−OH), 125.8 (4 Ar-C), 127.4 (2 Ar-C), 128.4 (4 Ar-C), 144.7 (2 Ar-C_q) ppm. ***anti*-5h:**[29b] ^{13}C NMR ($CDCl_3$): δ = 22.08 (CH_2), 38.73 (2 CH_2), 74.31 (2 C−OH), 125.8 (4 Ar−C), 127.4 (2 Ar−C), 128.4 (4 Ar−C), 144.7 (2 Ar-C_q) ppm.

1,6-Diphenyl-1,6-hexanediol (5i): Because of the low solubility of the substrate, the reduction was performed on 2.5 mmol of **4i**, dissolved in MeOH (40 mL) and CH_3CN (20 mL). After the usual workup, **5i** was recovered in quantitative yield (0.67 g, ^1H NMR purity > 95%) as a white solid melting at 118−120 °C. The ^1H NMR spectrum, run at 400 MHz, showed the presence of a 1:1 mixture of the two isomers: ^1H NMR ($CDCl_3$): δ = 1.2−1.5 (m, 4 H, 2 CH_2), 1.6−1.8 (m, 4 H, 2 CH_2), 1.82 (s, 2 H, 2 OH, D_2O exch.), 4.630 (dd, *J* = 5.8. 7.3 Hz, 2 H, 2 CH, *meso* isomer), 4.636 (dd, *J* = 6.0, 7.5. Hz, 2 H, 2CH, *dl* isomer), 7.2−7.4 (m, 10 H, Ph H) ppm. The crude **5i**, dissolved in hot $CHCl_3$, afforded a crop of pure *dl* isomer on standing overnight: M.p. 131−133 °C (ref.[29b] 132−134 °C from MeOH), which allowed the above ^1H NMR assignment. The ^{13}C NMR spectra of the two isomers were identical: ^{13}C NMR ($CDCl_3$): δ = 25.5 (2 CH_2), 38.8 (2 CH_2), 74.5 (2 CH), 125.8 (2 Ar-C), 127.5 (Ar-C), 128.4 (2 Ar-C), 144.7 (Ar-C_q) ppm. IR (KBr): $\tilde{\nu}$ = 3360, 2941, 2857, 1455, 1385, 1017, 761 cm^{-1}. MS (EI): *m*/*z* (%) = 234 (3) [$M^{+\bullet}$ − 2 H_2O], 146 (71), 130 (21), 117 (52), 107 (73), 105 (24), 104 (51), 91 (25), 79 (100), 77 (60).

Indan-1,3-diol (5j): After workup, **5j** was recovered in quantitative yield (0.75 g) as a white, solid mixture of two isomers (*cis*/*trans* = 60:40) as shown by ^1H NMR. Two recrystallizations of the crude **5j** from hot EtOAc afforded two crops (0.35 g) of analytically pure *cis*-**5j** as white crystals, m.p. 195 °C. ^1H NMR ($CDCl_3$ + DMSO): δ = 1.60 (dt, *J* = 12.3, 7.8 Hz,1 H, CH_2,), 2.81 (dt, *J* = 12.3, 7.3 Hz, 1 H, CH_2), 4.85 (2 t, *J* = 7.8, 7.3 Hz, 2 H, 2 CH), 7.25 (m, 2 H, Ar H), 7.33 (m, 2 H, Ar H) ppm. ^{13}C NMR (DMSO): δ = 46.4 (CH_2), 69.9 (2 C−OH), 123.1 (2 Ar-C), 126.8 (2 Ar-C), 145.0 (2 Ar-C_q) ppm. IR (KBr): $\tilde{\nu}$ = 3311, 1324, 1038, 767 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 150 (22) [M^+], 132 (95), 131 (65), 104 (100), 103 (58), 77 (83). HRMS ($C_9H_{10}O_2$): calcd. 150.06808; found 150.06810. All efforts to obtain analytically pure *trans*-**5j** were unsuccessful: ^1H NMR ($CDCl_3$ + DMSO): δ = 2.12 (2 t, *J* = 5.6, 5.0 Hz, 2 H, CH_2), 5.18 (2 t, *J* = 5.6, 5.0 Hz, 2 H, 2 CH), 7.26 (m, 2 H, Ar H), 7.33 (m, 2 H, Ar H) ppm.

1-Phenyl-1,3-propanediol (5k): After workup and purification by flash column chromatography (hexane/EtOAc, 7:3), **5k** was recovered as an oil (0.66 g, 87%), which was identified by comparison of the ^1H and ^{13}C NMR spectra with those reported in the literature.[34]

1-(4-Chlorophenyl)-1,3-propanediol (5l): After workup and purification of the crude residue by flash column chromatography (hexane/EtOAc, 6:4), **5l** was recovered as a pale yellow oil (0.79 g, 85%): ^1H NMR ($CDCl_3$): δ = 1.90 (m, 2 H, CH_2), 3.40 (s, br, 2 H, 2 OH, D_2O exch.), 3.80 (2 dd, *J* = 1.9, 4.6 and 1.2, 5.8 Hz, 2 H, CH_2OH), 4.88 (dd, *J* = 4.6, 8.1 Hz, 1 H, CHOH), 7.2−7.4 (m, 4 H, Ar H) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.3 (CH_2), 61.0 (CH_2OH), 73.2 (CHOH), 127 (2 Ar-C), 128.5 (2 Ar-C), 133.1 (Ar-C_q), 142.7 (Ar-C_q).) ppm. IR (neat): $\tilde{\nu}$ = 3345, 1492, 1091, 1052, 1014, 828 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 188 (16) [M^+], 186 (44) [M^+], 169 (10), 143 (30), 141 (100), 133 (16), 113 (10), 77 (25). HRMS ($C_9H_{11}ClO_2$): calcd. 186.0448; found 186.0445.

1-(4-Methoxyphenyl)-1,3-propanediol (5m): After purification by flash column chromatography (hexane/EtOAc, 7:3), **5m** was recovered (0.78 g, 86%) as a yellow liquid, which crystallized on standing, m.p. 34−36 °C. ^1H NMR[35] ($CDCl_3$): δ = 2.0 (m, 2 H, CH_2), 2.3 (s, br, 2 H, 2OH, D_2O exch.), 3.80 (s, 3 H, OCH_3), 3.85 (m, 2 H, CH_2), 4.85 (dd, *J* = 3.8, 8.7 Hz, 1 H, CH), 6.88 (d, *J* = 8.7 Hz, 2 H, Ar H), 7.25 (d, *J* = 8.7 Hz, 2 H, Ar H) ppm.

2-Methyl-1-phenyl-1,3-propanediol (5n): The ^1H NMR spectrum of the crude residue showed the presence of **5n** as a mixture of two isomers (*syn*/*anti*, 70:30) which were separated by thin layer chromatography ($CHCl_3$/MeOH, 9:1). ***syn*-5n**[36] (0.49 g, 60%, pale yellow oil): ^1H NMR ($CDCl_3$): δ = 0.81 (d, *J* = 6.9 Hz, 3 H, CH_3), 2.04 (m, 1 H, CH), 3.0 (s, 2 H, 2 OH, D_2O exch.), 3.62 (ABX system, *J* = 10.9, 5.9, 4.9 Hz, 2 H, CH_2), 4.91 (d, *J* = 3.5 Hz, 1 H, CH), 7.2−7.4 (5 H, Ar H, m). *anti*-**5n**[36] (0.21 g, 26%, pale yellow oil): ^1H NMR ($CDCl_3$): δ = 0.68 (d, *J* = 7.4 Hz, 3 H, CH_3, 2.04 (m, 1 H, CH), 3.0 (s, 2 H, 2 OH, D_2O exch.), 3.65 (dd, *J* = 10.9, 7.4 Hz, 1 H, CH_2), 3.73 (dd, *J* = 10.9, 3.9 Hz, 1 H, CH_2), 4.50 (d, *J* = 8.4 Hz, 1 H, CH), 7.2−7.4 (m, 5 H, Ar H).

Methyl 3-Hydroxy-3-phenylpropanoate (5o): After workup, **5o** was recovered in quantitative yield (0.90 g) as an oil and identified by comparison with the spectroscopic data reported in the literature.[37]

5-Phenyldihydrofuran-2-one (5p): The reaction mixture was acidified with an HCl solution (1.0 M) and then extracted with EtOAc (3 × 50 mL). Upon evaporation of the solvent in vacuo, **5p** was recovered in quantitative yield (0.80 g, ^1H NMR purity > 95%) as an oil that solidified on standing, m.p. 36−37 °C. The spectroscopic data were identical to those of an authentic commercial sample (Aldrich).

6-Phenyltetrahydropyran-2-one (5q): After workup as for **5p**, **5q** was recovered in quantitative yield (0.88 g, ^1H NMR purity > 95%) as an oil that slowly solidified, m.p. 73−75 °C (ref.[38] 74−76). The spectroscopic data were identical to those reported in the literature.[39]

3-Hydroxy-3-phenylpropionanilide (5r): After workup, **5r** was recovered in quantitative yield (1.20 g, ^1H NMR purity > 95%) as a white solid, m.p. 152 °C ($CHCl_3$). ^1H NMR (DMSO): δ = 2.61 (dd, *J* = 14.1, 4.8 Hz, 1 H, CH_2), 2.71 (dd, *J* = 14.1, 8.8 Hz, 1 H, CH_2), 5.06 (m, after D_2O exchange dd, *J* = 8.8, 4.8 Hz, 1 H, CH), 5.55 (d, *J* = 4.1 Hz, D_2O exch., 1 H, OH), 7.1 (m, 1 H, Ph H), 7.3 (m, 7 H, Ph H), 7.6 (m, 2 H, Ph H), 9.9 (D_2O exch., 1 H, NH) ppm. ^{13}C NMR (DMSO): δ = 47.0 (CH_2), 69.7 (CH), 118.9 (2 Ar-C), 123.0 (Ar-C), 125.6 (2 Ar-C), 126.9 (Ar-C), 128.0 (2 Ar−C), 128.6 (2 Ar−C), 139.1 (Ar-C_q), 145.3 (Ar-C_p), 169.1 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 3296, 1664, 1605, 1558, 1443, 752 cm^{-1}. MS (EI): *m*/*z* (%) = 241 (10) [M^+], 107 (10), 104 (11), 93 (100), 79 (32), 77 (50), 65 (20). $C_{15}H_{15}NO_2$ (241.3): calcd. C 74.67, H 6.27; found C 74.52, H 6.30.

3,3-Dimethoxy-1-phenylpropan-1-ol (8k): The crude **8k** (0.84 g, 86%, pale yellow oil) was not subjected to further purification (^1H NMR purity > 95%). ^1H NMR ($CDCl_3$): δ = 1.93−2.15 (m, 2 H, CH_2), 2.6 (s, br, D_2O exch., 1 H, OH), 3.36 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 4.57 (t, *J* = 5.4 Hz, 1 H, CH), 4.89 (dd, *J* = 3.5, 8.9 Hz, 1 H, CH), 7.35 (m, 5 H, Ar H) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.43 (CH_2), 50.61 (OCH_3), 53.61 (OCH_3), 70.75 (CHOH), 103.33 (CH), 125.68 (2 Ar-C), 127.36 (2 Ar-C), 128.36 (Ar-C), 143.92 (Ar-C_q) ppm. IR (film): $\tilde{\nu}$ = 3433, 2935, 1453, 1126, 1056, 702 cm^{-1}. MS (EI): *m*/*z* (%) = 165 (25) [M^+ − OCH_3], 135 (20), 121 (45), 105 (100), 75 (83), HRMS ($C_{11}H_{16}O_3$): calcd. 196.1099; found 196.1095.

1-(4-Chlorophenyl)-3,3-dimethoxypropan-1-ol (8l): The crude **8l** (0.98 g, 85%, pale yellow oil) was not subjected to further purifica-

tion (^{1}H NMR purity > 95%). ^{1}H NMR ($CDCl_3$): δ = 1.89−2.10 (m, 2 H, CH_2), 3.36 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 4.55 (t, *J* = 5.6 Hz, 1 H, CH), 4.84 (dd, *J* = 3.4, 8.5 Hz, 1 H, CH), 7.30 (m, 5 H, Ar H).^{13}C NMR ($CDCl_3$): δ = 41.4 (CH_2), 53.0 (OCH_3), 53.7 (OCH_3), 70.0 (CHOH), 103.2 (CH), 126.9 (2 Ar-C), 128.4 (2 Ar-C), 132.8 (Ar-C_q), 142.5 (Ar-C_q) ppm. IR (film): $\tilde{\nu}$ = 3437, 2934, 1491, 1127, 1090, 1014, 832 cm^{-1}. MS (EI): *m/z* (%) = 200/198 (10/30) [$M^+ - CH_3OH$], 168/166 (5/15), 143/141 (13/40), 77 (50), 75 (100). HRMS ($C_{11}H_{15}ClO_3$): calcd. 231.0788; found 231.0785.

3,3-Dimethoxy-1-(4-methoxyphenyl)propan-1-ol (8m): The crude **8m** (1.0 g, 90%, pale yellow oil) was not subjected to further purification (^{1}H NMR purity > 95%): ^{1}H NMR ($CDCl_3$): δ = 1.95 (ddd, *J* = 3.5, 5.4, 14.4 Hz, 1 H, CH_2), 2.08 (ddd, *J* = 6.2, 8.9, 14.4 Hz, 1 H, CH_2), 2.5 (s, br, D_2O exch., 1 H, OH), 3.36 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.55 (dd, *J* = 5.4, 6.2 Hz, 1 H, CH), 4.85 (dd, *J* = 3.5, 8.9 Hz, 1 H, CH), 6.9 (m, 2 H, Ar H), 7.3 (, 2 H, Ar H, m) ppm. ^{13}C NMR ($CDCl_3$): δ = 41.4 (CH_2), 52.9 (OCH_3), 53.5 (OCH_3), 55.1 (OCH_3), 70.3 (CHOH), 103.3 (CH), 113.7 (2 Ar-C), 126.8 (2 Ar-C), 136.2 (Ar-C_q), 158.8 (Ar-C_q) ppm. IR (film): $\tilde{\nu}$ = 3448, 2935, 1612, 1514, 1248, 1176, 1127, 1058, 1127, 834 cm^{-1}. MS (EI): *m/z* (%) = 226 (30) [M^+], 209 (10), 194 (55), 137 (80), 136 (50), 135 (100), 75 (50). HRMS ($C_{12}H_{18}O_4$): calcd. 226.1205; found 226.1208.

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