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Asymmetric benzaldehyde methylation with titanium TADDOLate complexes

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ABSTRACT

The Lewis acid catalyst derived from $Ti(O^iPr)_4$ and (4*R*,5*R*)-(−)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol, (*R*,*R*)-TADDOL, [**1**], in the presence of Me_2Zn, mediates the complete conversion of 4-chlorobenzaldehyde to (*S*)-1-(4-chlorophenyl)ethanol with 96% enantiomeric excess. With unsubstituted benzaldehyde, the maximum enantiomeric excess observed under the same conditions is 91%. Application of chlorinated (*R*,*R*)-TADDOL derivatives to the methylation of unsubstituted benzaldehyde reveals that addition of chloro substituents to the ligand also induces the result of increasing the enantioselectivity of the catalysis. The reaction of (−)-dimethyl 2,3-*O*-isopropylidene-L-tartrate with 3,4-dichlorophenyl magnesium bromide or 3,5-dichlorophenyl magnesium bromide yields the octachlorinated (*R*,*R*)-TADDOL derivatives (4*R*,5*R*)-(−)-2,2-dimethyl-α,α,α′,α′-tetra-3,4-dichlorophenyl-1,3-dioxolane-4,5-dimethanol, 3,4-[**1**] and (4*R*,5*R*)-(−)-2,2-dimethyl-α,α,α′,α′-tetra-3,5-dichlorophenyl-1,3-dioxolane-4,5-dimethanol, 3,5-[**1**]. Catalysis screenings showed that 3,4-[**1**], in conjunction with $Ti(O^iPr)_4$ and Me_2Zn, forms a Lewis acid titanium TADDOLate catalyst capable of converting benzaldehyde to (*S*)-1-phenylethanol with >99% conversion and >96% enantiomeric excess.

1. Introduction

Chemical synthesis by asymmetric catalysis is an intensely investigated field in modern chemical science and technology, assisting with the preparation of enantioenriched compounds on scales both small and large [1–3]. In the synthesis of enantiopure secondary alcohols, the addition of organometallic reagents to aldehydes, generally in the presence of an added titanium(IV) compounds such as $Ti(O^iPr)_4$, exemplifies an active area of research. These organometallic compounds include alkyl or aryl (i) lithium [4,5], (ii) magnesium halide (Grignard) [6,7], (iii) aluminum [8–10], (iv) titanium [11–16] and (v) zinc [11,14,17–31] reagents. Of these, several of the zinc catalysts have been shown to mediate alkylation without added titanium(IV) compounds [17,20,23,26,29,31]. Anchored catalysts [32] and porous materials for heterogeneous catalysis, including a recyclable chiral material [33], that mediate the addition of diethyl zinc to arylaldehydes in the presence of titanium(IV) isopropoxide, have also been reported.

We have been investigating the methylation of benzaldehyde with dimethyl zinc catalyzed by titanium complexes of resolved, chiral diols. Our initial work showed that it is possible to modestly increase the enantiomeric excess (*ee*) of 1-phenylethanol obtained from the methylation of benzaldehyde by dichiral double asymmetric induction with a titanium(IV) complex of BINOL (BINOL = 1,1′-bi-2-naphthol), and the resolved chiral alkoxides, $Ti(O^{R\text{-}2}Bu)_4$ or $Ti(O^{S\text{-}2}Bu)_4$ [34]. Whereas *R*- or *S*- BINOL in combination with achiral $Ti(O^iPr)_4$ results in *ee* of 1-phenylethanol in the range of 50% [14], resolved BINOL in combination with chiral, resolved $Ti(O^2Bu)_4$ of the opposite configuration designation results in *ee*'s of 1-phenylethanol in the range of 60% [34].

Including BINOL [14,16,18,19,21,24,27], other catalytically useful ligands for titanium mediated alkylation for aldehydes include octahydroBINOL [15,16,21,23,24], amino alcohols [20,26,30,31], bis(sulfonamides) [14,22,28], tetrahydrosalen [35], hydroxyamides [29], and TADDOL [11–13,16,25]. Whereas the alkylation of aldehydes with diethyl zinc can be achieved with very good conversion and high *ee*, dimethyl zinc typically results in much lower enantiomeric excess in similar catalytic systems [13,14,34], with the exception of a few notable examples. With (*R*,*R*)-TADDOL [**1**] (Scheme 1), Seebach and co-workers have extensively investigated the alkylation of aldehydes with dialkyl zinc compounds in the presence of $Ti(O^iPr)_4$, achieving nearly 100% *ee* in ethylation with diethyl zinc [11] and 94% *ee* in methylation with dimethyl zinc [11,36]. With a stoichiometric amount of $CH_3Ti(O^iPr)_3$ in the absence of dimethyl zinc at −25 °C, the selectivity can be increased to 96% *ee* (*S*)-1-phenylethanol [11].

More recently, reports of new derivatives of chiral ligands based on TADDOL and amino alcohol frameworks have shown that it is possible to observe high enantiomeric excess in the addition of di-

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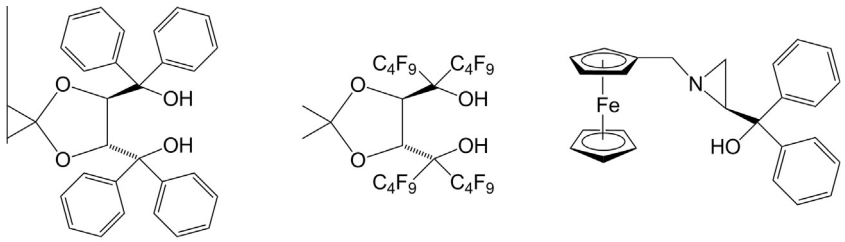


(*R,R*)-TADDOL [**1**]

Scheme 1. Chiral diol (*R,R*)-TADDOL, [**1**], a perfluorobutyl derivative of the 1,3-dioxolane-4,5-dimethanol scaffold, and a ferrocenyl methylaziridin methanol amino alcohol.

methyl zinc to arylaldehydes. Ando and coworkers have shown that perfluoroalkyl substituents on the 1,3-dioxolane-4,5-dimethanol scaffold found in TADDOL can mediate the methylation of an array of arylaldehydes in the presence of $Ti(O^iPr)_4$; in the case of benzaldehyde, a perfluorobutyl derivative (Scheme 1) yielding 99% conversion and 95% *ee* (*R*)-1-phenylethanol [25]. Wang et al. used the chiral ferrocene containing β-amino alcohol shown in Scheme 1 to observe 96% conversion of benzaldehyde to (*S*)-1-phenylethanol with 90% *ee* [26], remarkably in the absence of any added titanium Lewis acid.

In this paper we report results on an application of the TADDOL ligand framework, a highly useful framework for asymmetric synthesis [37], in the asymmetric methylation of benzaldehydes with dimethyl zinc. Specifically, octachlorinated (*R,R*)-TADDOL ligands have been investigated as they may lead to even more Lewis acidic titanium catalysts with even greater steric hindrance at the metal active site, further activating and constraining the possible conformations of the substrate bound to the catalyst leading to enhanced enantiomeric selectivity.

2. Experimental section

2.1. General experimental

Unless otherwise stated, all manipulations were carried out at room temperature in an inert atmosphere glove box or under a nitrogen atmosphere using standard Schlenk techniques. All glassware was oven dried at a temperature of 235 °C prior to use. Anhydrous solvents were purchased from Aldrich and stored under nitrogen. Dimethyl zinc (2.0 M in toluene), titanium(IV) isopropoxide (97%), (−)-dimethyl-2,3-*O*-isopropylidene-L-tartrate (97%), benzaldehyde (99.5%), 4-chlorobenzaldehyde (97%), 1-phenylethanol (98%), and (*R*)-(+)-1-(4-chlorophenyl)ethanol (95%) were purchased from Aldrich. (*R*)-(+)-1-phenylethanol was obtained from Fluka, and 1-(4-chlorophenyl)ethanol (97%) from Alfa-Aesar. (4*R*,5*R*)-(−)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol, (*R,R*)-TADDOL, was purchased from Strem. 3,4- and 3,5-dichlorophenyl magnesium bromide, 0.5 M in tetrahydrofuran, 97%, were purchased from Aldrich or Novel Chemical Solutions. All reagents were used as received. TADDOL derivatives (4*R*,5*R*)-(−)-2,2-dimethyl-α,α,α′,α′-tetra-3,4-dichlorophenyl-1,3-dioxolane-4,5-dimethanol, 3,4-[**1**] and (4*R*,5*R*)-(−)-2,2-dimethyl-α,α,α′,α′-tetra-3,5-dichlorophenyl-1,3-dioxolane-4,5-dimethanol, 3,5-[**1**] were prepared in a manner similar to that previously reported for another chlorinated TADDOL derivative [38].

^{1}H NMR spectra were recorded at room temperature using a Bruker Avance DPX 300 MHz spectrometer. Chemical shifts are reported referenced to the solvent resonances of δ 5.31 (^{1}H) and δ 53.84 (^{13}C) ppm for dichloromethane-d_2. Elemental analyses were carried out by Columbia Analytical Services, Tucson, AZ, USA; samples were dried under vacuum at 105 °C for 2 h. prior to analysis. The combustion analysis returns results that are higher than the theoretical values; this could be attributable to the fact that the compounds do not crystallize analytically pure and are obtained as powders. Infrared spectra were recorded as pressed KBr pellets on a Thermo Nicolet Nexus 670 FT-IR spectrometer and are reported in cm^{-1}. For mass spectrometry analysis, samples, dissolved in $CHCl_3$:CH_3OH:NH_4OH (800:195:5, v/v/v), were directly infused using an Agilent 1100 HPLC system into an Agilent 6520 electrospray ionization quadrupole time-of-flight mass spectrometer detecting in the negative ion mode. Mass spectra were obtained using settings described previously [39]. Chiral GC analyses with were carried out on an HP 6890 Series gas chromatograph using 50:1 split mode capillary injection (200 °C) with a flame ionization detector (220 °C) and an Alltech Chirladex B-DM column (0.25 mm × 30 m). Samples were injected as a diethyl ether solution, with an initial oven temperature of 90 °C for 5 min, followed by ramping 0.5 °C per min to 95 °C and holding for 15 min at 95 °C. Retention times for 1-phenylethanol 6.6 min (*R*), 7.0 min (*S*); for 1-(4-chlorophenyl)ethanol 22.5 min (*R*), 24.1 min (*S*).

2.2. General procedure for the asymmetric addition of Me_2Zn to benzaldehyde

Following a procedure derived from that of Chan [18] and Nakai [19]: to a stirring solution of (*R,R*)-TADDOL ligand (0.21 mmol) in CH_2Cl_2 (5 mL) was added $Ti(O^iPr)_4$ (1.4 mmol). After 1 h stirring, the reaction mixture was cooled to 3 °C and 3 mL of dimethylzinc solution (2.0 M in toluene, 6.0 mmol) was added. After stirring for 30 min, benzaldehyde was added (1.0 mmol) and the mixture was stirred for 24 h. The reaction was quenched with 1 M HCl (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated. The remaining oil was analyzed by ^{1}H NMR and chiral GC (Alltech Chiraldex B-DM), to determine the percent conversion to 1-phenylethanol and its enantiomeric excess, respectively. An identical procedure was used for the methylation of 4-chlorobenzaldehyde.

2.3. Synthesis of (4R,5R)-(−)-2,2-dimethyl-α,α,α′,α′-tetra-3,4-dichlorophenyl-1,3-dioxolane-4,5-dimethanol, 3,4-[*1*], and (4R,5R)-(−)-2,2-dimethyl-α,α,α′,α′-tetra-3,5-dichlorophenyl-1,3-dioxolane-4,5-dimethanol, 3,5-[*1*]

The octachlorinated TADDOL derivatives 3,4-[**1**] and 3,5-[**1**] were prepared with Grignard reagents in a manner similar to that previously reported for another chlorinated TADDOL [38]. (−)-Dimethyl-2,3-*O*-isopropylidene-L-tartrate (1.0 mL, 5.5 mmol) was added dropwise to the Grignard reagent 3,4- or 3,5-dichlorophenyl magnesium bromide (50 mL, 0.5 M in tetrahydrofuran, 25 mmol) with stirring at 0 °C. After the reaction was allowed to reach room temperature, it was refluxed at 70–80 °C under argon for 2 h. Once cooled, approximately 20 mL of ammonium chloride was added and the mixture was stirred for at least 1 h. The reaction was ex-

tracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated, purified by column chromatography (ethyl acetate/hexanes), concentrated again, dried on a vacuum line, triturated multiple times with dry tetrahydrofuran to remove bulk water, and finally dried with warming under vacuum. The resulting off-white to yellow powders were obtained in variable yields depending on the success of the synthesis, purification and drying steps, but could be obtained in up to 70% yield for 3,4-[**1**] and 60% for 3,5-[**1**].

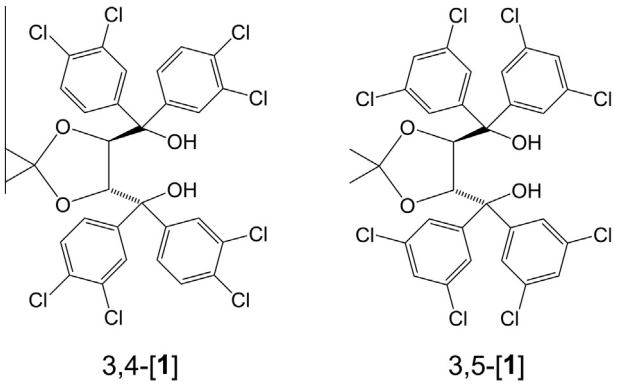
*Data for 3,4-[**1**]:* ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.22 (s, 6H, C*H*$_3$), 4.17 (s, 2H, O*H*), 4.39 (s, 2H, C*H*), 7.1–7.6 (m, 12 H, Ar–C*H*). ^{13}C NMR (^{13}C–{^{1}H}, 75.5 MHz, CD_2Cl_2): δ 27.41 (*C*H$_3$), 77.30 (*C*OH), 81.41 (*C*H), 110.81 (*C*(CH$_3$)$_2$), 127.23 (*C*$_{aryl}$H), 127.68 (*C*$_{aryl}$H), 129.79 (*C*$_{aryl}$H), 130.24 (*C*$_{aryl}$H), 130.53 (*C*$_{aryl}$H), 130.63 (*C*$_{aryl}$H), 132.43 (*C*$_{aryl}$), 132.46 (*C*$_{aryl}$), 132.53 (*C*$_{aryl}$), 132.72 (*C*$_{aryl}$), 142.70 (*C*$_{aryl}$), 144.69 (*C*$_{aryl}$). *Anal.* Calc. for $C_{31}H_{22}Cl_8O_4$: C, 50.17; H 2.99; N, 0. Found: C, 51.68; H, 3.09; N, <0.05%. IR Data (KBr pellet, cm^{-1}): 3544 (m, OH str), 3351 (s, br, OH str), 2986 (m, CH str), 2933 (m, CH str), 2888 (m, CH str), 1907 (w), 1769 (w), 1704 (w), 1590 (w), 1556 (w), 1470 (vs), 1437 (m), 1419 (m), 1382 (vs), 1337 (m), 1237 (s), 1169 (s), 1137 (s), 1098 (m), 1066 (s), 1031 (vs), 943 (w), 883 (s), 822 (s), 758 (s), 741 (s), 707 (w), 677 (s), 607 (w), 557 (w), 508 (w), 438 (w). The *m/z* observed for the [M−H]$^-$ ion was 736.896 (calculated exact mass: 736.8954). This *m/z* matches the molecular formula of the compound with 1.09 ppm error.

*Data for 3,5-[**1**]:* ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.26 (s, 6H, C*H*$_3$), 4.06 (s, 2H, O*H*), 4.43 (s, 2H, C*H*), 7.20 (d, 4H, Ar–C*H*, *J* 1.85 Hz), 7.25 (t, 2H, Ar–C*H*, *J* 1.84 Hz), 7.35 (t, 2H, Ar–C*H*, *J* 1.87 Hz), 7.42 (d, 4H, Ar–C*H*, *J* 1.88 Hz). ^{13}C NMR (^{13}C–{^{1}H}, 75.5 MHz, CD_2Cl_2): δ 27.49 (*C*H$_3$), 77.48 (*C*OH), 81.39 (*C*H), 111.30 (*C*(CH$_3$)$_2$), 126.17 (*C*$_{aryl}$H), 126.79 (*C*$_{aryl}$H), 128.59 (*C*$_{aryl}$H), 128.82 (*C*$_{aryl}$H), 135.10 (*C*$_{aryl}$), 135.33 (*C*$_{aryl}$), 145.81 (*C*$_{aryl}$), 147.22 (*C*$_{aryl}$). *Anal.* Calc. for $C_{31}H_{22}Cl_8O_4$: C, 50.17; H 2.99; N, 0. Found: C, 52.49; H, 3.71; N, 0.12%. IR Data (KBr pellet, cm^{-1}): 3543 (m, OH str), 3363 (s, br, OH str), 3086 (m, C$_{aryl}$H str), 2987 (m, CH str), 2959 (m, CH str), 2929 (m, CH str), 2854 (m, CH str), 1728 (w), 1585 (vs), 1567 (vs), 1419 (vs), 1384 (s), 1337 (w), 1261 (m), 1238 (m), 1192 (m), 1169 (s), 1101 (s), 1070 (s), 969 (w), 862 (vs), 801 (vs), 733 (s), 713 (m), 510 (w), 435 (w). The *m/z* observed for the [M−H]$^-$ ion was 736.895 (calculated exact mass: 736.8954). This *m/z* matches the molecular formula of the compound with 0.44 ppm error.

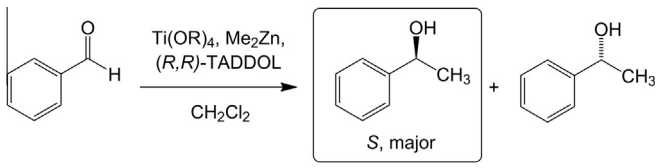
3. Results and discussion

3.1. Synthesis and characterization

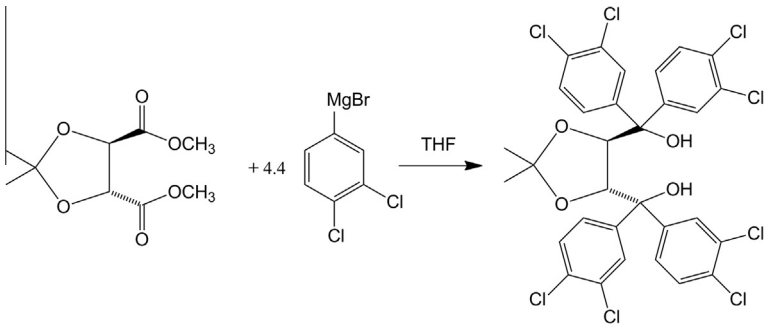
The synthesis of two octachlorinated (*R,R*)-TADDOL derivatives (Scheme 2) was accomplished *via* a Grignard reaction in a fashion similar to that previously reported for the synthesis of TADDOL derivatives [38]. The reaction of relatively inexpensive resolved, chiral starting material (−)-dimethyl-2,3-*O*-isopropylidene-L-tartrate with 3,4-dichlorophenyl magnesium bromide or 3,5-dichlorophenyl magnesium bromide yields (4*R*,5*R*)-(−)-2,2-dimethyl-α,α,α′,α′-tetra-3,4-dichlorophenyl-1,3-dioxolane-4,5-dimethanol, 3,4-[**1**] and (4*R*,5*R*)-(−)-2,2-dimethyl-α,α,α′,α′-tetra-3,5-dichlorophenyl-1,3-dioxolane-4,5-dimethanol, 3,5-[**1**] (Scheme 3). Purification of the ligands proved difficult, and off-white or slightly yellow powders were obtained only after silica gel column chromatography and repeated trituration with dry tetrahydrofuran to remove water and the other solvents used in the synthesis and purification. The ligands were characterized by NMR, IR, LC/MS and elemental analysis. The NMR spectra show that there are two inequivalent aryl groups in each compound. The ^{13}C NMR of 3,5-[**1**], with symmetrically substituted 3,5-dichlorophenyl groups, contains eight unique aryl carbon resonances, and that of 3,4-[**1**] with unsymmetrical 3,4-dichlorophenyl groups reveals all twelve unique aryl carbon resonances. Attempts were also made to synthesize the (*R,R*)-TADDOL derivatives from 2,3- and 2,4-dichlorophenyl magnesium bromide. These resulted in product mixtures containing only a low yield of the desired product.



Scheme 2. Octachloro (*R,R*)-TADDOL derivatives 3,4-[**1**] and 3,5-[**1**].



Scheme 4. Conversion of benzaldehyde to 1-phenylethanol.



Scheme 3. Synthetic scheme for the preparation of (4*R*,5*R*)-(−)-2,2-dimethyl-α,α,α′,α′-tetra-3,4-dichlorophenyl-1,3-dioxolane-4,5-dimethanol, 3,4-[**1**].

Table 1
Data for the addition of dimethyl zinc to benzaldehyde with $Ti(OR)_4$ and (*R,R*)-TADDOL [**1**] and the octachloroTADDOL derivatives 3,4-[**1**] and 3,5-[**1**].[a]

Entry	Aldehyde	Ligand	mmol L	mmol Ti, OR	Time (hr)	%[b]	*ee*[c]
1	PhCHO	[**1**]	0.21	1.4, O^iPr	24	>99	91
2	"	"	0.21	5.6, O^iPr	24	>99	92
3	"	"	0.21	0.5, O^iPr	24	45	61
4	4-Cl–PhCHO	"	0.21	1.4, O^iPr	24	>99	96
5	PhCHO	3,4-[**1**]	0.21	1.4, O^iPr	24	>99	96.5
6	"	"	0.105	1.4, O^iPr	96	>99	90
7	"	"	0.0525	1.4, O^iPr	120	>99	93
8	"	"	.105	1.4, O^iPr	24	>99	90
9	"	"	0.0525	1.4, O^iPr	24	>99	87
10	"	3,5-[**1**]	0.21	1.4, O^iPr	24	>99	95
11	"	"	0.105	1.4, O^iPr	72	>99	90
12	"	"	0.0525	1.4, O^iPr	120	>99	94
13	"	"	.105	1.4, O^iPr	24	>99	88
14	"	"	0.0525	1.4, O^iPr	24	>99	83
15	"	[**1**]	0.21	1.4, $O^{R\text{-}2}Bu$	24	>99	85
16	"	"	0.21	1.4, $O^{S\text{-}2}Bu$	24	>99	89

[a] $Ti(OR)_4$ (in 5 mL CH_2Cl_2), 6.0 mmol Me_2Zn/toluene, 1.0 mmol ArCHO, 3 °C.
[b] As determined by ^1H NMR.
[c] Determined by chiral GC, Alltech Chiraldex B-DM.

3.2. Asymmetric methylation of benzaldehyde

Catalysis screenings for the conversion of benzaldehyde to 1-phenylethanol (Scheme 4) were conducted with (*R,R*)-TADDOL [**1**] and the octachloro (*R,R*)-TADDOL ligands 3,4-[**1**] and 3,5-[**1**] under varying conditions (Table 1). With unsubstituted (*R,R*)-TADDOL ligand [**1**], entries 1–3 reveal that the maximum enantiomeric excess obtained under the conditions used is 91% (*S*)-1-phenylethanol. Increasing the relative amount of $Ti(O^iPr)_4$ does not improve the *ee* (entry 2), whereas decreasing the amount negatively impacts both the conversion and *ee* (entry 3). When 4-chlorobenzaldehyde was employed as the substrate, the *ee* of (*S*)-1-(4-chlorophenyl)ethanol was observed to be 96% (entry 4). We reasoned that the electron withdrawing ability of the chloride substituent assisted in activating the carbonyl group for alkylation, and that chlorination of the ligand would have a similar effect, in addition to added steric hinderance from the dichlorophenyl groups versus only phenyl substituents, and result in increased *ee* when unsubstituted benzaldehyde was used. This was observed to be the case. Entries 5 and 10 show that TADDOLs 3,4-[**1**] and 3,5-[**1**] lead to 96.5% and 95% (*S*)-1-phenylethanol, respectively. These are comparable with results achieved recently by Ando [25] and Wang [26] with different catalytic ligands, and by Seebach with TADDOL and stoichiometric $CH_3Ti(O^iPr)_3$ in the absence of dimethyl zinc [11]. Catalysts screening were then performed with reduced amounts of the octachloro (*R,R*)-TADDOL ligands. From these experiments, we were able to determine that for both octachloro (*R,R*)-TADDOL derivatives, less ligand could be used in the catalysis without compromising the percent conversion and with only a minor decrease in the *ee*, however, the later requiring increased reaction times. Entries 8, 9, 13, and 14 indicated that decreasing the relative amount of the ligand results in a decrease in the observed *ee* at a reaction time of 24 h, whereas entries 6, 7, 11, and 12 show that decreasing the relative amount of ligand while increasing the reaction time leads to observed *ee*'s that are closer to those that employed the larger amount of ligand. For example, in the case of 3,4-[**1**], comparison of entries 5 and 7 reveals a decrease in the *ee* of 1-phenylethanol from 96.5% to 93% when the amount of ligand used is reduced by a factor of four while the reaction time is increased by a factor of five. Similarly, in the case of 3,5-[**1**], comparison of entries 10 and 12 reveals a decrease in the *ee* of 1-phenylethanol from 95% to 94% when the amount of ligand used is reduced by a factor of four while the reaction time is increased by a factor of five. In every case, (*R,R*)-TADDOL results in an excess of (*S*)-1-phenylethanol or (*S*)-1-(4-chlorophenyl)ethanol, as determined by GC analysis of authentic samples of 1-phenylethanol, (*R*)-(+)-1-phenylethanol, 1-(4-chlorophenyl)ethanol and (*R*)-(+)-1-(4-chlorophenyl)ethanol. This is consistent with what has been reported by Seebach in investigation the alkylation of aldehydes with dialkyl zinc compounds in the presence of titanium TADDOLates [11,12]. Remarkably, when the TADDOL aryl groups are replaced with perfluoroalkyl substituents, the enantiomer produced in excess is reported to be (*R*)-1-phenylethanol [25].

Further, it is notable that in using achiral $Ti(O^iPr)_4$ and (*R,R*)-TADDOL [**1**], (i) we have been able to observe higher enantiomeric excesses in the methylation of benzaldehyde than with resolved BINOL and the resolved chiral alkoxides, $Ti(O^{R\text{-}2}Bu)_4$ or $Ti(O^{S\text{-}2}Bu)_4$, up to 91% from 60%, as expected based on previous observations for this system [11], and (ii) that the matched pair effect is less prominent with TADDOL than it is with BINOL when $Ti(O^iPr)_4$ is substituted with the resolved chiral alkoxides, $Ti(O^{R\text{-}2}Bu)_4$ or $Ti(O^{S\text{-}2}Bu)_4$. Comparison of entry 1 with 15 and 16 in Table 1 reveals a negligible matched pair effect, and in fact suggests that the larger *sec*-butoxides impart less enantioselectivity to the catalysis with (*R,R*)-TADDOL than does isopropoxide.

4. Conclusions

In the alkylation of arylaldehydes with dialkyl zinc and titanium (IV) alkoxides, we have found that (*R,R*)-TADDOL can mediate the methylation of 4-chlorobenzaldehyde with dimethyl zinc in the presence of titanium(IV) isopropoxide with >99% conversion and 96% enantiomeric excess, greater than the selectivity observed for unsubstituted benzaldehyde under the same conditions, >99% conversion and 91% enantiomeric excess. Likewise, addition of chloro substituents to the ligand also induces the result of increasing the enantioselectivity of the catalysis. The octachlorinated (*R,R*)-TADDOL ligands described lead to enhanced enantiomeric selectivity, resulting >99% conversion and >96% enantiomeric excess (*S*)-1-phenylethanol.

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