

## On the Mechanism of Phenolic Formylation Mediated by TiCl<sub>4</sub> Complexes: Existence of Diradical Intermediates Induced by Valence Tautomerism

Carlos Heras,<sup>[a]</sup> Iván Ramos-Tomillero,<sup>[a,b]</sup> Marc Caballero,<sup>[c]</sup> Marta Paradís-Bas,<sup>[a,b]</sup>
 Ernesto Nicolás,<sup>\*[a,d]</sup> Fernando Albericio,<sup>\*[a,b,e]</sup> Ibérico de P. R. Moreira,<sup>\*[c,f]</sup> and
 Josep Maria Bofill<sup>\*[a,f]</sup>

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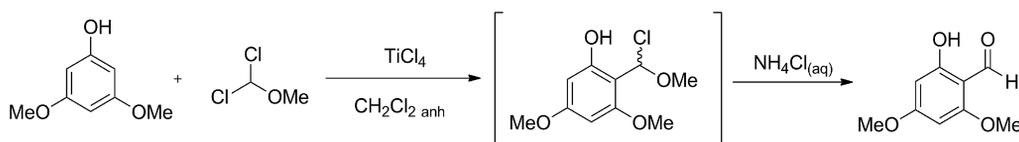
The conventional electrophilic intramolecular aromatic substitution pathway proposed by Cresp et al. [*J. Chem. Soc., Perkin Trans. 1* **1973**, 340–345] is confirmed by the observed products of phenolic formylation mediated by TiCl<sub>4</sub>. However, when the nucleophilic path is quenched by appropriate ligand modification, the initial equilibria between the possible neutral complexes of TiCl<sub>4</sub> with 3,5-dimethoxy-

phenol and/or diethyl ether lead to different stable diradical intermediates induced by valence tautomerism that provide valuable activated reagents. Some of these species have been detected by EPR, characterized theoretically and captured by TEMPO, thus providing a consistent mechanism for the reaction with one or more equivalents of TEMPO per phenol.

### Introduction

Phenolic aldehydes are valuable intermediates in many synthetic protocols. These derivatives can be readily accessed by formylation of phenols by using the TiCl<sub>4</sub>/

Cl<sub>2</sub>CHOCH<sub>3</sub> system,<sup>[1,2]</sup> which has proved to be of considerable synthetic potential.<sup>[3]</sup> In our hands, this methodology afforded key electron-rich phenolic aldehydes for the synthesis of de novo designed handles and protecting groups to be used in solid-phase chemistry.<sup>[4,5]</sup> The most interesting



Scheme 1. Formylation of phenols by using TiCl<sub>4</sub> and Cl<sub>2</sub>CHOCH<sub>3</sub>.

[a] Departament de Química Orgànica, Universitat de Barcelona, Martí i Franquès 1, 08028 Barcelona, Catalunya, Spain  
E-mail: jmbofill@ub.edu  
albericio@ub.edu  
enicolas@ub.edu  
http://www.ub.edu

[b] Institute for Research in Biomedicine, Barcelona Science Park, Baldiri Reixac 10, 08028 Barcelona, Catalunya, Spain  
http://www.irbbarcelona.org

[c] Departament de Química Física, Universidad de Barcelona, Martí i Franquès 1, 08028 Barcelona, Catalunya, Spain  
E-mail: i.moreira@ub.edu  
http://www.ub.edu

[d] Institut de Biomedicina, University of Barcelona, Martí i Franquès 1, 08028 Barcelona, Catalunya, Spain  
http://www.ub.edu

[e] CIBER-BBN, Networking Centre on Bioengineering, Biomaterials and Nanomedicine

[f] Institut de Química Teòrica i Computacional (IQTCUB), University of Barcelona, Martí i Franquès 1, 08028 Barcelona, Catalunya, Spain  
http://www.iqtc.ub.edu

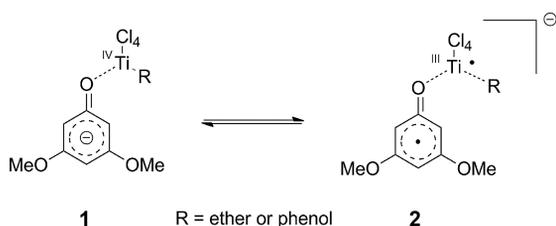
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feature of this synthetic methodology deals with the regioselectivity of formylation towards the *ortho*-position to the hydroxy phenolic group, that is more specific than in other formylation protocols.<sup>[6,7]</sup> The process seems to go through the formation of a 1-chloro-1-methoxymethyl aromatic intermediate resulting from titanium mediated C–C bond formation and further hydrolysis of this intermediate to afford the phenolic aldehyde (Scheme 1). In principle, an electrophilic aromatic substitution pathway could account for this result, as shown by Cresp et al.<sup>[2]</sup> However, it is well known that titanium can promote free radical reactions.<sup>[8]</sup> Thus, the diradical character of titanium enolates has been proven by some of us<sup>[9]</sup> and confirmed by Zakarian et al.,<sup>[10]</sup> suggesting that this diradical, which belongs to a large manifold, termed [R'–O(TiCl<sub>4</sub>)O–R]<sup>–</sup>, enables a range of transformations, including those such as polyene cyclization. In this sense, from a structural point of view, phenol

can be considered as the enolic form of cyclohexan-2,4-dienone, thus becoming a candidate for the generation of radical species promoted by  $\text{TiCl}_4$ . These precedents prompted us to get a deeper insight into the mechanism of phenolic formylation.

## Results and Discussion

In an effort to understand the mechanism of this formylation process, we initiated an investigation into the role of 3,5-dimethoxyphenolate– $\text{TiCl}_4$  as a purported diradical-ophile in the reaction shown in Scheme 1. With this in mind, we undertook mechanistic studies to determine whether the reaction proceeds through a diradical activation pathway via **2**, involved in the tautomeric equilibrium, or through **1** by a direct intramolecular nucleophilic attack that takes place when the  $\text{TiCl}_4$  complex is formed (see Scheme 2). To this end we substituted 1,1-dichloromethyl ether with diethyl ether to preclude the intramolecular nucleophilic substitution of  $\text{Cl}^-$  ions in the formylation process and to detect the possible intermediate  $\text{TiCl}_4$  complex in anhydrous  $\text{CH}_2\text{Cl}_2$ . The use of diethyl ether provides an equivalent quenched complex and largely facilitates the experimental procedure (dimethyl ether is a gas at ambient conditions). The comparison of the experimental results by using 1,1-dichloromethyl ether confirmed that the formylation reaction in Scheme 1 proceeds through the traditional (intramolecular) nucleophilic substitution pathway proposed by Cresp et al.<sup>[2]</sup> involving intermediate **1** shown in Scheme 2.



Scheme 2. The valence tautomerism in  $\text{TiCl}_4$ -phenolate complexes.

However, the use of the equivalent quenched complex with diethyl ether provides an excellent opportunity to analyze fine details of the nature of the essential intermediate and possible derivatives. To this end, we performed a series of NMR and EPR spectroscopy experiments of the quenched intermediate complex shown in Scheme 2 including  $\text{TiCl}_4$  and 3,5-dimethoxyphenol in  $\text{CH}_2\text{Cl}_2$  alone or in the presence of diethyl ether. In both experiments, a series of pre-equilibria between the neutral  $\text{TiCl}_4$ -diphenol,  $\text{TiCl}_4$ -diether and phenol– $\text{TiCl}_4$ -ether takes place and the presence of the diradical complex **2** was detected and assigned to the  $\text{TiCl}_4$ -diphenol diradical after proton subtraction (see Figure S4 in the Supporting Information).

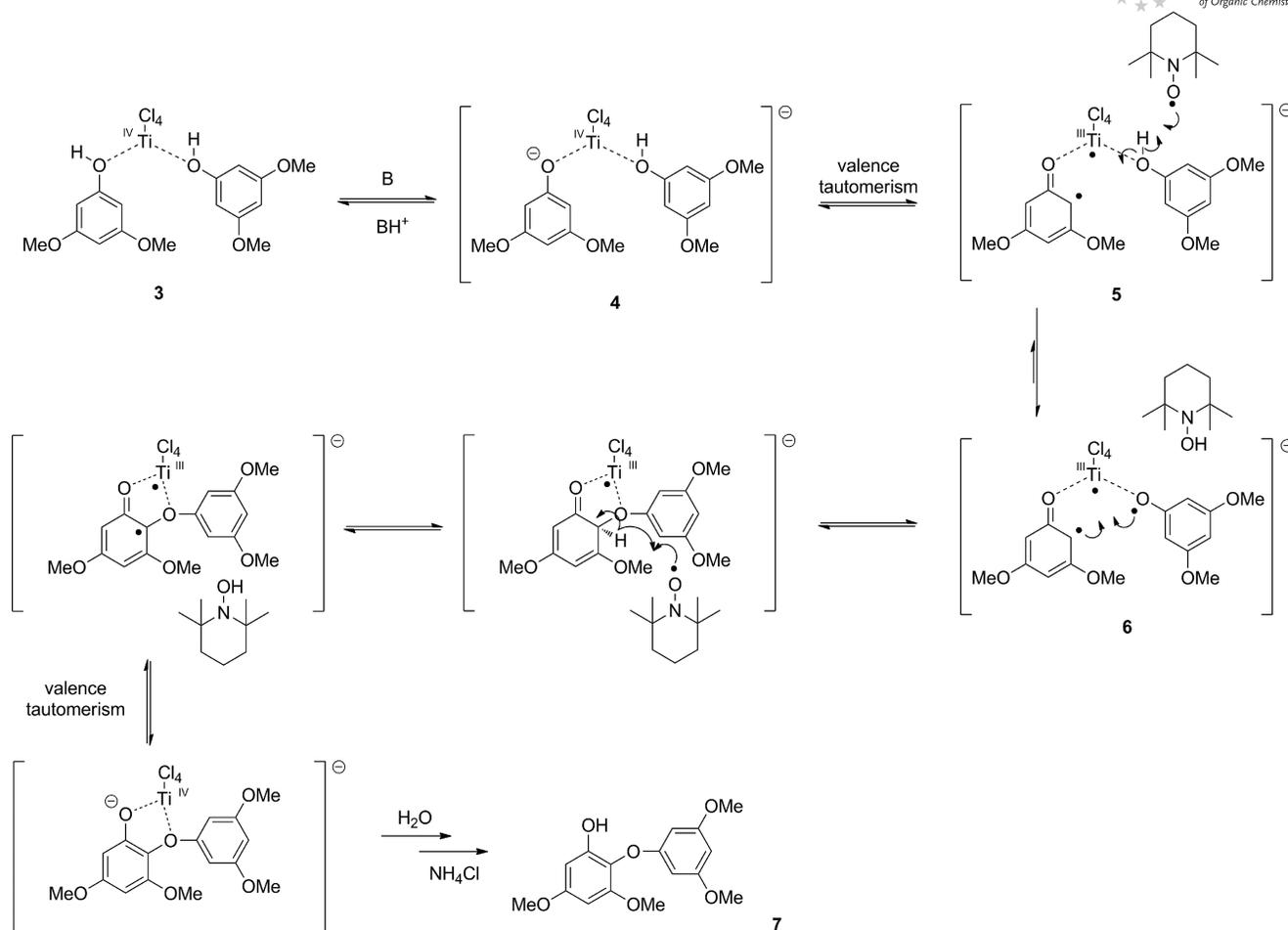
The next series of experiments was designed to probe the reaction mechanism. As a first hypothesis we suggested that the mechanism of the reaction takes place through the

tautomer **1**. To prove this assertion we initiated an investigation into the role of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO).

The unconventional diradical character of the Ti complex (Scheme 2) suggests that this intermediate should be an efficient radical acceptor. Indeed, when the initial  $\text{Cl}_2\text{CHOCH}_3$  reactant was replaced with dimethyl ether to avoid the nucleophilic substitution pathway, the resulting Ti complex was treated with TEMPO (1.1 equiv.) in anhydrous  $\text{CH}_2\text{Cl}_2$  under an argon atmosphere, a product was obtained in an essentially quantitative yield. Hydrolysis of such species would liberate the observed 2-(3,5-dimethoxyphenoxy)-3,5-dimethoxyphenol, **7**. A plausible mechanism that justifies the generation of product **7** is reported in Scheme 3. In the first step of this mechanism, namely the proton subtraction in anhydrous  $\text{CH}_2\text{Cl}_2$ , one molecule of 3,5-dimethoxyphenol acts as a base (B) to accept the acidic proton of complex **3** in the present experimental set up.

The mechanistic hypothesis in Scheme 3 is based on the well-established radical activity of TEMPO widely used in radical reactions and its action is similar to that proposed by Greci et al.<sup>[11]</sup> In the present case, however, the resulting triradical anion **6** after hydrogen abstraction by TEMPO should be strongly stabilized by electron delocalization onto both titanium and the phenyl ring. This effect has been found in a series of electronic structure calculations in a model system described below and in the Supporting Information. After the intramolecular rearrangement of the triradical anion **6**, the resulting radical anion recovers the aromatic character of the tetrasubstituted ring by hydrogen abstraction by the action of TEMPO. Thus, in the last step of the process, there is a new tautomeric equilibrium and, after water addition, **7** is formed.

To provide a theoretical justification of the proposed mechanism several wave function calculations were performed to show the stability of the intermediate diradical and triradical structures essential for this mechanism (i.e., those corresponding to structures **3**, **4**, **5**, and **6** in the mechanism and the competing equilibria involving one or two ether molecules). The electronic structure of these complexes and their molecular structures were investigated by using a simplified molecular model in vacuo that is representative of the description of the formation process of the  $\text{TiCl}_4$ -enolate complexes described in Scheme 3 by means of ab initio wave function electronic structure calculations. Hence, benzene-1,3,5-triol was adopted as a model system to represent 3,5-dimethoxyphenol and 3,5-dihydroxyphenolate to represent 3,5-dimethoxyphenolate, TEMPO was substituted by  $\text{H}_2\text{NO}$  (see the Supporting Information). The proton extraction by 3,5-dimethoxyphenol (see description of Scheme 3) was modelled by means of a tertiary amine to simplify the calculations. Using this simplified model, we investigated the stability of the intermediate species (neutral, anionic, diradical, and triradical) involved in the initial equilibria and the following reactions with a base and TEMPO. A sketch of the resulting minimum energy stable structures is reported in Figure 1 in the Experimental Section.

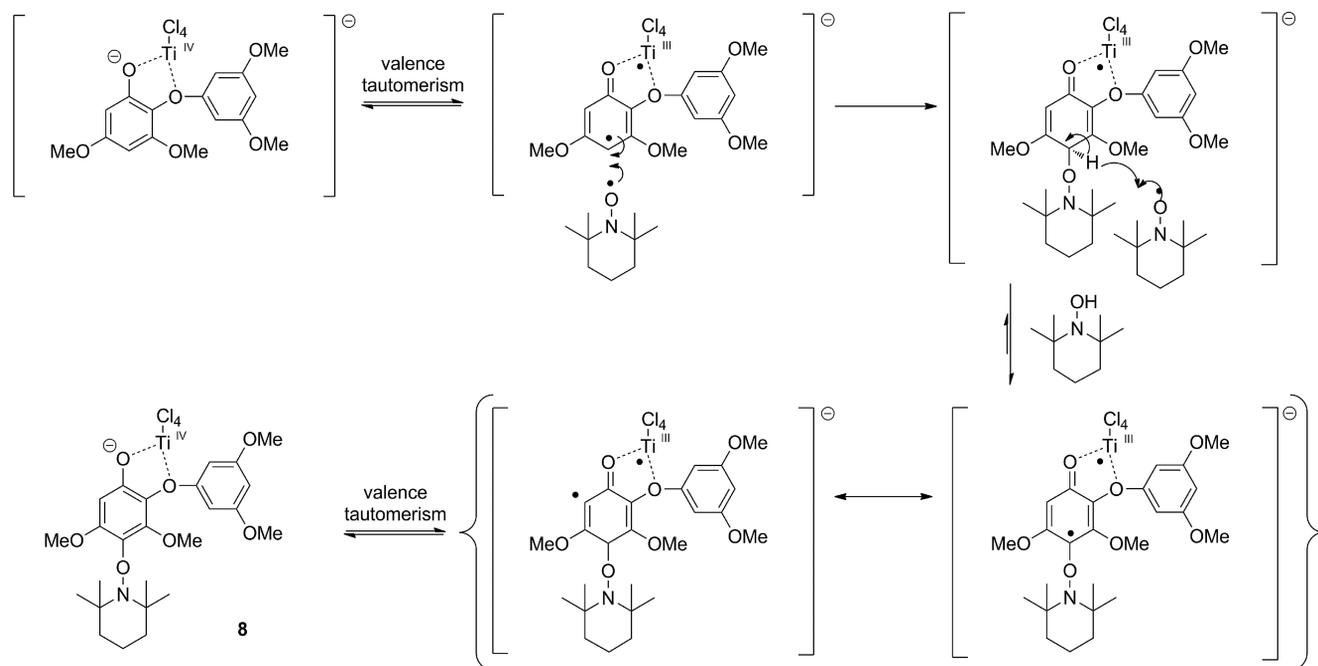


Scheme 3. Proposed mechanism for 1 equiv. of TEMPO per phenol.

In a first step, the initial equilibria between the possible complexes that can be formed between  $\text{TiCl}_4$  with benzene-1,3,5-triol and/or diethyl ether was analyzed to elucidate the stable precursors of the possible radical structures observed in EPR experiments. As shown in Figure 1 (panel a) in the Experimental Section, the three possible complexes have a very similar stability and the calculations suggest a slightly larger dominance of the  $\text{Ph-Ti}^{\text{IV}}\text{-Eth}$  complex. The addition of a tertiary amine to these species to model the proton extraction by benzene-1,3,5-triol (see description of Scheme 3), has different effects as shown in Figure 1 (panels b and c). The  $\text{Eth-Ti}^{\text{IV}}\text{-Eth}$  complex is not reactive in front of the base or the  $\text{H}_2\text{NO}$  species and will not be relevant for the rest of the mechanism. However, the base extracts a proton from the phenol group of the phenolic complexes to generate the anionic structures that exhibit valence tautomerism, showing an accessible, stable, diradical electronic state. In both cases, the open shell singlet is 0.3 kcal more stable than the triplet state. The relative stability of the two possible diradical species is clearly favorable to the  $[\text{Ph-Ti}^{\text{III}}\text{-Ph}]^-$  complex that, overall, displaces the previous equilibrium as long as the reaction proceeds. In Figure 1 (panel c) the key structures of the present proposed mechanism are shown. Addition of one equivalent of  $\text{H}_2\text{NO}$  radi-

cal per phenol to the  $[\text{Ph-Ti}^{\text{III}}\text{-Ph}]^-$  complex leads to a stable anion triradical  $[\text{Ph-Ti}^{\text{III}}\text{-Ph}]^-$  complex that provides a consistent pathway to reach the final product 7 by an internal bond formation between both aromatic rings (Scheme 3). The  $[\text{Ph-Ti}^{\text{III}}\text{-Ph}]^-$  anion triradical complex is the key structure for the proposed mechanism and the subsequent rearrangement is clear from the observed products using an increasing number of TEMPO equivalents per phenol as described in the Experimental Section. Clearly, a competition between both mechanisms takes place if the number of TEMPO equivalents per phenol present in the reaction medium is between 1 and 6. When more than one equivalent of TEMPO was added the 3-(3',5'-dimethoxyphenoxy)-4,6-dimethoxy-5-[(2',2',6',6'-tetramethylpiperidin-1-yl)oxy]benzene-1,2-diol (9) begins to form and with 6 or more TEMPO equivalents formation of compound 7 is not observed anymore, as shown in Scheme 4.

This compound can be mechanistically justified through an addition of TEMPO to the last tautomeric equilibrium drawn in Scheme 4, and briefly illustrated in Scheme 5. The justification of this mechanism is supported by the well-known fact that TEMPO easily reacts with radical species.<sup>[12]</sup> A TEMPO molecule can abstract hydrogen. Finally, in the formation of product 9, the addition of a hydroxyl

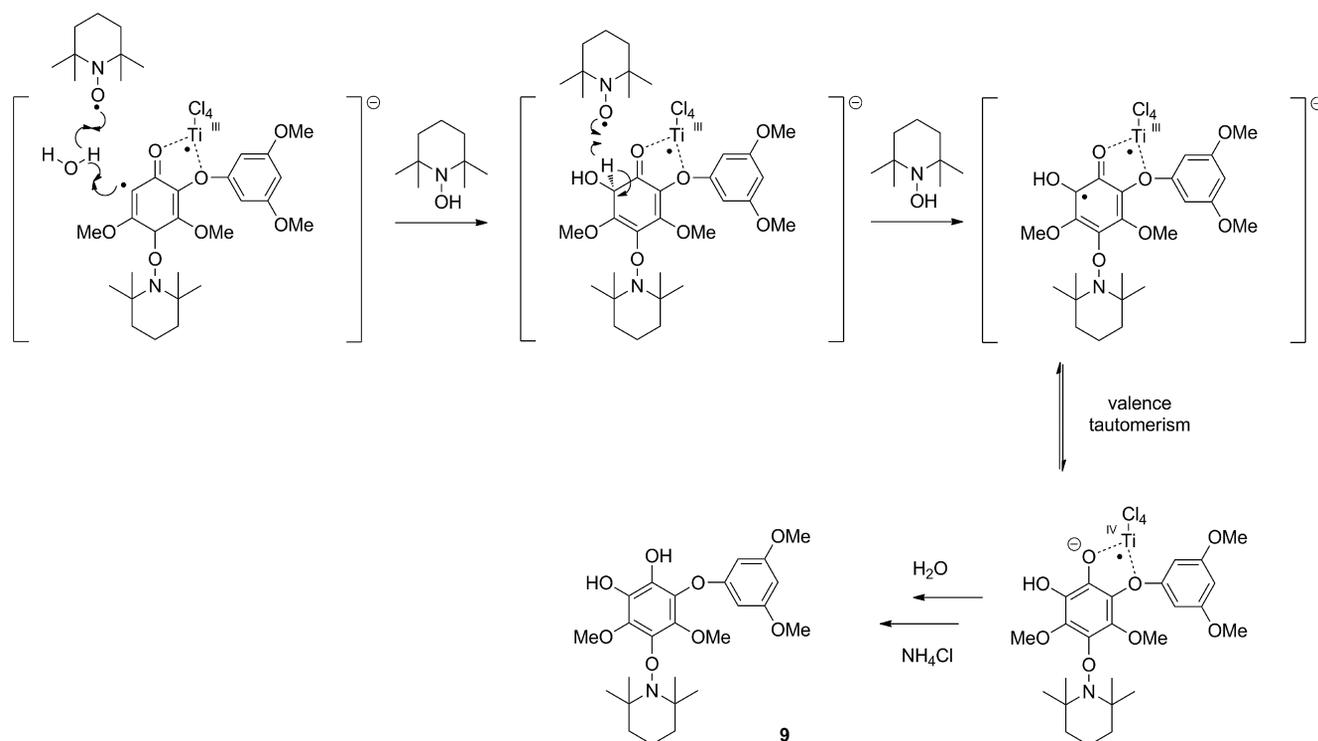


Scheme 4. Proposed mechanism for more than 1 equiv. of TEMPO per phenol.

group can be justified by the action of TEMPO on a water molecule to produce a hydroxyl radical that is added to the last Ti complex, **8**, in Scheme 4. Water is added (as a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ ) to the anhydrous reaction solution when complex **8** has been formed as part of the workup procedure. This last step is shown in Scheme 5.

## Conclusions

In conclusion, we have reported a comprehensive mechanistic description for the  $\text{TiCl}_4$ -mediated phenolic formylation confirming the intramolecular nucleophilic substitution pathway proposed by Cresp et al.<sup>[2]</sup> and, simulta-



Scheme 5. Proposed mechanism for hydroxyl addition.

neously, this research has provided theoretical and experimental evidence of diradical and triradical intermediates that lead to new and interesting active reagents for general use. It is found that the valence tautomerism is essential to understand the different nature of the active species for possible nucleophilic or radical processes in all the proposed mechanisms. In this sense, the implication of these kinds of diradical complexes in this and related reactions is expected to be of fundamental significance in organic and bioorganic chemistry. In particular, the formation of products such as lignines<sup>[17]</sup> or reactivity of phenolic derivatives<sup>[18]</sup> may occur through diradical mechanisms similar to the ones reported in the present study.

## Experimental Section

### EPR Experiments

**Experiment 1:** Following the conventional procedure for the formylation reaction, a solution of 3,5-dimethoxyphenol (231.0 mg, 1.50 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was stirred at 0 °C. Then, TiCl<sub>4</sub> (170 μL, 1.55 mmol) was added dropwise, then the mixture was left for a period of 30 min. Afterwards, anhydrous Et<sub>2</sub>O (170 μL, 1.62 mmol) [instead of dichloromethyl methyl ether] was added and after 30 min, 400 μL of the mixture, which presumably contains the blocked intermediate (compound **3** in Scheme 3), was introduced into an EPR tube for characterization. The complete procedure was carried out under Ar to avoid contamination by O<sub>2</sub>. The mixture was prepared the day before and kept at –80 °C in the EPR tube under Ar. The reference sample used as a blank in the EPR experiment contained 3,5-dimethoxyphenol in anhydrous CH<sub>2</sub>Cl<sub>2</sub> in the same concentration as the experiment mixture (0.15 M). The EPR spectra in solution at 4 K shows a clear |Δ*m<sub>s</sub>*| = 1 signal at ≈ 3350 G (*g* ≈ 2.000) without fine structure and the spin forbidden half field |Δ*m<sub>s</sub>*| = 2 signal at ≈ 3350 G (*g* ≈ 4.392). The observation of the half field signal at low temperature and the decrease in intensity of the observed signals with temperature suggest that the diradicals formed in the solution have a triplet ground state. However, these signals are almost undistinguishable from the background signal above 100 K in this experiment. This fact suggests that the pre-equilibria suggested by the theoretical model described in Figure 1 (panel a) start to play a role since the signal in experiment 2 is observable even at ambient temperature.

**Experiment 2:** A solution of 3,5-dimethoxyphenol (500.0 mg, 3.25 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and under an argon atmosphere was stirred at 0 °C. Then, TiCl<sub>4</sub> (800 μL, 7.30 mmol) was added by syringe and the mixture was left for a period of 30 min. The mixture was introduced into an EPR tube for characterization also under an argon atmosphere. The mixture was prepared and analyzed at the same time. The EPR spectra in solution shows a clear |Δ*m<sub>s</sub>*| = 1 signal even at 300 K at ≈ 3350 G. To justify the EPR signal observed in this experiment we propose what we believe is the most plausible explanation, an intermediate coordination consisting of two phenols bonded with TiCl<sub>4</sub> in an open shell singlet or triplet state. In the case of experiment 1, the competing pre-equilibria between TiCl<sub>4</sub> with phenol and/or ether molecules (neutral, anions and diradical tautomers described in Figure 1) is responsible for the rapid decay of the intensity of the EPR signal above 50 K.

**TEMPO Experiments:** A solution of 3,5-dimethoxyphenol (500 mg, 3.25 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was purged

with Ar and cooled with an ice bath. Then, TiCl<sub>4</sub> (800 μL, 7.30 mmol in anhydrous CH<sub>2</sub>Cl<sub>2</sub>) was added dropwise. The reaction mixture was left to react for 1 h. Since the reaction occurs even without adding a base, the proton extraction in anhydrous CH<sub>2</sub>Cl<sub>2</sub> is performed by one molecule of 3,5-dimethoxyphenol acting as a base to form complex **3** in the present experimental set up. Afterwards, a solution of different equivalents of TEMPO in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added by syringe to the solution and the mixture left to react for a further 45 min. The reaction was quenched by the addition of a saturated aqueous NH<sub>4</sub>Cl solution (10 mL) and the mixture was left to stand for 2 h. The organic layer was separated and washed with 0.1 N HCl solution (3 × 50 mL) and brine (3 × 50 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was evaporated under reduced pressure. The crude reaction mixtures were analyzed by HPLC with 5% MeCN for 2 min and from 5 to 95% MeCN in 10 min. Products **7** and **9** were obtained in different proportions according to the equivalents of TEMPO used, as shown in Table 1.

Table 1. Amounts of TEMPO used in this study and yields of **7** and **9** obtained under these conditions.

TEMPO ([g]/[mmol])	TEMPO [equiv.]	<b>7</b> [%] <sup>[a]</sup>	<b>9</b> [%] <sup>[a]</sup>
0.608/3.9	1.2	quant.	– <sup>[b]</sup>
1.267/8.1	2.5	35	65
2.534/16.2	5.0	18	82
3.042/19.5	6.0	– <sup>[b]</sup>	quant.

[a] Determined by integration of chromatographic areas. [b] Not detected.

From 6 equiv. of TEMPO the reaction stops progressing and shows the same chromatographic profile, only with product **9**. No variation of the temperature in the reactions improved the ratio of the desired products. Conversely, a lower yield was obtained due to what we believe is the stability of the titanium complex with increasing temperature.

A notable result was obtained when a solution of product **7** (500 mg, 3.25 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (10 mL) purged with Ar and cooled with an ice bath was mixed with one equivalent of TEMPO in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL) added by syringe to the solution. The mixture did not show any change or reaction for 45 min since in the analysis only the initial reactants and no other product could be seen. This negative result is a clear indication that only the radical reaction proceeds in the presence of TiCl<sub>4</sub> in front of other possible chemical equilibria such as H<sup>•</sup> or H<sup>+</sup> extraction by TEMPO on phenols.

Products **7** and **9** were isolated by flash chromatography and characterized as follows:

**2-(3,5-Dimethoxyphenoxy)-3,5-dimethoxyphenol (7):** White solid. TLC: *R<sub>f</sub>* = 0.77 (AcOEt). HPLC-MS: (X-Terra MS C<sub>18</sub>, H<sub>2</sub>O/MeCN from 95:5 to 0:100 over 11 min) *t<sub>R</sub>* = 7.3 min, *m/z* = 307.1 [M + H]<sup>+</sup>. HRMS (ESI): calcd for (C<sub>16</sub>H<sub>19</sub>O<sub>6</sub>) 307.1182; found 307.1175 [M + H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, [D<sub>6</sub>]DMSO): δ = 6.04 (s, 1 H, Ar-H), 6.03 (s, 2 H, Ar-H), 6.01 (s, 1 H, Ar-H), 5.93 (s, 1 H, Ar-H), 3.66 (s, 3 H), 3.52 (s, 3 H), 3.51 (s, 6 H) ppm. UV/Vis (methanol): λ<sub>max</sub> = 243.6 nm.

**2-(3,5-Dimethoxyphenoxy)-3,5-dimethoxy-4-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]phenol (9):** Brown oil. TLC: *R<sub>f</sub>* = 0.71 (AcOEt). HPLC-MS: (X-Terra MS C<sub>18</sub>, H<sub>2</sub>O/MeCN from 95:5 to 0:100 over 11 min) *t<sub>R</sub>* = 9.1 min, *m/z* = 478.2 [M + H]<sup>+</sup>. HRMS (ESI): calcd for (C<sub>25</sub>H<sub>37</sub>NO<sub>8</sub>) 478.2442; found 478.2439 [M + H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, [D<sub>6</sub>]DMSO): δ = 6.17 (s, 1 H, Ar-H), 6.08 (s, 1 H, Ar-

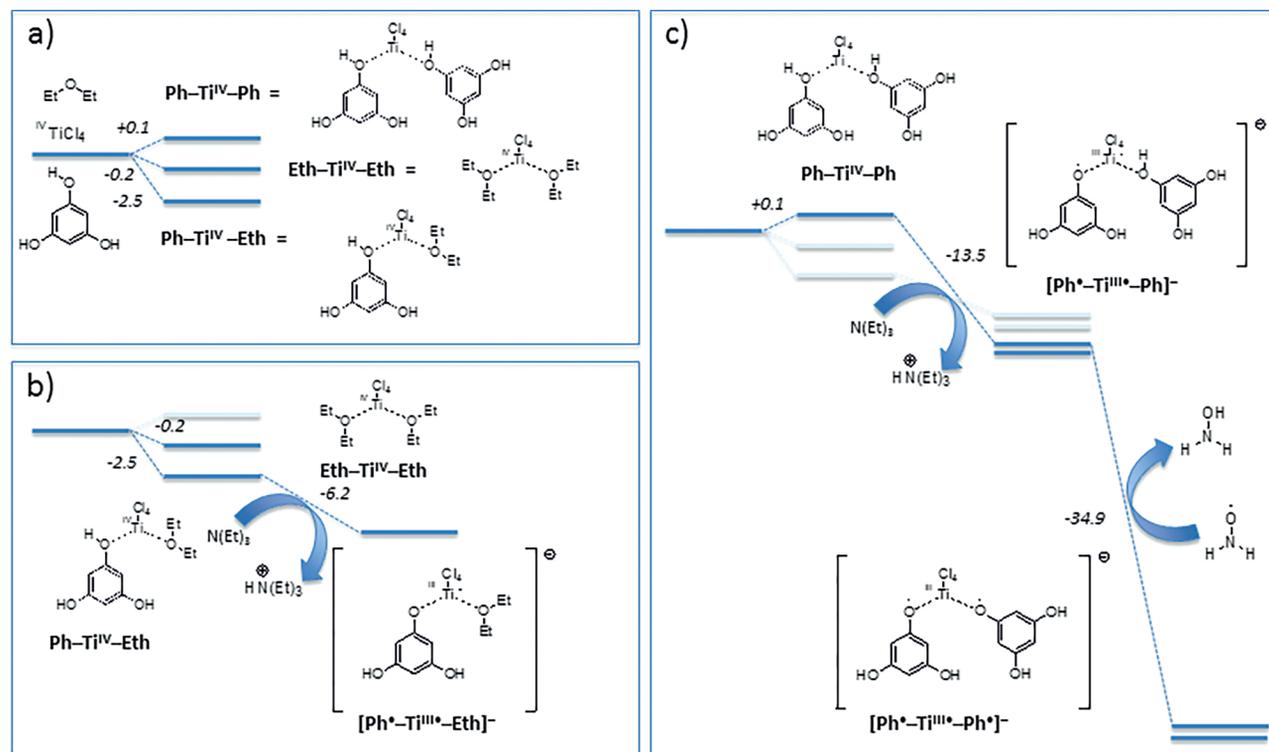


Figure 1. Optimized geometries of the calculations on the simplified model described in the text. In panel a) the preliminary equilibria present in the  $\text{TiCl}_4/1,3,5\text{-benzenetriol/diethyl ether}$ . Panel b) equilibrium process leading to the  $[\text{Ph}^\bullet\text{-Ti}^{\text{III}}\text{-Eth}]^-$  diradical. Panel c) equilibrium processes leading to the  $[\text{Ph}^\bullet\text{-Ti}^{\text{III}}\text{-Ph}]^-$  diradical and  $[\text{Ph}^\bullet\text{-Ti}^{\text{III}}\text{-Ph}]^\bullet$  triradical. Level of theory: HF/6-31G\* for reactants and neutral complexes in panel a; ROHF/6-31G\* for  $\text{H}_2\text{NO}/6\text{-31G}^*$ , CASSCF(8,8)/6-31G\* for diradical structures ( $[\text{Ph}^\bullet\text{-Ti}^{\text{III}}\text{-Eth}]^-$  and  $[\text{Ph}^\bullet\text{-Ti}^{\text{III}}\text{-Ph}]^-$ , either triplet or open-shell singlet states; in panels b and c) and CASSCF(11,11)/6-31G\* for the triradical structure  $[\text{Ph}^\bullet\text{-Ti}^{\text{III}}\text{-Ph}]^\bullet$  either quartet or doublet states (in panel c). ZPE correction has been included for each minimum energy structure.

H), 5.56 (s, 1 H, br. s, OH), 5.22 (s, 1 H, Ar-H), 4.39 (s, 1 H, br. s, OH), 3.75 (s, 3 H), 3.71 (s, 6 H), 3.62 (s, 3 H), 2.2–1.0 (m, 18 H, b.s.) ppm. UV/Vis (methanol):  $\lambda_{\text{max}} = 255.6 \text{ nm}$ .

**Ab Initio Calculations on the Model System:** To provide a theoretical justification of the proposed mechanism several wave function calculations were performed to show the stability of the intermediate diradical and triradical structures essential for this mechanism. The electronic structure of these complexes and their molecular structures were investigated by using a simplified molecular model in vacuo representative for the description of the formation process of the diradical  $\text{TiCl}_4$ -phenolate complexes by means of ab initio wave function electronic structure calculations. Hence, 3,5-dihydroxyphenol was adopted as a model system to represent 3,5-dimethoxyphenol, the TEMPO radical was substituted by  $\text{H}_2\text{NO}$ . The addition of a tertiary amine to these species [trimethylamine,  $\text{N}(\text{Me})_3$ ], a base to model the proton extraction (see comment in Scheme 3), has different effects as shown in Figure 1 (panels b and c). Using this simplified model we investigate the stability of the intermediate species (neutral, anionic, diradical and triradical) involved in the initial equilibria and the following reactions with base and TEMPO, shown in Scheme 3. A sketch of the resulting minimum energy stable structures is reported in Figure 1.

All calculations presented herein have been carried out by employing the standard 6-31G\* basis set and the GAMESS 2012 package.<sup>[13]</sup> The all electron basis sets correspond to the standard basis sets reported by Pople and collaborators: [4s/2s] for H, [10s4p1d/3s2p1d] for C, N, and O,<sup>[14]</sup> [16s10p1d/4s3p1d] for Cl<sup>[15]</sup> and [22s16p4d1f/5s4p2d1f] for Ti.<sup>[16]</sup>

For the first stage of the reaction we explore the stability of the possible complexes between  $\text{TiCl}_4$  with 1,3,5-triphenol and/or diethyl ether. We employed a theoretical approach based on the Hartree–Fock (HF) functional since the electronic ground states of all these structures are closed-shell in nature. The extraction of a proton from the  $\text{Ph-Ti}^{\text{IV}}\text{-Eth}$  or the  $\text{Ph-Ti}^{\text{IV}}\text{-Ph}$  complexes is modeled by addition of a tertiary amine to these species to simplify the calculations. Notice that in the present experimental set up the reaction occurs without adding a base and the proton extraction in anhydrous  $\text{CH}_2\text{Cl}_2$  is performed by one molecule of 3,5-dimethoxyphenol acting as a base to form complex 3 (neither  $\text{CH}_2\text{Cl}_2$  nor the ether can act as a proton acceptor). In the case of the  $\text{Eth-Ti}^{\text{IV}}\text{-Eth}$  complex, it is not reactive in the presence of the base or the  $\text{H}_2\text{NO}$  species and will not be relevant for the rest of the mechanism. However, the base extracts a proton from the phenolic complexes to generate the anionic structures that exhibit valence tautomerism, showing an accessible and stable diradical electronic state. In both cases, the open shell singlet is  $0.3 \text{ kcal mol}^{-1}$  more stable than the triplet state, which suggests that the triplet and the open-shell singlet are quasi-degenerate (the closed-shell singlet solution is significantly higher in energy: the  $^3\text{A}$  at UHF level is lower than the  $^1\text{A}$  RHF solution by almost  $20 \text{ kcal mol}^{-1}$ ). Indeed, the EPR spectrum at 4 K suggests that the ground state of the diradical species is a triplet since the intensity of the observed peaks decrease with temperature and the half-field signal at  $g \approx 4.392$ . Here, it is worth noting that in the case of the original formulation process shown in Scheme 1 of the main text the tautomeric equilibrium involving this anionic complex provides the essential step to reach the products through an intramolecular

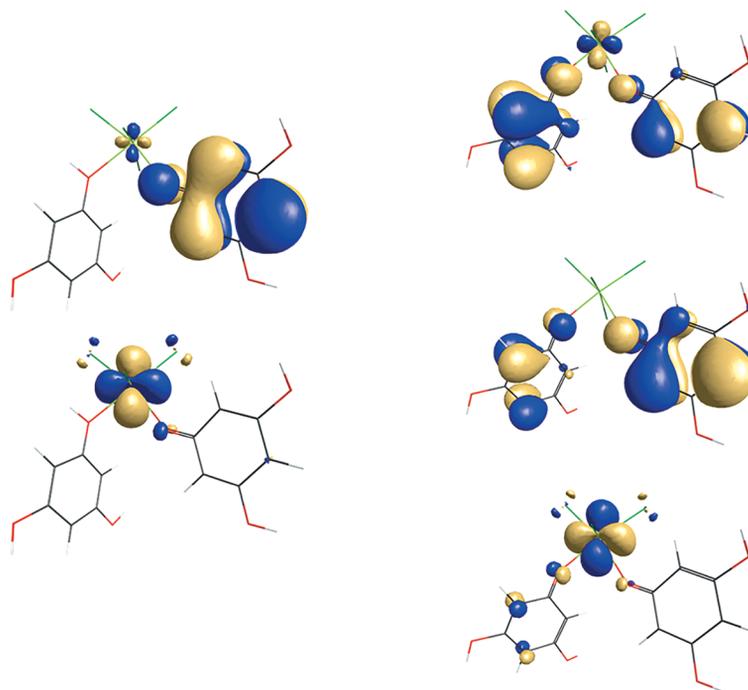


Figure 2. The most relevant natural orbitals (open shells) of the triplet state of  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{III}}\text{-Ph}]^{\cdot-}$  (left) and the quartet state of  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{III}}\text{-Ph}]^{\cdot-}$  (right). Contour value for orbital isosurfaces is  $0.03 \text{ |e|bohr}^{-3}$ .

nucleophilic attack on the Cl substituent situated on the ether group.

The relative stability of the two possible diradical species is clearly favorable to the  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{III}}\text{-Ph}]^{\cdot-}$  complex that, overall, displaces the previous equilibrium as long as the reaction proceeds. Notably, in the case of the original formylation process shown in Scheme 1, the tautomeric equilibrium involving the  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{III}}\text{-Eth}]^{\cdot-}$  anionic complex provides the essential step to reach the products through an intramolecular nucleophilic attack on the Cl substituent situated on the ether group. The valence tautomerism between the two forms of the anionic and diradical intermediates, namely  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{III}}\text{-Ph}]^{\cdot-}$  and  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{IV}}\text{-Ph}]^{\cdot-}$  or  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{III}}\text{-Eth}]^{\cdot-}$  and  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{IV}}\text{-Eth}]^{\cdot-}$  requires the use of a multi-reference approach as the complete active space self-consistent field (CASSCF). From the natural orbital occupations between 1.98 and 0.02 of the triplet state it has been established that the appropriate CASSCF wave function requires 8 electrons in 8 orbitals. This fact precludes the application of DFT methods based on a single Kohn–Sham determinant to represent the electronic states of the reported  $\text{TiCl}_4$ -enolate structures as discussed by us in previous papers. In addition, Schreiner and co-workers have shown that, even for closed shell organic molecules, the accuracy of standard hybrid DFT potentials is questionable.

The same scheme leads to a CASSCF(11,11) active space to properly describe the triradical anion  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{III}}\text{-Ph}]^{\cdot-}$ , either the  $^4\text{A}$  or the  $^2\text{A}$  states (the  $^2\text{A}$  state is  $0.4 \text{ kcal mol}^{-1}$  more stable than the  $^4\text{A}$  state, suggesting that these states are almost degenerate). The most relevant CASSCF(8,8) and CASSCF(11,11) natural orbitals (NOs) of the triplet state of the diradical and the quartet state of the triradical are those reported in Figure 2 with the corresponding occupation numbers close to 1.00. The topology of these NOs allows us to assign these orbitals to the nonbonding orbital of the phenol rings combined with one Ti d orbital.

The triradical anion along with the diradical structures  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{III}}\text{-Ph}]^{\cdot-}$  and  $[\text{Ph}^{\cdot-}\text{-Ti}^{\text{III}}\text{-Eth}]^{\cdot-}$  are the key stable intermediates to pro-

vide a plausible and consistent mechanism for the overall process as described in Figure 1.

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