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Diastereoselective and enantioselective photoredox pinacol coupling promoted by titanium complexes with a red-absorbing organic dye†

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The pinacol coupling reaction, a reductive coupling of carbonyl compounds that proceeds through the formation of ketyl radicals in the presence of an electron donor, affords the corresponding 1,2-diols in one single step. The photoredox version of this transformation has been accomplished using different organic dyes or photoactive metal complexes in the presence of sacrificial donors such as tertiary amines or Hantzsch's ester. Normally, the homo-coupling of such reactive ketyl radicals is neither diastereo- nor enantio-selective. Herein, we report a highly diastereoselective pinacol coupling reaction of aromatic aldehydes promoted by 5 mol% of the non-toxic, inexpensive and available Cp_2TiCl_2 complex. The key feature that allows the complete control of diastereoselectivity is the employment of a red-absorbing organic dye in the presence of a redox-active titanium complex. Taking advantage of the well-tailored photoredox potential of this organic dye, the selective reduction of Ti(IV) to Ti(III) is achieved. These conditions enable the formation of the D,L (*syn*) diastereoisomer as the favored product of the pinacol coupling (d.r. > 20 : 1 in most of the cases). Moreover, employing a simply prepared chiral SalenTi complex, the new photoredox reaction gave a complete diastereoselection for the D,L diastereoisomer, and high enantiocontrol (up to 92% of enantiomeric excess).

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Introduction

Photoredox catalysis¹ has become a powerful methodology to access radical intermediates.² The ability to convert visible light into chemical energy, mainly by SET (single electron transfer) processes, enables the exploration of new challenging chemical transformations.³ Thus, avoiding the use of classical radical initiators or stoichiometric metal reagents, visible light-mediated photoredox catalysis can serve as a simple method to generate ketyl radicals, allowing interesting transformations and providing alternative methods to the traditional approaches for the generation of these reactive intermediates.⁴ The first example of generation of a ketyl radical by visible light

was described in 1979 by Kellogg and co-workers, exploiting the ability of $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ to act as a photocatalyst for the SET reduction and fragmentation of phenacyl sulfonium salts.⁵ After this report, different photoredox methodologies have been applied for the formation of new C–C bonds *via* the generation of ketyl radicals from aldehydes and ketones.⁶ A photocatalytic pinacol coupling was described by Rueping and co-workers.⁷ This simple and catalytic methodology provides access to symmetrical pinacol and diamine products with good functional group tolerance. This study attracted considerable interest in the chemistry community, and many different alternative procedures were reported. In particular, the use of $[\text{Ir(III)}]$ and $[\text{Ru(II)}]$ complexes,⁸ organic dyes,⁹ and semiconductors¹⁰ has been described in photoredox-mediated pinacol coupling. However, the redox potential of the photocatalyst at the excited state is often not sufficient for the direct formation of aryl ketyl radicals.¹¹ Key studies reported by Rueping and other authors have clarified that tributylamine $[(n\text{-Bu})_3\text{N}]$, the sacrificial stoichiometric reductant, plays another important role. The amine radical cation – formed upon reductive quenching of the photocatalyst by amine – activates the carbonyl group lowering its reduction potential, thus leading to the formation of the ketyl radical. The ketyl radicals dimerize and, after protonation, the 1,2-diol products are obtained. In almost all the described catalytic processes, the

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† Electronic supplementary information (ESI) available: Screening tests, and further substrates studied. Photophysical measurements, and electrochemical and quenching studies. Detailed procedures, description and copies of NMR spectra for all compounds. See <https://doi.org/10.1039/d2sc00800a>

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promptness of the radical–radical dimerization step is responsible for the formation of a diastereoisomeric mixture of diols, generally in 1 : 1 ratio (d,l : *meso*), and the observed diastereoselection is generally low (d.r. up to 1.4 : 1).

We have hypothesized that the generation of [Ti(III)] complexes under photoredox conditions could be a straightforward method to perform the pinacol coupling with high diastereocontrol, as was reported by Gansäuer more than 20 years ago, employing manganese as the stoichiometric reductant, and Me₃SiCl as the scavenger.¹² Recently, Gansäuer,¹³ our group,¹⁴ and Shi¹⁵ have reported the generation of [Ti(III)] under photoredox conditions for radical chemistry (allylation reactions,^{14a,15b} opening of epoxides,^{13,15a} propargylations^{14b}). Unfortunately, any attempt to use organic dyes,¹⁷ as well as [Ru(II)] or [Ir(III)] photocatalysts, with [Ti(IV)] complexes, in the presence of Hantzsch's ester or amine-based reductants, gave almost a 1 : 1 ratio of the diastereomeric diols in a model reaction with *p*-chlorobenzaldehyde. This was probably due to a fast and effective reaction performed by the photoredox catalysts, with no participation of the titanium complex. In addition, Hantzsch's ester, used in stoichiometric amount in our attempts, displays a non-negligible absorption feature at 400 nm and it is a strong reductant in its excited state.¹⁸ In order to avoid the direct formation of ketyl radicals due to the photocatalyst or Hantzsch's ester, a milder photochemical system is needed. This photocatalyst needs to show the capability of reducing titanium, either in its excited state (*via* a direct oxidative quenching with titanium), or in its reduced form (upon reductive quenching in the presence of a sacrificial reductant). In addition, titanium complexes used in photoredox reactions can absorb visible light themselves, acting as the active photocatalysts as illustrated by Gansäuer.^{13b}

Based on all these limitations, we decided to use a red-absorbing dye, so that the photocatalyst can be selectively excited without concomitant absorption of light by titanium complexes and Hantzsch's ester. Excitation in the low-energy portion of the visible spectrum (orange and red) brings the advantages of decreased harmfulness and high penetration depth through various media, as evidenced by Rovis, who employed red-absorbing osmium complexes to perform metallaphotoredox catalysis.¹⁹ However, due to the potential toxicity of osmium and the difficulties related to the preparation of the complexes, we investigated the use of an organic dye for this metallaphotoredox chemistry.²⁰ Among all organic dyes with the capability of absorbing red light, dimethoxyquinacridinium (DMQA⁺), a helical carbenium ion, presents interesting photo-physical²¹ and electrochemical²² properties. Lacour *et al.* used *N,N'*-dipropyl-1,13-dimethoxyquinacridinium tetrafluoroborate ([*n*Pr-DMQA]⁺[BF₄][−]) in aerobic photooxidation of benzylamine.²³ More recently, the use of [*n*Pr-DMQA]⁺[BF₄][−] as a new organic photoredox catalyst for photoreduction and photooxidation upon excitation with red light (λ_{max} = 640 nm) with broader applications has been reported.²⁴ The use of this dye in metallaphotoredox catalysis, combining a photoredox catalytic cycle with metal catalysts such as gold and palladium complexes, has also been reported (Fig. 1A).^{24a} The organic dye was prepared in a few steps, and it was robust, and could be isolated by simple

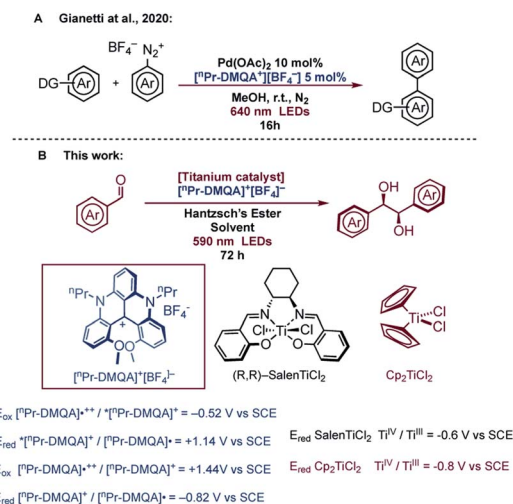
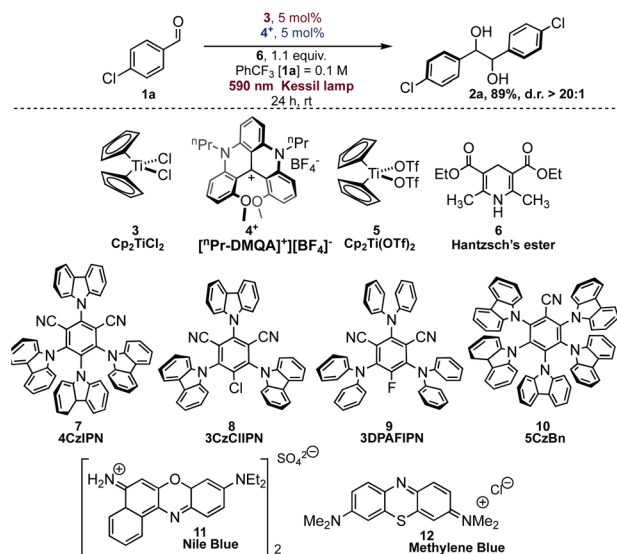


Table 1 Optimization of the pinacol coupling reaction mediated by Cp_2TiCl_2 

Entry ^a	Deviation from standard conditions	Yields ^b	d.r. (D,L : meso) ^c
1	None	>99(89) ^d	>20 : 1
2	No photocatalyst	No reaction	—
3	No 3	Traces	1 : 1
4	No light	No reaction	—
5 ^e	7 instead of 4*	>99	1 : 1
6 ^e	8 instead of 4*	>99	1 : 1
7 ^e	9 instead of 4*	>99	1 : 1
8 ^e	10 instead of 4*	>99	1 : 1
9 ^e	11 instead of 4*	No reaction	—
10 ^e	12 instead of 4*	No reaction	—
11 ^e	7 Instead of 4* and No 3	>99	1 : 1
12 ^{e,f}	No photocatalyst, No 3	50	1 : 1
13	Toluene instead of PhCF_3	>99	7 : 1
14	Benzene instead of PhCF_3	No reaction	—
15	DMF instead of PhCF_3	53	1 : 2
16	MeCN instead of PhCF_3	Traces	—
17	PhCN instead of PhCF_3	Traces	—
18	PhF instead of PhCF_3	23	3 : 1
19	THF instead of PhCF_3	Traces	—
20	5 Instead of 3	No reaction	—

^a Reactions performed on a 0.1 mmol scale. ^b Determined by ^1H NMR analysis using the internal standard method. ^c Determined by ^1H NMR analysis of reaction crude. ^d Reaction performed on a 0.2 mmol scale; the value in parentheses is the isolated yield after chromatographic purification; **4*** was recovered (>90%) after chromatographic purification. ^e Irradiation at 456 nm. ^f Reaction time 72 h.

titanium complex (Table 1, entries 5 and 11), likely due to the direct formation, *via* SET from the photocatalyst, of the ketyl radical on the activated carbonyl substrate (see a detailed discussion below).²⁶ Furthermore, Hantzsch's ester itself is capable of promoting the pinacol coupling reaction under blue light irradiation (Table 1, entry 12). The success of the reaction with dye **4*** and orange light irradiation is also highly dependent on the solvent (Table 1, entries 13–19).

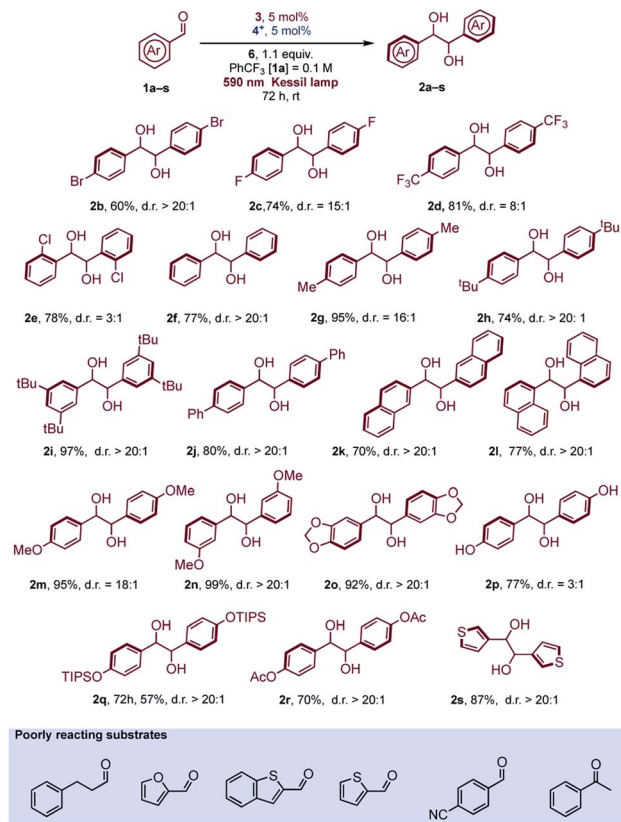
While THF or MeCN gave only traces of the desired product, the reaction proceeded with good diastereoselection in aromatic solvents (benzene excluded). Among all the aromatic solvents, yield and diastereoselectivity were optimal in

trifluorotoluene due to its documented inertness towards free-radical intermediates.²⁷ When these reactions were conducted in more conventional solvents, such as MeCN, benzene, or THF, yields are diminished, or no reaction is observed.

No formation of the pinacol product was observed for the titanium complex **5**, suggesting that the presence of stronger O-based ligands in place of weakly bound chloride is detrimental for the titanium complex reactivity (Table 1, entry 20).

The reaction conditions were found to be suitable with a variety of aromatic aldehydes (Scheme 1) but a prolonged reaction time of 72 h was necessary for full conversion of the substrates. Some limitations of the methodology were





Scheme 1 Scope of the diastereoselective pinacol coupling promoted by Cp₂TiCl₂.

observed with heterocyclic aldehydes, due to reaction conditions (formation of acidic oxidized Hantzsch's ester) or inherent reduced reactivity, while ketones or aliphatic aldehydes were found to be unreactive (see Scheme 1 and Fig. S6† for details).

In general, aromatic aldehydes bearing alkoxy groups (R = alkyl, Scheme 1) at the *para* position were found to be more reactive and the products were isolated in high yields. This behavior was also observed with moderate activating groups such as a methyl substituent. For aromatic aldehydes, the protection of the oxygen at the *para* position is not required since aldehyde **1p** was found to be reactive under the reaction conditions. Introduction of hindered substituent (**1q**) or electron withdrawing substituent (**1r**) onto the *para* OH group was found to reduce the reactivity. In any case, the diastereoselective outcome with these substrates was always excellent. Naphthyl aldehydes (α **1l** and β **1k**) were both reactive substrates, and, as reported in various studies with titanium mediated pinacol coupling,²⁸ no hindrance was observed with these two substrates. Some aldehydes bearing electron withdrawing groups gave satisfactory yields but a slight drop of diastereoselectivity was observed. This was particularly evident with *ortho*-chlorobenzaldehyde (**1e**), probably for a concomitant steric hindrance. Limitations due to the presence of bulky

groups close to carbonyl were also observed in Ti-mediated pinacol coupling with overstoichiometric Zn as sacrificial reductant.^{28a}

Enantioselective variant

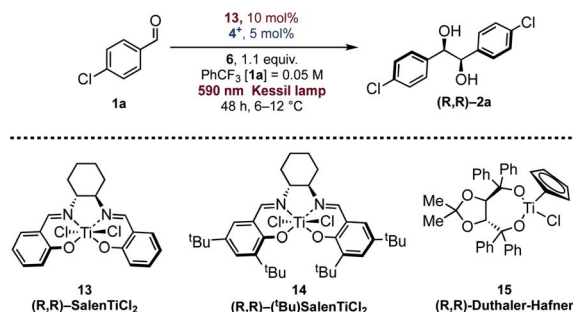
Different examples of enantioselective catalytic pinacol coupling of aldehydes were reported in the literature, based on the pioneering work developed by Gansäuer.¹² Although chiral titanium cyclopentadienyl complexes were employed in enantioselective pinacol couplings with moderate results,²⁹ titanium-Schiff base complexes³⁰ were found to be quite suitable promoters for catalytic titanium-mediated pinacol coupling reactions,³¹ and good scope and high enantioselectivity were obtained using different types of these complexes.³²

Riant^{32a} and Joshi^{28a} have reported interesting pinacol coupling protocols that gave high enantioselectivities using a titanium-Schiff base complex. Joshi published a particularly noteworthy study, featuring the use of an unsubstituted chiral SalenTiCl₂ complex (**13**, Table 2), simply prepared from Ti(OiPr)₄ and the bis-imine ligand by treatment with TMSCl. The titanium complex was converted *in situ* into the active Ti(III) species, through reduction with a stoichiometric amount of Zn. As well evidenced by Gansäuer, the presence of TMSCl in the reaction mixture was also crucial in order to close the catalytic cycle, upon pinacol silylation and concomitant liberation of Ti(IV) for a successive reduction. Recently, Ti(Salen) was found to be active in other radical mediated processes.³³

Since Schiff bases are modular and simply prepared from commercially available diamines, and both complexation and isolation of titanium complexes are quite straightforward, we selected two chiral Salen complexes **13** and **14** for a detailed investigation of our photoredox pinacol coupling. We were pleased to find promising results with **13**, while **14** and **15** were found to be unreactive (Table 2, entries 1–3). The conditions were optimized by varying the reaction parameters, as illustrated in Table 2. The presence of light, the titanium complex, and the photocatalyst is crucial for the reaction (Table 2, entries 4–6). It is worth mentioning that the reaction proceeds smoothly in trifluorotoluene, while other solvents are ineffective (Table 2, entries 8–12). The stereoselectivity depends on the temperature, whose optimal value was found to be close to 10 °C (Table 2, entry 13). With these indications, a series of aromatic aldehydes were subjected to our reaction, and we were pleased to observe good results, reported in Scheme 2. In general, the reaction was found to be effective with unhindered aldehydes. Electronic effects seem not to play a relevant role in the reactions, contrary to Ti(Salen)/Zn mediated reactions.^{28a} Sterical effects, in contrast, are detrimental for the enantioselectivity, as *ortho* substituted aromatic aldehydes were found to be less reactive. Hindrance in the *para* position lowers the stereoselectivity of the process. Compared to Cp₂TiCl₂, the SalenTiCl₂ mediated protocol was found to feature a slightly reduced reactivity, probably due to the scarce solubility of the complex in the reaction solvent.

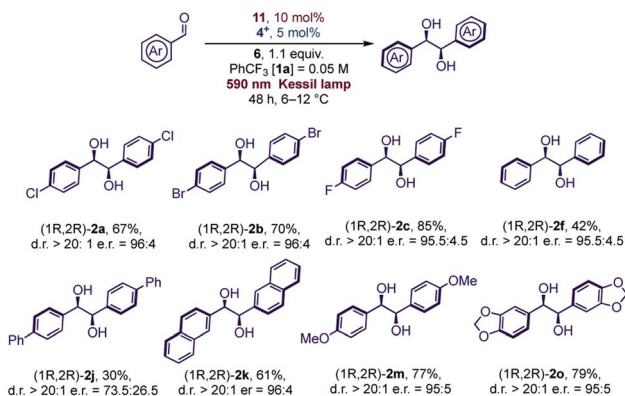


Table 2 Optimization of the pinacol coupling reaction mediated by chiral titanium complexes



Entry ^a	Deviation from standard conditions	Yields ^b	d.r. (D,L : meso) ^c	e.r. ^d (R,R/S,S)
1	None	74(67) ^e	>20 : 1	96 : 4
2 ^f	14 instead 13, [1a] 0.1 M	Traces	—	—
3 ^f	15 instead 13, [1a] 0.1 M	n.r.	1 : 1	—
4	No photocatalyst	n.r.	—	—
5	No titanium	Traces	1 : 1	50 : 50
6	No light	n.r.	1 : 1	—
7 ^g	10 mol% of (S,S) 11	49	1 : 1	3 : 97
8	Toluene instead of PhCF ₃	Traces	1 : 1	—
9	MeCN instead of PhCF ₃	n.r.	1 : 1	—
10	Benzene instead of PhCF ₃	n.r.	1 : 1	—
11	THF instead of PhCF ₃	Traces	7 : 1	—
12	DME instead of PhCF ₃	Traces	—	—
13	25 °C instead 6–12 °C	92	9 : 1	64.5 : 35.5

^a Reactions performed on a 0.1 mmol scale. ^b Determined by ¹H NMR analysis using the internal standard method. ^c Determined by ¹H NMR analysis of reaction crude. ^d Determined by HPLC analysis on a column with a chiral stationary phase. ^e Reaction performed on a 0.2 mmol scale. The value in parentheses is the isolated yield after chromatographic purification. ^f 5 mol% of titanium catalyst was used in the reaction. ^g Reaction time 16 h.

Scheme 2 Scope of the enantioselective photoredox pinacol coupling with (R,R)-SalenTiCl₂.

Photophysical and mechanistic analyses

To shed light on the reaction mechanism, as for the synthetic protocol, PhCF₃ was chosen as the main solvent for the photophysical characterization of photocatalyst 4⁺. In agreement with published results,^{24a} compound 4⁺ shows a low energy-lying

absorption band with the maximum at 614 nm ($\epsilon_{614 \text{ nm}} = 10\,300 \text{ M}^{-1} \text{ cm}^{-1}$ in CH₂Cl₂, $\lambda_{\text{onset}} \sim 680 \text{ nm}$; see Fig. 2A and S8†) allowing its excitation with orange light (LED source at $\lambda_{\text{max}} = 590 \text{ nm}$, see Fig. S1†). The emission band of 4⁺ is peaked at 648 nm – with a lifetime of 12.8 ns and a quantum yield of 0.26 in air-equilibrated PhCF₃ solution – corresponding to a spectroscopic energy E_{0-0} of 1.96 eV. The emission decay is not dramatically affected by the presence of molecular oxygen, as expected for fluorescent dyes: a lifetime of 13.8 ns is determined in oxygen-free solutions (Fig. 2B). No phosphorescence has been detected in the visible and NIR spectral regions from deoxygenated PhCF₃ solutions at r.t. or in a rigid matrix at 77 K in diethylether : ethanol : PhCF₃ mixtures (2 : 1 : 1 v/v/v). The compound shows excellent photostability in solution with no degradation upon prolonged irradiation at 570 nm and 590 nm (see ESI†), making it a good candidate for an active initiator in photoredox processes. Since 4⁺ is isolated and used as a racemic mixture, no investigations on electronic circular dichroism nor circular polarized luminescence have been carried out.

With this in hand, the analysis of the luminescence quenching in the presence of the reaction components has been undertaken to draw a mechanistic picture of the chemical reaction occurring upon visible-light excitation of 4⁺. The reduction potentials of 4⁺ have been reported as: $E_0(4^+/4^*) =$



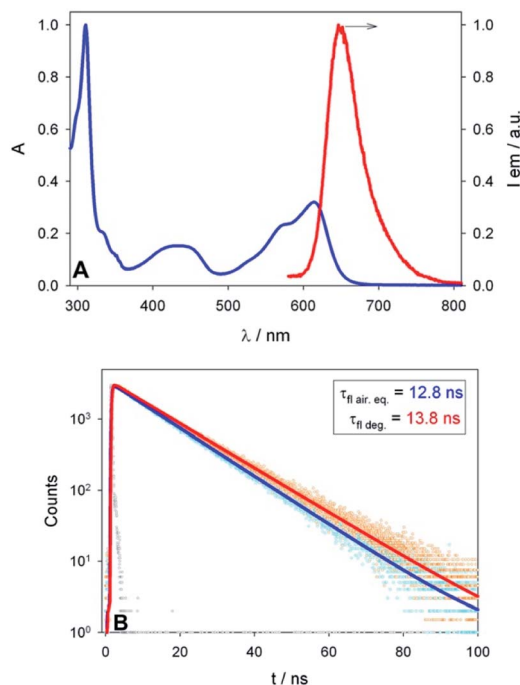


Fig. 2 (A) Absorption (blue line) and fluorescence spectra (red line) of a PhCF_3 solution of 4^+ ($31 \mu\text{M}$) at r. t. ($\lambda_{\text{ex}} = 575 \text{ nm}$). (B) Comparison between fluorescence decays of air-equilibrated (blue dots) and N_2 -saturated (red dots) PhCF_3 solutions of 4^+ (ca. $30 \mu\text{M}$) at r. t. The corresponding monoexponential fitting functions are shown as solid lines. The instrument response function (IRF) is also reported (grey dots).

-0.82 V vs. SCE , and $E_0(4^{2+}/4^+) = +1.44 \text{ V vs. SCE}$ in CH_2Cl_2 ,^{24a} whose polarity is comparable to that of PhCF_3 .³⁴ It follows that the excited state of 4^+ is able, on a thermodynamic basis, to oxidize substrates whose potential does not exceed $+1.14 \text{ V vs. SCE}$ and to reduce others whose potential is as low as -0.52 V

vs. SCE. No relevant quenching mechanism has been observed upon addition of *p*-chlorobenzaldehyde (**1a**, up to ca. 0.06 M , see Fig. S10†), as expected by its low reduction potential ($E_{\text{pc}} = -1.82 \text{ V vs. SCE}$, irreversible electron transfer process).¹¹ On the other hand, quenching processes have been observed for the two $[\text{Ti}(\text{IV})]$ complexes (**3** and **13**) and Hantzsch's ester **6** in air-equilibrated solutions, with compound **6** displaying the highest quenching constant ($k_{\text{q}} = 1.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$; see Fig. S11–S13†). By taking into account the concentrations used for the photocatalytic reaction, comparison between contributions of all substrates to the quenching efficiencies indicates that **6** is the most efficient quencher with a quenching efficiency of ca. 67% compared to ca. 3% in the case of the $\text{Ti}(\text{IV})$ complexes (see Fig. S14†). **6** can act as an efficient reductant of the dye's excited state ($E_0(6^{+}/6) = 1.0 \text{ V vs. SCE}$),¹⁸ leading to the formation of radical 4^+ , which is able, in a second stage, to reduce the $\text{Ti}(\text{IV})$ complexes and ultimately triggering the redox activity of the titanium centre towards aldehydes (Fig. 3A). Indeed, $\text{Ti}(\text{IV})$ species are characterized by the following reduction potentials: ca. -0.8 V vs. SCE for **3** in CH_2Cl_2 ;²⁵ ca. -0.6 V vs. SCE for **11** in CH_2Cl_2 ,^{28a} (see Fig. S16†), compatible with the reduction potential $E_0(4^+/4^*) = -0.82 \text{ V vs. SCE}$.

We can now compare the above-mentioned photochemical mechanism upon orange light excitation (Fig. 3A) with the one responsible for the photoreaction in the presence of photocatalysts **7–12** upon blue light excitation (Fig. 3B and Table 1, entries 5–9). In the latter case, the excited state of the photocatalyst is reductively quenched by Hantzsch's ester **6** and its reduced form can reduce the aldehyde activated by the oxidized species 6^{+} , as previously reported in the literature.²⁶ Therefore, the titanium complex is not involved in the catalytic mechanism (Table 1, entry 9) and the reaction does not show any stereoselectivity.

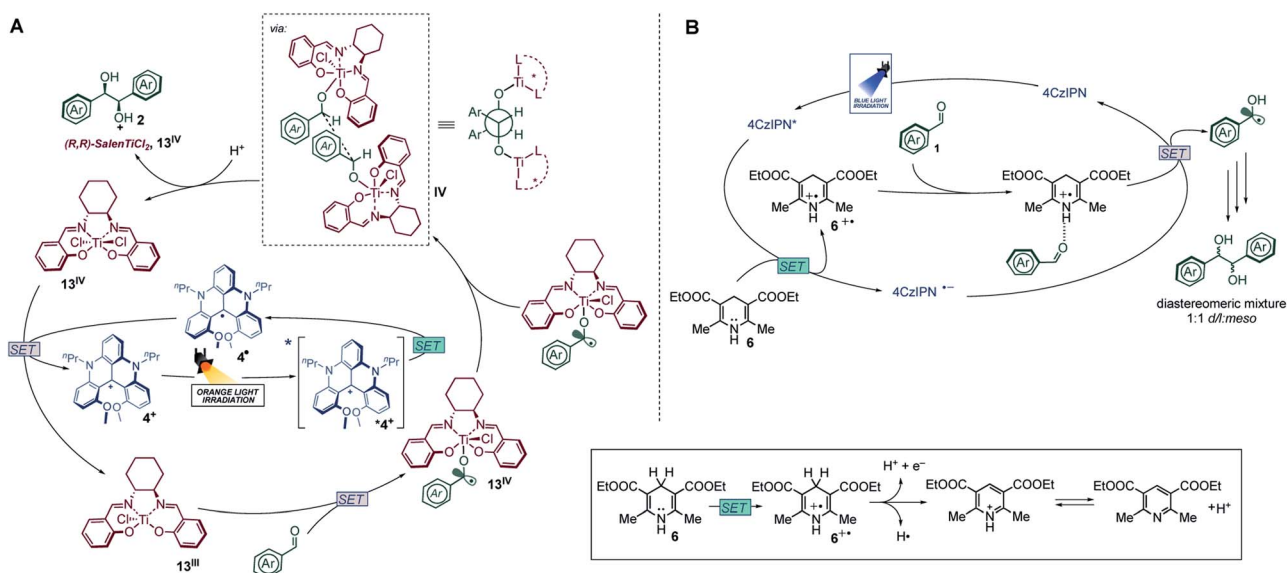


Fig. 3 Mechanistic proposal for the photoredox pinacol coupling catalyzed by 4^+ in the presence of titanium complexes (A) and by TADF dye **7** (B).

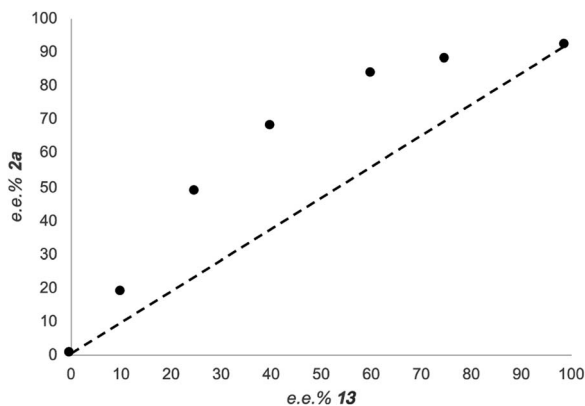


Fig. 4 Enantiomeric excess of the product **2a** vs. enantiomeric excess of **13** (see ESI† for the reaction setup and conditions).

In the case of the carbenium photocatalyst **4**⁺, the first photochemical event is again the reductive quenching by **6**, but the reduced photocatalyst **4**[•] can reduce only the titanium complex and not the aldehyde, giving a high stereocontrol (Fig. 3A). The stereoselective process involves the coupling of two ketyl radicals mediated by two molecules of Ti(Salen). In Fig. 3A we have depicted the diastereoselective/enantioselective step suggesting the encounter of two ketyl radicals. Based on sterical reasons, the approach in which the oxygen and phenyl substituent are in *anti*-positions is the most favourable, but it was not considered as it would lead to the meso product. Formation of *D/L* products could be rationalized by a transition state in which the two aryl groups are in a *gauche* relationship, and the titanium complexes are in the *anti*-position.³⁵

As pointed out in a recent calculation carried out by Streuff³⁶ on the reaction of carbonyl compounds with nitrile, the radical-radical coupling is the favoured pathway and, as far as the relative position of the titanium complex (Cp₂TiCl) coordinated fragment is concerned, the *anti*-coordination of the titanium is favoured from the energetic point of view. We assume that this coordination is favourable also in the case of pinacol coupling due to the positive non-linear effect (two molecules of titanium are involved in the stereoselective process). This led to the depicted transition states with *anti*-titanium and *gauche* configurations for the phenyl.

Since many stereoselective protocols involving two M(Salen) complexes (where M is either Co, Cr or Ti) usually display non-linear effects,³⁷ due to cooperative bimetallic mechanisms,³⁸ we have conducted a non-linear effect study by preparing the enantiomerically pure (*R,R*)- and (*S,S*)-SalenTiCl₂ complexes, and using different ratios of the two complexes to promote the reaction. The result of the study is depicted in Fig. 4. Clearly, a non-linear effect is registered in our reaction. Since Ti(III) complexes are involved in associative or dissociative equilibria (in the case of Cp₂TiCl₂, the loss of the chloride ligand with the formation of the corresponding cationic complex),^{26,39} the effective concentration of active titanium species can be hardly estimated.⁴⁰ Although it is difficult to attribute the suitable model to fit the data reported in Fig. 4, the best fitting model to

describe the observed curve is (ML)₂, indicating a cooperative role played by two Ti(Salen) complexes in the enantio-determining step.⁴¹

Conclusions

In conclusion, we have described an effective photoredox diastereo- and enantioselective pinacol coupling mediated by titanium complexes. The application of a red-absorbing organic dye, readily available and stable under the reaction conditions, is crucial to obtain excellent yields and avoid the use of stoichiometric amounts of metals as the reductants. The use of orange light in combination with this dimethoxyquinacridinium organic dye **4**⁺ allows the stereoselective coupling of aldehydes mediated by titanium, avoiding undesired processes lacking stereocontrol. The enantioselective process is mediated by a simply prepared Ti(Salen) complex, and good enantiomeric excesses are obtained. These results open new directions and possibilities to many stereoselective photoredox reactions promoted by titanium or other metals with low reduction potentials. In addition, titanium complexed ketyl radicals generated under these conditions could be used in different types of couplings. These directions will be subjected to further investigations in our laboratory.

Author contributions

P. G. C. and A. G. conceived the study. Photoredox reactions and preparation of chiral SalenTiCl₂ were carried out by F. P., F. C., G. M., and S. P. The latter three authors contributed equally to the experimental studies. Photophysical analysis and interpretation of photophysical data were carried out by A. F., P. C. and G. B. The manuscript was written with the contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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