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A Dual Photoredox- and Cp_2TiCl_2 -Catalyzed Approach for the Direct Access to α -Vinyl- β -hydroxy Esters

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For the first time, a dual photoredox- and titanocene-catalyzed methodology for the regioselective access to α -vinyl- β -hydroxy esters towards aldehyde allylation with 4-bromobut-2-enoate is reported. The protocol is based on the Barbier-type properties of the inexpensive and available Cp_2TiCl_2 in catalytic amount (5 mol%). The developed mild reaction conditions gave access to a library of differently functionalized α -vinyl- β -hydroxy esters in moderate diastereoselectivity, employing the commercially available ethyl 4-bromobut-2-enoate and both aromatic and aliphatic aldehydes. The reaction was realized under visible light irradiation, in the presence of an organophotocatalyst (3DPA-

FIPN, 2 mol%) combined with Hantzsch's ester as the sacrificial reductant. In contrast to other Barbier-type reactions employing ethyl 4-bromobut-2-enoate, the photoredox system ensures a better regioselectivity. Moreover, the use of preformed organometallic nucleophilic species (e.g., dienolborinates), and the need of metal reductants or stoichiometric amount of transition metals in low oxidation state for Barbier-type reactions, is avoided. To support the experimental evidence, a detailed photophysical study shed light on the mechanism of the reaction.

Introduction

The development of new catalytic methodologies concerning the generation of transient nucleophilic organometallic reagents for the realization of multi-decorated molecular scaffolds represents a continuously growing research topic in organic synthesis.^[1] Carbonyl compounds (*i. e.*, aldehydes, ketones, and imines) due to their electrophilic nature, are extensively employed as ideal counterparts for the development of new reactions designed both for the formation of new C–C bonds and consecutive stereocenters.^[2] In this scenario, α -vinyl- β -hydroxy esters, are a class of compounds exhibiting high potential from a synthetic point of view and have found

applications, not only for the synthesis of natural products, but also as synthons for pharmacologically active lactones.^[3] These molecular frameworks are also quite useful as they contain many functional groups such as: i) a secondary hydroxyl group that allows further functionalizations, ii) an electrophilic ester group, iii) an enolizable α -position and, iv) an unsubstituted and unconjugated β - γ -alkene (Figure 1.1).

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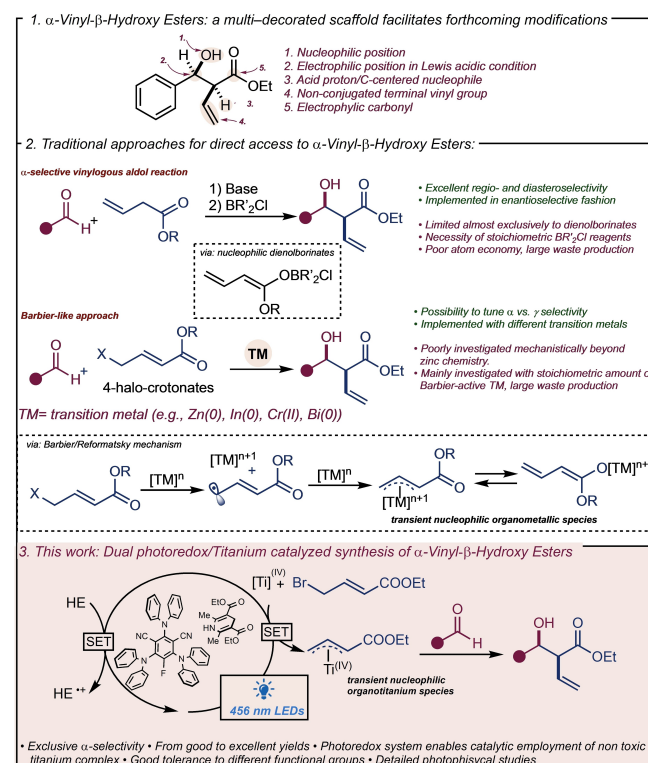


Figure 1. Approaches to α -vinyl, β -hydroxy esters.

Despite the several attractive points, a careful study for a diastereo- and regio-selective catalytic approach for the synthesis of this class of compounds lacks or has been addressed only occasionally quite recently. At the present state of the art, apart from a few seldom examples, the realization of these products has been faced mainly through two approaches: a) α -selective vinylogous aldol/Mukaiyama reaction in presence of suitable dienolates; b) Barbier-type reactions combined with 4-halo-crotonates for the generation of transient organometallic nucleophiles (Figure 1.2). The vinylogous approach^[4] consists in the transmission of the electronic effects of a functional group in a molecule to a distal position through interposed conjugated multiple bonds.^[5] According to this well-established principle, the introduction of a double bond in silyl enol ethers allowed the establishment of the vinylogous Mukaiyama aldol reaction.^[6] The transformation gives access to the exclusive formation of the γ -aldol product. Enantioselective variants of vinylogous Mukaiyama reactions were also reported.^[6,7] Unfortunately, the exclusive γ -selectivity partially fades moving from silicon-based dienolates to other nucleophilic metal systems.^[8] Although the vinylogous Mukaiyama reactions are selective for the γ -alkylated adducts, other nucleophilic metal systems display a competition between α - vs γ -selectivity together with poor diastereoselectivity. In 2013 Ramachandran and co-workers presented a possible solution for these drawbacks, describing the preparation of α -vinyl- β -hydroxy esters using preformed dienolborinates with excellent regio- and diastereo-selectivity.^[9] The key element of the methodology could be attributed to the well-known ability of boron enolates to react through a Zimmerman-Traxler transition state, enabling the exclusive α -selectivity.^[10] The report, although it represents a cornerstone for the synthesis of diastereo-defined α -vinyl- β -hydroxy esters and for enantioselective variants of the reaction,^[11] remains limited to the use of a stoichiometric amount of boron-based reagents.

The approach towards α -vinyl- β -hydroxy esters through Barbier-type methodologies is also addressed in literature as *α -selective vinylogous Reformatsky reaction*,^[12] and it is a quite-known topic, tracing back to the second half of the last century.^[13] Early examples in this regard involved the use of stoichiometric quantities of Zn(0) and 4-halo-crotonates or preformed zinc-dienolates obtained through a well-known Barbier/Reformatsky mechanism (Figure 1.2).^[14] The reactivity of these nucleophilic organometallic reagents was studied both in the presence of simple carbonyl compounds (*e.g.*, aldehydes and ketones) and with unsaturated α,β -carbonyls. The polarity of the reaction medium was identified to influence the α - vs γ -competition and, in the case of unsaturated carbonyls, the 1,2 vs. the 1,4 addition.^[15] Interestingly, beyond the well-established stoichiometric zinc chemistry, the development of similar methodologies with different metals was poorly investigated.^[16] Stoichiometric amounts of Sn(0) and In(0) metals were studied in aqueous conditions with 4-halocrotonates, in the presence of few selected aldehydes.^[17] However, Goldup and coworkers, employed this methodology with a stoichiometric amount of indium for an highly diastereoselective transformation in the total synthesis of viridiumfungin derivatives.^[18] Additionally,

Bi(0) was also applied in the presence of 4-halo-crotonates with aromatic aldehyde for the diastereoselective allylation in good yields, via a Zimmerman-Traxler transition state.^[19] Analogously, Cr(II) chemistry, has been applied in stoichiometric fashion for similar transformations also in the presence of 4-halo-crotonic acids with both aldehydes and ketones.^[20]

At the present time, the α -selective vinylogous Reformatsky-type reaction not only remains a greatly underdeveloped transformation, but, with a few exceptions, the use catalytic amounts of active metal complexes is not fully realized.^[21]

In the last decade dual metallaphotoredox catalysis, that is the combination of metal-promoted processes with photoredox cycles has reached an extraordinary level of advancement. The synergistic use of metal catalysis in combination with photoredox catalysis allowed the development of innovative, practical, and conceptually new strategies in organic synthesis.^[22] In recent years our and other laboratories were engaged in the development of photoredox methodologies for the preparation of transient nucleophilic organometallic reagents.^[23] The presence of catalytic amounts of nickel^[24] and titanium^[25,26] complexes allowed selective and mild C–C bond formation with carbonyl electrophiles.

To further expand our repertoire of methods, we tackled the underdeveloped synthesis of α -vinyl- β -hydroxy esters, also considering previous studies in titanium mediated catalytic Reformatsky reactions.^[27] Herein, we present for the first time a dual photoredox and titanium^[28] catalyzed synthesis of α -vinyl- β -hydroxy esters. We have employed in our optimized conditions the organophotocatalyst 3DPAFIPN (2,4,6-tris(diphenylamino)-5-fluoroisophthalonitrile),^[29] and stoichiometric amount of Hantzsch's ester as the sacrificial organic reductant. A valid, reproducible, highly-regioselective and moderately-diastereoselective dual photoredox protocol, with the commercially available ethyl 4-bromobut-2-enoate is here presented (Figure 1.3). The mild reaction conditions developed were found suitable in presence of different functional groups decorating the aldehydes tested, and the need of over-stoichiometric amount of preformed metal-based nucleophiles was avoided.

Results and Discussion

The salient results that brought us to establish a valid protocol for the synthesis of α -vinyl- β -hydroxy esters are summarized in the Table 1. Among the several photocatalysts that could trigger the desired methodology, we avoided the use of metal photocatalysts based on iridium and ruthenium considering their cost and sustainability. Accordingly, we mainly focused our attention on organophotocatalysts based on carbazole and diphenylamine substituted cyanoarenes exhibiting the peculiar photophysical property of TADF (Thermally Activated Delayed Fluorescence).^[30] This class of organic dyes is attracting more and more interest in dual metallaphotoredox catalysis,^[22b] thanks to the possibility of tuning their photoredox properties modifying the electronic character of their substituents.

Table 1. Optimization of the reaction conditions.

Entry ^[a]	Deviation from standard conditions	d.r. ^[b]	Conversion [%] ^[c]
1	None	3.7:1	> 97(91) ^[d,e]
2	No photocatalyst	–	No reaction
3	No light	–	No reaction
4	No Cp ₂ TiCl ₂	–	99(0) ^[f]
5	No Hantzsch's ester (HE)	–	No reaction
6	5 mol% of 3DPAFIPN, 10 mol% of Cp ₂ TiCl ₂ , [1 a] = 0.05 M	2.8:1	98(91) ^[e]
7	1.8 equiv. of Hantzsch's ester (HE)	3.2:1	88(83)
8 ^[g]	1.5 equiv. of Hantzsch's ester (HE)	3.2:1	88(85)
9	5 mol% of 3DPAFIPN	3.2:1	> 98(90) ^[d]
10 ^[g]	[1 a] = 0.1 M	2.9:1	99 (69) ^[h]
11 ^[g]	[1 a] = 0.2 M	2.8:1	75(0) ^[f]
12 ^[g]	5 h irradiation time, 0 °C	3.7:1	89(84) ^[e]
13 ^[g]	6 h irradiation time	3.7:1	99(91) ^[e]
14	3CZCIIPN instead of 3DPAFIPN	3.0:1	93(87) ^[e]
15	4CZIPN instead of 3DPAFIPN	3.0:1	93(88) ^[e]
16	Ru(bpy) ₃ Cl ₂ ^[i] instead of 3DPAFIPN	–	No reaction
17	Et ₂ O instead of THF	–	99(0) ^[f]
18 ^[g]	Toluene instead of THF	3.0:1	88(80) ^[e]
19 ^[g]	CH ₂ Cl ₂ instead of THF	2.0:1	50(32) ^[e]
20 ^[g]	MeCN instead of THF	2.8:1	71(63) ^[e]
21	TiCl ₄ instead of Cp ₂ TiCl ₂	–	99(0) ^[f]

[a] Reactions performed on 0.1 mmol scale. [b] d.r.s reported as *syn:anti* and determined by ¹H-NMR analysis by integration of the vinylic protons at H_{syn} = 5.88 ppm and H_{anti} = 5.62 ppm. [c] Determined by ¹H-NMR. [d] Reaction performed on 0.2 mmol scale. [e] The value in parenthesis is the isolated yield (chromatographic purification). [f] No product detected. Pinacolization of 1 a as major byproduct. [g] Reaction conditions based on our previous results: 5 mol% of 3DPAFIPN, 10 mol% of Cp₂TiCl₂, [1 a] = 0.05 M, HE 2 equiv. [h] 3 a formed as major product. Non-negligible undefined parasitic by products detected. [i] 1 mol% employed.

We began our investigation selecting 4-chlorobenzaldehyde (1 a) as model substrate and the commercially available ethyl 4-bromobut-2-enoate (2 a) as pro-nucleophile. We started the optimization process, based on the conditions employed for the development of dual photoredox and titanium-mediated propargylation and allylation reactions.^[26a,b] We were pleased to observe a full conversion of 1 a in presence of 4-bromobut-2-enoate (Table 1, Entry 6).

The use of 2 a in the reaction did not prevent the efficient reduction of Cp₂TiCl₂ (10 mol%) to Cp₂TiCl, employing 3DPA-

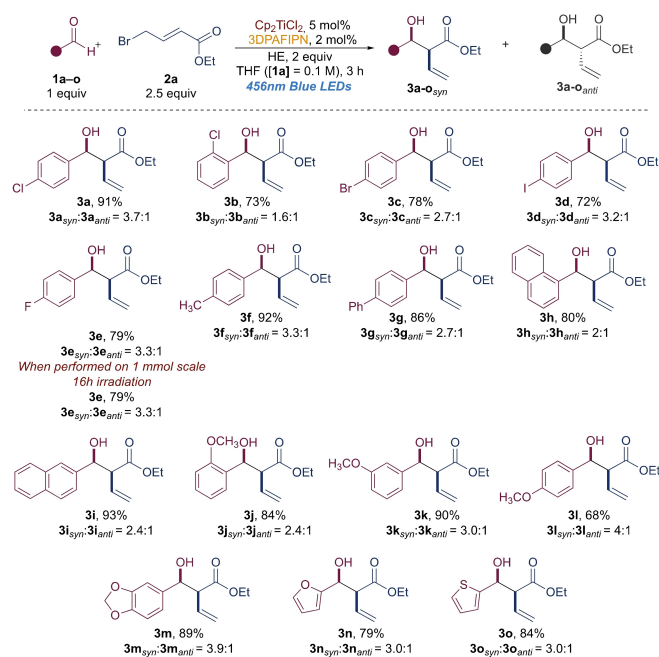
FIPN (5 mol%) and the Hantzsch's ester (2 equiv.) as stoichiometric organic reductant under blue light irradiation. The photoredox-generated RajanBabu reagent (Cp₂TiCl) proved capable to promote the formation of the desired α -vinyl- β -hydroxy ester (3 a) in moderate diastereoselectivity with the exclusive α -selectivity. Considering the positive preliminary results, a series of control experiments were carried out to establish the importance of all variables in our protocol. (Table 1, Entry 2–5) No conversion and no consumption of starting material 1 a were detected performing the reaction in the absence of 3DPAFIPN, Hantzsch's ester or light radiation. On the contrary, in the absence of Cp₂TiCl₂, a complete non-diastereoselective pinacolization of 1 a was observed.^[26d] The underlying reasoning for the outcome can be explained by the ability of 3DPAFIPN, in its excited state, to oxidize the Hantzsch's ester to HE^{•+} (E_(3DPAFIPN^{*}/3DPAFIPN^{•-}) = 1.1 V vs SCE; E_(HE^{•+}/HE) = 1.0 V vs SCE). This latter, proceeding in its oxidative pathway, is converted into its corresponding pyridinium salt. The concurrently formed 3DPAFIPN^{•-} cannot directly reduce an aromatic aldehyde generating a ketyl radical and restoring the photocatalyst in its pristine oxidation state (E_(3DPAFIPN/3DPAFIPN^{•-}) = –1.6 V vs SCE; E_(PhCHO/PhCHO^{•-}) < –1.9 V vs SCE). The reduction of 1 a and its subsequent pinacolization, is presumably achieved by activation of the carbonyl by the so-formed pyridinium salt. This latter, acting as Brønsted acid, coordinates the aldehyde moving to less negative value its reduction potential.

To our delight, the reaction could be promoted by different organophotocatalysts belonging to the same class of 3DPAFIPN. Commercially available, or easily accessible, 4CZIPN and 3CZCIIPN led to the formation of the desired product 3 a with a slight decreased conversion and without affecting the diastereoselectivity (Table 1, Entry 14–15). Noteworthy, Ru(bpy)₃Cl₂, although suitable for the photoinduced reduction of Cp₂TiCl₂, was found inadequate for the protocol (E_{(Ru(III)/Ru(II)^{*})} = –0.9 V vs SCE; E_{(Ti(IV)/Ti(III))} = –0.75 V vs SCE; Table 1, Entry 16).^[22,26] Regarding the reaction solvent for the transformation, we have briefly investigated the suitability of the protocol in various solvents. While THF, provided the best results in terms of both yield and diastereoselectivity, Et₂O was found poorly effective, due to the limited solubility of Cp₂TiCl₂ (Table 1, Entry 17). Commonly employed organic solvents for dual metallaphotoredox protocols, such as, acetonitrile, toluene, and CH₂Cl₂ lead to a severe drop in reactivity and diastereoselectivity (Table 1, Entry 18–20). Regarding the employment of other titanium complexes, although the use TiCl₄ in photoredox reaction was recently reported by Kanai,^[31] in our conditions only a non-diastereoselective pinacolization of 1 a was observed (Table 1, Entry 18–21). Finally, altering the reaction temperature was not influential for the stereochemical outcome of the reaction, even by lowering the temperature to 0 °C (Table 1, Entry 12). We were able to reduce the amount of Cp₂TiCl₂ and 3DPAFIPN to 5 mol% and 2 mol%, respectively (Table 1, Entry 1). Remarkably, under these conditions it was possible to decrease the irradiation time to 3 h. In our previous reported protocols dealing with Cp₂TiCl₂, the reaction was carried out under diluted conditions due to the absorption properties of the red titanium complex (concentration was [1 a] = 0.05 M). However, in the presented reaction,

decreasing the amount of transition metal complex, it was possible to use slightly more concentrate conditions ($[1a] = 0.1$ M). On the other hand, 2 equivalents of Hantzsch's ester remained mandatory to maximize the yields (Table 1, Entry 7,8).

After the systematic evaluation of all reaction parameters, in the optimized conditions, the synthesis of **3a** was performed in 91% isolated yield after only 3 h of blue light irradiation. The reaction exhibits an exclusive regioselectivity promoting the unique formation of the α -alkylation adducts. No trace of other regioisomer was observed by NMR analysis of crude reaction mixture. **3a** was obtained with a moderate diastereoselectivity ($3a_{syn}:3a_{anti} = 3.7:1$) in favor of the *syn* diastereoisomer, suggesting a plausible mechanism involving a Zimmerman-Traxler transition state.^[11,26a]

Having identified the optimal reaction conditions, the generality of the presented reaction was investigated with different aromatic and aliphatic aldehydes. The reaction was found effective with several differently substituted aromatic and heteroaromatic aldehydes (Scheme 1). In all cases, from excellent to good yields in favor of the *syn* diastereoisomer were obtained. ¹H-NMR conversion was always above 90% after 3 hours of irradiation for all the substrates. The small discrepancy observed with respect to the isolated yield mainly depended on detectable traces (*ca.* 5–10%) of non-diastereoselective pinacolization of the starting material. Moreover, in all cases the presence of the γ -alkylation product was not detected. While exploring the survey of substrates, we observed that the diastereoselective outcome of the reaction was strongly influenced both by the steric and the electronic properties of the tested aldehydes. 2-chlorobenzaldehyde (**1b**) and 2-methoxybenzaldehyde (**1j**), were effective in the reaction conditions and the desired products could be obtained in good

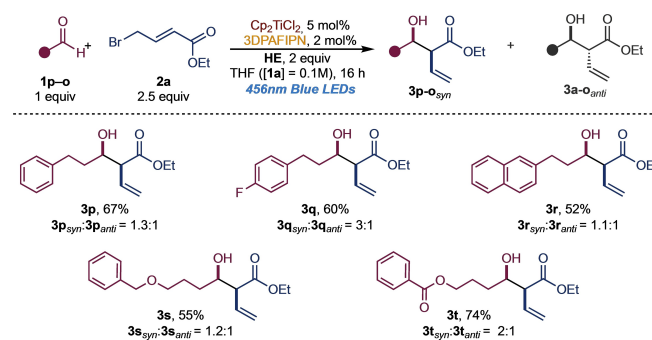


Scheme 1. Reaction scope with aromatic aldehydes. Isolated yields are reported.

yields. However, the presence of a substituent proximal to the carbonyl group resulted in a severe drop in diastereoselectivity ($3b_{syn}:3b_{anti} = 1.6:1$ and $3j_{syn}:3j_{anti} = 2.4:1$).

At the same time, the presence of electron donating groups in other positions of the aromatic ring (*i.e.* **1l**) has a beneficial effect in terms of diastereoselectivity ($3l_{syn}:3l_{anti} = 4.0:1$). Probably, this result is caused by the high electronic density characterizing the aldehydes which positively affects the coordination on titanium of it in the cyclic transition state. On the other hand, neither electronic nor steric effects hampered the reactivity of the reported protocol. Electron-neutral aromatic aldehydes (**1f-i**), as well as electron deficient 4-bromobenzaldehyde (**1c**), 4-iodobenzaldehyde (**1d**) and 4-fluorobenzaldehyde (**1e**) were found particularly suitable for the presented methodology leading to the formation of the corresponding α -vinyl- β -hydroxy esters with a yield range between 78% and 93%. Substrate **1e**, was also selected to test the scalability of the method. To our delight, extending the irradiation time from 3 to 16 hours it was possible to reproduce the results on 1 mmol scale. Remarkably, while other aldehydes bearing electron-donating groups (**1j**, **1k**, **1m**) afforded the desired products with good yield, in the presence of the electron rich **1l** we observed a slight decrease of the reactivity. Moreover, although during the reaction the oxidation of Hantzsch's ester generates a strong Brønsted acid,^[26a] sensitive substrates such as **1n** were found reactive in the reaction conditions and no presence of by-products was detected.^[32] When we turned our attention towards aliphatic aldehydes, we selected few examples to test the applicability of the protocol and a moderate reactivity was found (Scheme 2). Noteworthy, due to the general reduced reactivity of aliphatic aldehydes with organometallic reagents that reacts coordinating the carbonyl group, the reaction time was increased to 16 hours, while keeping constant the other reaction parameters.

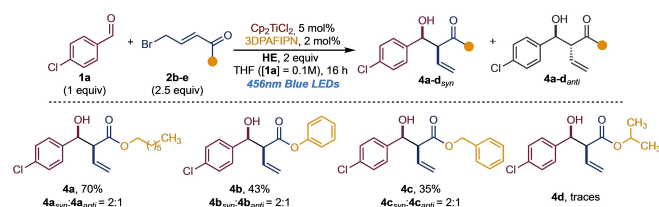
For the same reason, a lower diastereomeric control was evidenced. Since aliphatic aldehydes present a more negative reduction potential than their aromatic counterparts, the lowered yields observed in the above-mentioned cases do not depend on pinacolization processes.^[27] On the contrary, from the analysis of crude reaction mixture, the main parasitic pathway that determines the consumption of the aliphatic aldehyde was imputed to aldol auto-condensation processes.



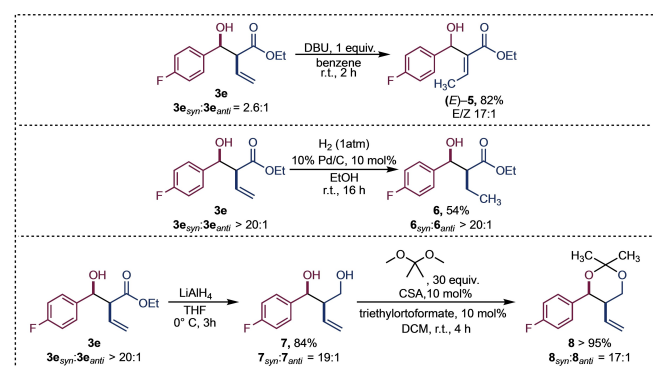
Scheme 2. Reaction scope with aliphatic aldehydes. Isolated yields are reported.

Probably, the presence of acid pyridinium salt, derived from the oxidation of the Hantzsch's ester, promotes this undesired process facilitating the formation of enols. Hydrocinnamic aldehyde derivatives (**1 p-r**) were suitable for the proposed protocol. Similarly, aliphatic substrates bearing differently protected hydroxy-groups (**1 s-t**) were tolerated in the reaction. Furthermore, our protocol resulted suitable in presence of secondary aliphatic aldehydes (cyclohexylcarboxaldehyde) and linear unsubstituted aldehydes. However, in these latter cases, issues related to the purification of products were encountered (see SI for further details). To evaluate the role of the ester moiety in the reaction outcome, the methodology was extended towards non-commercially available bromocrotonates (Scheme 3). However, moving from ethyl ester derivatives resulted in a reduced reactivity and the reaction conditions were slightly modified extending the irradiation time. Hindrance of the ester group was found to play a crucial role in the reaction outcome. While a longer alkyl chain results in a slight decrease in yield (**4 a**), the use of a phenyl or benzyl ester produces a reactivity drop. Consequently, a total shutdown of the catalytic system was found using the corresponding isopropyl ester (**2 e**). Other pro-nucleophiles were further explored but unfortunately, only 4-halo-crotonates were found reactive. Bromo unsaturated ketones or amides were not reactive under the reported reaction conditions (see SI for further details).

Once the generality of the protocol has been explored, we have briefly investigated the reactivity and the synthetic utility of the presented products performing some further functionalization, as depicted in Scheme 4. Firstly, from a diastereoisomeric mixture $3e_{syn}:3e_{anti}=2.6:1$ the isomerization of terminal double bond was performed. Employing a stoichiometric



Scheme 3. Reactions scope with non-commercially 4-bromo-crotonates. Isolated yields are reported.



Scheme 4. Functionalization of the derivatives.

amount of 1,5-diazabicyclo(5.4.0)undec-7-ene (DBU) in benzene at room temperature, the thermodynamically more favored α,β -unsaturated ester **5** was obtained in 82 % yield with preferred *E*-selectivity. Moreover, starting from diastereodefined **3 e** ($3e_{syn}:3e_{anti} > 20:1$), the reduction of the double bond was accomplished in diastereospecific fashion and in moderate yield employing a catalytic amount of palladium on carbon (10 mol% w/w) under hydrogen atmosphere (1 atm).

Lastly, to highlight the synthetic utility of the electron withdrawing ester moiety, **3 e** ($3e_{syn}:3e_{anti} > 20:1$) this was firstly reduced in presence of lithium aluminum hydride leading to the formation of the corresponding 2-vinyl-1,3-diol **7**. This latter was further treated in presence of an excess of 2,2-dimethoxypropane and a catalytic amount of camphorsulfonic acid (10 mol%), giving access to *syn*-4-(4-fluorophenyl)-2,2-dimethyl-5-vinyl-1,3-dioxane (**8**) in quantitative yield.

Mechanistic photochemical studies

To clarify the possible mechanism of the reaction, we performed a careful photophysical investigation. As outlined in some recent reports from our group,^[24b,26] 3DPAFIPN is an ideal candidate as a photocatalyst in the presence of HE and Cp_2TiCl_2 , due to a proper balance between photophysical and redox properties that allow i) efficient visible-light excitation ($\lambda_{onset} \approx 470$ nm, in THF), ii) a long-lasting excited state due to its delayed fluorescence to favor its diffusional quenching ($\tau = 110$ μs , in deaerated THF), and iii) thermodynamically favorable SET both towards the Ti(IV) species and the sacrificial donor HE ($E_{(Ti(IV)/Ti(III))} = -0.75$ V vs SCE; $E_{(HE\bullet+/+HE)} = 1.0$ V vs SCE),^{[33][34]} Analyses of the luminescence quenching of the visible light-activated 3DPAFIPN by the reactants present in the reaction mixture were carried out by employing the Stern-Volmer kinetics in order to trace a possible mechanistic picture. It is important to underline that, in the presence of HE at concentrations close to its solubility limit in THF (0.1 M), 3DPAFIPN is considered to quantitatively form with HE a photoactive complex (3DPAFIPN•HE), as previously demonstrated by a combined photophysical and computational study (Figure 2).^[24b]

The so-formed complex still possesses suitable redox potentials to provide efficient photo-induced electron transfer to substrates involved in the reaction: specifically, a quenching constant k_q equal to 2.1×10^8 $M^{-1} s^{-1}$ has been determined in the presence of excess HE, which is able to dynamically quench the excited state of 3DPAFIPN•HE at concentrations higher than 130 μM .^[24b] Along these lines, Cp_2TiCl_2 can also determine an efficient quenching of the luminescence lifetime of the complex, with a $k_q = 1.1 \times 10^9$ $M^{-1} s^{-1}$ (see figure S4, supporting information). On the other hand, aldehyde **1 a** and bromide **2 a** do not significantly affect the luminescence lifetime ($k_q < 1.0 \times 10^6$ $M^{-1} s^{-1}$), pointing out that photo-induced electron transfer processes are not favored in the presence of increasing amount of these substrates (see figure S5, supporting information).^[24b] By taking into account the difference in concentration between Cp_2TiCl_2 and HE in the reaction mixture, the corresponding quenching efficiency is higher for HE (20%

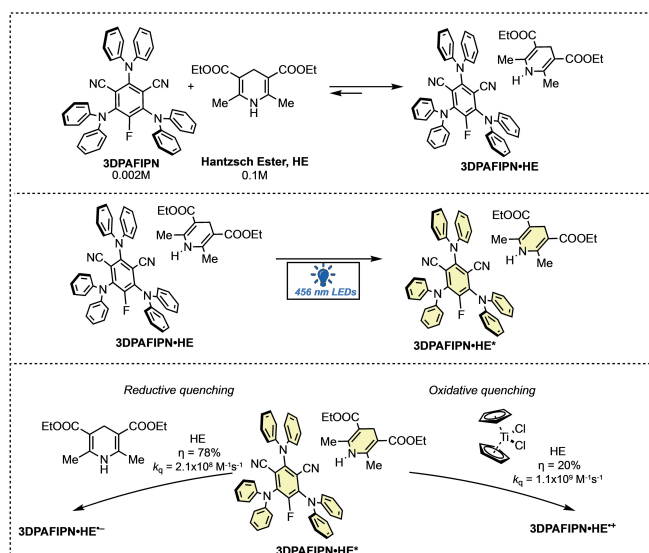


Figure 2. Photophysical behavior of 3DPAFIPN and HE under the reaction conditions.

and 78%, respectively; see supporting information), indicating that the first SET is most probably the one that leads to the reduction of 3DPAFIPN·HE* and concomitant oxidation of HE to HE*⁺ (Figure 2). The so-formed 3DPAFIPN·HE*⁻ is a strong reductant ($E_{\text{red}} = -1.63$ V vs. SCE)^[23b] and its thus able to restore the pristine 3DPAFIPN·HE undergoing to a single electron transfer in the presence of Cp₂TiCl₂, closing the photocatalytic cycle. We believe that the so formed Cp₂TiCl₂^[28c] in the presence

of the pro-nucleophile 4-bromobut-2-enoate (2), is involved in a Barbier/Reformatsky-type mechanism leading to the formation of the transient nucleophilic titanium-organometallic species. Since a Barbier/Reformatsky-type mechanism formally requires two molecules of Barbier-active transition metal for the generation of one transient nucleophilic organometallic reagent, we cannot exclude a possible role played by the strong reductant HE*⁺ in further reductive events, leading to a short radical chain (Figure 3).^[26] Once formed the nucleophilic organometallic species can interact in the presence of the carbonyl compound (*i. e.*, 1 a) leading to the formation of the corresponding product, as titanium alcoholate.

The diastereoselective outcome, moreover, is attributable with a plausible Zimmerman-Traxler transition state. The release of the product and the re-generation of the active Cp₂TiCl₂ is most probably a consequence of the oxidative pathway of the Hantzsch's ester, that, upon the single electron oxidation evolves into the corresponding protonated pyridine that can act as the active scavenger of the product, preventing the use of further additives such as Pyridinium hydrochloride I or TMSCI.

Conclusions

In conclusion, we have reported a complete study for the dual photoredox and titanocene catalyzed synthesis of a quite extended library of α -vinyl- β -hydroxy esters. The use of a catalytic amount (5 mol%) of inexpensive and commercially available Cp₂TiCl₂ combined with the organic dye 3DPAFIPN

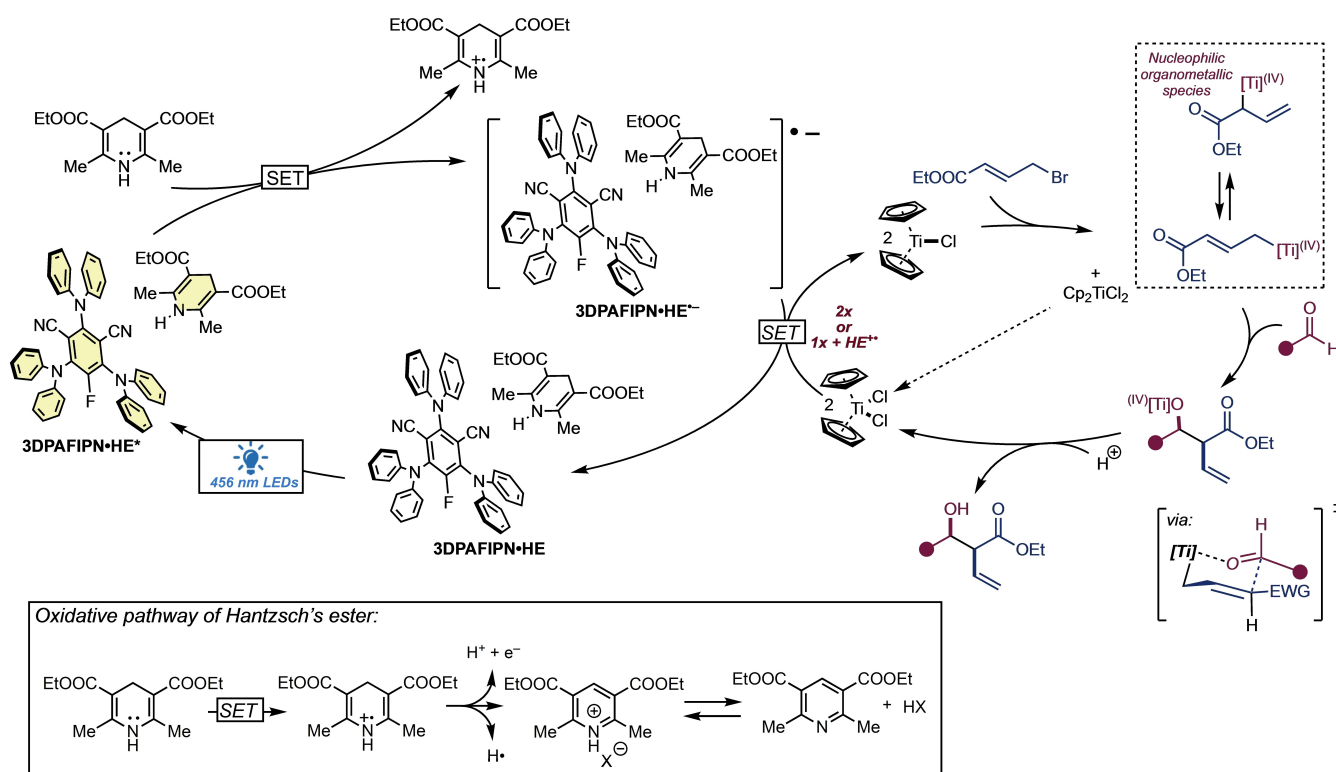


Figure 3. Proposed reaction mechanism.

(2 mol%) as the photocatalyst and Hantzsch's ester as sacrificial organic reductant under visible light irradiation afforded a rapid reaction with aromatic aldehydes (3 hours). In general, high yields, moderate diastereoselectivity in favor of *syn* diastereoisomer and exclusive regioselectivity in favor of the α -alkylation adducts were appreciated. Although aliphatic aldehydes were found less reactive and the diastereoselectivity was lower, for both aromatic and aliphatic aldehydes only one regioisomer was isolated. Moreover, a detailed photophysical investigation shed light on the mechanism of the reaction, highlighting the peculiar role played by the combination of 3DPAFIPN and the Hantzsch's ester. Further studies, directed towards a general Reformatsky reaction promoted by titanium or other metals are in progress in our laboratory.

Experimental Section

All the reactions were performed on 0.2 mmol scale, unless otherwise noted. A heat-gun dried 10 mL Schlenk tube, equipped with a Rotaflo stopcock, magnetic stirring bar and an argon supply tube, was first charged under argon with the substrate **1** if solid or not volatile (0.2 mmol), organic photocatalyst 3DPAFIPN (2 mol%, 0.004 mmol, 2.6 mg), Cp_2TiCl_2 (5 mol%, 0.01 mmol, 2.5 mg) and diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate Hantzsch's ester (2 equivalents, 0.4 mmol, 101 mg). THF (2 mL to obtain a 0.1 M substrate solution) was then added, and the reaction mixture was further subjected to a freeze-pump-thaw procedure (three cycles) and the vessel was refilled with argon. Then, ethyl 4-bromobut-2-enoate **2a** (0.5 mmol, 2.5 equiv., 97 mg, 69 μL) and the **1** (if volatile, 0.2 mmol) were added. The reaction was irradiated with Kessil® 456 nm LED lamp under vigorous stirring for the desired time (3 h for aromatic substrates **1a–o** or 16 h for aliphatic substrates **1p–t**). After that the reaction mixture was quenched with 2 M HCl (ca. 5 mL) and extracted with AcOEt (3 \times 10 mL). The reaction crude was analyzed by $^1\text{H-NMR}$ for the evaluation of the diastereomeric ratio. The NMR sample was carefully recovered, and the solvent was removed under reduced pressure. The title compounds were isolated by flash column chromatography (SiO_2). In most cases, unless otherwise noted, two consecutive separations were needed (1st Hexane/DCM, 2nd AcOEt/Hexane).

Supporting information

Additional references cited within the Supporting Information.^[24b,35–48]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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