

# Enantioselective C–P Bond Formation through C(*sp*<sup>3</sup>)–H Functionalization

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**Abstract:** An enantioselective C–P bond formation has been developed through a C(*sp*<sup>3</sup>)–H activation in an oxidation step followed by an organocatalyzed hydrophosphonylation protocol. The asymmetric organocatalytic Pudovik reaction has been achieved following a one-pot strategy, starting from different benzylic and allylic alcohols and dibenzyl phosphite, using MnO<sub>2</sub> as the oxidant and a chiral squaramide as organocatalyst. The scope of the reaction provides enantiomerically enriched  $\alpha$ -hydroxy phosphonates with yields from 40% to >95% and enantioselectivities from 64% to >99%. Furthermore, the use of this methodology has been demonstrated to form a tetrasubstituted carbon stereocenter, generating an acetophenone derivative *in situ*, using diphenyl phosphite. Therefore, this approach represents an asymmetric strategy for constructing chiral C–P bonds, which are of interest to the pharmaceutical industry.

**Keywords:** C–H activation; cascade; oxidation; Pudovik; one-pot

molecules. As a result, this tool has become one of the greatest milestones in organic synthesis, trying to emulate nature in its way of proceeding.<sup>[1]</sup> Nevertheless, it is well known that the strength of the C–H bond has limited its transformation for a long time to a few methods, such as free-radical halogenation, electrophilic aromatic substitution, and deprotonation of acidic C–H bonds, as the pioneering ones, using organometallic complexes or strong conditions and more sophisticated systems.<sup>[1,2]</sup> Over time, the usefulness of these strategies have allowed the C–H functionalization of increasingly complex backbones as key step in their preparation, using the advantages offered by metal-, enzymatic- and photo-catalysis, and succeeding where other synthetic methodologies had failed.<sup>[2]</sup>

Interestingly, among the diverse modes of C–H transformations, it is possible to find many examples of the introduction of versatile functional groups such as C–X bonds (for X: C, N, O, S, B and halogen) at both *sp*<sup>2</sup> and *sp*<sup>3</sup> centers.<sup>[2]</sup> However, its functionalization to C–P bonds has been considerably less explored, and the scarce examples reported in the literature work through free-radical activation using mainly transition metal catalysts.<sup>[3]</sup> Among them, the  $\alpha$ -C(*sp*<sup>3</sup>)–H activation involved in a phosphonylation reaction of *in situ* generated iminium species, for the formation of C–P bonds, has received more attention in recent years (Scheme 1, a),<sup>[3]</sup> than the analogous transformation of

Functionalization of inert or non-activated C–H bonds has been a powerful and challenging strategy for a long time, given the abundance of this bond in organic

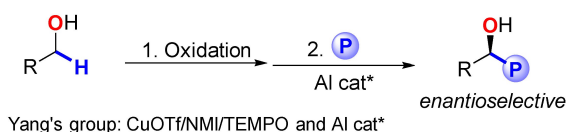
a) Previous studies of  $C(sp^3)\text{--}H$  activation adjacent to nitrogen<sup>[3]</sup>



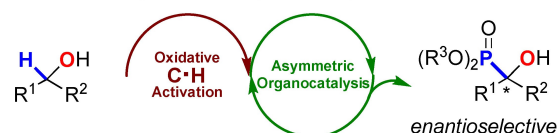
b) Previous studies of  $C(sp^3)\text{--}H$  activation adjacent to oxygen<sup>[4]</sup>



c) Previous work of  $C(sp^3)\text{--}H$  activation generating enantioselective  $C\text{--}P$  bond using a chiral metal-based catalyst<sup>[7]</sup>



d) This work:  $C(sp^3)\text{--}H$  activation generating enantioselective  $C\text{--}P$  bonds using a chiral organocatalyst



**Scheme 1.**  $C(sp^3)\text{--}H$  activation for the formation of  $C\text{--}P$  bonds.

$C(sp^3)\text{--}H$  bonds adjacent to an oxygen atom (Scheme 1, b).<sup>[4–6]</sup> Among these scarce examples, Tang and co-workers pioneered a copper-catalyzed  $C(sp^3)\text{--}H$  phosphonylation of alcohols and ethers using CuCl<sub>2</sub>/TBHP (*tert*-butyl hydroperoxide) as a catalyst and oxidant, with moderate to good yields of final  $\alpha$ -hydroxy phosphonates.<sup>[5]</sup> More recently, Chen, Huo and co-workers reported a photocatalyzed and additive-free visible-light-induced  $\alpha\text{-}C(sp^3)\text{--}H$  phosphinylation of unactivated ethers with moderate to good yields (Scheme 1, b).<sup>[6]</sup> Lately, Yang and coworkers reported the first asymmetric oxidation addition reaction for the synthesis of enantioenriched  $\alpha$ -hydroxy phosphonates using an aluminum-based catalyst (Scheme 1, c).<sup>[7]</sup> More interesting is the fact that none of the latter processes disclosed in Scheme 1 a), b) and c) imply an asymmetric organocatalytic transformation.

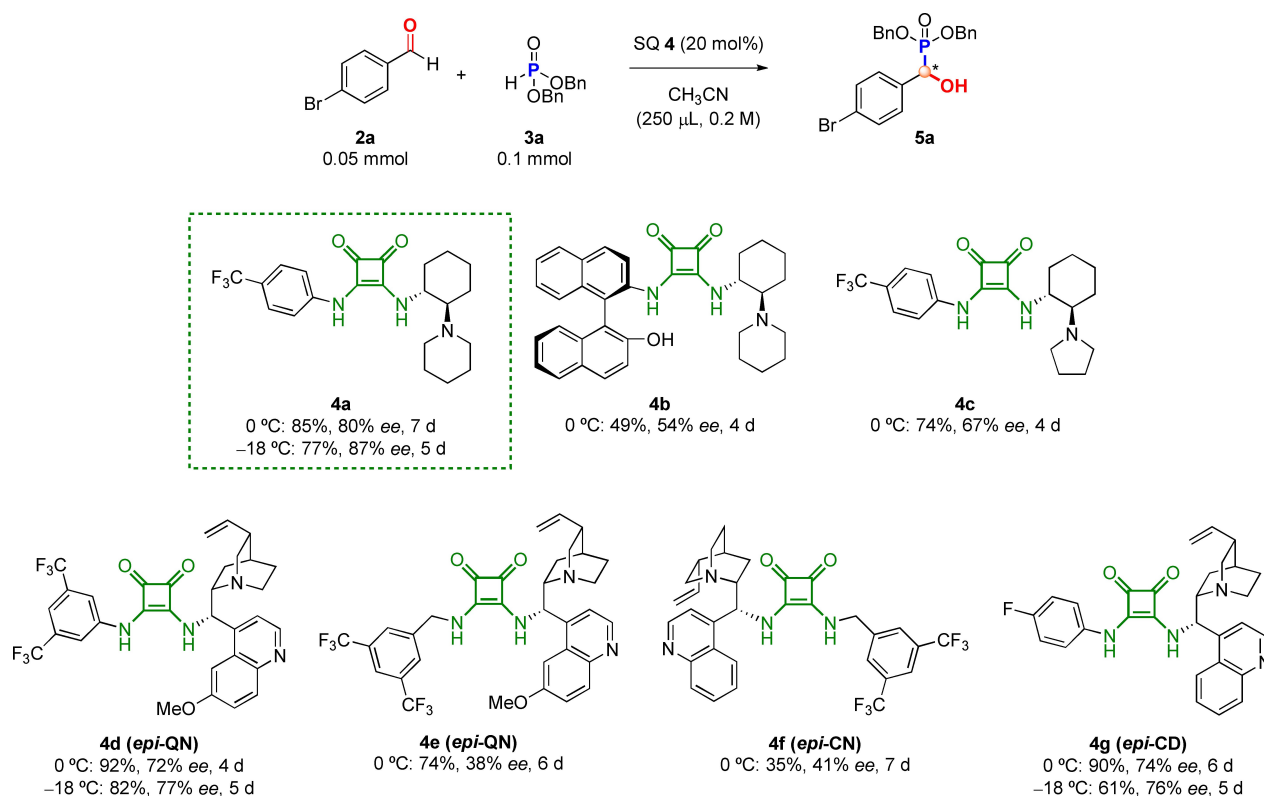
Furthermore, in all these examples, an oxidation process (through a cross-dehydrogenative coupling) represents an excellent opportunity to functionalize a specific  $C\text{--}H$  bond in a subsequent step.<sup>[8]</sup> However, to the best of our knowledge, the use of this approach

involving an asymmetric organocatalytic process has been overlooked so far in the literature (Scheme 1, d).

Due to the presence of  $C\text{--}P$  bonds in many biologically active compounds,<sup>[9]</sup> we have invested efforts in developing new enantioselective methodologies. Herein, we envisioned the use of an oxidative step followed by an asymmetric organocatalytic process in a one-pot procedure to convert benzylic  $C\text{--}H$  bonds into chiral  $C\text{--}P$  bonds, using mild reaction conditions (Scheme 1, d). Additionally, the direct condensation of simple phosphonates with alcohols is found to be a more convenient route than reactions in which aldehydes are used as reagents for practical and environmental reasons. Interestingly, the asymmetric catalytic version for obtaining  $\alpha$ -hydroxy phosphonates has been scarcely studied using an organocatalytic approach.<sup>[10]</sup> Based on these previous studies and the importance of developing alternative synthetic protocols, herein we describe the first formal  $C\text{--}H$  activation that leads to  $C\text{--}P$  bonds in an efficient organocatalytic asymmetric Pudovik methodology, starting from benzylic and allylic alcohols.

Before beginning with the oxidation process, we considered necessary to perform a preliminary and exhaustive screening of different organocatalysts **4** and reaction conditions starting from 4-bromobenzaldehyde (**2a**) (see the supporting information for a complete screening of this process). For this study, we chose the model reaction depicted in Scheme 2 using dibenzyl phosphite (**3a**) as nucleophile, since the use of this phosphite has been neglected in the literature until now, perhaps due to its lower reactivity in comparison to diphenyl phosphite.<sup>[10]</sup> More interesting is the fact that if it were necessary to remove the OBn groups, this operation would be easier than the use of the common diphenyl phosphite derivative. Hence, the development of new Pudovik protocols with new reagents and conditions is also a challenging task of high interest in organic synthesis.

Based on our experience in the hydrophosphonylation reactions,<sup>[11]</sup> and considering the need for a plausible bifunctional role played by the organocatalyst, we foresaw that squaramides (SQ) **4a–g** could be good candidates to start this study (Scheme 2).<sup>[12]</sup> In this pursuit, we initially explored the reactivity and the enantioselectivity of the process at 0 °C, and only when promising values were achieved (with **4a** and **4d**), we also investigated the decrease of temperature. To our delight, the initial exploration of catalysts revealed that squaramide **4a** was the best compromise in terms of both enantioselectivity and reactivity. After that, we continued exploring **4a** in a variety of solvents (see the supporting information for a complete screening of this process, Table S1). Furthermore, the concentration of the reaction, the amount of phosphite and the catalyst loading were some of the parameters also taken into consideration. Among all the studied



**Scheme 2.** Screening of squaramide-based organocatalysts **4a–g**.

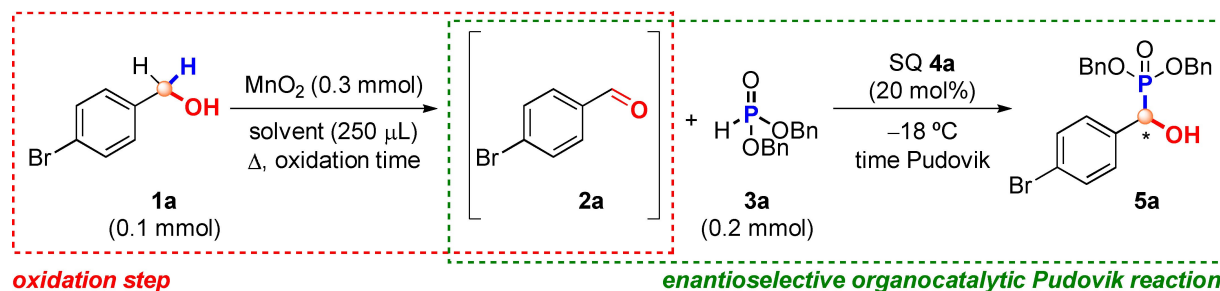
solvents,  $\text{CH}_2\text{Cl}_2$  was found to be the best option for this protocol in terms of enantioselectivity and reactivity. Moreover, cooling down the reaction mixture to  $-38^\circ\text{C}$  did not have a remarkable positive effect on the enantioselectivity of the process, and harmed the levels of reactivity (Table S1). From this screening, we concluded that the best reaction conditions were  $\text{CH}_2\text{Cl}_2$  (250  $\mu\text{L}$ ), at  $-18^\circ\text{C}$  using 20 mol% of catalyst **4a**.

After that, we began with the study of the oxidation process (Table 1). For this purpose, we used our own best conditions previously reported to oxidize benzylic alcohols.<sup>[13]</sup> To ensure that the oxidation process is stopped at the corresponding aldehyde, we used  $\text{MnO}_2$  as the mildest and most efficient oxidant.<sup>[14]</sup> It is worth noting that the *in situ* generated aldehyde **2a** was used without being purified, following a one-pot protocol in the ensuing hydrophosphonylation reaction. This means, the  $\text{MnO}_2$  is not removed from the medium until final purification of product **5a**. It is remarkable the importance of one-pot approaches, not only for their potential to efficiently construct highly complex molecules in a single reaction vessel, but also because they avoid difficult purifications and enable saving time, solvents, and reagents.<sup>[15]</sup>

In this study, we also considered potential green solvents and although very encouraging results were obtained for the first time in this protocol using green

solvents, such as 2-methyltetrahydrofuran (2-MeTHF) and cyclopentyl methyl ether (CPME) (entries 2 and 4), the best outcomes were found with  $\text{CH}_2\text{Cl}_2$  (entry 1). We tried to reduce the amount of  $\text{MnO}_2$  using 0.2 mmol (entry 6), but the yield was lower for a similar reaction time. Nevertheless, it is also remarkable that the common conditions when  $\text{MnO}_2$  is used require greater amounts of this oxidant.<sup>[16]</sup> Therefore, we have successfully optimized the reaction conditions for this oxidative step.

Then, we investigated the time necessary for the total conversion of each alcohol **1a–n** in its corresponding carbonyl compound **2a–n** (Scheme S1). As the solvent of choice was  $\text{CH}_2\text{Cl}_2$ , the initial oxidation step was carried out under mild conditions at  $30^\circ\text{C}$ . There is not a clear correlation between the reactivity observed and the electronegativity of each alcohol, but in most of the cases, almost complete conversion is accomplished. Finally, with the optimized reaction conditions in hand, we explored the scope and limitations of this one-pot procedure for alcohols **1a–n** (Scheme 3). Upon analyzing the results reported in Scheme 3, we can conclude that the Pudovik reaction proceeded smoothly, yielding the desired  $\alpha$ -hydroxy phosphonates **5** in moderate to excellent yields (up to  $>95\%$ ) and high enantioselectivities (up to  $>99\%$ ). The utility of this procedure is well-demonstrated as it was successfully applied to all the alcohols explored

**Table 1.** Screening of conditions joining both oxidative step and Pudovik reaction.<sup>[a]</sup>

Entry	Solvent	Oxidation		Pudovik		yield (%) <sup>[b]</sup>	% ee <sup>[c]</sup>
		t (h)	T (°C)	t (h)	T (°C)		
1	CH <sub>2</sub> Cl <sub>2</sub>	24	30	96	−18	82	85
2	2-MeTHF <sup>[d]</sup>	96	80	92	−18	64	73
3	Et-L-lac <sup>[d]</sup>	n.r. <sup>[e]</sup>	80	—	—	—	—
4	CPME <sup>[d]</sup>	15	30	96	−18	60	67
5	ClCH <sub>2</sub> CH <sub>2</sub> Cl	7	70	90	−18	48	70
6 <sup>[f]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	24	30	88	−18	50	86

<sup>[a]</sup> Reaction conditions. Oxidation: MnO<sub>2</sub> (0.3 mmol), solvent (250 µL) and alcohol **1a** (0.1 mmol) at different temperature; Pudovik: catalyst **4a** (0.02 mmol) and phosphite **3a** (0.2 mmol), −18 °C.

<sup>[b]</sup> After purified by column chromatography.

<sup>[c]</sup> Determined by chiral HPLC analysis (Daicel ChiralPak IA column (*n*-hexane/*i*-PrOH = 9:1, flow = 1 mL/min, λ = 215.0 nm)).

<sup>[d]</sup> 2-MeTHF: 2-methyltetrahydrofuran; Et-L-lac: (−)-ethyl L-lactate; CPME: cyclopentyl methyl ether.

<sup>[e]</sup> n.r. = No reaction observed (after 3 days).

<sup>[f]</sup> 0.2 mmol of MnO<sub>2</sub>.

**1a–n.** The electronic effects on the enantioselectivity and reactivity of the process were studied using different substituted *ortho*-, *meta*- and *para*-benzyl alcohols (**1a–f, h, i**) as well as an heteroaromatic group (**1i**), even in the absence of any substituents in the aromatic ring (**1g, m**) or interestingly, with an allylic alcohol (**1j**). However, there is not clear correlation between the reactivity and the electronegativity of the aromatic systems, since excellent results were achieved even with electron-donating groups (**5h**) or in the absence of substituents in the aromatic ring (**5g, m**). Moreover, excellent results were obtained for an upper scale of the process using **1a** and, interestingly, better *ee* was obtained for product **5a** (Scheme 3).

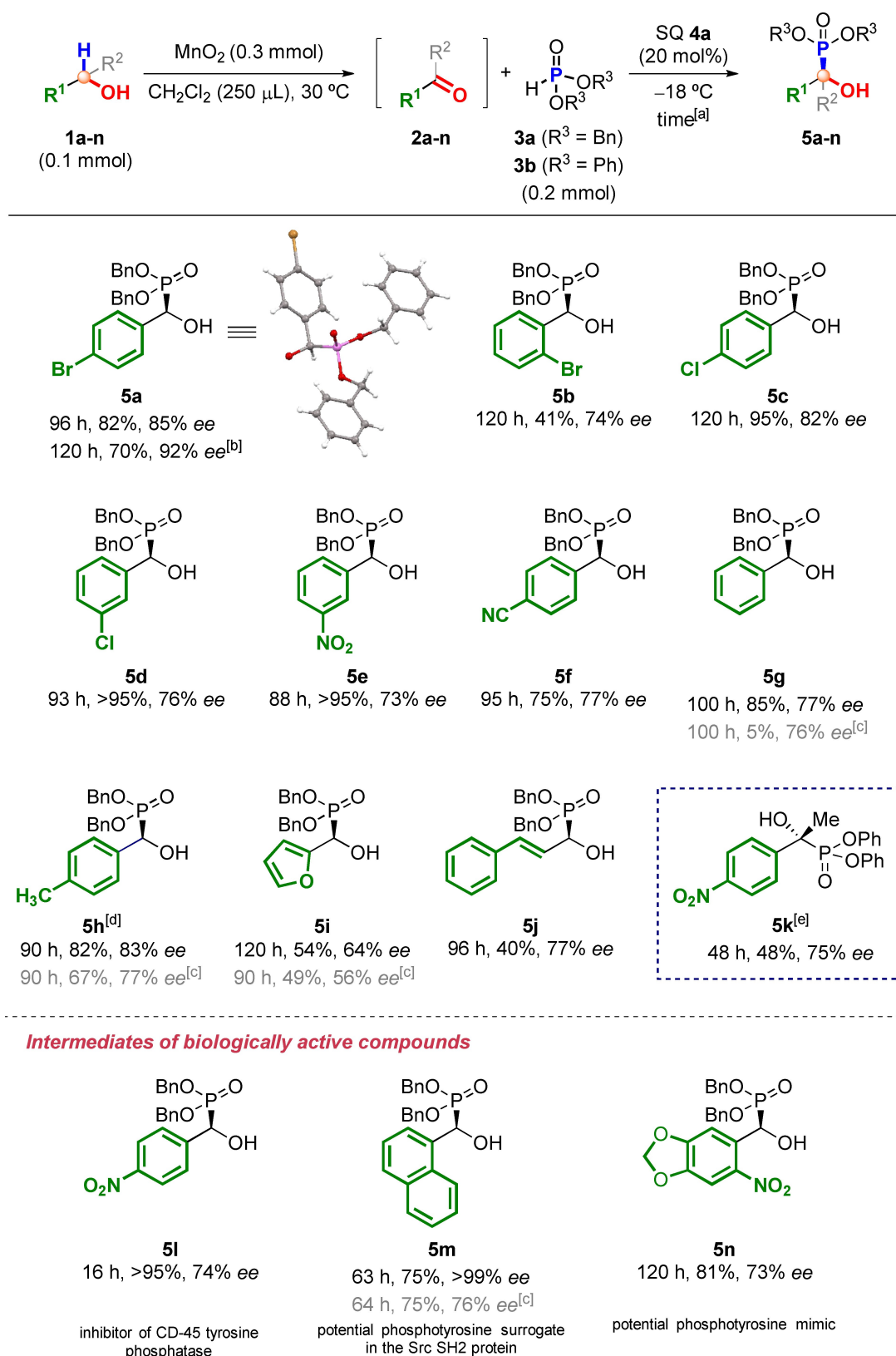
The efficiency of this protocol was also compared with the results obtained when using the corresponding commercially available liquid aldehydes (**2g–i, m**) as initial reagents without purification (Scheme 3, results in gray), since we have previously realized about the importance and the negative effect that traces of acid generated in liquid aldehydes could cause by inactivating the amount of catalyst used in the process.<sup>[13a,17]</sup> Although the enantiomeric excesses observed are very similar starting from **2g** and **2h**, in comparison with the corresponding alcohols **1g** and **1h**, the reactivity is better when starting from alcohols. Interestingly, using recently acquired aldehyde **2g**, the same results are

obtained as when starting from the alcohol **1g**. In contrast, a decrease in enantioselectivity is observed when using **2m**. The use of furfuryl aldehyde **2i** afforded the same yield as starting from the corresponding alcohol **1i**, albeit with a lower enantioselectivity. Herein, we reconfirm that the presence of traces of acid can have a negative and random impact on the catalyst's activity and the outcomes of the reactions. Hence, these finding support that starting from alcohols is consistently more advantageous than from the aldehydes.

We were able to extend our methodology for the construction of tetrasubstituted carbon stereocenters by initiating the process from 1-(4-nitrophenyl)ethan-1-ol (**1k**). This resulted in the formation of the tetrasubstituted α-hydroxy phosphonate **5k** with a moderate yield and good enantioselectivity. In this example, we improved the reactivity by using diphenyl phosphite (**3b**) due to the poor reactivity of the *in situ*-generated ketone **2k**.

Moreover, it is worth mentioning that three of these adducts (**5l–n**) are intermediates of biologically active products that could be obtained through a simple reduction process. The resulting phosphonic acid from **5l** is an inhibitor of CD-45 tyrosine phosphatase,<sup>[18]</sup> **5m** is a potential phosphotyrosine surrogate in the Src





**Scheme 3.** Scope of squaramide-catalyzed Pudovik reaction of the carbonyl compound generated *in situ* after oxidation of starting benzylic and allylic alcohols **1a–n**.<sup>[a]</sup> Time indicated is for the organocatalytic step.<sup>[b]</sup> Reaction at 1 mmol scale.<sup>[c]</sup> Outcomes starting from the corresponding aldehydes **2** (in gray).<sup>[d]</sup> The reaction was carried out at 5 °C.<sup>[e]</sup> Diphenyl phosphite (**3b**) was used at  $-50^\circ\text{C}$ .

SH2 protein<sup>[19]</sup> and **5n** is a potential phosphotyrosine mimic.<sup>[20]</sup>

Since the final  $\alpha$ -hydroxy phosphonates generated by this protocol have not been previously reported in their chiral version, single crystals were grown from adduct **5a** to establish the absolute configuration of our products. The stereochemical outcome was determined to be *R* (Scheme 3).<sup>[21]</sup>

We have also tested different phosphites **3b–e** under the best reaction conditions, as depicted in Scheme 4, but only using diphenyl phosphite (**3b**) provided the final product **5o** with good results of reactivity and enantioselectivity. This fact may be attributed to the less reactivity exhibited by the other aliphatic phosphites in comparison.<sup>[22]</sup>

In summary, herein we report an organocatalytic procedure for the construction of enantioselective C–P bonds as a proof of concept. Interestingly, this C–P bond formation occurs through a  $C(sp^3)$ –H activation in a cascade procedure, starting from stable and commercially available benzylic and allylic alcohols **1**, in an organocatalytic asymmetric reaction for the first time.<sup>[23]</sup> The protocol involves an asymmetric organocatalytic Pudovik reaction, in which a first oxidation step is carried out using  $MnO_2$  as oxidant and a second organocatalyzed step using a chiral squaramide catalyst. The scope of the reaction has conducted to a series of enantiomerically enriched  $\alpha$ -hydroxy phosphonates **5** with yields from 40% to >95% and enantioselectivities from 64% to >99%, some of them, intermediates of biologically active products. We have increased the scale up to 1 mmol, getting 92% ee and 70% yield. In general, the results obtained were better than those associated to the use of the corresponding liquid aldehydes. Several substituted benzylic alcohols including a secondary one and even an allylic derivative, have been used in the reaction in order to elucidate the electronic factors of the enantioselectivity and reactivity in this process, although a clear correlation has not been observed. To corroborate the absolute configuration of these  $\alpha$ -hydroxy phosphonates, X-ray diffraction studies have been performed

determining the *R* enantiomer. This protocol opens the possibilities for the construction of C–P bonds in an asymmetric way *via*  $C(sp^3)$ –H activation, which could be of importance for the pharmaceutical industry.

## Experimental Section

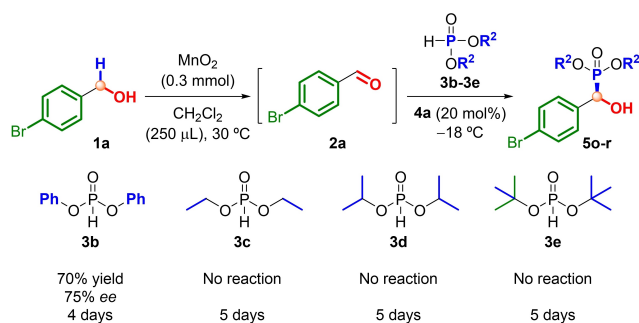
To a suspension of  $MnO_2$  (0.3 mmol) in dichloromethane (0.25 mL) placed in a test tube, the alcohol **1** (0.1 mmol) was added. The reaction mixture was stirred at 30 °C until TLC indicated total consumption of the starting material or no evolution was observed (Scheme S1). Then, the reaction mixture was cooled down to –18 °C and the catalyst **4a** (0.02 mmol) and phosphite **3** (0.2 mmol) were further added. The reaction mixture was stirred at that temperature until TLC indicated total consumption of the starting material or no evolution was observed (Scheme 3). Then, adducts **5** were purified by flash chromatography. Eluants, yields, enantioselectivities, reaction times, spectra and analytical data for compounds **5a–o** are reported in the supporting information. The spectroscopic data recorded for the products **5j**<sup>[24]</sup> and **5o**<sup>[11c]</sup> are in agreement with values previously reported by other authors.

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**Scheme 4.** Screening of phosphites **3b–e** in the Pudovik reaction.

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