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Asymmetric Organocatalyzed Phospha-Michael Addition for the Direct Synthesis of Biologically Active Chromenylphosphonates

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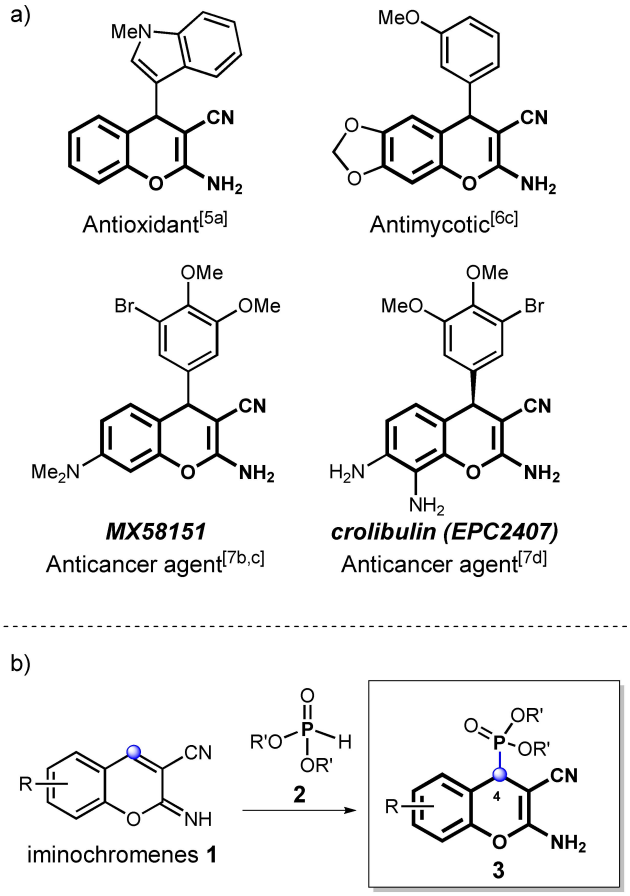
Abstract: The potential of phosphites as nucleophiles for the asymmetric synthesis of chiral chromene derivatives has been overlooked in the literature. Herein, we report a promising approach via asymmetric organocatalyzed phospha-Michael addition to iminochromenes, using a bifunctional squaramide, which gives access to chromenylphosphonates, an interesting family of bioactive compounds. Our optimized protocol provides very good reactivity, affording yields of up to 95% and with chiral products exhibiting an enantiomeric excess of up to 98%.

Keywords: asymmetric synthesis; phosphite; chromene; organocatalysis; phospha-Michael; biological activity

The structural core of chromenes is abundantly present in both natural and synthetic compounds, making them a subject of extensive investigation.[1] Numerous studies have focused on exploring their fascinating medicinal and pharmacological properties.[2] Notably, their role as antitumoral agents[3] and cognitive enhancers in the treatment of illnesses such as schizophrenia, myoclonus, and various neurodegenerative diseases has garnered significant attention.[4] In particular, the 2-amino-3-cyano-4*H*-chromene family has emerged as a topic of growing interest due to the unique properties exhibited by this specific structural core.[5] These properties include antimicrobial activity[6] and pro-apoptotic potential,[7] suggesting their possible application as promising therapeutic drugs for anticancer treatment and other diverse applications (Scheme 1a). While several racemic syntheses of this compound family have been reported using organocatalytic methods, the number of examples following an enantioselective approach remains limited.[8] Furthermore, there are even fewer reports on asymmetric metal-catalyzed procedures.[9]

Organophosphorus compounds, which encompass natural products and synthetic compounds featuring a P–C bond, have demonstrated significant potential in terms of their biological activities.[10] Among the various methods for constructing P–C bonds, such as the Pudovik reaction[11] or the Michaelis–Arbuzov reaction,[12] the phospha-Michael addition stands out as one of the most widely employed and straightforward approaches.[13] Despite its importance, the repertoire of enantioselective organocatalytic examples for this pivotal and valuable method remains limited.

Therefore, the introduction of a phosphonate moiety on the 2-amino-4*H*-chromene ring may have a synergistic effect. In recent years, there has been significant interest in the synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonates through the phospha-Michael addition of dialkyl and diphenyl phosphites to 2-amino-3-cyano-4*H*-chromenes. However, to date, only a limited number of racemic approaches have been reported for constructing these compounds (Scheme 1b).[14] Studies conducted with the racemic



Scheme 1. a) Biologically active 2-amino-3-cyano-4*H*-chromene derivatives. b) Phospha-Michael addition to iminochromenes **1**.

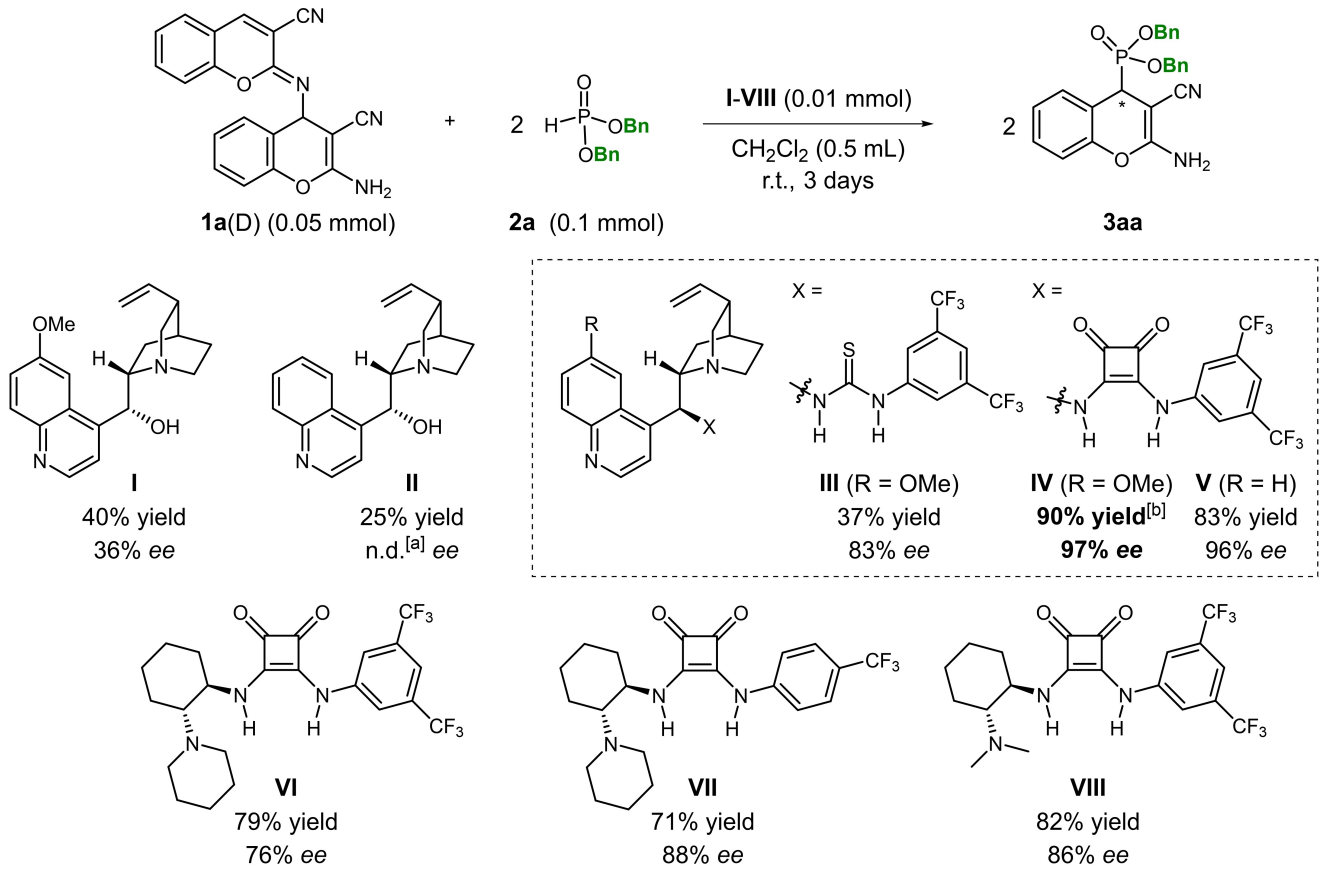
mixtures have unveiled a diverse range of biological activities associated with these products, including antioxidant, antimicrobial, anticancer, and anticoagulant properties.[15] Notably, the configuration of the stereogenic center in 2-amino-4*H*-chromenes has been found to impact their biological activity.[7e] Despite the importance of this aspect, to the best of our knowledge, there are no enantioselective catalytic procedures available for the synthesis of this intriguing scaffold, representing a highly desirable and challenging task. Consequently, we have successfully developed the first asymmetric phospha-Michael addition reaction utilizing the iminochromene conjugated system as the electrophile, leading to the formation of enantioenriched (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonates with exceptional enantioselectivity (Scheme 1b).

To explore the previously overlooked approach, we recognized the necessity of incorporating both hydrogen-bonding donor and acceptor groups within the catalyst structure, considering our prior expertise in developing new asymmetric Pudovik[16] and phospha-Michael[17] reactions. This led us to envision the importance of employing a bifunctional catalytic strategy: the basic moiety to facilitate the phosphonate-phosphite equilibrium shift (see mechanistic proposal in Figure 3),[18] and the squaramide capable of activating the substrates through hydrogen-bond interactions.[19] Consequently, our study was initiated by investigating the feasibility of the addition of dibenzylphosphite (**2 a**) to iminochromene **1 a**(D), employing chiral catalysts **I**–**VIII** (Scheme 2). We first used the dimer **1 a**(D) as the substrate, since it was obtained as the major compound following the method reported by Proença and co-workers (see supporting information),[20] and we found that it successfully led to the desired chromenylphosphonate **3 aa** (Scheme 2). Thus, the initial catalyst screening unveiled that squaramides **IV**–**VIII** exhibited remarkable performance in terms of both reactivity and enantioselectivity, demonstrating excellent values (up to 90% yield and up to 97% ee, obtained with catalyst **IV**, Scheme 2).

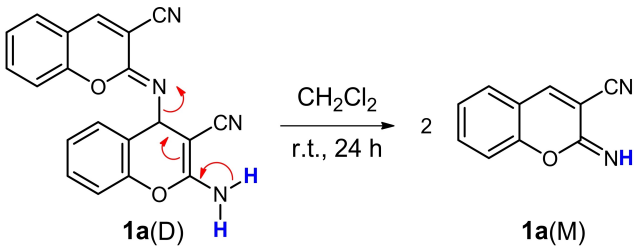
Furthermore, it was observed that stirring dimeric substrate **1 a**(D) in dichloromethane for 24 hours led to dedimerization, allowing the isolation of the monomer **1 a**(M), as the major component (Scheme 3). Notably, when using the monomer **1 a**(M) as the substrate in the reaction with dibenzylphosphite (**2 a**), same enantioselectivity and very similar yield were obtained (Scheme 2, catalyst **IV**). This intriguing finding encouraged us to utilize the iminochromenes **1** as obtained after their synthesis, normally a mixture enriched in the monomeric form (see supporting information).[20,21]

Subsequently, variations in solvent, reaction medium concentration, and catalyst loading revealed no improvement of the results (see the supporting information). Then, with the optimal reaction conditions established (10 mol% of catalyst **IV**, CH_2Cl_2 as the solvent of choice and at room temperature) the efficiency and scope of this protocol were further investigated using a range of phosphites and iminochromenes. As summarized in Figure 1, the phospha-Michael reaction takes place rendering the desired final chromene derivatives in good to high yields (up to $>95\%$) and excellent enantioselectivities in most cases (up to 98% ee, $>99\%$ ee after recrystallization). It seems that neither the enantioselectivity nor the reactivity of the process are extensively affected by the electronic effects of the iminochromenes **1**.

Among the different phosphites **2** tested, dibenzyl derivative **2 a** (OR' = OCH_2Ph) was indeed the one that



Scheme 2. Screening of catalysts **I–VIII** in the phospha-Michael reaction. Iminochromene **1a**(D) (0.05 mmol), dichloromethane (0.5 mL) and dibenzylphosphite (**2a**) (0.1 mmol) are added to the reaction vial containing the catalyst **I–VIII** (0.01 mmol).[a] N.d. = no determined.[b] 80% yield starting from monomer **1a**(M) (Scheme 3), and same enantioselectivity (97% ee) was observed.



Scheme 3. Dedimerization of the dimer **1a**(D) to the monomer **1a**(M).

provided the best results. It seems that the order of reactivity can be justified by attending to the steric effects of the dialkylphosphite, with the most sterically hindered being the least reactive one (**2e**, OR' = ^{t}Bu). Therefore, the order of reactivity agrees with the results of yields observed (**3aa** > **3ac** > **3ad** > **3ae**). In these cases, very high enantioselectivities were found for aliphatic phosphites (**2c**,**d**). In contrast, the diphenylphosphite (**2b**, OR' = OPh), being the most acidic and reactive one,[23] gave rise to the poorest enantiomeric values due to the competition of both, the racemic and the selective pathways.

Remarkably, for some of the obtained compounds there are few reports about the biological activities of their racemic version. For instance, some *dibenzyl* (2-amino-3-cyano-4*H*-chromen-4-yl)phosphonates (**3aa**, **3ea**, **3ia** and **3ja**) showed to be the most active compounds in comparison with *dimethyl* or *dibutyl* phosphonate substituted ones, since they showed cytotoxicity (IC_{50}) in the 3–7 μM range against the human promyelocytic leukemia (HL-60) cell line.[15e] On the other hand, compound **3ac**, *ethyl* substituted in the phosphonate moiety without any substitution on the chromene ring, showed potent *in vitro* dose dependent antioxidant activity and reasonable antibacterial (*Escherichia coli* and *Staphylococcus aureus*) and antifungal (*Aspergillus niger* and *Helminthosporium oryzae*) activity;[15a] as well as, cytotoxic activity (inhibition, 40 μM) in 50.96 ± 4.73% against the adenocarcinomic human alveolar basal epithelial (A549) and in 60.08 ± 2.02% against the human epidermoid cancer (KB) cell lines.[15b]

In order to determine the absolute configuration of final products, single crystals were grown from adducts

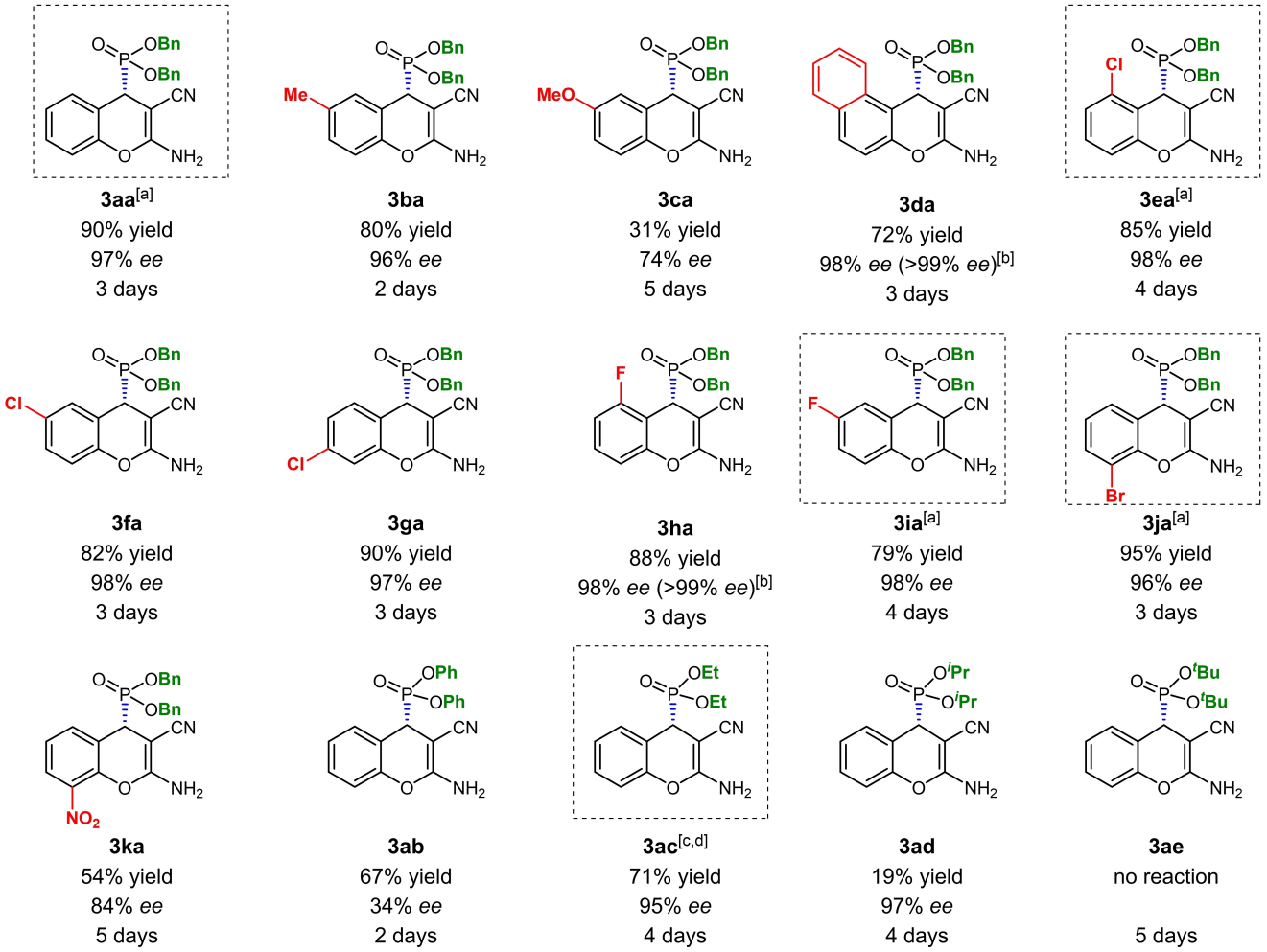


Figure 1. Scope of the phospha-Michael reaction. Corresponding iminochromene **1** (0.1 mmol monomer or 0.05 mmol dimer), dichloromethane (0.5 mL) and phosphite **2** (0.1 mmol) are added to the reaction vial containing the catalyst **IV** (0.01 mol). [a] Cytotoxic against HL-60 cells (racemic **3 aa**, **3 ea**, **3 ia** and **3 ja**).[15e] [b] After recrystallization. [c] Cytotoxic against A549 and KB cells (racemic **3 ac**).[15b] [d] Potent *in vitro* dose dependent antioxidant activity, as well as, reasonable antibacterial and antifungal activity (racemic **3 ac**).[15a]

3 da and **3 ha**, and the stereochemical outcome was determined to be *S* and *R*, respectively, by X-ray analysis (Figure 2). Hence, it was assumed the same nucleophilic approach applies to all obtained chromenylphosphonates **3** (Figure 1).[22]

Based on all experimental results, very preliminary DFT calculations (unpublished results) and our own experience, we propose a plausible mechanism supporting the absolute configuration found (Figure 3). On one hand, it is known that the phosphite, and not the phosphonate, forms the actual nucleophile of this kind of reactions.[21] Hence, the tautomeric equilibrium depicted in Figure 3, which under neutral conditions is shifted towards the unreactive phosphonate form, can be affected by the presence of a base, in this case, the quinuclidine nitrogen of the organocatalyst. On the other hand, the squaramide could activate the iminochromene through hydrogen bonding with the acidic

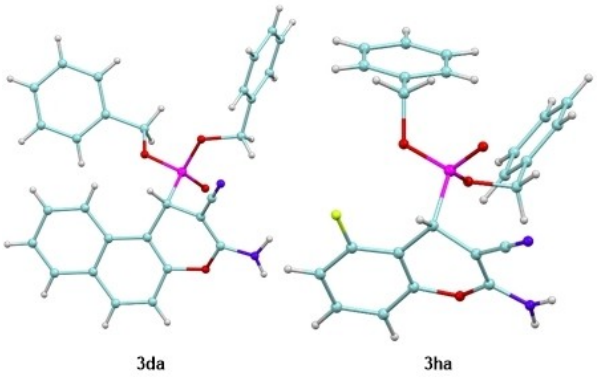


Figure 2. X-ray structures for compounds (*S*)-**3 da** and (*R*)-**3 ha**.

NH groups (in a monodentate or a bidentate fashion). The quinuclidine nitrogen would drive the attack of the

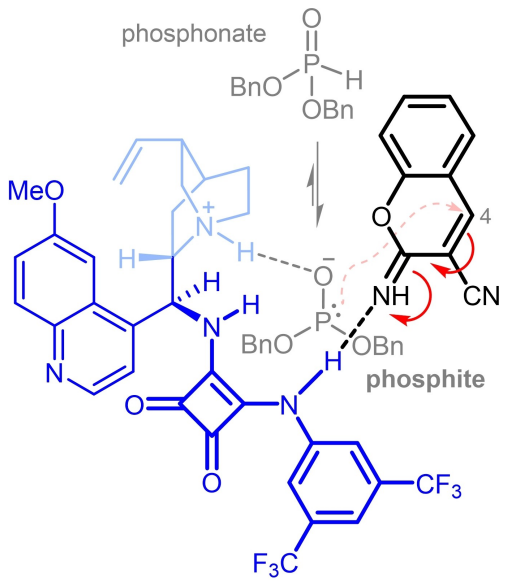


Figure 3. Mechanistic proposal, including the tautomeric equilibrium between the unreactive phosphonate and the phosphite, the actual nucleophile.

active phosphite form in a concomitant bifunctional activation over the *Si*-face of the double bond of the iminochromene (Figure 3). This would afford the *S* configuration in the final product, which is consistent with what was observed experimentally.

As mentioned before, the dimer **1a**(D) is slowly transformed into the monomeric species **1a**(M) in dichloromethane, the solvent used for the reaction (see the supporting information). In the process, two molecules of monomer **1a**(M) are released into the medium, which could take part as substrate in the phospha-Michael reaction (Scheme 3). Consequently, the mechanism would be assumed to be the same as described in Figure 3 when starting from both monomer and dimer. This would justify the same values of reactivity and enantioselectivity obtained using indistinctly both species.

In conclusion, marking an advancement in the field, our research has resulted in the successful development of the first reported example of an enantioselective organocatalytic phospha-Michael addition, employing dialkylphosphites and chromenes with a squaramide catalyst.[24] Notably, the process demonstrates equal efficacy when initiated from either monomeric or dimeric chromene substrates, offering a practical advantage by enabling a broader range of substrates to be utilized without the need for selective synthesis of one form over the other. Remarkably, we have also demonstrated that the phospha-Michael addition can be accomplished using various dialkylphosphites without compromising the enantioselectivity, although the reactivity of the reaction may be affected. Ongoing investigations in our laboratory involve further exploration of the mechanistic aspects and biological studies of the resulting products. These efforts aim to expand the applications of these valuable products, some of them with already demonstrated biological properties in their racemic version, and deepen our understanding of their potential uses.

Experimental Section

The starting material (**1**) (0.1 mmol; or 0.05 mmol of the corresponding dimer, if the case), dichloromethane (0.5 mL) and the corresponding phosphite (**2**) (0.1 mmol) are added to the reaction vial containing the squaramide (**IV**)[25] (0.01 mol). The mixture is stirred at room temperature for the time needed for total consumption of the starting reagent or until no further progress is observed (2–5 days), monitoring the evolution by thin-layer chromatography. After the corresponding time (Figure 1), the residue is purified by column chromatography using a mixture of *n*-hexane/ethyl acetate to afford the pure adducts **3aa-ka**,**ab-ad**. Enantiomeric excesses (ee) of isolated products are obtained via chiral HPLC analysis using mixtures of *n*-hexane/ethyl acetate or *n*-hexane/*i*-propanol as eluent. The yield and selectivity of distinct products are collected in Figure 1. Spectra and analytical data are reported in the supporting information.

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