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One-pot $Mo(CO)_6$-facilitated transformation of anilines into benzophenones *via in situ* pyridinium reconfiguration

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A novel, mechanochemical, one-pot transformation of anilines to benzophenones using molybdenum hexacarbonyl ($Mo(CO)_6$) was achieved, avoiding pre-functionalization steps inherent in such conversions. The reaction capitalizes on the activation of the C(sp^2)–NH_2 bond in anilines *via in situ* formation of pyridinium salts: a strategy impeded by the inertness of the C–N bond. For this envisioned methodology, pyrylium tetrafluoroborate was used to convert anilines into reactive pyridinium intermediates, which undergo carbonylation in the presence of $Mo(CO)_6$. The corresponding acyl pyridinium intermediates, in turn, are amenable for C–C coupling under transition metal catalyst-free conditions, driven by the piezoelectric nature of barium titanate in a mechanochemical reaction setup. This approach shows a very general substrate scope, good functional group tolerance, and fair-to-excellent yields (50–92%, depending on the aniline derivative used) of benzophenone analogues. This acyl-intermediate-based method has been further applied to the synthesis of 3-benzoylchromones, attesting to its broad scope. Therefore, the described late-stage functionalization strategy, free of transition metals, represents progress in the scope of bioactive compound syntheses for medicinal chemistry.

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Introduction

In modern synthetic methodologies, emphasis is given to the late-stage functionalization of bioactive compounds without recourse to *a priori* functionalization of given molecular fragments to improve their reactivity profiles (Scheme 1).[1] The inertness of the C–N bond in anilines[2] and their status as important precursors for a number of pharmaceuticals, agrochemicals, dyes, electronic materials, and polymers give them the advantage of being ideal candidates for LSF methodologies.[3] Hence, activation of the C(sp^2)–NH_2 bond in anilines represents a promising development in the field of late-stage functionalization of anilines to engineer new synthetic strategies for producing a diverse range of bioactive compounds.

Initial approaches for tackling the inert nature of the amine bond were set forth by Katritzky *via* his work on the interconversion of primary alkyl amines, C(sp^3)–NH_2, into reactive pyridinium salts.[4–6] This set the precedent for the development of various pyrylium salts, or Katritzky salts, with the capacity to activate the C–N bond across various molecular systems, altering the view of inactive aliphatic amines towards efficient electrophiles capable of undergoing S_N2 substitution.[7] In continuation of these results, further studies from Cornella *et al.* regarding the application of unsubstituted pyrylium tetrafluoroborate salts have extended to S_NAr functionalization in aromatic amines, with focal activities on the selective activation of the C(sp^2)–NH_2 bond in primary aromatic amines for further deamination and derivatization, offering an efficient route for late-stage functionalization of aromatic amines.[8–11]

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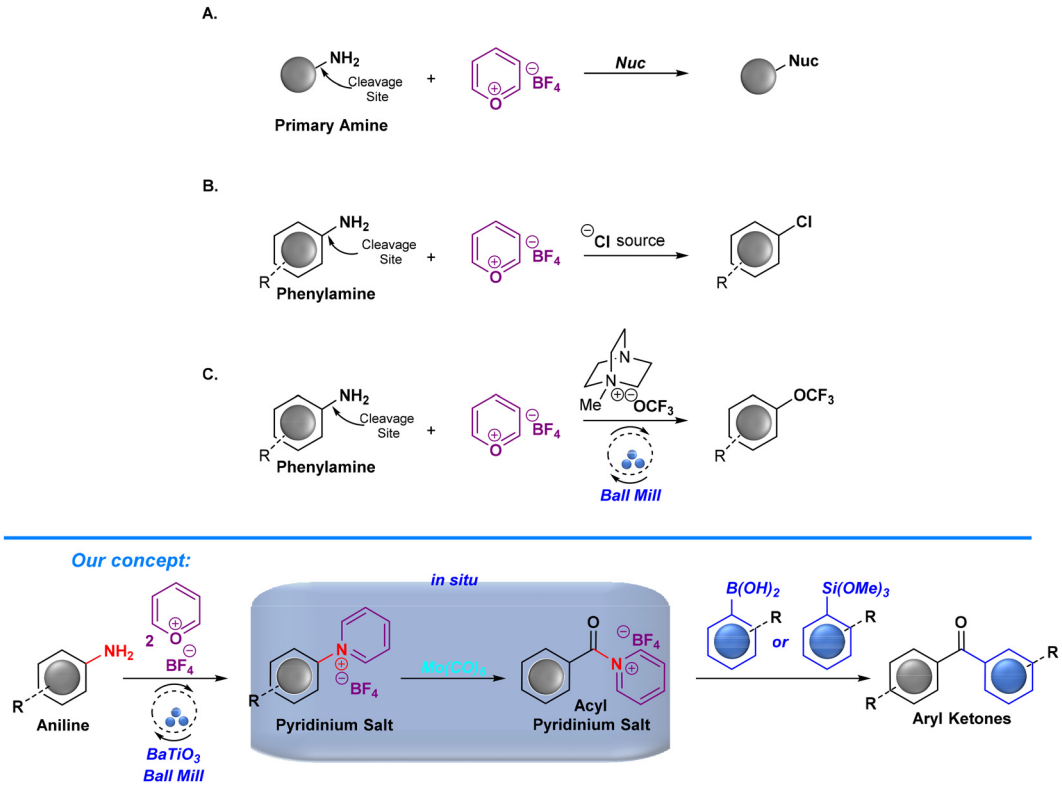


Scheme 1 Sample reported strategies for activation and late-stage functionalization plus our concept.

Recent advances in the field of mechanochemistry by Ito[12,13] and Bolm[14] have propelled us to develop numerous organic synthetic protocols aimed at utilizing mechanochemistry for developing green approaches that involve piezoelectric materials to produce *in situ* specialized chemicals.[15–22] Herein, we incorporate pyrylium tetrafluoroborate to design a mechanochemical protocol for late-stage modification of C(sp^2)–NH_2 in anilines without resorting to *de novo* synthesis of organic precursors. Consequently, we expand upon the scope of LSF of anilines to produce benzophenone derivatives *via* incorporation of molybdenum hexacarbonyl, $Mo(CO)_6$, which induces reconfiguration of the pyridinium salt intermediate into acyl pyridinium through *in situ* carbonylation.

Benzophenones represent a prominent class of bioactive molecules distinguished by their structural diversity, which enables a wide range of biological activities, including anti-inflammatory, antibacterial, antiviral, and anticancer properties, making them highly valuable in medicinal chemistry.[23] The organic synthesis transformation of primary amines to benzophenone functional groups is of great significance to medicinal chemistry due to the potential of benzophenones as bioactive compounds.[24–26] A major drawback in their synthesis from primary amines is the requirement for specific amine configurations, activation through pre-functionalization of the C–N bond, and the need for specific reaction conditions for ketone transformation.[24–26] This in turn limits the scope and compatibility with late-stage functionalization due to the need for a defined starting material structure or pre-functionalization steps to synthesize product intermediates. Typical methods for ketone formation from amines are based on the precedent of carbonylation of primary amines, R_2CHNH_2, to R_2CO *via* transamination of isomeric Schiff bases.[24,25] More recently, methodologies have placed emphasis on LSF by synthesizing several ketones from protected anilines *via* C(sp^2)–O/N bond cleavage to the corresponding imine-ketal core following the reaction with α-bis(boryl)carbanions, which results in the formation of aromatic ketones from bioactive anilines. However, this process requires the isolation of the intermediate at the quin-ketal stage in order to provide a good yield, resulting in product isolation at the intermediate step of the overall synthesis, thereby limiting the scope of the method and making it unsuitable for LSF.[27]

The inherent stability and inert character of anilines underscore the challenges associated with their use in ketone formation, since there is a requirement for pre-functionalization steps in order to activate them. The C(sp^2)–NH_2 bond is almost unreactive in terms of interconversion to other functionalities; it possesses poor heterolytic nucleofugality and a high C–N bond dissociation energy (BDE of C_6H_5–NH_2: 102.6 ± 1.0 kcal mol^{-1}),[28] with further consideration of basicity.[29–31] Advancements in the field of C(sp^2)–NH_2 bond activation for deaminative functionalization by Cornella led to successful S_NAr reactions in a single step *via* formation of a pyridinium ion (Scheme 1A and B).[7,11] Inspired by this work, our group

previously achieved selective mechanochemical interconversion of primary aromatic amino groups into the $-OCF_3$ functionality (Scheme 1C).[20] This process involved the condensation of anilines, amides, and sulfonamides with the pyrylium reagent (Pyry-BF_4) to form reactive pyridinium salts, followed by an S_NAr reaction with the $-OCF_3$ source, 1-methyl-1,4-diazabicyclo[2.2.2]octan-1-ium trifluoromethanolate, which resulted in the production of several derivatives.

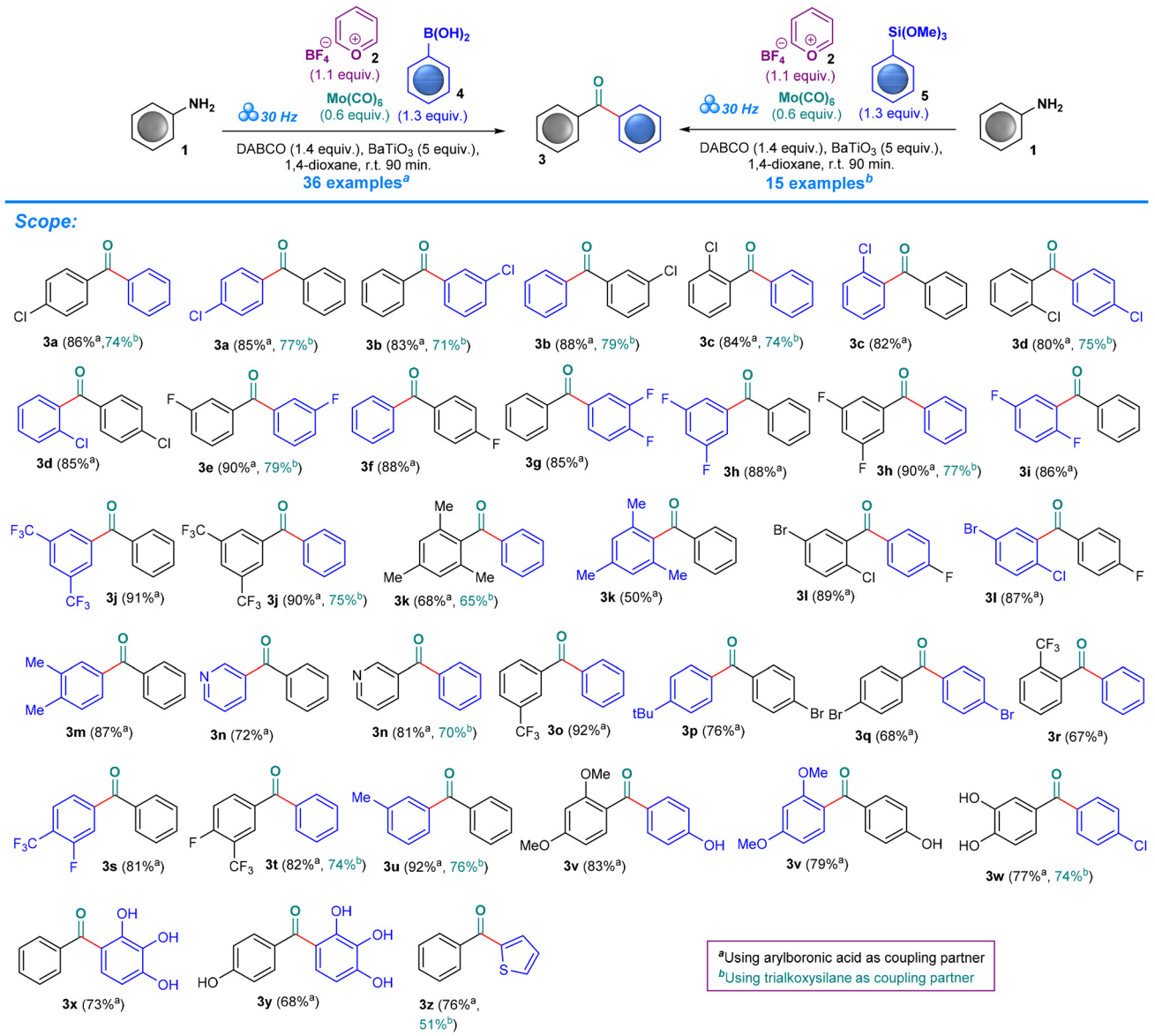
Since selective activation of anilines entails an *in situ*, one-pot approach, it is logical to devise an approach that retains the advantages conferred by late-stage functionalization by changing the reaction conditions according to the target compound. In this context, typical CO insertion proceeds *via* a 1,1-insertion into palladium(II) complexes generated through oxidative coordination of electrophiles to unsaturated palladium (0) species, leading to the formation of a Pd(0)/Pd(II) catalytic cycle.[32–35] The gaseous nature of CO presents a disadvantage in mechanochemical settings due to potential difficulties in experimental design with regard to gas pressurization[36] and the toxic, flammable nature of CO.[37] A more pragmatic approach involves employing a solid reagent as a CO source, which simplifies the experimental design and enhances safety. In the work of Larhed and co-workers, solid $Mo(CO)_6$ was utilized as a reliable source of CO for *in situ* carbonylation reactions, with established precedents in palladium-catalyzed carbonylation of aryl halides.[38,39] In this study, we incorporated $Mo(CO)_6$ within our specialized mechanochemical protocol to modify the mechanistic pathway responsible for benzophenone formation. CO insertion into the pyridinium intermediate leads to the formation of a reactive acyl pyridinium intermediate, which undergoes direct coupling with organoboron compounds without the requirement of a transition metal catalyst (Scheme 1). Organoboronic acids, as nucleophiles, find their most common utilization in Suzuki–Miyaura transition metal-catalyzed couplings of pyridinium salts for the formation of C–C bonds. However, these couplings are almost exclusively focused on *N*-alkyl[40,41] and benzylic pyridinium salts,[42,43] as the BDE of the $C(sp^3)$–NH_2 bond is significantly lower than that of the $C(sp^2)$–NH_2 bond (CH_3–NH_2: BDE = 85.1 ± 0.5 kcal mol^{-1}).[28] The activation of the $C(sp^2)$–NH_2 bond is more challenging, which explains why deaminative coupling of $C(sp^2)$–NH_2 with organoboron reagents has not been extensively studied.

Results and discussion

Building on the foundation of mechanochemical transformations in organic synthesis, our study explores novel C–C bond formation *via* $C(sp^2)$–NH_2 coupling with boronic acids and trialkoxysilanes (Scheme 2). In our study, we conducted a series of solid-phase reactions that were systematically performed to examine the effect of various metal carbonyls on the yield of the reactions. Various anilines (**1**), pyrylium tetrafluoroborate (**2**), boronic acids (**4**) or trialkoxysilanes (**5**) were consistently used in proportions of 1 equivalent, 1.1 equivalents, and 1.3 equivalents, respectively, under a constant milling frequency of 30 Hz for 90 minutes, with the addition of 0.20 mL of 1,4-dioxane as a liquid-assisted grinding (LAG) additive.[44,45]

In the optimization procedure shown in Table S1 (entries 1–15), various metal carbonyls were employed under optimized conditions for the reaction of boronic acids and tested for their potential to produce the desired benzophenone product (**3a**) from aniline (**1a**). The milling was conducted at a frequency of 30 Hz for 90 min; the yields changed significantly according to the type of the carbonyl source. A series of metal carbonyls (1.6 equiv.): $Fe(CO)_5$, $Co_2(CO)_8$, $Ni(CO)_4$, $Cr(CO)_5$, $Ru_3(CO)_{12}$, and $V(CO)_6$ were evaluated for the formation of benzophenone (**3a**) based on the first series of entries (1–6). The solid metal carbonyl reagents were employed in combination with DABCO (1.4 equiv.) and $BaTiO_3$ (5 equiv.)[12] in a mechanochemical setting, resulting in yields ranging from 0% to 67%. The highest yield was achieved as shown in entry 7 for $Rh_4(CO)_{12}$ (0.8 equiv.), which produced a 91% yield. In a general approach, the results showed that $Mo(CO)_6$ was the most versatile among all of the CO sources considered for the optimization of reaction conditions. Accordingly, in entry 8, 1.6 equivalents of $Mo(CO)_6$ were used, affording an 86% yield. Despite further reducing the quantity to 1 equivalent as in entry 9, a high yield of 87% was maintained. As in entry 10, 0.6 equivalents of $Mo(CO)_6$, 1.4 equivalents of DABCO, and 5 equivalents of $BaTiO_3$ were used, and the yield was also 86%. Thus, it was considered the optimum amount due to its balance of efficiency and cost-effectiveness. Further testing of $Mo(CO)_6$ was performed as shown in entries 11 and 12. In this case, changing the quantity of $BaTiO_3$ provided yields of 70% and 87%, correspondingly, for 4 or 6 equivalents. The control experiments, entries 13, 14, and 15, in which either DABCO, $BaTiO_3$, or both were not used, resulted in no product formation, thus stressing the importance of these constituents in guarantying reaction completion. This way, the obtained data allowed for setting the optimal reaction conditions as in entry 10, where 0.6 equiv. of $Mo(CO)_6$, 1.4 equiv. of DABCO, and 5 equiv. of $BatiO_3$ were employed for studying the scope of the reaction. Lastly, it may be worth mentioning that $Rh_4(CO)_{12}$ was not further elaborated as this compound is expensive, and the budget did not give the chance to move forward in this study. It is well known that DABCO is sufficiently basic to promote a variety of coupling reactions by elevating the nucleophilicity of the substrates, which in turn impacts the efficiency and yield of the reactions. For example, DABCO was used in mechanochemical C–N bond formation reactions by the Ito group to obtain high yields with a nickel(II) catalyst and a piezoelectric material under ball-milling conditions.[12] Moreover, our previous studies have shown the remarkable potential of DABCO as a base in a variety of mechanochemically induced cross-coupling reactions. Thus, we opted DABCO to be used directly as the base in the present transformation.

To elaborate further on the role of the mechanochemical conditions in the success of the reaction, a series of control experiments were conducted in the liquid-phase to compare



Scheme 2 Reaction scope for boronic acid and trialkoxysilanes.

the reaction efficiency with results obtained under mechanochemical conditions (see Table S1). In the solvent-based control experiments, the same reagents and proportions were employed as in the optimized mechanochemical conditions (entry 10: 0.6 equivalents of $Mo(CO)_6$, 1.4 equivalents of DABCO, and 5 equivalents of $BaTiO_3$). We tested several different solvents and temperatures for their impact on the efficiency of the reaction and product formation. Entries 16–24 show the conditions that employed several solvents and high temperatures in a classical approach. In methanol (entry 16) and ethanol (entry 17) solutions, the reaction mixtures were subjected to reflux at 100 °C for 20 hours, resulting in no observable product formation of the mixture at the proportions mentioned above. Similarly, using 1,4-dioxane (entry 18) and acetonitrile (entry 19) under reflux conditions at 100 °C for 20 hours also yielded no product. Further experiments with dimethylformamide (DMF) at 100 °C (entry 20) and 130 °C (entry 21), as well as *N*,*N*-dimethylacetamide (DMA) at 130 °C (entry 22), resulted in no product formation. In the same manner, benzene at 120 °C (entry 23) and toluene at 120 °C (entry 24) did not result in product formation. The yield for solution-based systems resulted in the formation of 0% target product in contrast to results obtained in a mechanochemical setting, hence putting emphasis on the vital role of mechanochemical activation of $BaTiO_3$ in driving the reaction to completion. This places emphasis on the importance of mechanical stimulation of $BaTiO_3$ to generate the necessary energy to drive the reaction by creating temporary polarized particles.

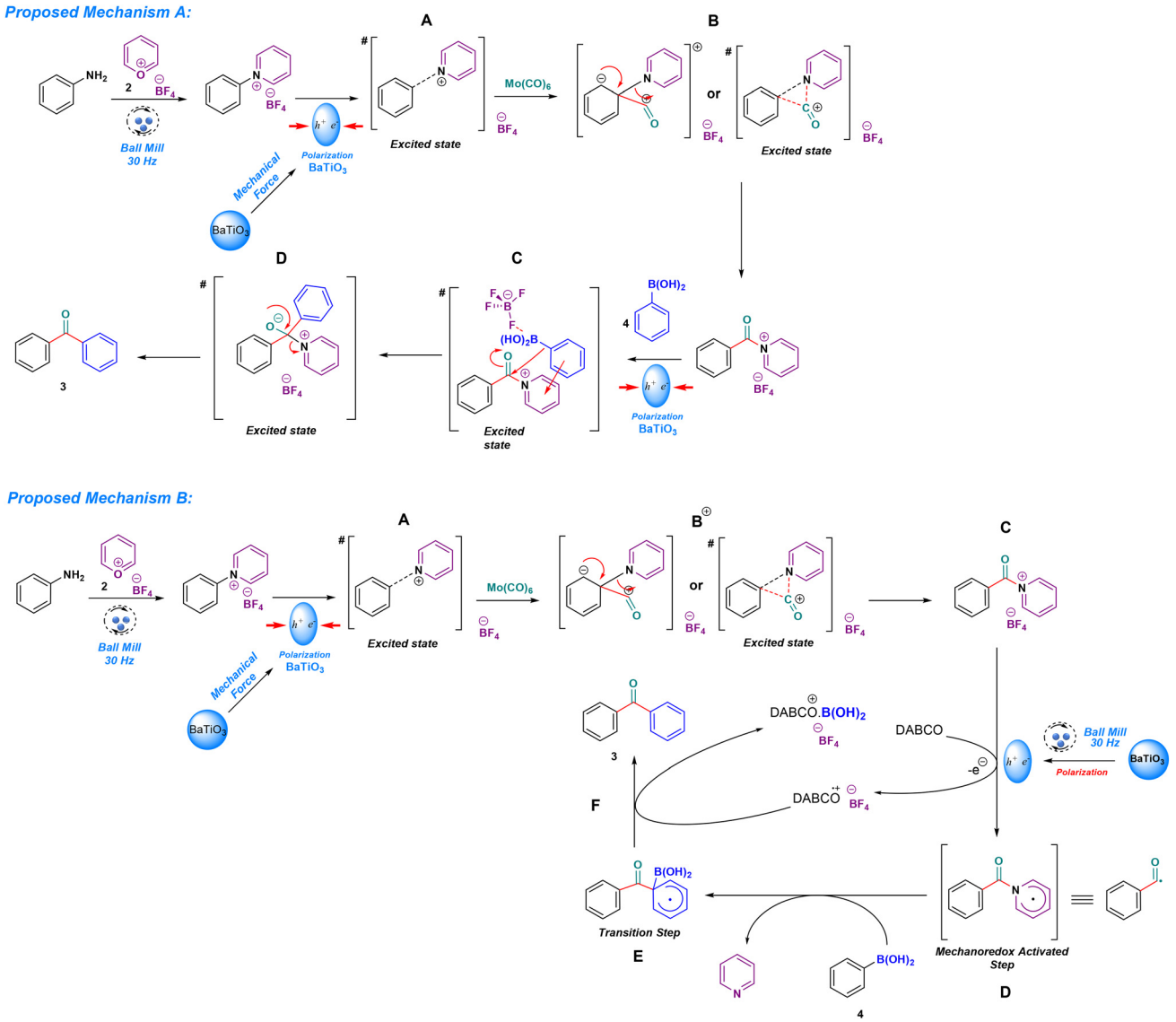
Optimization of the reaction conditions leading to the preparation of benzophenone derivatives involved a detailed evaluation of the applicability of the method using substrates

and coupling agents with substituents at the *ortho*, *meta*, and *para* positions. The isolated target products **3a–3z** obtained in isolated yields of 50%–92% with boronic acid as the coupling agent confirm the efficiency of the method over a wide scope of the parameters investigated (Scheme 2). The effect of substituent's position on yield efficiency was tested by synthesizing the same product, which are the compounds displaying the same labels in the scope. The results obtained for compounds **3a** (86% and 85%), **3b** (83% and 88%), **3c** (84 and 82%), and **3d** (80% and 85%) were quite high in yield and low in variability. Compound **3e** was isolated in a fair amount of 90% yield, while both **3f** and **3g** were obtained in 88% and 85% yields, respectively. Yields of 88% and 90% were obtained for compound **3h**, whereas for compounds **3i** and **3j**, the resulting yields were 86% and 91%, 90% respectively. Compound **3k** gave low yields of 68% and 50%. On the other hand, **3l** presented higher isolated yields of 89% and 87%, while **3m** yield was 87%. For **3n**, the yields were a bit more varied at 72% and 81%. For compounds **3p–3r**, the yields were 76%, 68%, and 67%. Compounds **3s** and **3t** provided yields of 81% and 82%. The compounds **3u–3z** provided yields of 92%–68%. The viability of the method was evaluated also with respect to reactions employing trialkoxysilanes as the coupling agent, although the efficiency of such reactions was slightly less than that of the reactions that employed boronic acid as the coupling agent. Target products **3a–3z** gave yields that ranged from 51% to 79% (Scheme 2). Yields obtained for compound **3a** ranged from 74% to 77%, showing good reproducibility regardless of the substituent placement. Compound **3b** also gave similar results, with isolated yields of 71% and 79%, which is in line with the trend for efficiency. Compounds **3c** and **3d** gave yields of 74% and 75%, respectively. Compound **3e** produced a high yield of 79%, and similarly the yield for compound **3h** was 77%. Products **3j**, **3k**, and **3n** displayed yields of 75%, 65%, and 70%, and the trend remained similar for the series of compounds **3t**, **3u**, and **3w** (74%, 76%, and 74%). The lowest yield of 51% was obtained for compound **3z**; in this way, such results allow us to surmise the efficiency of the protocol based on the series of different substituted benzophenones obtained with boronic acid and trialkoxysilanes as coupling agents.

In a similar manner to the reaction series of boronic acids and trialkoxysilanes (Scheme 2), the scope was studied for *ortho*-hydroxyarylenaminones to further extend the method for targeted production of 3-benzoylchromones (Scheme 4), which are important precursors for compounds with bioactive properties and require a complicated mechanistic pathway for their production.[46] Isolated yields for this reaction series ranged from 80% to 91%, showing the high efficiency of the approach with *ortho*-hydroxyarylenaminones. High yields of 83% and 91% were obtained for compounds **7a** and **7b**. Compound **7c**, in turn, accounted for 87% of the total product. **7d** and **7e** gave yields of 85% and 81%, respectively. Lastly, excellent to acceptable results were obtained for compounds **7f** and **7g** (90% and 80%). All these data show that the method retains its wide scope of application and efficiency with different substrates, performing with the same high efficiency for *ortho*-hydroxyarylenaminones, is very versatile, and thus has very good chance to be further optimized for the sake of synthesizing products in high yields.

The mechanochemically driven, transition metal catalyst-free C–C coupling of boronic acids with aniline derivatives to form benzophenones involves *in situ* reconfiguration to acyl pyridinium (Scheme 3 – mechanism A). Initially, an aniline derivative undergoes condensation with pyrylium tetrafluoroborate under the influence of mechanochemical ball-milling to form active pyridinium species. The mechanochemical polarization of the barium titanate ($BaTiO_3$) provides necessary energy input to excite the pyridinium intermediate to lead to an active pyridinium species **A**, which is here used as an on–off switch to access the carbonylation (step **B**).[12,13,47] Solid Mo$(CO)_6$ in the ball mill is used as the CO ligand source. CO ligands are released during mechanochemical activation. The CO ligands of the carbonyl complex then aid in promoting carbonylation of the pyridinium salt, which converts it to the acyl pyridinium intermediate. During this step, the pyridinium species changes shape, where the bound CO replaces a pyridinium molecule, allowing the formation of the acyl pyridinium intermediate, which is then attacked by the nucleophile in the next step. This acyl pyridinium subsequently undergoes a mechanochemically driven nucleophilic attack by boronic acid coupling on the source of acyl pyridinium, affording the arylated carbonyl moiety (step **C**). The benzophenone target is generated by releasing the pyridine moiety (step **D**). This is the fourth and last step of the C–C coupling reaction, establishing a fully mechanochemical pathway toward benzophenones by late-stage functionalization of anilines. Mechanochemical C–C coupling is a simple, highly efficient example of mechanochemistry in organic synthesis, representing one of the clean and effective ways of realizing sustainable synthesis of complex organic molecules, such as benzophenones.

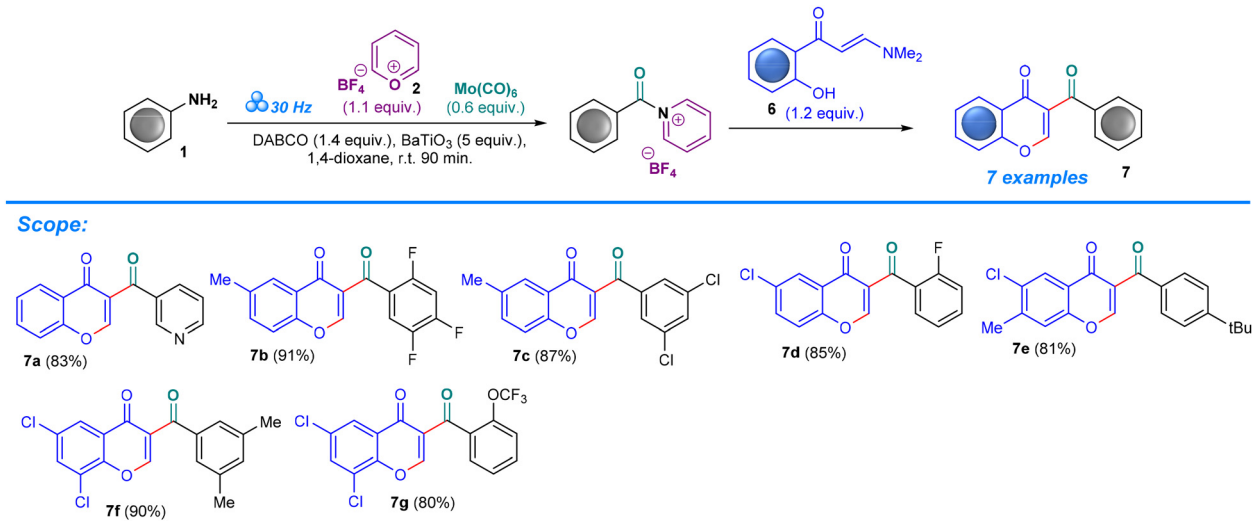
Another important mechanistic proposal was devised according to the principles of redox chemistry, which finds basis in the mechanoredox catalysis precedent of electron transfer from barium titanate to commence a redox cycle within the system (Scheme 3 – mechanism B).[12–14] In the first step, aniline undergoes condensation with pyrylium tetrafluoroborate, resulting in pyridinium species. The mechanical stimulation of barium titanate ($BaTiO_3$) produces an electrical field that assists in the excitation of the pyridinium salt, which undergoes carbonylation (step **A**) by Mo$(CO)_6$ to form the acyl pyridinium intermediate (steps **B** and **C**). The mechanochemical polarization of the piezoelectric material $BaTiO_3$ induces single-electron transfer (SET) from DABCO to the acyl pyridinium intermediate (step **D**), generating the acyl pyridinium radical intermediate, which acts as a synthetic equivalent of the acyl radical. The resulting acyl pyridinium radical intermediate adds to the *ipso* position of the arylboronic acid **4** (step **E**), resulting in the formation of an aryl radical transition state. Finally, the electron transfer from the aryl radical transition state to DABCO (step **F**) leads to the formation of the expected benzophenone **3**, with DABCO cycling between its reduced and oxidized forms.



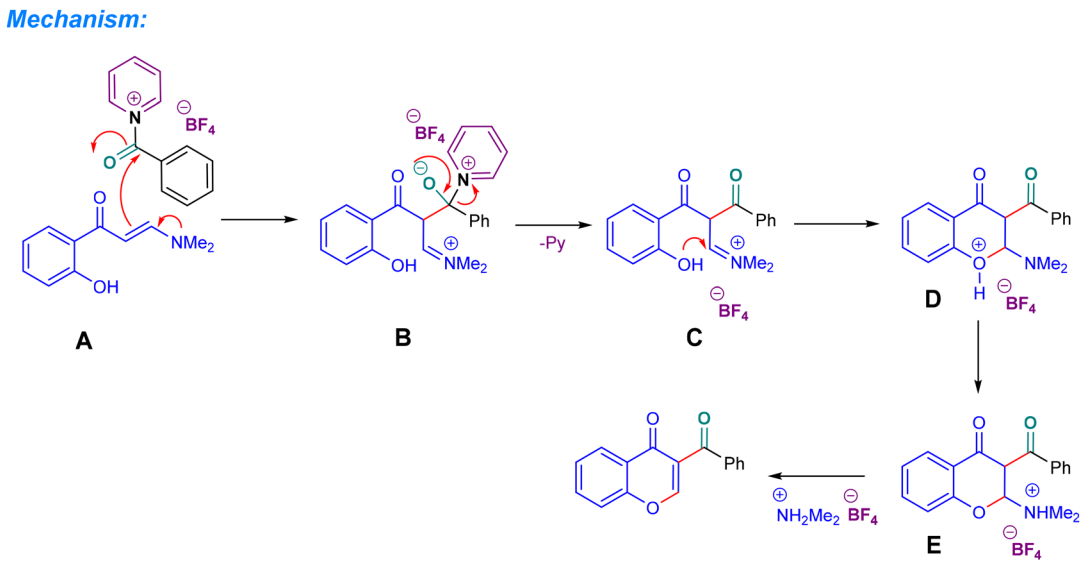
Scheme 3 Proposed mechanisms for benzophenone formation.

In the mechanistic account displayed in Scheme 5, *ortho*-hydroxyarylenaminones are used as coupling agents to give 3-benzoylchromones. Scheme 5, for which the formation of acyl pyridinium in Scheme 4 is the basis, explains the mechanistic steps that lead to the formation of 3-benzoylchromones. In the first step (step **A**), the acyl pyridinium intermediate is subjected to a nucleophilic attack by the *ortho*-hydroxyarylenaminones. The alpha carbon of the *ortho*-hydroxyarylenaminone attacks the carbonyl carbon of the acyl pyridinium intermediate. A tetrahedral intermediate is formed, leading to the next step (step B), in which the tetrahedral intermediate undergoes a rearrangement (step **C**), facilitating the elimination of the pyridine moiety. This elimination results in a new C–C bond between the *ortho*-hydroxyarylenaminone and the former acyl pyridinium moiety, from which the reaction can proceed towards the attachment of the aromatic moiety from the acyl intermediate. The hydroxyl group (–OH) on the benzene ring attacks a carbon atom of the side-chain adjacent to a nitrogen atom bearing a positive charge in a dimethylamine group (NMe_2^+). Subsequently, this step leads the formation of a new C–O bond and cyclisation of a six-membered ring (step **D**). The BF_4^- anion balances the positive charge of the oxonium intermediate (positively charged oxygen), which then transfers its proton to the neighboring nitrogen forming an ammonium leaving group, which upon elimination leads to the formation of 3-benzoylchromone (step **E**).

DFT calculations were performed to gain insights into the proposed reaction mechanisms (mechanisms A and B, Scheme 3), and the resulting reaction energy profiles are reported in Fig. 1 and 2. Mechanism A starts with the formation of the van der Waals complex involving reactants **R**, *i.e.*, a pyridinium species and hexacarbonyl molybdenum, *i.e.*,



Scheme 4 Reaction scope for *ortho*-hydroxyarylenaminones.



Scheme 5 Proposed mechanism for 3-benzoylchromone formation.

$Mo(CO)_6$ (Fig. 1). In the van der Waals complex (or reactant), one CO group (ligand) of $Mo(CO)_6$ interacts with the active pyridinium species at a distance of 3.62 Å. In this step, the length of the Mo–CO bond increases to 2.05 Å. The first step in the mechanism is the carbonylation of the pyridinium species by the CO ligand. The activation barrier for this step is 30.28 kcal mol^{-1}. In the transition state *i.e.*, **TS1**, the bond length of the Mo–CO bond increases to 2.44 Å and that of CO to pyridinium decreases to 3.10 Å, resulting in the formation of the acyl pyridinium intermediate (see Fig. 1). In **Int1**, the bond length of pyridinium to CO further decreases to 2.70 Å, along with the release of $Mo(CO)_5$. The acyl pyridinium intermediate then undergoes a nucleophilic attack by boronic acid, resulting in the arylated carbonyl moiety through coupling at the acyl pyridinium source. **Int2** lies at −50.53 kcal mol^{-1}. In **Int2**, the bond distance between the boronic acid and CO of acyl pyridinium is 3.46 Å, whereas the bond length of CO to the pyridine ring in acyl pyridinium is 1.49 Å. The activation barrier for this step (*i.e.*, nucleophilic attack) is 32.38 kcal mol^{-1}. The bond distance between boronic acid and acyl pyridinium decreases to 2.22 Å in **TS2**. Similarly, the bond length of CO to the pyridine ring (in acyl pyridinium) increases to 2.53 Å in **TS2**. After **TS2**, in **Int3**, the bond distance between boronic acid and acyl pyridinium further decreases, and the bond distance of CO to the pyridine ring further increases, resulting in the formation of benzophenone (**P**) along with the release of a pyridine moiety. This is the last step of the C–C coupling reaction, establishing a fully mechanochemical pathway toward benzophenones by late-stage functionalization of anilines.

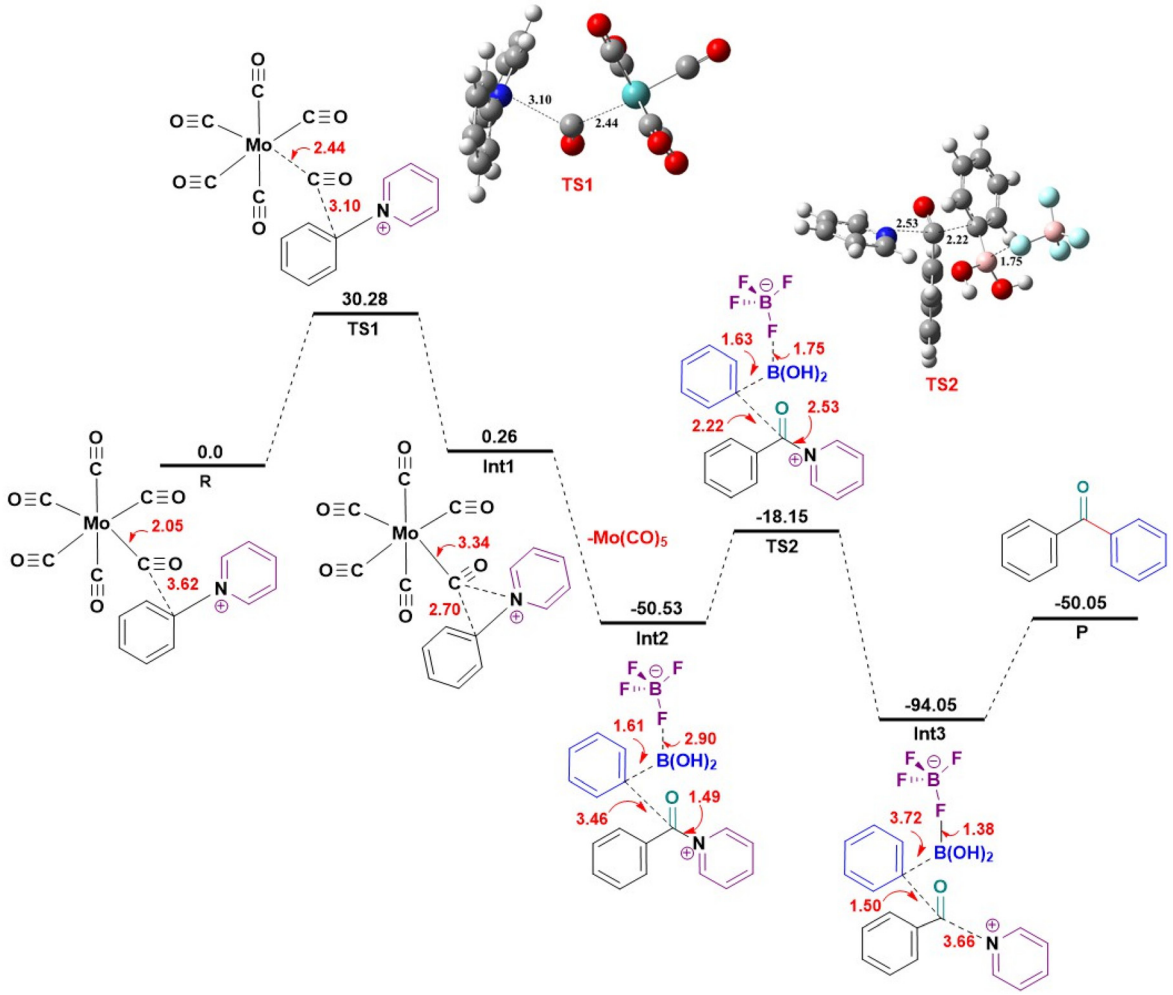


Fig. 1 Free energy diagram showing the proposed free radical mechanism for benzophenone formation *via* mechanism A (Scheme 4). All the reported energy values are presented in kcal mol^{-1} with reference initial reactant (**R**) at 0.00 kcal mol^{-1}. The measured bond lengths are presented in angstroms (Å).

Another plausible mechanism *i.e.* mechanism B (Scheme 3) is the free radical mechanism for the formation of benzophenones. As shown in Fig. 2, the initial steps in mechanism B are similar (up to the formation of **Int1**) to mechanism A, *i.e.*, the formation of the acyl pyridinium intermediate by the attack of the CO ligand on the active pyridinium species, requiring an energy barrier of 30.28 kcal mol^{-1}. The subsequent step is the deamination of the acyl pyridinium intermediate *i.e.*, the removal of aryl amide from acyl pyridinium, resulting in the formation of a radical intermediate. After the deamination of the acyl pyridinium species, the radical intermediate couples with boronic acid. This step of the mechanism proceeds through a free radical mechanism. **Int2** is a stable species involving boronic acid and a radical intermediate. The formation of benzophenone through the free radical mechanism involves an activation barrier of 4.15 kcal mol^{-1}. The bond distance between the C of boronic acid and the CO of the free radical in **Int2** is 3.51 Å, which decreases to 2.16 Å in **TS2**, and finally to 1.53 Å in **Int3**. $B(OH)_2$ leaves **Int3**, resulting in the formation of the final product **P**, *i.e.*, benzophenone. The final product obtained through this mechanism is very stable *i.e.*, lying at an energy of −69.27 kcal mol^{-1}.

The outcomes of the DFT calculations are much appropriate for the reactions that are carried out in the gaseous phase or in the solution phase. It has been well established that mechanochemically promoted reactions proceed along the synthetic pathways different from those described in the solution.[48–51] In a solvothermal process, the interaction between reactant molecules takes place by collisions in the liquid phase, while in the mechanochemical ball-milling process, the reactants are ground between the balls and the vessel surface as well as the between the surface of balls, where the collision between the balls and the vessel supplies the mechanical energy.[48]

During the mechanochemical ball milling, the substrates are subjected to mechanical forces, such as shear and non-hydrostatic compression forces, and combinations thereof.[52] As a result, the solid reactants undergo several associated physical processes including particle size reduction (comminu-

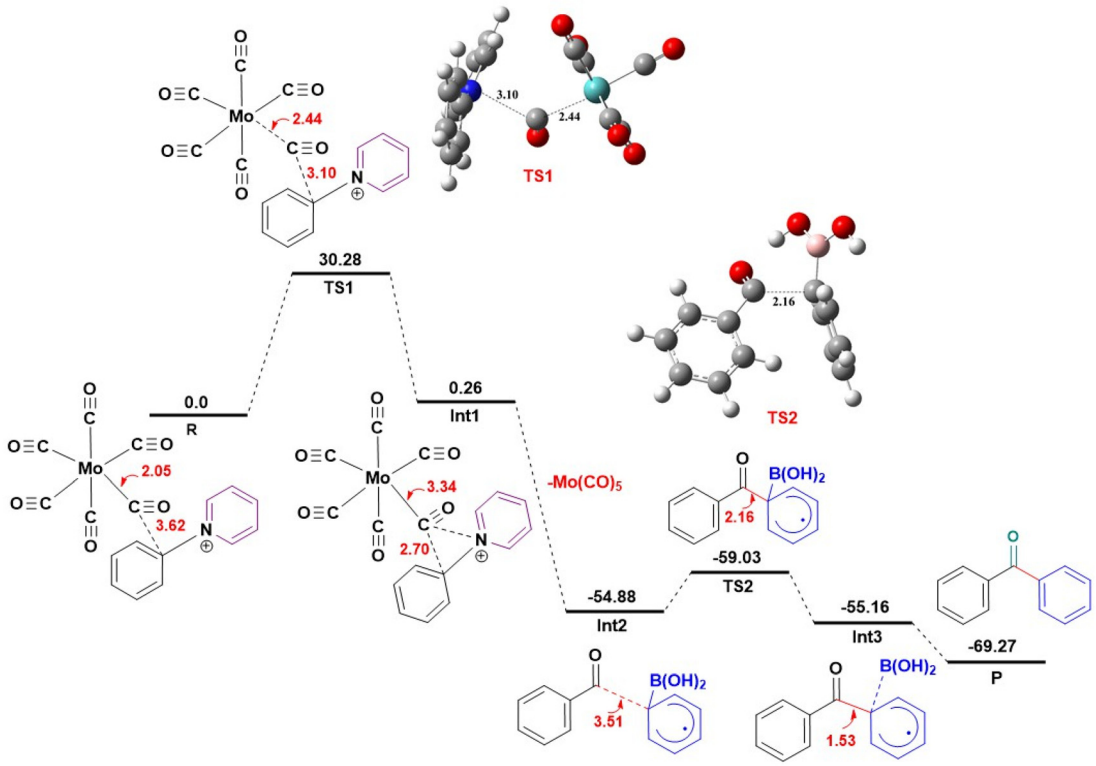


Fig. 2 Free energy diagram showing the proposed free radical mechanism for benzophenone formation *via* mechanism B (Scheme 4). All the reported energy values are presented in kcal mol^{-1} with reference initial reactant (**R**) at 0.00 kcal mol^{-1}. The measured bond lengths are presented in angstroms (Å).

tion), with a consequent surface area increase, and the formation of lattice defects of various types, wherein the reactivity is enhanced due to the reduction of the strength of the attractive interactions that hold the solid together, which also ultimately leads to amorphization. Furthermore, the mechanical energy acts synergistically with the internal energy of the chemical system due to its temperature, further increasing the chemical reactivity of the matter. Herein, the combined effects of grinding, crushing, pulverizing, impacting, and shearing forces can induce a chemical reactivity different from that of solution-based processes.[53] These force-induced perturbations induce a change in the energy landscape of chemical reactions and accelerate the dissociation of unloaded bonds and the change sets in the electronic configuration of covalent bonds, enabling a different chemical selectivity than that of conventional solution-based reactions. Moreover, the ball-milling process ensures the feasibility of the reaction by the creation of hot spots (which has a temperature of about 600–1000 K), enhanced solid–solid mixing and contact area, the creation of metastable or unstable structural configurations, or producing reactive surfaces *in situ*.[48] Thus, by managing the milling parameters, such as the ball/powder weight ratio, milling frequency, milling time, and atmosphere, it is possible to drive the kinetics of mechanochemical reactions to overcome the energy barrier, which is quite difficult in solution phase processes.

Conclusion

Herein, we developed a novel mechanochemical approach for the transformation of anilines to benzophenones, with Mo $(CO)_6$ being the solid source of CO. This addresses the challenge of activating the inert $C(sp^2)$–NH_2 bond of anilines without pre-functionalization in a one-pot process, which considerably simplifies the synthetic route. The formation of pyridinium salts followed by *in situ* carbonylation leads to C–C bond formation without employing a transition metal to drive the coupling aspect of the reaction. Moreover, we present evidence from different control experiments supporting the need for mechanochemical activation, as traditional solvent-based methods fail to deliver the target product in a solvothermal environment, thereby emphasizing the need for mechanochemical stimulation of the piezoelectric material through ball milling. The protocol was expanded to include the production of 3-benzoylchromones, underlining the broad scope and applicability of the approach for bioactive compound synthesis. Therefore, this novel approach will not only realize the potential of simplifying the synthesis of benzophenone analogues but also provide many more possibilities for late-stage functionalization of potentially bioactive molecules. Overall, the mechanochemical approach for deamination and functionalization conceptualizes a greener and more efficient way for the preparation of important classes of bioactive mole-

cules, which will permit the possible establishment of this new synthetic strategy in medicinal chemistry and related areas.

Conflicts of interest

The authors declare no competing financial interests.

Data availability

The datasets supporting this article have been uploaded as part of the SI: general information, synthetic procedures, spectral data, copies of ^{1}H and ^{13}C{1H} NMR spectra, and the data of DFT calculations of the postulated mechanisms. See DOI: **https://doi.org/10.1039/d5qo00920k**.

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