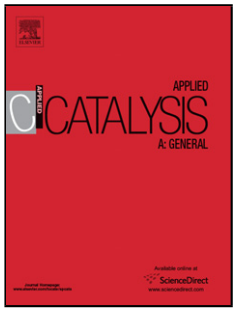

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Author: Maria J. Climent Sara Iborra Maria J. Sabater Juan D. Vidal

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Bifunctional acid-base ionic liquid for the one-pot synthesis of fine chemicals: thioethers, 2H-chromenes and 2H-quinoline derivatives

*Maria J. Climent, Sara Iborra, Maria J. Sabater, * Juan D. Vidal*

Instituto de Tecnología Química (UPV-CSIC), Universitat Politècnica de València, Consejo Superior de Investigaciones Científicas, Av. de los Naranjos s/n, 46022 Valencia, Spain.

Fax: 34 96 387 7809

E-mail: mjsabate@itq.upv.es

Abstract

A bifunctional organocatalyst with ionic liquid properties and with an optimized distance between the acid and basic sites efficiently activates electron deficient olefins for 1,4 conjugated addition, which can be incorporated in different one-pot transformations for the preparation of cyclic and acyclic compounds of biological and synthetic interest.

More specifically, the catalyst can be successfully applied for different carbon-carbon (C-C) and carbon-heteroatom (C-N, C-O, C-S) bond forming reactions integrated in a cascade sequence. The activity of the organocatalyst has been compared with that of structurally related monofunctional and bifunctional catalysts.

The most attractive features of this procedure are the high atom economy and the use of inexpensive starting materials as well as the use of an environmentally friendly catalyst that can be easily recovered thanks to its ionic liquid properties.

Keywords: organocatalysis, bifunctional, acid-base, one-pot, Michael addition, condensation, fine chemicals, chromenes, quinolines

1. Introduction

One possibility to improve activity and selectivity of chemical processes is the design of multisite catalysts that can jointly act and minimize the energy of the reaction transition state. The cooperative interactions occurring between two different catalytic centers and a given reaction transition state enable transformations that are not possible, or are done less efficiently, by using each catalyst separately. [1-3] For example a dual cooperation between acid and base centers placed on the same support and between complexes has been described. [1-3] In those cases where both active sites intervene in the transition state, the distance between the centers will be a key parameter to achieve high catalytic activities and selectivities. This mode of activation can also occur with organocatalysts, [4] as is the case for protonated *gem*-diamine piperidinomethane piperidium tetrafluoroborate (**A**), a molecule with an acid-base pair in close proximity, which has shown high activity and selectivity for condensation reactions. [5] Along with this, the combination of the acid and basic sites in the same molecule could make the organocatalyst behave as an ionic liquid hence facilitating its recovery and reuse. Thus, the interesting structural and chemical features as well as the good results obtained with *gem* diamine **A** for condensations, led us to explore the ability of this molecule as organocatalyst to perform multiple transformations in a single pot. Hence we will show that synthetic strategies involving a Michael reaction coupled with other acid/base catalyzed reactions in a sequential mode, allow gains of complexity in the synthesis of cyclic and acyclic organic structures of interest in the fine chemicals industry. [6] For achieving this, the ability of compound **A** for catalyzing the conjugated 1,4-addition of olefins will be studied and the results will be compared with the performance of other structurally related catalysts. Then, the ability of *gem* diamine **A** to couple an aldol

condensation reaction with a sulfa-Michael addition for forming new sulfur containing compounds in an expeditious way will be studied (Scheme 1).

INSERT SCHEME 1

It has to be said that a sulfa-Michael addition is an important synthetic tool for forming carbon sulfur bonds, since other synthetic alternatives such as the aldol reaction involving thiocarbonyl compounds are of limited synthetic viability. [7, 8] These limitations come from the fact that thiocarbonyl compounds are generally poor electrophiles, unstable under the aldol reaction conditions and are difficult to synthesize. [8,9]

Finally, we have also shown that the above working methodology is successful for performing two different cascade reactions involving a 1,4-conjugated addition (Michael reaction) and a cyclocondensation reaction, leading to the synthesis of types of heterocyclic compounds containing a 2H-chromene (**3**) and a 2H-quinoline (**4**) core. [10, 11]

INSERT SCHEME 2

Chromenes and quinolines are structural motifs that are usually found in natural products and drug-like compounds. In fact, chromenes have pharmacological activity as anti HIV, antitumor, antibacterial, fungicidal and insecticidal agents among other things; [10] whereas the quinoline ring occurs in general in natural products (especially in alkaloids), as is often involved in the design of synthetic compounds in the areas of

medicine, food, catalysis, dyes, and electronics. [11] For example, in the area of pharmacology the activity of quinolines in the treatment of leishmaniasis, malaria, as antitumor agents, antibiotics and antifungals is well-known. [11]

Due to the wide variety of applications, the synthesis of chromenes and quinolines has been an attractive goal for most synthetic organic chemists. The non-availability of many of these substrates and/or the limitations for achieving a specific substitution pattern as the main incentives for searching alternatives for the synthesis of these scaffolds by means of green and efficient processes should also be taken into account. To this respect, synthetic organic chemists have made use of new catalysts and/or different methodologies to obtain the chromene as well as the quinoline structures. [12-15]

However, despite many efforts, the catalytic synthesis of 2H-chromenes (**3**) and 2H-quinolines (**4**) has been reported to still proceed with large catalyst to substrate ratios, in occasions with the intervention of additives and usually with the impossibility of recovering and recycling the catalyst. [14, 15]

One will see here that is possible to prepare these molecules with high efficiency, while overcoming many of the above described drawbacks, by using a bifunctional acid-base catalyst with ionic liquid properties.

2. Experimental

Reagents solvents and basic and neutral Al_2O_3 were obtained from commercial sources and were used as received.

1) Synthesis of catalysts **A** and **B.** The catalysts were synthesized according to a procedure described in the literature. [5b]

Synthesis of catalyst ***A:*** A 100 mL round-bottomed flask was charged with dipiperidinomethane (10 g, 54.85 mmol) and diethyl ether (30 mL). Then equimolar amounts of tetrafluoroboric acid/diethyl ether were added dropwise into an ice bath. The mixture was stirred at room temperature for 1 h. A solid was formed which was recovered by filtration being exhaustively washed with diethyl ether. Then the solid was dried under vacuum to give the organic salt as a yellow solid (8.1 g, 55%).

Synthesis of catalyst ***B:*** 100 mL round-bottomed flask was charged with 1,2-di(N-piperidine)ethane (5.0 g, 25.47 mmol) and diethyl ether (30 mL). Then equimolar amounts of tetrafluoroboric acid/diethyl ether were added drop-wise into an ice bath. The mixture was stirred at room temperature for 1 h. A solid was formed and was recovered by filtration being washed exhaustively with diethyl ether. Finally it was dried under vacuum to give the organic salt as a yellow solid (4.25 g, 58.7%).

2) General procedure for the Michael addition reaction: In a typical experiment 0.1 mmol (or 0. 28 mmol) of catalyst and 1.5 mmol (or 2.8 mmol) of nucleophile were incorporated into a reactor while stirring under inert atmosphere. After temperature adjustment (80 ºC or 110 ºC), 1 mmol (or 2.8 mmol) of the carbonyl compound were added the reaction being periodically monitored by GC. The products were characterized by GC-MS and ^{1}H and ^{13}C-NMR by comparing with spectroscopic data of authentic samples.

3) General procedure for the condensation/sulfa-Michael one-pot sequence:

In a typical experiment 0.1 mmol of the catalysts were added to a solvent free solution of acetophenone (1 mmol) while stirring under inert atmosphere. After temperature

adjustment (100ºC), benzaldehyde (1 mmol) was added the reaction being periodically monitored by GC. After completing the formation of the condensation product chalcone, a stoichiometric amount of thiol was incorporated in the reactor and the reaction was monitored by GC. The products were characterized by GC-MS and ^{1}H and ^{13}C-NMR by comparing with spectroscopic data of authentic samples.

4) General procedure for the Michael addition/cyclization one-pot sequence

4a) Synthesis of 2H-chromene derivatives

In a typical experiment catalyst **A** (10% mol) was added to a solution containing a net solution of salicylaldehyde (1 mmol) and the alkene (1 mmol) while stirring under inert atmosphere. The temperature was adjusted to 100ºC, and the reaction was periodically monitored by GC. The products were characterized by GC-MS and ^{1}H and ^{13}C-NMR by comparing with spectroscopic data of authentic samples.

4b) Synthesis of 2H-quinoline derivatives

In a typical experiment catalyst **A** (10% mol) was added to a solution containing a solvent free solution of 2-aminobenzaldehyde (1 mmol) and the alkene (1 mmol) while stirring under inert atmosphere. After temperature adjustment (80ºC), the reaction was periodically monitored by GC. The products were characterized by GC-MS and ^{1}H and ^{13}C-NMR by comparing with spectroscopic data of authentic samples.

Experimental techniques: NMR spectra were recorded using a Bruker Avance 300 spectrometer at 300 (^{1}H) and 75 (^{13}C) in deuterated solvents with TMS as an internal standard.

Gas Chromatography coupled to Mass Spectrometry (GC-MS) was carried out using an Agilent 6890N GC /5973 Network model.

Gas chromatography was carried out using a Varian CP8400 equipment.

3. Results and Discussion

Given that previous studies have already shed light on the best conditions to carry out condensation reactions, [5] we have conducted preliminary experiments on the Michael addition in order to search a common operational window (temperature and solvent) for the desired multistep process that involves a condensation and a Michael addition.

Study of the Michael addition

Initially the Michael addition (1,4-conjugated addition) of different nucleophiles to the α,β-unsaturated carbonyl compounds 1,3-diphenyl-2-propenone and 2-cyclohexen-1-one were chosen as model reactions, and the activity and selectivity of bifunctional catalyst **A** was compared with that of other monofunctional (**C, D, E**) and bifunctional **B** related catalysts depicted below.

INSERT CHART 1

For example, in the acid-base organocatalyst **B** the separation between both active centers has been increased with respect to catalyst **A**, whereas compound **C** (the basic catalyst **A** precursor) is a strong basic catalyst which has shown high activity for aldol condensations. [4b] Finally, methylpiperidine **D** and N-methylpiperidinium

tetrafluoroborate **E** are organocatalysts commonly used for basic and acid catalyzed reactions respectively. [16]

In the first part of the work, a Michael addition between the nucleophile benzenethiol and the enone 1,3-diphenyl-2-propenone (chalcone) acting as Michael acceptor was performed with the organocatalysts depicted in chart 1 and the results are collected in Table 1 (see entry 1, Table 1).

INSERT TABLE 1

As shown in Table 1, the organocatalyst **A** exhibited an excellent activity and selectivity towards the Michael adduct when reacting 1,3-diphenyl-2-propenone (chalcone) and benzenethiol in the absence of solvent, whereas catalysts **B**, **C** and **D** were less active and selective than the former (entries 1-4, Table 1). Indeed, the resulting adduct was obtained at 110ºC with very good yields and in a relative short period of time with catalyst **A** (entry 1, Table 1), while no by-products were generated from 1,2-addition or polymerization or even hydrolytic reactions, under our experimental conditions.

It is interesting to notice that the activity of the catalyst decreased when the separation between both active centres was increased in the related organocatalyst **B (**see Chart 1 and results in Table 1 when going from catalyst **A** to catalyst **B**). This fact highlights the importance of keeping the appropriate distance between both catalytic functions to stabilize a given transition state (entries 1-2, Table 1). [5]

The higher activity of catalyst **A** can be attributed to a cooperative effect in where the carbonyl group of chalcone interacts with the acid site increasing the electron deficiency of the β-carbon of the enone in close analogy to previous studies on condensation

reactions [5], while the lone pair of the nearby N-basic center of **A**, abstracts the acidic proton of benzenethiol to generate a sulphur anion. The activation of both reactant molecules (protonated chalcone and anion) in the transition state complex at the proper distance facilitates the formation the Michael adduct (Scheme 3).

INSERT SCHEME 3

Just for comparison it is necessary to indicate that the bifunctional amino acid L-proline has been reported to catalyze the Michael addition between the same nucleophile /Michael acceptor pair with very good yields albeit working in ionic liquids as solvents. [17]

Since the Michael reaction can be catalyzed by stronger bases or acids, which will activate either the nucleophile or the acceptor component of the reaction [18] we have also used catalysts **C** and **D**. The Michael 1,4-adduct was obtained, albeit with moderated yields, under the same experimental conditions (entries 3-4, Table 1).

In view of these results, the conjugated enone 2-cyclohexen-1-one was selected as Michael acceptor being reacted with benzenethiol as S-nucleophile in the presence of the organocatalysts **A-D**, again in the absence of solvent at moderate temperature. The results collected in Table 1 show that again the conjugated addition of benzenethiol to a hexacyclic enone can selectively be conducted in the presence of the bifunctional catalyst **A** to afford the corresponding sulfa-Michael adduct with very good conversion (98%) and selectivity (95%), as compared with the rest of catalysts **B-D** (entries 5-8, Table 1).

In this case, it is necessary to indicate that the diphenyldisulfide compound could be detected as by-product, especially with the more basic catalysts **C** and **D**. Indeed,

disulfides form spontaneously by autooxidation of thiols upon exposure to air. [19] Since deprotonation of thiol to thiolate is the first step in disulfide formation, this reaction will be fast under neutral and basic conditions explaining why the more basic catalysts **C** and **D** are less selective towards the formation of the Michael adduct, whereas less basic conditions or even acidic conditions will stabilize thiols. [19]

It has to be pointed out that the Michael addition of thiols to α,β-unsaturated carbonyl compounds has been described to also occur without catalyst, albeit using an excess of thiol. [20] Taking into account this precedent, a blank reaction was carried out in the absence of catalyst showing that the reaction did not occur under our reaction conditions.

Finally, it is important to remark that the Michael addition is a highly demanding reaction in basic catalyzed reactions, showing the interest of applying bifunctional organocatalyst **A** with acid/base sites.[4] In other words a bifunctional acid-base catalyst with lower basicity can catalyze reactions that would require stronger basicities with a monofunctional base catalyst.

In summary, organocatalyst **A** has shown to be active and selective for the Michael addition with two different unsaturated carbonyl compounds and thiophenol as sulphur nucleophile (see Table 1), and we are now really ready to combine a conjugated 1,4-addition with different condensation reactions in order to prepare a variety of fine chemicals in one-pot processes.

Two-step reactions catalyzed by organocatalyst **A** in one-pot

a) *Sequential condensation/sulfa-Michael addition for obtaining sulphur-containing compounds in one-pot process.*

We have devised a one-pot sequence in which the formation of 1,3-diphenyl-2-propenone **1** as Michael acceptor, was followed by the 1,4 conjugated addition with

different aliphatic and aromatic thiols. The general structure of the resulting Michael adducts **2a-f** as well as the yields obtained by reacting benzaldehyde, acetophenone and diverse thiols are summarized in Table 2.

INSERT TABLE 2

In an initial approach benzaldehyde and acetophenone reacted in the presence of bifunctional catalyst **A** to form chalcone, which reacted *in situ* with different thiols acting as nucleophiles, to afford different sulphur containing compounds with very good yields in a two-step one-pot strategy (Scheme 1 and Table 2).

The combination of these two individual reactions in a single pot requires a change in the reaction conditions in order to maximize the yield of the final Michael adducts. Then the first step was carried out at 130ºC and the second one was performed at lower temperature (100ºC) under solventless conditions (see Table 2).

b) Sequential Michael addition/cyclocondensation reactions for forming 2H-chromenes and 2H-quinolines in a one-pot process.

The synthesis of important heterocycles such as 2H-chromenes or 2H-benzopyrans and 2H-quinolines was also accomplished in the presence of organocatalyst **A**. For achieving this, a tandem reaction comprising a Michael addition followed by an intramolecular cyclocondensation furnished chromenes and quinolines derivatives in one-pot. With this objective, different salicylaldehydes were reacted with a variety of α-functionalized alkenes in presence of catalyst **A**, resulting in the formation of diverse 2H-benzopyran structures under solventless conditions.

The most important results obtained on this reaction are detailed in Table 3.

INSERT TABLE 3

From the results collected there, we can conclude that, in general, organocatalyst **A** efficiently catalyzes the synthesis of 2H-chromenes starting from salicylaldehyde derivatives and *trans*-β-nitrostyrene as electron acceptor (entries 1-7, Table 3). Moreover, we found that selectivitities toward the corresponding chromene derivatives were in all cases 100%. *A priori*, these good results can be explained on the bases of the strong inductive effect of the nitro group on the double bond that makes the latter more prone to an electrofilic attack *versus* other electrowithdrawing groups, *vs.* a formyl group (compare entries 1-7 and 8-11 in Table 3). Therefore the utility of this strategy is evident if we take into account that both the nitro and formyl groups are valuable precursors for producing a wide variety of target molecules.

In order to complete the scope of the reaction, other selected examples were assessed by using salicylaldehyde derivatives, as well as differently substituted *trans*-β-nitrostyrenes. The most interesting results are collected in Table 4.

INSERT TABLE 4

From results presented in Table 4, other substituent effects were inferred on the synthesis 2H-chromene derivatives as will be described below. For example, the resonant effect transmitted by the OCH_3 group was differently manifested when this group moved from the salicylaldehyde derivative to the Michael acceptor. Indeed when the OCH_3 group at the *ortho* position (of the OH) in the salicylaldehyde moved to the

para position in the *p*-methoxy-*trans*-β-nitrostyrene, the yield of the corresponding 2(H) chromene decreased from 100% to 89% respectively (compare entries 2 in Table 3 and entry 1 in Table 4).

The same effect was observed when *p*-methoxy-*trans*-β-nitrostyrene reacted with different substituted salicylaldehydes, as the yields of chromene derivatives were in general lower than those obtained when reacting with the unsubstituted alkene *trans*-β-nitrostyrene (compare entries 1, 3, 5, 6 in Table 4 and entries 1-4 in Table 5).

Other inductive electrowithdrawing substituents such as the halogen Br and the NO_2 groups afforded lower yields of the desired heterocycle when placed at the *para* and *ortho* positions of the alkene respectively (entries 5-7, Table 5).

It is important to indicate that the synthesis of 2H-chromenes has been reported in the literature [14] to proceed with lower yields, while requiring higher amounts of catalysts than those reported in the present work. Indeed, the following table shows a collection of results obtained with different catalysts under different reaction conditions for the synthesis 3-nitro-2-phenyl-2H-chromene **3a** and 3-formyl-2-phenyl-2H-chromene **3h** as model compounds (Table 5).

INSERT TABLE 5

From the results given in Table 5 it follows that, in general, catalyst **A** is more efficient than some classical organocatalysts (DABCO, pipecolinic acid, etc), classic solid acid catalysts such as basic and neutral Al_2O_3, as well as other structural related catalysts (**B**, **C** and **D** employed in this study (see Table 5).

Besides this, other advantages of using catalyst **A** deserve to be highlighted. These are the lower amount of catalyst required, the no need of using solvent and, as we will see

later, the possibility of recovering and recycling catalyst **A** given its characteristics of ionic liquid.

Finally a library of differently substituted 2H-quinoline derivatives could be easily prepared from readily available starting reagents such as 2-aminobenzaldehyde [21] and appropriately substituted electron deficient alkenes in the presence of bifunctional catalyst **A** (Table 6).

INSERT TABLE 6

In this series of one-pot reactions, an initial 1,4-Michael addition between 2-aminobenzaldehyde and an electron deficient alkene, was followed by the formation of the respective intermediate which underwent cyclocondensation assisted by bifunctional acid-base catalyst **A.** The final result is the one-pot synthesis of a variety of quinolines (Scheme 1).

In general, the reactions were very fast since all of them went to completion in less than half an hour under solventless conditions. However in contrast to 2H-chromenes, the catalyst were less selective towards the desired 2H-quinoline. Interestingly the secondary product that could be detected in all cases was the respective fully aromatic quinoline derivative **5a-h** (see Table 6).

The importance of this route for the synthesis of 2H-quinolines is evident since the molecules obtained are intermediates for the synthesis of quinolines and 1,2,3,4-tetrahydroquinolines (both compounds mainly used as a feedstocks in the production of other specialty chemicals). [11, 13, 22] Again in this case we could find significant differences between the bifunctional catalyst **A** and other reported organocatalysts

(DABCO and pipecolinic acid) for the synthesis of some quinoline derivatives, which require the use of large catalyst to substrate ratios. [14c, 14f, 15]

Reusability of catalyst **A**

The reusability of the bifunctional catalyst **A** for the one-pot preparation of chromene **3a** has been shown here. The key point is that due to the ionic liquid characteristics the catalyst can be efficiently extracted from the reaction media by using the appropriate solvent. Thus, after extracting the products with diethyl ether, catalyst **A** was extracted with dichloromethane from the crude left. After solvent elimination the recovered catalyst (90%wt recovering) was dried at 50 ºC under vacuum. The catalyst was reused in successive runs for the synthesis of chromene **3a** and the results are depicted in Figure 1.

INSERT FIGURE 1

As can be deduced from the Figure 1, catalyst **A** retained its high activity and selectivity at least after three reaction cycles, whereas the ^{1}H and ^{13}C NMR spectra of the recovered catalyst **A** showed that this organocatalyst was stable under the described reaction and extraction process.

4. Conclusion

We have presented that the use of a bifunctional catalyst piperidinomethane piperidium tetrafluoroborate (**A**) in the Michael addition of different nucleophiles to activated α,β-unsaturated compounds, can afford the corresponding 1,4-adducts in good yields and selectivities.

In this case, the bifunctional catalyst **A** works better than monofunctional basic catalysts **C** and **D** or than bifunctional acid basic catalysts **B** in where the distance between the acid and basic site was increased.

This last observation points out to a plausible cooperative effect between the acid and basic site in the catalyst, leading to the stabilization of the reaction transition state for different condensation reactions (Knoevenagel and aldol condensation) using compound **A** as catalyst. In this case DFT mechanistic studies corroborated the existence of this cooperative effect and similar computational studies for the Michael addition are now underway.

The fact that organocatalyst **A** simultaneously activates electrophiles and nucleophiles for condensation reactions has been used to design the preparation of more complex molecules by means of a series of one-pot reactions. In this case, diverse conjugate systems that are initially formed *in situ* through a condensation reaction are further activated by bifunctional catalyst **A**, and have been used as reactants in a subsequent Michael addition by reacting with a variety of sulphur nucleophiles.

The application of organocatalyst **A** in one-pot reactions that strive for atom economy has been extended to the synthesis of heterocycles, leading into complex molecules that are of pharmacological and synthetic interest.

Moreover the resulting multi-functionalized compounds would serve as useful intermediates for further chemical manipulations.

The catalyst can be recovered and reused several times without loss of activity and selectivity.

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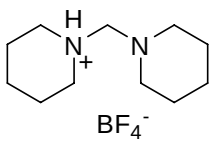
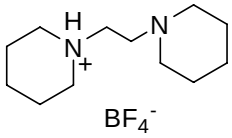


A



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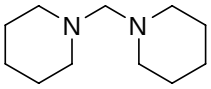

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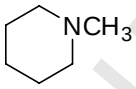
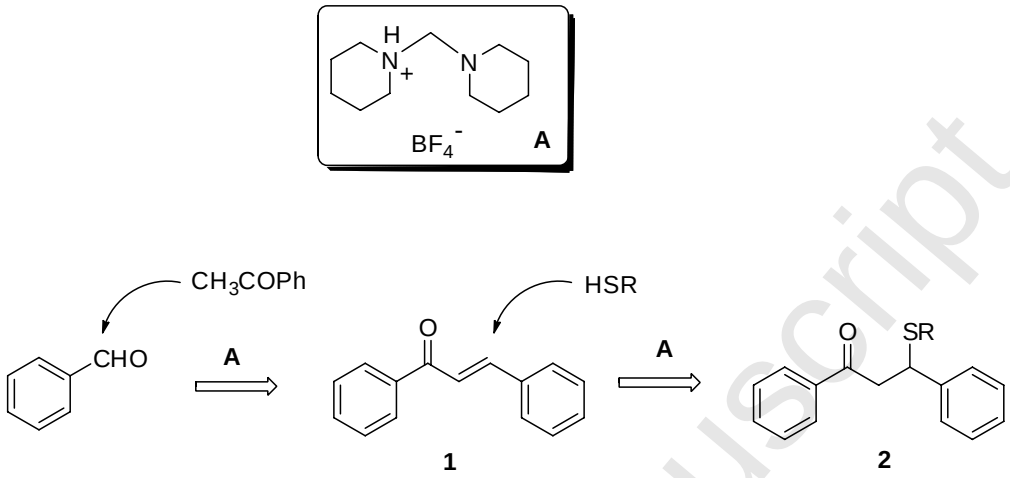


D

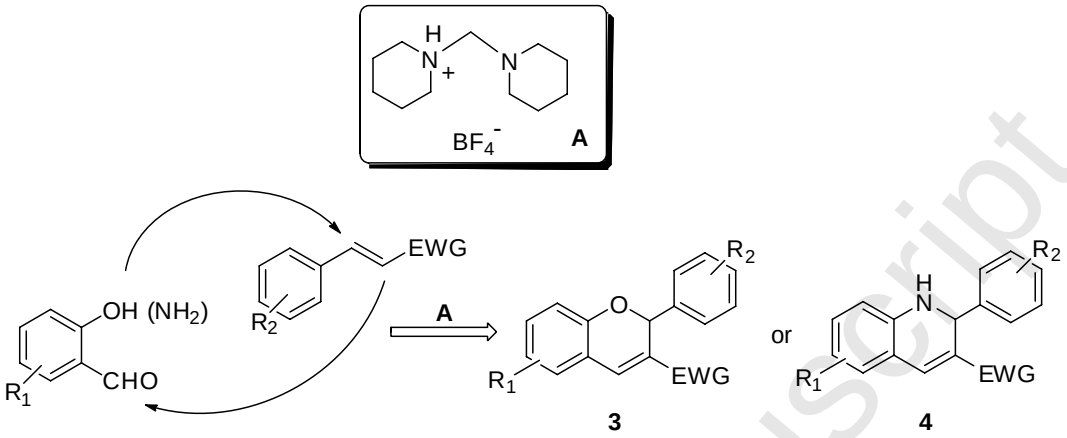
Chart 1

Aldol condensation/Michael addition

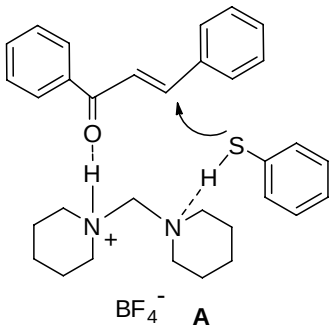


Scheme 1. Two step aldol condensation/Michael addition sequence catalyzed by **A** for the synthesis of S-compounds in one-pot.

Michael addition/Cyclocondensation



Scheme 2. Two step Michael addition/cyclocondensation sequence catalyzed by **A** for the synthesis of 2H-chromenes (**3**) and 2H-quinolines (**4)** in one-pot.



Scheme 3 Transition state complex for the Michael addition reaction of chalcone and benzenethiol

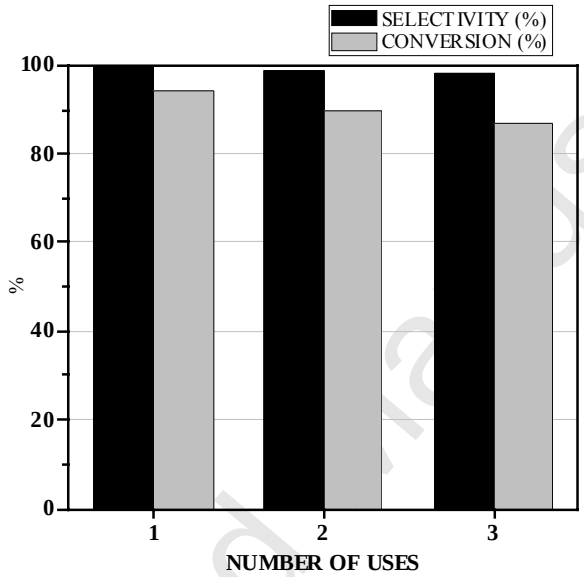
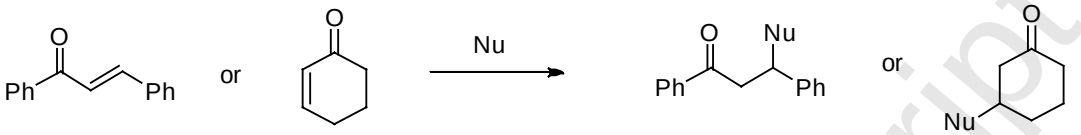
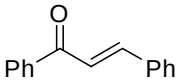
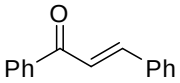
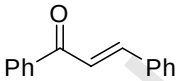
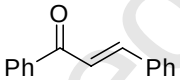
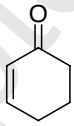
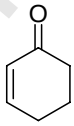
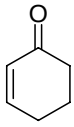
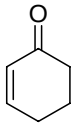


Figure 1. Graphic representation of the catalytic parameters obtained with catalyst **A** for the synthesis of chromene **3a** after successive uses.

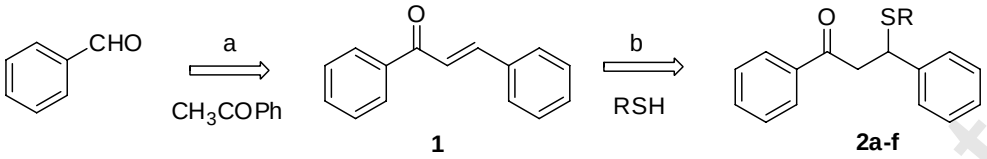
Table 1. Results on the Michael addition of α, β-unsaturated compounds (1,3-diphenyl-2-propenone and 2-cyclohexen-1-one) with benzenethiol with different catalysts.[a,b]

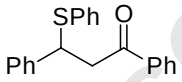
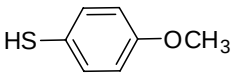
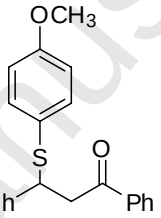
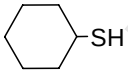
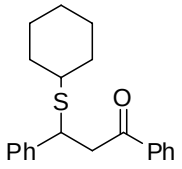
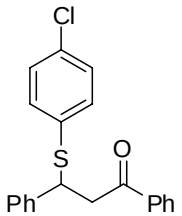
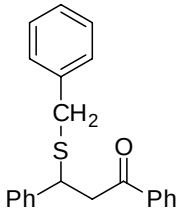
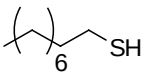
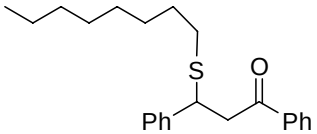


Entry	Catalyst	α, β-Unsaturated compound	Nucleophile	C(%)[a]	S(%)[b]
1	**A**[c]		PhSH	90	100
2	**B**[c]		PhSH	69	100
3	**C**[c]		PhSH	64	100
4	**D**[c]		PhSH	66	100
5	**A**[d]		PhSH	98	95
6	**B**[d]		PhSH	96	92
7	**C**[d]		PhSH	90	78
8	**D**[d]		PhSH	93	86

[a] Conversion (%) calculated by GC on the amount of unsaturated compound transformed; [b] Selectivity (%) calculated by GC towards the Michael adduct; [c] Reaction conditions (Michael addition of 1,3-diphenyl-2-propenone and benzenethiol): 1,3-diphenyl-2-propenone (1 mmol), benzenethiol (1.5 mmol), 0.1 mmol catalyst, n-dodecane: 0.1 mmol, T 110 ºC, t = 1h; [d] Reaction conditions (Michael addition of cyclohexenone and benzenethiol): cyclohexenone (2.8 mmol), PhSH (2.8 mmol), 0.28 mmol catalyst, T 80 ºC; t = 2h.

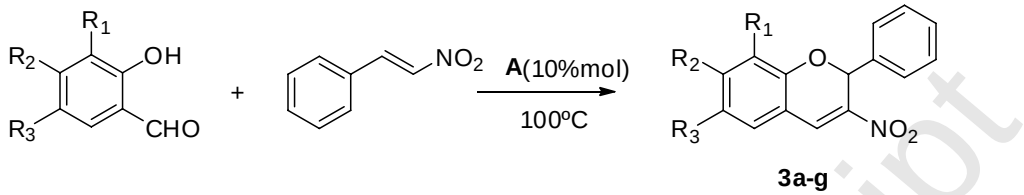
Table 2. Results on the condensation/sulfa-Michael one-pot sequence by reacting benzaldehyde, acetophenone and diverse thiols catalyzed by **A**.[a]



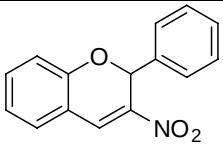
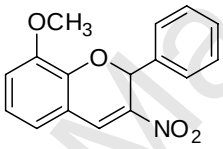
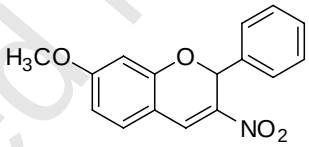
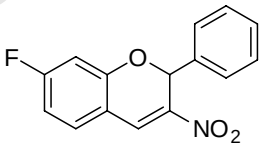
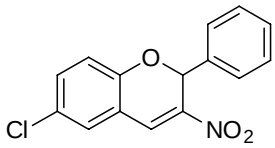
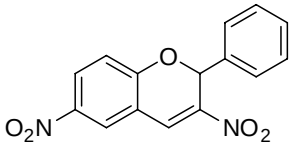
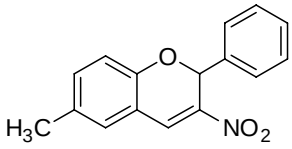
Entry	Catalyst	Time(h)	Nucleophile	Michael adduct	Yield(%)[b]	
					1	**2a-f**[c]
1	**A**	4	PhSH	 **2a**	95	80
2	**A**	5		 **2b**	95	78
3	**A**	5		 **2c**	95	86
4	**A**	4.5		 **2d**	95	79
5	**A**	5	$PhCH_2SH$	 **2e**	95	83
6	**A**	6		 **2f**	95	76

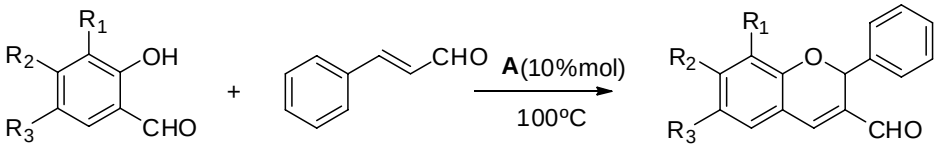
[a] Reaction conditions: Step a: benzaldedyde (1 mmol); acetophenone (1 mmol), catalyst (0.1 mmol), T 130 ºC; step b: nucleophile (an equimolar amount of nucleophile was added on the amount of condensation product formed; T 100 ºC; [b] yield was calculated by GC; [c]: isolated yield.

Table 3. Results on the synthesis of 2H-chromene derivatives from salicylaldehydes and the electron deficient alkenes *trans*-β-nitrostyrene and cinnamaldehyde catalyzed by **A** under solventless conditions.[a]

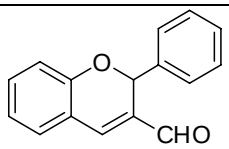
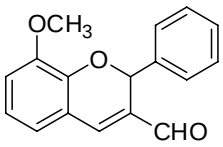
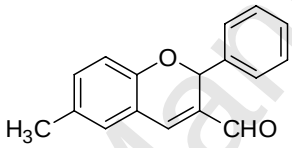
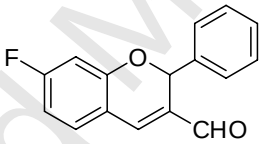


3a-g

Entry	R_1	R_2	R_3	Product	Time (h)	Yield[b,c] (%)
1	H	H	H	 **3a**	24	94
2	OCH_3	H	H	 **3b**	24	100
3	H	OCH_3	H	 **3c**	48	56
4	H	F	H	 **3d**	24	90
5	H	H	Cl	 **3e**	24	89
6	H	H	NO_2	 **3f**	24	68
7	H	H	CH_3	 **3g**	24	62

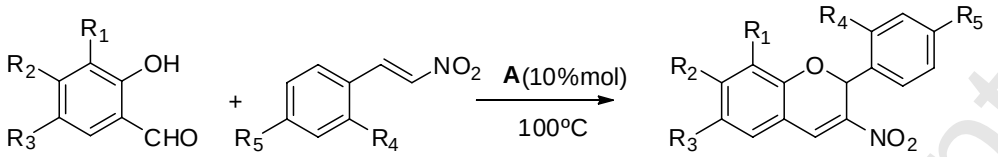


3h-k

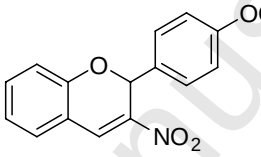
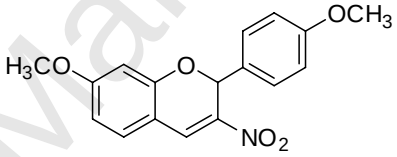
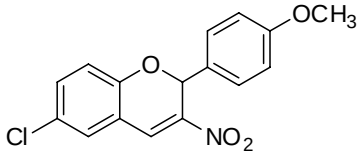
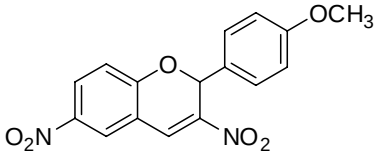
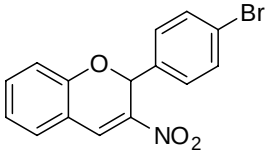
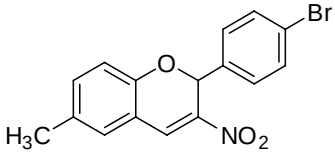
8[d]	H	H	H	 **3h**	24	78
9[d]	OCH_3	H	H	 **3i**	24	87
10[d]	H	H	CH_3	 **3j**	24	70
11[d]	H	F	H	 **3k**	24	72

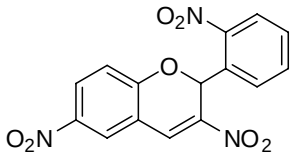
[a] Reaction conditions: salicylaldehyde (1 mmol), alkene (1 mmol), catalyst (10% mol), N_2, T 100 ºC; [b] calculated by GC with respect to the amount of converted alkene, [c] selectivity: 100% (in all cases); [d] catalyst: 20% mmol.

Table 4. Results on the synthesis of 2H-chromene derivatives from differently substituted salicylaldehydes and *trans*-β-nitrostyrenes catalyzed by **A** under solventless conditions.[a]



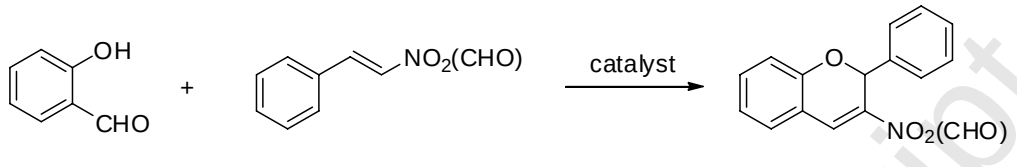
3l-r

Entry	R_1	R_2	R_3	R_4	R_5	Product	Time (h)	Yield[b,c] (%)
1	H	H	H	H	OCH_3	 **3l**	24	89
2	H	OCH_3	H	H	OCH_3	 **3m**	24	67
3	H	H	Cl	H	OCH_3	 **3n**	24	55
4	H	H	NO_2	H	OCH_3	 **3o**	24	43
5	H	H	H	H	Br	 **3p**	24	82
6	H	H	CH_3	H	Br	 **3q**	48	61

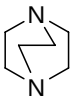
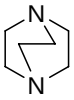
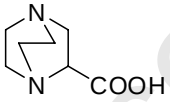
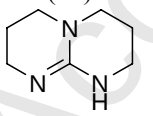
7	H	H	NO_2	NO_2	H	 **3r**	24	45

[a] Reaction conditions: salicylaldehyde (1 mmol), alkene (1 mmol), catalyst (10% mol), N_2, T 100 ºC;[b] calculated by GC with respect to the amount of converted alkene, [c] selectivity: 100% (in all cases).

Table 5. Results on the synthesis of 3-nitro-2-phenyl-2H-chromene **3a** and 3-formyl-2-phenyl-2H-chromene **3h** with different catalysts and references herein.

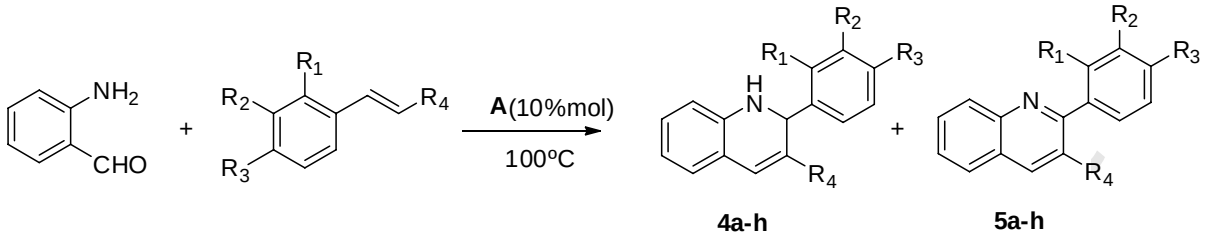


3a (or 3h)

Entry	Catalyst (% mol)	Compound	Solvent	Additive	T(ºC)	Time (h)	Yield (%)	Ref.
1	**A** (10)	**3a**	---	---	100	2	99	This work
2	**B** (10)	**3a**	---	---	100	6	0	This work
3	**C** (10)	**3a**	---	---	100	6	0	This work
4	**D** (10)	**3a**	---	---	100	6	0	This work
5	 (50-100)	**3a**	---	---	40	1.5	98	14a-b
6	 (10)	**3a**	----	----	100	6	----	This work
7	 (20)	**3a**	toluene	---	80	24	81	14c
8	 (5)	**3a**	---	---	80	15	55	14d
9[a]	Basic Al_2O_3	**3a**	CH_2Cl_2	sonication	25	2	85	14e
10[b]	Basic Al_2O_3	**3a**	---	---	100	6	---	This work
11[a]	Neutral Al_2O_3	**3a**	---	---	50	3	83	14f
12[b]	Neutral Al_2O_3	**3a**	---	---	100	6	---	This work
13	**A** (10)	**3h**	---	---	100	24	78	This work

[a)] Catalyst: 1g/mmol substrate, [b)] 0.1g/mmol substrate.

Table 6. Results on the synthesis of 2H-quinoline derivatives from 2-aminosalicylaldehyde and different alkenes catalyzed by **A** under solventless conditions.[a]



4a-h **5a-h**

Entry	R_1	R_2	R_3	R_4	Conv (%)[b]	Yield (%)[c]	
						4a-h	**5a-h**
1	H	H	H	NO_2	91	73	18
2	H	H	H	CHO	85	63	22
3	H	H	Br	NO_2	85	71	14
4	H	H	Br	NO_2	79	68	11
5	H	H	OCH_3	NO_2	86	72	14
6	OCH_3	H	H	NO_2	78	67	11
7	NO_2	H	H	NO_2	88	69	19

[a] Reaction conditions: 2-aminosalicylaldehyde (1 mmol), alkene (1 mmol), catalyst (10% mol), N_2, T 80ºC, time: 6 h; [b] calculated by GC with respect to the amount of converted alkene, [c] yield (%) calculated by GC.

Highlights

The bifunctional acid-base catalyst piperidinomethane piperidium tetrafluoroborate (**A**) catalyzes the Michael addition.

Piperidinomethane piperidium tetrafluoroborate (**A**) catalyzes a condensation reaction and subsequent Michael addition in one-pot.

A plausible cooperative effect between the acid and basic sites of the catalyst stabilizes the transition state.

This bifunctional catalyst **A** has been extensively applied to the one-pot synthesis of thioethers, 2H-chromenes and 2H-quinolines.

Graphical Abstract