The Acidity of a Carbon Nucleophile Dictates Enantioselectivity and Reactivity in Michael Additions to Aromatic and Aliphatic Enals *via* Iminium Activation

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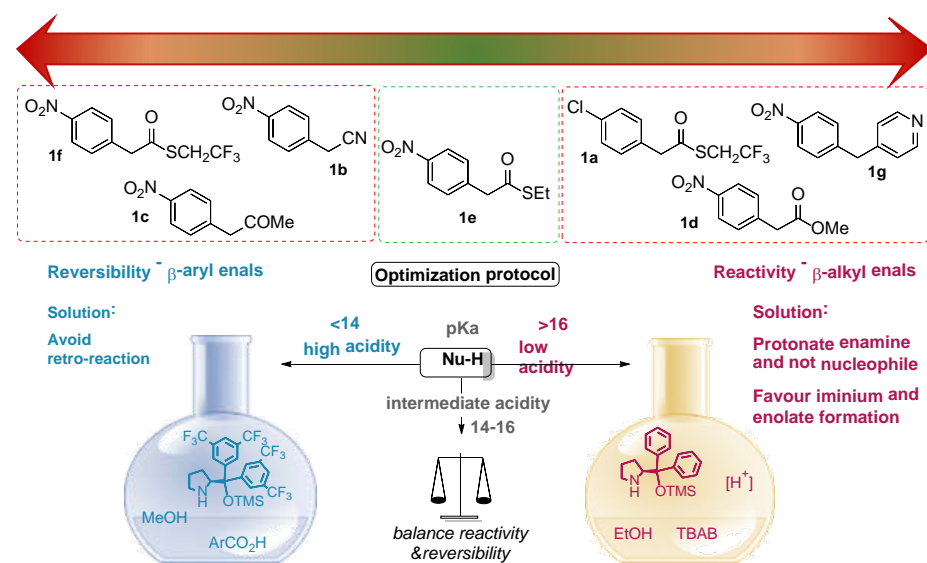
ABSTRACT: The Michael addition of activated methylenes to β-substituted α,β-unsaturated aldehydes (enals) *via* iminium catalysis takes place following reactivity and enantioselectivity patterns which depend on the electronic nature of the substituent in the β position (β-aryl or β-alkyl). Application of the same reaction conditions to both families of enals may result in erratic levels of asymmetric induction in the reactions of β-aryl enals, or low reactivity with β-alkyl enals. A systematic analysis of this behavior using phenylacetic acid derivatives as case study has led us to find a general trend: the different problems found for β-aryl and β-alkyl enals depend on the acidity of the nucleophile, and the outcome of the reaction for both types of enals can be improved substantially by careful choice of catalyst, solvent, and additive. Furthermore, this study has allowed us to understand subtle aspects of this transformation, and has enabled the formulation of a general and reliable protocol to obtain high yields and enantioselectivities consistently, regardless of the acidity of the nucleophile and the nature of the substituent (aromatic or aliphatic) at the β position.

KEYWORDS: asymmetric organocatalysis, Michael addition, iminium activation, enals, acidity.

INTRODUCTION

Iminium catalysis using chiral secondary amines has become a powerful method to introduce a carbon nucleophile at the β position of α,β-unsaturated aldehydes (β-substituted enals) via Michael addition in an asymmetric fashion.[1] The success of this transformation relies on the LUMO-lowering effect that the amine exerts on the starting enal, which results in a marked activation towards nucleophilic addition. Although a general mechanism for the reaction is widely accepted (Scheme 1), and despite the wealth of methods that have been reported which

capitalize on this strategy, several aspects that pertain to the generality of the transformation remain unclear. With the notable exception of sequences that involve cascade reactions in which mechanistic details are not easy to identify,[2] the behavior that enals display in terms of enantioselectivity and reactivity *frequently depends on the electronic nature of the substituent at the β-position*:[1c] β-aromatic enals often display enantioselectivities across the board,[3,4] while low reactivity is a frequent problem when exploring β-aliphatic enals.[5] Thus, it is relatively

common to find very similar reactions that require different catalysts, solvents, and/or additives, and information on this topic is often contradictory.

The accumulated knowledge on this reaction class indicates that *non-aromatic carbon nucleophiles must bear an acidic proton at the reactive site* for the reaction to proceed. The importance of the pK_a value of the nucleophile on the reactivity was first hinted at by Barbas III,[5d] who suggested that the relative acidity of the proton at the α-position of a given nucleophile must be lower than 16-17 for a reaction to take place. However, factors such as the lack of more specific information on the effect of the acidity range of that proton, or the impact of different additives in the reaction outcome, render the optimization process purely empirical.

Among the breadth of carbon nucleophiles that have been added successfully to enals, 2-phenylacetic acid derivatives have attracted interest in light of their applicability as synthetic building blocks for agrochemicals and active pharmaceutical ingredients,[6] such as nonsteroidal anti-inflammatory drugs. Attracted by this versatile structural motif, we have recently developed methods for the enantioselective Michael addition of 2-phenylacetic acids derivatives to α,β-unsaturated aldehydes, and the resulting adducts have been transformed into valuable synthetic intermediates in enantio- and diastereomerically pure form.[7] However, as detailed in the next section, the results obtained by us and other research groups are clearly indicative of a need for a general solution to the issues mentioned above. Here, we present a systematic analysis of the effect of several parameters on the reaction, along with NMR studies and theoretical calculations. Our studies suggest that both problems, *i.e.* reversibility with β-aromatic enals and low reactivity with β–aliphatic ones, are closely associated to the relative acidity of the nucleophile. In addition, we present data that support the hypothesis that inconsistency issues in asymmetric induction are also related to this relative acidity. From a synthetic standpoint, we have developed a reliable protocol that consistently affords high yields and asymmetric induction values for the Michael addition of multiple carbon nucleophiles to both types of enals.
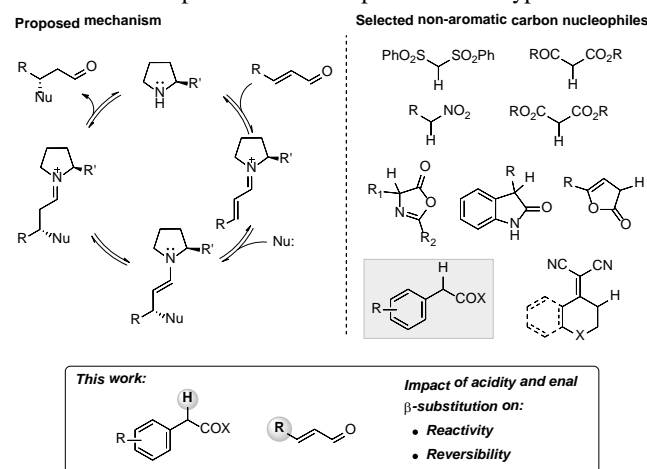

Scheme 1. Aim of this work

RESULTS AND DISCUSSION

1. Context of this work. Table 1 summarizes the observations made by different research groups for the Michael addition of arylacetic acid derivatives catalyzed by the widely used Jorgensen-Hayashi TMS-prolinol derivatives. The results obtained

with nucleophiles of similar structural features such as those studied by Barbas,[5d] Melchiorre,[5i] Kim[8] and us[7] represent a clear example of the apparently erratic behavior observed when employing β-aromatic and β-aliphatic enals. Barbas[5d] described the reaction of nucleophile **1a,** cinnamaldehyde derivatives and an acidic additive[9] to obtain Michael adducts in high enantioselectivities (entry 1). However, this set of conditions afforded the corresponding adducts with crotonaldehyde in low yields and optical purities. These findings are in sharp contrast with the results obtained by us for nucleophiles **1b-c**[7a,7b] using LiOAc as additive,[10] which showed very high enantioselectivity for β-aliphatic α,β-unsaturated aldehydes (R^1= aliphatic), and only erratic in the case of β-aromatic ones (R^1= aromatic). Entries 4 and 5 show the contradictory results reported recently and almost simultaneously by us[7c] and Kim[8] respectively for nucleophile **1d**: under our reaction conditions (catalyst **II** and TBAB-[11] tetrabutylammonium bromide- as additive) we observed excellent reactivity and enantioselectivities for β-aliphatic enals but lower and time dependent enantioselectivities for β-aromatic ones. In sharp contrast with our findings, Kim reported a combination of catalyst **I** and BzOH as additive to obtain high *ee* values with β-aromatic enals, whereas no reactivity was observed for β-aliphatic ones.[8] Nucleophile **1e**[7d] displays a trend similar to nucleophile **1d** (entry 7, Table 1): β-aryl enals perform better in the presence of acidic additives, whereas TBAB enhances the reactivity of the less reactive β-alkyl enals (compare entries 6 and 7 with 4 and 5). Entries 4-7 strongly suggest that optimization processes have to be performed considering the different behavior of β-alkyl and β-aryl enals[1c] and that acidic additives seem to slow down the reactions of aliphatic enals. The importance of the structural features of the nucleophiles is highlighted in entries 1, 5, 7 and 8, where similar conditions (catalyst **I** and BzOH as additive) are used in the reaction of nucleophiles **1a**, **1d**, **1e** and **1f**. We reasoned that the lower reactivity observed for nucleophile **1d** (entry 5)[8] in comparison with **1e** (entry 7)[7d] in their reaction with β-aliphatic enals could be due to the lower acidity of the former; moreover, the erratic behavior of **1f** (entry 8)[5d] compared to **1a** (entry 1)[5d] with aromatic enals could be due to the higher acidity of **1f**. The null reactivity of nucleophile **1g** with the aliphatic enals (entry 9)[5i] could be attributed to its low acidity.

Table 1. Trends in reactivity and enantioselectivity reported for the Michael addition of **1a-g** to β-substituted enals.
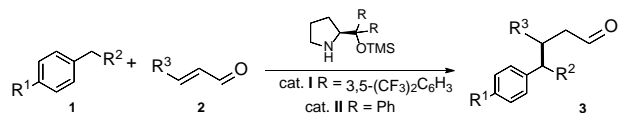
Entry	Nu	Ref.	Cond.	R³ = Aryl	R³ = alkyl
1	**1a**, R¹ = Cl, R² = COSCH₂CF₃	5d	I	BzOH	High ee	Low reactivity & ee
2	**1b**, R¹ = NO₂, R² = CN	7a	I	LiOAc	Erratic ee	High yields & ee
3	**1c**, R¹ = NO₂, R² = COMe	7b	I	LiOAc	Erratic ee	High yields & ee
4	**1d**, R¹ = NO₂, R² = CO₂Me	7c	II	TBAB	Erratic ee	High yields & ee
5	**1d**, R¹ = NO₂, R² = CO₂Me	8	I	BzOH	High ee	No reaction
6	**1e**, R¹ = NO₂, R² = COSEt	7d	II	TBAB	Erratic ee	High yields & ee
7	**1e**, R¹ = NO₂, R² = COSEt	7d	I	BzOH	High ee	Moderate reactivity & high ee
8	**1f**, R¹ = NO₂, R² = COSCH₂CF₃	5d	I	BzOH	Erratic ee	--
9	**1g**, R¹ = NO₂, R² = Py	5i	II	DABCO	High ee	No reaction

The following sections describe our efforts along two different lines: firstly, we sought for a clarification on the *influence of the pKₐ of the pronucleophile* on the Michael addition *via* iminium activation on reversibility and reactivity. Secondly, we explored the *parameters that modulate the different behavior of β-alkyl and β-aryl enals* in hopes of determining practical experimental conditions to sort out problems in each case.

2. Relative acidity of the pronucleophiles. In order to establish a connection between the acidity, the reversibility and reactivity of a given nucleophile, it became necessary to determine the acidity range for substrates **1a-1g** under conditions similar to those employed in the Michael addition. However, precise pKₐ values for all these substrates in CH₂Cl₂ or ROH (most common solvents used in Michael additions of this substrate class to enals) are not known,[12] which forced us to find an alternative way to determine the facility of deprotonation of a given pronucleophile. We reasoned that the deuteration degree of **1a-1g**, obtained when these are dissolved in the presence of a certain catalyst (**I** or **II**) could be indicative of the relative acidity of the nucleophile as well as the relative basicity of the catalyst. The results obtained in these studies are shown in Figure 1.
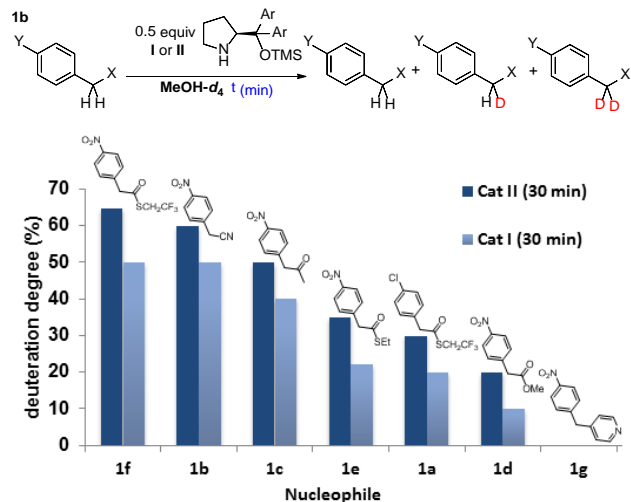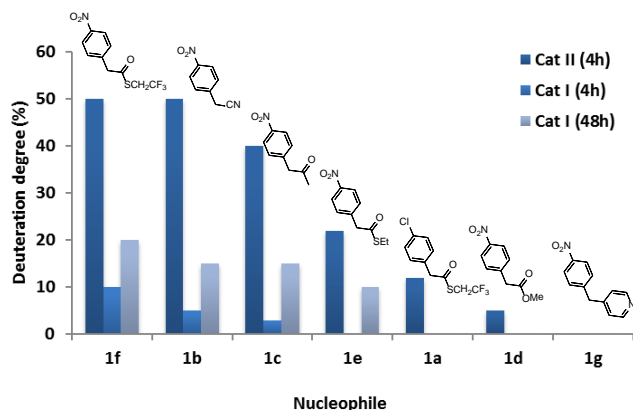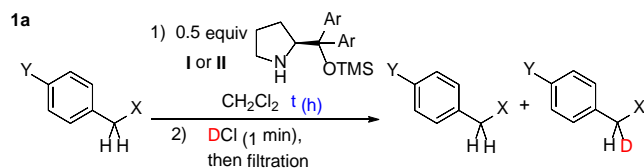

We found that after 4h in CH₂Cl₂ as solvent and treatment of the resulting enolate with deuterium chloride (DCl), the degree of deuteration was consistently higher in all cases when catalyst **II** was employed, which suggests that catalyst **II** is significantly more basic than catalyst **I** (Figure 1a). These experiments show an acidity order as follows: **1f~1b>1c**>**1e>1a**>**1d>1g**. Notably, the exact same trend was observed when reactions were performed in MeOD (Figure 1b). In this case, a higher degree of deuteration was detected due to the use of MeOD as solvent.

In order to obtain further theoretical support for our results, we performed a series of DFT calculations. The estimation, at M06-2X/6-311++G(3df,2p)//M06-2X/6-311G** level of theory,[13] of the acidity of these pronucleophiles in gas-phase, CH₂Cl₂ and EtOH as solvents showed the same trends as the experimental ones. The acidity was quantified as the free energy of the proton lost process: AH→A⁻ + H⁺.[14] The values are summarized in table 2. From these results, we can conclude that **1f** is the most acidic compound followed closely by **1b**. **1g** is the less acidic pronucleophile, which is in agreement with experiment. More important is the increment of acidity when the medium is changed: if **1f** is taken as example, the gas phase free energy for deprotonation is about 1296 kJ·mol⁻¹ whereas in EtOH this value decreases by about 128 kJ·mol⁻¹, which shows that protic solvents have an important effect.[15]

Table 2. The deprotonation free energy of the different pronucleophiles. All values expressed in kJ·mol⁻¹

Solvent	Gas Phase	CH₂Cl₂	EtOH
1f	1296	1178	1168
1b	1327	1189	1179
1c	1357	1217	1205
1e	1333	1197	1185
1a	1371	1223	1217
1d	1355	1208	1197
1g	1367	1234	1222

Figure 1. Deuteration exchange in compounds **1a-1g** in combination with catalysts **I** and **II** in a) CH₂Cl₂ and b) MeOD.

With a qualitative and quantitative range of acidity for the specific set of nucleophiles studied in our hands, we sought to clarify whether the different outcome of the reactions was determined by the acidity of the given nucleophile. Also, we envisioned that this outcome could be modulated by tuning the reaction conditions in accordance with the nature of the enal (i.e., aromatic or aliphatic).

3. On the reversibility of the system. Our experimental observation was that the use of more acidic and reactive nucleophiles (**1f**, **1b** and **1c**) resulted in lower and erratic values of asymmetric induction when aromatic enals were employed. In agreement with previous reports, we attributed the variable enantioselectivities to the reversibility of the process.[3] This scenario is outlined in Scheme 2a: enantiomer **A**, formed by attack of the nucleophile to the less hindered face of the iminium ion, would reenter the catalytic cycle by reaction with the catalyst to afford enamine **A**. Subsequent retro-Michael reaction would generate an iminium ion and a nucleophilic enolate. Then, the slower nucleophilic addition to the more hindered face of the iminium would yield enamine **B**, and consequently enantiomer **B**, thus enabling thermodynamic equilibration and racemization of the initial adduct **A**. This hypothesis is supported by the fact that retro-Michael reactions often occur if the nucleophiles are stabilized ions, in particular in the case of more acidic NuH, as they are better leaving groups. Moreover, and as opposed to β-aliphatic enals, aromatic ones may stabilize the corresponding iminium ion and aldehydes by virtue of a more extended π-conjugation, hence favoring the retro-reaction (Scheme 2b).
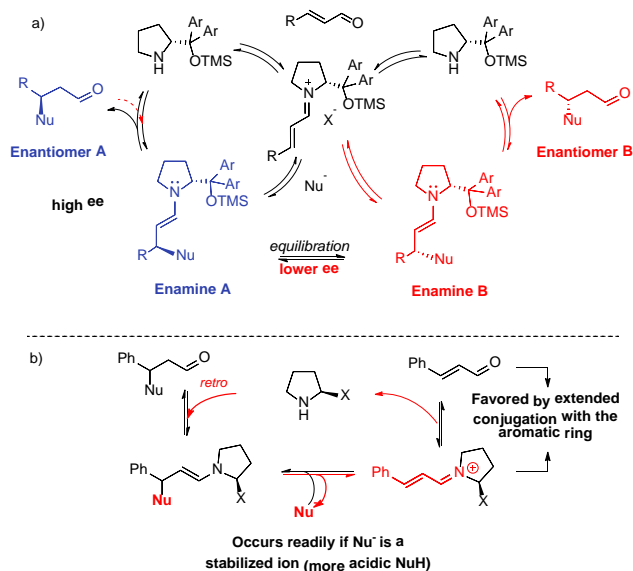
Scheme 2. a) Equilibration of enamines as cause for racemization. b) Michael (black) and retro-Michael (red) pathways.

To find theoretical support for these assumptions, we studied the structure of the iminium ion derived from catalyst **II,** in combination with crotonaldehyde **2a** (**II2a**) and cinnamaldehyde **2b** (**II2b**) using DFT calculations to highlight the structural differences between both intermediates. NBO and AIM population analysis were also carried out to underscore the electronic and bonding changes. Indeed, the stabilization issued by π conjugation in the aryl species is manifested by these combined techniques. Looking at the atoms which participate in the resonance (atoms 1-5 in figure 2), it can be observed that the electronic delocalization is more pronounced in the aryl substituted iminium ion than in the alkyl case. The lengths of single and double C-C bonds in **II2b** are shorter and longer respectively than in **II2a**.
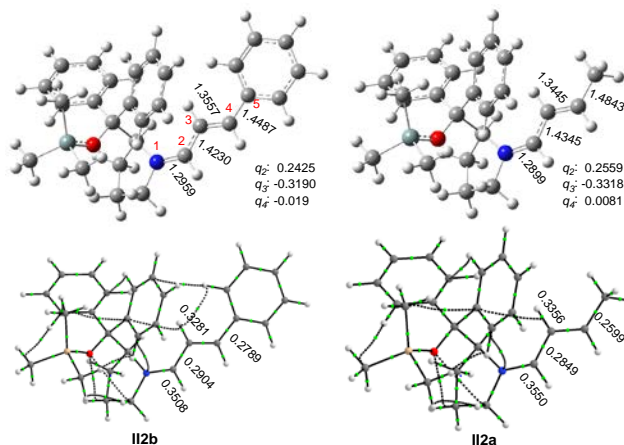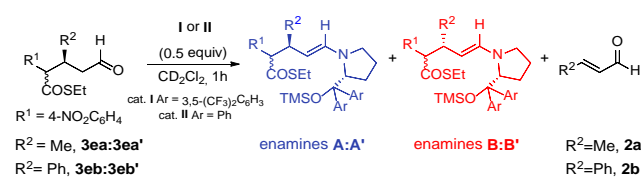

Figure 2. The optimized structures and the AIM graphs of the β-aryl and β-alkyl iminium ions (**II2b** and **II2a**). The bond lengths (in Å) and the electronic density of the BCP and natural charges (in a.u.) for relevant bonds /atoms are indicated.

The density of the bond critical points (BCPs) of these bonds ratify these findings. The relative charges found in both structures agree with the experimental observation that reactivity takes place through C-4. Additionally, the ΔG values obtained for the reaction of pronucleophiles **1a-1g** with **2a** or **2b** at the M06-2X/6-311G++G(3df,2p)//M06-2X/6-311G** level of theory[13] were found to be less favorable for **2b** in all cases, which supports its easier retro-Michael processes (see SI).

3.1 Parameters that affect reversibility. Experimental support for the importance of the nature of the enal, catalyst, additives and solvents in the reversibility (and therefore enantioselectivity) of the process was obtained by resubmission of Michael adducts **3ea** and **3eb**[16] under different reaction conditions, and detailed analysis of the evolution of the reaction. We studied the behavior of the adduct mixtures **3ea:3ea'** (R^2=Me) and **3eb:3eb'** (R^2=Ph) in the presence of 0.5 equivalents of catalyst[17] in CD$_2$Cl$_2$ under different conditions (Table 3 and SI for details). In the case of **3eb:3eb'** (R^2=Ph)**,** after 1 h and in the absence of additives, ^{1}H NMR analysis revealed a mixture of the corresponding diastereomeric enamines **A:A'** (16 %) and **B:B'** (18 %), as well as cinnamaldehyde[18] (29 %) (entry 1). Formation of enamines **B** strongly suggests that equilibration is taking place, which lends support to the equilibration hypothesis postulated in Scheme 2. In marked contrast, the reaction of **3ea**:**3ea'** (where R^2=Me) under identical conditions resulted in exclusive formation of enamines **A:A'** (40 %, entry 2), while the signals of the crotonaldehyde or enamines **B:B'** were not detected.[19] This finding suggests that although the substrate reacts with **II** to form the corresponding enamines, the equilibration with their diastereoisomers does not take place. These two results are in agreement with the experimental observation that compounds derived from β-aryl enals easily undergo racemization, whereas those that arise from addition to β-alkyl enals do not suffer from noticeable erosion of the enantioselectivity. When the mixture **3eb:3eb'** (R^2=Ph) was treated with 0.5 equivalents of the catalyst **I**, exclusive formation of enamines **A:A'** was detected even after 72 h of reaction (28 %, entry 3): this observation indicates that reversibility (and hence erosion of the enantioselectivity) is minimized when this catalyst was used. This effect could be due to two factors: 1) the lower nucleophilicity of catalyst **I** compared with catalyst **II**, and 2) the

lower stability of the iminium derived from **I** due to the electron-withdrawing effect exerted by the CF_3 groups.

**Table 3.** Retro-Michael reaction of compounds **3ea:3ea'** and **3eb:3eb'**.

R¹ = 4-NO₂C₆H₄
R² = Me, **3ea:3ea'**
R² = Ph, **3eb:3eb'**
enamines **A:A'** enamines **B:B'** R²=Me, **2a**
R²=Ph, **2b**

Entry	R²	Cat.	Additive (0.5 equiv)	3 (%)	A+A´ (%)	B+B´ (%)	2 (%)
1	Ph	II	--	37	16	18	29 (**2b**)
2	Me	II	--	60	40	--	-- (**2a**)
3[a]	Ph	I	--	72	28	--	-- (**2b**)
4	Ph	II	TBAB	23	16	23	38 (**2b**)
5	Ph	II	BzOH	53	8	10	29 (**2b**)
6	Ph	II	4-NO₂BzOH	68	32	--	-- (**2b**)

[a]Reaction time 72 h.

The effect of additives was also explored: we observed that addition of 0.5 equivalents of TBAB increased the amount of cinnamaldehyde (38 %, entry 4), which is in agreement with the low enantioselectivity control observed in the examples in Table 1 where this additive was used with aromatic enals.[7d,11b] In contrast, the addition of benzoic acid seems to slightly slow down formation of enamines (8 % **A:A'** and 10 % **B:B'**, entry 5). Consequently, the erosion of the enantioselectivity is partially reduced. This effect is even more pronounced with a stronger acid (4-NO₂C₆H₄CO₂H, entry 6, exclusive formation of enamines **A:A'**).[20]
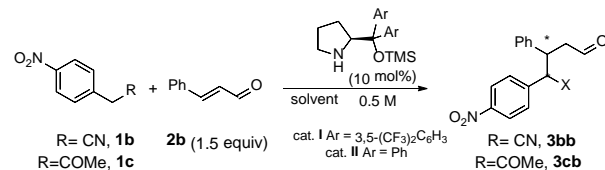
Finally, we studied the influence of the solvent. Interestingly, reactions of **3eb:3eb'** with either catalyst (**I** or **II**, 0.5 equiv) in CD_3OD resulted in exclusive and quantitative formation of the hemiacetals **4eb:4eb'** (Scheme 3). The absence of peaks corresponding to the starting unsaturated aldehyde **2b** or the enamines **A:A'** suggests that once the adduct is formed it reacts faster with MeOH than with the catalyst, thus blocking formation of the enamines and therefore preventing the final adduct from entering the catalytic cycle[21] (Scheme 4).

3eb:3eb' hemiacetals **4eb:4eb'**

cat. **I** Ar = 3,5-(CF₃)₂C₆H₃
cat. **II** Ar = Ph
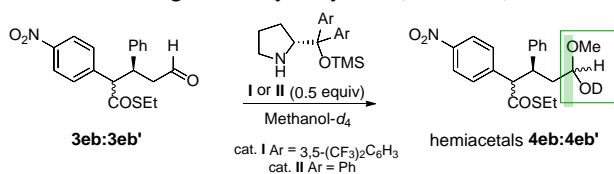
Scheme 3. Hemiacetalization process

3.2. Avoiding reversibility. The information obtained from the combined experimental and theoretical observations described above suggests that the introduction of an acidic additive in MeOH as solvent would result in a slower retro-Michael reaction, and hence the overall enantioselectivity should be increased. These conclusions were tested on problems reported in the literature with the more acidic pronucleophiles **1b**[7a] and **1c**[7b] (Table 1, entries 2 and 3) in combination with cinnamaldehyde **2b** (Table 4).

Table 4. Results obtained in reactions of **1b**-**1c** and **2b** under different conditions

R= CN, **1b** **2b** (1.5 equiv) cat. **I** Ar = 3,5-(CF₃)₂C₆H₃ R= CN, **3bb**
R=COMe, **1c** cat. **II** Ar = Ph R=COMe, **3cb**

Entry	1	solvent	cat	T(h)	Additive	Yield	ee
1[a]	**1b**	THF/H₂O	I	48	LiOAc	79	80[a]
2	**1b**	MeOH	I	6	---	92	**95/95**[a]
3	**1b**	MeOH	II	6	---	90	73/71[b]
4	**1b**	MeOH	II	6	4-NO₂C₆H₄CO₂H	91	**93/95**[b]
5[c]	**1c**	EtOH	I	2,5	LiOAc	69	66[c]
6	**1c**	MeOH	I	1	---	60[d]	**92**[e]
7	**1c**	MeOH	II	6	---	89	73[e]
8	**1c**	MeOH	II	6	4-NO₂C₆H₄CO₂H	89	**90**[e]

[a]Measured in a cyclized derivative (see ref. 7a) [b]Measured for both diastereoisomers obtained as a 1:1 mixture of diastereoisomers. [c]Measured in a cyclized derivative (see ref. 7b) [d]Reaction is not complete (20 % of starting material was recovered). [e]Measured for one of the diastereomeric alcohols obtained by reduction of the aldehyde mixture.

Entries 1-4 describe the Michael addition of nucleophile **1b**, which bears a cyano group, to cinnamaldehyde **2b** to form adduct **3bb**. Entry 1 shows the conditions that provided the best enantioselectivity described in the original report (80 % ee, catalyst **I** in THF/H₂O, LiOAc as additive).[7a] A switch to MeOH as solvent, in the absence of base, and in combination with catalyst **I**, had an immediate impact on the asymmetric induction, which was increased by 15 points (from 80 % to 95 %, compare entries 1 and 2). Additionally, a combination of catalyst **II** with an acidic additive also resulted in improved enantioselectivities (compare entries 3 and 4). Application of this set of conditions to the reaction of nucleophile **1c** (bearing a ketone group) with **2b** followed a similar trend (compare entries 5-8). These results led us to propose the use of either catalyst **I** in MeOH (entry 6, 92 % ee), or a combination of catalyst **II** and an acidic additive (entry 8, 90 % ee), as the best conditions to avoid erosion of the enantioselectivity in Michael additions to β-aromatic enals.

4. On the reactivity of the system. The information available in the literature regarding the differential reactivity of aromatic and aliphatic enals is often contradictory. We have only detected reactivity problems with the aliphatic enals (see Table 1). The most representative examples that illustrate this controversy have been summarized and discussed in the Supporting Information (figures S1, S2 and S3). From these data, it is difficult to clarify if the different behavior is a consequence of the structural features of each nucleophile and electrophile; additionally, limited conclusions can be extracted on the influence of catalyst, additives, or solvents, on the enantioselectivity and reactivity of the processes. Our hypothesis is that the confusion about the relative reactivity of β-aromatic and β-aliphatic enals derives from the fact that *this notion is often extrapolated from the degree of conversion determined after extended reaction times*, and it does not take into account that incomplete or lower conversions could be due to the reversible character of these reactions. This effect is more pronounced on heteronucleophiles, while it is minimized in cascade processes that prevent retro- Michael reactions.

4.1 Parameters that affect the reactivity of the addition. With these precedents in mind, we set out to explore the impact of the acidity of the nucleophile on the reactivity of the system.

This effect was evaluated by studying the same reaction parameters as in the previous section. Specifically, we analyzed the conversion in the reactions of nucleophiles **1b-e** with the model substrates cinnamaldehyde **2b** and crotonaldehyde **2a**, under different reaction conditions including additives (none, PhCO$_2$H, LiOAc, and TBAB), solvents (CH$_2$Cl$_2$ and EtOH), and catalysts (**I** and **II**). Nucleophiles are listed according to the order of acidity found in section 2. All these reactions were performed using aldehydes as purchased, stopped after the same time, and the conversions established by ^{1}H NMR analysis of the crude mixtures immediately after quenching. The most representative results obtained of these studies are summarized in figures 3 and 4 (complete results can be found in the SI section).

First analyses quickly showed that those reactions performed using catalyst **II** were too fast to detect appreciable differences between different reaction conditions. For that reason, catalyst **I** was chosen for this study. We next sought to identify differences in the reactivity of both types of enals, aromatic or aliphatic. When the reactions were analyzed after very short times, the conversions observed indicated that additions to aromatic enals were faster than additions to aliphatic enals (Figure 3). Using CH$_2$Cl$_2$ as solvent, in the absence of additives, we detected high conversion with cinnamaldehyde **2b** after only 15 minutes, and very low with crotonaldehyde **2a** even after 6h.

The influence of the solvent was next analyzed (Figure 4). Using catalyst **I** in the absence of additives, we observed that the reactions of nucleophiles **1b-1e** with the less reactive crotonaldehyde **2a** were notably faster in EtOH than in CH$_2$Cl$_2$. This is in agreement with studies that suggest that alcoholic solvents assist in the formation of the iminium ion acting as proton shuttle[22] and the higher acidity of nucleophiles in this solvent (see section 2). This effect was also observed in reactions with cinnamaldehyde **2b** (see SI for details), although the differences in reactivity were less notable. The unexpected low reactivity of nucleophile **1b** in EtOH may be attributed to its low solubility in this solvent.
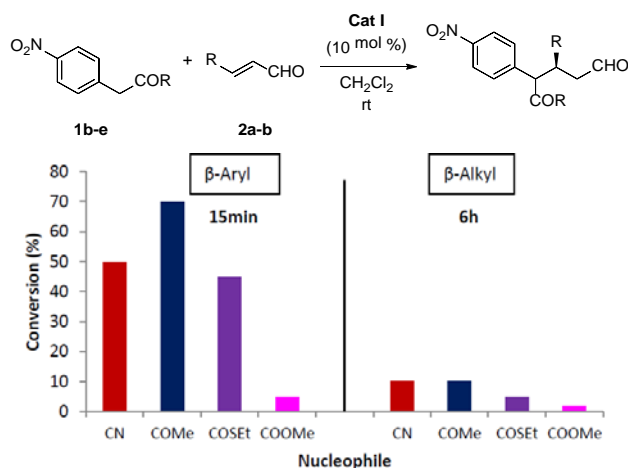
Figure 3. Conversion degrees observed for the reaction of **1b-1e** with cinnamaldehyde (left) and crotonaldehyde (right).
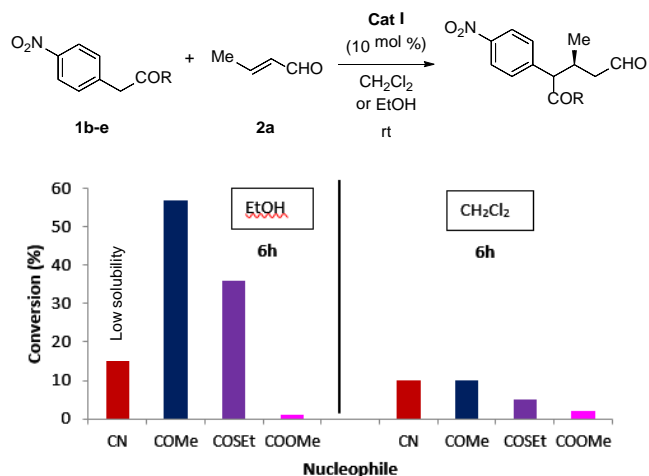
Figure 4. Influence of the solvent. EtOH (left) vs. CH$_2$Cl$_2$ (right).

We also analyzed systematically the effect of additives on the reaction of nucleophiles **1d-e** with crotonaldehyde **2a** and cinnamaldehyde **2b**, using catalysts **I** and **II** in EtOH and CH$_2$Cl$_2$ (see SI). The most significant observation derived from these measurements was that the effect of the additives depended on the nucleophile (see summary in Figure S26): the more acidic nucleophiles work better in combination with acidic additives, the less acidic nucleophiles react faster in the presence of LiOAc or TBAB. During these studies, we observed that different batches of aldehydes afforded different conversions. This fact led us to hypothesize that traces of acid present in commercially available aldehydes could have a non-negligible influence on the reactivity of a given nucleophile. Therefore, these results have to be interpreted qualitatively.

4.2. Study of the reactivity using different additives: identification of relevant reaction intermediates. To obtain more accurate data, we monitored the reaction of nucleophiles **1c** and **1d** (chosen as representative nucleophiles of higher and lower acidity, respectively) by ^{1}H NMR using freshly distilled aldehydes and purified catalyst[23] in CD$_2$Cl$_2$.[24] Studies on the reactions performed using distilled **2a** turned out to be complex due to decomposition of the aldehyde in the absence of stabilizers (see SI). Nevertheless, formation of the corresponding dienamine as the main species was rapidly detected (Scheme 4).[25] As an obvious consequence of the catalyst being kept away from the catalytic cycle, these reactions only took place in low conversion. This result strongly suggests that *the lower reactivity showed by aliphatic enals in some cases -and often ascribed to their inherently low reactivity- is a direct consequence of the low amount of free catalyst that is present in the catalytic cycle*.[26]
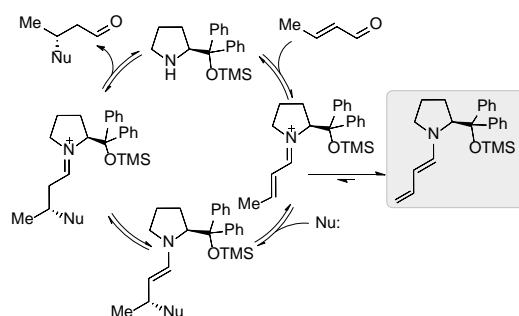
Scheme 4. Relevant reaction intermediate (β-alkyl enals).

Using distilled cinnamaldehyde we could clarify the initial apparent inconsistencies. The most representative results obtained when monitoring by ^{1}H NMR the reactions using redistilled cinnamaldehyde are compiled in Table 5, which includes the ratio of final products observed and the state of the catalyst (free or as enamine intermediates) after 45 minutes under different conditions.[27] As expected, results obtained with both nucleophiles were very different. We started this study with the most acidic nucleophile **1c**, and could clearly confirm the higher reactivity of catalyst **II** compared to catalyst **I** by comparing entries 1 and 2. Whereas the use of catalyst **I** did not lead to the final adduct and only 30 % of catalyst was able to evolve towards enamines **A** and **A'** (entry 1), use of catalyst **II** completely shifted the equilibrium towards the corresponding enamines (free catalyst/enamines: 5/95) and even 22 % of Michael adduct was observed (entry 2). This may be attributed to the above demonstrated higher basicity (and presumably nucleophilicity) of catalyst **II**. The use of acid increased the conversion to 49 % (entry 3). The lower reactivity of the less acidic nucleophiles was verified by comparing the conversion and free catalyst/enamines ratio of both **1c** and **1d** nucleophiles (entries 2 and 4). Results in entries 4 and 5 show that the less acidic nucleophile **1d** was able to react with freshly distilled **2b** (presumably free of the corresponding acid) to afford enamines **A** and **A'** (entry 4), *but adducts 3db were only formed when another source of acid was added to the reaction mixture* (entry 5). Thus, even if one may think that the attack of the anion to the iminium is prevented due to the lower acidity of the nucleophile, this step is possible, but the evolution to the Michael adducts **3db** with concomitant liberation of the catalyst requires the presence of the acid. Use of TBAB translated into an almost complete shift of the equilibrium towards the enamines resulting from the attack of **1d** (entry 6). Nevertheless, it also required the presence of acid to evolve towards the Michael adduct (entry 7).

Table 5. Results obtained in reactions of **1c** and **1d** with **2b** under different conditions and relevant reaction intermediate.
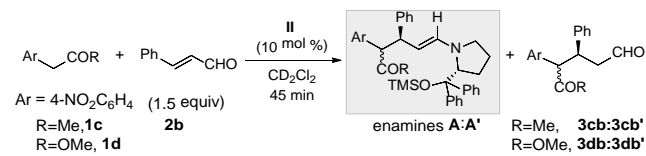
Entry	R	Cat	Additive	Free Cat/ enamines A+A´	Conv. (%)
1	Me, **1c**	I	--	70:30	0 (**3cb**)
2	Me, **1c**	II	--	5:95	22 (**3cb**)
3	Me, **1c**	II	BzOH	29:71	49 (**3cb**)
4	OMe, **1d**	II	--	37:63	0 (**3db**)
5	OMe, **1d**	II	BzOH	61:49	18 (**3db**)
6	OMe, **1d**	II	TBAB	7:93	0 (**3db**)
7	OMe, **1d**	II	BzOH+TBAB	6:94	66 (**3db**)

The graphic in Figure 5 plots conversion versus time for the reaction of the less reactive nucleophile **1d** with distilled cinnamaldehyde **2b**. The corresponding adduct **3db** was only detected when acid was present, while their formation in its absence was very low even after 5 h. Notably, although diastereomeric enamines **A/A'** were clearly observed (Table 5 and SI Figures S32-34), the presence of the acid was required to form the adduct **3db**. The synergistic effect observed when using TBAB and BzOH (compare entry 7 with entries 5 and 6 in Table 5) is also illustrated in Figure 5.
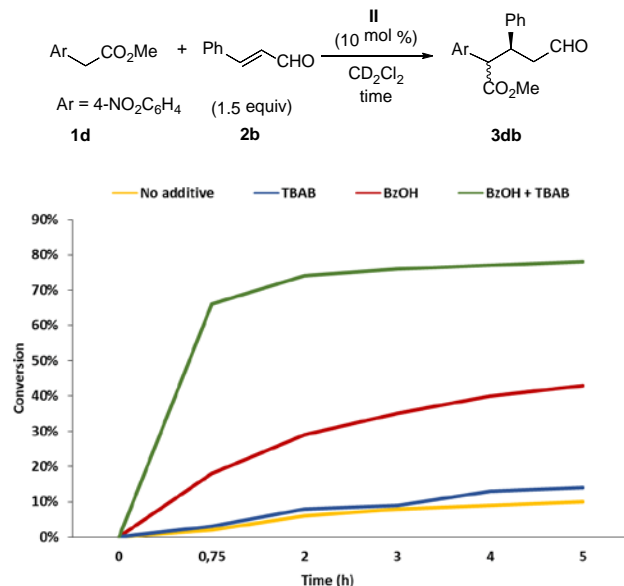

Figure 5. Importance of the acid and synergistic effect observed for TBAB and BzOH.

Our interpretation of this data is that the acid is essential for the reaction to occur, probably to protonate the enamine intermediate and subsequently release the catalyst, hence allowing turnover. One important observation from our NMR experiments is that traces of acid are formed by oxidation of the enal over time, hence producing an increase of the conversion. Therefore, in the absence of an external source of acid, the acidic media required for the reaction to take place could be provided by the acidic protons present in the nucleophile (according to its acidity) or/and by oxidation of the enal.[28] The acceleration observed previously by us when using TBAB,[7c-d,11] might be a consequence of the effect of TBAB in combination with traces of acid present in commercial aldehydes.[29] Thus, while TBAB promotes deprotonation of the nucleophile pushing the equilibrium towards the enamines, the presence of acid is crucial to afford high conversions by hydrolysis of the intermediate enamine.

However, this role of the acid proposed above is in apparent contradiction with the results detailed in Table 1 -entries 4 and 5 in particular- where BzOH seems to inhibit the reaction with alkyl enals.[7d] To explain this discrepancy, we reasoned that the amount of acid tolerated by each nucleophile is different. At this point we carried out several parallel experiments using different amounts of BzOH as additive (from 0 to 100 mol %), with nucleophiles of relatively high and low acidity (**1c** and **1d**, respectively), and measured the conversion by ^{1}H NMR after different reaction times (See SI). Figure 6 represents the conversions after 30 minutes. In agreement with our hypothesis, we observed that in the case of nucleophile **1c** a large amount of acid (100 mol %) was required to decrease the conversion significantly. However, the conversion for the reaction with nucleophile **1d** dropped down significantly using under 20 mol % BzOH.
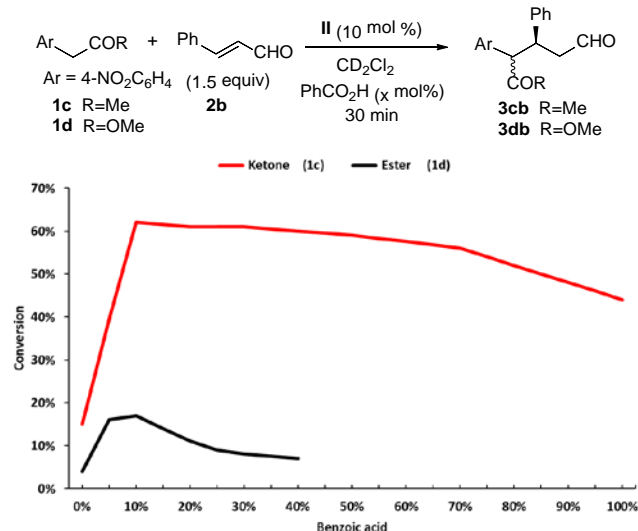
7

Figure 6. Experiment of conversion of two representative nucleophiles using different amounts of acid.

The fact that the acidic media turned out to be so decisive is in sharp contrast with reported data where the presence of bases like DABCO seems to accelerate these reactions.[5i] Scheme 5a shows the reaction of **1g** with **2b** catalyzed by **II** -using aldehyde directly from the commercial sources, as indicated by the authors- which takes place in 75 % yield.[5i] However, when we repeated this reaction under identical conditions (catalyst loading, solvent, concentration, temperature, etc.) but using freshly distilled **2b** we observed 0 % conversion after 18 h (Scheme 5a). The same result was obtained when no additive was employed. In turn, when BzOH (0.5 equiv) was added to the reaction mixture **3gb** was detected in 30 % conversion, which suggests that the high conversion reported[5i] is a consequence of the synergistic influence of basic additives and traces of acid present in the starting aldehydes. This synergy was also shown in the case of Et$_3$N when using dimethyl malonate[30] (Scheme 5b) and using our nucleophiles (see SI): Et$_3$N was only able to promote the reaction when some acid is present.[31]

The synergistic effect of both types of additives and the importance of the pK$_a$ of the nucleophile on the reactivity show the importance of a balance between two processes: 1. *Formation of an enolate*[32] to attack the iminium intermediate (favored by basic additives and hampered by acidic media). 2. *Protonation of the intermediate enamine*, necessary for the regeneration of the organocatalyst (favored by acidic media and hampered under basic conditions).
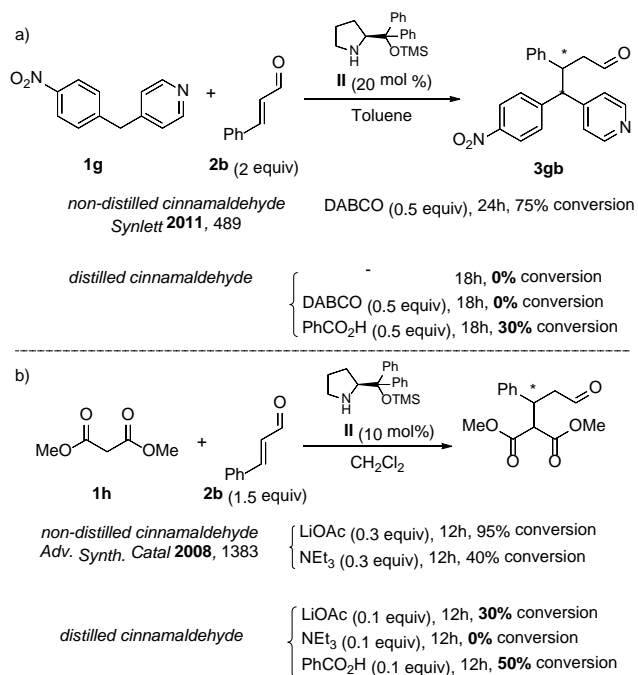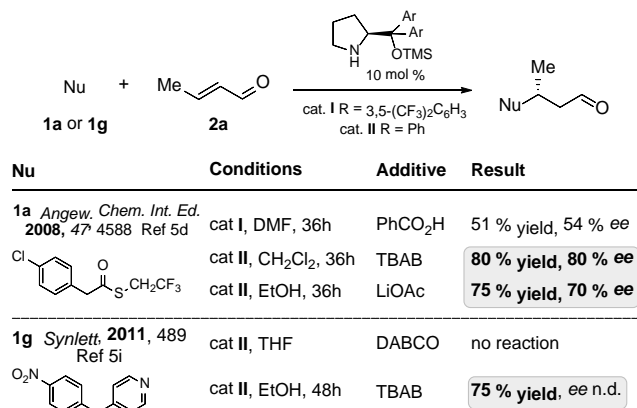

Scheme 5. Reaction of **1g** and **1h** with cinnamaldehyde under different conditions (Refs 5i and 30).

The reactivity studies above can be summarized as follows:

1. Reactions catalyzed by **I** were slower than those catalyzed by **II**, probably due to the more nucleophilic and basic character of the latter.

2. The use of protic solvents (MeOH or EtOH) accelerates the reactions,[33] presumably favoring both deprotonation of the nucleophile and proton transfer in enamine hydrolysis.

3. For less acidic nucleophiles -and therefore less reactive-, a combination of acid and TBAB turned out to be the most effective combination to promote the reaction with the less reactive aliphatic enals.

4.3. Increasing reactivity. With this information in hand, we next directed our efforts at addressing selected representative reactivity problems found for aliphatic enals (outlined in Table 1). Assuming that in all cases aldehydes were used as received from commercial sources, and taking into account that crotonaldehyde presents stability problems in the absence of a stabilizer, for the sake of practicality, we used commercial enals assuming that traces of acid were present. Firstly, the reaction of **1a** with **2a** had provided poor results using DMF in the presence of catalyst **I** and BzOH as the additive (entry 1, Table 1).[5d] These results were significantly improved by applying our optimized conditions: specifically, changing the catalyst (**II** instead of **I**) and using either TBAB or LiOAc as additives (Scheme 6) resulted in a raise in both reactivity and enantioselectivity in the range of 25 % (from 51 % yield and 54 % ee to 80 % yield and 80 % ee). Secondly, Melchiorre reported the unsuccessful reaction of **1g** with crotonaldehyde, using catalyst **II**, DABCO as additive, and THF as solvent[5i] (entry 9, Table 1). To our delight, switching to EtOH and using TBAB as additive (**1g** is even less acidic than **1e**) we obtained the corresponding addition product in 75 % yield (Scheme 6).[34]

Nu	Conditions	Additive	Result
1a *Angew. Chem. Int. Ed.* **2008**, *47*, 4588 Ref 5d	cat **I**, DMF, 36h	PhCO₂H	51 % yield, 54 % *ee*
(Cl-C₆H₄-CH₂-C(O)-S-CH₂CF₃)	cat **II**, CH₂Cl₂, 36h	TBAB	**80 % yield, 80 % *ee***
	cat **II**, EtOH, 36h	LiOAc	**75 % yield, 70 % *ee***
1g *Synlett,* **2011**, 489 Ref 5i	cat **II**, THF	DABCO	no reaction
(O₂N-C₆H₄-CH₂-pyridine)	cat **II**, EtOH, 48h	TBAB	**75 % yield**, *ee* n.d.

Scheme 6. Experimental solutions to reactivity problems found for β-alkyl enals.

5. Shifting the pK$_a$ limit. As mentioned in the introduction, Barbas suggested a pK$_a$ limit in the 16-17 range for arylacetic acid pronucleophiles in reactions with β-substituted α,β-unsaturated aldehydes.[5d] However, applying the findings described in the paragraphs above, nucleophile **1i** (pK$_a$ = 17.8) was found to react with **2a** and **2b** using catalyst **II** (Scheme 7). Reactions with cinnamaldehyde **2b** were faster in EtOH than in CH₂Cl₂, but slower when catalyzed by **I**, and did not require the presence of additives. In contrast, reactions with less reactive crotonaldehyde did not take place under catalysis of either **I** or **II**, unless TBAB or LiOAc were used. Pronucleophiles with higher pK$_a$ values, such as **1j** (pK$_a$ = 18.1) and **1k** (pK$_a$ ~18-19), were found to react smoothly with cinnamaldehyde (catalyst **II** and EtOH) but not with crotonaldehyde **2a**. Therefore, the pK$_a$ limit for a nucleophile to react in these processes is above 18 when the appropriate conditions are used. This limit is slightly different for reactions with aromatic and aliphatic enals, probably due to a lower concentration of effective catalyst due to dienamine formation (see section 4.2, Scheme 4).
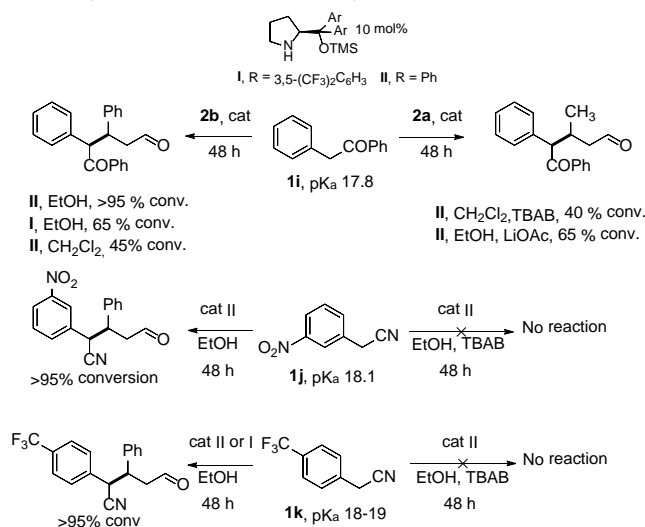
Scheme 7. Examples in which the pK$_a$ limit proposed by Barbas is overcome under different conditions.

6. Mechanistic overview: summary and conclusions

Scheme 8 is intended as an overall mechanistic proposal that incorporates all the aspects explored throughout our studies. The usually accepted mechanism for the Michael addition of 1-arylacetic acid derivatives to enals includes the following key steps: 1) Formation of an iminium ion (by reaction of the catalyst with the aldehyde), 2) attack of the nucleophile, and 3) hydrolysis of the resulting enamine.[1d] Acidic additives[1a,1d] have been proposed to activate the aldehyde towards iminium formation and protonate the enamine intermediate to form the reaction products. In addition, the role of catalysts is almost exclusively taken into account in the context of stereocontrol. Our experimental and theoretical studies have provided additional information regarding the influence of the structure of the enal (β-aryl and β-alkyl substituted) and the nucleophile, the effect of the catalysts on the reactivity, and the variation of the optical activity overtime (observed in some reactions), as well as the role of additional additives and/or solvents. A modified mechanistic proposal is as follows:

• **A first step** involves the attack of the nitrogen atom of the catalyst to the carbonyl of the enal that leads to sequential formation of hemiaminal **A** and iminium intermediates **B**. Formation of the latter takes place by elimination of a hydroxyl ion, a process that can be facilitated by the presence of additives. In this context, TBAB and other ammonium salts assist the elimination process by formation of NBu₄OH,[7c] providing a basic media capable of promoting enolate formation. Alternatively, the presence of acid may result in protonation of the OH, favoring the elimination of H₂O. In the case of aliphatic enals, dienamine **C** was the main species detected. This species, formed after deprotonation by OH⁻, keeps a *significant portion of the catalyst in an off-cycle pathway, which is consistent with the generally observed lower reactivity of aliphatic enals*.

• A **second step** involves a Michael addition of the different pro-nucleophiles to the iminium ion to afford enamine **D**, which does not evolve in the absence of a suitable proton. Also, our findings indicate that the corresponding enolate are the reactive species in these reactions,[7c] and not the enol as has been proposed in some cases. At this point, either the catalyst or the OH⁻ generated in the first step could be responsible for the deprotonation of the pronucleophiles to form the corresponding anions. An increase in [OH⁻] would also increase the concentration of reacting nucleophile, and as a direct consequence the rate of the Michael addition step that yields enamine **D**.

• The **third step** corresponds to the hydrolysis of enamine **D** to yield a Michael adduct, and subsequent release of the catalyst to reenter the catalytic cycle. The fact that the reactions were accelerated in the presence of acid, or slowed down in its absence, suggests that *the protonation of the enamine is the slowest step of the catalytic cycle*.
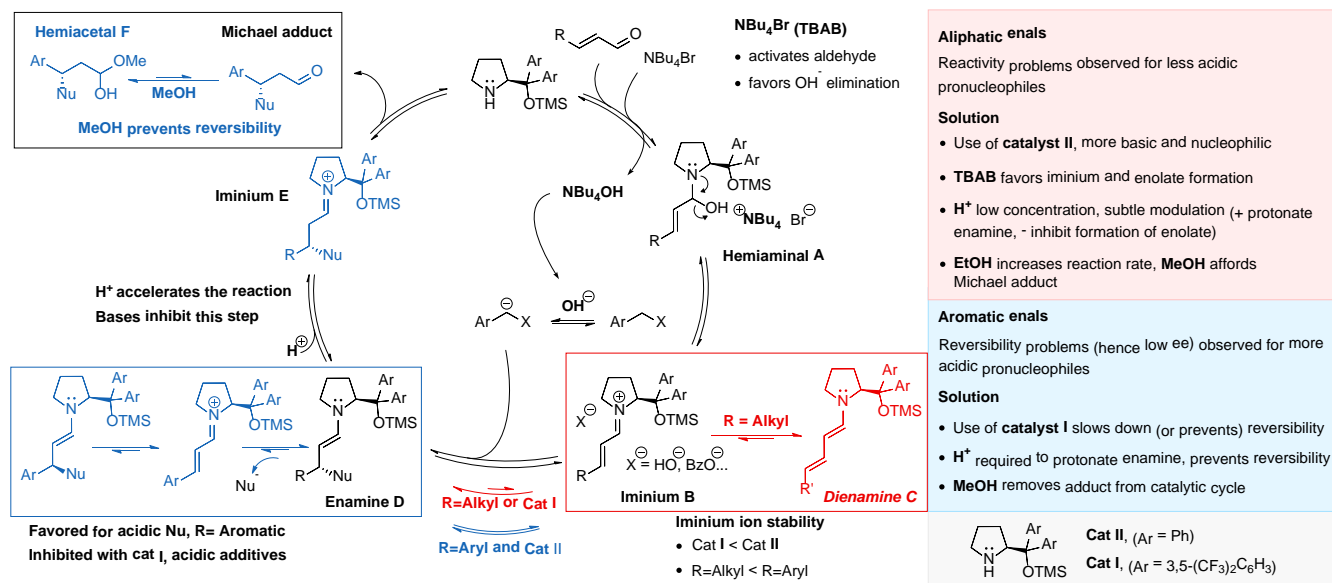
Scheme 8. Catalytic cycle and conclusions.

Other significant aspects of this transformation:

· **Importance of the catalyst on reactivity**: Reactions performed using catalyst **II** were faster than those catalyzed by **I**. We propose that the higher basic character of **II** would increase the ratio of enamines and provide larger concentrations of the enolates, which may be critical for the reactions of less acidic nucleophiles with the less reactive β-alkyl enals.

· The **influence of the catalyst on the asymmetric induction** of reactions with β-aryl enals has been studied. It appears that the reversibility of the reactions, which is responsible of the erosion of the enantioselectivity, is less favored using catalyst **I**. The instability of the iminium species derived from **I** (due to the -I effect of the CF_3 groups) would make a retro-Michael reaction from the enamine species **D** more difficult, slowing down the reversibility (down left in Scheme 8).

· The **role of the solvent** on reactivity: We have observed a role of MeOH in controlling the enantioselectivity, which can be ascribed to the fast formation of hemiacetals **F** from the corresponding Michael adducts: this side reaction minimizes the reversibility by preventing the final products to reenter the catalytic cycle. EtOH is a suitable solvent to increase the reactivity of aliphatic enals (MeOH affords Michael adducts with less reactive nucleophiles).

In summary, we have studied the influence of several parameters that control the enantioselectivity due to the reversibility of aromatic enals, determining that the Michael adducts reenter the catalytic cycle via retro-Michael reaction reaching the equilibrium with the starting products. This process is favored with β-aryl enals (conjugation with aromatic ring is lost after reaction of the enal and the aryl ring could stabilizes the iminium ions), more acidic pro-nucleophiles (generating more stable enolates as leaving groups), and using the more nucleophilic catalyst **II**, thus favoring enamine formation from the final adduct and form more stable iminium ions. With respect to the role of the solvents, we have demonstrated that MeOH exerts a very efficient control of the enantioselectivity, due to the fast formation of the

hemiacetals from the final aldehydes that precludes their reentering the catalytic cycle.

In a second part of our studies, we have demonstrated the importance of acidic additives in the catalytic process. The amount of acid has a pivotal role in the success of the reaction as although it is mandatory to protonate the resulting enamine, it can preclude a deprotonation of the pronucleophile, which is necessary for the reaction to take place, imposing a fine modulation of the reaction conditions. This modulation is especially significant for the reaction of not very acidic nucleophiles and aliphatic enals, as the favored formation of a dienamine species dramatically decreases the amount of available catalyst. Furthermore, our optimization protocol has allowed us to correct the postulated pK_a barrier (16-17 pK_a units) to pronucleophiles of 18-19 pK_a.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, characterization of products, computational methods and NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Most of the Michael additions described in the literature that follow an iminium activation pathway employs acidic additives.

(10) For some initial selected examples using basic additives, see: (a) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.*, **2006**, *128*, 14986-14991. (b) Ref 4e. For other examples in which LiOAc has been used, see: (c) Wang, Y.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem. Commun.,* **2008**, *44*, 1232-1234. (d) Ref 4k.

(11) (a) Nucleophile **1c** showed very low reactivity when acidic additives were used in combination with aliphatic aldehydes. This observation led us to introduce quaternary ammonium salts as a new kind of efficient additives in organocatalyzed Michael addition *via iminium* intermediate. Our studies suggest that TBAB salts favor iminium formation and stabilization, and activate the nucleophile via enolate formation by the action of tetrabutylammonium hydroxide, a soluble base generated only after iminium formation. See: Ref 7c. (b) See also Rodrigo, E.; García Ruano, J. L.; Cid, M. B. *J. Org. Chem.* **2013**, *78*, 10737−10746; use of TBAB resulted in erosion of the enantioselectivity when aromatic enals were used.

(12) Bordwell, F. G.; Cheng, J. -P.; Bausch, M. J.; Bares, J. E. *J. Phys. Org. Chem.* **1988**, *1*, 209.

(13) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.,* **2008**, *120*, 215-241.

(14) Alongi, K. S.; Shields, G. C., *Annual Reports in Computational Chemistry* **2010**, *6*, 113–138. Cartesian coordinates and energies of structures **1** (HA) and **1.dep** (A⁻) are collected in the Supporting Information.

(15) It is worth noting that the nucleophiles in this study are as acidic as most of the species studied in the gas phase. It should be mentioned that the acidity of nitric acid, estimated at approximately 1338 kJ·mol⁻¹, is above the acidity of most of these nucleophiles: Koppel, I. A.; Burk, P.; Koppel, I.; Leito, I.; Sonoda, T.; Mishima, M. *J. Am. Chem. Soc.,* **2000**, *122,* 5114–5124.

(16) These adducts were chosen because of its intermediate acidity. They were obtained and used as 1:1 diastereomeric mixtures at the α-position relative to the thioester in the reactions of **1e** with crotonaldehyde **2a** and cinnamaldehyde **2b**, respectively.

(17) Although the synthetic experiences were performed by using only a 10-20 mol % of catalyst, in order to identify more clearly the formed species we have studied these retro-Michael reactions using 0.5 equivalents of catalyst. The different tendency of aromatic and aliphatic enals can be unambiguously stated.

(18) Diagnostic signals in the ¹H NMR spectrum corresponding to thioester **1e** were also identified. However, the signals corresponding to the aldehyde were easier to analyze.

(19) A crossover experiment between product **3ea** and **2b** was conducted in hopes of assessing the potential reversibility, or lack thereof, of the conjugate addition to β-alkyl enals. Unfortunately, this experiment led to inconclusive results due to the formation of complex mixtures.

(20) Although we cannot rule out a competitive back reaction promoted by TBAB, the combination of this additive with the catalyst (the

actual reaction conditions) promotes a back reaction that led to low enantioselectivities in the forward sense, whereas the back reaction showed high concentration of enamines. Therefore, the enamine intermediates seem to be the main responsible for the epimerization of the adducts. On the other hand, entries 5 and 6 suggest that the effect of acids alone must not be enough for a competitive retro reaction to take place, since this would result in erosion of the enantioselectivity. We thank a reviewer for bringing up this issue.

(21) Interestingly, the less reactive starting enal **2a** does not form the corresponding hemiacetal when treated with catalysts **I** or **II** in MeOH, hence allowing its incorporation to the catalytic cycle.

(22) See: Patil, M. P.; Sunoj, R. B., *J. Org. Chem.* **2007**, *72*, 8202-8215, and references cited therein.

(23) As TMS cleavage has been observed for diarylprolinol silyl ethers, the catalysts used in this experiment were purified prior to their use: Haindl, M. H.; Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *RSC Adv.* **2012**, *2*, 5941-5943.

(24) Use of CD_2Cl_2 from different commercial sources also resulted in slightly different results, which was attributed to the existence of variable amounts of HCl.

(25) For a seminal precedent on dienamine chemistry, see: Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K.A. *J. Am. Chem. Soc.,* **2006**, *128*, 12973 -12980.

(26) Although it is reasonable to assume that the presence of acid would shift the equilibrium towards the reactive iminium intermediate, we have observed that it also favors side reactions such as self-condensation that compete with the desired pathway, especially in the case of the less reactive nucleophiles.

(27) These results are in sharp contrast with those obtained using non-distilled aldehydes as shown in the previous study (See SI pgs. S32-S38), which suggests an important influence of the acid on the reaction rate.

(28) Other explanations for the formation of acidic species in the reaction medium could be considered: It has been reported that the pirrolydine reacts with dichloromethane to release HCl: Mills, J. E.; Maryanoff, C. A.; McComsey, D. F.; Stanzione, R. C.; Scott, L. *J. Org. Chem.* **1987**, *52*, 1857-1859. Although our experimental conditions are different, this type of process cannot be ruled out.

(29) It is important to point out that during our studies we have found small inconsistencies when the reactions were repeated using different batches of enals, presumable due to traces of acid found in commercially available aldehydes. This fact highlights the importance of the amount of acid in the outcome of the reaction and would explain some contradictions found in the literature, since aldehydes are often used as obtained from commercial sources

(30) Wang, Y.; Li, P.; Liang, X.: Ye, J. *Adv. Synth. Catal.* **2008**, *350*, 1383-1389.

(31) Presumably, the same effect could be expected for catalysts bearing tertiary amines. See: Guevara-Pulido, J. O.; Andres, J. M.; Pedrosa, R. *RSC Adv*. **2015**, *5*, 65975-65981.

(32) The existence of a good correlation between the acidity of the pronucleophiles and their observed reactivity supports the notion that enolates could be the nucleophilic partners in these reactions. Even if the enolate is present in very low amounts, the reactivity of the charged species is much higher than the corresponding neutral ones (Nucleophilicity database: http:// www.cup.lmu.de/oc/mayr/reaktionsdaten-bank/), access date 3 November 2017. Our DFT calculations to study the reaction between ester **1d** and the iminium ion **II2a** pointed out that activation barriers were significantly higher for attack of the enol than for attack of the enolate form of the nucleophile (ref 7c).

(33) We have observed the Michael addition of MeOH when using not very reactive nucleophiles. This side reaction have been avoided using EtOH.

(34) Unfortunately, all attempts at determining the enantiomeric excess of this reaction were unsuccessful.