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A General Aminocatalytic Method for the Synthesis of Aldimines

Sara Morales, Fernando G. Guijarro, José Luis García Ruano,* M. Belén Cid*

Department of Organic Chemistry. Universidad Autónoma de Madrid, Cantoblanco 28049, Madrid, Spain

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ABSTRACT: A general and efficient biomimetic method for the synthesis of aldimines from aldehydes and compounds bearing the NH_2 group in the presence of pyrrolidine as catalyst has been developed. These organocatalytic reactions, based on the application of the concept of nucleophilic catalysis, proceed with outstanding yields in the absence of acids and metals under simple conditions and minimum experimental manipulation. The method has been mainly applied to the synthesis of *N*-sulfinyl and *N*-sulfonyl imines, but its general validity has been proven with the preparation of representative *N*-phosphinoyl imines, *N*-alkyl and *N*-aryl imines. These unprecedented reactions, presumably occurring *via* iminium activation without requiring acidic conditions, are an interesting and competitive alternative to the classical methods for preparing aldimines.

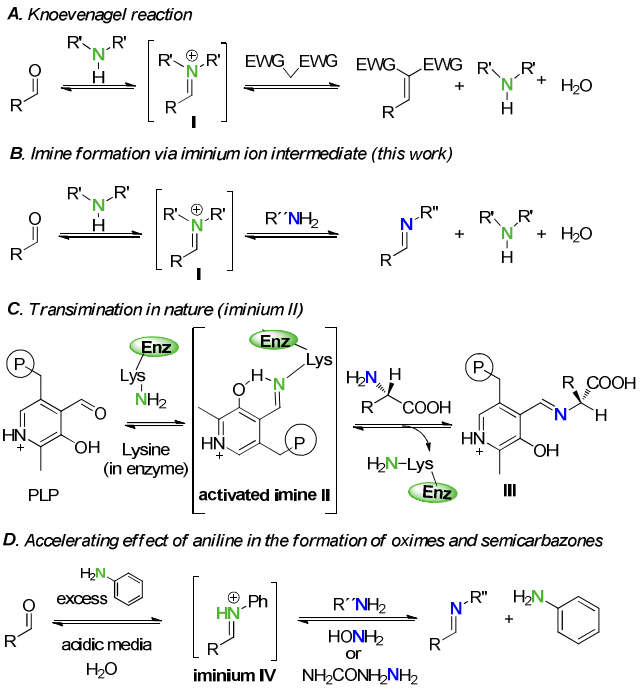
INTRODUCTION

The formation of the C=N bond by condensation of C=O and NH_2 groups has been a priority in organic synthesis due to the relevance of imines in the fields of chemistry and biology.[1] But more importantly, imines are versatile electrophiles that give rise to nitrogen-containing compounds,[2] widely distributed in nature and with many important pharmacological activities. Most of the methods for the direct imine formation require acidic activation (protic or metallic) of the corresponding carbonyl compound and/or irreversible water removal.[3]

To our knowledge, aminocatalytic methods for the direct preparation of imines from aldehydes and amines have never been reported, which is surprising taking into account the great advances achieved in organocatalytic processes.[4] Contrasting with the profusion of enantioselective reactions involving carbonyl compounds using proline derivatives as catalysts,[5] affecting to α–,[5a] β–,[5b,c] or γ–,[5e] positions, those concerning the nucleophilic attack to carbonyl carbon involving iminium intermediates **I** are mostly limited to the Mannich and Knoevenagel reactions (Scheme 1*A*).[6] We reasoned that compounds containing NH_2 groups could act as nitrogenated nucleophiles and evolve in a similar way under appropriated catalytic conditions, allowing the formation of any kind of C=N bonds (Scheme 1*B*). This transformation, astonishingly unexploited so far, could be considered as a new application of nucleophilic catalysis, an old concept conceived many years ago.[7]

Reactions *A* and *B* indicated in Scheme 1 can be considered as organocatalytic $C=N^+/C=C$ and $C=N^+/C=N$ interchanges,

Scheme 1. Organocatalyzed functionalization of aldehydes using iminium activation.



respectively. Interestingly, the transimination process indicated in Scheme 1*B;* would mimic transformations occurring in nature. In particular, the formation of imines **III** derived from pyridoxal phosphate (PLP) and aminoacids (Scheme 1*C*), which are pivotal intermediates in transformations of aminoacids, are not formed by direct condensation of these components, but through transimina-

tion reaction with activated imines **II** resulting in the reaction of pyridoxal phosphate and a lysine residue.[8]

The accelerating effect of aniline on the formation of semicarbazones and oximes in water at acidic pH, probably *via* transamination of a protonated imine **IV** (Scheme 1*D*), is known since 1962[9] and it has been recently used in the preparation of hydrazones and oximes as linkage of bioconjugates.[10] It is important to note that this is a non-catalytic process that requires high concentration of aniline in a strong acidic media.[11] On the contrary, the use of a secondary amine in catalytic amount to generate iminium intermediate **I** (instead of the protonated imine **IV** intermediate) would allow the reaction of a variety of amines in organic solvents without requiring acidic aqueous medium (Scheme 1*B*).

Some recently published results put forward the viability of our hypothesis. Mayr has reported that the electrophilicity of the aromatic iminium intermediate **I** (Scheme 1*B*) is more than ten orders of magnitude higher than that of the carbonyl group at the precursor aldehyde in reactions with carbon nucleophiles and even higher (3 to 5 orders) for heteronucleophiles.[12] Moreover, Mayr also describes the reaction of 2 equiv of benzylamine with the preformed *N,N*-dimethyliminium triflate derived from *p*-methoxybenzaldehyde to form the corresponding imine, thus demonstrating that the $C=N^+/C=N$ interchange is favored. Thus, it suggests that the pathway proposed in Scheme 1B to obtain imines could take place satisfactorily, even considering a low concentration of the iminium species **I** and the low nucleophilic character of some R-NH_2 (unable to react with aldehydes in the absence of a appropriated activator). It would confer the method a very general scope, allowing the preparation of imines with electron-withdrawing groups joined to the nitrogen, probably the most valuable precursors in the synthesis of amines.

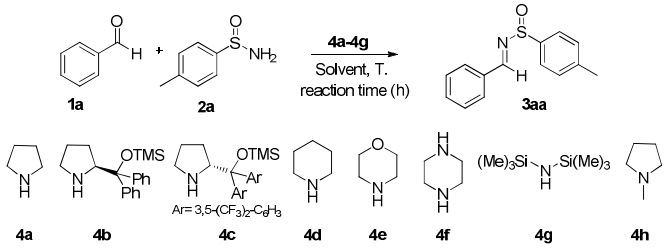
In this paper we describe the scope and limitations of the first aminocatalytic procedure for preparing almost any type of aldimine, including *N*-sulfinyl, *N*-sulfonyl and *N*-phosphinoyl derivatives in very high yields under mild conditions and clear environmental advantages with respect to those used by the methods so far reported.

RESULTS AND DISCUSION

We focused our initial efforts in the organocatalytic preparation of aldimines activated by electron-withdrawing groups because of their synthetic importance. Enantiomerically pure *N*-sulfinyl imines are one of the activated imines most used in the asymmetric synthesis of primary amines due to the dual role played by the sulfinyl group as activating and stereodirecting group and its easy removal.[13] The method most commonly used for preparing these compounds is based on the reaction of aldehydes with optically pure R-$SONH_2$ (R = *p*-Tol or *t*-Bu) in the presence of a large excess of $Ti(OEt)_4$ (usually 5 equiv) which activates the aldehyde and acts as dehydrating reagent.[14] The main drawback of this method, that provides imines in usually high yields, is the excess of the Lewis acid required, generating a large amount of environmentally undesired waste (titanium salts) that imposes purification process, sometime tedious.

The condensation of benzaldehyde and *p*-tolylsulfinamide **2a** was used as model reaction. Results obtained under different conditions are indicated in Table 1. All reactions were accomplished at 60 °C in a sealed vial using solutions containing equimolar amounts of the reagents. In the absence of catalyst the reaction did not take place (entry 1) as could be expected from the low nucleophilicity of the nitrogen at *p*-tolylsulfinamide **2a**.

Table 1. Evaluation of different amines as catalysts in the synthesis of imines.



Entry[a]	Cat (mol%)	Solvent	T (°C)	time (h)	Conv %[b] (yield %)[c]
1	-----	CH_2Cl_2	60	7	0
2	**4a** (20)	CH_2Cl_2	60	7	100
3	**4b** (20)	CH_2Cl_2	60	7	50
4	**4c** (20)	CH_2Cl_2	60	7	0
5	**4d** (20)	CH_2Cl_2	60	7	50
6	**4e** (20)	CH_2Cl_2	60	7	30
7	**4f** (20)	CH_2Cl_2	60	7	60
8	**4g** (20)	CH_2Cl_2	60	7	20
9	**4h** (20)	CH_2Cl_2	60	6	0
10	**4a** (20)	EtOH	60	7	99
11	**4a** (20)	THF	60	7	80
12	**4a** (20)	CH_3CN	60	7	79
13[d]	**4a** (20)	Toluene	40	7	66
14	**4a** (20)	CH_2Cl_2	40	7	83
15	**4a** (10)	CH_2Cl_2	60	8	89
16	**4a (10)**	**CH_2Cl_2/4ÅMS**	**60**	**1**	**100**
17[e]	**4a** (10)	CH_2Cl_2/4ÅMS	60	2	100 (94)
18	**4a** (10)	THF/4ÅMS	60	4.5	100 (90)
19	**4a** (10)	CH_3CN/4ÅMS	60	4.5	100 (92)
20	**4a** (10)	Toluene/4ÅMS	60	4.5	100 (91)

[a] Reactions were performed in a sealed vial using equimolar amount of aldehyde and *p*-tolylsulfinamide in a 0.2 mmol scale and the indicated catalyst (20 or 10 mol%) in 0.6 mL of solvent. [b] Determined by ^{1}H-NMR on the spectrum of the crude material. [c] Isolated yield after filtration through a short pad of silica gel. [d] 1.5 equiv of **1a** were used. [e] Reaction performed starting from 1 g of **2a**.

We studied the efficiency of a variety of secondary amines **4** (20 mol %) as catalysts in CH_2Cl_2 (entries 2-8). Almost all of them provided the desired *N*-sulfinyl imine **3aa** in some extent, demonstrating the potential of nucleophilic catalysis. In the presence of the tertiary amine **4h** as catalyst, the reaction did not work (entry 9). Pyrrolidine **4a** was the only amine that afforded full conversion after 7 h (entry 2). Other five membered ring amines, like **4b** and **4c**, widely used in asymmetric organocatalysis[15] are less efficient (entries 3 and 4). Analogously, in the presence of pyperidine (**4d**, entry 5), other six-membered cyclic secondary amines

(**4e** and **4f**, entries 6 and 7), and the bulky bis-trimethylsilyl amine **4g** (entry 8), conversions observed after 7h were lower than those achieved with **4a**.

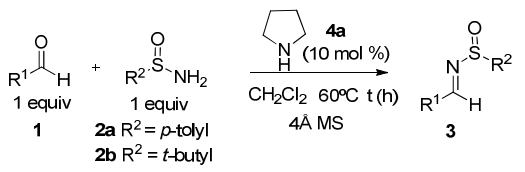
We then checked the role of the solvent. The reaction progressed in all the used solvents but, after 7 h under the studied conditions, complete conversion is only observed in CH_2Cl_2 and EtOH (entry 2 and 10). By lowering the temperature (entry 14) or the catalyst loading (to 10 mol%, entry 15) in CH_2Cl_2, conversions after 7 hours are not complete.

Better results were obtained in the presence of molecular sieves (4Å) as water scavenger. Thus, the time to get a complete conversion by using only 10 mol% of catalyst loading decreased to 1 h (entry 16).[16] The use of these conditions, considered as the optimal ones, allowed us to obtain pure **3aa** in almost quantitative yield by simple filtration through a short pad of silica gel to remove pyrrolidine and 4Å MS. Similar results were obtained at the gram scale, being possible to obtain **3aa** in 94 % isolated yield after 2 h in sealed tube (entry 17) and after 75 min under conventional CH_2Cl_2 reflux (see SI). Remarkably, these smooth conditions are also efficient in other solvents, like THF, MeCN, and toluene (entries 18-20), which could be interesting for connecting the preparation of the imines with their reactions with different nucleophiles in one-pot processes. Finally, we have checked that all these reactions take place without epimerization at the sulfur atom.[17]

We next investigated the scope of the reaction with different aromatic aldehydes. The reactions have been performed using two sets of conditions. The results obtained under conditions of entry 2, Table 1 (without 4Å MS) are recorded in SI, whereas those obtained under conditions of entry 16, Table 1 (in the presence of 4Å MS) are gathered in Table 2. All compounds were obtained in high purity after a simple filtration through a short pad of silica gel.

Starting from substituted benzaldehydes (entries 2-10) almost quantitative yields were obtained regardless the electronic character and the position of the substituents. A similar result was obtained from 2-naphthyl carbaldehyde (entry 11).

Table 2. Scope of the synthesis of *N*-sulfinyl imines derived from aromatic aldehydes.



Entry[a]	Aldehyde R^1	Amide	t(h)	Product (yield %)[b]	Previous method[c] Conditions	yield (%)
1	**1a** C_6H_5	**2a**	1	**3aa** (100)	$Ti(OEt)_4$ (5),4h	99[14]
2	**1b** *p*-NO_2-C_6H_4	**2a**	2.5	**3ba** (93)	$Ti(OEt)_4$ (5)	85[18]
3	**1c** *p*-OMe-C_6H_4	**2a**	2	**3ca** (96)	$Ti(OEt)_4$ (5),4h	92[14]
4	**1d** *p*-CN-C_6H_4	**2a**	4	**3da** (92)	$Ti(OEt)_4$ (5),4h	60[19]
5	**1e** *p*-Cl-C_6H_4	**2a**	3	**3ea** (95)	$Yb(OTf)_3$ (0.1)[d],12h	84[20]
6	**1f** *o*-NO_2-C_6H_4	**2a**	5	**3fa** (90)	$Yb(OTf)_3$ (0.1)[d],12h	81[20]
7	**1g** *o*-OH-C_6H_4	**2a**	3	**3ga** (89)	-Not described-	[i]
8	**1h** *o*-Br-C_6H_4	**2a**	4	**3ha** (96)	$Ti(OEt)_4$ (5),4h	65[19]
9	**1i** *o*-OMe-C_6H_4	**2a**	3	**3ia** (99)	KF (2), THF,-78 °C,12h	91[21]
10	**1j** *m*-OMe-C_6H_4	**2a**	3	**3ja** (91)	$Ti(OEt)_4$ (5), 4h	92[14]
11	**1k** 2-naphthyl	**2a**	4	**3ka** (90)	$Ti(OEt)_4$ (5), 4h	94[22]
12	**1l** 2-pyridyl	**2a**	4	**3la** (88)	$CsCO_3$ (5), 45 °C, 8h.	95[23]
13	**1m** 2-pyrrolyl	**2a**	4	**3ma** (91)	-Not described-	[i]
14[e]	**1n** 2-Methylindolyl	**2a**	8	**3na** (70)	-Not described-	[i]
15	**1o** 5-NO_2-tiophenyl	**2a**	4	**3oa** (90)	-Not described-	
16[f]	**1p** C_6H_4-CH=CH-	**2a**	4	**3pa** (99)	$Ti(OEt)_4$ (5),4h	80[22]
17[f]	**1q** *p*-NO_2-C_6H_4-CH=CH-	**2a**	3	**3qa** (97)	-Not described-	
18[f]	**1r** *p*-OMe-C_6H_4-CH=CH-	**2a**	3.5	**3ra** (88)	-Not described-	
19[f]	**1s** *o*-OMe-C_6H_4-CH=CH-	**2a**	3.5	**3sa** (98)	-Not described-	
20	**1t** CO2Et	**2a**	5	**3ta**(93)	4Å MS,rt,1h	67[27]
21	**1a** C_6H_4	**2b**	4	**3ab** (99)	$CuSO_4$ (2), rt [g]	91[24]
22	**1b** *p*-NO_2-C_6H_4	**2b**	4	**3bb** (91)	$CuSO_4$ (2), rt,24h [h]	96[25]
23	**1c** *p*-OMe-C_6H_4	**2b**	4	**3cb** (99)	$CuSO_4$ (2), rt [g]	81[24]

[a]All reactions were carried out in a 0.2 mmol scale. [b]Isolated yield. [c]Conditions providing the highest yield found in the literature. Unless otherwise stated, reactions were carried out under reflux of CH_2Cl_2 using 1 equiv of the starting aldehyde. [d] Reported procedure in THF at rt using 3.5 equiv of aldehyde.[e] 1.2 equiv of **1n** in the absence of 4Å MS. [f] Reaction was carried out at room temperature. [g] 1.1 equiv of aldehyde were used. [h] 1.5 equiv of aldehyde were used. [i] We have proven that these reactions also work in high yields using $Ti(OEt)_4$ (5) as shown in SI.

The reaction was also effective with heteroaryl aldehydes (entries 12-15) providing *N*-sulfinyl imines that in some cases (**3ma**, **3na**, and **3oa**) had never been reported. Under the standard conditions, 2-pyridyl, 2-pyrrolyl and 5-NO_2-

tiophenyl carboxaldehydes respectively produce **3la** (88%), **3ma** (91%), and **30a** (90 %) in 4 hours (entries 12, 13 and 15), whereas unprotected 2-methylindolyl carboxaldehyde afforded **3na** (70%) after 8 h, but using 1.2 equiv of **1n** without 4Å MS (entry 14).

Unsaturated aldehydes **1p-1s** (entries 16-19) also reacted to form the imines **3pa-3sa** in almost quantitative yields. This complete regioselectivity towards the products resulting in the attack of sulfinamide **2a** to C-1 is remarkable because carbonated nucleophiles only produce the attack to C-3 in reactions catalyzed by **4b** or **4c**. This change in the regioselectivity could be due to the reversibility observed in the attack to C-3 of some heteronucleophiles,[26] and/or to the fact that the reaction of *N*-nucleophiles with C-1 is more favored than that of C-nucleophiles, as a consequence of the anomeric stabilization of the aminal species resulting in the first case.[12] The incorporation of electron donating and electron withdrawing groups to the aromatic ring of these enals has not any consequence on the efficiency of the process (entries 17-19), being possible to obtain excellent yields of the *N*-sulfinyl imines **3qa-3sa**, so far never reported.

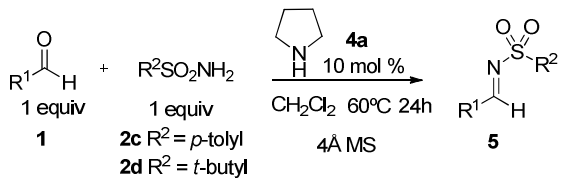
Finally, the excellent result obtained in the synthesis of **3ta** from ethyl glyoxylate (93% yield, entry 20) is remarkable due to the relevance of this compound as amino acids precursor as well as to the rather modest yield (67%) previously reported in the literature.[27]

Our method is also appropriate for obtaining *N*-*t*-butylsulfinyl imines, one of the most used for synthetic purposes.[13b-c] We have illustrated this fact with the synthesis in high yields of three representative *N*-*t*-butylsulfinyl imines (**3ab-3cb,** entries 21-23) derived from benzaldehyde and aromatic aldehydes bearing electron-withdrawing and electron donating substituents.

With comparative purposes, we have indicated in the right part of Table 2 the conditions of the best yields so far reported in the literature to obtain the different *N*-sulfinyl imines that we have prepared. Almost all of these methods use acidic catalysts, whereas pyrrolidine is employed in our method, constituting an interesting alternative for avoiding possible undesired reactions. Moreover, the yields obtained with pyrrolidine (left part of Table 2) are always comparable and, in many cases better than those provided by using acidic catalysis (right part of Table 2). It is also remarkable the simplicity of the experimental manipulation required for obtaining pure *N*-sulfinyl imines (by NMR) under pyrrolidine catalysis (filtration of the reaction crude through a short pad of silica gel), which fulfills the main requirements of the green chemistry[28] (minimal waste, no hazardous materials and catalytic conditions), conferring to our procedure a potential interest in its application at industrial scale.

Encouraged by the excellent results obtained by using nucleophilic catalysis for the synthesis of *N*-sulfinyl imines we set up to investigate the preparation of other synthetically important imine derivatives, like *N*-sulfonyl imines,[29] by condensation of the aromatic aldehydes with RSO_2NH_2. The main problem associated to this reaction is related to the large electron-withdrawing character of the sulfonyl group, determining a very low nucleophilicity of the nitrogen at the RSO_2NH_2 (much lower than that of the $RSONH_2$) and, therefore, the need of a very high activation of the carbonyl. The use of acid catalysts under very strong conditions allows solving this problem, but the instability of the resulting *N*-sulfonyl imines, more prone to hydrolysis than the *N*-sulfinyl ones, imposes restrictions to the catalysts that can be used. Despite these drawbacks, there is a plethora of methods for the preparation of the synthetically important *N*-sulfonyl imines.[30]

Table 3. Scope of the synthesis of *N*-sulfonyl imines with aromatic aldehydes.



Entry[a]	Aldehyde R^1	Amide	Product (yield,%)[b]	Previous highest yield[c] Conditions	yield (%)
1[d]	**1a** C_6H_5	**2c**	**5ac** (99)	$BF_3.Et_2O$ (0.8 equiv) Tol, 120 °C, 12 h	(95)[31]
2	**1b** *p*-NO_2-C_6H_4	**2c**	**5bc** (87)	Amb. 15, 5Å MS, Tol, Dean-Stark, 16 h.	(95)[32]
3[e]	**1c** *p*-OMe-C_6H_4	**2c**	**5cc** (97)	*p*-TsOH, Tol, 120 °C Dean-Stark, 16 h	(99)[33]
4	**1d** *p*-CN-C_6H_4	**2c**	**5dc** (95)	BF_3Et_2O (0.8 equiv), 120 °C Dean-Stark	(99)[34]
5[d]	**1i** *o*-OMe-C_6H_4	**2c**	**5ic** (86)[f]	$Si(OEt)_4$ (1.1 equiv), 160 °C, 10 h	(94)[35]
6[g]	**1p** C_6H_5-CH=CH-	**2c**	**5pc** (99)	Oxidation of *N*-sulfinyl imines with MCPBA	(95)[22]
7[g]	**1q** *p*-NO_2-C_6H_4-CH=CH-	**2c**	**5qc** (98)	$BF_3{\cdot}Et_2O$, Benzene, Dean-Stark, 2h	(80)[36]
8[g,h]	**1r** *p*-OMe-C_6H_4-CH=CH-	**2c**	**5rc** (92)	$Si(OEt)_4$ (1.1 equiv), 160 °C, 5 h	(82)[37]
9[i]	**1u** 2,4-$(OMe)_2$-C_6H_3	**2c**	**5uc** (86)	$BF_3{\cdot}Et_2O$ (0.8 equiv), Tol, 120°C, 12 h	(68)[31]
10[d]	**1v** 3,4,5-$(OMe)_3$-C_6H_2	**2c**	**5vc** (83)j	BF_3Et_2O (0.8 equiv), 120 °C Dean-Stark	(99)[34]
11	**1a** C_6H_5[d]	**2d**	**5ad** (96)	Oxidation of *N*-sulfinyl imines with MCPBA	(96)[22]

[a]All the reactions were carried in a 1.2 mmol scale. [b] Isolated yield. [c] Conditions providing the highest yield found in the literature. [d] 1.2 equiv of aldehyde were used. [e] Reaction time 20 h. [f] Purified by precipitation in THF/hexane. [g] Reaction carried out at rt. [h] Reaction time 16 h. [I] Reaction time 6 h. [j] Purified by flash chromatography.

The results obtained in the reactions of aromatic aldehydes with sulfonamides under similar conditions to those used for obtaining *N*-sulfinyl imines (4Å MS[38] and 10 mol% of pyrrolidine) are depicted in Table 3. Sulfonamide **2c** reacts with benzaldehyde yielding pure **5ac** (after filtration of the reaction mixture through a short pad of celite to remove both pyrrolidine and 4Å MS) in quantitative yield (entry 1, Table 3) after 24 h. The reaction times required for getting the complete conversion into **5ac** are longer (24 h) than those of the *N*-sulfinyl imine **3aa** (1 h, entry 1, Table 2), which was expected from the lower nucleophilicity of the sulfonamide **2c** with respect to the sulfinamide **2a**. Under similar conditions, substituted benzaldehydes with electron-withdrawing (entries 2 and 4) and electron-donating substituents (entries 3 and 5), and unsaturated aldehydes **1p**-**1r** (entries 6-8) provided excellent yields. Finally, compounds **1u** and **1v**, bearing 2 and 3 OMe groups also gave very good results (entries 9 and 10). We also carried out the preparation of **5bc** in a 1.1 g scale without losing efficiency (see SI). Moreover, we have demonstrated that 4Å molecular sieves could be successfully reused after MW activation without erosion of the yield (see SI).

t-Butylsulfonyl imines can be prepared under similar conditions, as we have demonstrated in the case of the reaction of *t*-butylsulfonamide **2d** with benzaldehyde (entry 11).

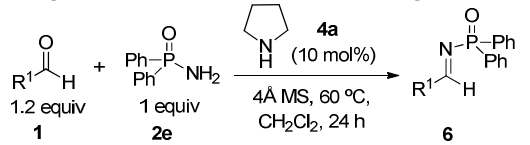
The comparison of our conditions and yields with those of the previously reported methods affording the highest yields for the different *N*-sulfonyl imines (right, Table 3) reveals similar advantages to those mentioned in the synthesis of *N*-sulfinyl imines (analogous or better yields, softer conditions, and simpler experimental manipulation). Moreover, the dispersion of methods based on acidic catalysis used for preparing the different *N*-sulfonyl imines shown in Table 3, contrasts with the fact that all of them are accessible under the same conditions employing pyrrolidine as catalyst.

The reaction of sulfinamides and sulfonamides with ketones was unsuccessful. Probably due to the high steric interactions around the iminium carbon at the tetrasubstituted generated intermediates.[39]

We have also checked that the aminocatalytic conditions used for preparing *N*-sulfinyl and *N*-sulfonyl imines are appropriated for *N*-diphenylphosphinoyl imines, which have particular importance in some catalytic processes leading to enantioenriched primary amines.[40]

Under similar conditions to those of tables 2 and 3, benzaldehyde (**1a**) and aromatic aldehydes bearing electron-withdrawing (**1b**) and electron-donating (**1c**) substituents, can be easily transformed into the *N*-phosphinoyl imines **6ae**-**6ce** in high yields by reaction with *N,N*-diphenyl phosfinic amide **2e** (Table 4). The indicated results were obtained starting from a little excess of aldehyde (1.2 equiv), and thus, for obtaining pure phosphinoyl imines, reaction crudes were filtered through a short pad of celite and then crystallized or column chromatographied. Despite this, the experimental manipulation is much simpler than that of the so far used methods for preparing these compounds (right, Table 4).[41,42,43]

Table 4. Synthesis of some *N*-phosphinoyl imines 6

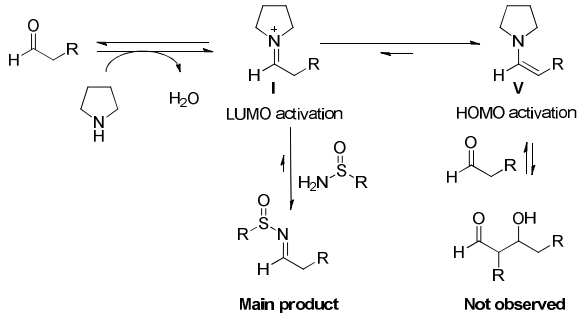


Entry[a]	Aldehyde R^1	Product (yield%)	**Previous method[b]** (yield, %)
1	**1a** C_6H_5	**6ae** (90)[c]	In 3 steps (82) [41b]
2	**1b** *p*-NO_2-C_6H_4	**6be** (98)[c]	In 2 steps (20) [42b]
3	**1c** *p*-OMe-C_6H_4	**6ce** (85)[d]	(85)[43]

[a] All reactions were carried out in a 0.4 mmol scale. [b] Method providing the highest yield found in the literature. [c] Purified by precipitation from CH_2Cl_2/pentane. [d] Purified by flash chromatography.

A priori, the synthesis of imine derivatives from aliphatic aldehydes should be troublesome because it is well established that they react with secondary amines to form mainly enamines **V** (Scheme 2), thus activating their α-position towards its reaction with electrophiles (HOMO activation).[4] However, to our surprise, we were also successful in applying our aminocatalytic approach (involving LUMO activation *via* iminium intermediates) to the synthesis of aliphatic *N*-sulfinyl imines, which suggests that the reaction of the sulfinamide with the iminium **I** is fast enough to shift the equilibrium shown in Scheme 2 towards the *N*-sulfinyl imine.

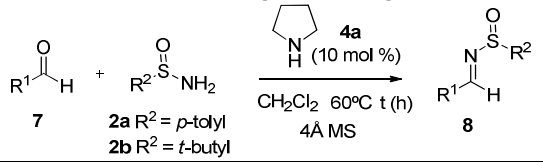
Scheme 2. Formation of *N*-sulfinyl imines from aliphatic aldehydes under pyrrolidine catalysis.



Reaction of **2a** with propanal **7a**, under conditions of the entry 16 at Table 1, afforded complex mixtures containing **8aa**. Cleaner reactions and higher yields of **8aa** were obtained after longer reaction times than those required for aromatic aldehydes by using an excess of the aldehyde, with the best results being obtained starting from 2 equiv of **7a** after 24 hours (entry 1, Table 5). A similar behavior was observed for 2-methybutanal, which afforded **8ba** in 72% yield after 6h, using 3 equiv of **7b** (entry 2). Chromatographic purification of the *p*-tolylsulfinyl imines was necessary. Better yields were achieved with *t*-butylsulfinamide **2b** than with **2a**. Reactions with different aliphatic aldehydes evolved in high yields regardless the primary, secondary and even tertiary nature of the alkyl

residue (entries 3-7). The isolated *N*-*t*-butylsulfinyl imines were obtained by using an excess of aldehyde (1.5 or 3 equiv) after simple filtration through a short pad of silica gel and elimination of the excess of aldehyde under vacuum with similar yields to the best ones described in the literature, which mainly use a large excess of $Ti(OEt)_4$[20,44,45] (see previous method, Table 5).

Table 5. Preparation of alkyl *N*-sulfinyl imines.



7 **2a** R^2 = *p*-tolyl **2b** R^2 = *t*-butyl **8**

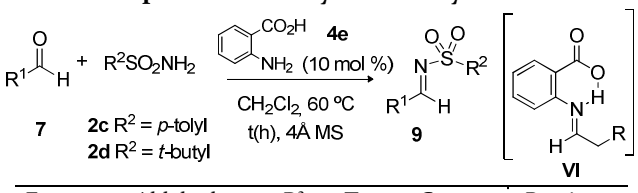
Entry[a]	Aldehyde R^1 (equiv)	Amine	t(h)	Product (yield,%)	Previous method (yield%)[c]
1	**7a** Et (2)	**2a**	24	**8aa** (83)[b]	87[20]
2	**7b** *s*-Bu (3)	**2a**	6	**8ba** (72)[b]	80[20]
3	**7c** *n*-Bu (2)	**2b**	24	**8cb** (99)[d]	81[46]
4	**7d** *i*-Bu (1.5)	**2b**	18	**8db** (89)[d]	96[47]
5	**7b** *s*-Bu (1.5)	**2b**	18	**8bb** (92)[d]	87[20]
6	**7e** Cy (1.5)	**2b**	18	**8eb** (99)[d]	98[44]
7	**7f** *t*-Bu (3)	**2b**	45	**8fb** (70)[d]	87[45]

[a] All reactions were carried out in a 0.4 mmol scale. [b] Isolated yield after column chromatography. [c] Highest yield found in the literature. [d] Yield after filtration through short pad of silica gel and removed the excess of aldehyde under vacuum.

Unfortunately, the reactions of the less nucleophilic sulfonamides with aliphatic aldehydes in the presence of pyrrolidine were not successful, yielding complex reaction mixtures. These negative results suggested us that the formation of the enamine must be avoided in order to achieve a general aminocatalytic method allowing the preparation of sulfonylimines derived from aliphatic aldehydes. We reasoned that the use of a similar strategy to those depicted in scheme 1*D*, consisting in the formation of a protonated imine, could provide a possible solution. It would require the use of primary amines as catalysts in the presence of a protons source, thus precluding the undesired enamine pathway.[48] By assuming that intramolecular protonation of the imine could facilitate the process (scheme 1*C*), we though in a β-amino acid as the catalyst, and chose the anthranilic acid because the aromatic ring would act as rigid tether between both functionalities, thus avoiding flexibility and making the protonation more effective (see specie **VI** in Table 6).[49]

We were glad to observe that a catalytic amount (10% mol) of anthranilic acid, in the presence of 4Å MS, was able to promote the direct condensation of aliphatic aldehydes with sulfonamides. By using an excess of the starting aldehydes (2 or 3 equiv), almost quantitative conversions were obtained, regardless the linear or ramified nature of the alkyl chain and the *p*-tolyl or *t*-butyl residue joined to sulfur (Table 6). As these imines are extremely prone to hydrolysis no chromatographic purification was undertaken. Nevertheless, after removal of the excess of aldehyde under vacuum, the crude products are pure enough to be used in further reactions (see ^{1}H-NMR spectra in SI). The experimental simplicity and the yields obtained with this method are clear advantages in comparison with the other ones reported in the literature to prepare aliphatic *N*-sulfonyl imines. These methods are based on their *in situ* generation from the corresponding amidosulfones[50] or on the oxidation of their *N*-sulfinyl imine precursors.[22]

Table 6. Preparation of alkyl *N*-sulfonyl imines.



7 **2c** R^2 = *p*-tolyl **2d** R^2 = *t*-butyl **9** **VI**

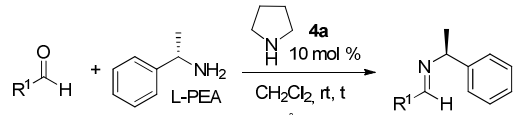
Entry	Aldehyde R^1 (equiv)	R^2	T (h)	Conv (%)[a]	Previous method (yield%)[b]
1	**7c** n-Bu (3)	**2c**	24	**9cc** (90)	78[50]
2	**7g** n-Octyl (3)	**2c**	24	**9gc** (100)	80[51]
3	**7d** *i*-Bu (3)	**2c**	24	**9dc** (88)	64[50]
4	**7f** *t*-Bu (2)	**2c**	72	**9fc** (99)[c]	96[22]
5	**7a** Et (3)	**2d**	36	**9ad** (80)	(-)[52]

[a] *D*etermined by ^{1}H-NMR on the spectrum of the crude material after filtration through a short pad of silica gel. [b] Highest yield found in the literature. [c] Yield obtained after filtration through a short pad of silica and removed the excess of **7f**.

Finally, we have tested the power of our methodology by preparing representative examples of *N*-alkyl and *N*-aryl imines derived from both aromatic and aliphatic aldehydes (Tables 7 and 8).[53]

As aliphatic amine model we chose L-PEA **2f** due to its synthetic interest.[54] Reaction of this amine with benzaldehyde in the presence of pyrrolidine and 4Å MS afforded **10af** in almost quantitative yield after 20 min (entry 1, Table 7). This reaction also occurs in the absence of catalysts, but it is clearly slower (see SI). The procedure was also very efficient with the more challenging aliphatic aldehydes **7b** and **7c** (entries 2 and 3), also affording the scarcely stable imines **10bf** and **10cf**, so far never reported, in almost quantitative yield, by using a small excess (1.2 equiv) of the starting aldehydes.

Table 7. Preparation of *N*-alkyl aldimines.



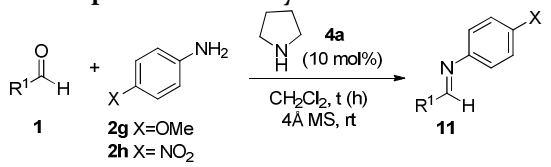
1 **2f** **10**

Entry	Aldehyde R^1 (equiv)	t	Yield (%)[a]	Previous method (yield%) [b]
1	**1a** C_6H_5 (1)	20 min	**10af** 90	99[c]
2	**7b** *s*-Bu (1.2)	1.5 h	**10bf** 99	not described
3	**7c** *n*-Bu (1.2)	1.5 h	**10cf** 98	not described

[a] Isolated yield after filtration through a short pad of celite without further purification. Excess of aldehyde in entries 2 and 3 was eliminated by evaporation. [b] Highest yield found in the literature. [c] Conditions: $NaHCO_3$ (5 equiv), reflux of benzene, 16h[54b]

As aromatic amine model for preparing *N*-aryl imines we chose the *p*-methoxyaniline (**2g**) because of the easy conversion of the *N*-PMP moieties into the free NH_2.[3] We have studied reactions of **2g** with aromatic (**1c**, entry 1, Table 8) and aliphatic aldehydes (**7b**, **7d**, and **7f**, entries 2-4), all of them evolving with excellent yields. Reaction with the ethyl glyoxylate **1t** (entry 5) is interesting because of the usefulness of the resulting imine **11tg** in the synthesis of aminoacids. Finally we have studied the reaction of the poorly nucleophilic *p*-nitroaniline (**2h**) with the scarcely electrophilic *p*-methoxy benzaldehyde **1c**, with analogously good result (entry 6) and where the accelerating role of both pyrrolidine and 4Å MS can also be clearly appreciated (see SI).

Table 8. Preparation of *N*-aryl aldimines.

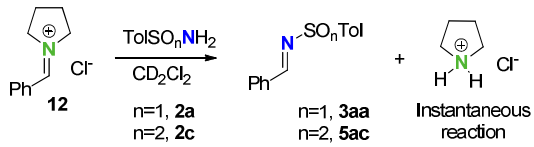


Entry	Aldehyde R^1 (equiv) / amine	t (h)	Product Yield(%)[a]	Previous method (yield%)[d]
1	**1c** *p*-OMe-C_6H_4 (1)/**2g**	0.25	**11cg** (89)[b]	99[55]
2	**7b** *s*-Bu (1.2) / **2g**	0.5	**11bg**(86)[b]	99[56a]
3	**7d** i-Bu (2) / **2g**	0.5	**11dg**(87)[b]	88[57]
4	**7f** t-Bu(2) / **2g**	22	**11fg** (99)	93[58]
5[c]	**1t** CO_2Et (1) / **2g**	1	**11tg** (94)	99[56b]
6	**1c** *p*-OMe-C_6H_4 (1)/**2h**	16	**11ch** (100)	95[59]

[a] Isolated yield after filtration through a short pad of silica gel. [b] Conversion determined by ^{1}H-NMR on the spectrum of the crude material. [c] 5 mol% of **4a** was used. [d] Highest yield found in the literature.

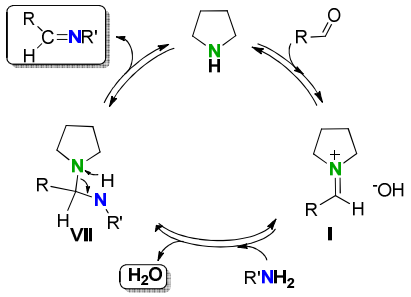
In order to corroborate our $C=N^+/C=N$ transimination hypothesis outlined in Scheme 1B, we carried out some NMR studies (see SI). We demonstrated that the preformed iminium chloride of pyrrolidine and benzaldehyde **12** reacted instantaneously with both *p*-tolylsulfinamide **2a** and *p*-tolylsulfonamide **2c** to afford the corresponding imines **3aa** and **5ac** (Scheme 3).

Scheme 3. Instantaneous reaction of iminium 12 with *p*-tolylsulfinamide 2a and *p*-tolylsulfonamide 2c.



A mechanistic proposal explaining the nucleophilic catalysis exerted by pyrrolidine in the synthesis of different types of aldimines is depicted in Scheme 4. The secondary amine would react to some extent with the starting aldehyde to form an iminium ion **I**. As it has been demonstrated with the previous experiment (Scheme 3), the attack of the amino derivative to the highly electrophilic iminium **I**, must be highly favored, even for scarcely nucleophilic compounds, like those bearing electron-withdrawing groups joined to the NH_2. The transformation of the so formed aminal **VII** into the imine could occur through a favored concerted process involving a four membered transition state according the route recently proposed by Di Stefano *et al.*[60] The liberation of the pyrrolidine would complete the catalytic cycle, reacting with another molecule of aldehyde, more reactive than the resulting imine in most of the cases. The water scavenger would prevent the hydrolysis of the formed imine (mainly the more reactive *N*-sulfonyl and *N*-phosphinoyl derivatives) into the starting products, shifting the equilibrium shown in Scheme 4 and therefore accelerating the reaction.

Scheme 4. Mechanistic proposal.



CONCLUSIONS

We have applied the concept of nucleophilic catalysis to the synthesis of different types of aldimines, including those bearing EWG at the nitrogen (*N*-sulfinyl, *N*-sulfonyl, and *N*-phosphinoyl derivatives), which are of special synthetic relevance. Contrasting with the so far reported methods, usually based on the activation of the carbonyl with a large amount of acid, our surprisingly unprecedented procedure takes place under smooth catalytic conditions in the presence of pyrrolidine (10% mol) and 4Å MS, providing excellent yields of aldimines from a wide variety of aldehydes (aryl, heteroaryl, alkyl and unsaturated), after minimum lab manipulation. We envision a great potential for this biomimetic and organocatalytic methodology as useful tool in imine preparation. The search of new aminocatalytic systems for these and similar reactions is currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION.

Corresponding Author

Belen.cid@uam.es, joseluis.garcia.ruano@uam.es

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Belowich, M. E.; Stoddart, J. F. *Chem. Soc. Rev*. **2012**, *41*, 2003 and references cited therein.
(2) (a) Bloch R. *Chem. Rev.* **1998**, *98*, 1407. (b) For chiral amines see: *Chiral Amine Synthesis: Methods, Developments and Applications* Thomas C. Nugent, Wiley-VCH: Weinheim, Germany, 2010. 494 pp.
(3) (a) Tehrani, K. Abbaspour; De Kimpe, N. Product class 7: imines. *Science of Synthesis,* Georg Thieme Verlag: Germany 2004, *27*, 245-312. (b) Charette, A. B. in ref 2 Chapter 1.
(4) (a) MacMillan, D. W. C. *Nature*, **2008**, *455*, 304. (b) Gaunt, M. J.; Johansson, C.C.C.; McNally, A.; Vo, N. T. *Drug Discov. Today* **2007**, *12*, 8. (c) *Science of Synthesis, Asymmetric Organocatalysis.* Edited by List, B., Maruoka, K. Thieme Chemistry: Germany, 2012, 1928 pp. 2-volume set.
(5) (a) Mukherjee, S.; Yang, J. W.; Hoffmann. S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (c) Vicario, J. L.; Reyes, E.; Badia, D.; Carrillo, L. *Catalytic Asymmetric Conjugate Reactions.* Ed. A. Cordova, Wiley-VCH: Weinheim, Germany, 2010, chapter. 6. (d) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K.A. *Chem. Commun*. **2011**, *47*, 632. (e) For a review see: Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. C*hem. Commun.*, **2013**, *49*, 4869.
(6) (a) Knoevenagel, E. *Chem. Ber.*, **1894**, *27*, 2345. (b) Ingold, C. K. In *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca N. Y. 1953, 685 pp.
(7) See for example: (a) Crowell, T. I. Peck, D.W. *J. Am. Chem. Soc*., **1953,** *75,* 1075. (b) Schroeder, C. Preis, S., Link, K. P. *Tetrahedron Lett*. **1960**, *13*, 23. (c) Spencer, T. A. In *Bioorganic Chemistry*. Chapter 13 *Studies of Amine Catalysis via Iminium Ion Formation*. Academic Press: New York, 1977, 313-337.
(8) McMurry, J. E.; Begley, T. In *The Organic Chemistry of Biological Pathways,* 7ª ed.; Roberts and Company Publishers: Colorado, USA, 2005, 490 pp.
(9) Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc,* **1962**, *84*, 826.
(10) (a) Dirksen, A.; Hackeng, T. M.; Dawson, P. E. *Angew. Chem. Int. Ed*. **2006**, *45*, 7581. (b) Dirksen, A.; Dirksen, S.; Hackeng, T. M.; Dawson, P. E. *J. Am. Chem. Soc*. **2006**, *128*, 15602.
(11) Aniline has also been used in transimination reactions: (a) Kovaříček, P.; Lehn J-M. *J. Am. Chem. Soc*. **2012**, *134*, 9446. (b) The use of proline in DMF as moderate accelerator of these interchanges has been recently reported by Lehn and used in dynamic covalent chemistry: Wilhelms, N.; Kulchat, S.; Lehn, J-M. *Helv. Chim. Acta* **2012**, *95*, 2635.
(12) R. Appel, S. Chelli, T. Tokuyasu, K. Troshin, H. Mayr. *J. Am. Chem. Soc*. **2013**, *135*, 6579.
(13) (a) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res*. **2002**, *35*, 984.(c) Robak, M.T.; Herbage, M.A.; Ellman, J.A. *Chem. Rev.* **2010,** *110,* 3600.
(14) Davis, F. A.; Zhang, Y.; Andemichae, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem*. **1999**, *64*, 1403.
(15) (a) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T.C.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, 127, 18296. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 4212.
(16) Reaction of **1a** with **2a** in the presence of 4Å MS affords **3aa** in a modest 52 % yield, after 24 hours (see ref. 14)
(17) We have compared the optical rotation value of compound **(S)-(+)-3aa** obtained following our method $[\alpha]_D^{20}$ +117.7° (c= 1,77, $CHCl_3$)with the one described in the literature: $[\alpha]_D^{20}$ +119.3° (c = 1.77, $CHCl_3$), Davis, F. A.; Reddy, R.E.; Szewczyk, J. M. *J. Org. Chem*. **1995**, *60*, 7037.
(18) García Ruano. J.L.; Alemán, J.; Fajardo, C.; Parra, A. *Org. Lett*. **2005**, *7*, 5493.
(19) García Ruano J. L.; Alemán, J.; Soriano, J. F. *Org. Lett*. **2003**, *5*, 677.
(20) Jiang, Z-Y.; Chan, W.H.; Lee, A.W. *J. Org. Chem.* **2005**, *70*, 1081.
(21) Davis, F.A.; Reddy, R. E.; Szewczyk, J.M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy; T. R.; Zhou, P.; Carroll, P. J. *J. Org. Chem*. **1997**, *62*, 2555.
(22) García Ruano J. L.; Alemán, J.; Cid, M.B.; Parra, A. *Org. Lett*. **2005**, *7*, 179.
(23) Higashibayashi, S; Tohmiya, H; Mori, T; Hashimoto, K; Nakata, M. *Synlett* **2004**, 457.
(24) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.
(25) Forbes, D.C.; Bettigeri, S.V.; Amin, S.R.; Bean, C.J.;. Law, A. M.; Stockman, R.A. *Synth. Commun*. **2009**, *39*, 2405.
(26) (a) Marigo, M.; Schulte. T.; Franzén, J.; Jørgensen. K.A. *J. Am. Chem. Soc*. **2005**, *127*, 15710.(b) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen. K.A. *Angew. Chem. Int. Ed*. **2007**, *46*, 1983.
(27) Davis, F.A.; McCoull, W. *J. Org. Chem*. **1999**, *64*, 3396.
(28) Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice*, Oxford University Press: New York, 1998. A more detailed description of the environmental advantages is included in SI.
(29) (a) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131. (b) Gohain, N. *Synlett* **2003**, 2097.
(30) See references 22 and 31-37 in Table 3.
(31) Yoshida, K.; Akashi, N.; Yanagisawa, A. *Tetrahedron: Asymmetry* **2011**, *22*, 1225.
(32) Barbarotto, M.; Geist, J.; Choppin,S.; Colobert. F. *Tetrahedron: Asymmetry* **2009**, *20*, 2780.
(33) Regiani, T.; Santos, V.G.; Godoi, M. N.; Vaz, B. G.; .Eberlin, M.N.; Coelho, F. *Chem. Commun*. **2011**, *47*, 6593.
(34) Fuyuhiko, T. Ohyun, K.; Masaru, W.; Hannah, F. WO 2007111948, 2007.
(35) Love, B. E.; Raje, P. S.; Williams II, T. C. *Synlett* **1994**, 493.
(36) Stokes, S.; Bekkam, M.; Rupp, M.; Mead K. T. *Synlett* **2012**, 389.

(37) Yamada, K.; Umeki, H.; Maekawa, M.; Yamamoto, Y.; Akindele, T.; Nakano, M.; Tomioka. K. *Tetrahedron* **2008**, *64*, 7258.
(38) 4Å MS has been used to accelerate the formation of *N-p*-tolylsulfonyl imines and their use in tandem processes, see: Guo, Q.; Zhao J. C-G *Org. Lett*. **2013**, *15*, 508. Nevertheless, we have proven, in the case of the imine **5cc** derived from *p*-anisaldehyde, that the combination of pyrrolidine and 4Å MS is more efficient than the use of only the molecular sieves or pyrrolidine where reactions do not go to completion (see SI).
(39) Primary amines and acidic additives have been used to sort out this problem and have been successfully employed for the Michael addition of unsaturated ketons *via* iminium activation, see for example: Bartoli, G.; Melchiorre, P. *Synlett* **2008**, *12*, 1759. It could be expected that this strategy could be used in the future to apply the methodology presented herein to the preparation of ketimines.
(40) For a review: Weinreb, S. M.; Orr, R. K. *Synthesis* **2005**, 1205.
(41) Experimental procedure requires three steps: i) preparation of $TolSO_2H$ from $TolSO_2Na$; ii) Formation of amidosulfone with RCHO (1.5 equiv), $TolSO_2H$ (1,5 equiv) and $Ph_2P(O)NH_2$ (1 equiv); iii) generation of the imine with K_2CO_3 (5 equiv) See: (a) Desrosiers, J-N.; Cote, A.; Boezio, A.A.; Charette, A. B *Proc. Natl. Acad. Sci., USA* **2004**, *101*, 5405. (b) Desrosiers, J-N.; Cote, A.; Boezio, A.A.; Charette, A. B. *Org. Synth.* **2006**, *83*, 5.
(42) Experimental procedure requires two steps: i) formation of aldoxime ii) alkylation with chlorodiphenylphosphine at low temperature under inert anhydrous conditions. See: (a) Boyd, D. R.; Malone, J. F.; McGuckin, M. R.; Jennings, W. B.; Rutherford, M.; Saket, B. M. *J. Chem. Soc., Perkin Trans. 2*, **1988**, 1145; (b) Krzyzanowska, B. Stec, W. *Synthesis*, **1978**, 521; **1982**, 270.
(43) Experimental procedure: Et_3N (3,5 equiv), $TiCl_4$ (0.5 equiv), CH_2Cl_2, rt. 1.5h. See: (a) Banerjee, S.; Groeper, J.A.; Standard, J.M.; Hitchcock, S.R. *Tetrahedron: Asymmetry* **2009**, *20*, 2154.(b) Jennings, W.B.; Lovely, C.J. *Tetrahedron Lett.* **1988**, *29*, 3725.
(44) Experimental procedure: $Ti(OEt)_4$ (5 equiv), refluxing DCM, 4h. Bolshan, Y.;.Batey, R.A. *Org.Lett*. **2005**, *7*, 1481.
(45) Experimental procedure: $Ti(OEt)_4$ (2 equiv), neat, MW, 70ºC, 40W, 10 min. Collados, J. F.; Toledano, E., Guijarro, D.; Yus, M. *J. Org. Chem*. **2012**, *77*, 5744.
(46) Experimental procedure: $KHSO_4$, toluene, 45 °C, 24h. See: Huang, Z.; Zhang, M.; Wang, Y.; Qin, Y. *Synlett* **2005**, 1334.
(47) Experimental procedure: PPTS (5 mol%), aldehyde (2 equiv), $MgSO_4$ (5 equiv), DCM, rt, 5h. See: Asada, M.; Obitsu, T.; Kinoshita, A.; Nagase, T.; Yoshida, T.; Yamaura, Y.; Takizawa, H.; Yoshikawa, K.; Sato, K.; Narita, M.; Nakai, H.; Toda, M.; Tobe, Y. *Bioorg. Med. Chem*. **2010**, *18*, 3212.
(48) This strategy is commonly used for activating unsaturated ketones in enantioselective aminocatalysis. See ref. 39
(49) Antranilic acid has also been recently used in a large excess to form hydrazones and oximes in aqueous media. See: (a) Crisalli, P.; Kool, E. T. *J. Org. Chem*. **2013**, *78*, 1184. (b) Crisalli, P.; Kool, E. T. *Org. Lett*. **2013**, *15*, 1646.
(50) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75.
(51) Experimental procedure: cyanuric chloride (0.15 equiv), neat, 110 °C, 2.5h. See: Wua, L.; Yang ,X.; Wang, X.; Yan, F. *J. Sulf. Chem*. **2010**, *31*, 509.
(52) This compound was prepared by MCPBA oxidation of the corresponding *N*-sulfinyl imine following the procedure of ref 26. See: Lanter, J C.; Chen, H.; Zhang, X.; Sui, Z. *Org. Lett*. **2005**, *7*, 5905. The yield is not reported.
(53) For a method to form N-alkyl and N-aryl imines in water see: Simion, *A.;* Simion, C.; Kanda, T.; Nagashima, S.; Mitoma, Y.; Yamada, T.; Mimura, K.; Tashiro, M. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2071.
(54) (a) Patel, M.S.; Worsley, M. *Can. J. Chem*. **1970**, *48*,1881. (b) Samec, J.S.M.; Bäckvall, J-E. *Chem. Eur. J*. **2002**, *8*, 2955. (c) Huang,L.; Zhang, Y.; Staples, R J.; Huang, R.H.; Wulff, W.D. *Chem. Eur. J*. **2012**, *18*, 5302.
(55) Experimental procedure: SiO_2 (5 equiv), EtOH, US, rt, 10 min. See: Guzen, K.P.; Guarezemini, A.S.; Órfão, A.T.G.; Cella, R.; Pereira, C.M.P.; Stefani, H.A. *Tetrahedron Lett*. **2007,** *48*, 1845.
(56) Experimental procedure: $MgSO_4$, DCM, 1h ,rt. See: (a) Rodríguez-Solla, H.; Concellón, C.; Alvaredo, N.; Soengas, R.G. *Tetrahedron* **2012**, *68*, 1736. (b) Künzi, S.A.; Morandi, B.; Carreira, E.M. *Org. Lett*. **2012**, *14*, 1900.
(57) A modified Wadsworth-Emmons procedure was used: Ciufolini, M.A.; Spencer, G.O. *J. Org. Chem*. **1989**, *54*, 4739.
(58) Vara, Y.; Bello, T.; Aldaba, E.; Arrieta, A.; Pizarro, J.L.; Arriortua, M.I.; López, X.; Cossio, F.P. *Org. Lett*. **2008**, *10*, 4759.
(59) Experimental procedure: $Mg(ClO_4)_2$ (5%), DCE, 8h. Chakraborti, A. K.; Bhagat, S.; Rudrawar, S. *Tetrahedron Lett*. **2004**, *45*, 7641.
(60) M. Ciaccia, R. Cacciapaglia, P. Mencarelli, L. Mandolini and S. Di Stefano. *Chem. Sci.* **2013,** *4*, 2253.