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A General Aminocatalytic Method for the Synthesis of Aldimines

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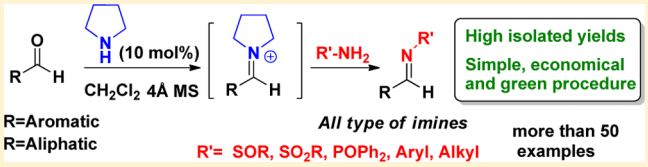
Supporting Information

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 a 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, *N*-alkyl, and *N*-aryl imines. These unprecedented reactions, which presumably occur via iminium activation without requiring acidic conditions, are an interesting and competitive alternative to the classical methods for preparing aldimines.



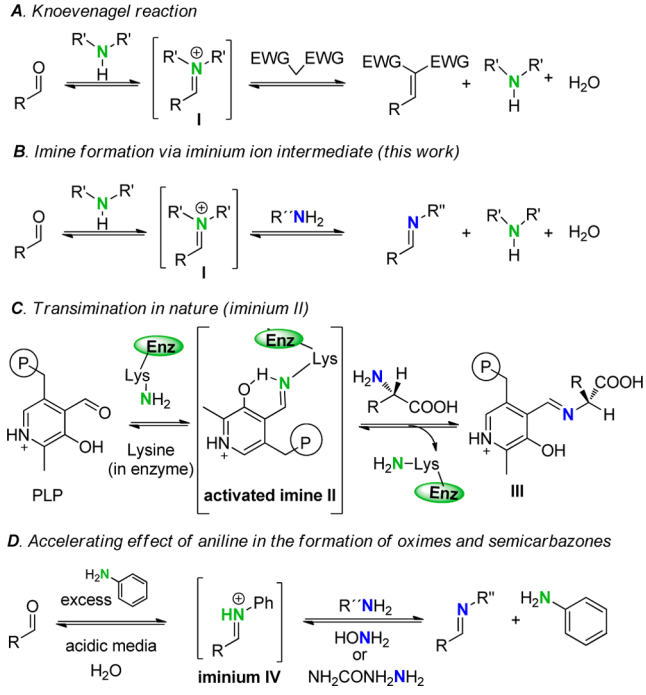
INTRODUCTION

The formation of C═N bonds by condensation of C═O and NH_2 groups has been a priority in organic synthesis because of the relevance of imines in the fields of chemistry and biology.[1] More importantly, however, imines are versatile electrophiles that give rise to nitrogen-containing compounds,[2] which are widely distributed in nature and have many important pharmacological activities. Most of the methods for 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] In contrast to the profusion of enantioselective reactions involving carbonyl compounds using proline derivatives as catalysts,[5] affecting the α-,[5a] β-,[5b,c] and γ-positions,[5e] those concerning nucleophilic attack at the carbonyl carbon involving iminium intermediates **I** are mostly limited to the Mannich and Knoevenagel reactions (Scheme 1A).[6] We reasoned that compounds containing NH_2 groups could act as nitrogenated nucleophiles and evolve in a similar way under appropriate catalytic conditions, allowing the formation of any kind of C═N bonds (Scheme 1B). This transformation, astonishingly unexploited to date, 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, respectively. Interestingly, the transimination process indicated in Scheme 1B would mimic transformations occurring in nature. In particular, the formation of imines **III** derived from pyridoxal phosphate (PLP) and amino acids (Scheme 1C), which are pivotal intermediates in transformations of amino acids, are not formed by direct condensation of these components but instead through transimination reactions with

Scheme 1. Organocatalyzed Functionalization of Aldehydes Using Iminium Activation



activated imines **II** that result 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 1D), has been known since 1962[9] and was recently used in the

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preparation of hydrazones and oximes as linkages of bioconjugates.[10] It is important to note that this is a noncatalytic process that requires a high concentration of aniline in a strongly acidic medium.[11] On the contrary, the use of a secondary amine in a catalytic amount to generate iminium intermediate **I** (instead of the protonated imine intermediate **IV**) would allow the reaction of a variety of amines in organic solvents without requiring an acidic aqueous medium (Scheme 1B).

Some recently published results put forward the viability of our hypothesis. Mayr reported that the electrophilicity of the aromatic iminium intermediate **I** (Scheme 1B) is more than 10 orders of magnitude higher than that of the carbonyl group in the precursor aldehyde in reactions with carbon nucleophiles and even higher (3 to 5 orders) for heteronucleophiles.[12] Moreover, Mayr also described 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. These results suggest 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 weakly nucleophilic character of some RNH_2 species (unable to react with aldehydes in the absence of an appropriate 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 with clear environmental advantages with respect to those used by the methods reported to date.

RESULTS AND DISCUSSION

We focused our initial efforts on the organocatalytic preparation of aldimines activated by electron-withdrawing groups because of their synthetic importance. Enantiomerically pure *N*-sulfinyl imines are one of the types of activated imines most used in the asymmetric synthesis of primary amines because of the dual role played by the sulfinyl group as an activating and stereodirecting group and its easy removal.[13] The method most commonly used to prepare these compounds is based on the reaction of aldehydes with optically pure $RSONH_2$ (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 a dehydrating reagent.[14] The main drawback of this method, which provides imines in usually high yields, is the excess of the Lewis acid required, which generates a large amount of environmentally undesired waste (titanium salts), imposing a sometimes tedious purification process.

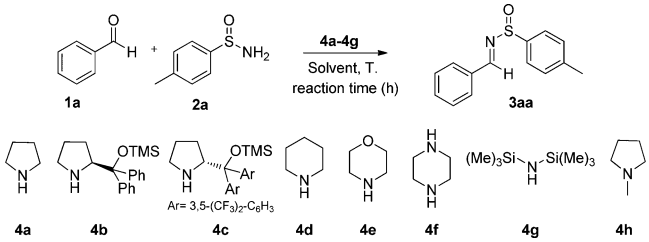
The condensation of benzaldehyde (**1a**) and *p*-tolylsulfinamide (**2a**) was used as model reaction. The results obtained under different conditions are indicated in Table 1. All of the reactions were accomplished at 60 °C in a sealed vial using solutions containing equimolar amounts of the reagents. In the absence of catalyst the reaction did not take place (entry 1), as could be expected from the low nucleophilicity of the nitrogen in **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** to some extent, demonstrating the potential of nucleophilic catalysis. In the presence of the tertiary amine **4h** as the 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, such as **4b** and **4c**, which are widely used in asymmetric organocatalysis,[15] were less efficient (entries 3 and 4). Analogously, in the presence of piperidine (**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), the conversions observed after 7 h were lower than those achieved with **4a**.

We then checked the role of the solvent. The reaction progressed in all of the solvents used, but after 7 h under the studied conditions, complete conversion was observed only in CH_2Cl_2 and EtOH (entries 2 and 10). At lower temperature (entry 14) or catalyst loading (10 mol %; entry 15) in CH_2Cl_2, conversion after 7 h was not complete.

Better results were obtained in the presence of 4 Å molecular sieves (4 Å MS) as a water scavenger. Thus, the time to get complete conversion with a catalyst loading of only 10 mol % decreased to 1 h (entry 16).[16] The use of these conditions, considered as the optimal ones, allowed us to obtain pure **3aa**

Table 1. Evaluation of Different Amines as Catalysts in the Synthesis of Imines



entry[a]	cat (mol %)	solvent	*T* (°C)	*t* (h)	% conv.[b] (% yield[c])
1	none	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_2/4 Å MS**	**60**	**1**	**100**
17[e]	**4a** (10)	CH_2Cl_2/4 Å MS	60	2	100 (94)
18	**4a** (10)	THF/4 Å MS	60	4.5	100 (90)
19	**4a** (10)	CH_3CN/4 Å MS	60	4.5	100 (92)
20	**4a** (10)	toluene/4 Å MS	60	4.5	100 (91)

[a]Reactions were performed in a sealed vial using equimolar amounts of aldehyde and *p*-tolylsulfinamide on 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 analysis of the crude material. [c]Isolated yields after filtration through a short pad of silica gel. [d]1.5 equiv of **1a** was used. [e]Reaction was performed starting from 1 g of **2a**.

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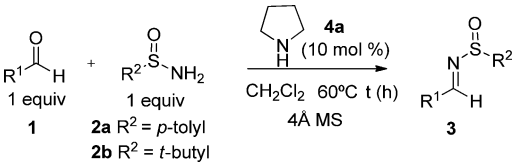
Table 2. Scope of the synthesis of *N*-sulfinyl imines derived from aromatic aldehydes



					previous method[c]	
entry[a]	aldehyde, R^1	amide	t (h)	product (% yield[b])	conditions	% yield
1	**1a**, C_6H_5	**2a**	1	**3aa** (95)	$Ti(OEt)_4$ (5), 4 h	99[14]
2	**1b**, p-$NO_2C_6H_4$	**2a**	2.5	**3ba** (93)	$Ti(OEt)_4$ (5)	85[18]
3	**1c**, p-$MeOC_6H_4$	**2a**	2	**3ca** (96)	$Ti(OEt)_4$ (5), 4 h	92[14]
4	**1d**, p-CNC_6H_4	**2a**	4	**3da** (92)	$Ti(OEt)_4$ (5), 4 h	60[19]
5	**1e**, p-ClC_6H_4	**2a**	3	**3ea** (95)	$Yb(OTf)_3$ (0.1),[d] 12 h	84[20]
6	**1f**, o-$NO_2C_6H_4$	**2a**	5	**3fa** (90)	$Yb(OTf)_3$ (0.1),[d] 12 h	81[20]
7	**1g**, o-HOC_6H_4	**2a**	3	**3ga** (89)	not described	–[i]
8	**1h**, o-BrC_6H_4	**2a**	4	**3ha** (96)	$Ti(OEt)_4$ (5), 4 h	65[19]
9	**1i**, o-$MeOC_6H_4$	**2a**	3	**3ia** (99)	KF (2), THF, −78 °C, 12 h	91[21]
10	**1j**, m-$MeOC_6H_4$	**2a**	3	**3ja** (91)	$Ti(OEt)_4$ (5), 4 h	92[14]
11	**1k**, 2-naphthyl	**2a**	4	**3ka** (90)	$Ti(OEt)_4$ (5), 4 h	94[22]
12	**1l**, 2-pyridyl	**2a**	4	**3la** (88)	$CsCO_3$ (5), 45 °C, 8 h	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-thiophenyl	**2a**	4	**3oa** (90)	not described	–
16[f]	**1p**, $C_6H_4CH{=}CH$	**2a**	4	**3pa** (99)	$Ti(OEt)_4$ (5), 4 h	80[22]
17[f]	**1q**, p-$NO_2C_6H_4CH{=}CH$	**2a**	3	**3qa** (97)	not described	–
18[f]	**1r**, p-$MeOC_6H_4CH{=}CH$	**2a**	3.5	**3ra** (88)	not described	–
19[f]	**1s**, o-$MeOC_6H_4CH{=}CH$	**2a**	3.5	**3sa** (98)	not described	–
20	**1t**, CO_2Et	**2a**	5	**3ta**(93)	4 Å MS, rt, 1 h	67[27]
21	**1a**, C_6H_5	**2b**	4	**3ab** (99)	$CuSO_4$ (2), rt[g]	91[24]
22	**1b**, p-$NO_2C_6H_4$	**2b**	4	**3bb** (91)	$CuSO_4$ (2), rt, 24 h[h]	96[25]
23	**1c**, p-$MeOC_6H_4$	**2b**	4	**3cb** (99)	$CuSO_4$ (2), rt[g]	81[24]

[a]All reactions were carried out on a 0.2 mmol scale. [b]Isolated yields. [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 4 Å MS. [f]Reaction was carried out at room temperature. [g]1.1 equiv of aldehyde was used. [h]1.5 equiv of aldehyde was used. [i]We have proven that this reaction also works in high yield using $Ti(OEt)_4$ (5), as shown in the SI.

in almost quantitative yield by simple filtration through a short pad of silica gel to remove pyrrolidine and 4 Å MS. Similar results were obtained on a gram scale, where **3aa** was obtained in 94% isolated yield after 2 h in a sealed tube (entry 17) and after 75 min under conventional CH_2Cl_2 reflux [see the Supporting Information (SI)]. Remarkably, these smooth conditions were also efficient in other solvents, including THF, MeCN, and toluene (entries 18−20), which could be interesting for connecting the preparation of the imines and their reactions with different nucleophiles in one-pot processes. Finally, we checked that all of 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 were performed using two sets of conditions. The results obtained under the conditions for entry 2 of Table 1, (without 4 Å MS) are recorded in the SI, whereas those obtained under the conditions for entry 16 of Table 1, (in the presence of 4 Å MS) are gathered in Table 2. All of the compounds were obtained in high purity after simple filtration through a short pad of silica gel.

Starting from substituted benzaldehydes (Table 2, 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).

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

Unsaturated aldehydes **1p−s** (entries 16−19) also reacted to form the imines **3pa−sa** in almost quantitative yields. This complete regioselectivity toward the products resulting from the attack of sulfinamide **2a** at C-1 is remarkable because carbonated nucleophiles produce only the attack at C-3 in reactions catalyzed by **4b** or **4c**. This change in the regioselectivity could be due to the reversibility observed in the attack at C-3 by some heteronucleophiles[26] and/or to the fact that the reaction of N-nucleophiles at C-1 is more favored than that of C-nucleophiles as a consequence of the anomeric stabilization of the aminal species that results in the first case.[12] The incorporation of electron-donating and electron-withdrawing groups on the aromatic ring of these enals has no consequence on the efficiency of the process (entries 17−19), and it was possible to obtain excellent yields of the *N*-sulfinyl imines **3qa−sa** that have not been reported previously.

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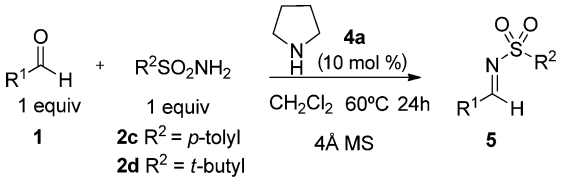
Table 3. Scope of the Synthesis of *N*-Sulfonyl Imines with Aromatic Aldehydes



				previous method[c]	
entry[a]	aldehyde, R^1	amide	product (% yield[b])	conditions	% yield
1[d]	**1a**, C_6H_5	**2c**	**5ac** (99)	$BF_3{\cdot}OEt_2$ (0.8 equiv), Tol, 120 °C, 12 h	95[31]
2	**1b**, *p*-$NO_2C_6H_4$	**2c**	**5bc** (87)	Amb. 15, 5 Å MS, Tol, Dean–Stark, 16 h	95[32]
3[e]	**1c**, *p*-$MeOC_6H_4$	**2c**	**5cc** (97)	*p*-TsOH, Tol, 120 °C, Dean–Stark, 16 h	99[33]
4	**1d**, *p*-NCC_6H_4	**2c**	**5dc** (95)	$BF_3{\cdot}OEt_2$ (0.8 equiv), 120 °C, Dean–Stark	99[34]
5[d]	**1i**, *o*-$MeOC_6H_4$	**2c**	**5ic** (86)[f]	$Si(OEt)_4$ (1.1 equiv), 160 °C, 10 h	94[35]
6[g]	**1p**, $C_6H_5CH{=}CH$	**2c**	**5pc** (99)	oxidation of *N*-sulfinyl imines with MCPBA	95[22]
7[g]	**1q**, *p*-$NO_2C_6H_4CH{=}CH$	**2c**	**5qc** (98)	$BF_3{\cdot}OEt_2$, benzene, Dean–Stark, 2h	80[36]
8[g,h]	**1r**, *p*-$MeOC_6H_4CH{=}CH$	**2c**	**5rc** (92)	$Si(OEt)_4$ (1.1 equiv), 160 °C, 5 h	82[37]
9[i]	**1u**, 2,4-$(MeO)_2C_6H_3$	**2c**	**5uc** (86)	$BF_3{\cdot}OEt_2$ (0.8 equiv), Tol, 120 °C, 12 h	68[31]
10[d]	**1v**, 3,4,5-$(MeO)_3C_6H_2$	**2c**	**5vc** (83)[j]	$BF_3{\cdot}OEt_2$ (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 of the reactions were carried out on a 1.2 mmol scale. [b]Isolated yields. [c]Conditions providing the highest yield found in the literature. [d]1.2 equiv of aldehyde was 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.

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

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

For comparative purposes, we have indicated in the right part of Table 2 the conditions of the best yields reported to date in the literature to obtain the different *N*-sulfinyl imines that we 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). Also remarkable is the simplicity of the experimental manipulation required for obtaining pure (by NMR) *N*-sulfinyl imines under pyrrolidine catalysis (filtration of the crude reaction mixture through a short pad of silica gel), which fulfills the main requirements of 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 using nucleophilic catalysis for the synthesis of *N*-sulfinyl imines, we investigated the preparation of other synthetically important imine derivatives, such as *N*-sulfonyl imines,[29] by condensation of aromatic aldehydes with RSO_2NH_2. The main problem associated with this reaction is related to the strong electron-withdrawing character of the sulfonyl group, which results in very low nucleophilicity of the RSO_2NH_2 nitrogen (much lower than that of $RSONH_2$) and therefore the need of a very strong activation of the carbonyl. The use of acid catalysts under very strong conditions provides a solution to this problem, but the instability of the resulting *N*-sulfonyl imines, which are more prone to hydrolysis than the *N*-sulfinyl ones, imposes restrictions on the catalysts that can be used. Despite these drawbacks, there are a plethora of methods for the preparation of synthetically important *N*-sulfonyl imines.[30]

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

tert-Butylsulfonyl imines can be prepared under similar conditions, as we have demonstrated in the case of the reaction of *tert*-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 (Table 3 right) reveals advantages similar to those mentioned in the synthesis of *N*-sulfinyl imines (analogous or better yields, softer conditions,

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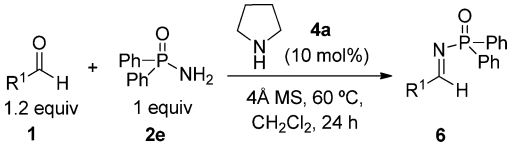
and simpler experimental manipulation). Moreover, the dispersion of methods based on acidic catalysis used to prepare the different *N*-sulfonyl imines shown in Table 3 contrasts with the fact that all of them are accessible under the same conditions employing pyrrolidine as a catalyst.

The reaction of sulfinamides and sulfonamides with ketones was unsuccessful. This is probably due to the large steric interactions around the iminium carbon in the tetrasubstituted intermediates that would be generated.[39]

We also checked that the aminocatalytic conditions used to prepare *N*-sulfinyl and *N*-sulfonyl imines are appropriate for *N*-diphenylphosphinoyl imines, which have particular importance in some catalytic processes leading to enantioenriched primary amines.[40] Under conditions similar 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**−**ce** in high yields by reaction with *N*,*N*-diphenylphosphinic amide (**2e**) (Table 4). The indicated results were obtained starting

Table 4. Synthesis of Some *N*-Phosphinoyl Imines 6



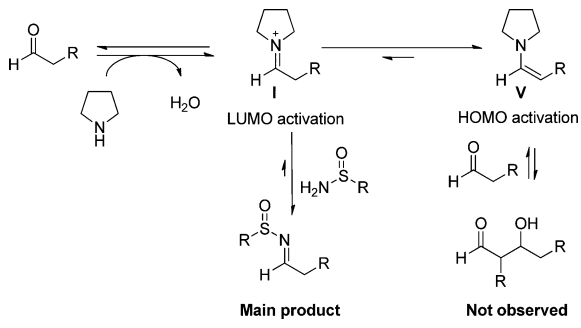
entry[a]	aldehyde, R^1	product (% yield)	previous method[b] (% yield)
1	**1a**, C_6H_5	**6ae** (90)[c]	in three steps (82)[41b]
2	**1b**, *p*-$NO_2C_6H_4$	**6be** (98)[c]	in two steps (20)[42b]
3	**1c**, *p*-$MeOC_6H_4$	**6ce** (85)[d]	(85)[43]

[a]All reactions were carried out on 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.

from a small excess of aldehyde (1.2 equiv), and thus, to obtain pure phosphinoyl imines, the crude reaction mixtures were filtered through a short pad of Celite and then crystallized or subjected to column chromatography. Despite this, the experimental manipulation is much simpler than in the methods used to date for the preparation of these compounds (Table 4 right).[41−43]

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-positions for reaction with electrophiles (HOMO activation).[4] However, to our

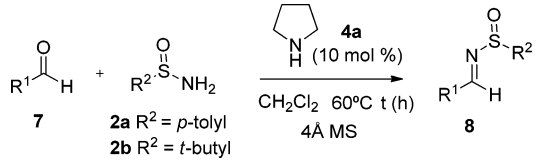
Scheme 2. Formation of *N*-Sulfinyl Imines from Aliphatic Aldehydes under Pyrrolidine Catalysis



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 iminium **I** is fast enough to shift the equilibrium shown in Scheme 2 toward the *N*-sulfinyl imine.

The reaction of **2a** with propanal (**7a**) under the conditions for entry 16 of 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 h (Table 5, entry 1). Similar behavior was observed for 2-

Table 5. Preparation of Alkyl *N*-Sulfinyl Imines



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 on a 0.4 mmol scale. [b]Isolated yield after column chromatography. [c]Highest yields found in the literature. [d]Yield after filtration through a short pad of silica gel and removal of the excess aldehyde under vacuum.

methylbutanal, which afforded **8ba** in 72% yield after 6 h with the use of 3 equiv of **7b** (entry 2). Chromatographic purification of the *p*-tolylsulfinyl imines was necessary. Better yields were achieved with *tert*-butylsulfinamide (**2b**) than with **2a**. Reactions with different aliphatic aldehydes evolved in high yields regardless the primary, secondary, or even tertiary nature of the alkyl residue (entries 3−7). The isolated *N*-*tert*-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 aldehyde under vacuum, and the yields were similar to the best ones described in the literature, which mainly were obtained using a large excess of $Ti(OEt)_4$[20,44,45] (see the "previous method" column in Table 5).

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 to us that formation of the enamine must be avoided in order to achieve a general aminocatalytic method allowing the preparation of sulfonyl imines derived from aliphatic aldehydes. We reasoned that the use of a strategy similar to that depicted in Scheme 1D, consisting of 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 proton source, thus precluding the undesired enamine pathway.[48] On the basis of the assumption that intramolecular protonation of the imine could facilitate the process (Scheme 1C), we decided to use a

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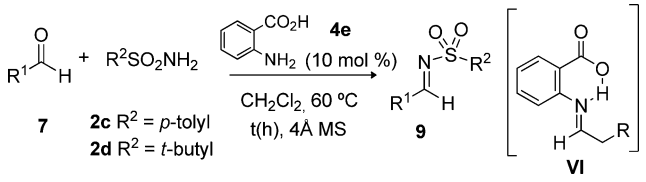
β-amino acid as the catalyst, and we chose anthranilic acid because the aromatic ring would act as rigid tether between the two functionalities, thus avoiding flexibility and making the protonation more effective (see species **VI** in the Table 6 scheme).[49]

We were glad to observe that a catalytic amount (10 mol %) of anthranilic acid in the presence of 4 Å MS was able to promote the direct condensation of aliphatic aldehydes with sulfonamides. With an excess of the starting aldehyde (2 or 3 equiv), almost quantitative conversions were obtained, regardless of the linear or ramified nature of the alkyl chain and the *p*-tolyl or *tert*-butyl residue joined to sulfur (Table 6).

Table 6. Preparation of Alkyl *N*-Sulfonyl Imines



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]Determined by ^{1}H NMR analysis 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 removal of the excess **7f**.

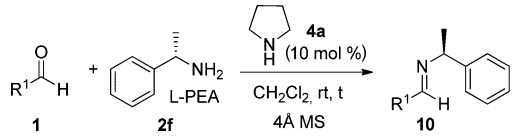
As these imines are extremely prone to hydrolysis, no chromatographic purification was undertaken. Nevertheless, after removal of the excess aldehyde under vacuum, the crude products were pure enough to be used in further reactions (see the ^{1}H NMR spectra in the SI). The experimental simplicity and the yields obtained with this method are clear advantages in comparison with the other ones reported in the literature for the preparation of 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]

Finally, we 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-1-phenylethylamine (L-PEA, **2f**) because of its synthetic interest.[54] Reaction of this amine with benzaldehyde in the presence of pyrrolidine and 4 Å MS afforded **10af** in almost quantitative yield after 20 min (Table 7, entry 1). This reaction also occurred in the absence of catalysts, but it was clearly slower (see the SI). The procedure was also very efficient with the more challenging aliphatic aldehydes **7b** and **7c** (entries 2 and 3), which also afforded the previously unreported scarcely stable imines **10bf** and **10cf** in almost quantitative yield when a small excess (1.2 equiv) of the starting aldehydes was used.

As an aromatic amine model for preparing *N*-aryl imines, we chose *p*-methoxyaniline (**2g**) because of the easy conversion of the *N*-(*p*-methoxyphenyl) moieties into free NH_2 groups.[3] We studied the reactions of **2g** with aromatic aldehyde **1c** (Table 8,

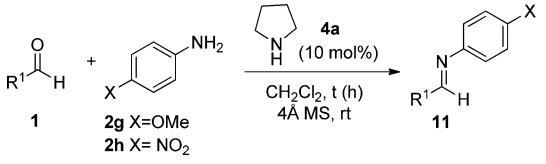
Table 7. Preparation of *N*-Alkyl Aldimines



entry	aldehyde, R^1 (equiv)	t (min)	**10** (% yield)[a]	previous method % yield[b]
1	**1a**, C_6H_5 (1)	20	**10af** (90)	99[c]
2	**7b**, *s*-Bu (1.2)	90	**10bf** (99)	not described
3	**7c**, *n*-Bu (1.2)	90	**10cf** (98)	not described

[a]Isolated yields after filtration through a short pad of Celite without further purification. The excess 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, 16 h.[54b]

Table 8. Preparation of *N*-Aryl Aldimines



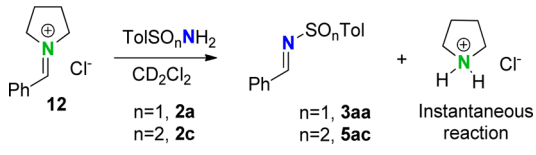
entry	aldehyde, R^1 (equiv)/amine	t (h)	product (% yield)[a]	previous method % yield[d]
1	**1c**, *p*-$MeOC_6H_4$ (1)/**2g**	0.25	**11cg** (89)[b]	99[55]
2	**7b**, *s*-Bu (1.2)/**2g**	0.5	**11bg** (86)[b]	99[56a]
3	**7d**, *i*-Bu (2)/**2g**	0.5	**11dg** (87)[b]	88[57]
4	**7f**, *t*-Bu (2)/**2g**	22	**11fg** (99)	93[58]
5[c]	**1t**, CO_2Et (1)/**2g**	1	**11tg** (94)	99[56b]
6	**1c**, *p*-$MeOC_6H_4$ (1)/**2h**	16	**11ch** (100)	95[59]

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

entry 1) and aliphatic aldehydes **7b**, **7d**, and **7f** (entries 2–4), and all of them evolved with excellent yields. The reaction with ethyl glyoxylate **1t** (entry 5) is interesting because of the usefulness of the resulting imine **11tg** in the synthesis of amino acids. Finally, we studied the reaction of poorly nucleophilic *p*-nitroaniline (**2h**) with scarcely electrophilic *p*-methoxybenzaldehyde (**1c**), in which an analogously good result was obtained (entry 6) and the accelerating role of both pyrrolidine and 4 Å MS can also be clearly appreciated (see the SI).

In order to corroborate our C=N$^+$/C=N transimination hypothesis outlined in Scheme 1B, we carried out some NMR studies (see the SI). We demonstrated that iminium chloride **12** preformed from pyrrolidine and benzaldehyde 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)



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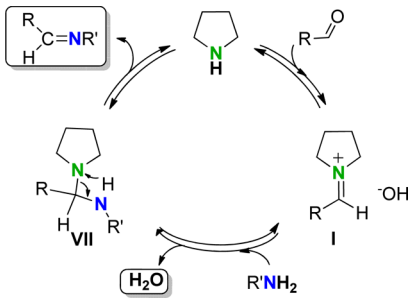
A mechanistic proposal explaining the nucleophilic catalysis exerted by pyrrolidine in the synthesis of different types of aldimines is depicted in Scheme 4. The secondary amine would

Scheme 4. Mechanistic Proposal



react to some extent with the starting aldehyde to form iminium ion **I**. As demonstrated by the previous experiment (Scheme 3), the attack of the amino derivative on the highly electrophilic iminium **I** must be highly favored, even for scarcely nucleophilic compounds such as 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 and co-workers.[60] Liberation of the pyrrolidine would complete the catalytic cycle, reacting with another molecule of aldehyde, which would be 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.

CONCLUSIONS

We have applied the concept of nucleophilic catalysis to the synthesis of different types of aldimines, including those bearing electron-withdrawing groups at the nitrogen (*N*-sulfinyl, *N*-sulfonyl, and *N*-phosphinoyl derivatives), which are of special synthetic relevance. In contrast to the methods reported to date, which are 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 4 Å MS, providing excellent yields of aldimines from a wide variety of aldehydes (aryl, heteroaryl, alkyl, and unsaturated) after minimal lab manipulation. We envision a great potential for this biomimetic and organocatalytic methodology as a useful tool in imine preparation. The search for 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.

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Notes

The authors declare no competing financial interest.

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