Solvent-free enantioselective organocatalyzed aldol reactions

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Abstract: The use of proline as catalyst for the aldol process gave a boost to the development of organocatalysis as a research area. Since then, a plethora of organocatalysts of diverse structures have been developed for this and other organic transformations under different reaction conditions. The use of an organic molecule as catalyst to promote a reaction meets several principles of Green Chemistry. The implementation of solvent-free methodologies to carry out the aldol reaction was soon envisaged. These solvent-free processes can be done using conventional magnetic stirring or applying ball milling techniques and are even compatible with the use of supported organocatalysts as promoters, which allows the recovery and reuse of the organocatalysts. In addition, other advantages such as the reduction of the required amount of nucleophile and the acceleration of the reaction are accomplished by using solvent-free conditions leading to a "greener" and more sustainable process.

Keywords: aldol, enamine, green chemistry, organocatalysis, proline, solvent-free, asymmetric catalysis

1. INTRODUCTION

The aldol reaction [1] discovered in 1872 by Wurtz [2] is one of the most important tools in organic chemistry to perform the synthesis of products ranging from simple building blocks to rather complicated natural products. In this reaction, a nucleophile, generally an enolizable carbonyl compound, reacts with itself or with another carbonyl compound, which acts as electrophile. As a result, a β-hydroxy carbonyl compound known as aldol product is achieved through the formation of a C-C bond, with the generation of one or more stereoregenic centers being possible. This transformation is carried out in Nature by aldolase [3] in a very selective way but with a limitation in the substrate scope. The discovery of the Mukaiyama-aldol reaction [4] gave a definitive impulse of the catalytic enantioselective version [5] of this transformation with an enlarged substrate scope. However, the need of stoichiometric amounts of bases and silylating reagents for the generation of the required silyl enol ether (or its chemical equivalent) led to low atom efficiencies [6]. To increase the atom economy of the aldol process maintaining the stereoselectivity of them, several synthetic strategies based in the application of the direct aldol reactions [7], in which the use of preformed enolates (or their equivalents) is avoided, have been developed. The use of small organic molecules, so-called organocatalysts [8], to perform this task supposed a revolution for the enantioselective organocatalyzed processes.

The application of organocatalysts to the aldol reaction [9] has several advantages such as the enhancing of the atom economy due to the unnecessary use of preformed enolates, the mild reactions conditions needed for the process, the lack of contamination with toxic metals of the final product and therefore the requirement of less purification steps, which agreed with the criteria of green chemistry [10]. Despite this, a great effort has been made in the recent years to carry out this reaction even in a more sustainable way [11]. Therefore, several advances in this field such as the use of supported catalyst and the application of other reaction media such water or ionic liquids have been achieved. Also, the implementation of solvent-free reaction conditions to accomplish this type of transformations has been studied. Several organocatalysts have demonstrated their efficiency under these reaction conditions, with the aldol products being achieved in excellent results in terms of yields, diastereo- and enantioselectivities. The aim of this review is to compile the catalysts based in their structure and the substrates for which the solvent-free aldol reaction is applicable, showing the advantages and also the problems of this methodology.

2. PROLINE AS ORGANOCATALYST UNDER SOLVENT-FREE CONDITIONS

(*S*)-Proline (**1**) is considered as an epitome of an organocatalyst due to the fact that it can be used in a wide range of enantioselective processes, giving excellent results. The application of proline, as the "simplest, enzyme" [12], as catalyst in the aldol reaction, marked a milestone in this research field. For instance, proline was used for the first time in 1971 as organocatalyst to perform the enantioselective intramolecular aldol reaction (Robinson-type annulation) [13]. This process showed the great potential of the enantioselective catalyzed reactions for the synthesis of natural products [14] and even its application at large scale was demonstrated [15]. However, this annulation process was generally carried out in toxic solvents such as acetonitrile or DMF, with long reaction times being required for the completion of the reaction. The use of the proline catalyzed intramolecular aldol reaction under solvent-free conditions was first described more than twenty years later [16]. Thus, prochiral triketones **2** in the presence of 0.26 mol% of proline (**1**) gave after 3 d the Wieland-Miescher ketone **4** (n = 2) in 49% yield and 63% ee. Starting from triketone **2** (n = 1) and using a smaller amount of catalyst (0.05 mol%), product **3** was obtained, being necessary to carry out an dehydration step using benzene as solvent, to achieve product **4** (n = 1) in 63% yield and 68% ee (Scheme 1). Although these results were not very promising, they showed the possibility of performing this type of processes under solvent-free conditions using conventional magnetic stirring.

Scheme 1. Solvent-free intramolecular aldol reaction catalyzed by proline.

With the use of proline as catalyst for the intermolecular aldol reaction [17], a revolution in the application of small organic molecules as promoters for asymmetric organic transformations occurred. However, this process suffered from some drawbacks such as the high catalyst loading employed, the huge excess of starting ketone required and the long reaction times needed to have full conversions. Most

of these inconveniences were associated with the poor solubility displayed by the proline in organic media. Therefore several modifications such as the use of water as solvent in the absence or presence of additives [18], the use of ionic liquids [19], or the use of high pressure [20], or microwaves [21] to perform the reaction have been described.

All these modifications have some beneficial effect on the reaction, but the use of solvent-free reaction conditions to carry out this transformation overcome most the pointed drawbacks and increases the greenness of the process (Scheme 2). These solvent-free conditions must be differentiated from the use of neat conditions, which implies the use of a large excess of the nucleophilic ketone, which in fact is the solvent media. The first solvent-free intermolecular aldol reaction involved the use of a ball mill [22]. This technique [23] is widely applied in grinding minerals and solids into fine particles and it was used in this transformation in order to enhance the efficient mixing of reagents and the catalyst. The best results were achieved using only one equivalent of ketone **5** and 10 mol% of (*S*)-proline, without requiring either dry conditions nor inert atmosphere or the use of purified materials. The advantages of the use of ball milling compared to the conventional magnetic stirring under similar reaction conditions were that the reaction time was reduced from days to hours (5-36 hours) leading to mostly clean crystalline solids in good diastereo- and enantioselectivities (42-99% yield, 1:1-96:4 dr, 55-99% ee). Furthermore, the reaction was performed in a 10 g scale giving similar results to those achieved in a small scale. This technique was also used to study the phase behavior of the proline-catalyzed aldol reaction under solvent-free conditions. A nonlinear relationship between the ee of the proline and the product, similar to the one observed in DMSO solutions with proline concentrations above 0.1 M [24] was found. Thus, under ball milling conditions the coexistence of the three proline phases, dissolved, racemic and enantiopure with the two latter being solids was proposed [23c].

Scheme 2. Solvent-free intermolecular aldol reaction catalyzed by L-proline using ball milling.

The same process was performed under conventional magnetic stirring. In this case a slight excess of the nucleophile, ketone **5** (5 equiv), and 30 mol% of catalyst **1** must be used to afford the aldol products **7** in longer reaction times but with similar enantioselectivities if a small amount of water (up to 5 equiv) was added to the reaction media (24-96 h, 67-89% yield, 74:26-93:7 dr, 96-99% ee). These solvent-free conditions were also applied to the cross aldol reaction between aldehydes providing after in situ reduction with $NaBH_4$, the corresponding 1,3-diols **9** in excellent enantioselectivities (Scheme 3). In this case only a 10 mol% of proline was required and no addition of water was needed if the temperature of the reaction was lowered to 4 ºC [25].

Scheme 3. Cross-aldol reaction between aldehydes catalyzed by L-proline under solvent-free conditions.

The ability of guanidinium salts to bind carboxylic acids and carboxylates has led to study their influence as additives in the aldol reaction catalyzed by proline (**1**) under *quasi* solvent-free conditions, using an small excess of the nucleophilic ketone (10 equiv) to carry out the reaction. Thus, when the aldol reaction between cyclohexanone (10 equiv) and *p*-chlorobenzaldehyde was tested using 15 mol% of proline under vigorous stirring, a 94% conversion was achieved being the enantioselectivity 56% for the main *anti*-isomer. The use of a trifluoroborate guanidium salt **10** (10 mol%) as additive for the same process afforded better results in terms of diastereo- and enantioselectivities. This reaction conditions were applied to the aldol reaction between several ketones, including the prochiral 4-methylcyclohexanone, and aldehydes giving the corresponding products in 70-92% yield, 76:26-95:5 dr and 74-99% ee. Remarkably, the process was done in a closed-cap test tube inside a standard laboratory fridge, without agitation or mechanical stirring, which requires very long reaction times (20 d) [26a]. These reaction conditions were extended to the reaction between α-chloroacetone and aryl aldehydes (Scheme 4), providing products **12**, mainly as *anti*-isomers in good results. However, when the corresponding α,β-epoxy ketones were prepared from compounds **12** by treatment with triethylamine, ~~being~~ these epoxides isolated in lower yields and lower enantioselectivities [26b].

Scheme 4. Solvent-free aldol reaction between α-chloroacetone and aldehydes without stirring.

3. PROLINAMIDES AS ORGANOCATALYST UNDER SOLVENT-FREE CONDITIONS

Some of the drawbacks associated with the use of proline as catalyst in organic media, have been overcome using proline derivatives in order to increase the solubility, modulate the reactivity and to fine-tuning of catalytic activities. Among these derivatives, prolinamides are the the most frequently used group, probably due to their easy preparation, robustness and the possibility of activation of the electrophiles through a hydrogen bond due to the acidity of the NH group. Prolinamides derived from 1,1'-binaphthyl-2,2'-diamine (Binam) (**14** and **15**, Figure 1) have been evaluated as catalysts in the aldol reaction between cyclic, acyclic, alkyl and α-functionalized ketones and aldehydes under different reaction conditions, including aqueous conditions [27].

Fig (1). Prolinamides derived from 1,1'-binaphthyl-2,2'-diamine (Binam).

Table 1. Intermolecular aldol reaction catalyzed by 14 and 15 under solvent-free conditions

Entry	Catalyst	Major product	t (h)	Yield (%)	dr (*anti*/*syn*)	ee (%)
1	**14**	*anti*-**7a**	2	80	90:10	86
2	**15**	*anti*-**7a**	4	98	99:1	98
3	**14**	*anti*-**7b**	22	54	96:4	86
4	**15**	*anti*-**7b**	72	74	99:1	98
5	**14**	*anti*-**7d**	48	76	94:6	72
6	**14**	**7f**	3	86	-	74

7	**15**	**7f**	16	88	-	86
8	**14**	*anti*-**9a**	7	60	59:41	40
9	**14**	*anti*-**9b**	5	96	89:11	94

Diastereomeric (S_a)-Binam-D-prolinamide (**16**, 20 mol%), instead of (S_a)-Binam-L-prolinamide **14**, combined with 100 mol% chloroacetic acid promoted the direct aldol reaction between α-keto esters **17** as electrophiles and alkyl and α-functionalised ketones (5 equiv). Chiral quaternary γ-keto α-hydroxyesters **18** were mainly obtained with up to 92% ee (Scheme 5). DFT computational studies indicate that steric effects between the phenylketo ester and the binaphthyl moiety of the bulky catalyst dictate the stereoselectivity [28c], while the possibility of a double activation of carbonyl group through hydrogen bonds with the NH group of catalyst **16** compare to a single activation found for catalyst **14** explained the better results achieved with catalyst **16**.

Scheme 5. Aldol reaction of α-keto esters and ketones under solvent-free conditions.

The application of ESI-MS techniques in the reaction between acetone and *p*-nitrobenzaldehyde catalyzed by **14** showed that enamine-iminium intermediates ~~derived~~ from one or both proline moieties are formed but only one prolinamide is working as catalyst, with the addition of benzoic acid being crucial to the provided the enamine-iminium species and therefore to accelerate the reaction rates [28b]. Therefore, one of the proline residues in catalyst **14**, was replaced by an acidic moiety such as a sulfonamide group, leading to catalyst **15** [29]. This catalyst was evaluated in the ketone-aldehyde or aldehyde-aldehyde intermolecular aldol reaction under solvent-free conditions. Best results were achieved

by using 2 equiv. of ketone, 5 mol% of **15** in the presence of 1 mol% benzoic acid at 0 ºC. The addition of small amount of water (3 to 7 equiv) to the reaction mixture leads to an increase on the reaction rates. These results are superior in terms of diastereo- and enantioselectivities to those previously reported using L-proline or prolinamide **14** as catalyst under solvent-free conditions.

Furthermore, catalyst **15** was very active under solvent-free conditions in the intramolecular aldol reaction, whereas bis(prolinamide) **14** gave very poor results. For instance, 93% overall yield and 94% ee was achieved in the synthesis of the Wieland–Miescher ketone (10-g scale) through a one-pot two-step solvent-free Robinson annulation procedure. This process involved the use of only 1 mol% triethylamine as the base in the initial Michael process and 2 mol% of the catalyst **15** in the presence of 0.5 mol% benzoic acid for the intramolecular aldol process. This green protocol was applied to the synthesis of a wide range of valuable building block analogues of the Wieland–Miescher ketone, affording them in 54-93% yield and 84-97% ee (Scheme 6) [29b-d] and in the total synthesis of the anominine [29e]. A comparative study for the synthesis of compound **4b**, which is the key intermediate in the total synthesis of anominine, using different catalysts such as proline (**1**, 14d, 74% yield, 46% ee), simple prolinamide (24h, 96% yield, 82% ee), (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine (24h, 93% yield, 8% ee), catalyst **14** (24h, 87% yield, 32% ee) and **16** (24h, 93% yield, 94% ee) was performed under solvent-free conditions, with the best results obtained obtained with the latter [29b].

Scheme 6. Synthesis of Wieland-Miescher ketone analogues under solvent-free conditions.

Very successful was the use of (*R*)-1-aminoindane prolinamide or prolinethioamide (**20**, 5 mol%) as catalyst in the reaction between aliphatic ketones (2 equiv) and aromatic aldehydes under solvent-free or in the presence of water (Scheme 7) [31]. Prolinethioamide **20b** in the presence of *p*-nitrobenzoic acid (5 mol%) was more effective as catalyst than **20a**, for the intermolecular aldol reaction between cyclic ketones such as cyclohexanone or heterocyclic cyclohexanones with aldehydes, affording mainly the *anti*-aldol products in good yields (40-93%), diastereo- (95:5-98:2 dr) and enantioselectivities (80-96%). In the case of cyclopentanone, a nearly 1:1 mixture of both diasteroisomers was achieved with 92% ee for the *syn*-**7** isomer. The reaction could be extended to acyclic ketones, such as acetone, butanone or α-alkoxyacetones (**5**, R^2 = MeO or BnO in Scheme 7), giving aldols *anti*-**7** as major products in good diastereo- (80:20-90:10 dr) and enantioselectivities (87-94% ee). This solvent-free reaction conditions were also applied to the intramolecular aldol reaction, affording bicyclic compounds **4** in good yields (71-99%) and high enantioselectivities (84-88% ee) [31b].

Scheme 7. Solvent-free intermolecular aldol reaction catalyzed by proline derivatives **20**.

Sugar based-prolinamides such as compound **21** (20 mol%, Figure 2) was also evaluated in the aldol reaction of aromatic aldehydes with cyclic ketones and acetone under solvent-free conditions providing the corresponding products in excellent results (82-97%, 52:48-98:2 dr, 83-99% ee) [32].

Fig. (2). Sugar based-prolinamide used as organocatalyst under solvent-free conditions.

4. OTHER PROLINE DERIVATIVES AS CATALYSTS

Small peptides that contain a (*S*)-proline residue have been used as catalysts in the aldol reaction under different reaction conditions, including solvent-free conditions [33]. These types of catalysts are easily modified allowing the fine tuning of their catalytic properties. Thus, the methyl ester of dipeptide **22a** (7 mol%, Figure 3) was used as catalyst under ball-mill solvent-free conditions for the aldol reaction of acetone and *p*-nitrobenzaldehyde giving aldol **7f** in moderate results (82% yield, 69% ee). Better results were achieved in the reaction between cyclohexanone with aromatic aldehydes, yielding mainly the *anti*-**7** aldol product in good results (62-94% yield, 67.5:32.5-98:2 dr, 55-95% ee) [33a]. Slightly better results in terms of diastereo- and enantioselectivities were obtained by using thiodipeptide **22b** under similar reaction conditions (51-89% yield, 70:30-98:2 dr, 50-96% ee) [33b]. A more complex sulfoimidamide proline derivative **23** (10 mol%, Figure 3), has been tested in the aldol reaction between cyclohexanone (5 equiv) and aromatic aldehydes to give the corresponding aldol products, with best yields and being achieved under ball-mill solvent-free conditions (22-84% yield, 92:8-96:4 dr, 89-98% ee) [34].

Fig. (3). Other proline derived catalysts used under solvent-free conditions.

5. OTHER ORGANOCATALYSTS IN THE DIRECT SOLVENT-FREE ALDOL REACTION

The use of other catalytic systems that do not contain proline or a pyrrolidine motif in their structures has been proven to be very efficient in the aldol reaction. Thus, a simple chiral primary amine **24** (10 mol%, Figure 4) as its trifluoroacetate salt catalyzed, in the presence of 5 mol% of *m*-nitrobenzoic acid,

the intramolecular aldol reaction, yielding the corresponding Wieland-Miescher ketone analogues **4** in excellent results (75-95% yield, 65-96% ee). The reaction was carried out in gram scale by using only 1 mol% of catalyst without changing the results [35]. The use of a chiral primary tertiary salt, bearing a tropos dibenz[c,e]azepine ring **25** (5 mol%, Figure 4) was tested as catalyst under solvent-free conditions in the reaction of cyclohexanone (3 equiv) and aromatic aldehydes providing main *anti*-aldols **7** in excellent enantioselectivities (up to 99% ee). When the same catalysts was applied in the reaction of other aliphatic ketones, *quasi* solvent-free conditions (10 equiv of ketone were used) were required in order to achieve good yields (76-99%) and also good enantioselectivities (87-99%) [36].

Fig. (4). Primary amines used as organocatalysts under solvent-free conditions.

2-Hydroxycyclobutanone derivatives have interesting application as building blocks in organic chemistry. Their desymmetrization process using the amino acid threonine (**26**, 20 mol%) as catalyst in the aldol reaction of 2-hydroxycyclobutanone (**27**, 5 equiv) and aromatic aldehydes, led to compounds **28** mainly as *syn*-isomers in moderated yields, diastereo and enantioselectivities (Scheme 8), with the reaction taking place only with activated aldehydes [37].

Scheme 8. Threonine catalyzed solvent-free aldol reaction between 2-hydroxycyclobutanone and aldehydes.

Not only bases, but also Lewis acids have been used as catalysts in the aldol reaction under solvent-free conditions. Thus, TADDOL derivative **29** (10 mol%) was able to catalyze the vinylogous aldol reaction

of Chan´s diene **30** (1.3 equiv) under solvent-free conditions giving only the aldol product **31** when non-activated aromatic aldehydes were used as nucleophiles and a mixture of the aldol product and the hetero Diels-Alder cycloaddition product **32** in the case of using electron-poor aromatic aldehydes with ee´s up 61% (Scheme 9). The use of imidazolium-based ionic liquids as additives to perform this reaction allowed the use of microwaves at very low power (10 W), which accelerates the reaction and increases the enantioselectivities for product **32** to 71% ee [38].

Scheme 9. Vinylogous aldol reaction catalyzed by TADDOL derivatives under solvent-free conditions.

6. SUPPORTED PROLINAMIDES AS ORGANOCATALYST IN THE ALDOL REACTION

The use of immobilized organocatalysts to carry out the aldol reaction [39] would enhance the greenness of the processes, due to possibility of the separation and reuse of the catalysts. Generally, the immobilization of organocatalysts has been carried out by using polymeric supports by means of two different synthetic strategies: the post-modification of a polymeric support and the bottom-up synthesis by copolymerization of several monomers, one of them containing the catalysts.

N-Tosyl-(R_a)-binam-D-prolinamide derivative **15**, which has been shown to be very efficient as organocatalyst for the intra- and intermolecular aldol reactions, can only be recovered by direct column chromatography from the reaction media. Therefore, a vinyl derivative of similar structure to compound **15** was synthesized and anchored into a polystyrene resin to give a supported prolinamide system **33** (Figure 5). This polymeric organocatalyst (**33**, 20 mol%) was used as catalyst for the intermolecular aldol reaction in the presence of benzoic acid (5 mol%) under dry and wet (55 equiv of water added) solvent-free conditions affording the corresponding aldol products **7** in high yields, regio-, diastereo-, and enantioselectivities (22-83% yield, 26-100% regioselectivity, 63:37-95:5 dr, 73-88% ee). These results (Table 2, entries 1-3) are comparable to those obtained under homogeneous conditions using soluble catalyst **15**. This polymer was also able to catalyse the reaction between propanal and *p*-

nitrobenzaldehyde in moderate results (54% yield, 81:19 dr, 84% ee). This polymeric material was recovered by filtration and reused up to six times without detrimental results [40].

The bottom up immobilization, where the polymeric catalyst is prepared by a copolymerization strategy of a catalyst-functionalized monomer with other monomers and cross-linkers, has several advantages compare to the post-modification strategy: it is cheaper, scalable, the degree of incorporation of the active monomer to the polymeric matrix is controllable and by with only changing the monomers ratios or structures, the chemical reactivity and physical properties, such as solubility, can be fine-tuned. However, this strategy has been less studied probably because is more synthetic challenging. This strategy has been used to the synthesis of several polymers, which contains the *N*-tosyl-(R_a)-binam-D-prolinamide framework by a styrene copolymerization strategy and has been used the aldol reaction under different reaction media including solvent-free conditions. Polymer **34** (10 mol%, Figure 5) showed a good performance (25-88% yield, 30-100% regioselectivity, 55:45-89:11 dr, 53-93% ee) as catalyst in the presence of a small amount of water (20 equiv) and benzoic acid (2.5 mol%) in the aldol reaction between several ketones, including functionalized ones, and aromatic aldehydes under solvent-free conditions (Table 2, entries 4-6). These reaction conditions were also extended to the cross-aldol reaction propanal and *p*-nitrobenzaldehyde giving the corresponding diol **9** in moderate results (74% yield, 71:29 dr, 74% ee). The catalyst can be recovered after filtration and reused up to seven times without changes on the achieved results [41].

The same bottom-up strategy was used for the synthesis of a recoverable silica-gel supported organocatalyst **35** (Figure 5) [42]. This catalyst (10 mol%) in combination with benzoic acid (5 mol%) and in the presence of a small amount of water (12 equiv) was very efficient in the intermolecular process, affording the aldol products (Table 2, entries 7-9) in high yields, regio-, diastereo- and enantioselectivities (48-95% yield, 36-100% regioselectivity, 71:29-95:5 dr, 50-95% ee). Under these reaction conditions, also the cross-aldol reaction between propanal and *p*-nitrobenzaldehyde gave good results (75% yield, 88:12 dr, 97% ee). The recovered catalyst can be reused up to nine times providing similar results. More remarkably, this heterogeneous organocatalyst **35** can be used in the intramolecular aldol reaction under solvent-free conditions allowing the synthesis of the Wieland-Miescher ketone and analogues **4** (Table 2, entries 10-12) in good results (73-91% yield, 80-91% ee), being possible its reuse up to five times without observing changes in the results.

Fig. (5). Supported organocatalyst used in the aldol reaction under solvent-free conditions.

Table 2. Aldol reaction catalyzed by supported organocatalyst under solvent-free conditions

Entry	Catalyst	Major product	t (h)	Yield (%)	dr (*anti*/*syn*)	ee (%)
1	**33**	*anti*-**7a**	24	83	95:5	88
2	**33**	*anti*-**7b**	192	69	94:6	86
3	**33**	**7f**	72	76	-	76
4	**34**	*anti*-**7a**	24	88	89:11	93
5	**34**	*anti*-**7d**	72	74	60:40	85
6	**34**	**7f**	72	78	-	58
7	**35**	*anti*-**7a**	6	90	94:6	95
8	**35**	*anti*-**7b**	72	85	93:7	91
9	**35**	**7f**	24	93	-	76

10	**35**	**4a**	120	88	-	80
11	**35**	**4b**	168	77	-	92
12	**35**	**4d**	240	73	-	91

CONCLUSIONS

Solvent-free conditions for the inter- and intramolecular aldol process can be used, providing the corresponding aldol products in similar results to those achieved under solvent media, with the advantage that only a few equivalents of the nucleophile is required and generally shorter reaction times are need for the reaction completion. Using some of the catalysts shown in this review, the process can be done in gram scale pointing the scalability of this process. Furthermore, one of the catalysts has been supported in polymeric supports or in silica-gel, allowing the reuse and recovery of the catalytic species and therefore enhancing the sustainability of the process. With these results, a promising future application of all these systems, even at large scale, can be envisaged.

ACKNOWLEDGMENTS

This research was supported by the Ministerio de Ciencia e Innovación (MICINN: Projects CTQ2007-62771/BQU, CTQ2010-20387, and Consolider Ingenio 2010 CSD2007-00006), FEDER, the Generalitat Valenciana (Project PROMETEO/2009/039), the University of Alicante and the EU (ORCA action CM0905). A.B.-C. thanks the Spanish MICINN for a predoctoral fellowship (FPU AP2009-3601).

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