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Synthesis A. C. Alvarez et al. Short Review

Computer-Aided Insight into the Relative Stability of Enamines

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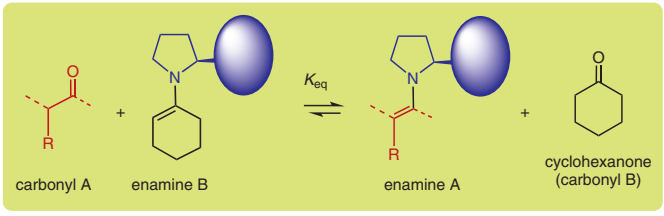
Dedicated to Pere Mir, *in memoriam*



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Abstract Venerable aldol, Michael, and Mannich reactions have undergone a renaissance in the past fifteen years, as a consequence of the development of direct organocatalytic versions, mediated by chiral amines. Chiral enamines are key intermediates in these reactions. This review focuses on the formation of enamines from secondary amines and their relative thermodynamic stability, as well as on the reverse reactions (hydrolysis). Experimental results and predictions based on MO calculations are reviewed to show which enamine forms may predominate in the reaction medium and to compare several secondary amines as organocatalysts.

Key words organocatalysis, enamine formation, enamine hydrolysis, DFT and MP2 calculations, pyrrolidine enamines, Jørgensen–Hayashi catalyst, proline enamines, catalyst comparison

1 Introduction

Conversion of enolizable aldehydes and ketones into enamines, although first reported around 1930, underwent considerable development after the 1960s.[1] As is well known, a further leap forward in the chemistry of enamines occurred with the advent of organocatalysis, at the beginning of the current century.[2] Conversion of enolizable enals and enones into conjugate dienamines (α-/γ-nucleophiles) and of enolizable dienals and dienones into trienamines (α-/γ-/δ-nucleophiles) can be included in this same basket. The effect of large substituents at the α position of the *sec*-amine moiety (see, e.g., the Jørgensen–Hayashi catalyst, henceforward J–H catalyst)[2m,n] and of H-bond donors at the

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same position (e.g., the COOH group of proline) may favor the attack of the electrophile from one face or another[3,4] of the most abundant and/or reactive enamine species or forms.

A general view of the reaction of chiral enamines with polarized double bonds (such as carbonyl compounds, activated imines, nitroalkenes, alkenes with other strong EWGs, etc.) is shown in Scheme 1. The secret of success, high yields, d.r., and/or e.r., acceptable reaction rates or, in other words, that the desired stereoisomer becomes the major product to a great extent in a reasonable time, lies in the formation of sufficient concentrations of the starting enamines in the reaction medium and the appropriate reactivity of these nucleophiles with the polarized double bonds or other electrophilic reagents. Although only enamines adopting the *E* configuration, in their s-*trans* conformations, are depicted in Scheme 1 (left) for the simple case of α-unsubstituted aldehydes, several enamine species (*E*/*Z*, s-*trans*/s-*cis*, pyrrolidine ring conformations) may obviously be present in the reaction medium.[5]

The easy hydrolysis of the reaction intermediates, with regeneration of the catalyst (the *sec*-amine), is important for the turnover and to reduce their equilibration with the product enamines (Scheme 1, first row, right). If the initial enamines (monosubstituted) were largely converted into product enamines (disubstituted), loss of diastereoselectivity could occur during the hydrolysis steps, in the absence of any stereocontrol. Besides, the *Z*/*E* equilibrium between these final enamines, probably mediated by protonation and/or addition of water, could also affect the configuration of the carbon atom labeled with a red dot in Scheme 1; it is unlikely that the hydrolysis of enamines *Z* and *E* gives rise to the same stereoisomer or the same stereoisomeric mixture.

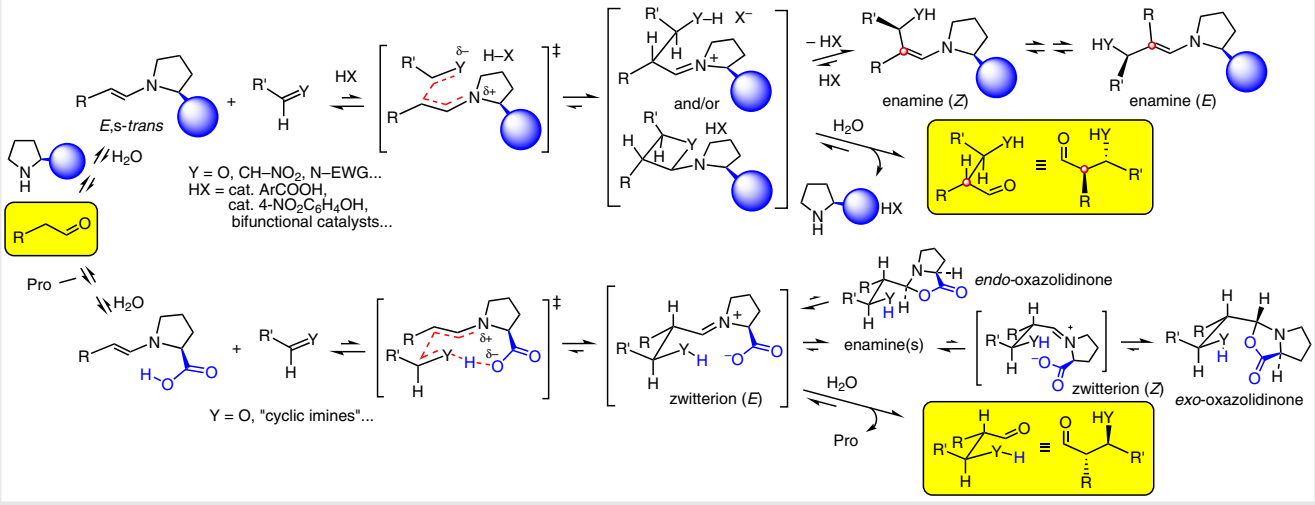
Scheme 2 summarizes the main enamine conformers that can be formed from chiral pyrrolidines and either α-unbranched aldehydes (shown in Scheme 1), α-branched aldehydes, cyclic ketones, or α-branched cyclic ketones. Linear and α-branched ketones, which have a lower tendency to produce enamines than cyclic ketones and α-branched cyclic ketones,[1,6] respectively, are not included in Scheme 2.

Historically, (*S*)-proline (henceforward proline or Pro) was the first and has been the most commonly used *sec*-amine in aminocatalysis. However, it is treated later on in this review, as it is a more complex case for several reasons, namely:

(a) Its COOH may act as a directing group, via hydrogen bonding with the O atom of the partner carbonyl group (the Houk–List model, see Scheme 1, second row)[3] or with the N atom of some imines.

(b) The COOH group should not be partially or fully deprotonated otherwise the directing effect will disappear and the approach of the partner may partially take place from behind, with the corresponding loss of selectivity, unless the Seebach–Eschenmoser model[4] is operative: anchimeric assistance of the carboxylate group to electrophilic attacks on the *E*,s-*cis* tautomer, with direct formation of the bicyclic *exo*-oxazolidinone of the adduct.

(c) The zwitterionic nature of solid proline makes it insoluble in most organic solvents (although the presence of reactive carbonyl compounds in the medium help to solubilize it[6]).



Scheme 1 Examples of plausible mechanisms for the reactions of chiral enamines of simple aldehydes with polarized double bonds. In the first row, a large substituent on the pyrrolidine ring favors the approach of the polarized double bond to the rear face (backside attack); HX is not always necessary; the enamine hydrolysis (which may occur via iminium salts and/or zwitterions) is not indicated. In the second row, an enamine of (*S*)-proline is depicted; in some cases R′–CH=Y may approach the front face due to the directing effect of the H donor (the Houk–List model of the corresponding transition state is shown). The hydrolysis of zwitterion(s) is expected to give rise to the enantiomer of the aldehyde drawn above.

(d) The starting enamines are in equilibrium with bicyclic oxazolidinones (which often predominate, mainly as the more stable *exo* isomers, causing the catalyst 'to disappear') and, in polar media under special conditions, with iminium carboxylates[1d] (zwitterions, which are prone to hydrolysis).

(e) The adducts can also equilibrate with enamines, oxazolidinones, and zwitterions (Scheme 1, second row, right) again with a possible loss of diastereoselectivity, unless the hydrolysis of zwitterions *E* is very rapid or that of enamine(s) occurs in a stereoselective manner.

(f) The dehydration of some intermediates (Mannich-type species, in particular)[7] to afford, for example, enals as byproducts (aldol condensation) rather than aldols often occurs. Decarboxylation of some zwitterionic intermediates (mainly of aromatic aldehydes) may take place,[2] also with loss of yield.

Proline surrogates, with an alternative acidic proton in the side chain of the pyrrolidine ring or with analogous heterocyclic rings,[8] have been developed to overcome one or other of these drawbacks. In spite of this, if in aldol reactions both partners have α-enolizable protons, the number of possible species that exist together for hours in the reaction medium may be huge. Fortunately, some are present in minute amounts and some are hardly reactive. All in all, it is extremely pleasing when only one stereoisomer of one aldol is obtained.

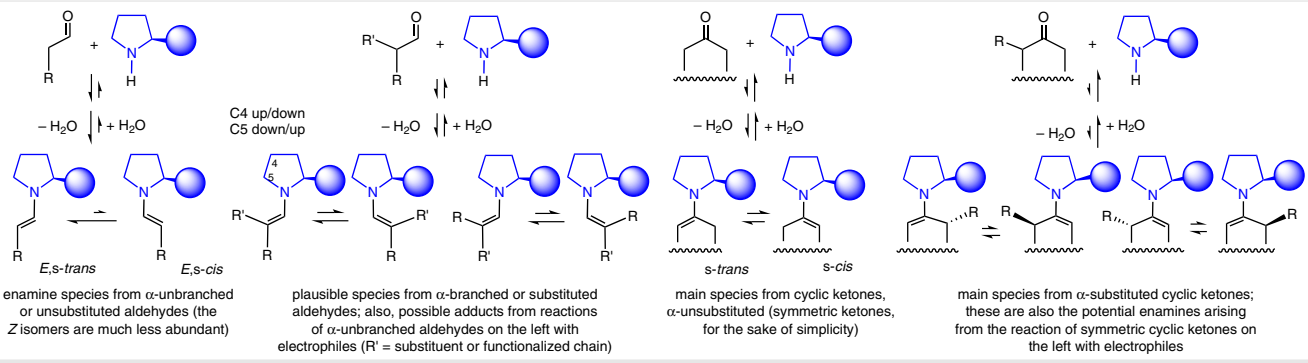
In this context, knowledge of the relative tendency of carbonyl compounds to form enamines (Scheme 2), or of the relative tendency of enamines to be hydrolyzed, which is the reverse reaction, is essential for initial and final steps of aminocatalytic reactions. The study of these equilibria, which are often reached rapidly, can throw light on all aspects of the process except perhaps for the fine-tuning of the stereoselectivity.

Here we review the relative energies of a long series of reactions of carbonyl compounds with amines to give enamines. A few of these values were determined experimentally and many were calculated by quantum chemical methods in our lab over the past twelve years[6,9] and then revised and presented in a uniform fashion in recent months. We mostly examine enamines from pyrrolidine, the J–H catalyst, and proline, for which many more calculations are available. The results and predictions may be useful to explain why: (a) some *sec*-amine-catalyzed reactions do not work at all or are too slow; (b) many aldol-like reactions (e.g., addition of methyl ketones or ethyl ketones to linear and α-branched aldehydes) cannot be carried out by organocatalysis; (c) double α-substitutions to a carbonyl group or α,α′ to a ketone are seldom observed; (d) the J–H catalyst and MacMillan catalysts[10] are not efficient with ketones; MacMillan catalysts are instrumental in reactions involving iminium ions from enals and in the SOMO activation of aldehyde enamines.[11]

Moreover, the results and predictions may also be useful when there are two or more enolizable carbonyl groups in a substrate, for example in an advanced synthetic intermediate of a total synthesis. They could shed light on questions such as 'which one will show the highest tendency to be converted into an enamine?' or 'will the more electrophilic carbonyl compound be preferably converted into its enamine (nucleophilic Cα)?' Similar puzzles exist if the catalyst contains two or more amino groups, or if there are two or more potential organocatalysts in the medium.

2 Relative Stability of Enamines as Determined Experimentally

How shifted to the right the enamine formation equilibria are, when a set of carbonyl compounds react with *O*-TBDPS-protected prolinol (Figure 1)[12] or, *vice versa*, how shifted to their components the hydrolysis of these enamines are, was measured by ^{1}H NMR spectroscopy in DMSO-d_6 at room temperature (rt) a few years ago (2012).[9a]



Scheme 2 Main enamine species or forms, main conformers of the more favored configurational isomers, expected to be formed from chiral pyrrolidines and four subclasses of carbonyl compounds: α-unbranched or unsubstituted aldehydes, α-branched or substituted aldehydes, cyclic ketones, and α-branched cyclic ketones.

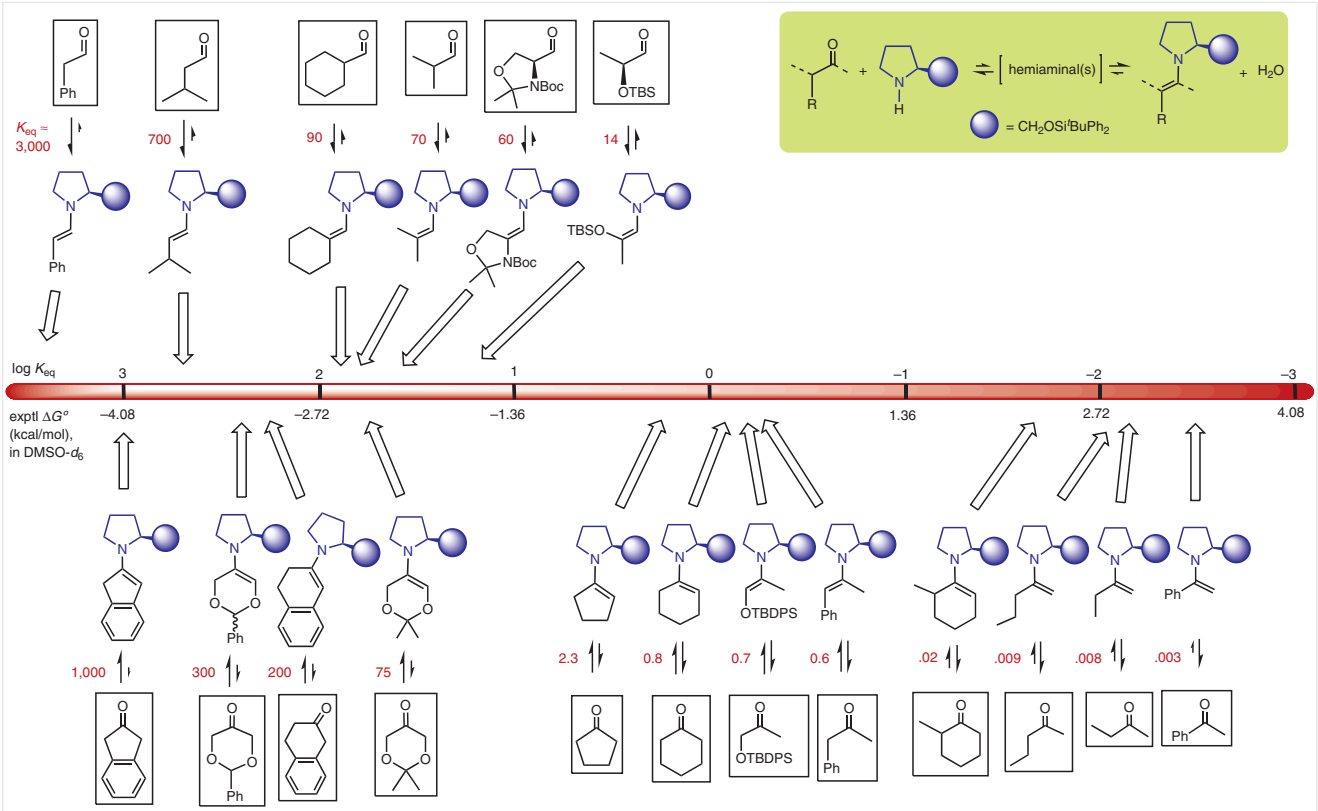


Figure 1 Range of equilibrium constants, from ^{1}H NMR spectra in DMSO-d_6 at 25 °C, for the formation of enamines of the *O*-TBDPS derivative of (*S*)-prolinol.[9a]

On the left side, there are aldehydes the enamines of which are particularly stable (log K_{eq} > 2.5). α-Branched and α-substituted aldehydes show values of log K_{eq} between 1 and 2. The range for ketones is wider: (a) those that yield enamines in which the conjugation is extended to an aromatic ring or those with oxygen atoms in appropriate positions are located to the left (the corresponding enamines are relatively favored); (b) cyclic ketones, as well as acyclic ketones with substituents that stabilize the enamine forms, show log K_{eq} values close to 0 (are in the middle of the scale); (c) finally, linear ketones and crowded cyclic ketones show log K_{eq} values around –2.

To summarize, carbonyl compounds on the left side show a high tendency to form enamines, whereas enamines to the right show a high tendency to be hydrolyzed. The hydrolysis rates and completion times will then depend on the concentration of water, presence of acid additives, steric hindrance, etc., but the relative K_{eq} values are essential.

The scale cannot be easily expanded experimentally, either to the left (as these carbonyls are fully converted into enamines, so the NMR signals of the starting substrates cannot be integrated to determine the K_{eq} value) or to the right, since for sterically crowded substrates the enamine forms are below the detection limit of the ^{1}H NMR instruments.

One possibility for expanding the scale slightly is to examine exchange reactions such as ***carbonyl A + enamine B = enamine A + carbonyl B***.[9a] The preparation of an enamine is forced under very anhydrous or drastic conditions, a second carbonyl, which is not very different, is then added, and the relative K_{eq} value for the exchange is determined.

To expand the scale shown in Figure 1 further, one can take advantage of quantum chemical calculations (QCC). The outcomes will be approximate, as will be commented on below, but any enolizable carbonyl compound, even the worst candidate, can be evaluated. This is the subject of the following sections.

3 Pyrrolidine Enamines

Enamines of pyrrolidine, especially 1-(cyclohex-1-enyl)pyrrolidine, have been known since the 1950s[1] and have been the subject of QCC, mainly at the DFT level.[13] A larger set of results has been obtained in our group over more than a decade for a long series of enamines of pyrrolidine, for our private use. We utilized the Gaussian 09 suite of programs,[14a–h] ORCA[14i,j] and, formerly, Gaussian 03 and MacSpartan. These results have recently been checked or recalculated with updated revisions of Gaussian 09, after a

conformational search with MacroModel[15] or with MMFFs[16] for molecules with many degrees of freedom, of as many as possible relative energy minima of each carbonyl compound (several conformers) and of each 'enamine' (many conformers for each possible regioisomer and/or stereoisomer).

Once optimized at the B3LYP/6-31G(d) level, single-point calculations were systematically carried out on the most stable conformers, at the MP2/6-31G(d) level. In many cases, for confirmation of results, calculations were also carried out at the MP2/6-311+G(d,p) and M06-2X/6-311+G(d,p) levels (see Appendix). For practically all the 125 reactions included herein, the MP2/6-31G(d) results were almost the mean between these two higher-level values and quite close to top-level CCSD results previously obtained by us for a few equilibria.[9k] Thus, MP2/6-31G(d) was taken as the appropriate method for the present overall comparison, providing us with a high reliability-to-cost ratio. The stationary points were characterized by frequency calculations, as usual. Gibbs free energies (free enthalpies) at rt were only recalculated for a few representative cases, to save time. We assumed that, except for equilibria with some very crowded partners on one side of equation, the differences after considering the thermal and entropic corrections would be small. Thus, the sum and subtraction of the total electronic energies may provide quite reliable relative free enthalpies of enamine formation and, in the opposite direction, of enamine hydrolysis. Additional geometry optimizations at other levels of theory and solvent effects with the SMD method[14h] will be commented on in a few cases; however, let us advance that no significant differences were noted in the reaction energies using more Gaussians and when corrections due to the presence of polar solvents, either implicit water or DMSO, were included in around 20 out of the 125 pairs reviewed.

Of the different energy minima obtained at the B3LYP and MP2 levels for each carbonyl compound and for each corresponding pyrrolidine enamine, the lowest energy minima at the MP2 level was selected (which usually, but not always, turned out to be the same as at the B3LYP level).

The equilibria examined *in silico* were exchanges of the type shown in Figure 2, that is, from ***carbonyl A + enamine B*** to ***enamine A + cyclohexanone (carbonyl B).*** It is a transfer of pyrrolidine from cyclohexanone to the other carbonyl compound. In practice, we demonstrated that these transfers occur quite rapidly in solution at rt.[9,17,18] In Figure 2, those carbonyl compounds the enamines of which we had studied by NMR are shown within a square.

Those carbonyl compounds with a high tendency to be converted into their pyrrolidine enamines are found on the left side of Figure 2. 1,3-Dicarbonyl compounds, which produce conjugate enaminones, are the most prone to such

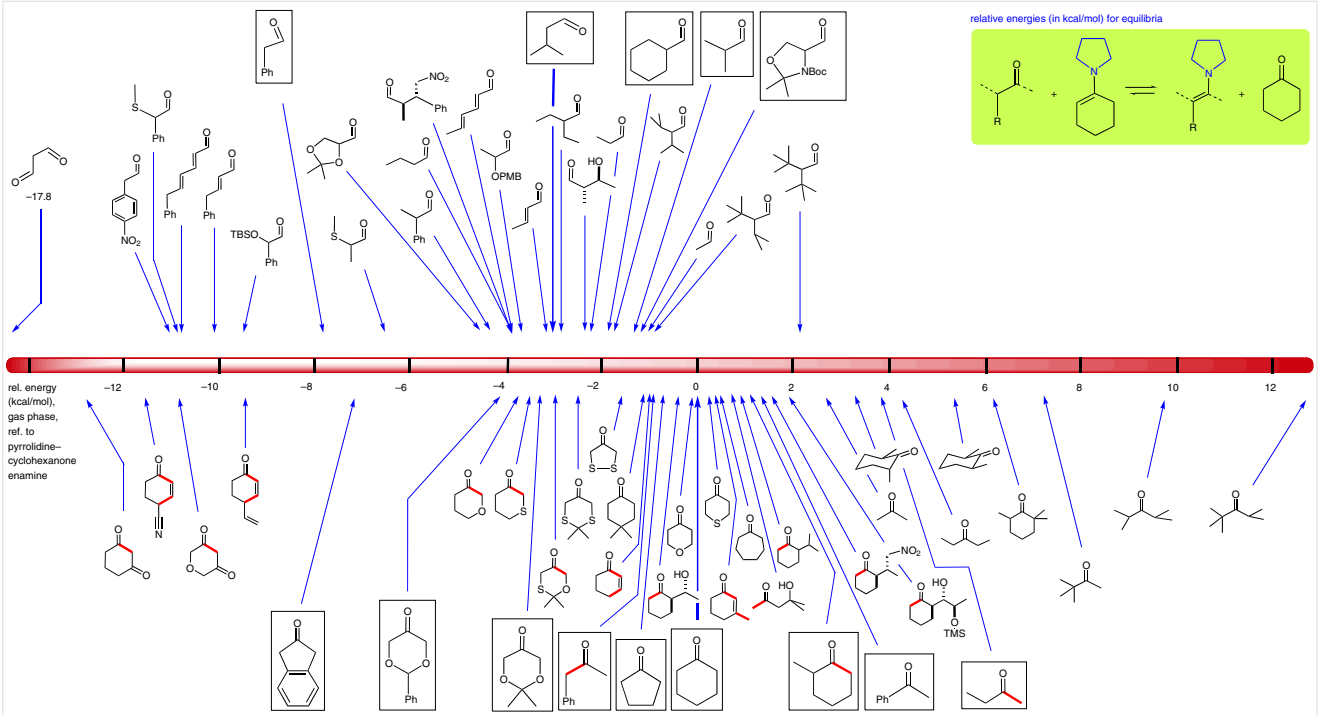


Figure 2 Calculated energies (ΔE_r in kcal/mol) for the exchange equilibria between carbonyl compounds and pyrrolidine enamines, at the MP2/6-31G(d)//B3LYP/6-31G(d) level (1 a.u. or hartree = 627.5 kcal/mol). Cyclohexanone (bold blue arrow) and its enamine were taken as the main reference pair (ΔE_r = 0); 3-methylbutanal and its enamine were sometimes taken as the second reference pair (a reference for aldehydes). Red bonds indicate where the double bond is located in the enamine.

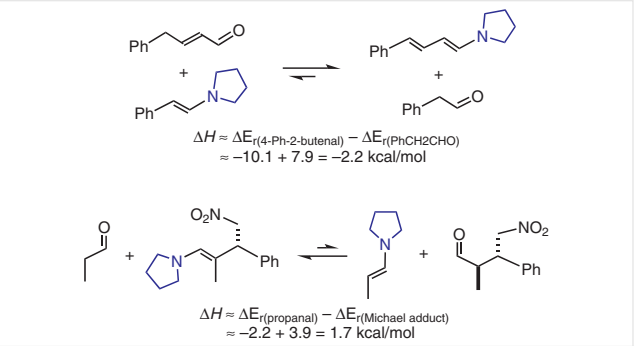
conversion; although enol forms can be present in these dioxo derivatives[19] and enaminones can be considered amide vinylogues, we calculated these pairs to get insight into the effect of hypothetic EWGs.[19]

Other conjugate enamines, including trienamines and dienamines conjugated with phenyl groups, are also very favored. Thus, these sets of enamines may survive much longer in aqueous media than standard enamines, which are very easily hydrolyzed. Carbonyl compounds that gave large amounts of the enamines in Figure 1, in DMSO, are also found to the left of the zero point (of our chief reference, which is cyclohexanone), in the gas phase and, at least, in apolar solvents. The parallelism is clear. An exact correspondence is unlikely or would be fortuitous, since in solution at rt there are many forms in equilibrium, whereas in the calculations we have only considered, as a first approximation, the energies at 0 K of the more stable carbonyl conformer and the more stable 'enamine form'. The individual total energies are given in the Appendix.

In Figure 2, those carbonyl compounds that exhibit a low tendency to be converted into their pyrrolidine enamines are located on the right side. There is one aldehyde that shows a lower tendency than cyclohexanone to produce its enamine: *t*-Bu_2CH-CHO. Or what is equivalent, the pyrrolidine enamine of this aldehyde, without any conformation in which its pyrrolidine ring can be more or less coplanar with the double bond, is the only one that has a higher tendency to be hydrolyzed than the well-known pyrrolidine enamine of cyclohexanone. Incidentally, *t*-Bu(*i*-Pr)CH-CHO, with one Me group fewer, is located to the left of cyclohexanone. Thus, it is expected that only aldehydes of general formula $(R_3C)_2$CH-CHO and $(Ar_3C)_2$CH-CHO will hardly form any pyrrolidine enamines.

The corollary is important, since aldehydes arising from nitro-Michael reactions, such as PhCH(CH_2NO_2)-CH(CH_3)-CHO (ΔE_r = –3.9 kcal/mol), and from aldol reactions, such as CH_3-CH(OH)-CH(CH_3)-CHO (ΔE_r = –2.3 kcal/mol), are thermodynamically more stable as enamines than the well-known enamine of our general reference, cyclohexanone (E_r = 0.0 by definition). These nitro-Michael and aldol adducts are close to butanal (ΔE_r = –3.9 kcal/mol), 3-methylbutanal (isovaleraldehyde, ΔE_r = –3.1 kcal/mol), and propanal (ΔE_r = –2.2 kcal/mol). In other words, unless an excess of water is present or added, the hydrolysis of the enamines of these adducts may not be complete.

Moreover, from these numbers the approximate energies for exchange or metathesis reactions can be predicted. For example, Scheme 3 shows that by subtraction of two enamine formation equilibria one can predict the energy of hundreds of possible exchange reactions.[9,17,18] The first example indicates that an aldehyde that may give a dienamine may steal the pyrrolidinyl group from an ordinary enamine. The second example of Scheme 3 suggests that, if an enamine is sufficiently stable in relation to its α-branched aldehyde (a nitro-Michael adduct), whatever the electronic or steric effect responsible for it, the exchange with the precursor (propanal in the example shown, the starting material of the nitro-Michael reaction) will not be favored.



Scheme 3 Examples of exchange reactions with pyrrolidinyl group transfer.

The dienamines and trienamines[20] shown in Figure 2 are also the predicted lowest-energy stereoisomers in their lowest-energy conformations. For the sake of comparison, we provide here the gaps for the main *N*-(butadienyl)pyrrolidine and *N*-(hexatrienyl)pyrrolidine species (Figure 3). The s-*cis* conformers, those prone to undergo Diels–Alder reactions rather than aldol or Michael reactions, are in both cases ≥ 3 kcal/mol above the most stable arrangement (*E* configurations, s-*trans* conformations). Assuming that the thermal and entropic corrections will not change these gaps very much, the chances of synchronous Diels–Alder reactions, with these unsubstituted substrates acting as dienes, seems lower than those of standard electrophilic substitutions or formal D–A reactions after an initial electrophilic attack. For substituted dienyl and trienyl groups, the situation may be more complex: some *Z* isomers (e.g., of the C3–C4 double bond of dienamines) are kinetically preferred and react more rapidly with electrophiles.[20l]

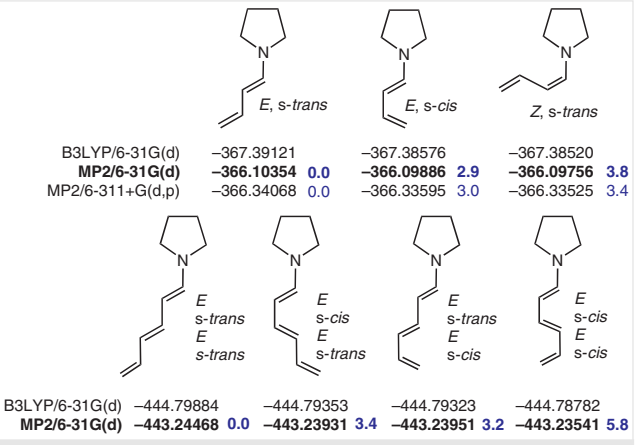


Figure 3 Relative energies in kcal/mol (in blue) of representative dienamine and (*E*,*E*)-trienamine systems. The indicated MP2 single-point calculations gave practically the same numbers starting from geometries optimized at the B3LYP/6-31G(d) or B3LYP/6-311+G(d,p) levels.

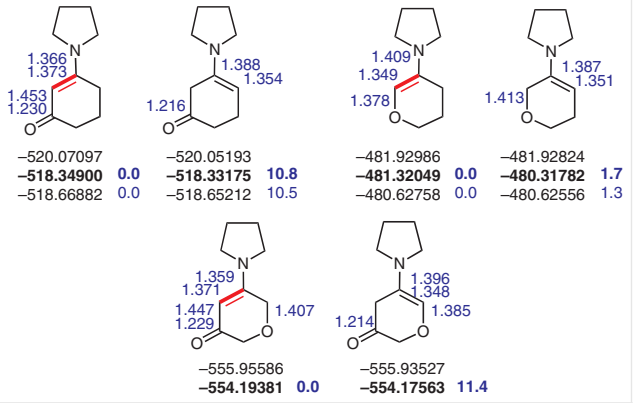


Figure 4 Comparison of the total electronic energies (in a.u. or hartrees) of regioisomers. First row numbers: B3LYP/6-31G(d). Second row: MP2/6-31G(d)//B3LYP/6-31G(d). Third row: MP2/6-311+G(d,p)//B3LYP/6-31G(d). Relative energies in kcal/mol, in blue. Relevant bond lengths, in Å, also in blue.

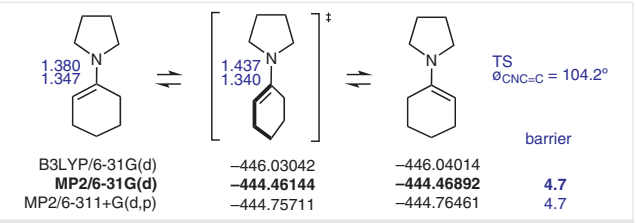
When standard ketones are compared, there are many in the neighborhood of cyclohexanone, including the cyclohex-2-enone derivatives that can yield conjugate dienamines. Those with heteroatoms, oxa and thia derivatives up to now, at position 3 of the ring, and then at both positions 3 and 5, are predicted to give more stable enamines. There are possible explanations for this, 'destabilization' of CO groups due to the presence of electronegative substituents, or a slight stabilization of double bonds with two σ-EWG/π-EDG substituents instead of one, but the stabilizing effect of an electronegative atom is obviously much smaller than that of a π-EWG, as summarized in Figure 4.

Predictions for sulfur compounds can be obtained from the data in Figure 2. There are no important differences between the effect of oxa- and thiacyclohexanones regarding enamine formation. To discard any poor description of sulfur atoms conjugated with double bonds, the geometries were optimized at higher levels of theory [B3LYP/6-311+G(d,p) and M06-2X/6-311+G(d,p)] and the energies were recalculated at different levels but no significant changes were noted.

Also according to Figure 2, cyclopentanone is 'better' than cyclohexanone while cycloheptanone is slightly 'worse'. As expected,[1] α-substituted cyclohexanones are predicted to form their enamines through the less substituted position and are found to the right of cyclohexanone. Enamines from α,α′-disubstituted or trisubstituted cyclohexanones, as well as branched ketones, have very low chances of producing organocatalytic reactions via their enamines. This is a well-known experimental fact. Nitro-Michael and cross-aldol adducts of cyclohexanone are located 0.8–1.3 kcal/mol to the right of cyclohexanone; this means that the hydrolysis of pyrrolidine enamines of these adducts may be even more shifted towards the components than that of the reference enamine.

The case of acetone (propan-2-one) deserves a comment. Its ΔE_r value (2.6) suggests that the concentration of its pyrrolidine enamine may be ca. 9 times lower (calculated $K_{eq} \approx 81$) than that of cyclohexanone ($\Delta E_r = 0$) and more than 100 times lower than that of 3-methylbutanal ($\Delta E_r = -3.1$). As with other *sec*-amines that are less reactive than pyrrolidine,[9i] the concentration of the corresponding enamines will be even lower. The acetone dimer, 4-hydroxy-4-methylpentan-2-one, occupies a better position in the ranking ($\Delta E_r = 0.6$). One may take advantage of this fact.

The rotational barrier calculated for the reference enamine, to evaluate the energy of breaking the almost coplanar arrangement of the N atom and the double bond, turned out to be 4.7 kcal/mol (Scheme 4). It is a true TS (only one imaginary frequency). We considered unnecessary to calculate the thermal and entropic corrections to obtain $\Delta G^{‡}$ values. The barrier is low, which allows for almost free rotation around the N–C_{sp2} bond at rt, in agreement with the NMR spectra.



Scheme 4 Rotational energy barrier, in kcal/mol, calculated for the pyrrolidine–cyclohexanone enamine at different levels; relevant bond lengths in Å.

4 Enamines of the Jørgensen–Hayashi Catalyst

Seebach and co-workers[21] reported the first crystal structure of an enamine from the Jørgensen–Hayashi (J–H) catalyst in 2008, while in 2011 Gschwind and co-workers[5a] described the conformational preferences, in several solvents, of related enamines from propanal and 3-methylbutanal, where the puckering of the pyrrolidine ring was also examined. The crystal structures of several adducts from enamines of the J–H catalyst have also been published in recent years.[22] DFT calculations have been reported.[23] Therefore, there are data to which our results, which are expanded to a large set of carbonyl compounds, can be compared. Figure 5 (top) shows the three more stable conformers of the J–H catalyst at the MP2/6-31G(d) level (our standard level for 'intermolecular' comparisons), which is compared 'intramolecularly', as always, with other methods to check the reliability of the results. We used the *sc-endo* value of the J–H catalyst for subsequent calculations.

Figure 5 (bottom) also contains the three most stable conformers of the enamine arising from the J–H catalyst and 3-methylbutanal out of the 18 conformers we calculat-

ed,[9l] starting with MacroModel and optimizing all of them with B3LYP/6-31G(d), followed by single-point MP2/6-31G(d), M06-2X/6-311+G(d,p), and Grimme's dispersion-corrected[24] B3LYP-D3/6-311+G(d,p) calculations.

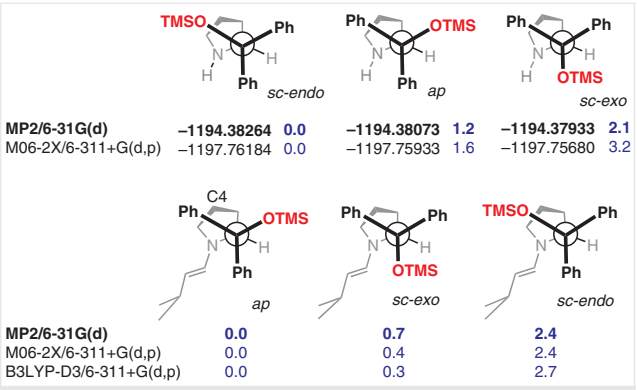


Figure 5 Lowest-energy conformers of the J–H catalyst (above) and its 3-methylbutanal enamine. As always, the gaps (in kcal/mol) between the different enamine forms (rotamers) are indicated in blue.

The results agree with the precedents mentioned above at other levels of theory.[21,23] We also support the explanations of Hayashi and co-workers,[5b,23g] which will not be repeated here, concerning the interactions that make the *ap* conformation for the related phenylethanal enamine slightly more stable, in the gas phase. The fact is that crystals of the *sc-exo* were obtained[21] from solutions of such a phenylethanal enamine. Therefore, for aldehydes, since the calculated energy differences between the *sc-exo* and *ap* forms of enamines were below 1 kcal/mol, we considered these forms to be almost equivalent and used one of the two values, mainly that of the *sc-exo* forms, in subsequent calculations.

The pyrrolidine ring usually adopts a conformation in which its C4 is up (and its C5 down), as shown in Figure 5, also in agreement with reported data,[21,23] which has an energy minimum 1.0–1.8 kcal/mol below that of the conformation with C4 down and C5 up. We have found few exceptions to this rule.

The rotational barrier associated with the interconversion between the *ap* and *sc-exo* conformers of the 3-methylbutanal enamine was predicted to be ≤ 10 kcal/mol at the MP2/6-31G(d)//B3LYP/6-3G(d) level (Figure 6). The barriers linked to the 360° rotation of the 3-methylbut-1-enyl group of the *ap* conformer are also represented in Figure 6. The numbers are not large, which means that many enamine species of such an aldehyde are in rapid equilibrium in the medium at rt. It is usually hoped that only one is productive.

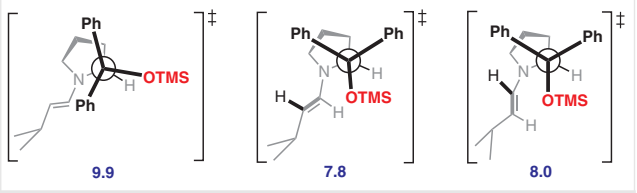


Figure 6 Rotational barriers, in kcal/mol, from the MP2/6-31G(d)//B3LYP/6-31G(d) energies, for the conversion of conformer *ap* into *sc-exo* (see Figure 5) and of conformer s-*trans* to s-*cis* of the *sc-exo* form.

The conformational analysis of the ketone enamines was more cumbersome, as shown in Figure 7 for the cyclohex-1-enyl derivative, since several conformers were very close together in terms of energy (less than 1.0 kcal/mol in the gas phase at 0 K).

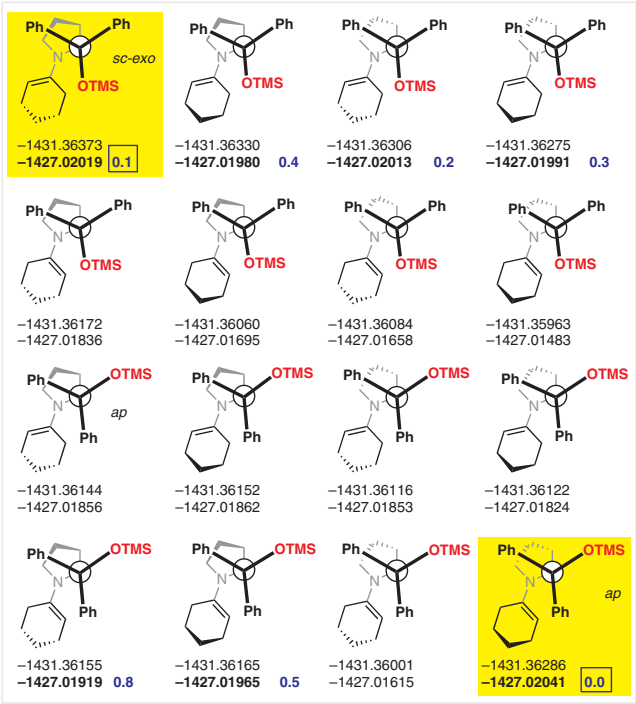
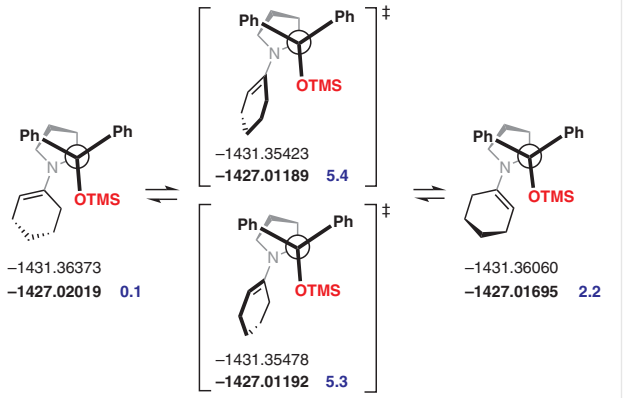


Figure 7 Main conformers of the cyclohex-1-enyl enamine of the J–H catalyst. B3LYP/6-31G(d) and single point MP2/6-31G(d) energies (below), as always.

The populations of the *sc-exo* and *ap* conformers of these cyclohexenyl derivatives were predicted to be quite similar. The calculation of all the barriers or the construction of the potential hypersurface would have required titanic efforts, and would probably be unnecessary. We did not undertake them, but we evaluated one of the barriers as a representative case.[9l] The highest barrier (around 5 kcal/mol, see Scheme 5) was relatively small. Thus, we assumed that, except for the most congested ketone enamines (which will hardly be formed in practice), many of the enamine forms are in rapid equilibrium at rt.



Scheme 5 Rotational barriers for the cyclohexenyl group of one of the main *sc-exo* conformers in Figure 7. Relative energies, in kcal/mol, in blue, as usual.

With these results in hand, we examined additional pairs of carbonyl-to-enamine conversions, as before. The following exchanges were calculated: ***carbonyl A + J–H enamine B*** gives ***J–H enamine A + cyclohexanone (carbonyl B)***. Thus, the J–H enamine of cyclohexanone was our main reference compound, that is, the $E_{r(J-H)}$ for cyclohexanone is 0.0 by definition. The outcome is shown in Figure 8. Our second reference compound (an aldehyde, to which other aldehydes can be compared) is again 3-methylbutanal, $E_{r(J-H)}$ = –5.0. This is a large number, since the K_{eq} for the formation of the enamine of cyclohexanone may then be almost 10^4 times lower than for that of 3-methylbutanal. It is understandable that the J–H catalyst is incapable of catalyzing reactions involving standard ketones. Fifteen carbonyl–enamine pairs are included in Figure 8. Those for which we had most NMR data or information related to their equilibria are again shown within a square.

Once more, those carbonyl groups that show a higher tendency than cyclohexanone to give the J–H enamine are found on the left; those with a very low tendency to give such an enamine on the right.

The number of pairs could have been expanded up to over 60, as we did in Figure 2, but that would have required several months of calculations, and was deemed unnecessary since a parallel was soon drawn between Figures 2 and 8, namely:

(a) The scale for aldehydes is similar. It is wider, since the $E_{r(J-H)}$ values, which go from –19.7 to 6.9 kcal/mol, are proportionally larger than the E_r values of Figure 2 (–17.8 to 2.0 kcal/mol). This may be explained on the basis of a better discrimination by steric hindrance.

(b) For the seven ketones that were compared to cyclohexanone (Figure 8, bottom) the $E_{r(J-H)}$ values (–7.9, –4.0, –1.3, –1.1, 1.0, 6.3) were almost identical to the values shown in Figure 2 (–7.1, –3.3, –1.3, –0.8, 1.1, 7.3).

Thus, Figures 2 and 8 can be used together to predict which of the envisaged *sec*-amine-catalyzed reactions are possible or which exchanges between carbonyl compounds and enamines can be shifted to the right. For pyrrolidines that are α-substituted with groups smaller than CPh_2OTMS (such as $CH_2OTBDPS$ or CH_2OTBS), an intermediate scale may be expected. Meanwhile, for pyrrolidines that are α-substituted with groups larger than CPh_2OTMS (and with a higher EW character), the percentages of enamines that may appear in the medium will be even lower; probably too low to observe any reaction, unless aldehydes well-positioned on the scale and very strong electrophiles are used.

5 Proline Enamines

The presence of a carboxyl group in the α- or C2-position of the pyrrolidine ring introduces several known issues that have been mentioned in the introduction. We should

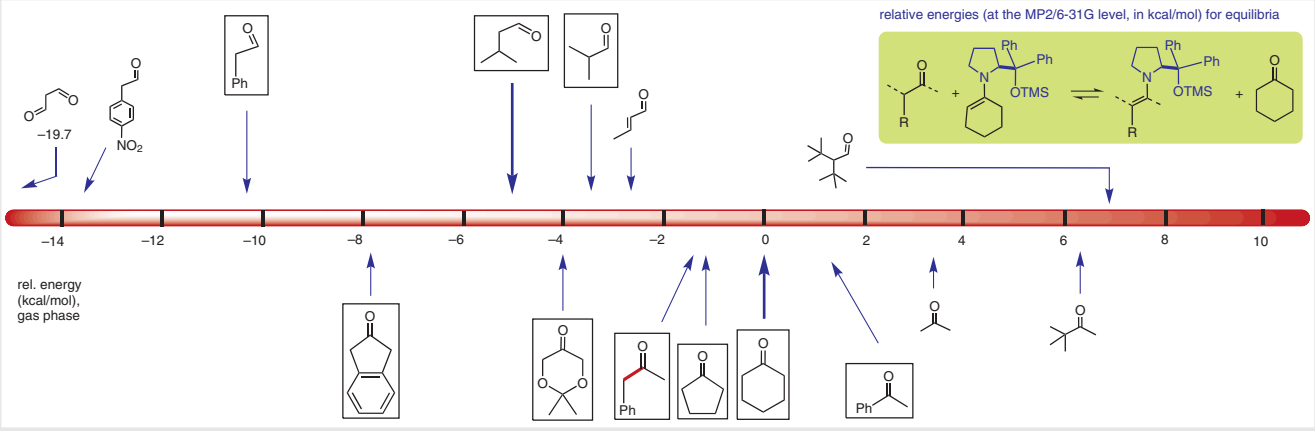
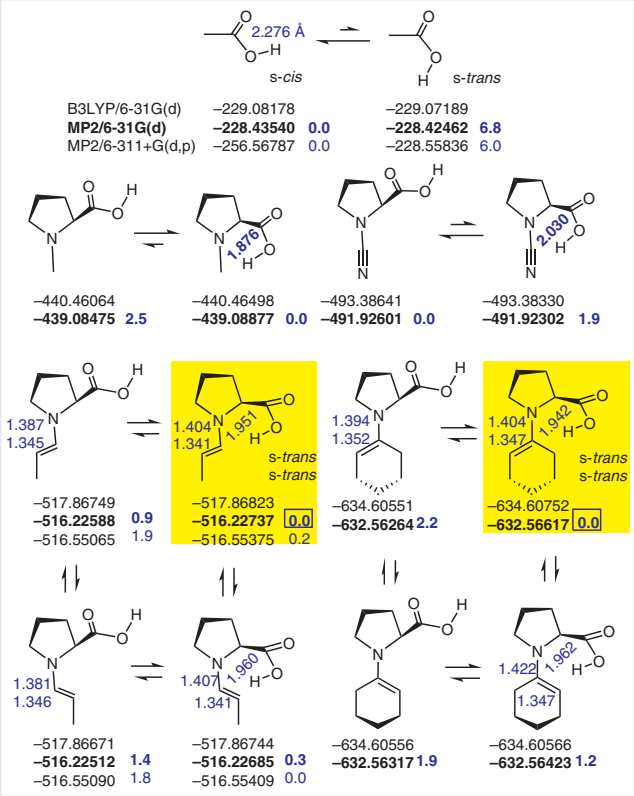


Figure 8 Calculated energies ($\Delta E_{r(J-H)}$ in kcal/mol) for the exchange equilibria between carbonyl compounds and enamines of the J–H catalyst. The cyclohexanone–enamine pair is taken as the main reference. The enamine of 3-methylbutanal (isovaleraldehyde) is our secondary reference (for aldehydes).

also recall that: (a) the s-*cis* conformer of standard carboxylic acids is predominant[25] in the gas phase (Scheme 6, top) and in most solvents; (b) crystal structures of enamines of proline or proline derivatives have been reported,[4a] although they are conjugate enaminones (amide vinylogues); (c) key calculations, mainly at the DFT level, on the mechanisms of proline-catalyzed aldol and related reactions, have been reported,[26] but the reader should go to these references since this subject is not dealt here.



Scheme 6 Total electronic energies (a.u.) of the main conformers of relevant carboxylic acids. Comparison of s-*cis* and s-*trans* arrangements of carboxy groups. Relative energies in kcal/mol, in blue.

The important point here is that, in the presence of a basic N atom in an appropriate position, the *status quo* can change. Scheme 6 shows that the internal hydrogen bonding (N···H–O) in *N*-methylproline overcomes the tendency of COOH groups to adopt s-*cis* arrangements. However, if the N atom is linked to an EWG (such as CN), such a hydrogen-bonding stabilization of the s-*trans* conformer does not occur or is lower, as expected.

For enamines of simple aldehydes and of cyclohexanone (Scheme 6, bottom), the strength of the N···H–O bond still overcomes the preference of COOH for the s-*cis* conformation, but the differences calculated are minimal. It is apparent that the s-*trans*,s-*trans* arrangements, s-*trans* carboxyl group and s-*trans* alkenyl or cyclohexenyl group, with the pyrrolidine ring and the six-membered ring in the depicted conformations, are predicted to predominate slightly, in multiple equilibria containing many enamine forms.

A simple comparison of the pyrrolidine–propanal enamine with the proline–propanal enamine (of the N–C and C=C bond lengths, from 1.380 and 1.347 Å to 1.404 and 1.341 Å, respectively, and of the electron densities on Cα) indicated that the resonance is lower in the second case, as expected. 'Fortunately', the approach of polarized double bonds (C=O bonds, for example) to such s-*trans*,s-*trans* conformers is often favored, according to the Houk–List model.[3a] Thus, although the enamine nucleophilicity is partially reduced due to hydrogen bonding, the approach of the CO group of the acceptor and its interaction with the HO proton may partially release the N atom and proportionally restore the standard enamine reactivity.

We also calculated, besides the two conformers of the carboxyl s-*trans* form of the reference enamine shown in Scheme 6 (bottom right), all the remaining conformers, with C4 of the pyrrolidine ring up and down and with C4 of the cyclohexenyl ring up and down (see Figure 9). It is clear that there are many 'species' that are very close together.

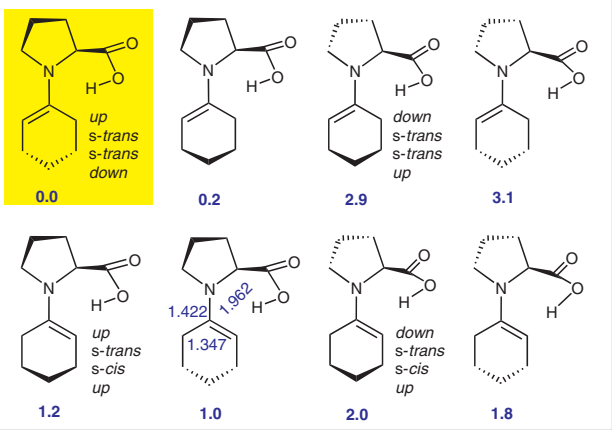


Figure 9 Additional forms of the reference enamine from cyclohexanone and proline. Relative energies at the MP2/6-31G(d)//B3LYP/6-31G(d) level, in kcal/mol.

Another question is whether this hydrogen bonding can affect the interconversion barriers between s-*trans* and s-*cis* enamine conformers:

(a) For the enamine from 3-methylbutanal and proline the barriers turned out to be 6.2 and 3.6 kcal/mol [MP2/6-31G(d) level].

(b) For the enamine of an α-branched aldehyde (2-methylpropanal, isobutyraldehyde), the highest barrier was only 5.5 kcal/mol, at the MP2/6-31G(d) level (see Figure 10).

(c) For the enamine from cyclohexanone and proline, the results are summarized in Scheme 7. The barriers were 5.5 kcal/mol (counterclockwise) and 5.1 kcal/mol (clockwise). The values are similar to those shown in Scheme 5.

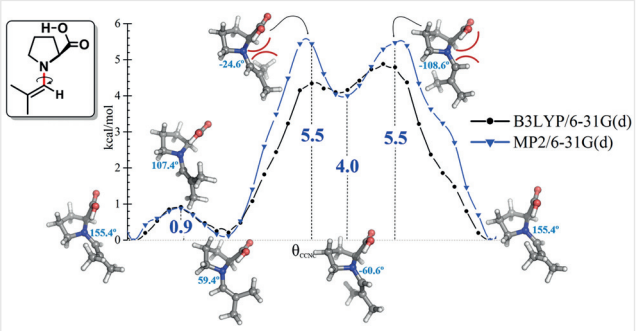
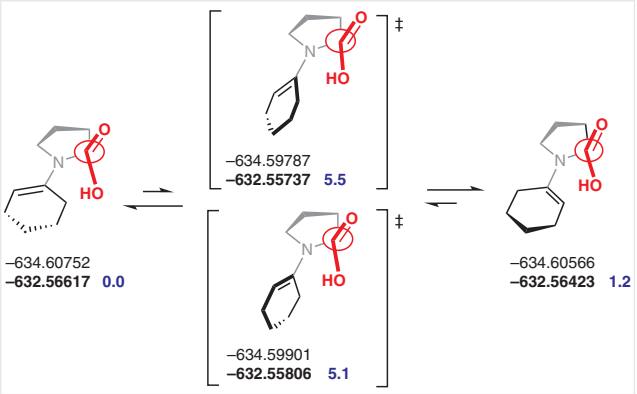


Figure 10 Conformational analysis of the 2-methylpropanal–proline enamine. Energy barriers in kcal/mol, indicated in blue, at the MP2/6-31G(d) level.



Scheme 7 Energy barriers corresponding to the s-*trans*-to-s-*cis* rotation of the cyclohexenyl group, at the MP2/6-31G(d)//B3LYP/6-31G(d) level. Units of numbers in blue: in kcal/mol, as always.

Finally, as for pyrrolidine enamines and the J–H enamines, we also calculated the relative energies for the transfer of proline from one carbonyl to another (Figure 11), that is, for the ***carbonyl A + proline enamine B = proline enamine A + cyclohexanone (carbonyl B)*** equilibrium. Thus, we once again established cyclohexanone as the first reference, although for some comparisons between aldehydes we used 3-methylbutanal as a second reference. The reason is simple: we had much more NMR data on the enamines of these two carbonyl compounds. We chose a series of 18 additional carbonyl compounds.

As above, those carbonyl compounds that have a high tendency to be converted into their proline enamines are found to the left of cyclohexanone, while those with a lower tendency to give enamines to the right. There is a parallelism between Figures 11 and 8. The differences lie in the fact that the scale is more compressed in Figure 11 (aldehydes and the most favorable ketones are closer to cyclohexanone), whereas the enamines of the less reactive ketones, such as methyl ketones, are far to the right. It seems that the corresponding enamines (vinyl-like enamines) are not particularly stable. Acetone, in particular, lies far to the right.[27] It is not surprising that the cross-aldol reactions of acetone are slow. This handicap has been overcome by using acetone as co-solvent and allowing the reaction to proceed for many days.[28]

For aldehyde–proline enamines conjugated with EWG (propanedial derivative, see Figure 11), with aryl groups, and with additional double bonds (dienamines and trienamines), and only for these cases, not for the 'best' ketone–proline enamines, the tautomers/rotamers with the s-*cis* carboxyl groups were predicted to be between 2.8 and 0.1 kcal/mol more stable than their s-*trans* forms, as shown in the Appendix, Section C (Figure 22); in other words, for these substrates the conjugation of the N atom with the double bonds overcomes the stabilization due to its interaction with the proton of the carboxyl group.

The cases of 3-methylcyclohexanone and 4-methylcyclohexanone did not pose any particular difficulties. In Figure 11 they are very close to cyclohexanone, as expected. Figure 12, which only includes the most stable conformers,

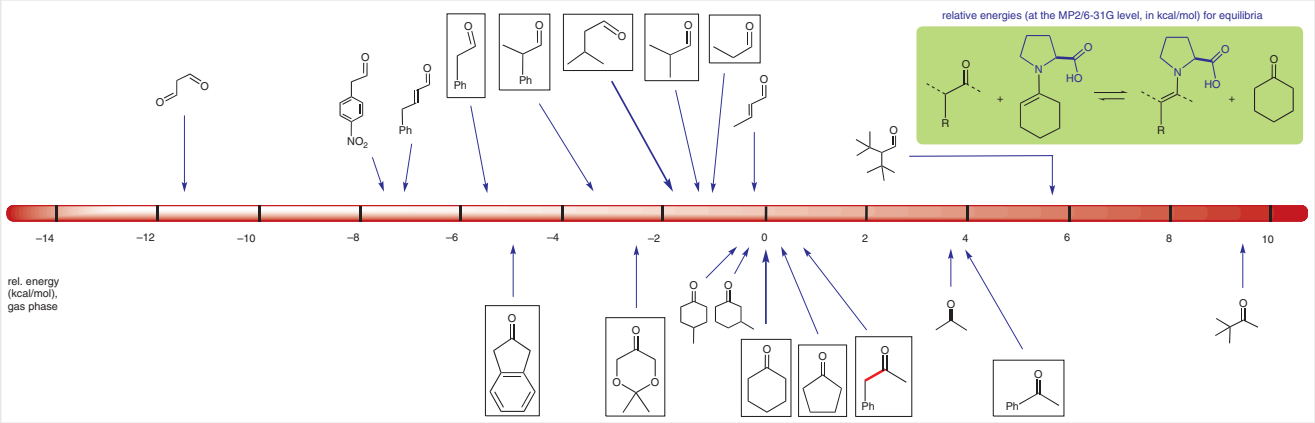


Figure 11 Calculated energies ($\Delta E_{r(pro)}$ in kcal/mol) for the exchange equilibria between carbonyl compounds and proline-derived enamines. Cyclohexanone and its enamine are taken as the general reference pair. Sometimes, we also compare the aldehydes with 3-methylbutanal, which we use as a secondary reference.

C4 of the pyrrolidine up and s-*trans* carboxyl group, almost equatorial Me groups, shows that the gaps between the forms are small.[29]

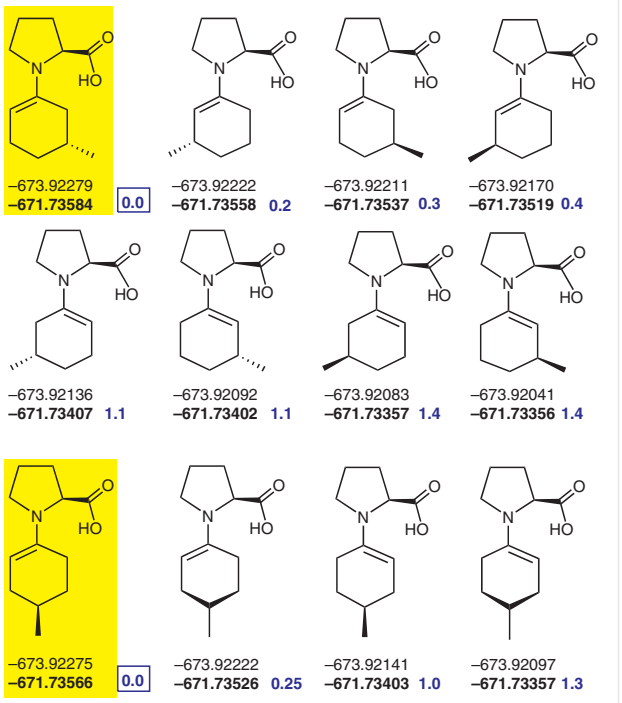


Figure 12 Enamine forms, from 3-methylcyclohexanone and proline and from 4-methylcyclohexanone and proline. First row, B3LYP/6-31G(d) results; second row, single point MP2/6-31G(d) results in bold, as usual. Relative energies in kcal/mol, in blue.

In contrast, 2-methylcyclohexanone was expected to be to the right of cyclohexanone,[1] with a high $\Delta E_{r(Pro)}$ value, because of the steric hindrance of the methyl group. The MP2 energies of all the forms (Figure 13) were above those of their regioisomers (Figure 12), as expected. However, a cautionary note is in order, since showing only the lowest-energy form in a table is an oversimplification when there are many isomers and rotamers quite close in energy, as happens in this case (Figure 13). Taking into account only those forms with an internal hydrogen bond, there are 24 possible minima (otherwise there could be up to 96). This deserves a detailed study of the populations of all the isomers. However, such a study is of little practical interest, since most α-branched or substituted cyclohexanones seldom participate in aminocatalytic reactions; usually they only appear as the reaction products of cyclohexanone enamines.

Last but not least, it is well known that the enamines of several of the carbonyl compounds in Figure 11 are in equilibrium with the corresponding bicyclic oxazolidinones (mainly with their *exo* oxazolidinones). When the enamines are highly stabilized by conjugation, those from the

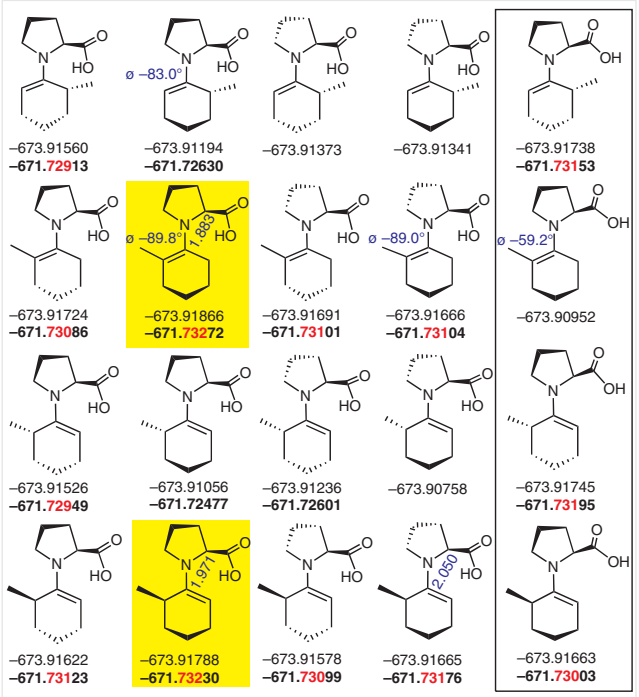
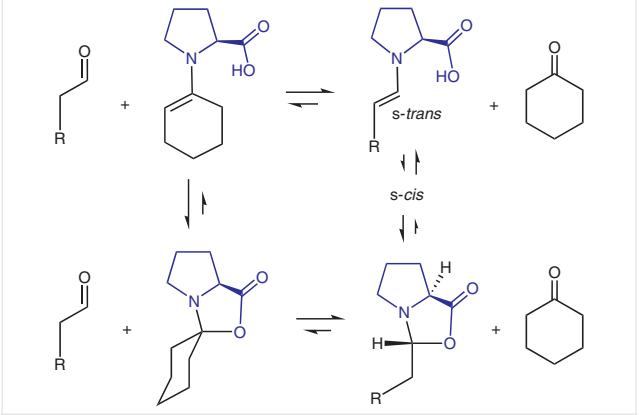


Figure 13 A few of the enamine forms potentially arising from the reaction of 2-methylcyclohexanone with proline. The four lowest-energy forms with the carboxy group in the s-*cis* conformation are depicted inside a rectangle. Relevant dihedral angles (CNC=C) and N···H distances, in Å, in blue.

carbonyl compounds on the left side of Figure 11, oxazolidinones are not detected: the equilibria in Figure 11 apply. In other cases, oxazolidinone-like tautomers may predominate over enamine-like tautomers. The equilibria to be studied are then those shown in Scheme 8 (bottom). We cannot deal with this subject here,[6,9d] due to a lack of space. What matters is that the right side of Figure 11 has to be

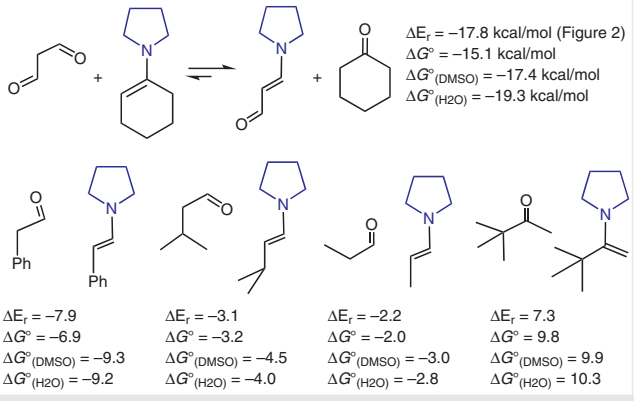


Scheme 8 Examples of the real equilibria that appear in the presence of proline when both carbonyl compounds, an aldehyde vs. cyclohexanone in the drawing, are more prone to form bicyclic oxazolidinones than enamines.

modified. Nevertheless, when the organocatalyst contains carboxyl surrogates not prone to produce bicyclic species (such as tetrazole rings, triazoles, azolium salts, COOR, CONH-EWG, CH_2NH-EWG, CH_2-NHR_2^+, etc. instead of COOH), the scale is fully valid, if appropriately adapted. See Section 7 for examples.

6 Free Enthalpies and Polar Solvent Effects

For a selection of representative carbonyl–enamine pairs we calculated the free enthalpies (Gibbs free energies) and, hence, the values of ΔG^e for ***carbonyl A + cyclohexanone enamine B = enamine A + cyclohexanone (carbonyl B)*** equilibria, as depicted above in Figures 2, 8, and 11, also at the MP2/6-31G(d)//B3LYP/6-31G(d) level. Our purpose was straightforward: to establish the degree to which the inclusion of the thermal and entropic corrections would modify these Figures. We followed the approximations made in a previous full paper,[9k] which will not be repeated here. Moreover, we also estimated by means of the SMD solvation model[14h] the effect that polar solvents such as DMSO and H_2O may have on the above equilibria. Results are summarized in Scheme 9.[30]



Scheme 9 ΔG^e values (in kcal/mol) for the indicated equilibria, with cyclohexanone and its enamine as the references, at the MP2/6-31G(d)//B3LYP/6-31G(d) level.

It is noted that for carbonyl compounds at the extremes in Figure 2, the ΔG^e values are > 2 kcal/mol above the total energies; for carbonyl compounds that are more close to cyclohexanone in Figure 2, the differences are smaller. The effect of polar solvents is strong when one of the enamines in the equilibrium equation is much more conjugated, the conjugation is extended with an EWG or with an aryl group, than the other, that is, than the reference cyclohexanone enamine; otherwise, the effect of polar solvents is predicted to be very small (see the last example in Scheme 9). What matters is that qualitatively the results agree and that the order is the same. In short, it seems that if we had been able to build up a Figure based on calculated ΔG^e(DMSO) values instead of on calculated total energies (ΔE), it would have been similar.

7 Comparison of Organocatalysts

Experimentally, some of us demonstrated[9i] that the relative tendency of popular aminocatalysts and of diisopropylamine to give the corresponding 3-methylbutanal enamines, either in DMSO-d_6, CD_3CN, or $CDCl_3$, followed the order shown in Figure 14 (where the enamines are depicted). The equilibrium constants for the enamine formation are much higher in DMSO than in the other solvents.

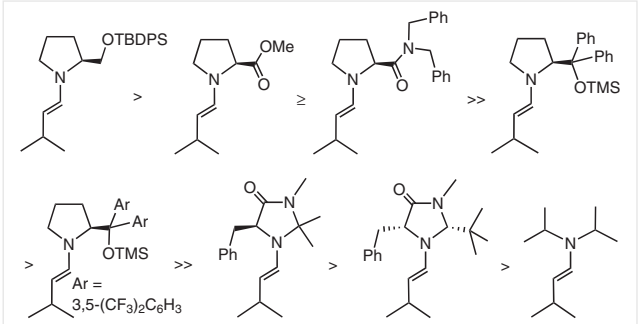


Figure 14 Relative thermodynamic stability of enamines of 3-methylbutanal, as determined experimentally by ^{1}H NMR, i.e., ordering of popular organocatalysts according to their tendency to yield enamines with 3-methylbutanal.

We expanded the scale by comparing the calculated ΔE_r values for exchange reactions ***enamine A*** + sec-***amine B*** = sec-***amine A*** + ***enamine B***. First, the enamine from pyrrolidine and 3-methylbutanal (our second reference throughout this review) was compared to other 3-methylbutanal enamines of pyrrolidine derivatives and proline surrogates, mainly at the MP2/6-31G(d)//B3LYP/6-31G(d) level, as always; the results are shown in Figure 15.

Calculations with other methods were also carried out in several cases to check the reliability of the outcomes. Thus, the same transfer reactions between aldehyde enamines and *sec*-amines were calculated at the M06-2X/6-311+G(d,p) level. The results are summarized in Figure 16. The scale is wider, but a clear parallel can be drawn between Figures 15 and 16.

None of the *sec*-amines examined surpasses pyrrolidine. Pyrrolidines methylated at position α have a slightly more basic N atom, but the steric effect counteracts the electron-donor capacity. TBS-protected prolinol,[9b] which can be compared to the TBDPS-protected prolinol studied by Peng and co-workers,[12] is almost 'as good as' pyrrolidine, so small corrections are expected to be required to correlate Figure 1 (experimental data, in DMSO) with Figure 2, when aldehydes are compared among them. (We did not calculate the

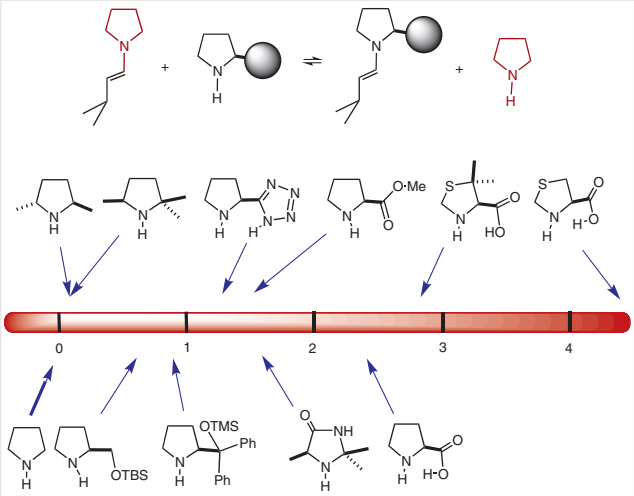


Figure 15 Energies for the indicated exchange reactions (Δ*E*), in kcal/mol, at the MP2/6-31G(d) level.

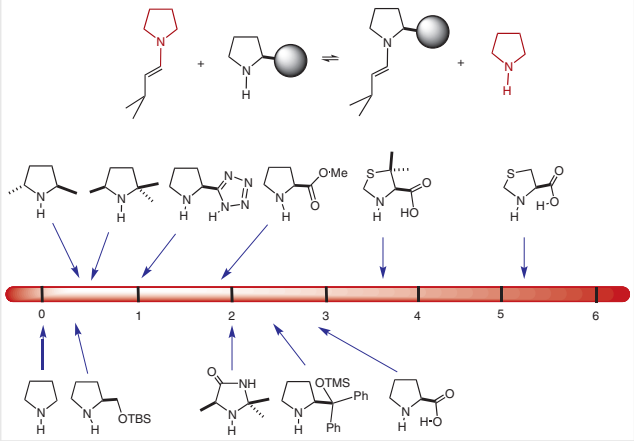


Figure 16 Energies for exchange reactions, at the M06-2X/6-311+G(d,p) level. The scale numbers are in kcal/mol.

TBDPS derivatives because of the huge number of conformers involved.) The stronger the EW character and the larger the substituents, the lower the tendency to produce the corresponding 3-methylbutanal enamines, of course. Methyl prolinate may be taken as a model of prolinamides and related proline-derived dipeptides or tripeptides. The imidazolidinone shown in Figures 15–18 is a simplified model of the MacMillan catalysts. All these catalysts may give enamines of α-unbranched aldehydes more easily than proline, whereas thiazolidine-4-carboxylic acids are predicted to be worse than proline.

The scales of Figures 2 and 15 can be combined, in an approximate way. For example, for α-unbranched aldehydes, the use of 5-[(*S*)-pyrrolidin-2-yl]tetrazole would give rise to a scale such as that of Figure 2 but with all the Δ*E* values corrected by 1.2 (i.e., with the arrows shifted nearly 1.2 points to the right).

Moreover, for α-unbranched aldehydes, the use of the J–H catalyst would require a correction of $\Delta E_r = 0.9$ to Figure 2, to convert it into the scale of Figure 8. And so on.

With respect to ketones, we mention in Section 3 that those with Δ*E* >> 2 in Figure 2 have few chances of participating in enamine-like reactions catalyzed by pyrrolidine, at least in an efficient way. The comparison of pyrrolidine–ketone enamines with other enamines of pyrrolidine analogues containing EWG and/or large substituents led to Figure 17. The steric effects, the well-known steric inhibition of the resonance, play a more important role than in the case of aldehydes, in such a way that 2,2,5-trimethylpyrrolidine, the J–H catalyst, and 2,2,5-trimethylimidazol-4-one were shifted to the right along the scale. Thiazolidine-5-carboxylic acid continued to be the worst catalyst in this regard. Again, the combined use of Figures 2 and 17 provides qualitative or approximate values for the relative stability against hydrolysis of any enamine arising from a ketone and a catalyst.

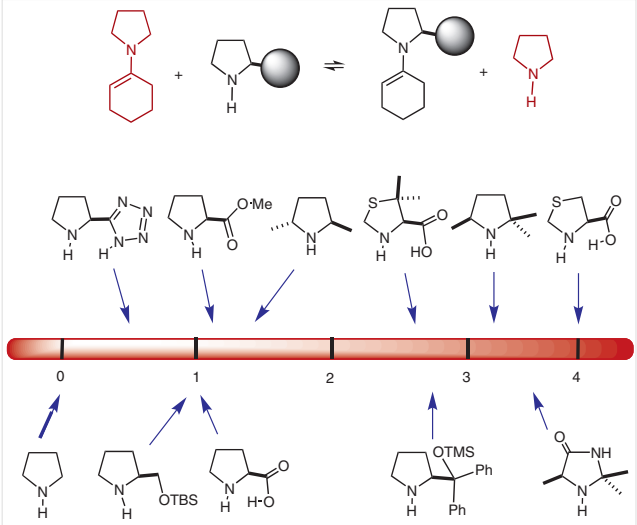


Figure 17 Energies for the indicated exchange reactions (Δ*E*), in kcal/mol, at the MP2/6-31G(d) level.

When the same reactions were calculated at the M06-2X/6-311+G(d,p) level, the range was similar (Figure 18), but expanded, as the sterically more demanding derivatives were shifted further to the right.

The number of DFT calculations of pyrrolidine-derived catalysts other than those reviewed here[31] is smaller. The results may be accommodated into Figure 8, for large substituents at C2 of the five-membered ring, or into Figure 11, if the substituent on the five-membered ring contains an acidic proton that may intervene in the initial or final steps of the organocatalytic process.

Finally, we should again recall that enamines formed from catalysts containing COOH groups may be in equilibrium with the corresponding bicyclic oxazolidinones (a sub-

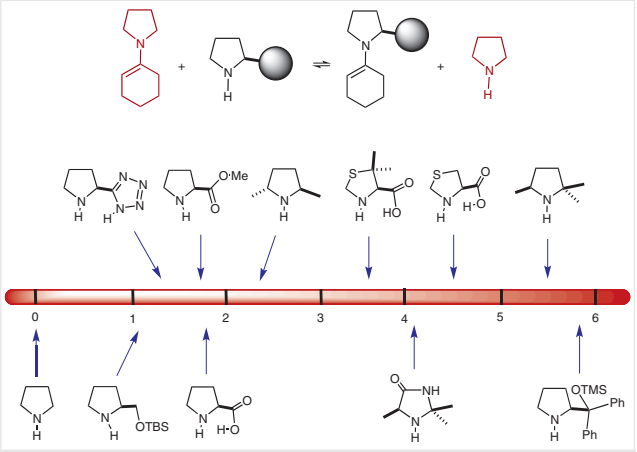


Figure 18 Energies for the indicated reactions at the M06-2X/6-311+G(d,p) level. The numbers are in kcal/mol.

ject that, as mentioned, is outside the scope of the present review). The true concentration of some enamines is then lower than that deducible from Figures 15–18. In other words, Pro and thiazolidine-5-carboxylic acids may in practice be found more on the right of Figures 15–18 than they appear; however, in aldol reactions, where hydrogen bonding between an acidic proton at the pyrrolidine-ring side chain and the carbonyl group approaching the enamine is essential, such a disadvantage may be compensated for.

8 Summary and Outlook

For equilibria between carbonyl compounds and sterically congested enamines, the MP2/6-31G(d) and M06-2X/6-311+G(d,p) predictions agreed with the experimental results we have accumulated. The MP2/6-311+G(d,p) results were less reliable, since crowded enamines were often predicted to be too stable (as the London dispersion forces are overestimated).[9k] Since we cannot rely upon B3LYP energies,[9k] we used the MP2/6-31G(d) method for all the comparisons: it provided us the highest performance-to-cost ratio. For branched and polyfunctional substrates, the use of higher level methods, the calculation of the $\Delta G^{\ddagger}$ values for all reactions (not only for a few), and a systematic evaluation of the effect of different solvents could have been undertaken. At present, however, the results seem consistent and very useful for synthetic purposes, as well as to explain the causes of disappointing trials.

For enamines, the rotational barriers were calculated to be quite small: usually below 5 kcal/mol, for α-unbranched and α-branched aldehydes as well as for α-unbranched cyclic ketones. That is to say, several rotamers of each isomer very rapidly interconvert at rt. As expected, with the J–H catalyst the rotational barriers were predicted to be higher (but still <10 kcal/mol). For α-substituted or branched cyclic ketones and for many acyclic ketones it is likely that the barriers would be higher, but we had no interest in evaluating these values as most of the corresponding enamines, especially those with large substituents at the pyrrolidine C2 position, were experimentally inaccessible.

It is likely that only if the real concentration and/or reactivity of one enamine species greatly surpasses those of the others, and only if the approach of the electrophile in a suitable orientation is favored from one of the two faces of such an enamine species, can high yields and stereoselectivites be expected. If enamines are not formed at all or are formed in such tiny amounts that their concentrations are practically zero, reactions will hardly occur at all, even in the presence of good electrophiles. Meanwhile, if the enamines of adducts are less prone to hydrolysis than the enamines of the substrates, there will not be a good turnover and the catalytic reaction will halt. Obviously, the reaction might still progress stoichiometrically but not under catalytic conditions.

Aldehydes are not very susceptible to steric effects. In general, with the exception of $(R_3C)_2CH\text{-}CHO$, all α-branched aldehydes can be converted into their enamines more easily than cyclohexanone (Figures 2, 8, and 11) and much more easily than any linear ketone. When catalysts other than pyrrolidine, the J–H catalyst, and Pro are considered (Figures 15 and 17), α-unbranched aldehydes are predicted to give enamines in sufficiently productive amounts, except for the case of thiazolidine-5-carboxylic acid.

In contrast, only a few cyclic ketones give sufficient amounts of enamines. Some cyclic ketones (especially α-branched ones) and many non-cyclic ketones are incapable of producing any trace of an enamine. Those ketones that lie > 3 kcal/mol to the right of cyclohexanone in Figure 2 are very bad candidates for *sec*-amine-catalyzed reactions; those that lie around 2 kcal/mol to the right of cyclohexanone may work provided that a large excess of ketones is used. Furthermore, since all the real or potential catalysts in Figure 17 are worse than pyrrolidine, it would be surprising or bizarre if any of them gave rise to excellent conversions in short times, of aldol, Michael, and Mannich reactions from ketone enamines. This is confirmed by looking at Figures 8 (J–H catalyst) and 11 (Pro).

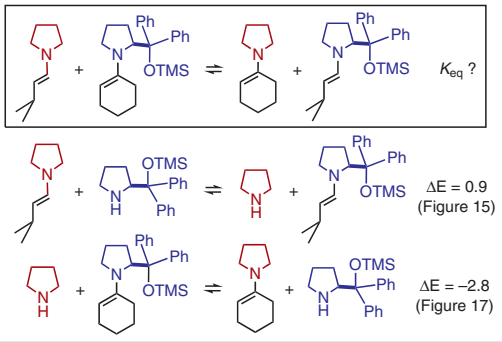
As far as exchange reactions are concerned, involving either one *sec*-amine and two different carbonyl compounds or one carbonyl compound and two different *sec*-amines, the equilibrium positions can be predicted with an acceptable accuracy by subtraction of the corresponding ΔE values. It does not matter if the exchange or metathesis reaction is catalyzed by a trace of water, a trace of acid, or whatever reagent, intermediate, or adduct present in the medium, since we are dealing with equilibrium positions.

The scales given in Figures 2, 8, 11, 15, and 17, together with, if necessary, the known experimental values of K_{eq} for the formation of enamines in different solvents may be combined to predict which reactions are feasible, as well as

whether some exchanges will be shifted far enough to the right or not. For example, when there is one *sec*-amine and two carbonyl groups in the reaction medium, as in any desired cross-aldol reaction between two enolizable aldehydes, one can predict in advance which enamine form will predominate (often that one with the greater 'real enamine character', probably with a 'better' conjugation between the N atom and the double bond). This does not ensure that such an enamine form will react more rapidly in every case, since that will also depend on the relative steric hindrance (around its nucleophilic C atom) when an electrophile is approaching, but it may help to explain why some reactions go and others do not. A sufficient concentration of the active species in the medium and a sufficient nucleophilicity[32] are both necessary to achieve good yields and turnover frequencies.

Finally, let us suppose a hypothetical case with two *sec*-amines and two carbonyl groups in the reaction medium; the oxo and/or formyl groups may be in the same or different molecule. With the available data, we can estimate which enamine form will predominate. Also, it can be calculated the relative percentage or approximate concentration in the medium of each of the possible active forms, that is, of the main conformers and stereoisomers of the four possible 'combinations' arising from the condensation reaction of the two *sec*-amines with the two carbonyl groups.

Another hypothetical case is shown in Scheme 10. Let us imagine that we have independently prepared and isolated the two enamines on the left and let us consider the possible exchange reaction (in the presence of a trace of water, pyrrolidine, or the J–H catalyst) that will take place on mixing them. The corresponding reaction energy can be obtained from two individual reactions. In this case, ΔE = 0.9 – 2.8 = –1.9 kcal/mol. Assuming again that the thermal, entropic, and solvent effect corrections will change this value only slightly, i.e., that in such an isodesmic reaction the individual changes of each term will be compensated by the other changes, the equilibrium position is shifted quite far



Scheme 10 Hypothetical exchange between two enamines (expected equilibria when two carbonyl compounds and two different pyrrolidines are present in the medium).

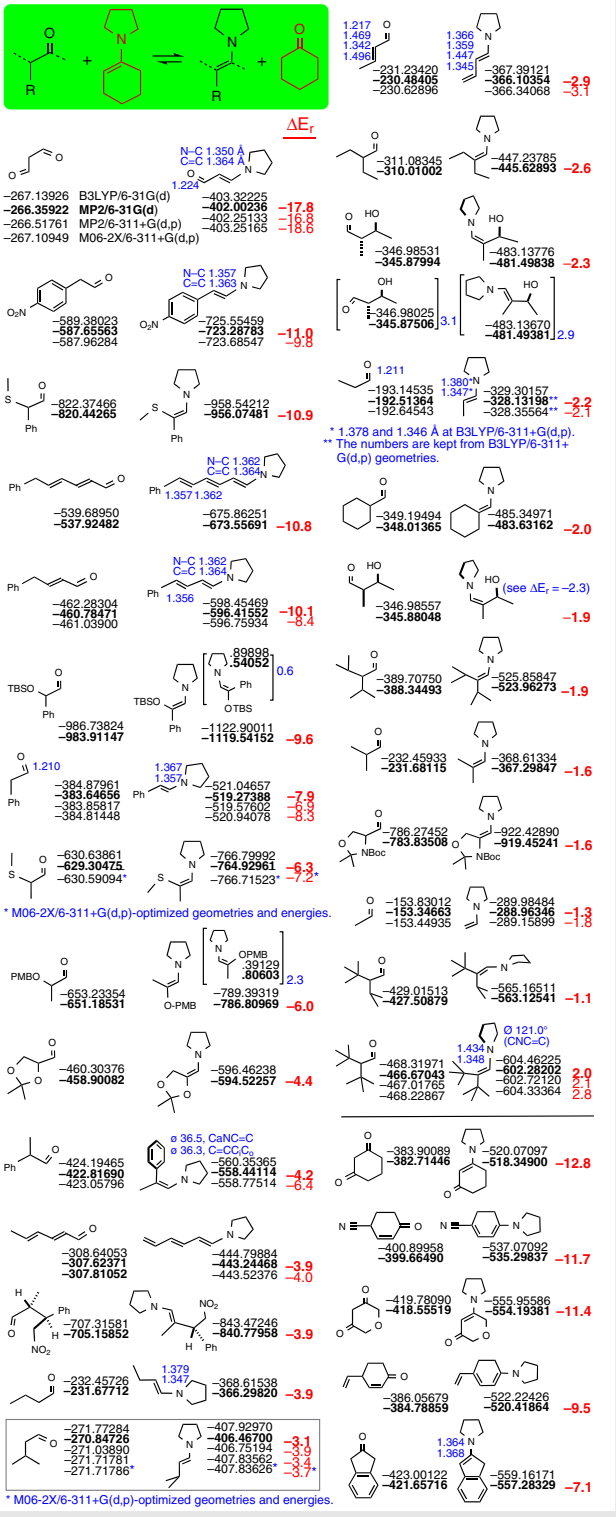


Figure 19

to the right (log K_{eq} = $-\Delta G^{\circ}/2.303\ RT \approx -\Delta G^{\circ}/1.36$). Obviously, this value can also be obtained from the total energies of the four enamines. Apparently, in the simple case of Scheme 10 the sterically demanding combination of cyclohexanone and the J–H catalyst is disfavored; in other words, the 'large' J–H catalyst prefers to be linked to the 'small' 3-methylbut-1-enyl group.

Analogously, dozens of other potential equilibria, with not so simple carbonyl compounds, may be examined by taking into account these scales or, alternatively, the energies given in the Appendix. We hope that they will be of help to predict, develop, or account for any reactions involving enamines.

9 Appendix

The relative energies (ΔE, in kcal/mol) for the equilibria shown in Figures 19–23 are indicated in bold red. Numbers in bold black are the total electronic energies in a.u. at the MP2/6-31G(d)//B3LYP/6-31G(d) level. The total energies and relative energies at other levels of theory are also given.

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Acknowledgment

This Account is dedicated to the chemist and former owner of Derivados Forestales S. A., Dr. Pere Mir Puig (deceased 10 March 2017). After his retirement he created the Fundació Privada Cellex de Barcelona and provided funds to hospitals, research institutes, and the Col·legi de Químics de Catalunya, as well as special studentships and fellowships.

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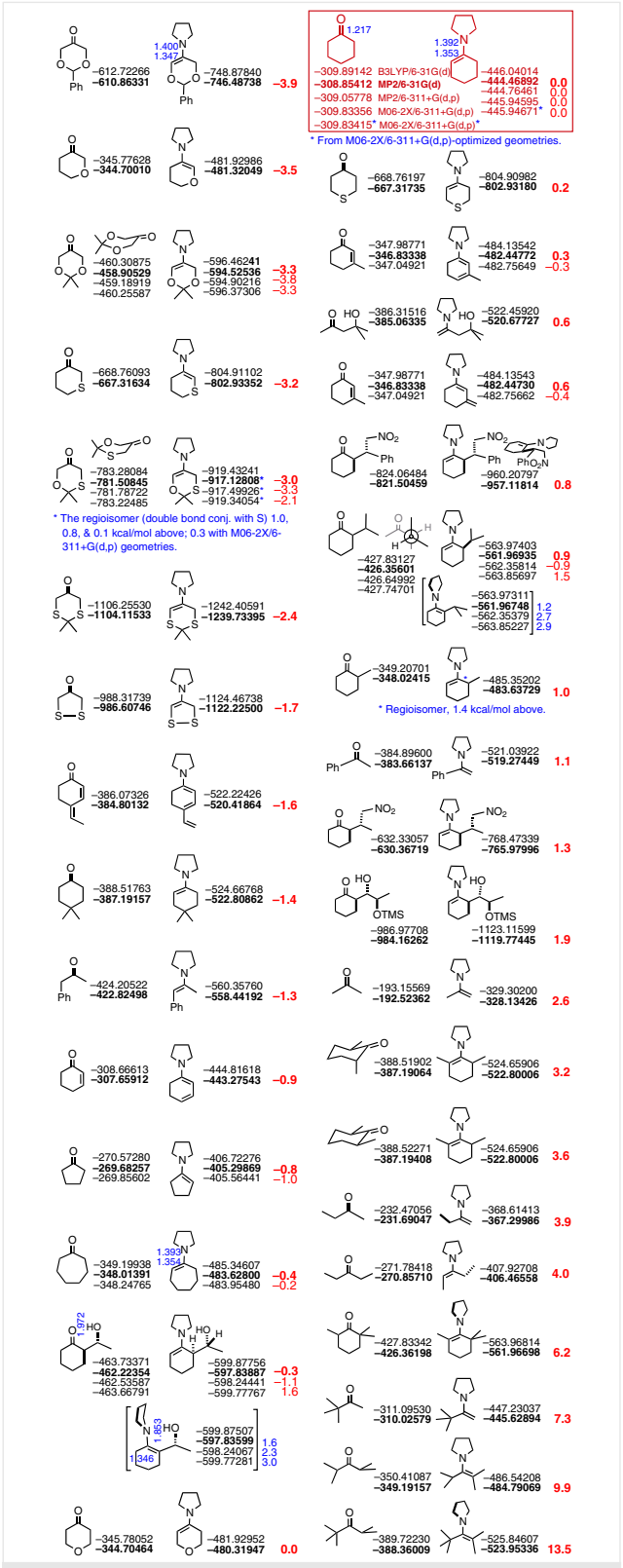

Figure 20

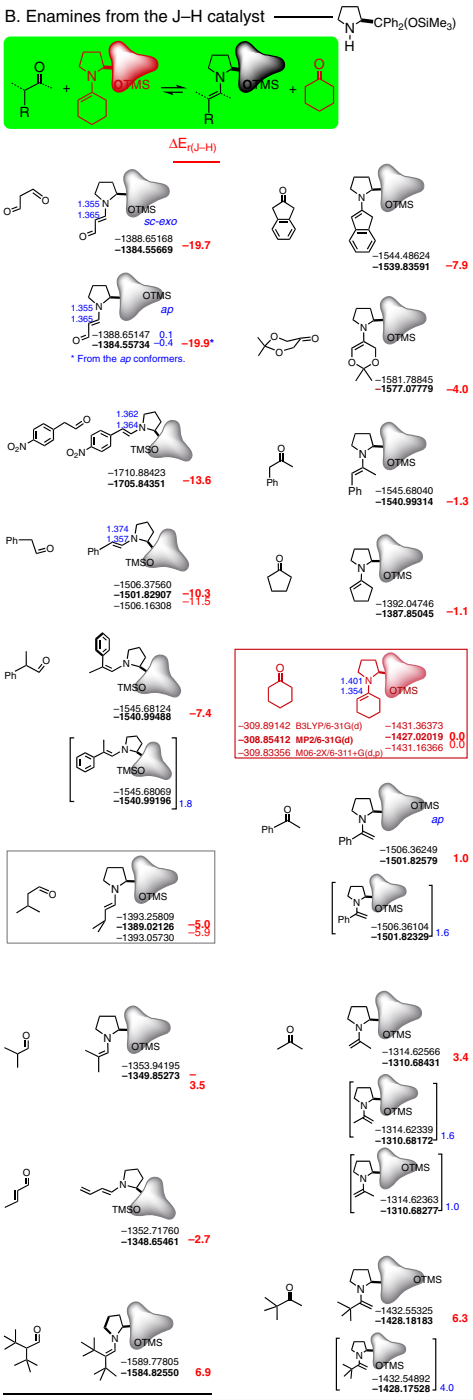

Figure 21

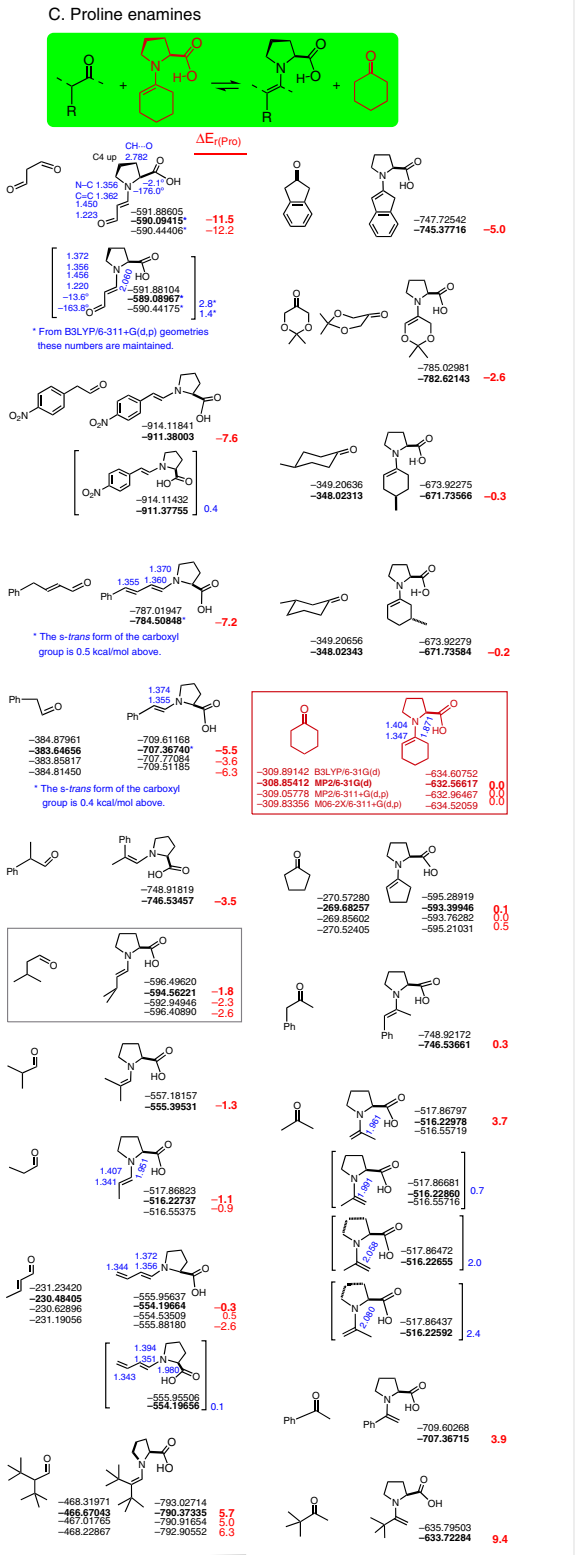

Figure 22

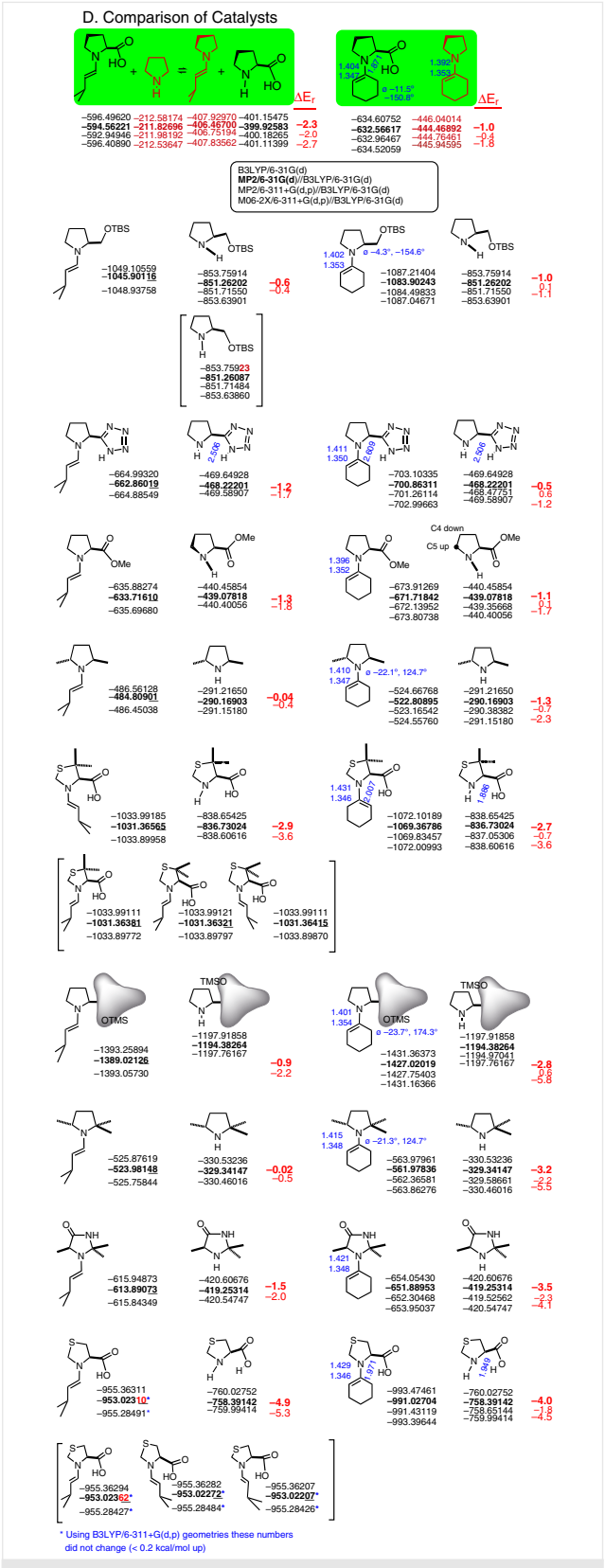

Figure 23

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(17) We carried out additional experiments that confirm the relative position of 2-methylpropanal (isobutyraldehyde) and 2-methylcyclohexanone (2MC) in Figure 2 and the Appendix. For example, when a solution of the pyrrolidine–cyclohexanone enamine was prepared from its components in the presence of 3-Å molecular sieves and CaH_2, and 100 mol% of 3-methylbutanal was added, we observed by ^{1}H NMR that in DMSO-d_6 the peaks at δ = 4.10 (enamine proton, t, J = 3.9 Hz) and 2.92 (4 H α to the N atom) started to disappear and signals at δ = 5.57 (new enamine proton) and 2.85 (4 H α to the N atom) appeared, and the equilibrium was reached in less than 1 h (K_{eq} ≈ 28); three days later the ratios between carbonyl compounds and their enamines were maintained. A similar result was observed in CD_3CN. In contrast, when we added commercially available 2MC to the pyrrolidine–cyclohexanone enamine, in DMSO-d_6, only a slight decrease of the peaks of the cyclohexanone enamine was observed whereas the peaks of the 2MC enamine were hardly observable; however, by adding 10 equiv of 2MC the exchange was clearly seen; an approximate value of K_{eq} (0.03) was determined.

(18) A trace of water or of pyrrolidine may catalyze these exchange reactions. For example, a trace of water hydrolyzes a small amount of pyrrolidine–cyclohexanone enamine and the resulting pyrrolidine reacts with carbonyl A leading to the production of water, which repeats the cycle■■*OK? (... unclear)*■■. Eventually, equilibrium is reached. Similarly, a trace of pyrrolidine remaining in the vial, by reacting with carbonyl compound A gives some enamine A plus some water, which continues the exchange process, as above. Although other exchange mechanisms might be operative, they have not yet been demonstrated.

(19) For malonaldehyde (propanedial) the calculated total energies of the main conformer are –267.13926 [B3LYP/6-31G (d)], –266.35922 [MP2/6-31G (d)//B3LYP/6-31G (d)], and –266.51761 a.u. [MP2/6-311+G(d,p)//B3LYP/6-31G (d)]. For its enol with an intramolecular hydrogen bond, (*Z*)-3-hydroxypropenal, the values are –267.14885, –266.36273, and –266.52384 a.u., respectively (that is, a few kcal/mol lower at every level). Thus,

ΔE_r in Figure 2 would be –15.6 instead of –17.8 (still the 'best' carbonyl compound in Figure 2); this is the only case of our series in which an enol form is more stable than the lowest-energy carbonyl form, in the gas phase.

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