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Transfer of 1-Alkenyl Groups between Secondary Amines. Relative Stability and Reactivity of Enamines from Popular Organocatalysts

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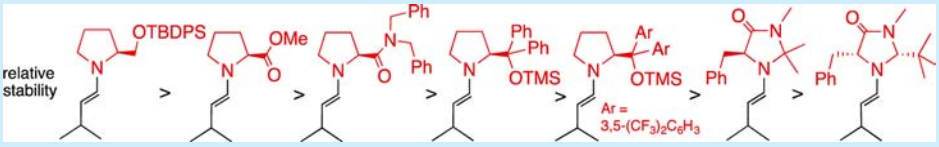
Supporting Information



ABSTRACT: Enamines from 3-methylbutanal and several Pro- and Phe-derived secondary amines were prepared in DMSO-d_6, CD_3CN, and $CDCl_3$. For the first time, the relative thermodynamic stabilities of these and other enamines were compared, and rapid exchanges of 1-alkenyl groups were demonstrated. Competition experiments showed that the most favored enamines (without significant steric inhibition of resonance) react more rapidly with electrophiles.

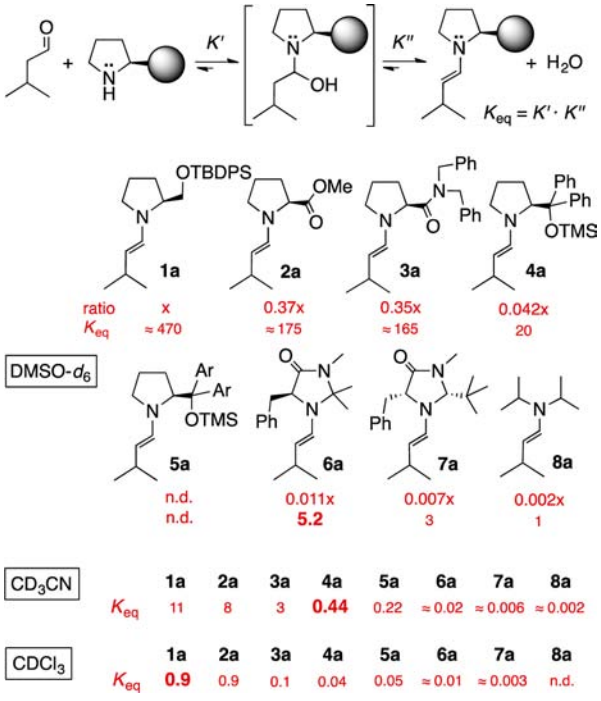
Asymmetric aminocatalysis is an extremely useful tool for the synthesis of chiral building blocks (chiroblocks, chirons).[1,2] Among the most popular enantiopure secondary amines used as organocatalysts, apart from α-amino acid proline (Pro), are the Phe-derived MacMillan catalysts[3] and Pro-derived Jørgensen–Hayashi catalysts.[4] Primary amines prepared from Cinchona alkaloids[1b,e,5] are also worth noting.

Choosing the most suitable aminocatalyst for the generation of the desired enamines is often an empirical process. To be aware of the relative thermodynamic stability of the enamines (of all the stereoisomers and conformers) could help in the selection, if it could be rapidly determined by NMR or calculated. This is our objective. Moreover, the relative percentage of the possible enamines in equilibrium (for example, when two carbonyl groups and/or two secondary amines are present) may also be useful to explain or predict the course of cascade or domino reactions.

The NMR spectra of mixtures of 3-methylbutanal (isovaleraldehyde) with chiral secondary amines (containing a pyrrolidine ring, mainly proline or prolinol derivatives, but also imidazolidinones) were registered in DMSO-d_6, CD_3CN, and $CDCl_3$. After reaching equilibrium (in general, within 15 min), the K_{eq} values for the formation of enamines **1a**–**7a** were calculated from the integrations (Scheme 1, for details see the Supporting Information). For the sake of comparison, although it is of no interest from the point of view of asymmetric synthesis, we also prepared the enamine of diisopropylamine (**8a**). We chose 3-methylbutanal because, in relation to linear aliphatic aldehydes, a very low percentage of aldol adducts were formed. Some of their enamines have been described,[6] but we were interested in the comparison of the K_{eq} of a long series, in an attempt to find a useful general rule.

As expected, the equilibria were shifted furthest to the right (Scheme 1) for those pyrrolidines substituted with groups of smaller size and/or of weaker electron-withdrawing character. In the first step, it is likely that the most nucleophilic N atoms will interact more strongly with the CO group, so the first equilibrium will be shifted further toward the hemiaminal(s), or *N*,*O*-acetal(s), a study of the relative stability of which is

Scheme 1. K_{eq} Values Determined by ^{1}H NMR[a]



[a]Ar = 3,5-bis(trifluoromethyl)phenyl. Holes in the series (n.d. = not determined) are due to the partial hydrolysis of the O–Si bond of **5** and the lack of detection of **8** in the less polar solvent.

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beyond the scope of this work. In the second step, the dehydration step, the most stable enamines (those in which the resonance is not inhibited or diminished by steric effects and/or by an EWG close to the N atom) will be formed in larger amounts. Thus, both steps depend on the "practical" electron-donating ability of the N atom.

The equilibria were more shifted to the right in DMSO-d_6 than in CD_3CN and $CDCl_3$ (Scheme 1). Apart from the polarity, the hygroscopic nature of DMSO may also play a role.[7]

It is clear that the sterically less hindered amines, such as *O*-TBDPS-prolinol (**1**, first examined by Peng et al.[8]), methyl prolinate (**2**), and *N*,*N*-dibenzylprolinamide (**3**)[9] give the most stable enamines (**1a**−**3a**). The Jørgensen−Hayashi catalyst (**4**) and Jørgensen's tetrakis-CF_3 derivative (**5**) follow. At the other extreme, the most crowded amines, the first- and second-generation MacMillan catalysts (**6** and **7**) and diisopropylamine (**8**), afford the lowest concentrations of enamines (**6a**−**8a**).[10]

The K_{eq} values that are very high or very low are approximate. They were obtained by mixing equimolar amounts of pairs of amines and adding up to 120 mol % of 3-methylbutanal (see spectra in the Supporting Information) and referred to reliable values, highlighted in bold. For equilibria shifted too far to the left or to the right the K_{eq} values cannot be obtained directly, properly, as they come from the integrations of the corresponding ^{1}H NMR peaks, some of which can hardly be seen. What matters is the relative order.

Exchange experiments were in agreement with the relative order shown in Scheme 1. For example, when a solution of **2a** in DMSO-d_6, prepared independently (Figure 1a), was treated

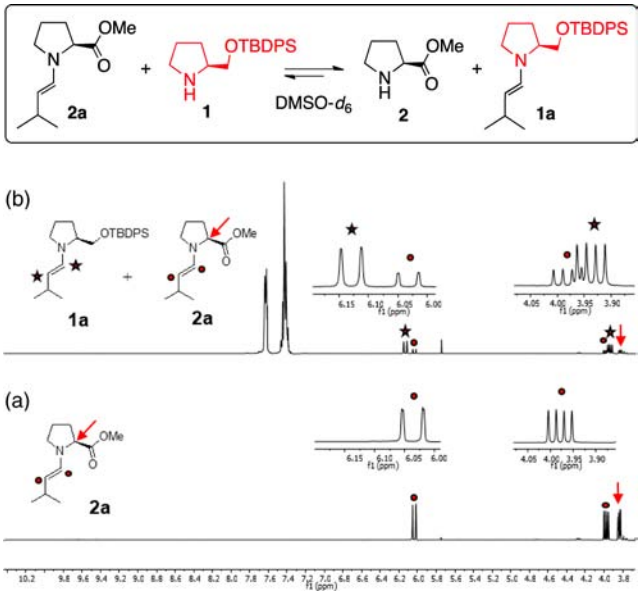

Figure 1. ^{1}H NMR spectra of the exchange of the 3-methyl-1-buten-1-yl group between **2a** and **1** in DMSO-d_6: (a) Portion of the spectrum of **2a**; (b) 10 min after the addition of 1 equiv of *O*-TBDPS-prolinol (**1**), enamine **1a** already predominated.

with *O*-TBDPS-prolinol (**1**) in an NMR tube, the equilibrium was reached in 10−15 min, with partial transfer of the alkenyl group, to give enamine **1a** (Figure 1b). In CD_3CN, the addition of **1** to **4a** (Figure 2a) gave quickly an equilibrium shifted far to the right (Figure 2b).

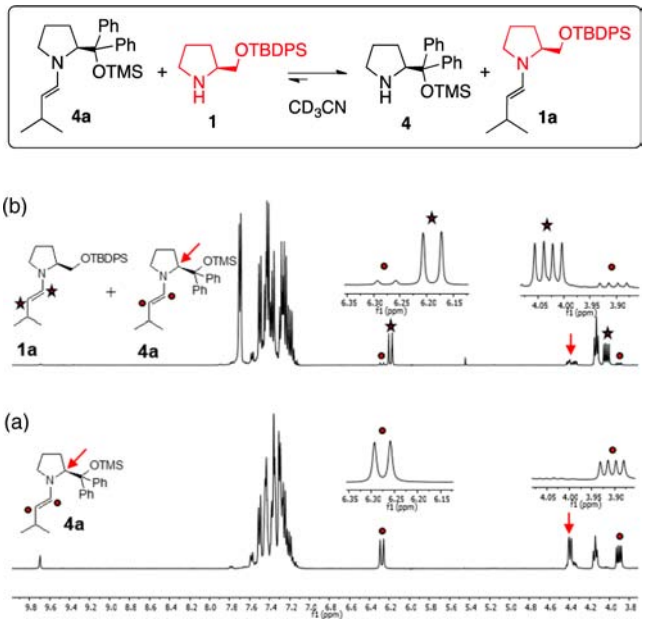

Figure 2. ^{1}H NMR spectra of the exchange of the 3-methyl-1-buten-1-yl group between **4a** and **1** in CD_3CN: (a) portion of the spectrum of **4a**, with a small amount of aldehyde remaining in the equilibrium; (b) 10 min after the addition of 1 equiv of *O*-TBDPS-prolinol (**1**), **4a** almost disappeared, while **1a** largely predominated.

Enamines from primary amines cannot be included in the scale of Scheme 1, as they give imines. Enamine signals were not detected. Nevertheless, using $PhCH_2CHO$ (phenylacetaldehyde), which is more prone than 3-methylbutanal to give enamines because of the conjugation of the enamino with the Ph group, a comparison is feasible (Figure 3). In practice, when

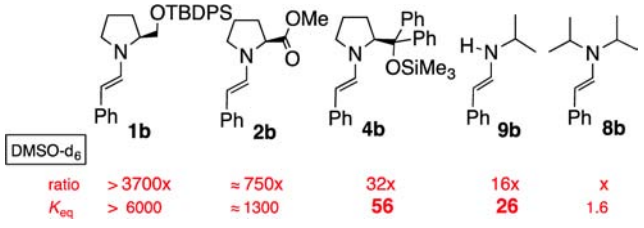

Figure 3. Relative stabilities of enamines from $PhCH_2CHO$.

isopropylamine was treated with $PhCH_2CHO$, the expected imine (δ 7.72) was formed, which slowly (overnight) but fully isomerized to its enamine, **9b**. On the other hand, when the experiment was carried out in the presence of PhCOOH (1 equiv), **9b** appeared immediately.

Mixing equimolar amounts of **1a** and **2b**, prepared independently, a slow exchange was observed, with appearance of the crossed enamines, **2a** and **1b**. Three days later, the ^{1}H NMR spectrum indicated a mixture of **1a** (20%), **1b** (9%), **2a** (32%), and **2b** (40%).

Experiments with 2-indanone, a ketone prone to yielding enamines, and representative amines, including (9*R*)-6′-methoxycinchonan-9-amine,[1b,e,5,11] are shown in Figure 4. The parallelism between Scheme 1, Figure 3, and Figure 4 indicates that there are general rules or patterns, so the ordering may be extended with other enamines.

Although the enamines from pyrrolidine[6a,12] have no interest in asymmetric catalysis, we determined their relative K_{eq} ratios

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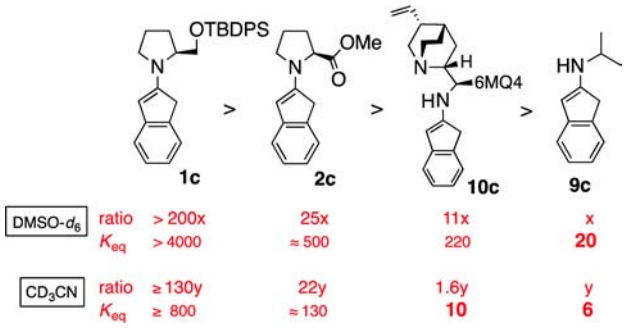

Figure 4. Relative stabilities of 2-indanone enamines. 6MQ4 = 6-methoxyquinolin-4-yl.

for comparison. As it could be expected, they are thermodynamically more stable than **1a**, **1b**, and **1c**: 1.1 (DMSO-d_6), 1.7 (CD_3CN), and 1.4 ($CDCl_3$) in series **a**; 2.8 (DMSO-d_6) in series **b**; 20 (DMSO-d_6) and 10 (CD_3CN) in series **c**.

Mechanistically, the exchanges between enamines and amines shown in Scheme 1 and Figures 1 and 2 may be mediated by water (that is, via hydrolysis). However, it is more interesting to evaluate if the exchanges may also take place by formation of an aminal (enamine A + amine B = aminal = amine A + enamine B), in other words, via an addition−elimination mechanism (hydroamination of the double bond of an enamine), either noncatalyzed or catalyzed by a trace of acid. The chemistry of aminals is known,[13] but the question is to demonstrate a significant participation in the exchanges reported here. At rt we never detected the corresponding aminals by mixing equivalent amounts of enamines and amines, nor by mixing 200 mol % of pyrrolidine with 3-methylbutanal in CD_3CN. However, in this last case decreasing the temperature to −30 °C (VT-^{1}H NMR) the aminal appeared (1:3 aminal/enamine ratio, methine of the aminal at δH 3.21, t, J = 6.3 Hz, methine δC 75.8, see the Supporting Information for more details). Also, even at rt, aminal signals were clearly detected by adding an excess of pyrrolidine (5 equiv) to pyrrolidine−3-methylbutanal enamine in DMSO-d_6 at rt; EXSY peaks correlating enamine and aminal (δ 6.09/3.21, δ 3.96/1.35) were clearly observed in the NOESY spectrum (see the Supporting Information). A detailed study of the relative stability of aminals is outside the scope of this communication, but the experiments just mentioned indicate that aminals can be involved as reaction intermediates in the exchange reactions of Figures 1 and 2.

Until now, we have dealt only with thermodynamics.[14] Let us now comment on the kinetic differences between enamines.

By addition of standard Michael acceptors, such as (*E*)-1-nitro-2-phenylethene (*E*-PhCH═CHNO$_2$, henceforward "nitrostyrene") to pairs of two enamines in practically identical percentage (prepared independently and mixed in appropriate ratios into the NMR tube), we observed that the most favored enamine disappeared more rapidly. For example, a mixture of **1b** and **4b** in CD_3CN, treated from 0 °C to rt with nitrostyrene (CD_3CN solution added in portions), caused a more rapid disappearance of **1b** than of **4b** (see Figure 5).

Besides, the reaction of an equimolar mixture of **1b** and **4b** in CD_3CN with DEAD (toluene solution, added in portions), from −40 °C to rt, gave rise to the disappearance of **1b** rather than of **4b** (see Figure 6).

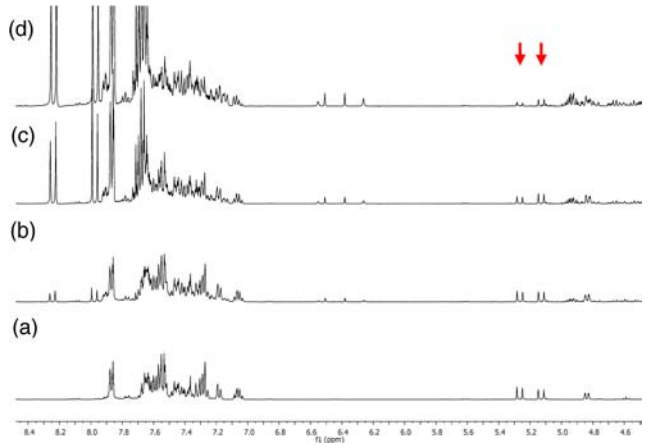

Figure 5. (a) Mixture of enamines **1b** (Hβ doublet at δ 5.30) and **4b** (Hβ doublet at δ 5.15) in CD_3CN, in 1.12:1.00 ratio; (b) 10 min after addition of 20 mol % of nitrostyrene, the ratio was 0.92:1; (c) 10 min after the addition of further 30 mol % of nitrostyrene, the ratio diminished to 0.69:1; (d) 10 min after the addition of further 50 mol % of nitrostyrene, the **1b**/**4b** ratio was 0.55:1.

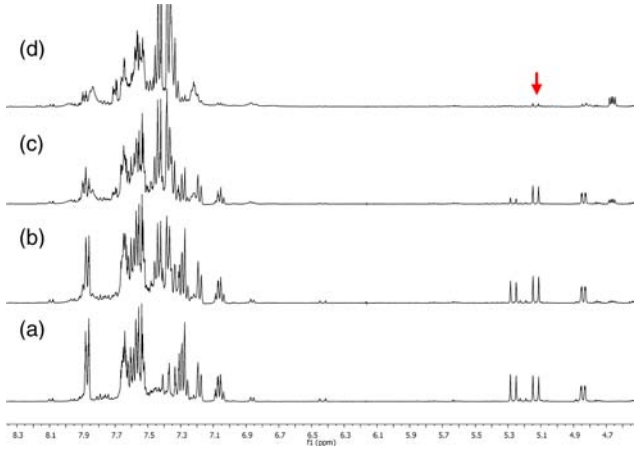

Figure 6. (a) Mixture of enamines **1b** (see Hβ doublet at δ 5.30) and **4b** (Hβ doublet at δ 5.15) in CD_3CN, in 1:1 ratio; (b) 10 min after addition of 10 mol % of DEAD (40% in toluene), the ratio was 0.75:1; (c) 10 min after the addition of further 40 mol % of DEAD, the ratio diminished to 0.35:1; (d) with 100 mol % of DEAD, **1b** disappeared completely, while **4b** was still detectable.

These preliminary experiments suggest that the thermodynamically more favored enamines (the less crowded enamines, if there are no strong EWG in the close neighborhood) may be the most reactive as nucleophiles.[15]

In conclusion, series of enamines of 3-methylbutanal, phenylacetaldehyde, and 2-indanone from the most popular organocatalysts have been compared for the first time. The relative thermodynamic stabilities of these enamines are predictable (mainly on the basis of the steric effects). Their reactivity as nucleophiles is also related, not unexpectedly, on their "true enamine character" (again depending on the more or less large inhibition of resonance by steric and electronic factors). Standard, cheap, quick NMR experiments such as those shown here can throw light on the understanding of some organocatalytic reactions and can assist the selection and/or development of appropriate catalysts, as we hope to show in the near future.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and copies of NMR and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) The values given are without addition of molecular sieves or other dehydrating agents into the vials or NMR tubes. We only did this in independent vials to increase the peaks in $CDCl_3$ in order to attribute enamine signals that we were hardly able to observe starting from the less nucleophilic amines.

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(10) This only means that the real concentrations of some enamines in the medium are much lower than others (longer reaction times, lower conversions). Reactions involving less favored enamines may give rise to higher stereoisomeric ratios (either due to the larger predominance of the *E*/*s-trans* arrangement—the major species, depicted in Scheme 1—or to the easier approach of the electrophile to C2 via its *Si* face). This is not a matter for discussion in this work.

(11) Isolated from its commercially available trihydrochloride. For the pioneering preparation of this cinchonanamine, see: Brunner, H.; Schmidt, P. *Eur. J. Org. Chem.* **2000**, 2119−2133.

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(14) Which chiral amine would produce a higher concentration of the enamine or which enamine would be most formed if two catalysts were added to the medium aimed at producing cascade-like reactions.

(15) (a) It has been reported that imidazolidinone-derived enamines of phenylacetaldehyde show scarce nucleophilicity (lower than analogous enamines from **5**) against Ar_2CH^+ (benzhydrylium) ions. See: Lakhdar, S.; Maji, B.; Mayr, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5739−5742. (b) For the nucleophilicity of achiral enamines, see: Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem.—Eur. J.* **2003**, *9*, 2209−2218.