Aminocatalyzed Reactions of Aldehydes with Chiral Nitroalkenes

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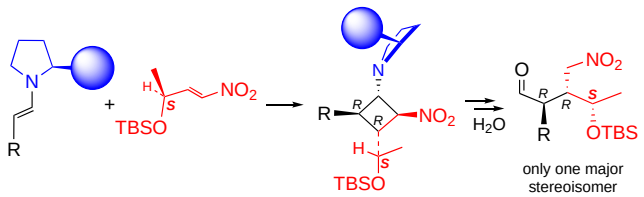
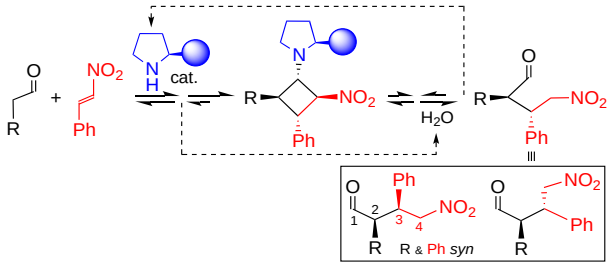


ABSTRACT: Chiral nitroalkenes are used for the first time in Michael additions of aldehydes, catalyzed by pyrrolidine derivatives. They yield the same major stereoisomer with either (*S*)-proline or (*R*)-proline, but this asymmetric induction does not overcome the effect of sterically more congested catalysts. Nitrocyclobutane intermediates are often formed, which are more stable than those from (*E*)-1-nitro-2-phenylethene. The cyclobutanes and final products were characterized by 2D NMR and chemical correlations.

A SciFinder-n search indicates that over 1,000 articles contain additions of carbonyl/carboxyl compounds to (*E*)-1-nitro-2-phenylethene (*β*-nitrostyrene), although the number is reduced to ca. 670 or 170 if the words "asymmetric" or "organocatalytic", respectively, are entered. In fact, to check the performance of chiral catalysts, the reaction of cyclohexanone with *β*-nitrostyrene has been used as a paradigmatic example.[1] The nitro-Michael reactions of aldehydes and nitroalkenes, as Seebach, Hayashi et al.[2] and Burés, Amstrong, and Blackmond demonstrated,[3] are (2+2)-cycloadditions (formal or stepwise).[4] Depending on the temperature, solvent polarity, and concentration of H_2O and organic acid in the medium, these cyclobutanes undergo quick or slow ring opening and hydrolysis to 4-nitrobutanals, as summarized in Scheme 1.

Scheme 1. The Asymmetric Nitro-Michael Reaction, Catalyzed by Chiral Secondary Amines (Simplified View)

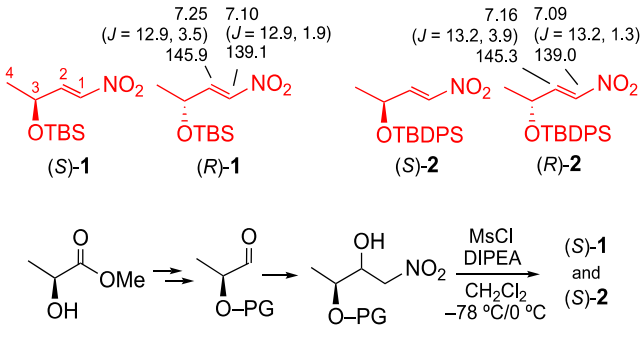


The final nitroaldehydes may be manipulated to obtain an array of fragments/synthons/chiroblocks. However, the presence of an aromatic or heteroaromatic ring in position 3 of a 4-nitrobutanal, 4-nitrobutanol, or 4-aminobutanoic acid is rare in bioactive natural products and enantiopure drugs. Use of functionalized non-aromatic nitroalkenes would be more interesting in this regard but has few precedents.[5]

In this context, we studied the performance of nitroalkenes (*S*)-**1**, (*R*)-**1**, (*S*)-**2**, and (*R*)-**2** as Michael acceptors. These reactions have not been reported. We first evaluated the possible asymmetric induction caused by these nitroalkenes.

We prepared both enantiomers of **1** and **2** from methyl lactate according to the standard procedure[6] shown in Scheme 2: addition of nitromethane to the appropriate aldehyde followed by dehydration, via activation with methanesulfonyl chloride and elimination with diisopropylethylamine. TBS-protected **1** and TBDPS-protected **2** are representatives of functionalized nitroalkenes that could be obtained from any chiral aldehyde. Compound (*S*)-**1** was known;[7] (*R*)-**1**, (*R*)-**2**, and (*S*)-**2** have not been reported previously.

Scheme 2. Chiral Nitroalkenes Examined in This Work, with Relevant NMR Data in $CDCl_3$

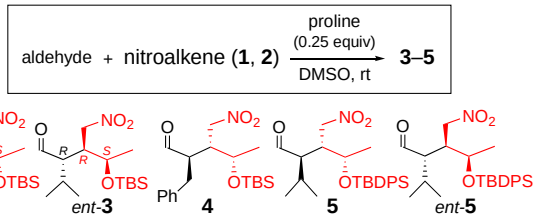


In preliminary experiments, when nitroalkene (*S*)-**1** was treated with cyclohexanone (2.5 equiv), in the presence of (*S*)-proline (L-Pro, 0.3 equiv), in DMSO at rt for 6 h, the nitroalkene disappeared and a very major stereoisomer (95:5) of the Michael adduct (see the Supporting Information, SI)

was obtained. To our initial surprise, when we used (*R*)-proline, a major stereoisomer was also formed, which was identical to the former. Racemic proline (DL-Pro), of course, afforded the same main product. Since the beginnings of aminocatalysis,[8] it has been known that the COOH group of proline exerts a modest effect on enantioselection (ee% ≤ 23%) in additions to *β*-nitrostyrene. Thus, the asymmetric induction of the simple chiral CHMe(OTBS) group appears to overcome the effect of the proline configuration.

However, as mentioned, our objective was to evaluate whether this was the case or not for aldehydes. The results with two representative aldehydes are summarized in Table 1.

Table 1. Reaction of Aldehydes with 1 and 2[a]



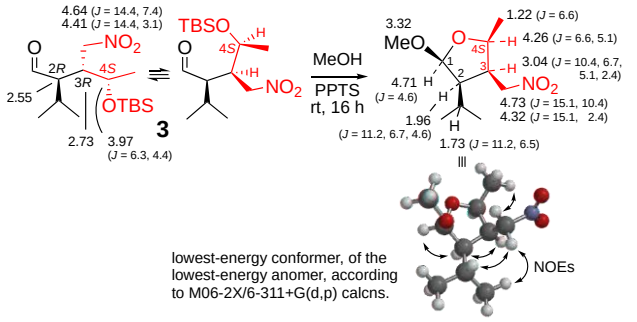
entry	aldehyde	nitroalkene	catalyst	time	dr[b]	yield[c]	major adduct
1	$(CH_3)_2CHCH_2CHO$	(*S*)-**1**	(*S*)-proline	16 h	98:2	86	**3**
2	$(CH_3)_2CHCH_2CHO$	(*S*)-**1**	(*R*)-proline	16 h	90:10	81	**3**
3	$(CH_3)_2CHCH_2CHO$	(*S*)-**1**	*rac*-proline	16 h	93:7	84	**3**
4	$(CH_3)_2CHCH_2CHO$	(*R*)-**1**	(*S*)-proline	16 h	90:10	82	*ent*-**3**
5	$PhCH_2CH_2CHO$	(*S*)-**1**	(*S*)-proline	12 h	86:14	79	**4**
6	$PhCH_2CH_2CHO$	(*S*)-**1**	(*R*)-proline	12 h	90:10	81	**4**
7	$(CH_3)_2CHCH_2CHO$	(*S*)-**2**	(*S*)-proline	16 h	90:10	83	**5**
8	$(CH_3)_2CHCH_2CHO$	(*R*)-**2**	(*S*)-proline	18 h	90:10	80	*ent*-**5**

[a] At rt, from 0.67 mmol of *β*-nitrostyrene in 2 mL of DMSO, with 2.5 equiv of aldehyde and 0.25 equiv of catalyst (proline). The reactions were quenched by addition of water when TLC indicated the disappearance of the starting nitroalkene (≈ 12 h), but they were usually stirred overnight. [b] Diastereomeric ratios in the crude products between diastereomers *RRS* and *SSS*; between *SSR* and *RRR* in entries 4 and 8. [c] Isolated yields of the major diastereomer after flash column chromatography.

The absolute configuration of **3**, the major stereoisomer from the reaction of 3-methylbutanal (isovaleraldehyde) with (*S*)-**1**, was supposed to be 2*R*,3*R*,4*S* rather than 2*S*,3*S*,4*S* on the basis of the known reactivity of 3-methylbutanal with *β*-nitrostyrene (to give major adducts with ^{i}Pr and Ph in *syn*).[1] It was confirmed by removal of the TBS group with methanol in the presence of pyridinium *p*-toluenesulfonate, which afforded one very major cyclic acetal. The observed nuclear Overhauser enhancements (NOESY) pointed to the structure depicted in Scheme 3. Coupling constants agree with those predicted by DFT calculations (see SI). The configurations of **4** and **5** were attributed by analogy, by comparison of their 1D and 2D NMR spectra with those of **3**.

Table 1 shows that: (a) the nitroalkene configuration determines the configuration of the final product ("dominates" over the proline configuration), in general; (b) the CHMe(OTBS) group afforded the highest stereoselectivity, so we used this substrate

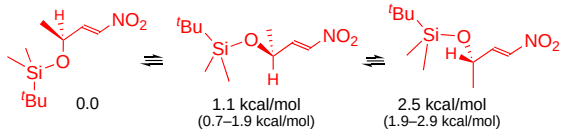
Scheme 3. Conversion of 3 into an Oxolane (THF) Derivative



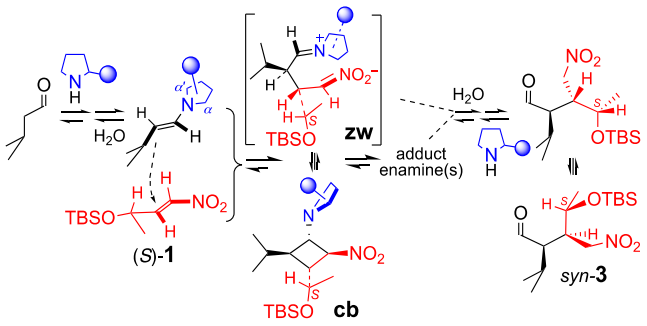
after this point; (c) despite the low concentrations of the reactive enamines in the corresponding enamine–oxazolidinone equilibria,[1] the reaction times were generally short (compared to many other aminocatalytic reactions); and (d) the difference between the supposed matched and mismatched cases was small.

A possible explanation of these observations, for the representative case of (*S*)-**1**, is as follows. The $^{3}J_{H2H3}$ and $^{4}J_{H1H3}$ values for **1** and its NOESY spectrum suggest the predominance in solution of the first of the three conformers of **1** shown in Scheme 4, in agreement with the calculated total energies at different levels (ωB97, M06-2X, MP2, and CCSD, see SI), also including the effect of polar solvents and an estimation of the Gibbs free energies.[9] As shown in Scheme 5, the main conformer of (*S*)-**1** may react through its less hindered face with the depicted face of the enamine conformer,[10] which is also the less sterically hindered. The small groups, such as COOH, however, cannot determine this approach: it does not matter if COOH is at position *α* (L-Pro) or at position *α*′ (D-Pro) of the pyrrolidine ring in Scheme 5, that is, there is no significant energy difference between the two conformers (s-*trans* and s-*cis*) of the starting *E*-enamine (SI). The reaction would afford the kinetically and thermodynamically preferred zwitterion (**zw**, the "ionic form", which is probably only significant in very polar solvents and which immediately reacts with water if present) and its corresponding all-*trans* cyclobutane (**cb**, the "covalent form" of **zw**, largely predominant in organic solvents), which isomerizes to the trisubstituted enamine(s), or adduct enamine(s), which are slowly hydrolyzed to **3** (*syn*-**3**).

Scheme 4. Relative Energies of the Conformers of (*S*)-1 at Different Levels of Theory. Mean Values are Given

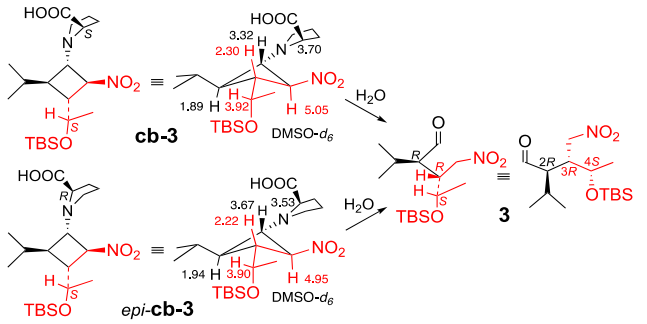


Scheme 5. Suggested Mechanism for the Formation of 3



The reaction of entry 1 in Table 1 was repeated under stoichiometric conditions, that is, by mixing equivalent amounts of aldehyde, nitroalkene, and L-Pro. A very major cyclobutane derivative was formed, which was readily characterized due to its cyclic structure (with diagnostic $^3J_{HH}$ = 7–9 Hz values for the hydrogen atoms of the cyclobutane) and which survived for hours in the NMR tube (in DMSO-d_6!, without any special precaution against moisture); analogous cyclobutane intermediates from β-nitrostyrene are quite unstable in polar solvents.[11] This relative stability allowed us to register NOESY, COSY, HSQC, and ^{13}C NMR spectra (**cb-3**, see Scheme 6 and SI). The configuration and main conformation of the major adduct **3** was thus confirmed.

Scheme 6. Compounds Characterized under Stoichiometric Conditions, from 3-Methylbutanal, (*S*)-1, and (*S*)- or (*R*)-Proline



Similarly, the major compound from the stoichiometric reaction related to entry 2 in Table 1 afforded another cyclobutane derivative, *epi*-**cb-3**. The addition of water and 3-methylbutanal to the NMR tubes, to favor the cleavage and hydrolysis of these cyclobutanes,[12] in both cases afforded **3** (*RRS*) and only trace amounts of a diastereomer.

Parallel results were obtained starting from (*R*)-**1** instead of (*S*)-**1**. As expected, the combination of (*R*)-**1** with (*R*)-proline led to *ent*-**cb-3** and the use of (*R*)-**1** and (*S*)-proline produced *ent-epi*-**cb-3**. Ring opening and hydrolysis of both gave *ent*-**3**.

Using (*S*)-**1** and pyrrolidine a very major cyclobutane was formed (**cb-3a**, see Figure 1), which was hydrolyzed as indicated above, to yield **3**. From (*R*)-**1** and pyrrolidine the same NMR spectra (of the cyclobutane intermediate, *ent*-**cb-3a**) were obtained. After hydrolysis, the product has the opposite optical rotation to that of **3**, that is to say, it turned out to be *ent*-**3**, as expected. These cyclobutanes could not be purified by *flash* column chromatography, as they were partially converted into **3**.

Catalysts other than proline and pyrrolidine were also studied, such as the popular Jørgensen–Hayashi catalyst (JH, 2-CPh$_2$-OTMS),[13a,b] the catalyst of Peng et al. (*O*-TBDPS-prolinol),[13c,d] and other chiral pyrrolidines (such as the bis-silylated 4-*cis*-hydroxyprolinol),[11a] to check whether the asymmetric induction caused by these pyrrolidines was greater or smaller than that induced by the chirality of nitroalkenes **1** and **2**.

To our surprise, none of the catalytic reactions tested by us with 3-methylbutanal and **1** or **2**, under standard conditions (nonpolar solvents, 0.2–0.3 equiv of catalyst and of PhCOOH) progressed: conversions lower than 30% were always observed after 24 h. Analysis of the reaction mixtures indicated that cyclobutanes were immediately formed and appeared to be quite resistant to the hydrolysis in non-polar solvents (as above mentioned, they are relatively more stable than those from β-nitrostyrene).

The reactions were thus repeated under stoichiometric conditions (3-methylbutanal/**1**/catalyst/PhCOOH in equimolar ratios). Within 20–60 min, the cyclobutanes depicted in Figure 1 were always the major products, in different solvents. That is, some experiments repeated in non-deuterated organic solvents, followed by careful evaporation, addition of $CDCl_3$ or C_6D_6, and registration of the NMR spectra, afforded the same results indicated in Figure 1. When (*R*)-**1** or "(*R*)-catalyst" was used, this stereodescriptor is indicated in the figures. For NOESY and other 2D NMR experiments see SI.

With (*S*)-**1** and methyl (*S*)-prolinate, a 3:1 mixture of cyclobutanes was obtained (which we called **cb-3b** and **cb-3c**, see Figure 1). When we used (*R*)-**1** instead, another 3:1 mixture of epimers was formed. Thus, it seems that the stereocenter on the nitroalkene and the CHCOOMe stereocenter exert a different

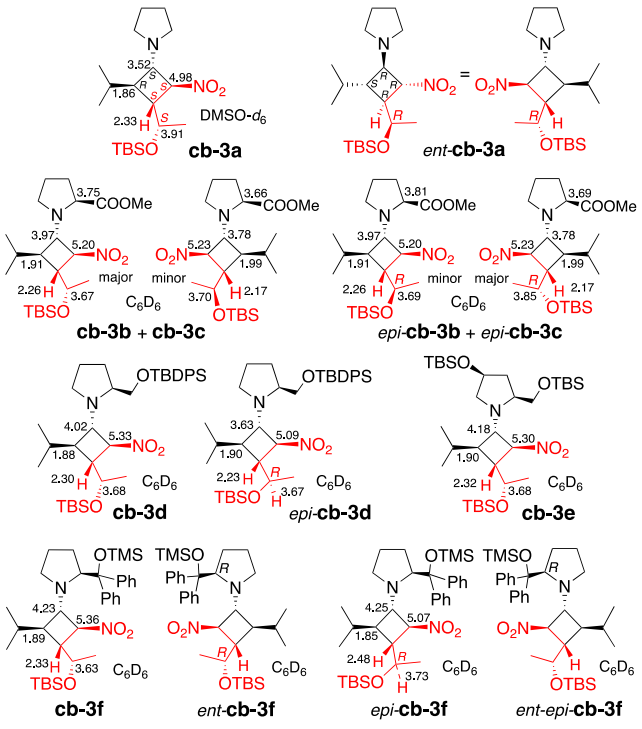
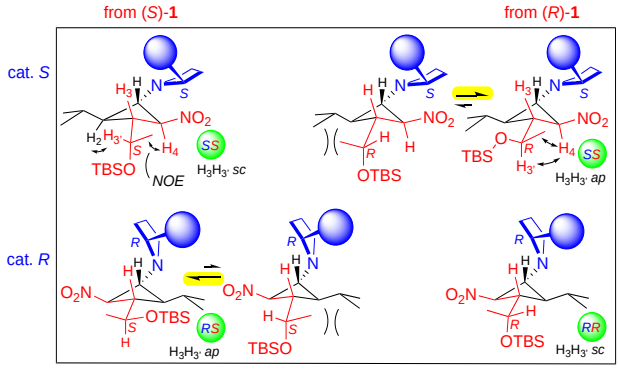


Figure 1. Relevant ^{1}H NMR signals of the series of new nitrocyclobutyl-pyrrolidine derivatives from 3-methylbutanal

effect, but of the same order of magnitude. Ring opening and hydrolysis of these pairs of diastereomers can only afford mixtures (*syn/syn'* mixtures), as we observed by NMR. This case has no practical interest.

In contrast, with the $CH_2OTBDPS$ group[13c,d] and (*S*)-**1**, the resulting cyclobutane was **cb-3d**, exclusively. With (*R*)-**1**, epimeric cyclobutane *epi*-**cb-3d**, with the NO_2 group on the right in Figure 1, was almost exclusively formed as well (signals due to other isomers were hardly observed by ^1H NMR). Thus, in the first case, the *S*-configuration catalyst and the (*S*)-CHMeOTBS group matched: they led to the formation of a cyclobutane with the NO_2 group on the right (in the figure). In the second case, supposedly mismatched, the effect of the catalyst predominated. Coupling constants and NOESY indicated that the main species were those shown in Scheme 7 (top row). It seems that the (*R*)-CHMeOTBS group (Scheme 7, bottom row) is not so well accommodated in the structure due to van der Waals repulsions and a loss of favorable polar interactions, and adopts a different lower energy conformation.

Scheme 7. Main Conformers of Cyclobutanes 3d–3f



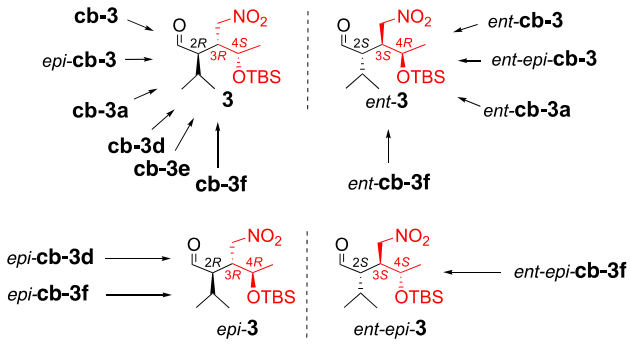
The addition of DMSO–H_2O–3-methylbutanal to the reaction vials allowed us to hydrolyze them at rt: **cb-3d** afforded **3**, a (2*R*,3*R*,4*S*)-pentanal derivative; *epi*-**cb-3d** yielded its 2*R*,3*R*,4*R*-epimer.

Cyclobutane **cb-3e**, which was formed as a stereopure sample from a bis-TBS prolinediol[11a] and (*S*)-**1**, confirmed the **cb-3d** case.

With the JH catalyst, we carried out the four possible independent reactions, by also using its commercially available enantiomer together with (*S*)- and (*R*)-**1**. In each experiment, only one stereoisomer was formed (see **cb-3f**, *ent*-**cb-3f**, *epi*-**cb-3f**, and *ent-epi*-**cb-3f** in Figure 1). The configuration of the chiral catalyst determined the final configuration of the cyclobutane intermediate (the asymmetric induction produced by this crowded secondary amine was much greater than that caused by a simple CHMeOTBS substituent). This was expected but it had to be demonstrated. The $^3J_{HH}$ coupling constants and NOESY spectra indicated that the main conformers were those shown in Scheme 7 (bottom row). Treatment of the contents of these four vials with DMSO–H_2O–$(CH_3)_2CHCH_2CHO$ at rt allowed us to obtain stereopure isomers **3** (2*R*,3*R*,4*S*), *ent*-**3** (2*S*,3*S*,4*R*), *epi*-**3** (2*R*,3*R*,4*R*), and *ent-epi*-**3** (2*S*,3*S*,4*S*), respectively. Thus, four stereopure products are accessible by using the same methodology, by combining appropriate *R* or *S* organocatalysts with *R* or *S* enantiopure nitroalkenes.

A summary of the chemical correlations or connections that we have experimentally established, by hydrolysis of the various nitrocyclobutanes to the corresponding nitrobutanals, is shown in Scheme 8.

Scheme 8. Summary of Chemical Correlations



Further examples, by using propanal, are shown in Figure 2. The reactions were carried out in NMR tubes. By mixing equivalent amounts of propanal, the JH catalyst, and (*S*)-**1** or (*R*)-**1**, nitrocyclobutanes **cb-6f** and *epi*-**cb-6f**, respectively, were rapidly formed. They were stable, at least in nonpolar solvents. Thus, the formation of nitrocyclobutanes seems to be general.

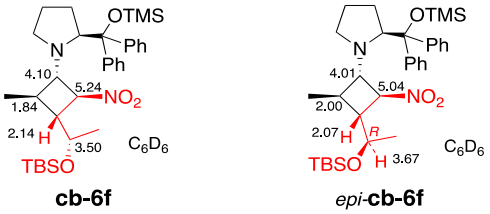


Figure 2. Nitrocyclobutylpyrrolidine derivatives from propanal

In conclusion, chiral nitro-alkenes are used for the first time in aminocatalyzed Michael additions. The reactions take place with substrate control (asymmetric induction) when proline and pyrrolidine were used. However, the Jørgensen–Hayashi and Peng catalysts clearly determine the stereochemical outcome of the reaction. Series of stereoisomers of chiral fragments can be made accessible by iteratively applying the procedure.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglet. .....

Preparation of chiral nitroalkenes, standard procedure for the addition of aldehydes to chiral nitroalkenes, relative energies of the conformers of **1**, reaction of cyclohexanone with (*S*)-**1**, nitro-Michael additions of cyclic ketones to (*S*)-**2**, NMR spectra of the new compounds, detection of nitrocyclobutanes by NMR (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Addition of water obviously helps to hydrolyze some final enamines that are apparently quite resistant and also increases the polarity of the medium (which relatively favors the zwitterionic and ionic species, more susceptible to hydrolysis). Addition of the starting aldehyde (a large excess of the starting aldehyde in the medium) shifts the hydrolysis equilibria to the right, by capturing part of the released secondary amine, resembling an exchange reaction. It may also favor the mixing of the two phases if the starting aldehyde has a small size (is partially miscible with water). For exchange reactions between enamines and carbonyl compounds, see: (a) Carneros, H.; Sánchez, D.; Vilarrasa, J. *Org. Lett.* **2014**, *16*, 2900. (b) Sánchez, D.; Bastida, D.; Burés, J.; Isart, C.; Pineda, O.; Vilarrasa, J. *Org. Lett.* **2012**, *14*, 536.

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