Direct Experimental Evidence for the Epimerization of Diastereoisomers in the Enantioselective Organocatalyzed Michael Addition of Acetoacetates to Nitroolefins

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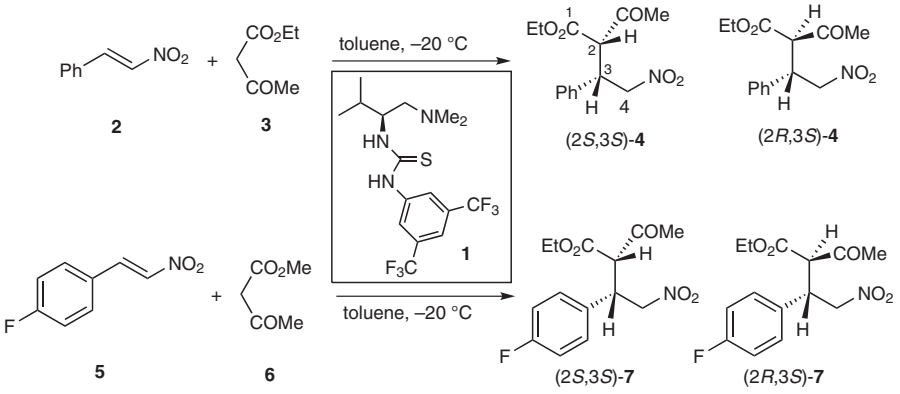
Abstract: The evolution of the addition of acetoacetates to nitrostyrene catalyzed by a bifunctional thiourea has been followed by ^{19}F NMR. The results show for the first time that the diastereoselectivity varies along the reaction time and that both the major and minor diastereoisomers epimerize in the presence of the catalyst.

Key words: asymmetric synthesis, epimerization, Michael addition, organocatalysis, thioureas

The conjugate addition of nucleophiles to electron-poor olefins is one of the most powerful reactions in organic synthesis because, in addition to the formation of carbon–carbon or carbon–heteroatom bonds, it allows the creation of up to three contiguous stereocenters.[1] Enantioselective organocatalytic transformations have been shown in the last decade as a useful tool to get enantioenriched addition products,[2] and one of the most studied reactions is the conjugated addition of carbonyl derivatives to β-substituted nitroolefins promoted by bifunctional thioureas. In that reaction it is possible to create one[3] or two contiguous stereocenters, depending on the prochirality of the carbonyl derivative.

In general, good to excellent enantioselectivities are obtained in the formation of a single stereocenter for addition of methyl ketones,[4] malonates,[5] 2-substituted malonates,[5a,6] and acetylacetone[7] to nitroalkenes promoted by chiral thioureas or guanidines. Very high ee values were also obtained in the construction of two adjacent stereocenters by the same methodology but, in that case, the diastereoselectivity was dependent on the prostereogenic nature of the methylene or methine groups acting as nucleophiles. For instance, good to excellent dr was obtained in the addition of unsymmetrical[4] and cyclic ketones,[8] or cyclic ketoesters[5a,9] but only moderate stereoselection was observed in the addition of acyclic 2-substituted β-keto esters to nitrostyrene.[9d,10] In contrast, excellent enantioselectivity, but low or no diastereoselection was reported for the reaction of the same olefin with unsubstituted β-keto esters.[5a,11] These differences have been explained on the basis of the stereochemical lability of the tertiary stereocenter owing to the acidity of the hydrogen attached to a carbon bearing two different electron-withdrawing groups but, to the best of our knowledge, there are no data supporting that fact.

Now we report here our results on the stereoselective Michael addition of ethyl acetoacetate and methyl acetoacetate to *trans* nitrostyrene and *trans* 4-fluoro nitrostyrene respectively by using valine-derived thiourea **1** as bifunctional organocatalyst.[5e,9d] The reaction of a 0.5 M solution of nitrostyrene (**2**) in toluene with two equivalents of ethyl acetoacetate (**3**), for four hours at –20 °C in the presence of 10 mol% of **1**, yielded 99% of the addition products as a mixture 54:46 of diastereoisomers (2*S*,3*S*)-**4** and (2*R*,3*S*)-**4**.[12] Under these conditions, the diastereose-



Scheme 1 Addition of acetoacetates to nitrostyrenes catalyzed by thiourea **1**

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lection was very poor but the enantioselection was excellent because both diastereoisomers were obtained in 96:4 enantiomeric ratio. The reaction was scaled up to 4 mmol by using only 2 mol% of catalyst **1** obtaining the same results but at the expense of increasing the reaction time to 48 hours.

Interestingly, the temperature plays an important role in both the reaction rate and the diastereoselectivity. At room temperature the reaction led to a mixture (1.4:1) of diastereoisomers in 62% yield after stirring for 70 minutes. The same yield but an increase of the diastereoselectivity to 2.8:1 was obtained if the reaction was carried out at –20 °C for 130 minutes. The comparison of the last data with those obtained after four hours of reaction indicates that the diastereoselectivity also decreases with the time, pointing to the epimerization of the addition products under the reaction conditions.

To test that fact, we decided to study the evolution of the reaction mixture by ^{19}F NMR spectroscopy because the ^{1}H NMR spectra were too complex to determine the diastereomeric ratios in the mixtures accurately. The reaction of *trans*-4-fluoronitrostyrene (**5**) with two equivalents of methyl acetoacetate (**6**) was chosen as the model reaction (Equation 2 in Scheme 1), and we first tested whether the fluoro nitroolefin behaves in a similar way as nitrostyrene, because under the same conditions (0.5 M toluene solution, –20 °C, 4 h) a mixture (58:42) of diastereoisomers (2*S*,3*S*)-**7** and (2*R*,3*S*)-**7** was formed in 98% yield in excellent 96:4 enantiomeric ratio for both of them. To study the evolution of the reaction, 0.15 mmol of **4**, 0.30 mmol of **5** and 0.015 mmol of thiourea **1** was dissolved in 0.6 mL of toluene-d_8 (0.25 M solution with respect to the nitroolefin) and $CFCl_3$ as internal standard in an NMR tube, and monitored by ^{19}F NMR at 253 K (Figure 1).[13]

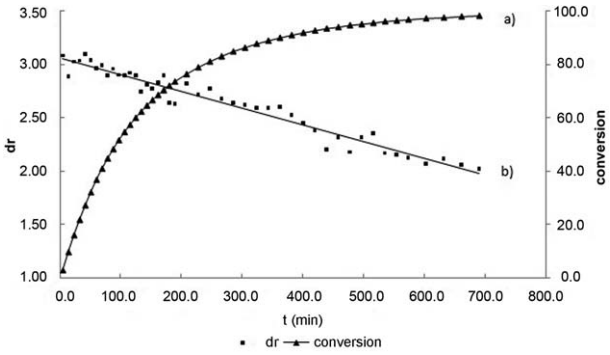


Figure 1 Evolution of the conversion (a) and dr (b) of the reaction of *trans*-4-fluoro-β-nitrostyrene with methyl acetoacetate catalyzed by thiourea **1**

Figure 2 shows part of some representative ^{19}F NMR traces that indicate the evolution of the reaction mixture along the time. In these spectra, the signal at δ = –106.8 ppm corresponds to *trans*-4-fluoro-β-nitrostyrene, whereas the signals at δ = –113.3 and –113.5 ppm correspond to (2*S*,3*S*)-**7** and (2*R*,3*S*)-**7**, respectively.

In fact, after 60 minutes of reaction, a 3.0:1 mixture of diastereoisomers was formed in 37% yield (trace 1), but the

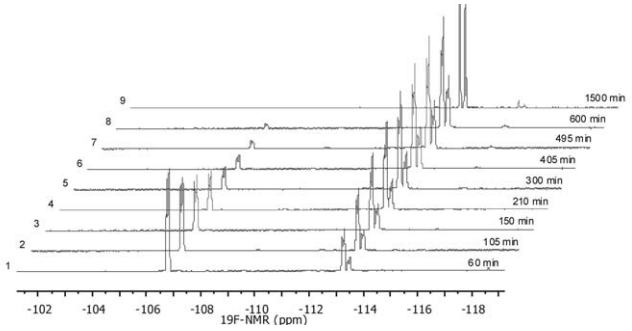
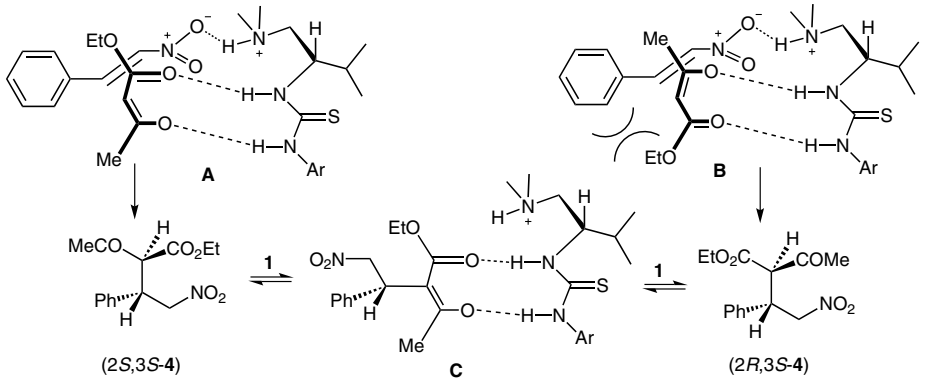


Figure 2 ^{19}F NMR traces of the reaction mixture of *trans*-4-fluoro-β-nitrostyrene with methyl acetoacetate catalyzed by thiourea **1**

diastereoselection diminished over time, and only a 2.1:1 mixture of epimers was obtained after consumption of the nitroolefin (about 600 min, trace 8). Interestingly, if the reaction mixture was left standing for a long period of time (1500 min) practically total epimerization occurred and the diastereoisomers were obtained in near equimolar ratio (trace 9). Interestingly, an equimolar mixture of epimers was obtained when the pure minor diastereoisomer (2*R*,3*S*)-**4** was dissolved in chloroform and stirred in the presence of a catalytic amount of **1**, but remained unchanged after six days in chloroform solution in the absence of the catalyst. An additional important fact is that the enantioselectivity of the reaction did not change along the reaction, because chiral HPLC analysis of the reaction mixtures at different times showed that the enantiomeric ratio in all cases varied from 95:5 to 96:4 for both diastereoisomers.[13]

Although diastereoisomers **4** had been previously described,[5a,14] only the absolute configuration at C-3 was unequivocally determined, and no information about the configuration at C-2 had been provided. It was necessary to know the geometry of both diastereoisomers, and fortunately we have now been able to obtain the relative stereochemistry by X-ray diffraction analysis[13] of the racemate and assigned the absolute configuration as (2*R*,3*S*)-**4** for the minor diastereoisomer. Then, the stereochemistry of diastereoisomers **7** was assigned by extension of that of compounds **4**.

The reaction has been previously well studied from both the chemical[5a] and computational[11b,15] points of view, and the generally accepted mechanism supposes a dual activation of the reagents by the catalyst leading to a ternary complex (Scheme 2). In our case, the stereochemistry of the addition products could be explained by accepting that, after deprotonation of the acetylacetonate by the amine group, the nitrostyrene derivative is coordinated by the protonated amino group while the anion is stabilized by the hydrogen donors of the thiourea moiety. The major diastereoisomer (2*S*,3*S*)-**4** will be formed from the ternary complex **A**, whereas complex **B**, less stable by steric interactions, will be the responsible of the formation of the minor (2*R*,3*S*)-**4** isomer. Once formed, the mixture of diastereoisomers equilibrates in the presence of the catalyst through the enolate **C**. That enolization, in both α-po-



Scheme 2 Models for the formation of diastereoisomers and epimerization in the presence of catalyst **1**

sitions of the carbonyl and the nitro groups, has been previously observed by us in some related reactions.[16]

Alternatively, although adducts **4** and **7** are very prone to be deprotonated and form enolates, an enol-mediated epimerization pathway might also be suggested, which would involve the activation of the enol of the corresponding adduct by both the amino group and the thiourea moiety of the catalyst, as previously proposed for different reactions.[17]

In summary, the described results showed that the diastereoselection in the addition of prochiral dicarbonyl compounds to nitroolefins is dependent on a series of experimental parameters, especially on the reaction time. Only a careful control of the reaction evolution could get acceptable diastereomeric ratios.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **(3*S*)-Ethyl 2-Acetyl-4-nitro-3-phenylbutanoate (4)**: To a stirred solution of *trans*-β-nitrostyrene (**2**; 0.30 mmol, 45.6 mg) and catalyst **1** (0.03 mmol, 12.0 mg) in toluene (0.6 mL) was added ethyl acetoacetate (**3**; 0.60 mmol, 0.08 mL) at –18 °C. The reaction mixture was stirred until disappearance of the nitroolefin (observed by TLC). The solvent was removed in vacuo and the residue was purified by flash chromatography (hexane–EtOAc, 20:1 to 15:1 as eluent) to afford the desired product **4** (0.30 mmol, 83 mg, 99% yield, 54:46 dr, 96:4 er).
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