JOC The Journal of Organic Chemistry

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Anti-Selective Organocatalytic Michael Addition between Phenylacetaldehyde and Nitrostyrene

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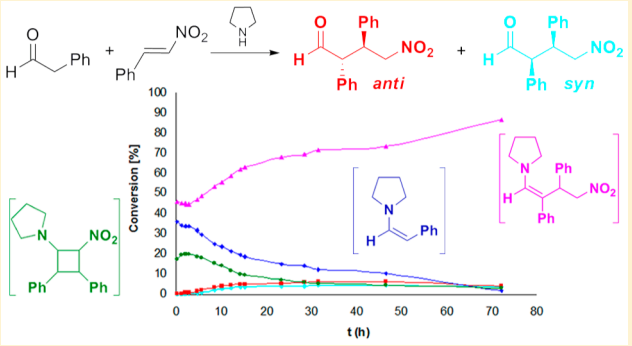
Supporting Information

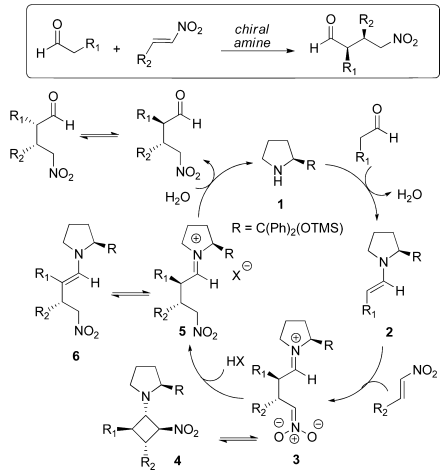
ABSTRACT: Using the reaction between phenylacetaldehyde and nitrostyrene catalyzed by pyrrolidine as a simple model, we have studied the diastereochemical outcome of the organocatalytic Michael reactions between benzylic aldehydes and nitrostyrenes. We found that the *anti* adduct was obtained in high yield and diastereoselection as was demonstrated by the X-ray structure of the product. *In situ* NMR studies showed a different reaction pathway when compared to aliphatic aldehydes that yield the *syn* adduct as major isomer.



The stereoselective conjugate addition of chiral enamines to prochiral nitro alkenes to provide γ-nitro carbonyl derivatives is widely recognized as a powerful tool to install two adjacent stereogenic centers with high enantio- and diastereoselectivity using a wide range of substrates. In fact, the organocatalytic version has become a benchmark reaction for assessing new catalysts performance[1,2] as well as for the development of cascade reaction sequences.[3−5] Accordingly, many new organocatalysts displaying high *syn* diastereo- and enantioselectivity were developed.[6−8] Among them, the silylated diphenylprolinol **1** proved to be particularly efficient (Scheme 1).

The diastereochemical outcome of the reaction has been generally rationalized assuming Seebach model that postulates the attack of an enamine nucleophile to a Michael acceptor. The *syn* selectivity is explained according to a preferential acyclic synclinal transition state, where there are favorable electrostatic interactions between the enamine nitrogen atom and the nitro group in the transition state.[9] Recent studies have shed light on the mechanism of the catalytic process, but some controversy regarding the reaction route still remains.[10−13] For the case of monosubstituted nitro olefins, *in situ* NMR spectroscopy, reaction calorimetry, and crystallographic studies showed that cyclobutane species **4** are formed rapidly at the onset of the reaction most likely through a zwitterionic intermediate **3**. At higher conversions, product enamine **6** becomes prevalent and thus, erosion of the diastereoselectivity is observed (Scheme 1).

Scheme 1. Organocatalyzed Conjugate Addition of Aldehydes to Nitro Olefins



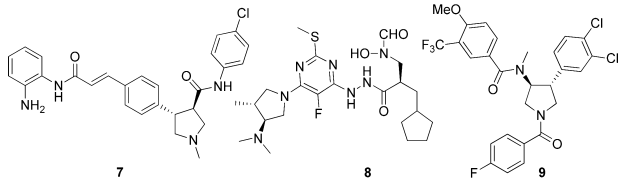
The simplicity and mildness of reaction protocol and the opportunity for further elaboration of γ-nitro carbonyl derivatives into valuable building blocks represents an important synthetic transformation that allows for the preparation of many products in a diastereo- and enantioselective manner. A remarkable example is the synthesis of anti-

Received: May 6, 2016
Published: July 21, 2016

DOI: 10.1021/acs.joc.6b01061
J. Org. Chem. 2016, 81, 7952−7957

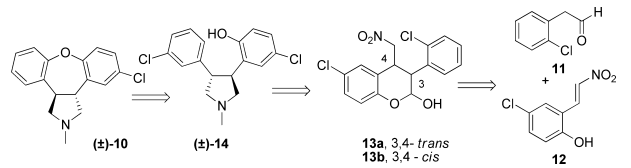
influenza drug (−)-Oseltamivir,[14,15] developed by Hayashi and co-workers. In addition to cascade reaction, its synthetic versatility has been applied for the synthesis of γ-butyrolactones and 3,4-disubstituted pyrrolidines that are common structural units of natural products[6] and pharmaceutically relevant compounds, such as the histone deacethylase inhibitor **7** developed by Roche,[16] the bacterial peptide deformylase inhibitor **8**,[17] and the NK2 receptor antagonist **9** (Scheme 2).[18]

Scheme 2. Pharmaceutically Relevant Compounds with *trans* 3,4-Disubstituted Pyrrolidine Moiety



When designing an original synthetic route toward antipsychotic drug (±)-Asenapine (**10**), we envisioned that an organocatalyzed Michael addition between known aldehyde (**11**) and nitrostyrene (**12**) could be used as key step for the installation of the required substitution pattern at its central disubstituted *trans*-pyrrolidine ring in a diastereoselective fashion through the *cis* hemiacetal **13b** (Scheme 3).

Scheme 3. Retrosynthetic Strategy Toward (±)-Asenapine (10)

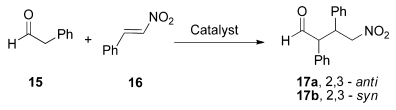


Surprisingly, under all conditions assayed, we obtained diastereomeric mixtures favoring the *trans* isomer **13a**, derived from the *anti* Michael adduct after spontaneous hemiacetal formation.

The stereochemical outcome was different than that observed for aliphatic aldehydes during this type of cascade reactions.[4] The desired hemiacetal product was isolated as a 5:1 diastereomeric mixture favoring the *trans* isomer **13a** as deduced from its crystal structure (Figure S1). This result showed that in this case, the Michael addition preferentially yielded the *anti* adduct.

Despite extensive studies on aliphatic aldehydes, very few reports have addressed α-unsubstituted benzylic aldehydes as substrates.[19−23] So, in order to understand this result, we studied the reaction between commercially available phenylacetaldehyde (**15**) and nitrostyrene (**16**) as a simple model in more detail (Scheme 4). In the case of **15**, reported results showed low *syn* diastereo- and enantioselectivity when compared to the aliphatic counterparts.

Scheme 4. Organocatalytic Reaction between Phenylacetaldehyde (15) and Nitrostyrene (16)



We first optimized reaction conditions. As the starting point, we employed toluene as solvent, 0.5-fold excess of aldehyde,[24] and a quantitative clean reaction occurred in the presence of 20 mol% of pyrrolidine as organocatalyst. There was no need to use a large excess of aldehyde as no competing aldol pathways were observed.[1,6,19,25] Then, the effect of solvent nature on reaction performance was established. A high diastereoselection was observed in most cases with only a small variation on the product diasteriomeric ratio. In contrast, reaction rate was strongly modulated by the solvent. Overall, toluene gave the best results, smooth reaction occurred to generate the Michael adduct in high conversions (≥99%) and excellent diastereoselectivities (dr = 98:2) (Table S1). We then explored the influence of catalyst's nature on diastereoselection and reaction rate (Table S2). So, we tested different secondary amines as organocatalysts. Pyrrolidine and 3-pyrrolidinol gave the best results in terms of both diastereoselection and conversion. Consequently, pyrrolidine was selected for further studies due to its wider availability. When the catalyst loading was reduced, the diastereoselection was affected and low conversion was observed within the same reaction period (Table S3).

Once the best reaction conditions were established, the reaction was scaled up and the products were characterized in detail. No variations in conversion and in diastereoselection were observed during this process and we were able to perform the reaction in a 36 mmol scale with excellent results. The NMR spectroscopic data of the major diastereomer obtained was in accordance with that already described for the *syn* diastereomer[19−23] but, surprisingly, when the absolute relative configuration was established through X-ray diffraction the major product was identified as the *anti* isomer **17a** (Figure S2).

This result unequivocally shows that, in contrast to the generally observed trend, the major diastereomer obtained by the Michael reaction between **15** and **16** under our optimized experimental conditions was *anti*. So, in this case, the course of the reaction does not follow the stereochemical pathway predicted by Seebach model. At least two possible explanations could be given both related to the more acidic nature of phenylacetaldehyde's α protons. First, an alternative mechanism involving deprotonation by pyrrolidine to give an enolate favoring the *anti* product could be postulated. Second, the higher thermodynamic stability of the conjugated product enamine **18** could favor its formation over the hydrolysis of the corresponding iminion ion of type **5** again favoring the formation of the *anti* adduct. In this regard, we observed that *anti* **17a** is favored at higher conversions (Tables S3, entries 2, 3, and 4) while *syn* **17b** is formed preferentially at lower conversions (Table S3, entry 1) suggesting that the *anti* nitro aldehyde **17a** might be the thermodynamic product.

Therefore, in order to see if the enolate mechanism was active, we tried the same reaction but using triethylamine instead of pyrrolidine as catalyst. In this case, in spite of the usually observed difficulty of generating enols or enolates from naked aldehydes,[26] a clean reaction took place and the desired Michael adduct **17** was obtained as a 94:6 diastereomeric mixture favoring the *anti* isomer **17a** in quantitative yield.

For the sake of comparison, we tested our experimental set of conditions on *n*-hexanal (**19**) as a model of aliphatic aldehydes. In accordance with published data,[1,27,28] the reaction proceeded cleanly favoring the *syn* adduct **20b** (dr 62:38). In this case, when pyrrolidine was replaced by triethylamine no reaction was observed, indicating that the enolate pathway was not relevant.

DOI: 10.1021/acs.joc.6b01061
J. Org. Chem. 2016, 81, 7952−7957

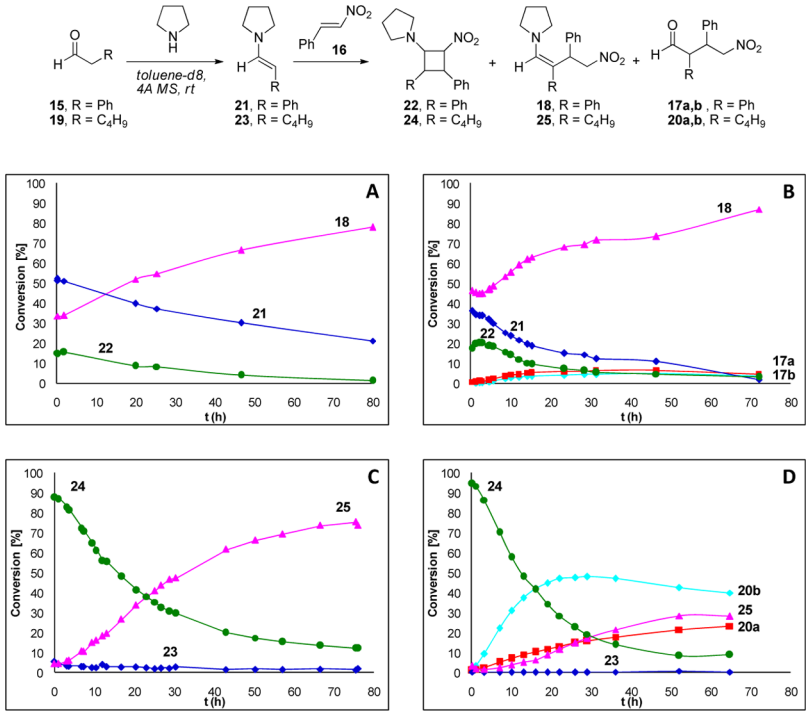


Figure 1. (A) Michael addition between **15** and **16** in the presence of an equimolar amount of pyrrolidine (ratio 1:1:1). The reaction was carried out in an NMR tube: an equimolar amount of **16** was added to a suspension of preformed enamine **21** in the presence of 4 Å molecular sieves in toluene-d_8. (B) Idem A but without 4 Å molecular sieves. (C) Michael addition between **19** and **16** in the presence of equimolar amount of pyrrolidine (ratio 1:1:1). The reaction was carried out in an NMR tube: an equimolar amount of **16** was added to a suspension of preformed enamine **23**, in the presence of 4 Å molecular sieves in toluene-d_8. (D) Idem C but without 4 Å molecular sieves.

With the aim of gaining understating on the reaction pathway when pyrrolidine was used as organocatalyst, several ^{1}H NMR experiments were performed. Recent mechanistic studies on reactions between aliphatic aldehydes and nitrostyrenes catalyzed by diaryl prolinol ethers[12,24,29] have identified four (cyclobutane, CB) and six (oxazine *N*-oxides)-membered cyclic intermediates that play a central role in the reaction cycle. These species are formed via [2+2] or [4+2] cycloadditions between the enamine and the nitroalkene, respectively. Therefore, we hypothesized that if we were able to detect the presence of one of these intermediates for the model in study, we could show that this mechanism was active. Consequently, NMR experiments in stoichiometric conditions that would give us evidence about possible intermediates of the organocatalytic process were designed. In fact, the use of stoichiometric model reactions proved to be a useful tool for the recognition of key steps and for the understanding of the stereochemical courses of the catalytic process.[11] First, we examined the formation of enamine **21** from equimolar amounts of phenylacetaldehyde and pyrrolidine in the presence of molecular sieves that prevents enamine hydrolysis. Indeed, **21** was formed quantitatively in less than 20 min. So, an equimolar amount of nitrostyrene was then added and the formation of the products and the intermediates were monitored (Figure 1A). After 10 min, only a maximum ca. 15% of cyclobutane **22** was detected that then decayed while product enamine **18** grew. We were not able to isolate the cyclobutane intermediate because of its low concentration and stability. Nonetheless, ^{1}H NMR spectra of the stoichiometric reaction showed signals that share the same pattern with those previously described.[24] Moreover, as previously observed for the case of monosubstituted nitro olefins, no oxazine *N*-oxides were detected.

The same NMR experiment was made without molecular sieves in order to study the formation of cyclobutane versus Michael adducts (Figure 1B). In this case, an initial low concentration of cyclobutane **22** (ca. 20%) was observed while the emergence of product enamine **18** was predominant. The amount of Michael adducts **17a** and **17b** was low, indicating that deprotonation of the corresponding iminium ion intermediate to give conjugated enamine **18** was much more rapid than the nucleophilic attack on the iminiun C atom to give **17**.

Again, we performed the same sequence of NMR experiments on an aliphatic aldehyde (*n*-hexanal, **19**). In the presence of molecular sieves, we observed the spontaneous, fast, and almost quantitative formation of cyclobutane intermediate **24** that then gradually converts into product enamine **25** (Figure 1C). Similar profiles have been reported for others aliphatic aldehydes.[12,24,29,30] The structure of cyclobutane **24** was confirmed by 2D NMR experiments (Supporting Information). Lastly, in the absence of molecular sieves, the Michael addition between *n*-hexanal and nitrostyrene yielded cyclobutane **24** almost quantitatively (95% maximum) at the beginning of the reaction and it then gradually decreased while Michael adducts **20a,b** and product enamine **25** increased. In contrast to what we have observed for phenylacetaldehyde, in the case of *n*-hexanal, the rate of formation was higher for the *syn* Michael adduct **20b** than for product enamine **25** (Figure 1D). So, NMR data confirms the typical reaction behavior for these kind of aldehydes and suggests that the different results obtained were only inherent to aldehydes nature. Indeed, a remarkable difference in the rate of product enamine formation was observed between both cases. As already mentioned, enamine **18** grows fast during the first hours of the reaction and is

DOI: 10.1021/acs.joc.6b01061
J. Org. Chem. 2016, 81, 7952−7957

indeed the major product over Michael adducts **17a** and **17b** at any time. On the contrary, in case of *n*-hexanal, the major product observed since the beginning of the reaction is the *syn*-Michael adduct **20b** and only at higher conversions values, product enamine **25** concentration increases. Other important difference observed is that for the benzylic aldehyde, the *anti* adduct **17a** is always formed preferentially over the *syn* isomer **17b**, whereas for *n*-hexanal, the *syn* isomer **20b** is prevalent at all conversion values.

It is well documented that acid additives play an important role in accelerating the enamine-mediated Michael reactions.[24,31,32] So, we also studied its influence on our simple model. When phenylacetaldehyde was used as substrate, no rate acceleration (in fact the reaction was slower) and no changes in the diastereochemical outcome were observed. In contrast, in the case of *n*-hexanal, the reaction was complete within 50 min, more than three times faster than without the additive. These results add further evidence that for phenylacetadehyde both mechanisms are active (Table S4).

In conclusion, we have shown that the Michael reaction between benzylic aldehydes and nitrostyrenes derivatives afford the *anti*-product with high diastereoselection as demonstrated by its X-ray structures. From the NMR experiments, we can conclude that in the case of phenylacetaldehyde the organocatalytic reaction does not show the typical profile. Under stoichiometric conditions, the cyclobutane intermediate is formed in a relative low ratio during the initial phase of the reaction. The major product is the conjugated enamine **18** that facilitates, as it is well documented,[11,30] the erosion of the diastereomeric ratio yielding the thermodynamic *anti* adduct **17a**. On the contrary, in the case of *n*-hexanal, the cyclobutane **24** is formed quantitatively and the *syn*-Michael adduct **20b** is formed preferentially over the corresponding product enamine **25**. These results evidence the different reaction pathways that are prevalent in each case. For benzylic aldehydes two mechanisms are likely to be coexisting. The occurrence of the enolate mechanism was demonstrated by the experiment where triethylamine was used as catalyst and by the different reaction profiles observed in the NMR experiments. On the other hand, the presence of cyclobutane **22** evidenced the enamine-mediated reaction route. Moreover, the effect of an acid additive further proves the differences in reaction pathways in agreement with the idea that probably not a single catalytic cycle could be postulated for different reactants.[11] The important factor that may be governing the diastereochemical outcome is the major thermodynamic stability of conjugated product enamines derived from benzylic aldehydes that yield toward the *anti* Michael adducts as was exemplified by **18**. Further work could probably lead to the development of new asymmetric versions of antiselective Michael additions.

EXPERIMENTAL SECTION

General. All reactions were carried out under an atmosphere of argon. Solvents were purified by standard procedures and distilled before use. Reagents and starting materials obtained from commercial suppliers were used as received unless otherwise stated. TLC was performed on 0.2 mm silica gel 60 F254 aluminum supported plates. Detection was effected by exposure to UV light or by spraying with 5% (v/v) sulfuric acid in EtOH and charring. Mass spectra were recorded on a GCMS mass spectrometer operating at 70 eV ionizing energy. NMR spectra were recorded on a 400 MHz instrument, and chemical shifts of protons are reported in parts per million downfield from tetramethylsilane and are referenced to the proton resonances of the solvent or TMS. The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. Chemical shifts of carbon are referenced to the carbon resonances of the solvent.

General Procedure for the Organocatalytic Michael Addition between Aldehydes and Nitrostyrenes. To a stirred solution of aldehyde (0.45 mmol) and nitrostyrene (0.30 mmol) in solvent (0.3 mL), catalytic amine (x mol%) was added. The reaction mixture was stirred at room temperature. After complete consumption of the nitrostyrene (as monitored by TLC), aq. 1 M HCl (1 mL) was added. The mixture was stirred for 10 min at room temperature and extracted with ethyl acetate (3 × 3 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed *in vacuo*.

*6-Chloro-3-(2-chlorophenyl)-4-(nitromethyl)chroman-2-ol (**13**).* Prepared from 5-chlorophenylacethaldehyde (**11**) and nitrostyrene derivative (**12**), catalytic pyrrolidine (20 mol%), and toluene as solvent according to general procedure. Starting materials **11**[33] and **12**[34] were synthesized from commercially available compounds following published procedures. ^{1}H NMR of the crude showed a mixture of two diastereomers (83:17) each one as a mixture of anomers. The two diastereomers could be separated by column chromatography and analyzed by NMR. After flash column chromatography purification (hexane to 10% EtOAc in hexanes), the major product **13a** was isolated in 79.5% yield (558 mg) as pale yellow crystals: mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60−6.85 (m, 7 H), 5.71 (s, 0.2 H, minor anomer), 5.59 (s, 0.8 H, major anomer), 5.13 (dd, 0.2 H, J = 13.1, 7.8 Hz), 4.81 (dd, 0.2 H, J = 13.1, 6.3 Hz), 4.57 (m, 1.6 H), 4.31 (m, 0.8 H), 4.04 (d, 0.8 H, J = 12.1 Hz), 3.92 (s, 0.2 H), 3.87 (t, 0.2 H, J = 7.1 Hz), 3.30 (d, 0.2 H, J = 3.3 Hz), 3.08 (d, 0.8 H, J = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.6, 149.5, 136.0, 135.5, 134.0, 133.5, 130.1, 130.0, 129.7, 129.6, 129.4, 128.6, 127.8, 127.6, 127.5, 127.1, 126.9, 126.4, 123.3, 121.0, 119.4, 119.3, 93.4, 91.8, 80.5, 77.2, 41.2, 40.3, 36.5, 33.8; MS (EI) m/z (relative intensity) 353.05 (M^+, 17.37), 306.05 (11.49), 291.05(10.79), 195.00 (12.62), 165.05 (13.07), 154.00 (100), 125.00 (83.66), 91.10 (53.01), 89.05 (51.58); Anal. Calcd for $C_{16}H_{13}Cl_2NO_4$: C, 54.26; H, 3.70; N, 3.95. Found: C, 53.93; H, 3.80, N, 3.77.

*Anti-4-nitro-2,3-diphenylbutanal (**17a**) and syn-4-Nitro-2,3-diphenylbutanal (**17b**).* Compounds **17a** and **17b** were prepared from phenylacethaldehyde (**15**) and nitrostyrene (**16**) and catalytic pyrrolidine (20 mol%) and toluene as solvent according to general procedure. ^{1}H NMR of the crude mixture showed a dr (*anti*:*syn*) = 96:4. After flash chromatography (hexanes to 5% EtOAc in hexanes), the diastereomeric mixture (*anti*:*syn*, 96:4) was isolated as a white solid (80.5%, 7.60 g). Pure translucent white crystals corresponding to the major isomer could be selectively isolated from a chloroform solution; mp 157−160 °C, lit.[19] 168−171 °C. Compound **17a** (*anti* major isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.56 (d, 1 H, J = 2.2 Hz), 7.45−7.25 (m, 10 H), 4.49 (dd, 1 H, J = 10.3, 12.8 Hz), 4.39 (dd, 1 H, J = 4.4, 12.8 Hz), 4.30 (dt, 1 H, J = 4.4, 10.3 Hz), 4.07 (dd, 1 H, J = 2.0, 10.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 196.8, 137.0, 132.3, 129.8, 129.4, 129.1, 128.9, 128.2, 128.1, 78.4, 61.6, 44.3. Compound **17b** (*syn* isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.75 (d, 1 H, J = 1.1 Hz), 7.74−6.95 (m, 10 H), 4.92 (dd, 1 H, J = 5.2, 12.6 Hz), 4.78 (dd, 1 H, J = 8.8, 12.6 Hz), 4.26 (dt, 1 H, J = 5.5, 9.3 Hz), 4.01 (dd, 1 H, J = 0.9, 9.2 Hz).

*(2-Nitro-1-phenylethyl)hexanal (**20**).* Compound **20** was prepared from hexanal, nitrostyrene, and catalytic pyrrolidine (20 mol%) and toluene as solvent according to general procedure. The reaction mixture was stirred at room temperature for 20 h. Compound **20** was isolated as a colorless syrup (62:38 *syn*/*anti* diastereomeric mixture, 89%, 633 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.71 (d, 0.62 H, J = 2.8 Hz, *syn* isomer), 9.48 (d, 0.38 H, J = 3.0 Hz, *anti* isomer), 7.41−7.14 (m, 5 H), 4.84−4.75 (m, 0.76 H, *anti* isomer), 4.73−4.61 (m, 1.24 H, *syn* isomer), 3.86−3.72 (m, 1 H), 2.70 (m, 0.62 H, *syn* isomer), 2.61 (m, 0.38 H, *anti* isomer), 1.76−1.10 (m, 6 H), 0.90 (m, 1.14 H), 0.78 (t, 1.86 H, J = 6.7 Hz).[28]

NMR Analysis of Reaction Intermediates under Stoichiometric Conditions. *Reaction between Phenyl Acetaldehyde (**15**) and Nitrostyrene (**16**).* A NMR tube was charged with phenylacetaldehyde (**15**, 7 μL, 0.06 mmol), MS (4 Å), pyrrolidine (5 μL, 0.06

DOI: 10.1021/acs.joc.6b01061
J. Org. Chem. 2016, 81, 7952−7957

mmol), and toluene-d_8 (500 μL) under argon atmosphere. The suspension was shaken and this time was taken as time zero. Enamine formation was monitored by NMR. After 10 min, the ^{1}H NMR spectra showed total conversion to enamine **21** (lit.[35]): ^{1}H NMR (400 MHz, toluene-d_8) δ ppm 7.21−7.10 (m, 5 H), 6.84 (d, 1 H, J = 13.9 Hz), 6.93 (m, 1 H), 5.14 (d, 1H, J = 13.9 Hz), 2.83 (m, 4 H), 1.50−1.36 (m, 4H). At this point, 100 μL of a 0.6 M (toluene-d_8) fresh stock solution of nitrostyrene (**16**) was added. After the mixture was shaken, NMR recordings were run until no further changes were observed in the reaction profile.

Cyclobutane 22, 1-(2-Nitro-3,4-diphenylcyclobutyl)-pyrrolidine. ^{1}H NMR (400 MHz, toluene-d_8) δ (ppm) 7.17−6.76 (m, 10 H), 4.85 (dd, 1 H, J = 7.2, 8.7 Hz), 3.88−3.91 (m, 1 H), 3.65 (dd, 1 H, J = 7.2, 8.7 Hz), 2.98 (m, 1 H), 2.31 (m, 4 H), 1.50−1.36 (m, 4 H)); ^{13}C NMR (100 MHz, toluene-d_8) δ (ppm) 140.33 (C), 138.9 (C), 132.9−126.3(CH), 84.8 (CH), 69.8 (CH), 51.6 (CH_2), 48.9 (CH), 47.7 (CH), 26.6 (CH_2).

Product Enamine 18, (*E*,*Z*)-1-(4-Nitro-2,3-diphenylbut-1-enyl)pyrrolidine. *E*/*Z* mixtures were observed during the course of the reaction. ^{1}H NMR signals were assigned based on 2D spectra. Compound **18a**: ^{1}H NMR (400 MHz, toluene-d_8) δ (ppm) 7.42−6.89 (m, 10 H), 6.88 (s, 1 H), 4.28 (m, 1 H), 3.90 (m, 2 H), 2.15 (m, 4 H), 1.15−1.36 (m, 4 H); ^{13}C NMR (100 MHz, toluene-d_8) δ (ppm) 141.5 (C), 140.4 (C), 132.9−126.3(CH), 137.0 (C), 108.9 (C), 79.3 (CH_2), 52.51 (CH), 52.49 (CH_2), 26.2 (CH_2). Compound **18b**: ^{1}H NMR (400 MHz, toluene-d_8) δ (ppm) 7.42−6.89 (m, 10 H), 6.07 (s, 1 H), 4.37 (m, 2 H), 4.13 (dd, 1 H, J = 4.7, 9.7 Hz), 2.56 (m, 4 H), 1.19 (m, 4 H); ^{13}C NMR (100 MHz, toluene-d_8) δ (ppm) 141.7 (C), 138.2 (C), 132.9−126.3 (CH), 133.3 (C), 108.9 (C), 80.5 (CH_2), 67.5 (CH), 52.1 (CH_2), 26.3 (CH_2).

*Reaction between Hexanal (**19**) and Nitrostyrene (**16**).* A NMR tube was charged with hexanal (7.4 μL, 0.06 mmol), MS (4 Å), pyrrolidine (5 μL, 0.06 mmol), and toluene-d_8 (500 μL) under argon atmosphere. The suspension was shaken and this time was taken as time zero. Enamine formation was monitored by NMR. After 10 min, the ^{1}H NMR spectra (400 MHz, toluene-d_8) δ ppm 6.11 (d, 1 H, J = 13.6 Hz), 4.18 (dt, 1 H, J = 13.6, 7.0 Hz), 2.79 (t, 4 H, J = 6.4 Hz), 2.05−2.15 (m, 2 H) 1.48−1.57 (m, 4 H) 1.36−1.46 (m, 4 H), 0.94 (t, 3 H, J = 7.1 Hz) showed total conversion to enamine **23**; and 100 μL of a 0.6 M (toluene-d_8) fresh stock solution of nitrostyrene was added. The suspension was shaken and this time was taken as time zero. ^{1}H NMR spectra were recorded until no further changes were. The acquired spectra were processed manually to obtain the concentration of each species during the reaction.

Cyclobutane 24, 1-(2-Butyl-4-nitro-3-phenylcyclobutyl)-pyrrolidine. ^{1}H NMR (400 MHz, toluene-d_8) δ (ppm) 7.13−7.01 (m, 5 H), 4.68 (dd, 1 H, J = 6.8, 8.6 Hz), 3.36 (t, 1 H, J = 8.9 Hz), 3.17 (t, 1 H, J = 7.86 Hz), 2.48−2.29 (m, 4 H), 2.02 (m, 1 H), 1.51 (m, 4 H), 1.37 (m, 2 H), 1.08 (m, 4 H), 0.74 (m, 3 H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01061.

X-ray crystallographic data for **13a** and **17a** (CIF)

Tables of reaction optimization, NMR spectra of new compounds and intermediates, and X-ray experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research was supported in part by The National Institute of Industrial Technology (INTI), Consejo Nacional de Investigación Científica y Tecnológica (CONICET), Chem-essentia SRL, and University of Siena. Authors acknowledge Ing. Leandro Santos for NMR support.

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J. Org. Chem. 2016, 81, 7952−7957