Concentration Effect in the Asymmetric Michael Addition of Acetone to β -Nitrostyrenes Catalyzed by Primary Amine Thioureas

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Dedicated to Professor Dieter Enders on the occasion of his 70th birthday

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Abstract Bifunctional primary amine thiourea (PAT) organocatalysts show remarkable improvement in enantioselectivity and catalytic activity (turnover frequency) in the asymmetric Michael addition of acetone to β -nitrostyrenes upon dilution. Mechanistic investigations indicate that this behavior corresponds to the inhibition of off-cycle catalyst deactivation at low concentration, rather than to the operation of aggregation phenomena at high concentration. Reaction at low concentration (≤ 0.2 M in β -nitrostyrene) leads to the minimization of catalyst deactivation and, thus, to the optimization of yield and ee of the Michael addition products.

Key words primary amine thioureas, Michael addition, asymmetric catalysis, organocatalysis, concentration effect

The bifunctional primary amine thiourea (PAT) catalysts developed by Tsogoeva¹ and Jacobsen² and their co-workers in 2006 represented the first truly effective organocatalysts for the asymmetric Michael addition of challenging substrates like ketones. Indeed, the use of additives (water and/or organic acids) was found to be crucial for the development of efficient and highly enantioselective Michael additions of such challenging substrates. Since then, many examples have been described, due to the interest of the asymmetric Michael addition in organic synthesis and as a benchmark for the development of new catalysts.^{3,4} Likewise, the occurrence of primary amines in the active site of enzymes such as class I aldolases and pyridoxal phosphate dependent enzymes, among many others, has also contributed to stimulating the interest in this kind of catalyst.⁵ Furthermore, this type of catalyst can perform efficiently in reactions not belonging to the 1,4-addition archetype, such as the Mannich reaction, α -alkylation of aldehydes, cyclizations and cycloadditions, and vinylogous

aldol and multi-component Biginelli reactions.^{3a,b}

During mechanistic analysis of the catalytic system comprising **I**, we disclosed the subtle yet decisive effects that acetic acid and water exert over PAT catalysts in the asymmetric Michael addition of acetone to β -nitrostyrene (**1**, Scheme 1).⁶ These additives modify the reaction mechanism: water minimizes catalyst deactivation by the nitrostyrene, and acetic acid, which provides the catalyst turnover, prevents the formation of an undesired double addition side product. Although water actually slows down the reaction rate, the overall result is an enhancement in the yield of the desired Michael adduct **2a**.⁶

Scheme 1 Michael addition of acetone to β -nitrostyrene catalyzed by bifunctional PAT catalysts I–IV

In continuation of our efforts in asymmetric organocatalysis in general, and Michael additions in particular,⁷ we now show that PAT catalysis results in significant changes in conversion and enantioselectivity upon changes in the reactants concentration. Essentially, dilution leads consistently to Michael adducts with higher ee values. This behavior was found to be identical for the five PAT catalysts studied herein (Scheme 1). Finally, we show that, under these new reaction conditions, catalyst **IV** behaves as a simple yet efficient PAT catalyst for the Michael addition of acetone to β -nitrostyrenes without the need for a precise control of the amount of water present in the reaction medium.

Several PAT organocatalysts were synthesized according to literature methods and evaluated under the reaction conditions outlined in Scheme 1. It is important to note that water did not need to be added to the reaction mixture, since the presence of sufficient water was secured by adventitious traces present in solvents, reagents and the atmosphere.⁸ Catalysts **I**, *epi-I* and **II** were successfully developed for this reaction by Tsogoeva and co-workers.¹ Catalyst **III**, developed initially by Yan and co-workers, lacks additional stereocenters and therefore can be considered a simplified version of **I** and *epi-I*.⁹ Finally, catalyst **IV**, at first designed and tested for asymmetric hydrocyanation reactions by Fuerst and Jacobsen, with little success,¹⁰ features a bulkier benzhydryl side moiety, again with no additional stereocenters (Scheme 1).

Hence, acetic acid was used as the only controlled additive to promote the Michael addition. The amount of AcOH was re-optimized for catalyst **I**. Indeed, Figure 1 shows that it is important not to surpass 10 mol% AcOH; above this value, a decrease in conversion takes place. We also observed that the ee remained unaffected by the amount of acid (83–86% ee). Therefore, the optimal amount of AcOH must be set in a narrow range of 5–10 mol%. Thereafter, 10 mol% AcOH was used in our work to ensure that there was always enough acid, but being especially accurate not to surpass that amount (Figure 1).

Figure 1 Effect of the AcOH amount in the Michael addition of acetone to β -nitrostyrene (**1**). Reagents and conditions: catalyst **I** (10 mol%), $[1]_0 = 0.45$ M, acetone (10 equiv), toluene, r.t., 24 h.

Then, the benchmark Michael addition was studied at several concentrations with PAT catalysts **I–IV**, using 10 mol% catalyst and 10 mol% AcOH. In all cases, a clear improvement in ee was observed upon dilution, the amount of solvent being the only variable. For reactions using 0.335 mmol of β -nitrostyrene, enantioselectivity increased asymptotically for all catalysts studied (Figure 2) from experiments performed at high concentration (toluene volume of 0.15 mL plus acetone volume of 0.25 mL, $[1]_0 = 0.84$ M) to experiments at low concentration (toluene volume of 5 mL plus acetone volume of 0.25 mL, $[1]_0 = 0.06$ M). For catalyst **I**, the increase in ee was 14%, whereas for *epi-I* it was 24%. Catalyst **II** also exhibited an improvement of 14% ee. For catalyst **III**, the improvement was 17% ee, and for catalyst **IV**, up to 15% ee. Clearly, the stereoselectivity of the Michael addition significantly increased, reaching above 90% ee (product **2a**) for most catalysts under the more diluted conditions (5 mL toluene added, $[1]_0 = 0.06$ M). Further dilution below 0.06 M (not shown) led to poorer results, though, likely due to a decrease in catalytic efficiency. For the analogous results for *epi-I*, see the Supporting Information.

Regarding conversion, it was also clear that higher concentrations (0.15 mL toluene, $[1]_0 = 0.84$ M) are not suitable for running this reaction with any of the catalysts studied. Dilution improved the conversion as well, with best results being obtained for an initial concentration of β -nitrostyrene around 0.3 M (1 mL toluene added). Further dilution led, in general, to a slight but still acceptable decrease in conversion. Finally, $\geq 95\%$ conversion can be safely achieved for all five catalysts **I–IV** in the range of $[1]_0 = 0.06$ –0.30 M (1–5 mL toluene added, Figure 2).

In this way, these experiments show the importance of optimizing the reactant concentration as a key parameter in PAT catalysis. For the catalysts studied herein, a compromise between the optimal reagent concentration for enantioselectivity and conversion must be decided upon. An initial concentration of β -nitrostyrene of 0.15 M seems a good choice in view of our results (2 mL toluene plus acetone for 0.335 mmol β -nitrostyrene), and this value was therefore used as the optimal conditions to test the synthetic utility and substrate scope of catalyst **IV** (*vide infra*). Our data also suggest that the side moiety of the thiourea in PAT catalysts might not be of great importance in determining activity and enantioselectivity, once a catalytic scaffold (enantiopure *trans*-1,2-diaminocyclohexane) has been set. Reaction conditions, including additives and concentration, might play a much more important role in defining the final results of PAT-based catalytic systems.

Then, we evaluated the substrate scope under the optimal concentration (initial concentration of nitrostyrene of 0.15 M, 10 mol% catalyst **IV** and 10 mol% AcOH), as shown in Table 1. High isolated yields and enantioselectivities in

Figure 2 Effect of reactant concentration on ee (left y axis) and conversion (right y axis) for the addition of acetone to β -nitrostyrene (**1**; 50 mg, 0.335 mmol) catalyzed by I–IV, plotted against the amount of toluene added to the reaction. *Reagents and conditions:* catalyst (10 mol%), AcOH (10 mol%), acetone (10 equiv), toluene, r.t., 24 h. Conversion determined by ^1H NMR spectroscopy of the crude samples; ee determined by HPLC on a chiral stationary phase.

the range 84–96% ee were obtained for a variety of substituted β -nitrostyrenes, bearing electron-donating (entries 2, 3 and 5) or electron-withdrawing (entries 4

Table 1 Asymmetric Michael Addition of Acetone to Substituted β -Nitrostyrenes^a

Entry	Product	Yield ^b (%)	ee ^c (%)
1	2a	72	93
2	2b	76	96
3	2c	80	91
4	2d	81	89
5	2e	55	87
6	2f	77	92
7	2g	80	92
8	2h	54	84

^a Reaction conditions: [nitrostyrene]₀ = 0.15 M, catalyst IV (10 mol%), AcOH (10 mol%), acetone (10 equiv), toluene, r.t., 24 h.

^b Isolated yield after purification by flash chromatography on silica gel.

^c Determined by chiral-phase HPLC.

and 6–8) groups. No particular dependence of enantioselectivity on electronic effects was observed, although the most modest result corresponds to a β -

nitrostyrene containing a strong electron-withdrawing group (p -CF₃, entry 8). These results

demonstrate that **IV** is a simple yet reliable catalyst for this particular reaction.

The most common explanation for the correlation between dilution and enantioselectivity observed in this study would invoke catalyst self-aggregation, since some thioureas and squaramides are known to undergo concentration-dependent aggregation that has a strong impact on their performance as asymmetric catalysts.^{11,12} High aggregation phenomena because of gelation can even lead to inversion of stereoselectivity.¹³ In these compounds, aggregation usually takes place through the establishment of intermolecular hydrogen bonds between thiourea (or squaramide) groups.

However, we have discarded catalyst aggregation phenomena in PAT catalysis because NMR dilution experiments on **I** proved specifically that no aggregation takes place in solution in the presence of AcOH, although a weak dimerization constant ($K_{\text{dimer}} = 25 \text{ M}^{-1}$ at 25 °C) can be associated with the acid-free catalyst in solution (see the Supporting Information for details). Moreover, the absence of nonlinear effects in the asymmetric Michael addition catalyzed by **IV** (see the Supporting Information), as also occurs with Takemoto's catalyst (a tertiary amine thiourea catalyst), further supports this observation.¹⁴ Finally, we were able to obtain single crystals of **IV**·AcOH suitable for X-ray diffraction analysis (Figure 3). No thiourea–thiourea contacts were observed in the solid state either; instead, thiourea–acetate and thiourea–ammonium hydrogen bonding are the norm.

Figure 3 Unit cell of **IV**·AcOH showing intra- and intermolecular hydrogen bonding. Sulfur, yellow; nitrogen, blue; oxygen, red; carbon, gray. Non-H-bonding hydrogen atoms have been omitted for clarity. Ellipsoid probability level set at 50%. CCDC 1437478.

Therefore, the explanation for such a concentration effect must respond to other mechanistic aspects of the reaction. Reversibility, which has a decisive impact on yield and stereoselectivity of the Michael addition of α,α -disubstituted aldehydes to nitroolefins,¹⁵ must be of negligible importance for the Michael addition of acetone since, for example, the ee of the reaction product remains constant over time when catalyst **IV** is used. Likewise, product inhibition or a reverse reaction of the addition product with the free PAT catalyst was never

detected (see the Supporting Information).⁶

It could be argued that these changes in conversion and enantioselectivity can be due to changes in pH due to different concentrations of AcOH that might affect a non-asymmetric background reaction. However, assuming an aqueous solution, it can be calculated that the pH would only decrease from 3.5 to 2.9 when going from the most diluted conditions to the most concentrated ($[1]_0 = 0.06 \text{ M}$ to 0.84 M). Moreover, Michael addition was never observed in the absence of a PAT catalyst.

Therefore, once the occurrence of product inhibition is discarded,⁶ the most likely explanation for the observed concentration effect must rely on the higher stability of the PAT catalyst at low concentration. Indeed, catalyst deactivation by the nitrostyrene is an off-cycle process in direct competition with the main catalytic cycle leading to the Michael adduct.⁶ If dilution makes this process kinetically disfavored (e.g., upon dilution, a second order reaction like nitrostyrene polymerization should be disfavored ahead of a first order reaction),¹⁶ a higher amount of active catalyst would be available at a given reaction time for the main, enantioselective, cycle.

To further prove this assumption, we used quantitative ¹H NMR analysis to study changes in the concentration of β -nitrostyrene (**1**) with time for three different initial concentrations ($[1]_0 = 0.45, 0.34$ and 0.23 M) using catalyst **I**. In order to check the effect of the β -nitrostyrene concentration exclusively, all other concentrations (catalyst, acetone, AcOH and water) were kept constant. By applying reaction progress kinetic analysis,¹⁷ we were able to construct turnover frequency (TOF) vs $[1]$ plots for the three sets of reactions (Figure 4 and Supporting Information). The results of this study are clear: reactions performed under more diluted conditions are faster and exhibit higher TOF. This is indeed in agreement with our previous conclusion that cata-

Figure 4 Effect of the initial concentration of **1** on TOF in the Michael addition of acetone to β -nitrostyrene (**1**). Reagents and conditions: $[1]_0 = 0.045 \text{ M}$, $[\text{acetone}]_0 = 4.5 \text{ M}$, $[\text{AcOH}]_0 = 0.011 \text{ M}$, $[\text{water}]_0 = 0.045 \text{ M}$, toluene, r.t. $[1]_0 = 0.45 \text{ M}$, diamonds; $[1]_0 = 0.34 \text{ M}$, squares; $[1]_0 = 0.23 \text{ M}$, circles.

lyst deactivation by the nitrostyrene takes place at high concentration. From these results, the apparent first-order kinetic constants for the three concentrations could be calculated, and showed a threefold increase in TOF by just diluting the initial β -nitrostyrene concentration from $[1]_0 = 0.45$ M to 0.23 M (Table 2).

Table 2 Observed First-Order Kinetic Constants for the Reactions Plotted in Figure 4

$[1]_0$ [M]	k_{obsd} [M ⁻¹ ·h ⁻¹]	Error
0.45	2.20	± 0.11
0.34	3.96	± 0.11
0.23	7.00	± 0.02

The observed increase in ee of the Michael adduct upon dilution can be simply attributed to this increase in TOF of the catalytic asymmetric process ahead of non-asymmetric background reactions. The conclusion is that a reaction run under diluted conditions keeps side reactions hampering the Michael addition under control, resulting in an efficient process.

To sum up, we have found a remarkable and general concentration effect in the asymmetric Michael addition of acetone to β -nitrostyrenes catalyzed by primary amine thioureas. When the reactant concentration is decreased (dilution), the ee values increase significantly while conversion remains high. Under the optimal concentration ($[1]_0 = 0.15$ M), excellent results can be obtained. Finally, we have successfully applied catalyst **IV** to the asymmetric Michael addition of acetone to β -nitrostyrenes for the first time. It thus has become apparent that, in these PAT-catalyzed Michael additions, reaction concentration plays a fundamental role and must be thoroughly optimized to ensure the highest performance of the catalyst.

All reagents were purchased and used without any further purification. 4-Trifluoromethyl- β -nitrostyrene was synthesized according to a literature procedure.¹⁸ Solvents were directly used from the bottle, unless otherwise indicated. Unless otherwise stated, all reactions were performed in air. Column chromatography and TLC were performed on silica gel using UV light and/or indicator stains to visualize the products. ¹H and ¹³C NMR spectra were measured in the indicated deuterated solvent at 25 °C on an Automatic Varian VNMRs 400 MHz spectrometer with OneNMR Probe. Chemical shifts are reported in ppm downfield and upfield from TMS, and referenced to solvent resonances.

Synthesis of Catalyst **IV**^{1a,10}

Benzhydryl isothiocyanate (1.97 g, 8.75 mmol) was added over a period of 1 h to a stirred solution of (*S,S*)-1,2-diaminocyclohexane (1 g, 8.75 mmol) in anhyd CH₂Cl₂ (17 mL). The reaction mixture was stirred for a further 3 h at r.t. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with hexane–EtOAc mixtures of increasing polarity. Catalyst **IV** was isolated as a white foam; yield: 2.3 g (6.83 mmol, 78%). The spectroscopic characterization of **IV** matched the literature data.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.20 (br, 1 H, NHCS), 7.42 (br d, *J* = 6.0 Hz, 1 H, NHCS), 7.40–7.20 (m, 10 H, CH

Ar), 6.68 (s, 1 H, CHPh₂), 3.75 (br, 1 H, CHNH), 2.43 (m, 1 H, CHNH₂), 2.00 (m, 1 H, CH Cy), 1.78 (m, 1 H, CH Cy), 1.58 (m, 2 H, CH Cy), 1.25–0.95 (m, 4 H, CH Cy).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 182.1 (C=S), 142.7 (C Ar), 128.4 (CH Ar), 127.2 (CH Ar), 126.9 (CH Ar), 60.4 (CHNH), 59.8 (CHPh₂), 54.3 (CHNH₂), 34.7 (CH₂ Cy), 31.4 (CH₂ Cy), 24.5 (CH₂ Cy), 24.3 (CH₂ Cy).

Michael Addition Dilution Studies; General Procedure

In a vial, the catalyst (0.0335 mmol, 0.1 equiv) and β -nitrostyrene (50 mg, 0.335 mmol, 1 equiv) were weighed, then dissolved in toluene (2 mL, varied for other reaction concentrations). To this solution, AcOH (0.1 equiv) was added [10 μ L of a stock solution of AcOH (200 μ L, 3.5 mmol) in toluene (1 mL)]. Finally, acetone (250 μ L, 3.35 mmol, 10 equiv) was added and the reaction mixture was stirred at r.t. for 24 h. To quench the reaction, water was added, and the organic phase was extracted with EtOAc and dried over MgSO₄. The solvent was evaporated in vacuo and the crude mixture was analyzed by ¹H NMR spectroscopy to determine the conversion. HPLC samples were prepared from the crude reaction mixture and analyzed using a Phenomenex Lux 5 μ m Amylose-2 column (hexane–*i*-PrOH, 90:10, 1 mL/min, 209 nm).

Preparative Michael Addition ($[1]_0 = 0.15$ M); General Procedure

In a 10-mL flask, catalyst **IV** (34 mg, 0.1 mmol, 0.1 equiv) and the corresponding nitroalkene (1 mmol, 1 equiv) were weighed, then dissolved in toluene (6 mL). To this solution, AcOH (5.7 μ L, 0.1 mmol, 0.1 equiv) and acetone (0.75 mL, 10 mmol, 10 equiv) were added. The reaction mixture was stirred at r.t. for 24 h. Then, water was added, and the mixture was transferred to a separation funnel. The organic phase was extracted with EtOAc and dried over MgSO₄. The solvent was evaporated in vacuo and the crude mixture was purified by flash chromatography on silica gel (EtOAc–hexane, 1:4). All adducts are known compounds, and our spectroscopic data match the literature data.

(*R*)-5-Nitro-4-phenylpentan-2-one (**2a**)^{1a,19}

The preparative Michael addition procedure was followed using *trans*- β -nitrostyrene (149 mg, 1 mmol). Product **2a** (149 mg, 0.72 mmol, 72% isolated yield; 93% ee (*R*)) was obtained as a white solid.

$[\alpha]_D^{20}$ –6.8 (*c* 0.4, CHCl₃). HPLC (Phenomenex Lux 5 μ m Amylose-2 column, hexane–*i*-PrOH, 90:10, 1 mL/min, 209 nm): t_R = 19.8 (major), 22.4 (minor)

min. ¹H NMR (400 MHz, CDCl₃): δ = 7.40–7.10 (m, 5 H), 4.75–4.55 (m, 2 H), 4.02 (m, 1 H), 2.90 (d, *J* = 7.0 Hz, 2 H), 2.12 (s, 3 H). (*R*)-4-(4-

Methoxyphenyl)-5-nitropentan-2-one (**2b**)^{1a,19}

The preparative Michael addition procedure was followed using *trans*-4-methoxy- β -nitrostyrene (179 mg, 1 mmol). Product **2b** (180 mg, 0.76 mmol, 76% isolated yield; 96% ee (*R*)) was obtained as a white solid.

HPLC (Phenomenex Lux 5 μ m Amylose-2 column, hexane–*i*-PrOH, 90:10, 1 mL/min, 209 nm): t_R = 28.8 (major), 30.4 (minor) min.

¹H NMR (400 MHz, CDCl₃): δ = 7.18 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 4.70–4.50 (m, 2 H), 3.90 (m, 1 H), 3.75 (s, 3 H), 2.89 (m, 2 H), 2.08 (s, 3 H).

(R)-4-(2-Methoxyphenyl)-5-nitropentan-2-one (2c)²⁰

The preparative Michael addition procedure was followed using *trans*-2-methoxy-β-nitrostyrene (179 mg, 1 mmol). Product **2c** (190 mg, 0.80 mmol, 80% isolated yield; 91% ee (*R*)) was obtained as a white solid.

HPLC (Phenomenex Lux 5 μm Amylose-2 column, hexane–*i*-PrOH, 90:10, 1 mL/min, 209 nm): *t*_R = 21.0 (major), 23.2 (minor) min.

¹H NMR (400 MHz, CDCl₃): δ = 7.25–6.83 (m, 4 H), 4.70 (m, 2 H), 4.22 (m, 1 H), 3.80 (s, 3 H), 3.00 (m, 2 H), 2.08 (s, 3 H).

(R)-4-(4-Bromophenyl)-5-nitropentan-2-one (2d)²⁰

The preparative Michael addition procedure was followed using *trans*-4-bromo-β-nitrostyrene (228 mg, 1 mmol). Product **2d** (232 mg, 0.81 mmol, 81% isolated yield; 89% ee (*R*)) was obtained as a white solid.

HPLC (Phenomenex Lux 5 μm Amylose-2 column, hexane–*i*-PrOH, 90:10, 1 mL/min, 209 nm): *t*_R = 26.8 (major), 31.1 (minor) min.

¹H NMR (400 MHz, CDCl₃): δ = 7.48 (d, *J* = 8.4 Hz, 2 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 4.70–4.50 (m, 2 H), 4.02 (m, 1 H), 2.88 (m, 2 H), 2.14 (s, 3 H).

(R)-5-Nitro-4-(*p*-tolyl)pentan-2-one (2e)²¹

The preparative Michael addition procedure was followed using *trans*-4-methyl-β-nitrostyrene (163 mg, 1 mmol). Product **2e** (122 mg, 0.55 mmol, 55% isolated yield; 87% ee (*R*)) was obtained as a white solid.

HPLC (Phenomenex Lux 5 μm Amylose-2 column, hexane–*i*-PrOH, 90:10, 1 mL/min, 209 nm): *t*_R = 18.5 (major), 20.7 (minor) min.

¹H NMR (400 MHz, CDCl₃): δ = 7.30–6.80 (m, 4 H), 4.70 (m, 2 H), 4.21 (m, 1 H), 3.82 (s, 3 H), 3.05–2.85 (m, 2 H), 2.10 (s, 3 H).

(R)-4-(2,4-Dichlorophenyl)-5-nitropentan-2-one (2f)²²

The preparative Michael addition procedure was followed using *trans*-2,4-dichloro-β-nitrostyrene (218 mg, 1 mmol). Product **2f** (213 mg, 0.77 mmol, 77% isolated yield; 92% ee (*R*)) was obtained as a white solid.

HPLC (Phenomenex Lux 5 μm Amylose-2 column, hexane–*i*-PrOH, 90:10, 1 mL/min, 209 nm): *t*_R = 23.8 (major), 28.5 (minor) min.

¹H NMR (400 MHz, CDCl₃): δ = 7.45–7.10 (m, 3 H), 4.75 (m, 2 H), 4.41 (m, 1 H), 3.10–2.80 (m, 2 H), 2.16 (s, 3 H).

(R)-4-(4-Fluorophenyl)-5-nitropentan-2-one (2g)²⁰

The preparative Michael addition procedure was followed using *trans*-4-fluoro-β-nitrostyrene (167 mg, 1 mmol). Product **2g** (180 mg, 0.80 mmol, 80% isolated yield; 92% ee (*R*)) was obtained as a white solid.

HPLC (Phenomenex Lux 5 μm Amylose-2 column, hexane–*i*-PrOH, 90:10, 1 mL/min, 209 nm): *t*_R = 15.8 (major), 17.2 (minor) min.

¹H NMR (400 MHz, CDCl₃): δ = 7.22 (m, 2 H), 7.02 (m, 2 H), 4.75–4.50 (m, 2 H), 4.01 (m, 1 H), 2.83 (m, 2 H), 2.12 (s, 3 H).

(R)-5-Nitro-4-(4-trifluoromethyl)phenyl)pentan-2-one (2h)²²

The preparative Michael addition procedure was followed using *trans*-4-trifluoromethyl-β-nitrostyrene (217 mg, 1 mmol). Product **2h** (149 mg, 0.54 mmol, 54% isolated yield; 84% ee (*R*)) was obtained as a white solid.

HPLC (Phenomenex Lux 5 μm Amylose-2 column, hexane–*i*-PrOH, 90:10, 1 mL/min, 209 nm): *t*_R = 13.7 (major), 14.9 (minor) min.

¹H NMR (400 MHz, CDCl₃): δ = 7.23 (m, 2 H), 7.01 (m, 2 H), 4.75–4.50 (m, 2 H), 4.01 (m, 1 H), 2.82 (m, 2 H), 2.10 (s, 3 H).

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Supporting Information

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