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Effect of High Pressure on the Organocatalytic Asymmetric Michael Reaction: Highly Enantioselective Synthesis of γ-Nitroketones with Quaternary Stereogenic Centers

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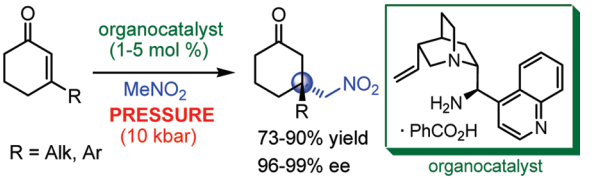
ABSTRACT



The significant effect of hydrostatic pressure on the difficult organocatalytic 1,4-conjugate addition of nitroalkanes to prochiral sterically congested β,β-disubstituted enones is demonstrated. This approach allows for the synthesis of γ-nitroketones containing quaternary stereogenic centers with good yields, excellent enantioselectivity, and low loading (1−5 mol %) of simple chiral primary amine catalysts.

The high-pressure methodology in liquid systems has been quite well recognized as a very powerful tool in organic synthesis,[1] but the influence of pressure on asymmetric metallo-[1a,2] and organocatalytic[3] reactions still remains a poorly explored area of catalysis. These facts, as well as the remarkable progress made in organocatalysis in recent years,[4] prompted us to study the effect of pressure on selected difficult organocatalytic reactions requiring a high catalyst loading, long reaction time, and reactions which are still beyond the reach of classical organocatalysis. Increased pressure can assist in overcoming organocatalytic reactions with a negative volume of activation,[1] which are ineffective under thermal conditions because of steric and electronic constraints.

The high-pressure technique was successfully introduced to organic synthesis by Dauben in the mid-1970s.[5] In the early 1980s Matsumoto[3a] investigated the first high-pressure asymmetric organocatalytic reaction, including natural cinchona alkaloids as catalysts in Michael-type reactions, with a positive influence on the rate but unfortunately with low or moderate enantioselectivity. The literature also describes a few other examples of high-pressure asymmetric organocatalytic reactions catalyzed by chiral tertiary or secondary amines, usually with low or moderate enantioselectivity.[3b−f,h] To date, the highest positive effect of pressure on the asymmetric organocatalytic process was observed by Hayashi[3g] in a Mannich-type reaction catalyzed by proline.

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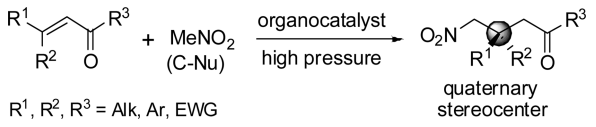
Scheme 1. Creation of All-Carbon Quaternary Stereocenters by 1,4-Conjugate Addition to β,β-Disubstituted Enones



In our high-pressure studies we focused attention on challenging 1,4-conjugate additions of carbon nucleophiles to prochiral β,β-disubstituted Michael acceptors enabling the generation of quaternary stereogenic centers (Scheme 1).[6] Asymmetric organocatalytic Michael-type reactions are practically restricted to β-monosubstituted unsaturated carbonyl compounds and nitroalkenes.[7] The literature describes only a few examples of such organocatalytic reactions of sterically congested β,β-disubstituted acceptors with C-nucleophiles,[6c,8] usually with a very limited scope, and some examples of intramolecular reactions,[9] e.g. Diels–Alder, Friedel–Crafts, and Stetter. Moreover, this type of Michael acceptors was also applied in asymmetric organocatalytic hydrogenation[10] and some additions of heteronucleophiles including epoxidation and aziridination.[11] In contrast, transition-metal-catalyzed asymmetric conjugate addition reactions to β,β-disubstituted Michael acceptors have been quite extensively explored in recent years.[6d]

In this communication we demonstrate the positive effect of hydrostatic pressure (up to 10 kbar) on enantioselective 1,4-conjugate addition of nitroalkanes to prochiral sterically congested β,β-disubstituted enones, catalyzed by simple chiral primary amines **1a**–**1h** (Figure 1).[12,13] We have found that a combination of pressure and bifunctional catalysis with primary amines derived from cinchona alkaloids can remarkably accelerate the reaction rate. This approach allows for efficient asymmetric synthesis of γ-nitroketones[14] containing all-carbon quaternary stereogenic centers with high enantioselectivity.

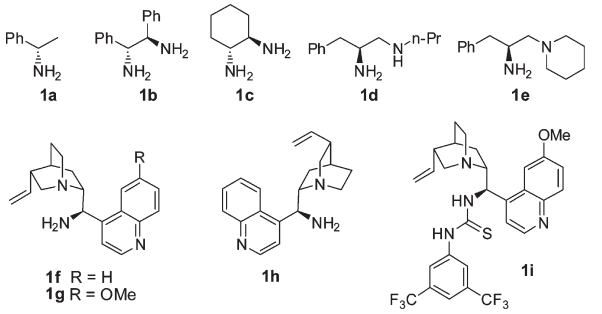


Figure 1. Organocatalysts examined in the Michael reaction.

As a model reaction for our studies, we chose the addition of nitromethane to 3-methylcyclohexenone (**2a**, Table 1). This particular reaction was investigated by the research groups of Ley[8a,b] and Amedjkouh[8c] in the presence of chiral secondary amines. More promising results were obtained recently by Ye's group,[8d] with 10–20 mol % of the primary amine-thiourea catalyst containing 1,2-diaminocyclohexane and a cinchona alkaloid moiety. The product **3a** was isolated after 5 days with 82% yield and 94% ee; however, the presented scope of enones is limited only to 3-*n*-alkylcyclohexenones.

In our preliminary investigations we applied 5 mol % of simple chiral primary amines **1a**–**f** as catalysts with TFA as a cocatalyst (Figure 1, Table 1). Screening under ambient conditions revealed a very low conversion of 3-methylcyclohexenone. In contrast, application of 10 kbar of pressure and a catalytic amount of 1,2-diamines **1b**–**f** remarkably accelerated the reaction rate (Table 1).

The best results in terms of conversions were observed with amines **1c**, **1e**, and **1f**. The significantly lower yield

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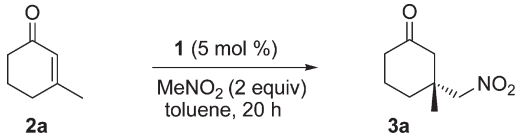
Table 1. Catalyst Screening in the Model Reaction[a]



			1 bar	10 kbar	
entry	amine (5 mol %)	acid additive (5 mol %)	yield (%)[b]	yield (conv) (%)[b]	ee (%)[c]
1[d]	**1a**	TFA	<1	11 (23)	34 (*S*)
2	**1b**	TFA	2	55 (60)	98 (*R*)
3	**1c**	TFA	6[f]	55 (95)	75 (*R*)
4	**1d**	TFA	9[g]	70 (77)	82 (*S*)
5	**1e**	TFA	<1	55 (99)	73 (*S*)
6	**1f**	TFA	1	78 (91)	96 (*R*)
7	**1f**	BzOH	3	75 (99)	98 (*R*)
8[e]	**1f**	BzOH	<2	80 (96)	98 (*R*)
9	**1f**	No acid	1	36 (89)	85 (*R*)
10	**1i**	No acid	<0.1	36 (43)	92 (*R*)

[a] Reaction conditions: **2a** (1 mmol, c = 1.0 mol/L), nitromethane (2 mmol), amine **1** (0.05 mmol), acid (0.05 mmol) in toluene (*ca.* 0.75 mL), 20–25 °C, 20 h, 10 kbar (or 25 °C, 24 h, 1 bar). [b] Determined by GC analysis with internal standard. [c] Determined by GC analysis using β-dex 225 column. [d] 2.5 mol % of TFA was used. [e] 2 mol % of **1f** and 2 mol % of benzoic acid was used. [f] 83% ee at 1 bar. [g] 80% ee at 1 bar.

than those by conversion with some catalysts (Table 1, entries 3 and 5) can be explained by subsequent nitromethane (2 equiv) addition to the carbonyl group.[3e] The highest efficiency in terms of yield and enantioselectivity was achieved with 9-amino-9-deoxy-*epi*-cinchonine **1f** (entry 6). After screening of an acid additive we found that the addition of a weaker acid (e.g., benzoic) gave higher conversion and enantioselectivity (entry 7).[15] To our surprise, lowering the catalyst loading to 2 mol % in fact improved the yield to 80% (entry 8). A higher concentration of catalyst **1f** gave practically full conversion and promoted the subsequent Henry reaction, lowering the yield of the desired product. Reaction without an acid additive is less enantioselective and favors byproduct formation (entry 9).

We studied the influence of pressure in more detail, with 2 mol % of catalyst **1f**·1.5 BzOH. Figure 2 illustrates that pressure increase has a significant effect on the reaction rate with enantioselectivity kept on a very high level (98 ± 1% ee). We found that 8–10 kbar of pressure and 2 mol % of amine **1f** with an excess of benzoic acid in the range of 3–4 mol % are optimal for the model reaction (Table 2, entry 1).[15]

We also tested other derivatives of cinchona alkaloids **1g**–**i**. Application of pseudoenantiomeric catalyst **1h** resulted in opposite enantioselectivity (Table 2, entry 3, 97% ee). Promising results were observed with quinidine-derived thiourea **1i** (Table 1, entry 10);[16] however, the use of natural cinchonidine under the same conditions resulted in low yield and enantioselectivity (< 10%, 18% ee).

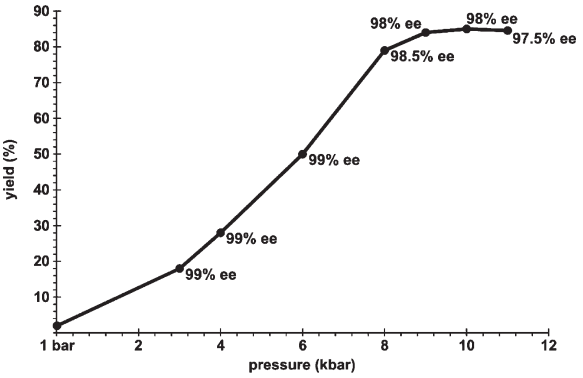


Figure 2. Effect of pressure on the model reaction.

The model reaction is very efficient under 10 kbar even with 1 mol % of **1f** during 20 h (Table 2, entry 4) and 5 mol % after 5 h (entry 6). Comparable results are also attainable under lower pressure (4–8 kbar, entries 7 and 8). We also demonstrated that this methodology is applicable with 1–2 mol % of **1f** for multigram scale synthesis (20 mmol) with good yield (> 75%) and > 97% ee.[15] For comparison the reaction with 10 mol % of catalyst **1f** under atmospheric pressure at 60 °C allows product **3a** with 25% yield (entry 10).

Table 2. Model Reaction Optimization Studies[a]

entry	amine	mol % of **1**·1.5 BzOH	pressure	conv (%)[b]	yield (%)[b,c]	ee (%)[d]
1	**1f**	2	10 kbar	96	87 (85)	98 (*R*)
2	**1g**	2	10 kbar	96	91	98 (*R*)
3	**1h**	2	10 kbar	96	90 (87)	97 (*S*)
4	**1f**	1	10 kbar	87	84	98
5	**1f**	0.2	10 kbar	27	26	98
6[e]	**1f**	5	10 kbar	93	87	98
7	**1f**	5	8 kbar	96	88	98.5
8[f]	**1f**	2	4 kbar	80	75	98
9[g]	**1f**	10	1 bar	5	4	~98
10[h]	**1f**	10	1 bar	26	25	98

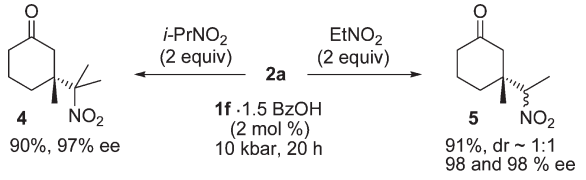
[a] Reaction conditions: **2a** (1 mmol, c = 1.0 mol/L), nitromethane (2 mmol), amine **1**·1.5 BzOH in toluene (*ca.* 0.75 mL), 20–25 °C, 20 h. [b] Determined by GC analysis with internal standard. [c] Numbers in parentheses refer to isolated yield of **3a** starting from 3 mmol of **2a**. [d] Determined by GC analysis using β-dex 225 column. [e] 5 h. [f] Reaction carried out at 60 °C. [g] 24 h. [h] Reaction carried out at 60 °C, 24 h.

Having established the optimal conditions for high-pressure asymmetric reactions of 3-methylcyclohexenone (**2a**) with nitromethane, we extended investigations of the Michael reaction to other nitroalkanes and enones. Ketone

(15) For more details, see Supporting Information.
(16) Vakulya, B.; Varga, S.; Csaámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

2a reacts with higher nitroalkanes, e.g. nitroethane[17] and 2-nitropropane, under 10 kbar of pressure with very high yield and enantioselectivity (Scheme 2).

Scheme 2. Reaction of **2a** with Higher Nitroalkanes



We focused more attention on reactions of nitromethane with various β,β-disubstituted enones, especially cyclic enones. As shown in Figure 3, this reaction works well for a broad range of 3-substituted cyclohexenones usually affording good to very good yields and enantioselectivity (usually >95% ee, products **3b**–**h**).

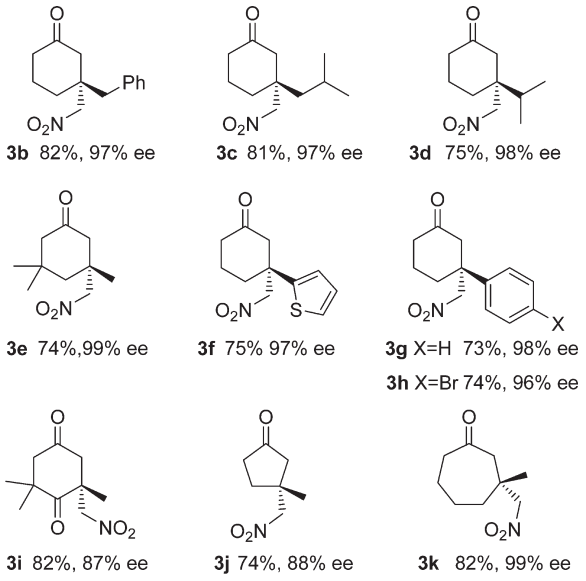


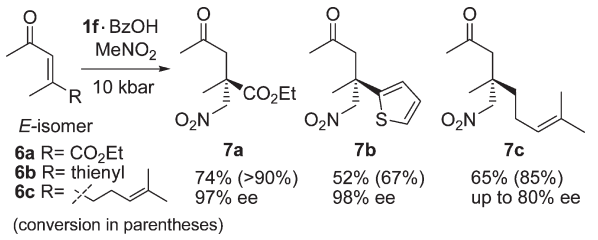
Figure 3. Products of nitromethane reaction with cyclic enones catalyzed by 2–5 mol % of **1f**·1.5 BzOH (isolated yield given).

Cyclohexenones containing more sterically demanding substituents (e.g., *i*-Pr) and aryl groups in the 3-position are less reactive, and to obtain a good yield they require 5 mol % of catalyst **1f** and in some cases more than 2 equiv of nitromethane.[15] This protocol also works quite effectively with more substituted cyclohexenones like isophorone (see product **3e**) and regioselectively with 2,6,6-trimethylcyclohexene-1,4-dione (see product **3i**). Moreover, we demonstrated that this approach is readily applicable with five- and seven-membered cyclic enones (see products **3j** and **3k**).

(17) The use of 1-nitroalkanes (e.g., $EtNO_2$) introduces two stereogenic centers, unfortunately with no diastereoselectivity because of unselective formation of the center with the nitro group.

The organocatalytic high-pressure method can also be employed for selected reactions of nitromethane with acyclic β,β-disubstituted enones (**6a**–**c**, Scheme 3). This group of enones is generally less reactive in the presence of catalyst **1f** in comparison to cyclic ones. The best results in terms of yield and enantioselectivity was obtained with ketone **6a** containing an electron-withdrawing group in the β-position (74%, 97% ee with 5 mol % of **1f**·BzOH). Enones with aryl and alkyl substituents in the β-position require a higher loading of catalyst (10 mol %). For instance, the Michael reaction of ketone **6b**, containing a thienyl group, furnished product **7b** with high enantioselectivity and moderate yield. The situation is more complicated with enones having two different alkyl groups in the β-position (e.g., **6c**). Starting from the *E*-isomer of **6c** we obtained acceptable yields and an enantioselectivity up to 80%. Surprisingly, with the *Z*-isomer the same direction of asymmetric induction was observed but with very low enantioselectivity.[15] Such results can be explained by *E*/*Z*-isomerization of enone **6c** in the presence of a catalyst during the reaction and the higher reactivity of the *E*-isomer.[15]

Scheme 3. Reactions of Acyclic Enones with Nitromethane



In conclusion, we have developed efficient high-pressure enantioselective organocatalytic 1,4-conjugate addition of nitromethane to prochiral sterically hindered β,β-enones. This approach works especially well with various cyclic enones and allows for the synthesis of γ-nitroketones containing quaternary stereogenic centers with good yields, excellent enantioselectivity, and low loading of a simple catalyst (1–5 mol %). We also presented promising preliminary results of the reaction with acyclic enones. Moreover, this work demonstrates the significant effect of hydrostatic pressure on the rate of an organocatalytic reaction while retaining very high enantioselectivity. To the best of our knowledge, this is the first example of pressure influence studies on an organocatalytic reaction proceeding via an iminium activation mode.

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Supporting Information Available. Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.