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Efficient and Highly Enantioselective Construction of Trifluoromethylated Quaternary Stereogenic Centers via High-Pressure Mediated Organocatalytic Conjugate Addition of Nitromethane to β,β-Disubstituted Enones

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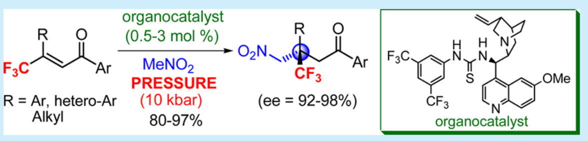
Supporting Information

ABSTRACT: A very effective high-pressure-induced acceleration of asymmetric organocatalytic conjugate addition of nitromethane to sterically congested β,β-disubstituted β-CF_3 enones has been developed. A combination of pressure (8−10 kbar) and noncovalent catalysis with low-loading of chiral tertiary amine-thioureas (0.5−3 mol %) is shown to provide very efficient access to a wide range of γ-nitroketones containing trifluoromethylated all-carbon quaternary stereogenic centers in the β-position (80−97%, 92−98% ee).



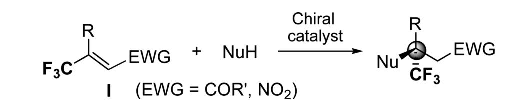
The growing role of organofluorine compounds in medicinal chemistry,[1] agrochemistry,[2] and material sciences[3] is stimulating the development of new synthetic methods, with particular attention to strategies providing access to novel types of fluorinated molecules. In recent years, there has been increasing interest in the asymmetric synthesis of compounds containing the trifluoromethyl group at secondary and tertiary carbon stereogenic centers.[4] Methods yielding enantiomerically enriched compounds with all-carbon quaternary stereogenic centers[5] containing the CF_3 group are still rare and very challenging for organic synthetic chemists.[6,7]

This goal can be achieved by utilizing sterically congested prochiral β,β-disubstituted β-CF_3 alkenes of type **I** as Michael acceptors (Scheme 1). In 2010, Shibata[8] demonstrated, for the first time, the application of enones representing this group (**I**) in asymmetric 1,4-addition. The reaction of hydroxylamine with β-CF_3-chalcones catalyzed by *Cinchona*-based ammonium salts resulted in the formation of trifluoromethyl-substituted 2-isoxazolines with 80−99% yield and 82−94% ee. Since this work, only a few examples of asymmetric catalytic conjugate additions of C-nucleophiles (e.g., cyanide, nitromethane, indoles)[7] and heteronucleophiles (e.g., methylhydrazine, H_2O_2 and thioles)[9] to enones or nitroalkenes of type **I** have been reported.

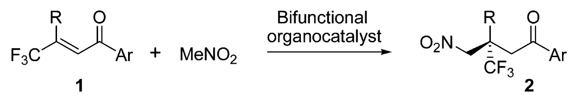
Here, we demonstrate the remarkable effect of hydrostatic pressure[10] on the asymmetric organocatalytic 1,4-conjugate addition[11] of nitromethane[12] to sterically congested β,β-disubstituted β-CF_3 enones **1** (Scheme 2) in the presence of easily available bifunctional tertiary amine-thiourea catalysts (Figure 1) in a homogeneous system. This reaction opens access to interesting γ-nitroketones **2** with trifluoromethylated all-carbon quaternary stereogenic centers, as well as to trifluoromethylated diarylpyrrolines, their *N*-oxides,[7c] and β-CF_3-GABA analogs.[7f,13]

In the first stage, we tested well-defined bifunctional tertiary amine−thiourea catalysts[14] (Figure 1) in the model reaction of nitromethane and (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-one (**1a**, Table 1). The application of organocatalysts **3a−3f**, effective in an analogous reaction with simple chalcones,[15] failed in the model reaction of **1a** under classical conditions. With 2 mol % of catalysts **3a−h** at rt, traces of product **2a** were usually observed after 2 weeks (Table 1) and the best result was obtained

Scheme 1. Construction of Quaternary Stereocenters Containing CF_3 Group via 1,4-Conjugate Addition



Scheme 2. Addition of Nitromethane to β-CF_3-β-R Enones



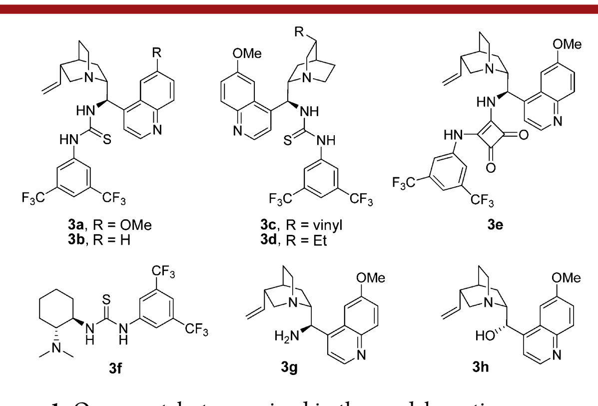


Figure 1. Organocatalysts examined in the model reaction.

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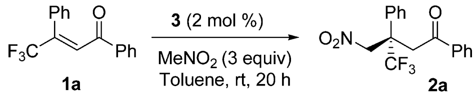
Table 1. Catalyst Screening in the Model Reaction[a]



entry	catalyst (2 mol %)	1 bar (14 days) yield GC (%)[b]	8 kbar (20 h) yield (%)[b]	8 kbar (20 h) ee (%)[c]	10 kbar (20 h) yield (%)[b]	10 kbar (20 h) ee (%)[c]
1	**3a**	~0.5	75	95	97	94
2	**3b**	1.5	68	95	96	94
3	**3c**	4	85	96[d]	98	95[d]
4[f]	**3d**	9[e]	93	96[d]	99	95[d]
5	**3e**	1	46	93	80	90
6	**3f**	2	81	93	99	90
7	**3g**[g]	0	0	–	0	–
8	**3h**	~0.5	33	50[d]	56	45[d]

[a]Reaction conditions: **1a** (E/Z ~98:2, 0.25 mmol, c = 0.5 mol/L), nitromethane (0.75 mmol, 3 equiv), and catalyst **3** (0.005 mmol, 2 mol %) in toluene (ca. 0.75 mL), 20–25 °C. [b]Determined by GC analysis using biphenyl as the internal standard. [c]Determined by HPLC analysis using the Chiralpak IC column. [d]Product **2a** with opposite absolute configuration, (R). [e]ee = 96.5 (~0.5% yield after 1 day). [f]Experiment at 4 kbar (20 h): 24% yield, ee = 97.5%. [g]Also with additive of $PhCO_2H$ (2 mol %).

for **3d** (9% yield and 96% ee, Table 1, entry 4). A higher loading of **3d** (10 mol %), an excess of nitromethane (≥5 equiv), and elevated temperature (50 °C) improved the yield after 1 week to ca. 15–28%.[16] A similar observation in this reaction has been reported by Shibata[7c] with 10 mol % of catalyst **3c** (14% yield, ee = 93% ee; 50 °C for 7 days). This group finally succeeded in performing the reaction under phase-transfer catalysis conditions with 10–30 mol % of ammonium salt of cupreidinium n-butyl ether.[7c] Using this method, diarylated products of type **2** were obtained after 1.5–3 days with 80–99% yields and 90–93% ee's.

Our preliminary experiments with well-known organocatalysts **3a–f** confirmed their very low activity (Table 1) in the model reaction under atmospheric pressure. Inspired by the pioneering work of Matsumoto[17] in the high-pressure activation of a cinchona alkaloid-catalyzed Michael reaction and our recent discoveries in high-pressure conjugate additions with primary amine catalysis,[12c,18] we decided to investigate the influence of hydrostatic pressure in this case as well. High-pressure methodology in liquid systems has been quite well recognized as a powerful tool in organic synthesis,[10] but the influence of pressure on asymmetric organocatalytic reactions still remains a very poorly explored area of catalysis.[19,20]

In 2011, our group demonstrated that a combination of pressure and catalysis with primary amines of type **3g** remarkably accelerate the enantioselective addition of nitroalkanes to congested β-substituted cyclic enones.[12c] This class of organocatalysts failed in the reaction of β-CF_3-chalcone (**1a**) with $MeNO_2$ (Table 1, entry 7). The use of quinidine (**3h**)[17] improved the yield under high-pressure conditions, although the enantioselectivity was moderate (entry 8).

Application of 2 mol % of cinchona alkaloid-thiourea catalysts **3a–d**[15a,21] or the corresponding squaramide **3e**[15c,22] under 8 and 10 kbar of pressure remarkably accelerated the reaction rate (Table 1, entries 1–5). From traces of product **2a** observed at atmospheric pressure (after 2 weeks), the yield dramatically increased to 68–93% at 8 kbar and >95% at 10 kbar (after 20 h) with very high enantioselectivity (ee = 94–96%). Results at 8 kbar indicate that quinine derived thioureas **3c** and **3d** are slightly more active in comparison to thioureas **3a** and **3b** derived from quinidine and cinchonine, offering the opposite enantiomer of **2a**. Also, the Takemoto catalyst **3f**[23] turned out to be very active under high-pressure conditions, however, the enantioselectivity is lower (ee = 90%, entry 6).

Table 2. Model Reaction Optimization Studies[a]

entry	catalyst (mol %)	pressure	time	yield (%)[b,c]	ee (%)[d]
1	**3a** (2%)	6 kbar	20 h	60	97
2	**3a** (2%)	8 kbar	20 h	87	96
3	**3a** (2%)	10 kbar	20 h	97 (92)	95.5 (S)
4[e]	**3a** (2%)	10 kbar	20 h	96	86
5	**3a** (1%)	10 kbar	20 h	84 (80)	95.5
6[f]	**3a** (0.5%)	10 kbar	20 h	90	94
7	**3a** (2%)	10 kbar	5 h	86	95.5
8	**3a** (2%)	10 kbar	2 h	58	96
9	**3d** (1%)	10 kbar	20 h	97 (91)	96.5 (R)
10	**3d** (0.5%)	10 kbar	20 h	81 (78)	96
11	**3d** (1%)	10 kbar	5 h	83	97.5
12	**3d** (2%)	10 kbar	2 h	72	97.5
13	**3d** (2%)	6 kbar	20 h	81	98
14	**3d** (1%)	8 kbar	20 h	89	97.5

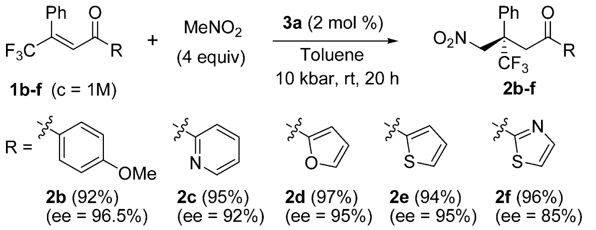
[a]Conditions: **1a** (E/Z 99:1, c = 1.0 mol/L), **3a** or **3d**, $MeNO_2$ (3–4 equiv) in toluene at 20–25 °C. [b]Determined by GC analysis using biphenyl as the internal standard. [c]Numbers in parentheses refer to isolated yield of **2a**. [d]Determined by HPLC analysis using Chiralpak IC column. [e]**1a**, E/Z ratio 94:6. [f]Reaction carried out at 50 °C.

Based on catalyst screening at 8 and 10 kbar (Table 1) for further optimization studies we selected cinchona thiourea **3a**, as well as catalyst **3d** offering the opposite product enantiomer (Table 2). A higher concentration of enone **1a** (1.0 M in Table 2 vs 0.5 M in Table 1) improved the yield from 75% to 87% at 8 kbar with 2 mol % of **3a**. Experiments at lower pressure, e.g. 6 kbar, resulted in a decreased reaction rate (60% yield) (Table 2, entry 1). Based on these results further optimization studies were performed with **3a** for a more concentrated reaction mixture (1.0 M) at the 8–10 kbar pressure range (Table 2).

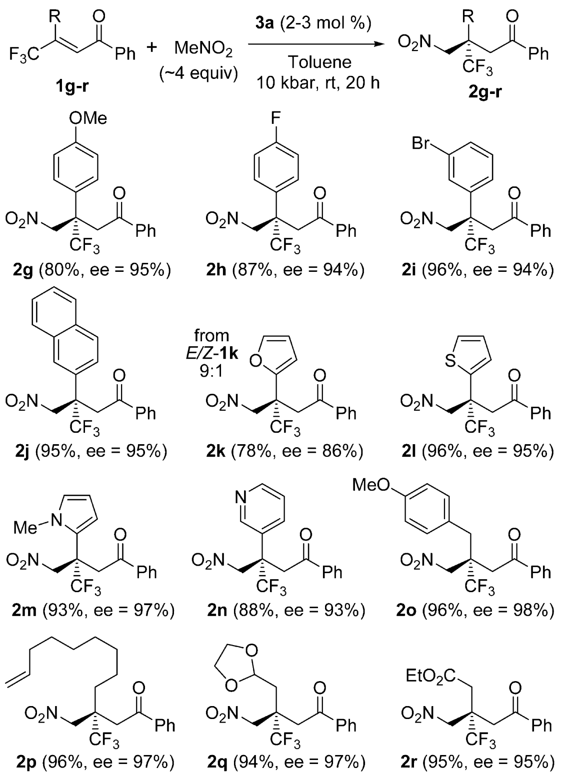
The E/Z ratio of enone **1a** used in the reaction has a very important influence on the enantioselectivity. Application of **1a** as a 94:6 E/Z mixture decreased the enantiomeric purity of the product to 86% (Table 2, entry 4). The model reaction is effective under 10 kbar even with 1 mol % of **3a** at rt or 0.5 mol % at 50 °C after 20 h (Table 2, entries 5 and 6). With 2 mol % of the catalyst satisfactory results were obtained also after shorter reaction times (5 and 2 h, Table 2, entries 7 and 8). To obtain optically pure product **2a** with opposite absolute configuration (R), more active catalyst **3d** (1–0.5 mol %) derived from quinine was applied (Table 2, entries 9–14). In this case good yield and very high enantioselectivity (81%, 98% ee) were observed even at 6 kbar after 20 h (Table 2, entry 13). We also demonstrated that this methodology is applicable with 1 mol % of **3a** and 0.5 mol % of **3d** for multigram scale synthesis (5–12 mmol) with good isolated yields (78–92%, Table 2, entries 3, 5, 9, and 10) and high enantioselectivity (ee = 94–97%). For comparison, the reaction with 10 mol % of **3d** under atmospheric pressure at 50 °C gives product **2a** with up to a 28% yield after 7 days.[16]

Having established the optimal conditions for the model reaction, we extended our investigations to reactions of other enones with nitromethane. All experiments were carried out under 9–10 kbar of pressure in the presence of **3a** (usually 2–3 mol %).[24] The reaction tolerates different heteroaromatic

Scheme 3. Products 2b−2f Modified in the Aryl-Ketone Part



Scheme 4. β-CF_3 Products 2g−2r Modified in β-Position



substituents neighboring the carbonyl group in enone (e.g., 2-pirydyl, 2-furyl, and 2-thienyl, Scheme 3). Except for **2f** (with a 2-thiazole), very high yields and enantioselectivity (92−96.5%), comparable to those of the model reaction, were observed.

We focused more attention on reactions of various β-trifluoromethylated enones with different aryl, heteroaryl, and alkyl substituents in the β-position. The structures of synthesized products **2g**−**2r** are presented in Scheme 4. The reaction tolerates different *para*- and *meta*-substituted phenyl groups in the β-position (see examples **2g**−**i**) including 2-naphtyl (**2j**).[25] Moreover, we extended the reaction scope to enones with different heteroaryl (products **2k**−**2n**) and alkyl (**2o**−**2r**) substituents in the β-position. As shown in Schemes 3 and 4, this reaction works very well for a broad range of β-CF_3 enones, affording good to very good yields and high enantioselectivity (ee = 92−98%) with a low loading of **3a** (2−3 mol %).[24,26] In all cases, control experiments under atmospheric pressure were performed and only traces of products were detected.

The structure and absolute configuration of products **2f** and **2l** was confirmed by X-ray crystallographic analysis.[24] The use of catalyst **3a** afforded enantiomerically enriched products (*S*)-**2f** and (*S*)-**2l**. Application of the more active pseudoenantiomeric catalyst **3d** leads to the opposite enantiomer.

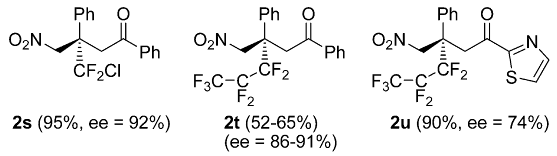
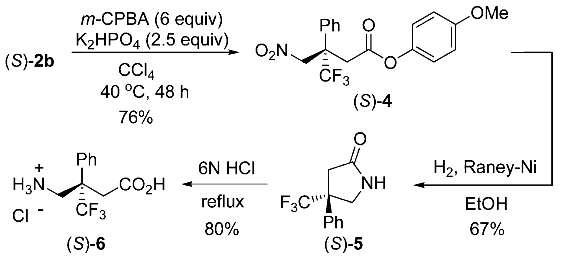


Figure 2. Products with CF_2Cl and $CF_2CF_2CF_3$ groups.

Scheme 5. Synthesis of β-CF_3−GABA Analog



Nitroketones with CF_2R type groups (e.g., CF_2Cl and $CF_2CF_2CF_3$) are also attainable using the high-pressure approach, and promising preliminary results are presented in Figure 2. The synthesis of **2t** with a perfluoro-*n*-propyl group is much more demanding and requires a higher catalyst loading (5−10 mol %)[24] compared to the model reaction of **1a**. Use of a 2-thiazole analog improved the yield but unfortunately reduced the enantioselectivity (see product **2u**).

The high-pressure approach has several advantages over the method under phase transfer catalysis conditions with *Cinchona*-based ammonium salts:[7c] a considerably lower loading of very well-defined and commercially available thiourea-organocatalysts (0.5−3 mol %), shorter reaction time (5−20 h), and slightly higher enantioselectivity (ee = 93−98% vs 90−93%). Moreover, the high-pressure method offers a much broader reaction scope, including products with heteroaromatic substituents as well as alkyl groups in the β-position.

Trifluoromethylated γ-nitroketones **2** are very interesting precursors for further applications. Shibata[7c] utilized them to synthesize trifluoromethyl diarylpyrrolines and their *N*-oxides. We demonstrate the synthesis of β-CF_3-β-aryl functionalized γ-aminobutyric acid **6** (Scheme 5) from nitroketone **2b**. Analogous β-monosubstituted-γ-aminobutyric acids (e.g., baclofen, pregabalin) are very important molecules in medicine and psychopharmacology.[27] Baeyer−Villiger oxidation of (*S*)-**2b** under optimized conditions followed by reduction with Raney nickel provide (*S*)-β-trifluoromethyl-β-phenyl-butyrolactam **5**. Finally, hydrolysis of the lactam afforded β-trifluoromethylated γ-amino acid hydrochloride **6**, the analog of phenibut (Scheme 5).

In summary, we have found that a combination of pressure (8−10 kbar) and cinchona alkaloid-thioureas **3a** and **3d** (0.5−3 mol %) can remarkably accelerate the reaction rate of nitromethane addition to sterically congested β-trifluoromethyl enones.[28] This approach allows for a very efficient asymmetric synthesis of γ-nitroketones containing all-carbon quaternary stereogenic centers bearing a trifluoromethyl group with very high enantioselectivity (ee = 92−98%). This work has also demonstrated the first example of a highly enantioselective (>90% ee) organocatalytic reaction proceeding via a noncovalent activation under high-pressure conditions (8−10 kbar).

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data, including NMR spectra, crystallographic data, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (d) Ojima, I. *J. Org. Chem.* **2013**, *78*, 6358.

(2) Theodoridis, G. In *Agrochemicals, Archaeology, Green Chemistry & Water*, Vol. 2; Tressaud, A., Ed.; Elsevier: 2006; Vol. 2, pp121−175.

(3) (a) Pagliaro, M.; Ciriminna, R. *J. Mater. Chem.* **2005**, *15*, 4981. (b) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496.

(4) (a) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119; Update 1 *Chem. Rev.* **2008**, *108*, PR1−PR43. (c) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633. (d) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (e) Zheng, Y.; Ma, J.-A. *Adv. Synth. Catal.* **2010**, *352*, 2745.

(5) (a) Christoffers, J.; Baro, A., Eds. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, 2005. (b) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583.

(6) (a) Kimura, M.; Yamazaki, T.; Kitazume, T.; Kubota, T. *Org. Lett.* **2004**, *6*, 4651. (b) Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625. (c) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 10769.

(7) (a) El Qacemi, M.; Smits, H.; Cassayre, J. Y.; Mulholland, N. P.; Renold, P.; Godineau, E.; Pitterna, T. WO 2011/154555 A1, 2011. (b) Kawai, H.; Okusu, S.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4959. (c) Kawai, H.; Yuan, Z.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5575. (d) Gao, J.-R.; Wu, H.; Xiang, B.; Yu, W.-B.; Han, L.; Jia, Y.-X. *J. Am. Chem. Soc.* **2013**, *135*, 2983. (e) Chen, Q.; Wang, G.; Jiang, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2014**, *16*, 1394. (f) Ma, C.-H.; Kang, T.-R.; He, L.; Liu, Q.-Z. *Eur. J. Org. Chem.* **2014**, 3981.

(8) Matoba, K.; Kawai, H.; Furukawa, T.; Kusuda, A.; Tokunaga, E.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5762.

(9) (a) Kawai, H.; Okusu, S.; Yuan, Z.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 2221. (b) Wu, S.; Pan, D.; Cao, C.; Wang, Q.; Chen, F.-X. *Adv. Synth. Catal.* **2013**, *355*, 1917. (c) Su, Y.; Ling, J.-B.; Zhang, S.; Xu, P.-F. *J. Org. Chem.* **2013**, *78*, 11053. (d) Liu, F.-L.; Chen, J.-R.; Feng, B.; Hu, X.-Q.; Ye, L.-H.; Lu, L.-Q.; Xiao, W.-J. *Org. Biomol. Chem.* **2014**, *12*, 1057. (e) Chen, W.; Jing, Z.; Chin, K. F.; Qiao, B.; Zhao, Y.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2014**, *356*, 1292.

(10) (a) Van Eldik, R., Klaerner, F. G., Eds. *High Pressure Chemistry: Synthetic Mechanistic and Supercritical Applications*; Wiley-VCH: Weinheim, 2002. (b) Matsumoto, K.; Acheson, R. M., Eds. *Organic Synthesis at High Pressure*; Wiley: New York, 1991. (c) Jurczak, J.; Baranowski, B., Eds. *High Pressure Chemical Synthesis*; Elsevier: Amsterdam, 1989.

(11) For reviews on asymmetric organocatalytic conjugate additions, see: (a) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, *2*, 42. (b) Vicario, J.; Badía, D.; Carillo, L.; Reyes, E. *Organocatalytic Enantioselective Conjugate Addition Reactions. A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*; RSC Publishing: Cambridge, 2010. (c) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2561.

(12) For examples of asymmetric organocatalytic 1,4-conjugate addition of nitromethane to *β*,*β*-disubstituted enones and enals, see: (a) Mitchell, C. E. T; Brenner, S. E.; Ley, S. V. *Chem. Commun.* **2005**, 5346. (b) Li, P.; Wang, Y.; Liang, X.; Ye, J. *Chem. Commun.* **2008**, 3302. (c) Kwiatkowski, P.; Dudziński, K.; Łyżwa, D. *Org. Lett.* **2011**, *13*, 3624. (d) Akagawa, K.; Kudo, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12786. (e) Hayashi, Y.; Kawamoto, Y.; Honda, M.; Okamura, D.; Umemiya, S.; Noguchi, Y.; Mukaiyama, T.; Sato, I. *Chem.—Eur. J.* **2014**, *20*, 12072. (f) Mukaiyama, T.; Ogata, K.; Sato, I.; Hayashi, Y. *Chem.—Eur. J.* **2014**, *20*, 13583 and ref 7a, 7c.

(13) By analogy to the synthesis of (*R*)-baclofen: Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257.

(14) For selected reviews on bifunctional amine−thiourea catalysis, see: (a) Siau, W.-Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499.

(15) (a) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (b) Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475. (c) Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450.

(16) Product (*R*)-**2a** was obtained: (a) 28% yield, 96% ee (reaction conditions based on ref 15a: $c_{[\mathbf{1a}]}$ = 1.0 mol/L, **3d** (10 mol %), 5 equiv of $MeNO_2$ in toluene, 1 bar, at 50 °C, 7 days). (b) 15% yield, 95% ee (reaction conditions based on ref 7a: $c_{[\mathbf{1a}]}$ = 0.5 mol/L, **3d** (10 mol %), 40 equiv of $MeNO_2$, 1 bar, at 50 °C, 7 days.

(17) (a) Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673. (b) Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157.

(18) Łyżwa, D.; Dudziński, K.; Kwiatkowski, P. *Org. Lett.* **2012**, *14*, 1540.

(19) For other representative examples of enantioselective organocatalytic reactions under high pressure, see: (a) Misumi, Y.; Bulman, R. A.; Matsumoto, K. *Heterocycles* **2002**, *56*, 599. (b) Sekiguchi, Y.; Sasaoka, A.; Shimomoto, A.; Fujioka, S.; Kotsuki, H. *Synlett* **2003**, 1655. (c) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208. (d) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *Tetrahedron Lett.* **2004**, *45*, 4353. (e) Mori, K.; Yamauchi, T.; Maddaluno, J.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Synlett* **2011**, 2080.

(20) Kwiatkowski, P.; Dudziński, K.; Łyżwa, D. Non-Classical Activation of Organocatalytic Reactions. In *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Dalko, P., Ed.; Wiley-VCH: Weinheim, 2013.

(21) (a) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (b) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (c) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

(22) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

(23) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(24) For more details see Supporting Information.

(25) The reaction is very difficult with enones containing *ortho*-substituted phenyls or 1-naphtyl in *β*-position. Shibata (ref 7c) also presented only products with *para*- and *meta*- substituted *β*-aryls.

(26) For less reactive enone **1k**, 4 mol % of **3a** was added. Only for product **2k** is the enantioselectivity lower (86% ee), because a difficult-to-separate *E*/*Z*-mixture (∼9:1) of enone **1k** was used.

(27) Gajcy, K.; Lochyński, S.; Librowski, T. *Curr. Med. Chem.* **2010**, *17*, 2338.

(28) Preliminary results were presented by P.K. at the 18th European Symposium on Organic Chemistry in Marseille, 7−12 July, 2013.