Efficient Organocatalytic Hetero-Diels–Alder Reactions of Activated Ketones under High Pressure for Direct Access to δ-Lactones[1]

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Abstract: A general and efficient protocol for the high-pressure-promoted hetero-Diels–Alder reactions of activated ketones has been developed. The reactions are successfully achieved by thiourea-derived organocatalysts, and the desired adducts, convenient precursors of δ-lactones, are obtained in good to high yields.

Key words: Hetero-Diels–Alder reaction, activated ketones, δ-lactones, thiourea catalyst, high pressure

δ-Lactones and related compounds are an important family of molecules that are present in many biologically active synthetic and naturally occurring products. δ-Lactones, as well as their open-chain homologues, are key components of the world's best-selling drugs, such as Lipitor and Zocor.[2] Hence, a variety of methods for the synthesis of δ-lactones have been developed to date.[3] These can be simply classified into four categories: (a) intramolecular lactonization of ω-hydroxy acids or their synthons,[4] (b) Baeyer–Villiger oxidation of cyclopentanone derivatives,[5] (c) ring-closing metathesis of acrylic esters,[6] and (d) hetero-Diels–Alder (HDA) reaction of carbonyl compounds.[7] Among these, the latter is particularly attractive, since the adducts can be easily transformed into the corresponding δ-lactones by simple oxidation.[8]

However, this synthetic protocol still has some significant limitations; that is, there are few known examples that involve the use of metal-free organocatalysis, and the reactions are mostly limited to aldehyde dienophiles.[8d,9] In fact, extension of this method to ketone dienophiles would provide an effective tool for the construction of a highly congested quaternary carbon center in a single step.[10]

We thought that the first issue might be solved by taking advantage of organocatalysts that can activate carbonyl dienophiles by using multiple hydrogen-bonding interactions, and the second limitation could be overcome by applying a high-pressure technique to accelerate sluggish Diels–Alder reactions under normal conditions (Scheme 1).

Recently, it has been recognized that hydrogen-bonding activation plays a critical role in organocatalytic DA reactions, and for this purpose thiourea-type catalysts (Figure 1)[11] have attracted considerable attention from synthetic chemists since the first report by Schreiner and Wittkopp.[12] In addition, high pressure can serve as an elegant means to not only promote DA reactions but also to stabilize hydrogen-bond scaffolds.[13]

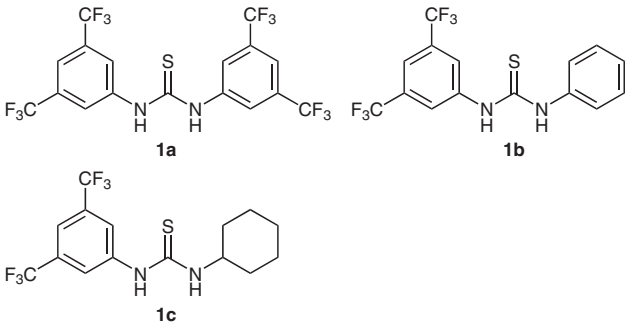
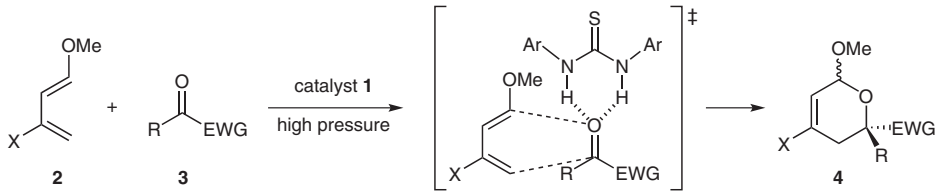


Figure 1 Structures of thiourea-based organocatalysts **1**

Against this background, we started our investigation by using the reaction between 1-methoxybutadiene (**2a**) and methyl benzoylformate (**3a**) in the presence of thiourea catalyst **1** in toluene as a model system.[14] The results are summarized in Table 1.[15]



Scheme 1

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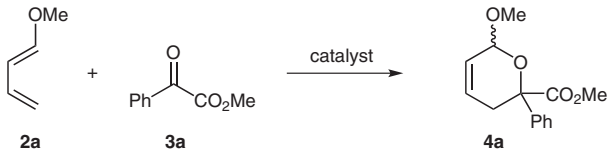
Table 1 Effects of Pressure, Catalyst, and Solvent[a]



2a **3a** **4a**

Entry	Catalyst (mol%)	Conditions	Yield (%)[b] (dr)
1	**1a** (30)	0.1 MPa, r.t., 72 h	trace
2	**1a** (30)	1.0 GPa, r.t., 10 h	91 (3.4:1)
3	**1a** (30)	0.8 GPa, r.t., 72 h	82 (4.9:1)
4	**1a** (30)	0.4 GPa, r.t., 72 h	58 (3.6:1)
5	–	1.0 GPa, r.t., 10 h	8 (1:2.1)
6	**1a** (20)	1.0 GPa, r.t., 10 h	86 (4.3:1)
7	**1a** (10)	1.0 GPa, r.t., 10 h	72 (4.9:1)
8[c]	**1a** (30)	1.0 GPa, r.t., 10 h	80 (2.6:1)
9[d]	**1a** (30)	1.0 GPa, r.t., 10 h	71 (3.4:1)
10[e]	**1a** (30)	1.0 GPa, r.t., 10 h	trace
11	**1b** (30)	1.0 GPa, r.t., 10 h	58 (2.6:1)
12	**1c** (30)	1.0 GPa, r.t., 10 h	40 (2.4:1)

[a] Unless otherwise noted, all reactions were carried out using **2a** (1.0 mmol) and **3a** (0.25 mmol) in the presence of catalyst **1** in toluene (ca. 2.5 mL).
[b] Isolated yield; dr was determined by ^{1}H NMR.
[c] In CH_2Cl_2.
[d] In CH_2Cl_2–toluene (1:1).
[e] In THF.

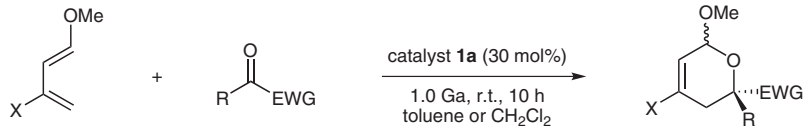
Increased pressure dramatically accelerated the rate of the reaction: at atmospheric pressure only a trace amount of **4a** was obtained even in the presence of 30 mol% of **1a**, whereas at 1.0 GPa, the reaction proceeded efficiently to give **4a** in 91% as a 3.4:1 diastereomeric mixture (Table 1, entries 1 and 2). As expected, the yields decreased at lower pressures (Table 1, entries 3 and 4).

The profound effect of catalyst activity is evident: in the absence of **1a** essentially no reaction was observed, and at lower loadings of the catalyst the product yields gradually decreased (Table 1, entries 5–7). Among the catalysts screened, **1a** was the best in terms of efficiency, which indicated that the presence of a 3,5-bis(trifluoromethyl)phenyl moiety on both sides of a thiourea framework was essential (Table 1, entry 2 vs. entries 11 and 12).

We also briefly examined the solvent effect in this HDA reaction: in dichloromethane or in dichloromethane–toluene mixture a similar result was obtained (71–80%), while THF led to insufficient conversion, suggesting that the polar coordinating solvent inhibits the formation of an effective hydrogen-bonding network between **1a** and **3a** (Table 1, entry 2 vs. entries 8–10).

With these optimized conditions in hand for α-keto ester **3a**, we then investigated the general scope of this method by using various combinations of dienes and activated ketones (Table 2).[15] In all of these examples, parallel experiments were performed in toluene and dichloromethane. For ethyl pyruvate (**3b**) and its trifluoro analogue **3c**, toluene appeared to be a better solvent than dichloromethane, and the adducts **4b** and **4c** were obtained in respective yields of 63% and 89% (Table 2, entries 1 and 2).[16]

Table 2 High-Pressure-Promoted HDA Reactions of Activated Ketones[a]



2a: X = H
2b: X = OTMS
3 **4**

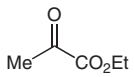
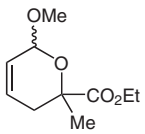
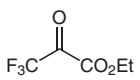
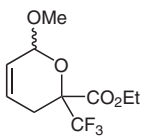
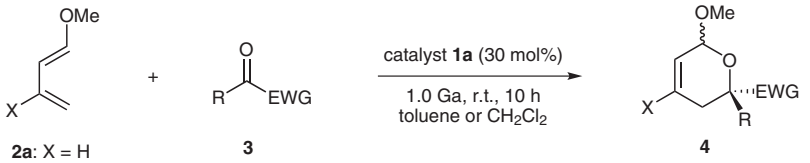
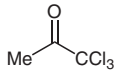
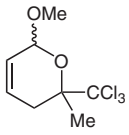
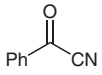
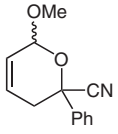
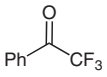
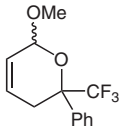
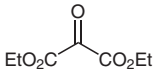
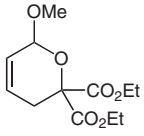
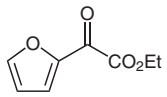
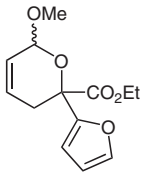
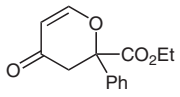
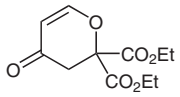
Entry	Diene **2**	Ketone **3**	Product **4**	Yield (%)[b] in toluene	Yield (%)[b] in CH_2Cl_2
1	**2a**	 **3b**	 **4b**	63 (dr 3.7:1)	26 (dr 2.4:1)
2	**2a**	 **3c**	 **4c**	89 (dr 2.1:1)	81 (dr 1.7:1)

Table 2 High-Pressure-Promoted HDA Reactions of Activated Ketones[a] (continued)



2a: X = H
2b: X = OTMS

3 4

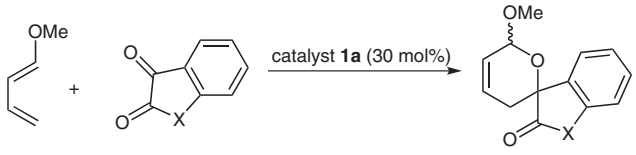
Entry	Diene **2**	Ketone **3**	Product **4**	Yield (%)[b] in toluene	Yield (%)[b] in CH_2Cl_2
3	**2a**	 **3d**	 **4d**	complex	complex
4	**2a**	 **3e**	 **4e**	64 (dr 1:0)	79 (dr 1:1)
5[c]	**2a**	 **3f**	 **4f**	76 (dr 2.2:1)	91 (dr 2.3:1)
6	**2a**	 **3g**	 **4g**	91	71
7	**2a**	 **3h**	 **4h**	78 (dr 4.8:0)	56 (dr 3.4:1)
8[d]	**2b**	**3a**	 **4i**	86	81
9[d,e]	**2b**	**3g**	 **4j**	38	62

[a] Unless otherwise noted, all reactions were carried out using **2** (1.0 mmol) and **3** (0.25 mmol) in the presence of 30 mol% of **1a** in toluene or CH_2Cl_2 (ca. 2.5 mL).
[b] Isolated yield; dr was determined by ^1H NMR.
[c] The amount of **1a** used was 10 mol%.
[d] In the absence of catalyst **1a**.
[e] At 0.8 GPa for 12 h.

Although 1,1,1-trichloroacetone (**3d**) gave only a complex mixture of products, ketones **3e–h** produced the corresponding adducts **4e–h** in yields of 56–91% in either solvent (Table 2, entries 3–6). Finally, Danishefsky's diene **2b** was quite reactive, and, even in the absence of the catalyst, the reaction with **3a** or **3g** afforded the respective dihydropyrone derivatives **4i** and **4j** in good to high yields after conventional workup (TFA in Et_2O).

Encouraged by these results, we further examined the application of the present method to cyclic ketone systems such as benzofuran-2,3-dione (**3i**) and *N*-Boc-isatin (**3j**) as an unprecedented carbonyl-dienophile component (Table 3).

Table 3 HDA Reactions of Benzofuran-2,3-dione (**3i**) and *N*-Boc-isatin (**3j**)[a]



Entry	Ketone **3**	Conditions	Yield (%)[b] in toluene	Yield (%)[b] in CH_2Cl_2
1	**3i**	0.1 MPa, r.t., 72 h[c]	21[d]	17[d]
2		0.1 MPa, r.t., 36 h	63	12[e]
3		0.8 GPa, r.t., 12 h[c]	90	79
4		0.8 GPa, r.t., 12 h	74	23[e]
5	**3j**	0.1 MPa, r.t., 72 h[c]	6[d]	13[d]
6		0.1 MPa, r.t., 36 h	62	94
7		1.0 GPa, r.t., 10 h[c]	60	95
8		1.0 GPa, r.t., 10 h	82	62

[a] Unless otherwise noted, all reactions were carried out using **2a** (1.0 mmol) and **3i** or **3j** (0.25 mmol) in the presence of 30 mol% of **1a** in toluene or CH_2Cl_2 (ca. 2.5 mL).
[b] Isolated yield. The product was obtained as a mixture (ca. 1:1) of diastereomers determined by ^{1}H NMR analysis.
[c] No **1a** catalyst was used.
[d] Incomplete reaction.
[e] The reaction gave a complex mixture of products.

Interestingly, **3i** and **3j** were sufficiently reactive even at atmospheric pressure and under **1a**-catalyzed conditions the corresponding spirocyclic adducts **4k** and **4l** were obtained, albeit slowly, while the uncatalyzed systems were again useless (Table 3, entries 1, 2, 5, 6).[17] On the other hand, at 0.8–1.0 GPa, the reactions proceeded quite smoothly for both substrates regardless of the use of catalyst **1a** (Table 3, entries 3, 4, 7, 8).

In summary, we have developed a new efficient method for the HDA reaction of a variety of activated ketones with dienes in the presence of **1a** as an organocatalyst under high pressure. Notably, since HDA products **4** can be easily oxidized to the corresponding δ-lactone derivatives,[18] the overall process constitutes a rapid means for preparing this important family of compounds. Furthermore, it may be easy to extend the present method to asymmetric versions using chiral thiourea catalysts,[11] and further studies along these lines are now in progress in our laboratory.

Acknowledgment

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References and Notes

(1) High-Pressure Organic Chemistry, Part 35. For Part 34, see: Azad, S.; Kobayashi, T.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron Lett.* **2009**, *50*, 48.
(2) Istvan, E. S.; Deisenhofer, J. *Science* **2001**, *292*, 1160.
(3) Reviews: (a) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377. (b) Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 225.
(4) Selected recent examples: (a) Perez, L. J.; Micalizio, G. C. *Synthesis* **2008**, 627. (b) Habel, A.; Boland, W. *Org. Biomol. Chem.* **2008**, *6*, 1601. (c) Evans, D. A.; Burch, J. D.; Hu, E.; Jaeschke, G. *Tetrahedron* **2008**, *64*, 4671. (d) Jung, W.-H.; Guyenne, S.; Riesco-Fagundo, C.; Mancuso, J.; Nakamura, S.; Curran, D. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1130. (e) Crimmins, M. T.; Dechert, A.-M. R. *Org. Lett.* **2009**, *11*, 1635. (f) Su, Y.; Xu, Y.; Han, J.; Zheng, J.; Qi, J.; Jiang, T.; Pan, X.; She, X. *J. Org. Chem.* **2009**, *74*, 2743.
(5) Selected recent examples: (a) Wu, F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4301. (b) Pichlmair, S.; de Lera Ruiz, M.; Vilotijevic, I.; Paquette, L. A. *Tetrahedron* **2006**, *62*, 5791. (c) Kumar, I.; Rode, C. V. *Tetrahedron: Asymmetry* **2007**, *18*, 1975. (d) Hanessian, S.; Auzzas, L. *Org. Lett.* **2008**, *10*, 261.
(6) Selected recent examples: (a) Shibahara, S.; Fujino, M.; Tashiro, Y.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2008**, *10*, 2139. (b) Akaike, H.; Horie, H.; Kato, K.; Akita, H. *Tetrahedron: Asymmetry* **2008**, *19*, 1100. (c) Chandrasekhar, S.; Rambabu, Ch.; Reddy, A. S. *Tetrahedron Lett.* **2008**, *49*, 4476. (d) Ding, F.; Jennings, M. P. *J. Org. Chem.* **2008**, *73*, 5965.
(7) Selected recent examples: (a) Lucas, B. S.; Gopalsamuthiram, V.; Burke, S. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 769. (b) Jensen, K. H.; Sigman, M. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 4748. (c) Dilger, A. K.; Gopalsamuthiram, V.; Burke, S. D. *J. Am. Chem. Soc.* **2007**, *129*, 16273. (d) Yu, Z.; Liu, X.; Dong, Z.; Xie, M.; Feng, X. *Angew. Chem. Int. Ed.* **2008**, *47*, 1308. (e) Yang, X.-B.; Feng, J.; Zhang, J.; Wang, N.; Wang, L.; Liu, J.-L.; Yu, X.-Q. *Org. Lett.* **2008**, *10*, 1299. (f) Lin, L.; Chen, Z.; Yang, X.; Liu, X.; Feng, X. *Org. Lett.* **2008**, *10*, 1311. (g) Tiseni, P. S.; Peters, R. *Org. Lett.* **2008**, *10*, 2019.
(8) Reviews of HDA reactions: (a) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S.; Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, **2002**. (b) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558. (c) Carmona, D.; Lamata, M. P.; Oro, L. A. *Coord. Chem. Rev.* **2000**, *200-202*, 717. (d) Jørgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093. (e) Gouverneur, V.; Reiter, M. *Chem. Eur. J.* **2005**, *11*, 5806. (f) Lin, L.; Liu, X.; Feng, X. *Synlett* **2007**, 2147.
(9) Recent examples: (a) Moreau, X.; Bazán-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 7288. (b) Broustal, G.; Ariza, X.; Campagne, J.-M.; Garcia, J.; Georges, Y.; Marinetti, A.; Robiette, R. *Eur. J. Org. Chem.* **2007**, 4293. (c) Chen, I.-H.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 5151.

(10) (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (c) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591. (d) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (e) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J.; Baro, A., Eds.; Wiley-VCH: Weinheim, **2005**. (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (g) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (h) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647. (i) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853.

(11) (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (e) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (f) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (g) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785. (h) Connon, S. J. *Chem. Commun.* **2008**, 2499. (i) Connon, S. J. *Synlett* **2009**, 354.

(12) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217.

(13) (a) *Organic Synthesis at High Pressures*; Matsumoto, K.; Acheson, R. M., Eds.; Wiley: New York, **1990**. (b) For a huge compilation of high-pressure reactions, see: Matsumoto, K.; Hamana, H.; Iida, H. *Helv. Chim. Acta* **2005**, *88*, 2033.

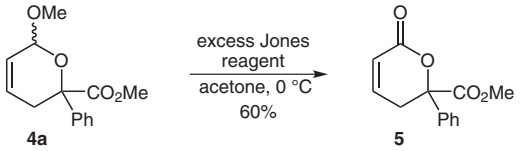
(14) Review of DA reactions of 1-alkoxydienes, see: Maddaluno, J. *Synlett* **2006**, 2534.

(15) **General Procedure**
A mixture of diene (**2**, 1.0 mmol) and ketone (**3**, 0.25 mmol) in the presence of **1a** (0.1 mmol) in toluene or CH_2Cl_2 (ca. 2.5 mL) was placed in a Teflon reaction vessel, and the mixture was allowed to react at 1.0 GPa and r.t. for 10 h. After the pressure was released, the mixture was concentrated and purified by silica gel column chromatography (elution with hexane–Et_2O) to afford the pure adduct **4**.

(16) (a) Under uncatalyzed conditions, much higher pressures (2.0 GPa) are necessary to gain satisfactory results: Jurczak, J.; Chmielewski, M.; Filipek, S. *Synthesis* **1979**, 41. (b) For $Eu(fod)_3$-catalyzed reactions at 1.0 GPa and 50 °C, see: Jurczak, J.; Golebiowski, A.; Bauer, T. *Synthesis* **1985**, 928.

(17) For a formal synthesis of the **4k**-type compound, see: Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346.

(18) Typically, treatment of **4a** with excess Jones' reagent in acetone (0 °C, 3 h) gave the corresponding dihydropyranone **5** in 60% yield: colorless needles (Scheme 2); mp 104–105 °C (hexane–CH_2Cl_2). FTIR (KBr): ν = 1745, 1718 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.85 (1 H, dt, *J* = 18.2, 2.5 Hz), 3.49 (1 H, ddd, *J* = 18.2, 5.8, 1.0 Hz), 3.73 (3 H, s), 6.12 (1 H, ddd, *J* = 9.8, 2.5, 1.0 Hz), 6.91 (1 H, ddd, *J* = 9.8, 5.8, 2.5 Hz), 7.33–7.44 (3 H, m), 7.60–7.63 (2 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.0, 53.4, 84.2, 121.8, 124.9 (2×), 128.7 (2×), 128.9, 137.1, 143.6, 162.2, 171.0. Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.13; H, 5.35.



Scheme 2