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Reversal of Chemoselectivity in Diels–Alder Reaction with α,*β*-Unsaturated Aldehydes and Ketones Catalyzed by Brønsted Acid or Lewis Acid

Daisuke Nakashima and Hisashi Yamamoto*

Department of Chemistry, University of Chicago, 5735 South Ellis Avenue,
Chicago, Illinois 60637

yamamoto@uchicago.edu

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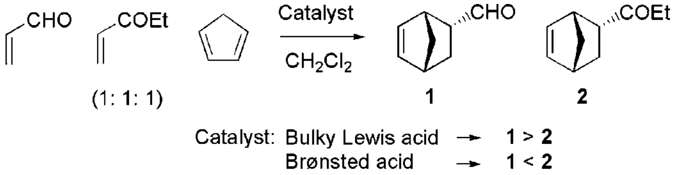
ABSTRACT



High chemoselectivity was observed in the Diels–Alder reaction of α,*β*-unsaturated aldehyde and α,*β*-unsaturated ketone with cyclopentadiene. Using Tf_2NH as catalyst, the reaction gave Diels–Alder adduct derived from α,*β*-unsaturated ketone as a major product. On the other hand, bulky Lewis acid, $B(C_6F_5)_3$, gave mainly the cycloadduct of α,*β*-unsaturated aldehyde and cyclopentadiene.

The Brønsted acid catalyzed Diels−Alder reaction was reported by Wassermann in 1942.[1] This was almost two decades earlier than the discovery of the Lewis acid accelerated Diels−Alder reaction.[2] The Lewis acid-catalyzed Diels−Alder reaction is one of the most investigated areas in organic synthesis. Many regio-, chemo-, diastereo-, and enantioselective Diels−Alder reactions catalyzed by various Lewis acids have been developed to date.[3] In contrast, the Brønsted acid-catalyzed Diels−Alder reaction has not received much attention for a long time. Only a few reports describe the diastereo- and enantioselective Diels−Alder reactions catalyzed by Brønsted acid.[4] To the best of our knowledge, research on the chemoselective Brønsted acid catalyzed Diels−Alder reaction has not been reported. Control of the chemoselectivity in the Diels−Alder reaction is still of great synthetic interest. Herein we describe a highly chemoselective Diels−Alder reaction catalyzed by Brønsted acid and the unprecedented reversal of the chemoselectivity by the choice of acid catalyst.

Our studies began with the chemoselective Diels−Alder reaction using numerous Brønsted acids. In the presence of various Brønsted acid catalysts, the Diels−Alder reaction of cyclopentadiene with acrolein and ethyl vinyl ketone (1 equiv of each), was carried out at −78 °C for 1 h. After the reaction, the ratio of Diels−Alder adducts of α,*β*-unsaturated aldehyde **1** and of α,*β*-unsaturated ketone **2** was determined

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[1] (a) Wassermann, A. *J. Chem. Soc.* **1942**, 618. (b) Wassermann, A. *J. Chem. Soc.* **1942**, 623.

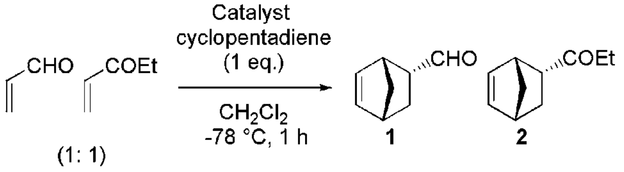
[2] Yate, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.

[3] For recent reviews, see: (a) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jøgensen, K. A., Ed.; Wiley-VCH: Weinheim, 2002. (b) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinhelm, 2000; Vols. 1 and 2. (c) *Lewis Acid Reagent: A Practical Approach*; Yamamoto, H., Ed.; Oxford University Press: Oxford, 1999.

[4] (a) Sammakia, T.; Berliner, M. A. *J. Org. Chem.* **1995**, *60*, 6652. (b) Schuster, T.; Bauch, M.; Dürner, G.; Göbel, M. W. *Org. Lett.* **2000**, *2*, 179. (c) Palmo, C.; Oiarbide, M.; Garcia, J. M.; González, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 10288. (d) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (e) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature.* **2003**, *424*, 146. (f) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846. (g) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

10.1021/ol047341s CCC: $30.25

Table 1. Chemoselective Diels–Alder Reaction with Brønsted Acids



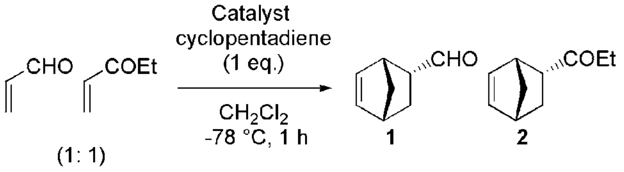
entry	catalyst, mol %	yield[a] (%)	ratio of **1**/**2**
1	Tf_2NH, 5	86	12:88
2[b]	Tf_2NH, 5	93	5:95
3	$C_6F_5CHTf_2$, 5	86	8:92
4[b]	$C_6F_5CHTf_2$, 5	84	1:99
5	TfOH, 5	79	9:91
6	MsOH, 5	45	29:71
7	*p*-TsOH·H_2O, 5	8	38:63

[a] Isolated yield. [b] The reaction was carried out at −96 °C.

by ^{1}H NMR. The results are summarized in Table 1. Surprisingly, most Brønsted acids gave **2** almost exclusively. Although the reaction with super Brønsted acids, which are triflylimide (Tf_2NH), triflic acid (TfOH), and pentafluorophenylbistriflylmethane ($C_6F_5CHTf_2$),[5] proceeded smoothly and gave desired the cycloadducts quantitatively (entries 1, 3, and 4), the reactivity of methanesulfonic acid and *p*-toluenesulfonic acid were relatively poor (entries 5 and 6). Thus, super Brønsted acids seem to be a suitable catalyst for the Diels–Alder reaction. It was noted that the ratio of **1**/**2** was improved from 12:88 to 5:95 when the reaction with Tf_2NH was carried out at −96 °C (entry 2).

Typical Lewis acids, BF_3•OEt_2, $TiCl_4$, $EtAlCl_2$, $SnCl_4$, and $B(C_6F_5)_3$, were also examined for the same reaction, and the results are summarized in Table 2. When BF_3•OEt_2, $TiCl_4$, or $EtAlCl_2$ was used as a catalyst, the reaction gave mainly **2**. However, the ratios of **1**/**2** were lower than those of super Brønsted acids (entries 1−3). Furthermore, in the presence of $SnCl_4$ or $B(C_6F_5)_3$, the reaction gave **1** as a major product. Thus, Tf_2NH showed high ketone selectivity and $SnCl_4$ and $B(C_6F_5)_3$ revealed high aldehyde selectivity.

Table 2. Chemoselective Diels–Alder Reaction with Various Lewis Acids

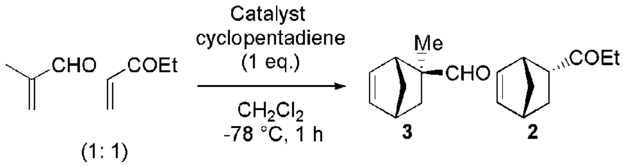


entry	catalyst, mol %	yield[a] (%)	ratio of **1**/**2**
1	BF_3·OEt_2, 5	25	26:74
2	$TiCl_4$, 5	92	25:75
3	$EtAlCl_2$, 5	89	28:72
4	$SnCl_4$, 5	73	97:3
5	$B(C_6F_5)_3$, 50	88	85:15

[a] Isolated yield.

To explore the generality of such a chemoselective Diels–Alder reaction catalyzed by super Brønsted acids or Lewis acids, we studied other α,*β*-unsaturated aldehydes and ketones. The reactivity of methacrolein and ethyl vinyl ketone with cyclopentadiene was compared, and the results are summarized in Table 3. In the presence of $SnCl_4$ the reaction unexpectedly proceeded ketone selectively (entry 3 in Table 3). This would be due to the lower reactivity of methacrolein than acrolein. However, Tf_2NH and $B(C_6F_5)_3$ still revealed ketone selectivity (11:89) and aldehyde selectivity (75:25), respectively (entries 2 and 4 in Table 3).

Table 3. Scope and Limitation of Dienophile

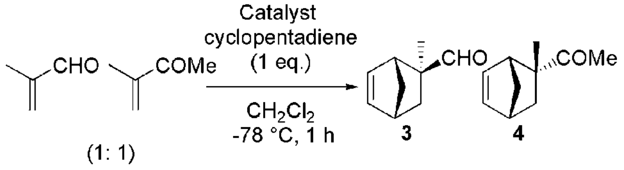


entry	catalyst, mol %	yield[a] (%)	ratio of **3**/**2**
1	Tf_2NH, 5	93	20:80
2[b]	Tf_2NH, 5	94	11:89
3	$SnCl_4$, 5	94	40:60
4	$B(C_6F_5)_3$, 20	87	75:25

[a] Isolated yield. [b] The reaction was carried out at −96 °C.

Unfortunately, the ketone selectivity was completely lost for methacrolein and 3-methyl-3-buten-2-one (Scheme 1). This would be due to the significantly decreased reactivity of α,*β*-unsaturated ketone by the substituent on the α-position. A substituent on the *β*-position also decreases the reactivity of both α,*β*-unsaturated aldehyde and ketone. The reaction was conducted at a higher temperature. Nevertheless,

Scheme 1. Chemoselective Diels–Alder Reaction with Methacrolein and 3-Methyl-3-butene-2-one



Tf_2NH (5 mol %) : 91 % yield, **3**: **4** = 71: 29
$B(C_6F_5)_3$ (20 mol%) : 95 % yield, **3**: **4** = 91: 9

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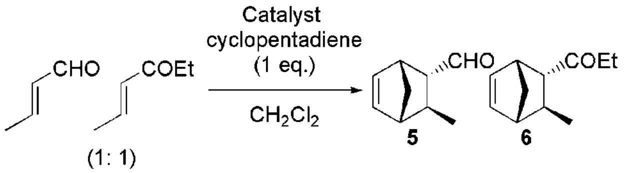
[5] (a) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4077. (b) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett.* **2002**, 1296. (c) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett.* **2002**, 1299. (d) Hasegawa, A.; Ishihara, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5731.

Tf_2NH and $B(C_6F_5)_3$ showed high ketone and aldehyde selectivity, respectively (Scheme 2).

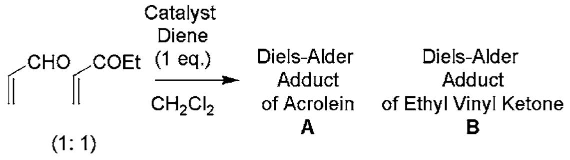
Scheme 2. Chemoselective Diels−Alder Reaction with Crotonaldehyde and 2-Hexen-4-one

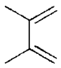
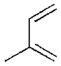


Tf_2NH (5 mol %) (-40 °C, 1 h) :75 % yield, **5**: **6** = 10: 90
$B(C_6F_5)_3$ (30 mol%) (-20 °C, 1 h) :84 % yield, **5**: **6** = 92: 8

These chemoselectivities were observed for other dienes; thus, 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene, and isoprene with Tf_2NH and $B(C_6F_5)_3$ expectedly gave the corresponding Diels−Alder adduct with high chemoselectivity (Table 4).

Table 4. Scope and Limitation of Diene



entry	diene	catalyst, mol %	conditions	yield (%),ratio of **A**: **B**
1		Tf_2NH, 5	-40°C, 2 h	64, 39: 61
2		$B(C_6F_5)_3$, 30	-40°C, 2 h	85, 94: 6
3		Tf_2NH, 5	-40°C, 2 h	81, 19: 81
4		$B(C_6F_5)_3$, 30	-40°C, 2 h	75, 95: 5
5		Tf_2NH, 5	-40°C, 4 h	51, 22: 78
6		$B(C_6F_5)_3$, 30	-40°C, 4 h	62, 90: 10

Previously, we reported high chemoselective Diels−Alder reactions using exceptionally bulky Lewis acids.[6] Bulky Lewis acid can recognize the two different carbonyl groups by the steric effect. The present chemoselectivity can be explained as follows: Brønsted acid could be regarded as the smallest Lewis acid, which would be insensitive to the steric effect. Therefore, Brønsted acid selectively coordinates a more basic carbonyl group such as α,β-unsaturated ketone.[7] On the other hand, bulky Lewis acid, $B(C_6F_5)_3$, preferentially coordinates to α,β-unsaturated aldehyde due to the severe steric repulsion present in α,β-unsaturated ketone (Figure 1).

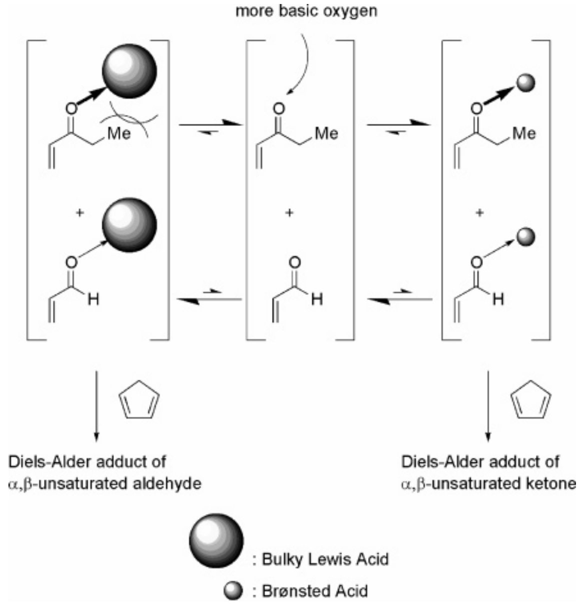


Figure 1. Coordination of acid catalysis for the high chemoselectivity.

In conclusion, we have described the utility of Brønsted acid as an effective catalyst for the Diels−Alder reaction of α,β-unsaturated ketone. Brønsted acid and bulky Lewis acid catalyst showed high chemoselectivity in the Diels−Alder reaction, and we propose that this high chemoselectivity arises from a combination of steric as well as electronic effects of the dienophile.

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Supporting Information Available: Experimental procedure and full characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[6] (a) Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 1089. (b) Maruoka, K.; Imoto, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 12115. (c) Maruoka, K.; Saito, S.; Yamamoto, H. *Synlett* **1994**, 439. (d) Saito, S.; Maruoka, K.; Yamamoto, H. *Kagaku* **1995**, *50*, 190.

[7] The importance of the Lewis basisity of the carbonyl compounds on chemoselectivity between aldehyde and ketone in Lewis acid catalysis have been reported. (a) Mikami, K.; Terada, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 6, 5456. (b) Chen, J.-x.; Sakamoto, K.; Orita, A.; Otera, J. *J. Org. Chem.* **1998**, *63*, 9739. (c) Asao, N.; Asano, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3206.