A Simple Route to Selective Diels-Alder Reactions Using Modified Zeolite Y

H. Mahmoudi Najafi, M. Ghandi,* and F. Farzaneh†
Department of Chemistry, Faculty of Science, University of Tehran, P.O. Box 14155-6455, Tehran, Iran
† *Department of Chemistry, University of Az-Zahra, Tehran, Iran*

(Received November 9, 1999; CL-990958)

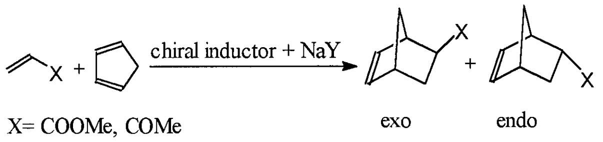
Synthetically useful Diels-Alder reactions of different dienophiles with cyclopentadiene in the presence of chirally modified zeolite Y as simple and accessible medium led to high rate and diastereoselectivity and low to moderate enantioselectivity.

In the absence of catalyst, the Diels-Alder reactions sometimes require high temperature and/or high pressure. It was therefore a major breakthrough when it was found that Lewis acids (e.g. $AlCl_3$) catalyze the Diels-Alder reactions allowing running in very mild conditions often below 0 °C to afford high rate and stereoselectivity. In order to enhance the rate and selectivity, the reaction has been performed using a variety of catalysts or under specific reaction conditions: 1) by using homogeneous Lewis acids[1] or heterogeneous acids,[2] 2) under high pressure,[3] 3) in aqueous media,[4] 4) in confined spaces.[5]

The asymmetric Diels-Alder reaction was first investigated by introducing a chiral auxiliary on the dienophile and then successfully followed by using chiral Lewis acids,[6] as the efficient work of Corey which afforded the ee of 96:4 in the reaction of 2-bromoacrolein with furan.[7] Although, recent work of Itsuno,[8] which has used new chiral polymeric catalyst, and the results of moderate to high ee is remarkable, the method cannot be recommended to organic synthetic chemists due to the complexity of the catalyst.

Combined characters of acidic sites (Lewis and Brønsted) and shape medium which both enhance the rate and diastereoselectivity of Diels-Alder cycloadducts are remarkably present in the simple system of crystalline microporous solid which is called zeolite. The reports on the observation of catalysis by zeolite electron acceptors have prompted several investigators to use the zeolites as catalysts in Diels-Alder reactions.[9] It has been observed that zeolites can dramatically enhance the rate, which is comparable with the use of elevated pressure.[10] Moreover, using these catalysts have afforded highly regioselective and diastereoselective reactions and good to excellent yields.[11] Our main goal of this research was to design a very simple and easily accessible system, which can promote the asymmetric Diels-Alder reaction. Since, a part of our recent research group has been concentrated on zeolite chemistry and its applications,[12] and due to a recent communication which has described using of zeolite Y included chiral inductor successfully as a remarkable medium for the intramolecular photocyclization reaction,[13] we decided to study the Diels-Alder reactions using chirally modified zeolite Y. Our literature survey showed that these chirality inducing systems have not been used before in Diels-Alder reactions.

The catalysts were prepared by exchanging (-)-ephedrine hydrochloride and (-)-histidine hydrochloride within NaY zeolite. The loading (or exchanging) level of the chiral inductor was maintained such that every supercage on an average contained one molecule of the chiral compound. In a typical synthetic procedure, 1 mmol of the dienophile (methyl vinyl ketone and methyl acrylate) and 1.2 mmol of freshly distilled cyclopentadiene were added to 20 ml of CH_2Cl_2 containing 1 g of vacuum pre-dried zeolite catalyst. The mixture was stirred for 4 h under nitrogen atmosphere at 0 °C. After filtration the filtrate was concentrated under reduced pressure by a rotary evaporator. We used the NMR method to analyze the products in the presence of chiral shift reagent $Eu(hfpc)_3$.[14] The results are shown in Table 1. The reaction in the presence of zeolite loaded with (-)-ephedrine and (-)-diethyl tartrate could not be conducted since the chiral compound will immediately diffuse out of the cavities in moderate to high polar solvents (CH_2Cl_2).



We also used the loading method in order to compare the results of reactions taking place inside the cavities with those obtained in the aforementioned synthetic procedure (see Table 1).[15] Under the synthetic conditions, the diene and dienophile have a lower chance to condense and form the cycloadduct outside the supercages due to lack of the required activation energy available at 0 °C. The reaction takes place as soon as the substrates collide with each other within the supercages, where the rate enhances due to the presence of Lewis and Brønsted acidic sites. The product will then be expelled outside with the aim of solvent molecules and makes the microreactor host available for reception of the reactant guest molecules. The lower enantioselectivity observed in the synthetic method might be resulted either from the change in the reactivity of chirally modified sites in different solvents or from that part of reactions taking place outside the supercages. In both methods the best results obtained with (-)-histidine·HCl as chiral inductor in NaY.

From the results presented in Table 1, we tentatively conclude that a three-point interaction between the dienophile molecule, the chiral inductor and the zeolite interior is necessary to induce the chirality in the cycloadducts. The fact that low functional chiral inductors fail to yield significant enantioselectivity supports this idea (compare ephedrine with histidine). The recognition points in the case of (-)-histidine·HCl are most likely the carboxyl, amino and the imidazole groups of the chiral inductor, the cations of the zeolite and the carbonyl group of the dienophile. The cations present in the zeolite help to anchor the chiral inductor to the interior surface. This arrangement is expected to favor one of the modes of cycloaddition.

Due to rapid polymerization of such dienophiles and cyclopentadiene, the yield decreases with longer reaction times in homogeneous Diels-Alder reactions with or without catalyst.[16] In all of our reactions no trace of dicyclopentadiene

Table 1. Endo and ee percentages for Diels-Alder reactions of methyl acrylate (MA) and methyl vinyl ketone (MVK) with cyclopentadiene in dichloromethane and hexane using chirally modified zeolite NaY[a,b]

Chiral Inductor	Dichloromethane[c]		Hexane[d]	
	MA	MVK	MA	MVK
(-)-Histidine·HCl	93 (13)	92.5 (14)	95 (18)	94 (18.5)
(-)-Ephedrine·HCl	90 (10)	92 (6)	96 (12.5)	93.5 (8)
(-)-Ephedrine	---	---	90 (6)	91 (5)
(-)-Diethyl tartrate	---	---	94 (16)	92 (12)

[a] The products were analyzed by GC for the endo and by NMR using a chiral shift reagent for the ee percentages. The ee percentages are presented in parentheses. [b] The yields were in the range of 70-90%. [c] The reactions ran at 0 °C for 4 h. [d] The reactions ran at room temperature for 4 h.

Table 2. Endo and yield percentages for Diels-Alder reactions with cyclopentadiene in zeolite MY[a,b]

Dienophile	Li	Na	K	Cs	Standard[c]
Methyl acrylate (MA)	91.9 (85)	94.5 (87)	99 (95)	99 (95)	78.7 (70)
Methyl vinyl ketone (MVK)	91.1 (72)	92 (68)	92.5 (75)	96.4 (78)	82.9 (61)
Methyl propenyl ketone (MPK)	97 (65)	97.8 (62)	98 (67)	98.5 (70)	73.6 (55)
Acrylonitrile (AN)	46.5 (75)	63.2 (67)	81.6 (87)	89 (78)	47.1 (63)
Methacrylonitrile (MAN)	16.1 (58)	20.5 (64)	25.1 (63)	40.7 (68)	13.4 (35)

[a] All the reactions ran in dichloromethane at 0 °C for 4 h. The products were analyzed by GC using an internal standard. [b] The yields are presented in parentheses. [c] The standard reactions ran without zeolite under the same conditions.

was observed in the products, a material which accompanies the products even after preparative GC separation.[17]

In another part of our research, we used alkali metal exchanged zeolites Y to see the cation size effect on the diastereoselectivity of the Diels-Alder reactions. For this, five different dienophiles have been used which consist of different functional groups of ketone, ester and nitrile. These dienophiles were reacted with cyclopentadiene in the presence of zeolites Y exchanged with alkali metals (Li, Na, K, and Cs) in CH_2Cl_2 at 0 °C. The results are presented in Table 2.

We observed that by increasing the cation size (ionic radii) the endo:exo ratio increases. This trend supports the shape selectivity behavior of zeolite Y resulted in the formation of the more compact endo adduct which has less molecular volume. It is evident that even the smallest cation of the group (Li^+) exchanged within zeolite has a dramatic change on the endo:exo ratio of cycloadducts of MA, MVK and MPK with cyclopentadiene (see Table 2). CsY shows good to excellent ratios with the maximum amount of about 99% in the case of MA. Moreover, the improvement of synthetic yield percentage compared to the standard procedure is consistent with the acidic behavior of zeolite Y used in these reactions. Applying the loading method in these reactions in *n*-hexane showed slight diastereoselectivity improvement with respect to the synthetic method. Therefore, the more diastereoselectivity is the consequence of maximum shape selectivity since the reaction is taking place totally inside the cavities.

In summary we have shown that high rate, diastereoselectivity and low to moderate enantioselectivity have been obtained using modified zeolite Y as microreactor.

Acknowledgment is made to the Research Council of the University of Tehran for support of this research.

References and Notes

1 S. Yamabe, T. Dai, and T. Minato, *J. Am. Chem. Soc.*, **117**, 10994 (1995).

2 C. Cativiela, J. M. Fraile, J. I. Garcia, J. A. Mayoral, F. Figueras, L. C. de Menorval, and P. J. Alonso, *J. Catal.*, **137**, 394 (1992); M. Onaka and R. Yamasaki, *Chem. Lett.*, **1998**, 259.

3 G. Isaacs, *Chem. Ber.*, **1987** , 47.

4 D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, **102**, 7816 (1980).

5 J. Kang and J. Rebek ,Jr., *Nature*, **385**, 50 (1997); E. Endo, T. Koike, T. Sawaki, O. Hayashida, H. Masuda, and Y. Aoyama, *J. Am. Chem. Soc.*, **119**, 4117 (1997).

6 H. B. Kagan and O. Riant, *Chem. Rev.*, **92**, 1007 (1992)

7 E. J. Corey and T. P. Loh, *Tetrahedron Lett.*, **34**, 3979 (1993).

8 K. Kamahori, K. Ito, and S. Itsuno, *J. Org. Chem.*, **61**, 8321 (1996).

9 S. Ghosh and N. Blaud, *J. Catal.*, **95**, 300 (1985).

10 U. Pindur, G. Lutz, and C. Otto, *Chem. Rev.*, **93**, 741(1993).

11 L. Eklund, A. Axelsson, A. Nordahl, and R. Carlson, *Acta Chem. Scand.*, **47**, 581 (1993); N. Murthy and C. N. Pillai, *Synth. Commun.*, **21**, 783 (1991).

12 F. Farzaneh and F. Nikkhoo, *J. Sci. I.R. Iran*, **6**, 155 (1995); M.M. Akbarnejd, F. Farzaneh, and M. Khatamian Oskooi, *Iran. J. Chem. & Chem. Eng.*, **10**, 14 (1991); F. Farzaneh, J. Soleimannejad, and M. Ghandi, *J. Mol. Catal. A*, **118**, 223 (1997); R. Sadeghpoor, M. Ghandi, H. Mahmoudi Najafi, and F. Farzaneh, *J. Chem Soc., Chem. Commun.*, **1998**, 329; F. Farzaneh and M. Ghandi, *J. Mol. Catal. A*, **132**, 255 (1998).

13 A. Joy, J. R. Scheffer, D. R. Corbin, and V. Ramamurthy, *J. Chem Soc., Chem. Commun.*, **1998**, 1379.

14 Due to the presence of methyl groups in MA and MVK and their simple characterization in NMR spectra we used the NMR method to obtain the endo:exo ratio and the ee of the products using chiral shift reagent.

15 Loading procedure: The zeolites were exchanged by the chiral compound according to the reported procedure (reference 13). The vacuum dried zeolite was added to the dienophile (1 mmol) solution in *n*-hexane (zeolite:dienophile weight ratio = 25:1) and the mixture was stirred at room temperature for 3 h. After filtration and washing with *n*-hexane, GC or UV analysis of the hexane layer revealed that no dienophile was left. To the magnetically stirred slurry of dienophile-zeolite complex in *n*-hexane a solution of cyclopentadiene in *n*-hexane was added at once (2:1 molar ratio of diene:dienophile) and the mixture stirred for 4 h at room temperature. After filtration and washing with more *n*-hexane and small portions of diethyl ether, GC analysis of the filtrate revealed no product in the filtrate. The product was readily extracted into the ether layer by stirring the zeolite in diethyl ether overnight (mass balance ~ 90%). The product was analyzed by GC (using 10 ft. OV-17 on Chromosorb column with cyclohexanone as internal standard) and NMR for endo:exo ratio and ee using a chiral shift reagent. The absolute configuration has not been determined.

16 M. Avalos, R. Babiano, J. L. Bravo, P. Cintas, J. L. Jimenze, J. C. Palacios, and B. C. Rano, *Tetrahedron Lett.*, **39**, 2013 (1998).

17 Y. Kobuke, T. Fueno, and J. Furukawa, *J. Am. Chem. Soc.*, **92**, 6548 (1976).