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ORGANOCATALYTIC ASYMMETRIC DIELS-ALDER REACTION OF FURAN UNDER HIGH PRESSURE¹

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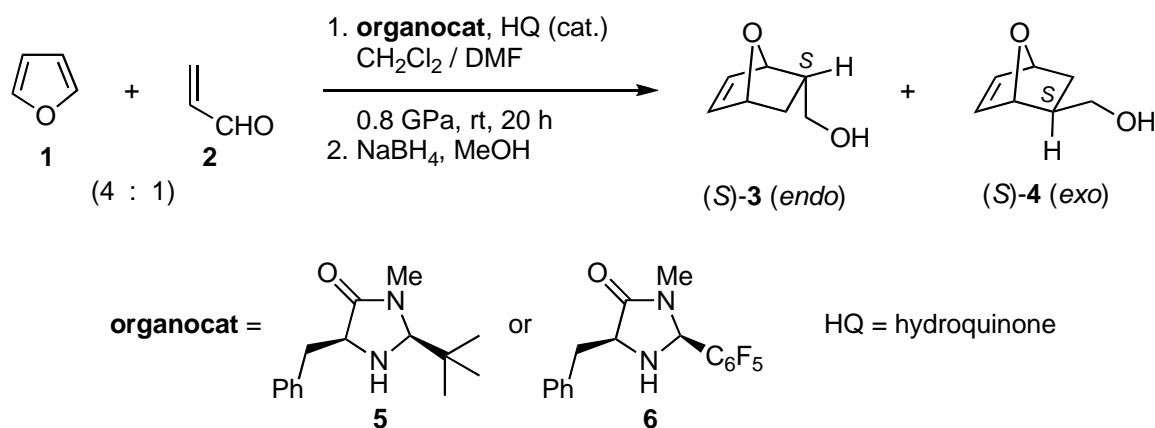
Abstract – A new method for the asymmetric Diels-Alder reaction between furan and acrolein has been developed through the combined use of chiral organocatalysts and high pressure (yield up to 91%; *endo*-adduct up to 19% ee, *exo*-adduct up to 26% ee).

The Diels-Alder reaction is one of the most important synthetic methodologies in furan chemistry, since it has been well-established that the corresponding cycloadducts, 7-oxabicyclo[2.2.1]heptene derivatives, are useful for producing both natural and unnatural biologically interesting molecules.² However, furans are generally less-reactive dienes for the Diels-Alder reaction due to their intrinsic aromaticity,³ and hence additional activation techniques, e.g., Lewis acid catalysis and high-pressure chemistry, are required to obtain a sufficient amount of the desired adducts.⁴ In addition, whereas the asymmetric version in this field is very important for preparing optically active substances, a few examples of catalytic asymmetric processes have been reported, and the development of new methods remains a significant challenge.^{5,6}

Over the past decade, remarkable progress has been achieved in the development of asymmetric organocatalysis as modern synthetic transformations, mainly because they are less toxic and more environmentally friendly than traditional metal-catalyzed systems.⁷ In particular, recent reports of successful organocatalytic asymmetric Diels-Alder reactions by MacMillan and his group⁸ prompted us to examine the applicability of their synthetic strategy to the asymmetric Diels-Alder reaction of furan.⁹ We describe here our preliminary results on this subject with the combined use of asymmetric organocatalysis and high pressure.

To investigate the catalyst activity and enantioselectivity, we first examined the utility of MacMillan-type

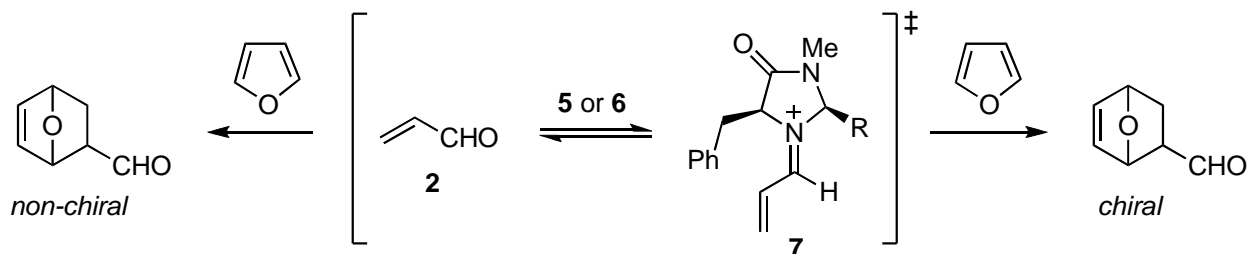
This paper is dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.



Scheme 1. Organocatalytic asymmetric Diels-Alder reaction of furan at high pressure

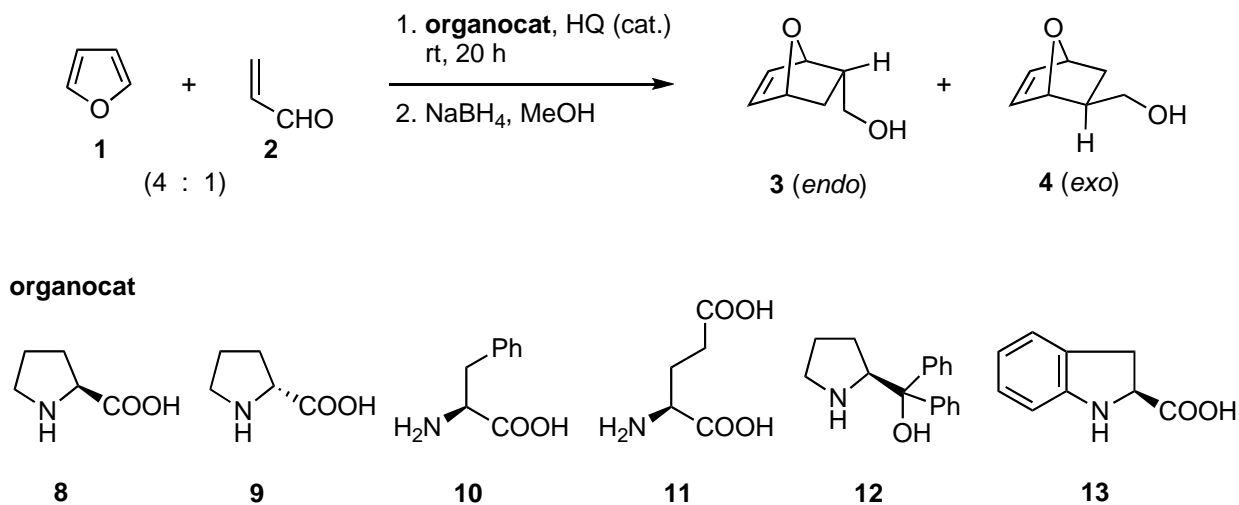
organocatalysts, chiral imidazolidinones **5** and **6**, in our system (Scheme 1). For example, when a mixture of furan (**1**, 4 equiv) and acrolein (**2**) containing 10 mol% of **5** together with PhCO_2H in $\text{CH}_2\text{Cl}_2/\text{DMF}$ (4 : 1) was reacted at 0.8 GPa and rt for 20 h,¹⁰ the desired *endo*- and *exo*-adducts **3** and **4** were obtained, after NaBH_4 reduction, in a combined yield of 59% and in a ratio of 56 : 44. Chiral HPLC analysis using a Chiralpak AS column revealed that the enantioselectivity of each adduct was disappointingly low: 7% ee for (*S*)-**3** and 3% ee for (*S*)-**4**.¹¹ We also carried out the same reaction at a lower pressure: the reaction slowed sharply at 0.2 GPa, and the adducts were obtained in only 15% yield with no appreciable enhancement in enantioselectivity. Similar results were obtained with catalyst **6**: 0.2 GPa, 20 h, 22% yield; **3/4** = 46 : 54, 7% ee for (*R*)-**3** and 8% ee for (*R*)-**4**.

The fact that bond-formation and ionization both have a large negative activation volume¹² implies that the iminium ion-activation mode through intermediate **7** proposed by MacMillan et al.⁸ should also be favorable in our system (Scheme 2). Despite this expectation, the essentially non-asymmetric induction shown in Scheme 1 means that the subtle differences in a LUMO energy between acrolein (**2**) and iminium ion **7** may be overridden at high pressure.^{13,14}

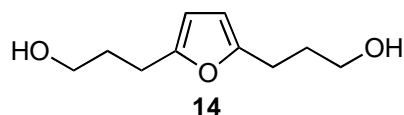


Scheme 2. Proposed transition state for the organocatalytic asymmetric Diels-Alder reaction

Based on this consideration, we then searched for other types of chiral amine-based organocatalysts. The results are summarized in Table 1.¹⁰

Table 1. Organocatalytic asymmetric Diels-Alder reaction of furan at high pressure

entry	organocat	pressure (GPa)	solvent	yield (%) ^a	endo/exo ratio ^b	ee (%) ^c	
						3	4
1	8 (20 mol%)	0.8	CH ₂ Cl ₂	38	53 : 47	3 (<i>R</i>)	2 (<i>R</i>)
2	8 (20 mol%)	0.8	MeCN	70	55 : 45	1 (<i>S</i>)	0 (–)
3	8 (20 mol%)	0.8	<i>i</i> -PrOH	62	61 : 39	4 (<i>S</i>)	1 (<i>S</i>)
4	8 (10 mol%)	0.8	CH ₂ Cl ₂ / <i>i</i> -PrOH (4 : 1)	72	56 : 44	7 (<i>R</i>)	5 (<i>R</i>)
5	8 (20 mol%)	0.8	DMF	74	57 : 43	3 (<i>S</i>)	3 (<i>S</i>)
6	8 (10 mol%)	0.8	CH ₂ Cl ₂ / DMF (4 : 1)	89	51 : 49	3 (<i>S</i>)	1 (<i>S</i>)
7	8 (50 mol%)	0.8	CH ₂ Cl ₂ / DMF (4 : 1)	18 ^d	64 : 36	13 (<i>S</i>)	25 (<i>S</i>)
8	8 (20 mol%)	0.4	CH ₂ Cl ₂ / DMF (4 : 1)	33	51 : 49	3 (<i>S</i>)	2 (<i>S</i>)
9	8 (20 mol%)	0.2	CH ₂ Cl ₂ / DMF (4 : 1)	5	56 : 44	11 (<i>S</i>)	21 (<i>S</i>)
10	9 (10 mol%)	0.8	CH ₂ Cl ₂ / DMF (4 : 1)	76	57 : 43	3 (<i>R</i>)	5 (<i>R</i>)
11	9 (50 mol%)	0.8	CH ₂ Cl ₂ / DMF (4 : 1)	26 ^d	42 : 58	19 (<i>R</i>)	20 (<i>R</i>)
12	10 (10 mol%)	0.8	CH ₂ Cl ₂ / DMF (4 : 1)	91	54 : 46	1 (<i>R</i>)	1 (<i>R</i>)
13	11 (10 mol%)	0.8	CH ₂ Cl ₂ / DMF (4 : 1)	82	56 : 44	0 (–)	1 (<i>R</i>)
14	12 (10 mol%)	0.8	CH ₂ Cl ₂ / DMF (4 : 1)	41	54 : 46	3 (<i>S</i>)	1 (<i>R</i>)
15	13 (10 mol%)	0.8	CH ₂ Cl ₂ / DMF (4 : 1)	45 ^e	44 : 56	10 (<i>R</i>)	6 (<i>S</i>)
16	13 (10 mol%)	0.4	CH ₂ Cl ₂ / DMF (4 : 1)	33	41 : 59	13 (<i>R</i>)	14 (<i>S</i>)
17	13 (10 mol%)	0.2	CH ₂ Cl ₂ / DMF (4 : 1)	22	48 : 52	4 (<i>R</i>)	26 (<i>S</i>)

^a Isolated yield.^b Determined by ¹H NMR (400 MHz).^c Determined by chiral HPLC using a Chiralpak AS column.^d Considerable polymerization was observed.^e The Michael adduct **14** was formed as a major by-product.

The use of L- or D-proline (**8** or **9**) as a chiral organocatalyst showed no remarkable improvement in enantioselectivity, even under a variety of conditions (entries 1-11). However, the enantioselectivity tended to be enhanced with an increase in the amount of catalyst and with a decrease in pressure (entries 7, 9, 11).¹⁵ Furthermore, the chirality of the catalyst directs the enantiofacial attack of the reagent, which leads to a reversal of enantiomers of the respective cycloadducts **3** and **4** (entries 7 and 11). Other types of organocatalysts such as L-phenylalanine (**10**), L-glutamic acid (**11**), and diphenylprolinol **12** were found to be less effective (entries 12-14).

Finally, when L-indolinecarboxylic acid (**13**) was used as a catalyst at 0.2 GPa, a slightly improved result (26% ee) was obtained for the *exo*-isomer **4** (entry 17). However, carrying out the experiments under a variety of conditions could not provide a significant improvement in both enantioselectivity and product yield, but the formation of Michael-type adduct **14** was observed as a major by-product (entry 15).

The combined use of high pressure and organocatalysis was shown to be quite useful for promoting the asymmetric Diels-Alder reaction of furan with acrolein.¹⁶ The enantioselectivity observed here is not yet high enough for practical application, and hence additional studies are needed to identify much more effective chiral organocatalysts. Further studies are now in progress in our laboratory.

ACKNOWLEDGEMENTS

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 11. HPLC conditions: Chiralpak AS, $\lambda = 210$ nm, 5% 2-propanol/hexane, flow rate = 1.0 mL/min; retention times: 20.04 min for (*S*)-**3**, 21.94 min for (*R*)-**3**, 15.51 min for (*S*)-**4**, 17.95 min for (*R*)-**4**. The absolute configuration of each isomer was determined by comparison of the sign of the optical rotation with reported data after conversion to the corresponding carboxylic acid. See, S. Ogawa, Y. Iwasawa, and T. Suami, [Chem. Lett., 1984, 355](#): (*R*)-*endo*-acid, $[\alpha]_D^{22} +110.7$ (EtOH); (*S*)-*endo*-acid, $[\alpha]_D^{22} -111.8$ (EtOH). Ref 6b: (*R*)-*exo*-acid, $[\alpha]_D^{22} +27.6$ (EtOH).
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 14. It can not preclude the possibility that the reaction of furan with iminium ion **7** may be a kinetically disfavored process under high pressure due to its sterically crowding structure.
 15. In many cases the longer reaction periods reduced the enantioselectivity of cycloadducts.
 16. Unfortunately, crotonaldehyde and cinnamaldehyde gave no Diels-Alder adducts under the standardized conditions (10 mol% of **13**, CH₂Cl₂/DMF = 4 : 1, 0.2 GPa, rt, 24 h).