Site-recognition of one of the two alkoxy carbonyl groups present in the dienophile for Diels–Alder reaction

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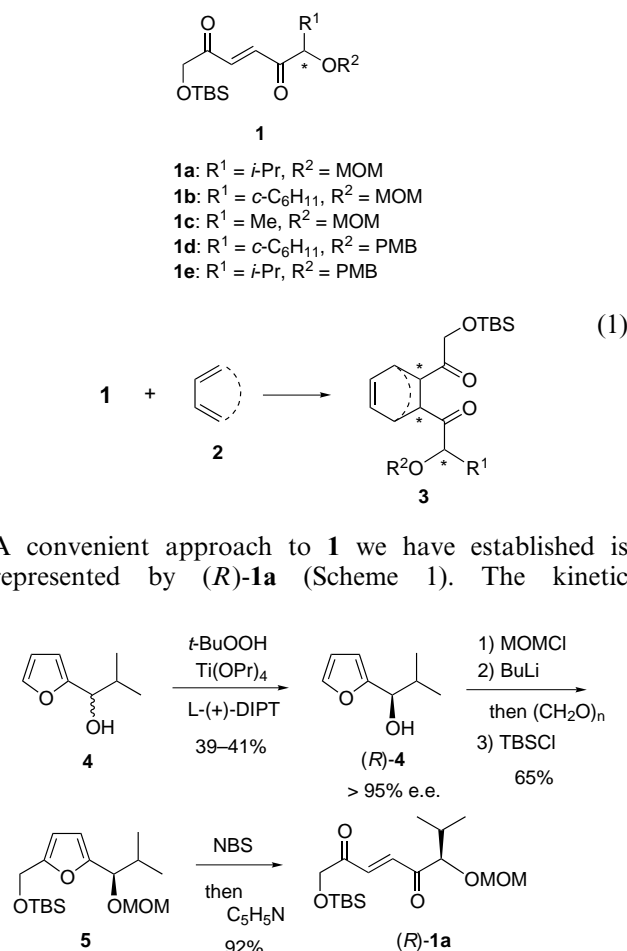
Abstract—Recognition of one alkoxy carbonyl group from the two in a molecule by a Lewis acid was investigated using **1a**–**e** in the Diels–Alder reaction with diene **6**. Combination of **1a** and $BF_3 \cdot OEt_2$ provided the highest efficiency to afford **7a**, thus showing evidence for the site-selective coordination of $BF_3 \cdot OEt_2$ to the MOM-oxy carbonyl group in **1a**. Furthermore, the generality and high reactivity of this combination were confirmed with dienes **11**–**14**. © 2001 Elsevier Science Ltd. All rights reserved.

Chelation control of α- or β-alkoxy carbonyl compounds by a Lewis acid is a powerful method to furnish high stereoselectivity in their reactions. Simple compounds possessing *one* alkoxy carbonyl group in a molecule have been studied extensively, and the preferable combinations of alkoxy groups and Lewis acids are elucidated.[1] However, compounds with *two* types of alkoxy carbonyl sites have been paid little attention,[2] though products derived from these compounds are more useful intermediates in organic synthesis because of their greater possibility for further conversion by taking advantage of these alkoxy carbonyl groups. Fundamentally, differentiation of the two carbonyl groups in a coordination step by a Lewis acid is an important process to produce one stable conformer of a given compound. Although the previous investigation with the simple compounds can suggest a Lewis acid capable of strong coordination to a given alkoxy carbonyl group, a guideline to attain the maximum differentiation has not been fully established. We chose a 2-ene-1,4-dicarbonyl compound of the general structure **1**, and the Diels–Alder reaction of **1** (Eq. (1)) was investigated.[3] In practice, high selectivity and reactivity were observed. In addition, the synthetic potential of the products **3** was demonstrated by several successful transformations.

1a: R^1 = *i*-Pr, R^2 = MOM
1b: R^1 = *c*-C_6H_{11}, R^2 = MOM
1c: R^1 = Me, R^2 = MOM
1d: R^1 = *c*-C_6H_{11}, R^2 = PMB
1e: R^1 = *i*-Pr, R^2 = PMB

(1)

A convenient approach to **1** we have established is represented by (*R*)-**1a** (Scheme 1). The kinetic

Scheme 1. Synthesis of (*R*)-**1a**.

Table 1. Diels–Alder reaction of **1a–d** with cyclopentadiene (**6**)[a]

Entry	For **1** and **7**		Dienophile	Lewis acid (equiv.)	Temp. (°C)	Major isomer	Ratio of isomers[b]	Combined yield (%)
	R^1	R^2					Major:others[c]	
1	Pr-i	MOM	**1a**	–	0	**7a**	1:1	Nd[d]
2	Pr-i	MOM	**1a**	$BF_3 \cdot OEt_2$ (1.5)	−78	**7a**	10:1	87
3	Pr-i	MOM	**1a**	$BF_3 \cdot OEt_2$ (1.5)	−50	**7a**	6:1	85
4	Pr-i	MOM	**1a**	$BF_3 \cdot OEt_2$ (2.0)	−78	**7a**	13:1	90
5	Pr-i	MOM	**1a**	Ti(OPr-i)$_4$ (2.0)	−78	**7a**	1:1	Nd[d]
6	Pr-i	MOM	**1a**	$ZnCl_2$ (2.0)	−78	**7a**	7:1	87
7	Pr-i	MOM	**1a**	Et_2AlCl (2.0)	−78	**7a**	4:1	Nd[d]
8	C_6H_{11}-c	MOM	**1b**	$BF_3 \cdot OEt_2$ (2.0)	−78	**7b**	5:1	77
9	Me	MOM	**1c**	$BF_3 \cdot OEt_2$ (2.0)	−78	**7c**	3.5:1	91
10	C_6H_{11}-c	PMB	**1d**	$BF_3 \cdot OEt_2$ (2.0)	−78	**7d**	5:1	Nd[d]

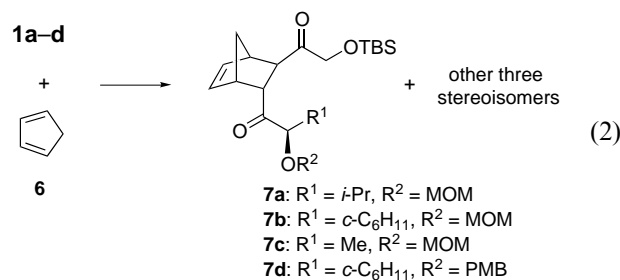[a] Reactions were examined using racemic **1a–d** and **6** (3 equiv.) in CH_2Cl_2 for 1–2 h.
[b] Determined by ^1H NMR (300 MHz) spectroscopy.
[c] The other three corresponding isomers were combined as 'others'.
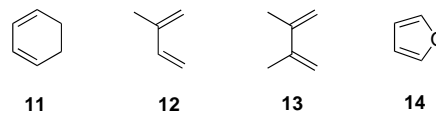[d] Not determined.

resolution[4] of racemic furyl alcohol **4** by using the Sharpless reagent[5] (t-BuOOH, L-(+)-DIPT, Ti(OPr)$_4$) is a key step of this method to afford (R)-**4** with >95% e.e. (determined by ^1H NMR spectroscopy of the MTPA ester) in 39–41% yields (78–82% yields based on the enantiomer). The other steps involved in the method also proceeded efficiently. Needless to say, use of D-(−)-DIPT in the kinetic resolution affords (S)-**1a**. For the preliminary investigation, the racemic dienophile **1a** was synthesized by this method without carrying out the kinetic resolution. Similarly, other dienophiles, **1b** ($R^1 = c$-C_6H_{11}, $R^2 =$ MOM), **1c** ($R^1 =$ Me, $R^2 =$ MOM), **1d** ($R^1 = c$-C_6H_{11}, $R^2 =$ PMB (p-methoxybenzyl)), and **1e** ($R^1 = i$-Pr, $R^2 =$ PMB) were prepared in racemic forms with comparable efficiency.

First, racemic **1a** with the i-Pr and MOM groups as R^1 and R^2, respectively, was subjected to a Diels–Alder reaction with cyclopentadiene (**6**), the most reactive diene, in order to find the best conditions in terms of stereoselectivity and reactivity (Eq. (2)). The results are summarized in Table 1. In the presence of $BF_3 \cdot OEt_2$ (1.5 equiv.), the reaction in CH_2Cl_2 at −78°C afforded diastereoisomer **7a**[6] as a major isomer in a 10:1 ratio of **7a** and three other stereoisomers (entry 2), while a control experiment without $BF_3 \cdot OEt_2$ even at higher temperature (0°C) was sluggish, furnishing a mixture of **7a** and the isomers in a 1:1 diastereomeric ratio (entry 1). The low temperature of −78°C was critical in order to attain the high diastereoselectivity, since a reaction at −50°C resulted in a lower ratio of 6:1 (entry 3). Significantly important also is the stoichiometry of $BF_3 \cdot OEt_2$, as is indicated in entry 4, where use of 2.0 equiv. improved the ratio to 13:1. A larger quantity (3.0 equiv.), however, changed the selectivity marginally.[7]


$$
\text{1a–d} + \text{6} \longrightarrow \text{[bicyclic product with OTBS, } R^1, OR^2\text{]} + \text{other three stereoisomers} \quad (2)
$$

7a: $R^1 = i$-Pr, $R^2 =$ MOM
7b: $R^1 = c$-C_6H_{11}, $R^2 =$ MOM
7c: $R^1 =$ Me, $R^2 =$ MOM
7d: $R^1 = c$-C_6H_{11}, $R^2 =$ PMB

Catalytic ability of other Lewis acids such as Ti(OPr-i)$_4$, $ZnCl_2$, and Et_2AlCl was investigated. These catalysts, however, did not provide a better result than $BF_3 \cdot OEt_2$ (entries 5–7). In entry 7, alcohol **8** was produced in a 3:1 ratio of **8** and **7a**.

Next, other dienophiles **1b–e** were examined in order to optimize the R^1 and R^2 groups in dienophile **1**. The cyclohexyl candidate **1b** under the conditions elucidated for **1a** (Table 1, entry 4) furnished **7b** and the other three isomers in a 5:1 ratio (entry 8). This result implies the bigger cyclohexyl group obstructs the coordination of $BF_3 \cdot OEt_2$ to the MOM-oxy carbonyl group. On the other hand, a mixture of **7c** and the other isomers was obtained from **1c** in a ratio of 3.5:1 (entry 9), thus indicating that the methyl group was much smaller than the i-Pr group for discrimination of the olefin face in the transition state. Examined next was the PMB ether **1d**, which gave a mixture of **7d**, the other three isomers, and alcohol **9** in a ratio of 10:2:5 (entry 10). The alcohol was formed probably by $BF_3 \cdot OEt_2$-induced deprotection of the PMB group. The observed instability of the PMB group against $BF_3 \cdot OEt_2$ led us to abandon investigation of **1e**. Taking together these results, it can be concluded that i-Pr and MOM groups are the most suitable substituents as R^1 and R^2, respectively, in dienophile **1**.[8]

The reaction was repeated with (*R*)-**1a** of 95% e.e. and diene **6** under the best conditions exploited above (Table 1, entry 4), producing (2*R*,3*R*)-**7a** in 90% yield (Scheme 2). The chirality of the product was determined by the specific rotation of the derived ester **10** ((1) H$^+$; (2) H$_5$IO$_6$, THF/H$_2$O; (3) CH$_2$N$_2$; 59% yield; $[\alpha]_D^{25}=+100$ (*c* 1.00, MeOH); lit.[9] $[\alpha]_D^{25}=+135$ (*c* 1.455, MeOH).

Other dienes **11–14** were subjected to the Diels–Alder reaction with dienophile **1a** in the presence of BF$_3$·OEt$_2$. The results are summarized in Table 2, and the major products are presented in Fig. 1. Although **11–14**, especially **14**,[10] are less reactive dienes in the Diels–Alder reaction than **6**, as were reconfirmed by us (entries 2, 4, 6, and 8; cf. Table 1, entry 1), the high reactivity of **1a** compensated the low reactivity of these dienes to produce diastereoisomers **15–18** at −78°C within 7 h (entries 1, 3, 5, and 7). When acyclic dienes **12** and **13** were the substrates, somewhat lower selectivities for production of **16** and **17** were observed, while cyclic diene **11** furnished the almost same selectivity as diene **6**. Noteworthy is that furan (**14**) could participate in the reaction even at −78°C to provide **18**, though the somewhat unstable nature of product **18** restricted the quantity of BF$_3$·OEt$_2$ to 1.3 equiv., thus furnishing a slightly lower yield of 68% as listed in entry 7.
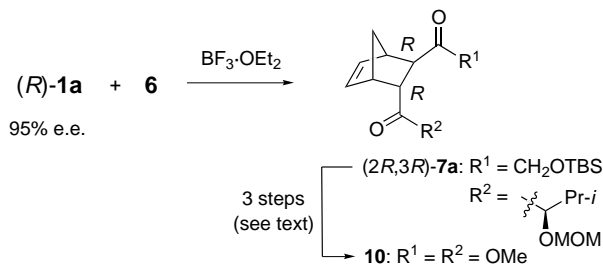
The relative stereochemistry of products **15–18** is speculated as drawn in Fig. 1 in analogy to **7a**.[6] The position of the methyl group was tentatively assigned as **16**.

In addition to the important role of the substituent (*i*-Pr) and the protective groups (TBS, MOM) in **1a** to achieve the diastereoselective Diels–Alder reaction, these groups in adducts **7a**, **15–18** are potentially useful for further transformations. This synthetic advantage was successfully practiced with adduct **7a**, as is presented in Scheme 3. Treatment of **7a** with 10% HCl in MeOH furnished diol **19** in 77% yield. Oxidation of **19** with KIO$_4$ in THF/H$_2$O proceeded regioselectively to afford, after esterification, ester **20**, which upon oxidation with H$_5$IO$_6$ produced half-acid **21** in 52% yield. On the other hand, AcOH furnished selective deprotection of the TBS group in **7a** to provide alcohol **22** in 95% yield. Subsequent reduction with simple NaBH$_4$ proceeded in a highly site-selective manner,[11] and the resulting diol **23**, upon oxidation with H$_5$IO$_6$, furnished aldehyde **24** in good yield.
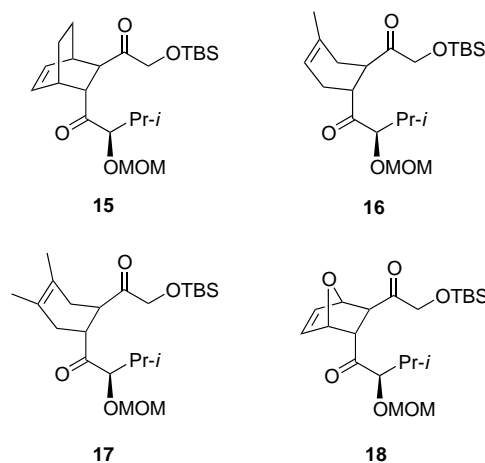

Figure 1. Products derived from **1a** and dienes **11–14**.

Scheme 2.

**Table 2.** Diels–Alder reaction of **1a** and dienes **11–14**[a]

Entry	Diene	Equiv. of BF$_3$·OEt$_2$	Temp. (°C)	Major product	Product ratio[b]	Yield (%)[c]
1	**11**	2.0	−78	**15**	12:1	84
2[d]	**11**	0	0	–	–	–
3	**12**	2.0	−78	**16**	10:1	85
4[d]	**12**	0	0	–	–	–
5	**13**	2.0	−78	**17**	9:1	85
6[d]	**13**	0	0	–	–	–
7	**14**	1.3	−78	**18**	10:1	68
8[d]	**14**	0	0	–	–	–

[a] Reactions were carried out with three (3) equiv. of dienes in the presence or absence of BF$_3$·OEt$_2$ for 7 h.
[b] Major:other three isomers, which were determined by ^{1}H NMR (300 MHz) spectroscopy.
[c] Combined yields.
[d] No reaction proceeded.
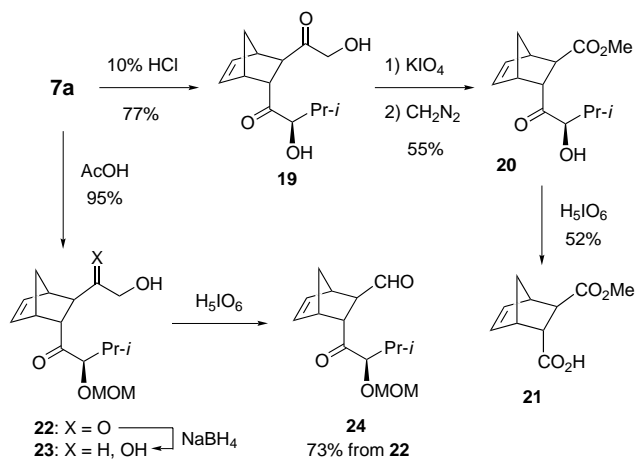
**Scheme 3.**

In summary, one of the alkoxy carbonyl groups in **1a** was recognized selectively by $BF_3 \cdot OEt_2$ in the Diels–Alder reaction with several dienes **6**, **11–14** affording **7a**, **15–18** efficiently.[12] In addition, the synthetic advantage of this method was demonstrated by the further transformation of the representative adduct **7a**.

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6. The related stereochemistry of **7a** was unambiguously determined by NOE experiment of **24**, which was synthesized by the method shown in Scheme 3.
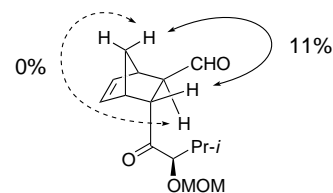
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8. To a solution of **1a** (198 mg, 0.573 mmol) in CH_2Cl_2 (0.5 mL) was added $BF_3 \cdot OEt_2$ (0.147 mL, 1.16 mmol) at −78°C. The resulting light yellow solution was stirred at −78°C for 30 min, and **6** (0.180 mL, 1.81 mmol) was added. After 1 h of stirring at −78°C, the mixture was quenched with saturated $NaHCO_3$, and chromatography on silica gel (hexane/EtOAc) afforded **7a** (211 mg, 90%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 and 0.09 (2s, 6H), 0.85 (d, $J = 7$ Hz, 3H), 0.93 (s, 9H), 1.02 (d, $J = 7$ Hz, 3H), 1.39 (dd, $J = 8.5$, 2 Hz, 1H), 1.71 (d, $J = 8.5$ Hz, 1H), 2.05–2.19 (m, 1H), 3.07–3.12 (m, 2H), 3.33–3.37 (m, 4H), 3.68 (t, $J = 4$ Hz, 1H), 4.14 (d, $J = 5$ Hz, 1H), 4.22 (d, $J = 17$ Hz, 1H), 4.27 (d, $J = 17$ Hz, 1H), 4.56 (d, $J = 7$ Hz, 1H), 4.63 (d, $J = 7$ Hz, 1H), 5.94 (dd, $J = 6$, 3 Hz, 1H), 6.30 (dd, $J = 6$, 3 Hz, 1H).

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11. Ratio of **23** and the corresponding triol was 10:1 by ^1H NMR spectroscopy.

12. On the basis of the following references, we are speculating complexes such as $[\mathbf{1a} \cdot BF_2]^+ (BF_4)^-$ and $[\mathbf{1a} \cdot BF_2]^+ F^-$: BF_2 forms chelation at the α-MOM-oxy carbonyl site to produce one reactive conformer in which the *i*-Pr group efficiently blocks one of the olefin faces. See: (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256; (b) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778–1784.