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Enhancement of Diastereofacial Selectivity by Protecting Groups: Asymmetric Diels-Alder Reactions of 2-Siloxyfurans Derived from L-Ascorbic Acid

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Abstract: Diastereoselectivity in asymmetric Diels-Alder reaction of chiral 2-siloxyfurans with dimethyl acetylenedicarboxylate (DMAD) depending on the protecting groups in the allylic stereogenic centers of the molecules in the presence of the (+)-Eu(hfc)₃ catalyst was described.

The asymmetric Diels-Alder reaction is a highly efficient method for preparation of chiral six-membered ring compounds, in which several chiral centers can be established in one step.¹ Although chiral auxiliaries are commonly used in dienophiles,² dienes² or catalysts³ to induce diastereofacial selectivity, Diels-Alder reactions of dienes with an adjacent chiral center have been also extensively studied.⁴ As part of our project on the total synthesis of natural products, we studied asymmetric Diels-Alder reactions of 2-siloxyfurans **3a-f** derived from L-ascorbic acid. We report here the exceptional enhancement of diastereofacial selectivity by protecting groups on the allylic stereogenic centers of **3**.

Siloxyfurans **3a-f** were prepared from compound 1^5 Protection of the diol moiety of 1 by *t*-butyldimethylsilyl or dialkyl- and diaryl-methylidene ketal group by conventional methods gave **2a-f**,⁶ which can be converted into **3a-f** by treatment with *t*-butyldimethylsilyl triflate and triethylamine.⁷ Diels-Alder reactions of **3a-f** with 10 equiv. dimethyl acetylene-dicarboxylate (DMAD) without solvent at room temperature gave cycloadducts **5 a-f** and **6a-f**. The results are summarized in Table 1. For Entries 1 and 2 using the *t*-butyldimethylsilyl group as the protecting groups, Diels-Alder reactions of **3a** gave either no diastereofacial selectivity (**5a** : **6a** = 1:1) without a catalyst or poor diastereofacial selectivity (1.3:1) with (+)-Eu(hfc)₃ catalyst.⁸ When the protecting group was altered to the isopropylidene ketal group (Entries 3 and 4), the diastereofacial selectivity improved slightly (1.8:1 and 2.2:1)



Table 1. Asymmetric Diels-Alder Reactions of Siloxyfurans 3

Entry		2-Siloxyfurans 3	Catalyst	Reaction	Diastereofacial	Yield/%
				Time	Selectivity (5:6)	
1	3a	$R_1 = R_2 = TBS$		5 days	1:1	60
2			(+)-Eu(hfc)3	37 h	1.3 : 1	73
3	3b	R_1 and $R_2 =$	_	22 h	1.8 : 1	81
4		(CH ₃) ₂ C <	(+)-Eu(hfc)3	15 h	2.2 : 1	83
5	3c	R_1 and $R_2 =$	-	48 h	2.1:1	82
6		(Ph) ₂ C <	(+)-Eu(hfc)3	24 h	9.3 : 1	90
7	3d	R_1 and $R_2 =$	_	48 h	2.1 : 1	92
8		$(p-MeOPh)_2C \leq$	(+)-Eu(hfc)3	24 h	9.3 : 1	86
9			Eu(fod)3	24 h	3.7 : 1	79
10	3e	R_1 and $R_2 =$	_	48 h	2.1:1	88
11		$(PhCH_2)_2C \leq$	(+)-Eu(hfc)3	22 h	7.5 : 1	84
12	3f	R_1 and $R_2 =$		24 h	6.4 : 1	86
13		(Cyclohexyl) ₂ C <	(+)-Eu(hfc)3	12 h	7.6 : 1	91

without or with the (+)-Eu(hfc)3 catalyst. However, when diphenylmethylidene ketal group was employed as the protecting group, the diastereofacial selectivity was enhanced greatly to 9.3: 1 in the presence of the (+)-Eu(hfc)₃ catalyst (Entry 6). In contrast, without the (+)-Eu(hfc)₃ catalyst the selectivity was only 2.1 : 1. Similarly, compound 3d with the di-pmethoxyphenylmethylidene ketal protecting group gave high diastereofacial selectivity (9.3 : 1. Entry 8). On the other hand, with an achiral Eu(fod)3 catalyst (Entry 9) compound 3d gave much lower diastereofacial selectivity (3.7:1).8 Compound 3e with a dibenzylmethylidene ketal protecting group also gave cycloadducts in high diastereofacial selectivity (7.5 : 1. Entry 11) with the (+)-Eu(hfc)3 catalyst. An X-ray analysis of the major cycloadduct **5e** confirmed its absolute stereochemistry, Figure 1.⁹ In order to confirm the stereochemistry of 5d, correlation of the stereochemistry of 5d with 5e was undertaken. Hydrogenation of 5d and 5e gave compounds 7d and 7e, respectively. Reaction of 7d or 7e with tetrabutylammenium fluoride afforded compound 8d or 8e. When compound 8d was treated with dibenzyl ketone dimethyl acetal and a catalytic amount of p-toluenesulfonic acid, 8d was converted into a compound identical to 8e. These correlation experiments proved that major cycloadducts 5d and 5e have the same stereochemistry.



In addition, we also found that compound **3f** using dicyclohexylmethylidene ketal protecting group underwent Diels-Alder reaction in good diastereofacial selectivity (Entries 12 and 13), Table 1. From these results, we attribute this exceptional enhancement in asymmetric induction to the steric bulkiness of the aryl rings and the double differentiation due to the chiral (+)-Eu(hfc)₃ catalyst. π -stacking effect¹⁰ of the aryl rings in **3c** and **3d** is probably not as important in view of comparable effectiveness of diarylmethylidene ketal groups in **3c** and **3d** versus the dibenzylmethylidene and dicyclohexylmethylidene ketal groups in **3e** and **3f**.

In summary, we report herein that diphenylmethylidene and di-*p*-methoxyphenylmethylidene ketal protecting groups on the allylic stereogenic centers of **3c** and **3d** enhanced the diastereofacial selectivity of the Diels-Alder reactions of **3c** and **3d** significantly in the presence of the (+)-Eu(hfc)₃ catalyst. The application of this discovery to other asymmetric reactions and the use of Diels-Alder adducts **5c** and **5d** as the starting materials for total synthesis of natural products are under current investigation.



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References and Notes

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