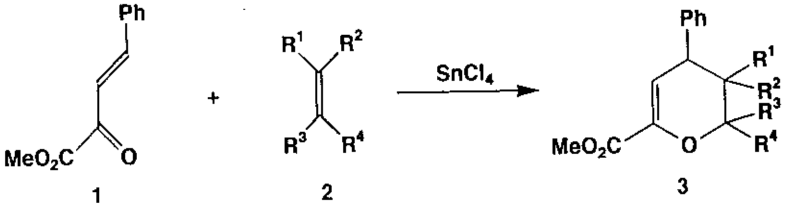
TIN(IV) CHLORIDE CATALYZED HETERO-DIELS-ALDER REACTION OF METHYL 2-OXO-4-PHENYL-3-BUTENOATE WITH STYRENE

Akira Sera,* Naohiro Ueda, Kuniaki Itoh* and Hiroaki Yamada

Department of Chemistry, Faculty of Science, Kobe University, Nada, Kobe 657, Japan

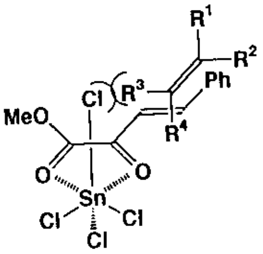
Abstract - Hetero-Diels-Alder reactions of methyl 2-oxo-4-phenyl-3-butenoate with styrene to give dihydropyran derivatives were found to proceed through an *exo*-selective concerted as well as an ionic stepwise mechanisms concurrently.

Recently we reported tin(IV) chloride catalyzed inverse electron demand hetero-Diels-Alder reactions of methyl 2-oxo-3-alkenoates with simple alkenes to give substituted 3,4-dihydro-2*H*-pyran derivatives.[1] The addition reaction proceeded with high regio- and stereoselectivities to yield cycloadducts, in which substituents on C-2 and C-4 possessed configuration. Representative examples are the reactions of methyl 2-oxo-4-phenyl-3-butenoate (**1**) with 1-hexene (**2a**) and *trans*-3-hexene (**2b**) (Scheme 1 and Entries 1 and 2 in Table 1). The reaction of **1** with **2a** gave methyl *trans*-2-butyl-4-phenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**3a**) as a sole product, while the reaction with **2b** yielded methyl *r*-2,*t*-3-diethyl-*t*-4-phenyl-2*H*-pyran-6-carboxylate (**3b**) which possessed C_2/C_4 *trans* as well as C_2/C_3 *trans* configurations. Thus these inverse electron demand hetero-Diels-Alder reactions proceeded through a concerted *exo* transition state in which an incoming dienophile molecule perferred an *exo* approach to the diene molecule[1] (Scheme 2).



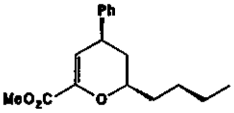
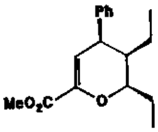
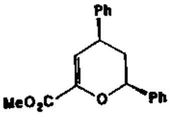
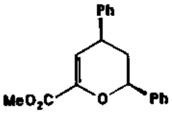
2	R¹	R²	R³	R⁴
a	H	H	H	Bu
b	Et	H	H	Et
c	H	H	H	Ph
d	D	H	H	Ph

Scheme 1



Scheme 2

Table 1. Tin(IV) Chloride Catalyzed Cycloaddition of Methyl 2-Oxo-4-phenyl-3-butenoate (**1**) with Alkenes[a)]

Entry	Alkene	Product (Yield/%)
1	1-Hexene (**2a**)	 **3a** (63)
2	*trans* -3-Hexene (**2b**)	 **3b** (34)
3	Styrene (**2c**)	  *trans* -**3c** *cis* -**3c** (94, *trans* : *cis* =73:27)

a) Conditions; molar ratio of 1:alkene:$SnCl_4$=1:2:0.09 in dichloromethane at 0 °C for 3 h.

A similar tin(IV) chloride mediated reaction of **1** with styrene (**2c**), however, yielded products as a mixture of methyl *trans* - and *cis* -2,4-diphenylpyran derivatives (*trans* -**3c** and *cis* -**3c**, Entry 3, Table 1). The rigorous *exo* selectivity observed in all reactions with simple alkenes[1] disappeared in the reaction with styrene. The formation of a *trans*- and *cis*-**3c** mixture in this case may be caused by one of following possibilities.

a) The cycloaddition proceeded through a concerted mechanism only. However, the *exo* selectivity diminished in the case of styrene as a dienophile, and no isomerization between *trans*- and *cis*-**3c** occurred; b) the concerted and highly *exo* selective cycloaddition gave *trans*-**3c** as a kinetically predominant product, but *trans*-**3c** isomerized by tin(IV) chloride to give *cis*-**3c** as just observed in the reaction of **1** with vinyl ethers;[2] c) only a stepwise cycloaddition reaction with intervention of an ionic intermediate took place to give the mixture; d) the concerted and the ionic stepwise additions occurred concurrently with succeeding isomerization.

The reaction of **1** with **2c** was examined at various temperatures. Temperature dependence of the reaction given in Table 2 revealed that the *trans*-**3c**/*cis*-**3c** ratio decreased at higher temperatures or longer reaction times. It implied the presence of a *trans*-*cis* isomerization of **3c** under the reaction conditions, although 4-alkyl-3,4-dihydropyran derivatives obtained by the reaction of **1** with simple alkenes (for example, **3a** and

Table 2. Temperature Dependence of Isomer Distribution in the Reaction of Methyl 2-Oxo-4-phenyl-3-butenoate (**1**) with Styrene

Entry	Reaction conditions[a)] temp./°C	time	Isomer distribution[b)] *trans*-**3c** : *cis*-**3c**
1	-64	3 h	86 : 14
2	0	5 min	77 : 23
3	0	3 h	73 : 27
4	r.t.[c)]	5 min	67 : 33
5	r.t.	3 h	59 : 41
6	reflux	3 h	54 : 46

a) The same molar ratio as given in Table 1, and in dichloromethane. b) Determined by ^{13}C nmr. c) At room temperature (28-30 °C).

3b) did not isomerize under the reaction conditions. Hence the tin(IV) chloride catalyzed isomerization of **3c** was examined, and the results given in Table 3 showed that neither *trans*- **3c** nor *cis*-**3c** isomerized at -64 °C. At 0 °C, however, the isomerization of *trans*-**3c** gave a mixture composed of *trans*-**3c** and *cis*-**3c** (71:29, Entry 6, Table 3), while that of *cis*-**3c** also gave a mixture having nearly the same isomer distribution (*trans*-**3c**:*cis*-**3c**= 70:30, Entry 10, Table 3). This observation excluded the above mentioned possibility a). *trans*-**3c** was found to isomerize more slowly than *cis*-**3c** (Entries 3-10, Table 3).

Table 3. Tin(IV) Chloride Catalyzed Isomerization of Methyl 2,4-Diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (**3c**).

Entry	Starting isomer	Reaction conditions[a)] temp./°C	time	Isomer distribution[b)] *trans*-**3c** : *cis*-**3c**
1	*trans*-**3c**	-64	3 h	-[c)]
2	*cis*-**3c**	-64	3 h	-
3	*trans*-**3c**	0	10 min	-
4		0	1 h	91 : 9
5		0	2 h	84 : 16
6		0	3 h	71 : 29
7	*cis*-**3c**	0	10 min	12 : 88
8		0	1 h	38 : 62
9		0	2 h	49 : 51
10		0	3 h	70 : 30
11	*trans*-**3c**	r.t.[d)]	3 h	59 : 41
12	*cis*-**3c**	r.t.	3 h	55 : 45

a) Molar ratio of $3c:SnCl_4=1:0.09$ in dichloromethane. b) Determined by ^{13}C nmr. c) No isomerization. d) Room temperature (28-30°C).

In order to elucidate the reaction mechanism operating in the present addition, we prepared (*E*)-(ß-$^2H_1$)styrene (**2d**)[3] as a keying dienophile, and its reaction with **1** was thoroughly examined. The expected products of the reaction should be *trans*- and *cis*-**3d** and *trans* - and *cis* -**3d'**. As depicted in Scheme 3, the addition through a concerted Ph- *exo*-oriented transition state (the same mechanism operated in the reactions of **1** with simple alkenes[1]) must give *trans* -**3d** having an *r*-2, *t*-3, *t*-4 configuration, whereas that through a concerted Ph- *endo* oriented transition state must yield *cis* -**3d** having an *r*-2, *t*-3, *c*-4 configuration. The both adducts must preserve the starting dienophile geometry at their C_2 and C_3 positions. All four isomeric adducts will be formed more or less by a stepwise addition mechanism through ionic intermediates.

The results summarized in Table 4 revealed interesting feature of the reaction. The predominantly formed isomer was *trans*-**3d** in all conditions, which was produced through the concerted Ph-*exo*-oriented transition state as depicted in Scheme 2 (R^1=D, $R^{2,3}$=H, R^4=Ph). A tin(IV) chloride catalyzed isomerization of isolate *trans*-3d afforded a mixture composed of *trans*-**3d** and *cis*-**3d'**, in which neither *trans*-**3d'** nor *cis* -**3d** was detected. Thus the isomerization did not involve cleavage of the C_3-C_4 bonds, that is no retrograde Diels-Alder reaction occurred during the isomerization. The presence of *cis* -**3d** in all the conditions could not be explained by the possibility b). The possibility c), in which only an ionic stepwise addition mechanism was supposed, may predict overwhelming formation of *cis*-**3d** and *cis*-**3d'** having equatorial phenyl groups on their C_3 positions. However, this was not the case, and hence the possibility c) was discarded.

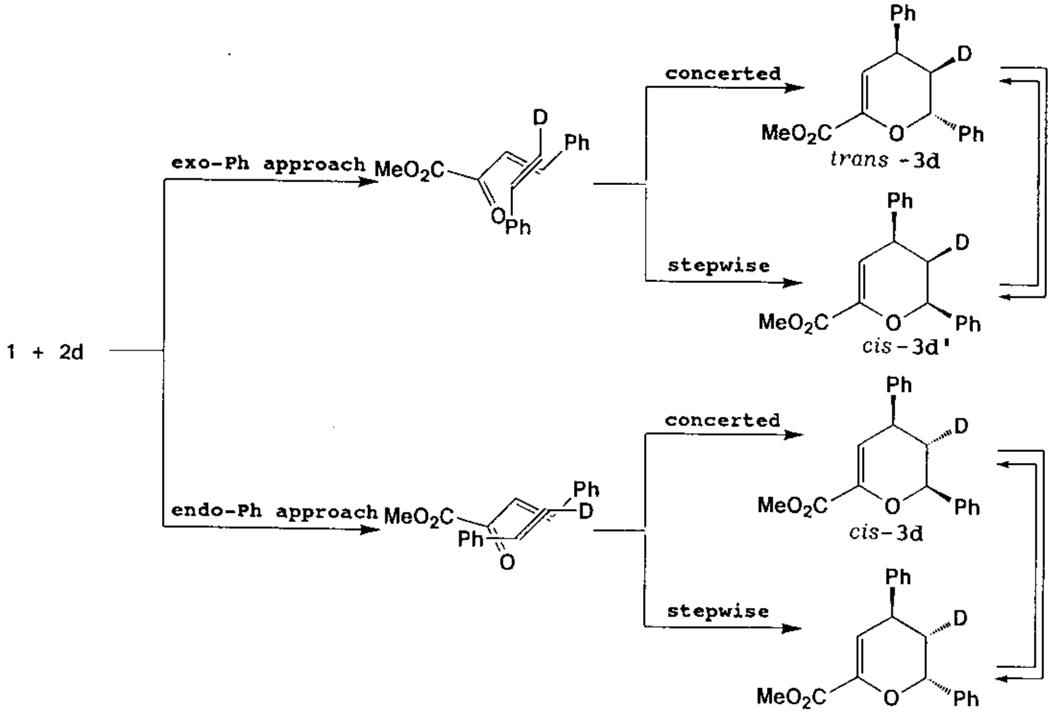
The fact that *cis*-**3d'** was produced even at -64 °C (conditions of no isomerization) indicated the operation of an ionic stepwise addition to give this isomer having an *r*-2,*c*-3 configuration (Entry 1, Table 4). The yield of *trans*-**3d** exceeded that of *cis* -**3d** in all cases. Generally the *exo*-Ph approach is sterically more favored than the *endo* Ph approach,[1] and this steric factor is responsible for the restricted formation of *cis*-**3d** and the absence of *trans*-**3d'** at -64 °C. Temperature and reaction time dependences of the yield of *trans*-**3d'** suggested that this isomer was the secondary product produced solely by the isomerization of *cis* -**3d** (Entries 2,3 and 4,5, Table 4).

It was thus deduced that the concerted Ph-*exo* addition predominated over the concerted Ph-*endo* addition, and even at -64 °C the ionic stepwise addition proceeded in part to give *cis* -**3d'**. At higher temperatures both the concerted and the ionic stepwise additions took place concurrently followed by the isomerization of the isomers.

Table 4. Isomer Distribution of the Reaction of 2-Oxo-4-phenyl-3-butenoate (1) with (*E*)-(β-$^2H_1$)-Styrene at various Temperatures[a)]

Entry	Temp./°C	Reaction time	Isomer distribution[b)] *trans*-**3d**	: *trans*-**3d'**	: *cis*-**3d**	: *cis*-**3d'**
1	-64	3 h	86	c)	8	6
2	0	15 min	66	11	14	9
3	0	3 h	58	15	13	14
4	r.t.[d)]	5 min	55	12	21	12
5	r.t.	3 h	41	18	14	27

a) Conditions; the same molar ratio as given in Table 1, and in dichloromethane. b) Determined by ^{1}H nmr. c) Trace. d) At room temperature (28-30°C).



Scheme 3

EXPERIMENTAL

Infrared spectra were recorded on a JASCO IRA-3 spectrophotometer. ^{1}H and ^{13}C nmr spectra were recorded on JEOL FX 90Q and Bruker AC-250 spectrometers. The chemical shifts are given in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on ESCO EMD-05A and Shimadzu GCMS QP-2000A spectrometers. Melting points were determined on a Yanaco micro hot-plate apparatus, and are uncorrected.

Methyl 2-oxo-4-phenyl-3-butenoate (1) was prepared by the method described in the previous paper.[1]

Synthesis of (*E*)-(ß - $^2H_1$)Styrene (2d).[4] A two-necked round bottomed flask equipped with a reflux condenser and a dropping funnel was flame dried under nitrogen, and phenylacetylene (2.79 g, 27.3 mmol) in dry ether (40 ml) was placed in the flask. Diisobutylaluminum hydride (DIBAH, 23 ml of a 1.5 mol/l toluene solution, 34.5 mmol) was added slowly to the flask cooled in an ice-bath. After addition, the mixture was heated at 80 °C for 5 h. The solvent and unchanged phenylacetylene were evaporated off under reduced pressure at room temperature, and dry ether (15 ml) was added to the flask. Deuterium oxide (99.6 atom % D, 3.0 ml) was added slowly through a syringe to the ice cold mixture. After decomposition of the organoaluminum compound, resulted inorganic mass was filtered off and the filtrate was washed twice with saturated sodium chloride solutions, and dried over sodium sulfate. The dried solution was carefully concentrated by distillation under atmospheric pressure to give an oil, which was chromatographed on a silica gel column (eluent; hexane) to give (*E*)-(ß-$^2H_1$)styrene containing a small amount of hexane. Hexane was carefully evaporated off as much as possible by distillation under atmospheric pressure, and the yield and deuterium content of (*E*)-(ß-$^2H_1$)styrene were determined by ^1H nmr. Yield; (44.7%), D atom content; 96.1 %. Colorless oil; ^1H nmr[4] ($CDCl_3$) δ =7.37-6.80 (5H, m), 6.45 (1H, dt, *J*=17.0 and 1.6 Hz), and 5.52 (1H, d, J=17.0 Hz); ms m/z 105 (M^+) and 91.

Tin(IV) Chloride Catalyzed Reaction of Methyl 2-Oxo-4-Phenyl-3-butenoate (1) with Styrene (2). General Procedure. Tin(IV) chloride (0.01 ml, 0.09 mmol) was added through a syringe to a dry dichloromethane solution (20 ml) of 1 (286 mmg, 1.5 mmol) and styrene (0.34 mml, 3 mmol) in an ice bath. The mixture was stirred under a nitrogen atmosphere for 3 h. The reaction was quenched by adding a small amount of a saturated aqueous sodium hydrogen carbonate solution. The mixture was washed successively with a saturated sodium hydrogen carbonate solution, a saturated sodium chloride solution, and water, and then dried over sodium sulfate. The solvent was evaporated off under reduced pressure to give an oil, which was chromatographed on a silica gel column (eluent: hexane:ether=8:1) to give methyl 2,4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylates (**3c**) in a 94 % yield (415 mg, the isomer ratio, *trans* -**3c**: *cis* -**3c** =73:27, determined by ^{13}C nmr), which was rechromatographed on a silica gel column (eluent; hexane:ether=8:1) to give *trans*- and *cis* - **3c**, respectively.

Methyl *trans*-2,4-Diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (*trans*-3c): Colorless oil; ir (neat) 2970, 2930, 1725, 1635 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ=7.38-7.23 (10H, m), 6.27 (1H, dd, J=4.1 and 1.1 Hz), 5.01 (1H, dd, J=9.5 and 1.3 Hz), 3.88 (3H, s), 3.64-3.57 (1H, m), 2.40-2.28 (1H, m), and 2.18-2.09 (1H, m); ^{13}C nmr (CDCl$_3$) δ =163.06, 144.89, 140.40, 128.63, 128.55, 128.36, 127.90, 127.66, 127.06, 126.74, 125.98, 111.98, 74.21, 52.00, 37.32, and 36.19; ms m/z 294 (M$^+$), 276 and 236. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.46; H, 6.23.

cis-**3c**: Colorless oil; ir (neat) 3050, 2950, 1735, 1610, and 1500 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ =7.45-7.21 (10H, m), 6.24 (1H, br. t, J=2 Hz), 5.10 (1H, dd, J=11.5 and 1.8 Hz), 3.82 (3H, s), 3.88 (1H, dq, J=11.5, 6.3 and 2.7 Hz), 2.38 (1H, tq, J=13.5, 6.2 and 2.2 Hz), and 1.96 (1H, dt, J=13.8 and 12.0 Hz); ^{13}C nmr (CDCl$_3$) δ =163.3, 145.10, 143.02, 140.28, 128.69, 128.44, 128.04, 127.12, 126.87, 126.06, 125.76, 114.20, 78.82, 52.06, and 39.63; ms m/z 294 (M$^+$) and 276. Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.43, H, 6.19.

Methyl *t*-3-Deuterio- *r*-2, *t*-4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (*trans* -3d): Colorless oil; ir (neat) 3028, 2952, 1738 and 1648 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ =7.37-7.23 (10H, m), 6.26 (1H, d, J=4.7 Hz), 4.99 (1H, d, J=9.3 Hz), 3.85 (3H, s), 3.58 (1H, t, J=5.4 Hz), and 2.30 (1H, dd, J=9.3 and 6.3 Hz); ^{13}C nmr ($CDCl_3$) δ=163.10, 144.74, 143.84, 140.27, 128.48, 124.40, 128.29, 127.83, 127.59, 126.64, 125.61, 112.04, 74.12, 51.99, 37.5-35.5, and 35.93; ms m/z 295 (M^+), 277, and 236. Anal. Calcd for $C_{18}H_{17}O_3D$: C, 77.27; H, 6.54. Found: C, 77.14; H, 6.46.

Methyl *t*-3-Deuterio-*r*-2, *c*-4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (*cis*-3d): Colorless oil; ir (neat) 3028, 2952, 1736, and 1646 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ =7.61-7.05 (10H, m), 6.23 (1H, br. d, J=2.4 Hz), 5.00 (1H br. t, J=5.8 Hz), 3.93-3.73 (1H, m), 3.82 (3H, s), and 2.35 (1H, br. d, J=6.1 Hz); ^{13}C nmr δ =163.35, 145.03, 140.27, 128.73, 128.48, 128.08, 127.16, 126.89, 126.13, 114.34, 78.78, 52.15, 38.0-40.0, and 39.48; ms m/z 295 (M^+), 277, 236, and 205. Anal. Found: C, 77.24; H, 6.64.

Methyl *c*-3-Deuerio-*r*-2, *t*-4-diphenyl-3,4-dihydro-2*H*-pyran-6-carboxylate (*trans*-3d'): ^{1}H nmr ($CDCl_3$) δ =7.39-7.23 (10H, m), 6.27 (1H, dd, J=4.8 and 1.1 Hz), 5.00 (1H, m), 3.87 (3H, s), 3.60 (1H, t, J=2.3 Hz), 2.12 (1H, br. s).

***cis*-3d':** ^{1}H nmr ($CDCl_3$) δ =7.48-7.21 (10H, m), 6.24-6.22 (1H, m), 5.09 (1H, br. t, J=6 Hz), 3.82 (3H, s), 3.49 (1H, q, J=7 Hz), and 2.36 (1H, br. d, J=7 Hz).

This work was supported by a Grant-in Aid for Scientific Research No. 60430008 from the Ministry of Education, Science and Culture. We indebted to Miss Masuko Nishinaka for ms determination and microanalysis.

REFERENCES

1. A. Sera, M. Ohara, H. Yamada, E. Egashira, N. Ueda, and J. Setsune, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1912 , and references cited therein.

2. D. L. Boger and K. D. Robarge, *J.Org.Chem.*, 1988, **53**, 3373 and 5793.
3. (*E*)-(β-$^{2}H_{1}$)Styrene (**2d**) did not isomerize to (*Z*)-(β-$^{2}H_{1}$)styrene under the reaction conditions.
4. J. T. Wood, J. S. Arney, D. Cortes, and J. A. Berson, *J.Am.Chem.Soc.*, 1978, **100**, 3855.

Received, 14th June, 1996