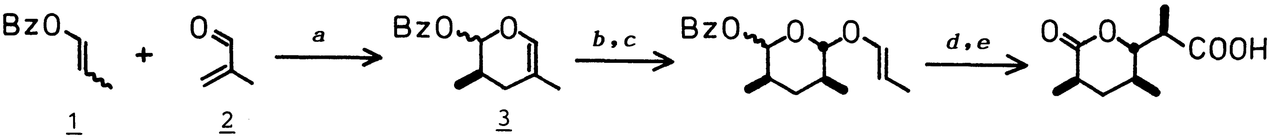
CHEMISTRY LETTERS, pp. 73-76, 1986.

$MoO_2(acac)_2$ CATALYZED HETERO DIELS-ALDER REACTION OF BENZYL PROP-1-EN-1-YL ETHER WITH METHACROLEIN

Yasuo YAMAMOTO, Hiroharu SUZUKI,* and Yoshihiko MORO-OKA*
Research Laboratory of Resources Utilization, Tokyo Institute
of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 227

Molybdenyl acetylacetonate, $MoO_2(acac)_2$ (acac = $CH_3COCHCOCH_3^-$), effectively catalyzes hetero Diels-Alder reaction of benzyl prop-1-en-1-yl ether with methacrolein under mild conditions to yield 3,4-dihydro-2-benzyloxy-3,5-dimethyl-2H-pyran.

A few years ago we discovered a new route to PDLA (Prelog-Djerassi lactonic acid) by using benzyl prop-1-en-1-yl ether, 1, and methacrolein, 2, as starting materials via a sequence of transformations including Ir-catalyzed C-C double bond migration and $BF_3 \cdot OEt_2$-catalyzed 1,3-alkyl migration reaction (Scheme 1).$^{1)}$



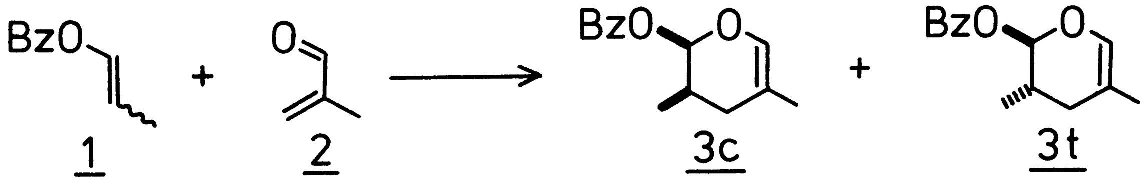
a, neat, 250 °C; b, $CH_2=CHCH_2OH$, $BF_3 \cdot OEt_2$ (1/100 equiv.), rt; c, $[(1,5\text{-COD})Ir(PMePh_2)_2]PF_6$ (1/500 equiv.), THF, rt; d, $BF_3 \cdot OEt_2$ (1/2 equiv.), CH_2Cl_2, -78 °C; e, CrO_3, H_2SO_4, H_2O, CH_3COCH_3.

Scheme 1.

In this route, Diels-Alder reaction of benzyl propenyl ether, 1, with methacrolein would be a step of crucial importance for the stereoselective synthesis of PDLA. Although the Diels-Alder reaction of dienes with dienophiles proceeds under relatively mild conditions without any catalysts, it generally needs rigorous reaction conditions, high reaction temperature and/or strong Lewis acids as catalysts, to complete the hetero Diels-Alder reaction.$^{2)}$ While it has been shown in recent years that hetero Diels-Alder reaction of ketones with dienes was greatly accelerated in the presence of lanthanides reagents such as $Eu(fod)_3$, $Eu(hfc)_3$, or $Yb(fod)_3$,$^{3)}$ only a few successful example of hetero Diels-Alder reactions between α,β-unsaturated carbonyl compounds and vinylic ether have been reported because of instability of both starting materials and the products towards heat and Lewis acid.$^{2)}$

We report herein that molybdenum(VI) complex, $MoO_2(acac)_2$ (acac = $CH_3COCHCOCH_3^-$), effectively catalyzed stereoselective hetero Diels-Alder reaction between benzyl prop-1-en-1-yl ether and methacrolein to give 3,4-dihydro-2-benzyloxy-3,5-dimethyl-

2H-pyran (Eq.1).



(1)

Experimentally, benzyl prop-1-en-1-yl ether, two equivalents of methacrolein, and catalytic amounts (2 mol%) of $MoO_2(acac)_2$ were placed in a pyrex tube filled with argon. After the tube was sealed, the reaction mixture was allowed to warm at 100 °C for 5 h. To the resulting reaction mixture was added 20 ml of n-hexane and the solution was passed through a column packed with Celite 545. Then the phase was poured into aqueous sodium hydrogen carbonate, and was extracted with three portions of 20 ml of n-hexane. The combined organic layers were dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, followed by purification of residual oily substance by Kugelrohr distillation afforded the mixture of *cis*-3,4-dihydro-2-benzyloxy-3,5-dimethyl-2H-pyran (3c)[4] and the *trans*-isomer (3t)[5]. The products, 3c and 3t, were characterized on the basis of ^1H-NMR (400 MHz) spectra and the isomeric ratio of 3c to 3t was determined by means of GLC (3m × 3m/m, 20% PEG 20M on Celite 545).

Catalytic activity of several metal salts and transition metal complexes to the Diels-Alder reaction of 1 with 2 was examined. The selected results are summarized in Table 1.

Table 1. Catalytic Diels-Alder Reaction of 1 with Methacrolein[a]

Entry	Cat.	[1]/[Cat.]	Temp/°C	Time/h	Yield of 3[e] %	Recovery of 1
1	none[b]		120	10	0	100
2	none[b]		250	10	13	tr.
3	$AlCl_3$[c]	1	r.t.	3	63	0
4	$Eu(fod)_3$[d]	20	30	720	0	100
5	$PdCl_2$	100	100	6	0	0
6	$RuCl_3(H_2O)_n$	100	100	6	0	0
7	$RuHCl(PPh_3)_3 \cdot tol$	300	160	12	20	67
8	$VO(C_2O_4) \cdot H_2O$	50	100	5	16	0
9	$MoO_2(acac)_2$	50	100	5	58	15

a) Reaction was conducted without solvent under Ar. b) Hydroquinone (1/5 equiv.) was added. c) In THF. d) In $CDCl_3$. e) Isolated based on 1.

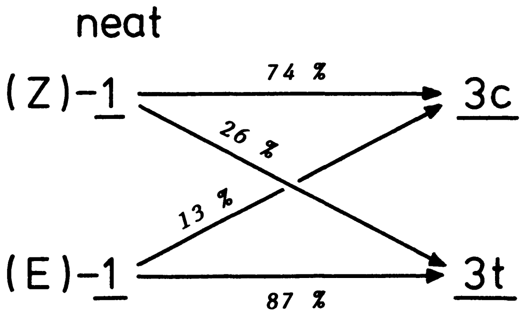
In the absence of catalyst, the reaction hardly proceeded even at high temperature. The lanthanide complex, Eu(fod)$_3$, did not affect the reaction under the same conditions as that adopted by Danishefsky. The use of $PdCl_2$, $RuCl_3 \cdot nH_2O$, $RuCl_2(PPh_3)_3$, $Mn(acac)_2 \cdot 2H_2O$, $Mn(acac)_3$, NH_4VO_3, $VO(acac)_2$, $CoCl_2$, $TiCl_4$, or $BF_3 \cdot Et_2O$ in the reaction resulted in vain. While $AlCl_3$ greatly accelerated the reaction, it had disadvantage of considerable loss of stereoselectivity in the reaction of (Z)-1 with 2.6) The best result was obtained when the reaction was conducted in the presence of molybdenyl acetylacetonate, $MoO_2(acac)_2$ (entry 9).

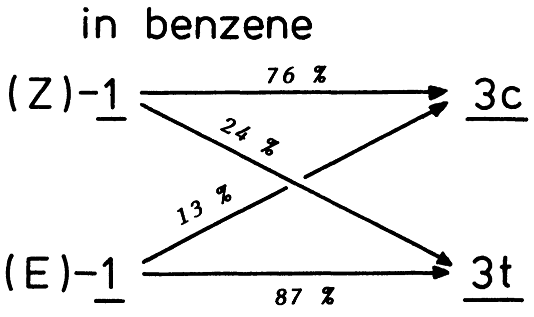
The stereochemistry of the reaction was examined by using the isomerically pure prepared (*Z*)- and (*E*)-benzyl prop-1-en-1-yl ether, (*Z*)-1 and (*E*)-1, as dienophiles. The stereochemical outcome of the reaction catalyzed by $MoO_2(acac)_2$ is given in Table 2.

Table 2. Stereoselectivity in $MoO_2(acac)_2$ Catalyzed Diels-Alder Reaction

Solvent	1 (*Z*/*E*)a)	Recovery of 1 / %	Yield of 3b) / %	3c/3ta)
none	99.6/ 0.4	40	57	74/26
none	5.2/94.8	10	59	15/85
benzene	99.9/ 0.1	44	43	76/24
benzene	3.5/96.5	9	67	15/85
acetonitrile	99.9/ 0.1	24	25	54/46
acetonitrile	3.5/96.5	12	40	17/83

a) Determined by means of GLC. b) Isolated yield based on consumed 1.





The results may be summarized as follows: the reaction of (*E*)-1 with 2 gave *trans*-dihydropyran 3t predominantly and the reaction of (*Z*)-1 led to the formation of *cis*-dihydropyran 3c with the diminution of the stereoselectivity. The reaction in benzene solution gave almost the same results as that in the absence of solvent while the reaction in acetonitrile diminished the stereoselectivity.

We thank Dr. T. Ikariya for collecting NMR data with JEOL GX-400. Financial support for this work was generously provided in part grant from the Ministry of Education, Science and Culture of the Japanese Government (No. 60550581).

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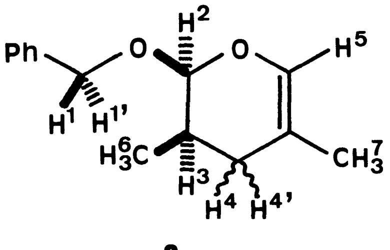
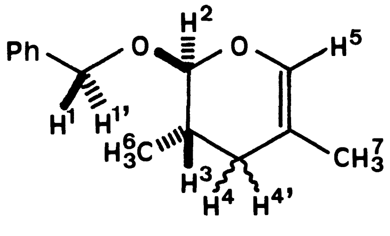


3c



3t

4) ^{1}H-NMR (400 MHz, CDCl$_3$) δ 4.78 (d, $J_{H^1H^{1'}}$=12.37 Hz, 1H, H^1 or $H^{1'}$), 4.55 (d, $J_{H^1H^{1'}}$=12.37 Hz, 1H, $H^{1'}$ or H^1), 4.79 (d, $J_{H^2H^3}$=2.13 Hz, 1H, H^2), 1.90 (m, 1H, H^3), 1.76 (m, 1H, H^4 or $H^{4'}$), 0.96 (m, 1H, $H^{4'}$ or H^4), 6.02 (d, $J_{H^5H^7}$=1.22 Hz, 1H, H^5), 1.00 (d, $J_{H^3H^6}$=6.41 Hz, 3H, H^6), 1.55 (d, $J_{H^5H^7}$=1.22 HZ, 3H, H^7), 7.32 (m, 5H, Ph).

^{13}C-NMR (25 MHz, CDCl$_3$) δ 97.8 (C-2), 31.0 (C-3), 29.7 (C-4), 109.7 (C-5), 133.8 (C-6), 16.2 ($\underline{C}H_3$-C-2), 18.3 ($\underline{C}H_3$-C-5), 69.1 ($\underline{C}H_2$-Ph), 127.4, 127.5, 128.2, and 138.4 (Ph).

5) ^{1}H-NMR (400 MHz, CDCl$_3$) δ 4.82 (d, $J_{H^1H^{1'}}$=12.21 Hz, 1H, H^1 or $H^{1'}$), 4.57 (d, $J_{H^1H^{1'}}$=12.21 Hz, 1H, $H^{1'}$ or H^1), 4.60 (d, $J_{H^2H^3}$=3.97 Hz, 1H, H^2), 1.98 (dddt, $J_{H^2H^3}$=3.97 Hz, $J_{H^3H^4}$ or $J_{H^3H^{4'}}$=6.74 Hz, $J_{H^3H^{4'}}$ or $J_{H^3H^4}$=4.27 Hz, $J_{H^3H^6}$=7.02 Hz, 1H, H^3), 2.24 (dd, $J_{H^4H^{4'}}$=16.79 Hz, $J_{H^3H^4}$ or $J_{H^3H^{4'}}$=6.74 or 4.27 Hz, 1H, H^4 or $H^{4'}$), 1.53 (dd, $J_{H^4H^{4'}}$=16.79 Hz, $J_{H^3H^{4'}}$ or $J_{H^3H^4}$=6.74 or 4.27 Hz, 1H, $H^{4'}$ or H^4), 6.03 (d, $J_{H^5H^7}$=1.22 Hz, 1H, H^5), 0.96 (d, $J_{H^3H^6}$=7.02 Hz, 3H, H^6), 1.54 (d, $J_{H^5H^7}$=1.22 Hz, 3H, H^7), 7.33 (m, 5H, Ph).

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6) The reaction of (*Z*)-1 (purity > 99.6) with 2 gave the mixture of isomers, 3c and 3t (41 : 59), in 63 % combined yield.

(Received October 29, 1985)