A Lewis Base-catalyzed Hetero Diels–Alder Reaction between Aldehydes and the Danishefsky's Diene

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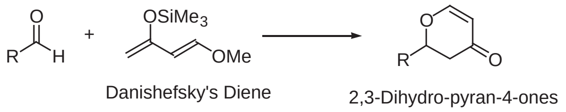
A lithium methoxide-catalyzed hetero Diels–Alder reaction of aromatic and aliphatic aldehydes with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) is described. It proceeds through the Mukaiyama-Aldol reaction pathway and affords the corresponding 2,3-dihydropyran-4-one skeletons in good to excellent yields.

2,3-Dihydropyran-4-one is a characteristic hetero-cyclic compound and is found in many biologically active compounds. It is well known that the 2,3-dihydropyran-4-one skeleton is formed by treating aldehydes with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) via hetero Diels–Alder reaction (Scheme 1).[1]

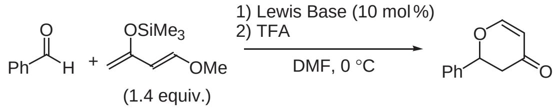


Scheme 1. Hetero Diels–Alder reaction of an aldehyde and the Danishefsky's diene.

Recently, it was reported from our laboratory that various types of Lewis base catalysts were used effectively in such carbon–carbon bond forming reactions as Aldol,[2] Michael,[3] and Mannich-type reactions.[4] In these reactions, it was assumed that the silicon–oxygen bond of silyl enolates were activated by the Lewis base catalysts. To demonstrate the usefulness of these Lewis base catalysts, it was planned then to activate a different type of silyl enolates such as Danishefsky's diene (1-methoxy-3-trimethylsilyloxy-1,3-butadiene) under the same conditions. There are no examples of Lewis base used as a catalyst in hetero Diels–Alder reaction though many Lewis acids were known to be effective. Here, a new method for the formation of 2,3-dihydropyran-4-ones via the Lewis base-catalyzed hetero Diels–Alder reactions is described.

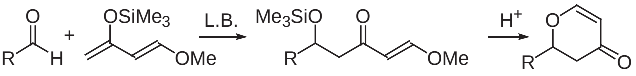
In the first place, a reaction between benzaldehyde and the Danishefsky's diene was tried in the presence of a catalytic amount of various Lewis base catalysts and the reaction conditions were carefully examined (Table 1). Whereas Lewis base catalysts prepared from carboxylic acids were less effective, those prepared from phenol and alcohol were found more potent. Then, effect of the counter cation was screened and the lithium ion gave the best result. When THF and pyridine was used as a solvent, the yield was lowered dramatically. Further investigation using various lithium alkoxides showed that lithium methoxide promoted the reaction smoothly to give the cycloadduct in excellent yield. When the reaction was carried out in the presence of 5 mol % of the catalyst, the yield lowered slightly. Although the desired cycloadduct was not observed under this reaction condition, the corresponding aldol adduct was obtained instead as the major product. The reaction is thus assumed to proceed via a stepwise procedure through Mukaiyama-Aldol reaction (Scheme 2).

Table 1. Screening of catalyst and reaction conditions in the hetero Diels–Alder reaction



Entry	Lewis Base	Yield/%	Entry	Lewis Base	Yield/%
1	AcOLi	9	9	PhONBu$_4$^{c}	34
2	AcOCs	6	10^{g}	MeOLi	96(79)^{f}
3	AcONBu$_4$	36	11	MeOLi^{a}	50
4	PhOLi^{a}	57	12	MeONa	28
5	PhOLi^{a}	N.R.^{d}	13	BnOLi^{a}	43
6	PhOLi^{a}	18^{e}	14	^{i}PrOLi^{a}	40
7	PhONa^{b}	5	15	^{t}BuOLi^{a}	59
8	PhOK^{b}	20	16	^{t}BuOK	25

^{a}Prepared from alcohols (phenol) and MeLi. ^{b}Prepared from phenol and aq. MOH (M = Na and K). ^{c}Prepared from phenol and Bu$_4$NOH in MeOH. ^{d}The reaction was carried out in THF. ^{e}The reaction was carried out in pyridine. ^{f}Yield given in parenthesis is the result using 5 mol % catalyst. ^{g}Ref. 5.

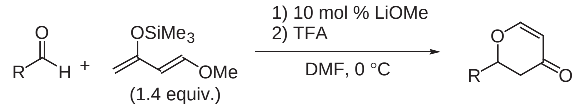


Scheme 2. Assumed reaction pathway of hetero Diels–Alder reactions promoted by Lewis Base catalysts.

Next, the above hetero Diels–Alder reaction were examined by using various aldehydes (Table 2). Aromatic aldehydes having an electron-withdrawing group and an electron-donating group reacted smoothly and the corresponding cycloadducts were obtained in excellent yields (Entries 2 to 8). It is noteworthy that a substrate having Lewis basic moiety (Entry 9) reacted under these conditions as well and gave the corresponding cycloadducts, which is often difficult to be prepared by the Lewis acid catalyzed reactions. Other aromatic aldehydes with naphthalene ring and heteroaromatic ring gave the corresponding cycloadducts in good to excellent yields as shown in Entries 10 to 13. Aliphatic aldehydes of primary, secondary, and tertiary aldehydes and α,β-unsaturated aldehyde also gave the corresponding cycloadducts in good yield (Entries 14 to 18).

Next, this hetero Diels–Alder reaction was tried by using other Danishefsky's dienes (Table 3). Then, it was found that the Danishefsky's diene with a methyl group at 2-position reacted smoothly and the desired cycloadducts were obtained in ex-

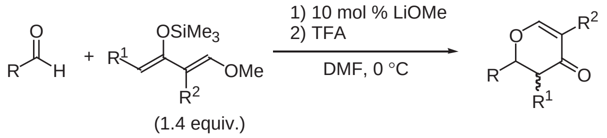
Table 2. LiOMe-catalyzed hetero Diels–Alder reactions with various aldehydes



Entry	R	Yield/%	Entry	R	Yield/%
1	Ph	96	10	1-Naphthyl	93
2	2-ClPh	88	11	2-Naphthyl	88
3	4-ClPh	94	12[a]	2-Pyridyl	60
4	4-NCPh	93	13	2-Furyl	75
5	4-MeOOCPh	91	14	Ph(CH$_2$)$_2$	81
6	2-MeOPh	80	15	*c*-Hex	78
7	4-MeOPh	79	16[a]	^{t}Bu	54
8	4-MePh	76	17	BnOCH$_2$	75
9[a]	4-Me$_2$NPh	50[b]	18	(*E*)-PhCH=CH	80

[a]2.0 equiv. of Danishefsky's diene was used. [b]Determined by ^{1}H NMR analysis (270 Hz) using 1,1,2,2,-tetrachloroethane as an internal standard.

Table 3. LiOMe-catalyzed hetero Diels–Alder reactions with substituted Danishefsky's dienes



Entry	R	R^1	R^2	Yield/%	d.r.
1	Ph	H	Me	96	—
2		Me	Me	quant.	65/35
3	4-MeOOCPh	H	Me	quant.	—
4		Me	Me	94	64/36
5	4-MeOPh	H	Me	97	—
6		Me	Me	quant.	72/28
7[a]		Me	Me	73	75/25
8	Ph(CH$_2$)$_2$	H	Me	68	—
9		Me	Me	80	59/41

[a]The reaction was carried out at −20 °C.

cellent yields. The reactions of those with the methyl groups at 2- and 4-position also went smoothly but their diastereoselectivities turned out to be low even at lower temperatures.

It is noted that the lithium methoxide-catalyzed hetero Diels–Alder reactions using both aromatic and aliphatic aldehydes proceeded smoothly to construct the corresponding 2,3-dihydropyran-4-one skeletons in good to excellent yields under the Lewis basic conditions. Thus, the present method provides an efficient route to the preparation of substrates having a basic moiety that is frequently found in biologically active compounds such as in pharmaceuticals and in natural products. Further studies on this type of reactions are in progress.

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5 Typical experimental procedure is as follows (Table 1, Entry 10): to a stirred solution of LiOMe (1.6 mg, 0.0421 mmol) in dry DMF (0.1 mL) was added a solution of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (104.4 mg, 0.603 mmol) in DMF (0.3 mL) and a solution of benzaldehyde (44.0 mg, 0.415 mmol) in DMF (0.6 mL) at 0 °C under argon atmosphere. The mixture was stirred for 15 h at the same temperature and 5 mL of saturated NH$_4$Cl solution was added to quench the reaction. The mixture was extracted with EtOAc and the combined organic layer was washed with water and brine, dried over anhydrous Na$_2$SO$_4$, and evaporated. The residue was dissolved in Et$_2$O (5 mL) and TFA (0.3 mL) was added at 0 °C. The mixture was stirred for 30 min at the same temperature and saturated NaHCO$_3$ solution was added carefully. After usual workup, the crude product was purified by preparative TLC (hexane/EtOAc/benzene = 10/2/1) to give the corresponding 2,3-dihydropyran-4-one (70.6 mg, 96%) as a colorless oil.

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