

Dilithium 2,2'-Methylenebis(4,6-di-*tert*-butylphenoxide) as a Bidentate Lewis Acid in Organic Synthesis

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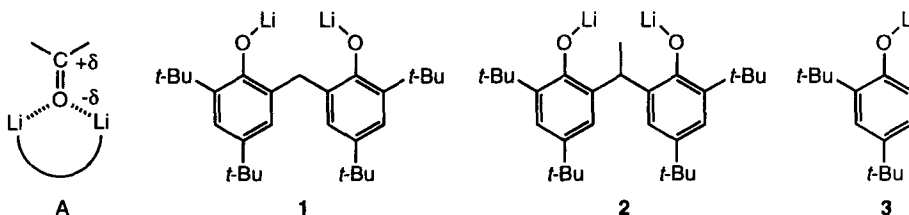
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Abstract: Dilithium 2,2'-methylenebis(4,6-di-*tert*-butylphenoxide) can be successfully utilized as a bidentate Lewis acid for simultaneous coordination to carbonyl groups, thereby accelerating the Diels-Alder reactions. The double activation ability of the bidentate lithium reagent toward carbonyls is emphasized in comparison with the corresponding monodentate lithium reagent. © 1998 Elsevier Science Ltd. All rights reserved.

Since the pioneering work of $\text{LiClO}_4/\text{Et}_2\text{O}$ -promoted electrophilic reactions in organic synthesis by Grieco *et al.*,^{1,2} a variety of lithium-cation reagents have been elaborated for this purpose. LiBF_4 is found to be highly effective for aminolysis of oxetanes.³ Lithium trifluoromethanesulfonimide (LiNTf_2) can be utilized as a safe alternative to LiClO_4 in diethyl ether.⁴ The recently discovered $\text{LiAl}(\text{OC}(\text{Ph})(\text{CF}_3)_2)_4$, which is soluble in hydrocarbon solvents, is applicable to conjugate addition of silyl ketene acetals to α,β -unsaturated carbonyl compounds and for the direct substitution of allylic acetates by silyl ketene acetals.⁵ Lithium cobalt-bis-dicarbollide ($\text{LiCo}(\text{B}_9\text{C}_2\text{H}_{11})_2$) has also been introduced as a mild and efficient Lewis acid for catalyzing the conjugate addition of silyl ketene acetals to α,β -unsaturated carbonyl compounds and for the substitution of allylic acetates.⁶ In addition to the development of these lithium-based reagents, we here disclose a conceptually new approach based on the simultaneous coordination and activation of carbonyl moiety, illustrated in A, by dilithium 2,2'-methylenebis(4,6-di-*tert*-butylphenoxide) (**1**) as a bidentate lithium Lewis acid.⁷ The distinct advantage of the dilithium reagent **1** is its solubility in a nonpolar solvent such as toluene, which obviously stems from the four *t*-butyl groups,⁸ and also the ready availability of the ligand synthesized from 2,4-di-*tert*-butylphenol in one-pot procedure.⁹



Lithium phenoxides have usually been recognized as an organic base and therefore have not been utilized as a Lewis acid in selective organic synthesis. Indeed, the Diels-Alder reaction of acrolein with cyclopentadiene (2 equiv) under the influence of lithium 2,4-di-*tert*-butylphenoxide (**3**) (1.1 equiv) at -78°C for 1 h and -20°C for 7.5 h resulted in formation of a product mixture which was totally deteriorated. In marked contrast, however, treatment of acrolein with 1.1 equiv of bidentate lithium reagent, dilithium methylenebis(4,6-di-*tert*-

butylphenoxide) (**1**) and subsequent reaction with cyclopentadiene (2 equiv) under similar reaction conditions produced the corresponding Diels-Alder adduct **4** ($R^1 = R^2 = R^3 = H$) in 77% yield (*endo/exo* = 76 : 24), demonstrating the effectiveness of **1** as a bidentate lithium Lewis acid.¹⁰ The comparable reactivity was observed using **2** (prepared from a commercially available 2,2'-ethylidenebis(4,6-di-*tert*-butylphenol)) as a bidentate Lewis acid: 50% yield of **4** ($R^1 = R^2 = R^3 = H$); *endo/exo* = 81:19. Other representative results are summarized in Table 1.

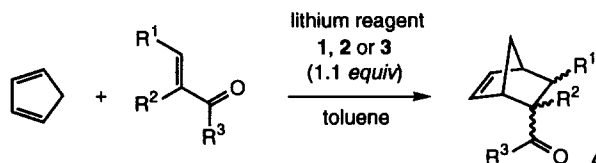


Table 1. Lithium Lewis Acid-Promoted Diels-Alder Reaction of Cyclopentadiene with Several Dienophiles ^a

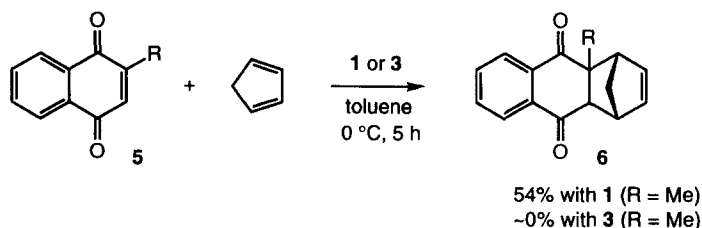
entry	dienophile	lithium reagent	condition (°C, h)	yield, % ^b (<i>endo/exo</i>) ^c
1	CH ₂ =CHCHO	1	-78, 1; -20, 7.5	77 (76:24) ^d
2		1		n.r. ^{e f}
3		2		50 (81:19)
4		3		trace
5		LiClO ₄		16 (88:12) ^f
6	CH ₂ =C(CH ₃)CHO	1	-78, 0.5; 20, 17	70 (12:88) ^d
7		2		50 (12:88)
8		3		25 (17:83) ^d
9	CH ₂ =CHCOCH ₃	1	-78, 0.5; 0, 1.5; 20, 3	71 (89:11)
10		2		67 (85:15)
11		3		19 (80:20)
12	CH ₃ CH=CHCHO	1	20, 15	trace

^a The reaction was carried out in distilled toluene with 1.1 equiv of lithium phenoxide reagent under the given reaction conditions. ^b Isolated yield. ^c The *endo/exo* ratio was determined by ¹H NMR analysis. ^d Isolate yield and the *endo/exo* ratio were determined after conversion to the corresponding *primary* alcohol by NaBH₄ reduction. ^e n.r.: no reaction. ^f Use of diethyl ether as solvent.

As shown in the Table, a variety of α,β -unsaturated aldehydes and ketones can be utilized as dienophiles under the influence of both dilithium reagents **1** and **2** to promote Diels-Alder reactions, while monolithium phenoxide **3** lacks the ability of effecting the cycloadditions.¹¹ Substituents on the β position of dienophile

significantly retard the reaction as evident from the case of crotonaldehyde (entry 12).¹² When LiClO₄ was used as promoter in diethyl ether (the same molar concentration of Li as **1**), the reaction proceeded sluggishly under similar reaction conditions yielding Diels-Alder adduct **4** ($R^1 = R^2 = R^3 = H$) in only 16% yield (entry 5).¹³ The dilithium Lewis acid **1** consistently gave better results than **2** probably due to the more flexible structure of **1**, thereby allowing the efficient simultaneous coordination of lithium to carbonyl moiety. Notably, switching the reaction solvent from toluene to diethyl ether tremendously diminished the Lewis acidity of dilithium reagent (entry 2).

We also studied the Diels-Alder reaction between 2-methyl-1,4-naphthoquinone (**5**, $R = Me$) and cyclopentadiene. This cycloaddition proceeds very slowly even at room temperature, and indeed the product **6** ($R = Me$) is obtained in only 3.6% yield after 40 h stirring. However, the dilithium reagent **1** was found to accelerate the Diels-Alder reaction at 0 °C giving the corresponding cycloadduct **6** ($R = Me$) in 54% yield, while the reaction did not proceed at all with the monodentate counterpart **3** under similar reaction conditions. The stereochemistry of the product **6** ($R = Me$) is that anticipated for the usual *endo* orientation of reactants in the transition state. The cycloaddition of naphthoquinone (**5**, $R = H$) with cyclopentadiene was also effected by **1** at -20 °C for 3.5 h to afford **6** ($R = H$) in 90% yield without any aromatization.



The typical experimental procedure is as follows (Table 1, entry 1): To a solution of 2,2'-methylenebis(4,6-di-*tert*-butylphenol) (233.6 mg, 0.55 mmol) in distilled toluene (5 mL) was added a 1.6 M hexane solution of BuLi (687.5 μ L, 1.1 mmol) dropwise at 0 °C under argon and the mixture was stirred for 1 h at room temperature. After the resulting mixture was cooled to -78 °C, freshly distilled acrolein (33.4 μ L, 0.5 mmol) and cyclopentadiene (83 μ L, 1.0 mmol) were added sequentially. The whole reaction mixture was then allowed to warm to -20 °C and stirred there for 7.5 h. The reaction was quenched with 1 N HCl and extractive workup was performed with ether. The combined organic extracts were washed with saturated NaHCO₃ solution and dried over Na₂SO₄. After removal of solvents, the residual oil was dissolved in methanol and then treated with NaBH₄ at 0 °C for 30 min. The reaction mixture was poured into water and extracted with ether. The organic extracts were washed successively with brine and dried over Na₂SO₄. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/pentane = 1:2 as eluant) gave reductant of the Diels-Alder adduct (47.8 mg, 0.385 mmol; 77% yield). The *endo/exo* ratio of the product was determined by ¹H NMR analysis (*endo/exo* = 76: 24).

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References and Notes

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- (8) 2,7-Dimethyl-1,8-biphenylenediol is already found to be an appropriate spacer for designing bidentate aluminum reagent (see ref 7). However, dilithium reagent derived from 2,7-dimethyl-1,8-biphenylenediol and BuLi is sparingly soluble in toluene and even in diethyl ether.
- (9) For the preparation of 2,2'-dihydroxydiphenylmethanes: (a) Casiraghi, G.; Casnati, G.; Pochini, A.; Puglia, G.; Ungaro, R.; Sartori, G. *Synthesis* **1981**, 143. (b) Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, A.; Puglia, G.; Sartori, G.; Ungaro, R. *J. Chem. Soc. Perkin I* **1974**, 318.
- (10) We have not yet been able to obtain convincing physical evidence of the simultaneous coordination of **1** to carbonyl substrate. However, it has been fairly implicated by the fact that the bisaluminum reagent derived from 2,2'-methylenebis(4,6-di-*tert*-butylphenol) and 2 equiv of Me₃Al exhibits almost the same reactivity with that of (2,7-dimethyl-1,8-biphenylenedioxy)bis(dimethylaluminum).
- (11) Simple mixing of methyl vinyl ketone and 2 equiv of cyclopentadiene in toluene at room temperature for 3 h afforded the Diels-Alder adduct **4** (R¹ = H, R² = Me) in 16.6% yield.
- (12) Attempted cycloaddition of methyl acrylate and cyclopentadiene with **1** proceeds quite reluctantly at room temperature.
- (13) The cycloaddition with LiClO₄/diethyl ether system proceeds faster at room temperature and it is apparently possible to obtain synthetically useful chemical yield employing more concentrated conditions.