Selective Conjugate Alkylation of Alkyllithium Nucleophiles to α, β, γ, δ-Unsaturated Aldehydes with Functionalized Lewis Acid Receptors

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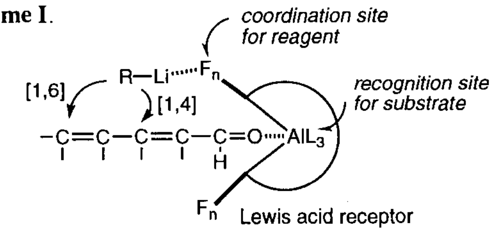
Selective 1,4- and 1,6-addition of alkyllithium reagents to $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes has been successfully realized with fluorinated aluminum tris(2,6-diphenylphenoxide) (ATPH) derivatives as functionalized Lewis acid receptors.

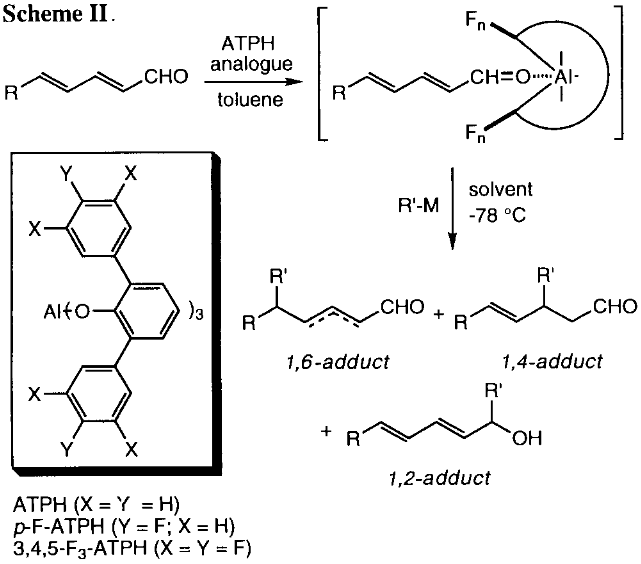
In contrast to the smooth conjugate alkylation to α,β-unsaturated aldehydes by organocopper chemistry, little is known about the application of such alkylation to $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes.[1] Indeed, attempted conjugate alkylation of $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes with R_2CuLi was totally ineffective, and resulted in deteriorated reaction mixtures with only a trace of the desired conjugate adducts. This observation prompted us to examine the reaction of $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes using our recently developed amphiphilic conjugate alkylation system (Scheme I).[2] Here we wish to report that the selective 1,4- or 1,6-alkylation of reactive organometallics to $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes can be effected with aluminum tris[2,6-bis(3,4,5-trifluorophenyl)phenoxide] (3,4,5-F_3-ATPH) as a functionalized Lewis acid receptor. Representative results are summarized in Table I.

Scheme I.



Initial complexation of (*E*,*E*)-5-phenyl-2,4-pentadienal[3] with aluminum tris(2,6-diphenylphenoxide) (ATPH)[4] (1.1 equiv) in toluene and subsequent reaction of BuLi (1.2 equiv) in hexane at -78 °C for 15 min gave rise to 1,2-adduct predominantly (ratio of 1,6-/1,4-/1,2-adducts = 6:7:87; 97% combined yield) (entry 1). Switching carbon nucleophiles from BuLi to BuMgBr slightly enhanced the selectivity (ratio of 1,6-/1,4-/1,2-adducts = 0:23:77; 50% combined yield) (entry 2). This selectivity is markedly different from the case of α,β-unsaturated aldehydes, where high 1,4-selectivity is generally observed with ATPH/RMgX.[4a] However, the 1,4-selectivity is further enhanced with aluminum tris(2,6-di(*p*-fluorophenyl)phenoxide) (*p*-F-ATPH)[2] and aluminum tris[2,6-bis(3,4,5-trifluorophenyl)phenoxide] (3,4,5-F_3-ATPH)[2c] in the reaction of (*E*,*E*)-5-phenyl-2,4-pentadienal with BuLi or BuMgBr: *p*-F-ATPH/BuLi (ratio of 1,6-/1,4-/1,2-adducts = 4:55:41; 99% combined yield); 3,4,5-F_3-ATPH/BuLi (10:65:25, 99%); 3,4,5-F_3-ATPH/BuMgBr (24:70:6, 81%) (entries 3, 5 and 6). In contrast, modest 1,6-selectivity is achievable with 3,4,5-F_3-ATPH and BuLi in ether or DME (64:31:5 with ether; 71:18:11 with DME) (entries 7 and 8). Here, the solvation of BuLi with ethereal solvent is quite appropriate to increase the steric size of the nucleophile (BuLi), while still maintaining the coordination ability of Li^+ to fluorine atoms of 3,4,5-F_3-ATPH.[5]

Scheme II.



Conjugate addition of other organolithium reagents such as *sec*-BuLi, PhLi and isopropenyllithium appeared to be feasible with excellent selectivities (entries 9-11). The effectiveness of the 3,4,5-F_3-ATPH/BuLi system was further demonstrated with (*E*,*E*)-2,4-nonadienal (entries 12-14). The unique selectivity observed herein could be ascribed not only to the eminent metal-fluorine interaction but also to the increase in overall depth of the cavity resulting from the fluorine atoms.[5,6] Further development of a more sophisticated reaction system based on designer Lewis acid engineering to improve the selectivity is certainly our ongoing project.

The typical experimental procedure is as follows (Table I, entry 7): A solution of 2,6-di(3,4,5-trifluorophenyl)phenol (585 mg, 1.65 mmol) in toluene (5 mL) was degassed, and a 1M hexane solution of Me_3Al (0.55 mL, 0.55 mmol) was added at room temperature under argon. Methane gas evolved immediately. The resulting yellow solution was stirred for 30 min and used without purification. After the addition of a solution of (*E*,*E*)-5-phenyl-2,4-pentadienal in toluene (1 mL) at -78 °C, a 1.6 M hexane solution of BuLi (375 μL, 0.6 mmol) in ether (2 mL) at -78 °C was added dropwise by cannular transfer. The solution was stirred at -78 °C for 15 min and then poured into 1N HCl solution. After extraction with ether, the organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (dichloromethane/hexane = 1:3 to ethyl acetate/hexane = 1:4 as eluant) gave the mixture of 1,6-, 1,4- and 1,2-adducts as a pale yellow oil (93.0 mg, 0.43 mmol, 86% yield). The ratio of 1,6-/1,4-/1,2-adducts was determined by ^1H NMR analysis to be 64:31:5.

Table I. Conjugate Addition of Alkyllithiums to $\alpha,\beta,\gamma,\delta$-Unsaturated Aldehydes with Modified ATPH [a]

entry	aldehydes	ATPH analogue	RLi/solvent	yield, [b] %	ratio [c]
1	PhCH=CHCH=CHCHO	ATPH	BuLi/hexane	97	6 : 7 : 87
2			BuMgBr/ether	50	0 : 23 : 77
3		*p*-F-ATPH	BuLi/hexane	99	4 : 55 : 41
4			BuMgBr/ether	49	0 : 53 : 47
5		3,4,5-F_3-ATPH	BuLi/hexane	99	10 : 65 : 25
6			BuMgBr/ether	81	24 : 70 : 6
7			BuLi/ether	86	64 : 31 : 5
8			BuLi/DME	81	71 : 18 : 11
9	PhCH=CHCH=CHCHO	3,4,5-F_3-ATPH	*sec*-BuLi/hexane	77	64 : 36 : <1
10			PhLi/ether	85	27 : 67 : 6
11			$CH_2=C(CH_3)Li$/ether	87	46 : 48 : 6
12	BuCH=CHCH=CHCHO	3,4,5-F_3-ATPH	BuMgBr/ether	76[d]	30 : 70 : 0[d]
13			BuLi/hexane	96[d]	26 : 55 : 19[d]
14			BuLi/ether	88[d]	44 : 40 : 16[d]

[a] An alkyllithium (1.2 equiv) was added to $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes by complexation with ATPH analogue (1.1 equiv) in toluene at -78 °C, and stirred there for 15 min. [b] Isolated yield. [c] Ratio of 1,6-/1,4-/1,2-adducts. [d] Isolated yield and product ratio were determined after conversion of conjugate adducts to the corresponding alcohols by DIBAH reduction in toluene at -78 °C.

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6 Electron withdrawing substituents directly attached to the phenoxy ring dramatically affect the Lewis acidity of aluminum. However, the influence of fluoro substituents introduced to the *ortho*-phenyl groups of fluorinated ATPH derivatives on the Lewis acidity seems to be negligible compared to the parent ATPH, since the increase of the Lewis acidity of fluorinated ATPH derivatives would cause the preferential 1,2-addition of BuLi to the dienals. See: a) K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973). b) B. Deschamps, *Tetrahedron*, **34**, 2009 (1978).