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Evaluation of Several Fluorinated ATPH Derivatives as Functionalized Lewis Acid Receptors for Conjugate Alkylation to α,β-Unsaturated Aldehydes with Alkyllithium Nucleophiles

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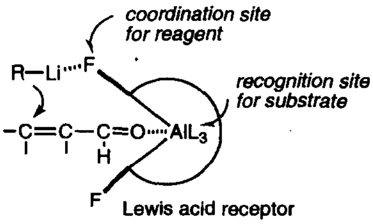
Abstract: Several fluorinated aluminum tris(2,6-diphenylphenoxide) (ATPH) derivatives have been synthesized to evaluate, as functionallized Lewis acid receptors, the conjugate alkylation ability to α,β-unsaturated aldehydes by the combined use of alkyllithium nucleophiles. Among these, 3,4,5-F_3-ATPH was found to be the most satisfactory. © 1997 Elsevier Science Ltd.

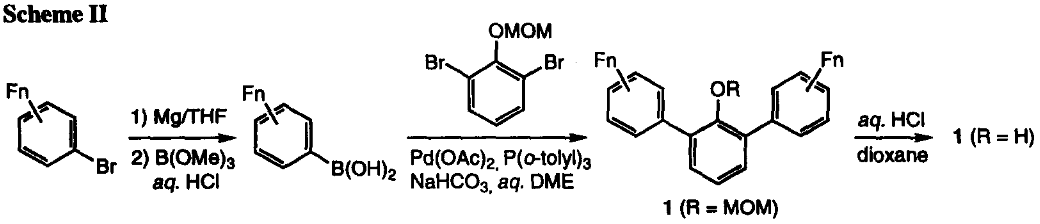
The design of new host molecules for application in molecular recognition is a subject of much current interest, and a variety of recognition systems capable of reversible binding interactions have been developed for this purpose.[1-4] In particular, Lewis acid receptors are found to be highly promising as host molecules in view of their tighter binding behavior with effective coordination bondings than hydrogen-bonding interactions.[5] Our recent design of a new Lewis acid receptor, aluminum tris[2,6-di(*p*-fluorophenyl)phenoxide] (*p*-F-ATPH) featured a recognition site for carbonyl substrates as well as an effective coordination site for an alkyllithium nucleophile in the conjugate alkylation to α,β-unsaturated aldehydes by the combined use of alkyllithium nucleophiles (Scheme I).[6,7] Without the *p*-fluoro coordination site in the parent ATPH, the 1,4-selectivity is dramatically lowered,[8] suggesting that the effective lithium/fluorine coordination ensures the smooth conjugate alkylation. This observation prompted us to examine several other fluorinated ATPH derivatives as functionallized Lewis acid receptors to attain the more effective lithium/fluorine coordination for selective delivery of alkyllithium nucleophiles to a remote β position of α,β-unsaturated aldehydes.[9]

Scheme I



Several fluorinated 2,6-diphenylphenols **1** (R = H) can be synthesized according to procedures in the literature: (i) conversion of fluorinated phenyl bromide to fluorinated phenylboronic acid by treatment with Mg in THF followed by addition of $B(OMe)_3$; (ii) Suzuki coupling of the fluorinated phenylboronic acid and 2,6-dibromophenol MOM ether with $Pd(OAc)_2/P(o\text{-tolyl})_3/NaHCO_3$ in *aq.* DME; (iii) deprotection of the MOM group with *aq* HCl-dioxane (Scheme II).[10]

Scheme II



Fluorinated ATPH is conveniently prepared by treatment of a fluorinated phenol 1 (R = H) (3 equiv) in toluene with a 1 M hexane solution of Me_3Al at 25 °C for 30 min and its ability as a functionallized Lewis acid is evaluated in the conjugate addition of alkyllithiums to α,β-unsaturated aldehydes (Scheme III and Table I). Initial complexation of cinnamaldehyde with *p*-F-ATPH (1.1 equiv) in toluene and subsequent reaction of BuLi (1.5 equiv) in hexane at -78 °C for 15 min gave rise to a mixture of 1,4- and 1,2-adducts in a ratio of 76:24 (87% yield); this is bettter than the case of parent ATPH (entries 1 and 2). Interestingly, the 1,4-selectivity of this alkylation was improved almost linearly as the number of fluorine atoms on phenoxy ligands increased (entries 1-4).[11] Using ether as solvent of BuLi greatly enhanced the selectivity, especially with 3,4-F_2-ATPH and 3,4,5-F_3-ATPH. Here, the coordination of ether increased the steric size of BuLi without interfering with the interaction between Li^+ and fluorine atoms. The effectiveness of 3,4,5-F_3-ATPH/BuLi system was further demonstrated with aliphatic aldehyde, 2-heptenal (entries 8-10). A similar tendency was observed in the conjugate addition of PhLi in hexane under the influence of fluorinated ATPH analogues (entries 11-14), and virtually complete 1,4-selectivity was obtained with 3,4,5-F_3-ATPH (entry 14). These results strongly indicate that the effective lithium/fluorine coordination is responsible for the selective delivery of the reactive alkyllithium reagents to a β position of α,β-unsaturated aldehydes. As clearly illustrated in the space-filling model of each fluorinated ATPH analogue, fluorine atoms are neatly lined up and create attractive coordination sites right on top of the reaction cavity, the effectiveness of which is certainly exploited with 3,4,5-F_3-ATPH.

Scheme III

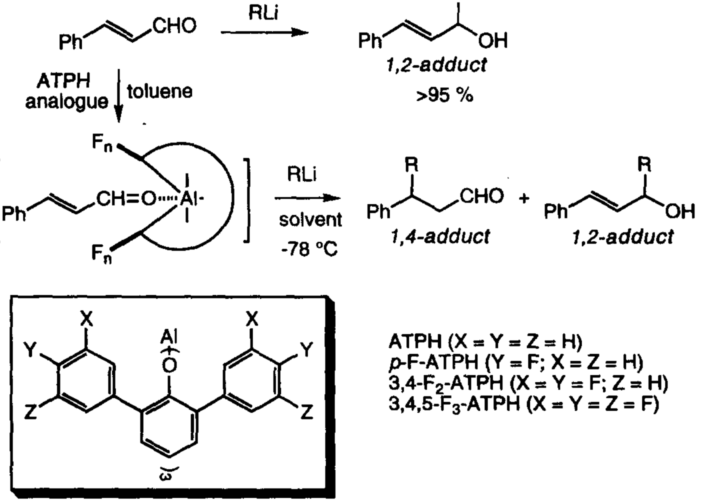
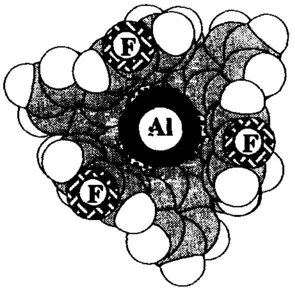


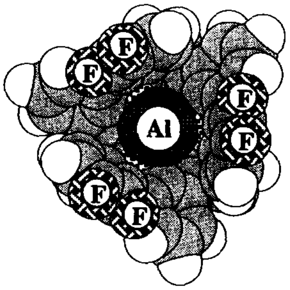
Table I. Conjugate Addition of Alkyllithiums to α,β-Unsaturated Aldehydes with Modified ATPH[a]

entry	Aldehydes	ATPH analogue	RLi/solvent	yield,[b] %	ratio[c]
1	PhCH=CHCHO	ATPH	BuLi/hexane	92	50 : 50
2	PhCH=CHCHO	*p*-F-ATPH	BuLi/hexane	87	76 : 24
3	PhCH=CHCHO	3,4-F_2-ATPH	BuLi/hexane	83	79 : 21
4	PhCH=CHCHO	3,4,5-F_3-ATPH	BuLi/hexane	91	86 : 14
5	PhCH=CHCHO	*p*-F-ATPH	BuLi/ether	90	79 : 21
6	PhCH=CHCHO	3,4-F_2-ATPH	BuLi/ether	99	93 : 7
7	PhCH=CHCHO	3,4,5-F_3-ATPH	BuLi/ether	93	95 : 5
8	BuCH=CHCHO	ATPH	BuLi/hexane	67	52 : 48
9	BuCH=CHCHO	3,4,5-F_3-ATPH	BuLi/hexane	78	82 : 18
10	BuCH=CHCHO	3,4,5-F_3-ATPH	BuLi/ether	77	93 : 7
11	PhCH=CHCHO	ATPH	PhLi/hexane	68	68 : 32
12	PhCH=CHCHO	*p*-F-ATPH	PhLi/hexane	73	89 : 11
13	PhCH=CHCHO	3,4-F_2-ATPH	PhLi/hexane	91	91 : 9
14	PhCH=CHCHO	3,4,5-F_3-ATPH	PhLi/hexane	99	98 : 2

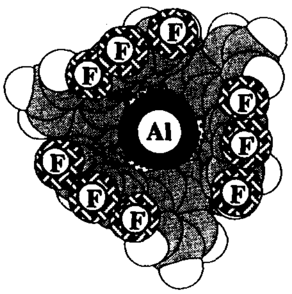
[a] An alkyllithium (1.5 equiv) was added to cinnamaldehyde by complexation with ATPH analogue (1.1 equiv) in toluene at -78 °C, and stirred there for 15 min. [b] Isolated yield. [c] Ratio of 1,4-/1,2-adducts.



p-F-ATPH



3,4-F_2-ATPH



3,4,5-F_3-ATPH

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