

# Unprecedented Nucleophilic Addition of Organolithiums to Aromatic Aldehydes and Ketones by Complexation with Aluminum Tris(2,6-diphenylphenoxide)

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The selective functionalization of an aromatic nucleus has become increasingly important in synthetic organic chemistry.<sup>1</sup> Despite the availability of various procedures for arene substitution via nucleophilic addition to electron-deficient arenes, such as nitroarenes, aryldiazonium compounds, and oxazolines,<sup>1c,2</sup> little is known about nucleophilic addition to an aromatic nucleus with simple carbonyl and carboxyl functionalities which act as electron-withdrawing groups with weak activating capabilities. Recent progress in this field has been achieved only by Tomioka and Koga using the conjugate addition of organolithiums to sterically hindered 2,6-di-*tert*-butyl-4-methoxyphenyl naphthalenecarboxylates.<sup>3</sup> In this Communication, we describe the first example of the regioselective conjugate addition of organolithiums to simple aromatic aldehydes and ketones by complexation with aluminum tris(2,6-diphenylphenoxide) (ATPH)<sup>4,5</sup> as an efficient carbonyl stabilizer (Scheme 1).

Reactive organometallic reagents normally add to benzaldehyde (**1**) or acetophenone (**2**) in a 1,2 fashion. For example, alkylation of benzaldehyde with *t*-BuLi in ether or THF at  $-78^{\circ}\text{C}$  gives rise to the 1,2-adduct 2,2-dimethyl-2-phenyl-1-propanol **4** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ) exclusively in a yield of 92–95%. Initial complexation of benzaldehyde in toluene/THF (1:1 v/v)<sup>6</sup> with ATPH (1.5 equiv), followed by treatment of the resulting complex **5** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ) with *t*-BuLi (2 equiv) in pentane at  $-78^{\circ}\text{C}$ , gave, after quenching with concentrated HCl, 1,6-adduct **6** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ) in a yield of 81% along with 7% 1,2-adduct **4** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ).<sup>5</sup> No 1,4-adducts were detected by TLC or NMR analyses. Using  $\text{CH}_2\text{Cl}_2$  as a solvent and quenching the reaction with 1 N HCl under otherwise similar reaction conditions,<sup>6</sup> only aromatization product **7** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ) was obtained in a yield of 48% accompanied by 6% 1,2-adduct **4** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ). Other selected examples are listed in Table 1, which also shows the conjugate alkylation of acetophenone (**2**) and its derivative **3** with the ATPH/ $\text{R}^3\text{Li}$  system. Primary, secondary, and tertiary alkylolithiums can be introduced equally well by a 1,6-addition (entries 5–14). In general, the ratio of dearomatization to aromatization products is highly dependent on the choice of solvents and quenching methods. For example, the ratio of **6** to **7** ( $\text{R}^1 = \text{Me}$ ;  $\text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ) in the

Scheme 1

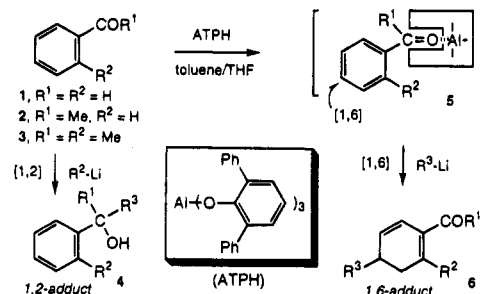
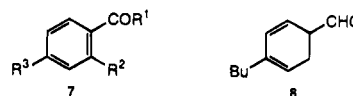


Table 1. Conjugate Alkylation of Aromatic Carbonyl Substrates with the ATPH/ $\text{R}^3\text{Li}$  System<sup>a</sup>

entry	sub- strate	nucleo- phile	solvent	conditions ( $^{\circ}\text{C}$ , h)	% yield <sup>b</sup> (ratio of <b>6</b> to <b>7</b> ) <sup>c</sup>
1	<b>1</b>	<i>t</i> -BuLi	toluene/THF	$-78^{\circ}\text{C}$ , 3	81 (>99:<1) <sup>d</sup>
2			toluene/THF	$-78^{\circ}\text{C}$ , 3.5	69 (10:90) <sup>e</sup>
3			$\text{CH}_2\text{Cl}_2$	$-78^{\circ}\text{C}$ , 5	49 (<1:>99) <sup>f</sup>
4		<i>n</i> -BuLi	toluene/THF	$-78^{\circ}\text{C}$ , 2	47 (>99:<1) <sup>d,g</sup>
5	<b>2</b>	<i>t</i> -BuLi	toluene/THF	$-78^{\circ}\text{C}$ , 3	93 (>99:<1) <sup>d</sup>
6			toluene/THF	$-78^{\circ}\text{C}$ , 0.5	74 (91:9) <sup>e</sup>
7			toluene/THF	$-78^{\circ}\text{C}$ , 7.5	92 (74:26) <sup>f</sup>
8			toluene/ether	$-78^{\circ}\text{C}$ , 3	74 (88:12) <sup>d</sup>
9			toluene/DME	$-78^{\circ}\text{C}$ , 4	35 (54:46) <sup>f</sup>
10			$\text{CH}_2\text{Cl}_2$	$-78^{\circ}\text{C}$ , 12	71 (53:47) <sup>d</sup>
11			$\text{CH}_2\text{Cl}_2$	$-78^{\circ}\text{C}$ , 2.5	43 (<1:>99) <sup>f</sup>
12		<i>sec</i> -BuLi	toluene/THF	$-78^{\circ}\text{C}$ , 1.5	80 (>99:<1) <sup>d</sup>
13		<i>n</i> -BuLi	toluene/THF	$-78^{\circ}\text{C}$ , 7	45 (>99:<1) <sup>d</sup>
14			toluene/THF	$-78^{\circ}\text{C}$ , 7.5	41 (73:27) <sup>f</sup>
15	<b>3</b>	<i>t</i> -BuLi	toluene/THF	$-78^{\circ}\text{C}$ , 12	89 (>99:<1) <sup>d</sup>

<sup>a</sup> The conjugate alkylation of benzaldehyde or acetophenone was carried out with ATPH (1.5 equiv) and organolithium (2 equiv) under the given reaction conditions. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR analysis. <sup>d</sup> Workup with concentrated HCl. <sup>e</sup> Workup with AcOH. <sup>f</sup> Workup with 1 N HCl. <sup>g</sup> The isomeric **8** was obtained in a yield of 13%.

alkylation of acetophenone with ATPH/*t*-BuLi varies tremendously (entries 5–11): >99:<1 (toluene/THF as solvent; quenching with concentrated HCl); 91:9 (toluene/THF; AcOH); 74:26 (toluene/THF; 1 N HCl); 88:12 (toluene/ether; concentrated HCl); 54:46 (toluene/DME; 1 N HCl); 53:47 ( $\text{CH}_2\text{Cl}_2$ ; concentrated HCl); <1:>99 ( $\text{CH}_2\text{Cl}_2$ ; 1 N HCl).<sup>7–9</sup> In the conjugate butylation of benzaldehyde, the isomeric 1,6-adduct **8** was generated as a minor product in addition to the normal



1,6-adduct **6** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ;  $\text{R}^3 = \text{Bu}$ ) (entry 4). *o*-Methylacetophenone gave 1,6-adduct **6** ( $\text{R}^1 = \text{R}^2 = \text{Me}$ ;  $\text{R}^3 = t\text{-Bu}$ ) exclusively (entry 15). Unfortunately, the attempted reaction of *p*-methylacetophenone with ATPH/*t*-BuLi in THF/

(7) Attempted alkylation of benzaldehyde or acetophenone with ATPH/*t*-BuLi in toluene at  $-78^{\circ}\text{C}$  resulted in the recovery of most of the starting carbonyl compounds.

(8) The origin of the solvent and workup effect is unclear at present. Oxygen seems to be an important factor for aromatization, since bubbling of the oxygen gas by syringe to the reaction mixture in entry 5 before workup gave **6** ( $\text{R}^1 = \text{Me}$ ;  $\text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ) and **7** ( $\text{R}^1 = \text{Me}$ ;  $\text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ) in 81% and 13% yields, respectively. The concentration of the reaction mixture might be important in cases where aromatization occurs via a disproportionation to furnish tetrahydroaromatics as side products. This possibility, however, is excluded, since conjugate alkylation in a more concentrated solution gave comparable results. Consequently, aromatization would be mostly facilitated by trace amounts of oxygen in  $\text{CH}_2\text{Cl}_2$  solvent.

(9) Attempted oxidation of purified **6** ( $\text{R}^1 = \text{Me}$ ;  $\text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ) with oxygen gas (by bubbling) resulted in recovery of most **6** ( $\text{R}^1 = \text{Me}$ ;  $\text{R}^2 = \text{H}$ ;  $\text{R}^3 = t\text{-Bu}$ ). Oxidation with  $\text{MnO}_2$  in benzene under reflux for 12 h gave *p*-(*tert*-butyl)acetophenone in high yield.

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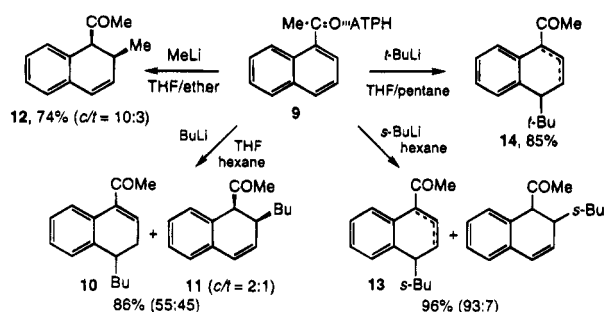
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(5) ATPH can be prepared by treating 2,6-diphenylphenol (3 equiv) in toluene or  $\text{CH}_2\text{Cl}_2$  with  $\text{Me}_3\text{Al}$  at room temperature for 1 h. See ref 4.

(6) Solvents are deoxygenated prior to reaction.

## Scheme 2

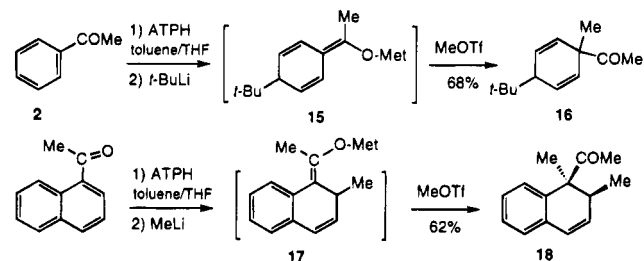


toluene (1:1) at  $-78^\circ\text{C}$  for 9 h was unsuccessful, and most of the starting ketone was recovered.<sup>10</sup>

A dramatic effect of nucleophiles on regiochemistry was observed in the case of methyl  $\alpha$ -naphthyl ketone (Scheme 2).<sup>11</sup> Initial complexation of methyl  $\alpha$ -naphthyl ketone in  $\text{CH}_2\text{Cl}_2$  with ATPH (1.5 equiv), followed by treatment of the resulting complex **9** with BuLi (1.5 equiv) in hexane at  $-78^\circ\text{C}$ , gave a mixture of the 1,6- and 1,4-adducts **10** and **11** (55:45) in a yield of 86%. Alkylation with MeLi as a small nucleophile in THF/

ether gave the 1,4-adduct **12** (74%) as the sole isolable product, whereas the use of the more bulky *sec*-BuLi and *t*-BuLi gave rise to 1,6-adducts **13** and **14**, respectively, as the major or exclusive products.

The existence of the hypothetical, intermediary dienolates **15** and **17** can be verified by trapping with MeOTf to furnish dialkylation products **16** (68%; *cis/trans* ratio = ~1:1) and **18** (61%; *trans* only), respectively.<sup>12,13</sup>



**Supporting Information Available:** Text describing the experimental procedure for the 1,6-addition of *t*-BuLi to acetophenone and spectral data of 1,6-adduct **6**, ketones **10–12**, and dialkylation products **16** and **18** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) In a similar manner, alkylation of *p*-methylbenzaldehyde with the ATPH/*t*-BuLi system in toluene/THF gave only trace amounts of 1,2-adduct.

(11) In the alkylation of naphthyl ketone substrates, the choice of solvents and quenching methods is not very important for aromatization, though use of the more polar THF solvent generally gave higher chemical yield without affecting the selectivity. For example, reaction of methyl  $\alpha$ -naphthyl ketone with ATPH/*t*-BuLi in  $\text{CH}_2\text{Cl}_2$ /pentane or  $\text{CH}_2\text{Cl}_2$ /THF gave **14** in 63% or 85% yield, respectively.