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Conjugate Allylation to α,β-Unsaturated Aldehydes with Amphiphilic Alkylation System, ATPH/Allylcerium Reagents

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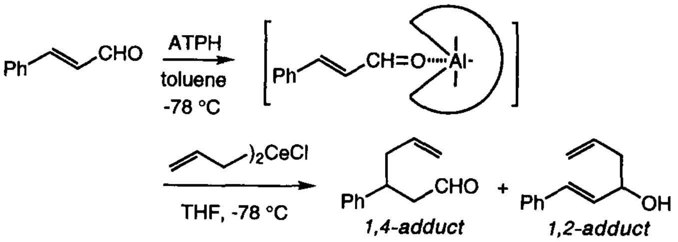
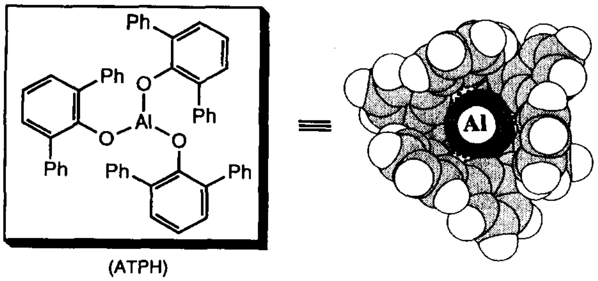
Abstract: Conjugate allylation to α,β-unsaturated aldehydes has been successfully accomplished with a new amphiphilic alkylation system, aluminum tris(2,6-diphenylphenoxide) (ATPH)/allylcerium reagents. Diallylcerium chloride was found to be the most satisfactory among several allylcerium reagents. © 1997 Elsevier Science Ltd.

Recently, we designed a new Lewis acid receptor, aluminum tris[2,6-di(*p*-fluorophenyl)phenoxide] (*p*-F-ATPH), which features a recognition site for carbonyl substrates as well as an effective coordination site for an alkyllithium nucleophile.[1] In combined use of allyllithium reagents, this amphiphilic alkylation system allows realization of the first successful conjugate allylation to α,β-unsaturated aldehydes by taking advantage of the eminent lithium/fluorine coordination to deliver allyllithium nucleophiles selectively to a remote β position of α,β-unsaturated aldehydes.[2] Continuing our research on development of new conjugate allylation techniques, we have investigated the possible use of other allylmetal reagents for the conjugate allylation to α,β-unsaturated aldehydes by complexation with readily available aluminum tris(2,6-diphenylphenoxide) (ATPH).[3] Here, we wish to disclose that among various allylic metal reagents, an allylcerium is the reagent of choice for the conjugate allylation to α,β-unsaturated aldehydes by complexation with ATPH.[4]

Scheme I





(ATPH)

Diallylcerium reagents were prepared by the addition of 2 equiv of allyltributyltin at -78 °C to a THF solution of dibutylcerium chloride which can be generated from BuLi and anhydrous $CeCl_3$ according to Imamoto's procedure.[5,6] Attempted reaction of cinnamaldehyde with diallylcerium chloride (1.2 equiv) in the presence of ATPH (1.2 equiv) at -78 °C for 15 min afforded 1,4- and 1,2-adducts in a ratio of 27:73 (94% combined yield). In contrast, however, when $CeCl_3•7H_2O$ was used without any pretreatment for the preparation of diallylcerium reagent, the reaction exhibited the opposite product distribution (1,4-/1,2-adducts = 74:26) even though the reaction did not complete (49% isolated yield), suggesting that the presence of H_2O molecules has significant influence on the structure of allylcerium species in THF and then leads to preferable 1,4-addition. These results prompted us to examine the effect of temperature of drying $CeCl_3•7H_2O$ prior to its use. As shown in Table I, the best result was obtained when $CeCl_3•7H_2O$ was dried with stirring at 80 °C for 1 h under reduced pressure (0.35 Torr) (entry 3, Table I).[7]

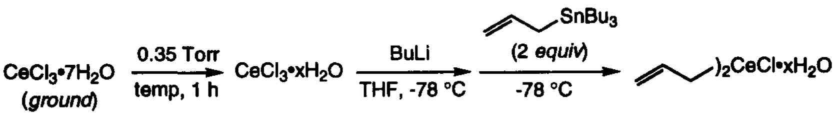


Table I. Temperature Effect of Drying $CeCl_3•7H_2O$ on the Conjugate Allylation to Cinnamaldehyde with ATPH [a]

entry	temp (°C)	yield [b] (%)	ratio [c]	S.M.recovery (%)
1	rt	49	74 : 26	42
2	70	60	82 : 18	24
3	80	91	87 : 13	–
4	90	92	80 : 20	–
5 [d]	–	90	34 : 66	–
6 [e]	140	94	27 : 73	–

[a] Diallylcerium chloride prepared from BuLi, dried $CeCl_3•xH_2O$ and $CH_2=CHCH_2SnBu_3$ under indicated conditions was transferred to the ATPH/cinnamaldehyde complex in toluene at -78 °C. [b] Isolated yield. [c] Ratio of 1,4-/1,2-adducts. [d] Commercially available anhydrous $CeCl_3$ was used without any treatment. [e] Dried according to Imamoto's procedure.[5]

Other selected examples of conjugate allylation to α,β-unsaturated aldehydes with the ATPH/allylcerium system are listed in Table II. The reaction proceeded with both good 1,4-selectivity and chemical yield using ATPH/diallylcerium chloride.[8] Use of either monoallyl or triallylcerium reagent gave less satisfactory results in terms of chemical yield and 1,4-selectivity (entries 2, 3, 7 and 8). Conjugate addition of diprenylcerium chloride, which was prepared from prenyltributyltin and dibutylcerium chloride, was also feasible and showed excellent 1,4-selectivity. Unfortunately, only moderate α-selectivity was observed in the 1,4-adducts.[9]

Table II. Conjugate Addition of Allylceriums to α,β-Unsaturated Aldehydes with ATPH [a]

entry	aldehyde	allylcerium [b]	% yield, [c] (ratio) [d]	α/γ [e]
	$PhCH{=}CHCHO$			
1		$(CH_2{=}CHCH_2)_2CeCl$	91 (87 : 13)	
2		$CH_2{=}CHCH_2CeCl_2$	49 (85 : 15)	
3		$(CH_2{=}CHCH_2)_3Ce$	97 (75 : 25)	
4		$((CH_3)_2{=}CHCH_2)_2CeCl$	77 (91 : 9)	64/36
5		$(CH_3)_2{=}CHCH_2CeCl_2$	40 (93 : 7)	60/40
	$BuCH{=}CHCHO$			
6		$(CH_2{=}CHCH_2)_2CeCl$	99 (81 : 19)	
7		$CH_2{=}CHCH_2CeCl_2$	48 (79 : 21)	
8		$(CH_2{=}CHCH_2)_3Ce$	83 (67 : 33)	
9		$((CH_3)_2{=}CHCH_2)_2CeCl$	70 (92 : 8)	52/48
10		$(CH_3)_2{=}CHCH_2CeCl_2$	38 (93 : 7)	58/42

[a] Unless otherwise noted, the allylation with allylceriums was carried out in the presence of ATPH (1.2 equiv) in toluene at -78 °C for 15 min. [b] Allylceriums were prepared as follows: (i) treatment of $CeCl_3{\bullet}xH_2O$, which was obtained by drying $CeCl_3{\bullet}7H_2O$ at 80 °C for 1 h *in vacuo* (0.35 Torr), with BuLi in THF at -78 °C for 1 h; (ii) subsequent reaction of allyltributyltin at -78 °C for 10 min. [c] Isolated yield. [d] Ratio of 1,4/1,2-adducts. [e] α/γ Ratio of 1,4-adducts.

A typical experimental procedure follows (entry 1, Table II). Commercially available $CeCl_3{\bullet}7H_2O$ (224 mg, 0.6 mmol) was quickly and finely pulverized in a mortar and placed in a dry, two-neck flask with stirring bar. The flask was immersed in an oil bath at 80 °C and the temperature was maintained for 1 h *in vacuo* (0.35 Torr) with continuous stirring. Argon was introduced and the flask was cooled to room temperature. Then, dry THF (2 mL) was added with vigorous stirring and the mixture was stirred for an additional 30 min at room temperature. After cooling to -78 °C, a 1.6 M hexane solution of BuLi (0.75 mL, 1.2 mmol) was added and stirring was continued for 1 h. Allyltributyltin (373 µL, 1.2 mmol) was added to furnish diallylcerium reagent after another 10 min of stirring at -78 °C. To a toluene solution of ATPH (0.6 mmol) freshly prepared from 2,6-diphenylphenol (443 mg, 1.8 mmol) and a 1 M hexane solution of Me_3Al (0.6 mL, 0.6 mmol) was added cinnamaldehyde (63 µL, 0.5 mmol) dropwise at -78 °C under argon. The solution immediately turned into deep orange indicating the formation of aldehyde-ATPH complex into which the diallycerium chloride prepared as above was transferred by cannula at -78 °C. The reaction mixture was stirred there for 15 min and poured into 1 N HCl. Extractive workup was performed with ether and the combined organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (dichloromethane/hexane = 1:4 to ether/hexane = 1:1 as eluant) gave a mixture of 1,4- and 1,2-adducts (79 mg, 0.453 mmol, 91% yield) as a colorless oil. The ratio of 1,4-/1,2-adducts was determined by capillary GLC analysis at the column temperature of 150 °C (1,4-/1,2-ratio = 87 : 13).

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(4) We examined the allylation reaction of cinnamaldehyde with various allyllic metal reagents, which uniformly exhibited the predominant 1,2-selectivity (1,4-/1,2-adducts = <5:>95) except an allyllithium[1] or an allylcerium reagent (1,4-/1,2-adducts = 28:72). This result gave us an implication that an allylcerium might be a suitable reagent to realize the amphiphilic allylation of α,β-unsaturated aldehydes with ATPH.

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(6) This new transmetallation process of Bu_2CeCl by allyltributyltin provides an operationally simple method. We confirmed that diallylcerium reagent prepared independently from $CeCl_3$ and allyllithium gave comparable reactivity and selectivity in the conjugate allylation reaction with ATPH (94% yield; 1,4-/1,2-adducts = 84 : 16).

(7) According to the literature, the thermal dehydration of $CeCl_3 \cdot 7H_2O$ gives four definitive intermediates: $CeCl_3 \cdot 6H_2O$, $CeCl_3 \cdot 3H_2O$, $CeCl_3 \cdot 2H_2O$, $CeCl_3 \cdot H_2O$, and $CeCl_3 \cdot 6H_2O$ releases three H_2O molecules in a second endothermic process (~102 °C). Therefore, generation of $CeCl_3 \cdot 3H_2O$ seems to be appropriate under our optimized conditions. See: Reuter, G.; Fink, H.; Seifert, H. J. *Z. anorg. allg. Chem.* **1994,** *620*, 665.

(8) Attempted reaction of cinnamaldehyde/ATPH complex with 0.5 equiv of diallylcerium reagent resulted in lower selectivity and chemical yield (54%; 1,4/1,2-adducts = 69 : 31).

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