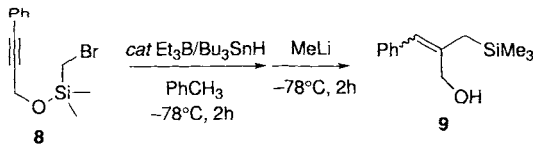

5% (*E*/*Z* = 28 / 72)

ATPH: 70% (*E*/*Z* = 54 / 46)

with ATPH under otherwise identical reaction conditions gave rise to **9** in 70% yield, again demonstrating the ability of ATPH as an efficient template to facilitate the cyclization step.

Experimental Section

Radical cyclization of **1** in the presence of ATPH: A solution of 2,6-diphenylphenol (740 mg, 3 mmol) in toluene (5 mL) was degassed and a 2M hexane solution of Me_3Al (0.5 mL, 1 mmol) was added at room temperature under argon. The slightly yellow solution was stirred for 30 min. After the solution had been cooled to −78 °C, **1** (143 mg, 0.5 mmol) in toluene (1 mL) was added and then Bu_3SnH (200 μL, 0.75 mmol) and Et_3B (100 μL, 0.1 mmol) were introduced sequentially. The solution was stirred at −78 °C for 1 h and then poured into an aqueous saturated solution of $NaHCO_3$. After extraction with ether, the combined ethereal extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/dichloromethane/hexane 1/2/16 as eluant) gave the cyclic ether **2** (79.6 mg, 0.496 mmol) as a colorless oil (99% yield, *E*/*Z* = 14/86): ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, TMS): δ = 7.10–7.40 (5H, m, Ph), 6.45 and 6.37 (1H, m, CH=C for *Z* and *E* isomer, respectively), 4.58 and 4.46 (2H, m, C=CCH_2–O for *Z* and *E* isomer, respectively), 4.01 and 3.90 (2H, t, *J* = 6.9 Hz, CH_2–O for *E* and *Z* isomer, respectively), 2.73–2.86 (2H, m, CH_2).

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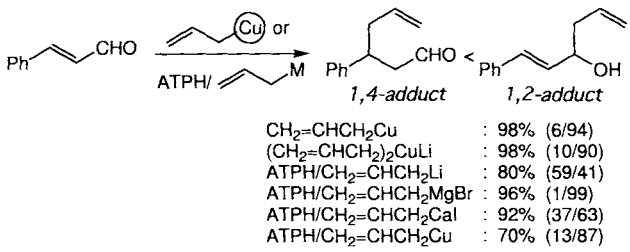
Conjugate Allylation to α,β-Unsaturated Aldehydes with the New Chemzyme *p*-F-ATPH**

Takashi Ooi, Yuichiro Kondo, and Keiji Maruoka*

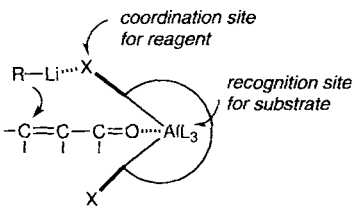
Conjugate allylation to α,β-unsaturated aldehydes is an extremely difficult, hitherto unattainable transformation in organic synthesis, and no effective procedure has yet been developed to a useful level due to the lack of a satisfactory reagent.[1,2] Even organocopper reagents, which have been employed successfully in the conjugate alkylation to α,β-unsaturated carbonyl compounds,[3] gave very disappointing results for the conjugate allylation. For instance, the reaction of cinnamaldehyde with allylcopper or lithium diallylcuprate gave predominantly the 1,2-adduct *trans*-1-phenyl-1,5-hexadien-3-ol (Scheme 1). Our recently developed new conjugate alkylation procedure with the Lewis acidic receptor aluminum tris(2,6-diphenylphenoxide) (ATPH)[4] was also found to be less effective for the present conjugate allylation, and only the ATPH/allyllithium system gave modest 1,4-selectivity (Scheme 1). This



CH_2=$CHCH_2Cu$	: 98% (6/94)
$(CH_2$=$CHCH_2)_2CuLi$	: 98% (10/90)
ATPH/CH_2=$CHCH_2Li$	: 80% (59/41)
ATPH/CH_2=$CHCH_2MgBr$	: 96% (1/99)
ATPH/CH_2=$CHCH_2CaI$	: 92% (37/63)
ATPH/CH_2=$CHCH_2Cu$	: 70% (13/87)

Scheme 1. Preliminary attempts at the conjugate allylation to cinnamaldehyde.

tendency is contradictory, for example, to our previous observations on the ATPH/BuM system for the conjugate alkylation to cinnamaldehyde, in which the 1,4-selectivity is enhanced by changing nucleophiles (BuM) from BuLi (ratio of 1,4-/1,2-adduct 50/50) to BuMgCl (90/10) and BuCaI (98/2).[4a] After consideration of the wide availability and versatility of organolithium reagents,[5] this lack of selectivity prompted us to design a new Lewis acidic receptor possessing appropriate coordination sites for alkyllithium nucleophiles (Scheme 2).[6] Here we report the realization of such a new system by presenting the first successful conjugate addition of allyllithium reagents to α,β-un-



Scheme 2. Schematic representation of the structural requirements for a Lewis acidic receptor in order for it to be a suitable for the conjugate allylation to α,β-unsaturated aldehydes.

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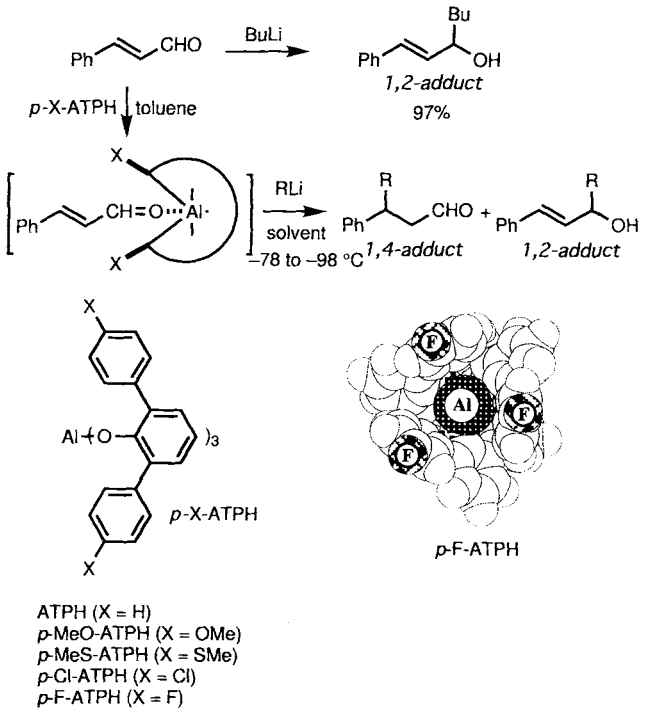
saturated aldehydes by complexation with a modified Lewis acidic receptor.

First, we examined the 1,4-selectivity of the conjugate alkylation to cinnamaldehyde with the modified ATPH/BuLi system (Scheme 3). Selected results are given in Table 1. *p*-(MeO)-ATPH and *p*-(MeS)-ATPH exhibited slightly better selectivity than ATPH (entries 2 and 3). The 1,4-selectivity was further enhanced with *p*-Cl-ATPH and *p*-F-ATPH (entries 4 and 5).[7, 8] In addition significant solvent and temperature effects on the 1,4-selectivity were observed (entries 6–10). The optimum reaction conditions for BuLi were achieved by using DME as solvent at low temperature (−98 °C) under the influence of *p*-F-ATPH in toluene. This gave the 1,4-adduct with 95% selectivity (entry 10). Here, the chelation of BuLi with DME is quite suitable for increasing the steric size of the nucleophile (BuLi) without suppressing the ability of Li^+ to coordinate to fluorine atoms of *p*-F-ATPH.[9]



Scheme 3. Conjugate addition of RLi to cinnamaldehyde in the presence of *p*-X-ATPH.

Table 1. Conjugate addition of alkyllithium compounds to cinnamaldehyde with *p*-X-ATPH compounds [a].

Entry	*p*-X-ATPH	RLi/solvent	*T* [°C]	Yield [%][b] (ratio)[c]
1	ATPH	BuLi/hexane	−78	92 (50/50)
2	*p*-MeO-ATPH	BuLi/hexane	−78	80 (55/45)
3	*p*-MeS-ATPH	BuLi/hexane	−78	91 (57/43)
4	*p*-Cl-ATPH	BuLi/hexane	−78	92 (63/37)
5	*p*-F-ATPH	BuLi/hexane	−78	87 (76/24)
6	*p*-F-ATPH	BuLi/Et_2O	−78	90 (79/21)
7	*p*-F-ATPH	BuLi/Et_2O	−98	87 (84/16)
8	*p*-F-ATPH	BuLi/THF	−78	82 (86/14)
9	*p*-F-ATPH	BuLi/DME	−78	75 (90/10)
10	*p*-F-ATPH	BuLi/DME	−98	83 (95/5)
11	*p*-F-ATPH	allyl-Li/Et_2O	−78	94 (77/23)
12	*p*-F-ATPH	allyl-Li/Et_2O	−98	87 (84/16)
13	*p*-F-ATPH	allyl-Li/THF	−78	89 (50/50)
14	*p*-F-ATPH	allyl-Li/DME	−78	75 (90/10)
15	*p*-F-ATPH	allyl-Li/DME	−98	83 (95/5)
16	*p*-F-ATPH	prenyl-Li/Et_2O	−98	82 (95/5)[d]
17	*p*-F-ATPH	prenyl-Li/DME	−98	77 (95/5)[e]

[a] The alkyllithium compounds (1.5 equiv) were added to cinnamaldehyde by complexation with the *p*-X-ATPH analogue (1.1 equiv) in toluene at −78 to −98 °C, and stirred for 15 min. [b] Yield of isolated product. [c] Ratio of 1,4-/1,2-adducts. [d] α/γ-Ratio of the conjugate adducts 10/90. [e] α/γ-Ratio of the conjugate adducts 72/28.

These results clearly demonstrate that the Lewis acidic receptor *p*-F-ATPH serves as a substrate recognition center for the aldehyde-carbonyl group as well as an effective coordination site for the nucleophile (BuLi). Thus, in this case the reactive BuLi reagent is appropriately placed in the proximity of the β-carbon atom of cinnamaldehyde to enable the smooth conjugate alkylation (Figure 1).

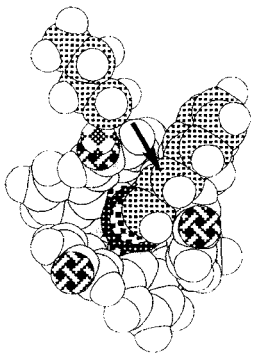
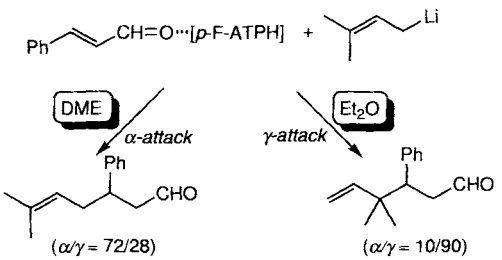


Figure 1. Proposed structure of the complex from cinnamaldehyde, *p*-F-ATPH, and BuLi, showing the favorable relative arrangement of the reaction partners for the desired conjugate alkylation.

With this information at hand, the present approach was applied to the conjugate allylation to α,β-unsaturated aldehydes, which has certainly proven to be a very difficult chemical transformation by conventional methodologies including the use of the otherwise most reliable organocopper reagents.[2, 3] In fact, use of the *p*-F-ATPH/allyllithium system for the conjugate allylation to cinnamaldehyde gave better 1,4-selectivity (entries 11, 12, and 14) than the ATPH/allyllithium counterpart (see Scheme 1). Synthetically useful conjugate allylation can be realized with *p*-F-ATPH/allyllithium in DME at −98 °C (entry 15).[10] Notably, use of the more basic solvent THF resulted in significant loss of 1,4-selectivity due to the reduced ability of Li^+ to coordinate in THF to fluorine atoms of *p*-F-ATPH (entry 13).

Conjugate addition of prenyllithium to cinnamaldehyde appears to be feasible. Indeed, the reaction proceeded with excellent selectivity under optimized reaction conditions (entry 17). Noteworthy is the fact that the α/γ ratio of the conjugate adducts was profoundly influenced by the solvent (Scheme 4).[11]



Scheme 4. Effect of solvent on the conjugate addition of prenyllithium to cinnamaldehyde with *p*-F-ATPH.

Experimental Section

Conjugate addition of allyllithium to cinnamaldehyde with *p*-F-ATPH (Table 1, entry 15): A solution of 2,6-di(*p*-fluorophenyl)phenol (466 mg, 1.65 mmol, prepared as described in ref. [7]) in toluene (4 mL) was degassed, and a 1 M 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 cinnamaldehyde (63.1 μL, 0.5 mmol) at −98 °C, allyllithium (prepared from allyltributyltin (233 μL, 0.75 mmol) and 1.6 M hexane solution of BuLi (469 μL, 0.75 mmol) [10]) in DME (2 mL) at −98 °C was added dropwise by cannular transfer. The solution was

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stirred at −98 °C for 15 min and then poured into 1 N HCl solution. After extraction with ether, the combined ethereal extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (dichloromethane/hexane 1/4 to ether/hexane 1/1 as eluant) gave the mixture of 1,4- and 1,2-adducts (72.3mg, 0.415 mmol, 83% yield) as a colorless oil. The ratio of 1,4-/1,2-adducts was determined by GLC analysis at the column temperature of 150 °C (1,4-/1,2-adducts 95/5). 1,4-adduct 3-phenyl-5-hexenal; ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, TMS): δ = 9.68 (1H, t, J = 2.0 Hz, CHO), 7.18–7.36 (5H, m, Ph), 5.59–5.75 (1H, m, CH=C), 4.90–5.06 (2H, m, C=CH_2), 3.30 (1H, quint, J = 7.3 Hz, PhCH), 2.68–2.84 (2H, m, CH_2C=O), 2.31–2.48 (2H, m, CH_2C=C).

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Strong, Rapid Binding of a Platinum Complex to Thymine and Uracil Under Physiological Conditions**

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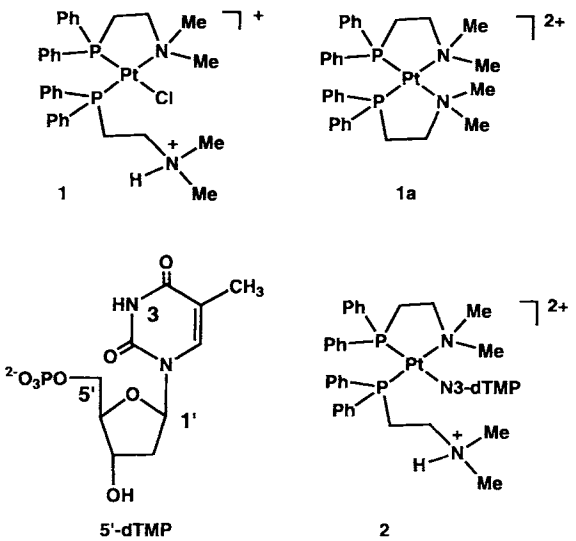
All four DNA bases adenine (A), cytosine (C), guanine (G), and thymine (T) (uracil, U, in RNA) are known to be capable of binding to metal ions through their ring N atoms and exocyclic N and O atoms. The major site of attack by platinum am(m)ine anticancer complexes is the N7 atom of guanine, which is readily accessible in the major groove of duplex DNA and is the strongest electron donor of the four bases, especially when situated next to another guanine residue.[1] Thus, over 90% of Pt is found in intrastrand G·G and A·G cross-links.[2] The N3 atom of thymine should provide a strong binding site for Pt[3] but has a high pK_a value (ca. 10),[4] and is usually inaccessible in double-stranded DNA due to involvement in A·T base pairs. Therefore cross-links involving thymine are not observed.[2] Even when the N3 atom of thymine is exposed in single strands of DNA or in thymine derivatives, reactions with Pt am(m)ine complexes are usually very slow.[5] It is of interest therefore to examine new methods of attaining kinetic control over attack by Pt on thymine bases. We report here the unusual ability of a cytotoxic platinum complex to bind strongly and rapidly to the N3 atom of thymine (and uracil) under physiological conditions.

The chloride salt of Pt^{II} complex **1**,[6] which we have used in this work, is cytotoxic to several cancer cell lines including cisplatin-resistant cells. In water it exists as a mixture of ring-closed (**1a**) and ring-opened forms. We find that **1** reacts rapidly (within minutes) with deoxythymidine 5′-monophosphate (5′-dTMP). The ^{31}P{^{1}H} NMR spectrum of a 1:1 solution of **1** and 5′-dTMP at pH* 7.1 (measured in D_2O, Figure 1) consists of



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