Michael Addition

Chiral Molecular Recognition by Aluminum Tris(2,6-diphenylphenoxide) in an Asymmetric 1,4-Addition**

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Asymmetric conjugate addition, the most popular reaction in organocopper chemistry, can be used to generate stereogenic centers, both stoichiometrically[1] and catalytically.[2] Recently there have been important advances in the strategies based on catalytic reagents. Earlier work focused on the stoichiometric approach, which required chiral conjugated esters, amides, and their variants, each bearing a chiral auxiliary.[1c,3] We report here an approach relying on molecular recognition, which broadens the potential of strategies based on stoichiometric reagents. This method involves the use of organolithium reagent, chiral ester, and aluminum tris(2,6-diphenylphenoxide) (ATPH) (Figure 1).[4] A wide range of the most reactive nucleophiles could be used with high selectivity and generality.

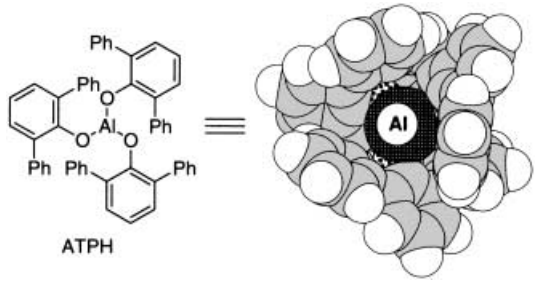

Figure 1. Molecular structure of aluminum tris(2,6-diphenylphenoxide) (ATPH).

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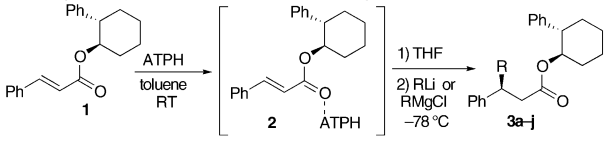
Precomplexation of the chiral ester **1** (1.0 equiv) with ATPH (1.1 equiv) in toluene at room temperature was followed by treatment with THF at −78 °C for 1 h and then subsequent addition of a solution of BuLi (1.5 equiv) in hexane. After 1 h the reaction was quenched, and subsequent purification by silica gel column chromatography gave the 1,4-adduct **3a** quantitatively in 97 % *de* (*S*). If precomplexation was performed at −78 °C, a somewhat lower diastereomeric excess was observed (88 % *de* (*S*)). If the equilibration period with THF is eliminated from the procedure and the reaction mixture is treated directly with a solution of BuLi in THF, the diastereoselectivity decreases slightly (94 % *de*). The use of 1.0 equiv BuLi slightly decreased the product yield (ca. 90 %). In each case the 1,2-adduct could not be detected by ^{1}H NMR analysis. The ester of the opposite chirality to **1** gave comparable results but with complete reversal of the diastereofacial selectivity (97 % *de* (*R*)). Other nucleophiles were also tested, and results are listed in Table 1. These results can be summarized by three points.

1) Optimal conditions resulted in clean reactions, affording **3a–f** in nearly quantitative yields and more than 91 % *de*. Several reagents favored the attack from the *si* face of **1**, which is consistent with the behavior of BuLi.
2) Surprisingly, unusual α-selectivity was observed from screening allylic reagents. With prenyllithium, the addition proceeded preferentially at its α-carbon to give good selectivity (91 % *de*; α:γ = 1.8:1), while the γ-addition was gave even better selectivity (99 % *de*). In contrast, prenylmagnesium chloride reacted exclusively by γ-addition[5] with 92 % *de* (entry 6).
3) A positive effect of lithium halide[6] was observed when **2** was formed at −78 °C (92 % *de* for BuLi–LiBr), in contrast to the negative halide effect when **2** was formed at room temperature (87 % *de*). Thus chiral recognition events by ATPH are strongly temperature-dependent. With the exception of the acetate enolate, the best results were obtained when the complexation was carried out at room temperature and the ATPH–ester complex **2** was "aged" with THF[7] at −78 °C for approximately 1 h in the absence of LiBr.

Table 1: Asymmetric 1,4-addition of **1** in the presence of ATPH.[a]



Entry	Nucleophile	Prod.	R	Yield [%][b]	*de* [%][c]	Abs. config.[d]
1	BuLi	**3a**	Bu	99	97	*S*
2	prenyl-Li	**3b**		98[g]	α:91	–
		3c			γ:99	–
3	2-propenyl-Li	**3d**		99	99	–
4	vinyl-Li	**3e**		94	98	*R*
5[e]		**3f**		90	93	–
6[f]	prenyl-MgCl	**3c**		98[h]	92	–

[a] Unless otherwise specified, the reaction was performed with ATPH (1.1 equiv), the chiral ester (1.0 equiv), THF (100 vol %), and RM (1.5 or 2.0 equiv) in toluene. Precomplexation was performed at room temperature. [b] Yield of the isolated, purified alcohols obtained by reduction of crude **3a–f**. [c] The *de* values were determined by chiral HPLC analysis of the corresponding alcohols. [d] The absolute configurations were determined by comparison to literature values. See the Supporting Information. [e] Precomplexation was performed at −78 °C, and a solution of the enolate with TMEDA (1.5 equiv) in THF was used. [f] A solution of the Grignard reagent with TMEDA (1.5 equiv) in THF was used. [g] α-Adduct **3b**:γ-adduct **3c** 1.8:1. [h] **3b**:**3c** < 5:> 95.

To better understand these unprecedented observations, we determined the X-ray single-crystal structure of the ATPH–**1** complex **2** (Figure 2).[8] In addition to resolving arguments concerning the conformational of **1** in the complex,[9,10] the X-ray data may also help explain the role of ATPH in the chiral recognition. A large portion of the chiral ester **1** is under the considerable steric influence of ATPH. Fortunately, however, from the X-ray crystal structure, the difference in steric bulk around both sides of the diastereoface involving the β-carbon is discernible. The *re* face is more shielded by ATPH, allowing a favorable attack from the *si* face, which is totally consistent with the configurations that have been assigned so far (Table 1, entries 1 and 4; Table 2, entries 1–3). In addition, the X-ray structure shows that the chiral auxiliary is relatively exposed, at least to the region distal from the β-carbon, and thus likely to have little influence on the diastereofacial events. Rather, the effective chiral environment that seems to induce the high diastereoselectivity is created by the conformational chirality of ATPH, which is induced by the chirality of the ester. Although ATPH possesses C_3 symmetry[11,12] and thus has conformational enantiomers rapidly interconverting in an equilibrium, these enantiomers are optically resolved. In other words, the conformational enantiomers are rendered homochiral by the chiral recognition of the optically pure ester (Figure 2).

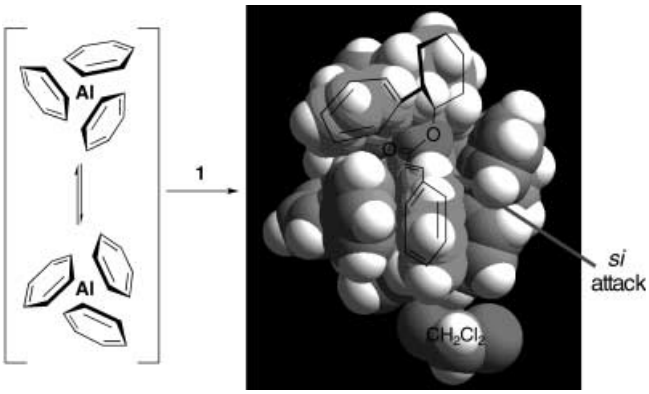
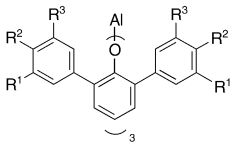


Figure 2. Possible inversion of the C_3 enantiomers of ATPH and the X-ray single-crystal structure of **2**.

Table 2: Asymmetric 1,4-addition of **1** in the presence of ATPH analogues.[a]

Entry	Organolithium	Al reagent	Product	R	Yield [%][b]	*de* [%][c]	Abs. config.[d]
1	MeLi	**5**	**3g**	Me	99	94	*S*
2	allyl-Li	**4**	**3h**		97	93	*S*
3	allyl-Li	**5**	**3h**		99	95	*S*
4	methallyl-Li	**5**	**3i**		92	97	–
5	prenyl-Li	**4**	**3b**		99	α: 98;	–
			3c		(6.0:1)[e]	γ: 97	
6	prenyl-Li	**5**	**3b**		99	α: 99;	–
			3c		(5.5:1)[e]	γ: 99	
7	prenyl-Li	**6**	**3b**		99	α: 99;	–
			3c		(8.5:1)[e]	γ: 98	
8		**5**	**3j**		99	99	–

[a] Unless otherwise specified, the reaction was performed with ATPH (1.1 equiv), the chiral ester (1.0 equiv), THF (100 vol%), and RM (1.5 or 2.0 equiv) in toluene.[b] Yield of isolated, purified alcohols derived by reduction of crude **3**. [c] Diastereomeric excess was determined by chiral HPLC analysis of the corresponding alcohols. [d] Absolute configurations were determined by comparison to literature values. See the Supporting Information. [e] α-Adduct **3b**:γ-adduct **3c**.



4: $R^1 = R^3 = H$, $R^2 = Me$
5: $R^1 = R^3 = H$, $R^2 = Et$
6: $R^1 = R^2 = Me$, $R^3 = H$

Although the reactions gave virtually complete yields and diastereoselectivities for several organolithium reagents, we found that MeLi and allylic reagents were less suitable. For example, attempts to use MeLi and allyllithium resulted in lower diastereoselectivities (86% and 78% *de*, respectively). The present strategy facilitates the rational molecular design of ATPH. Several ATPH analogues were synthesized based on the X-ray structure and used for the asymmetric 1,4-addition (Table 2). We observed considerable increase not only in diastereoselectivities for **3b**, **g**–**j** (entries 1–8) but also in the α-selectivity in the reaction with prenyllithium (entries 5–7). The effectiveness of these ATPH analogues in remote stereocontrol, such as asymmetric 1,6-addition, is now being investigated in our laboratory.

Experimental Section

The following procedure for the reaction of (1*R*,2*S*)-2-phenylcyclohexyl cinnamate and *n*-butyllithium is representative. To a solution of ATPH (0.33 mmol) in toluene (3.0 mL) was added (1*R*,2*S*)-2-phenylcyclohexyl cinnamate (**1**) (91.9 mg, 0.30 mmol) in toluene (0.5 mL) at room temperature under Ar. After the mixture had been stirred for 5 min, it was cooled to −78°C. THF (3.0 mL) was added dropwise, and the reaction mixture was stirred for 1 h. To the mixture was added *n*BuLi (1.55 M, 290 μL, 0.45 mmol) dropwise at the same temperature. The reaction mixture was stirred for 1 h and quenched with aqueous hydrogen chloride (1.0 M, 5 mL). The organic layer was extracted with ether, dried over Na_2SO_4, and concentrated. The residue was dissolved in THF (9.0 mL) and reduced with $LiAlH_4$ (92%, 63 mg, 1.5 mmol) under Ar at 0°C, and stirred for 1 h at room temperature. The reaction mixture was quenched by a dropwise addition of MeOH and neutralized with a 1.0 M aqueous HCl. The organic layer was extracted with ether, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (ether/hexane 1:3 to 1:2 as the eluent) to give 3-phenylheptanol (99% yield, 97% *de*) as the reduced 1,4-adduct. (*S*)-**3**-Phenylheptan-1-ol, known compound:[13] $[\alpha]_D^{20} = -1.28$ ($c = 1.02$, $CHCl_3$, for 94% *ee*); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.50$ (m, 5H), 3.50 (m, 2H), 2.67 (m, 1H,), 1.83 (m, 2H), 1.61 (m, 2H), 1.22 (m, 4H), 0.83 ppm (t, 3H, $J = 6.9$ Hz). HPLC analysis (OD-H, 1.0 mL min^{-1} flow rate, hexane/2-propanol 40:1 as eluent): $t_R = 12.8$ (minor) and $t_R = 15.4$ min (major; *S*, determined by comparing the value in ref. [13b]). After converting to the corresponding acid: $[\alpha]_D^{20} = +6.42$ ($c = 1.04$, $CHCl_3$).

Experimental procedures, spectroscopic, and analytical data for all new compounds, and the X-ray data for the ATPH complex **2** (PDF) are included in the Supporting Information.

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[7] We have no good explanation for the THF effect, which is now under investigation. However, one reasonable explanation might be that THF coordinates to the aluminum atom of ATPH to make a higher coordination complex. This was also invoked to explain the effect of Et_2O, which also enhanced asymmetric induction, see: M. Murakata, T. Jono, Y. Mizuno, O. Hoshino, *J. Am. Chem. Soc.* **1997**, *119*, 11713.

[8] CCDC-217071 (**2**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk). The ^{1}H NMR (300 MHz, [D_8]toluene) data showed a solution structure of the complex **2** adopting a single, presumably the most favorable conformation. ^{1}H NMR data: $\delta = 7.80$–6.40 (m, 50H), 5.16 (d, 1H, $J = 15.9$ Hz), 3.57 (td, 1H, $J = 10.0$, 4.0 Hz), 2.21 (td, 1H, $J = 11.1$, 3.9 Hz), 1.50–0.60 (m, 7H), 0.22 ppm (m, 1H).

[9] The complex **2** adopts the s-*trans* conformation with respect to the carbonyl compound and the *syn* coordination by ATPH. The alkoxy group of the ester prefers *Z* (or *trans*) orientation with respect to the carbonyl group and is arranged around the single-bond axis of (O=C)–(OR*). For the definition of conformations of conjugated carbonyl compounds, see: S. Saito, H. Yamamoto in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, pp. 33–65.

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