

Synthetic utility of bulky aluminium reagents as Lewis acid receptors

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1. Introduction

Organoaluminium compounds, little known until the 1950s, have been widely accepted and increasingly important in the field of industry and in the laboratory,¹⁻¹³ particularly after K. Ziegler and colleagues discovered the direct synthesis of trialkylaluminiums and their brilliant application to the polymerization of olefins.^{14,15} The chemistry of organoaluminium compounds has been understood in terms of the Lewis acidity of their monomeric species, which is directly related to the tendency of the aluminium atom to complete electron octets. Organoaluminium compounds possess a strong affinity for various heteroatoms in organic molecules, particularly oxygen. In fact, bond strength of aluminium and electronegative atoms such as oxygen is extremely strong; the bond energy of the Al-O bond is estimated to be 138 kcal mol⁻¹. In view of this high bond strength, most organoaluminium compounds are particularly reactive with oxygen and often ignite spontaneously in air. Accordingly, they easily generate 1:1 co-ordination complexes even with neutral bases such as ethers, which is in marked contrast with lithium and magnesium derivatives. Utilization of this property, commonly identified with 'oxygenophilicity', in organic synthesis allows facile reactions with hetero atoms particularly oxygen- and carbonyl containing compounds.

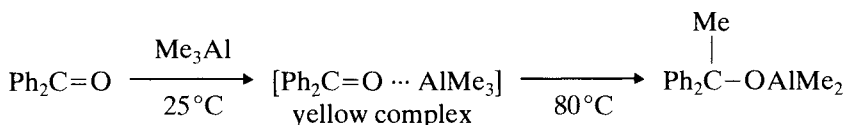


The major difference between organoaluminium compounds and more common Lewis acids such as aluminium chloride and bromide is attributable to the structural flexibility of organoaluminium reagents. Thus, the structure of an aluminium reagent is easily modified by changing one or two of its ligands. Described below are our recent practical strategies to selective organic synthesis with modified organoaluminium reagents.

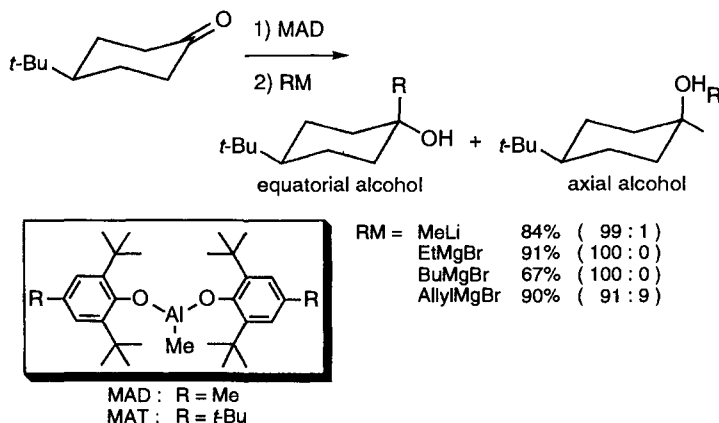
2. Amphiphilic alkylations

2.1 Amphiphilic carbonyl alkylations

Organoaluminium compounds are endowed with high oxygenophilic character, and hence are capable of forming long-lived monomeric 1:1 complexes with carbonyl substrates. For example, the reaction of benzophenone with Me_3Al in a 1:1 molar ratio gives a yellow, long-lived monomeric 1:1 species



which decomposed unimolecularly to dimethylaluminum 1,1-diphenylethoxide during some minutes at 80°C or many hours at 25°C .¹⁶ This unique property may be utilized for stereoselective activation of the carbonyl group. Among various organoaluminium derivatives examined, exceptionally bulky, oxygenophilic organoaluminium reagents such as methylaluminum bis(2,6-di-*tert*-butyl-4-alkylphenoxide) (MAD and MAT), have shown excellent diastereofacial selectivity in carbonyl alkylation.^{17,18} Thus, treatment of 4-*tert*-butyl cyclohexanone with MAD or MAT in toluene produced a 1:1 co-ordination complex which on subsequent treatment with methyl-lithium or Grignard reagents in ether at -78°C afforded the equatorial alcohol almost exclusively (Scheme 2.1). Methyl-lithium or Grignard reagents solely undergo preferential equatorial attack yielding axial alcohols as the major product. MAD and MAT have played a crucial role in the stereoselective synthesis of hitherto inaccessible equatorial alcohols from cyclohexanones as shown in Table 2.1.

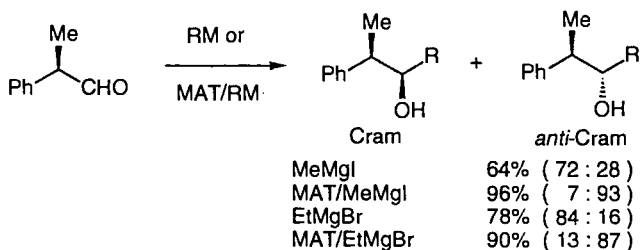
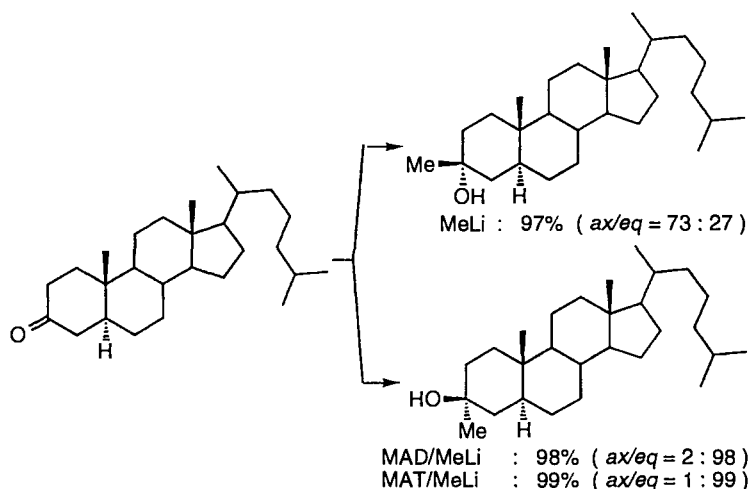


Scheme 2.1

Table 2.1 Stereoselective alkylation of cyclic ketones

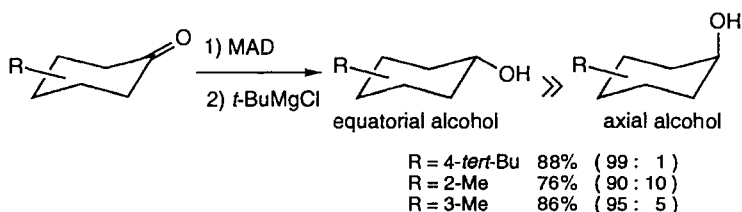
Entry	Alkylation agent	Chemical yield (ax/eq ratio)
1	MeLi	75% (79 : 21)
2	MAD/MeLi	84% (1 : 99)
3	MAT/MeLi	92% (0.5 : 99.5)
4	EtMgBr	95% (48 : 52)
5	MAD/EtMgBr	91% (0 : 100)
6	BuMgBr	58% (56 : 44)
7	MAD/BuMgBr	67% (9 : 100)
8	MeLi	73% (92 : 8)
9	MAD/MeLi	84% (14 : 86)
10	MAT/MeLi	80% (10 : 90)
11	MeLi	80% (83 : 17)
12	MAD/MeLi	69% (9 : 91)
13	MAT/MeLi	95% (3 : 97)
14	BuMgBr	86% (79 : 21)
15	MAD/BuMgBr	75% (1 : 99)
16	MeLi	77% (75 : 25)
17	MAD/MeLi	82% (1 : 99)

This approach has been quite useful in the stereoselective alkylation of steroidal ketones. Reaction of 3-cholestanone with MeLi gave predominantly 3 β -methylcholestan-3 α -ol (axial alcohol), whereas amphiphilic alkylation of the ketone with MAD/MeLi or MAT/MeLi afforded 3 α -methylcholestan-3 β -ol (equatorial alcohol) exclusively (Scheme 2.2). In addition, unprecedented *anti*-Cram selectivity was achievable in the MAD- or MAT-mediated alkylation of α -chiral aldehydes possessing no ability to be chelated.



Scheme 2.2

In contrast to the facile MAD- or MAT-mediated alkylation of cyclic ketones with primary organolithium or Grignard reagents, reduction takes precedence over alkylation with hindered alkylation agents such as *t*-butylmagnesium chloride in the presence of MAD¹⁸ (Scheme 2.3). This amphiphilic reduction system appears to be complementary to the existing methodologies using L-Selectride for obtaining axial selectivity.



Scheme 2.3

Protocol 1.

Synthesis of equatorial 4-*tert*-butyl-1-methylcyclohexanol. Amphiphilic alkylation of 4-*tert*-butylcyclohexanone with MAD/MeLi system

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles.

Equipment

- Magnetic stirrer
- Three-necked, round-bottomed flask (300 mL)
A three-way stopcock is fitted to the top of the flask and connected to a vacuum/argon source
- Teflon-coated magnetic stirring bar
- Medium-gauge needle
- All-glass syringe with a needle-lock Luer (volume appropriate for quantity of solution to be transferred)
- Vacuum/inert gas source (argon source may be an argon balloon)

Materials

- | | |
|--|--------------------------------|
| • 2,6-Di- <i>tert</i> -butyl-4-methylphenol (FW 220.4), 6.61 g, 30 mmol | irritant |
| • Trimethylaluminum in hexane (FW 72.1), 2 M solution in hexane, 7.5 mL, 15 mmol | Pyrophoric, moisture sensitive |
| • Dry toluene, 110 mL | flammable, toxic |
| • MeLi in ether (FW 22.0), 1.5 M solution in ether, 10 mL, 15 mmol | flammable, moisture sensitive |
| • 4- <i>tert</i> -butylcyclohexanone (FW 154.3), 1.54 g, 10 mmol | |
| • 1M HCl, 50 mL | toxic |
| • Technical ether for extraction, 100 mL | flammable, toxic |
| • Silica gel for flash chromatography 300 g, Merck Kieselgel 60 (Art. 9385) | irritant dust |
| • Ether for flash chromatography | flammable, toxic |
| • <i>n</i> -Hexane for flash chromatography | flammable, irritant |

1. Clean all glass wares, syringes, needles, and stirring bar and dry for at least 2 h in a 100°C electric oven before use.
2. Assemble the flask, stirring bar, and stop cocks under argon while the apparatus is still hot.
3. Support the assembled flask using a clamp and a stand with a heavy base.
4. Dry the apparatus with an electric heat gun under vacuum (1–2 mm Hg) for 5 min, then back-fill the flask with argon. Repeat to a total of three times.
5. Place 2,6-di-*tert*-butyl-4-methylphenol and flush with argon.
6. Charge dry toluene (100 mL).
7. Stir the mixture, degassed under vacuum, and replaced by argon.
8. Support the bottle containing trimethylaluminum in hexane using a clamp and a stand with a heavy base.
9. Fill a syringe with trimethylaluminum in hexane from the bottle containing trimethylaluminum using argon pressure. Apply the argon pressure to fill the syringe slowly with the required volume. Transfer the reagent in the syringe to the reaction flask at room temperature.
10. Stir the resulting solution at this temperature for 1 h to give methyl-

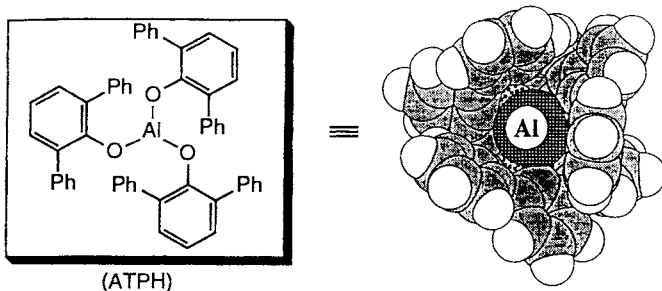
Protocol 1. Continued

aluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) almost quantitatively. During this operation, nearly 2 equivalents of methane gas are evolved per 1 equiv of trimethylaluminium.

11. Cool the reaction vessel to -78°C in a dry ice-methanol bath.
12. Transfer 4-*tert*-butylcyclohexanone, which is dissolved in 10 mL of dry toluene, to the syringe, and add to the reaction flask over 5 min at -78°C . Then add MeLi in ether over 10–15 min at -78°C . Stir the whole mixture at -78°C for 1 h in order to complete the alkylation.
13. Place 1M HCl solution and the stirring bar in the Erlenmeyer flask. While 1M HCl solution is stirred vigorously, add the reaction mixture slowly at 0°C to avoid excessive foaming on hydrolysis.
14. Remove the ice bath and stir the entire mixture vigorously at 25°C for 20 min.
15. Transfer the mixture to a separating funnel and separate the two layers. Extract the water layer with ether twice (2×50 mL).
16. Combine the ethereal extracts in a 500 mL flask. Dry over anhydrous magnesium sulfate, and filter through filter paper. Concentrate the filtrate under reduced pressure by means of a rotary evaporator.
17. Purify the oily residue by column chromatography on silica gel (ether/hexane as eluants) to give 625 mg (84%) of a mixture of axial and equatorial 4-*tert*-butylcyclohexanols (ratio = 1:99) as a colourless oil, the ratio of which is determined by capillary GLC analysis. Each isomer is characterized by ^1H NMR analysis.

2.2 Amphiphilic conjugate alkylations

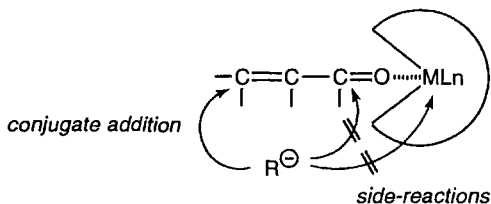
Conjugate addition to α,β -unsaturated carbonyl compounds is generally effected by soft organometallics as often seen in organocopper chemistry. In contrast, the use of organolithiums alone has never been developed to a useful level because of their hard nucleophilic character. This difficulty has been successfully overcome by using aluminium tris(2,6-diphenylphenoxide) (ATPH) (Scheme 2.4) as a carbonyl stabilizer.¹⁹ This type of conjugate alkyla-



Scheme 2.4

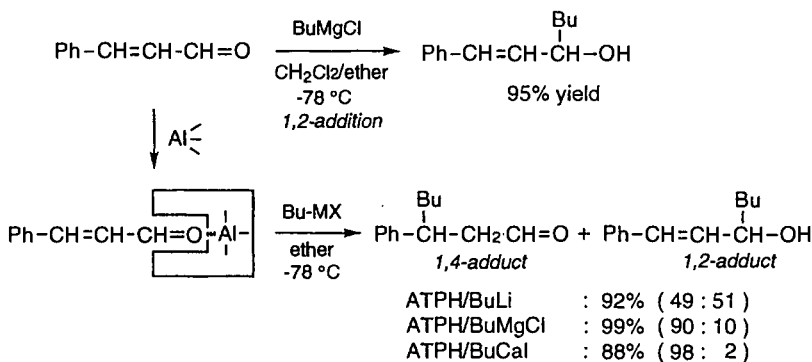
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tion can be classified as an amphiphilic conjugate alkylation that is markedly different from previously known nucleophilic and/or electrophilic conjugate alkylations (Scheme 2.5).

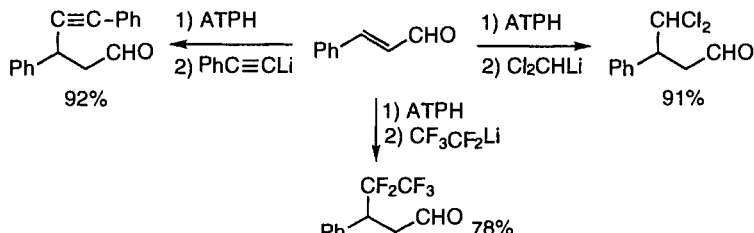


Scheme 2.5. Amphiphilic alkylation system.

This methodology is particularly effective for the conjugate alkylation to α,β -unsaturated aldehydes, which, among various conjugate acceptors, are prone to be more susceptible to 1,2 addition with a number of nucleophiles than α,β -unsaturated ketones, esters, and amides (Scheme 2.6). In addition, conjugate addition of lithium alkynides and thermally unstable lithium carbenoids, which are very difficult to achieve in organocopper chemistry, are realized with this amphiphilic conjugate alkylation system (Scheme 2.7).

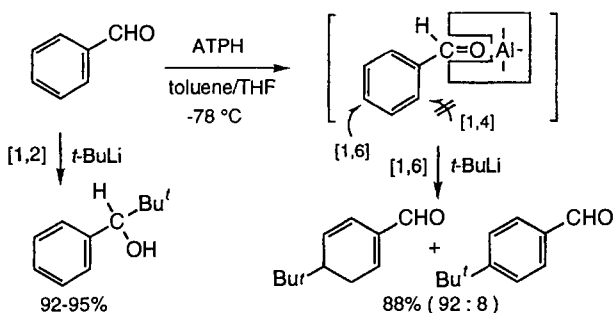


Scheme 2.6



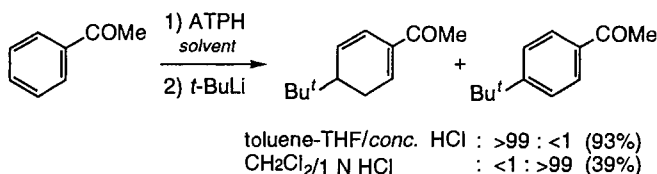
Scheme 2.7

This amphiphilic conjugate alkylation has been successfully applied for the nucleophilic alkylation to electron-deficient arenes based on the unprecedented conjugate addition of organolithiums to aromatic aldehydes and ketones by complexation with ATPH.²⁰ Thus, initial complexation of benzaldehyde or acetophenone with ATPH and subsequent addition of organolithiums affords 1,6-adducts with high selectivity (Scheme 2.8).



Scheme 2.8

The ratio of dearomatization to aromatization products is highly dependent on the choice of solvents and quenching methods as exemplified by the amphiphilic conjugate alkylation to acetophenone (Scheme 2.9).

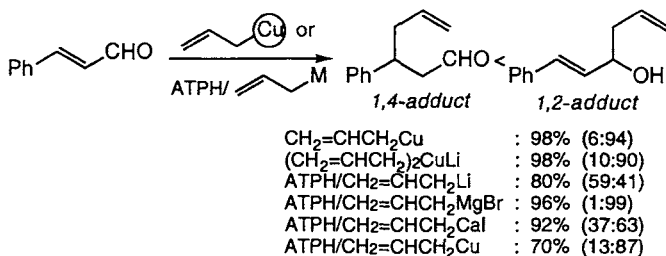


Scheme 2.9

2.3 Amphiphilic conjugate allylations

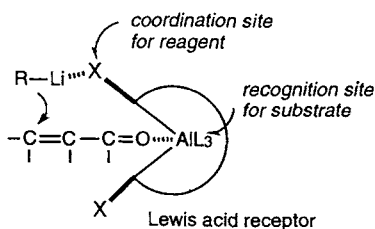
Conjugate allylation to α,β -unsaturated aldehydes is an extremely difficult, hitherto unattainable transformation in organic synthesis, and no effective procedure has yet been developed to a useful level due to the lack of a satisfactory reagent. Even organocopper reagents, which are quite powerful in the conjugate alkylation to α,β -unsaturated carbonyl compounds, gave disappointing results for the conjugate allylation. In fact, attempted reaction of cinnamaldehyde with allylcopper or lithium diallylcuprate gave rise to 1,2-adduct, *trans*-1-phenyl-1,5-hexadien-3-ol predominantly. The new, amphiphilic conjugate alkylation procedure with a Lewis acid receptor, ATPH,¹⁹ was also found to be less effective for the present conjugate allylation, and only the ATPH/allyl-lithium system gave modest 1,4-selectivity (Scheme 2.10).

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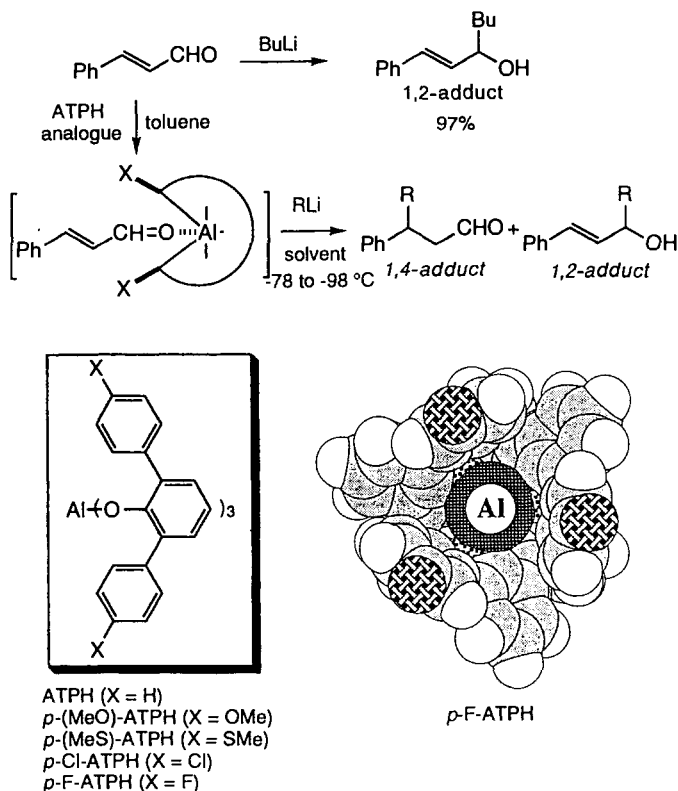


Scheme 2.10

This tendency is contradictory, for example, to our previous observation of the ATPH/Bu-M system for the conjugate alkylation to cinnamaldehyde, where the 1,4-selectivity is enhanced by changing nucleophiles (Bu-M) from BuLi (1.4-/1.2-ratio = 50:50) to BuMgCl (90:10) and BuAl (98:2).¹⁹ Considering the wide availability and versatility of organolithium reagents,²¹⁻²⁴ a new Lewis acid receptor possessing appropriate co-ordination sites for organolithium nucleophiles has been devised (Scheme 2.11). Among various functionalized ATPH derivatives as a Lewis acid receptor, *p*-F-ATPH (Scheme 2.12) was found to be highly effective for this transformation, which clearly demonstrated the synthetic utility of the strong lithium/fluorine participation in selective organic synthesis.²⁵ First, the 1,4-selectivity for the conjugate alkylation to cinnamaldehyde was examined with the modified ATPH/BuLi system in model experiments. Selected results are shown in Table 2.2. *p*-(MeO)-ATPH and *p*-(MeS)-ATPH showed slightly better selectivity than ATPH (Table 2.2, entries 2 and 3). The 1,4-selectivity was further enhanced by designing *p*-Cl-ATPH and *p*-F-ATPH (entries 4 and 5). Significant solvent and temperature effects on the 1,4-selectivity were also observed (entries 6-9), and eventually the optimum reaction condition was achieved using 1,2-dimethoxyethane (DME) solvent for BuLi at lower temperature under the influence of *p*-F-ATPH in toluene, giving the 1,4-adduct with 95% selectivity (entry 9). Here, the chelation of BuLi with DME is quite appropriate to increase the steric size of the nucleophile (BuLi), while still maintaining the co-ordination ability of Li⁺ to fluorine atoms of *p*-F-ATPH. This molecular recognition system is highlighted by the first successful conjugate addition of



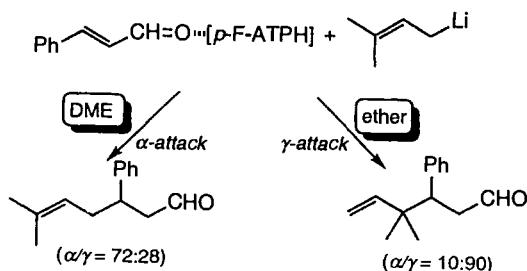
Scheme 2.11



Scheme 2.12

allyl-lithium reagents to α,β -unsaturated aldehydes by complexation with the modified Lewis acid receptor, *p*-F-ATPH (entry 13).

Furthermore, the conjugate addition of prenyl-lithium to cinnamaldehyde proceeded equally well with excellent selectivity under optimized reaction conditions, where the α/γ ratio of the conjugate adducts was profoundly influenced by the solvent effect (Scheme 2.13).



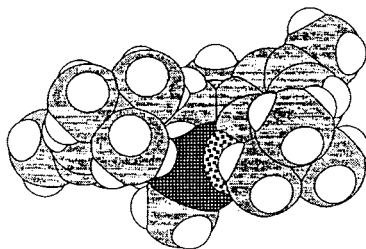
Scheme 2.13

Table 2.2 Conjugate addition of RLi to cinnamaldehyde with modified ATPH

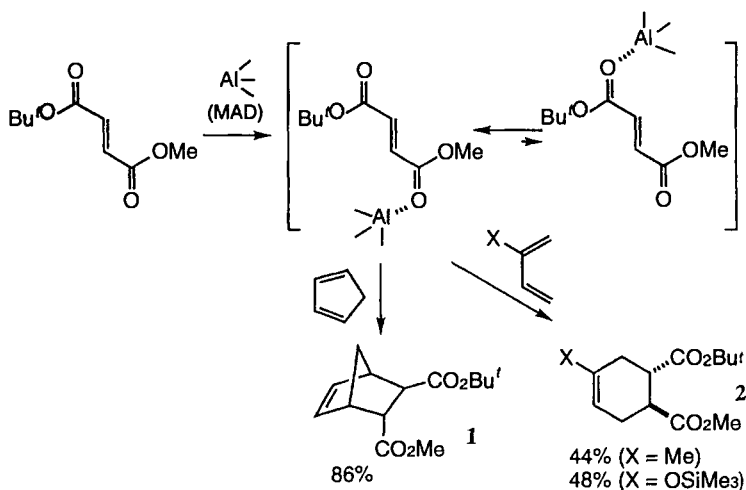
Entry	ATPH analogue	RLi/solvent	Temp (°C)	Yield (1,4/1,2 ratio)
1	ATPH	BuLi/hexane	−78	92% (50 : 50)
2	<i>p</i> -(MeO)-ATPH	BuLi/hexane	−78	80% (55 : 45)
3	<i>p</i> -(MeS)-ATPH	BuLi/hexane	−78	91% (57 : 43)
4	<i>p</i> -Cl-ATPH	BuLi/hexane	−78	92% (63 : 37)
5	<i>p</i> -F-ATPH	BuLi/hexane	−78	87% (76 : 24)
6	<i>p</i> -F-ATPH	BuLi/ether	−78	90% (79 : 21)
7		BuLi/THF	−78	82% (86 : 14)
8		BuLi/DME	−78	75% (90 : 10)
9		BuLi/DME	−98	83% (95 : 5)
10		Allyl-Li-ether	−78	94% (77 : 23)
11		Allyl-Li/THF	−78	89% (50 : 50)
12		Allyl-Li/DME	−78	75% (90 : 10)
13		Allyl-Li-DME	−98	83% (95 : 5)

3. Regio- and stereocontrolled Diels–Alder reaction

The Diels–Alder reaction is undoubtedly the best known and most thoroughly investigated of all cycloaddition reactions because of sustained interest in its mechanism and its exceptionally broad application to regio- and stereo-defined synthesis. The rate of this reaction is usually accelerated by the presence of certain Lewis acids. As revealed by the space-filling model, the exceptionally bulky aluminium reagent, MAD (Scheme 2.14), in addition to its Lewis acidity, provides an exceptionally bulky molecular cleft, which may feature a complementary size, shape, and co-ordination capacity for structurally similar ester substrates. Indeed, MAD allows the discrimination of two structurally different ester carbonyls of unsymmetrical fumarates such as *t*-butyl methyl fumarate, where the sterically less hindered methoxycarbonyl moiety binds selectively to the bulky molecular cleft of MAD as revealed by low-temperature ^{13}C NMR spectroscopy. This finding has been successfully applied to the regio- and stereocontrolled Diels–Alder reaction of unsymmetrical fumarates.²⁶ Thus, the Diels–Alder reaction of the *t*-butyl methyl

**Scheme 2.14.** MAD.

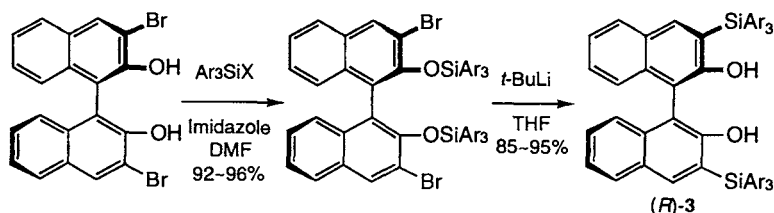
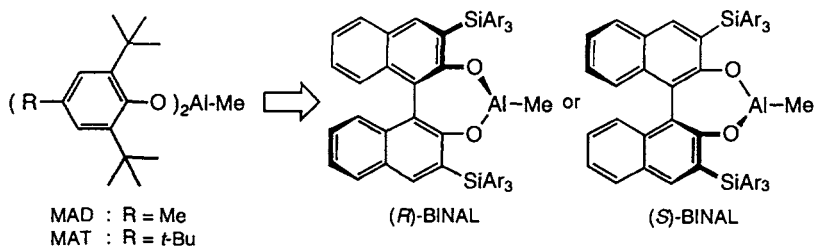
fumarate/MAD complex with cyclopentadiene at -78°C resulted in stereoselective formation of the cycloadduct **1** (Scheme 2.15) almost exclusively. In addition, treatment of the 1:1 co-ordination complex with 2-substituted 1,3-butadiene ($\text{X} = \text{Me}$, OSiMe_3) gave the cycloadduct **2** ($\text{X} = \text{Me}$, OSiMe_3) with high regioselectivity. In marked contrast, the cycloadditions with Et_2AlCl as an ordinary Lewis acid were found to have a total lack of selectivity.



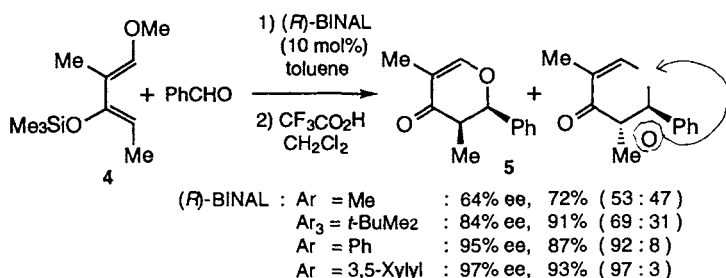
Scheme 2.15

4. Asymmetric hetero-Diels–Alder reaction

Based on the concept of the diastereoselective activation of carbonyl groups with MAD or MAT as described in the section 2.1, the first reliable, bulky chiral organoaluminium reagent, (*R*)-BINAL or (*S*)-BINAL has been devised for enantioselective activation of carbonyl groups. The sterically hindered, enantiomerically pure (*R*)-(+)-3,3'-bis(triarylsilyl)binaphthol((*R*)-**3**) required for the preparation of (*R*)-BINAL can be synthesized in two steps from (*R*)-(+)-3,3'-dibromobinaphthol by bis-triarylsilylation and subsequent intra-molecular 1,3-rearrangement of the triarylsilyl groups as shown in Scheme 2.16.²⁷ Reaction of (*R*)-**3** in toluene with trimethylaluminium produced the chiral organoaluminium reagent (*R*)-BINAL quantitatively. Its molecular weight, found cryoscopically in benzene, corresponds closely to the value calculated for the monomeric species. The modified chiral organoaluminium reagents, (*R*)-BINAL and (*S*)-BINAL were shown to be highly effective as chiral Lewis acid catalysts in the asymmetric hetero Diels–Alder reaction.²⁸ Reaction of various aldehydes with activated diene **4** (Scheme 2.17) under the influence of a catalytic amount of BINAL (5–10 mol%) at -20°C , after ex-



Scheme 2.16



Scheme 2.17

posure of the resulting hetero Diels–Alder adducts to trifluoroacetic acid, gave predominantly *cis*-dihydropyran **5** in high yield with excellent enantioselectivity. The enantioface differentiation of prochiral aldehydes is controllable by judicious choice of the size of trialkylsilyl moiety in BINAL, thereby allowing the rational design of the catalyst for asymmetric induction. In fact, switching the triarylsilyl substituent (Ar = Ph or 3,5-xylyl) to the *tert*-butyldimethylsilyl or trimethylsilyl group led to a substantial loss of enantio as well as *cis* selectivity in the hetero Diels–Alder reaction of benzaldehyde and activated diene **4**. In marked contrast, the chiral organoaluminium reagent derived from trimethylaluminium and (*R*)-(+)-3,3'-dialkylbinaphthol (alkyl = H, Me, or Ph) could be utilized, but only as a stoichiometric reagent and results were disappointing both in terms of reactivity and enantioselectivity for this hetero Diels–Alder reaction.

Protocol 2.**Synthesis of (5*R*, 6*R*)-3,5-dimethyl-6-phenyldihydropyran-4-one (5).
Asymmetric hetero-Diels–Alder reaction catalysed by (*R*)-BINAL**

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. Because of its high oxygen and moisture sensitivity, (*R*)-BINAL reagent should be prepared *in situ* and used immediately.

Equipment

- Magnetic stirrer
- Three-necked, round-bottomed flask (200 mL).
A three-way stopcock is fitted to the top of the flask and connected to a vacuum/argon source
- Teflon-coated magnetic stirring bar
- Medium-gauge needle
- All-glass syringe with a needle-lock Luer (volume appropriate for quantity of solution to be transferred)
- Vacuum/inert gas source (argon or nitrogen source may be an argon or a nitrogen balloon)

Materials

- (*R*)-(+)-3,3'-Bis(triphenylsilyl)binaphthol (FW 800), 0.88 g, 1.1 mmol irritant
- Trimethylaluminum in hexane (FW 72.1), 1 M solution in hexane, 1 mL, 1 mmol pyrophoric, moisture sensitive
- Dry toluene, 50 mL flammable, toxic
- Benzaldehyde (FW 106.1), 1.06 g, 10 mmol highly toxic, cancer suspecting agent
- (1*E*,3*Z*)-2,4-Dimethyl-1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (FW 200.4), 2.20 g, 11 mmol moisture sensitive
- 10% HCl, 50 mL toxic
- 1 M NaHCO₃, 50 mL
- Technical ether for extraction, 50 mL flammable, toxic
- Technical dichloromethane, 100 mL toxic, irritant
- Trifluoroacetic acid (FW 114.0), 1.37 g, 12 mmol corrosive, toxic
- Silica gel for flash chromatography, 200 g, Merck Kieselgel 60 (Art. 9385) irritant dust
- Ether for flash chromatography flammable, toxic
- *n*-Hexane for flash chromatography flammable, irritant

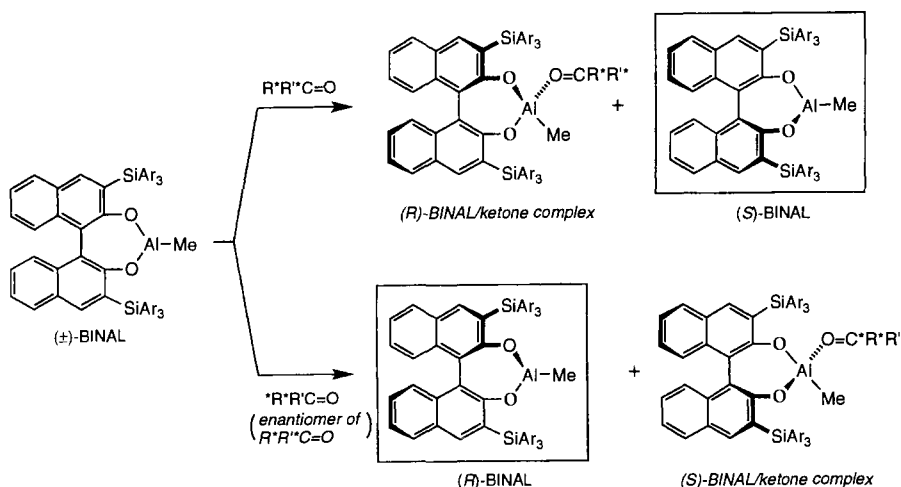
1. Clean all glassware, syringes, needles, and stirring bar and dry at least 2 h in an electric oven at 100°C before use.
2. Assemble the flask, stirring bar, and stop cocks under argon while the apparatus is still hot.
3. Support the assembled flask using a clamp and a stand with a heavy base.
4. Dry the apparatus with an electric heat gun under vacuum (1–2 mm Hg) for 5 min, then back-fill the flask with argon. Repeat to a total of three times.
5. Place (*R*)-(+)-3,3'-bis(triphenylsilyl)binaphthol in the flask and flush with argon.
6. Add dry toluene (50 mL).
7. Stir the mixture, degassed under vacuum, and replaced by argon.

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8. Support the bottle containing trimethylaluminium in hexane using a clamp and a stand with a heavy base.
9. Fill a syringe with trimethylaluminium in hexane from the bottle containing trimethylaluminium using argon pressure. Apply the argon pressure to fill the syringe slowly with the required volume. Transfer the reagent in the syringe to the reaction flask at room temperature.
10. Stir the resulting solution at room temperature for 1 h to give (*R*)-BINAL (Ar = Ph) almost quantitatively. During this operation, nearly 2 equivalents of methane gas are evolved per 1 equiv of trimethylaluminium.
11. Cool the reaction vessel to a temperature of -20°C in a dry ice/*o*-xylene bath. *o*-Xylene is recommended as refrigerant in place of carbon tetrachloride (toxic and cancer suspecting agent).
12. Add benzaldehyde and (1*E*,3*Z*)-2,4-dimethyl-1-methoxy-3-(trimethylsiloxy)-1,3-butadiene sequentially at -20°C . Stir the mixture at -20°C for 2 h in order to complete the cycloaddition.
13. Place 10% HCl solution and the stirring bar in the Erlenmeyer flask. While stirring the diluted HCl solution vigorously, add the reaction mixture slowly at 0°C to avoid excessive foaming on hydrolysis.
14. Remove the ice bath and stir the entire mixture vigorously at 25°C for 20 min.
15. Transfer the mixture to a separating funnel and separate the two layers. Extract the water layer with ether twice ($2 \times 25\text{ mL}$).
16. Combine the ethereal extracts to a 300 mL flask. Dry the layer over anhydrous magnesium sulfate, and filter through a filter paper. Concentrate the filtrate under reduced pressure by means of a rotary evaporator.
17. Dilute the oily residue with dichloromethane.
18. Add trifluoroacetic acid at 0°C , and stir the mixture at 0°C for 1 h.
19. Transfer the mixture to a separating funnel containing diluted Na/CO₃ solution, and separate the two layers. Extract the water layer with dichloromethane twice ($2 \times 25\text{ mL}$).
20. Combine the extracts in a flask. Dry the layer over anhydrous magnesium sulfate, and filter through a filter paper. Concentrate the filtrate under reduced pressure by means of a rotary evaporator.
21. Purify the oily residue by column chromatography on silica gel (ether/hexane = 1:3 as eluents) to give 1.56 g (77%, 95% ee) of (5*R*,6*R*)-3,5-dimethyl-6-phenyldihydropyran-4-one which is characterized by ¹H NMR analysis: $[\alpha]_{\text{D}} +7.1^{\circ}$ (*c* 1.0, chloroform).

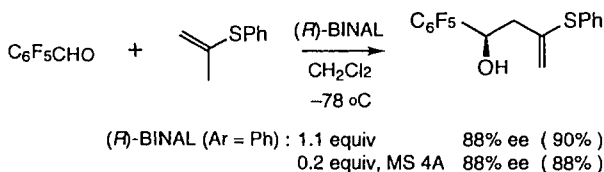
An interesting method for the preparation of chiral aluminium reagents has appeared recently. The chiral organoaluminium reagent, (*R*)-BINAL or (*S*)-BINAL can be generated *in situ* from the corresponding racemate (\pm)-BINAL by diastereoselective complexation with certain chiral ketones

(Scheme 2.18).²⁹ Among several terpene-derived chiral ketones, 3-bromocamphor was found to be the most satisfactory. The hetero Diels–Alder reaction of benzaldehyde and 2,4-dimethyl-1-methoxy-3-trimethylsiloxy-1,3-butadiene (**4**) with 0.1 equiv. of (\pm)-BINAL (Ar = Ph) and *d*-bromocamphor at -78°C gave rise to *cis*-adduct **5** as the major product with 82% ee. Although the level of asymmetric induction attained does not yet match that acquired with the enantiomerically pure BINAL (Ar = Ph, 95% ee), one recrystallization of the *cis*-adduct **5** of 82% ee from hexane gave essentially enantiomerically pure **5**, thereby enhancing the practicality of this method. This study demonstrates the potential for broad application of the *in situ* generated chiral catalyst via diastereoselective complexation in asymmetric synthesis.



Scheme 2.18

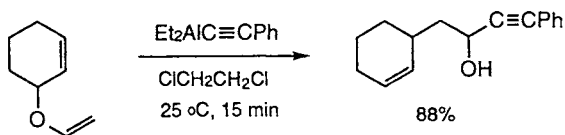
Since the enantioselective activation of carbonyl with the chiral aluminium, (*R*)-BINAL or (*S*)-BINAL, had been demonstrated, the asymmetric ene reaction of electron-deficient aldehydes with various alkenes, by using the latter reagent, could also be considered a feasible transformation.³⁰ Indeed in the presence of powdered 4Å molecular sieves, the chiral aluminium reagent, (*R*)-BINAL or (*S*)-BINAL can be used as a catalyst without any loss of enantioselectivity (Scheme 2.19).



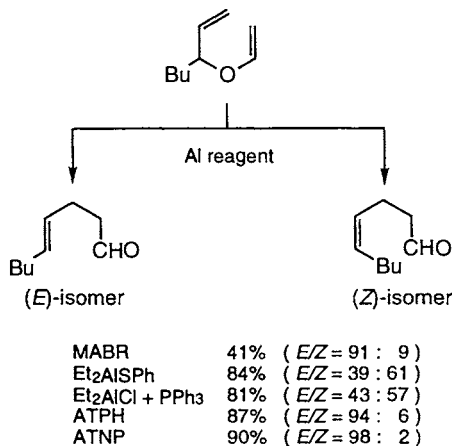
Scheme 2.19

5. Claisen rearrangement

Aliphatic Claisen rearrangements normally require high temperatures. However, in the presence of Lewis acidic organoaluminium reagents, the rearrangements have been accomplished under very mild conditions. Treatment of simple allyl vinyl ether substrates with trialkylaluminums resulted in the [3,3] sigmatropic rearrangement and subsequent alkylation on the aldehyde carbonyl group³¹ (Scheme 2.20). Notably, ordinary strong Lewis acids such as TiCl_4 , SnCl_4 , and $\text{BF}_3 \cdot \text{OEt}_2$ could not be used for this rearrangement. The rearrangement–reduction product was obtained exclusively with *i*- Bu_3Al or DIBAH. The aluminium thiolate, Et_2AlSPh or a combination of Et_2AlCl and PPh_3 was effective for the rearrangement providing the normal Claisen products, γ,δ -unsaturated aldehydes, however, without any stereoselectivity. Accordingly, a new molecular recognition approach for the stereocontrolled Claisen rearrangement of allyl vinyl ethers has been developed based on the stereoselective activation of ether moiety using aluminium-type Lewis acid receptors. Thus, treatment of 1-butyl-2-propenyl vinyl ether with ATPH in CH_2Cl_2 afforded *E*-Claisen products predominantly (*E/Z* ratio = 94:6) (Scheme 2.21). Use of sterically more hindered aluminium tris(2- α -naphthyl-6-phenylphenoxide) (ATNP) exhibited better selectivity (*E/Z* ratio = 98:2).³²



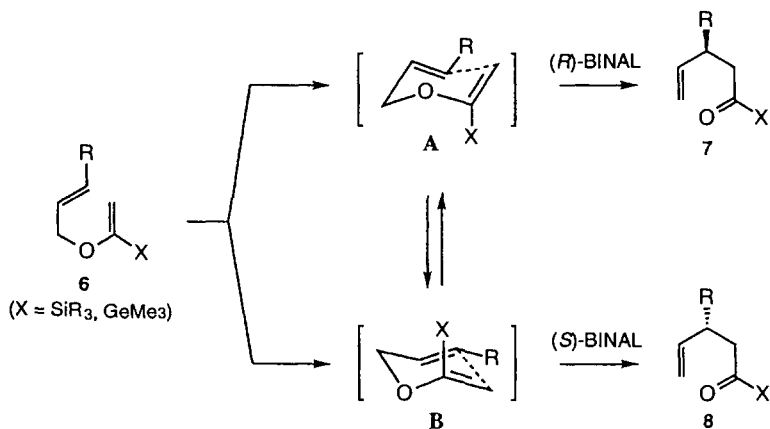
Scheme 2.20



Scheme 2.21

In marked contrast, use of exceptionally bulky, Lewis acidic receptor, methylaluminium bis(2,6-di-*tert*-butyl-4-bromophenoxide) (MABR) resulted in predominant formation of *Z*-Claisen products (*E/Z* ratio = 9:91), which was very difficult to attain by the conventional methodologies including thermal Claisen rearrangement and its variants (Carroll, the ortho ester, Eschenmoser, and Ireland rearrangements).³³

In a similar manner, the concept of the enantioselective activation of carbonyl groups with the bulky, chiral aluminums, (*R*)-BINAL or (*S*)-BINAL, has also been extended to the enantioselective activation of an ether oxygen, which gave rise to the first successful example of the asymmetric Claisen rearrangement of allylic vinyl ethers **6** catalyzed by (*R*)-BINAL or (*S*)-BINAL^{34,35} (Scheme 2.22). This method provides an easy asymmetric synthesis of various acylsilanes **7** or **8** ($X = \text{SiR}_3$) and acylgermane **7** ($X = \text{GeMe}_3$) with high enantiomeric purity (Table 2.3). Among the various trialkylsilyl substituents



Scheme 2.22

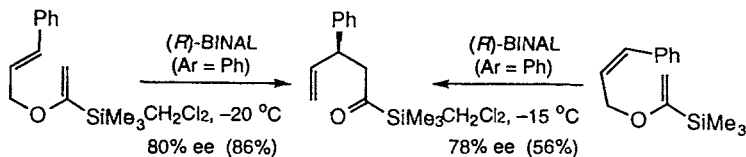
Table 2.3 Asymmetric Claisen rearrangement of allylic vinyl ether **6** (Scheme 2.22)

Allyl vinyl ether	(<i>R</i>)-BINAL	Product	Yield	Optical yield
6 (R=Ph, X=SiMe ₃)	Ar ₃ =Bu ^t Me ₂	7	22%	14% ee
6 (R=Ph, X=SiMe ₃)	Ar=Ph	7	86%	80% ee
6 (R=Ph, X=SiMe ₃)	Ar ₃ =Bu ^t Ph ₂	7	99%	88% ee
6 (R=Ph, X=SiMe ₃)	Ar=Ph ^a	8	85%	80% ee
6 (R=Ph, X=SiMe ₂ Ph)	Ar=Ph	7	65%	85% ee
6 (R=Ph, X=SiMe ₂ Ph)	Ar ₃ =Bu ^t Ph ₂	7	76%	90% ee
6 (R=cyclohexyl X=SiMe ₃)	Ar=Ph	7	79%	61% ee
6 (R=cyclohexyl X=SiMe ₃)	Ar ₃ =Bu ^t Ph ₂	7	84%	71% ee
6 (R=Ph, X=GeMe ₃)	Ar=Ph	7	73%	91% ee
6 (R=Ph, X=GeMe ₃)	Ar ₃ =Bu ^t Ph ₂	7	68%	93% ee

^aUse of (*S*)-BINAL as catalyst.

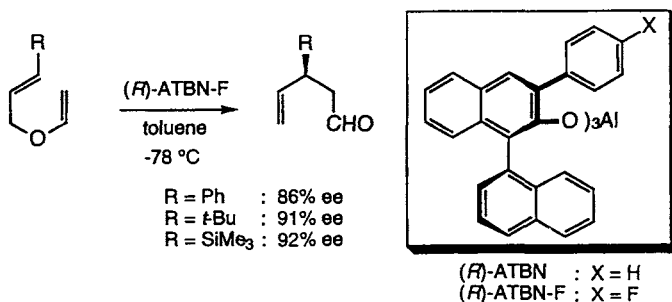
of BINAL, use of a bulkier *t*-butyldiphenylsilyl group gives rise to the highest enantioselectivity. Conformational analysis of two possible chairlike transition-state structures of an allyl vinyl ether substrate **6** reveals that the chiral organoaluminium reagent BINAL can discriminate between these two conformers **A** and **B**, which differ from each other only in the orientation of α -methylene groups of ethers.

Notably, the asymmetric Claisen rearrangement of *cis*-allylic α -(trimethylsilyl)vinyl ethers with (*R*)-BINAL produced optically active acylsilanes with the same absolute configuration as those produced from *trans*-allylic α -(trimethylsilyl)vinyl ethers³⁶ (Scheme 2.23).



Scheme 2.23

The bulky, chiral organoaluminium reagents of type (*R*)-BINAL or (*S*)-BINAL is only applicable for allyl vinyl ether substrates possessing bulky α -silyl and α -germyl substituents. Later, the asymmetric Claisen rearrangement of simple allyl vinyl ether substrates has been developed with the designing of chiral ATPH analogues, aluminium tris((*R*)-1- α -naphthyl-3-phenylnaphthoxide) ((*R*)-ATBN) or aluminium tris((*R*)-3-(*p*-fluorophenyl)-1- α -naphthyl-naphthoxide) ((*R*)-ATBN-F) with high enantioselectivity³² (Scheme 2.24).

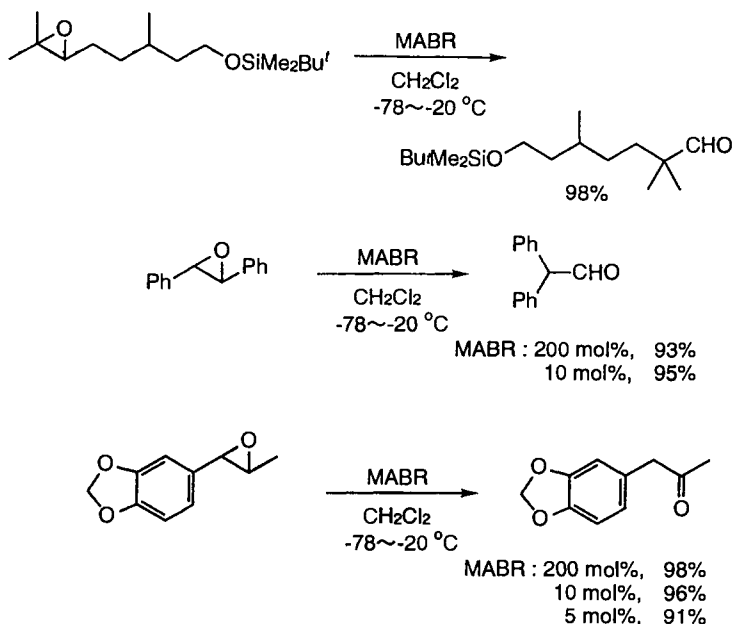


Scheme 2.24

6. Epoxide rearrangement

The exceptional bulkiness of the modified organoaluminium reagent, MABR, can also be utilized for the rearrangement of epoxy substrates under very mild conditions with high efficiency and selectivity. So far, BF₃•OEt₂ catalyst is regarded as a reliable Lewis acid catalyst for the epoxide rearrangement.

However, attempted rearrangement of *tert*-butyldimethylsilyl ether of epoxy citronellol with $\text{BF}_3 \cdot \text{OEt}_2$ resulted in the formation of a number of products. In contrast, treatment of this substrate with MABR under mild conditions (-78 to -20°C) gave the desired aldehyde almost quantitatively (Scheme 2.25). In addition, certain epoxy substrates can be rearranged with catalytic use of MABR.³⁷



Scheme 2.25

Protocol 3.

Synthesis of diphenylacetaldehyde. MABR-catalysed rearrangement of *trans*-stilbene oxide

Caution! Carry out all procedures in a well-ventilated hood, and wear disposable vinyl or latex gloves and chemical-resistant safety goggles. Because of its high oxygen and moisture sensitivity, MABR reagent should be prepared *in situ* and used immediately.

Equipment

- Magnetic stirrer
- All-glass syringe with a needle-lock Luer (volume appropriate for quantity of solution to be transferred)
- Teflon-coated magnetic stirrer bar
- Vacuum/inert gas source (argon source may be an argon balloon)
- Medium-gauge needle
- Three-necked, round-bottomed flask (1 L) fitted with a condenser and a pressure-equalizing dropping funnel. A three-way stopcock is fitted to the top of the condenser and connected to a vacuum/argon source

2: Synthetic use of bulky aluminium reagents as Lewis acid receptors

Materials

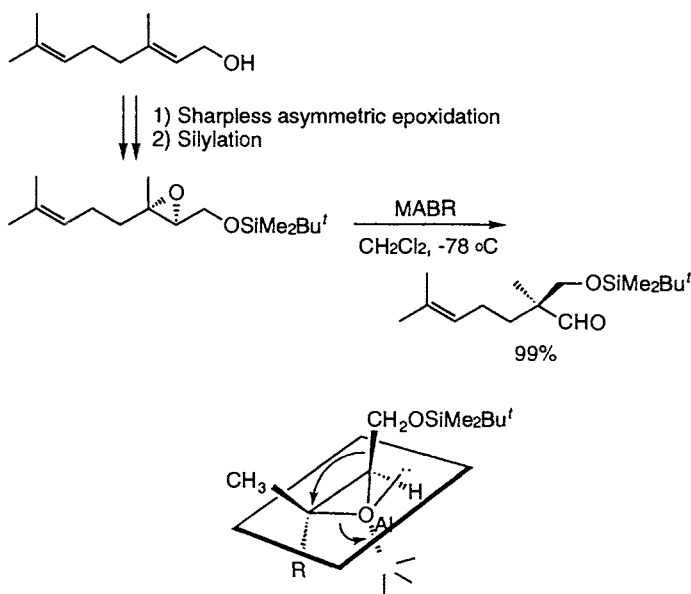
- 4-Bromo-2,6-di-*tert*-butylphenol (FW 285.2), 3.42 g, 12 mmol **irritant**
- Trimethylaluminium in hexane (FW 72.1), 2 M solution in hexane, 3 mL, 6 mmol **pyrophoric, moisture sensitive**
- Dry dichloromethane, 300 mL **toxic, irritant**
- *trans*-Stilbene oxide (FW), 11.78 g, 60 mmol
- Sodium fluoride (FW 42.0), 1.01 g, 24 mmol **moisture sensitive, toxic**
- Water (FW 18), 324 μ L, 18 mmol
- Technical dichloromethane **toxic, irritant**
- Silica gel for flash chromatography, 500 g, Merck Kieselgel 60 (Art. 9385) **irritant dust**
- Ether for flash chromatography **flammable, toxic**
- Dichloromethane for flash chromatography **toxic, irritant**
- *n*-Hexane for flash chromatography **flammable, irritant**

1. Clean all glassware, syringes, needles, and stirring bar and dry for at least 2 h in an electric oven at 100°C before use.
2. Assemble the flask, stirring bar, and stop cocks under argon while the apparatus is still hot.
3. Support the assembled flask using a clamp and a stand with a heavy base.
4. Dry the apparatus with an electric heat gun under vacuum (1–2 mm Hg) for 5 min, then back-fill the flask with argon. Repeat to a total of three times.
5. Place 4-bromo-2,6-di-*tert*-butylphenol and flush with argon.
6. Add freshly distilled dichloromethane (300 mL).
7. Stir the mixture, degas under vacuum, and replace by argon.
8. Support the bottle containing trimethylaluminium in hexane using a clamp and a stand with a heavy base.
9. Fill a syringe with trimethylaluminium in hexane from the bottle containing trimethylaluminium using argon pressure. Apply the argon pressure to fill the syringe slowly with the required volume. Transfer the reagent in the syringe to the reaction flask at room temperature.
10. Stir the resulting solution at this temperature for 1 h to give methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) almost quantitatively. During this operation, nearly 2 equivalents of methane gas are evolved per 1 equiv of trimethylaluminium.
11. Cool the reaction vessel to –20°C in a dry ice/*o*-xylene bath. *o*-Xylene is recommended as refrigerant in place of carbon tetrachloride (toxic and cancer suspecting agent).
12. Transfer *trans*-stilbene oxide, which is dissolved in 25 mL of dry dichloromethane, to the dropping funnel, and added to the reaction flask over 15–20 min at –20°C. Stir the mixture at –20°C for 20 min in order to complete the rearrangement.
13. Add sodium fluoride, and injected water dropwise at –20°C. To avoid excessive foaming on hydrolysis water should be added carefully by syringe.

Protocol 3. Continued

14. Stir the entire mixture vigorously at -20°C for 5 min at 0°C for 30 min.
15. Filter the contents of the flask with the aid of three 50 mL portions of dichloromethane. The sodium fluoride–water workup offers an excellent method for large-scale preparations, and is generally applicable for product isolation in the reaction of organoaluminium compounds.
16. Evaporate the combined filtrates under reduced pressure with a rotary evaporator. Purify the oily residue by column chromatography (column diameter: 9.5 cm) on silica gel (ether/dichloromethane/hexane = 1:2:20 to 1:1:10 as eluants) to give 11.02–11.17 g (94–95%) of diphenylacetaldehyde as a colourless oil, which is characterized by ^1H NMR analysis.

Although the acid-catalysed rearrangement of epoxides to carbonyl compounds is a well-known transformation and a number of reagents have been elaborated for this purpose, only a few reagents have been used successfully for the rearrangement of functionalized epoxides with respect to the efficiency and selectivity of the reaction. With the stoichiometric use of MABR, however, a new, stereocontrolled rearrangement of epoxy silyl ethers leading to β -siloxy aldehydes has been developed under mild conditions. Interestingly, used in combination with the Sharpless asymmetric epoxidation of allylic alcohols, this rearrangement represents a new approach to the synthesis of various optically active β -hydroxy aldehydes,^{38,39} (Scheme 2.26) which are

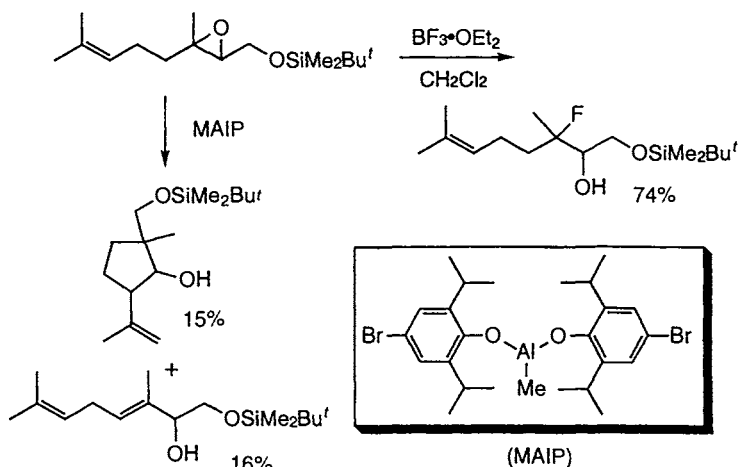
**Scheme 2.26**

2: Synthetic use of bulky aluminium reagents as Lewis acid receptors

quite useful intermediates in natural product synthesis. Based on the optical rotation sign and value of the β -siloxy aldehydes, this organoaluminium-promoted rearrangement proceeds with rigorous transfer of the epoxide chirality, and the observed stereoselectivity can be interpreted to arise from the *anti* migration of the siloxymethyl group to the epoxide moiety. Here

Table 2.4 MABR-catalysed rearrangement of optically active epoxy silyl ethers

Entry	Mol % of MABR	Conditions (°C, h)	Chemical yield
1	200	-78, 0.5	95%
2	20	-20, 0.3	82%
3	10	-20, 0.3	74%
4	200	-78, 1	99%
5	20	-78, 0.2; 0, 0.5	82%
6	10	-78, 0.2; 0, 1	74%
7	200	-78, 1; -40, 0.5	98%
8	20	-78, 0.2; 0, 1	79%
9	10	-78, 0.2; 0, 3	68%
10	200	-78, 0.5	87%
11	20	-40, 0.5	75%
12	10	-78, 0.2; -20, 0.5, 0, 0.5	71%
13	200	-78, 0.5; -20, 2	88%
14	20	-78, 0.2; 0, 5	77%



Scheme 2.26

again, the exceptional bulkiness of 2,6-di-*tert*-butyl-4-bromophenoxy ligands in MABR is essential for the smooth rearrangement of epoxy silyl ethers, and the less bulky methylaluminum bis(4-bromo-2,6-di-isopropylphenoxide) (MAIP) was found to be totally ineffective for the rearrangement of *tert*-butyldimethylsilyl ether of epoxygeraniol (Table 2.4). Again, $\text{BF}_3 \cdot \text{OEt}_2$ as an ordinary Lewis acid gave fluorohydrines as sole isolable products (Scheme 2.27).

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