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FEATURE ARTICLE

Designer Lewis acid catalysts—bulky aluminium reagents for selective organic synthesis

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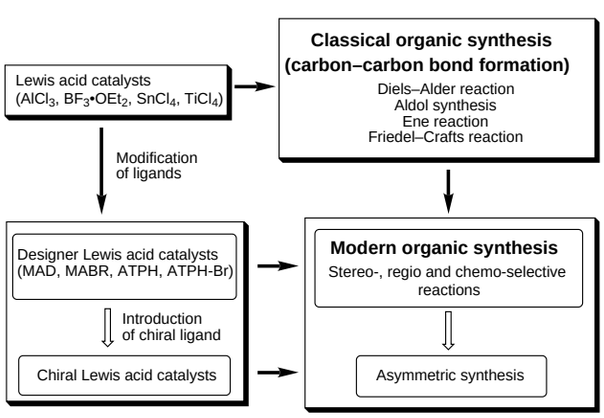
Sterically hindered aluminium aryloxides have been developed as designer Lewis acid catalysts for stereo-, regio- and chemo-selective carbon–carbon bond-forming reactions. Compared with classical Lewis acids, these aluminium reagents coordinate strongly with various oxygen-containing substrates, and this coordination is affected by the steric environment of their ligands. The carbonyl groups of the bound substrates are either electronically activated or sterically deactivated depending on the aluminium reagent used and the type of reaction. Designer chiral catalysts based on the structure of these bulky aluminium reagents have also been examined.

Introduction

Lewis acid-promoted carbon–carbon bond-forming reactions are some of the most important processes in organic synthesis. Traditionally, the Friedel–Crafts reaction,[1] the ene reaction,[2] the Diels–Alder reaction[3] and the Mukaiyama aldol synthesis[4] are catalysed by ordinary Lewis acids such as $AlCl_3$, $TiCl_4$, BF_3, and $SnCl_4$. These classical Lewis acids activate a wide variety of functional groups and the reactions usually proceed efficiently but with relatively low stereo-, regio- and chemoselectivities. The relatively simple design of ligands for these Lewis acids leads to monomeric Lewis acids in organic solvent and consequently to high Lewis acidity and reactivity. Furthermore, upon coordination with designed ligand(s), the well designed Lewis acid exhibits new selectivity (Scheme 1).

Several bulky aluminium reagents can be prepared from sterically hindered phenols. Most aluminium reagents in solution exist as dimeric, trimeric, or higher oligomeric structures.[5] In contrast, methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[6] and aluminium tris(2,6-diphenylphenoxide) (ATPH)[7] are monomeric in organic solvents. The Lewis acidity of these reagents decreases with the coordination of more electron-donating aryloxides, but this can be compensated for by loosening of the aggregation. Compared with classical Lewis acids, the steric effect of our aluminium reagents also plays an important role in selective organic synthesis, which is the subject of this article.



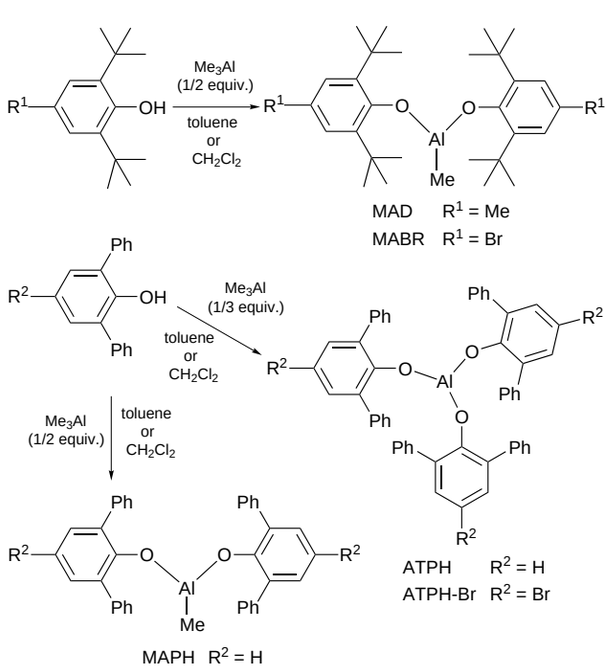
Scheme 1

Preparation of various aluminium phenoxides

MAD, ATPH, methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR)[8] and methylaluminium bis(2,6-diphenylphenoxide) (MAPH)[9] are readily prepared by treatment of Me_3Al with a corresponding amount of the phenol in toluene (or in CH_2Cl_2) at room temperature for 0.5–1 h with rigorous exclusion of air and moisture. These reagents can be used without further purification for all of the reactions described here. The reactivity of a phenol toward Me_3Al largely depends on the steric limitations of the phenol. For example, treatment of 3 equiv. of 2,6-di-*tert*-butyl-4-methylphenol with Me_3Al in CH_2Cl_2 at room temperature under argon results in the generation of bis(phenoxide) MAD together with the unreacted phenol. In contrast, 3 equiv. of 2,6-diphenylphenol react completely with 1 equiv. of Me_3Al to produce the tris(phenoxide) ATPH (Scheme 2).

Structural features of ATPH

The X-ray crystal structure of the *N*,*N*-dimethylformamide (DMF)–ATPH complex[7] disclosed that the three arene rings of ATPH form a propeller-like arrangement around the aluminium centre, and hence ATPH has a cavity with C_3 symmetry. By contrast, the X-ray crystal structure of the benzaldehyde–ATPH complex shows that the cavity surrounds the carbonyl substrate upon complexation with slight distortion from C_3 symmetry. A



Scheme 2

particularly notable structural feature of these aluminium–carbonyl complexes is the Al–O–C angles and Al–O distances (Fig. 1), which clarify that the size and the shape of the cavity changes flexibly depending on the substrates. According to these models, the cavity should be able to differentiate between carbonyl substrates, which, when accepted into the cavity, should exhibit unprecedented reactivity under the steric and electronic environment of the arene rings. ^{1}H NMR analysis of the crotonaldehyde–ATPH complex (300 MHz, CD_2Cl_2) revealed that the original chemical shifts of the aldehydic proton (H_a) at δ 9.50, and the α- and β-carbon protons (H_b and H_c) at δ 6.13 and 6.89, were significantly shifted upfield to δ 6.21, 4.92 and 6.40, respectively. The largest $\Delta\delta$ value of H_a of 3.29 suggests that the carbonyl is effectively shielded by the arene rings of the cavity. This observation is in contrast to the resonance frequencies of the crotonaldehyde–Et_2AlCl complex at −60 °C (H_a: δ 9.32; H_b: δ 6.65; H_c: δ 7.84), and those of crotonaldehyde complexes with other ordinary Lewis acids.[10]

Molecular recognition with bulky aluminium reagents

The monomeric aluminium phenoxides have sufficient Lewis acidity and thus bind with polar functionalities. The complexation is heavily dependent on the structural features of these functional groups. Thus, functional groups on the outside of a molecule bind to bulky aluminium reagents rather tightly, while functional groups on the inside of a molecule will not form stable complexes. In other words, the steric bulk of aluminium reagents appears to play a crucial role in discriminating between structurally or electronically similar substrates.

Discrimination of two different ethers

The 125 MHz ^{13}C NMR spectrum of a mixture of 1 equiv. each of MAD, methyl 3-phenylpropyl ether **1**, and ethyl 3-phenylpropyl ether **2** in $CDCl_3$ (0.4 M solution) at −50 °C (Scheme 3) showed that the original signal of methyl ether **1** at δ 58.7 shifted downfield to δ 60.1, whereas the signal of the α-methylene carbon of ethyl ether **2** remained unchanged. This unusual selectivity could not be observed with other Lewis acids as shown below. This method could be extended to the use of a polymeric aluminium aryloxide in complexation chromatography: heteroatom-containing solutes can be separated by complexation with a stationary, insolubilized organoaluminium polymer.[11]

Discrimination of two different ketones

Selective reduction of more hindered or electronically less polarizable ketones can be accomplished using MAD as a selective stabilizer of the carbonyls of less hindered or electronically more polarizable ketones.[12] Treatment of 1.0 equiv. each of acetophenone **3** and pivalophenone **4** in CH_2Cl_2 with 1.0 equiv of MAD at −78 °C, followed by subsequent addition of diisobutylaluminium hydride (DIBAL-H) at this temperature yielded alcohols **5** and **6** in a ratio of 1 : 10 (Scheme 4). Selective coordination of MAD with **3** was observed by ^{13}C NMR spectroscopy. These results suggest that the tight binding of MAD with sterically less congested **3** inhibited the attack of DIBAL-H at the carbonyl of **3**.

Discrimination of two different esters

Discrimination between two different ester carbonyls can be similarly achieved with MAD.[13] For example, reaction of *tert*-butyl methyl fumarate **7** with 1.1 equiv. of MAD in CH_2Cl_2 at −78 °C gave organoaluminium–fumarate complex **8** exclusively (Scheme 5), the structure of which was rigorously established by low-temperature ^{13}C NMR spectroscopy. Diels–Alder reaction of complex **8** with cyclopentadiene at −78 °C in

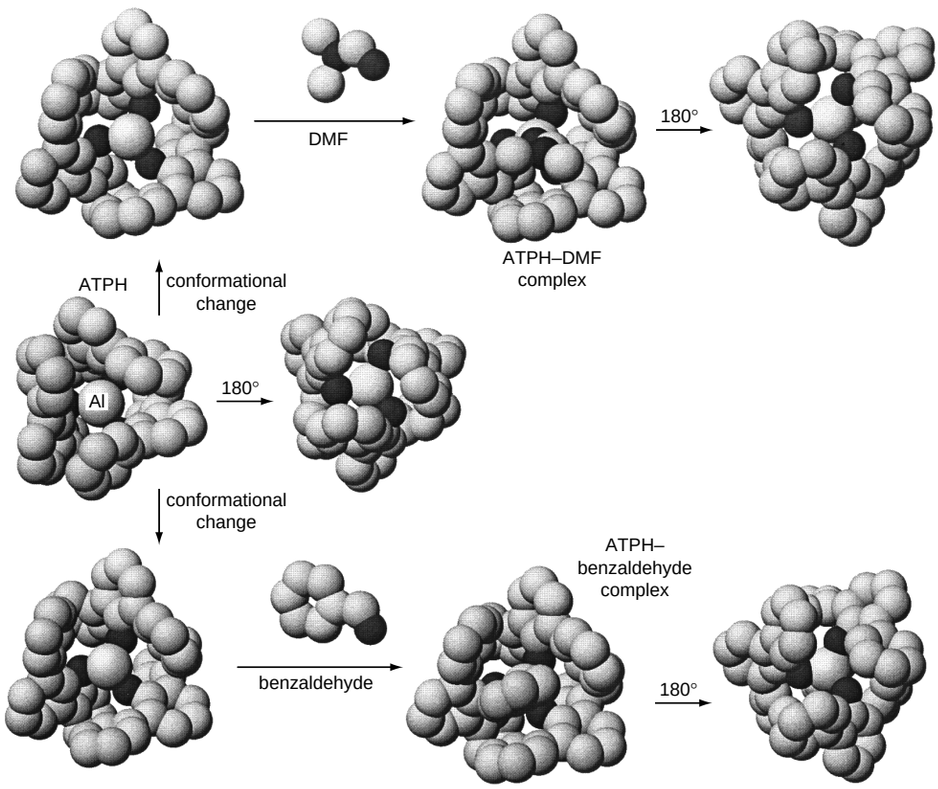
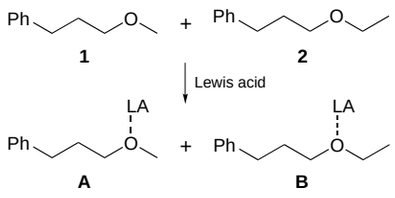


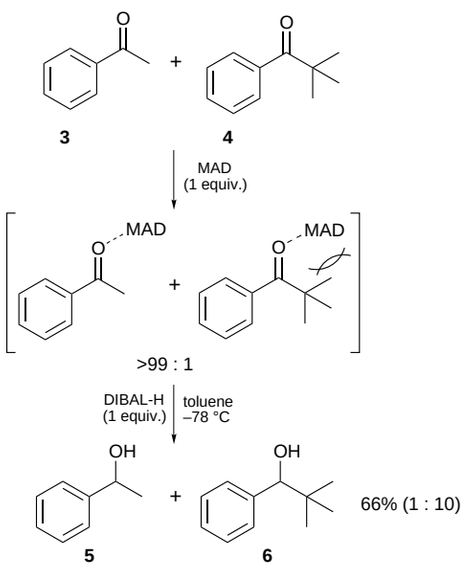
Fig. 1 Schematic complexation processes of DMF and benzaldehyde with ATPH, and the X-ray crystal structures of the ATPH–DMF and ATPH–benzaldehyde complexes. The protons are omitted for clarity. Front side view [looking down the O(sp^2)–Al bond] and back side view [180° rotation from the front side view around the axis perpendicular to the O(sp^2)–Al bond] are shown. Selected distances (Å) and angles (°): ATPH–DMF: Al–O(sp^3)–C 135.6(8), Al–O(sp^2)–C 138.1(3), Al–O(sp^3) 1.711(3), Al–O(sp^2) 1.795. ATPH-benzaldehyde: Al–O(sp^3)–C 149.6(5), 136.1(5) and 144.1(5), Al–O(sp^2)–C 135.7(9), Al–O(sp^3) 1.694(3), 1.728(5) and 1.709(5), Al–O(sp^2) 1.856(5).

toluene gave, after 1 h, cycloadduct **9**, predominantly with *endo* orientation of the methoxycarbonyl group. Thus, the methyl ester coordinated with the aluminium reagent gave us high *endo*-selectivity of the Diels–Alder reaction. Even methyl and isopropyl or methyl and ethyl can be fairly well discriminated with MAD.



Lewis acid	**A** : **B**
MAD	>99:1
Bu^i_3Al	4 : 1
$SnCl_4$	2 : 1 (ether : Lewis acid = 2:1)
$BF_3{\bullet}OEt_2$	no complexation
BEt_3	5 : 3

Scheme 3

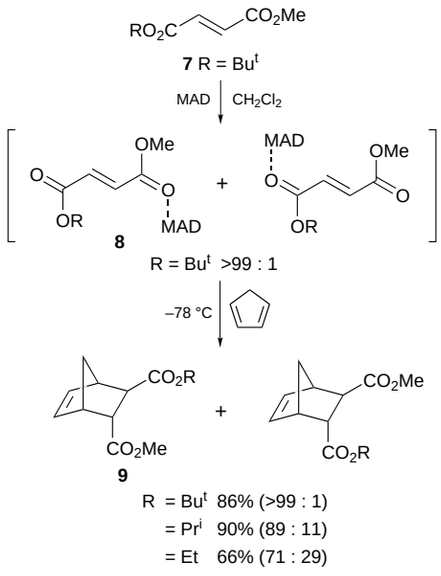


Scheme 4

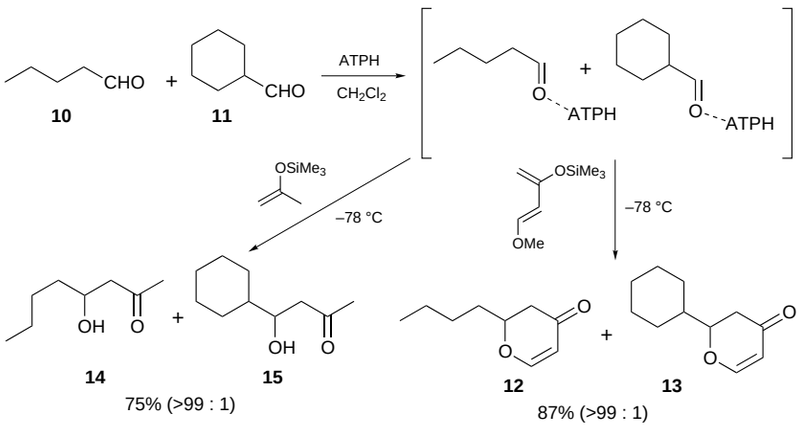
Discrimination of two different aldehydes

ATPH can discriminate between structurally similar aldehydes, thereby facilitating the selective functionalization of the less hindered aldehyde carbonyl.[14] Treatment of an equimolar mixture of valeraldehyde **10** and cyclohexanecarboxaldehyde **11** with 1.1 equiv. of ATPH in CH_2Cl_2 at −78 °C, followed by addition of Danishefsky's diene at this temperature, gave hetero-Diels–Alder adducts **12** and **13** in a ratio of >99 : 1 (Scheme 6). It should be noted that only the complexed aldehyde could react with the diene. The reaction gave relatively low chemoselectivity with other typical Lewis acids: [**12** : **13** ratios: $(Pr^iO)_2TiCl_2$ = 6.2 : 1; Me_3Al = 5 : 1; MAD = 3.7 : 1; $TiCl_4$ = 2 : 1; $BF_3{\cdot}OEt_2$ = 1.3 : 1; MAPH = 1 : 3.4]. This fact emphasizes that the cavity of ATPH plays an important role in differentiating between the reactivities of the two different aldehydes. In a similar manner, the aldol reaction of a mixture of **10** and **11** was effected equally well with ATPH to furnish 4-hydroxyoctan-2-one **14** without **15**.

Obviously, the coordinated aldehyde is electronically activated but sterically deactivated with bulky aluminium reagents. The selective functionalization of more sterically hindered aldehydes was accomplished by the combined use of MAPH and alkyllithiums (RLi; R = Bu^n or Ph) (Scheme 7).[15] In this system, MAPH acted as a carbonyl protector of a less hindered aldehyde such as **10**, and therefore the carbanions preferentially



Scheme 5



Scheme 6

react with more hindered carbonyl groups. It should be noted that alkyllithium reagents could react with aldehydes in the absence of the aluminium reagent.

Bulky aluminium reagents for selective organic syntheses

So far we have discussed the discriminating abilities of aluminium reagents. In this section, we will focus on the reactions promoted with bulky aluminium reagents which could not be achieved with ordinary Lewis acid catalysts.

Conjugate addition to α,β-unsaturated carbonyl compounds

Organocuprates are the most widely used reagents for Michael addition to α,β-unsaturated ketones, one of the most powerful and important carbon–carbon bond-forming reactions. ATPH can be used as a carbonyl protector upon complexation, which facilitates 1,4-addition to even α,β-unsaturated aldehydes,[10] for which 1,4-addition is virtually unexplored. Complexation of cinnamaldehyde **12** with 1.1 equiv. of ATPH in CH_2Cl_2 at −78 °C, followed by subsequent addition of 1.5 equiv. of *n*-butylmagnesium bromide (Bu^nMgBr), gave the 1,4-addition product preferentially (Scheme 8). The alkylation of **12** with MAD and Bu^nMgBr gave unsatisfactory results (95%; 1,4 : 1,2 adduct ratio = 7 : 93). The combination of MAPH with the same butylating agent gave an equal mixture of 1,4- and 1,2-adducts (98%; ratio = 49 : 51). Replacing organomagnesium reagents with organo-calcium, -strontium and -barium reagents enhanced 1,4-selectivity. One of the advantages of this method over organocopper-mediated conjugate addition is the availability of lithium alkynides and thermally unstable lithium carbenoids as Michael donors. With alkynides, raising the reaction temperature after the Michael addition triggered cyclopropanation to give a sole diastereoisomer (Scheme 9).

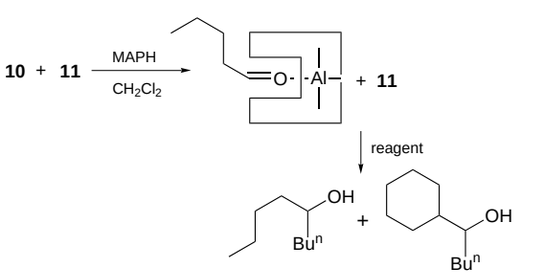
Application of this system to α,β-unsaturated ketones gave even more general and pronounced 1,4-selectivity (> 99 : 1).[16] In this case, various alkyllithiums can be used as Michael donors, and this ATPH–RLi system enables the introduction of perfluoroalkyl or perfluoroaryl substituents at the β-positions of carbonyl functions (Scheme 10).[17]

Several ketone lithium enolates and the dianions of β-dicarbonyl substrates similarly undergo highly selective 1,4-addition to various α-enones. Thus, tandem inter- and intramolecular Michael addition using the enolates of α,β-unsaturated ketones as Michael donors[18] was achieved successfully: treatment of **13**–ATPH complex in toluene with a THF solution of the benzylideneacetone lithium enolate at −78 °C, followed by refluxing for 13 h, gave stereochemically homogeneous annulation product **14** in 50% yield (> 84% de) (Scheme 11).

Michael addition of the dianions derived from β-dicarbonyl compounds facilitated another annulation: Michael addition of a dianion, followed by intramolecular aldol condensation.[19] Complexation of ATPH with *trans*-chalcone **15** in CH_2Cl_2 at −78 °C, followed by treatment with the dianion of methyl acetoacetate gave, after quenching with aq. HCl, bicyclic product **16** in high yield (Scheme 12). This system can also be used for elaboration of the bicyclo[3.5.1]undecane ring system in **17**, which can be found in the backbones of terpenoids[20] and the taxol family.[21]

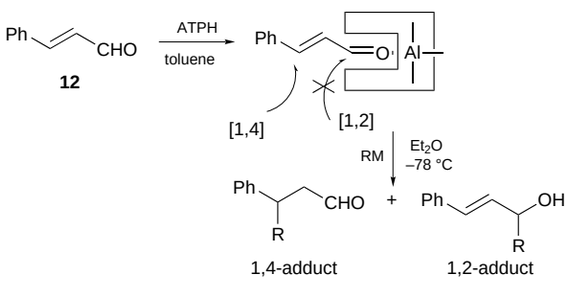
The exceedingly bulky aluminium reagent aluminium tris(2,6-di-*tert*-butyl-4-methylphenoxide) (ATD)[22] was superior to ATPH or MAD as a carbonyl protector in ynones.[23] Initial complexation of oct-3-yn-2-one **18** in toluene with ATD and subsequent addition of a hexane solution of Bu^nLi at −78 °C generated 1,4-adduct **19** in 92% yield together with a small amount of the 1,2-adduct (Scheme 13).

Selective 1,6-addition of alkyllithiums to aromatic carbonyl substrates such as benzaldehyde or acetophenone was achieved with ATPH to give cyclohexadienyl compounds **20** and **21**, respectively (Scheme 14).[24] According to the molecular structure of the benzaldehyde–ATPH complex (Fig. 2), it is



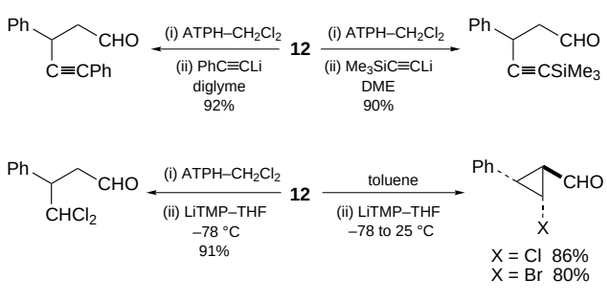
$Bu^nTi(OPr^i)_3$ (1 equiv.)	31% (2.5:1)
MAPH (1 equiv.)/ Bu^nLi (1 equiv.)	76% (1:6.5)
MAPH (2 equiv.)/ Bu^nLi (2 equiv.)	45% (1:14)

Scheme 7

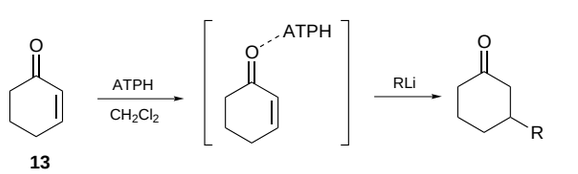


RM =	Bu^nLi	92% (49:51)
	Bu^nMgCl	99% (90:10)
	Bu^nCal	88% (98:2)
	Bu^nSrI	60% (95:5)
	Bu^nBal	97% (97:3)

Scheme 8

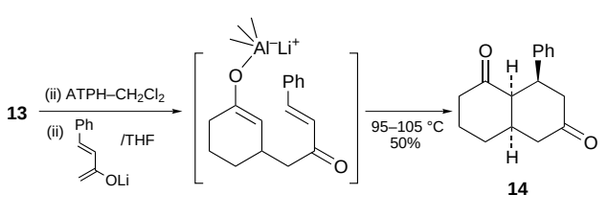


Scheme 9

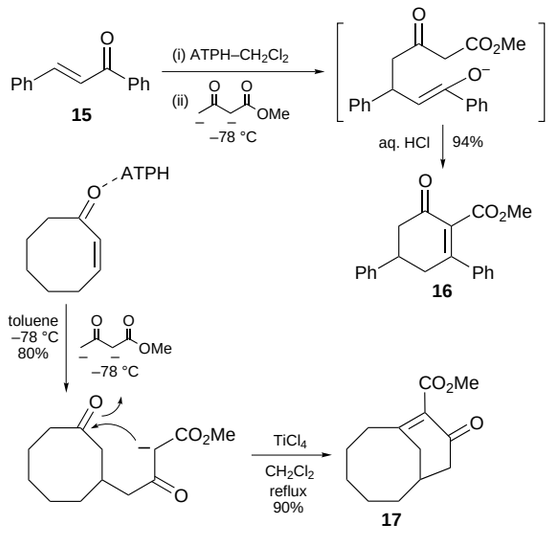


RLi = MeLi (83%), PhLi (86%), PhC≡CLi (99%), Cl_3CLi (60%), CF_3CF_2Li (75%)

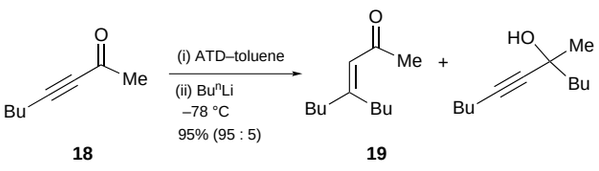
Scheme 10



Scheme 11

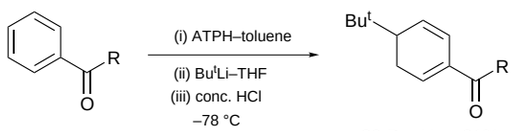


Scheme 12



18 **19**

Scheme 13



20 R = H 81%
21 R = Me 93%

Scheme 14

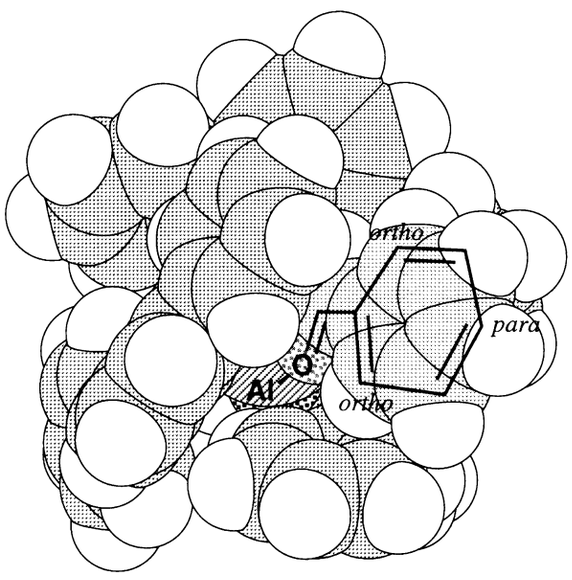


Fig. 2 X-Ray crystal structure (space-filling model) of the ATPH–benzaldehyde complex, which shows the more facile nucleophilic attack at the *para*-position

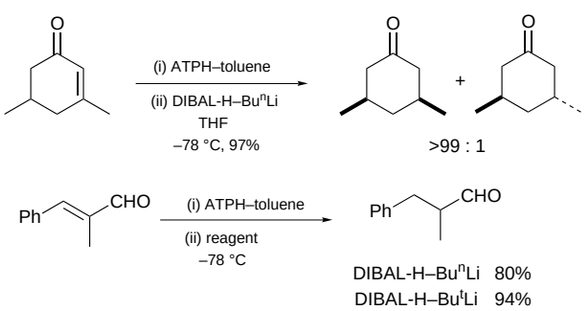
obvious that the *para* position of benzaldehyde is deshielded by the three arene rings, which effectively block the *ortho* position and the carbonyl carbon from nucleophilic attack.

Efficient conjugate reduction of several α,β-unsaturated carbonyl substrates was similarly realized by the combined use of ATPH and diisobutylaluminium hydride–butyllithium 'ate' complex (DIBAL-H–BunLi) as a reducing agent (Scheme 15).[25] Diisobutylaluminium hydride–*tert*-butyllithium (DIBAL-H-ButLi) was more effective for the 1,4-reduction of α,β-unsaturated aldehydes.

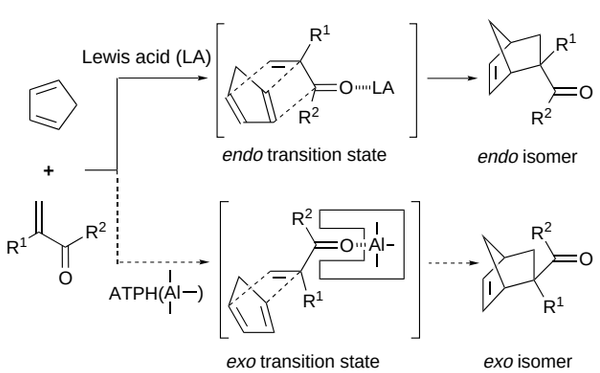
exo-Selective Diels–Alder reaction

One characteristic stereochemical feature of the Diels–Alder reaction is *endo* selectivity. The origin of the *endo* preference in Diels–Alder reactions can be ascribed to 'secondary orbital interactions'. If the carbonyl functions of dienophilic α,β-unsaturated carbonyl substrates are effectively shielded by complexation with ATPH, secondary interaction is decreased, thereby disfavouring the hitherto preferred *endo* transition state (Scheme 16).

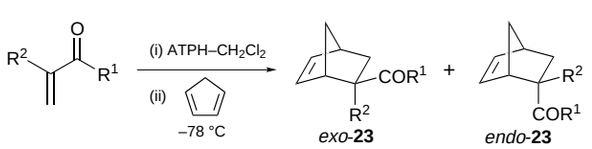
As expected, precomplexation of α,β-unsaturated ketone **22a** with ATPH in CH_2Cl_2 at −78 °C, followed by cyclization with cyclopentadiene, resulted in stereochemical reversal to furnish *exo*-**23a** as a major product (Scheme 17). Similarly, the Diels–Alder reaction with other dienophiles **22b,c** complexed with ATPH exhibited *exo* selectivity.[26]



Scheme 15



Scheme 16



22a R^1 = Ph, R^2 = H **a** 81% (73:27)
b R^1 = Ph, R^2 = Me **b** 81% (96:4)
c R^1 = R^2 = Me **c** 87% (87:13)

Scheme 17

This concept was extended intramolecularly to give *trans*-fused stereoisomer **25**, while an ordinary aluminium reagent gave *cis*-isomer **24** *via* an *endo* transition state (Scheme 18).

Stereoselective and asymmetric Claisen rearrangement

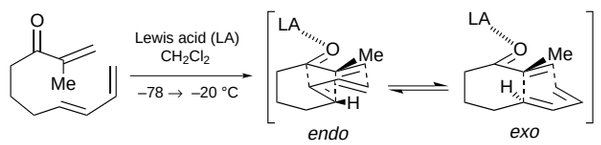
Claisen rearrangement[27] is accelerated significantly with bulky aluminium reagents. With MABR, the rearrangement of 1-substitutedprop-2-enyl vinyl ether derivatives **26**–**28** takes place in a few seconds even at −78 °C to give the (*Z*)-alk-4-enols after reduction with $NaBH_4$ (Scheme 19). When MABR is replaced by MAPH, (*E*)-isomers are formed preferentially.[28] This stereochemical reversal observed with MABR and MAPH can be accounted for by the two possible chair-like transition state structures *ax*-**29** and *eq*-**29**, respectively,[28,29] which are suggested by the absolute configuration of the double bonds and the allylic carbons of the produced aldehydes (Scheme 20).

Optically pure aluminium reagent (*R*)-**30** was synthesized from 1 equiv. each of (*R*)-(+)-3,3′-bis(triarylsilyl)-1,1′-bi-2-naphthol and Me_3Al,[30] based on the structure of MAPH. Chiral (*R*)-**30** is an excellent promoter for the asymmetric Claisen rearrangement of allyl vinyl ethers **31** or **32** which possess bulky substituents such as trialkylsilyl or trialkylgermyl groups,[31] but is totally ineffective for sterically less hindered substrates (Scheme 21).

Claisen rearrangement is considered to proceed *via* a six-membered transition state.[27,32] The preferential conformation of the reactant in the transition state might be due to the shape and the size of the cavity of ATPH. This hypothesis can be verified by treatment of 1-butylprop-2-enyl vinyl ether **33** with ATPH at 0 °C to give isomeric rearrangement products (*E*)- and (*Z*)-**34** in 87% yield in a ratio of 16 : 1 (Scheme 22). MAPH-mediated rearrangement of **33** gave fairly good stereoselectivity [(*E*)-**34** : (*Z*)-**34** = 5 : 1].

The effect of the electron-withdrawing group of the ATPH ligands on stereoselectivity and acceleration of the rearrangement was also investigated.[33] The rearrangement of **33** with ATPH-Br proceeded with prominent stereoselectivity [−78 °C, 13 h; (*E*)-**34** : (*Z*)-**34** = > 200 : 1], which suggests that both the cavity and the high Lewis acidity are responsible for the high degree of stereocontrol. The rearrangement of (*E*)-**35** and (*Z*)-**35** with various aluminium reagents indicates that the reaction rate was significantly enhanced with ATPH-Br to give **36** almost quantitatively (Scheme 23).

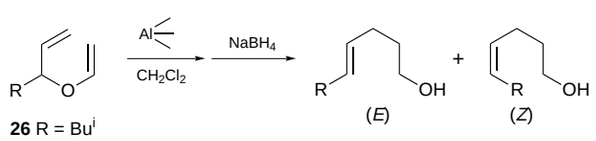
The catalytic Claisen rearrangement of 1,1-dimethyl-3-phenylprop-2-enyl vinyl ether **37** was achieved with 5–10 mol% of ATPH-Br by taking advantage of its high Lewis acidity



24 *cis* isomer **25** *trans* isomer

Lewis acid =	Me_3Al	75% (88:12)
	ATPH	69% (4:96)

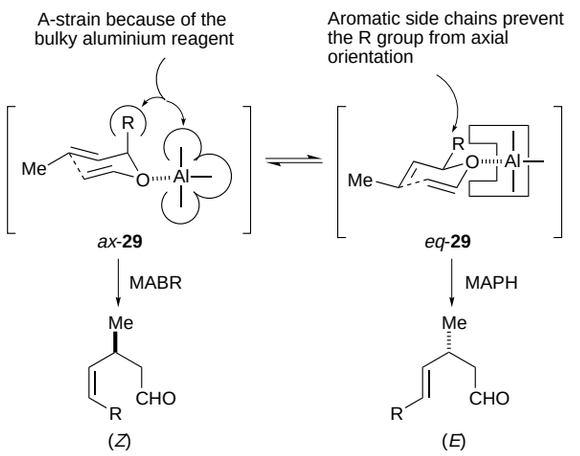
Scheme 18



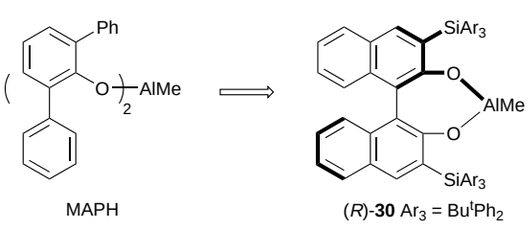
26 R = Bu^i
27 R = vinyl
28 R = allyl

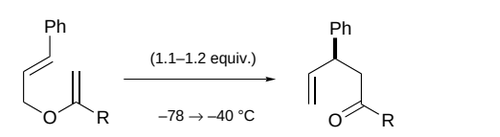
	MABR	MAPH
R = Bu^i	64% (7:93)	85% (97:3)
R = vinyl	97% (24:76)	91% (90:10)
R = allyl	40% (7:93)	97% (95:5)

Scheme 19



Scheme 20

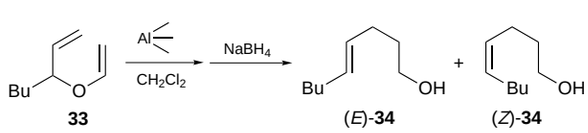




31 R = $SiMe_3$
32 R = $GeMe_3$

R = $SiMe_3$	76% (90% ee)
R = $GeMe_3$	68% (93% ee)

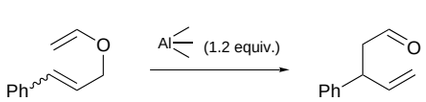
Scheme 21



33 (*E*)-**34** (*Z*)-**34**

MAPH	75% (5:1)
ATPH	87% (16:1)

Scheme 22



(*E*)- and (*Z*)-**35** **36**

−78 °C, 1 h, toluene	MAD	37%
	MABR	76%
	ATPH	93%
	ATPH-Br	98%
−20 °C, 1 h, CH_2Cl_2	ATPH	48%
	ATPH-Br	93%

Scheme 23

(Scheme 24). MABR was entirely ineffective for the catalytic rearrangement.

Based on the structure of ATPH, an optically active catalyst, aluminium tris[(*R*)-1-(1-naphthyl)-3-phenyl-2-naphthoxide] [(*R*)-ATBN], was synthesized, and was subjected to the asymmetric Claisen rearrangement of (*E*)-**35** and **38**–**40** to give the corresponding aldehydes in moderate enantioselectivities (> 60% ee) (Scheme 25). In contrast, the more elaborated (*R*)-ATBN analogue, aluminium tris[(*R*)-1-(1-naphthyl)-3-(*p*-fluorophenyl)-2-naphthoxide] [(*R*)-ATBN-F], generated products with up to 92% ee. Taking in account the decomposition of (*E*)-**35** which took precedence over the rearrangement with (*R*)-**30**, adequate design of Lewis acid catalysts was proven to be important for the stereoselective and asymmetric Claisen rearrangement.

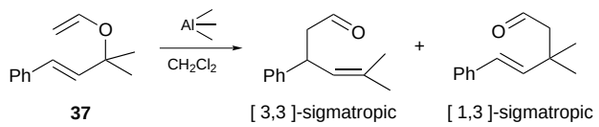
Selective alkylation at the α-carbon of unsymmetrical ketones

An unsymmetrical dialkyl ketone can form two regioisomeric enolates upon deprotonation under either kinetic or thermodynamic control. Ideal conditions for the kinetic control of less-substituted enolate formation are those in which deprotonation is irreversible using lithium diisopropylamide (LDA). On the other hand, at equilibrium, the more substituted enolate is the dominant species with moderate selectivity. A hitherto unknown method, *i.e.* the kinetically controlled generation of the more substituted enolate, was realized by the combined use of ATPH and LDA.[34]

Precomplexation of ATPH with 2-methylcyclohexanone **41** at −78 °C in toluene was followed by treatment with LDA in THF, and the mixture was stirred for 1 h (Scheme 26). Subsequent treatment with methyl trifluoromethanesulfonate (MeOTf) furnished 2,2-dimethylcyclohexanone **43** and 2,6-dimethylcyclohexanone **42** in an isolated yield of 53% in a ratio of 32 : 1. Similarly, highly regiocontrolled alkylation of unsymmetrical **44** and **46** with octyl trifluoromethanesulfonate ($C_8H_{17}OTf$) was achieved to give **45** and **47**, respectively (> 99 : 1) (Scheme 27). Replacing ATPH with MAD resulted in a lack of regioselectivity (**42** : **43** = *ca* 1 : 1).

Using *tert*-butyldimethylsilyl trifluoromethanesulfonate (Bu^tMe_2SiOTf) in place of alkyl trifluoromethanesulfonates in the present alkylation system produced silyoxybutylated product **48** as a result of THF ring-opening, where alkylation similarly occurred at the more hindered α-carbon of unsymmetrical ketone **41** (Scheme 28).[35]

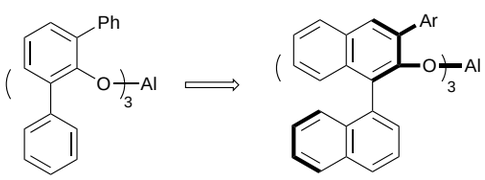
Generation of the kinetically deprotonated more substituted enolate can be explained in terms of the effect of ATPH on the inherent coordination preference of unsymmetrical ketones. Most likely, the bulky aluminium reagent ATPH prefers coordination with one of the lone pairs *anti* to the more hindered α-carbon of the unsymmetrical ketones. As a consequence, the aluminium reagent surrounds the less hindered site of the carbonyl group, thus obstructing the trajectory of the nucleophilic attack of LDA (Fig. 3).



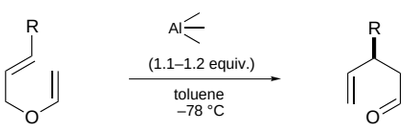
37 [3,3]-sigmatropic [1,3]-sigmatropic

ATPH-Br	(10 mol%), –78 °C, 2.5 h	90% (5:1)
ATPH-Br	(5 mol%), –78 °C, 20 h	82% (4.8:1)
MABR	(5 mol%), –78 °C, 20 h	<9%

Scheme 24



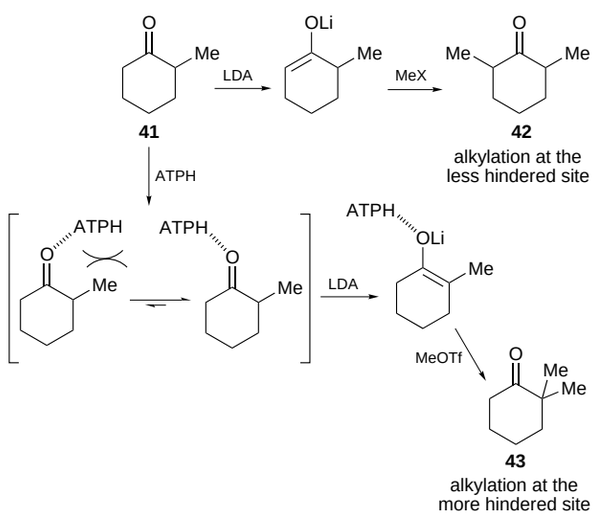
ATPH (*R*)-ATBN Ar = Ph
(*R*)-ATBN-F Ar = *p*-FPh



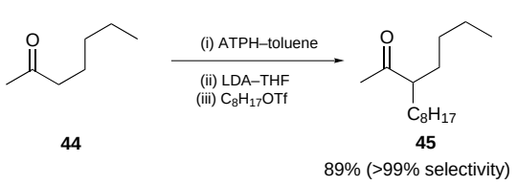
(*E*)- **35** R = Ph
38 R = c-hexyl
39 R = Bu^t
40 R = Me_3Si

R = Ph	(*R*)-ATBN	93% (61% ee)
R = Ph	(*R*)-ATBN-F	97% (76% ee)
R = c-hexyl	(*R*)-ATBN-F	85% (86% ee)
R = Bu^t	(*R*)-ATBN-F	70% (91% ee)
R = Me_3Si	(*R*)-ATBN-F	78% (92% ee)

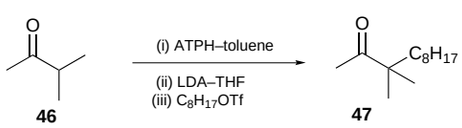
Scheme 25



Scheme 26

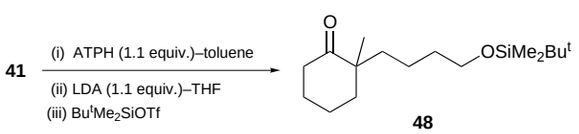


44 **45**
89% (>99% selectivity)



46 **47**
71% (>99% selectivity)

Scheme 27



Scheme 28

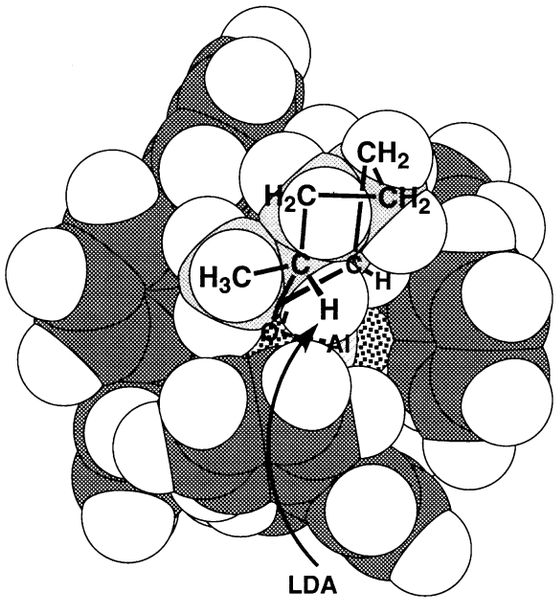


Fig. 3 Space-filling model of the ATPH–**41** complex. LDA attack is more feasible at the more substituted α-carbon.

Conclusion

The designer Lewis acids described here show several unique characteristics. In particular, these designer Lewis acids can (i) discriminate between structurally and electronically similar oxygen functionalities, (ii) protect the carbonyl groups of α,β-unsaturated carbonyl compounds from nucleophiles (this observation was extended to selective 1,4- and 1,6-additions, as well as new annulation processes), (iii) promote stereoselective Claisen rearrangement, and the chiral catalysts lead to an asymmetric rearrangement, (iv) selectively coordinate with unsymmetrical carbonyl compounds to generate more substituted enolates. The designer Lewis acid catalysts described here are only a few examples of what is possible. Thus, the search for a new and practical designer Lewis acid still remains a challenge in selective organic synthesis.

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