Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)

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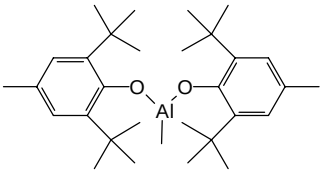
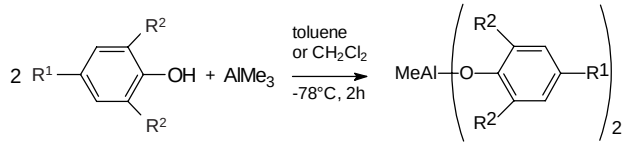
Bulky designer aluminum Lewis acids of type **1** [1], first introduced into organic synthesis by Yamamoto and coworkers [2], provide remarkably versatile reagents for the control of regio-, stereo- and chemoselective transformations. The first described compound of this class, methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) **1** proved to be a universal tool for the selective promotion of carbon–carbon bond formation, radical or pericyclic reactions. The reagent is readily available in a large scale from low cost commercial precursors [2].



MAD **1**

Aluminum alkoxide- and aryloxide compounds generally show the tendency to maximise their coordination number by association to give aggregates containing tetrahedral or octahedral centres. This aggregation leads to decreased Lewis acidity, and can be prevented by use of the steric hindered aryloxide derived ligand 2,6-di-*tert*-butyl-4-methylphenol (**2**) (BHT, from the trivial name butylated hydroxytoluene) [3], or structurally related phenolic ligands like **3** or **4** (scheme 1). The resulting monomeric aluminum Lewis acids like **1**, **5**, or **6** show different reactivities, depending on the number, electronic properties and steric hindrance of the ligands [4].



2 R^1 = Me; R^2 = *t*-Bu; **3** R^1 = Br; R^2 = *t*-Bu;
4 R^1 = H; R^2 = Ph

R^1 = Me; R^2 = *t*-Bu: MAD **1**
R^1 = Br; R^2 = *t*-Bu: MABR **5**
R^1 = H; R^2 = Ph: MAPH **6**

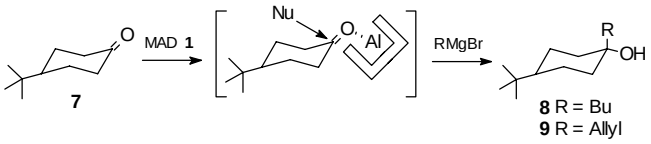
Scheme 1

In general, use of MAD **1** gives good to excellent selectivities and yields but, if required, screening of related reagents like **5**, **6** or even more bulky aluminium complexes with three phenolic substituents may result in improved results [4].

1. Unusual Regioselectivities in Nucleophilic Additions to Carbonyles

Due to the high oxophilicity of the monomeric MAD **1**, stable Lewis acid complexes are formed with carbonyl oxygen. This complexation leads to steric protection of initially less hindered substrate positions by the bulky ligands of the aluminium complex. MAD **1** can thus act as both Lewis acid catalyst and a protective agent to enhance selectivity, or often also reverse the stereo- or regiospecificity of reactions.

Complexation of a wide range of substituted cyclohexanones or cyclopentanones with MAD **1** inverts the facial selectivity of attacking nucleophiles by shielding the initially favoured equatorial side (scheme 2) [2, 5].



7

8 R = Bu
9 R = Allyl

Scheme 2

This sequence, leading nearly exclusively to tertiary axial substituted alcohols like **8** or **9** was carried out with different alkyl or allyl organolithium or Grignard reagents giving excellent to quantitative axial selectivities. The approach has also been used successfully in the stereoselective alkylation of the steroidal ketone 3β-methylcholestan-3α-ol [2].

Complexation of the α-chiral aldehyde **10** with MAD **1** has been shown to reverse the selectivity of amphiphilic alkylation [2]. After complexation with MAD **1**, an ethyl Grignard reagent preferentially attacks opposite to the bulky aluminum reagent (scheme 3) leading to the *anti* Cram **11a** and Cram product **11b** in a ratio of 75 : 25 (90% yield), while alkylation without preceding complexation gives a product ratio of 13 : 87 favouring the Cram product **11b**.

Another example of unusual selectivity in nucleophilic additions is the use of MAD **1** for directing organolithium addition to α,β-unsaturated carbonyl compounds. While conjugate addition to α,β-unsaturated carbonyl compounds is generally affected by soft organometallics (Cu, Ni, *etc*.), use of organolithium reagents for that purpose has long been a chal-

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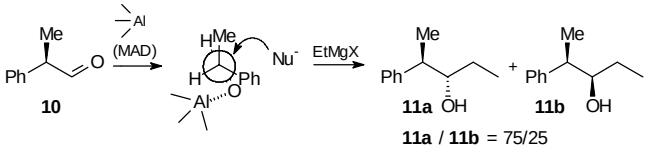
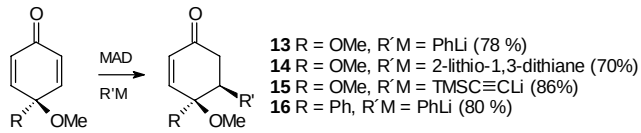


Scheme 3

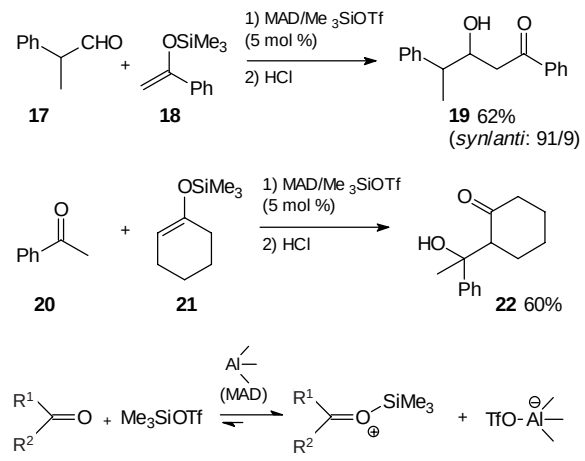
lenge due to their hard nucleophilic character [6]. Remarkable 1,4-selectivities were reported for the addition of organolithium compounds to substituted cyclohexenones and linear ketones in the presence of MAD **1** [7] or the structurally related aluminum tris(2,6-diphenylphenoxide) [8]. Complexation of the substrate with MAD **1** sterically disfavours the more reactive carbonyl position, directing attack of the nucleophile to the γ-position. For example, MAD **1** was used very efficiently for the direction of alkyllithium and Grignard reagent addition to quinone monoketals [9], thus providing a universal route to *meta* substituted *p*-methoxyphenols (scheme 4). Good yields were obtained in alkylations of the quinone monoketal **12a** and the quinone ether **12b** with aryl organometallics **13**, **16**, 2-lithio-1,3-dithiane **14**, and even the acetylenic lithium reagent **15**.



Scheme 4

2. Use of MAD in Mukaiyama Aldol Reactions and One Carbon Homologations

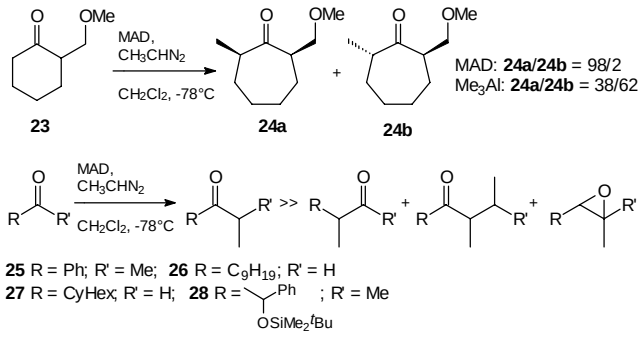
Oishi *et al*. recently reported a remarkable rate enhancement in the trialkylsilyl triflate-catalysed Mukaiyama aldol reaction of silyl enol ethers using MAD **1** or MABR **5** as cocatalysts [10]. The aliphatic aldehyde **17** and ketone **20** reacted smoothly with silylenolethers **18** and **21** in the presence of a catalytic amount of a mixture of MAD **1** and trimethylsilylsulfonates (scheme 5).



Scheme 5

The strategy involved was based on selective molecular recognition of a triflate anion by MAD **1**. The anionic species is trapped, and the equilibrium is shifted towards an electron deficient carbonyl species which reacts readily with the silyl enolether as shown in scheme 5.

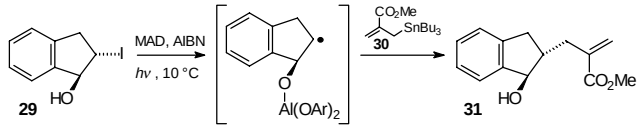
Organoaluminum promoted selective C1- homologation or ring expansion of ketones like **23**, **25** or **28** and aldehydes (**26**, **27**), using diazoalkanes, has been investigated using a variety of aluminum Lewis acids. MAD **1** was found to be highly effective as a complexing agent, suppressing multiple homologation and oxirane formation, often observed with unhindered aluminium reagents (scheme 6) [11].



Scheme 6

3. Radical Reactions

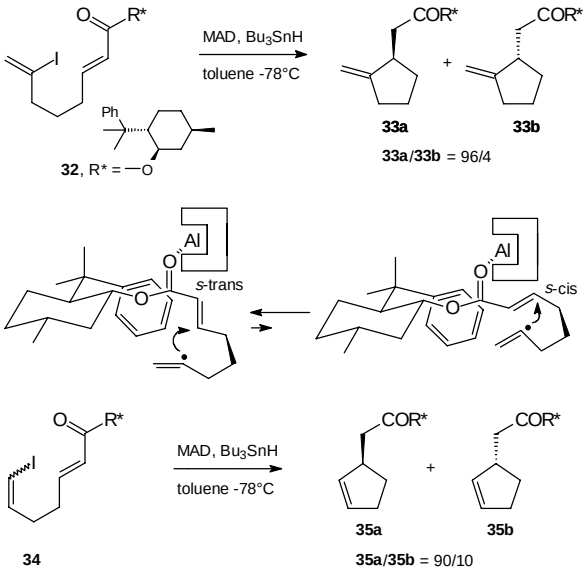
The use of Lewis acids to control the regio- and stereochemical course of radical reactions is an emerging field [12]. According to several recent studies, the use of sterically hindered Lewis acids of type **1** enhances the reactivity, and provides better control of the selectivity of radical reactions. Moufid and Renaud investigated the carbon–carbon bond formation of the iodohydrin **29** and methyl-2-[(tributyl-stannyl) methyl]propenoate **30** (Scheme 7) [13].



Scheme 7

In the absence of Lewis acids only moderate *trans* selectivity was observed for the alkylation of **30** (*trans*/*cis* **31**: 5/1). Furthermore, use of the covalently bound bulky (*tert*-butyl) diphenylsilyl group on the alcohol moiety of **29** did not significantly improve this ratio (protected *trans*/*cis* **31**: 7/1). In contrast, an almost complete control of the stereochemical course of the reaction (*trans*/*cis* **31**: 100 : 1) was observed after treating the free alcohol **29** with MAD. In this example, the production of methane during the addition of MAD indicated formation of an intermediate aluminum alkoxide.

Coordination of MAD to chiral esters like **32** and **34** enhances stereoselectivity of radical cyclisations (scheme 8) [14]. In the presence of MAD, the chiral radical acceptor **32** gave a 96 : 4 mixture of diastereomers **33a** and **33b**. This selectivity was attributed to a favoured *s-trans* conformation of the MAD complexed α,β-unsaturated ester radical as shown in scheme 8. Similar results were obtained for the cyclisation to the cyclopentene derivative **35**, opening a new approach to these versatile chiral building blocks.



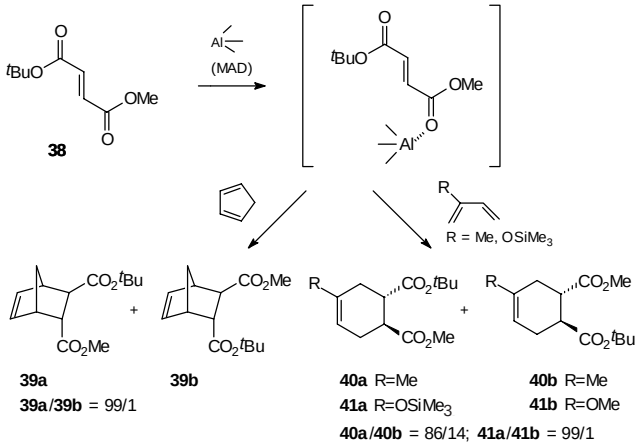
Scheme 8

The domino radical cyclisation of type **36** chiral sufoxides was recently reported by Lacote *et al.* (scheme 9) [15]. An *anti*-Michael-5-*exo*-*trig*-radical cyclisation/β-elimination sequence of the chiral sulfoxide **36** leads to the chiral cyclopentane **37** with 96% *e.e.* (*S*) in 93% yield (scheme 9A).

Remarkably, the stereochemical course of the cyclisation was inverted in the presence of MAD, and (*R*)-**37** could be isolated with 92% *e.e.* albeit with lower yield (52%). The stereochemical outcome of this reaction is directed by complexation of the sulfoxide oxygen with the bulky aluminum reagent as depicted in scheme 9B.

4. Cycloadditions

Discrimination of different hindered carbonyl groups using MAD can be employed to increase the selectivity of Diels–Alder reactions. As an example, complexation of *tert*-butyl methyl fumarate **38** with one equivalent of MAD **1** gave the organoaluminium-fumarate complex exclusively on the less hindered oxygen. It reacted readily at –78 °C with dienes to give the products **39**, **40** and **41** (scheme 10)[16].

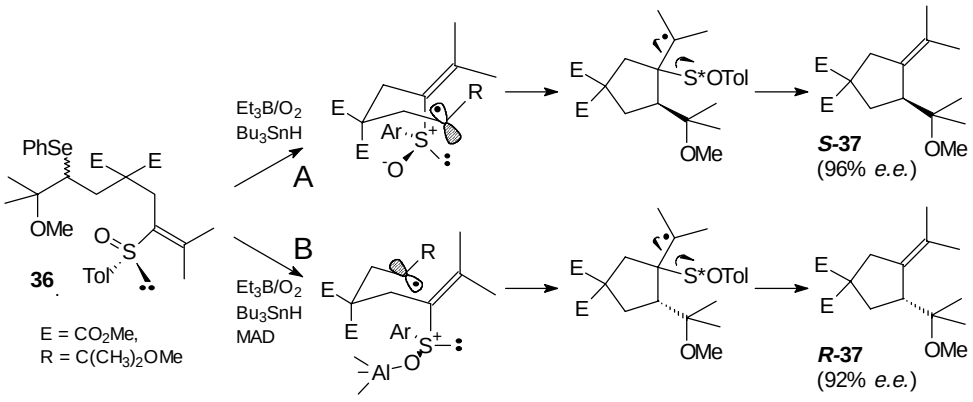


Scheme 10

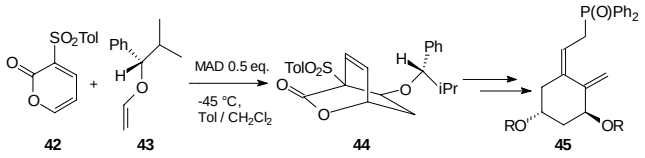
The unusual high selectivities of these reactions were in contrast to the nearly statistical product ratio obtained in the presence of the Lewis acid Et_2AlCl or in the absence of an appropriate catalyst. This concept could be also applied to the asymmetric Diels–Alder reaction of l-menthylmethylfumarate giving the cycloaddition products with 86% *d.e.* [16]. High regiochemical control was reported for the MAD assisted [2+2] cycloaddition of ketene diethyl acetal or ketene dimethyl thioacetal to **38** [17].

As a key step in the total synthesis of an A-ring precursor **45** to 1α,25-dihydroxyvitamin D_3, an inverse-electron-demand Diels–Alder reaction was catalysed by MAD **1** to promote cycloaddition between pyrone sulfone **42** and the vinyl ether (*S*)-**43** (Scheme 11) [18].

With 0.5 equivalents of MAD **1** as a catalyst, the cycloadduct **44** was isolated on a 1.5 g scale in 93% yield as a 98:2 ratio of *endo* : *exo* diastereomers. This high degree of asym-



Scheme 9



Scheme 11

metric induction could be obtained even though the spatial movement of the inducing chiral centre in **43** was not restricted by the chiral centre being bound to the reaction centre. In the absence of MAD, both the selectivity and yield of the reaction was reduced drastically.

The efficacy of MAD **1**, and related bulky Lewis acids as catalysts for the Claisen rearrangement were compared [19]. While MAD **1** results in only moderate rate enhancements and selectivities, the sterically more demanding aluminum tris(2,6-diphenylphenoxide) or the MAD-analogue with electronic withdrawing ligands **5** improved yields and selectivities significantly. This study demonstrated the use of various structurally related bulky aluminum Lewis acids with tuned properties for obtaining optimum results.

In conclusion MAD **1** provides a versatile Lewis acid catalyst that affects the regiochemical and stereochemical outcome of a wide array of reactions. The reagent allows the use of unusual reagents and substrates in carbon–carbon bond formation reactions like nucleophile additions, radical reactions and cycloadditions. With the predictable outcome of MAD **1** controlled reactions it allows the use of new strategies in synthesis.

Preparation of Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) [2]

MAD is readily prepared by treatment of a 1–2M solution of Me_3Al (Fluka, Deisenhofen) in hexane with two equivalents of 2,6-di-tert-butyl-4-methylphenol (**2**) *in dry toluene or CH_2Cl_2 at room temperature with exclusion of air and moisture. After 30 to 60 min the reaction is complete, and the crude product should be used directly for best results, no further purification is required. MAD solutions and the dry solid are inflammable and must be handled in the absence of air and moisture.*

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