# Trimethylaluminum[1]

$Me_3Al$

*[75-24-1]* $C_3H_9Al$ (MW 72.10)
InChI = 1S/3CH3.Al/h3*1H3;
InChIKey = JLTRXTDYQLMHGR-UHFFFAOYSA-N

(Lewis acid with methylation ability;[2–11,31–40,46–53] can effect useful C–C bond forming reactions including conjugate addition,[41–45] cross-coupling reaction,[12–13,54] carboalumination,[14,55–56] methylenation,[15–16,57–60] and cyclopropanation;[17] can serve as a catalyst for C–C bond formation[61–64] other than methylation, rearrangement,[65–67] and precursor to various well-designed Lewis acids[27,68,69,72,73] or chiral catalysts[28,29,70,71])

*Physical Data:* mp 15 °C; bp 127 °C; *d* 0.743 g cm$^{-3}$ (30 °C).

*Solubility:* freely miscible with saturated and aromatic hydrocarbons; reacts violently with $H_2O$ and protic solvents, as well as $O_2$ and air.

*Form Supplied in:* clear colorless liquid; widely available as a neat liquid in a stainless container or 1–2 M solution in hydrocarbon solvents (hexane, heptane, toluene).

*Analysis of Reagent Purity:* brochures from manufacturers describe an apparatus and method for assay.

*Handling, Storage, and Precautions:* indefinitely stable under an inert atmosphere. Neat trimethylaluminum or concentrated solutions are highly pyrophoric. Solutions that are more dilute are not pyrophoric and are safer to handle. The nonpyrophoric limits are 11 wt % in hexane and 14 wt % in heptane. Halogenated hydrocarbons should be avoided because of possible explosive reactions sometimes observed for mixtures of $CCl_4$ and organoaluminums.

# Original Commentary

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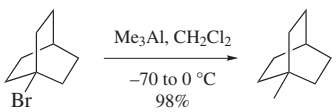
**Methylation.** The Lewis acidity of $Me_3Al$ has been used to activate electronegative atoms, such as oxygens, halogens, and other functional groups. It also methylates the resulting electrophilic species. Bridgehead methylation of bicyclo[2.2.2]octyl bromide (eq 1)[2a] and regioselective methylation of terpene derivatives[3a] are early examples that show these features. More recent examples include methylation of bromododecahedrane[2b] and unusual aromatic substitutions of *N*-hydroxyaniline derivatives (eq 2).[3b] Substitution reactions of glycosyl fluorides,[4] benzyl or glycal acetates,[5a,b] and sulfonyl groups[6] at activated positions can be effected with $Me_3Al$ (eqs 3–6).



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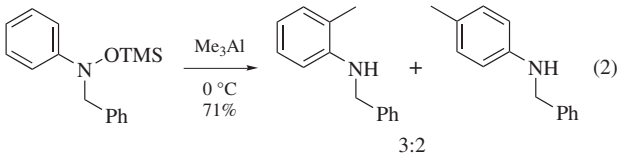

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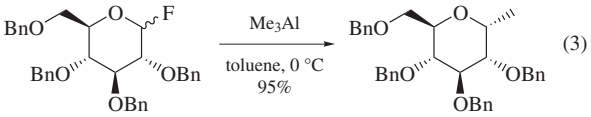

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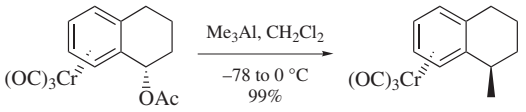

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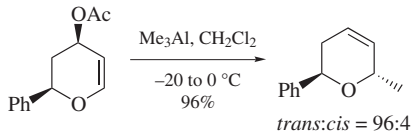
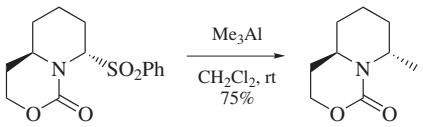
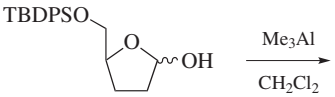


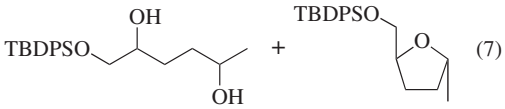
*trans*:*cis* = 96:4 (5)



(6)

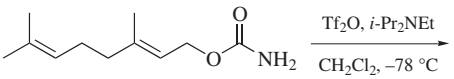
***Boron Trifluoride Etherate*** alters the reactivity of $\gamma$- or $\delta$-lactols toward $Me_3Al$ (eq 7).[7] $Me_3Al$ traps isocyanates generated from certain sigmatropic rearrangements (eq 8).[8]

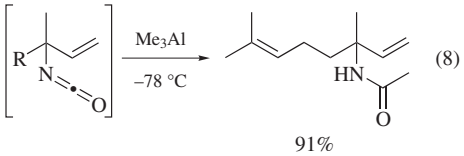



| | | |
|---|---|---|
| without $BF_3 \cdot OEt_2$ | 67% | 0% |
| with $BF_3 \cdot OEt_2$ | 0% | 75% |

*trans*:*cis* = 10:1 (7)

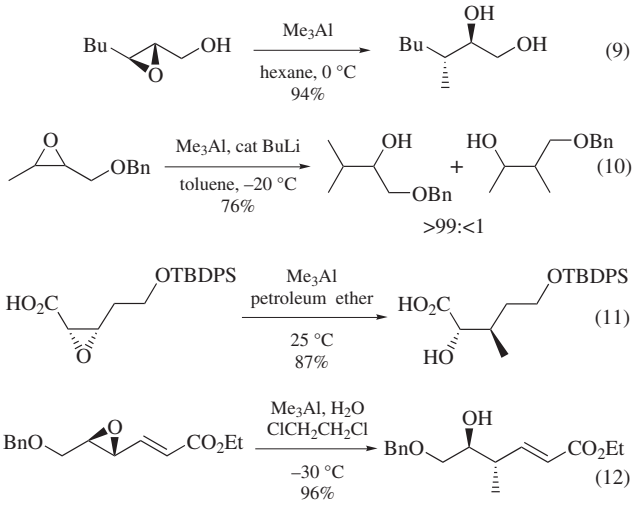


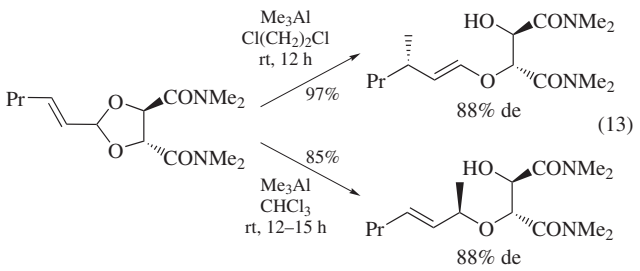
91% (8)

In connection with the asymmetric Sharpless epoxidation, the regioselective cleavage of 2,3-epoxy alcohols and their derivatives has been well studied. In contrast to organocuprates, which provide 1,3-diols via C-2 attack, trialkylaluminiums give 1,2-diols via C-3 attack (eq 9).[9a,b] It should be noted that substrates with a phenyl group at C-3 undergo the methylation largely in retentive manner.[9c,d] ***Butyllithium*** catalyzes the regioselective $\beta$-addition to $\alpha$- and $\beta$-alkoxy epoxides (eq 10).[10a,b] This regioselectivity also holds for epoxy acids (eq 11).[9d] A mixed reagent, $Me_3Al$ and

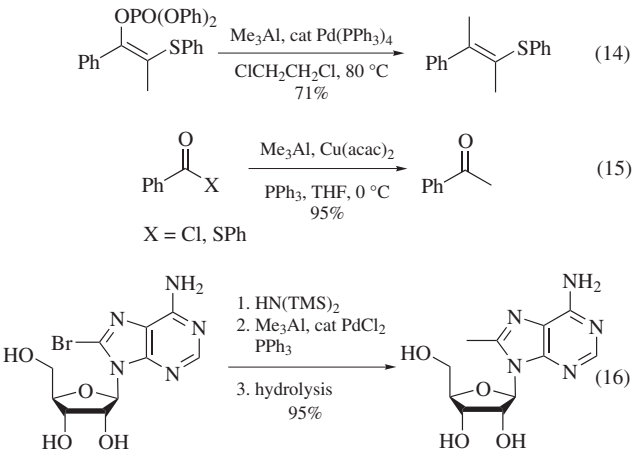
water (5:3), effects the regioselective and stereospecific methylation of $\gamma,\delta$-epoxy acrylates (eq 12).[10c,d]



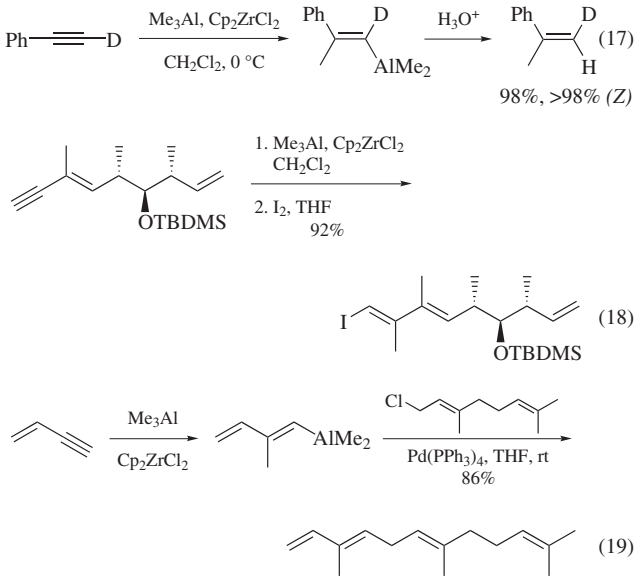

Asymmetric reactions via regioselective ring cleavage of chiral unsaturated acetals have been reported. The regioselectivity is sensitive to the solvent employed (eq 13).[11a,b] Recent developments have been described by Ishihara et al.[11c,d]



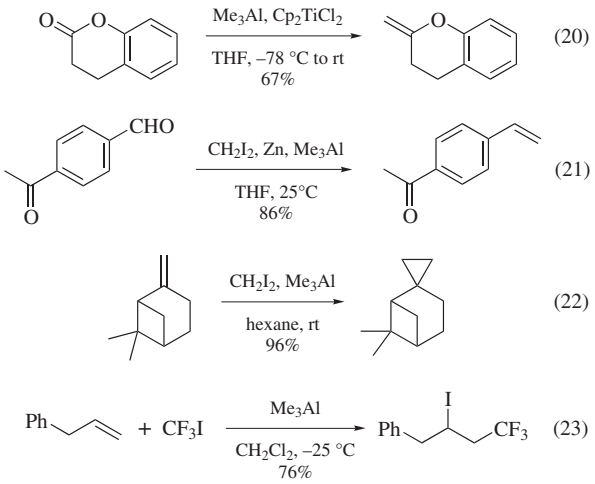

Cross couplings of organoaluminums with vinyl halides,[13b] enol phosphates,[12a] carboxylic acid chlorides, and thioesters[12b,c] are achieved by employing Pd or Cu catalysts (eqs 14 and 15). Unsaturated *N*-acylsulfoximines[13a] or *C*-alkylated purine nucleosides are thus prepared (eq 16).[13b]




Other useful C–C bond formations using $Me_3Al$ include the carboalumination of 1-alkynes. The procedure with ***Trimethylaluminum–Dichlorobis($\eta^5$-cyclopentadienyl)zirconium*** (eq 17) has broad applicability,[14a–c] and has been used in many natural product syntheses (eq 18).[14d] Direct manipulation of the alkenylalanes provides a stereoselective route to trisubstituted alkenes (eq 19).[14e,f]



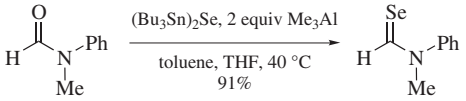

The Tebbe reagent (see ***μ-Chlorobis(cyclopentadienyl)(dimethylaluminum)-μ-methylenetitanium***) is conveniently generated in situ by the reaction of ***Dichlorobis(cyclopentadienyl)titanium*** and $Me_3Al$, which, in contrast to the Wittig reaction, methylenates ester carbonyls to provide enol ethers (eq 20).[15] See also ***Trimethylaluminum–Dichlorobis($\eta^5$-cyclopentadienyl)titanium***. A triad reagent, ***Diiodomethane–Zinc***–$Me_3Al$, effects chemoselective methylenation of aldehydes (eq 21),[16] while the combination of $CH_2I_2$ and $Me_3Al$ (or other organoaluminums) leads to cyclopropanation of alkenes (eq 22).[17] The regiochemical course of the latter reaction is markedly different from the Simmons–Smith reaction. Regioselective addition of polyhalomethanes to alkenes is induced by $Me_3Al$ (eq 23).[18]




Carbon–heteroatom bond formation is often facilitated by the co-addition of $Me_3Al$. Aminolysis of esters is achieved by the action of amines or their hydrochlorides in the presence of $Me_3Al$ (eq 24),[19a–c] the latter procedure being particularly useful when volatile amines are concerned (see ***Dimethylaluminum Amide***). The technique is also applicable to the synthesis of

acid hydrazides.[19d] Selenoformamides are available from the corresponding formamides by reaction with $(Me_2Al)_2Se$, generated in situ from $(Bu_3Sn)_2Se$ (eq 25).[20] The corresponding tellurium chemistry works also. $Me_3Al$–LiSPh offers a tandem Michael–aldol approach to the oxahydrindene subunit of avermectins (eq 26).[21a]

(24)



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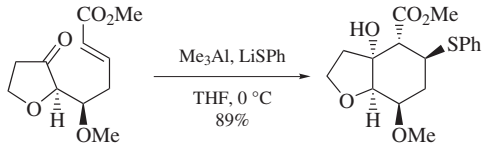
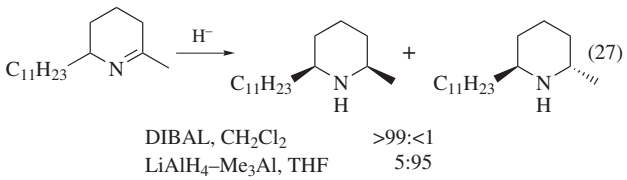


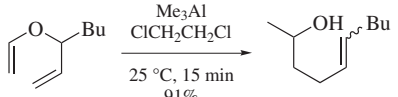
(26)

The steric course of reduction of cyclic imines is impressively reversed by a mixed reagent, ***Lithium Aluminum Hydride***–$Me_3Al$ (eq 27).[21b]



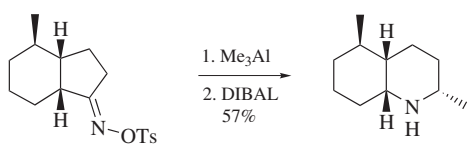
(27)

**Rearrangements.** Allyl vinyl ethers undergo [3,3]-sigmatropic rearrangements in the presence of $Me_3Al$, which also captures the resulting aldehyde (eq 28).[22] In contrast, use of ***Triisobutylaluminum*** results in a primary alcohol.



(28)

$Me_3Al$ effects sequential Beckmann rearrangement–methylation of oxime sulfonates. The rearranged imines can be stereoselectively reduced with ***Diisobutylaluminum Hydride*** to give amines (eq 29, cf. eq 27).[23a–c] Related alkylative ring enlargement[24] or alkylative Beckmann fragmentation[23d] reactions are also known (eqs 30 and 31).



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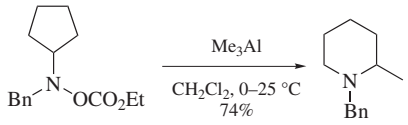

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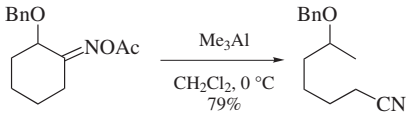
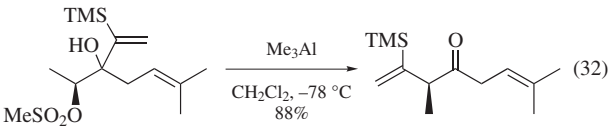


(31)

$\beta$-Hydroxy methanesulfonates or *N*-nitrosulfoximines have been activated by $Me_3Al$ to induce asymmetric pinacol-type rearrangement (eq 32)[25] or carbocyclization reactions (eq 33).[26]



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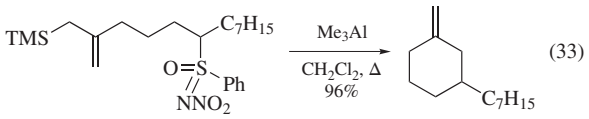
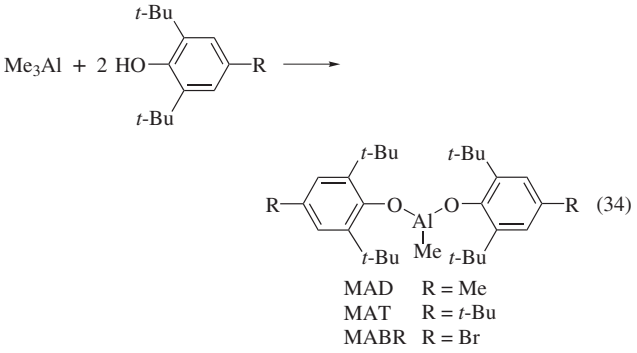


(33)

**Lewis Acid.** $Me_3Al$ serves as the precursor to various sophisticated Lewis acids with different acidities, such as $MeAl(OTf)_2$[26] and $MeAl(OC_6F_5)_2$,[11c,d] or other acids with unique spatial environments (eq 34).[27] Chiral Lewis acids, such as **1**[28] and **2**,[29] serve as catalyst for asymmetric Diels–Alder reactions. The catalyst generated from **3** and $Me_3Al$ has been used for asymmetric cyanohydrin synthesis.[30]



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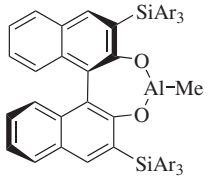

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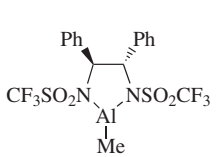

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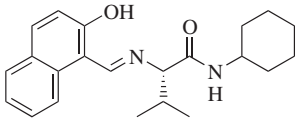

**(3)**

# First Update

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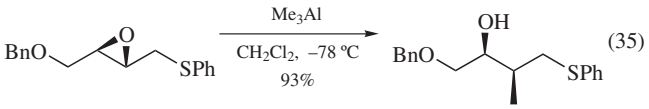
**Methylation of Epoxides.** The regioselective cleavage of 2,3-epoxy alcohols and their derivatives has been well studied. In contrast to organocuprates that provide 1,3-diols via C-2 attack, trialkylaluminums give 1,2-diols via C-3 attack.[9a,b] Upon exposure to $Me_3Al$ in the presence of a small amount of BuLi, 1-benzyloxy-2,3-epoxides undergo regioselective methylation at the C-3 distal from the benzyloxy group to give the 1-benzyloxy-3-methylalkan-2-ol.[10a,b] Similar trends are also observed in the regioselective and stereospecific substitution reaction of 1-(phenylthio)-2,3-epoxyalkanes (eq 35)[31] and epoxy selenides (eq 36).[32] Methylation occurs at the C-2 position with a high degree of stereoselectivity using BuLi and $Me_3Al$, albeit with exactly reversed regioselectivity to that obtained in the substitution reactions with $Me_3Al$ alone (eq 37).[33] Exclusive methylative cleavage at the oxirane ring of 1,5-dioxaspiro[3.2]hexanes proceeds regioselectively at the quaternary carbon (eq 38).[34] Methylation of nucleoside 1′,2′-epoxides furnishes the ribonucleosides branched at the anomeric position (eq 39).[35] Enantioselective conjugate addition of $Me_3Al$ to cyclic vinyl epoxides is achieved by using $Cu^I$ salts, such as copper thiophenecarboxylate (CuTC), and chiral phosphorus-based ligands (eq 40).[36]

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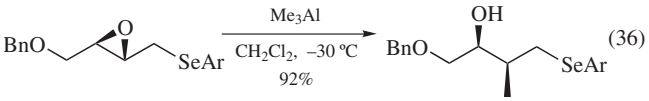


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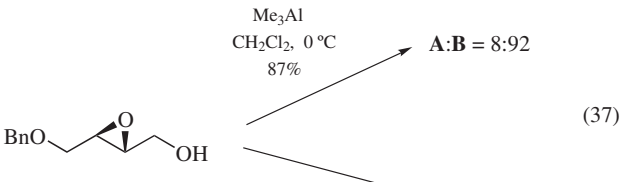


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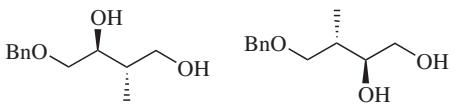


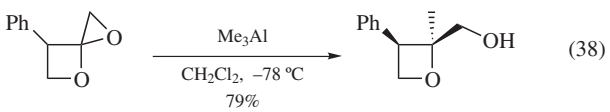


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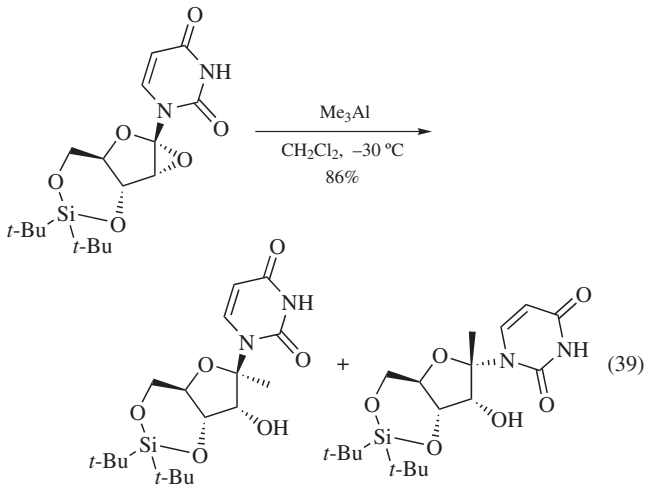


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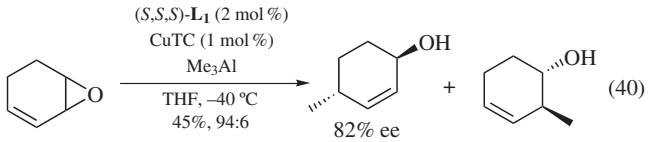


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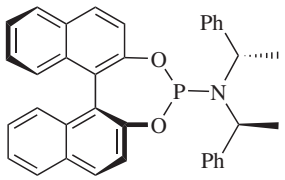
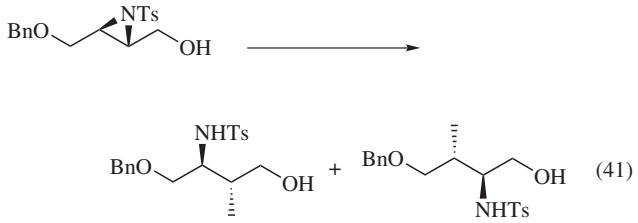



**Methylation of Aziridines.** Analogous to 2,3-epoxy alcohols, the ring-opening methylation proceeds with 1-hydroxy-2,3-aziridines under reflux conditions in toluene to give the $\gamma$-amino alcohol in fair to good yields (eq 41).[37]

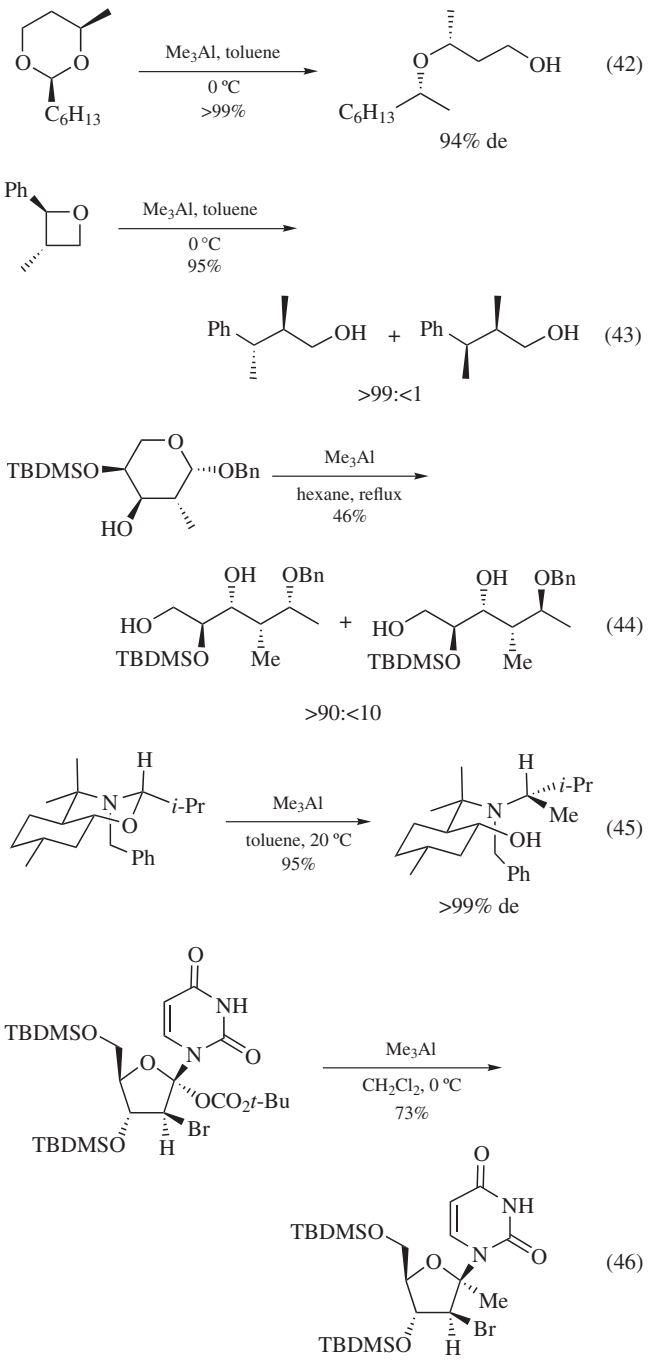



(41)

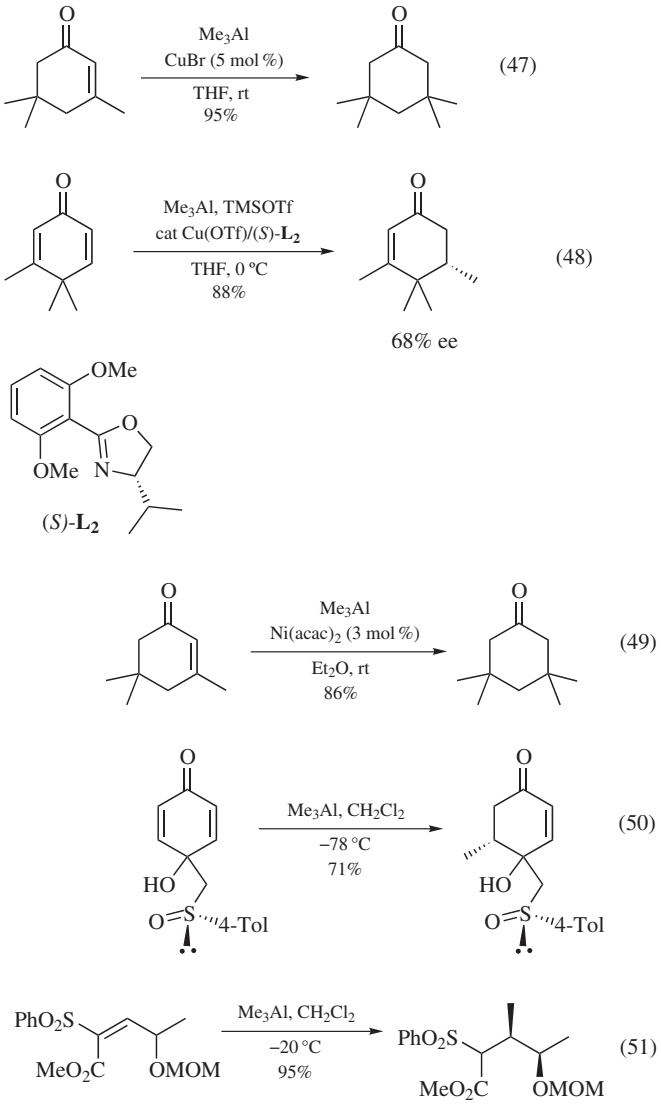
| | |
|---|---|
| $Me_3Al$, toluene, 75 °C | 80% (<1:>99) |
| $Me_2CuLi$, $Et_2O$, –20 °C | 71% (>99:<1) |

**Methylation of other Cyclic Ethereal Carbons.** Asymmetric reactions via regioselective ring cleavage of chiral unsaturated acetals and ketals have been reported.[11a,b] The regioselectivity is sensitive to the solvent used. More recent examples include addition of $Me_3Al$ to acetals derived from simpler chiral diols (eq 42),[11c,d] leading to a moderate to high diastereoselectivity. Alkylative cleavage of oxetanes accompanies strictly retentive stereochemistry (eq 43).[11e] Stereoselective methylation proceeds at the anomeric carbon to afford the ring opening of six-membered sugar derivatives (eq 44).[38] Enantioselective methylative ring opening

of 1,3-perhydrobenzoxazines gives chiral primary amines in an optically pure form (eq 45).[39] Substitution of the carbonate by a methyl group is successful without ring opening of furanosyl uracils (eq 46).[40]

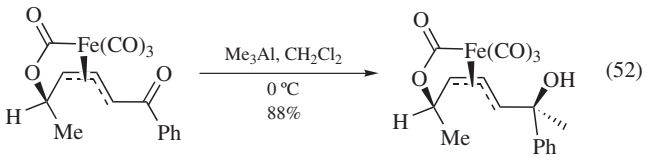



**Conjugate Addition to α,β-Unsaturated Carbonyl Compounds.** β-Disubstituted-α,β-unsaturated ketones undergo effective 1,4-addition of $Me_3Al$ in the presence of catalytic amounts of CuBr (eq 47).[41] A chiral $Cu^{I}$ catalyst, consisting of Cu(OTf) and the chiral ligand, was also tested in similar conjugate addition reactions of organoaluminums, but the ee and yield are uniformly moderate (eq 48).[42] A $Ni^{II}$ catalyst enables the conjugate addition of $Me_3Al$ to give a quaternary carbon center in high yield (eq 49).[43] Diastereoselective conjugate addition of $Me_3Al$ to chiral enones, such as [(4-tolylsufinyl)methyl]quinols, occurs to give the methylated chiral ketone in good yield (eq 50).[44] The two different electron-withdrawing groups, which doubly activate the substrate, accommodate conjugate addition of $Me_3Al$ under mild conditions (eq 51).[45] The diastereoselectivity and the chemical yield of this reaction are both high, giving the methylation product in 95% yield with *syn*-stereochemistry.




**Carbonyl Methylation.** Virtually complete 1,5-stereocontrol has been achieved in the nucleophilic addition of $Me_3Al$ to the ketone moiety distal from the π-allyltricarbonyliron lactone complex (eq 52).[46] In contrast, reaction with triisopropylaluminum or triethylaluminum yields significant amounts of the reduction product. In the methylation event of 3-phenylpropanoyl chloride, the addition order of $Me_3Al$ and $AlCl_3$ is critical (eq 53).[47] The addition of $Me_3Al$ is to be carried out prior to treatment with $AlCl_3$, otherwise intramolecular Friedel-Crafts alkylation predominates. The ketones are also readily accessible from carboxylic acid esters upon treatment with $Me_3Al$ in the presence of *N*,*N*′-dimethylethylenediamine (eq 54).[48] Methylation of carbamates gives rise to the corresponding amides (eq 55).[49] Chiral

$\beta$-trichloromethyl-$\beta$-propiolactone undergoes regioselective ring opening by $Me_3Al$ to give double alkylation (eq 56).[50]

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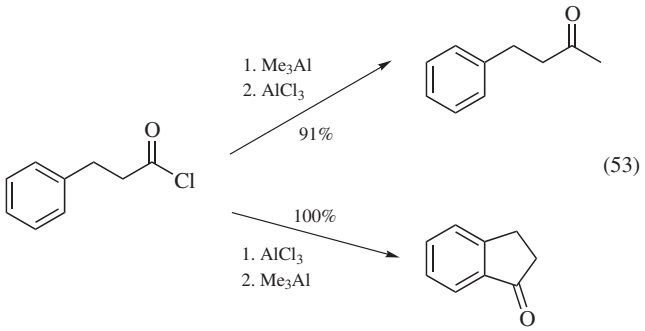


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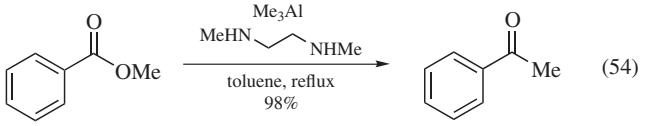


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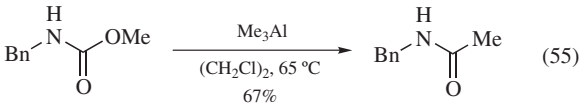


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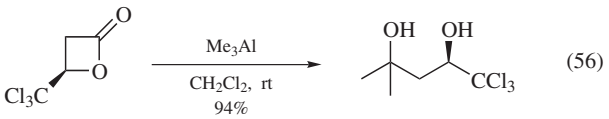
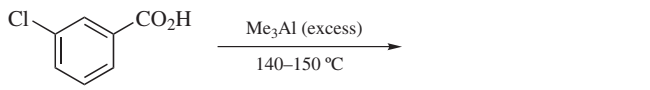
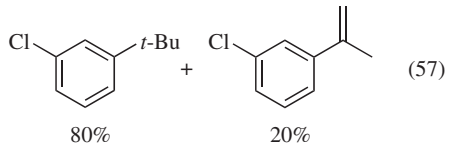



(56)

**Multiple Methylation.** Reaction of aromatic carboxylic acids with $Me_3Al$ at a high temperature (140–150 °C) gives triply methylated products (eq 57).[51] The alkylating ability of $Me_3Al$ is dramatically enhanced by trimethylsilyl trifluoromethanesulfonate (TMSOTf) (eq 58).[52] This characteristic feature was applied to the double-methylation of aromatic ketones, which provides a convenient synthetic route to arotinoid analogs.

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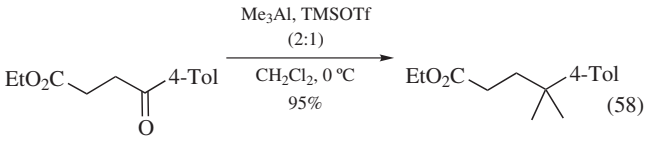
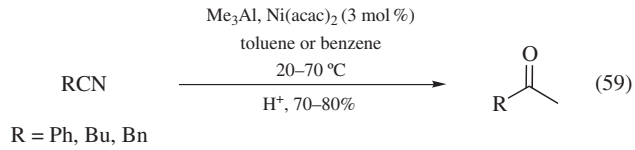


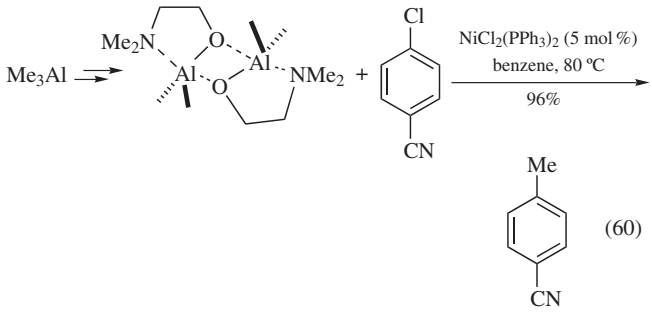

(58)

**Nitrile Methylation.** In the presence of 3 mol % of bis(acetylacetonato)nickel$^{II}$, methylation of various nitrile species proceeds in hydrocarbon solvents at nearly ambient temperature to give, upon hydrolysis, the acyl compounds in moderate to good yield (eq 59).[53]



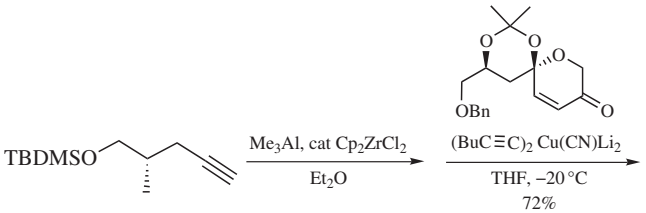

(59)

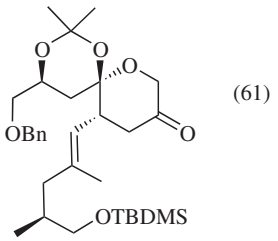
**Cross-coupling Methylation with the Aid of a Transition Metal.** Cross-coupling reactions between $Me_3Al$ and vinyl halides,[13b] enol phosphates,[12a] carboxylic acid chloride, or thioesters [12b,c] are achieved in the presence of catalytic amounts of $Pd^0$ or $Cu^{II}$ species. The dimethylaluminum species derived from $Me_3Al$, which are intramolecularly stabilized by the amine embedded into the ligand tether, have recently been introduced as a relatively stable methyl source for the cross coupling with aryl bromides and chlorides (eq 60).[54]




(60)

**Methylalumination of Alkynes and Alkenes.** Other useful carbon-carbon bond forming reactions include methylalumination of unsaturated carbon chains such as terminal alkynes or alkenes. The procedure involves the use of catalytic dichlorobis($\eta^5$-cyclopentadienyl)zirconium and $Me_3Al$ (cat. $Cp_2ZrCl_2$– $Me_3Al$) and has proved to possess broad applicability.[14a–c] The usefulness of this method has been demonstrated by the total synthesis of many natural products.[14d] In fact, alkenylaluminum species, generated by methylalumination of alkynes, serve as versatile synthetic intermediates, which undergo direct cross-coupling reactions with the aid of a transition metal catalyst to provide stereoselective formation of the trisubstituted alkenes (eqs 61–63).[14e,f 55] Asymmetric methylalumination of styrene and other terminal alkenes by a novel chiral zirconium reagent has also been reported (eq 64).[56]

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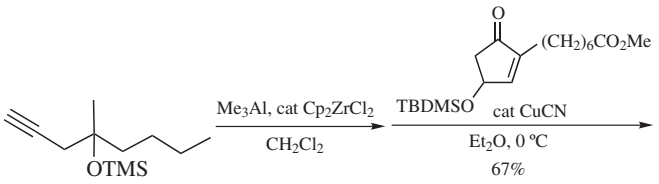
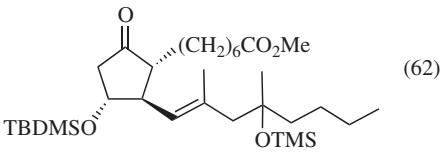
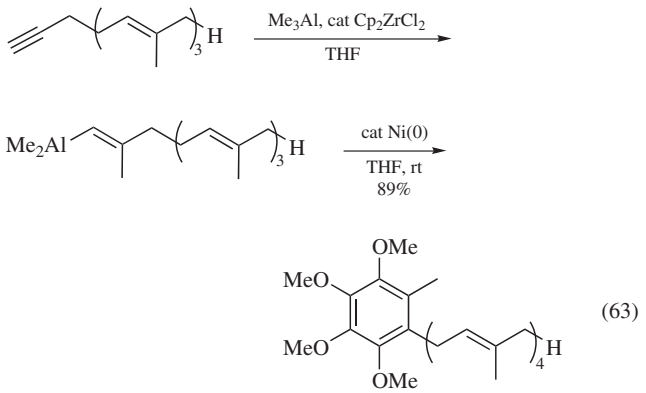



(62)

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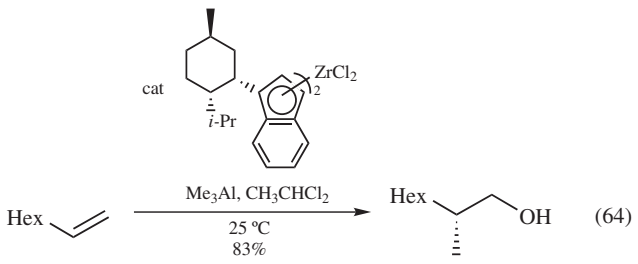
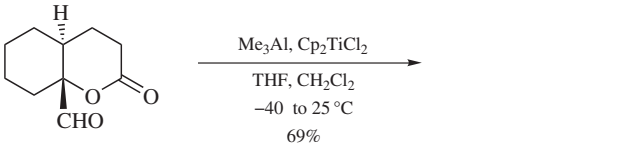


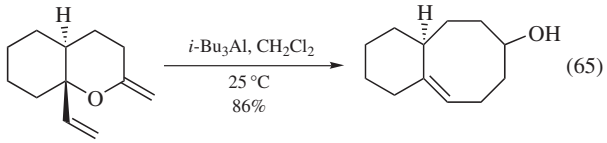

(64)

81% ee

**Methylenations.**

***Formation and Reaction of Tebbe Reagent.*** The Tebbe reagent (see $\mu$-chlorobis(cyclopentadienyl)(dimethylaluminum)-$\mu$-methylenetitanium) is a typical methylenation agent for both ketones and esters. Thus this reagent is conveniently generated in situ by the reaction of dichlorobis(cyclopentadienyl)titanium and $Me_3Al$, which, unlike the Wittig olefination, affords methylenation of ester carbonyls to provide vinyl ethers.[15] Double methylenation of the formyl $\delta$-lactone by the Tebbe reagent, followed by subsequent Claisen rearrangement in the presence of *i*-$Bu_3Al$, affords ring enlargement to give the cyclooctene framework (eq 65).[57] $(Cp_2)Ti=CH_2$ (+ $Me_2AlCl$) is in equilibrium with the Tebbe reagent. Therefore, in some cases, intramolecular metathesis follows the methylenation if a neighboring alkene exists (eq 66).[58] The Tebbe reagent also reacts with alkynes to give titanacyclobutene intermediates, which subsequently undergo alkenylation of carbonyl compounds to give the corresponding dienes (eq **67**).[59]

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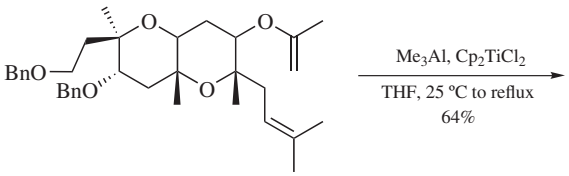


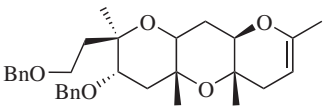


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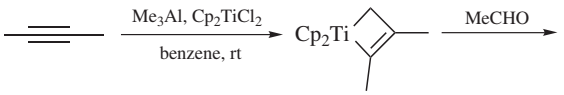
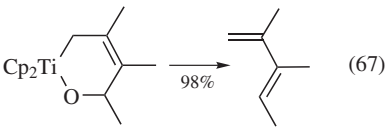
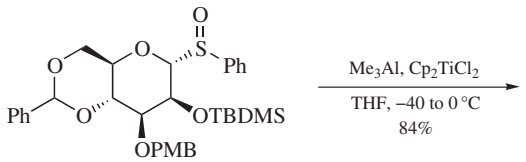
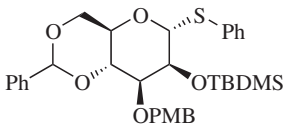



(67)

The Tebbe reagent not only deoxygenates sulfoxides and selenoxides, but also deoxygenatively methylates pyridine *N*-oxides (eqs 68–70).[60]

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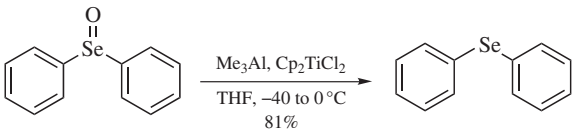


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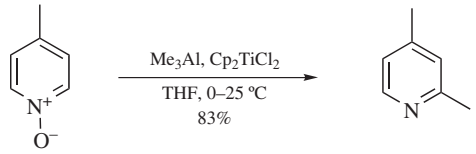
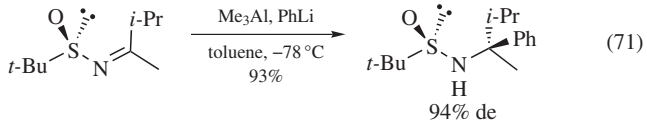



(70)

**Alkylations (Other than Methylation) Promoted by $Me_3Al$.**

***Alkylation of Imines.*** Results from Ellman's group demonstrated highly diastereoselective alkylation of *N-tert*-butylsulfinyl ketimines by alkyllithiums in the presence of $Me_3Al$ (eq 71).[61] The effect of $Me_3Al$ on the diastereoselective addition of an allylsamarium reagent to imines bearing a $\beta$-hydroxy group is notable and significantly increases both reactivity and stereoselectivity (eq 72).[62]

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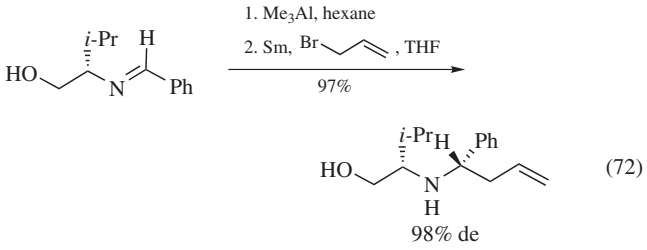
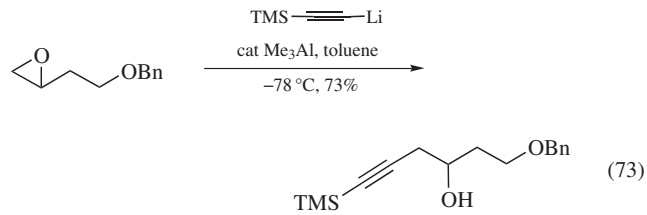


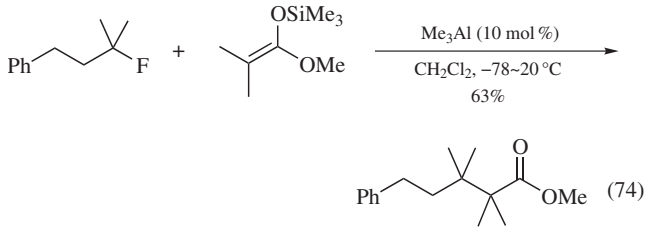

(72)

***Alkylation of Epoxides.*** When stoichiometric amounts of alkynyllithium reagents along with 10 mol % of $Me_3Al$ are employed in the alkynylation reaction of benzyloxy epoxides, a dramatic increase in chemical yield from those attained without $Me_3Al$ is observed (eq 73).[63] The relative mobility of the organic groups from an aluminum center is roughly of the order: alkynyl > alkenyl > alkyl. Alkynylation prevails over methylation of epoxides by taking advantage of this trend in mobility.




(73)

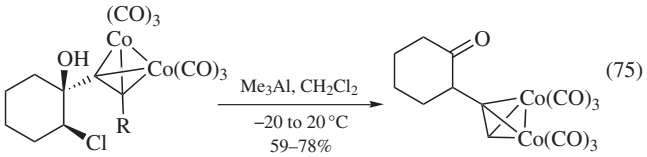
***Alkylation of Tertiary Alkyl Fluorides.*** Catalytic amounts of $Me_3Al$ effectively catalyze the substitution reaction of fluorides of tertiary alkanes by silyl vinyl ethers or by azide salts (eq 74).[64]




(74)

**Rearrangements.**

***Pinacol-type Rearrangement.*** An alkenyl moiety migrates in preference to an alkynyl moiety during competitive rearrangements when both are embedded onto the same carbon. $Co_2(CO)_6$ is used as a convenient masking agent for alkynyl groups to reinforce the migration ability of the parent alkynyl group. Taking into account the strong preference of Co–alkyne complexes for neighboring-group participation toward their adjacent carbocations, the Co–alkyne group migrates preferentially over an aryl or alkenyl group. In fact, the skeletal rearrangement of the alkyne–$Co_2(CO)_6$ group of 2-chloro-1-alkynylcyclohexan-1-ol derivatives is promoted by $Me_3Al$, giving the protected $\alpha$-alkynyl ketone in reasonable yield (eq 75).[65] Further studies indicate that the Me-group of $Me_3Al$ is capable of capturing an oxonium intermediate, generated by the rearrangement of the alkyne–$Co_2(CO)_6$ group from the parent acetal (eq 76).[66]

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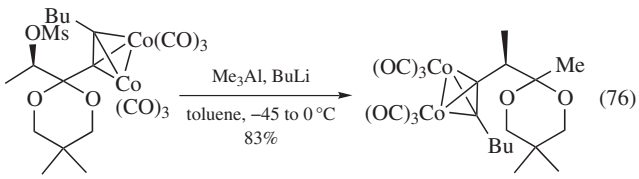
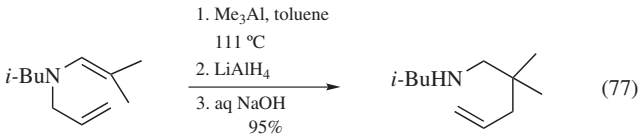



(76)

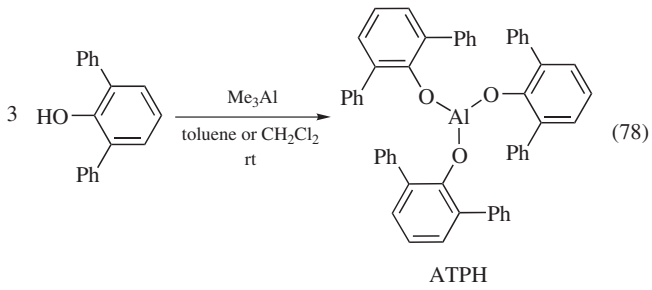
***Aza-Cope Rearrangement.*** Allyl vinyl ethers undergo [3,3] sigmatropic rearrangements in the presence of $Me_3Al$, followed by subsequent methylation of the resulting aldehydes.[22] 3 Aza-cope rearrangement of allyl vinyl amines is also achieved using $Me_3Al$ as a Lewis acidic promoter at a temperature of 80–111 °C (eq 77).[67] Unlike the Claisen rearrangement, methyl group transfer from the aluminum center to the resulting imine does not occur. To avoid hydrolysis during workup, products are isolated as the corresponding amines after treatment with lithium aluminum hydride (LAH).




(77)

**Synthesis of Well-designed Aluminum Reagents.** Several well-designed aluminum reagents, modified from $Me_3Al$, provide unique steric environments around the active metal center, achieving new reactivity and selectivity in organic synthesis. They are readily accessible simply by mixing $Me_3Al$ with the corresponding ligand(s). Each ligand possesses one to three protons that smoothly react with $Me_3Al$, thereby liberating 1–3 equiv of methane gas, respectively. For example, methylaluminum bis(2,6-di *tert* butyl 4-methylphenoxide) (MAD)[27] and aluminum tris(2,6-diphenylphenoxide) (ATPH)[68] are

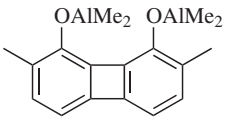
easily prepared by treatment of 2 or 3 equiv of the corresponding phenol with 1 equiv of $Me_3Al$ (eq 78).




(78)

ATPH

These aluminum reagents, including the bidentate Lewis acid **4**[69] show wide applicability in various carbon–carbon bond-forming reactions as well as skeletal rearrangements, including hetero-Diels–Alder reactions, 1,4 and 1,6-additions, vinylogous aldol reactions, enone fragmentations, and Claisen rearrangements.[68] Chiral Lewis acids, such as **5**[70] and **6**,[71] serve as homogeneous catalysts for asymmetric syntheses. Compound **7**[72] is the catalyst precursor for the polymerization of ethylene. Dimethylaluminum bis(trifluoromethanesulfonyl)imide ($Me_2AlNTf_2$)[73] and many other methylaluminum reagents are also prepared from $Me_3Al$.

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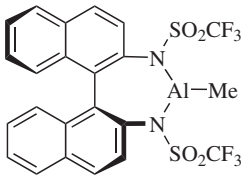


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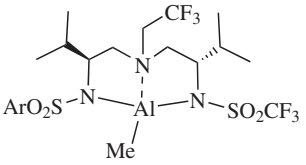


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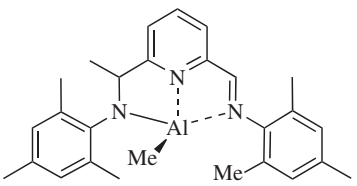


**7**

# Second Update

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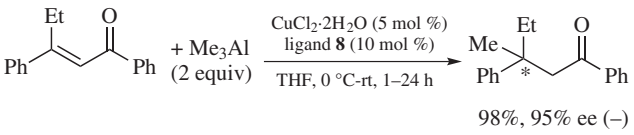
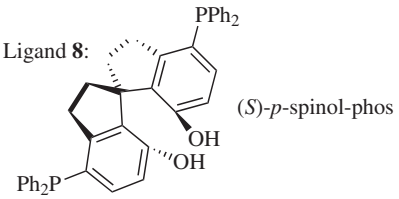
*BASF SE, Ludwigshafen, Germany*

### $Me_3Al$ as Alkylating Agent.

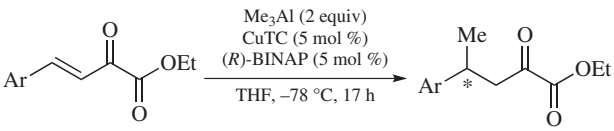
***Methylation via Conjugate Addition.*** The (enantioselective) conjugate alkylation of cyclic enones has already been described in the previous update. The scope of this transformation has been extended to additional acyclic substrates. For instance, $\beta$-substituted acyclic enones can be treated with $Me_3Al$ either in the presence of simple phosphoramidite ligands to provide enolates,[74] which can be trapped,[75] or in the presence of binol ligands[76] to provide good yields and good ee of the desired adducts (eq 79).[77] This transformation was successfully extended to various types of acyclic enones — to $\alpha$-keto esters and $\alpha$-keto amides in the presence of BINAP ligand and CuTC (copper(I) thiophene-2-carboxylate)[78] as source of copper(I) (eqs 80 and 81).[79,80] The transformation can be successfully performed with acyclic nitro olefins (eq 82)[81] and *N*-formylimines (eq 83).[82]




98%, 95% ee (–)



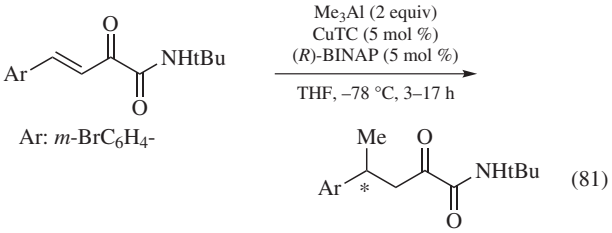

(79)




Ar: *m*-$BrC_6H_4$-

85%, 99.5% ee

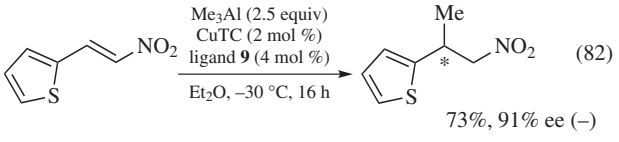
(80)




Ar: *m*-$BrC_6H_4$-

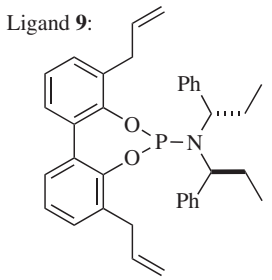
(81)

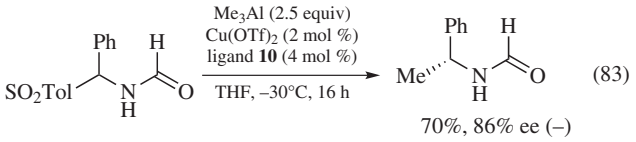
89%, 98% ee




(82)

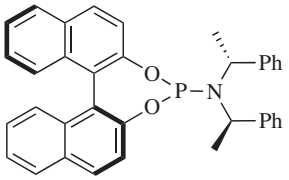
Ligand **9**:



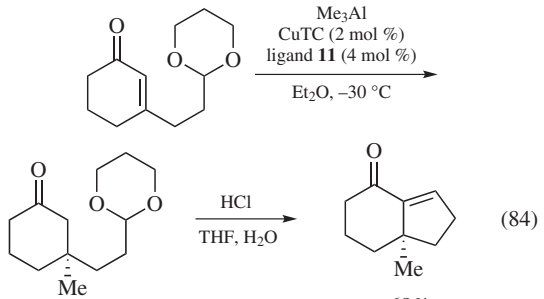




(83)

Ligand **10**:

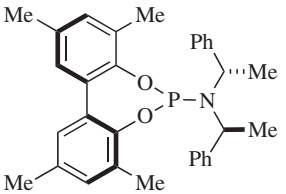


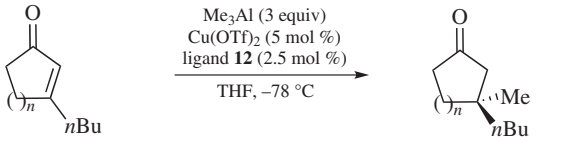

The scope of the enantioselective conjugate methylation on hindered cyclic enones was further explored. The type of functionality at the $\beta$-position was varied (eq 84),[83] the use of new enantiopure ligands was tested (eq 85),[84] and the efficiency with difficult substrates such as $\alpha$-halo enones was improved (eq 86).[85] The enantioselective conjugate methylation of cyclic enones without functionalization at the $\beta$-position can be combined with electrophilic trapping at the $\alpha$-position. Not only aldehydes (eq 87),[86] but also $\alpha$-aminoethers (as alternatives to the Eschenmoser salt) (eq 88)[87] and $\alpha,\beta$-conjugated systems such as nitro olefins or vinyl sulfones can be used as suitable electrophiles to provide the desired products with good enantioselectivity, good diastereoselectivity and in high yield.[88] Enantioselective conjugate addition was extended to other cyclic substrates such as $\alpha,\beta$-unsaturated imines[89] and $\alpha,\beta$-unsaturated lactams.[90]




(84)

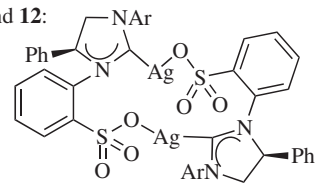
Ligand **11**:



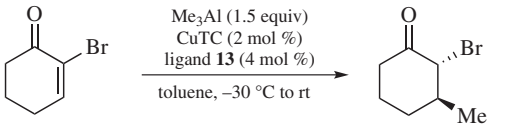




*n*=1 15 h 80%, 88% ee
*n*=3 12 h 90%, 85% ee

Ligand **12**:

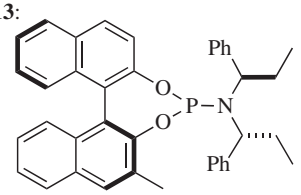



(85)

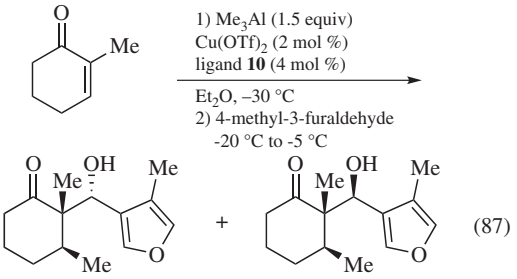



*trans*:*cis* 75:25
94% ee

Ligand **13**:

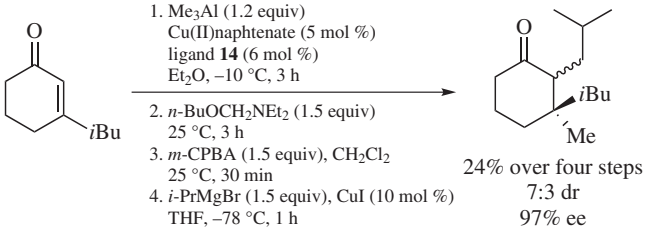



(86)



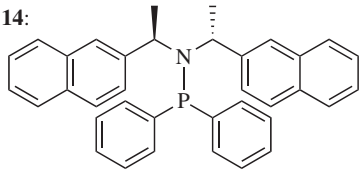

(87)

50–65%
5–7:1 (*syn*:*anti*)



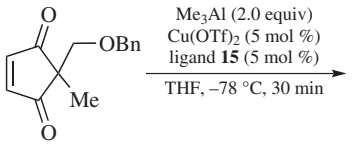

24% over four steps
7:3 dr
97% ee

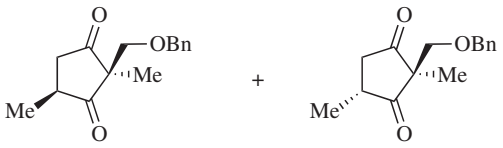
Ligand **14**:




(88)

Finally, it must be noted that this strategy can be used for the desymmetrization of cyclopentendiones (eq 89).[91]

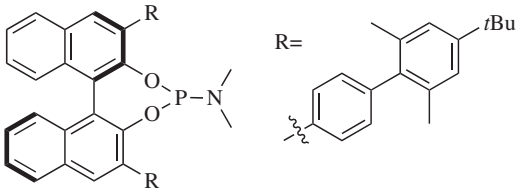


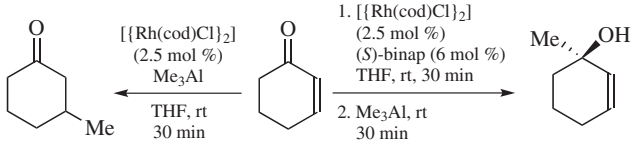
(2*R*,4*S*) (2*R*,4*R*) (89)

97%, >95:5 ((2*R*,4*S*) vs. (2*R*,4*R*))
97% ee (2*R*,4*S*)

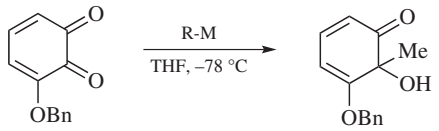
Ligand **15**:




***Methylation via Addition to Carbonyls.*** As mentioned in the previous update, $Me_3Al$ can react with carbonyl moieties (e.g., esters and acyl halides) to provide the corresponding ketones. Without copper catalyst, the 1,2-addition takes place smoothly with saturated ketones[92] and with high regioselectivity with $\alpha,\beta$-unsaturated ketones.[93] The regioselectivity of the 1,2-addition with $\alpha,\beta$-unsaturated ketones can be tuned in the presence of the enantiopure catalyst (eq 90).[94] Methylation with $Me_3Al$ can not only be diastereoselective and enantioselective but also chemoselective when the environment of the ketone permits it (eq 91).[95] Aldehydes are also suitable substrates for enantioselective 1,2-addition (eq 92).[96] The difference in reactivity between aldehydes and ketones makes chemoselective 1,2-addition to the keto moiety problematic. However, aldehydes can be masked in situ with "$Me_2AlN(OMe)Me{\cdot}LiCl$" prior to the addition of the nucleophile, thus leading to 1,2-addition on the ketone, leaving the aldehyde untouched after aqueous workup (eq 93).[97]

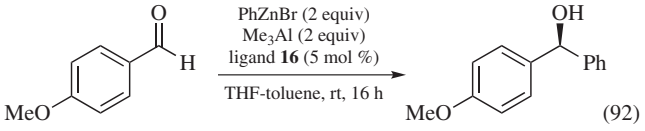



59% 84%, 96% ee (90)



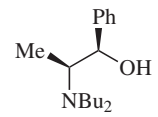

(91)

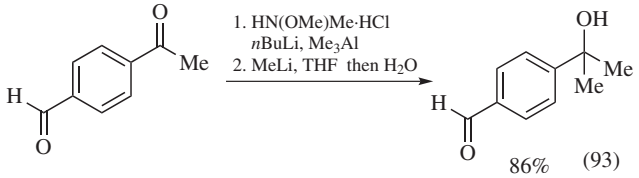
R-M = $Me_3Al$ 45%
R-M = MeMgCl 60%




70%, 86% ee (*S*) (92)

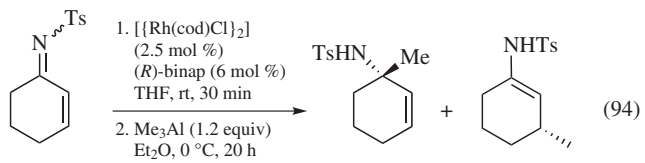
Ligand **16**:





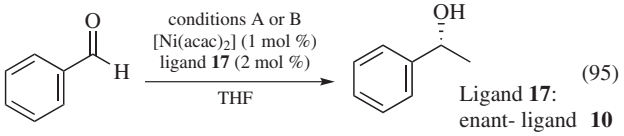

86% (93)

In a similar way, 1,2-additions can be performed with imines (eq 94)[98] and nitrones.[99]




(62:38 *E*/*Z*) 75%, 8:1 (1,2 vs. 1,4)
99% ee (94)

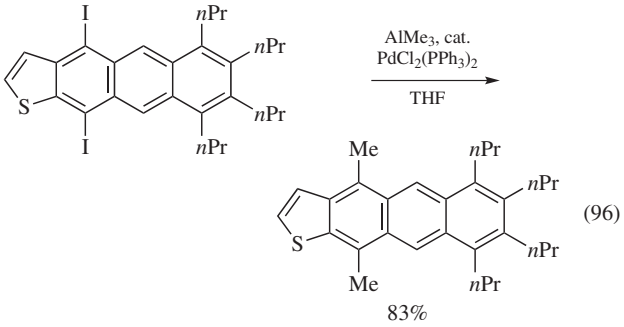
**DABCO·2$Me_3Al$, a Stable and Storable Alkylating Agent.** $Me_3Al$ is a highly pyrophoric organometallic, which can be treated with DABCO to provide a stable organometallic. DABCO·2$Me_3Al$ (also named DABAL) is suited for enantioselective 1,2-addition to aldehydes (eq 95)[100] and can react smoothly in cross-couplings.[101]




Ligand **17**:
enant- ligand **10** (95)

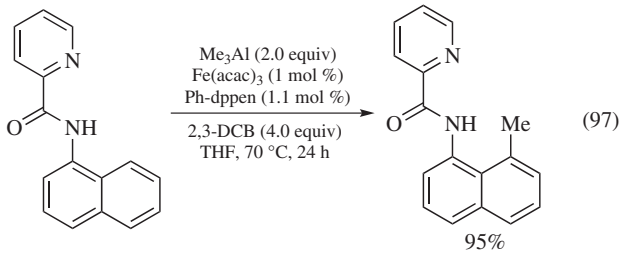
conditions A: DABAL (1.3 equiv), 5 °C, 1 h — 92%, 91% ee (*R*)
conditions B: $Me_3Al$ (2.0 equiv), –20 °C, 3 h — 60%, 85% ee (*R*)

**Methylation via Cross-coupling with Heavy Metals.** As described in the previous update, $Me_3Al$ is a suitable coupling partner for $Csp^3$–$Csp^2$ cross-coupling. The cross-coupling with vinyl phosphates was previously reported, but recently further explored.[102] In parallel, the cross-coupling with Al-based reagents (synthesized via transmetalation with $Me_3Al$) was extended to various $Csp^2$ electrophiles: iodoaryl (eq 96),[103] aryltosylates,[104] vinyl/arylbromides,[105] and aryl chlorides.[106]

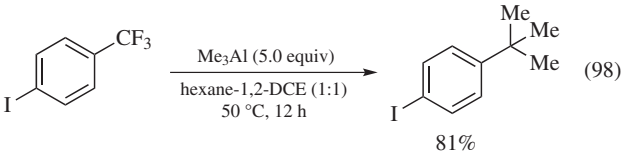


(96)

**Csp²-H and Csp³-H/F Methylation.** C–H methylations are attractive transformations, which, in comparison to cross-coupling, do not lead to significant by products and thus are more environmentally friendly. Examples of such transformations, especially using Al-based organometallics, are scarce. Nakamura and coworkers recently reported that $Me_3Al$ and its air stable version DABAL can achieve methylation of $Csp^2$-H (or $Csp^3$-H) bonds using Fe(III) catalysis and an amide as directing/activating group (eq 97).[107] Similarly, Kambe and coworkers reported the $Csp^3$-F methylation of benzotrifluorides using $Me_3Al$ as methylating agent (eq 98).[108] This last transformation is notable, given the strength of the C–F bond.

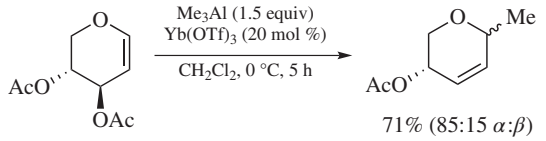


(97)

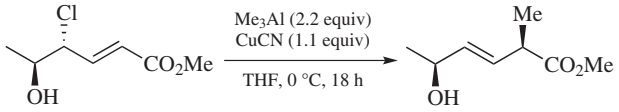


(98)

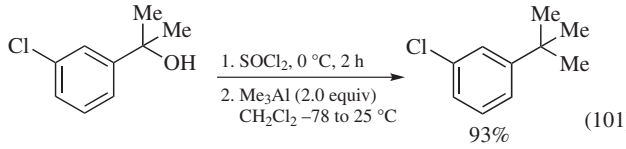
**Methylation via Allylic Displacement.** The previous update described the use of $Me_3Al$ as an efficient nucleophile for stereoselective allylic substitution (i.e., for glycal acetates), but this reaction sometimes leads to poor yields in the presence of acidic catalysts. Use of lanthanide triflates improves the yield of the methylation at the anomeric position (eq 99).[109] This transformation was extended to $\delta$-chloro vinyl esters, which undergo regioselective and stereoselective $S_N2'$ methylation (eq 100).[110] Benzyl alcohols are also methylated via in situ chlorination (eq 101).[111] Allyl phosphates also undergo enantioselective $S_N2'$ methylation using ligand **18** (eq 102).[112] Stereodefined epoxy vinylsulfones are privileged substrates for regioselective and stereoselective methylation with $Me_3Al$ in the presence of Cu catalyst (eq 103),[113] while the presence of directing groups (i.e., OH groups) can invert the regioselectivity of the reaction, thereby securing complementary stereoselectivity (eq 104).[114]



(99)



(100)



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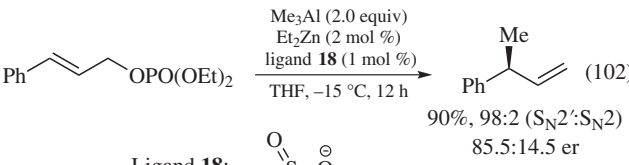

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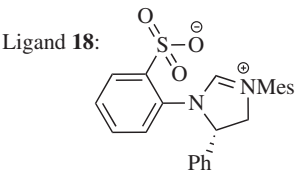
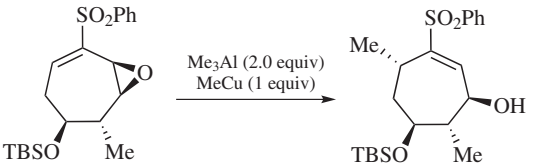
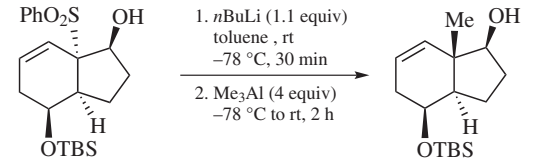


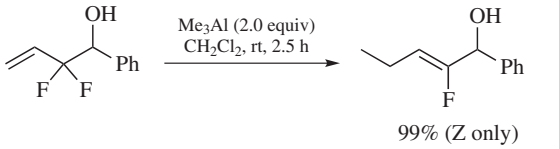



(103)



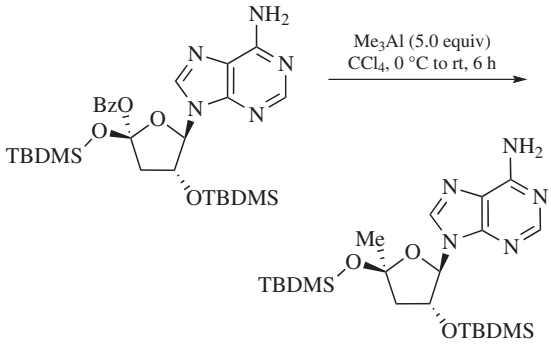
(104)

$Me_3Al$ can also perform $S_N2'$ methylation with difluorohomoallyl alcohols to provide the corresponding (*Z*)-fluoro-olefins in excellent yield (eq 105).[115]



(105)

**Substitution/Methylation at Other Activated (Nonallylic) Positions.** Other activated positions can undergo stereoselective and regioselective methylation with $Me_3Al$. For instance, the $Me_3Al$ based methylation can occur at the anomeric position using pivalates/benzoates (eq 106)[106] or methoxy groups (eq 107) as leaving groups.[117] Interestingly, such displacement can take place (presumably via the acylimine) with larger alkoxy leaving groups (i.e., –OTBMS) with formal retention of stereochemistry (eq 108).[118]

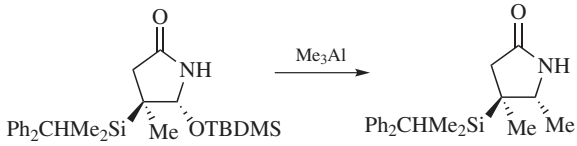



(106)

99% conversion, 98% de


(107)

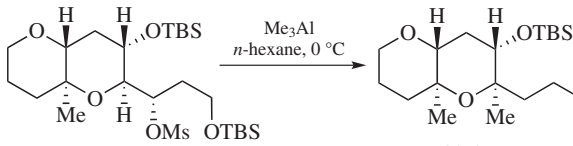
99%




(108)

75%

Pyrans are found in many natural products, especially marine polycyclic ethers. Some pyrans bear a methyl at the C2 position, which is difficult to stereoselectively install using traditional methods. It was recently demonstrated that $Me_3Al$ can provide access to such products with furans/pyrans bearing a 1′-mesyloxy group via trapping of the oxonium ion produced by a hydride rearrangement (eq 109).[119]

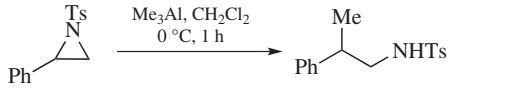



(109)

82%

**Methylation via Epoxide/Aziridine Opening.** The regioselective and stereoselective opening of epoxides with concomitant methylation with $Me_3Al$ is a well-known transformation (especially for 2,3-epoxy alcohols or epoxy acids via C3 attack, for $\gamma,\delta$-epoxy acrylates via C5 attack, or for activated epoxides bearing neighboring vinyl/aryl groups), as previously described (eqs 9–12 and eqs 35–40). Regioselective and diastereoselective epoxide opening of $\gamma,\delta$-epoxy acrylates with $Me_3Al/H_2O$ was recently featured for the synthesis of streptolic acid and tirandalydigin,[120] the formal synthesis of leucascandrolide A[121] and the synthesis of the C15–C27 segment of venturicidins.[122] Similarly, the stereoselective epoxide opening of activated epoxides bearing alkenyl groups (total syntheses of amphidinolides C and F),[123] alkynyl groups (total synthesis of herbimycin A),[124] and aryl groups (formal synthesis of rodgersinol, synthesis of the ABC ring of zoanthenol)[125,126] was described.

Similar to the epoxide opening, the stereoselective and regioselective opening of 1-hydroxy-2,3-aziridines with $Me_3Al$, has already been described in the previous update (eq 41). This transformation was recently extended to aryl functionalized aziridines bearing no hydroxyl directing functionality. This reaction can be achieved with high regioselectivity and in high yield due to the presence of the aryl group using non-ethereal solvents (eq 110).[127]

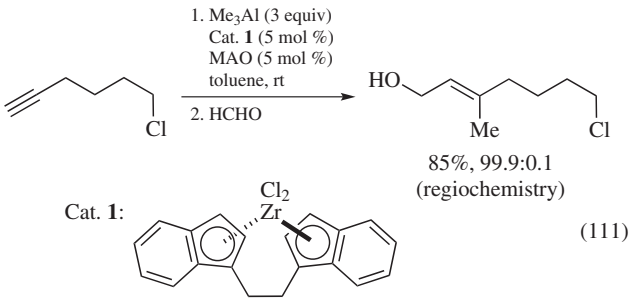



(110)

92%, 95:5 (regioselectivity)

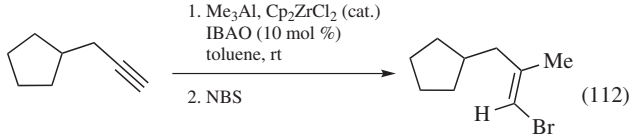
**Methylation via Carboalumination.** The carboalumination of olefins and alkynes is a well-established reaction discovered, developed, and used by Negishi and coworkers for the total synthesis of natural products. The functionalized vinylaluminum reagents can be quenched with various electrophiles (water, iodine, or $\alpha,\beta$-unsaturated ketones (eqs 17–18, 61, and 62) and undergo cross-coupling with Pd/Ni catalyst and allyl chlorides (eqs 19 and 63).

The regioselectivity of the carboalumination of terminal alkynes was problematic with the standard Negishi protocol since imperfect regioselectivities (95:5) were often observed with difficult substrates. The Wipf modification of the Negishi protocol based on the use of MAO (methylaluminoxane) as cocatalyst improved the regioselectivity with similar substrates (up to 97:3),[128] but this ratio was still unacceptable for commercial operations. Lipschutz et al. improved the regioselectivity of this reaction using the Brintzinger[129] Zr catalyst, thus obtaining regioselectivities >99:1 in the presence of MAO (eq 111).[130] However, such catalysts are too costly in comparison to $Cp_2ZrCl_2$. To solve this issue, Lipschutz and coworkers modified the design of the aluminum reagent; the $^i$Bu version of MAO (IBAO)[131] is an inexpensive and more sterically demanding congener of MAO, which successfully improved regioselectivity of the carboalumination (up to 99:1 or more) with a variety of substrates even in the absence of chlorinated solvents (eq 112).[132,133] It was additionally found that the cross-coupling of such alanes (synthesized with $Me_3Al$ and IBAO as cocatalyst) can proceed smoothly in high yield with aryl tosylates using a Ni catalyst (eq 113).[134]



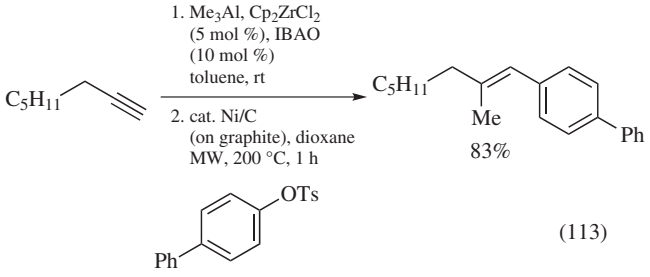

85%, 99.9:0.1 (regiochemistry)

(111)



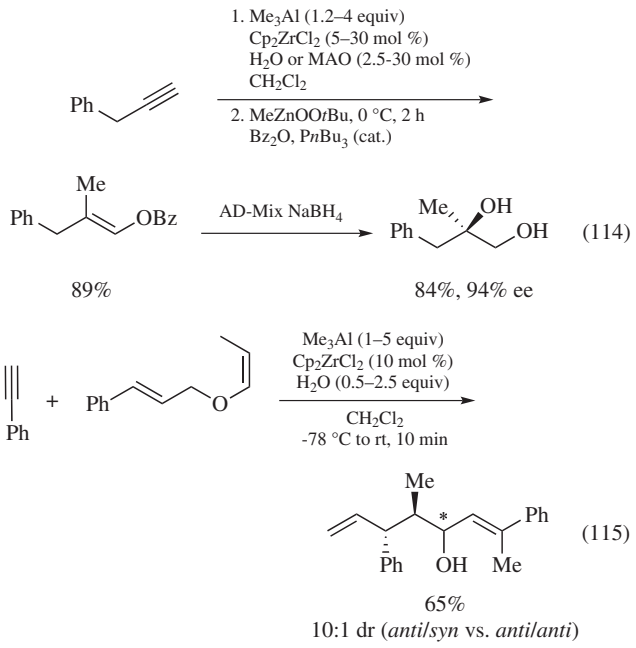

(112)

91%, 99.8:0.2 (regiochemistry)




(113)

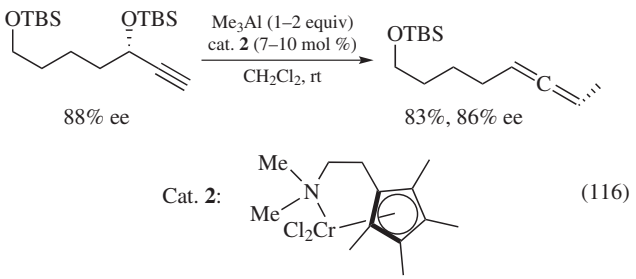
In 2008, Ready and coworkers provided an interesting extension to the Negishi carboalumination with the highly diastereoselective synthesis of enol ethers, thereby providing an appealing alternative to the troublesome and poorly selective enolization of $\alpha$-functionalized aldehydes (eq 114).[135] In 2005, Wipf et al. reported the trapping of vinyl alanes with aldehydes (obtained via in situ Claisen rearrangement) and the synthesis of the resulting allyl alcohols bearing up to three contiguous stereocenters in moderate to good yields and with good diastereoselectivity (eq 115).[136]




(114)

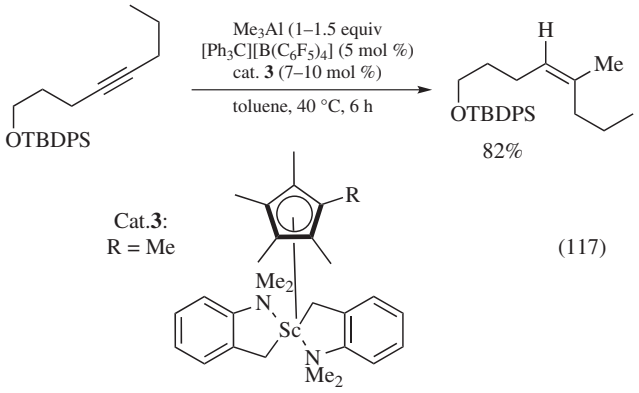
(115)

In 2005, Molander et al. reported the synthesis of allenes from alkynes using carbometalation with $Me_3Al$ followed by an elimination. The transformation was performed with a Cr catalyst and provided moderate to good optical yield (up to 96%) and low to moderate enantioselectivity (up to 86% ee) (eq 116).[137]

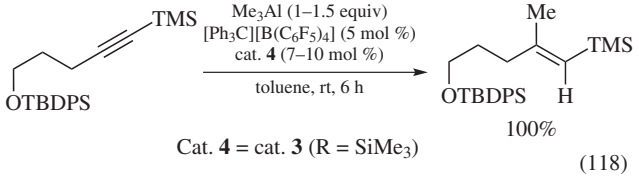



(116)

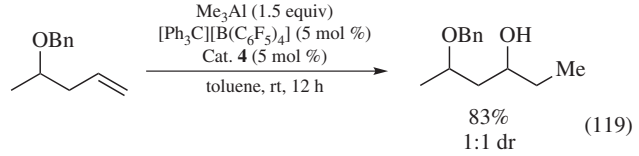
Several approaches to replace the traditional Zr catalyst with an enantiopure scandium catalyst for the carbometalation of silyloxy/alkoxy substituted alkynes/alkenes were reported by Hou and coworkers.[138] Such alkynes undergo regiospecific and stereospecific carboalumination, depending on the functionalization of the alkyne (eq 117 vs eq 118), in good yield (up to 100%). Similarly, the carbometalation on alkenes is accomplished in high yield, but sometimes with poor diastereoselectivity (eq 119).




(117)




(118)



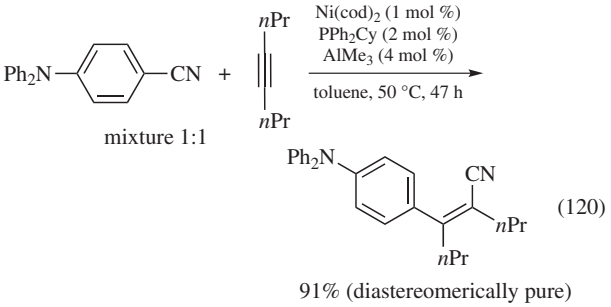

(119)

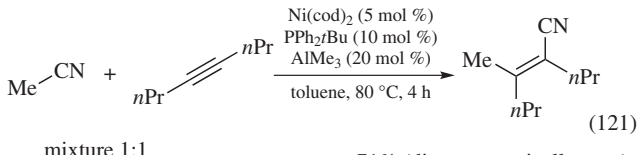
## C–C Bond Formation Mediated by $Me_3Al$ as Lewis Acid.

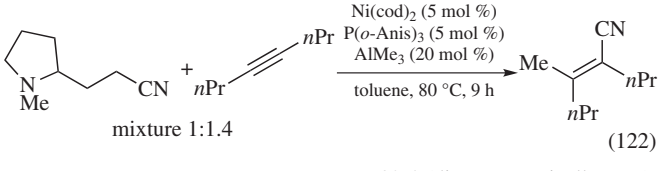
***C–C Bond Formation via 1,2- and 1,4-Additions Mediated by $Me_3Al$.*** $Me_3Al$ can act as a Lewis acid to promote a broad variety of reactions. Several of them have been described the in previous update: $Me_3Al$ can be used as activator for rearrangements ([3,3] sigmatropic rearrangements, Beckmann rearrangement/fragmentation, pinacol rearrangement, and aza-Cope rearrangement), epoxide openings and for the synthesis of enantiopure catalysts (i.e., ATPH: see eq 78). $Me_3Al$ can be used as Lewis acid to accelerate 1,2-additions of other organometallics to aldehydes,[139] *N-tert*-butanesulfinyl imines,[140,141] or accelerate conjugate-additions of silyl enol ethers with nitro olefins.[142]

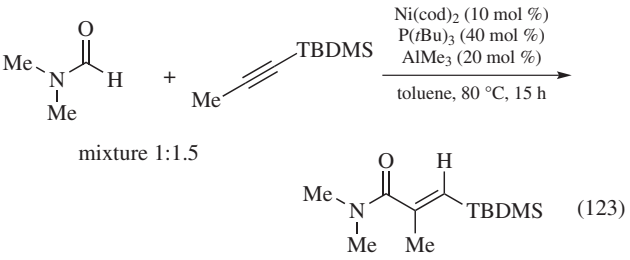
***C–C Bond Formation via C–H Insertion Mediated by $Me_3Al$.*** Nitriles are important intermediates and synthetic targets. C–CN bonds can be cleaved via oxidative insertion of metals and undergo addition to alkynes as demonstrated by Hiyama and coworkers: aryl alkynes undergo such transformation in good yield (up to 96%) and with high stereoselectivity, but the achievable level of regioselectivity is highly dependent on the nature/size of the groups surrounding the alkyne.[143] This reaction had previously been limited to electron poor aryl nitriles since the carbocyanation of electron rich aryl cyanides is sluggish. Recently, Hiyama and coworkers reported an improvement of this protocol, using $Me_3Al$ to accelerate the oxidative addition of Ni into the C–CN bond (eq 120).[144] This reaction can be extended to alkyl

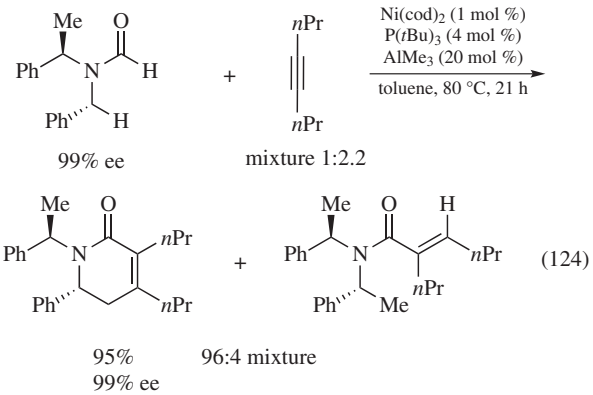
nitriles and alkenyl nitriles (eq 121), although $BPh_3$ proved to be a better Lewis acid for the latter transformation. The yield of the alkyl cyanation of alkynes is often reduced due to the low reactivity of the C($sp^3$)–CN bond and side reactions (i.e., $\beta$-hydride elimination leading to HCN). Hiyama and coworkers offered a solution by using alkyl cyanides bearing coordinating functionalities (pyrrolidines, piperazines, pyridines, aziridines, tetrahydrofurans, sulfides, and acetals). The resulting alkyl cyanation takes place in good yield (47–90%) and with good stereospecificity, depending on the nature and size of the neighboring groups to the alkyne (eq 122).[145] Parallel to their work on carbocyanation, Hiyama and coworkers reported a similar transformation using *N*,*N*-functionalized formamides as electrophiles in order to perform the hydrocarbamoylation of alkynes.[146] This reaction is performed under similar conditions and provides moderate to good yields of the resulting olefins, the regioselectivity being highly dependent on the nature and size of the neighboring groups of the alkyne (eq 123). Hiyama and coworkers extended the scope of this reaction to the synthesis of $\alpha,\beta$-unsaturated lactams via dehydrogenative [4 + 2] cycloaddition of formamides with alkynes through double C–H activation (eq 124).[147] This protocol was also successfully applied by Hiyama and coworkers to heteroarenes, especially for the *ortho*[148] vs *para* alkenylation of pyridines (eq 125)[149] and the alkenylation/alkylation of 2-pyridones (eqs 126 and 127).[150] The alkylation of 2-pyridones was enhanced by the work of Cramer who showed tuning the regioselectivity of the alkylation was a function of the ligand selection (eq 128).[151] Interestingly, the regioselectivity of the C–H insertion of imidazo[1,5-*a*] pyridines can be controlled via synergistic cooperation of Al and Ni. In practice, the C–H insertion takes place regioselectively at the C5 position in the presence of $Me_3Al$ and at the C3 position in the absence of $Me_3Al$ (eq 129).[152] Similarly, the regioselectivity of alkylation of benzimidazoles can be influenced with or without $Me_3Al$ in the presence of NHC ligands such as IPr and IMes (eq 130).[153]

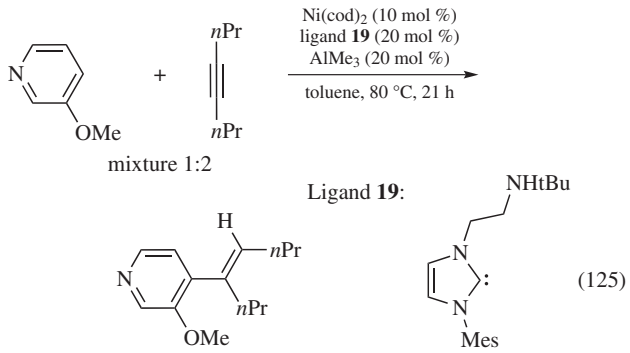


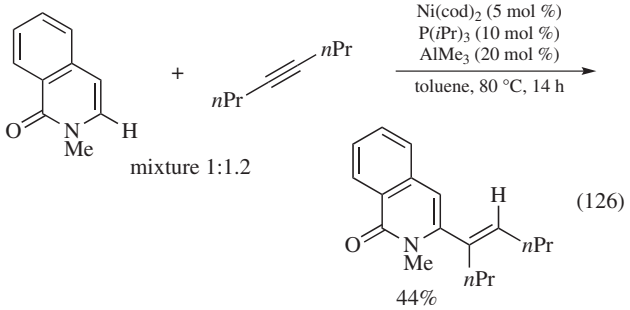



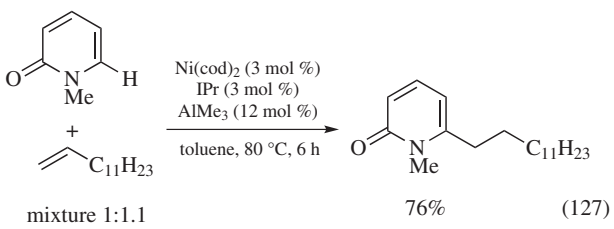



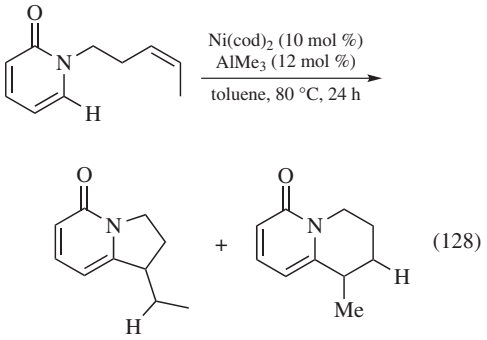



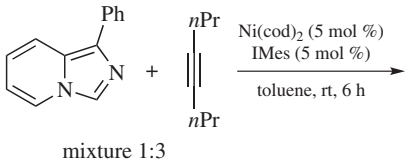



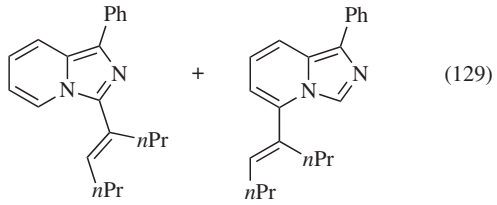



(128)

with no ligand 83%, regioselectivity >95:5
IPr (3 mol %) 77%, regioselectivity 6:94

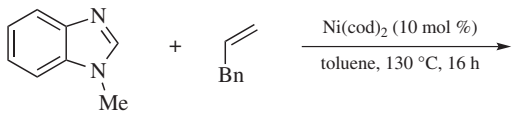


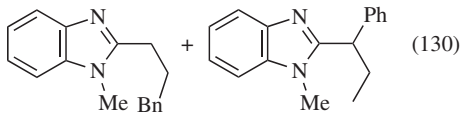

mixture 1:3



(129)

without $Me_3Al$ 96%, regioselectivity 4:1 98:2(*E*:*Z*)
with $Me_3Al$ (60 mol %) 98%, regioselectivity 1:10 99:1 (*E*:*Z*)

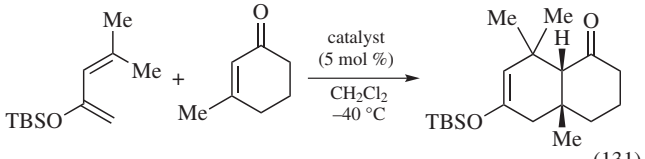


(130)

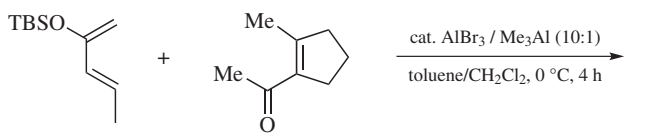
IPr (10 mol %), $Me_3Al$ (10 mol %), 92%, regioselectivity 92:8
IMes (10 mol %), 97%, regioselectivity 6:94

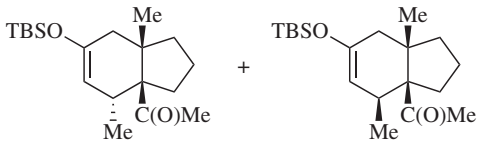
***C–C Bond Formation via $Me_3Al$ mediated Cycloaddition.*** As described in the previous update, $Me_3Al$ or reagents derived from $Me_3Al$ (i.e., $MeAl(OTf)_2$, $MeAl(OC_6F_5)_2$, MAD, MABR, catalysts **1** and **2**) are potent Lewis acids that trigger (enantioselective and diastereoselective) cycloadditions such as Diels–Alder cycloadditions. This well-studied transformation still attracts improvements for the construction of hindered cyclohexenes. As demonstrated by Jung, $MeAl(NTf_2)_2$ derived from $Me_3Al$[154] or the combination of $AlBr_3$ and $Me_3Al$[155] delivers high yields (up to 90%) of hindered cyclohexenes (eqs 131 and 132).[156,157] Similar work based on the combination $Tf_2CH_2/Me_3Al$ was reported by Taguchi and coworkers.[158] Ward and Abaee suggested a novel approach based on the self-assembly of the reaction partners.[159] The so-called LACASA-DA leads to higher reactivity, regioselectivity, and diastereoselectivity via an "intramolecular" process. Ward and Souweha also provided an asymmetric version of this transformation via the use of the binol ligand, but $Me_2Zn$ in combination with MeMgBr provides better reactivity, yield and enantioselectivity than $Me_3Al$ alone (eq 133).[160]




(131)

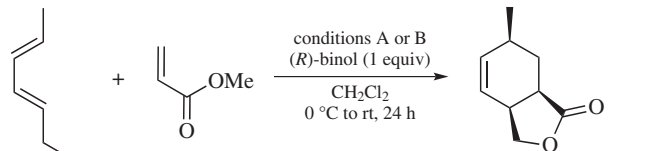
| catalyst | | |
|---|---|---|
| $Tf_2NH$ | 4 h | 92% |
| $Me_2AlNTf_2$ | 1.5 h | 96% |
| $MeAl(NTf_2)_2$ | 0.5 h | 94% |
| $Al(NTf_2)_3$ | 0.1 h | 0% |



(132)

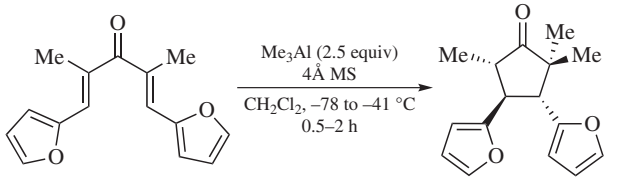
92%, 2.6:1 dr




(133)

conditions A: $Me_3Al$ (1 equiv) 60%, 90% ee
$Et_2AlCl$ (1 equiv)
conditions B: $Me_2Zn$ (1 equiv) 95%, 93% ee
$CH_3MgBr$ (1 equiv)

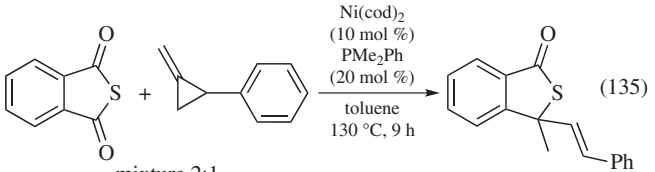
Interestingly, $Me_3Al$ with dienones can trigger interrupted Nazarov reactions, which involve activation of the dienone for the cyclization followed by intramolecular trapping of the resulting oxidocyclopentenyl cation formed after electrocyclization, without requiring alkylation of the dienone prior to the electrocyclization. Good yields and relatively good diastereoselectivities of the resulting highly functionalized cyclopentanones were observed (eq 134).[161] Trapping of the resulting oxidocyclopentenyl cation with triplet $O_2$ can be performed to provide the corresponding $\alpha$-hydroxy cyclopentanones in good yield but with only modest diastereoselectivity.[162]

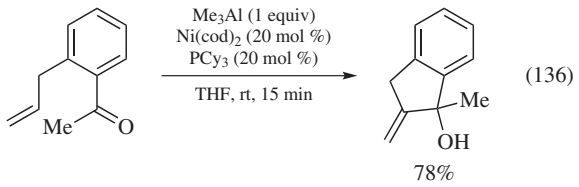



94% (134)

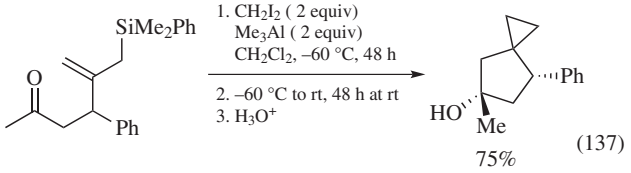
Use of $Me_3Al$ in the presence of Ni catalyst was extended by Matsubara and coworkers to [4+1] cycloadditions (although the

use of MAD provided better yields (eq 135)[163]) and by Ogoshi et al. to oxidative cyclizations of alkenes and ketones (eq 136).[164]

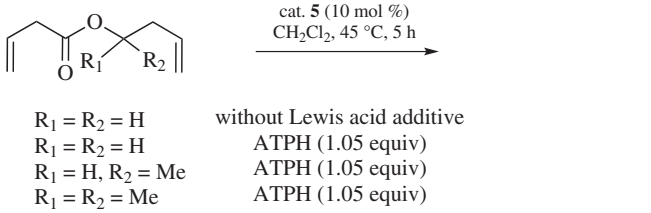


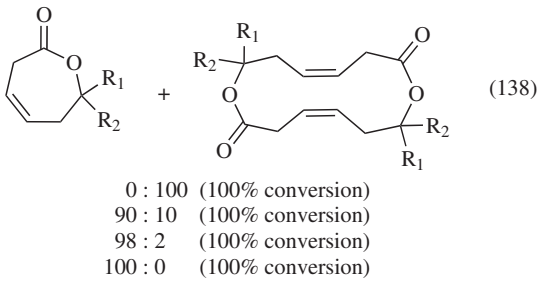




$Me_3Al$ combined with $CH_2I_2$ can perform spirocyclopropanation with oxoallylsilanes in medium to good yields (52–92%) at −60 °C (eq 137).[165] $Me_3Al$ can also accelerate the Pd catalyzed benzannulation of enynes and diynes in the presence of an appropriate phosphine ligand (however, MAO is a better catalyst).[166]

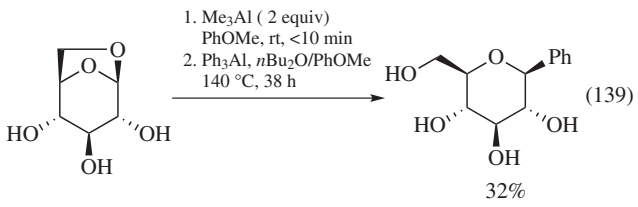



Finally, it is also advantageous to use a $Me_3Al$ derived additive of the type ATPH in order to facilitate access to $\epsilon$-lactones via RCM (eq 138).[167]

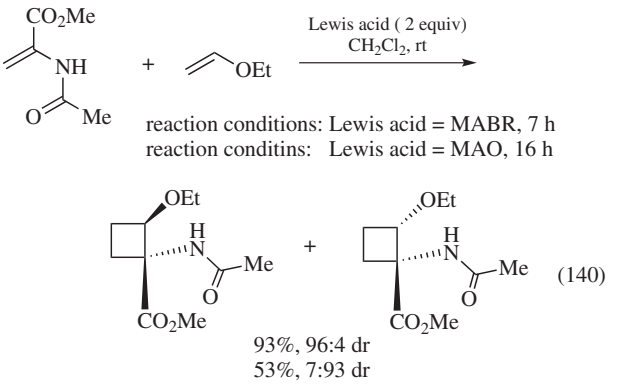


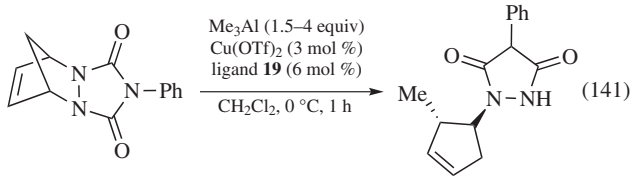

***$Me_3Al$ mediated Alkylation at the Anomeric Position.*** $Me_3Al$ can be used not only as alkylating agent for the alkylation at the anomeric positions of sugars but can also catalyze and orient the C–C bond formation with other organometallics with good *β/α* selectivity. According to Henschke et al.'s reports, hydroxyl directed arylation can take place using $Me_3Al$ as a bridging partner. Low to moderate yields and excellent *β*-stereoselectivities were obtained (eq 139).[168]




***C–C Bond Formation via Enols.*** $Me_3Al$ can be used for the synthesis of Al-based catalysts showing various acidities (i.e., triflimide based Al catalysts) or hindrance (i.e., eq 34: MAD, MAT, MABR; eq 78: ATPH). For example, $Me_3Al$ is used for the synthesis of $Me_2AlNTf_2$, a Lewis acid for complexation with aldehydes during C–C bond formation with silyl enol ethers.[169] Moreover, MABR or MAO can successfully promote tandem Michael–Aldol reactions and thus provide high diastereoselectivity and yields of highly functionalized cyclobutane rings (eq 140).[170]

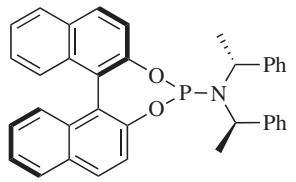


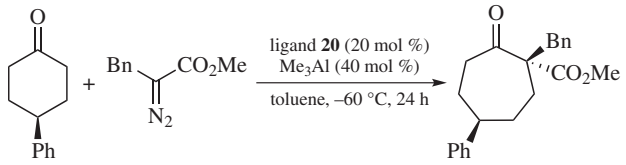

***$Me_3Al$ mediated Desymmetrization and Kinetic Resolution.*** Heteronorbornenes give access to various enantiomerically enriched building blocks via asymmetric ring opening. There are only few reports describing such reaction, especially in a catalytic fashion. Recently, Pineschi and Micouin/Alexakis separately reported the catalytic asymmetric ring opening using $R_3Al$ reagents as nucleophiles and enantiopure phosphine ligands for the enantioselection. Good reactivity, high yields and moderate enantioselection can be obtained (up to 86% ee) (eq 141).[171] Maruoka and coworkers reported in 2011 the desymmetrization of cyclic ketones via ring extension using $Me_3Al$ as activator, *α*-diazoacetate as nucleophile and binol as enantiopure ligand to provide enantiomerically enriched cyclic ketones in good yield and with an all-carbon quaternary center at the *α*-position (eq 142).[172] Finally, $Me_3Al$ can be used as Lewis acid in DKR (dynamic kinetic resolution) in combination with a lipase for the resolution of racemic alcohols (eq 143). Excellent ee can be obtained even with ketones bearing side chains of relatively similar size.[173]



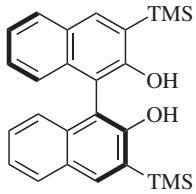

(141)

Ligand **19**:

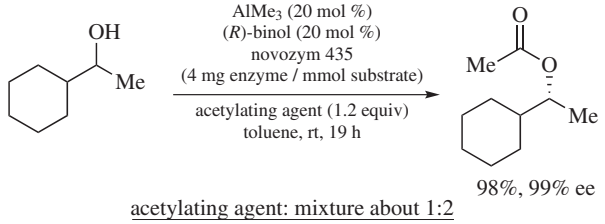




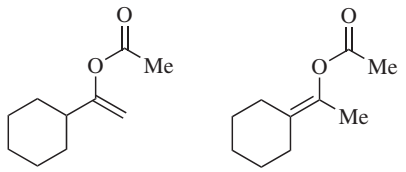

Ligand **20**:



(142)

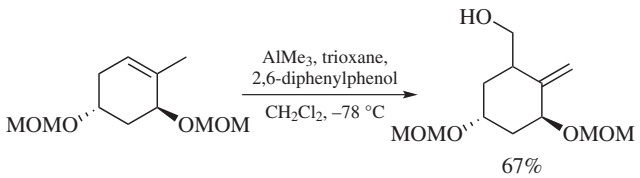



acetylating agent: mixture about 1:2



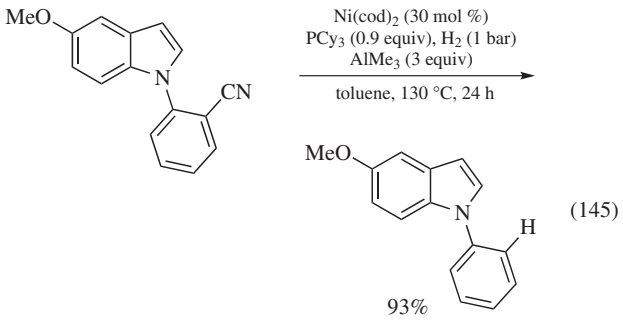
(143)

***Me$_3$Al mediated C–C Bond Formation via Ene Reaction.*** In 1993, Yamamoto and coworkers showed that Al species can activate aldehydes to boost their reactivity for C–C formation via ene reaction. This transformation was originally developed with MAPH as Al catalyst,[174] but it can be performed as successfully with ATPH (eq 144).[175]



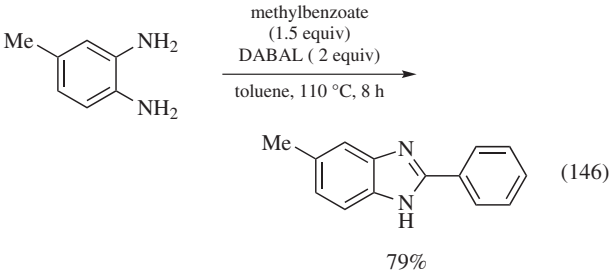

(144)

**C–C Bond Cleavage via Hydrogenolysis of Unactivated C–CN Bonds.** The nitrile moiety plays an important role in the functionalization of arenes since it can control regioselectivity and boost the reactivity of the $\pi$-system. After functionalization of the ring, it is possible to remove the nitrile directing group. In that application, Maiti and coworkers reported the hydrogenolysis of the activated nitrile using $Me_3Al$, which served as both Lewis acid and trapping agent for the HCN by-product (eq 145).[176]

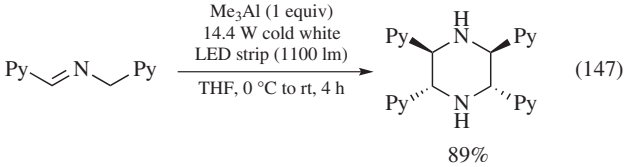



(145)

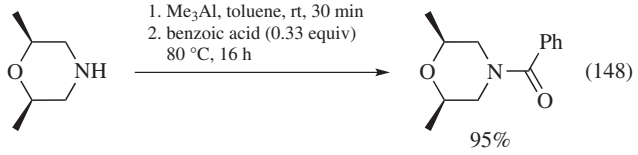
**C–N Bond Formation and Synthesis of *N*-Heterocycles.** Previous updates described $Me_3Al$ methylation of esters, acyl halides and carbamates. $Me_3Al$ acts as a Lewis acid with esters or amides to construct (other) amides (eq 24) or heterocycles of biological relevance. For instance, esters and 1,2-diaminobenzene in the presence of $Me_3Al$ affords benzimidazoles (eq 146),[177] imidazolines in the presence of TMEDA,[178] and piperazines with UV light via [3+3] cycloaddition of azomethine ylides (eq 147).[179] Interestingly, the synthesis of amides using $Me_3Al$ as Lewis acid can be extended to carboxylic acids, as described by Li and coworkers (eq 148).[180]




(146)

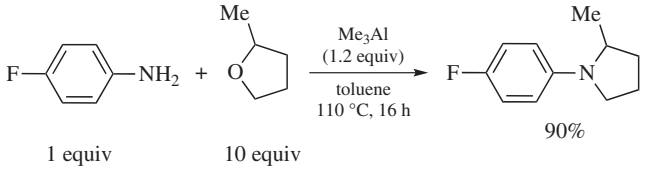



(147)



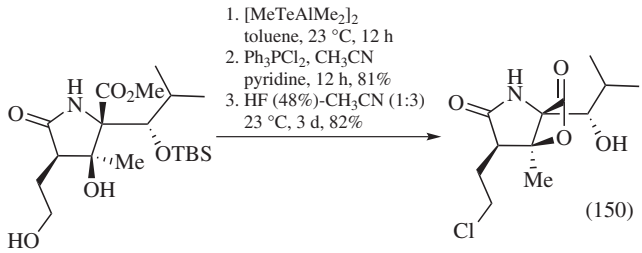

(148)

$Me_3Al$ is a potent Lewis acid that can be used for the synthesis of *N*-functionalized five- or six-membered azacycles such as pyrrolidines, piperidines, piperazines, tetraisoquinolines and isoindolines in good yield (eq 149).[181]



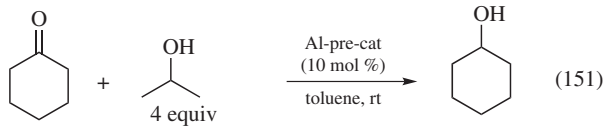

(149)

Interestingly, methyl esters can be chemoselectivity transformed with "$Me_3Al$" into the corresponding carboxylic acid under mild conditions even with hindered substrates without any formation of methyl ketone. A new Te-based reagent ($[Me_2AlTeMe]_2$) synthesized with $Me_3Al$ and Te powder effects this intriguing reaction (eq 150).[182]



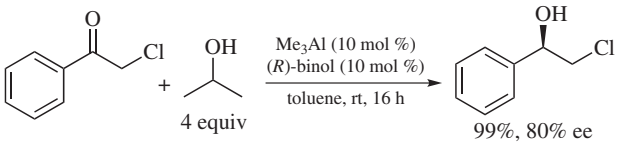

(150)

**Asymmetric Oppenhauer Oxidation vs Verley–Pondorf Reduction.** The MVP reduction (Meerwein–Verley–Pondorf reduction), first reported more than 90 years ago,[183] is a well-established method for the reduction of carbonyls to primary and secondary alcohols, but still suffers despite its benefits (mild conditions, chemoselectivity, easy removal from acetone via evaporation) from drawbacks that have limited its utility (use of stoichiometric amounts of aluminum alkoxide to achieve high yields in a reasonable time). In 2001, Nguyen and coworkers demonstrated that catalytic $Me_3Al$ afforded the desired alcohols in high yield and high reaction rate (eq 151).[184] The enantioselective version of this transformation can be accomplished with binol ligand, but the enantioselectivity remains modest (up to 83% ee) (eq 152).[185] Extension of this transformation to ketimines was only partly successful since stoichiometric $Me_3Al$ was required for high yields (eq 153).[186] Finally, given the efficiency of $Me_3Al$ as activator for the MVP reduction, Nguyen and coworkers developed the $Me_3Al$-catalyzed Oppenhauer oxidation, which can be successfully accomplished with 10 mol % of $Me_3Al$ and 3-nitrobenzaldehyde as oxidant to provide the desired ketones in high yield in less than 1 h (eq 154).[187]

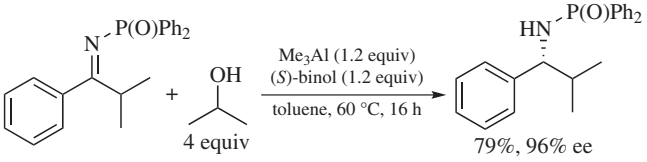



(151)

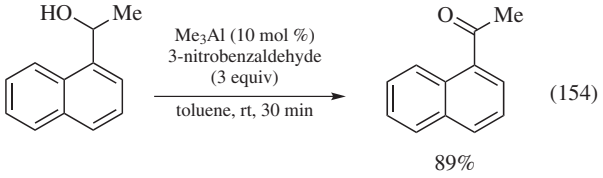
conditions: Al pre-cat = $AlMe_3$; reaction time 3 h 82%
Al pre-cat = $AlMe_2Cl$; reaction time 2 h 96%
Al pre-cat = $Al(OiPr)_3$; reaction time 12 h 7%




(152)




(153)

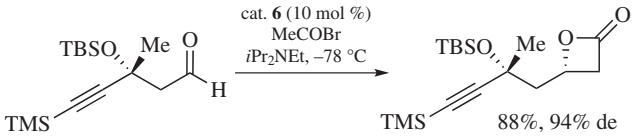


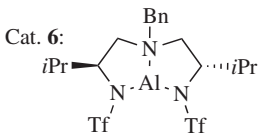

(154)

**Synthesis of Methyltrioxorhenium (MTO).** MTO has been recognized to be the most active available catalyst for olefin epoxidation and can also be used as catalyst for olefin metathesis and aldehyde olefination. Its large-scale synthesis suffered severe drawbacks, methylation being the most troublesome step.[188] These limitations have been solved via a new protocol by Kühn and coworkers and where $Me_3Al$ plays a pivotal role. $Me_3Al$ is used to produce methylzincacetate, which cleanly and efficiently effects the key step leading to MTO (eq 155).[189]

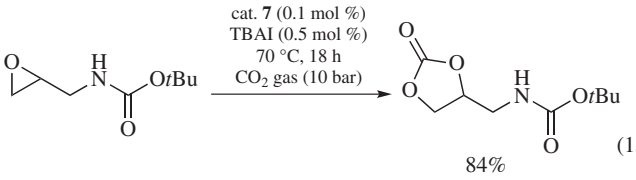
$$Re_2O_7 + 2\,[CH_3C{=}O)]_2O + 2/3\,Al(CH_3)_3 \longrightarrow 2\,CH_3ReO_3 + 2/3\,Al[OC{=}O)CH_3]_3 \quad (155)$$

**$Me_3Al$ as Precursor for New Al-based Ligands.** $Me_3Al$ was used as precursor for the synthesis of novel Al-based catalysts with tuned Lewis acidity and/or various three-dimensional environments. Such designs lead to unique interactions, with substrates bearing oxo- or amino-based functionalities and perform stereoselective transformations, necessitating increased reactivity and/or intimate interactions between reaction partners. MAO, MAD, MABR, ATPH (eq 78) and other chiral Lewis acids of types **4–7** have already shown wide synthetic utility. For instance, catalytic asymmetric acyl halide–aldehyde cyclocondensation can be performed with catalyst **6** (eq 156)[190] or with Salen complexes.[191] Aluminatrane complexes are used for catalytic enantioselective cyanation of aldehydes.[192] Kleij and coworkers reported the synthesis of a powerful aluminum catalyst (based on the novel ligand **21**) for the synthesis of functional organic carbonates (eq 157).[193] The catalytic asymmetric rearrangement of $\alpha,\alpha$-disubstituted $\alpha$-siloxy aldehydes to optically active acyloins using axially chiral organoaluminum Lewis acids (catalyst **8**) was reported by Maruoka and coworkers in 2007 (eq 158).[194] Finally, Shitama and Katsuki reported the use of $Me_3Al$ and enantiopure ligand **22** for the synthesis of Salalen complexes, which are suitable catalysts for asymmetric Simmons–Smith reaction of allylic alcohols (eq 159).[195]

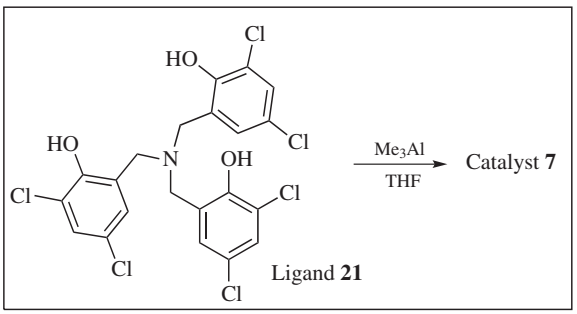


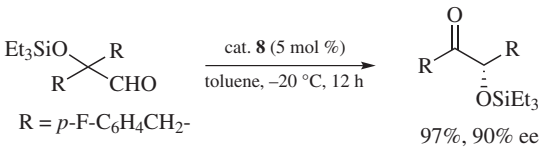



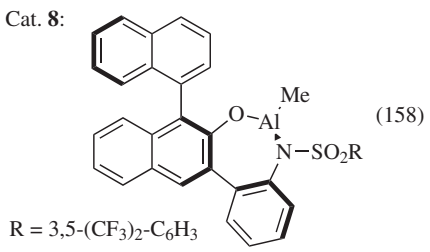

(156)



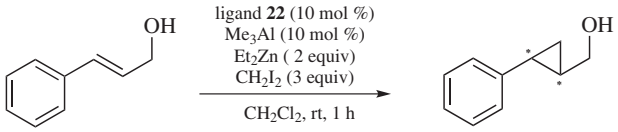

(157)

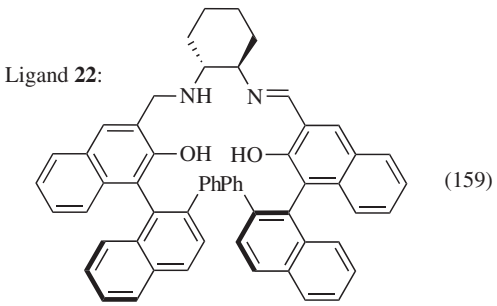



(158)




(159)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