Design and Exploration of Novel Chiral Organoaluminum Reagents Derived from *N*-Methylephedrine: A Study of Asymmetric 1,4-Addition to .. -Unsaturated Carbonyl Compounds

C500 Report

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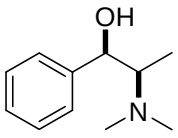
Design and Exploration of Novel Chiral Organoaluminum Reagents Derived from *N*-Methylephedrine: A Study of Asymmetric 1,4-Addition to .. -Unsaturated Carbonyl Compounds

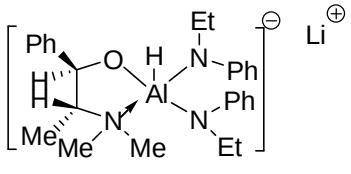
Background:-

The quest for an asymmetric reaction is significant because of its immense application to the chemical synthesis of small drug molecules, many of which are derived from natural products.[1] Among all types of asymmetric chemical reactions, reductions of carbonyl substrates play a major role in chemical synthesis. Thus, scientists have examined chiral reducing reagents capable of stereoselective reduction of different types of carbonyl compounds.

Towards this goal, Terashima[2] developed chiral reagent **1** derived from lithium aluminum hydride, which was modified with one equivalent of (+) or (−)-*N*-methylephedrine and two equivalents of an additive (amine ligand, *N*-ethylaniline in the case of **1**).



(+)-*N*-Methyl ephedrine

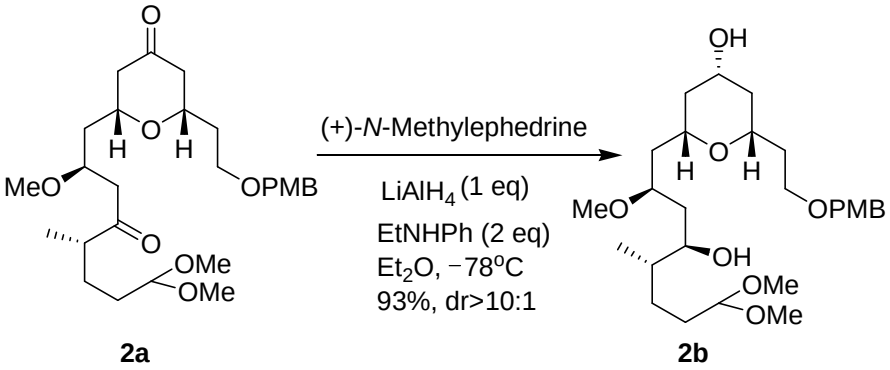


1

Terashima reagent

This reducing agent was initially designed for high diastereoselective and enantioselective delivery of hydride to various .~unsaturated carbonyl compounds. The facial selectivity arises from the chirality associated with either enantiomer of *N*-methylephedrine used to generate the chiral aluminate. Williams and co-workers have recently applied this methodology to the highly selective reduction of complex substrates, as exemplified in the

total synthesis of (−)-ratjadone[3], (−)-hennoxazole A[4] and (+)-leucascandrolide A[5] (Scheme 1). Moreover, a study of the scope and reactivity of the reducing agent has been initiated to extend its applications as a synthetic tool as well as to understand its mechanistic features.



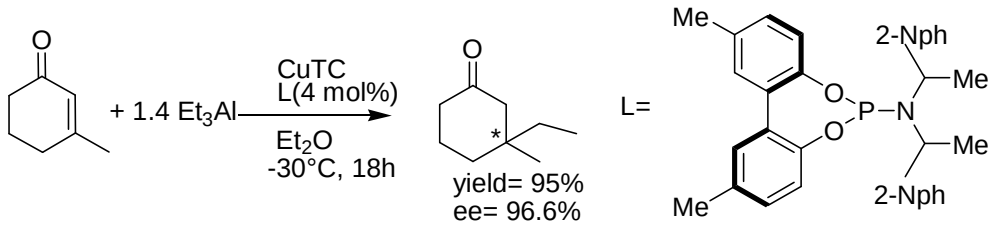
2a **2b**

Scheme 1

Among the prevalent methodologies for carbon-carbon bond formation, the conjugate addition of metal-alkyl reagents to . -unsaturated carbonyl compounds is an extensively used strategy to functionalize complex substrates with regio and stereoselectivity.[6,7,9] Although organocuprates prepared from Grignard reagents are early entrants to this field, those derived from organozinc reagents dominate the field.[10] Organocuprates derived from organoaluminum are the newest reagents for asymmetric conjugate addition (ACA).[10] Until recently, it was impossible to carry out asymmetric conjugate additions without employing stoichiometric amounts of copper salts.[8,11] Apart from this limitation, these methods also suffered from several drawbacks such as sluggish reactivity of alkylzinc reagents, and the exclusive use of dimethylzinc and diethylzinc reagents as successful alkylating agents.[7] On the other hand, organocuprates derived from Grignard reagents, suffer from several drawbacks in ACA reactions: these include side

reactions due to the presence of reactive organomagnesium species; the presence of both chiral and achiral complexes in solution, as well as halide ions, resulting in loss of enantioselectivity and excessive dependence on reaction parameters.[12] All of the reagents displayed a limited substrate scope in case of acyclic[13] and -substituted enones, resulting in low stereoselectivity and chemoselectivity.[8,14] To overcome the limitations of these reagents, researchers have tried to design chiral reagents which may react with a wide variety of substrates including tri-substituted enones with moderate to high reactivity and high stereoselectivity employing catalytic amounts of copper salts. Several research groups have advanced ACAs with high enantioselectivity using a diverse set of organocuprates prepared from organozinc species using catalytic amounts of copper salts and various chiral auxiliaries such as "BINOL-derived phosphoramidite ligands",[15] phosphoramidates,[7,16] chiral phosphates, TADDOL's derivatives,[11] oxazoline based chiral auxiliaries,[17] BINPO,[18] pyridine methanols, proline amides, amino alcohols and chiral triamide phosphane.[19] Studies have been initiated to improve this methodology for acyclic/ -substituted enones as well as using a diverse set of alkyl transfer groups. Hoveyda and coworkers first described highly enantioselective ACA using organocuprates derived from organozinc species other than simple dimethyl and diethylzinc reagents.[19] They have also reported highly enantioselective ACA's to -substituted enones using organocuprates derived from dialkylzinc and employing a complex peptide as chiral source.[20] Moreover, Imamoto and coworkers have shown that organocuprates derived from organozincs reagents can successfully undergo addition to acyclic enones with high enantioselectivity using P-chiral *o*-phosphinophenol as ligand.[24] Using organocuprates derived from Grignard reagents and employing commercially available ferrocenyl

diphosphines, Feringa and co-workers have successfully carried out ACA's to various acyclic enones with 96% enantioselectivity.[22] Alexakis and co-workers have shown that highly enantioselective ACA reactions of various -substituted enones can be achieved by using organocuprates derived from trialkylaluminum and employing phosphoamidites as chiral auxiliaries.[14] An example as shown in Scheme 2[14] illustrates the efficiency of this method with -substituted enones. One of the major disadvantages for most of the methodologies is that they employ a chiral auxiliary which requires multistep synthesis and is sometimes difficult to handle.[23]

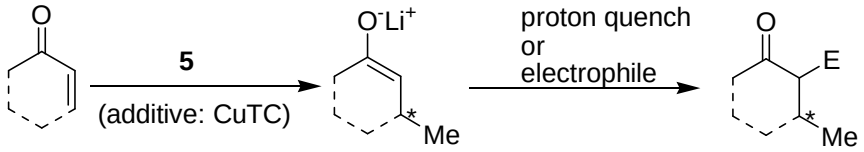


Scheme 2: 1,4- Conjugate addition of Et_3Al to 3-methyl-2-cyclohexenone using L as the catalyst

Proposal:-

The current proposal develops a research study of Terashima reagents in the Williams laboratories. It attempts the preparation and exploration of novel aluminum-based chiral reagents derived from *N*-methylephedrine. We propose to study this novel reagent for 1,4-conjugate addition of . -unsaturated carbonyl compounds, and extend the "existing methodologies" by using a novel aluminum reagent employing commercially available chiral auxiliaries which will make our reagent more accessible for widespread use. We also plan to explore the possibility of using various transferable groups to expand the scope of the proposed reagent.

The chiral agent would then survey a wide variety of Michael acceptors according to the general pattern as shown in **Scheme 3**.



Scheme 3: Asymmetric conjugate addition of an enone with reagent **5**

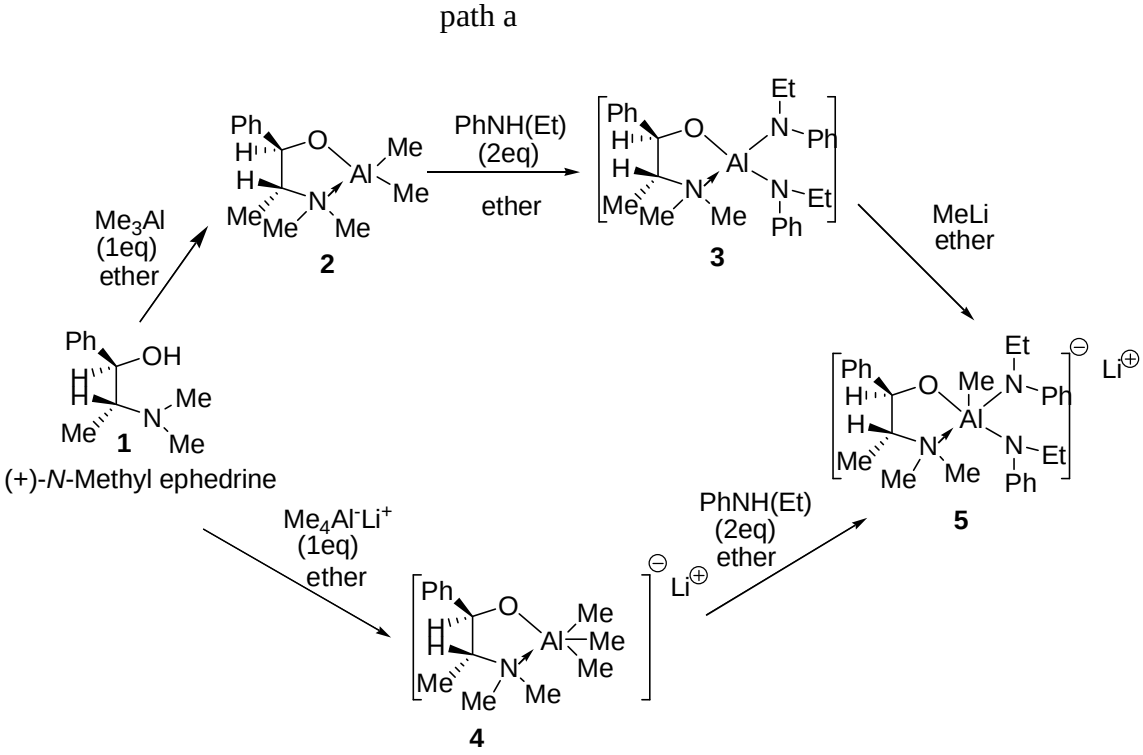
Results and Discussion:-

The initial objective of this project was to prepare the reagent (**5**), optimize the reaction conditions, and then explore the scope of the reagent by carrying out asymmetric conjugate addition with a diverse set of substrates.

Preparation of reagent:-

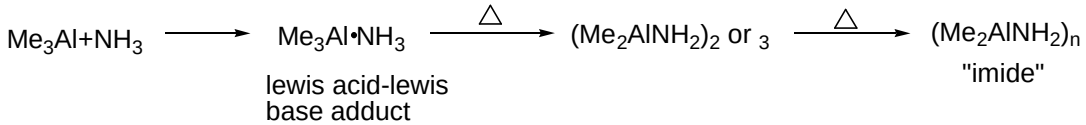
The preparation of the novel aluminate reagent (**5**) involves two different pathways starting from either (+) or (−) *N*-methylephedrine (**Scheme 4** illustrates for (+)-*N*-methylephedrine).

Initial reactions to prepare the reagent were carried out at low temperature (−78°C- −30°C) recognizing that, reaction of *N*-methylephedrine with trimethylaluminum might be exothermic. After the addition of trimethylaluminum to the *N*-methylephedrine solution, the reaction mixture was heated to make the solution homogeneous by allowing the di or tri alkoxy derivatives of trimethylaluminum to equilibrate forming compound **2** as shown in **Scheme 4** (path a):



Scheme 4: Preparation of the reagent **5**

The above assumption is based on similarity between reaction of trimethylaluminum and ammonia as reported by Sauls and co-workers and shown below in Scheme 5.[24]



Scheme 5: Reaction between trimethylaluminum and ammonia

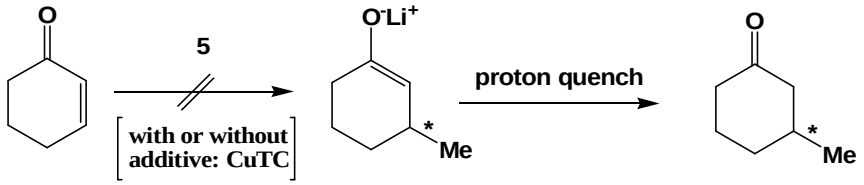
After the addition of *N*-ethylaniline, the reaction mixture was further refluxed for an hour and then it was cooled to −30°C. Finally, MeLi was added at low temperature (−30°C or 0°C) assuming that the reagent **5** might not be stable at room temperature or higher.

In a second protocol (**Scheme 4**, path b), trimethylaluminum was treated with methyllithium followed by dropwise addition of one equivalent of *N*-(+)-methylephedrine solution. The mixture was stirred at room temperature for an hour and then heated to reflux for one hour. This mixture was allowed to cool to room temperature, and two equivalents of *N*-ethylaniline were added slowly, stirred for an hour and refluxed for one hour resulting in a clear solution. At this stage, studies of asymmetric conjugate addition with the ethereal solution of the reagent were initiated.

Asymmetric Conjugate Addition (ACA):-

Asymmetric conjugate addition is more facile in case of monosubstituted . -unsaturated carbonyl compounds. Hence, 2-cyclohexenone was chosen as the initial substrate for ACA reaction as shown in **Scheme 6**. A complex mixture of products was obtained when the ACA reaction was carried out at low temperature. The mixture was subjected to flash column chromatography for purification. Apart from the isolation of significant amounts of *N*-(+)-methylephedrine and *N*-ethylaniline, and starting 2-cyclohexenone, the identification of the rest of the collected products remained inconclusive after ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis. Further spectral

analysis of these compounds using 1D-NOESY, gDQCOSY are in progress. When the reaction was carried out at room temperature (Et_2O) as well as at refluxing conditions (THF, toluene), we observed the similar results.



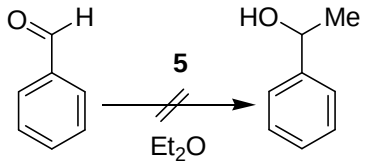
Scheme 6: Asymmetric conjugate addition of 2-cyclohexenone with reagent **5**

The ACA reaction in the presence of CuTC was investigated, but a similar product composition as observed with the non-CuTC catalyzed ACA reaction was obtained.

1,2-Addition:-

At this point, we reasoned that asymmetric 1,4-conjugate additions might be slower compared to 1,2-additions of the aluminate reagent (**5**) with the carbonyl functionality.

Thus, to test this hypothesis, we attempted the 1,2-addition of **5** to benzaldehyde, as shown in **Scheme 7**. Surprisingly we did not observe any 1,2-adddition product of benzaldehyde as the reagent.



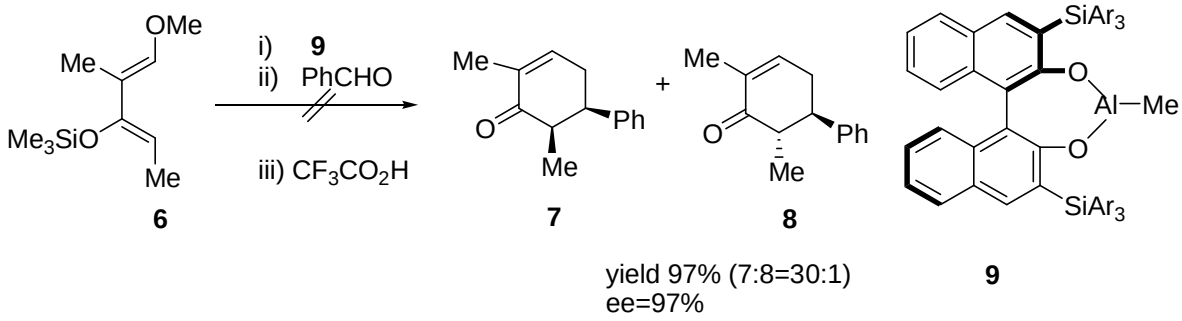
Scheme 7: 1,2-Additon of **5** with benzaldehyde

The failure of 1,2-addition product compelled us to verify the identity of the species generated during the course of the reagent preparation (**Scheme 4**, path a). We

hypothesized that it might be fruitful to explore the neutral alumina species (**3**), which is the precursor of our aluminate reagent (**5**), as a chiral Lewis acid in the hetero Diels Alder reaction.[26] The studies of the structure and properties of this neutral species might provide useful information about the aluminate species.

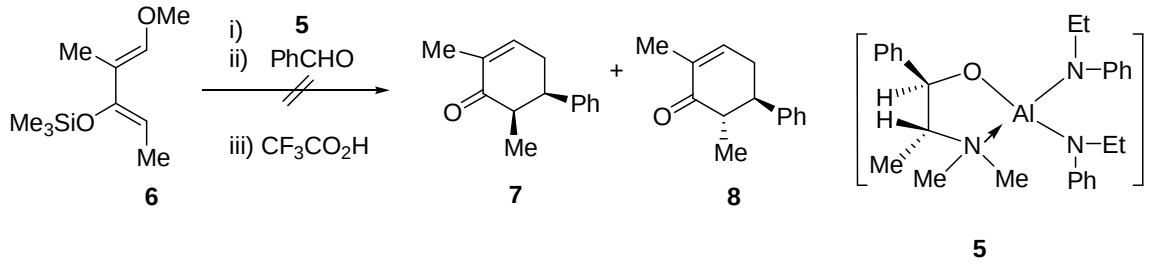
Asymmetric hetero Diels-Alder reaction:-

Yamamoto and co-workers have shown that binaphthol derived trimethyl aluminum derivative (**9**) can be used as a chiral Lewis acid for the asymmetric hetero Diels-Alder reaction for the preparation of optically active pyran with 97% ee (**Scheme 8**). We decided to study s this reaction in the presence of **3** to identify its role as a catalyst.



Scheme 8: Hetero Diels-Alder reaction between diene 6 and benzaldehyde using catalyst **9.**

To our surprise the reaction didn't proceed and we recovered mostly *N*-ethylaniline and unreacted benzaldehyde from the reaction mixture.



Scheme 9: Hetero Diels-Alder reaction between diene 6 and benzaldehyde using catalyst **5**

Future Work:-

Our future focus will to utilize various analytical tools to study the generation and characterization of the species of the organometallic species. The Variable Temperature NMR experiment will be carried out to follow the progress in reagent preparation. Once we unambiguously resolve the structure of the reagent, it will facilitate reaction development of ACA reactions and 1,2-additions of carbonyl functionality. Once optimized, this methodology could be applied in the total synthesis of various natural products to demonstrate its potential for the construction of complex molecules.

Experimental:-

General:-

All the solvents are dried before use unless mentioned otherwsie. All the chemicals are used without further purification unless mentioned otherwise. Deuterated chloroform, the residual peak of which also serves the purpose of internal standard, was dried over molecular sieves and was used for recording all the proton and carbon-13 NMR either in Varian-400 or Inova-400. All the reactions were carried out in flame dried glassware and under argon atmosphere unless otherwise mentioned. TLC was carried out on precoated

glass backed silica gel plates having thickness of 0.25 mm. The TLC plates were developed either in *p*-anisaldehyde or in ethanolic potassium permanganate solution. Silica gel from E. Merck having mesh size 230-400 mesh size was used for flash column chromatography.

I. Preparation of the Reagent (protocol 1):-

To degassed 10 ml freshly distilled toluene taken in a two-necked flame dried flask 447.5 mg (2.5mmol) of ephedrine was added and the solution was stirred for ten minutes. To the resulting solution 1.38ml of trimethylaluminum (2.5 mmol, 2.0 M in toluene) was added dropwise to the solution, during which gas evolution was observed. Then the solution was stirred at room temperature for two hours and then refluxed for two hours. The solution was then allowed to cool to room temperature and freshly distilled *N*-ethylaniline (0.69 ml, 10 mmol) over calcium hydride was added slowly, the solution turned light yellow by this time. The solution was stirred for two hours at room temperature and then refluxed for four hours. The solution was then allowed to cool down to room temperature and MeLi (1.6 ml, 2.5 mmol, 1.6 M in ether) solution was added slowly, during which gas evolution was observed. After the addition the solution is stirred at room temperature for two hours, the solution was then cooled down and the reagent was used for the asymmetric conjugate addition. Final reagent concentration was 0.25 M.

I. Asymmetric conjugate addition with 2-cyclohexenone:-

To a 4 ml toluene solution of 2-cyclohexenone (0.25 ml, 2.5 mmol) taken in a flame dried two necked flask, the above reagent (10ml, 2.5mmol) was added slowly. The reaction mixture was stirred for two hours and then refluxed for overnight. The solution

turned deep yellow colored as the reaction proceeded. The solution was cooled to room temperature and then the reaction solution was diluted with 100 ml ether solution and then 120 ml of pH 7 buffer solution was added. The solution was then stirred for two hours to get the organic and aqueous layers separated. The whole solution was then taken in a separating funnel and the ether layer separated. The aqueous layer was washed three times with ether and the combined organic fraction was dried over sodium sulfate and concentrated in vacuum. The crude product was then subjected to flash column chromatography with hexane/ethyl acetate mixture in 1:1 ratio.

II. Hetero Diels-Alder Reaction:-

In a two-necked flame dried flask, to a 5 ml degassed solution of dry toluene the above mentioned reagent (0.1 ml, 0.25 M) was added followed by the reaction flask was cooled to -20^0C. Then distilled benzaldehyde (0.102 ml, 1 mmol) followed by the diene (220mg, 1.1mmol) were added. The reaction mixture was stirred at this temperature for two hours. The reaction mixture was then poured into 10 ml of 10% HCl solution taken into separating funnel along with 50 ml ether solution. The ether layer was separated and the remaining aqueous layer was extracted twice with (2 x 20 ml) ether. The combined organic layer was concentrated under reduced pressure to obtain crude oil. The obtained liquid was dissolved in dichloromethane (30 ml) and then treated with trifluoroacetic acid (0.092 ml, 1.2 mmol) at 0^0C for one hour. The resulting mixture was then poured into saturated sodium bicarbonate solution and extracted three times with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate, concentrated under

reduced pressure and then subjected to flash column chromatography using 10% ethyl acetate in hexane.

III. 1,2-Addition:-

To a 2 ml ether solution of the benzaldehyde at 0^0C, the reagent was added dropwise and the reaction was stirred at that temperature for three hours. The reaction solution was diluted with 10 ml ether solution and then 12 ml of pH 7 buffer solution was added. The solution was then stirred for two hours to separate the organic and aqueous layers. The organic layer was then separated, and the aqueous layer was washed three times with ether. The combined organic fraction was dried over sodium sulfate and concentrated under reduced pressure. The crude product was then subjected to flash column chromatography with 2% ethyl acetate in hexane.

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