COMBINING ORGANOCATALYSIS WITH
TRANSITIONMETAL CATALYSIS

By

NARESH BABU MULPURI

Master of Science in Chemistry

University of Hyderabad

Hyderabad, India

2007

Submitted to the Faculty of the

Graduate College of the

Oklahoma State University

in partial fulfillment of

the requirements for

the Degree of

MASTER OF SCIENCE

July, 2014

COMBINING ORGANOCATALYSIS WITH

TRANSITIONMETAL CATALYSIS

Thesis Approved:

Dr. Ronald J. Rahaim

Thesis Adviser

Dr. Richard A. Bunce

Dr. Jimmie D.Weaver

Dr. Toby L. Nelson

Name: NARESH BABU MULPURI

Date of Degree: JULY, 2014

Title of Study:

COMBINING ORGANOCATALYSIS WITH TRANSITIONMETAL CATALYSIS

Major Field: CHEMISTRY

Abstract: The use of transition metals or small organic molecules established as catalysts powerful technique in organic synthesis. In recent years combining transition metal with organocatalysis (dual catalysis) has gained considerable attention. The advantage of the dual catalysis is the ability to access pharmaceutically relevant frameworks or building blocks, which is not possible by single catalytic systems. To explore this dual catalytic strategy we initiated a program to use tether technology to combine the transition metal catalysis and organocatalysis for library development. Chapter I deals with combining the organocatalysis with Hg(II) salts for direct α-alkylation of aldehydes with unactivated alkenes. In chapter II focus is on using a disiloxane linker to combine gold catalysis with enamine catalysis. In chapter III deals with the synthesis of dihydropyridines, which are found in many natural products and biologically active molecules. We attempted to develop a titanium promoted reductive coupling of π-unsaturated substrates with pyridinium salts to access highly substituted dihydropyridines.

TABLE OF CONTENTS

LIST OF TABLES

Table   Page

LIST OF SCHEMES

Scheme

LIST OF FIGURES

CHAPTER I

ALKYLATION OF ALDEHYDES WITH MERCURY (II) ACTIVATED ALKENES

Introduction

Organocatalysis has emerged as powerful tool which is an alternative to metal catalyzed reactions. It involves small molecules as catalysts for chemical transformations. Organocatalysts are commercially available and they are can be used under open air conditions; moreover they are less toxic than traditional metal catalyzed reaction. Due to these factors they have significant advantage over metal catalyzed reactions.[1] Recent publications in this field give a broad picture of organocatalysis.[2-7]

In the early 1970s Hajos, Parrish, Wiechert, Eder and Sauer first reported the proline-catalysed intermolecular aldol reaction (Scheme 1).[8] Nearly 25 years later, Barbas, List and Lerner published the first asymmetric aldol reactions catalyzed by L-Proline (Scheme 1).[7] Here we briefly look at enamine catalysis, by primary or secondary amines.[1-4] Enamines are reactive intermediates prepared by reaction between carbonyl compounds and amines. Nucleophilic enamines generally delocalize electron density on nitrogen with C=C π bond thus increase the sp^2 hybridization of enamine nitrogen. The structure amine has great influence on the p- π delocalization.[9] Usually five membered pyrimidine is more nucleophilic than six membered amine. Proline is an excellent secondary amine for catalyzing Mannich and Aldol reactions (Scheme 1).[5] Its reacts with aldehyde to form catalytic amounts of a nucleophilic enamines. These reactions do not require preformed enol equalents, which is a powerful tool for asymmetric aldol & mannich reactions.
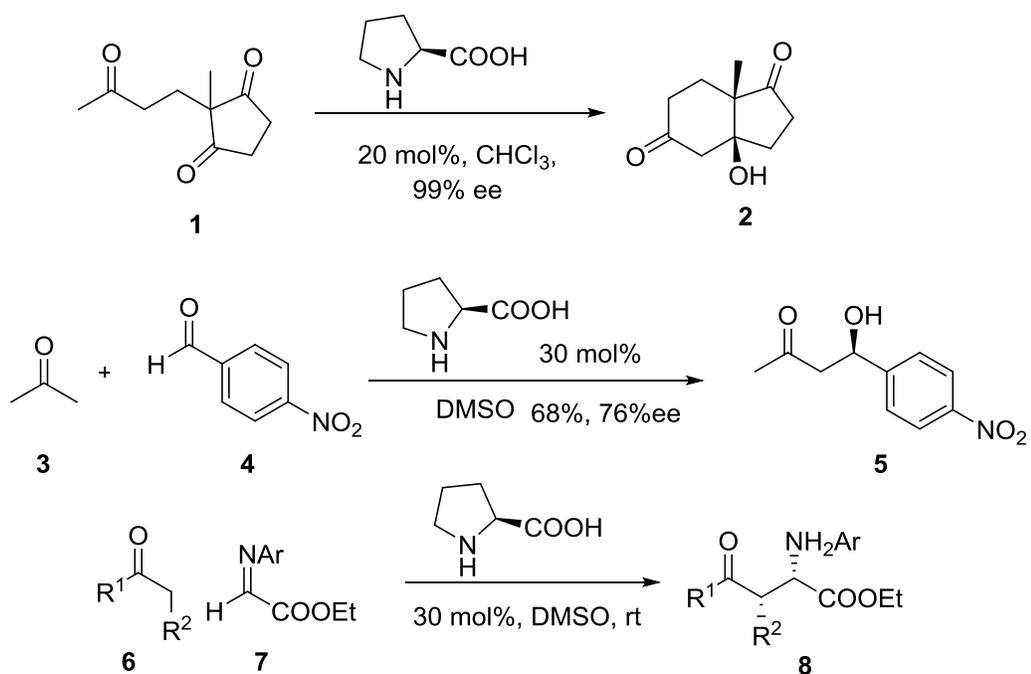
Scheme 1: Proline-catalysed intramolecular aldol reaction, Asymmetric Aldol, Mannich reaction.

Chiral pharmaceuticals are important for therapeutic uses which are difficult to synthesize by employing organocatalysis alone. In the last decade, the combination of transition metal catalysts and organocatalysts has become a powerful tool for developing new reactions.[10,11] Among them, the combination of gold catalysis to activate alkynes and organocatalysis has developed rapidly in the past six years.[12] Methods to activate alkenes in combination with organocatalysis has yet to be developed. We attempted to fill this gap by combining Hg (II) activated olefins with organocatalysis.

Activation of alkenes by Mercury Hg (II) salts:

In 1900, Hoffman and sand discovered the addition of mercury salts to alkenes. The addition of mercuric salts to olefins by solvomercuration followed by reductive demercuration with sodium borohydride is used to prepare alcohols, ethers and amines[13]. Mecury salts have been

used for intramolecular oxymercuration in natural product synthesis. [14,15] However its toxicity limits its use in the pharmaceutical industry.

Combining Organocatalysis with Mercury (II) metal catalysis: An approach to direct alkylation of aldehydes with unactivated alkenes:

Alkylation of aldehydes using orgnocatalysts has been developed over the years. But reactions involving unactivated alkenes towards enamine catalysis are underdeveloped. To solve this problem we attempted to activate alkenes with mercury (II) salts, which is viable to target for doing enamine catalysis (Scheme 2). The aim of this project is to synthesize of library of scaffolds which are found in many natural products.
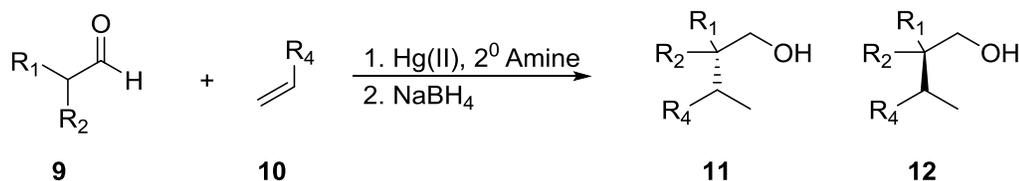
Scheme 2: Combining organocatalysis with mercury (II) activated alkenes

As starting point for combining the organocatalysis with mercury (II) activated alkenes, we selected 1-hexene as our desired alkene because of it more reactivity towards oxymercuration and related reactions. Nucleophic enamine prepared from 3- phenyl propanaldehyde and catalytic amount of pyrrolidine. 1- Hexene was chosen to react with variety of mercury salts such as Hg $(OAc)_2$, $Hg(OTFA)_2$, $Hg(Cl)_2$, $Hg(NO_3)_2$, $Hg(O_3SCH_3)_2$ to provide the required electrophilic site.
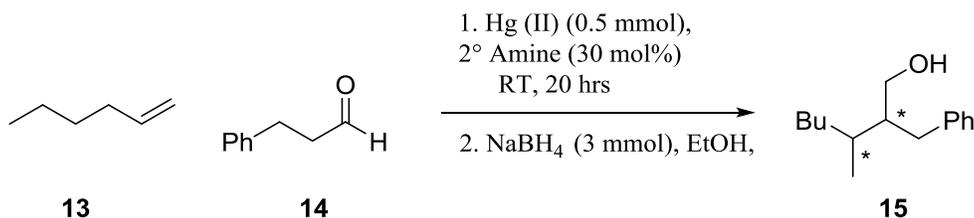
Scheme 3: The proposed reaction for alkylation of aldehydes with Hg (II) activated alkenes
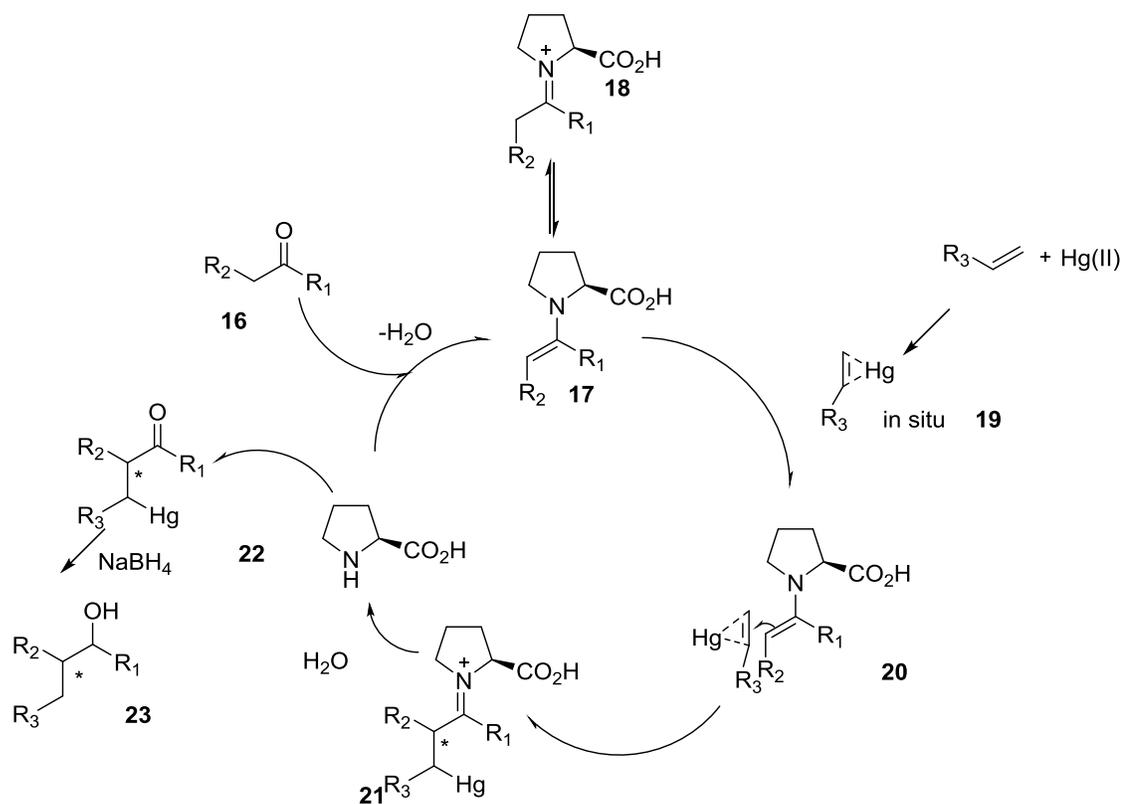
Scheme 4: The proposed catalytic cycle for alkylation of aldehydes with Hg(II) activated alkenes.[7,13]

The proposed catalytic cycle for organocatalysis towards Hg(II) activated alkenes is explained as follows. The 2^0 amine or L-proline reacts with aldehyde **16** to form enamine **17**, which is in equilibrium with iminium ion **18**. Enamine **17** is undergo nucleophilic attack on olefin **19** which is activated by Hg(II) salts affording intermediate **21**. The hydrolysis of intermediate **21** regenerates the catalyst and aldehyde **22**, which upon reduction with sodium borohydride affords alcohol **23**.

In order to effectively and quickly monitor the optimization reactions by GC, we synthesized the final product (2*R*,3*R*)-2-benzyl-3-methylheptan-1-ol (**15**) using standard literature procedures (scheme 5).

Preparation of (2*R*,3*R*)-2-benzyl-3-methylheptan-1-ol:
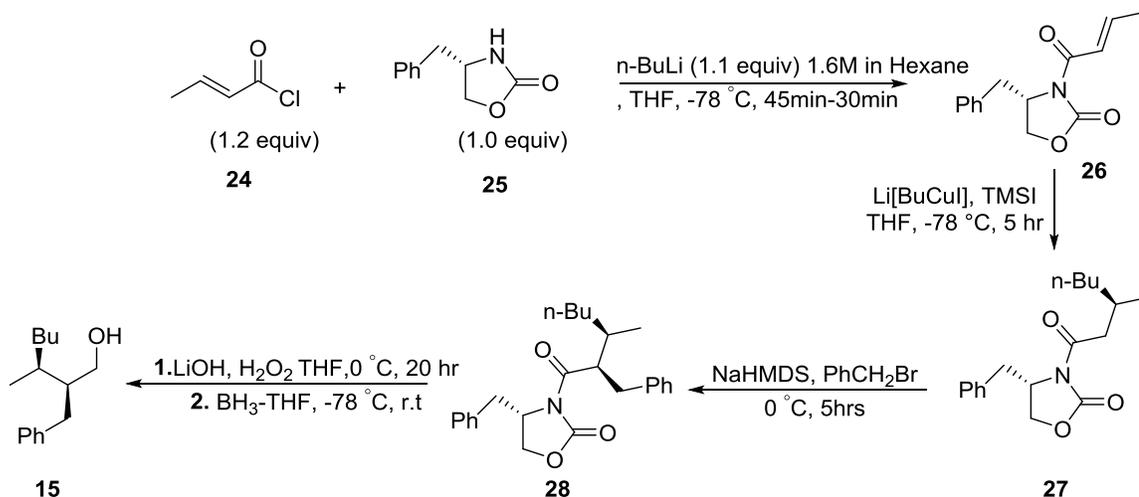
Scheme5: Preparation of 2-benzyl-3-methylheptan-1-ol from Evan's Chiral Auxilary.[14-20]

We started with crotonic acid converted to its acid chloride **24** using thionyl chloride.[17] It was reacted with Evan's chiral auxiliary **25** [(S)-4-benzyloxazolidin-2-one] provide the chiral N-enoyl substituted amide **26**. Chiral 2- oxazolidinones have been known for copper promoted asymmetric conjugate additions of Grigard reagents.[21] Li[BuCuI] monoorganocopper reagent with TMSI as additive known to be effective reagent for the asymmetric conjugate addition reaction.[21] It was important to prepare monoorgano copper reagent from CuI-dimethyl sulfide (DMS) complex. It is the main factor for obtaining good yields and good stereoselectivity in the 1,4- addition of monosilylcopper reagents.[23] The chiral imide **26** upon alkylation with monoorganocopper reagent provide compound **27**.[19] Alkylation chiral imide **26** react with benzyl bromide affording disubstituted chiral imide **28** and subsequent removal of chiral auxiliary with

lithium hydroxide[20] in the presence of hydrogen peroxide yielded acid, followed by reduction with BH_3.THF complex to yield alcohol **15**. [16]

The final compounds were subjected to GC analysis. Calirbration curve was plotted according to table 1.

Table 1: Calibration curve for of 2-benzyl-3-methylheptan-1-ol

% of 2-benzyl-3-methylheptan-1-ol(**6**)	2-benzyl-3-methylheptan-1-ol mmol	Calculated Volume **uL**	Mesitylene[a] (mmol)
100	0.002	25.3	0.002
90	0.0018	22.7	0.002
80	0.0016	20.2	0.002
70	0.0014	17.7	0.002
60	0.0012	15.1	0.002
50	0.0010	12.6	0.002
40	0.0008	10.0	0.002
30	0.0006	7.5	0.002
20	0.0004	5.0	0.002
10	0.0002	2.5	0.002

   a.   mesitylene used as internal standard. Retention time for alcohol **6** =9.515 min, for 3-phenyl propyl alcohol = 9.4 min

All starting material and the possible side products such as 1-hexene, 2-hexanol, 3-phenyl propanaldehyde, 3-phenypropyl alcohol were run on GC. The crude reactions were analyzed and product yields determined from calibration curve.

We attempted to follow general procedure A, we screened the solvents, CH_2Cl_2, DMF, DMSO, Dioxane, THF, with $Hg(OAc)_2$ afforded in 3-phenyl propyl alcohol, which is direct reduction of 3-phenyl propanaldehyde (Table 2).

Table 2: Optimization of reaction by changing solvent system[a]
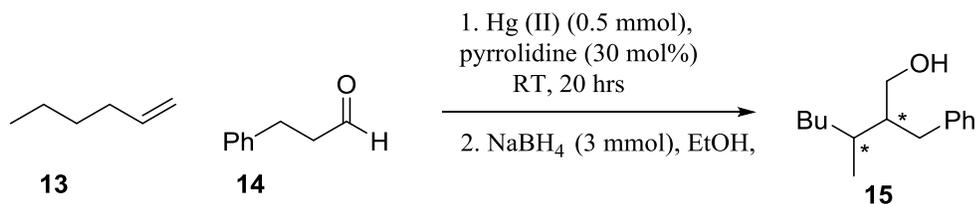
3-phenyl Propanal (mmol)	Solvent	Conc (M)	1-hexene/ Hg(OAc)$_2$(1:1)		Observations	Comment (15)%
0.5	CH$_2$Cl$_2$	0.2	0.5	0.5	No Color	0
0.5	DMF	0.2	0.5	0.5	Yellow	0
0.5	DMSO	0.2	0.5	0.5	Yellow	0
0.5	Dioxane	0.2	0.5	0.5	Yellow	0
0.5	THF	0.2	0.5	0.5	Slight Yellow	0

a. 1-hexene (0.5 mmol), Aldehyde (0.5 mmol), 3-phenyl propyl alcohol was recovered with 80% yield.

We incorporated additives like H$_2$O (1 equiv, 4equiv, 8 equiv), in which most organocatalysis employ water and acid additives to aid the generation of catalyst, but it did not result any observed product formation (Table 3).

Then we tried preformed amine salts by reacting pyrrolidine with, additives like TFA, HCl in stoichiometric amounts. The amine salts were used according to procedure A. The role of additives is to aid the formation of enamine by deprotonating iminium intermediate by conjugate base of co-catalyst. Addition to that we heated this reaction up 60 ^{0}C will always resulting reduced form of starting aldehyde.

Table 3: Optimization of reaction by changing additives concentration[a]
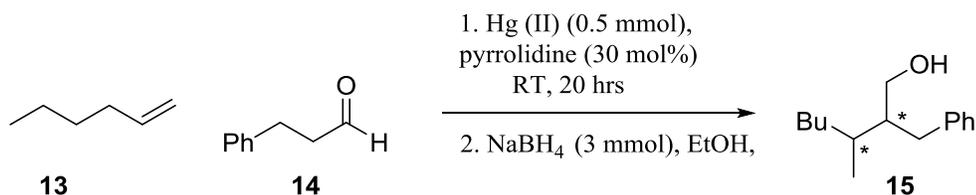
3-phenyl Propanal (mmol)	Solvent	Conc (M)	1-hexene/ Hg(OAc)₂(1:1)		Additive H₂O (1/4/8eq)	Comment **15 %**
0.5	CH₂Cl₂	0.2	0.5	0.5	1/4/8	0
0.5	DMF	0.2	0.5	0.5	1/4/8	0
0.5	DMSO	0.2	0.5	0.5	1/4/8	0
0.5	Dioxane	0.2	0.5	0.5	1/4/8	0
0.5	THF	0.2	0.5	0.5	1/4/8	0

a. 1-hexene (0.5 mmol), Aldehyde (0.5 mmol), 3-phenyl propyl alcohol was recovered with 80% yield.

Tabel 4: Optimization of reaction by changing Mercury (II) salts[a]
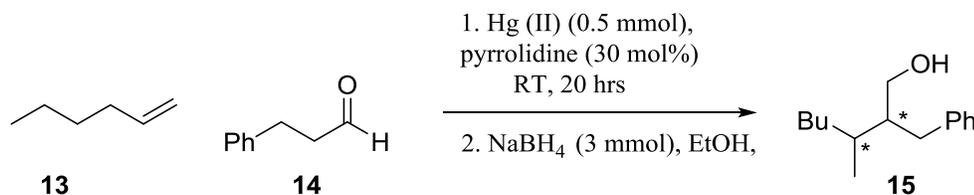
Hg(II)Salt	DCM	Dioxane	DMSO	DMF	THF
Hg(OTFA)₂	NP	NP	NP	NP	NP
Hg(OTf)2	NP	NP	NP	NP	NP
Hg(NO₃)	NP	NP	NP	NP	NP

a. 3-phenyl propyl alcohol was recovered. All reactions were carried at 0.2M. NP=No Product.

We also explored reaction under refluxing conditions and high loading, 1 equiv did not afford any product. In addition to that we did slow addition of enamine to Hg(II) contain mixture using by using syringe pump did not result any product formation.

Alkylation of aldehydes with mercury (II) activated alkenes using preformed enamines

As we can see from the above results with catalytic generated enamine equalents did not observe any product formation. The logical step is to increase the concentration of enamine or to use preformed enamine in stoichiometric quantities and then to react with mercury (II) activated alkenes. The enamine could be synthesized by reaction between cyclohexanone and pyrrolidine at reflux condition using dean-stork apparatus. The yellow oil cyclohexylenamine subjected to reaction with Hg(II) activated 1-Hexene. We tried with the following mercury salts and solvents shown in Table 5 and recovered about 75% of the cyclohexanol as side product without any product formation.

Table 5: Reaction of preformed enamine with Hg (II) activated alkenes
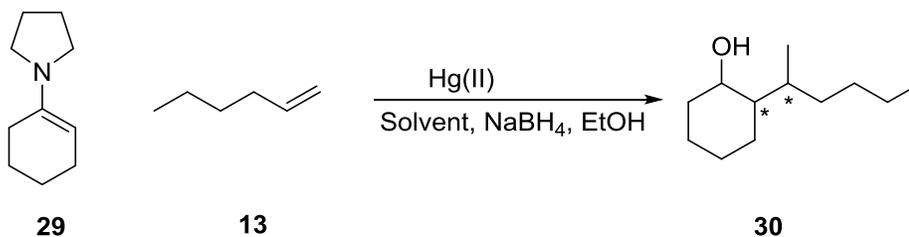
Hg(II)Salt	DCM	Dioxane	DMSO	DMF	THF
Hg(OTFA)$_2$	NP	NP	NP	NP	NP
Hg(OTf)2	NP	NP	NP	NP	NP
Hg(NO$_3$)	NP	NP	NP	NP	NP

Reaction conditions: 1-Hexene 0.5 mmol, Cyclohexylenamine 0.5 mmol, run at 0.2M, NaBH$_4$- 2 equiv, . Np=No Product. About 65-75% cyclohexanol recovered in the reactions.

Conclusions

A study to develop direct alkylation of aldehydes with unactivated alkenes using mercury (II) salts has been performed. We successfully made catalytic amounts of enamine from 3-phenyl propanaldehyde and pyrrolidine and reacted with 1-Hexene activated by variety of mercury salts such as Hg $(OAc)_2$, $Hg(OTFA)_2$, $Hg(Cl)_2$, $Hg(NO_3)_2$,$Hg(O_3SCH_3)_2$. The reactions were performed in various solvents such as THF, DMSO, DMF, CH_2Cl_2, DCE, dioxane at room temperature and reflux conditions. We recovered the reduced form of starting material. Exact reasons for not getting the product were unknown. Attempt to run this reaction at stoichiometric level with activated alkenes did not result any product formation. We suspect that the more reactive enamine was interacting with Hg(II) salts deactivating the alkene. This was corroborated in the mercuration of enamines.[24,28]

Experimental

General procedure for the α-alkylation of aldehydes with unactivated alkene:

General Procedure A

To 15ml round bottom charged with stir bar, 1 equiv mercury(II) salt then solvent was added stirred until the homogeneous solution was obtained. Then to the above solution 1 equiv 1-Hexene was added. In a separate container to 3-phenyl propanaldehyde solution catalytic amounts of pyrrolidine were added. To the above reaction mixture added to solution of 1-Hexene and stirred at room temperature for 24 hrs. Then sodiumborhydrate in ethanol is added. The reaction mixture is filtered through celite (with use 20 mL syringes) and then 30 micro liters of send for analysis over GC. The possible outcome of reaction is monitored with use of calibration

curve. All the reactions were done on 0.5 mmol scale with 1-hexene & 3-phenylpropanaldehyde, 0.2M solvent, 30 mol % of pyrrolidinone.

Preparation of (2*R*,3*R*)-2-benzyl-3-methylheptan-1-ol by Evan's chiral auxiliary:

31   **24**
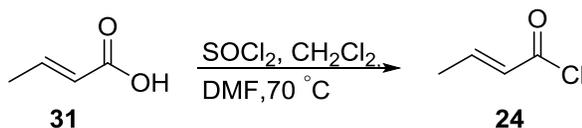
(*E*) **But-2-enoyl chloride (24)[17] :** Yield= 95%, obtained 1.0 g as a yellow color oil. To an oven-dried and argon-purged 10 ml round bottom flask was charged with thionyl chloride (2.55ml, 35mmol, 3.5 equiv) in CH_2Cl_2 is added to crotonic acid (0.86g, 10mmol, 1 equiv) and DMF (1drop). The reaction gradually heat to 70^0 C for 2 hrs. The reaction mixtures are cooled to r.t then concentrated yield a yellow color compound. The crude compound is sensitive to moisture. ^{1}H NMR, ^{13}C NMR was not taken to minimize exposure.

25   **24**   **26**
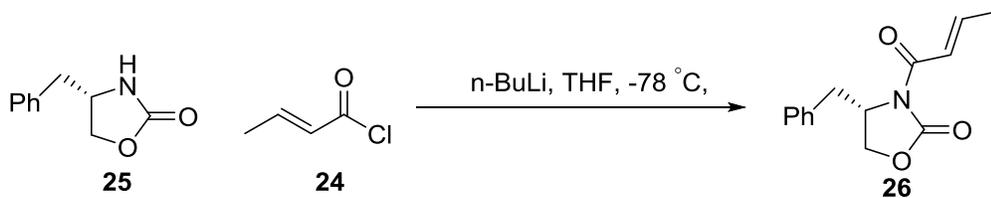
N-(2'*E*-Butenoyl)-4*S*-phenylmethyl-1,3-oxazolidin-2-one (26)[18]:   Yield 55%. To oven-dried and argon purged 25ml round bottom is charged with stir bar then butyl lithium (1.6 M in hexane, 1.1 equiv, 3.66 mmol, 2.25ml) was added to a solution of (*S*)-4-Benzyl-2-oxazolidinone (1.0 equiv, 3.32 mmol, 0.5894 g) in THF at -78 °C. The reaction mixture was stirred for 45 min and a solution of the acyl chloride (1.5 equiv, 5mmol, 0.5225g) in THF was added at -78 °C. The reaction mixture was stirred for 30 min and then warmed to room temperature.   The above reaction quenched with aqueous ammonium chloride and then diluted with distilled water.

11

Extraction with ether (3 x 20 mL), the combined organics was dried with MgSO$_4$, filtered and solvent was evaporated.

The crude product was purified using column chromatography (Hexanes/EtOAc: 95/5 then 50/50) afforded 82% of N-(2'E-Butenoyl)-4S-phenylmethyl-1,3-oxazolidin-2-one as white solid. The compound is subjected to recrystallization, yielded white crystalline compound. ^{1}H NMR (400 MHz, CDCl$_3$), δ 7.34-7.18 (m, Ar-H and olefinic, 7H), 4.74(m, J=2.3 Hz, 1H), 4.22(dd, J=7.02 and 10.15Hz, 1H), 3.40(dd, J=3.9 and 13.2 Hz, 1H), 2.87(dd, J=9.36 and 13.2Hz), 1.98(d, J=5.4Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 165.0, 153.5, 147.0, 135.4, 129.3, 129.1, 127.4, 122.0, 66.1,55.4, 38.0, 18.6

Preparation of CuI–DMS complex[25]: CuI is purified according to the following procedure. To 113 mol of NaI dissolved in water (40 mL) and boiled for 30 minits, then 10 mmol (1.9g) of CuI is added and heated it another 15 minits. Pure CuI is produced by cooling and diluting the solution with water, followed by filtration. Wash the solid with water, ethanol, Ethylacetate and ether. Let it dry for 24 hrs.

To 5g of pulverized CuI was added to 15ml of Et$_2$O and 20ml of Me$_2$S. The reaction mixture stirred at r.t until deep red solution is obtained. It is filtered and then 50 ml of hexanes is added which is resulting a crystalline material, which was filtered and washed with hexane resulting white crystals.
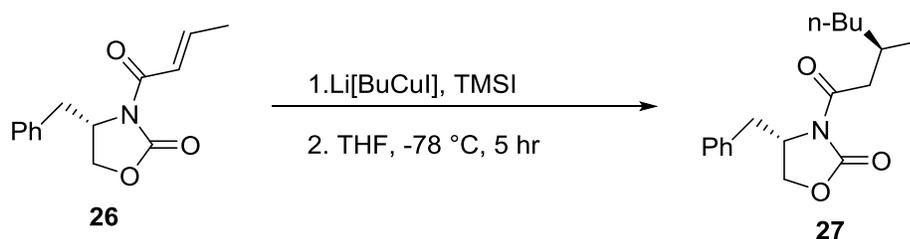
(S)-4-benzyl-3-((R)-3-methylheptanoyl)oxazolidin-2-one (27): Yield=70%, It was prepared by adding n-BuLi(1.6M in Hexanes, 1.83 equiv, 9.15 mmol, 5.71 mL) to a slurry of purified CuI-

DMS complex(1.3 equiv, 10.75 mmol, 2.04 g) in distilled THF at -40 °C. After stirring for about

20 min, temperature of orange heterogeneous butyl cupper was lowered to -78 °C and TMSI

added slowly via syringe. Thereafter a solution of chiral imide in THF added slowly to cooled

flask and stirred for about 4 hr at -78 °C then dry triethylamine was added. After stirring for 1

hour at -78 °C, a saturated solution of NH$_4$Cl was added. The reaction mixture warmed to room

temperature stirred until homogenous deep blue solution was obtained. The contents were then

transferred in to a mixture of ether (20 mL) and water (20 mL) and poured in to a separation

funnel. Seperatory funnel was used to separate the aqueous and organic layers. The aqueous

layer was extracted with ether (3 x 20 mL) and the combined organic layers dried with MgSO4

and solvent is removed under rotary evaporation. Crude compound is purified by column

chromatography (Hexanes/EtOAc : 90/10 then 50/50) afforded 1.51 g (70%) of (N-(3$^{'}$ R-

Methylheptanoyl)-4S-phenylmethyl-1,3-oxazolidin-2-one. ^{1}H NMR (400 MHz, CDCl$_3$), δ 7.35–

7.20 (m, 5H), 4.71 (m, 1H), 4.18 (dd, J=7.8 Hz and 9.36, 2H), 3.3(dd, J=3.1 and 16.3 Hz, 1H),

2.92 (dd, J=15.5, 4.5 Hz, 1H), 2.84 (dd, J=15.5 and 6.0 Hz, 1H), 2.78 (dd, J=12.0 and 9.0 Hz,

1H), 2.11(m, 1H), 1.47-1.1(m, 6H) 1.02 (d, J=6.2 Hz, 3H), 0.8(t, J= 7.02 Hz, 3H). ^{13}C NMR (100

MHz, CDCl$_3$) 172.9, 153.4, 135.4, 129.4, 129.0, 127.2, 66.1, 55.2, 42.5, 38.0, 36.5, 29.7, 29.3,

22.7, 19.6, 13.9
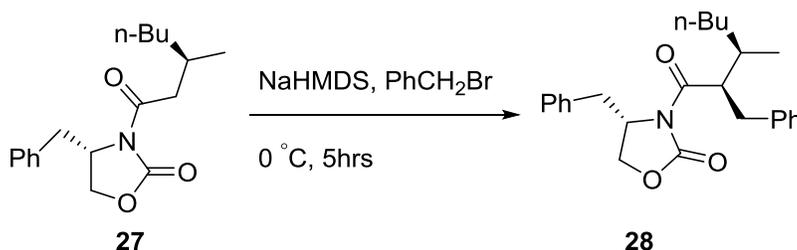
(S)-4-benzyl-3-((2R,3R)-2-benzyl-3-methylheptanoyl)oxazolidin-2-one (28)[19]: To oven dried

and argon purged round bottom charged with stir bar and solution of N-(3$^{'}$ R-Methylheptanoyl)-

4S-phenylmethyl-1,3-oxazolidin-2-one (1 equiv, 3.29 mmol, 1.0g) in THF at -78 °C. NaHMDS

(1.5 equiv, 4.935 mmol, and 0.929 g) is added slowly to the above solution and stirred for 30 min.

To the reaction mixture, benzyl bromide (3 equiv, 9.87 mmol, and 1.688 g) was added slowly via

syringe and the reaction stirred at 0°C before addition of saturated NH$_4$Cl solution. The solution

was extracted with EtOAc then washed with brine solution and dried over MgSO$_4$. The organic

extracts concentrated under reduced pressure and purified by column chromatography (Silica gel,

Hexanes/EtOAc : 90/10 then 75/25) afforded 1.29g (65%) of (4S)-4-benzyl-3-(2-benzyl-3-

methylheptanoyl)oxazolidin-2-one. . ^{1}H NMR (400 MHz, CDCl$_3$), δ 7.33–7.20 (m, 10H), 4.71

(m, 1H), 4.18 (dd, J=7.8 and 9.36 Hz, 2H), 3.3(dd, J=3.1 and 16.3 Hz, 1H), 2.92 (dd, J=15.5, 4.5

Hz, 1H), 2.84 (dd, t, J=15.5 and 6.0 Hz, 2H), 2.78 (dd, J=12.0 and 9.0 Hz, 2H), 2.11(m, 1H),

1.47-1.1(m, 6H) 1.02 (d, J=6.2 Hz, 3H), 0.8(t, J= 7.02 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$)

173.2, 152.1, 135.3, 129.2, 129.1, 127.2, 127.3, 66.1, 55.0, 42.3, 38.0, 36.5, 29.7, 22.8, 19.6, 14.1
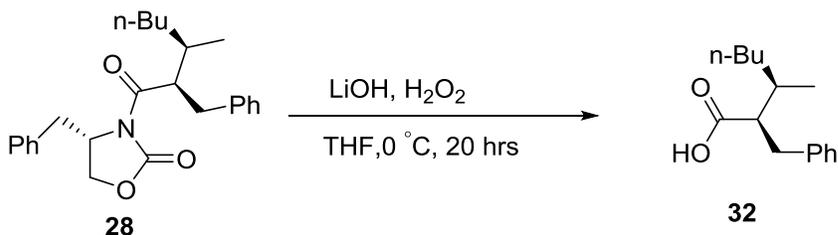
(2R,3R)-2-benzyl-3-methylheptanoic acid[20]: Yield=77%   To stirred solution of chiral imide (1

eq, 1.28 mmol, 0.5060 g) in THF/H$_2$O (3:1) 20 ml was added to LiOH (1.5 eq, 1.93 mmol, 0.04

g) at 0°C. After 2 min H$_2$O$_2$ (35%, 4eq, 5.12 mmol, 0.43 mL) was added and stirred at 0°C until

completion of the reaction. The reaction is quenched with Na$_2$S$_2$O$_3$ (1.5 M). The reaction mixture

is concentrated by evaporating THF. The solution is made slightly acidic (pH = 6) by addition of

HCl (5M). The mixture was treated with aqueous NaOH (2M) to pH 8-9. The organic layer was

extracted with EtOAc and it was washed with NaOH, brine and dried over MgSO$_4$, concentrated

under vacuum afforded chiral auxiliary. The basic layer treated with HCl (pH = 2-3). The mixture

was extracted with CH$_2$Cl$_2$ (pH 2-3). The organic layers were combined, washed with brine, dried

over MgSO4, and concentrated. The crude compounds is purified through column chromatography (Hexanes/EtOAc : 90/10) afforded 0.299 g (77%) of 2-benzyl-3-methylheptanoic acid. . ^{1}H NMR (400 MHz, CDCl$_3$), δ 7.1-7.3 (m, 5H), 2.9 (m, 2H), 2.65 (m, 1H), 1.94 (m, 1H), 1.55 (m, 1H), 1.3-1.4 (m, 5H), 1.05 (d, J=7.02 Hz, 3H), 0.95 (t, J=5.4 Hz, 3H).
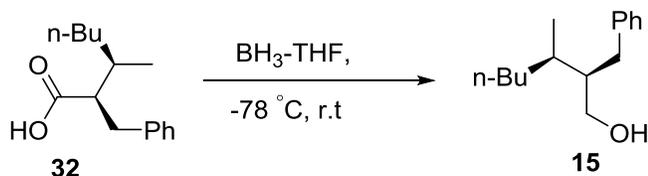
(2R,3R)-2-benzyl-3-methylheptan-1-ol (15)[16]: Yield=70%, obtained 0.174 g colorless oil. To a stirred solution of 2-benzyl-3-methylheptanoic acid (1 equiv, 0.85 mmol, 0.2g) in THF, solution of BH$_3$-THF complex (1.1 equiv, 0.939 mmol, 0.93 mL) added slowly at 78 °C. The mixture allowed to warm room temperature and stirred over 20 hrs. The excess reagent is quenched with HCl at 0 °C. After evaporation of the solvent, CH$_2$Cl$_2$ and NaHCO$_3$ were added. The phase's separated, aqueous phase extracted with CH$_2$Cl$_2$. The combined organics dried over MgSO$_4$ and the solvent is removed under reduced pressure. The crude compound is purified by column chromatography (Silica gel, Hexanes/EtOAc : 90/10) afforded 0.174 g (70%) of 2-benzyl-3-ethylheptan-1-ol as colorless oil. . ^{1}H NMR (400 MHz, CDCl$_3$), δ 7.15-7.28 (m, 5H), 3.55 (m, 2H), 2.7 (m, 2H), 2.42 (m, 1H), 1.6-1.8 (m, 3H), 1.0-1.57 (m, 4H), 0.89 (m, 6H); ^{13}C NMR (400 MHz, CDCl$_3$) δ 141.6, 129.0, 128.4, 125.8, 63.5, 47.6, 35.3, 33.9, 32.7, 33.1, 29.9, 23.07, 15.8, 14.2; IR 3350. The spectral data is consitstent with literature[14]

Preparation of Cyclohexylenamin[26,27]:
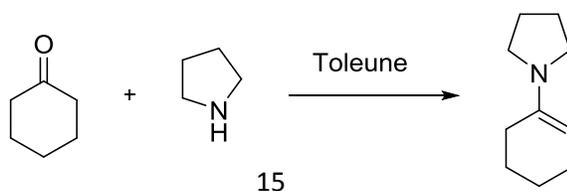
This reaction was carried using dean-stork apparatus. The oven dried argon purged round bottom charged with dean stork apparatus , solution of cyclohexanone (1equiv, 10 mmol, 0.9814g) and pyrrolidin (2 equiv, 20 mmol, 1.422g) , PTSA in catalytic amounts (1 or 2 drops) in toluene. The reaction mixture underwent azeotropic distillation until the reaction water was separated (approx. 5 hrs). $CaCl_2$ and MS were employed to absorb the water generated in the reaction. Reaction can be concentrated resulting cyclohexylenamine as yellow oil which was further purified by vacuum distillation.

References

(1)   Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8-27.

(2)   Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175.

(3)   Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726-3748.

(4)   List, B. *Acc. Chem. Res.* **2004**, *37*, 548-557.

(5)   Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580-591.

(6)   List, B. *Adv. Synth. Catal.* **2004**, *346*, 1021-1021.

(7)   List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

(8)   Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.

(9)   Pihko, P. M.; Majander, I.; Erkkila, A. *Top. Curr. Chem.* **2010**, *291*, 29-75.

(10)   Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, *2010*, 2999-3025.

(11)   Du, Z.; Shao, Z. *Chem. Soc. Rev.* **2013**, *42*, 1337-1378.

(12)   Loh, C. C. J.; Enders, D. *Chem.--Eur. J.* **2012**, *18*, 10212-10225.

(13)   Pasto, D. J.; Gontarz, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 7480-7482.

(14)   Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535-2538.

(15)   Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763-7772.

(16)   Toró, A.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 6847-6852.

(17)   Jung, M. E.; Im, G. Y. J. *J. Org. Chem.***2009**, *74*, 8739-8753.

(18)   Dambacher, J.; Anness, R.; Pollock, P.; Bergdahl, M. *Tetrahedron.* **2004**, *60*, 2097-2110.

(19)   Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2886-2899.

(20)   Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J.-x. *J. Org. Chem.* **2002**, *67*, 1738-1745.

(21)   Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766-770.

(22)   Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015-6018.

(23)   Dambacher, J.; Bergdahl, M. *Chem. Comm.* **2003**, 144-145.

(24)   Gasc, M. B.; Perie, J.; Lattes, A. *Tetrahedron* **1978**, *34*, 1943-1950.

(25)   House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.***1975**, *40*, 1460-1469.

(26)   Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207-222.

(27)   Tenora, L.; Buchlovič, M.; Man, S.; Potáček, M. *Tetrahedron Lett.* **2011**, *52*, 401-403.

(28)   Cadogan, J. I. G.; Mitchell, J. R.; Sharp, J. T.; Bach, R. D.; Mitra, D. K. *J. Chem. Soc D: Chem. Comm.* **1971**, 1433-1434.

CHAPTER II

COMBINING GOLD CATALYSIS WITH ORGANOCATALYSIS USING SILICON

TETHERS: DIRECT FUNCTIONALISATION OF CARBONYL COMPOUNDS WITH

ALKYNES

Introduction

Transition metal catalyzed reactions have been well known in organic synthesis. Over the past 14

years the use of small organic molecules in organocatalysis has grown tremendously. The unique

activation mode provided by organocatalysis has considerable advantage over the transition metal

catalysis. In recent years combination of the transition metal catalysis with organocatalysis (dual

catalysis) has gained considerable attention.   The main advantage of dual catalytic systems is the

ability to access certain molecular frameworks not currently possible using single catalytic

systems.   In our long term goal of the library development for accessing biologically active

complex molecules, we initiated to explore this dual catalytic system utilizing temporary silicon

tethers.

Organocatalysis is primarily connected with the use of small organic molecules as catalyst for

chemical transformations. List and Barbas[1] first reported the use of secondary amines as catalyst

for asymmetric functionalization of carbonyl compounds. The secondary amine catalyzed

reactions with carbonyl compounds preceeded through either enamine or iminium intermediates.

It reacts with aldehydes and ketones to provide reactive enamines whereas α, β-unsaturated

carbonyl compounds provide iminium intermediates. Hence the choice of substrate determines

the activation mode for the catalysis.

In 2006, Cardova first showed the utility of dual catalysis by combining enamine catalysis with transition metal (Pd) catalysis. As direct alkylation of aldehydes and ketones suffers unwanted side reactions.[2] He reported the direct catalytic intermolecular α-allylic alkylation of aldehydes and ketones (Scheme 6). They used catalytic amount of Pd(PPh$_3$) (5 mol %), pyrrolidine (10 mol %), obtained α-allylated carbonyls compounds in good yields (up to 95%). It was reported that enamine and Pd-π complexes[4] were the reactive intermediate in this reaction. Aldehydes react with secondary amines *in situ* to generate the catalytic enamine intermediate **37** and the nucleophilc attack on Pd-π allyl complex **38** followed by reductive elimination provides the iminium intermediate **39**, which is subjected to hydrolysis to furnish the alkylated aldehyde and the secondary amine (Scheme 7).
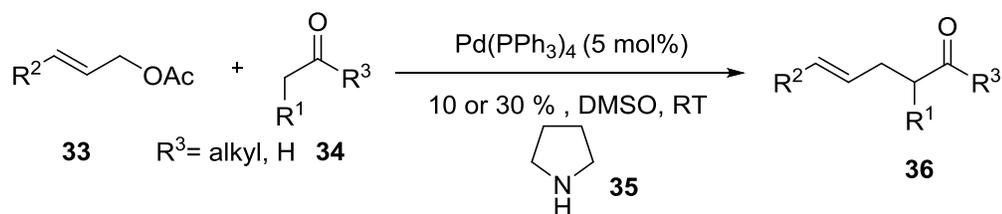
Scheme 6: Direct catalytic intermolecular α-allylic alkylation of aldehydes and ketones
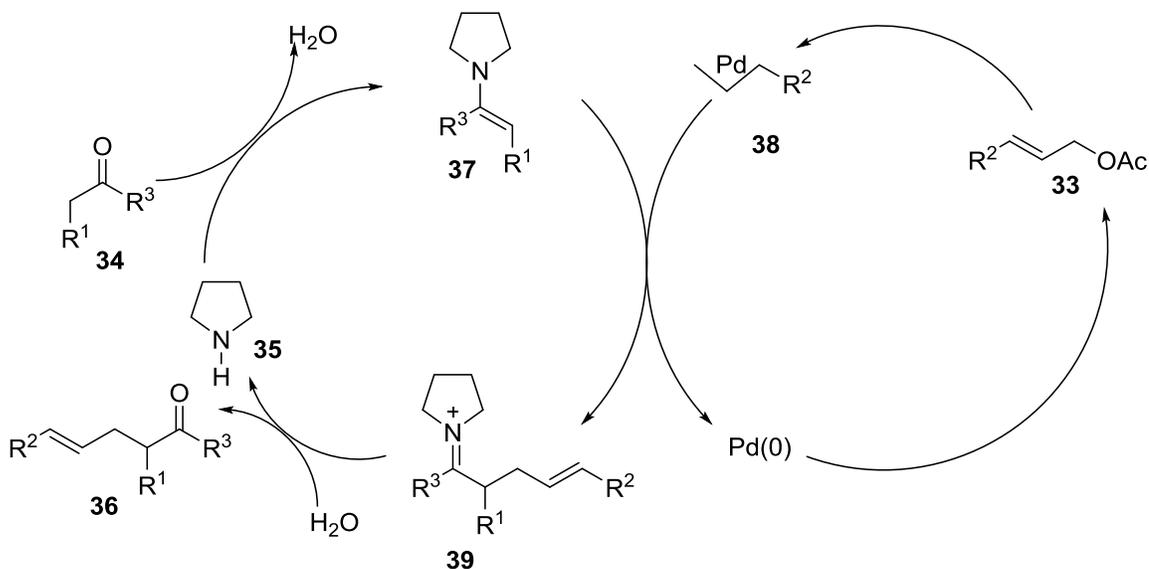
Scheme 7: Mechanism of intermolecular α-allylic alkylation of aldehydes and cyclic ketones.

Homogeneous gold catalysis

Homogeneous gold catalysis plays an important role in organic synthesis due to its unique carbophilicity towards alkynes, alkenes and allenes.[5-7] Gold catalysis is an excellent tool for cyclization reactions forming complex carbocycles.[8] The π-activation property of Au has been exploited in various cyclization reactions, carbon-carbon bond forming reactions and carbon-heteroatom bond forming reactions.[9] The advantage of gold catalysis mainly due to its tolerance to moisture and air, which allows us to perform reactions in an open flask. However, the catalytic system has certain limitations to overcome.

In our long term goal towards library development, we hope to combine transition metal catalysis with organocatalysis. In that direction, we want to explore the emerging gold catalysis with organocatalysis. Over the last five years very few reports on combining the gold catalysis with organocatalysis have emerged. Gold is an excellent metal for activating the alkyne containing substrates. With gold catalysis we can access cyclization modes which were not possible with

organocatalysis. Gold being a carbophilic π-acid activates the alkyne, alkene or allene through accepting the electron density from multiple bonds. The general gold catalyzed mechanism is explained in Scheme 3.[9] The substrate containing both nucleophile and alkyne is shown in the Scheme 8. The gold catalyst precursor LAuX, (X=Cl, Br, I) is a bidentate ligand. The silver salt $AgSbF_6$ is necessary to activate the catalyst by abstraction of halide ion, where the thermodynamically stable AgX salt precipitates out of the solution. The bulky SbF_6 ion counters the Au catalyst. This an ion exchange process provides the catalytic site for activating the multiple bonds such on the alkyne, alkene or allene. For substrate **40** gold activates the alkyne in The nucleophilic attacks the alkyne intermediate **41** to generate a new Au-C covalent bond in **42**, which undergoes proton exchange known as protodeauration to afford **43**. The Au-C bond must be cleaved to regenerate the active catalyst.
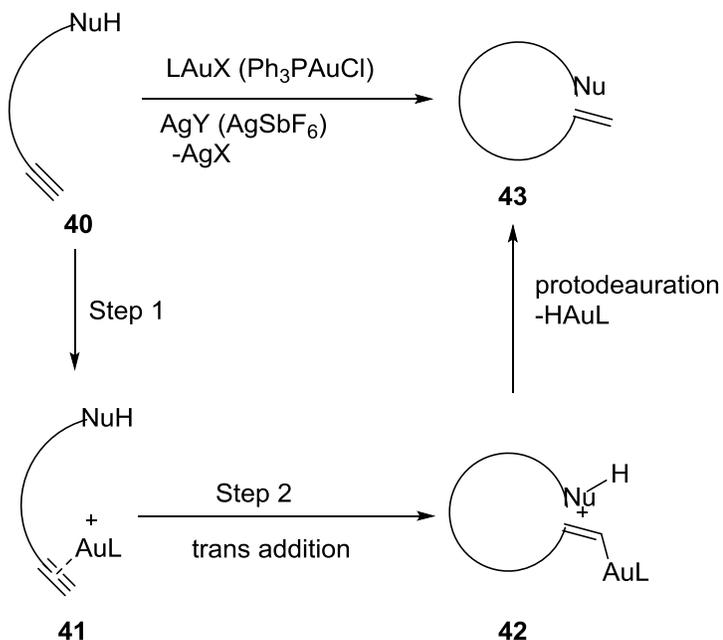
Scheme 8: Mechanism of homogeneous gold catalysis

Toste showed that active methylene compounds react with unactivated alkyne in the presence of catalytic Au(I) form complex carbocycles.[10] He obtained cyclopentenoid structures by gold

catalyzed 5-endo-dig addition of carbonyl compounds to unactivated alkynes. Akynyl gold complexes cannot react directly with the less enolizable carbonyl compounds. It was limited by its nucleophilicity to attack the gold-alkyne complex. Other nucleophilic sources such as alkyl enol ethers, silyl enol ethers,[11] and enamines[12] readily react with alkyne-gold complexes resulting new C-C bond formation, but it is limited due to additional step required for enol equivalents (Scheme 9).
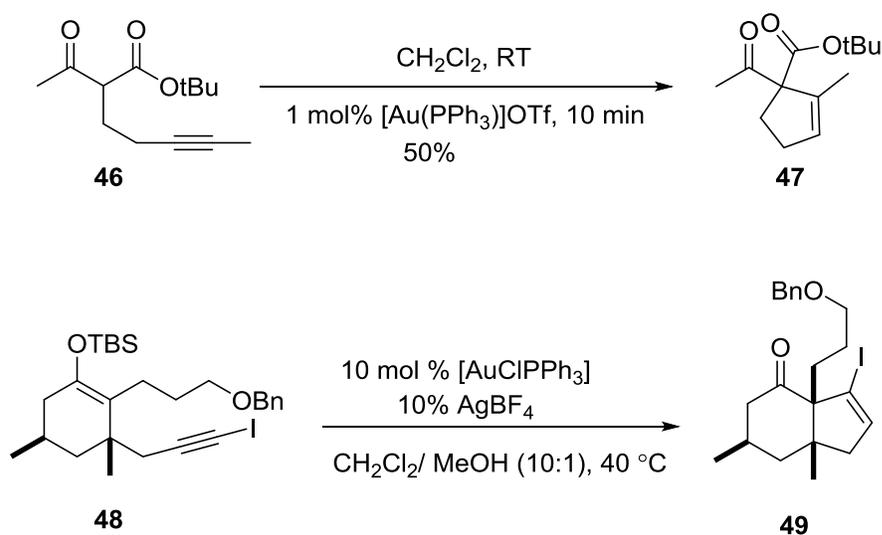
Scheme 9: Active methylene compounds, silyl enol ethers react with alkyne-gold complexes
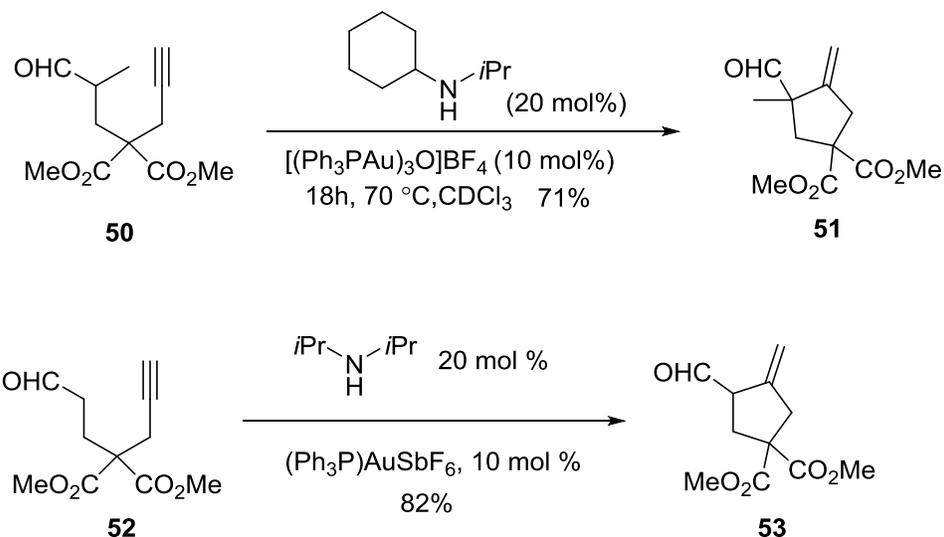
Scheme 10: Carbocyclization of aldehydes with alkynes.

Kirsch reported the direct carbocyclization of alkynes with aldehydes by combining gold catalysis with secondary amine catalysis (Scheme 10).[8] For combining organocatalysis with homogeneous gold catalysis, Kirsche reported cyclization through catalytically generated enol equivalents by reaction of secondary amine with aldehydes. [8,13-15] The intramolecular reaction of provides the direct α-functionalization of aldehydes with alkynes without use of preformed enol equivalents. Gold catalyst and enamine cooperate each other to enable cyclization. The products are rationalized by nucleophic attack of enamine on an alkynyl-Au complex. The product undergoes rearrangement to the thermodynamically more stable product (Scheme 6)
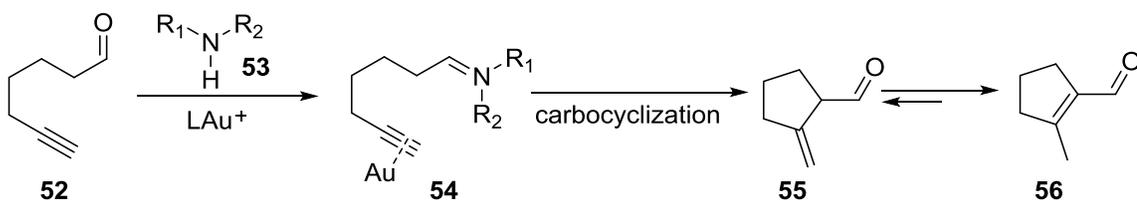
Scheme 11: Mechanism for direct carbocyclization of aldehydes with alkynes.

Our Approach
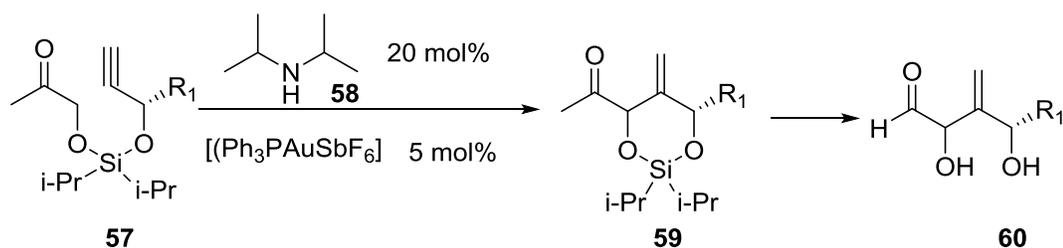
Scheme 12: Combining gold catalysis with organocatalysis using silicon tethers.

Only intramolecular cyclization's involving dual catalysis were reported. We want to do it via an intermolecular path by utilizing silicon tether technology and followed by cleavage of tether. Disiloxane and siloxane structural motifs are the most common linker used to achieve intramolecularization.

Introduction to silicon tethers

The development of organic synthetic methodology is an important process to reduce linear steps and achieve a more efficient synthesis.[16] Temporary tethers such as silicon,[17] boron,[18] phosphorous,[19] and esters[20] have been used to access biologically active complex molecules. However silicon tethers are most prominent due to its stability towards a variety of reaction conditions and easy removal following reaction. Organosilicon compounds are utilized in variety of areas such as medicinal chemistry, bio-molecular chemistry, solid-state and organic chemistry.[21] Their compatibility with biological system will make them possible drug additives and drug delivery regulators.[21] Organosilicon compounds such as allylsilanes, alkoxysilanes are widely utilized in organic synthesis.

Silicon tether technology is widely used to facilitate intramolecular reactions. In intramolecular reactions, rate increased due to the proximity effect.[16] In addition to that intramolecularization increase, conformational restriction of the transition may also increase regio and stereoselectivity. Thus, tethering increases the reactivity and selectivity of chemical reactions. Tethering can be achieved through an appropriate linker, and it should meet certain properties. The ideal tether

should be introduced in high yield and it must tolerate the reaction conditions. Additionally the tether could be easily removed or converted to other functional groups following the intramolecular reactions. By considering those in to account, it becomes obvious that silicon based functionalities are suitable tethers.[17] Silicon tethers are widely employed in stereospecific intramolecular reactions,[17] protecting agents,[22] substrates for solid support synthesis.[23] Itoh[24] and Stork and Kahn [25] first explained use of silicon tethers in radical cyclization reactions (Scheme 13). The use of silicon tethers in the Diels-Alder reaction gave complete control over the regio- and stereoselectivity.[26]

Itoh (1984)
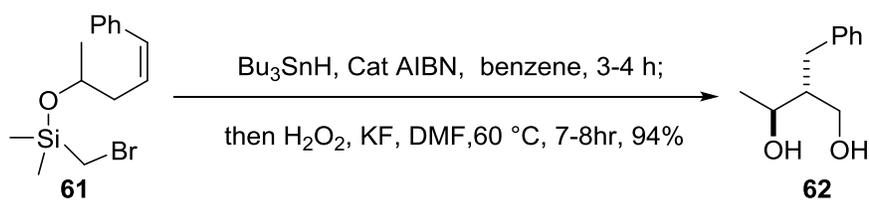
Stork (1985)
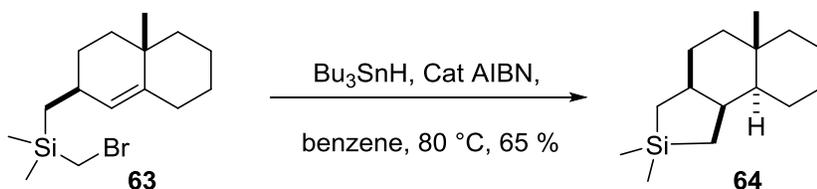
Craig (1990)
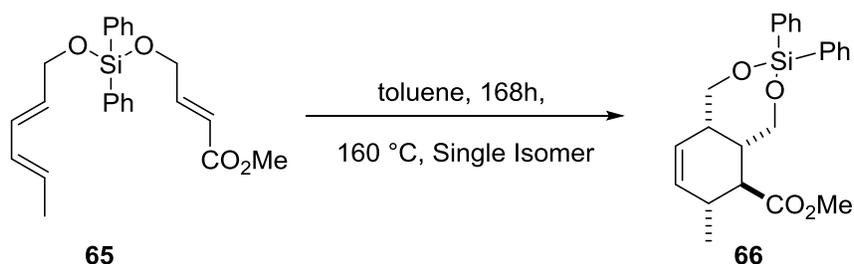
Scheme 13: Examples of the temporary silicon tether in radical cyclization.

The silyl ethers are safe and compatible with different reaction conditions. Use of silicon tethers has played a considerable role in the synthesis of complex compounds. Tethering permitted

25

reactants to undergo intramolecularization, thereby increasing the reaction rate as were as the regio and stereoselectivity.

$$R_2Si(Cl)_2 \; \textbf{67} \xrightarrow{R^1\text{-OH}} R_2Si(OR^1)(Cl) \; \textbf{68} \xrightarrow{R^2\text{-OH}} R_2Si(OR^1)(OR^2) \; \textbf{69}$$

$$R_2Si(Cl)(NMe_2) \; \textbf{70} \xrightarrow[R^2\text{-OH}]{R^1\text{-M}} R_2Si(R^1)(OR^2) \; \textbf{71}$$

$$R_2Si(Cl)(H) \; \textbf{72} \xrightarrow[M=MgX,\ Li,\ SnR_3]{R^1\text{-M}} R_2Si(R^1)(H) \; \textbf{73} \xrightarrow[\text{or NBS, } R^2\text{-OH}]{[M]\ cat,\ R^2\text{-OH}} R_2Si(R^1)(OR^2) \; \textbf{74}$$

$$R_2Si(Cl)(H) \text{ (or) } HN(SiMe_2H)_2 \; \textbf{75} \xrightarrow{R^1\text{-OH}} R_2Si(OR^1)(H) \; \textbf{76} \xrightarrow[R^2\text{-OH}]{\text{NBS, or [M] cat}} R_2Si(OR^1)(OR^2) \; \textbf{77}$$
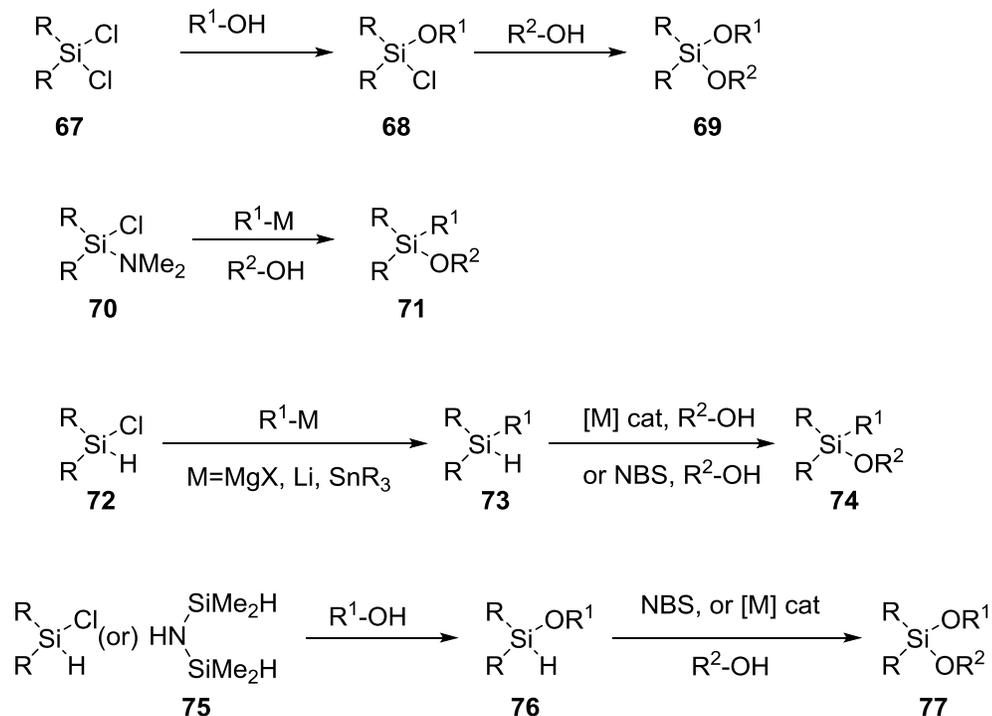
Scheme 14: Common routes for the preparation of disiloxane (bisalkoxysilane) and siloxane linker.

Common methods for tether incorporation

The most common linkers are disiloxans, containing two Si-O bonds and siloxans, one Si-O bond.[16] We will address only disiloxane linkers in the context of gold catalysis. Different routes have developed to synthesize disiloxane moiety (scheme 9). It is usually prepared by sequential addition of two alcohols to dichlorosilane. However it has certain limitations due to possible double substitution. The use of excess silane overcomes the problem of double substitution but this strategy is limited to the volatile dialkyldichlorosilanes such as dimethyl dichlorosilane. For more nonvolatile silanes, one usually observes a statistically determined mixture of mono and

dialkoxy silyl ethers. For better control over substitution, tetraalkyldisilazane, chlorosilanes, or aminochlorosilane were used to prepare siloxanes (Scheme 14).

Silyl ethers (siloxanes) and silyl ketals (disiloxanes) are most often used for protecting groups for the hydroxyl group. They are versatile and easy to remove under acidic conditions. Silyl ethers can be prepared by transition metal catalyzed alcoholysis of silanes. This process delivers hydrogen gas as a byproduct. It is atom economical and avoids the use of bases and excess silicon dichloride. Several reports on the use of trialkylsilanes to prepare silyl ethers have appeared.[27,28] The list of transition metal catalysts that were employed for synthesis of silyl ethers include Wilkinson's catalyst,[28] Stryker's catalyst,[29] Doyle's rhodium(II) perfluorobutyrate,[30] Cutler's $Mn(CO)_5Br$ and its dimer $[Mn(CO)_4Br]_2$, $IrCl(C_8H_{14})_2]_2$,[31] cationic complexes $([IrH_2(THF)_2(PPh_3)Fe^+]^{32}$ and cis-$PtCl_2(PhCH=CH_2)_2$.[33] Corriu and Moreau $et\ al$, reported $(Ph_3P)_3RhCl$ and $(Ph_3P)_3RuCl$ catalysts for synthesis of silyl ethers from dihydrosilanes.[34] Recently, Colleen $et\ al$ reported $Rh_2(OAc)_4$ and $Mn(CO)_5$ Br transition metal catalysts for the synthesis of bis-alkoxysilanes from dihydridosilanes in two steps (Scheme 15).[35]
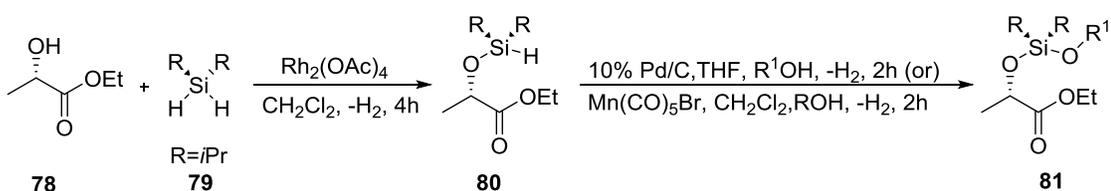
Scheme 15: Synthesis of unsymmetrical bisalkoxysilane from chlorosilane.

Results and Discussion

In order to find a suitable route to the synthesis of the our target molecules unsymmetrical bisalkoxysilane (disiloxane) bearing a propargyl group and a carbonyl functionality, we attempted many synthetic procedures. In our initial attempts we used dimethyl dichlorsilane and obtained a mixture of mono and dialkoxy chlorosilanes based on crude NMR. Attempts to isolate these

compounds using column chromatography failed due to similar Rf values. Silica is acidic enough to cleave the dimethyl alkoxy silane and could be a potential problem for isolation. We changed from dimethyldichlorosilane to less volatile diphenyldichlorosilane. The diphenyl substituted silyl ethers are more stable to chromatography conditions. We subjected the diphenyl dichlorosilane to sequential addition of alcohols. But we obtained mixture of mono and disubstituted products. We are not able to isolate the products in pure form using column chromatography. We found that the problem with double substitution is due to the symmetrical nature of the diphenyldichlorosilane. We thought that changing reactivity of the one chloride by reacting with diethyl amine to give aminochlorosilane (Et_2NPh_2SiCl).[36]

We subjected aminochlorosilane to sequential addition of alcohols (procedure A) and observed mono and di substituted disiloxanes with close Rf values. All the efforts to isolate pure disiloxane using column chromatography failed. Since the dichlorosilane and aminochlorosilane afforded little control over selectivity, we proceeded to use more expensive diisopropyl chlorosilane.

We hoped that reaction of diisopropylchlorosilane with alcohol would facilitate the addition of alcohol under mild conditions and to generate the mono alkoxysilane (Scheme 16).
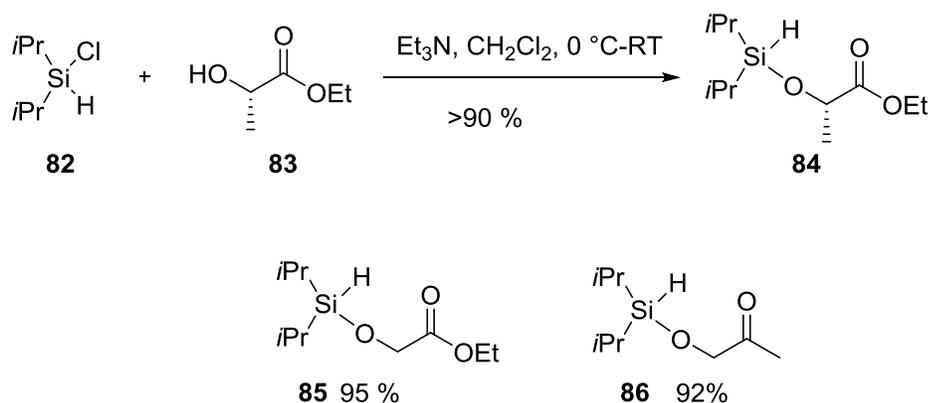
Scheme 16: Preparation of mono-alkoxy silane from chlorodiisopropyl silane

In second step of alcoholysis, we selected a catalytic system that was tolerable to alkynes. It was reported that Cutler's $Mn(CO)_5Br$ and its dimer were compatible with alkenes and alkynes.[35] Starting with mono-alkoxy product and it was treated with propargyl alcohol using $Mn(CO)_5Br$ as the catalyst in CH_2Cl_2 or toluene at RT in air. The results are shown in Table 1. When we tried with conditions reported by Scott *et al*, we obtained only a 26 % yield (entry 1). Increasing the catalytic loading from 4 mol% to 10 mol% and reaction temperature improved the **87** yield significantly (entry 2). It was found that changing the solvent system from dichloromethane to toluene yield also improved the yield (entry 3). Increasing the catalyst amount from 10 to 20 mol % did not improve returns
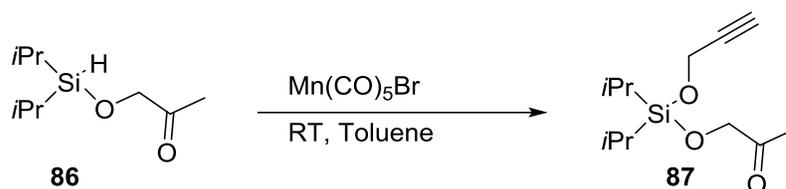
Table 6: Optimization of $Mn(CO)_5Br$ Catalyzed Reaction[a]

S. No	Solvent	$Mn(CO)_5Br$ (mol%)	Temp (°C)	Conc (M)	% Yield[b]
1	DCM	4	RT	0.5	26
2	DCM	10	Reflux	1	34
3	Toluene	10	Reflux	1	59
4	CH_3CN	10	Reflux	1	16
5	Toluene	20	Reflux	1	65

a. Conditions: alcohol 3 mmol, mono alkoxysilane 2 mmol
b. Isolated yield from column chromatography

88 74%   **89** 26%
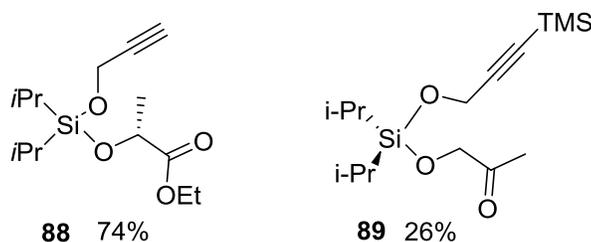
Mechanism of Silane Alcoholysis

General mechanism of silane alcoholysis is illustrated in Scheme 11.[21,32,34] Oxidative addition of the metal into an Si-H bond to form either a η^2 complex **B** or silylhydride **A**. The lone pair of oxygen in the alcohol coordinates to silicon resulting in intermediate **C**. Reductive elimination of intermediate **C** provides the silyl ether and metal dihydrogen complex **D**. Silane reacts with metal dihydrogen complex **D** to regenerate the catalyst with release of hydrogen gas. It was found that the intramolecular interaction between the Lewis basic carbonyl oxygen of hydroxyacetone and the silicon atom facilitates the oxidative addition of silicon to the metal catalyst; thereby increasing the rate of nucleophilic addition of alcohol.
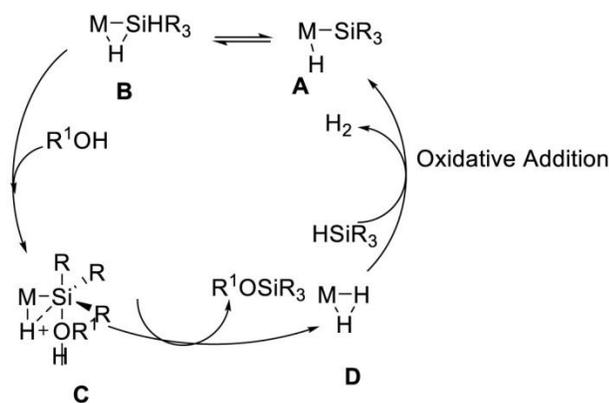
Scheme 17: Mechanism of silane alcoholysis.

Having successfully synthesized the disiloxane linker (unsymmetrical bisalkoxysilane) in two steps. We subjected it to dual catalysis. As a starting point for the investigation, we used the Kirsch procedure. However, we performed all the reactions in non deuterated solvents. The following gold catalysts were used in the dual catalytic system.

Ph₃PAuCl   [(Ph₃PAu)₃O]BF₄   Ph₃PAuNTf

B1   B2   B3

B4   B5
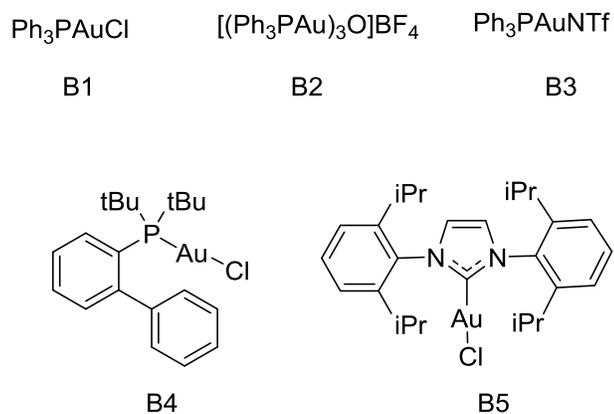
Figure 1: Gold complexes and silver salts in dual catalytic system.

The following silver salts are used for making the gold catalyst AgSbF6, AgBF$_4$, Ag (OTf).

Among all the gold catalysts listed, it was found that Au(PPh$_3$)NTf$_2$ gold complexes having NTf$_2$ counter ion show greater air and thermal stablitiy compared to other counter ions.[37] Silver salts are hygroscopic and light sensitive, and thus there are difficulties in weighing the reagent. Active gold(I) species are quite unstable when fluorine based counter ion is used. Bis(trifloriomethane sulfonyl) imidate is a weakly coordinating counter ion that provides greater stability than other fluoride base counter ions.

All gold catalyzed reactions were run in argon atmosphere using glove box conditions. A solution of bisalkoxysilane and diisopropylamine in DCE was added to mixture of AgSbF$_6$ and PPh$_3$AuCl in CH$_2$Cl$_2$ and the mixture was sealed, protected from light, and stirred at 70 °C for 48 hours. The mixture was filtered through celite, and concentrated and analyzed by ^{1}H NMR and GC.

The solvent concentration was 1M; crude products are analyzed by ^{1}H NMR. About 70% of starting material (SM) was recovered from the reactions. From Table 1 (entry 1), the combination of most popular gold complex B1 and AgSbF$_6$ did not result any product formation. We

recovered about 70% of starting material and did not observe any side reaction based on the crude spectra. By changing the counter ion (entry 2) we did not observe any reaction. Changing the gold catalyst B1 to B2 and B3 did not result in any product formation. The typical time for the cyclization procedure is 6 hours. But prolonging the reaction up to 48 hours did not result any product formation.
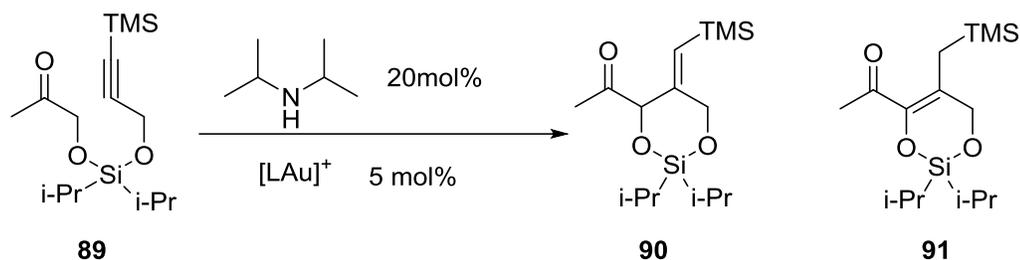
Table 7: Optimization of Dual Catalytic System: Effect of catalyst on cyclization[a]

S.NO	LAuCl (mol%)	Silver salt	Solvent	Temp (°C)	Time (h)	Comment[b]
1	B1	AgSbF$_6$	DCE	70	48	SM
2	B1	AgBF$_4$	DCE	70	48	SM
3	B2	-	DCE	70	48	SM
4	B3	-	DCE	70	48	SM
5	B1	AgSbF$_6$	DCE	90 (μw)	1	Lost tether
6	B1	AgBF$_4$	DCE	90 (μw)	1	Lost tether
7	B1	AgSbF$_6$	DCE	90 (μw)	0.5	SM
8	B1	AgSbF$_6$	DCE	130 (μw)	0.5	SM

a. Disiloxane 0.5 mmol,
b. SM –starting material, 70% recovered

Based on the above results, we attempted to vary the temperature of the reaction under microwave μW conditions. From table 7 entry 5 and 6, we carried the reaction for 1 h under μW conditions resulted cleavage of the tether. The reaction time is limited to 0.5 hr entry 7 and 8 but did not observe any reaction.

Table 8: Effect of catalyst on cyclization under microwave conditions.
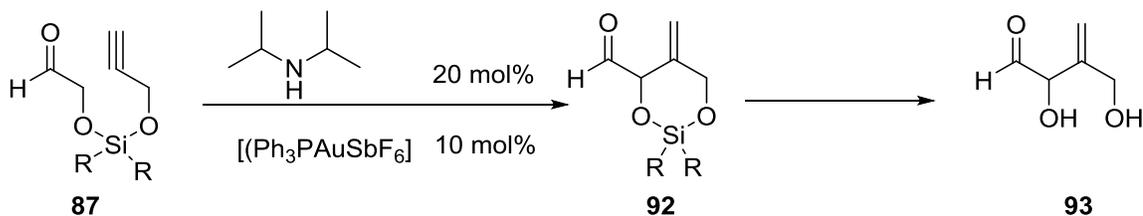
Entry	[LAuCl] 20 mol %	Additives 10 mol %	Solvent	Conc (M)	Temp (°C) (μw)	Time h	Comment (^{1}H NMR)
1	B2	-	DCE	0.5	90	0.5	SM
2	B2	-	DCE	0.5	130	0.5	SM
3	B2	-	DCE	0.5	170	0.5	SM
4	B3	-	DCE	0.5	90	0.5	SM
5	B3	-	DCE	0.5	130	0.5	SM
6	B3	-	DCE	0.5	170	0.5	SM
7	B4	AgSbF$_6$	DCE	0.5	90	0.5	SM
8	B4	AgSbF$_6$	DCE	0.5	130	0.5	SM
9	B4	AgSbF$_6$	DCE	0.5	170	0.5	SM
10	B5	AgSbF$_6$	DCE	0.5	90	0.5	SM
11	B5	AgSbF$_6$	DCE	0.5	130	0.5	SM
12	B5	AgSbF$_6$	DCE	0.5	170	0.5	SM

We selected the disiloxane containing a terminal alkyne and perormed the reactions with following gold complexes B2, B3, JohnPhosAuCl (B4) and NHCAuCl (B5) at 90, 130 and 170 ^{0}C under microwave (μw) conditions. Again we obtained the starting material (Table 8). The reaction conditions are 20 mol% of diisopropylamine and 10 mol% of gold catalyst at 0.5 M concentration.

Table 9: Effect of Bronsted acid pTSA on gold catalyst.
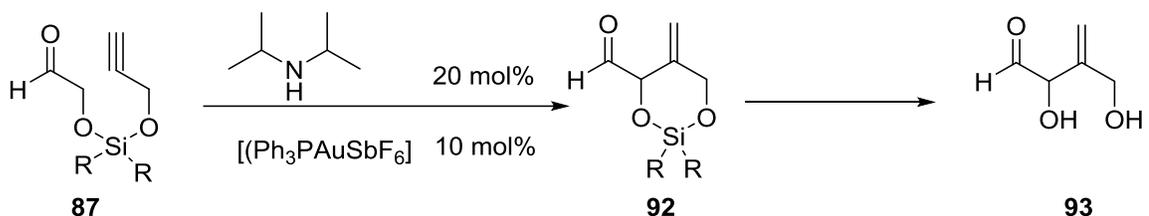
Entry	[LAuCl] 10 mol %	Silver salt 10 mol %	Bronsted acid 10 mol %	Solvent	Temp (°C)	Time (h)	Comment (^{1}H NMR)
1	B1	AgSbF$_6$	-	DCE	90 (μw)	0.5	SM
2	B1	AgOTf	^{P}TSA	DCE	90 (μw)	0.5	SM
3	B1	AgOTf	^{P}TSA	DCE	90 (μw)	0.5	SM
4	B4	AgSbF$_6$	^{P}TSA	DCE	130 (μw)	0.5	Lost tether
5	B4	AgSbF$_6$	^{P}TSA	Toluene	120	24	Lost tether
6	B4	AgOTf	^{P}TSA	DCE	130 (μw)	0.5	Lost tether
7	B4	AgOTf	^{P}TSA	Toluene	120	24	Lost tether

Base on the above results we suspect that catalyst deactivation occurs by the nucleophilic amine group by interaction of nitrogen with active site of the gold catalyst.[38] Other research groups evidenced this by ^{31}P NMR studies. In such conditions the use of Bronsted acids like ^{P}TSA can regenerate the catalyst.[39,40] Bronsted acids (^{P}TSA) prevent the catalyst deactivation by coordinating to the nitrogen atom of diisopropylamine. This study will help to clarify the influence of Bronsted acid on gold catalysis. We selected gold complexes B1 and B4 as they are the most popular gold complexes in homogenous gold catalysis. They are air stable and easy to handle. The silver salts AgSbF$_6$ and AgOTf were used under glove box conditions as they are more sensitive to light and moisture. Gold catalysts were prepared by stirring a mixture of the gold complex and the silver salt for about 30 min. The microwave vial, charged with amine, disiloxane and ^{P}TSA was added to the reaction flask before addition of the gold catalyst. The

reactions were protected from light and moisture by covering with alumina foil. We analyzed the crude product using NMR. We studied these reactions in both DCE and toluene. From entries 1, 2 and 3 with using the B1 gold complex and changing the counter ion under Bronsted acid conditions, we did not observe any product formation. With more stable JohnPhosAuCl complex we carried the reaction in both microwave at 130 °C in DCE and silica oil bath at 120 °C in toluene conditions entries 4, 5, 6 and 8. We observed cleavage of the tethers evidenced by absence of the propargyl group in the crude NMR. As we had difficulty in getting any product formation we wondered whether the formation of enamine could be problem for the substrate disiloxane. Thus performed this reaction to understand the amount enamine present in at different concentration of secondary amine.

Table 10: Relative tendency of formation of enamine in silyl ethers.

35
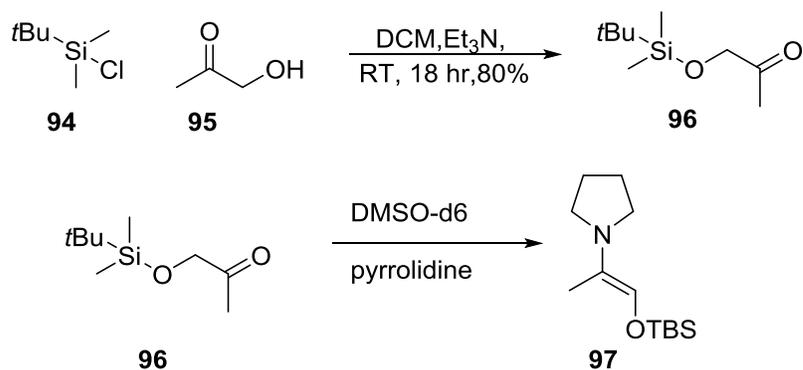
S. No	Silylether (eq)	Pyrrolidine (eq)	Enamine ^{1}HNMR
1	1	1	66 %
2	1	0.8	33 %
3	1	0.4	0 %
4	1	0.2	0 %

With 1 equiv of pyrrolidine with 1equiv of silyl ether we observed 66% enamine formation relative to the silyl ether (entry 1, Table 10). As the concentration of secondary amine decreased the enamine formation decreased significantly. With 0.8 equiv of pyrrolidine results only 33% of enamine formation (entry 2). We did not observe any enamine with 40 mol% or 20 mol% of pyrrolidine. From the above results we suspect that the lone pairs on the oxygen in silyl ether preventing the enamine formation by donating its electron density to the nearby carbon caused by inductive effect.

Conclusions

A study to combine the gold catalysis with organocatalysis using silicon tether technology has been performed. We successfully synthesized disiloxane (unsymmetrical bisalkoxysilane) linker in two steps. Monoalkoxysilane was prepared by treatment of diisopropylchlorosilane with hydroxyl acetone. In the second step it was treated with catalytic $Mn(CO)_5Br$ to reduce silane alcoholysis. All the other methods to prepare disiloxane with the use of dialkyldichlorosilane or aminochlorosilane, resulted in a mixture of products, which were difficult to separate. The disiloxane linker was subjected to dual catalysis using variety of gold catalyst and silver salts but no product was formed. Changing the reaction temperature, using microwave condition or a silica oil bath resulted no reaction. Changing solvent or catalyst also had no effect on the reaction.

Experimental Section

All the reactions were carried in oven dried and flame dried glassware under argon atmosphere. Tetrahydrofuran was freshly distilled from sodium/benzophenone under argon where as dichloromethane and 1,2-dichloroethane were distilled from calcium hydride under argon atmosphere. Commercially available reagents were used without additional purification unless otherwise stated. Reactions were monitored by thin-layer chromatography with 0.25 mm percolated silica gel plates, or gas chromatography. TLCs were staining with $KMnO_4$, or Seebach's stain or phosphomolybdic acid stain. Purifications were carried using silica gel flash chromatography with silica gel (Silicycle, 60 Å, 230-400 mesh) packed in glass columns . ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Inova 400 MHz NMR Spectrometer or a Bruker Avance 400 NMR Spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) with chemical shifts reported relative to chloroform solvent peaks as reference peaks ($\delta = 7.26$ ppm for ^{1}H and $\delta = 77.0$ ppm for ^{13}C).

General method for formation of Bisalkoxysilanes from dichlorodiphenylsilanes

General Procedure A[41]

The reaction was done in one pot to minimize exposure to moisture. To an oven dried round bottomed flask charged with a stirbar, dialkyldichlorosilane in CH_2Cl_2 was added. To the above solution, a solution of alcohol and Et_3N were added via syringe pump for 3 h at 0 °C. Then solution of alcohol in CH_2Cl_2 was added stirred at room temperature for 1 h. The reaction is washed with water, brine and aq. NH_4Cl solutions. The layers were separated then the combined organics extracted dried over $MgSO_4$. The solvent was removed under reduced pressure. Crude compound was subjected to column chromatography with silica gel.

General method for formation of Diisopropylsilylethers [35]

General Procedure B: Mono-Alkoxy silane

Chlorodiisopropyl silane (1.2 equiv.) added to the alcohol (1 equiv.) and triethylamine (1.5 equiv.) in dichloromethane (0.5 M) at 0 °C. The reaction mixture was stirred at room temperature until completion as indicated by TLC. The reaction mixture was cooled to 0 °C, the reaction was quenched with methanol (5 equiv.) and the solvent removed under rotary evaporation. The reaction mixture was suspended in hexane and filtered, washed with hexane. The solvent was removed under reduced pressure to provide the crude product, which was used without purification.

General Procedure C: Bisalkoxysilanes

To a solution 1.5 eq of alcohol (3.0 mmol) and 1 eq of monoalkoxysilane (2.0 mmol) in toluene, was added $Mn(CO)_5Br$ (10.0 mol%) and the reaction was stirred at room temperature for 2-4 h. The solvent was removed under vacuum and the crude mixture was purified by column chromatography (hexane/EtOAc 95:5) to give the pure product as a colorless liquid.

Ethyl 3-[(diisopropylsilyl)oxy]butanoate:
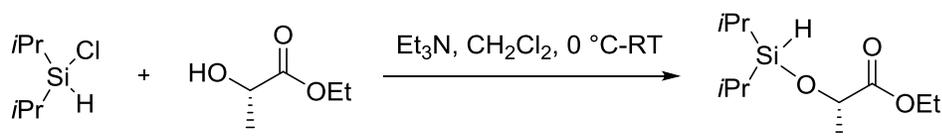
Prepared according to general Procedure B: Yield 92%, ^{1}H NMR (400 MHz, CDCl$_3$), δ 4.35 – 4.30 (m, 1H), 4.21- 4.13 (m, 3H), 1.42 (d, J = 7 Hz, 3H), 1.2 (t, J = 7 Hz, 3H), 1.03 – 0.96 (m, 14H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 174, 70.9, 61.2, 21.4, 17.7, 14.6, 12.8.

Ethyl (2S)-2-{[diisopropyl(prop-2-yn-1-yloxy)silyl]oxy}propanoate:
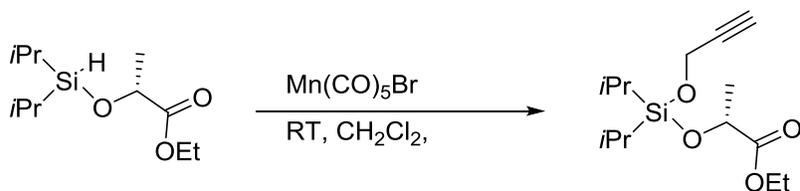
Prepared according to general Procedure C: Yield 74%, ^{1}H NMR (400 MHz, CDCl$_3$), δ 4.52 (q, J=6.2 Hz, 1H), 4.44 (s, 2H), 4.19 (q, J = 7 Hz, 2H,), 2.3 (s, 1H), 1.46 (d, J =7 Hz, 3H), 1.29 (t,

J= 7 Hz, 3H), 1.06-0.89 (m, 14H) ^{13}C NMR (100 MHz, CDCl$_3$), δ 174.2, 82.1, 72.9, 68.1, 61.0, 51.4, 21.5, 17.2, 14.3, 12.4. IR 3310, 2944, 2868, 1750, 1464, 1372, 1266, 1091.

1-((Diisopropylsilyl)oxy)propan-2-one:
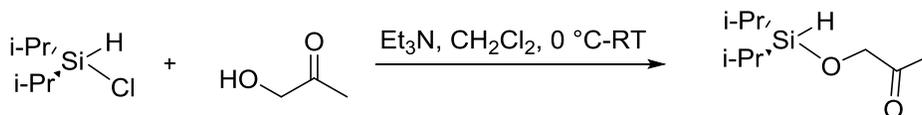
Prepared according to general Procedure B: Yield 92%, ^{1}H NMR (400 MHz, CDCl$_3$), δ 4.24 (s, 1H), 4.17 (s, 1H), 2.18 (s, 3H), 1.03 – 0.96 (m, 14 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 209, 71.7, 26.1, 17.3, 12.5.

1-((Diisopropyl(prop-2-yn-1-yloxy)silyl)oxy)propan-2-one:
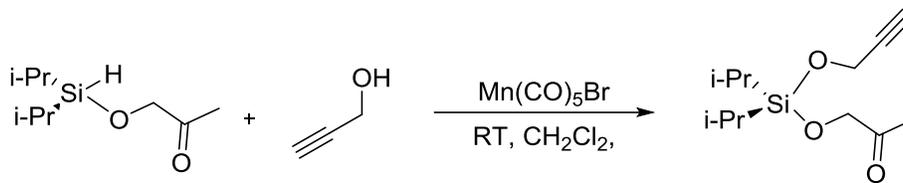
Prepared according to general Procedure C: Yield 26%, ^{1}H NMR (400 MHz, CDCl3), δ = 4.43 (s, 2 H), 4.34 (s, 2 H), 2.4 (t, J = 2.4 Hz, 1 H), 2.2 (s, 3 H), 1.07 (d, 14H). ^{13}C NMR (100 MHz, CDCl$_3$), δ 209.0, 82.4, 73.7, 69.8, 51.8, 26.6, 17.6, 12.5.

7,7-Diisopropyl-2,2-dimethyl-6,8-dioxa-2,7-disilaundec-3-yn-10-one :
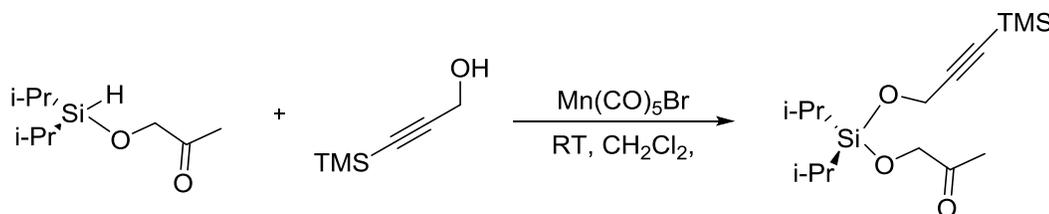
Prepared according to general Procedure C: Yield 26%, ^{1}H NMR (400 MHz, CDCl$_3$), δ 4.41 (s, 2 H), 4.33 (s, 2H), 2.21 (s, 3H), 1.07 (d, 14H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, CDCl$_3$), δ 208.9, 104.0, 90.2, 69.5, 26.3, 17.5, 17.3, 12.3, 0.04.

References

(1)   Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

(2)   Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, *2010*, 2999-3025.

(3)   Ibrahem, I.; Córdova, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1952-1956.

(4)   Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591-2594.

(5)   Hashmi, A. S. K. *Chem. Rev. (Washington, DC, U. S.)* **2007**, *107*, 3180-3211.

(6)   Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990-6993.

(7)   Hashmi, A. S. K. *Chem. Aust.* **2009**, *76*, 7-10.

(8)   Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 1025-1028.

(9)   Loh, C. C. J.; Enders, D. *Chem.--Eur. J.* **2012**, *18*, 10212-10225.

(10)   Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 5350-5352.

(11)   Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991-5994.

(12)   Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2006**, *9*, 367-370.

(13)   Duschek, A.; Kirsch, S. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 5703-5705.

(14)   Hashmi, A. S. K.; Hubbert, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1010-1012.

(15)   Chiarucci, M.; di Lillo, M.; Romaniello, A.; Cozzi, P. G.; Cera, G.; Bandini, M. *Chemical Science* **2012**, *3*, 2859-2863.

(16)   Bracegirdle, S.; Anderson, E. A. *Chem. Soc. Rev.* **2010**, *39*, 4114-4129.

(17)   Gauthier Jr, D. R.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289-2338.

(18)   Yamamoto, Y.; Ishii, J.-i.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712-3713.

(19)   Chegondi, R.; Maitra, S.; Markley, J. L.; Hanson, P. R. *Chem.--Eur. J.* **2013**, *19*, 8088-8093.

(20)   Saito, A.; Ono, T.; Hanzawa, Y. *J. Org. Chem.* **2006**, *71*, 6437-6443.

(21)   Scott, C. N. Ph.D., University of Pittsburgh, 2005.

(22)   Röver, S.; Wipf, P. *Tetrahedron Lett.* **1999**, *40*, 5667-5670.

(23)   Smith, E. M. *Tetrahedron Lett.* **1999**, *40*, 3285-3288.

(24)   Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298-2300.

(25)   Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500-501.

(26)   Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1990**, *31*, 6585-6588.

(27)   Corriu, R. J. P.; Kpoton, A.; Poirier, M.; Royo, G.; de Saxcé, A.; Colin Young, J. *J. Organomet. Chem.* **1990**, *395*, 1-26.

(28)   Mayasundari, A.; Young, D. G. J. *Tetrahedron Lett.* **2001**, *42*, 203-206.

(29)   Lorenz, C.; Schubert, U. *Chem. Ber.* **1995**, *128*, 1267-1269.

(30)   Doyle, M. P.; High, K. G.; Bagheri, V.; Pieters, R. J.; Lewis, P. J.; Pearson, M. M. *J. Org. Chem.* **1990**, *55*, 6082-6086.

(31)   Blackburn, S. N.; Haszeldine, R. N.; Parish, R. V.; Setchfield, J. H. *J. Organomet. Chem.* **1980**, *192*, 329-338.

(32)   Luo, X. L.; Crabtree, R. H. *J. Am. Chem. Soc.* **1989**, *111*, 2527-2535.

(33)   Caseri, W.; Pregosin, P. S. *Organometallics* **1988**, *7*, 1373-1380.

(34)   Corriu, R. J. P.; Moreau, J. J. E. *J. Organomet. Chem.* **1976**, *114*, 135-144.

(35)   Scott, C. N.; Wilcox, C. S. *J. Org. Chem.* **2009**, *75*, 253-256.

(36)   Matsui, R.; Seto, K.; Fujita, K.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 10068-10073.

(37)   Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133-4136.

(38)   Belot, S.; Vogt, K. A.; Besnard, C.; Krause, N.; Alexakis, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 8923-8926.

(39)   Jensen, K. L.; Franke, P. T.; Arróniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem.--Eur. J.* **2010**, *16*, 1750-1753.

(40)   Loh, C. C. J.; Badorrek, J.; Raabe, G.; Enders, D. *Chem.--Eur. J.* **2011**, *17*, 13409-13414.

(41)   Hutchinson, J. H.; Daynard, T. S.; Gillard, J. W. *Tetrahedron Lett.* **1991**, *32*, 573-576.

CHAPTER III

TITANIUM PROMOTED REDUCTIVE COUPLINGS OF ALKYNES WITH PYRIDINIUM

SALTS

Introduction

Pyridines are important synthetic precursors to dihydro, tetrahydropyridines and piperidines. These heterocyclic compounds are invaluable intermediates in the preparation of pharmaceutical, agrochemical, alkaloids, and other biologically active compounds.[1] Functionalization of pyridine possess significant challenges due to the low energy of its π-system. Electrophilic aromatic substitution and nucleophilic aromatic substitution are ineffective to pyridine containing substrates.[1] However its π-energy is activated through the formation of cationic pyridinium species (Figure 2). Pyridines are functionalized at nitrogen to pyridine ylides, N-acyl pyridinium salts, N-alkyl pyridinium salts. Among them N-acyl pyridinium salts are more reactive than alkyl pyridinium salts due to high activity of π-system. The resulting pyridine species are more electrophilic than the corresponding parent pyridine.[1]

X= COOMe, COCH$_3$, BF$_3$,CH$_3$
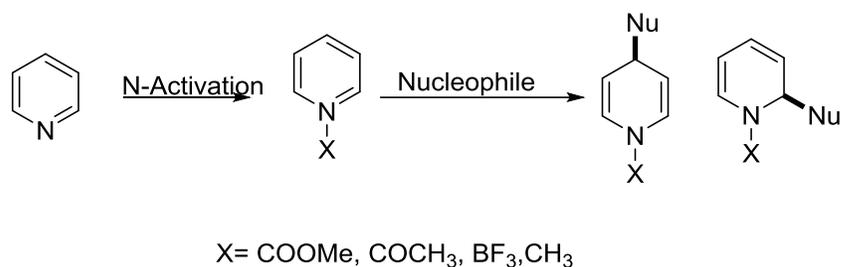
Figure 2: Regioselectivity of pyridinium species

Over the years functionalization of pyridine has been achieved by addition of electrophiles, nucleophiles, and transition metal mediated reagents. The addition of organometallic reagent to N-acyl pyridinium salts usually gives a mixture of 1,2- and 1,4-dihydropyridines. The regioselectivity can be explained by HSAB (hard,soft,acid,base) theory.[2] Soft nucleophiles such as organocuprates tend to add at 4-position whereas hard nucleophiles such as alkyl lithium reagents add at 2-position of pyridinium species. Comins & Abdullah reported the addition of Grignard reagent to N-acylpyridinium salts to 1,2 and 1,4 dihydropyridines.[3] Later Piers & Soucy reported the synthesis of 1,4 dihydropyrdines with soft nucleophiles like organocopper reagents.[4] Soft nucleophiles such as silylenol ethers generated from ketones and benzyl tin reagents has high preference for 1,4 addition.[5,6] The regioselectivity of addition to the pyridine can be influenced by the substituents on the ring. For example substituents at 4-position of pyridine ring allow addition only at 2-position. Comins reported 4 substituted pyridines react with alkyl zinc reagents at 2-position of N-acyl pyridinium species.[7]
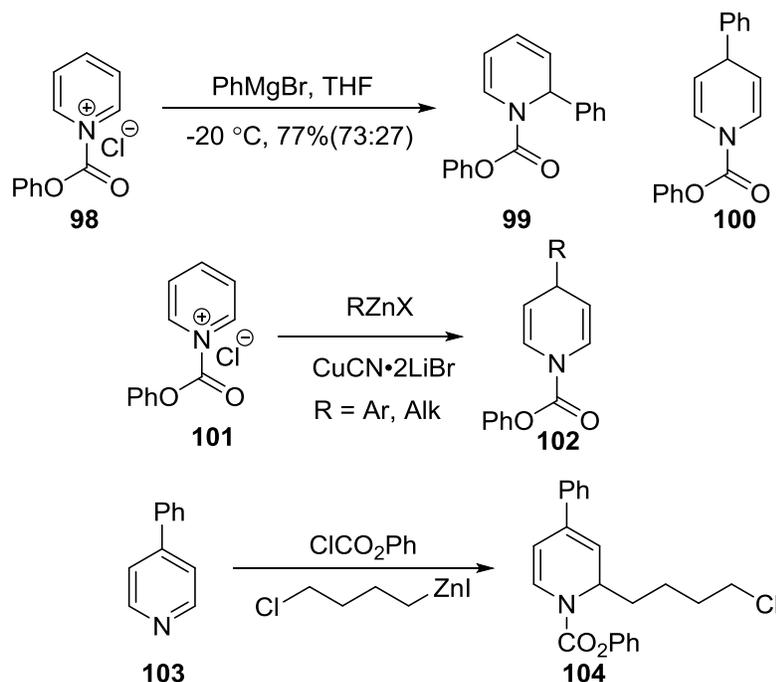
Scheme 18: Synthetic strategies for dihydropyridines

Titanium promoted reductive cross couplings: Introduction

Transition metals are known catalyze cross coupling reactions between organic halides and organometallic reagents derived from Mg, B, Al, B & Si species.[8,19] Many transition metal have been explored in cross coupling reactions but titanium-compounds as reactive intermediates in cross coupling is under developed.[8] Ti-mediated reagents such as titanium chloride, titanium alkoxide, dicarbanionic titanium regents are less expensive and easy to handle. Hayashi reported the first cross coupling reaction catalyzed by Pd/Ni between titanium reagents and Aryl triflates and halides.[9] Tshuji in 2003 reported the Ni(cod)₂ catalyzed cross coupling reactions between dialkoxytitanacyclopropenes complexes and aryl halides (Scheme 19).[8] Ti-alkyne complexes usually exist as dialkoxytitanacyclopropene form.[10] Micalizio showed the cross-coupling reactions between alkyne-alkyne using this powerful titancacylopropenes.[11]
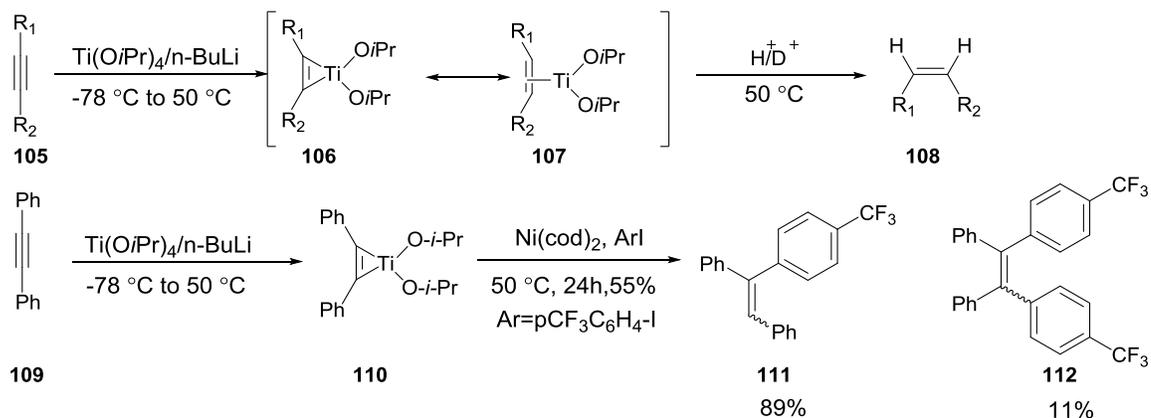
Scheme 19: Cross-coupling reaction between titanium (II)-alkyne complexes and aryl halides

Ti(II)-alkyne complexes are the reactive intermediates, prepared by adding n-Buli to mixture alkyne and $Ti(O-i-Pr)_4$ in THF at -78^0C, raising the temperature to $50\ ^0C$.[8] Ti-alkyne complexes generated from n-BuLi are thermally stable at room temperature. Sato reported the low valent titanium-acetylene complexes generated from slow addition of 2 equiv *i*-PrMgCl to the $Ti(O-i-Pr)_4$ and acetylene at $-78\ ^0C$ and then mixture stirred at $-50\ ^0C$ Scheme 19.[12] Dialkoxytitanacyclopropenes reacts with variety of functional groups such as aldehydes, ketones, carboxyl derivatives, imine derivatives, nitriles , alkenes, alkynes, allenes, alkynyl carboxylic derivatives, alkynyl aldehydes and ketones, alkynyl imines, enynes, diynes etc.[10]

Our Approach:

Even though many organometallic reagents such as alkyl Grignard reagents, organocuper reagents, alkenyl Grignard reagents, alkynyl reagents have been used for the synthesis of 1,2 and 1,4 dihydropyrdines, methods to functionalize pyridines with substituted alkenes are underdeveloped.   To address this gap we sought to develop a titanium promoted reductive coupling of alkynes with N-acylated pyridinium salts.   The hard nature of organotitanium reagents would favor 1,2 addition to the activated pyridines. This methodology allows us to synthesis complex dihydropyridines from readily available pyridines and highly substituted alkynes.
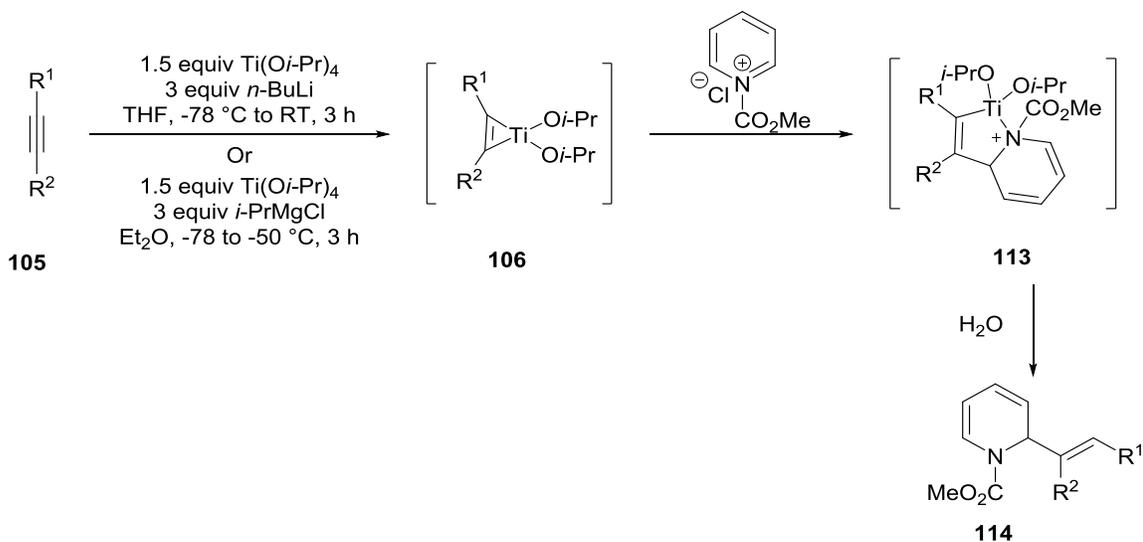
Scheme 20: Titanium Promoted Reductive Coupling of Alkynes with Pyridinium Salts

Results and Discussion

Table 11: Titanium promoted reductive coupling of 4-octyne with N-acyl pyridine
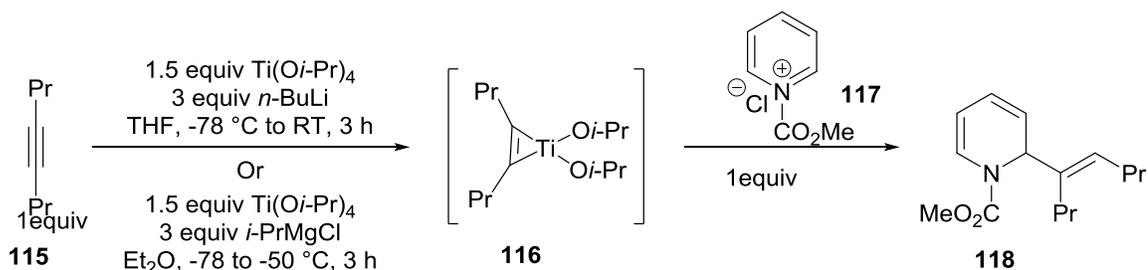
Entry	Reduct	Temp (°C) Ti-cycle	Temp (°C) Pyr	Solv	Yield
1	iPrMgCl	-50	-78	Et$_2$O	0
2	iPrMgCl	-50	-50	Et$_2$O	0
3	iPrMgCl	-50	0	Et$_2$O	0
4	iPrMgCl	-50	RT	Et$_2$O	0
5	n-BuLi	RT	-78	THF	0
6	n-BuLi	RT	-50	THF	0
7	n-BuLi	RT	0	THF	0
8	n-BuLi	RT	RT	THF	0

All reactions were run at 0.125 M and alkyne 0.5mmol (1 equiv), more than 95 % of starting material is converted to titanacycle. For coupling reaction carried using the reducing agent is iPrMgCl (see procedure A). The reductive coupling reactions were also carried in nBuLi in both THF, Et$_2$O (See Procedure B)

As starting point we synthesized the titanocycle from using procedure A for Grignard reagents and Procedure B for n-BuLi. The resulting Ti-alkyne complex made from Grignard reagent usually unstable above -50 ^{0}C whereas Ti—alkyne complex made from n-BuLi stable at room temperature. Having known the fact that Grignard reagent were good nucleophilic sources for 1,2 and 1,4 addition to N-acyl pyridinium species. The pyridinium salt prepared was added to the

Table 12: Titanium promoted reductive coupling of 4-octyne with N-acyl pyridine
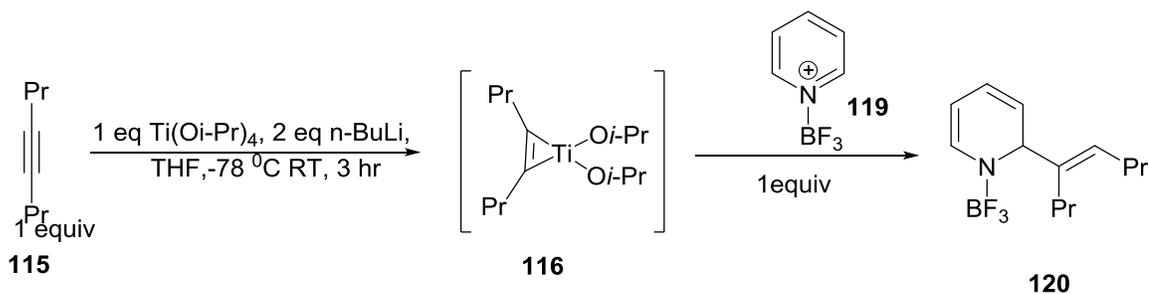
Entry	Reduct equiv.	Temp (°C) Ti-cycle	Temp (°C) Pyr	Solv	Yield[b]
1	n-BuLi	RT	-78	THF	0
2	n-BuLi	RT	-50	THF	0
3	n-BuLi	RT	0	THF	0
4	n-BuLi	RT	RT	THF	0
5	iPrMgCl	RT	-78	Et$_2$O	0
6	iPrMgCl	RT	-50	Et$_2$O	0
7	iPrMgCl	RT	0	Et$_2$O	0
8	iPrMgCl	RT	RT	Et$_2$O	0

The reaction were run at 0.5 mmol scale, at 0.125 M and alkyne 0.5mmol (1 equiv), more than 95 % of starting Material is converted to titanacycle.

Ti-alkyne complex at various temperatures as shown in Table 11. Unfortunately we did not observe any product. We recovered above 80% of 4-octene, which was the result of hydrolysis of Ti-Alkyne complex. We changed solvent system and nature of reducing agent for titanocyle formation. We carried this reaction at various temperatures. Ether solvents did not give any product (Table 11). The logical step is to change the nature of pyridinium ion we screened

Table 13: Titanium Promoted Reductive Coupling of 4-octyne with various pyridinium salts
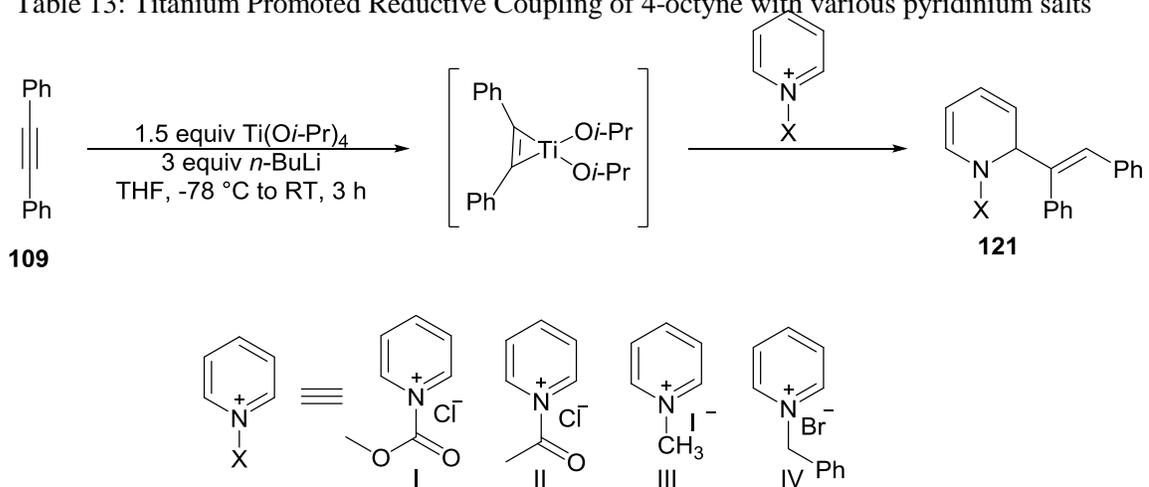
Entry	Alkyne equiv.	Pyridin 1equiv.	Ti(OiPr)$_4$ equiv.	Reduct equiv.	Temp (°C) Ti-cycle	Temp (°C) Pyr	Solv	Yield[b]
1	1	I	1.0	nBuLi	RT	RT	THF	0
2	1	II	1.0	nBuLi	RT	RT	THF	0
3	1	III	1.0	nBuLi	RT	RT	THF	0
4	1	IV	1.0	nBuLi	RT	RT	THF	0

b. All reactions were run in 0.125 M and alkyne 0.5mmol (1 equiv), more than 95 % of starting material is converted to titanacycle.

various pyridinium salts at different temperature and reaction conditions. We recovered more than 80 % of 4-octene. As we can conclude from table 11, 12, 13 that the changing the nature of solvent, titanocycle, temperature, pyridinium salt did not observe any signs of product formation.

Synthesis of 1,2 dihydropyridines by Grignard reagent: Since the Ti-promoted reductive coupling of alkynes and pyridinium satls did not result in any product formation. We thought to synthesize the final product through using standard Grignard procedure.[13] The following scheme 21 explains the result of Grignard addition to pyridinium salts. The alkyl Grignard reagents were
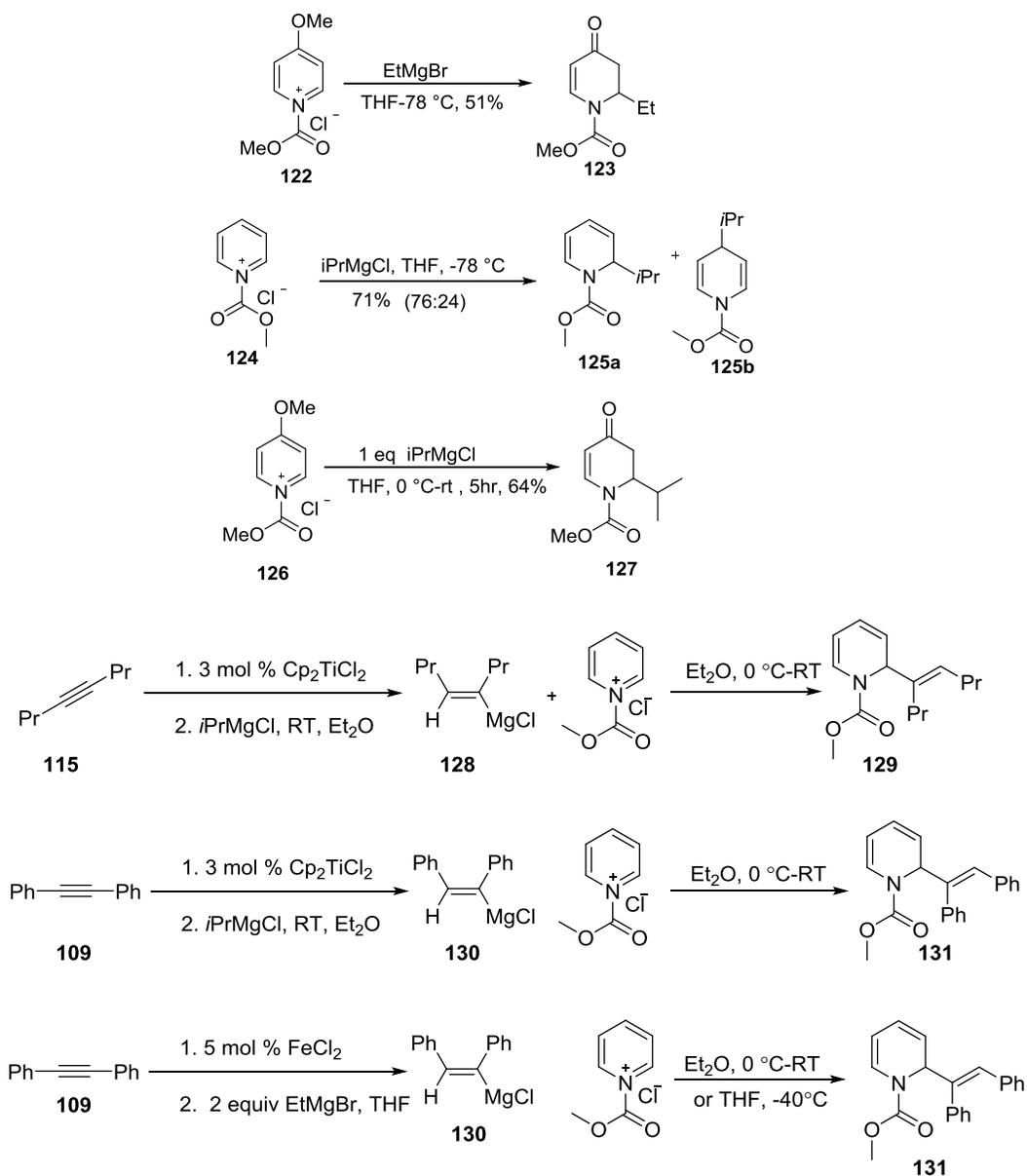
Scheme 21: Synthesis of 1,2 dihydropyridines by Grignard reagent

added successfully to N-acylpyridinium salts provided 1, 2 and, 1, 4 dihydropyridines. Ethyl Magnesium bromide and isopropyl magnesium chloride reacted with 4-methoxy pyridinium salt provided the 1,2 dihydropyridinone. In order to synthesize the final product through direct addition of *in situ* generated alkenyl Grignard reagent to pyridinium species. Internal Grignard reagents prepared from procedure C[14] and Procedure D[15] and added it to N-acylpyridinium salt. To our surprise we did not observed the product formation. We suspect that the synthesis of alkenyl 1,2 dihydropyridines by direct alkenylation of N-acyl pyridinium species was not favorable.

Reductive coupling of titanacyclopropane with pyridinium species:

Titanocyclopropane complexes reported by Kulinkovich are highly reactive intermediates generated after transmetallation reaction Scheme 22.[16,17] Titanocyclopropenes generated from Grignard reagents unstable below -30 ^{0}C whereas from n-BuLi stable at room temperature for 30 min. [18] The reactive species must be produced *in situ* in the presence of pyridinium salt.
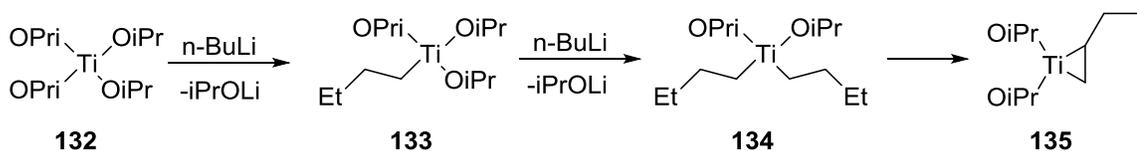
Scheme 22: Formation of a titanacyclopropane from Ti(O*i*Pr)$_4$

Table 15: Reductive coupling of titanacyclopropane with 4-methoxy pyridinium species[a]
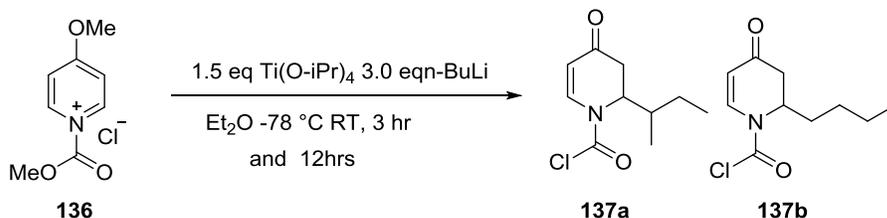
| Temp | Temp | Solvent | Comment |
Ti cylce	Pyr salt		
RT	-78	THF	SM
RT	-50	THF	SM
RT	0	THF	SM
RT	rt	THF	SM
RT	+50	THF	SM

a. Reactions were run at 0.125 M , 4-methoxy pyridine 0.25mmol

Table 16 : Reductive coupling of titanacyclopropane with N-acyl-3-chloro pyridine
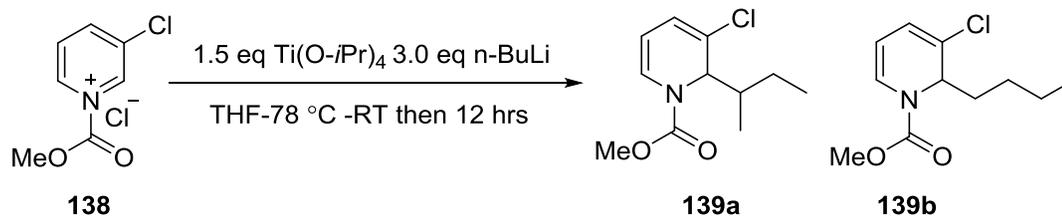
	1.5 eq Ti(O-*i*Pr)$_4$ 3.0 eq n-BuLi		
	THF-78 °C -RT then 12 hrs		
138		**139a**	**139b**

| Temp | Temp | Solvent | Comment |
Ti-cylce	Pyr salt		
RT	-78	THF	SM
RT	-50	THF	SM
RT	0	THF	SM
RT	rt	THF	SM
RT	+50	THF	SM

a. Reactions were run at 0.125 M, 3-chloropyridine 0.5mmol

Titanocyclopropene produced from n-Buli and Ti(O*i*Pr)$_4$ were added to pyridinium species. As we can see from table 15, 16, we did not observe the product.

Experimental

Procedure A: Titanium promoted reductive coupling of alkyne with N-acyl pyridine using Grignard reagents: To a dry and argon flushed 50 ml round bottom flask charged with stir bar, added alkyne in ether at -78 ^{o}C followed by addition of 1 equiv Ti(O-i-Pr)$_4$ and 2 equiv of isopropyl magnesium chloride. The reaction temperature is increase to -50 ^{o}C and stirred at that temperature for 3-4 hours. The amount of titanocycle formation was judged by taking an aliquot and quenching the reaction mixture with water and analyzed the resulting 4-octene over GC-MS. To a dry and argon flushed 50 mL round bottom flask charged with magnetic stir bar and added solution of pyridine in dry ether and cooled it to 0 °C. To the above solution (BF$_3$**.** OEt$_2$ or methyl chloroformat) was added drop wise and stirred for 1 hr at that temperature. The formation of pyridinium salt was indicated by the white precipitate. To the above reaction mixture above titanocycle added slowly and stirred it for 12 hours.

Procedure B: Titanium promoted reductive coupling of alkyne with N-acyl pyridine using n-BuLi reagents: To a dry and argon flushed 50 ml round bottom flask charged with stir bar, added alkyne in THF at -78 ^{o}C. To a mixture of Ti(O-i-Pr)$_4$ and alkyne in THF, 2 equiv of n-BuLi is added at -78 ^{o}C. The reaction temperature is increase to RT and stirred it at room temperature for 4 hours. The amount of titanocycle formation was judged by taking an aliquot and quenching the reaction mixture with water and analyzed the resulting 4-octene over GC-MS. To a round bottom flask charged with solution of pyridine in dry THF and cooled it to 0 °C. To the above solution methyl chloroformate was added drop wise and stirred for 1 hr at that temperature. The formation of pyridinium salt was indicated by the white precipitate. To the above reaction mixture above titanocycle at room temperature was added slowly and stirred it for 12 hours.

Procedure C: To oven dried round bottom flask, $FeCl_2$ is added to a solution of alkyne in Et_2O. After stirring for 15 min, a solution of EtMgBr in Et_2O is added to the reaction mixture at RT and the resulting black mixture was stirred at RT for additional 15 min and then added to pyridinium salt at room temperature.

Procedure D: Cp_2TiCl_2 was added to mixture of alkyne and isopropyl magnesium bromide in 0.6 mL ether at RT under argon. The reaction mixture is stirred for 1 hr. The resulting Grignard reagent was added to pyridinium salt at RT until completion of the reaction.

Conclusions

The reductive coupling of symmetrical alkyne with pyridinium species utilizing titanocycle as reactive species was performed. The titanocycle could be generated using Grignard reagent or n-BuLi as reductants. The pyridinium salts reacted with titanocycle did not give any product. Changing the reaction temperature, solvent, and pyridinium species did not provide any product. Given the amount of alkene recovered indicates that Ti-mediated reagents were not facilitating nucleophilic addition to pyridinium species. The exact reasons for direct nucleophilic addition of substituted alkenyl griganrd reagents to pyridinium salts were not known. Even the direct addition of *in situ* generated titanocyclopropane from $Ti(OiPr)_4$ and n-BuLi did not react with pyridinium species.

References

(1)   Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev* **2012**, *112*, 2642-2713.

(2)   Ho, T.-L. *Tetrahedron* **1985**, *41*, 3-86.

(3)   Comins, D. L.; Abdullah, A. H. *J. Org. Chem* **1982**, *47*, 4315-4319.

(4)   Piers, E.; Soucy, M. *Can. J. Chem.* **1974**, *52*, 3563-3564.

(5)   Akiba, K.-y.; Nishihara, Y.; Wada, M. *Tetrahedron Lett.* **1983**, *24*, 5269-5272.

(6)   Akiba, K.-y.; Matsuoka, H.; Wada, M. *Tetrahedron Lett.* **1981**, *22*, 4093-4096.

(7)   Comins, D. L.; O'Connor, S. *Tetrahedron Lett.* **1987**, *28*, 1843-1846.

(8)   Obora, Y.; Moriya, H.; Tokunaga, M.; Tsuji, Y. *Chem. Commun.* **2003**, 2820-2821.

(9)   Han, J. W.; Tokunaga, N.; Hayashi, T. *Synlett* **2002**, *2002*, 0871-0874.

(10)   Wolan, A.; Six, Y. *Tetrahedron* **2010**, *66*, 3097-3133.

(11)   Shimp, H. L.; Micalizio, G. C. *Org. Lett.* **2005**, *7*, 5111-5114.

(12)   Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203-3206.

(13)   Yamaguchi, R.; Nakazono, Y.; Matsuki, T.; Hata, E.-i.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215-222.

(14)   Ilies, L.; Yoshida, T.; Nakamura, E. *J. Am. Chem. Soc.* **2012**, *134*, 16951-16954.

(15)   Sato, F.; Ishikawa, H.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 85-88.

(16)   Averbuj, C.; Kaftanov, J.; Marek, I. *Synlett* **1999**, *1999*, 1939-1941.

(17)   Rassadin, V. A.; Six, Y. *Tetrahedron* **2014**, *70*, 787-794.

(18)   Santra, S.; Masalov, N.; Epstein, O. L.; Cha, J. K. *Org. Lett.* **2005**, *7*, 5901-5904.

(19)   Bolm, C. *J. Org. Chem.* **2012**, *77*, 5221-5223.

VITA

Naresh Babu Mulpuri

Candidate for the Degree of

Master of Science

Thesis: COMBINING ORGANOCATALYSIS WITH TRANSITIONMETAL CATALYSIS

Major Field: Organic Chemistry

Biographical:

Education:

Completed the requirements for the Master of Science in chemistry at Oklahoma State University, Stillwater, Oklahoma in July, 2014.

Completed the requirements for the Master of Science in chemistry at University of Hyderabad, Hyderabad, AP/ INDIA in   May, 2007.

Completed the requirements for the Bachelor of Science in chemistry at Andhra University, Visakhapatnam, AP/INDIA in 2005.