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Studies Directed Toward the Synthesis of Amphibian Alkaloids via Iridium Catalyzed N-Heterocyclization Reactions

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Studies Directed Toward the Synthesis of Amphibian Alkaloids via Iridium
Catalyzed N-Heterocyclization Reactions

A Dissertation

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
In
The Department of Chemistry

By

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M.S. from Pondicherry University, Pondicherry, India 2008
M.S from University of New Orleans 2013

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Abstract

The main focus of the research was on the selective conversion of terminal dienes to primary diols. This conversion has always had problems with regioselectivity and low yields due to polymer formation with carbon chains having more than seven carbon atoms. An improvement in the yield and regioselectivity was observed with disiamylborane prepared *in situ* using 2-methyl-2-butene and $\text{BH}_3 \cdot \text{DMS}$. The scope of this method with seven, eight and nine carbon chains and different alcohol protecting groups for synthesis of various triols is presented.

With a variety of diol and triol derivatives in hand the study focused on the synthesis of pyrrolidine and piperidine ring systems that are present in a variety of different classes of amphibian alkaloids. We have found the iridium catalyzed N-heterocyclization reaction of diols with amines to be very useful for the construction of novel pyrrolidine, piperidine and piperazine derivatives. The scope and utility of the iridium catalyzed N-heterocyclization reaction for the construction of novel anuran scaffolds using amino diols and triols are presented. Studies directed towards the total synthesis of 4,6-disubstituted quinolizidine and (\pm)-epiquinamide are also discussed.

Keywords: N-Heterocyclization, Catalysis, Microwave, N-Alkylation, Iridium, Amphibian Alkaloids, Hydroboration, Synthesis.

CHAPTER 1: Introduction – Iridium Catalyzed N-Heterocyclization with Alcohols

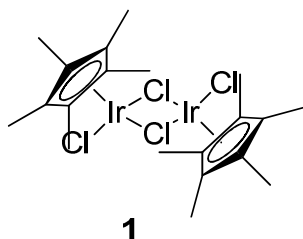
1.1 Iridium catalyzed N-alkylation using alcohols

N-Heterocyclic compounds have attracted considerable attention because of their functionality in pharmaceutical chemistry, material chemistry and synthetic organic chemistry.^{1a} They include pyrrolidine, piperidine, piperazine and morpholine derivatives, which are present in a plethora of biologically active natural products.^{14,15} There are a large number of reported reactions for the construction of these ring systems. They include reactions such as hydroamination of alkenes or alkynes,^{1c} amination of aryl halides^{1d} and reductive amination with carbonyl compounds.^{2b,2c} These reactions use alkyl halides or strong reducing agents which are undesirable from an environmental point of view and also generate equimolar amounts of wasteful salts as co-products. A versatile and highly atom economical catalytic system consisting of $[\text{Cp}^*\text{IrCl}_2]_2/\text{NaHCO}_3$ (Cp* = pentamethylcyclopentadienyl) for the N-alkylation of amines with primary and secondary alcohols as alkylating reagents has been developed by Fujita and co-workers.^{2a}

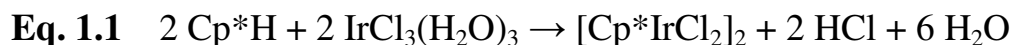
1.2 The catalyst

Pentamethylcyclopentadienyl iridium dichloride (**1**) is an organometallic compound with the formula $[\text{Cp}^*\text{IrCl}_2]_2$, a bright orange air stable diamagnetic solid.^{1b}

Fig 1.1: (Pentamethylcyclopentadienyl)iridium (III) chloride dimer catalyst



The compound has C_{2h} symmetry. Each metal is pseudo-octahedral. It was first prepared by the reaction of hydrated iridium trichloride with hexamethyl Dewar benzene. More conveniently, iridium trihydrate and pentamethylcyclopentadiene consistently yields the dimer in both high yield and purity according to the idealized equation (Eq 1.1).^{1b}



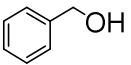
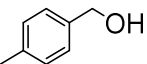
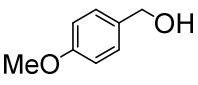
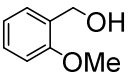
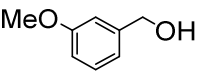
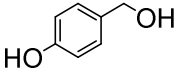
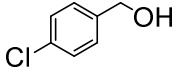
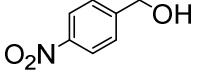
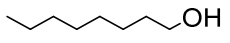
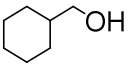
During the past few years, there has been numerous examples of the catalytic activity of $[\text{Cp}^*\text{IrCl}_2]_2$ towards hydrogen transfer reactions, which

includes Oppenauer-type oxidation of alcohols, carbon-nitrogen and carbon-carbon bond formations reactions as discussed below.

1.3 Oxidation of primary and secondary alcohols catalyzed by pentamethylcyclopentadienyliridium complex⁵

The oxidation of alcohols to aldehydes and ketones is one of the most fundamental reaction in organic synthesis. These reactions are usually achieved by using stoichiometric amounts of chromium reagents,⁶ which are harmful from an environmental view point. Oppenauer-type oxidations, which use a transition metal catalyst for the oxidation of alcohols, can be achieved under mild and less toxic conditions with high selectivity compared to many other oxidation methods.⁷ However, these hydrogen transfer oxidation reactions have been mainly applicable to secondary alcohols and only few reagents for the conversion of primary alcohols have been reported. To address this issue, Cp*Ir complex catalyzed oxidation of primary and secondary alcohols has been reported with equal efficiency, which proceed under mild and less-toxic conditions in presence of acetone as an oxidant. Results of the oxidation of various primary alcohols by a Cp*Ir catalytic system are summarized in Table 1.1. This method can be applied to various substrates with various functional groups. No formation of carboxylic acid products or condensation products of aldehydes was observed.

Table 1.1 Oxidation of primary alcohols to aldehydes catalyzed by a pentamethylcyclopentadienyliridium complex^a

Entry	Alcohol	Conv. of alcohol(%) ^b	Yield of aldehyde(%) ^{b,c}
1		87	87(74)
2		100	93(82)
3		100	99(90)
4		70	67(63)
5		85	85(77)
6 ^d		77	60 ^e
7		72	70(61)
8		32	20
9 ^f		59	57(44)
10 ^f		51	47

^aThe reaction was performed at room temperature for 6h with primary alcohol(1.0 mmol), [Cp*IrCl₂]₂ (2.0 mol% Ir) and K₂CO₃ (0.10 mmol) in acetone (30 ml).

^bDetermined by GC based on starting alcohol.

^cThe value in parenthesis is an isolated yield.

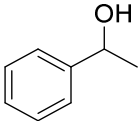
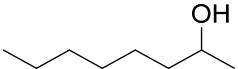
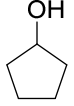
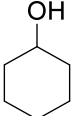
^dReaction was performed with 1.1 mmol of K₂CO₃.

^eDetermined by ¹H-NMR.

^fReaction was performed at reflux.

The yields of aldehydes with electron-donating groups at the para-position (entries 2 and 3) were found to be higher than those with electron-withdrawing groups (entries 7 and 8) while the ortho-substituted substrate showed less reactivity (entry 4). There was only a little effect shown by substrates with meta-directing group (entry 5). The p-hydroxybenzyl alcohol could only be oxidized with an excess amount of base (entry 6). The Cp*Ir catalytic system was also found to be applicable to oxidation of non-aromatic primary alcohols (Table 1.1 entries 9 and 10), but needed to be carried out at reflux temperature to obtain moderate yields. Results of the oxidation of secondary alcohols by the present catalytic system are summarized in Table 1.2.

Table 1.2. Oxidation of secondary alcohols to ketones catalyzed by a pentamethylcyclopentadienyliridium complex^a

Entry	Alcohol	Conv. of alcohol (%) ^b	Yield of ketone (%) ^{b,c}
1		100	100(94)
2 ^d		89	88(77)
3		100	100
4 ^d		79	79

^aThe reaction was performed at room temperature for 6 h with secondary alcohol (2.0 mmol), [Cp*IrCl₂]₂ (0.5 mol%/Ir) and K₂CO₃ (0.20 mmol) in acetone (2.0 ml).

^bDetermined by GC based on the starting alcohol.

^cThe value in parentheses is isolated yield.

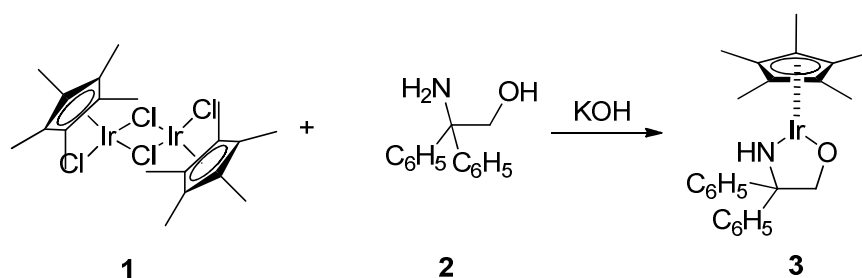
^dReaction was performed at reflux temperature.

Secondary alcohols which could be more easily oxidized compared to primary alcohols, gave higher yields even with the use of small amounts of catalyst.

1.4 Mild and chemoselective synthesis of lactones from diols using a novel metal-ligand bifunctional catalyst

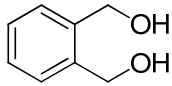
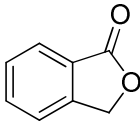
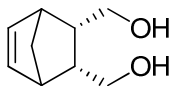
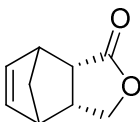
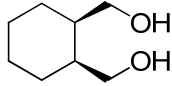
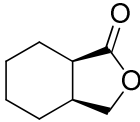
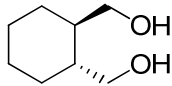
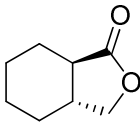
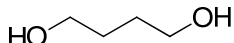
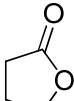

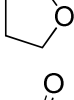
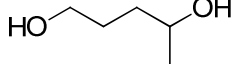
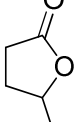
The oxidative lactonization of diols was found to be very useful for the synthesis of variety of natural products.^{8,9} The general approach for this type of reaction is to use a stoichiometric amount of silver carbonate on celite,¹⁰ which often uses a large excess (10-26 equiv) of expensive silver salts. In addition, lactonization has been achieved by catalytic reactions which use high temperature (> 180 °C)¹¹ co-oxidants such as toluene,^{11b} PhBr, α,β -unsaturated ketones,^{11d,e} allyl methyl carbonate, or N-methylmorpholine N-oxide. Some catalytic reactions¹² which use a clean co-oxidant such as acetone,^{12a,b,c} hydrogen peroxide^{12b} or molecular oxygen^{12c} has been reported. The use of the iridium catalyst Cp*Ir was found to be high-yielding, clean, operationally simple and chemoselective.¹³ The amino-alcohol based iridium bifunctional catalyst which is obtained from $[\text{Cp}^*\text{IrCl}_2]_2$ and the corresponding ethanol amine has been used as a catalyst for the oxidative lactonization of diols (Scheme 1.1).¹³

Scheme 1.1 Synthesis of amino-alcohol based iridium bifunctional catalyst

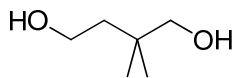
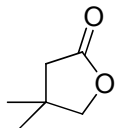
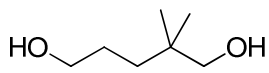
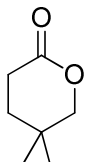
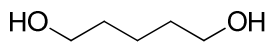
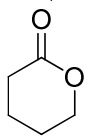
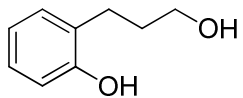
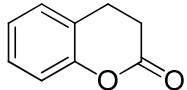


A variety of 1,4 or 1,5-diols have been transformed into the corresponding lactones using this novel metal-ligand bifunctional catalyst **3**. The results are summarized in Table 1.3.

Table 1.3 Oxidative lactonization of diols catalyzed by an Ir catalyst(3)

Entry	Diol	Time, h	Product	%yield ^b
1		4		>99
2		48		97
3		36		97
4		36		98
5		20		96
6 ^c		48		89
7 ^d		36		88

(table 1.3 continued)

8 ^e		20		98 ($\beta,\beta:\alpha,\alpha = >$ 99:1) ^f
9		26		>99 ($\gamma,\gamma:\alpha,\alpha = 93:7$) ^f
10		24		95
11 ^d		5		95

^aUnless otherwise stated, the reaction was carried out at room temperature using a 1.0 M solution of diol (1.0 mmol) in acetone. Diol/Ir = 200:1.

^b Isolated yield.

^c Reaction using 50 g in 140 mL of 2-butanone (4.0 M) under reflux with S/C = 1000.

^d Reaction using a 2.0 M acetone solution.

^e The reaction was carried out using a 0.25 M solution of 1g in CH₃CN containing 4 molar equiv of acetone.

^f Determined by ¹H NMR.

The substrates with chiral centers (entries 2-4) gave the corresponding lactones without epimerization. In the case of unsymmetrical diols (entries 9 and 10), the less hindered hydroxyl groups were selectively oxidized. A broad functional group tolerance was shown with high yields at room temperature. Thus, use of this novel amino alcohol-based Ir bifunctional complex found to be efficient for oxidative lactonization of 1,4- or 1,5-diols.

1.5 Cp*Ir complex-Catalyzed N-heterocyclization of primary amines with diols: A new catalytic System for environmentally benign synthesis of cyclic amines

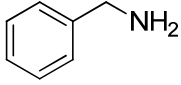
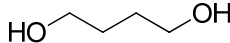
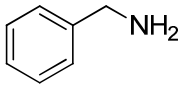
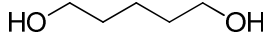
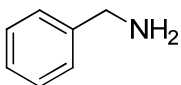
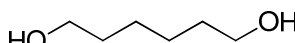
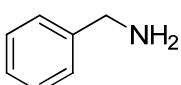
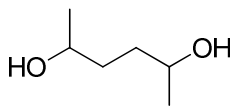
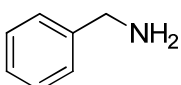
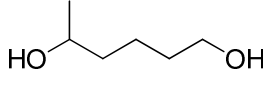
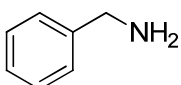
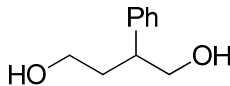
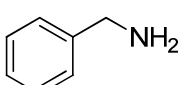
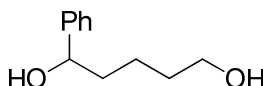
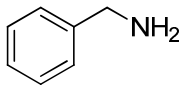
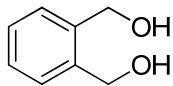
N-Heterocyclic compounds containing pyrrolidine, piperidine and morpholine ring systems form the basis for large class of biologically active natural products.¹⁴ These compounds have attracted considerable attention because of their importance in pharmaceutical chemistry, material chemistry and synthetic organic chemistry. Many efforts have been made to develop efficient methods for the synthesis of such compounds. Although some ruthenium catalyzed systems for N-heterocyclization of primary amines with diols have been reported, most of these reactions require high temperature (> 150 °C), and applicable substrates are rather restricted. Moreover, asymmetric synthesis using ruthenium catalytic systems has never been studied. The Cp*Ir catalyst was found to be an efficient system for synthesis of a variety of N-heterocyclic compounds from primary amines and diols under relatively mild conditions (90 – 110 °C) and has also been applied toward the asymmetric synthesis of (*S*)-2-phenylpiperidine.³ A summary of N-heterocyclization of benzyl amine with a variety of diols under optimized conditions can be found in Table 1.4.

Table 1.4 Cp*Ir complex-catalyzed N-heterocyclization of primary amines with a variety of diols^a

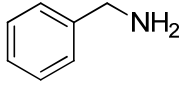
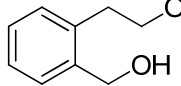
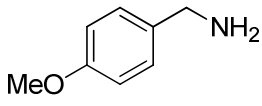
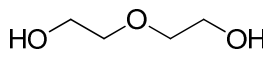
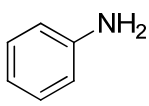
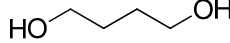
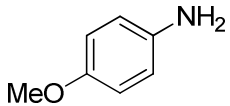
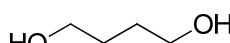
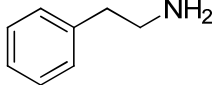
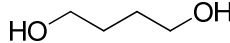
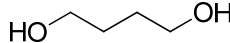
$$\text{R}^1\text{NH}_2 + \text{HO}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH} \xrightarrow[\text{NaHCO}_3]{\text{cat. [Cp}^*\text{IrCl}_2\text{]}_2}$$

$$\text{R}^1-\text{N}(\text{CH}_2)_n-\text{R}^2$$

 toluene, 110 °C, 17 h
 n = 1 - 3

Entry	amine	Diol	cat. (%Ir)	yield ^b (%)
1			1.0	72
2 ^c			1.0	91
3 ^d			2.0	73
4 ^e			1.0	94 ^f
5			1.0	79
6			2.0	90
7			4.0	78 ^g
8 ^{h,i}			2.0	63

(table 1.4 continued)

9			2.0	76
10			2.0	76
11 ^{j,k}			5.0	70
12 ^j			5.0	90
13			4.0	73
14	n-C ₈ H ₇ NH ₂		4.0	81 ^g

^a The reaction was carried out at 110 °C for 17 h with amine (3.0 mmol), diol (2.0 mmol), [Cp*IrCl₂]₂ (1.0-5.0% Ir), and NaHCO₃ (same number of equivalents as the iridium catalyst) in toluene (1 mL).

^b Isolated yield.

^c Reaction temperature was 90 °C.

^d Toluene (3 mL) was used.

^e Na₂CO₃ was used as base.

^f Cis/trans = 73:27 (determined by ¹H NMR analysis).

^g GC yield.

^h Amine (2.0 mmol) was used.

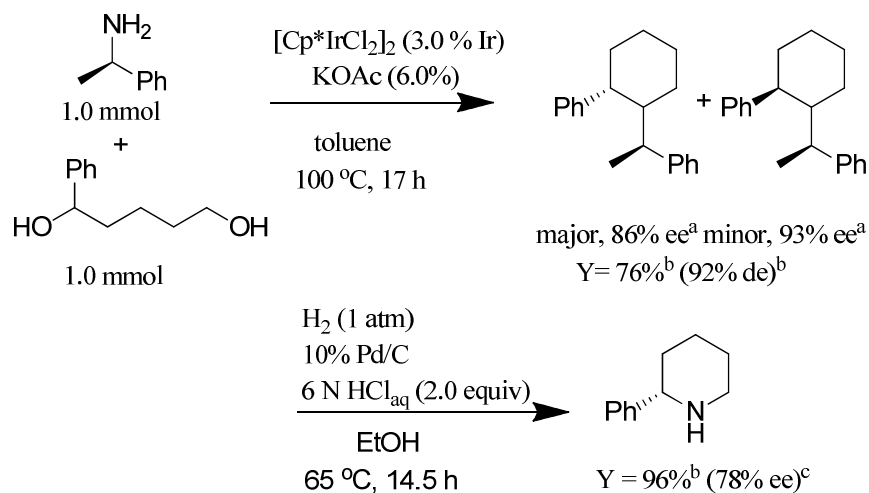
ⁱ Base was not added. ^j Reaction temperature was 130 °C.

^k Reaction time 40 h.

The reactions of benzyl amine with 4, 5 and 6 membered diols gave corresponding cyclic amines in good to excellent yield (entries 1-3). Diols with

different side chains (entries 4-7) can also be used as substrates to give substituted cyclic amines. Although aniline could be used as the starting primary amine, higher catalyst loading (5.0 mol% Ir) and a higher reaction temperature was required to obtain good yields (entries 11 and 12). Introduction of electron donating groups at the phenyl ring of aniline (entry 12) improved the yield considerably. Other primary amines such as phenylethylamine and octylamine, could also be used as starting primary amine (entries 13 and 14). The asymmetric synthesis of 2-substituted piperidines, which have considerable importance as natural and synthetic biologically active compounds, can also be prepared by the use of the Cp*Ir catalytic system.

Scheme 1.2 Asymmetric synthesis of (*S*)-2-Phenylpiperidine



^aDetermined by chiral GC analysis.

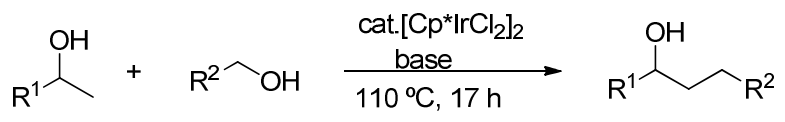
^bDetermined by GC analysis.


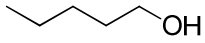










^cDetermined by chiral HPLC analysis.

1.6 Direct β -alkylation of secondary alcohols with primary alcohols catalyzed by Cp*Ir complex¹⁵

Alcohols are one of the most basic and important classes of organic compounds because of their wide variety of uses in industrial and laboratory chemistry. As we have already seen, alcohols are a good replacement for alkyl halides in most of the reactions, because alkyl halides are environmentally harmful. Although there is huge number of methods for the synthesis of alcohols, the synthesis of variety of alcohols having intricate structures requires tedious procedures using many reagents. For example, β -alkylation of a secondary alcohol can be obtained via three steps: oxidation, alkylation and reduction. Although, Ru catalyzed β -alkylation of a secondary alcohol with another alcohol gave higher alcohol with only harmless H₂O as co-product, a large amount of sacrificial hydrogen acceptor (5 equiv of 1-dodecane) and a hydrogen donor (dioxane solvent) is used in this system. To avoid these additives from the view point of atom economy, the [Cp*IrCl₂]₂ catalytic system was found to show high catalytic activity towards both oxidative and reductive hydrogen-transfer reactions. Electronic and steric effects of the catalyst are essential in achieving high performance as a hydrogen transfer catalyst. The reactions of various secondary alcohols with primary alcohols under optimized conditions are summarized below (Table 1.5).

Table 1.5 Cp*Ir complex catalyzed β -alkylation of various secondary alcohols with primary alcohols



Entry	2° alcohol(R ¹)	1° alcohol (R ²)	Catalyst [%Ir]	Base	Yield [%] ^b
1			1.0	NaO ^t Bu	88 ^c
2		C ₇ H ₁₅ -CH ₂ -OH	2.0	NaOH	77 ^c
3		iPr-CH ₂ -OH	2.0	NaOH	75(8)
4		iBu-CH ₂ -OH	2.0	NaOH	82 ^d (12)
5 ^e		Ph-CH ₂ -OH	2.0	NaO ^t Bu	75 ^c
6		4-MeC ₆ H ₄ -CH ₂ -OH	4.0	NaO ^t Bu	80 ^c
7 ^e		4-MeOC ₆ H ₄ -CH ₂ -OH	4.0	NaO ^t Bu	81 ^c
8 ^e		4-ClC ₆ H ₄ -CH ₂ -OH	4.0	NaO ^t Bu	80 ^c
9 ^e		4-CF ₃ C ₆ H ₄ -CH ₂ -OH	4.0	NaO ^t Bu	87 ^c
10		Ph-CH ₂ -CH ₂ -OH	2.0	NaO ^t Bu	74
11		Ph-CH ₂ -CH ₂ -CH ₂ -OH	2.0	NaOH	83

(table 1.5 continued)

12			4.0	NaOH	80(14)
13			4.0	NaOH	69(22)
14			2.0	NaOH	78(14)
15			1.0	NaO ^t Bu	77
16			4.0	NaO ^t Bu	58
17			2.0	NaO ^t Bu	78
18			4.0	NaO ^t Bu	65 ^f (34)

^aThe reaction was carried out with secondary alcohol (3.0 mmol), primary alcohol (3.6 mmol), catalyst, and base (3.0 mmol) in toluene (0.3 mL) at 110 °C for 17h.

^bIsolated yield based on secondary alcohol. Values in parentheses indicate the isolated yield of the corresponding ketone.

^cFormation of a small amount of the corresponding ketone which was not isolated was observed by GC analysis (5-10%).

^dMixture of diastereomers (1:1).

^eReaction was carried out in 3.0 mL of toluene.

^fMixture of diastereomers (cis/trans = 54:46).

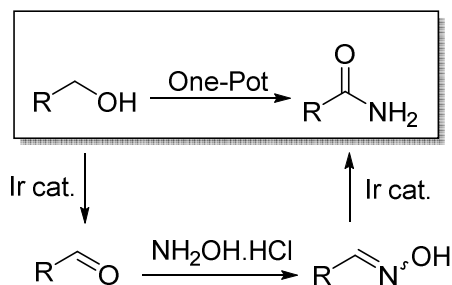
The β -alkylated products were obtained in good yields with aliphatic primary alcohols. The reaction with benzyl alcohols bearing an electron-donating or electron-withdrawing substituent (entries 5-9) were also found to be efficient with this catalytic system. The reaction with butanol gave the β -alkylated products (entries 12-15). A considerable amount of the corresponding ketone product was also isolated in these reactions, in addition to the desired alcohol product. Other secondary alcohols (entries 16-18) were found to be applicable to the present catalytic system to give moderate to good yields. The reaction of 1,2,3,4-tetrahydro-1-naphthol with butanol (entry 18) gave a diastereomeric mixture (cis/trans = 54:46) of 2-butyl-1,2,3,4-tetrahydronaphthalene-1-ol (3r, 65%) in addition to 3,4-dihydro-2-butyl-naphthalene-1(2*H*)-one (4r, 34%). Thus, Ir catalyst found to be an efficient system for β -alkylation of secondary alcohols with primary alcohols.

1.7 Iridium catalyzed conversion of alcohols into amides via oximes

We have already seen that iridium and ruthenium catalysts can be used for the conversion of alcohols into amines. First the alcohol is oxidized to aldehyde, which then allows simple imine formation in situ. These intermediates are reduced to corresponding amine without any overall change in oxidation state. However, an attempt to reduce benzaldehyde oxime to benzyl amine with iridium catalyst and

isopropanol showed unusual rearrangement reaction leading to corresponding amide (Scheme 1.3).¹⁶

Scheme 1.3 Amide bond formation from alcohols



Neither the alcohol nor the base was required for the rearrangement reaction to be effective. Either the (E)- or the (Z)- isomer of oxime could be used. Moreover, the interconversion of the (Z)-isomer to the (E)-isomer was more rapid than the rearrangement into the amide. It is interesting to note that O-alkylated amines were inert to this type of reaction. Therefore, the presence of an aldehyde as hydrogen acceptor in this reaction could also be converted in situ to the corresponding oxime and interfere with the desired product formation. This can be avoided by employing styrene as the sacrificial acceptor as shown in Scheme 1.4. Styrene is a convenient oxidant because it is cheap and can be removed easily by simple evaporation. The amides formed from alcohols are summarized in Table 1.6.

Scheme 1.4 Optimized oxidation conditions

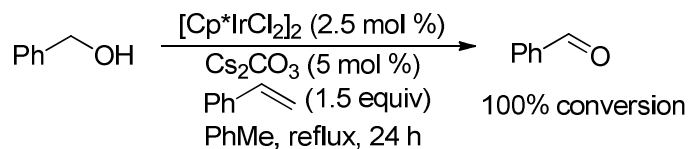
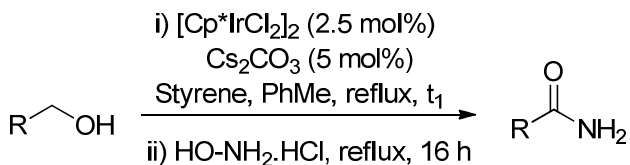


Table 1.6 One-pot synthesis of amides from alcohols



Entry ^a	R	t ₁ (h)	Yield (%) ^b
1	Ph	24	87
2	(4-Me)C ₆ H ₄	24	90
3	(4-F)C ₆ H ₄	24	84
4	(4-Br)C ₆ H ₄	30	79
5	(4-Cl)C ₆ H ₄	30	83
6	(4-OMe)C ₆ H ₄	24	91
7	(4-BnO)C ₆ H ₄	24	90
8	(4-O ₂ N)C ₆ H ₄	36	48
9	(4-F ₃ C)C ₆ H ₄	36	56

^aConditions: alcohol (1.0 mmol), [Ir(Cp*)Cl₂]₂ (2.5 mol%), PhMe (2 mL); 111 °C.


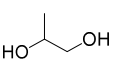

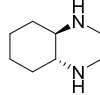

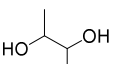

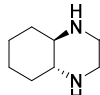

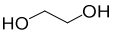
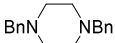
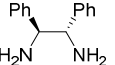
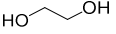

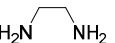
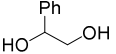

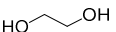
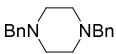
^bIsolated yields after recrystallization or column chromatography

The conversion to amides was found to be successful for a wide range of benzylic alcohols except those with electron-withdrawing groups which showed sluggish oxidations and lower yields. The reaction was found to be unsuccessful with aliphatic alcohols, as no oxidation products were observed.

1.8 Iridium catalyzed synthesis of piperazines from diols

The piperazine moiety is an important privileged structure which is found in large number of biologically active molecules. The synthesis of piperazine and substituted piperazines can be achieved by reduction of the corresponding (di)ketopiperazines or by various cyclization reactions like dialkylation of amines with bis(2-chloroethyl)amine or intramolecular reductive coupling of diimines.^{4a} Again, employing Cp*Ir catalyst here found to be an efficient method for the synthesis of piperazines by cyclocondensation of diols^{4b} with either primary amines or a 1,2-diamine.

Table 1.7 Synthesis of substituted piperazines^a

Entry	Amine	Diol	Product(s)	Solvent	Temp./	Yield ^b (%)
					°C	(dr) ^c
1			 + 	Toluene	110	87 (3:1)
					Water	110
2			 + 	Toluene	140	79 (1:1)
					Water	140
3				Toluene	140	74
					Water	140
4				Toluene	110	54 ^d
					Water	100
5				Water	120	Quant.
6	BnNH ₂			Neat	160 ^f	94

^a Reactions were performed overnight with equimolar amounts of amine and diol in the presence of 0.5 mol% [Cp*IrCl₂]₂ and 5% of NaHCO₃.

^b Isolated yield.

^c Determined from ¹H NMR spectroscopy.

^d Reaction time 64 h.

^e 10% of trifluoroacetic acid was used instead of NaHCO₃. ^f Reaction time 6 h.

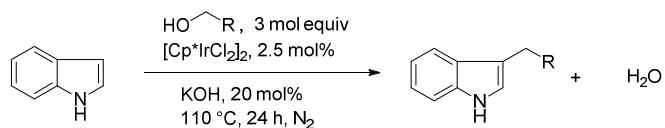
The dialkylation reaction to form piperazines proceeded very well in toluene and/or water. The reaction with trans-1,2-diaminocyclohexane (entry 1-2, 4) introduced a new stereocenter in this reaction with the diastereoselectivity highly dependent on the solvent. The secondary alcohol and the secondary amines react

significantly slower than the corresponding primary amines and alcohols, which require high temperature (140 °C) for complete conversion. Overall, the Ir catalyzed reaction is a green and atom-economical method for the synthesis of piperazines.^{4b}

1.9 [Cp*IrCl₂]₂ catalyzed indirect functionalization of alcohols: Novel strategies for the synthesis of substituted indoles

The indole ring is found in many structurally diverse natural products and pharmaceutical agents. New methods for indole synthesis and functionalization continue to attract attention. A long standing interest in direct catalytic alkylation with alcohols has been established. This offers an attractive green chemistry solution due to its high atom efficiency. An α -alkylation of ketones with alcohols, indirect Wittig reactions with alcohols and [Cp*IrCl₂]₂ catalyzed direct β -alkylation of secondary alcohols with primary alcohols are recent examples of these kind of reactions. However, two of the [Cp*IrCl₂]₂ catalyzed cascade reactions that afford substituted indoles have been recently reported¹⁷ (Table 1.8 and Table 1.9). First, as summarized in Table 1.8, the [Cp*IrCl₂]₂ catalyzed alkylation of indole was investigated with alcohols under essentially solvent free conditions using a slight excess of alcohol to achieve a substituted indole.

Table 1.8 Alkylation of indole with a variety of alcohols using [IrCp*Cl₂]₂ and KOH^a



Entry	Alcohol	Product	Yield (%) ^b
1			80
2			84
3			54
4			83
5			70
6			78
7			81 ^c
8			35 ^d

^a Reaction were carried out in a sealed tube at 110 °C for 24 h with indole (1.0 mmol), alcohol (3.0 mmol), [Cp*IrCl₂]₂ (2.5 mol%), and KOH (0.2 mmol). Bis-indolylmethane byproducts 11-20% were observed by ¹H NMR.

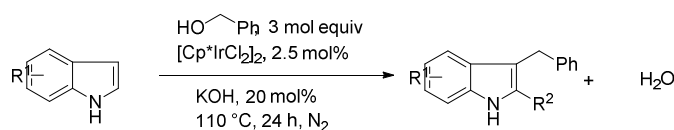
^b Isolated yield.

^c Reaction time 48 h.

^d Reaction time 48 h, ratio of product : bis-indolylmethane byproduct was 3.5:1.

Aromatic, hetero aromatic and aliphatic alcohols gave a variety of 3-substituted indoles in moderate to high yield. This was the first reported hydrogen transfer mediated alkylation of indoles with alcohols using a transition metal catalyst.

Table 1.9 Alkylation of substituted indoles with benzyl alcohol using [IrCp*Cl₂]₂ and KOH^a



Entry	Indole	Product	Yield (%) ^b
1			65 ^c
2			60 ^d
3			73
4			69
5		-	- ^e

^aReaction were carried out in a sealed tube at 110 °C for 24 h with the indole (1.0 mmol), benzyl alcohol (3.0 mmol), [Cp*IrCl₂]₂ (2.5 mol%), and KOH (0.2 mmol).

^bIsolated yield.

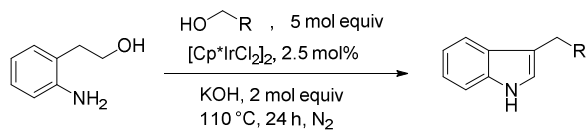
^cRatio of desired:bis-indolymethane byproduct was 6:1.

^dReaction time was 48 h.

^eNo product was observed after 72 h.

Secondly, as summarized in Table 1.9, alkylation of substituted indoles was investigated with electron-donating and electron-withdrawing groups. Both electron-withdrawing and electron-donating groups were tolerated as was substitution in 2-position. However, N-methyl indole failed to undergo alkylation, which indicates indole anion formation during alkylation.¹⁷ Apart from these studies, oxidative cyclization of 2-amino phenyl ethyl alcohols to give indoles has been reported as summarized in Table 1.10.

Table 1.10 One-Pot synthesis of substituted indoles from 2-aminophenyl ethyl alcohol and primary alcohols^a



Entry	Alcohol	Product	Yield (%)
1			75
2			71
3			68 ^c
4			71 ^c
5			68 ^c
6			53 ^c
7			74 ^c

^aReactions were carried out in a sealed tube at 110 °C for 24 h with amino alcohol (1.0 mmol), alcohol (5.0 mmol), [Cp*IrCl₂]₂ (2.5 mol%), and KOH (2.0 mmol). ^bIsolated yield. ^cReaction time 48 h.

The reaction was found to be highly selective for 3-benzylindole at higher base concentrations. N,N-Dimethyltryptamine analogues form a class of

commercially important anti-migraine drugs. Good yields of disubstituted indoles were achieved with substitution tolerated on the aromatic ring. Thus, two novel $[\text{Cp}^*\text{IrCl}_2]_2$ catalyzed methods has been developed for synthesis of substituted indoles.¹⁷

1.10 Cp*Ir-catalyzed N-alkylation of amines with alcohols. A versatile and atom economical method for synthesis of amines

Amines play a major role in many fields of organic chemistry including such as biological, medicinal, agrochemical, dyes and polymer chemistry. Therefore, development of versatile methods for the synthesis of amines has been an active area of research. In recent years, a number of transition metal catalyzed reactions for the synthesis of amines, such as hydroamination of alkenes or alkynes, and amination of aryl halides have been developed. Other methods include N-alkylation with alkyl halides and the reductive amination with carbonyl compounds. However, the use of alkyl halides or strong reducing agents is undesirable from environmental point of view, because it generates equimolar amounts of wasteful salts as co-products. This can be avoided by using alcohols and amines for N-alkylation of amines which can again be achieved using Cp*Ir complex catalyst.² Alcohols are more readily available than corresponding halides or carbonyl compounds and only harmless water is generated as co-product. The reaction with Cp*Ir catalyst proved to be efficient and extremely high atom economical system. Although, several catalytic systems has been studied for N-

alkylation of amines with alcohols using ruthenium and other transition metal catalysts. Most of them require a high reaction temperature ($>150\text{ }^{\circ}\text{C}$) and/or an excess use of alcohol to obtain high yields of the product. Cp^*Ir catalyst can also be effective in achieving N-alkylation of primary and secondary amines with primary and secondary alcohols.²

Scheme 1.5 Possible catalytic cycle for Ir catalyzed N-alkylation²

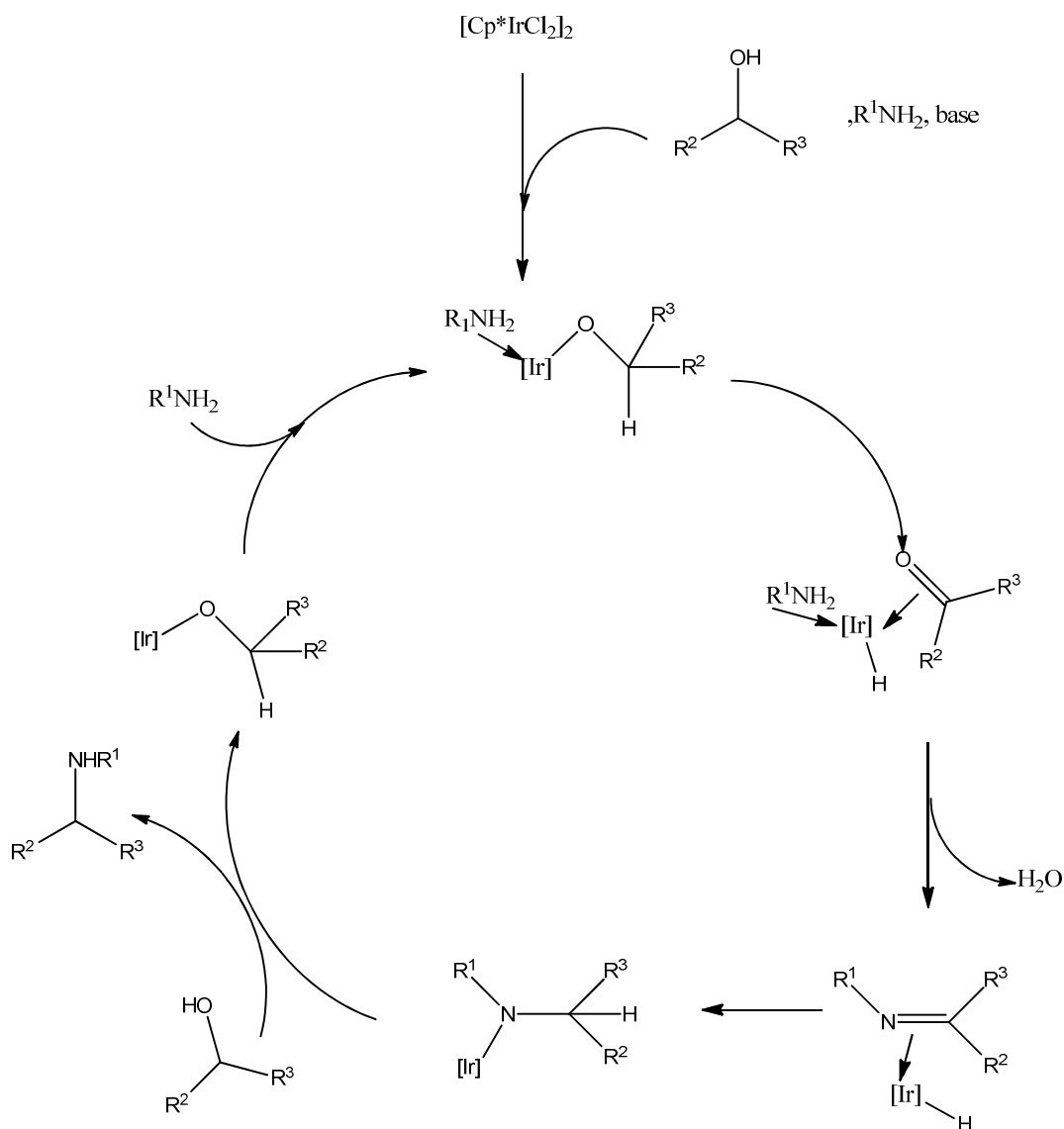
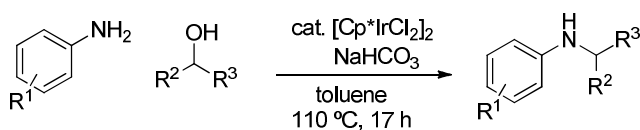


Table 1.11 N-Alkylation of anilines with various primary and secondary alcohols^a



Entry	Amine	Alcohol	Catalyst(mol%Ir)	Yield ^b (%)
1			1.0	94
2 ^{c,d}			3.0	88
3		n-C ₇ H ₁₅ -CH ₂ -OH	2.0	97
4 ^e		n-C ₇ H ₁₅ -CH ₂ -OH	5.0	63+36 ^f
5		n-C ₆ H ₁₃ -CH(OH)-CH ₃	3.0	91
6			1.0	93
7			3.0	92
8			1.0	94
9			1.0	92

^aThe reaction was carried out with aniline (1.0 mmol), alcohol (1.0 mmol), [Cp*IrCl₂]₂ (1.0-3.0 mol% Ir), and NaHCO₃ (same equivalent as that of the iridium catalyst) in toluene (0.1 mL) at 110 °C for 17 h.

^b Isolated yield.

^c At 130 °C.

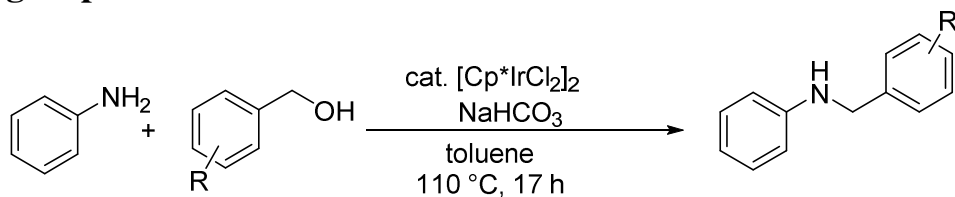
^d K₂CO₃ was used as base.

^e The reaction was carried out using aniline (1.0 mmol), 1-octanol (2.6 mmol), [Cp*IrCl₂]₂ (5.0 mol% Ir), and K₂CO₃ (5.0 mol%) in toluene (0.5 mL) at 110 °C for 40 h.

^f N-Octylaniline (63%) and N,N-dioctylaniline (36%) were isolated

N-Alkylation of amines with primary anilines and with primary alcohols resulted in the formation of monoalkylation product with high to excellent yields, although the reaction with 2-phenylethanol (entry 3) required high temperature to obtain good yields. When the reaction was performed with excess of 1-octanol, excess catalyst and for 40 h, the dialkylated product was obtained in 36% yield along with 63% monoalkylated product (entry 4), indicating that the second alkylation is sufficiently slow. Secondary alcohols also gave good yield of alkylated products. However, the reaction with tertiary alcohol resulted in no reaction. The reaction of aniline with benzyl alcohols bearing various functional groups were also explored and summarized in Table 1.12.²

Table 1.12 N-Alkylation of aniline with benzyl alcohols bearing functional groups^a



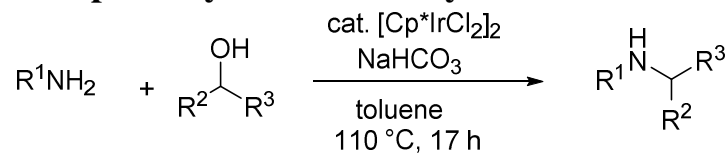
Entry	R	Catalyst (mol% Ir)	Yield ^b (%)
1	4-Me	1.0	92
2	2-OMe	2.0	93
3	3-OMe	2.0	97
4	4-OMe	1.0	92
5	4-Cl	1.0	96
6	4-Br	3.0	98
7	4-NO ₂	3.0	84
8	3-CN	3.0	87
9	4-COOMe	3.0	96

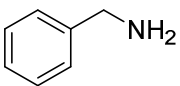
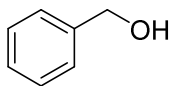
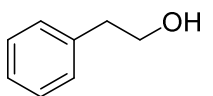
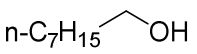
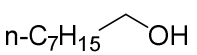
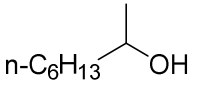
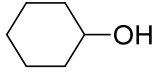
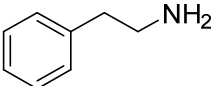
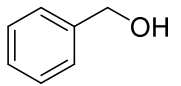
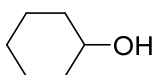
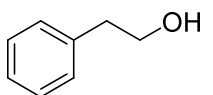
^a The reaction was carried out with aniline (1.0 mmol), benzyl alcohols (1.0 mmol), [Cp*IrCl₂]₂ (1.0-3.0 mol% Ir), and NaHCO₃ (same equivalent as that of the iridium catalyst) in toluene (0.1 mL) at 110 °C for 17 h.

^b Isolated yield.

The N-alkylation of aniline with benzyl alcohols bearing various electron-withdrawing and electron-donating groups gave similar yields with small variation in catalyst loading. The results of N-alkylation of other primary amines were also explored and are summarized in Table 1.13.²

Table 1.13 N-Alkylation of benzyl amine, phenethylamine, and octylamine with primary and secondary alcohols^a



Entry	Amine	Alcohol	Catalyst (mol% Ir)	Yield ^b (%)
1			1.0	93
2			1.0	80
3 ^c			1.0	86
4 ^d			5.0	80 ^e
5			2.0	86
6 ^c			1.0	98
7			3.0	86
8 ^f			3.0	71
9 ^g	$n\text{-C}_8\text{H}_{17}\text{NH}_2$		3.0	76

^a The reaction was carried out with primary amine (1.0 mmol), alcohols (1.0 mmol), $[Cp^*IrCl_2]_2$ (1.0-3.0 mol% Ir), and $NaHCO_3$ (same equivalent as that of the iridium catalyst) in toluene (0.1 mL) at 100 °C for 17 h.

^b Isolated yield.

^c At 90 °C.

^d The reaction was carried out using benzyl amine (1.0 mmol), 1-octanol (2.6 mmol), $[Cp^*IrCl_2]_2$ (5.0 mol% Ir), and K_2CO_3 (5.0 mol%) in toluene (0.5 mL) at 110 °C for 40 h.

^e N,N-Dioctylbenzylamine (80%) was isolated.

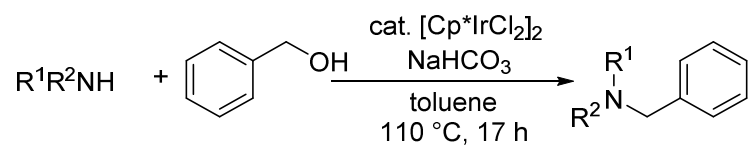
^f At 130 °C.

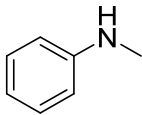
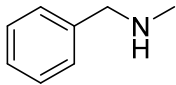
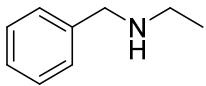
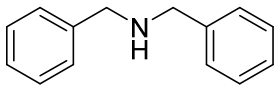
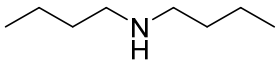

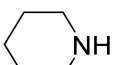
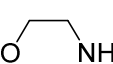
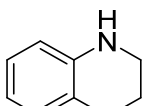
^g At 100 °C for 40 h.

The N-alkylation of benzyl amine, phenyl ethyl amine, and octyl amine with primary and secondary alcohols also gave good yields. However higher catalyst loading and higher reaction temperature were required. The results of the N-alkylation reaction of various secondary amines with alcohols are summarized in Table 1.14.²

The N-alkylation of various secondary amines was found to be tolerable with this catalytic system, although reaction required higher catalyst loading (4.0 mol% Ir) to afford excellent yields. However, the reaction of more basic and sterically unhindered N-methylbenzyl amine required only 1.0 mol% of Ir catalyst. The N-alkylation of various secondary alcohols with various secondary amines is summarized in Table 1.15.²

Table 1.14 N-Alkylation of various secondary amines with benzyl alcohol^a

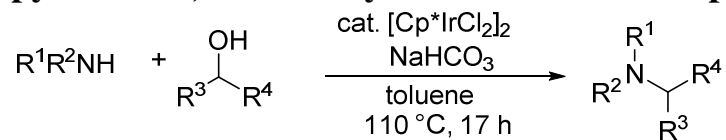


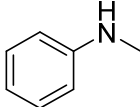
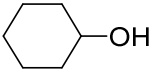
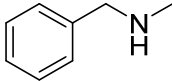
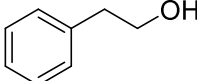
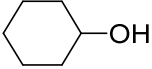

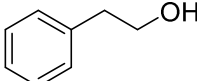
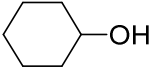
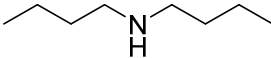
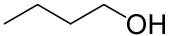
Entry	Amine	Catalyst (mol % Ir)	Yield ^b (%)
1		4.0	91
2		1.0	95
3		2.0	87
4		3.0	75
5		5.0	81
6		1.0	92
7		2.0	93
8		5.0	83
9		5.0	72

^a The reaction was carried out with secondary amine (1.0 mmol), benzyl alcohol (1.0 mmol), benzyl alcohol (1.0 mmol), [Cp*IrCl₂]₂ (1.0-5.0 mol% Ir), and NaHCO₃ (same equivalent as that of the iridium) in toluene (0.1 mL) at 110 °C for 17 h

^b Isolated yield.

Table-1.15. N-Alkylation of N-methylaniline, N-methylbenzylamine, pyrrolidine, and dibutylamine with various primary and secondary alcohols^a



Entry	Amine	Alcohol	Catalyst (mol% Ir)	Yield ^b (%)
1 ^c		n-C ₇ H ₁₅ -CH ₂ -OH	5.0	66
2			4.0	83
3			1.0	88
4		n-C ₇ H ₁₅ -CH ₂ -OH	1.0	95
5			4.0	44
6			5.0	77
7 ^d		n-C ₇ H ₁₅ -CH ₂ -OH	2.0	96
8 ^e			5.0	88
9 ^{f,g}			3.0	91 ^h

^a The reaction was carried out with secondary amine (1.0 mmol), alcohol (1.0 mmol), [Cp*IrCl₂]₂ (1.0-5.0 mol% Ir), and NaHCO₃ (same equivalent as that of the iridium catalyst) in toluene (0.1 mL) at 110 °C for 17 h.

^b Isolated yield. ^c At 130 °C.

^d 1-Octanol (2.0 mmol) was used.

^e Pyrrolidine (2.0 mmol) and 4.0 mmol of cyclohexanol were used.

^f 1-Butanol (5.0 mmol) was used.

^g At 90 °C. ^h GC yield.

The N-alkylation of secondary amines and secondary alcohols gave lower yields compared to above reactions. Thus, a variety of secondary and tertiary amines can be synthesized with high atom economy under mild and less toxic conditions, which also provide an environmentally benign and versatile protocol for the synthesis of amines.

1.11 N-alkylation of carbamates and amides with alcohols catalyzed by a Cp-Ir complex

Carbamates are known to have multiple applications as synthetic intermediates for the production of a variety of biologically active compounds. The carbamate moiety can be found in a number of agrochemicals and pharmaceuticals. An efficient method for the introduction of substituents therefore is quite important. Carbamates are regarded as ammonia equivalents, because the protecting alkoxy carbonyl group on nitrogen can be easily removed by simple procedures. The N-alkylation of carbamates is usually obtained by reductive amination with carbonyl compounds or with alkyl halides. However, both of these reactions generate equimolar amounts of wasteful salts or co-products which are dangerous from an environmental point of view. The $[\text{Cp}^*\text{IrCl}_2]_2$ catalytic system has been found to be a new atom economical system for the N-alkylation of carbamates and amides using alcohols as alkylating agents under solvent free conditions. This avoids generation of wasteful co-products. Both $[\text{Cp}^*\text{RhCl}_2]_2$ and $\text{RuCl}_2(\text{PPh}_3)_3$ have been used as catalysts in hydrogen transfer reactions, however

the catalysts showed inferior activity to $[\text{Cp}^*\text{IrCl}_2]_2$ catalytic system.¹⁸ The N-alkylation of N-butylcarbamate with various primary alcohols is summarized in Table 1.16.

Table 1.16 N-alkylation of n-butyl carbamate and methyl carbamate with various alcohols.

Entry	Carbamate	Alcohol	Product	Yield ^b (%)
1	R ¹ = n-Bu			87(94c)
2	R ¹ = n-Bu			92
3	R ¹ = n-Bu			67
4	R ¹ = n-Bu			55
5 ^d	R ¹ = n-Bu			67

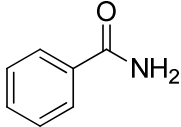
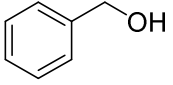
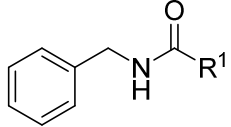
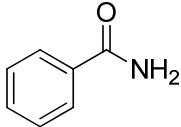
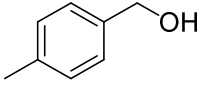
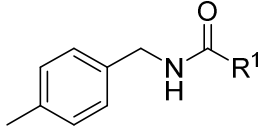
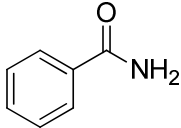
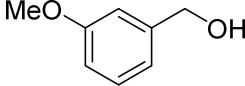
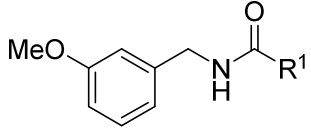
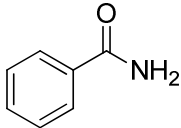
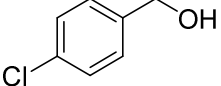
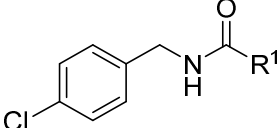
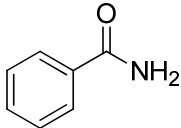
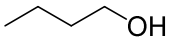
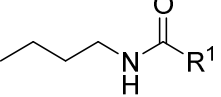
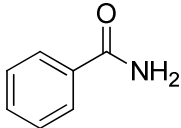
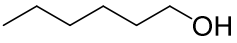
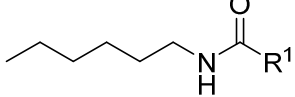
(table 1.16 continued)

6 ^d	R ¹ = n-Bu			58
7	R ¹ = n-Bu			53
8 ^d	R ¹ = n-Bu			57
9	R ¹ = n-Bu			69
10 ^d	R ¹ = n-Bu			50
11 ^d	R ¹ = n-Bu			65
12	R ¹ = Me			46

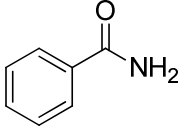
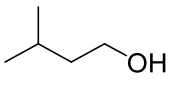
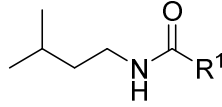
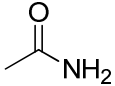
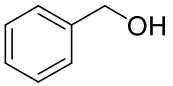
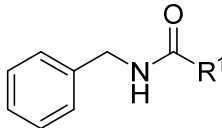
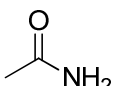
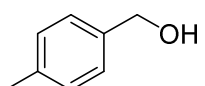
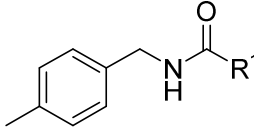
The reactions with benzyl alcohol bearing electron donating and electron withdrawing substituents at the aromatic ring gave moderate to good yields,

although the higher catalyst loadings (10 mol% Ir) were required in some cases (Table 1.17).

Table 1.17 N-Alkylation of benzamide and acetamide with various alcohols^a

Entry	Carbamate	Alcohol	Product	Yield ^b (%)
1				81
2				91
3				59
4 ^c				67
5				82
6				66

(table 1.17 continued)

7				70
8				64
9				66

^a The reaction was carried out with amide (1.0 mmol), alcohol (4.0 mmol), [Cp*IrCl₂]₂ (5.0 mol% Ir), and NaOAc (5.0 mol%) at 130 °C for 17 h.

^b Isolated yield.

^c [Cp*IrCl₂]₂ (10 mol% Ir) and NaOAc (10 mol%) were used.

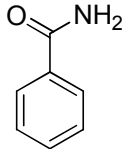
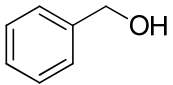
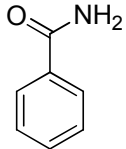
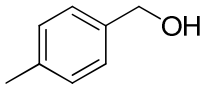
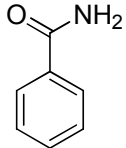
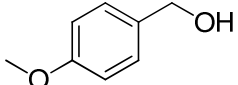
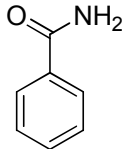
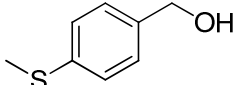
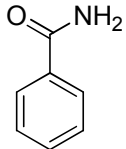
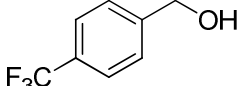
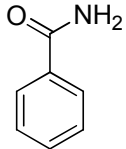
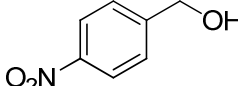
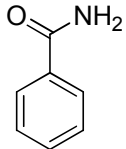
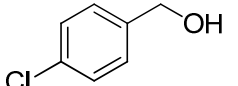
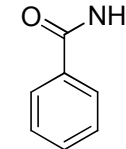
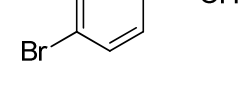
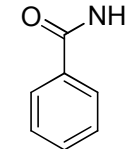
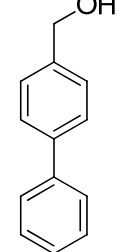
1.12 Solvent free, base free microwave mediated Iridium catalyzed N-alkylation of amides with alcohols

Recent studies by Xu and co-workers have demonstrated the solvent free conditions for N-alkylation of amides with primary alcohols using a variety of transition metal catalytic systems (Rh, Ru, Ir).^{19b} However, these systems typically required longer reaction times and high temperatures. Williams and co-workers reported the use of Ru catalysis under solvent free microwave conditions for N-alkylation of amides with alcohols. However, these reports were limited to the use of only primary alcohols as alkylating agent. Our lab reported the first solvent-free,

base-free microwave mediated N-alkylation of amides with both primary and secondary alcohols, using Ir catalysis.^{19a} The results are summarized in Table 1.18. The microwave approach provided N-alkylated product in shorter time period than the conventional reflux times for these reactions. The results were improved by omitting the use of base, increasing the quantity of alcohol to three equivalents and by increasing the reaction temperature to 160 °C. Further increase in temperature or decrease in catalyst loading decreased the yield of the product.

Substituted benzyl alcohols afforded good yields of the corresponding N-substituted benzyl amides. Benzyl alcohols with electron-donating and electron-withdrawing groups showed equal tolerance. Only 4-nitrobenzyl alcohol failed to give good yield of the amide, affording only an intractable mixture of material. Primary alcohols also furnished decent yields. Acetamide and the substituted benzamides also gave good yields of the corresponding N-benzyl benzamide derivatives. A variety of cyclic and acyclic secondary alcohols were also reported as summarized in Table 1.19.

Table 1.18 Reaction of variety of amides with various substituted primary alcohols

Entry ^a	Amide	Alcohol	Yield (%) ^b
1			85
2			85
3			72
4			75
5			77
6			IM ^[c]
7			65
8			68
9			60

(table 1.18 continued)

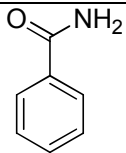
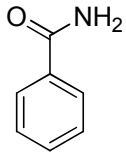
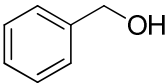
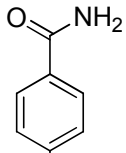
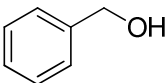
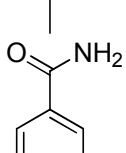
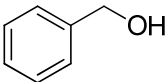
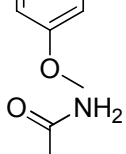
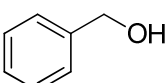
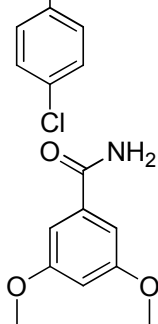
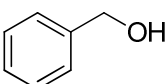
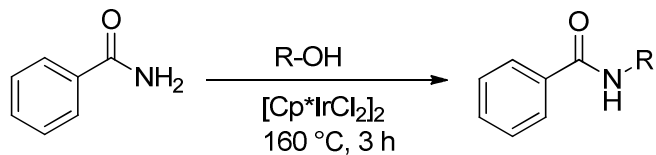
10		$\text{CH}_3(\text{CH}_2)_4\text{-OH}$	72
11		$\text{CH}_3(\text{CH}_2)_5\text{-OH}$	70
12	$\text{CH}_3\text{-NH}_2$		68
13			76
14			75
15			70
16			78

Table 1.19 Reaction of benzamide with secondary alcohols



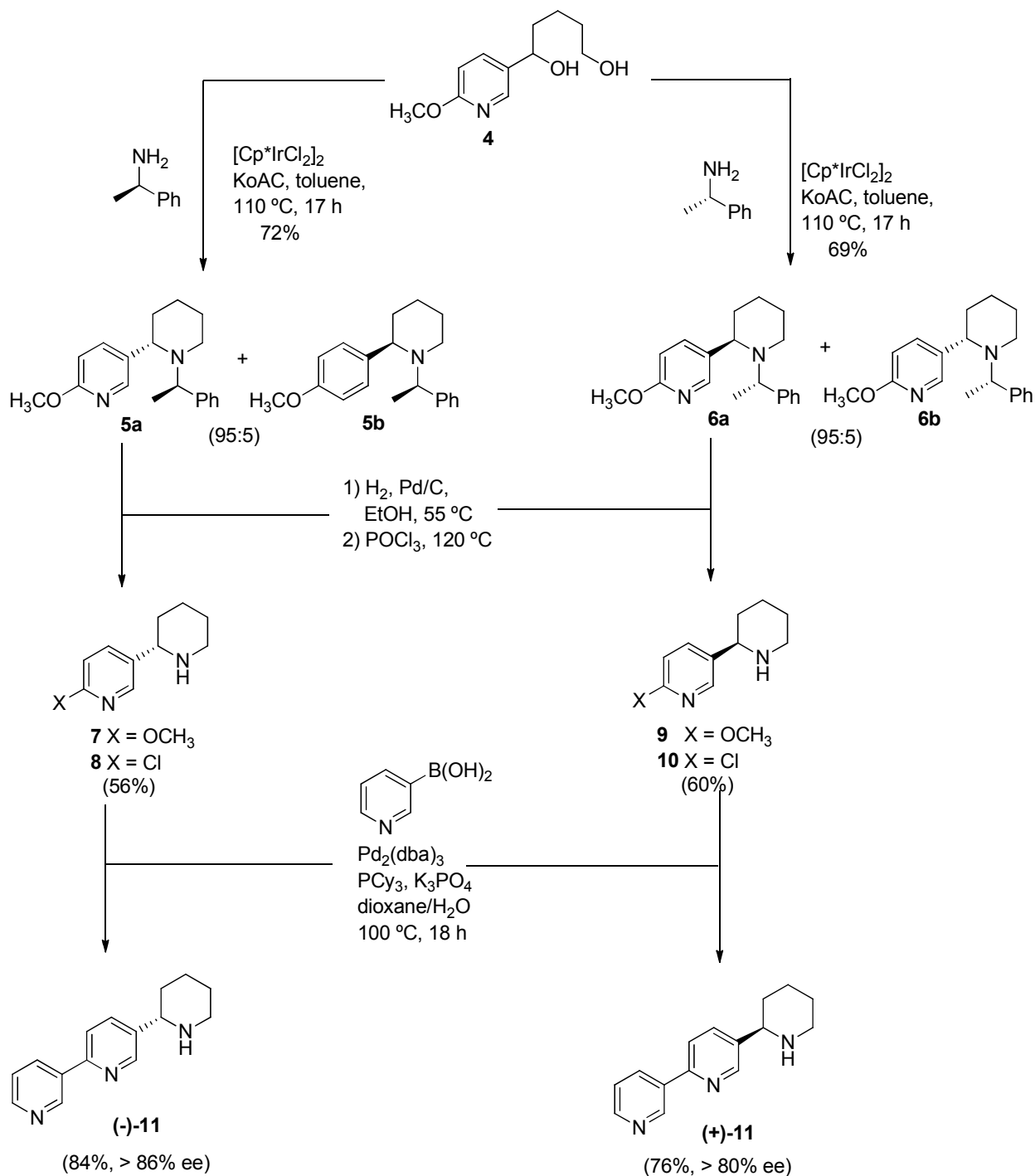
Entry	Alcohol	Product	Yield (%)
1			68
2			72
3			65
4			78
5			76
6			65
7			65

Both cyclic and acyclic alcohols gave decent yields. Even the sterically hindered benzhydrol derivatives afforded the N-benzhydryl amides in good yields.

1.13 Enantioselective synthesis of both enantiomers of Noranabasamine

Nicotine and anabasine are pyridine alkaloids commonly found in solanaceac plant family such as *Nicotina tobacum* and *Nicotina rustica*.^{20a,20b} Nicotina alkaloids modulate neuronal acetyl choline receptors, which affect the central nervous system. The pharmacological action of nicotine alkaloids and its derivatives on the central nervous system attracted considerable attention as they are potential therapeutic targets for a variety of disease states and pathological conditions mediated by nicotine acetyl choline receptors. However, toxicity and abuse potential has limited the use of nicotine related drugs for the central nervous system disorders. Therefore, new analogues of nicotine with unique nicotine acetyl choline receptor subtype selectively remain important pharmacological targets for the development of novel therapeutics with improved safety profiles. Our lab first reported the application of the iridium catalyzed N-heterocyclization reaction for the synthesis of nicotine-related compounds and the first total synthesis of both enantiomeric forms of the noranabasamine^{20c} as shown in Scheme 1.6.

Scheme 1.6 Synthesis of Noranabasamine



The diol **4** was heated at 110 °C in toluene in the presence of [Cp*IrCl₂]₂ catalyst with (R)-1-phenylethylamine in a sealed tube to obtain diastereomers of 2-substituted piperidine **5ab** in 72% yield (5a:5b, dr, 95:5). The other two diastereomers of 2-substituted piperidine **6ab** was obtained in similar fashion using (S)-1-phenylethylamine, in 69% yield with a diastereomeric ratio of 95:5. Presumably, N-heterocyclization proceeds through the formation of various imine and enamine intermediates. The N-substitution on the piperidine ring was subjected to hydrogenolysis condition to furnish **7,9** and concomitant treatment with POCl₃ gave chloro analogue **8** and **10** in 56% and 60% yield respectively.

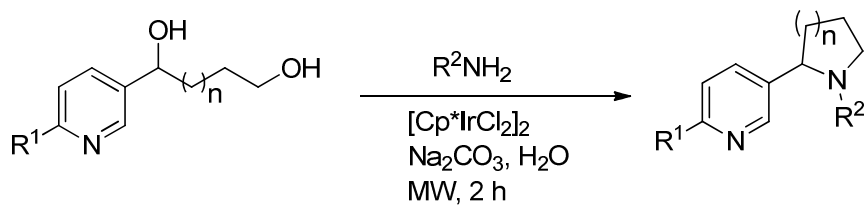
The Suzuki-Miyaura coupling conditions^{20d} developed by Fu and co-workers can be applied to **8** and **10** finally to obtain both enantiomers of noranabasamine **11**. Thus, iridium-catalyzed N-heterocyclization reaction is a facile method for the efficient and enantioselective construction of 2-(pyridine-3-yl)-piperidine alkaloids, which is a key step in the first total synthesis of both enantiomers of the amphibian alkaloid noranabasamine.

1.14 Application of Iridium catalyzed N-heterocyclization for synthesis of natural products^{19b}

In the past, we have described the application of iridium catalyzed N-heterocyclization reaction for the synthesis of nicotine related compounds, and the first total synthesis of the alkaloid, Noranabasamine. Further, studies by Zhao and

co-workers showed that the N-heterocyclization of simple amine/alcohol system proceeded under solvent free, base-free microwave-assisted conditions. Recently, our lab developed conditions for the green synthesis of nicotine and anabasine related analogues utilizing the above two concepts. N-Heterocyclization of 1,4-butanediols and 1,5-pentanediols were performed under microwave conditions. The reaction was optimized under aqueous conditions using Na_2CO_3 as a base to prepare a series of nicotine and anabasine derivatives. The results are summarized in Table 1.20.

Table 1.20 Synthesis of N-substituted nor-nicotine derivatives



Entry	Diol	Amine	Yield (%)
1		CH ₃ NH ₂	50
2			75
3			73
4			78
5			75
6			70
7			75
8			78

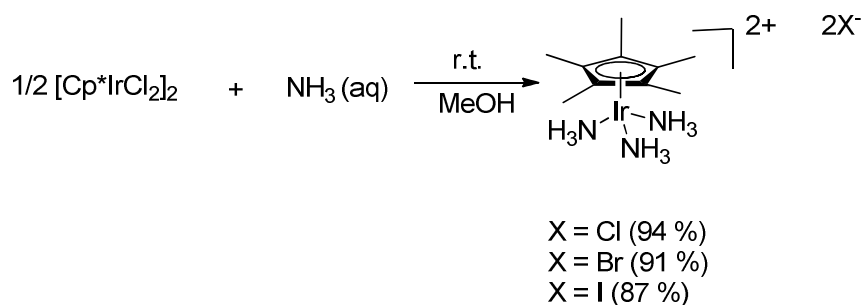
The reaction of 1,4-butanediols with methyl amine gave a moderate yield of product. This may be because of the high volatility of methyl amine in water at elevated temperatures. Instead, use of benzyl amine and 4-methoxyamine gave good yields of the corresponding cyclization products. Synthesis of quinolone derivative also found to give good yields using similar conditions.

1.15 Amination with ammonia

Ammonia has drawn much attention as a source of nitrogen for synthesis of organic molecules in the recent days, because of its abundance and low price.²⁴ Although there are many reports on homogeneous transition-metal-catalyzed reactions for the synthesis of organic amines using gaseous (or liquid) ammonia and its solution in organic solvent²⁵, aqueous ammonia is much easier to handle considering its advantages in terms of safety. Some reactions which utilize aqueous ammonia as a substrate for the synthesis of organic amines are Rh-catalyzed reductive amination of aldehydes²⁶ Rh- and Ir-catalyzed hydroaminomethylation of olefins,²⁷ Pd-catalyzed allylic amination,²⁸ Pd-catalyzed telomerization with butadiene,²⁹ Cu-catalyzed coupling with aryl halides,³⁰ and Cu-catalyzed coupling with aryl boronic acids.³¹ However, most of these reactions employ harmful organic halides as a reagent and use of excess quantities of ammonia. Although, Cp*Ir complexes show high catalytic performance in hydrogen transfer reactions for construction of N-alkylation of amines and ammonium salts with alcohols,^{32,33}

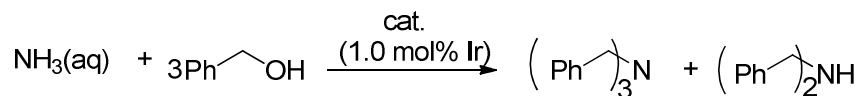
the utilization of aqueous ammonia as nitrogen source found to be most unsatisfactory because the catalyst is insoluble in aqueous conditions. A novel water-soluble Cp*Ir complexes having ammine ligands that is soluble and stable in water has been reported. This catalyst can be obtained by treating a suspension of $[\text{Cp}^*\text{IrCl}_2]_2$ in methanol and 28 % aqueous ammonia (Scheme 1.7).^{35, 37}

Scheme 1.7 Synthesis of water soluble iridium catalysts



A similar procedure starting with $[\text{Cp}^*\text{IrBr}_2]_2$ and $[\text{Cp}^*\text{IrI}_2]_2$ also gave dicationic catalyst having ammine ligands in 91 and 87% yield, respectively. These complexes are highly soluble in water and stable in air for months without decomposition. The geometry could be described as a three-legged piano stool, which is common in $\text{Cp}^*\text{Ir}^{\text{III}}$ complexes. The catalytic activity of the N-alkylation of aqueous ammonia³⁴ (28%) with benzyl alcohol under various conditions are shown in Table 1.21.

Table 1.21 N-Alkylation of aqueous ammonia with benzyl alcohol catalyzed by Cp*Ir complexes under various conditions^a



Entry	Catalyst	Temp (°C)	Time (h)	Yield(%) ^b	
				(3° amine)	(2° amine)
1	None	140	20	0	0
2	[Cp*IrCl ₂] ₂	140	20	29	21
3	[Cp*Ir(NH ₃) ₃]Cl ₂	140	20	70	18
4	[Cp*Ir(NH ₃) ₃]Br ₂	140	20	49	23
5	[Cp*Ir(NH ₃) ₃]Cl ₂	140	20	82	7
6	[Cp*Ir(NH ₃) ₃]I ₂	120	20	79	6
7 ^c	[Cp*Ir(NH ₃) ₃]I ₂	140	20	76	3
8	[Cp*Ir(NH ₃) ₃]I ₂	140	24	100	0

^aThe reaction was carried out with NH₃ (1.0 mmol, 28% aqueous solution), Cp*Ir catalyst (1.0 mol% Ir), and benzyl alcohol (4a, 3.0 mmol).

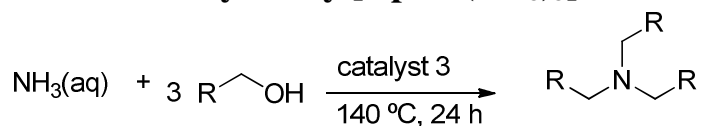
^bDetermined by GC.

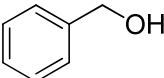
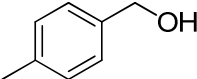
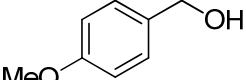
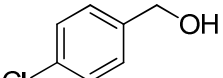
^cCatalyst 3 (0.50 mol% Ir) was used

It is clear that no product is formed in the absence of catalyst (entry 1). When the reaction of aqueous ammonia was carried out with 3 equivalents of benzyl alcohol at 140 °C for 20 h in the presence of [Cp*IrCl₂]₂ catalyst, the corresponding disubstituted and trisubstituted products obtained in low yields

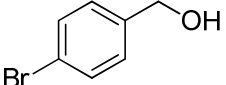
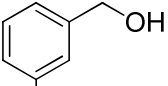
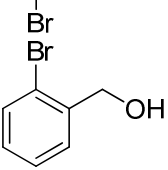
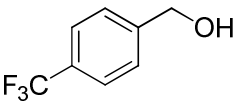
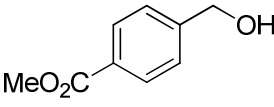
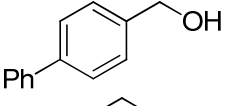
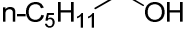
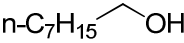
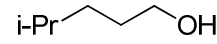
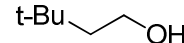
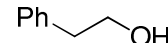
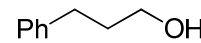
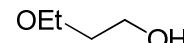
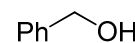
(entry 2). However, the reaction was considerably accelerated by using the water soluble catalysts (entries 3-5). Among the three water soluble catalysts, the one having iodide as a counter ion exhibited the highest catalytic activity with good selectivity towards tertiary amine (entry 5). There is no much effect on the selectivity even with lower amounts of catalyst (0.5 mol% Ir) or at lower temperature (120 °C). However, best results were achieved with longer reaction time (entry 8). The advantage of this catalytic system is there is no generation of waste. The reaction of aqueous ammonia with various primary alcohols was summarized in Table 1.22.

Table 1.22 N-Alkylation of aqueous ammonia with a variety of primary alcohols catalyzed by [Cp*Ir(NH₃)₃]I₂ affording tertiary amines^a



Entry	Primary alcohol	Catalyst 3 (mol% Ir)	Product yield (%) ^b
1		1.0	94
2		1.0	92
3		1.0	95
4		2.0	86

(table 1.22 continued)

5		2.0	81
6		2.0	85
7		3.0	81
8		3.0	84
9		2.0	89
10		1.0	94
11		1.0	96
12		1.0	86
13		1.0	86
14		1.0	87
15		1.0	85
16		1.0	86
17		3.0	65 ^c
18 ^d		1.0	89

^aThe reaction was carried out with NH₃ (1.0 mmol, 28% aqueous solution), catalyst 3 (1.0 – 3.0 mol% Ir), and primary alcohol (3.0 mmol) at 140 °C for 24 h.

^bIsolated yield.

^cDetermined by ¹H NMR.

^dThe reaction was carried out using 20 mmol of aqueous ammonia and 60 mmol of 4a.

The reactions with benzyl alcohol bearing electron-donating and electron-withdrawing substituents, both proceeded smoothly to give corresponding tertiary amines in good to excellent yields (entries 1-10). The reactions with a variety of aliphatic primary alcohols also proceeded smoothly (entries 11-16). The results of reaction of aqueous ammonia with various secondary alcohols are also summarized in Table 1.23.

The selective formation of secondary amines was observed here probably because of the steric factors. The reactions with cyclic alcohols showed good yields compared to aliphatic secondary alcohols. The aliphatic secondary alcohols gave mixture of diastereomers (entries 4-7).

The multialkylation reaction was extended for the synthesis of quinolizidine³⁶ by the use of aqueous ammonia with a water soluble 1,5,9-nonanetriol (Scheme 1.8). The reaction was carried out at 140 °C for 24 h in the presence of [Cp*Ir(NH₃)₃]₂I₂ (5.0 mol% Ir). It was reported that quinolizidine was obtained in 85 % yield based upon NMR.³⁶

Scheme 1.8 Synthesis of quinolizidine²⁴

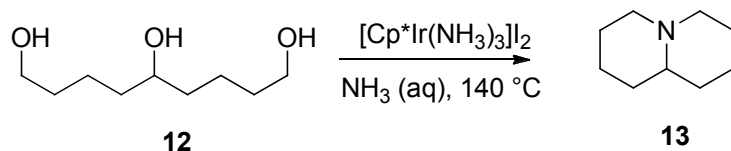
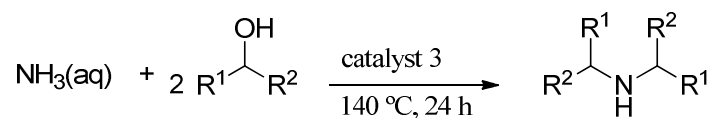
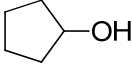
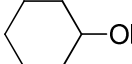
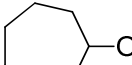
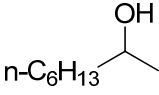

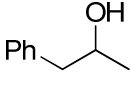
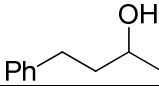


Table 1.23 N-alkylation of aqueous ammonia with a variety of secondary alcohols catalyzed by **3 affording secondary amines^a**



Entry	Secondary alcohol	Catalyst 3 (mol% Ir)	Product yield (%) ^b
1		1.0	84
2		1.0	85
3		1.0	86
4		1.0	83 ^c
5		3.0	89 ^d
6		3.0	81 ^c
7		3.0	63 ^c

^aThe reaction was carried out with NH₃ (1.0 mmol, 28% aqueous solution), catalyst **3** (1.0 – 3.0 mol% Ir), and secondary alcohol (2.0 mmol) at 140 °C for 24 h.

^bIsolated yield

^cIsolated as a mixture of diastereomers (50:50 by ¹H NMR).

^dIsolated as a mixture of diastereomers (*meso/dl* = 63:37 by ¹H NMR).

1.16 References

1. (a) *Comprehensive Heterocyclic Chemistry II*; Bird, C.W., Ed.; Pergamon: Oxford, 1996. (b) Kang, J.W.; Moseley, K.; Maitlis, P.M. *J. Am. Chem. Soc.* **1969**, *91*, 5970. (c) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708. (d) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348.
2. (a) Fujita, K. I.; Enoki, Y.; Yamaguchi, R. *Tetrahedron*. **2008**, *64*, 1943-1954. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928.
3. Fujita, K. I.; Fujii, T.; Yamaguchi, R. *Org Lett.* **2004**, *6*, 3525-3528.
4. (a) Mercer, G.J.; Signam, M. S. *Org. Lett.* **2003**, *5*, 1591-1594. (b) Nordstrom, L. Ulrik.; Madsen, R. *Chem. Comm.* **2007**, 5034-5036.
5. Fujita, K. I.; Furukawa, S.; Yamaguchi, R. *J. Organomet. Chem.* **2002**, *649*, 289-292.
6. Ley, S.V.; Madin, A. in: Trost, B.M.; Fleming, I. (Eds.), *Comprehensive Organic Synthesis*, vol. 7, Pergamon Press, Oxford, **1991**, p. 251.
7. (a) Namy, J. L.; Soupe, J.; Collin, J.; Kagan, H.B. *J. Org. Chem.* **1984**, *49*, 2045. (b) Ishii, Y.; Nakano, T.; Inada, A.; Kishigami, Y.; Sakurai, K.; Ogawa, M. *J. Org. Chem.* **1986**, *51*, 240. (c) Wang, G. Z.; Backwall, J. E. *J. Chem. Soc. Chem. Commun.* **1992**, 337. (d) Almeida, M. L. S.; Beller, M.; Wang, G. Z.; Backwall, J. E.; *Chem. Eur. J.* **1996**, *2*, 1533. (e) Krohn, K.; Knauer, B.; Kupke, J.; Seebach, D.; Beck, A. K.; Hayakawa, M. *Synthesis* **1996**, 1341
8. (a) Procter, G. In *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Ley, S. V., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 312-318. (b) Kano, S.; Shibuya, S.; Ebata, T. *Heterocycles* **1980**, *14*, 661-711.
9. For recent examples of the natural product synthesis, see: (a) Suzuki, T.; Ohmori, K.; Suzuki, K. *Org. Lett.* **2001**, *3*, 1741-1744. (b) Zhu, X.; Yu, B.; Hui, Y.; Higuchi, R.; Kusano, T.; Miyamoto, T. *Tetrahedron Lett.* **2000**, *41*, 717-719. (c) Amaike, M.; Mori, K.; *Liebigs Ann.* **1995**, 1451-1454. (d) Ley, S. V.; Norman, J.; Pinel, C. *Tetrahedron Lett.* **1994**, *35*, 2095-2098.
10. Fetizon, M.; Golfier, M.; Louis, J. M. *Tetrahedron* **1975**, *31*, 171-176.
11. (a) $2\text{CuO}\cdot\text{Cr}_2\text{O}_3$: Kyrides, J. P.; Zienty, F. B. *J. Am. Chem. Soc.* **1946**, *68*, 1385-1385. (b) $\text{Ru}_3(\text{CO})_{12}$ -tolane: Shvo, Y.; Blum, Y.; Reshef, D.; Menzin, M. *J. Organomet. Chem.* **1982**, *226*, C21-C25. (c) $\text{Pd}(\text{OAc})_2$ -PhBr: Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 1286-1292. (d) $\text{RhH}(\text{PPh}_3)_4$ - α,β -unsaturated ketone: Ishii, Y.; Suzuki, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2822-2824. (e) $\text{RuH}_2(\text{PPh}_3)_4$ - α,β -unsaturated ketone: Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2034-2039.

12. (a) Metal polyhydrides-acetone: Lin, Y.; Zhu, X.; Zhou, Y. *J. Organomet. Chem.* **1992**, *429*, 269-274. (b) Heteropolyacid-H₂O₂: Ishii, Y.; Yoshida, T.; Yamawaki, K.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 5549-5552. (c) Pd(OAc)₂-O₂: Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750-6755.
13. Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* **2002**, *4*, 2361-2363.
14. (a) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435.
15. Fujita, K. I.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* **2005**, *7*, 4017-4019.
16. Owston, N. A.; Parker, A. J.; Williams, M. J. *J. Org. Lett.* **2007**, *9*, 73-75
17. Whitney, S.; Grigg, R.; Derrick, A.; Keep, A. *Org. Lett.* **2007**, *9*, 3299-3302.
18. Fujita, K. I.; Komatsubara, A.; Yamaguchi, R. *Tetrahedron* **2009**, *65*, 3624-3628.
19. (a) Apsunde, T. D.; Trudell, M.L. *Synthesis* **2014**, *46*, 230. (b) Liu, C.; Liao, S.; Li, Q.; Feng, S.; Sun, Q.; Yu, X.; Xu, Q. *J. Org. Chem.* **2011**, *76*, 5759. (c) Apsunde, T. D.; Trudell, M. L. *Synthesis* **2014**, *45*, 2120.
20. (a) Leete, E. In *Alkaloids, Chemical and Biological Perspectives*; Vol. 1; Pelletier, S. W., Ed.; John Wiley & Sons: New York, **1983**, 85. (b) Strunz, G. M.; Findlay, J. A. In *The Alkaloids, Chemistry and Pharmacology*; Vol. 26; Brossi, A., Ed.; Academic Press: Orlando, **1985**, 89. (c) Miao, L. DiMaggio, S. C.; Shu, H.; Trudell, M. L. *Org. Lett.* **2009**, *11*, 1579-1582. (d) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282.
21. John, W. D.; Thomas, F. S.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556-1575
22. Gresser, M. J.; Keller, P. A.; Wales, S. M. *Tetrahedron Lett.* **2009**, *50*, 4899-4902.
23. Salmon, A.; Carboni, B. *J. Organomet. Chem.* **1998**, *567*, 31-37
24. (a) Roundhill, D.M. *Chem Rev.* 1992, *92*, 1. (b) Willis, M.C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3402.
25. (a) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354. (b) Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Enthaler, S.; Schallner, B.; Dumrath, A.; Spannberg, A.; Ncumann, H.; Borner, A.; Beller, M. *Chem. Eur. J.* **2009**, *15*, 4528.
26. Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055.
27. Zimmermann, B.; Herwig, J.; Beller, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2372.
28. Nagona, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2009**, *131*, 4200.
29. Prinz, T.; Driessen-Holscher, B. *Chem. Eur. J.* **1999**, *5*, 2069.
30. Wu, Z.; Jiang, Z.; Wu, D.; Xiang, H.; Zhou, X. *Eur. J. Org. Chem.* **2010**, 1854.

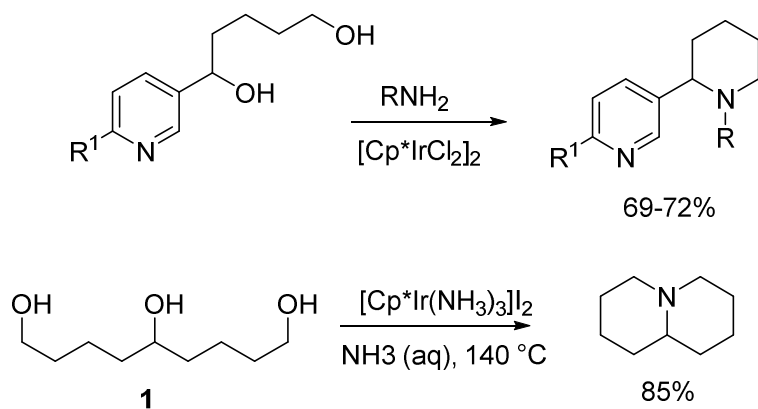
31. Kim, J.; Chang, S. *Chem. Commun.* **2008**, 3052.
32. Fujita, K.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943
33. (a) Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Banh, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4745. (b) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766.
34. He, J.; Kim, J. W.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 9888.
35. Blacker, A. J.; Brown, S.; Cligue, B.; Gourlay, B.; Headley, C. E.; Ingham, S.; Ritson, D.; Screen, T.; Stirling, M. J.; Taylor, D.; Thompson, G. *Org. Process Res. Dev.* **2009**, *13*, 1370.
36. Comins, D. L.; O'Conner, S. *Tetrahedron Lett.* **1987**, *28*, 1843. (b) Tehrani, K. A.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 3099.
37. Kawahara, R.; Fujita, K. I.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108-15111.

CHAPTER 2 Synthesis of Glycerol Homologues

2.1 Results and discussion

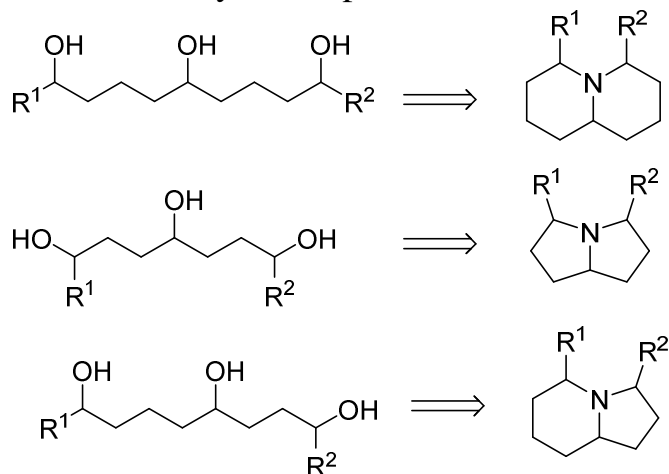
We have recently demonstrated the efficiency of the iridium catalyzed N-heterocyclization reaction¹ for the preparation of novel piperidine alkaloids from 1,5-diols (Fig. 1).² More recently Kawahara and coworkers, demonstrated that 1,5,9-nonanetriol (**1**) could be efficiently converted into quinolizidine in 85% yield (Scheme 2.1).³ Our interest in exploring the chemistry and biology of novel amphibian alkaloids has prompted an investigation to implement this methodology for the construction of more complex heterocyclic structures.

Scheme 2.1 Applications of the iridium catalyzed N-heterocyclization reaction



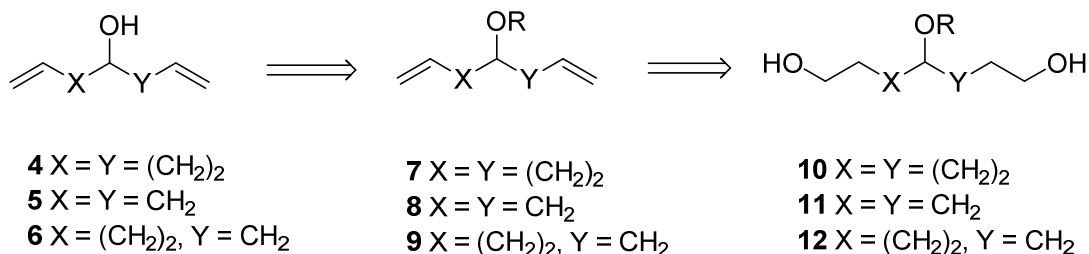
To this end we envisaged the application of the iridium catalyzed N-heterocyclization reaction for the preparation of quinolizidine, pyrrolizidine and indolizidine alkaloids from the corresponding triol-based molecular scaffolds. (Scheme 2.2).⁴

Scheme 2.2 Bicyclic amphibian alkaloids.



In an effort to identify precursors for the preparation of complex triols, we found that the 1,5,9-nonanetriol (**1**)^{3,5} the 1,4,7-heptanetriol (**2**)⁶ and the unsymmetrical 1,4,8-octanetriol (**3**)⁷ have been reported in the literature. However, these triols were deemed less than ideal substrates for further structural modifications, since like glycerol, they exhibit high polarity and low solubility in a variety of organic solvents (e.g. THF, CH₂Cl₂, toluene). Therefore it was of interest to develop an efficient method for the general construction of a series of glycerol homologues that would facilitate later structural modification of the core triol side chains.

Scheme 2.3 Target mono-protected triols.

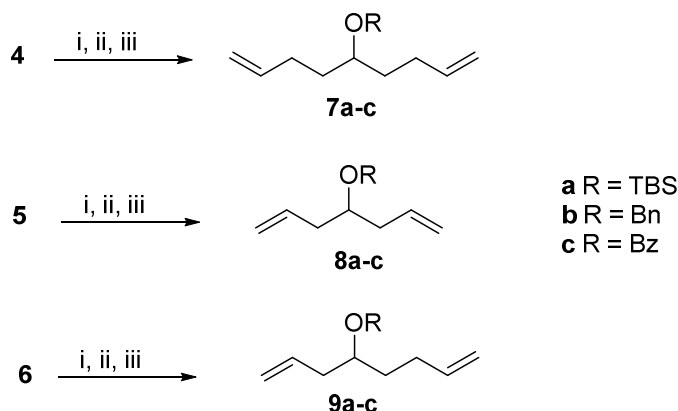


To achieve this goal we envisaged a hydroboration-oxidation strategy that would give a triol derivative with a protected secondary hydroxyl group (Scheme 2.3).⁸ Protection of the hydroxyl moiety of the readily available dienols **4**⁹ and **6**¹⁰ and commercially available **5** would provide the corresponding dienes **7-9**. Simultaneous hydroboration-oxidation of both double bonds of the dienes would then afford the mono-protected glycerol homologues **10-12**. This strategy would furnish a triol substrate that would likely have improved solubility in organic solvents and allow for further modification of the primary hydroxyl bearing appendages.

2.2 Hydroboration of dienes

In order to establish the viability of the approach for future studies, it was of interest to determine whether a series of hydroxyl protecting groups would tolerate the hydroboration-oxidation reaction. To this end (Scheme 2.4), the dienols **4-6** were converted into a series of the silyl ethers **7a - 9a**, benzyl ethers **7b - 9b** and benzoate esters **7c-9c** in straightforward fashion and in high yields (95-98%).

Scheme 2.4 Reagents and conditions for protection of dienol

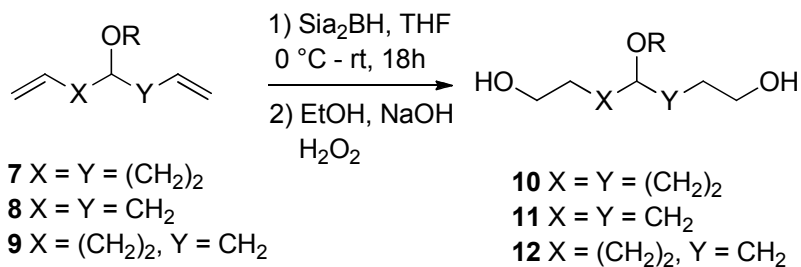


Reagents and Conditions: i) TBSCl, imidazole, DCM, 0 °C. ii) NaH, BnBr, DMF, 0 °C. iii) BzCl, Et₃N, DMAP, DCM, 0 °C.

With the dienes in hand, our attention was directed toward the identification of suitable hydroboration reagents and conditions to prepare the glycerol homologues.¹¹ Initially, diene **8a** was treated with BH₃•THF with concomitant alkaline oxidative work-up with NaOH/H₂O₂. This afforded an insoluble material that was impervious to the oxidative work-up. Subsequently the yield of any hydroxylated material was low (< 20%). Similar results were obtained with BH₃•DMS. The formation of intractable material was avoided with the dialkyl borane reagents, dicyclohexylborane and 9-BBN. However, these reagents gave low yields (< 50% yield of hydroxylated material) and mixtures of regioisomers resulting from the introduction of the hydroxyl group at C2 and/or C6 of **8a**. In light of these results it was clear that the dialkyl borane reagents offered the best chance for success if we could better control the regiochemistry of the reaction. In

this vein, we investigated the utility of disiamylborane, generated in situ from $\text{BH}_3 \cdot \text{DMS}$ and 2-methyl-2-butene. Treatment of **8a** with disiamylborane followed by oxidation with alkaline H_2O_2 afforded the silyl protected glycerol homologue **11a** in 95% isolated yield (Table 1). Under these conditions we observed no formation of insoluble materials and the high yield was quite satisfying given our previous results with the dicyclohexylborane and 9-BBN. In addition, we were unable to detect the formation of regioisomers resulting from C2 and/or C6 hydroxylation. Based upon the success of this reaction we employed the disiamylborane for the preparation of series of mono-protected glycerol homologues. These results are summarized in Table 2.1.

Table 2.1 Hydroboration-oxidation of diene derivatives 7 – 9



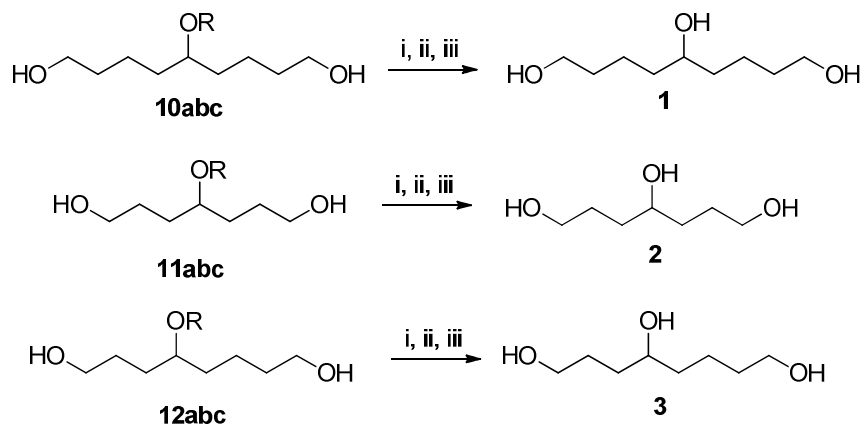
Entry	R	10 , % yield	11 , % yield	12 , % yield
1	TBS	96	96	96
2	Bn	97	97	98
3	Bz	95	95	96

Overall, the disiamylborane mediated hydroboration-oxidation was very effective in providing high yields (>95%) of the mono-protected glycerol homologues **10abc**, **11abc** and **12abc**. Clearly the reaction conditions were tolerant of the three protecting groups that were evaluated (TBS, Bn and Bz). This suggests that this method should be readily adaptable to other silyl ethers, substituted benzyl ethers or ester based protecting groups.

2.3 Glycerol homologues

To demonstrate the utility of the method for the preparation of glycerol homologues, **10abc**, **11abc** and **12abc** were converted into the corresponding triols. As illustrated in Scheme 2.5, the silyl ethers **10a**, **11a** and **12a** were treated with TBAF in THF to furnish the triols **1**, **2** and **3**, respectively, in high yields (97-99 %). In addition, hydrogenolysis over Pd(OH)₂ on carbon of the benzyl ethers **10b**, **11b** and **12b** afforded the triols **1**, **2** and **3** in quantitative yields (97-99 %). Finally, the triols **1**, **2** and **3**, were easily obtained by hydrolysis of the benzoate esters **10c**, **11c** and **12c** (96-98 % isolated yields).

Scheme 2.5 Reagents and conditions for triol formation:

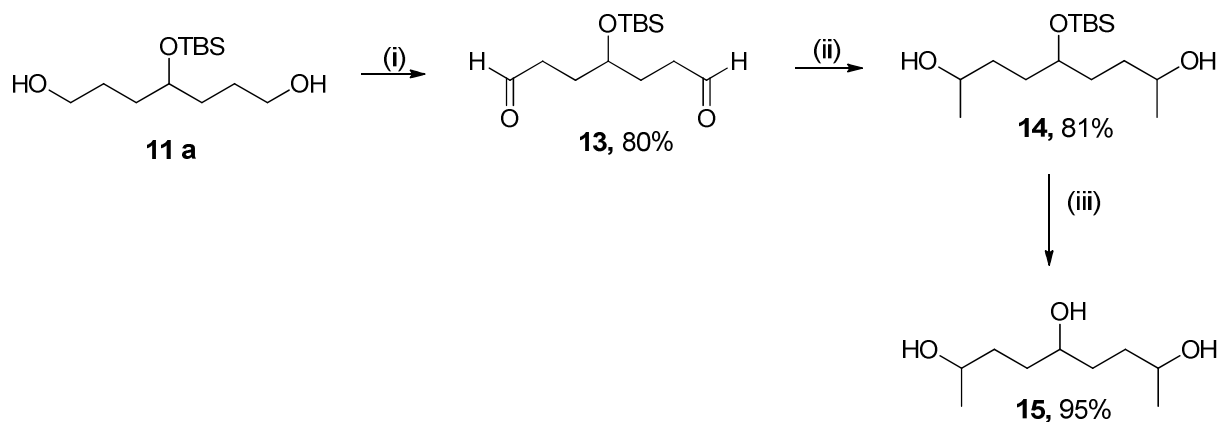


Reagents and Conditions: i) TBAF, THF, rt. ii) H₂ (1 atm), Pd(OH)₂/carbon, CH₃OH, rt. iii) KOH, CH₃OH, rt.

2.4 Substituted glycerol homologue

With the monoprotected glycerol homologues in hand, we selected the TBS homologue **11a** for further conversion into a substituted homologue. As illustrated in Scheme 2.6, oxidation of diol **11a** with excess Dess-Martin periodinane reagent furnished the dialdehyde **13** in 80% yield. The dialdehyde **13** was then treated with excess methylmagnesium bromide to afford the diol **14** in 81% yield. Removal of the TBS-protecting group was then activated with tetrabutylammonium fluoride to give the triol **15** in 95% yield. We were pleased with the efficiency of the oxidation, alkylation and deprotection sequence to furnish the substituted triol **15** in 58% overall yield (five steps) from commercially available dienol **5**.

Scheme 2.6 Reagents and conditions for synthesis of triol derivatives:



Reagents and Conditions: (i) Dess-Martin periodinane, 0 °C to rt, 6 hr. (ii) CH_3MgBr , -78 °C to rt, 3 hr. (iii) TBAF, THF, rt.

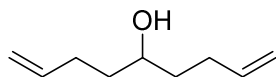
In conclusion, we have shown that the hydroboration-oxidation of mono-protected dienols with disiamylborane is a mild, high yielding and highly efficient method for the construction of glycerol homologues. Further conversion of the monoprotected glycerol homologues into more highly substituted triol derivatives proceeded in high overall yield. Having established an efficient route for the preparation of novel triols, the synthesis of structurally novel amphibian alkaloids is currently under investigation and will be reported in due course.

2.5 Experimental section

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Thin layer chromatography (TLC): silica gel (250 μm) on glass plates purchased from Sorbent Technologies. Visualization was

achieved with UV light, iodine or phosphomolybdic acid. Compounds were purified by flash chromatography on silica gel 60 Å (230-400 mesh) purchased from Sorbent Technologies. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in CDCl₃ or D₂O. ¹H NMR chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. ¹³C NMR chemical shifts are reported as δ values (ppm) relative to chloroform-*d* (77.0 ppm). Melting points were recorded on a Mel-temp apparatus and are uncorrected. Atlantic Microlab, Inc., Norcross, GA performed all CHN microanalyses.

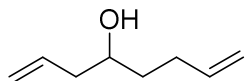
Nona-1,8-dien-5-ol (4)



To a dry 250-mL two-neck round bottom flask, magnesium turnings (2.7 g, 110 mmol) were added under an argon atmosphere followed by the addition of anhydrous THF (40 mL). To the stirred solution, 4-bromobutene (5.0 g, 37 mmol) was added slowly at room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C and ethylformate (1.5 mL, 19 mmol) was added dropwise then stirred at room temperature overnight. Saturated NH₄Cl (40 mL) was added at 0 °C and stirred for 3 h. The organic layer was separated, washed with brine solution, then dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The

residue was purified by flash chromatography (4% EtOAc-hexane) to furnish **4** (4.6 g, 90 %). as colorless oil. The spectroscopic data were consistent with those reported previously for this compound.⁹

Octa-1,7-dien-4-ol (6)



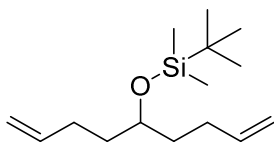
A dry 250 mL two necked round bottom flask was filled with a solution of allyl magnesium bromide (1M solution in diethyl ether, 17 mL, 18 mmol) under an argon atmosphere. The mixture was cooled to -78 °C and 4-pentenal (1.0 g, 12 mmol) was added dropwise. The mixture was stirred and allowed to warm to room temperature overnight. Saturated NH₄Cl (20 mL) was added and the mixture stirred for 1h. The organic layer was separated, washed with brine solution, then dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (5% EtOAc-hexane) to furnish **6** (1.41 g, 94 %) as a colorless oil. The spectroscopic data were consistent with those reported previously for this compound.¹⁰

***tert*-Butyldimethylsiloxydienes **7a**, **8a**, and **9a**; General procedure**

To a solution of dienol (1 equiv.) in CH₂Cl₂ (20 mL), imidazole (2 equiv.) was added at room temperature and stirred for 15 min. To the stirred solution, a solution of TBSCl (1.5 equiv.) in CH₂Cl₂ (5 mL), was added slowly at 0 °C with

continued stirring overnight. The reaction mixture was poured into water (50 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂) to afford the desired TBS ether.

5-(*tert*-Butyldimethylsilyloxy)nona-1,8-diene (7a).

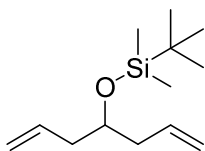


Prepared from **4** (1.0 g, 7.1 mmol), imidazole (1.0 g, 14 mmol) and TBSCl (1.6 g, 11 mmol). Purification by flash chromatography (1% EtOAc/hexane) furnished **7a** (1.8 g, 98%) as a colorless oil; yield: 1.8 g (98%).

¹H NMR (CDCl₃): δ 5.85-5.74 (m, 2H), 5.03-4.90 (m, 4H), 3.72-3.65 (m, 1H), 2.12-2.04 (m, 4H), 1.54-1.50 (m, 4H), 0.89(s, 9H), 0.05 (s, 6H).

¹³C NMR (CDCl₃): δ 139.1, 114.5, 71.4, 36.4, 29.7, 26.1, 18.3, -4.2.

4-(*tert*-Butyldimethylsilyloxy)hepta-1,6-diene (8a).

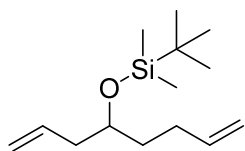


Prepared from **5** (1.0 g, 7.1 mmol), imidazole (1.0 g, 14 mmol) and TBSCl (1.6 g, 11 mmol). Purification by flash chromatography (1% EtOAc/hexane) furnished **8a** (1.8 g, 98%) as a colorless oil; yield: 1.8 g (98%).

^1H NMR (CDCl_3): δ 5.85-5.76 (m, 2H), 5.06-5.02 (m, 4H), 3.74 (p, $J = 5.8$ Hz, 1H), 2.27-2.15 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (CDCl_3): δ 135.5, 117.1, 72.0, 41.7, 26.1, 18.4, -4.3.

4-(*tert*-Butyldimethylsilyloxy)octa-1,7-diene (9a)



Prepared from **6** (1.0 g, 8.0 mmol), imidazole (1.1 g, 15 mmol) and TBSCl (1.8 g, 12 mmol). Purification by flash chromatography (1% EtOAc/hexane) furnished **9a** (1.9 g, 97%) as a colorless oil; yield: 1.9 g (97%).

^1H NMR (400 MHz, CDCl_3): δ 5.84-5.75 (m, 2H), 5.05-4.92 (m, 4H), 3.71 (p, $J = 6.0$ Hz, 1H), 2.22 (t, $J = 4.0$ Hz, 2H), 2.17-2.01 (m, 2H), 1.57-1.50 (m, 2H), 0.89 (s, 9H), 0.091 (s, 6H).

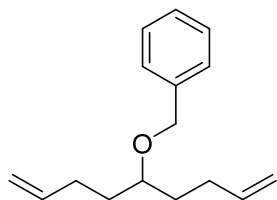
^{13}C NMR (100 MHz, CDCl_3): δ 139.1, 135.4, 117.0, 114.5, 71.6, 42.1, 36.2, 29.9, 26.1, 18.3, -4.3.

Benzyloxydienes 7b, 8b, and 9b; General procedure

To a solution of NaH (1.4 equiv.) in anhydrous DMF, the dienol (1 equiv.) was added dropwise at 0 °C. The mixture was stirred for 15 minutes followed by addition of benzyl bromide (1.1 equiv.). The mixture was allowed to warm to room temperature and stirred overnight. Excess NaH was quenched by adding ice at 0 °C

and the mixture was stirred for 10 minutes. The mixture was poured in water, extracted with EtOAc (3 × 50 mL). The combined organic layers were with water, brine solution, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by and flash chromatograph (SiO₂) to furnish the desired benzyl ether.

5-(Benzyloxy)nona-1,8-diene (7b).

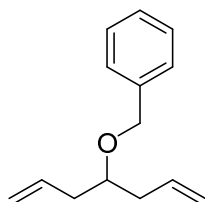


Prepared from **4** (1.2 g, 9.0 mmol), NaH (0.31 g, 13 mmol) and BnBr (1.7 g, 10 mmol). Purification by flash chromatography (2% EtOAc/hexane) furnished **7b** (1.8 g, 90 %) as a colorless oil; yield: 1.8g (90%).

¹H NMR (400 MHz, CDCl₃): δ 7.35-7.26 (m, 5H), 5.86-5.77 (m, 2H), 5.04-4.94 (m, 4H), 4.50 (s, 2H), 3.47-3.41 (m, 1H), 2.17-2.11 (m, 4H), 1.72-1.54 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ 139.1, 138.9, 128.5, 128.0, 127.7, 114.8, 77.1, 33.3, 29.8

4-(Benzyloxy)hepta-1,6-diene (8b).

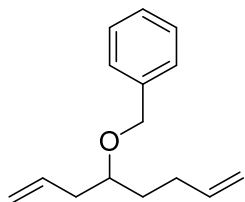


Prepared from **5** (1.0 g, 9.0 mmol), NaH (0.32 g, 13 mmol) and BnBr (1.7 g, 10 mmol). Purification by flash chromatography (2% EtOAc/hexane) furnished **8b** (1.6 g, 90%) as a colorless oil; yield 1.6 g (90%).

^1H NMR (400 MHz, CDCl_3): δ 7.36-7.26 (m, 5H), 5.87-5.81 (m, 2H), 5.08-5.06(m, 4H), 4.56 (s, 2H), 3.52 (p, $J = 6.0$ Hz, 1H), 2.34 (t, $J = 6.6$ Hz, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 138.9, 135.1, 128.5, 127.9, 127.7, 117.3, 78.4, 71.2, 38.3.

4-(Benzyloxy)octa-1,7-diene (**9b**).



Prepared from **6** (1.1 g, 9.0 mmol), NaH (0.31 g, 13 mmol) and BnBr (1.7 g, 10 mmol). Purification by flash chromatography (2% EtOAc/hexane) furnished **9b** (1.7 g, 91 %) as a colorless oil; yield: 1.7 g (91%).

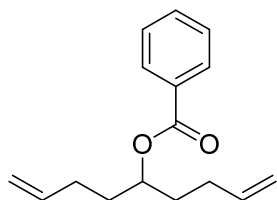
^1H NMR (400 MHz, CDCl_3): δ 7.35-7.26 (m, 5H), 5.88-5.76 (m, 2H), 5.06-4.94 (m, 4H), 4.58 (d, $J = 11.6$ Hz, 1H), 4.48 (d, $J = 11.6$ Hz, 1H), 3.48 (p, $J = 6.0$ Hz, 1H), 2.34-2.20 (m, 2H), 2.16-2.08 (m, 2H), 1.62-1.57 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 139.0, 138.8, 135.1, 128.6, 128.0, 127.7, 117.2, 114.8, 78.1, 71.2, 38.5, 33.3, 29.9.

Dienyl Benzoates **7c**, **8c**, and **9c**; General procedure

To a solution of dienol (1 equiv.) in dichloromethane (20 mL), triethylamine (3 equiv.) was added along with catalytic amount of DMAP (10%). The mixture was stirred for 30 minutes at room temperature. The solution was cooled to 0 °C and benzoyl chloride (1.1 equiv.) was added and the mixture was stirred overnight at room temperature. The mixture was poured into water (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatograph (SiO₂) to furnish the desired benzoate esters.

Nona-1,8-dien-5-yl benzoate (**7c**).

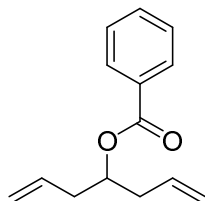


Prepared from **4** (1.0 g, 9.0 mmol), Et₃N (3.7 mL, 27 mmol) DMAP (0.1 g) and BzCl (1.2 mL, 10 mmol). Purification by flash chromatography (2% EtOAc/hexane) furnished **7c** (1.9 g, 91 %) as a colorless oil; yield: 1.9 g (91%).

¹H NMR (400 MHz, CDCl₃): δ 8.05 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 5.83-5.77 (m, 2H), 5.19-5.16 (m, 1H), 5.04-4.95 (m, 4H), 2.16-2.12 (m, 4H), 1.88-1.75 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.4, 138.0, 133.0, 130.8, 129.8, 128.6, 115.2, 74.1, 33.7, 29.8.

Hepta-1,6-dien-4-yl benzoate (8c).

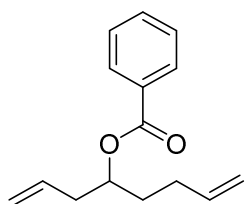


Prepared from **5** (1.0 g, 9.0 mmol), Et_3N (3.7 mL, 27 mmol), DMAP (0.1 g) and BzCl (1.2 mL, 10 mmol). Purification by flash chromatography (2% EtOAc /hexane) furnished **8c** (1.8 g, 92 %) as a colorless oil; yield 1.8 g (92%).

^1H NMR (400 MHz, CDCl_3): δ 8.04 (d, $J = 7.2$ Hz, 2H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 2H), 5.88-5.78 (m, 2H), 5.22 (p, $J = 6.0$ Hz, 1H), 5.15-5.07 (m, 4H), 2.47 (t, $J = 6.4$ Hz, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.3, 133.7, 133.1, 130.8, 129.8, 128.6, 118.3, 73.3, 38.2.

Octa-1,7-dien-4-yl benzoate (9c).



Prepared from **6** (1.0 g, 9.0 mmol), Et₃N (3.7 mL, 27 mmol) DMAP (0.1 g) and BzCl (1.2 mL, 10 mmol). Purification by flash chromatography (2% EtOAc/hexane) furnished **9c** (1.9 g, 91 %) as a colorless oil; yield: 1.9 g (91%).

¹H NMR (400 MHz, CDCl₃): δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 5.88-5.77 (m, 2H), 5.23-5.17 (m, 1H), 5.13-4.95 (m, 4H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.21-2.10 (m, 2H), 1.88-1.72 (m, 2H).

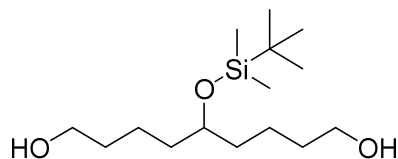
¹³C NMR (100 MHz, CDCl₃): δ 166.4, 137.9, 133.7, 133.0, 130.8, 129.8, 128.4, 118.4, 115.2, 73.6, 38.9, 33.1, 29.8.

Diols 10a-c, 11a-c, and 12a-c; General procedure

A 250 mL round bottom flask was filled with borane-DMS complex (4.4 equiv.) under an argon atmosphere and cooled to -10 °C. A solution of 2-methylbut-2-ene (2M in THF, 8.8 equiv) was added drop wise and stirred for 2 h at 0 °C. A solution of the diene (1 equiv.) in anhydrous THF (10 mL) was added drop wise at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 18-24 h until none of the diene was observed by TLC. Ethanol (50 equiv), 6N NaOH (6 equiv.) and H₂O₂ (25 equiv, 30 %) were added slowly and the reaction mixture was heated to 50 °C for 1-3 h (until the white solid suspension dissolved). After cooling to room temperature, the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and

concentrated under reduced pressure. The residue was purified by flash chromatography to furnish the desired mono-protected glycerol homologue.

5-(*tert*-Butyldimethylsilyloxy)-nonane-1,8-diol (10a).



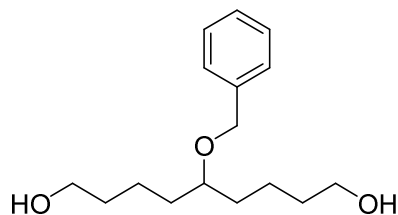
Prepared according to General Procedure D using **7a** (0.51 g, 2.0 mmol), $\text{BH}_3 \cdot \text{DMS}$ (0.75 mL, 8.0 mmol) and 2-methyl-2-butene (2M in THF, 7.3 mL, 16 mmol). The oxidation used EtOH (5.5 mL), 6 N NaOH (1.8 mL) and H_2O_2 (30%, 3.7 mL). Purification by flash chromatography (50% EtOAc/hexane) furnished **10a** (0.56 g, 96 %) as a colorless oil; yield: 0.56 g (96%).

^1H NMR (400 MHz, CDCl_3): δ 3.68-3.63 (m, 1H), 3.66-3.62 (t, $J = 6.4$ Hz, 1H), 1.59-1.52 (m, 4H), 1.49-1.42 (m, 4H), 1.40-1.30 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 72.3, 63.2, 36.9, 33.2, 26.1, 21.6, 18.4, -4.2.

Anal. Calcd. for $\text{C}_{15}\text{H}_{34}\text{O}_3\text{Si}$: C, 62.01; H, 11.80. Found: C, 61.75; H, 11.68.

5-(Benzyloxy)nonane-1,8-diol (10b).



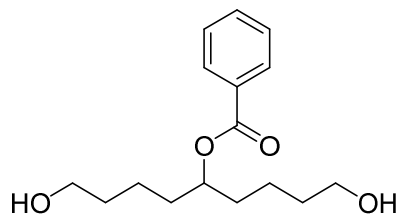
Prepared from **7b** (0.46 g, 2.0 mmol), $\text{BH}_3 \cdot \text{DMS}$ (0.75 mL, 8 mmol) and 2-methyl-2-butene (2M in THF, 7.3 mL, 16 mmol). The oxidation used EtOH (5.5 mL), 6 N NaOH (1.8 mL) and H_2O_2 (30%, 3.7 mL). Purification by flash chromatography (60% EtOAc/hexane) furnished **10b** (0.52 g, 97 %) as a colorless oil; yield: 0.52 g (97%).

^1H NMR (400 MHz, CDCl_3): δ 7.33-7.25 (m, 5H), 4.49 (s, 2H), 3.59 (t, $J = 6.4$ Hz, 4H), 3.39 (p, $J = 6.0$ Hz, 1H), 1.90 (br s, 2H), 1.61-1.34 (m, 12H).

^{13}C NMR (100 MHz, CDCl_3): δ 139.1, 128.6, 128.0, 127.7, 79.1, 71.1, 62.9, 33.7, 33.0, 21.7.

Anal. Calcd. for $\text{C}_{16}\text{H}_{26}\text{O}_3 \cdot \text{H}_2\text{O}$: C, 67.57; H, 9.92. Found: C, 67.98; H, 9.69.

1,5-Dihydroxynonane-5-yl benzoate (**10c**).



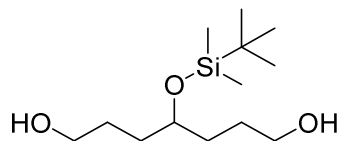
Prepared from **7c** (0.49 g, 2.0 mmol), $\text{BH}_3 \cdot \text{DMS}$ (0.75 mL, 8 mmol) and 2-methyl-2-butene (2M in THF, 7.3 mL, 16 mmol). The oxidation used EtOH (5.5 mL), 6 N NaOH (1.8 mL) and H_2O_2 (30%, 3.7 mL). Purification by flash chromatography (60% EtOAc/hexane) furnished **10c** (0.53 g, 95 %) as a colorless oil; yield: 0.53 g (95%).

^1H NMR (400 MHz, CDCl_3): δ 8.03 (d, $J = 6.8$, Hz, 2H), 7.55 (t, $J = 7.2$ Hz, 1H), 7.43 (t, $J = 7.2$ Hz, 2H), 5.19-5.12 (m, 1H), 3.62 (t, $J = 6.4$ Hz, 4H), 1.77-1.65 (m, 4H), 1.63-1.51 (m, 4H), 1.49-1.39 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.7, 133.1, 130.8, 129.8, 128.6, 74.9, 62.9, 34.2, 32.7, 21.8.

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{O}_4 \cdot 0.5\text{H}_2\text{O}$: C, 66.40; H, 8.73. Found: C, 66.00; H, 8.69.

4-(*tert*-Butyldimethylsilyloxy)-heptane-1,7-diol (**11a**).



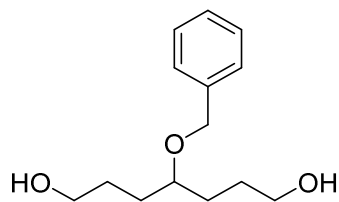
Prepared from **8a** (1.0 g, 5.0 mmol), $\text{BH}_3 \cdot \text{DMS}$ (1.7 mL, 22 mmol) and 2-methyl-2-butene (2M in THF, 17.6 mL, 44 mmol). The oxidation used EtOH (13 mL), 6 N NaOH (4.4 mL) and H_2O_2 (30%, 5.3 mL). Purification by flash chromatography (50% EtOAc/hexane) furnished **11a** (1.1 g, 96 %) as a colorless oil; yield: 1.1 g (96%).

^1H NMR (400 MHz, CDCl_3): δ 3.78-3.76 (m, 1H), 3.62-3.60 (m, 4H), 2.34 (br s, 2H), 1.62-1.52 (m, 8H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 72.1, 63.2, 33.2, 28.5, 26.1, 18.3, -4.3.

Anal. Calcd for $\text{C}_{13}\text{H}_{30}\text{O}_3\text{Si}$: C, 59.49; H, 11.52. Found: C, 59.23; H, 11.26.

4-(Benzyloxy)heptane-1,7-diol (**11b**).



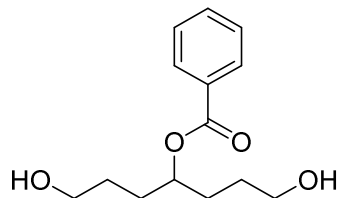
Prepared from **8b** (0.4 g, 2.0 mmol), $\text{BH}_3 \cdot \text{DMS}$ (0.75 mL, 8 mmol) and 2-methyl-2-butene (2M in THF, 7.3 mL, 16 mmol). The oxidation used EtOH (5.5 mL), 6 N NaOH (1.8 mL) and H_2O_2 (30%, 3.7 mL). Purification by flash chromatography (70% EtOAc/hexane) furnished a colorless oil; yield: 0.46 g (97%).

^1H NMR (400 MHz, CDCl_3): δ 7.34-7.25 (m, 5H), 4.51 (s, 2H), 3.61-3.59 (t, $J = 5.6$ Hz, 4H), 3.50-3.48 (m, 1H), 2.31 (br s, 2H), 1.67-1.58 (m, 8 H).

^{13}C NMR (100 MHz, CDCl_3): δ 138.5, 128.6, 128.1, 127.9, 78.8, 71.1, 63.0, 30.2, 28.6.

Anal. Calcd for $\text{C}_{14}\text{H}_{22}\text{O}_3 \cdot \text{H}_2\text{O}$: C, 65.60; H, 9.44; Found: C, 65.87; H, 8.91.

1,7-Dihydroxyheptan-4-yl benzoate (**11c**).



Prepared from **8c** (0.4 g, 2.0 mmol), $\text{BH}_3 \cdot \text{DMS}$ (0.75 mL, 8.0 mmol) and 2-methyl-2-butene (2M in THF, 7.3 mL, 16 mmol). The oxidation used EtOH (5.5

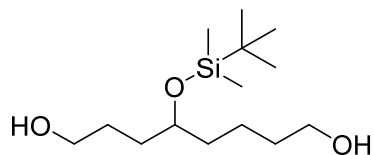
mL), 6 N NaOH (1.8 mL) and H₂O₂ (30%, 3.7 mL). Purification by flash chromatography (75% EtOAc/hexane) furnished a colorless oil; yield: 0.47 (95%).

¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 5.24-5.18 (m, 1H), 3.67 (t, *J* = 6.0 Hz, 4H), 1.82-1.76 (m, 4H), 1.69-1.62 (m, 4H).

¹³C NMR (100 MHz, CDCl₃): δ 166.8, 133.2, 130.6, 129.8, 128.6, 74.6, 62.7, 30.9, 28.6.

Anal. Calcd. for C₁₄H₂₀O₄•0.5H₂O: C, 64.35; H, 8.10. Found: C, 64.36; H, 8.12.

4-(*tert*-Butyldimethylsilyloxy)-octane-1,8-diol (12a).



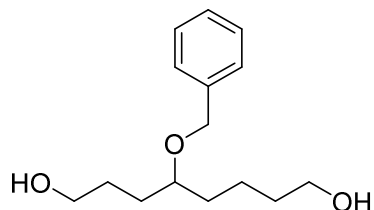
Prepared from **9a** (0.48 g, 2.0 mmol), BH₃•DMS (0.75 mL, 8.0 mmol) and 2-methyl-2-butene (2M in THF, 7.3 mL, 16 mmol). The oxidation used EtOH (5.5 mL), 6 N NaOH (1.8 mL) and H₂O₂ (30%, 3.7 mL). Purification by flash chromatography (50% EtOAc/hexane) furnished a colorless oil; yield: 0.53 (96%).

¹H NMR (400 Mhz, CDCl₃): δ 3.73 (p, *J* = 5.6 Hz, 1H), 3.64 (t, *J* = 5.6 Hz, 4H), 1.65-1.56 (m, 2H), 1.54-1.47 (m, 2H), 1.43-1.31 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 72.1, 63.4, 63.1, 36.5, 33.5, 33.1, 28.0, 26.1, 21.8, 18.3, -4.3.

Anal. Calcd. for $\text{C}_{14}\text{H}_{32}\text{O}_3\text{Si}$: C, 60.82; H, 11.67. Found: C, 60.80; H, 11.80.

4-(Benzyloxy)octane-1,8-diol (12b).



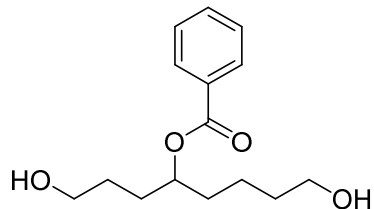
Prepared from **9b** (0.43 g, 2.0 mmol), $\text{BH}_3\cdot\text{DMS}$ (0.75 mL, 8 mmol) and 2-methyl-2-butene (2M in THF, 7.3 mL, 16 mmol). The oxidation used EtOH (5.5 mL), 6 N NaOH (1.8 mL) and H_2O_2 (30%, 3.7 mL). Purification by flash chromatography (70% EtOAc/hexane) furnished a colorless oil; yield: 0.49 g (98%).

^1H NMR (400 MHz, CDCl_3): δ 7.35-7.26 (m, 5H), 4.54 (d, $J = 11.6$ Hz, 1H), 4.50 (d, $J = 11.6$ Hz, 1H), 3.64 (t, $J = 6.4$ Hz, 4H), 3.48-3.42 (m, 1H), 1.58-1.38 (m, 10 H).

^{13}C NMR (100 MHz, CDCl_3): δ 138.8, 128.6, 128.1, 127.8, 78.9, 71.1, 63.3, 63.1, 33.5, 33.1, 30.4, 28.7, 21.8.

Anal. Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_3\cdot\text{H}_2\text{O}$: C, 66.64; H, 9.69; Found: C, 67.00; H, 9.38.

1,8-Dihydroxyoctan-4-yl benzoate (12c).



Prepared from **9c** (0.46 g, 2.0 mmol), $\text{BH}_3 \cdot \text{DMS}$ (0.75 mL, 8.0 mmol) and 2-methyl-2-butene (2M in THF, 7.3 mL, 16 mmol). The oxidation used EtOH (5.5 mL), 6 N NaOH (1.8 mL) and H_2O_2 (30%, 3.7 mL). Purification by flash chromatography (75% EtOAc/hexane) furnished a colorless oil; yield: 0.51 g (96%).

^1H NMR (400 MHz, CDCl_3): δ 8.03 (d, $J = 7.2$ Hz, 2H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 2H), 5.20-5.15 (m, 1H), 3.68-3.60 (m, 4H), 1.76-1.41 (m, 10 H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.7, 133.1, 130.7, 129.8, 128.6, 74.7, 62.8, 62.7, 34.3, 32.7, 30.8, 28.7, 21.8.

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_4 \cdot 0.5\text{H}_2\text{O}$: C, 65.43; H, 8.42. Found: C, 65.38; H, 8.47.

TBS deprotection of **10a**, **11a** and **12a**: General procedure

A solution of 1M solution of TBAF in THF (2 equiv.) was added to a solution of *tert*-butyldimethylsilyloxy diol (1 equiv.) in dry THF (10 mL) at room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (10 % MeOH/EtOAc) to furnish the corresponding triol in nearly quantitative yield.

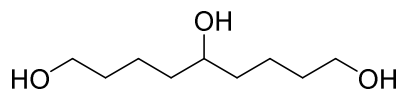
Debenzylation of 10b, 11b and 12b: General procedure

The benzyloxy diol (1 g) in anhydrous methanol (5 mL) was added to a solution of 10% Pd(OH)₂ on carbon (10% wt) and stirred for 3-4 h under an atmosphere of hydrogen (1 atm). After all of the starting material was consumed (TLC) the catalyst was filtered and concentrated under reduced pressure and dried under high vacuum (0.133 mbar) at room temperature to furnish triol in nearly quantitative yield.

Debenzylation of dihydroxy benzoates 10c, 11c and 12c; General procedure

To a solution of the benzoate ester (1 equiv.) in methanol (10 mL), KOH (1.1 equiv.) was added and stirred for 16 hrs. After the starting material had all been consumed (TLC), the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (10 % MeOH-EtOAc) to furnish the desired triol in nearly quantitative yield.

Nonane-1,5,9-triol (1).



Prepared from **10a** (1.1 g, 3.8 mmol) in THF and TBAF (1M in THF, 7.6 mL, 7.6 mmol). Purification by flash chromatography (10% MeOH/EtOAc) furnished a colorless oil; yield: 0.65 g (97%).

Prepared from **10b** (1.0 g, 3.8 mmol) in CH₃OH and Pd(OH)₂ (0.10 g). Purification by flash chromatography (10% MeOH/EtOAc) furnished a colorless oil; yield: 0.64 g (96%).

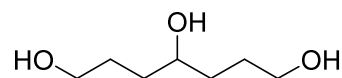
Prepared from **10c** (1.2 g, 4.4 mmol) in CH₃OH and KOH (0.26 g, 4.6 mmol). Purification by flash chromatography (10% MeOH/EtOAc) furnished a colorless oil; yield: 0.73 g (95%).

¹H NMR (400 MHz, D₂O): δ 3.53-3.50 (m, 1H), 3.45 (t, *J* = 6.4 Hz, 4H), 1.44-1.18 (m, 12H).

¹³C NMR (100 MHz, CDCl₃): δ 71.9, 62.9, 37.2, 32.7, 22.0.

Anal. Calcd. for C₉H₂₀O₃•0.75H₂O: C, 56.96; H, 11.42; Found: C, 56.77; H, 11.26.

Heptane-1,4,7-triol (**2**).



Prepared from **11a** (1.0 g, 3.8 mmol) in THF and TBAF (1M in THF, 7.6 mL, 7.6 mmol). Purification by flash chromatography (10% MeOH/EtOAc) furnished a colorless oil; yield: 0.53g (95%).

Prepared from **11b** (1.0 g, 4.2 mmol) in CH₃OH and Pd(OH)₂ (0.10 g). Purification by flash chromatography (10% MeOH/EtOAc) furnished a colorless oil; yield: 0.61 g (98%).

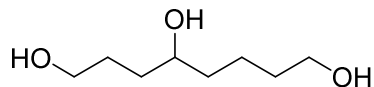
Prepared from **11c** (1.0 g, 4.0 mmol) in CH₃OH and KOH (0.26 g, 4.6 mmol). Purification by flash chromatography (10% MeOH/EtOAc) furnished **2** a colorless oil; yield: 0.56 g (95%).

¹H NMR (400 MHz, D₂O): δ 3.58-3.52 (m, 1H), 3.47 (t, *J* = 6.4 Hz, 1H), 1.56-1.28 (m, 8H).

¹³C NMR (100 MHz, CDCl₃): δ 71.9, 63.3, 35.2, 29.5.

Anal. Calcd. for C₇H₁₆O₃•H₂O: C, 50.58; H, 10.92. Found: C, 50.85; H, 10.77.

Octane1,4,8-triol (**3**).



Prepared from **12a** (1.1 g, 3.8 mmol) in THF and TBAF (1M in THF, 7.6 mL, 7.6 mmol). Purification by flash chromatography (10% MeOH/EtOAc) furnished a colorless oil; yield: 0.61 g (97%).

Prepared from **12b** (1.0 g, 4.0 mmol) in MeOH and Pd(OH)₂ (0.10 g). Purification by flash chromatography (10% MeOH/EtOAc) furnished a colorless oil; yield: 0.63 g (97%).

Prepared from **12c** (1.2 g, 4.5 mmol) in CH₃OH and KOH (0.26 g, 4.6 mmol). Purification by flash chromatography (10% MeOH/EtOAc) furnished a colorless oil; yield: 0.71 g (97%).

¹H NMR (D₂O): δ 3.53-3.42 (m, 1H), 3.45 (t, *J* = 6.4 Hz, 4H), 1.49-1.19 (m, 10 H).

^{13}C NMR (CDCl_3): δ 71.9, 63.3, 62.9, 37.3, 34.8, 32.7, 29.3, 22.1.

Anal. Calcd for $\text{C}_8\text{H}_{18}\text{O}_3 \cdot 0.5\text{H}_2\text{O}$: C, 56.11; H, 11.18. Found: C, 56.05; H, 10.95.

4-(*tert*-Butyldimethylsiloxy)heptane-1,7-dial (13)

To a stirred solution of mono protected triol **11a** (1.0 g, 3.8 mmol) in anhydrous CH_2Cl_2 was added Dess-Martin periodinane (3.55 g, 8.36 mmol) slowly at 0 °C. The mixture was allowed to warm to room temperature and then it was stirred until the diol was no longer observed by TLC. Sat. NaHCO_3 (20 mL) was added at 0 °C and a white suspension was formed. The suspension was then filtered and the organic layer was dried (anhydrous Na_2SO_4). The mixture was filtered and concentrated under reduced pressure, and the residue was purified by flash chromatography (10% E tOAc-hexane) to furnish **13** (0.78 g, 80%) as colorless oil.

^1H NMR (400 MHz, CDCl_3): δ = 9.78(s, 2H), 3.78 (p, J = 5.2 Hz, 1H), 2.50 (t, J = 7.2 Hz, 4H), 1.75-1.67 (m, 4H), 0.87 (s, 9H), 0.04 (s, 6H)

^{13}C NMR (100 MHz, CDCl_3): δ = 202.3, 70.1, 39.8, 28.9, 26.0, 18.2, -4.3

5-(*tert*-Butyldimethylsiloxy)nonane-2,8-diol (14)

To the stirred solution of MeMgBr (3.82 ml, 3.8 mmol) in anhydrous at -78 °C was added dialdehyde **13** (450 mg, 1.7 mmol) in THF (1 mL); the mixture was

stirred for 3 h. Sat. NH_4Cl solution (5 mL) was added at 0 °C and the mixture stirred for 1h. The mixture was extracted with EtOAc (3 × 10 mL) and the organic layer was dried (anhydrous Na_2SO_4). The mixture was filtered and the solution was removed under reduced pressure. The residue was purified by flash chromatography (25% EtOAc-hexane) to furnish 12 (0.40 g, 81%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3): δ 3.86-3.75 (m, 2H), 3.67-3.62 (m, 1H), 2.38 (s, 2H), 1.59-1.49 (m, 8H), 1.20 (d, 6.4 Hz, 6H), 0.90 (s, 9H), 0.09 (s, 6H)

^{13}C NMR (100 MHz, CDCl_3): δ 72.5, 72.3, 72.1, 68.5, 68.3, 35.1, 34.9, 34.7, 33.0, 32.4, 26.1, 23.7, 18.3, -4.2, -4.3

Anal. Calcd for $\text{C}_{15}\text{H}_{34}\text{O}_3\text{Si}$: C, 62.01; H, 11.80. Found: C, 61.89; H, 11.94.

Nonane-2,5,8-triol (15):

To the stirred solution of compound **14** (0.43 g, 1.47 mmol) in anhydrous THF (10 mL) was added 1M TBAF in THF (1.77 mL, 1.77 mmol) at r.t. and the mixture was stirred overnight. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (5% MeOH-EtOAc) to furnish the desired triol 15 (0.26g, 95% yield) as a colorless oil.

^1H NMR (400 MHz, D_2O): δ = 3.65-3.62 (m, 1H), 3.48-3.46 (m, 2H), 1.88 (s, 3H), 1.33-1.25 (m, 8H), 1.01-0.97 (m, 6H)

^{13}C NMR (100 MHz, CDCl_3): $\delta = 72.8, 72.1, 71.6, 68.7, 68.0, 36.5, 36.4, 35.2,$
 $35.1, 35.0, 34.6, 33.8, 33.3, 24.0, 23.5$

Anal. Calcd for $\text{C}_9\text{H}_{20}\text{O}_3$: C, 61.33; H, 11.44. Found: C, 61.07; H, 11.50.

2.6 References

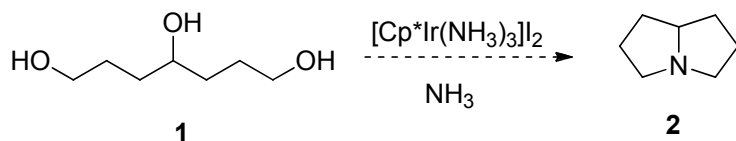
1. Fujita, K; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *16*, 3525-3528.
2. Miao, L. DiMaggio, S. C.; Shu, H.; Trudell, M. L. *Org. Lett.* **2009**, *11*, 1579-1582.
3. Kawahara, R.; Fujita, K; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108-15111.
4. For a review of amphibian alkaloids see: (a) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556-1575. (b) Daly, J. *J. Med. Chem.* **2003**, *46*, 445-451.
5. Schwartz, B. D.; McErlean, C. S. P.; Fletcher, M. T.; Mazomenos, B. E.; Konstantopoulou, M. A.; Kitching, W.; De Voss, J. J. *Org. Lett.* **2005**, *7*, 1173-1176.
6. Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* **2007**, *9*, 1821-1824.
7. Colonge, J.; Jeltsch, P. *Bull. Chim. Soc. Fr.* **1963**, *6*, 1296-1298.
8. Green, T. W.; Wutts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd Ed. John Wiley & Sons: New York, 1999.
9. (a) Nicolai, S.; Waser, J. *Org. Lett.* **2011**, *13*, 6324-6327. (b) Brown, H.C.; Negishi, E.; Diskason, W. C. *J. Org. Chem.* **1985**, *50*, 520-527.
10. (a) Chiruta, C.; Jachak, S.; Clive, D. L. J. *Tet. Lett.* **2007**, *48*, 3141-3143. (b) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977-988.
11. For a review of hydroboration chemistry see: Smith, K.; Pelter, A. in *Comprehensive Organic Synthesis*, Vol. 8. Trost, B. M.; Fleming, I. (Eds), Pergamon Press: Oxford 1991, 703-732.

CHAPTER 3: Synthesis of Amphibian Alkaloids using Intermolecular N-Heterocyclization Reactions

3.1 Results and discussion

Our interest in exploring the chemistry and biology of novel amphibian alkaloids has prompted an investigation to implement this methodology for the construction of more complex heterocyclic structures. To this end we envisaged the application of the iridium catalyzed N-heterocyclization reaction for the preparation of pyrrolizidine alkaloids from the corresponding hepta-1,4,7-triol using $[\text{Cp}^*\text{Ir}(\text{NH}_3)_3]\text{I}_2$ catalyst¹ as shown in scheme 3.1

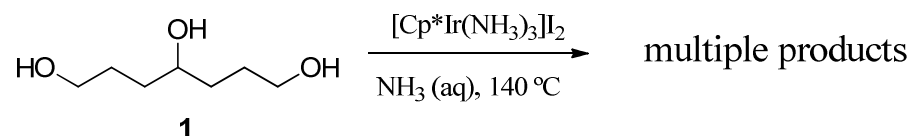
Scheme 3.1 Proposed synthesis of substituted pyrrolizidine



With the different triol derivatives in hand, our next step was to attempt triol cyclization in to corresponding izidines alkaloids, using aqueous ammonia as a source of nitrogen. An attempt was made with heptane-1,4,7-triol to see if the present catalytic system could cyclize it into pyrrolizidine ring as shown in Scheme 3.2. Unfortunately, the attempt was unsuccessful because of the formation of

multiple products formation as shown in Scheme 3.2. This made us difficult to analyze the formation of desired product exclusively.

Scheme 3.2 Attempted synthesis of pyrrolizidine



The selectivity of the product is reduced probably because of the triol system having multiple alcohol groups, which competes equally between intermolecular reaction and intramolecular reaction. We also employed dilution techniques to favor intramolecular product formation by using more solvent. Even then, the desired product formation is not improved. Employing different solvent systems, bases and also changing the catalyst found to be unsuccessful in obtaining the desired product. Moreover, increase in temperature leads to formation of intractable material which makes it much more difficult to analyze as shown in Table 3.1.

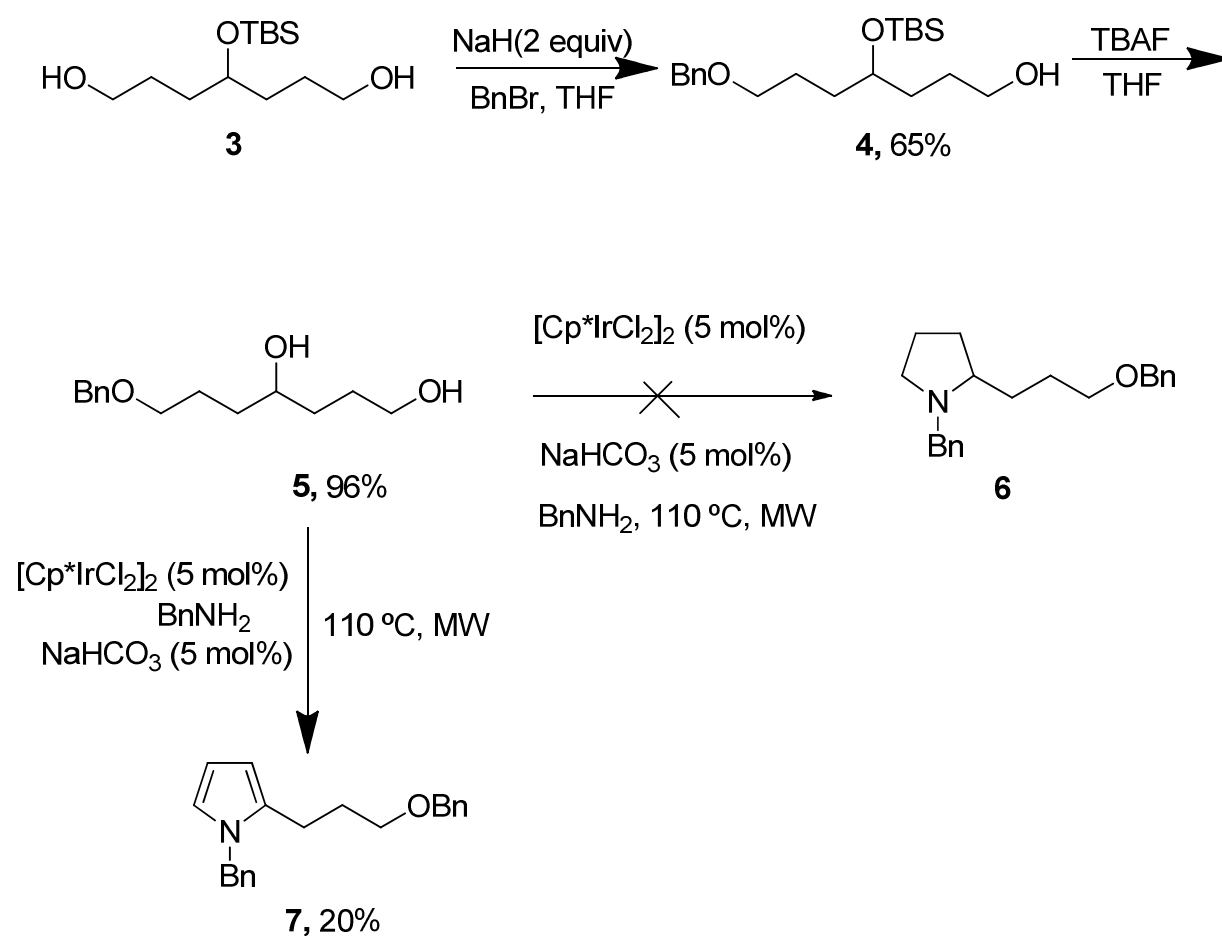
Table 3.1 Reaction conditions for Cp*Ir cyclization step

Entry	Catalyst	Solvent	Base	Amine	Conditions
1	[Cp*Ir(NH ₃) ₃] ₂ I ₂	No	no	aq. NH ₃	140 °C for 17 h to 48 h
2	[Cp*Ir(NH ₃) ₃] ₂ I ₂	H ₂ O	no	benzyl amine	140 °C for 17 h to 48 h
3	[Cp*Ir(NH ₃) ₃] ₂ I ₂	H ₂ O	no	aq. NH ₃	reflux/microwave
4	[Cp*Ir(NH ₃) ₃] ₂ I ₂	H ₂ O	no	benzyl amine	reflux/microwave
5	[Cp*IrCl ₂] ₂	toluene	NaHCO ₃ Or NaCO ₃	aq. NH ₃	Reflux
6	[Cp*IrCl ₂] ₂	Toluene	NaHCO ₃ Or NaCO ₃	benzyl amine	Reflux
7	[Cp*IrCl ₂] ₂	H ₂ O	NaHCO ₃ Or NaCO ₃	benzyl amine	reflux/microwave

With the intention of moving forward toward the target pyrrolizidine, the current scheme was abandoned and further trials were made by using monoprotected triols(diols) as starting alcohol systems (Scheme 3.3).

The 4-(*tert*-butyldimethylsiloxy)heptane-1,7-diol obtained previously² (Table 2.1) was monoprotected using benzyl bromide under basic conditions to obtain compound **4** in 65 % yield. The TBS protecting group was then deprotected using tetrabutylammonium fluoride to furnish compound **5** in 96% yield.

Scheme 3.3 Synthesis of N-substituted pyrrole



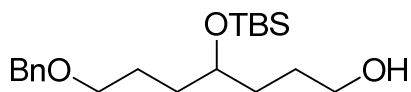
With the diol **5** in hand, the compound was subjected to general iridium catalyzed reaction condition to obtain N-substituted pyrrolidine ring system. Interestingly, the product obtained was found to be the N-substituted pyrrole **7**,

which is believed to have been formed because of O₂ (air) acting as a co-oxidant. The results however were not satisfying because of low yields (<20%).

The triol system for construction of izidine ring systems found to be unsuccessful with iridium catalyst. However, the results are found to be fairly convincing with the diol system. The N-substituted pyrrole thus obtained developed our interest towards constructing pyrrole derivatives which can be of biological importance. Further research in improving the reaction conditions for making pyrrole ring system is in progress.

3.2 Experimental section

1-(methoxyphenyl)-4-(tert-butyldimethylsiloxy)heptanol (4)



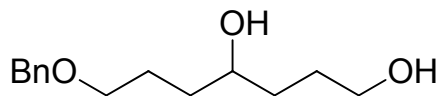
To a solution of NaH (0.09 g, 3.8 mmol) in anhydrous THF, the dienol **11** (1g, 3.8 mmol) was added dropwise at 0 °C. The mixture was stirred for 15 minutes followed by addition of benzyl bromide (0.45 mL, 3.8 mmol). The mixture was allowed to warm to room temperature and stirred overnight. Excess NaH was quenched by adding ice at 0 °C and the mixture was stirred for 10 minutes. The mixture was poured in water, extracted with EtOAc (3 × 50 mL). The combined organic layers were with water, brine solution, dried over anhydrous Na₂SO₄ and

concentrated under reduced pressure. The residue was purified by and flash chromatograph (SiO₂) to furnish the desired benzyl ether **12** as colorless oil; yield: 0.87g (65 %).

¹H NMR (400 MHz, CDCl₃): δ 7.34-7.25 (m, 5H), 4.5 (s, 2H), 3.76-3.74 (m, 1H), 3.72-3.52 (m, 2H), 3.46 (t, *J*=8Hz, 2H), 1.64-1.51 (m, 8H), 0.88 (s, 9H), 0.05 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 138.2, 128.6, 127.7, 127.8, 73.0, 70.2, 62.8, 33.2, 31.4, 29.8, 26.9, 26.6, 21.6, 18.3, -4.2

1-(methoxyphenyl)heptane-1,4-diol (5)

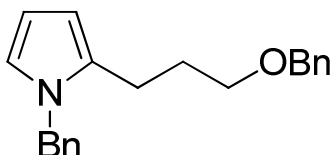


A solution of 1 M solution of TBAF in THF (2.83 mL, 2.8 mmol) was added to a solution of compound **12** (1g, 2.8 mmol) in dry THF (10 mL) at room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (30 % MeOH/EtOAc) to furnish the corresponding diol **13** as colorless oil; yield: 0.65 g (96 %)

¹H NMR (400 MHz, CDCl₃): δ 7.35-7.26 (m, 5H), 4.51 (s, 2H), 3.68-3.60 (m, 1H), 3.54-3.48 (m, 4H), 1.74-1.60 (m, 6H), 1.54-1.49 (m, 2H)

^{13}C NMR (100 MHz, CDCl_3): δ 138.2, 128.7, 127.9, 73.3, 71.7, 70.8, 63.2, 35.2, 34.8, 29.5, 26.6

1-(methyphenyl)-2(3-benzyloxypropyl)pyrrole (7)



The monoprotected diol **13** (0.1 g, 0.4 mmol) was added to the microwave reaction tube along with the catalyst $[\text{Cp}^*\text{IrCl}_2]_2$ (8.3 mg, 0.01 mmol) and NaHCO_3 (1.8 mg, 0.01 mmol) in H_2O and benzyl amine (0.045 mL, 0.4 mmol) was added and the mixture was irradiated at 110 °C for 2 h. The mixture was extracted with EtOAc (3×10 mL) and the combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5 % EtOAc-hexane) afforded **14** as colorless oil; yield: 23 mg (20 %)

^1H NMR (400 MHz, CDCl_3): δ 7.38- 7.21 (m, 8H), 6.98 (d, $J = 6.8$ Hz, 2H), 6.63 (t, $J = 2.4$ Hz, 1H), 6.14 (t, $J = 3.2$ Hz, 1H), 5.97 (s, 1H), 5.04 (s, 2H), 4.46 (s, 2H), 3.49 (t, $J = 6.4$ Hz, 2H), 2.57 (t, $J = 8$ Hz, 2H), 1.89 (p, $J = 8$ Hz, 3H)

^{13}C NMR (100 MHz, CDCl_3): δ 138.7, 133.1, 128.9, 128.6, 127.8, 127.5, 126.5, 121.2, 107.3, 106.2, 73.0, 69.8, 50.4, 29.1, 22.9

3.5 References

1. Kawahara, R.; Fujita, K. I.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108-15111.
2. Thota, K.K.; Trudell, M. L. *Synthesis* **2013**, *45*, 2280-2286

CHAPTER 4 Synthesis of Amphibian Alkaloids using Intramolecular N-Heterocyclization Reactions

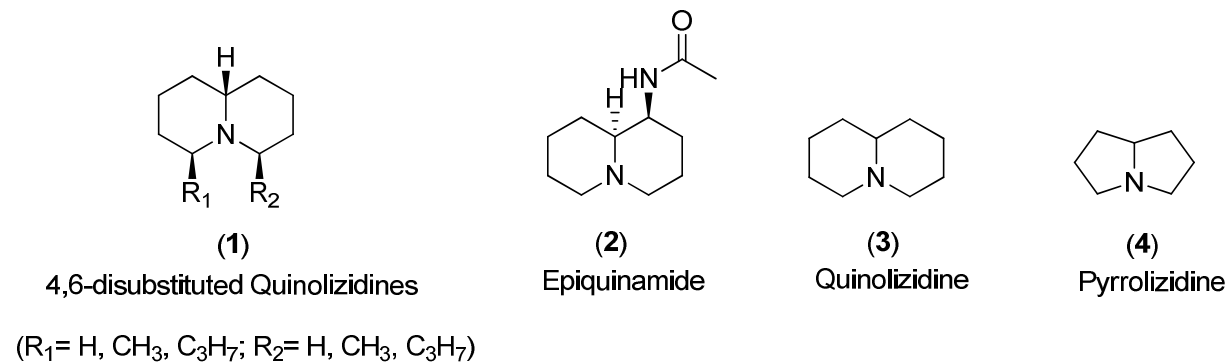
4.1 Results and discussion

All the reactions discussed in the introduction were performed with the alcohol and the amine as separate reactants, which proceed via an intermolecular N-heterocyclization reaction. To our knowledge, there are no reports corresponding to intramolecular N-heterocyclization reactions involving amine and alcohol functional groups in the same molecule. It has been envisaged that the development of an intramolecular approach could be applied to the synthesis of most of the pyrrolizidine and quinolizidine derivatives. This could then lead to the construction of diverse library of biologically active, lipid- soluble alkaloids that have been discovered in amphibian skin.

We are currently studying the catalytic activity of the iridium complex in constructing novel anuran scaffolds like quinolizidine (**14**) and pyrrolizidine (**15**) derivatives. We selected 4,6-disubstituted quinolizidines derivatives (**12**) and epiquinamide (**13**, a natural product) as shown in Figure 1.2, from a list of compounds that are taken from a diverse array of biologically active, lipid-soluble alkaloids that have been discovered in amphibian skin. These compounds can be made using the generalized Scheme 1.6 in making quinolizidine. Epiquinamide,

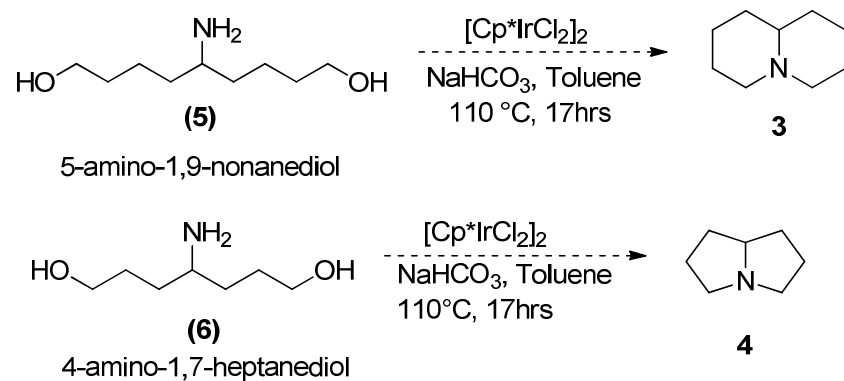
isolated in 2003 from an Ecuadoran dendrobatid frog as a trace alkaloid has been reported to act as an agonist at nicotinic receptors.¹

Figure 4.1 Structures of 4,6-disubstituted quinolizidines, epiquinamide, quinolizidine, and pyrrolizidine



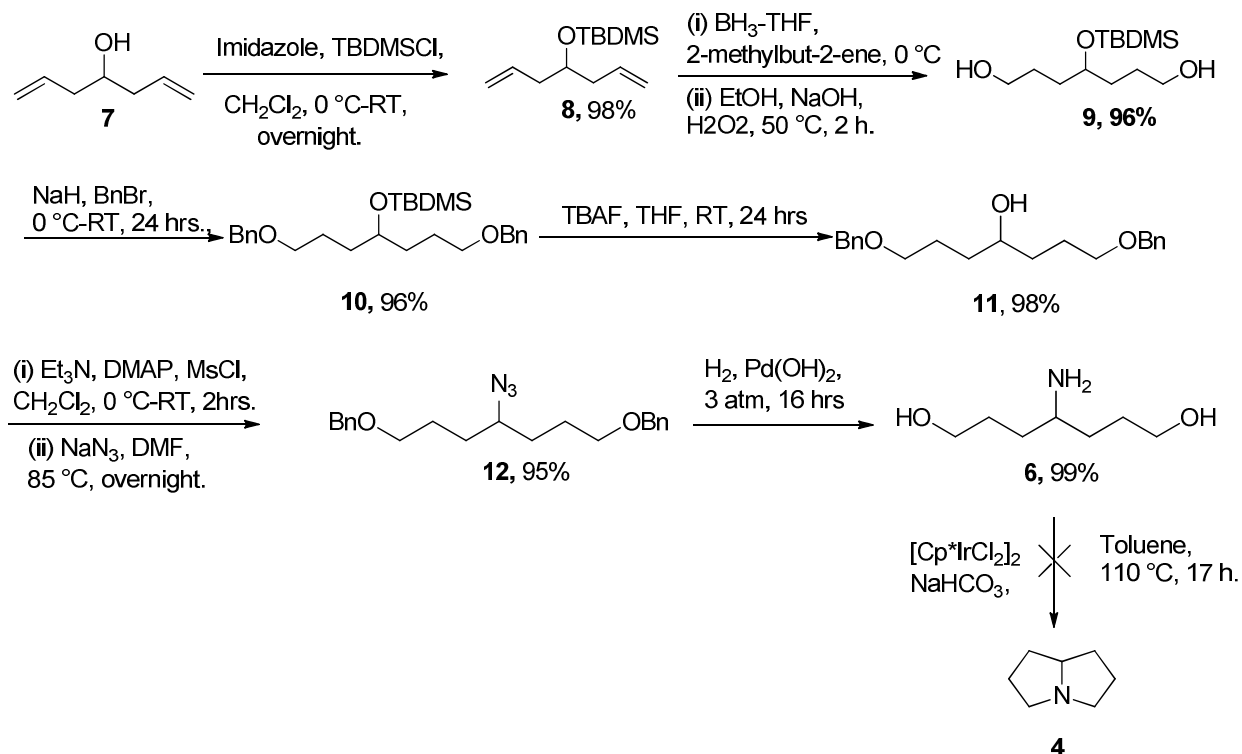
Our priority was to develop a method for the construction of quinolizidine and pyrrolizidine molecules using an iridium catalyzed system (Scheme 4.1) and then apply the same methodology for the construction of quinolizidine derivatives (1) and (±)-epiquinamide (2).

Scheme 4.1 Novel strategy for synthesis of quinolizidine and pyrrolizidine



The synthesis of precursor for pyrrolizidine **4** is shown in Scheme 4.2. The 1,6-heptadien-4-ol (**7**) is commercially available. Initially, the alcohol group was protected using TBDMSCl to afford silyl ether **8** in 98% yield. Subsequent treatment of **8** with disiamylborane prepared from $\text{BH}_3 \cdot \text{DMS}$ and 2-methyl-2-butene afforded the mono-protected triol **9** in 96 % yield. The primary alcohol groups of mono-protected triol **9** were then protected with benzyl groups using NaH and benzyl bromide, to furnish the dibenzyl ether **10** in 96% yield. The TBDMS group was then removed using TBAF which gave alcohol **11** with 98% yield. The hydroxyl group was converted to the azide via mesylation and concomitant nucleophilic substitution using NaN_3 . This afforded azide **12** in 95% yield. The azide group was reduced to the amine along with deprotection of benzyl group using $\text{Pd}(\text{OH})_2$, to give 4-aminoheptane-1,7-diol **6** in 99% yield and 83% overall yield starting from **7**. The aminodiol **6** was obtained in sufficient purity that it could be used directly in subsequent reactions. This was a significant advantage of this approach, because the polar amines are often difficult to purify by column chromatography.

Scheme 4.2 Synthesis of 4-amino-1,7-heptanediol



Unfortunately, the final step involving the iridium catalyzed N-heterocyclization was unsuccessful with various conditions summarized in Table 4.1. It had been reported that solvents like toluene and $\text{H}_2\text{O}/\text{NaHCO}_3$ were efficient for the intermolecular N-heterocyclization reactions. However, the same conditions were found not to be suitable for the intramolecular reaction. It is believed that the highly polar nature of 4-amino-1,7-heptanediol **6** made it insoluble in organic solvents such as toluene and too unreactive in polar solvents like water.

Table 4.1 Conditions for Cp*Ir cyclization step

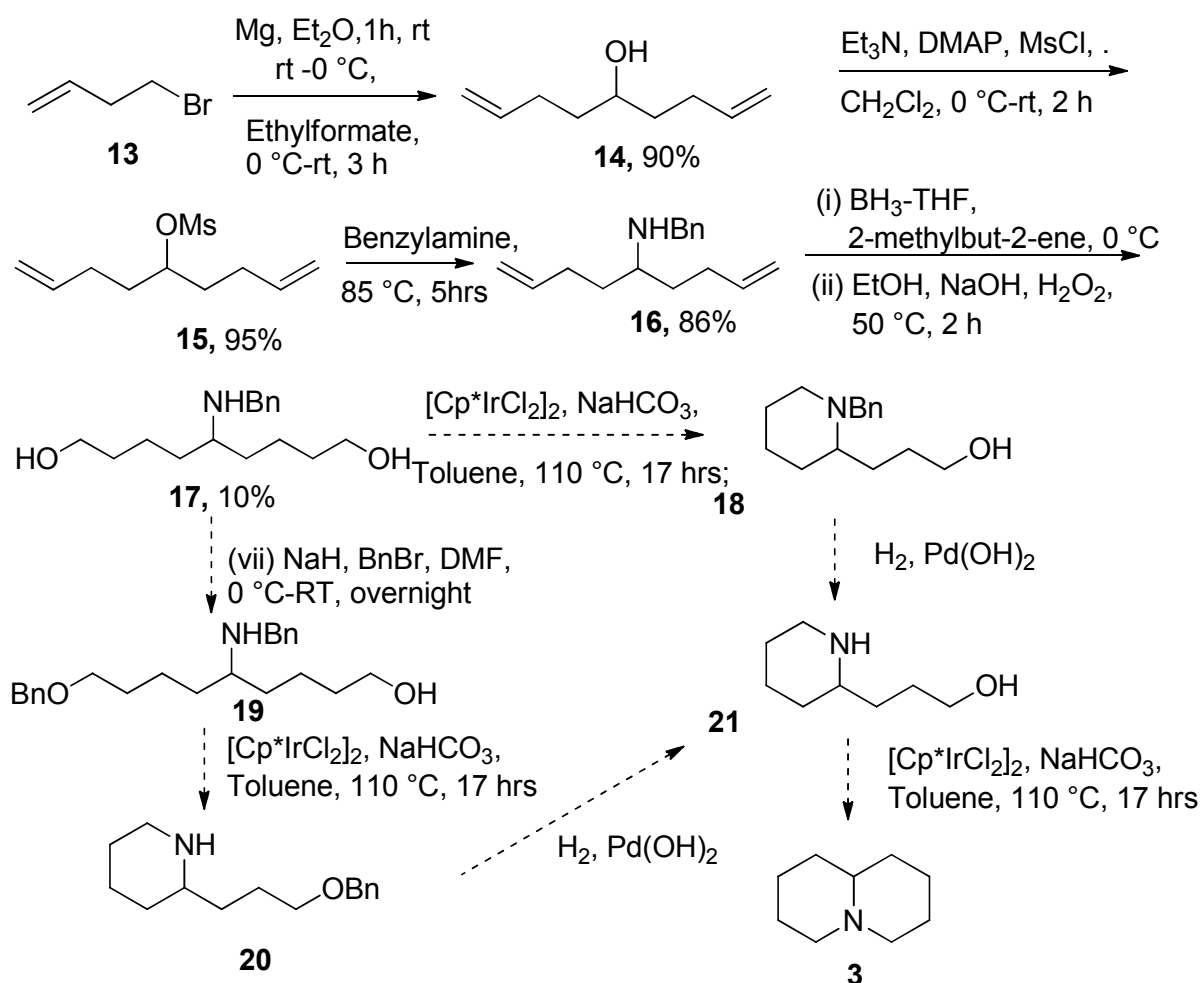
Solvent	Base	Temperature (°C)	Reaction time	Result
Toluene	NaHCO ₃	110	17 hrs	NR
Toluene	K ₂ CO ₃	110	17 hrs	NR
Toluene	TFAA	110	17 hrs	NR
H ₂ O	NaHCO ₃	100	17 hrs	NR
H ₂ O	K ₂ CO ₃	100	17 hrs	NR
H ₂ O	TFAA	100	17 hrs	NR
MeOH	NaHCO ₃	64	17 hrs	NR
THF	NaHCO ₃	66	17 hrs	NR
DMF	NaHCO ₃	152	17 hrs	NR

The N-heterocyclization reaction of **6** was determined to be unsuccessful in different solvents and with different bases. Therefore, our next step in developing our approach was to decrease the polarity of reactant amino alcohol compound in the final step (Scheme 4.3).

As illustrated in Scheme 4.3 the commercially available bromide **13** was converted into alcohol **14** in 80 % yield, using Grignard reagent conditions and ethyl formate. The alcohol group was mesylated using mesyl chloride under basic conditions to provide compound **15** in 95% yield. The nucleophilic substitution of the benzyl amine using benzyl amine itself as the solvent and heating up to 85 °C for 5 h, afforded compound **16** in 86% yield. The conversion of terminal alkenes into the primary diol was attempted using the same disiamyl borane.

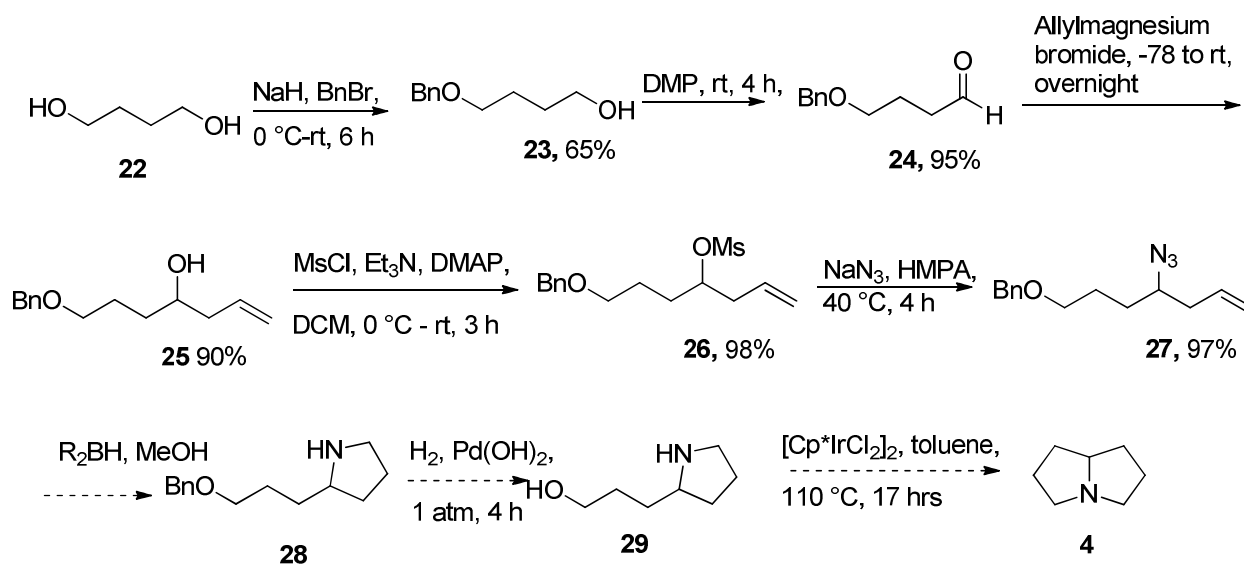
Unfortunately, this only gave a 10 % yield of the desired product this time. Presumably this is due to the competing of oxidation of amine group upon addition of H₂O₂ during the oxidative work-up, thus reducing the yield of desired product. Therefore, the synthetic approach illustrated in Scheme 4.3 was abandoned and an alternative approach was explored.

Scheme 4.3 Alternate strategy for synthesis of quinolizidine



As illustrated in Scheme 4.4, the alternative approach began with commercially available 1,4-butanediol (**22**). The diol was monoprotected² as the benzyl ether to give monoprotected diol **23** in 65% yield. The free alcohol group was converted into the aldehyde using Dess-Martin periodinane conditions,² to afford aldehyde **24** in 95% yield. The aldehyde group was converted into the secondary alcohol by adding allyl magnesium bromide to afford the alcohol **25** in 90% yield. The alcohol group was converted into the azide via nucleophilic displacement of the corresponding mesylate group to furnish **27** with 95% yield.

Scheme 4.4 Strategy for synthesis of pyrrolizidine



With the azide **27** in hand, the synthesis of the pyrrolizidine ring system **4** was envisaged to proceed from the alcohol **29**. The alcohol **29** will be obtained via

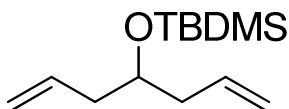
conversion of the azide **27** into pyrrolidine **28** using a tandem hydroboration-cycloalkylation reaction.³

The iridium catalyzed intramolecular N-heterocyclization reaction of aminodiols, was initially unsuccessful due to the highly polar nature and low solubility of the aminodiol precursors. The modified approach which involves the reduction of the the polar nature of the aminodiol will be the subject of future studies in the Trudell group.

4.2 Experimental section

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Thin layer chromatography (TLC): silica gel (250 μm). Visualization with UV light, iodine or phosphomolybdic acid. Chromatography: silica gel 60 Å (230-400 mesh). ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in CDCl_3 or D_2O . ^1H NMR chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. ^{13}C NMR chemical shifts are reported as δ values (ppm) relative to chloroform-*d* (77.0 ppm). Melting points were recorded on a Mel-temp apparatus and are uncorrected. Atlantic Microlab, Inc., Norcross, GA performed all CHN microanalyses.

4-(*tert*-Butyldimethylsilyloxy)hepta-1,6-diene(**8**)

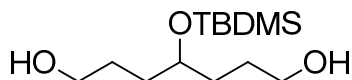


To a solution of dienol **7** (1.0 g, 7.1 mmol) in CH₂Cl₂ (20 mL), imidazole (1.0 g, 14 mmol) was added at room temperature and stirred for 15 min. To the stirred solution, a solution of TBSCl (1.6 g, 11 mmol) in CH₂Cl₂ (5 mL), was added slowly at 0 °C with continued stirring overnight. The reaction mixture was poured into water (50 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (1% EtOAc/hexane) furnished compound **8** as a colorless oil; yield: 1.8 g (98%).

¹H NMR (400 MHz, CDCl₃): δ 5.85-5.76 (m, 2H), 5.06-5.02 (m, 4H), 3.74 (p, *J* = 5.8 Hz, 1H), 2.27-2.15 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 135.5, 117.1, 72.0, 41.7, 26.1, 18.4, -4.3.

4-(*tert*-Butyldimethylsilyloxy)heptane-1,7-diol (**9**)



A 250 mL round bottom flask was filled with borane-DMS complex (1.7 mL, 22 mmol) under an argon atmosphere and cooled to -10 °C. A solution of 2-

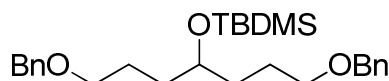
methyl-but-2-ene (2M in THF, 17.6 mL, 44 mmol) was added drop wise and stirred for 2 h at 0 °C. A solution of the diene **8** (1.0 g, 5 mmol) in anhydrous THF (10 mL) was added drop wise at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 18-24 h until none of the diene was observed by TLC. Ethanol (13 mL), 6N NaOH (4.4 mL) and H₂O₂ (30 %, 5.3 mL) were added slowly and the reaction mixture was heated to 50 °C for 1-3 h (until the white solid suspension dissolved). After cooling to room temperature, the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography to furnished **9** as a colorless oil; yield: 1.1g (96%).

¹H NMR (400 MHz, CDCl₃): δ 3.78-3.76 (m, 1H), 3.62-3.60 (m, 4H), 2.34 (br s, 2H), 1.62-1.52 (m, 8H), 0.88 (s, 9H), 0.06 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 72.1, 63.2, 33.2, 28.5, 26.1, 18.3, -4.3.

Anal. Calcd for C₁₃H₃₀O₃Si: C, 59.49; H, 11.52. Found: C, 59.23; H, 11.26.

4-(*tert*-Butyldimethylsilyloxy)1,7-bis(benzyloxy)-heptane (10)

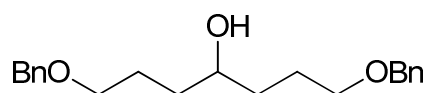


To a solution of NaH (0.2g, 8.3 mmol) in anhydrous THF(20 mL), the dienol **9** (1g, 3.8 mmol) solution in anhydrous THF was added dropwise at 0 °C. The mixture was stirred for 15 minutes followed by addition of benzyl bromide (0.95 mL, 7.9 mmol). The mixture was allowed to warm to room temperature and stirred overnight. Excess NaH was quenched by adding ice at 0 °C and the mixture was stirred for 10 minutes. The mixture was poured in water, extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (30 mL), brine solution (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by and flash chromatograph (SiO₂, 5 % EtOAc-Hexane) to furnish **10** as a colorless oil; yield: 1.62 g (96%).

¹H NMR (400 MHz, CDCl₃): δ 7.35-7.25(m, 10H), 4.53(s, 4H), 3.74-3.68(p, 1H), 3.49-3.45(t, 4H), 1.75-1.62(m, 4H), 1.56-1.48(m, 4H), 0.92(s, 9H), 0.05(s, 6H)

¹³C NMR (100 MHz, CDCl₃): δ 138.5, 129.6, 127.8, 127.6, 73.4, 72.1, 65.9, 38.4, 31.2, 18.5, -4.2

1,7-bis(benzyloxy)-heptane-4-ol (11)



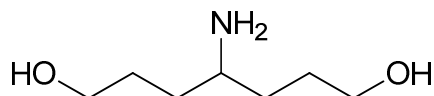
A solution of 1M solution of TBAF in THF (4.5 mL, 4.4 mmol) was added to a solution of compound **10** (1g, 2.2 mmol) in dry THF (10 mL) at room

and washed with water (3×50 mL) and then with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatograph (SiO₂) to furnish **12** as a colorless oil; yield: 1.02 g (95%).

¹H NMR (400 MHz, CDCl₃): δ 7.39-7.27 (m, 10H), 4.52(s, 4H), 3.53-3.44(m, 4H), 3.32-3.25(m, 1H), 1.82-1.53(m, 8H)

¹³C NMR (100 MHz, CDCl₃): δ 138.6, 129.7, 127.8, 127.8, 73.2, 71.9, 65.6, 37.8

4-amino-hetane-1,7-diol (**6**)

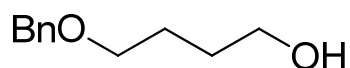


The compound **12** (1 g) in anhydrous MeOH (5 mL) was added to a solution of Pd(OH)₂ on carbon (10% wt) in a clean and dry parr hydrogenator reaction bottle and reaction is performed under hydrogen gas at 3 atm pressure using a parr hydrogenator for 16 hours. After all of the starting material was consumed (TLC) the catalyst was filtered using celite, concentrated under reduced pressure, and dried under high vacuum (0.133 mbar) at r.t to furnish **6** as a colorless oil; yield: 0.41 g (99%)

¹H NMR (400 MHz, CDCl₃): δ 3.52-3.43 (t, 4H), 2.69-2.59(p, 1H), 1.52-1.30(m, 6H), 1.26-1.15(m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 61.9, 50.1, 32.6, 27.4

4-(phenylmethoxy)butane-1-ol (**23**)

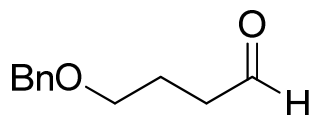


To a solution of NaH (0.27g, 11.0 mmol) in anhydrous THF(20 mL), the diol **22** (1.0 g, 11 mmol) solution in anhydrous THF was added dropwise at 0 °C. The mixture was stirred for 15 minutes followed by addition of benzyl bromide (1.5 mL, 12 mmol). The mixture was allowed to warm to room temperature and stirred overnight. Excess NaH was quenched by adding ice at 0 °C and the mixture was stirred for 10 minutes. The mixture was poured in water, extracted with EtOAc (3 × 50 mL). The combined organic layers were with water, brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by and flash chromatograph (SiO_2 , 15 % EtOAc-Hexane) to furnish **23** as colorless oil; yield: 0.65 g (65%).

^1H NMR (400 MHz, CDCl_3): δ 7.38-7.26(m, 5H), 4.54(s, 2H), 3.68-3.62(q, 2H), 3.56-3.51(t, 2H), 1.76-1.64(m, 4H)

^{13}C NMR (100 MHz, CDCl_3): δ 137.8, 127.9, 128.8, 127.6, 73.2, 70.4, 62.8, 28.4, 25.8

4-(phenylmethoxy)butane-1-al (**24**)

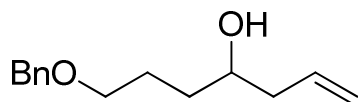


To a stirred solution of mono protected diol **23** (1.0 g, 5.5 mmol) in anhydrous CH_2Cl_2 was added Dess-Martin periodinane (2.4 g, 5.5 mmol) slowly at 0°C . The mixture was allowed to warm to room temperature and then it was stirred until the diol was no longer observed by TLC. Saturated NaHCO_3 (20 mL) was added at 0°C and a white suspension was formed. The suspension was then filtered and the organic layer was dried (anhydrous Na_2SO_4). The mixture was filtered and concentrated under reduced pressure, and the residue was purified by flash chromatography (SiO_2 , 10% E tOAc-hexane) to furnish **24** as colorless oil; yield: 0.94 g (95%).

^1H NMR (400 MHz, CDCl_3): δ 9.8(s, 1H), 7.39-7.24(m, 5H), 4.48(s, 2H), 3.53-3.48(t, 2H), 2.58-2.53(t, 2H), 1.99-1.92(p, 2H)

^{13}C NMR (100 MHz, CDCl_3): δ 202.2, 137.8, 127.9, 128.8, 127.6, 73.2, 69.4, 39.6, 21.4

7-(phenylmethoxy)hept-1-ene-4-ol (**25**)

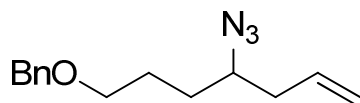


To the stirred solution of allyl magnesium bromide 1M in diethyl ether (6.7 mL, 6.7 mmol) in anhydrous at -78 °C was added aldehyde **24** (1.0 g, 5.6 mmol) in THF (1 mL). The mixture was stirred for 3 h. Saturated NH₄Cl solution (5 mL) was added at 0 °C and the mixture stirred for 1h. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried (anhydrous Na₂SO₄). The mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 25% EtOAc-hexane) to furnish **25** as colorless oil; yield: 1.12 g (90%).

¹H NMR (400 MHz, CDCl₃): δ 7.39-7.24 (m, 5H), 5.89-5.68 (m, 1H), 5.15-5.09 (m, 2H), 4.53 (s, 2H), 3.70-3.62 (m, 1H), 3.52 (t, *J* = 6.4 Hz, 2H), 1.82-1.52 (m, 4H)

¹³C NMR (100 MHz, CDCl₃): δ 137.8, 135.1, 127.9, 128.8, 127.6, 115.7, 73.2, 71.4, 70.3, 42.3, 34.2, 29.1

4-azido-7-(phenylmethoxy)hept-1-ene (**27**)



To the solution of compound **25** (1.0 g, 4.5 mmol) in DCM was added Et₃N(1.89 mL, 13.5 mmol) and a catalytic amount of DMAP. The solution is then stirred for 30 min before adding MsCl (0.35 mL, 4.5 mmol) at 0 °C and then stirred

at room temperature for another 2 hours. The disappearance of starting material indicated that the reaction was completed. The reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This gives compound **26** which is sufficiently pure to carry forward for the next step where NaN_3 (0.88 g, 13.5 mmol) is added in dry DMF and stirred at 80°C overnight. The compound is then extracted in to ether layer and washed with water(3×50 mL) and then with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatograph (SiO_2 , 2 % EtOAc-Hexane) to furnish **27** as colorless oil; yield: 1.06 g (95%).

^1H NMR (400 MHz, CDCl_3): δ 7.39-7.24 (m, 5H), 5.89-5.68 (m, 1H), 5.15-5.09 (m, 2H), 4.53 (s, 2H), 3.52 (m, 2H), 3.39-3.32 (m, 1H), 1.82-1.52 (m, 4H)

^{13}C NMR (100 MHz, CDCl_3): δ 137.8, 133.2, 127.9, 128.8, 127.6, 118.7, 73.2, 71.4, 58.6, 41.3, 32.2, 26.1

4.3 References

1. John, W. D.; Thomas, F. S.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556-1575
2. Gresser, M. J.; Keller, P. A.; Wales, S. M. *Tetrahedron Lett.* **2009**, *50*, 4899-4902.
3. Salmon, A.; Carboni, B. *J. Organomet. Chem.* **1998**, *567*, 31-37

VITA

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