CHAPTER II

LITERATURE REVIEW

Bioactivity of Eugenol on Analgesic Property

Anesthesia is performed by placing the fish in the anesthetic solution that is absorbed through the gills and into the blood by that acts on the central nervous system (CNS).[12] Prostaglandin (PHS) H synthase is a key control enzyme in the biosynthesis of eicosanoids[13]. These causes are increase of the stress hormone cortisol. The eugenol in clove oil has an analgesic property that affect to the inhibition of prostaglandin H synthase[14,15].Prostaglandin is a neurotransmitter that produced and secreted in the central nervous system and muscles when is outside stimulated and cause stress. Eugenol can affect on the production of prostaglandin *via* inhibition of cyclogenase enzyme that is function to change arachidonic acid to endoperoxidase and convert itself to thromboxane A_2 and prostacyclin [16]in shown the Figure 4.

The major area of entry and excretion of anesthetics in fish is the respiratory organ; through the gills and the rate of passage extremely depends on its degree of ionization and lipid solubility.[17] Because of its hydrophobicity property, eugenol's structure is highly lipid soluble and it can reach the relatively rapid onset to stage 4 and 5 of anesthesia. The range stages of anesthesia and recovery from anesthesia experiment in fish are present in Table 1. For the purposes of this experiment, loss of equilibrium refers to stage 4 of anesthesia, and is defined as the stage at which a fish is unable to recover and maintain an upright position in the water. Stage 5 of anesthesia refers to the stage at which a fish is unresponsive to slight pressure applied to the caudal fin with a net.

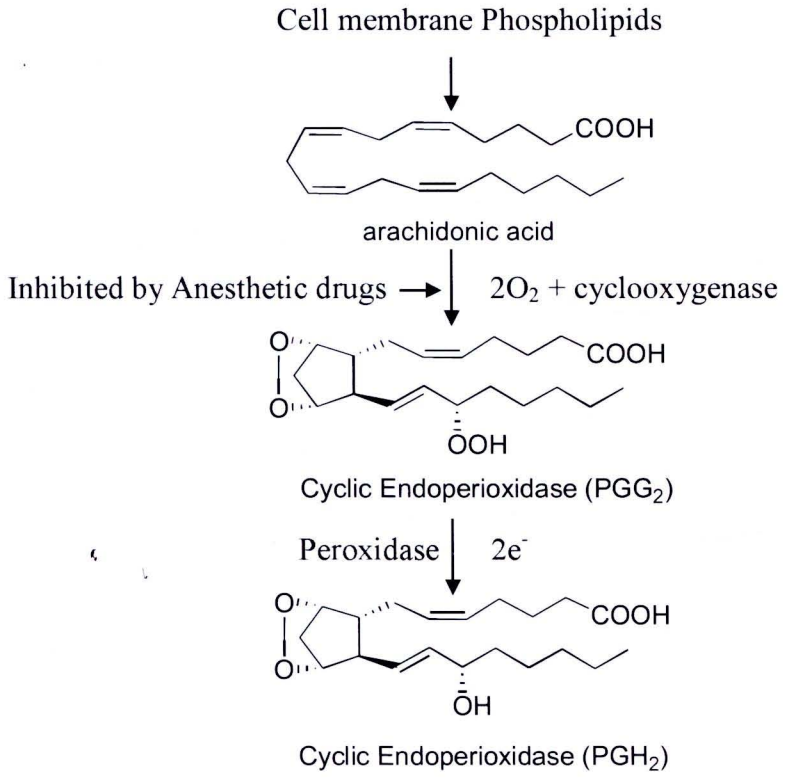


Figure 4 Biosynthesis of eicosanoids in the stress hormone cortisol and process inhibited by anesthetic drugs

Table 1 Stages of anesthesia in fish [18, 19]

Stage	Behavior exhibited
1	Sedation; partial loss of reaction to external stimuli.
2	Partial loss of equilibrium; uncoordinated movement followed by active, erratic swimming.
3	Total loss of equilibrium; fish usually turns over but retains swimming ability.
4	Anesthesia; loss of reflex activity, fish fails to respond to strong external stimuli.
5	Medullary collapse; respiratory movement ceases.

In 2006, Sergio Ne´stor Bolasina [20] reported the experiment about anesthetic treatment in *Urophycis brasiliensis* (Piscer, Phycidae) when the fishes were irritated until they get stress. It was found that the level of cortisol hormone and glucose in blood were increased. Moreover, they adapted themselves to get balance in order to decrease level of cortisol and glucose within 1-14 days (Figure 5)

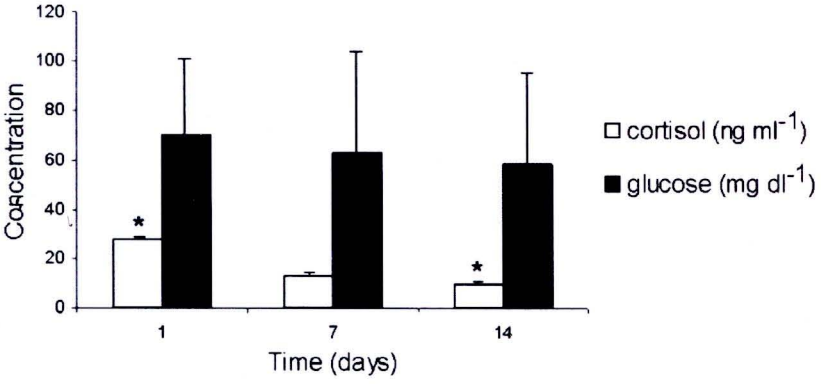


Figure 5 Cortisol and glucose plasmatic levels in *Urophycis brasiliensis* along 14 days after capture

Moreover, the study of plasma electrolytes of ordinary fish comparing to the treated fish with anesthetic agent, benzocaine, was found that it rarely lost ion when examine the concentration of Na^+, K^+ and Cl^- ion. Therefore, the anesthetized fishes can regularly breathe by getting enough oxygen and commonly still alive(Figure 6).In this literature, the chemical agent can be to the efficacy anesthetic and to control in plasma electrolytes of aquatic animal.

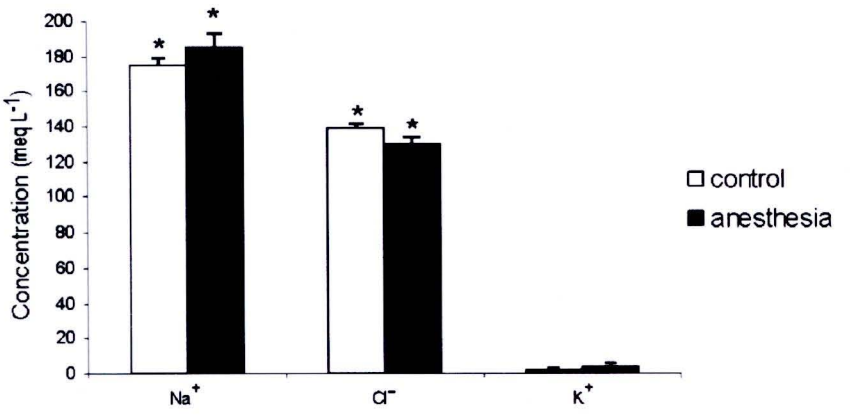


Figure 6 Plasmatic electrolytes concentration in control and anesthetized group

The selected examples of the use of eugenol and their derivatives in fish anesthetic research are described as following. Keene L.J. et.al [21]conducted the study of the efficiency of clove oil to make rainbow trout (*Oncorhynchus mykiss*) become unconscious. The 80 grams of rainbow trout was tested with 40-80 ppm of eugenol solution. The corresponding concentration of eugenol can cause the fish to be unconscious in stage 5 within 3-6 minutes. In additions, the unconscious period of time was approximately 6-8 hours which showed the safety LC_{50}value in both fish and human.

Hematological parameters are closely related to the response of the animal to the environment [22]. Anesthesia may affect blood parameters and hemolised tissues.[23] Sudagara M. and co-worker [24]reported the efficacy of clove powder that was produced from the dry flowers and flower stalks of the clove tree. Evaluation of the hemogram involves the determination of the total erythrocyte count (RBC), total White Blood Cell count (WBC), Hematocrit (HT), Hemoglobin concentration (Hb), erythrocyte indices (MCV, MCH, MCHC), white blood cell differential count and the evolution of stained peripheral blood films on juvenile Roach (*Rutilus rutilus*). Effects of clove powder on the hematological parameters are shown in Figure 7- 9.

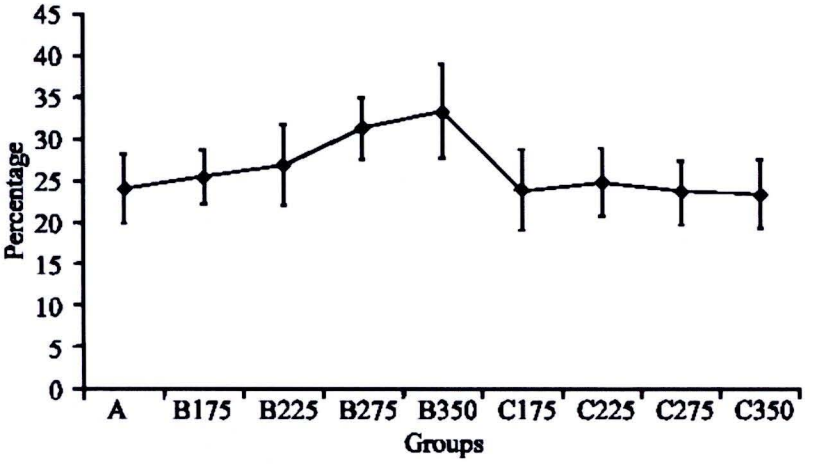


Figure 7 Effects of clove powder anesthesia on hematocrit. Control group A (without the anesthesia), group B (after 7 min of anesthesia at the concentrations of 175, 225, 275 and 350 mg L^{-1}) and group C (24 h after 7 min of anesthesia at the same concentrations)

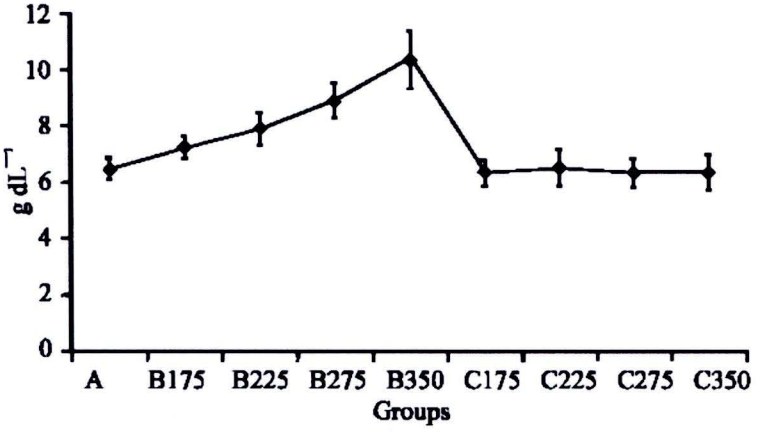


Figure 8 Effects of clove powder anesthesia on hemoglobin. Control group A (without the anesthesia), group B (after 7 min of anesthesia at the concentrations of 175, 225, 275 and 350 mg L^{-1}) and group C (24 h after 7 min of anesthesia at the same concentrations)

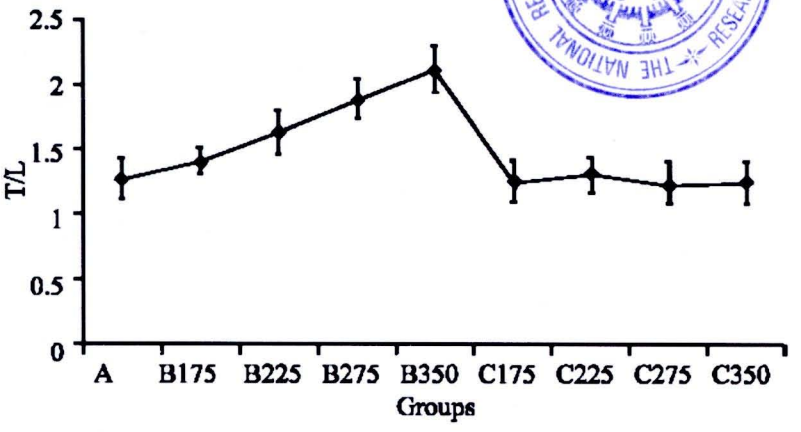
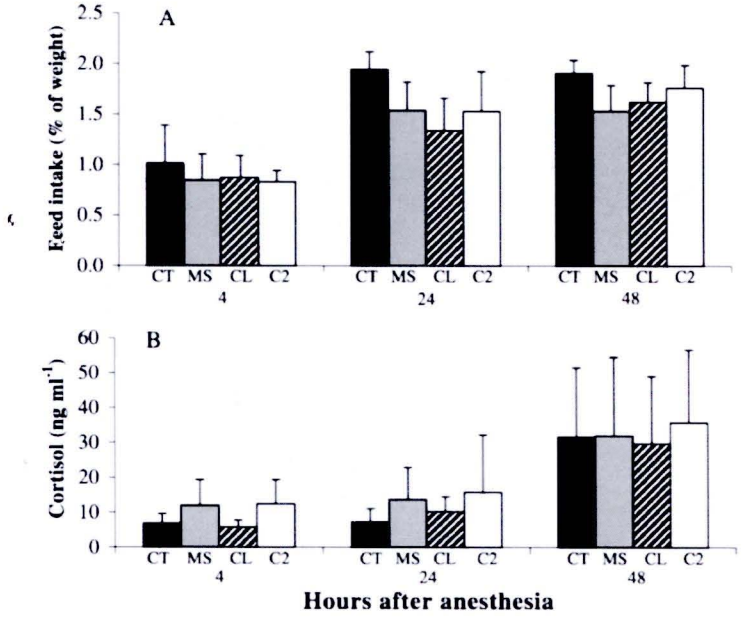


Figure 9 Effects of clove powder anesthesia on RBC. Control group A (without the anesthesia), group B (after 7 min of anesthesia at the concentrations of 175, 225, 275 and 350 mg L^{-1}) and group C (24 h after 7 min of anesthesia at the same concentrations)

In Figure 7-9, there were shown the times to achieve anesthesia response to concentration dose. The hematological parameters were assessed before, immediately after 7 min of anesthesia and 24 h, after the anesthesia at concentration of 175, 225, 275 and 350 mg L^{-1} of clove powder. The 7 minutes exposure to clove powder caused the hematocrit (Figure 7), hemoglobin (Figure 8) and total erythrocyte count (Figure 9) after anesthesia. These values returned back to normal within 24 h. These were revealed that clove powder anesthesia had not effect on other hematological parameters. Result of the examinations suggested that the use of clove powder at the concentrations of 175, 225, 275 and 350 mg L^{-1} does not cause irreversible damage of the blood parameters in Roach. It's main the advantages are low cost and the relative safety in the fish and humans.

Juhani Pirhonen and Carl B. Schreck [25] reported the impact comparison study of using MS-222, clove oil and carbondioxide (CO_2) for making steelhead trout (*Oncorhynchus mykiss*) to be unconscious. The objective of the study was to find the level of feed intake and plasma cortisol concentrations in a period of 4, 24 and 48 hours. After steelhead trout recover from unconscious state (Figure 10A and 10B), it can be found that the percentage of feed intake at every period when steelhead trout

get recover from treating with MS-222, clove oil and CO_2 was decreased comparing with the control. For cortisol concentration investigation, it was found that the clove oil gave a similar level of cortisol comparing with control. From the results, it can be concluded that the unconscious fish performing by clove oil was not significantly affected in the term of releasing of cortisol hormone when compare to control.



Figures 10 (A) Feed intake (percentage of weight per feeding) and (B) Plasma cortisol concentrations (ng/mL) of *Oncorhynchus mykiss* at 4, 24 and 48 hours after anesthesia. Treatments: CT = control, MS = MS-222, CL = clove oil and C2 = CO_2

In 2004, Melissa A. Kildea and co-worker [26]studied the toxicity and contamination of eugenol and iso-eugenol(Figure 11), that is a minor component found in the clove oil, test in silver perch (*Bidyanus bidyanus*).

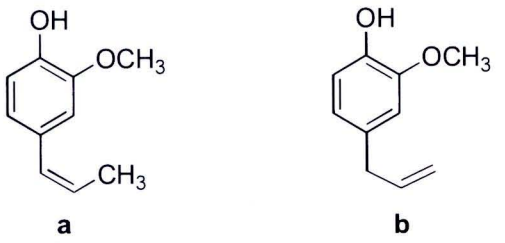


Figure 11 Chemical structures of (a) iso-eugenol and (b) eugenol

The accumulation of eugenol during harvest when treat at 15 and 50 ppm of eugenol to make silver perch become unconscious at both high temperature and ambient temperature were studied (Figure 12). Eugenol accumulated in the silver perch at harvesting stages 2, 4 and 6b. It was found that the suitable concentration of eugenol was 15 ppm to make the silver perch become unconscious at stage 4. The highest concentration of eugenol was measured in fish at stage 6b (killed by overdose) followed by those sedated for transport (stage 4). In this stage, the fish still alive and recover without no contamination of accumulation and depuration from eugenol. This means that eugenol is a possible anesthetic agent suitable for aquamarine transportation. However, the concentration at 50 ppm seems to be overdose and leads to the death.

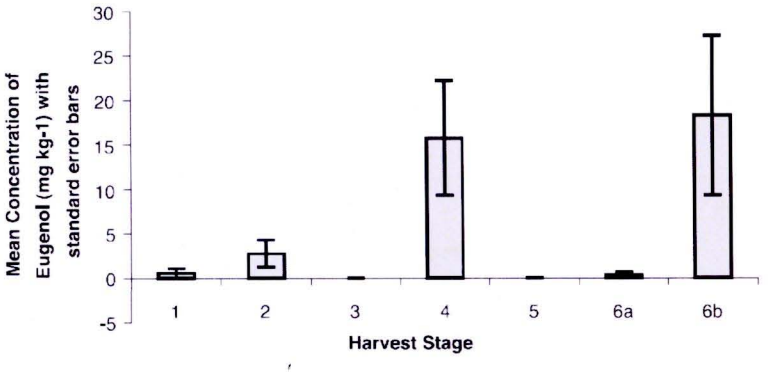


Figure 12 Mean accumulation and depuration of eugenol from silver perch during normal harvest

The contamination and dilution of eugenol and iso-eugenol were studied as shown in Figure 13 and Figure 14, and it was found that at dose 15 ppm of eugenol at both high temperature and ambient temperature the mean concentration is approximate 0.32 mg/kg for eugenol and iso-eugenol respectively after 6 hours which is acceptable. And after one week, the contamination of both eugenol and iso-eugenol was not found in fish.

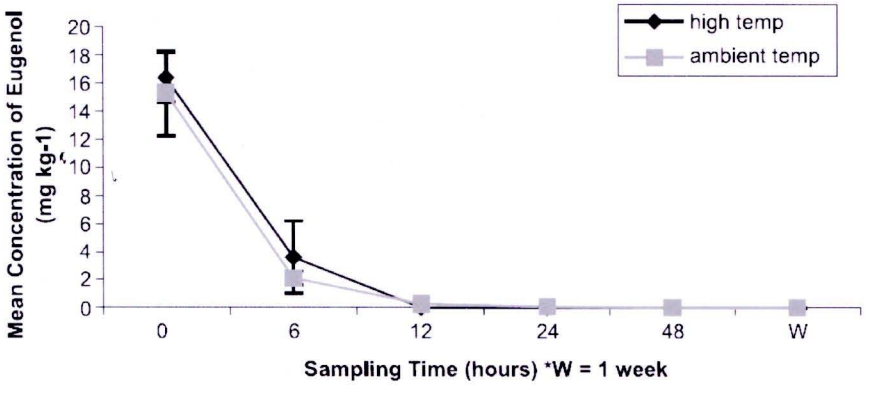


Figure 13 Accumulation and clearance of eugenol from silver perch exposed to 15 ppm eugenol at high temperature and ambient temperature

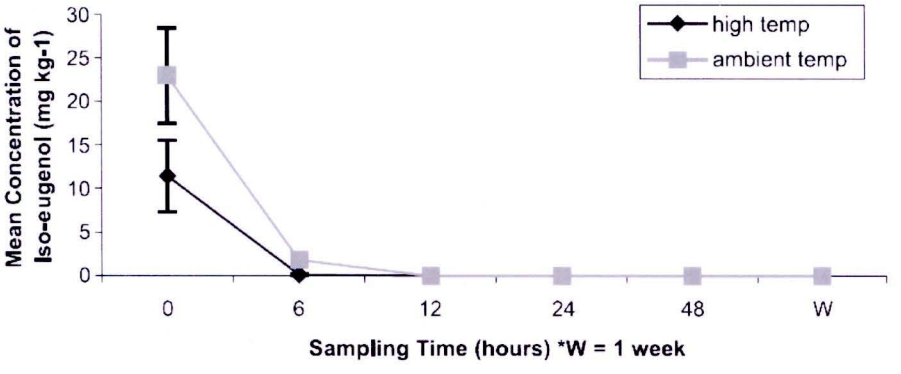
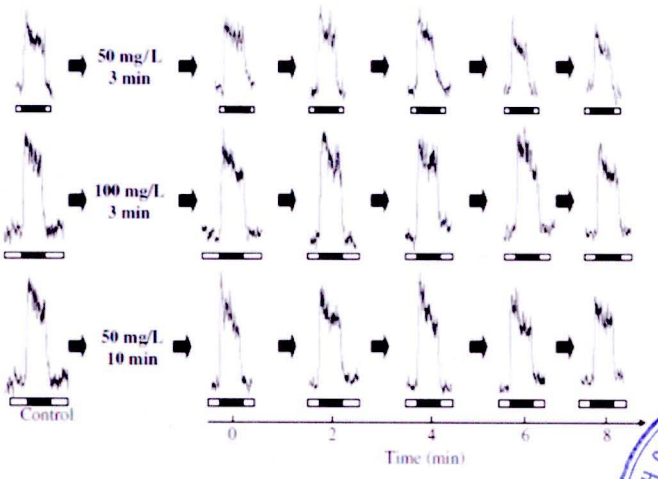


Figure 14 Accumulation and clearance of iso-eugenol from silver perch exposed to 15 ppm eugenol at high temperature and ambient temperature

From this research, it can be concluded that eugenol and iso-eugenol were rather than safety for consumer comparing with MS-222. Furthermore, eugenol and iso-eugenol were likely to take less time for fish recovery than MS-222.

In 2008, Yuzo Yamamoto and co-workers [27] studied the olfactory nerve response by clove oil of masu salmon (*Oncorthynchus masou Brevoot*) and rainbow trout (*O.mykiss Walbaum*). Olfactory nerve is a pair of nerve that controls the sense of smell for feed intake in fish. The olfactory nerve is in the forebrain that can be found in big fish more than small fish. In this work, the clove oil test at 50 ppm for 3 mins, 100 ppm for 3 mins and 50 ppm for 10 mins in both fishes and found that when fish swooned and revived at different time it showed a little change that indicated the concentration levels are safe for both of fish (Figure 15).

(a)



(b)

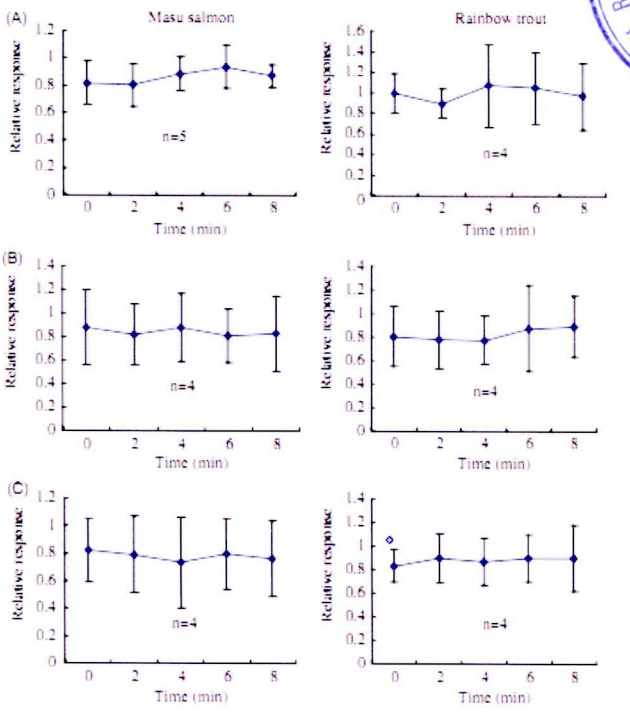


Figure 15 (a) Time course changes in typical integrated olfactory nerve response of masu salmon after exposure to three clove oil treatments. (b) Time course changes in relative magnitude of integrated olfactory nerve response of masu salmon and rainbow trout to different concentrations and anaesthetization time of clove oil. (A) 50 ppm, 3 min; (B) 100 ppm, 3 min; (C) 50 ppm, 10 min

In the same year, Zaikov A. and co-workers [28] reported the investigation of the possibilities for using clove oil as anesthetic in pike (*Esox Lucius* L.)The experiments were performed in four concentrations at 0.02 mL L^{-1}, 0.04 mLL^{-1}, 0.06 mLL^{-1} and 0.08 mLL^{-1}. Each concentration was tested with 12 pike having an average body weight of 244.4 to 284.9 g, and water temperature of 10 °C in 20 L of water. The results obtained from the experiment are show in Table 2. The pikes exposed to the lowest concentration of 0.02 mL L^{-1} did not reach stage 4 complete immobilization. Therefore, at the concentration 0.02 ml L^{-1} cannot be used for anesthetic of pike. The effect of clove oil on the pike at the next two concentrations of 0.04 and 0.06 ml L^{-1} is approximately the same. Fish lose equilibrium after 2:37 and 2:11 min, respectively and reach stage 4, at an average of 7:45 and 7:00 min, respectively. Their recovery of equilibrium and normal body position is done at an average in 3:57 min at 0.04 mL L^{-1} and 4:42 min at 0.06 mL L^{-1}. At the highest concentration of 0.08 mL L^{-1}, pikes lose equilibrium in the shortest time and reach stage 4 (complete loss of reactivity) at an average of 6:00 min, but at the highest degree of time variation (Cv, 33.09%) for reaching it. Therefore, the best results in regard to the time for reaching stage 4 (complete anesthesia) and the time for complete recovery at concentration of 0.06 ml L^{-1}.

Table 2 Time for induction and recovery from anesthesia of pike (*Esoxlucius*) exposed to different concentrations of clove oil

D[*1]	F[*2]	BW[*3] (g)	BL[*4] (g)	Induction of anesthesia			Recovery from anasthesia		
				Decreased locomotor activity (min'sec")	Total of equilibrium (min'sec")	Imobili-zation (min'sec")	Uncoordi-Natedlocomotor (min'sec")	Decreased activity (min'sec")	Normal position (min'sec")
0.02	X	224.4	28.7	5:45					
	SD	38.38	2.07	1.75					
	Cv%	15.7	7.21	30.57					
0.04	X	284.9	0.81	2:37	3:58	7:45	2:31	3:57	12:00
	SD	144.05	3.87	0.81	1.18	1.53	1.59	3.04	1.96
	Cv%	50.56	13.19	31.68	29.73	19.77	63.38	77.17	16.28
0.06	X	263.1	29.9	2:11	3:35	7:00	2:38	4:42	11:42
	SD	58.21	1.96	0.51	1.1	1.76	1.8	1.7	2.36
	Cv%	22.12	6.58	23.09	30.75	25.01	68.09	36.22	20.12
0.08	X	251.3	28.93	1:38	2:20	6:00	2:14	4:54	12:04
	SD	72.78	2.07	0.22	0.46	1.98	1.32	2.45	2.09
	Cv%	28.96	7.16	13.75	19.77	33.09	58.92	50.26	17.37

Note: [*1]Dose (mL L^{-1}), [*2]Feature, [*3]Bodyweight/BW/ (g), [*4]Bodylength/BL/ (g)

In 2010, Sohrab Akbari and co-workers had investigated the sedative properties of eugenol in post larvae (PL) of indian prawn (*Fenneropenaeus indicus*) which is the most target stage of animal for transportation. The median lethal concentration (LC_{50}) of eugenol for the PLs was also investigated to find out the safety margin of eugenol for application in transportation. The mortality of the experimental PLs exposed to various concentrations of eugenol test is shown in Table 3. Mortalities counted at each 4 hour intervals during 24 hours for five different concentrations and one control vary based on duration of exposure concentration of the eugenol. At 2 ppm is the best result concentration because there was no mortality at all in the PLs of *Fenneropenaeus indicus* exposed to sedation concentrations of eugenol during 24 hour test.

Table 3 Number of mortalities of the PLs of *Fenneropenaeus indicus* (n=500) exposed to different concentrations of eugenol in a 24 h test

Conc. of eugenol (ppm)	No. of replicate test	The number of shrimp mortalities at each time (h)						
		0	4	8	12	16	20	24
32	1	0	500	-	-	-	-	-
	2	0	500	-	-	-	-	-
	3	0	500	-	-	-	-	-
16	1	0	400	100	-	-	-	-
	2	0	450	50	-	-	-	-
	3	0	450	40	10	-	-	-
8	1	0	300	170	30	-	-	-
	2	0	300	50	50	-	-	-
	3	0	250	50	50	100	-	-
4	1	0	50	50	50	50	-	-
	2	0	50	-	-	-	-	-
	3	0	25	25	-	25	-	25
2	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0
Control	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0

The LC_{50} of eugenol for experimental PLs for each four hour interval are show in Table 4.The 24 h LC_{50} of eugenol for experimental PLs was found to be 5.2 ppm with minimum confidence limit of 5.0 ppm and maximum confidence limit of 5.3 ppm. In conclusion, the use of eugenol for transportation of PLs of *Fenneropenaeus indicus* at 2 ppm is higher safety.

Table 4 The LC_{50} values of eugenol and its Min-Max. Confidence limits for the PLs of *Fenneropenaeu sindicus* test

Time (h)	LC_{50} (ppm)	Min. confidence limit (ppm)	Max. confidence limit (ppm)
4	7.9	7.5	8.2
8	6.2	6.0	6.4
12	5.7	5.4	5.9
16	5.2	5.1	5.4
20	5.2	5.1	5.4
24	5.0	5.2	5.3

Literature Review for Synthetic Methodology

The general mechanism of the anesthesia activation undergoes interaction without breaking or forming covalent bonds *via* inhibition at synaptic neurotransmitter receptor located in the central nervous system where the NH or OH groups of amino acids such as tryptophan, tyrosine and phenylalanine is able to form H-bonding with functional group of anesthetic. Moreover, widely usages of anesthesia such as halothane, chloroform, isoflurane and methoxyflurane have acidic hydrogen which is able to form weak H-bonding with the C-H group as proton donor, or by the easily polarizable Cl or Br-atoms. In addition, they can be achieved the hydrophobic interaction too.[29] In this work, we design the eugenol derivatives in term of they can be achieved the H-bonding interaction and also remain hydrophobicity.

The syntheses of eugenol derivatives have been reported in several methods such as *O*-alkylation at hydroxy group of eugenol, demethylation at methoxy group of

eugenol, electrophilic aromatic substitution at aromatic ring of eugenol and allylation *via* Grignard reaction as following.

In 1994, Clas Sonesson and co-worker [30], studied the Sandmeyer reaction of (*S*)-phenylpiperidine used for the synthesis of aryl halides or allyl benzene from aryl diazonium salts. The mechanism of aromatic amine reacts with a nitrite to form an aryl diazonium salt, which decomposes in the presence of copper(I) chloride. Next, nucleophile such as bromide or allyl anion attacks diazonium salt to form the desired aryl bromide (Figure 16) and afforded (*S*)-phenylpiperidine in a moderate yield. The reaction is a radical-nucleophilic aromatic substitution type. Sandmeyer reaction was appropriate for commenting the amino group to chlorine and bromine into aromatic compounds of high yield.

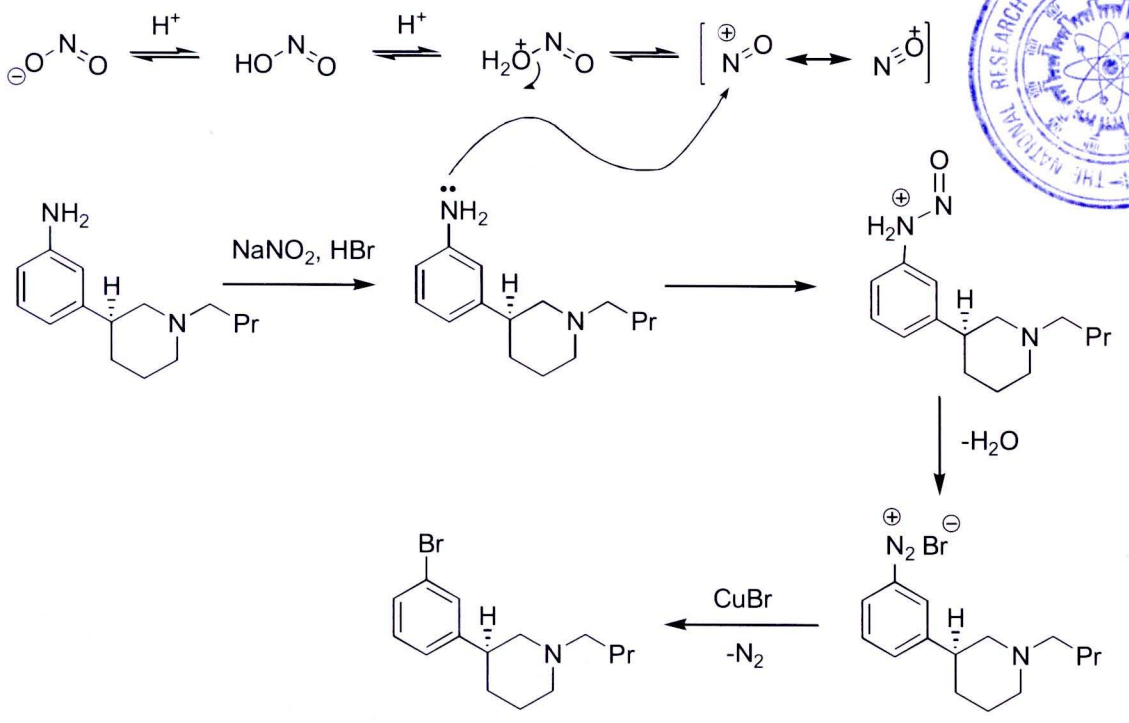


Figure 16 Proposed mechanism of (*S*)-phenylpiperidines *via* Sandmeyer reaction

In 1995, Judy L. Bolton and co-workers [31], studied the synthesis of 2-methoxy-4-propylphenol (PMP) by hydrogenation of eugenol with Pd on activated carbon in trifluoroacetic acid to give the PMP which is the saturated eugenol product in 41 % yield. (Figure 17)

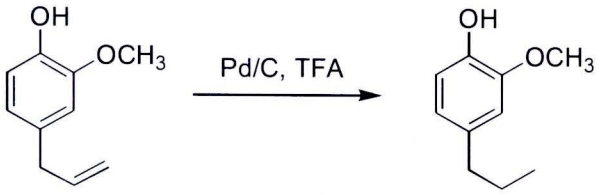


Figure 17 Synthesis of 2-methoxy-4-propylphenol (PMP)

In 2003, Xiaohong Cheng and co-workers [32], studied the synthesis of 3-allylanisole which is the dehydroxyeugenol derivative *via* Grignard reaction of 3-bromoanisole in 2 step (Figure 18) using magnesium in anhydrous ether at 50 °C and allylbromide to give the product in 48% yield.

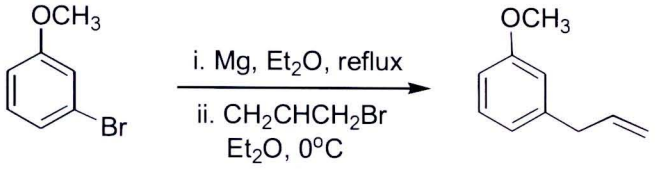


Figure 18 Synthesis of 3-allylanisole *via* Grignard reaction

In 2008, Hidenori Someya and co-workers [33], studied the silver-catalyzed in benzylation and allylation reaction of tertiary alkyl halides with Grignard reagent. It was found that tertiary alkyl bromide, with benzylic or allylic Grignard reagent in the presence of silver nitrate that acts as catalyst in ether can achieved the cross-coupling products in high yields (Figure 19).

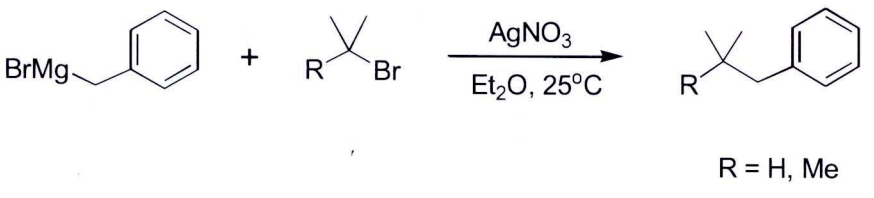


Figure 19 Scope of benzylic Grignard reagent

In 2009, Jeremy Ricci and co-worker [34], was reported the activity of various Lewis acids derived from metallic triflates catalysts, in the Friedel-Crafts allylation of aromatic derivatives (Figure 20 and Table 5).

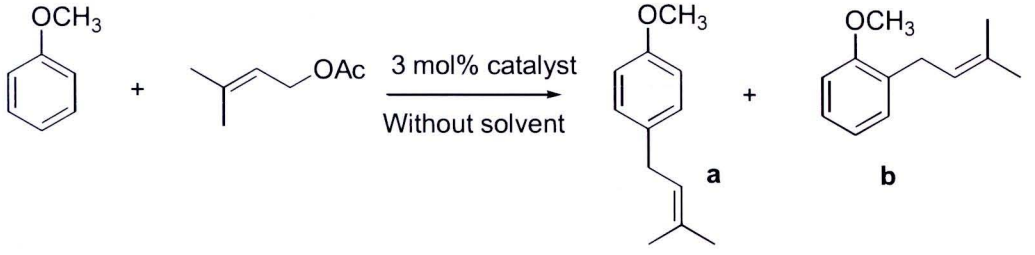


Figure 20 Scope of Friedel-Crafts allylation of anisole

Table 5 Influence of the catalyst and the temperature in the allylation reaction of Friedel-Crafts (ratio a:b =10:1, 3% molar of catalyst, without added solvent)

Entry	Catalyst	Temp (°C)	Reaction time	Yield of a/b (%)	Ratio a/b
1	$Cu(NTf_2)_2$	120	2 h	5	3.8/1
2	$W(NTf_2)_6$	120	5 h	16	2.7/1
3	$Zn(NTf_2)_2$	80	6 h	66	2.9/1
4	$Zn(NTf_2)_2$	100	3 h	93	2.8/1
5	$Zn(NTf_2)_2$	120	2 h	46	2.4/1
6	$Ni(NTf_2)_2$	80	24 h	55	2.8/1
7	$Ni(NTf_2)_2$	100	3 h	86	2.6/1
8	$Ni(NTf_2)_2$	120	2 h	52	2.3/1
9	$Zn(BF_4)_2$	120	4 h	62	-
10	$Ni(OTf)_2$	120	45 min	47	2.4/1

The reaction of anisole with isoproprenyl acetate was unsuccessful when performed in the presence of 3% molar of Fe (II), In (III), Sn (IV) or Al (III) triflimidates. Cu (II) and W (VI) catalysts gave low yields of 5-16% for **a/b** (Table 5, entry 1-2). The best results were obtained in the presence of 3 mol% of Zn (II) or Ni (II) triflimidates, at 100 °C, without added solvent, affording the mixture of two

isomers **a**/**b** with 93 and 86% yields, respectively (entry 4 and 7). With $Zn(NTf_2)_2$ and $Ni(NTf_2)_2$ at 80 °C, the reaction is resulting in lower yields (entry 3 and 6). In this at higher temperature (120 °C) of entry 5 and 8 it a moderated yields of **a**/**b**. $Zn(BF_4)_2$ and $Ni(OTf)_2$ were able to catalyse the coupling reaction to **a**/**b**, with 47 and 62% yields, respectively (entry 9-10). In the summery, the use of zinc *bis* (trifluoromethylsulfonyl) amide as a Lewis super acid catalyst was shown to be efficient for Friedel-Crafts allylation reaction. The reaction with good yields of high *para* selectivities in the mono-allylated isomers.

Zhuan Fang and co-worker [35], reported the lithium chloride-catalyzed demethylation reaction of aryl methyl ethers under microwave irradiation. It was found that microwave condition significantly improves the reaction yield. The mechanism of this reaction probably occurs by a nucleophilic attack of Li^+Cl^- on the methyl group followed by the release of CH_3Cl (Figure 18), and occurrence of this cleavage may be attributed to a nucleophilic attack from the strongly electron-withdrawing effect. The effect of the substituted group to selectivity and reactivity effect on the *para*-position more than meta-position, because of the influence of dipoles pairs which specifically help chloride ion in pulling off the leaving group.

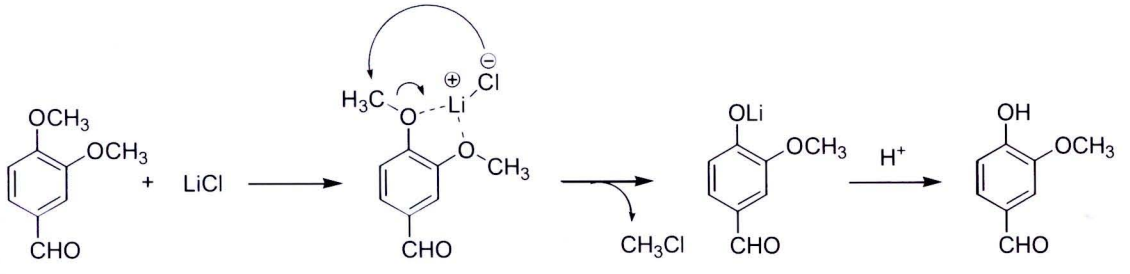


Figure 21 Proposed mechanism of catalytic de-alkylation of aryl ether by LiCl

Li Zuo and co-worker [36], researched the method of demethylation of aryl methyl ethers (Figure 22). In the Table 6 is a model reaction of 4-methoxy phenol with iodoalkanes in various solvent. Iodoalkanes can be produced in situ *via* an elimination process. Iodocyclohexane was identified to be the best one for this reaction, the process proceeded smoothly (4-methoxyphenol) to afford the desired product (4-hydroxyphenol) in 93% yield in dimethylformamide (DMF) under reflux and argon

condition (entry 5). For the other solvent, dimethyl sulfoxide (DMSO) and pyridine provide no reaction (entry 8 and 10). Although, *N*-methylpyrrolidinone (NMP) gave rise to product in good yield (81%), whereas a better reaction yield (93%) was achieved in DMF.

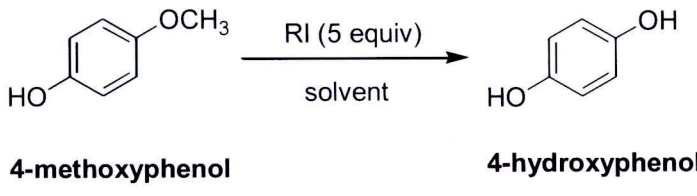


Figure 22 Scope of demethylation in aryl methyl ethers

Table 6 Optimization of reaction conditions for demethylation of 4-methoxyphenol

Entry	RI	Solvent	*T* (°C)	*t* (h)	Yield (%)
1	EtI	DMF	80	3	NR
2	2-Iodopropane	DMF	100	14	24
3	1-Iodobutane	DMF	Reflux	3	26
4	1-Iodopentane	DMF	Reflux	3	22
5	**Iodocyclohexane**	**DMF**	**Reflux**	**3**	**93**
6	Iodocyclohexane[a]	DMF	Reflux	3	57
7	Iodocyclohexane[b]	DMF	Reflux	3	81
8	Iodocyclohexane	DMSO	Reflux	2	NR
9	Iodocyclohexane	NMP	Reflux	2	81
10	Iodocyclohexane	Pyridine	Reflux	2	NR

Note: NR = No reaction, a = 3.0 equiv used, b = 4.0 equiv used.

In the 1999, J. Augusto R. Rodnigues and co-workers [37], studied the *ortho*-regioselectivity reaction of phenols (Figure 23) with acyl nitrates at room temperature for long periods of time (3-4 h). The results are summarized in Table 7. The reaction of phenol with acetyl nitrate in chloroform is rapid and quantitative giving an *ortho/para* ratio of 1:8 (entry 1) which is better than to the classical method using H_2SO_4-HNO_3 (1:4). When the reaction was carried out with acetyl nitrate pre-adsorbed on chrysotile or alumina, the *o/p* ratio increased to 2:3-2:5 (entry 2-3). In the presence of montmorillonite K10, the *ortho* selectivity went up to 2:9 (entry 4). The best result with the reagent previously adsorbed on dry silica which gave an *o/p* ratio of 13:3 (entry 5). By the entry 6, acetyl nitrate was less adsorbed on the support leaving more reagents in solution than in less polar solvent chloroform. As a result the regioselectivity decreases to 1:3 for a mixture of chloroform-dioxane. And the conditions of the reaction, 3-nitrophenol is non-reactive but competes with acetyl nitrate for the adsorption sites on the surface of the silica. In the presence of a 5:1 and 1:1 mixture of chloroform and 3-nitrophenol, the *o/p* ratio decreases to 1:1 and 0:4 (entry 7-8). This adsorbed on the support in order to obtain high *ortho*-selectivity. It was found that, similar results were achieved with benzoyl nitrate (entries 9 and 10) and with trimethylsilyl nitrate (entry 11-12). In conclusion, It is a highly ragioselective procedure for nitration of phenol using acetyl nitrate pre-adsorbed on silica gel giving an *o/p* ratio of 13:3 for the nitration of phenol derivatives.

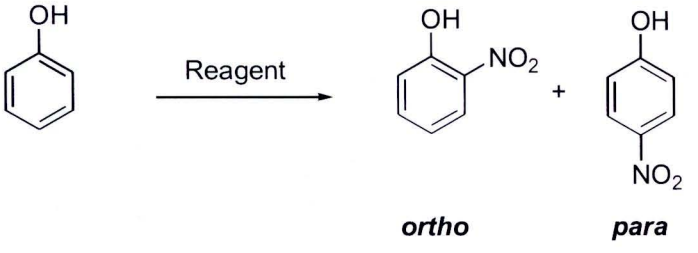


Figure 23 Nitration reaction of phenol

Table 7 Nitration of phenol with acyl nitrates in the presence of various supports

Entry	Reagent	Solvent	Ratio *ortho*/*para*
1	$AcONO_2$	$CHCl_3$	1:8
2	$AcONO_2$-chrys	$CHCl_3$	2:3
3	$AcONO_2$-Al_2O_3	$CHCl_3$	2:5
4	$AcONO_2$-K10	$CHCl_3$	2:9
5	$AcONO_2$-SiO_2	$CHCl_3$	13:3
6	$AcONO_2$-SiO_2	$CHCl_3$-dioxane	1:3
7	$AcONO_2$-SiO_2	1:5 $CHCl_3$: 3-nitrophenol	1:1
8	$AcONO_2$-SiO_2	1:1 $CHCl_3$: 3-nitrophenol	0:4
9	$BzONO_2$	$CHCl_3$	1:8
10	$BzONO_2$-SiO_2	$CHCl_3$	9:0
11	$TMSONO_2$	$CHCl_3$	1:1
12	$TMSONO_2$-SiO_2	$CHCl_3$	2:3

In the nine year later, Jae-Hwan Kwak and co-workers [38], studied the bromination conditions including the variety of brominating agent and solvent for synthesis of *ortho*-bromoeugenol as shown in Figure and Table 8.

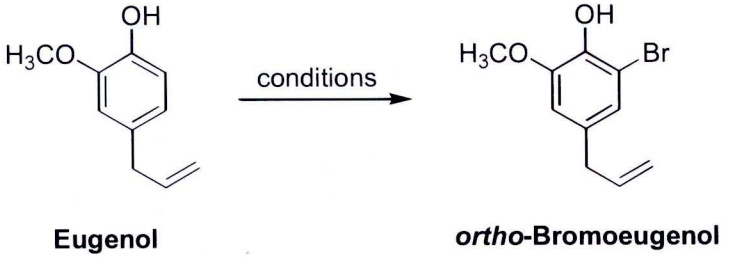


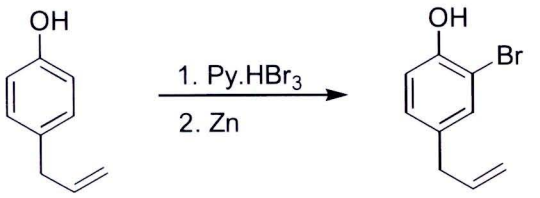
Figure 24 Bromination reaction of eugenol

Table 8 Optimization for chemoselective *ortho*-bromination

Entry	Condition	Yield of *ortho*-eugenol (%)
1	NBS, CH_2Cl_2	<20
2	NBS, DMF	35
3	NaOBr, *i*-Pr_2O	<20
4	Br_2, AcOH	DP
5	*n*-BuLi, NBS, THF	47
6	*n*-BuLi, NBS, Et_2O	30
7	*n*-BuLi, DBDMH, THF	25
8	***i*-PrMgCl, DBDMH, THF**	**78**
9	*i*-PrMgCl, DBDMH, CH_2Cl_2	45

Note: DP = Decomposed or unidentified byproducts

In Table 8 showed the decides to screen a variety of conditions including combination of base, brominating agent, and solvent. The bromination conditions failed to give the desired product, leading to substantial amount of decomposed byproduct (entry 1-4). However, the use of base additive as *n*-BuLi generally increased the chemical yield of the desired aromatic bromination product. Especially, treatment of eugenol with *iso*-propylmagnesium chloride (*i*-PrMgCl) as a base and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as an electrophile gave predominantly rise to the desired product in 78% yield. Chang-Ming Chen and Yeuk-Chen Liu [39], studied the chemoselective bromination on synthesis of 4-allyl-2-bromoanisole by pyridinium hydrobromide perbromide to give a 68% yield after further debromination by zinc in Figure 25.



4-allylanisole **4-allyl-2-bromoanisole**

Figure 25 Synthesis of 4-allyl-2-bromoanisole *via* chemoselective bromination

Xiuli Bu and co-workers [40], the very simple and convenient method to synthesize the phenyl ethers *via* the *O*-alkylation/etherification of phenols under solvent-free conditions were reported (Figure 26). Then the mixture of phenol, phenacyl bromide or benzyl bromide, organic base and anhydrous K_2CO_3 were grinded in a mortar. It was found that, other inorganic bases such as anhydrous Na_2CO_3, NaOH, and KOH can also be used in this reaction instead of anhydrous K_2CO_3.

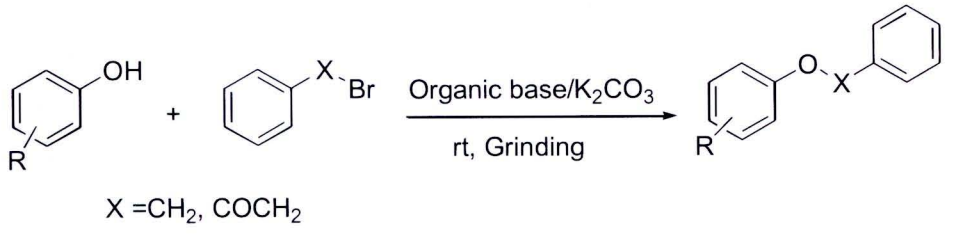


Figure 26 Synthesis the phenyl ethers *via* the *O*-alkylation reaction

Table 9 *O*-Alkylation of 4-methoxyphenol or ethers with benzyl bromide or phenacyl bromide

Entry	Organic base	Time (min)	Yield (%)
1	DABCO	40	85.0
2	DBU	42	75.3
3	DBN	50	73.3
4	DMAP	60	65.1
5	PPh_3/pyridine/picoline	60	0
6	None	35	0

The effect of organic base on the synthesis of 4-methoxyphenylbenzyl ethers and 4-methoxyphenolphenybenzyl was shown in Table 9. The weak organic bases such as triphenylphosphine, picoline, and pyridine cannot catalyze this coupling reaction (entry 5) and there was no reaction without organic base as catalyst (entry 6). The organic base 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 4-dimethylaminopyridine (DMAP) and 1,4-diazabicyclo[2,2,2] octane (DABCO) can catalyze this coupling reaction with different activity (entry 2-4). It can be seen that DABCO is the best catalyst in this *O*-alkylation reaction (entry 1). Therefore, the mixture of organic base and inorganic base (K_2CO_3) is the best for synthesis of 4-methoxyphenylbenzyl ethers.

Mizuno M. and Yamano M. [41], studied the modification of bases and solvents (Table 10) and discovered that an alkali metal hydroxide in a dipolar aprotic solvent in Smiles rearrangement. It was found that, the best result an sodium hydroxide in *N*,*N*-dimethylacetamide (DMA) at room temperature for 2 h (entry 3) give to product in high yield. Furthermore, it was found that the combination of an alkali metal and hydroxide in a dipolar aprotic solvent is successful not only in the Smiles rearrangement but also in the *O*-alkylation and the hydrolysis reaction. Therefore, it is one-pot method for the conversion of hydroxyl to amino group the most convenient method.

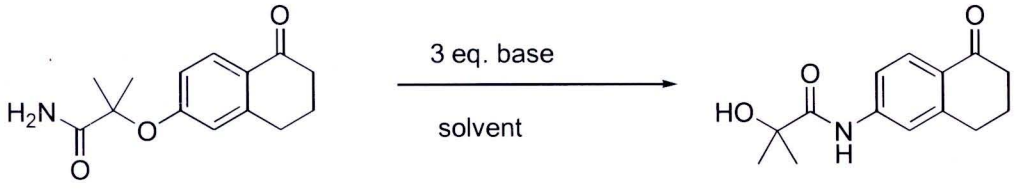


Figure 27 Scope of base conditions in Smiles rearrangement

Table 10 Reaction Conditions of Smiles Rearrangement

Entry	Base	Solvent	Temp./time	Yield (%)
1	NaH	DMA	rt/0.5 h	89
2	NaOH	DMA	rt/0.5 h	73
3	NaOH	DMA	rt/2 h	94
4	NaOH	MeOH	rt/2 h	0.3
5	NaOH	MeOH	reflux/2 h	13
6	$NaOCH_3$	MeOH	rt/2 h	0.1
7	$NaOCH_3$	MeOH	reflux/1 h	26
8	Na_2CO_3	DMA	rt/2 h	NR
9	Na_2CO_3	DMA	140 °C/1 h	72