

**INVESTIGATION OF SUBSTRATE-SELECTIVITY PATTERNS IN  
THE OXIDATION OF SECONDARY ALCOHOLS BY  
AMINO ACID-DERIVED IBX DERIVATIVES  
AND  
SELECTIVE OXIDATION OF SECONDARY ALCOHOLS USING  
*o*-IODOXYBENZOIC ACID (IBX)**



**A THESIS SUBMITTED IN PARTIAL FULFILLMENT  
OF THE REQUIREMENTS FOR  
THE DEGREE OF MASTER OF SCIENCE  
(ORGANIC CHEMISTRY)  
FACULTY OF GRADUATE STUDIES  
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Krisada Kittigowittana

PART I: INVESTIGATION OF SUBSTRATE-SELECTIVITY PATTERNS IN THE OXIDATION OF SECONDARY ALCOHOLS BY AMINO ACID-DERIVED IBX DERIVATIVES

PART II: SELECTIVE OXIDATION OF SECONDARY ALCOHOLS USING *o*-IODOXYBENZOIC ACID (IBX)

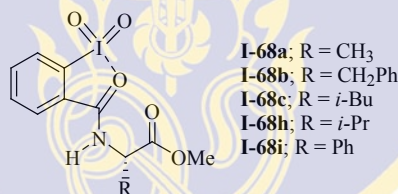
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M.Sc. (ORGANIC CHEMISTRY)

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### ABSTRACT

Part I: The chiral amino acid-derived 2-iodoxybenzamides **I-68a-c**, **I-68h-i** were prepared and employed for investigation of their synthetic potential for the oxidation of *sec*-alcohols. The results indicate that they can readily oxidize *sec*-alcohols to the corresponding ketones in good to excellent yields, however, with lack of selectivity.



Part II: A selective and efficient alternative method using *o*-iodoxybenzoic acid (IBX) at room temperature with 1:1 v/v of CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O as a solvent in the presence of phase transfer catalyst, tetrabutylammonium bromide (*n*-Bu<sub>4</sub>NBr), has been developed for the oxidation of secondary hydroxyl groups to ketones in moderate to good yields, in the presence of primary hydroxyl group within the same molecule.

KEY WORDS : HYPERVALENT IODINE/ OXIDATION/ IBX AMIDE

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ส่วนที่ 1 การศึกษารูปแบบตัวเกิดปฏิกิริยาต่อการเลือกทำปฏิกิริยาของปฏิกิริยาออกซิเดชันของอัลกอฮอล์ทุติยภูมิ โดยใช้อนุพันธ์ของไอบีเอ็กซ์ที่เตรียมได้จากกรดอะมิโน

(PART 1: INVESTIGATION OF SUBSTRATE-SELECTIVITY PATTERNS IN THE OXIDATION OF SECONDARY ALCOHOLS BY AMINO ACID-DERIVED IBX DERIVATIVES)

ส่วนที่ 2 การเลือกทำปฏิกิริยาออกซิเดชันของอัลกอฮอล์ทุติยภูมิ โดยใช้ 2-ไอโอดอกซีเบนโซอิกแอซิด (ไอบีเอ็กซ์) [PART 2: SELECTIVE OXIDATION OF SECONDARY ALCOHOLS USING *o*-IODOXYBENZOIC ACID (IBX)]

กฤษฎา กิตติโกวิทธนา 4536959 SCOC/M

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คณะกรรมการควบคุมวิทยานิพนธ์ : ชุตินา กูหากาญจน์, Ph.D., มนัส พรหมโคตร, Dr. rer. nat., วิชัย รวีตระกูล, Ph.D.

บทคัดย่อ

ส่วนที่ 1 ไครัล 2-ไอโอดอกซีเบนซอไมด์ ซึ่งเป็นอนุพันธ์ของกรดอะมิโน **I-68a-c, I-68h-i** ถูกเตรียมขึ้นและศึกษาคุณสมบัติในการทำปฏิกิริยาออกซิเดชันกับอัลกอฮอล์ทุติยภูมิ ผลการทดลองพบว่าอัลกอฮอล์ทุติยภูมิสามารถถูกออกซิไดซ์ไปเป็นคีโตนได้ดี แต่ไม่มีความจำเพาะในการเลือกทำปฏิกิริยากับไอโซเมอร์ที่สมบูรณ์


ส่วนที่ 2 ปฏิกิริยาออกซิเดชันของอัลกอฮอล์ โดยใช้ 2-ไอโอดอกซีเบนโซอิกแอซิด (ไอบีเอ็กซ์) ในไดคลอโรมีเทนกับน้ำอัตราส่วน 1 ต่อ 1 โดยปริมาตร และมีเตตระบิวทิลแอมโมเนียมโบรไมด์เป็นตัวเร่งปฏิกิริยาที่อุณหภูมิห้องได้รับการพัฒนาขึ้น ซึ่งปฏิกิริยานี้มีความสามารถในการเลือกออกซิไดซ์หมู่ไฮดรอกซิลชนิดทุติยภูมิในสารซึ่งมีหมู่ไฮดรอกซิลชนิดปฐมภูมิอยู่ด้วย

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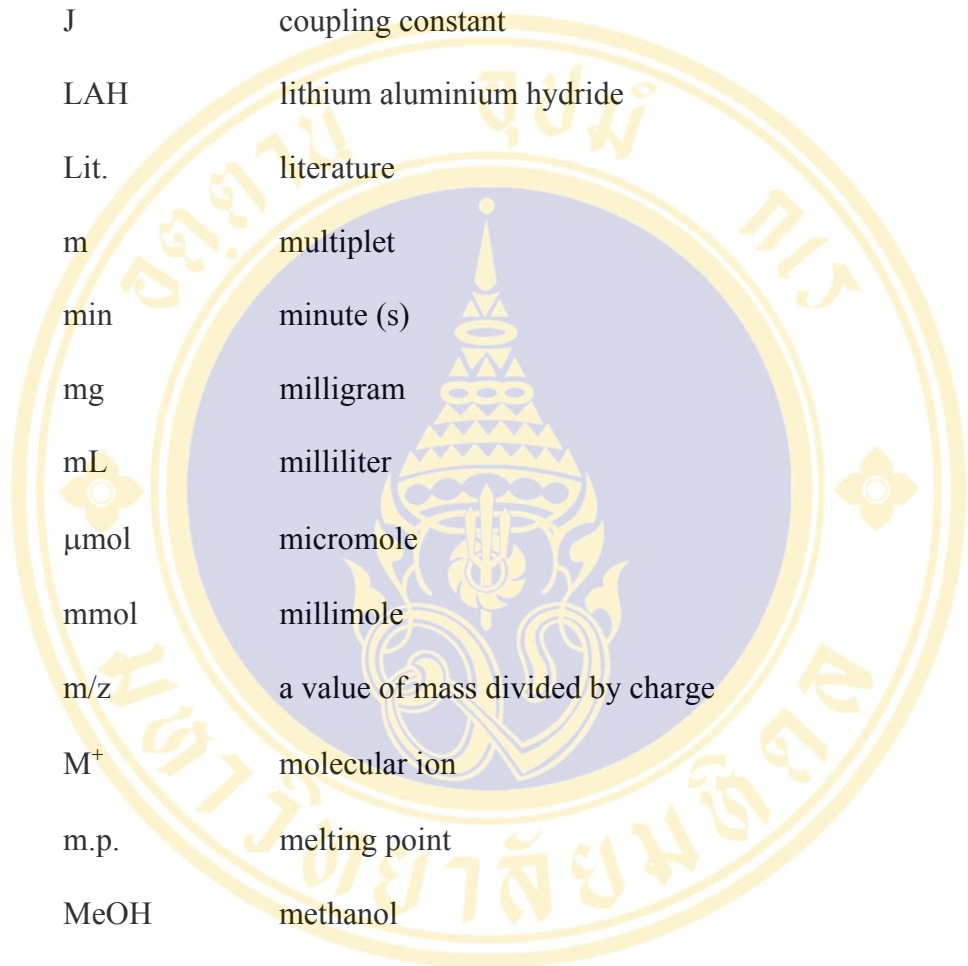
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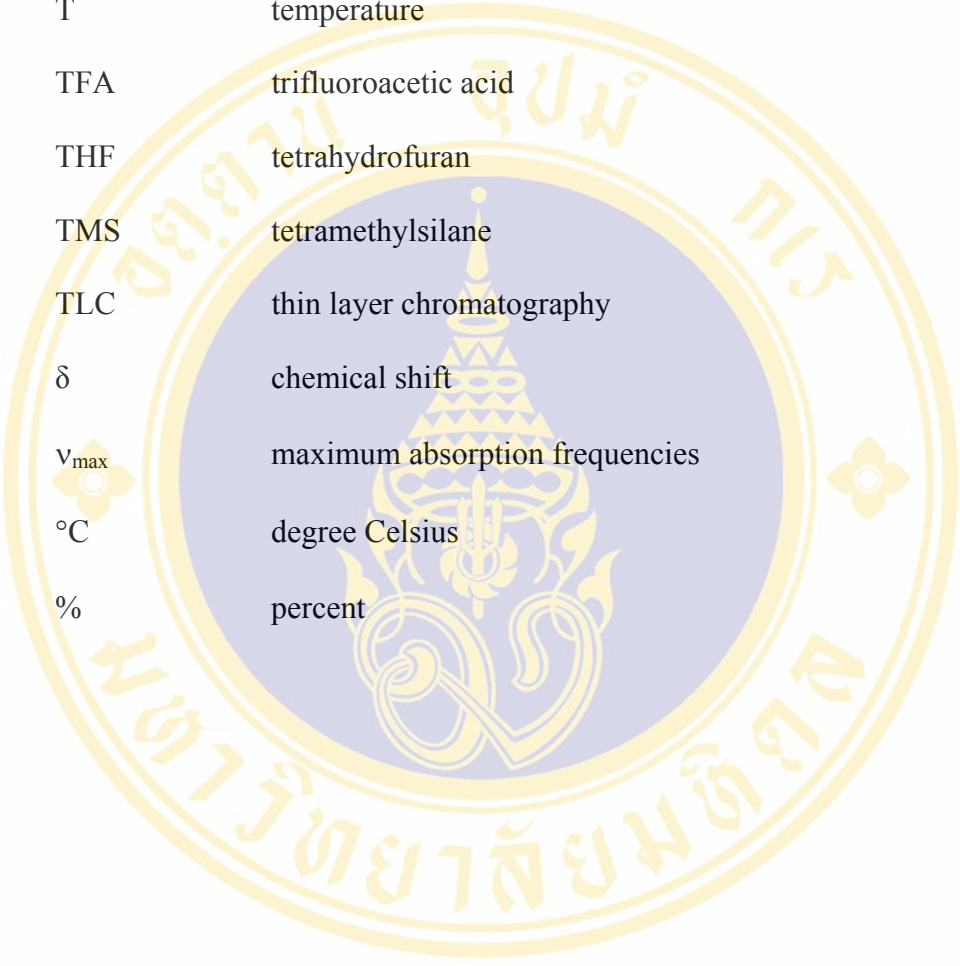
## LIST OF ABBREVIATIONS



Ac	acetyl
Ar	aryl
Bn	benzyl
br	broad
calcd.	calculated
CDCl <sub>3</sub>	deuteriochloroform
conc. or c	concentration
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
DMD	dimethyldioxirane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalent
<i>ee</i>	enantiomeric excess
EtOAc	ethyl acetate
Et <sub>3</sub> N	triethylamine
g	gram
h	hour (s)
Hz	hertz
HRMS	high resolution mass spectrometry

**LIST OF ABBREVIATIONS (Cont.)**

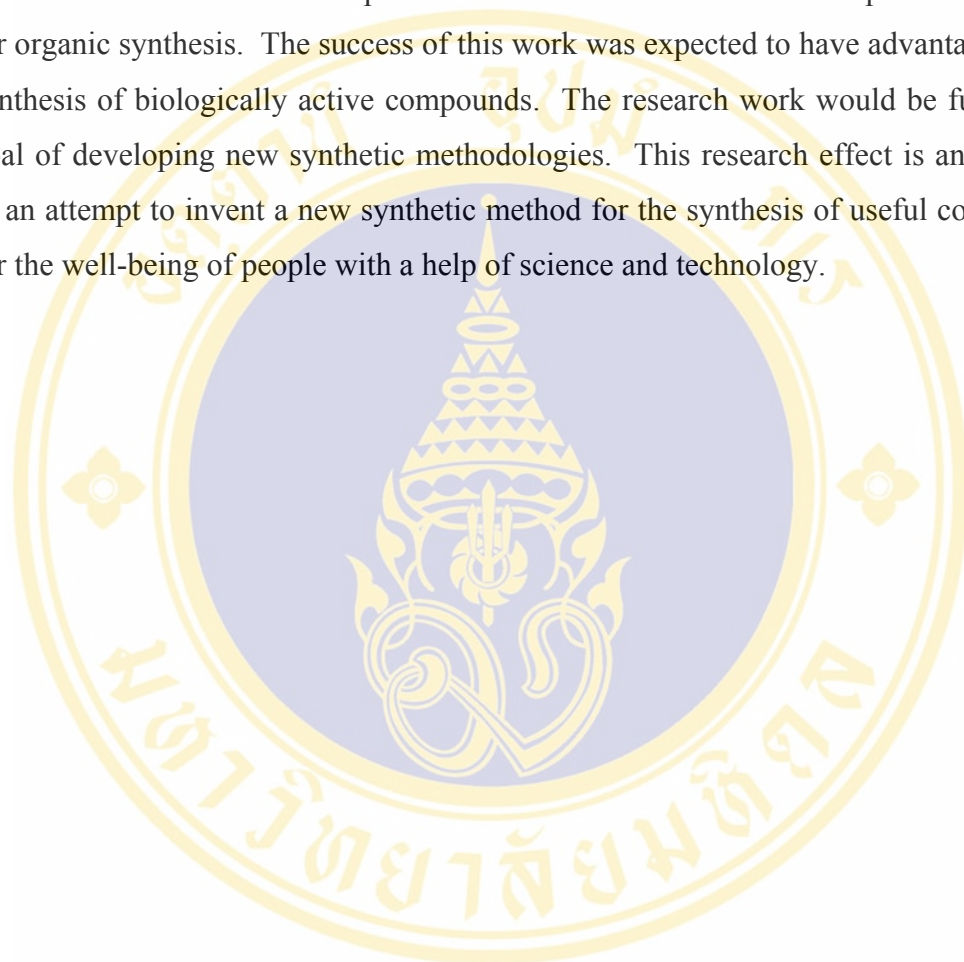
IR	infrared spectrum
J	coupling constant
LAH	lithium aluminium hydride
Lit.	literature
m	multiplet
min	minute (s)
mg	milligram
mL	milliliter
$\mu\text{mol}$	micromole
mmol	millimole
m/z	a value of mass divided by charge
$M^+$	molecular ion
m.p.	melting point
MeOH	methanol
Me	methyl
NMR	nuclear magnetic resonance
ppm	part per million
Ph	phenyl
q	quartet
ref.	reference
rt	room temperature
s	singlet

**LIST OF ABBREVIATIONS (Cont.)**

t	triplet
T	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	tetramethylsilane
TLC	thin layer chromatography
$\delta$	chemical shift
$\nu_{\max}$	maximum absorption frequencies
$^{\circ}\text{C}$	degree Celsius
%	percent

## THE RELEVANCE OF THE RESEARCH WORK TO THAILAND

The research work is a part of the basic research on the development of method for organic synthesis. The success of this work was expected to have advantage on the synthesis of biologically active compounds. The research work would be further the goal of developing new synthetic methodologies. This research effect is an example of an attempt to invent a new synthetic method for the synthesis of useful compounds for the well-being of people with a help of science and technology.





## CHAPTER I

### INTRODUCTION

Enantiomerically enriched secondary alcohols are important as intermediates and chiral auxiliaries in organic synthesis and are found in a number of natural products and pharmaceuticals. As a consequence, practical access to obtain enantiomerically enriched secondary alcohols is still of interest to many chemists. Among current methodologies developed for this purpose, kinetic resolution of racemic secondary alcohols is preferably attractive. The kinetic resolution of secondary alcohols have previously been accomplished through a number of strategies, i.e. the epoxidation of allylic alcohols,<sup>1</sup> oxidative methods,<sup>2</sup> acylation<sup>3</sup> and Mitsunobu strategies.<sup>4</sup>

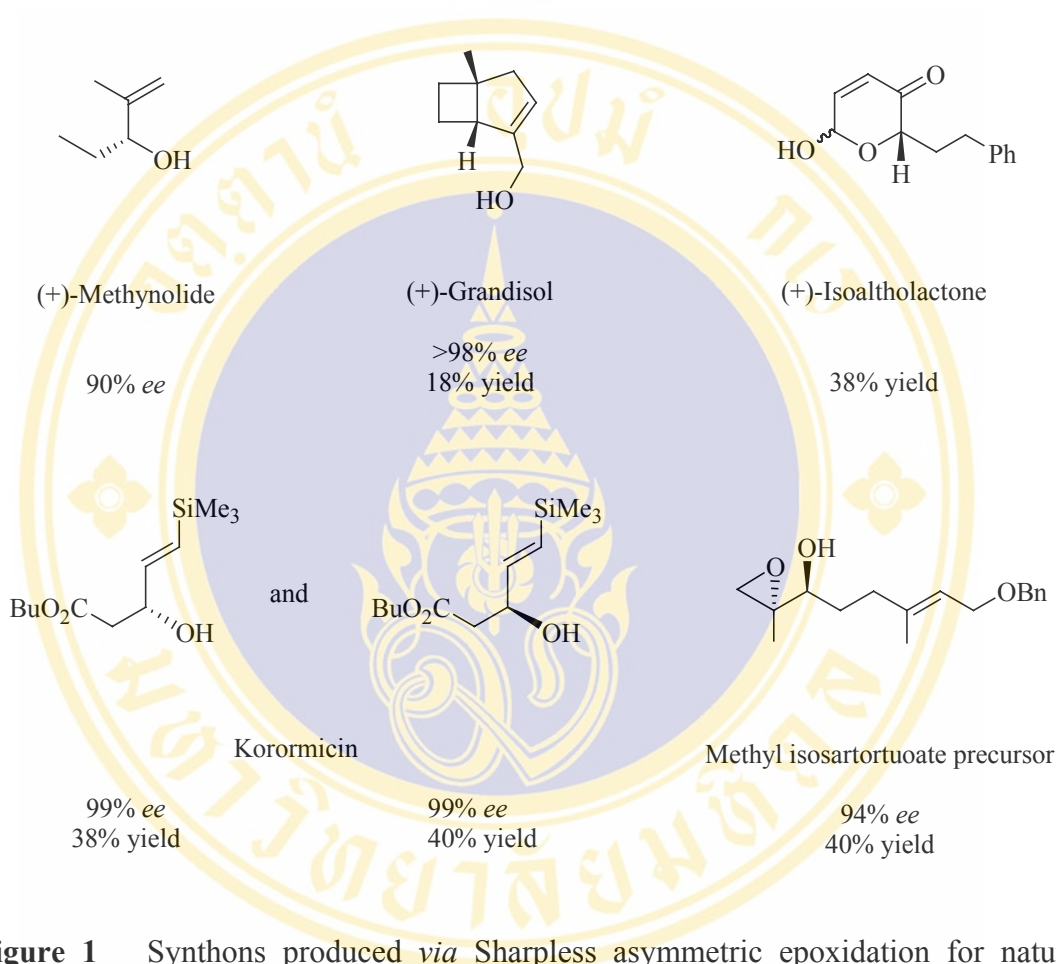
The seminal protocol for the catalytic kinetic resolution of allylic alcohols first reported by Sharpless et al. in 1981 (Scheme 1)<sup>1a</sup> continues to find favor amongst synthetic chemists for the preparation of a wide range of chiral synthons directed towards the synthesis of chiral drugs;<sup>5</sup> as substrates for new synthetic methodology; or for natural product synthesis.



DIPT = Diisopropyltartrate

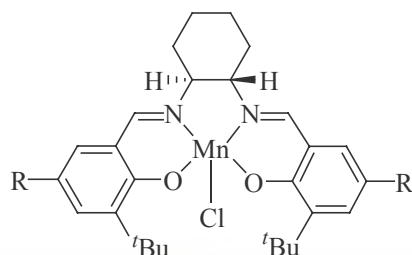
**Scheme 1** Kinetic resolution of racemic allylic alcohols using Sharpless asymmetric epoxidation.

A range of non-racemic chiral allylic alcohols or epoxides have been prepared using asymmetric epoxidation methodology as synthons for the asymmetric synthesis of a wide range of natural products such as (+)-grandisol,<sup>6</sup> korormicin,<sup>7</sup> (+)-isoalthalactone,<sup>8</sup> (+)-methynolide,<sup>9</sup> and methyl isosartortuoate<sup>10</sup> (Figure 1).



**Figure 1** Synthons produced *via* Sharpless asymmetric epoxidation for natural product synthesis.

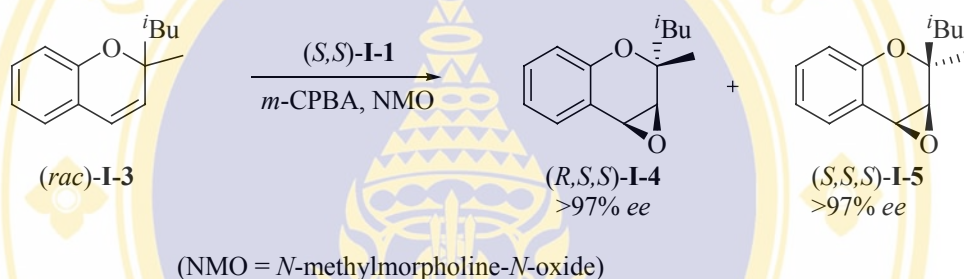
In 1995, Jacobson et al. reported the first example of a catalytic kinetic resolution using (salen)-Mn catalyst (*S,S*)-**I-1** (Figure 2), *m*-CPBA and *N*-methyl morpholine-*N*-oxide for the stereoselective epoxidation of 2,2-dialkylchromene (*rac*)-**I-3** with a modest *s* value of 3.1 to afford the two diastereoisomeric epoxychroman products, (*R,S,S*)-**I-4** and (*S,S,S*)-**I-5** both in greater than 97% ee (Scheme 2).<sup>11</sup>



(*S,S*)-**I-1**: R=OSi<sup>*i*</sup>Pr<sub>3</sub>

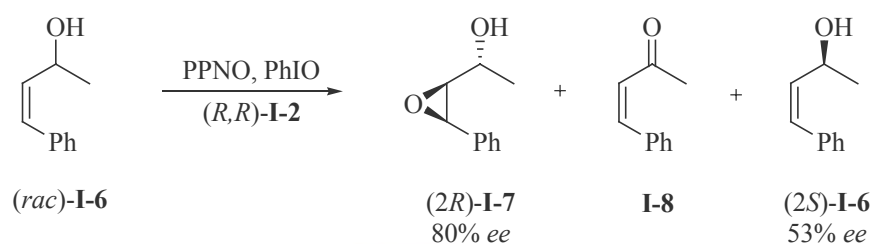
(*S,S*)-**I-2**: R=OMe

**Figure 2**



**Scheme 2**

This Mn-salen complex mediated epoxidation resolution was later successfully applied to the kinetic resolution of 1,2-dihydronaphthalenes for the synthesis of lignans,<sup>12</sup> while Adam et al. have recently applied it to the kinetic resolution of aryl-substituted allylic alcohols.<sup>1b</sup> For example, *cis*-allylic alcohol (*rac*)-**I-6** was resolved using catalyst (*R,R*)-**I-2**, and the (*R*)-enantiomer was preferentially epoxidized to give the *threo* or *cis*-epoxy alcohol (*2R*)-**I-7** in 80% *ee*, while the unreacted enantiomer (*S*)-**I-6** was recovered in 53% *ee* (Scheme 3). A small amount of the over-oxidation product enone **I-8** was also obtained in a ratio of (*2R*)-**I-7**:**I-8** of 95:5.

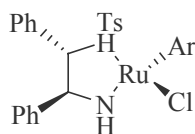


Scheme 3

A large number of kinetic resolution strategies that rely on the use of chiral catalysts for the enantioselective oxidation of one enantiomer of a racemic secondary alcohol to its corresponding ketone have been reported to date.<sup>13</sup>

Since Noyori's seminal report in 1997 on reversible catalytic asymmetric transfer hydrogenation for asymmetric catalysis, the use of chiral diamine Ru(II) complexes to transfer hydride from a racemic alcohol substrate to acetone has been widely used as a method for the kinetic resolution of secondary alcohols.<sup>14</sup>

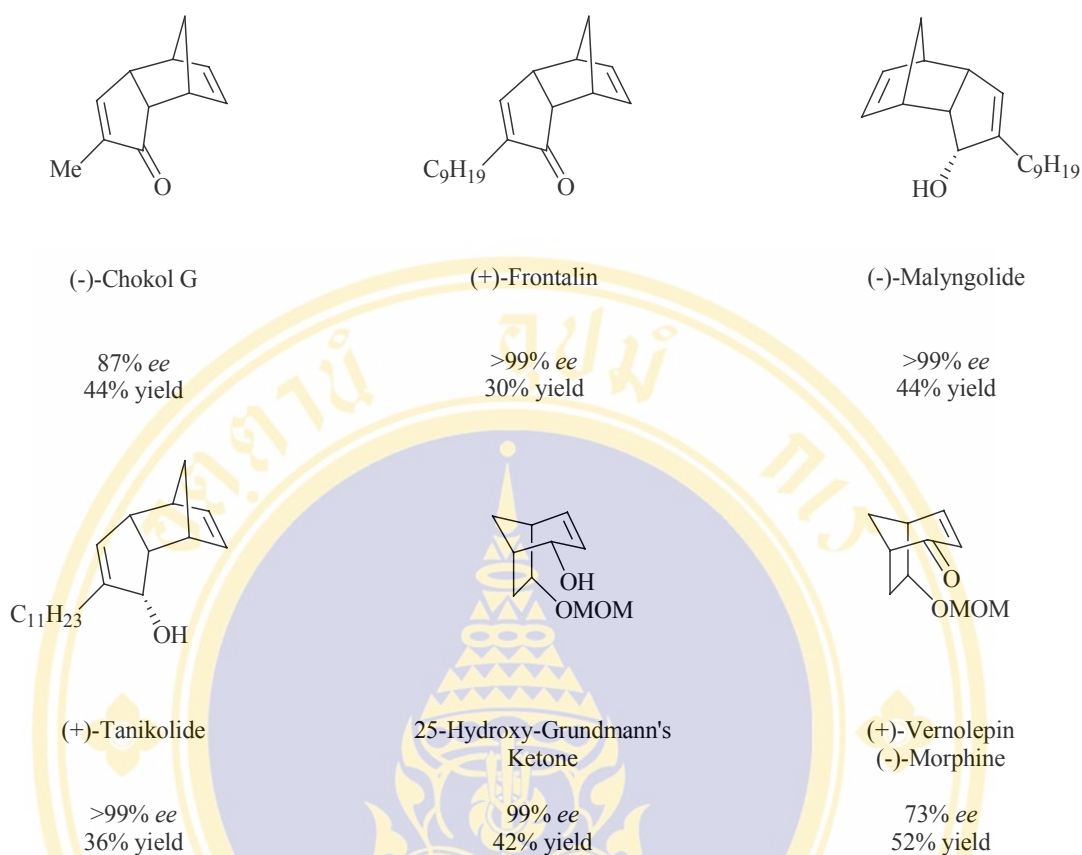
For example, Ogasawara et al. have employed complexes (*S,S*)-**I-9** or (*S,S*)-**I-10** (Figure 3) for kinetic resolution of a range of cyclic allylic alcohols in good *ee*, which were subsequently used as synthons for the asymmetric synthesis of a wide range of natural products including (-)-chokol G,<sup>15</sup> (+)-frontalin and (-)-malyngolide,<sup>16</sup> (+)-tanikolide,<sup>17</sup> (-)-morphine,<sup>18</sup> 25-hydroxy-grundmann's ketone<sup>19</sup> and (+)-vernolepin<sup>20</sup> (Figure 4).



(*S,S*)-**I-9**: Ar =  $\eta^6$ -mesitylene

(*S,S*)-**I-10**: Ar =  $\eta^6$ -cymene

Figure 3



**Figure 4** Synthons resolved for natural product synthesis *via* enantioselective oxidation using **I-9** or **I-10**.

In 2001, Sigman et al. and Stoltz et al. independently reported a Pd(II)-catalyzed oxidative kinetic resolution of the combined total of nine different secondary racemic aryl alcohols using (-)-sparteine **I-11** (Figure 5) as a chiral ligand using molecular oxygen as the terminal oxidant (Scheme 4).<sup>2a, 2b</sup> In a representative example, Sigman et al. used Pd(OAc)<sub>2</sub> as a palladium source, which gave unreacted alcohol (*S*)-**I-12** in 96% *ee*,<sup>2a</sup> while Stoltz et al. found that the alternative use of Pd(nbd)Cl<sub>2</sub> resulted in the *ee* of the recovered alcohol (*S*)-**I-12** being increased to 99%.<sup>2c</sup>

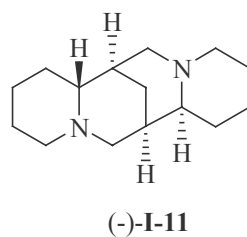
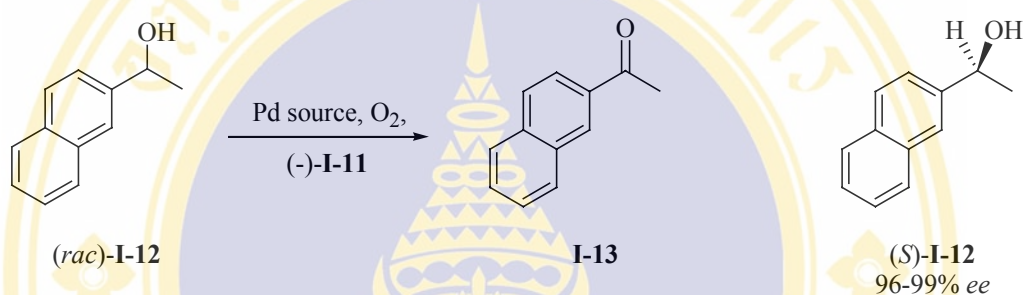
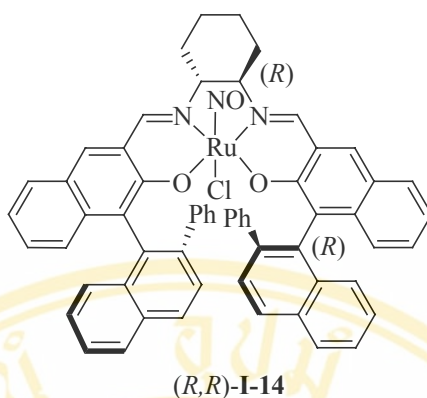
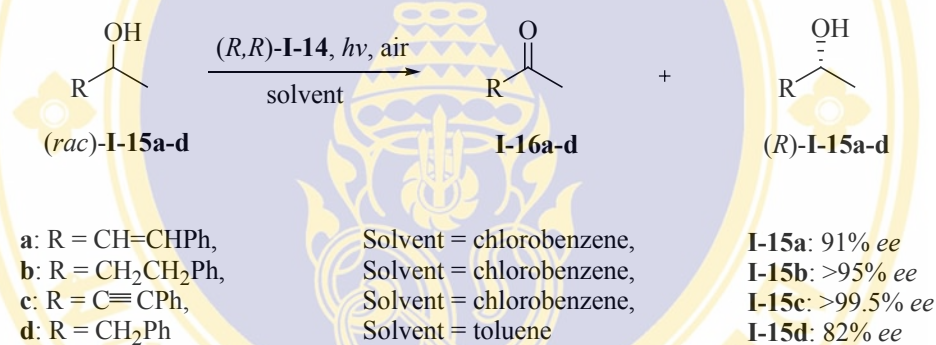


Figure 5



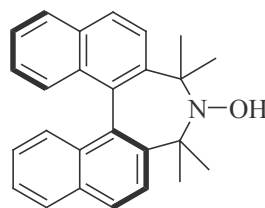
**Scheme 4** Kinetic resolution of secondary alcohols *via* Pd(II)-catalyzed oxidation.

An alternative approach to O<sub>2</sub>-mediated oxidative kinetic resolution has been disclosed by Katsuki et al. who employed chiral (nitroso)-salen-Ru complexes for stereoselective oxidation of a range of secondary alcohols under photolytic conditions. Thus, photolysis of a solution of alcohols (*rac*)-**I-15a-d** in aromatic solvents, in the presence of catalyst (*R,R*)-**I-14** (Figure 6) under aerobic conditions, resulted in efficient kinetic resolution to afford ketones **I-16a-d** and recovered alcohols (*R*)-**I-15a-d** in 82 to 99% *ee* (Scheme 5).<sup>2d</sup>

**Figure 6**

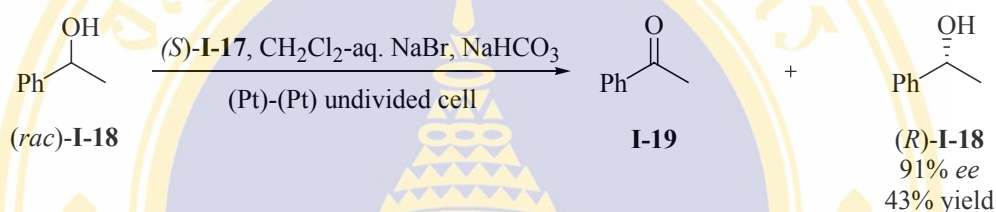
**Scheme 5** Kinetic resolution of secondary alcohols (*rac*)-**I-15a-d** catalysed by (*R,R*)-**I-14**.

Tanaka et al. reported the kinetic resolution of six racemic secondary aryl alcohols via electrochemical oxidation.<sup>2e</sup> This approach involved electro-oxidation in a presence of catalytic amount of an enantiomerically pure binaphthyl-*tert-N*-hydroxylamine (*S*)-**I-17** (Figure 7) and was performed using a single undivided cell under constant current. For example, electro-oxidation of 1-phenyl-1-ethanol (*rac*)-**I-18** proceeded to give acetophenone **I-19** in 57% yield and unreacted alcohol (*R*)-**I-18** in 91% *ee* and 43% yield (Scheme 6).



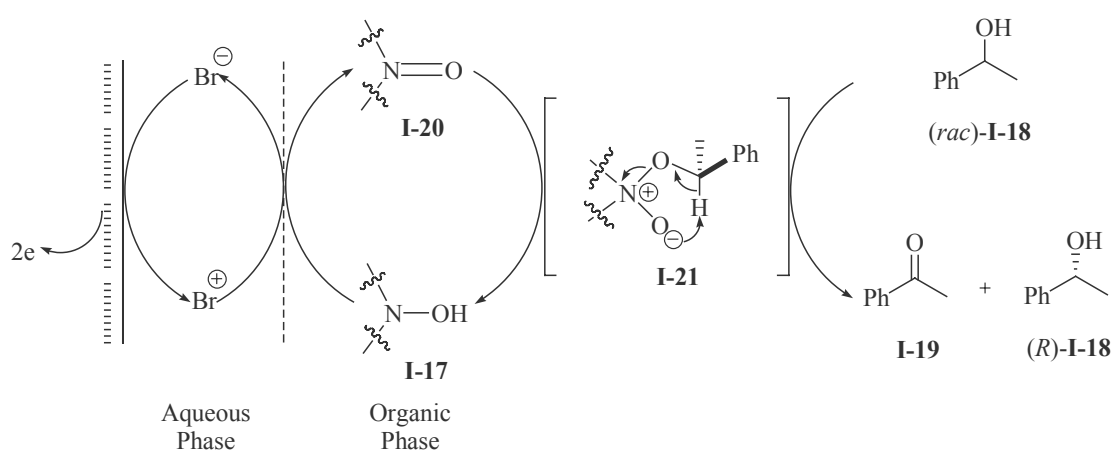
(S)-I-17

Figure 7



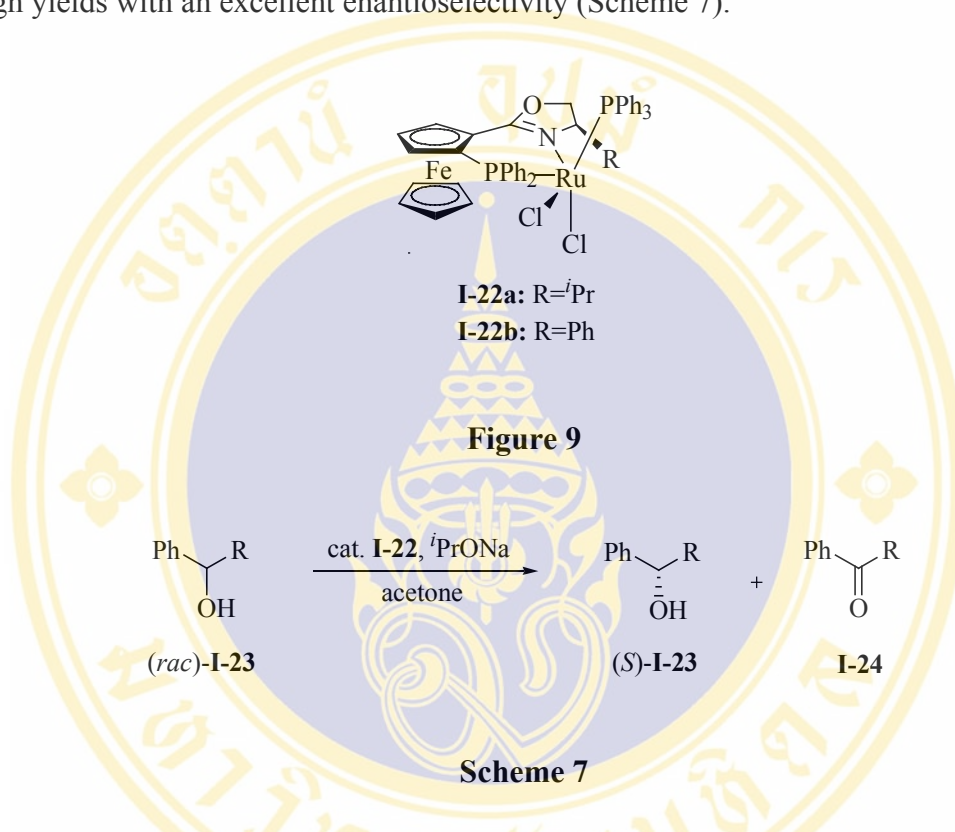
**Scheme 6** Kinetic resolution of (*rac*)-I-18 via electro-oxidation in the presence of catalyst (S)-I-17.

The oxidative catalytic cycle proposed for this kinetic resolution is described in Figure 8, in which catalyst (S)-I-17 is oxidized electrochemically to afford I-20, which then preferentially reacts with one enantiomer of 1-phenyl-1-ethanol (S)-I-18 to afford adduct I-21, that then decomposes *via* a cyclic transition state regenerating I-17, thus affording acetophenone I-19 and recovered 1-phenyl-1-ethanol (R)-I-18.



**Figure 8** The electro-oxidative cycle for the kinetic resolution of (*rac*)-I-18.

In 2003, Uemura and co-workers reported the oxidative kinetic resolution of a variety of racemic aryl alcohols using acetone as a hydrogen acceptor in the presence of a catalytic amount of  $[\text{RuCl}_2(\text{PPh}_3)(\text{ferrocenyloxazolinylphosphine})]$  (**I-22**) (Figure 9). The reaction proceeded quite effectively to recover the corresponding alcohols in high yields with an excellent enantioselectivity (Scheme 7).<sup>2f</sup>



Recently, Xia and co-workers found that Mn(salen) complexes (Figure 10) were effective catalysts for the oxidation of secondary alcohols to ketones in the presence of the cooxidant diacetoxyiodobenzene ( $\text{PhI}(\text{OAc})_2$ ) (Scheme 8).<sup>2g</sup> Water can be used successfully as a benign solvent in this reaction system. The use of water makes this reaction more significant in terms of potential industrial application.

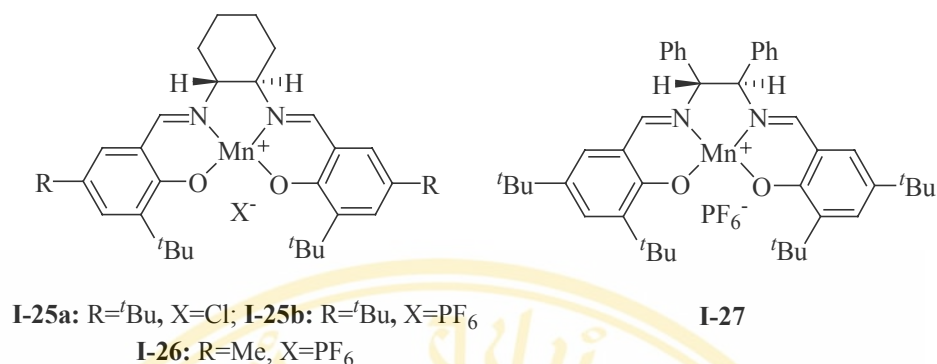
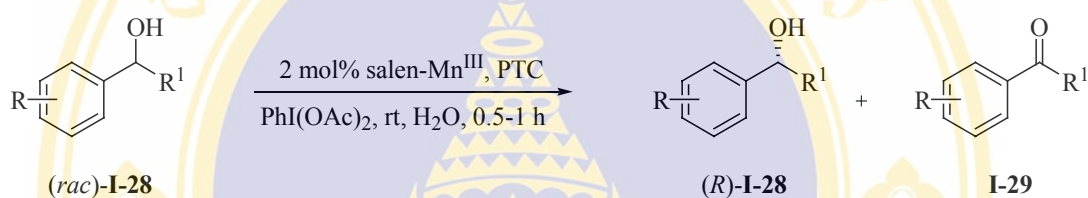
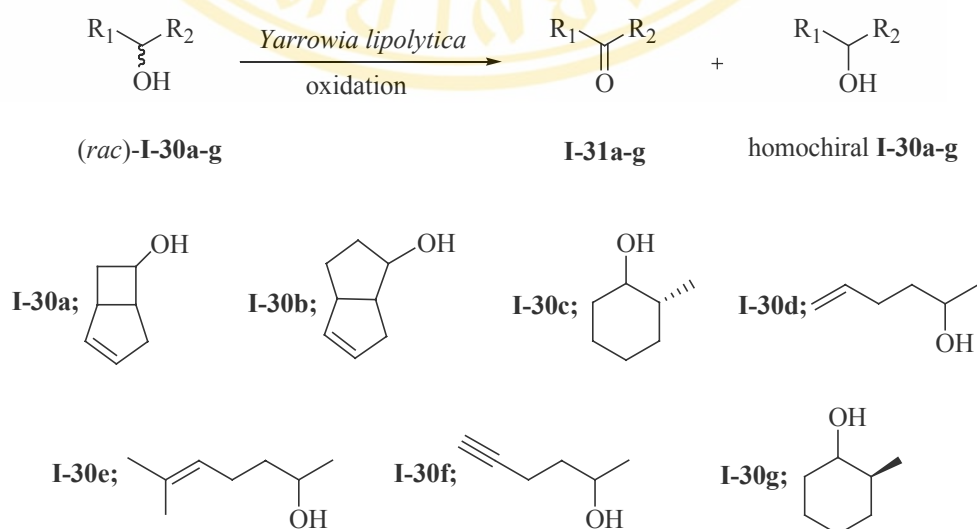


Figure 10



Scheme 8

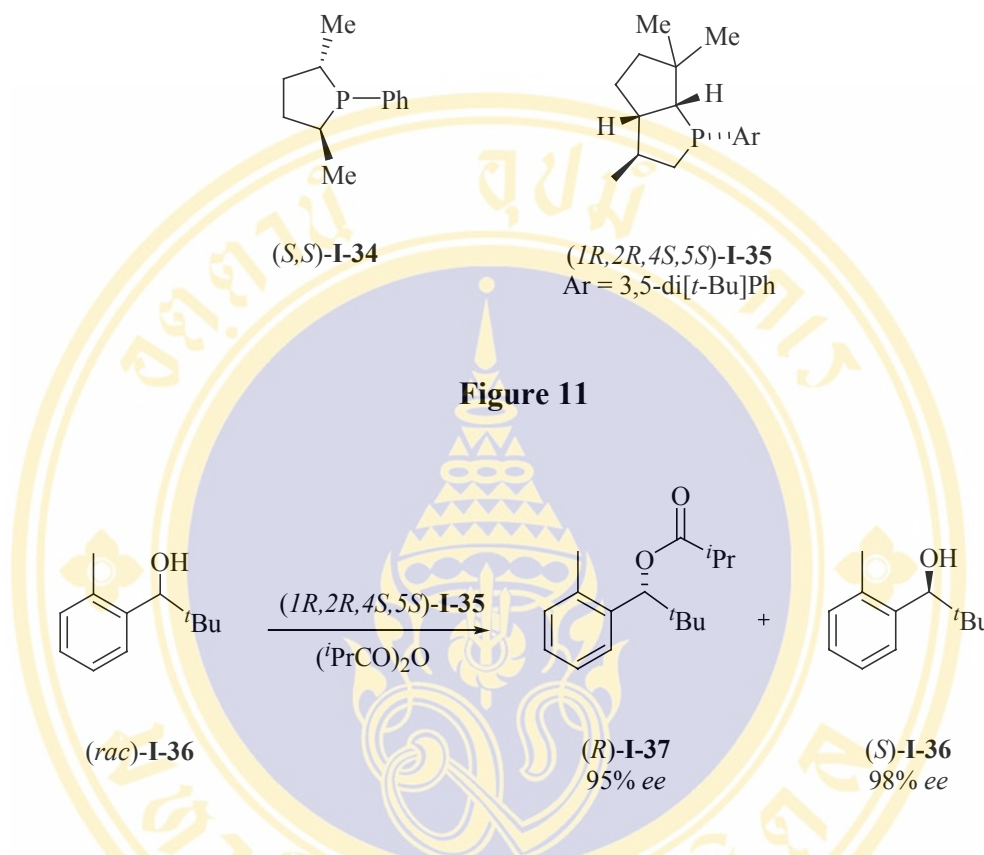
In 2000, Pedrini and co-workers reported a kinetic resolution of various cyclic and acyclic alcohols *via* oxidation with *Yarrowia lipolytica* strains (Scheme 9).<sup>2h</sup> These microorganisms are yeasts, distributed over a wide range of food systems.



Scheme 9

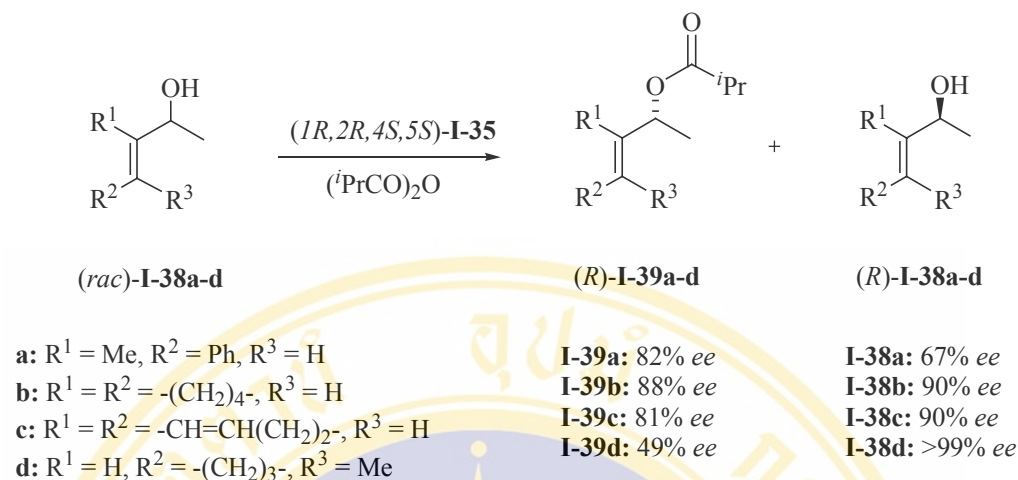


shown to resolve 1-(*o*-methylphenyl)ethanol (*rac*)-**I-36** to afford unreacted alcohol (*S*)-**I-36** in 98% *ee* and ester (*R*)-**I-37** in 95% *ee* at 51% conversion (Scheme 12).<sup>3b</sup>



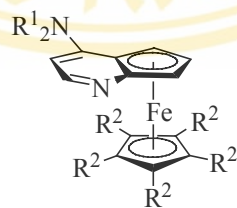
**Scheme 12** Kinetic resolution of (*rac*)-**I-36** with isobutyric anhydride and **I-35**.

The scope of this type of phosphine catalysts was subsequently demonstrated for the kinetic resolution of a small library of twelve allylic alcohols (*rac*)-**I-38a-d**, typically affording isobutyryl esters (*R*)-**I-39a-d** and unreacted alcohols (*S*)-**I-38a-d** in satisfactory to excellent *ee* (Scheme 13).<sup>3c</sup>



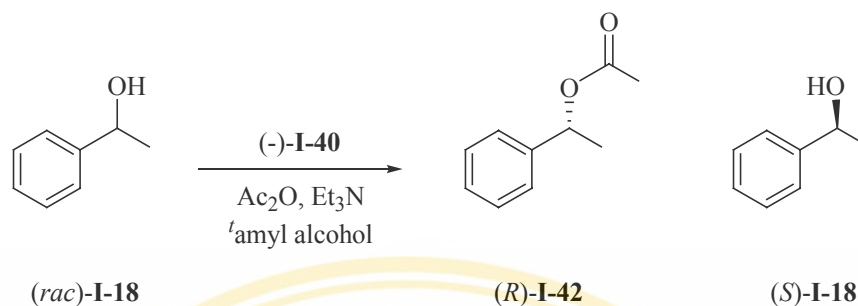
**Scheme 13** Kinetic resolution of allylic alcohols (*rac*)-**I-38a-d** with isobutyric anhydride and **I-35**.

The versatile ferrocene derived acyl transfer catalysts (-)-**I-40** and (-)-**I-41** (Figure 12) described by Fu et al. remain one of the most effective systems for the kinetic resolution of a wide range of racemic arylalkyl carbinols, including 1-phenyl-1-ethanol (*rac*)-**I-18** which gave ester (*R*)-**I-42** in 90% *ee* and unreacted alcohol (*S*)-**I-18** in 99% *ee*. (Scheme 14).<sup>3d</sup> These catalyst systems have recently been employed for the resolution of a series of racemic allylic alcohols to afford a wide range of structurally diverse chiral allylic alcohols such as (*R*)-**I-38a** in greater than 90% *ee*.<sup>3e</sup>



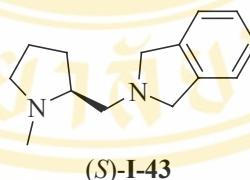
(-)-**I-40**: NR<sup>1</sup><sub>2</sub> = NMe<sub>2</sub>, R<sup>2</sup> = Ph  
 (-)-**I-41**: NR<sup>1</sup><sub>2</sub> = pyrrolidino, R<sup>2</sup> = Me

**Figure 12**

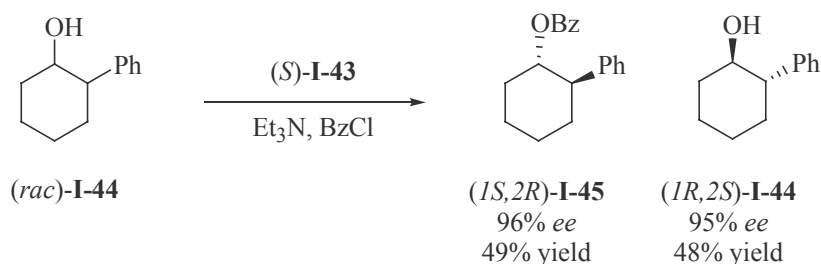


**Scheme 14** Kinetic resolution of  $(rac)\text{-I-18}$  with acetic anhydride and catalyst  $(-)\text{-I-40}$ .

In 1999, Oriyama et al. reported an alternative method for kinetic resolution of a wide range of cyclic racemic alcohols,<sup>3f</sup> involving treatment of benzoyl chloride in the presence of 0.3 mol% of chiral diamine  $(S)\text{-I-43}$  (Figure 13). Under these conditions benzoate ester  $(1S,2R)\text{-I-45}$  was formed in 96% *ee* and 49% yield, whilst the unreacted alcohol  $(1R,2S)\text{-I-44}$  was recovered in 95% *ee* and 48% yield (Scheme 15). This system has subsequently been employed for the kinetic resolution of cyclic racemic  $\beta$ -halohydrins to afford the corresponding benzoate esters and recovered alcohols in fair to excellent *ee*.<sup>3g</sup>



**Figure 13**



**Scheme 15**

This type of proline-based diamine has also been immobilized onto poly (ethylene glycol) (PEG) supports and was used as recyclable acylation catalysts for the kinetic resolution of a range of racemic secondary alcohols with *s* values similar to those obtained using the soluble catalyst (*S*)-**I-43**.<sup>3h</sup> This class of acyl transfer catalyst has also been attached to soluble polymer supports with JandaJel supported catalyst **I-46** (Figure 14), affording benzoate ester (*1S,2R*)-**I-45** in 96% *ee* and unreacted alcohol (*1R,2S*)-**I-44** in 85% *ee*.

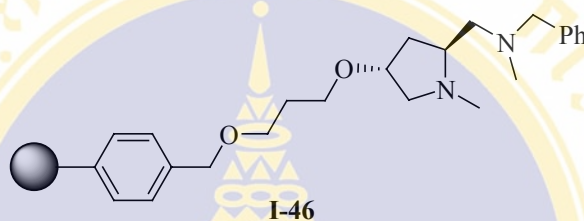


Figure 14

Another class of chiral dimethylaminopyridine like catalyst (+)-**I-47** (Figure 15) has been reported for the kinetic resolution of cyclic *N*-acyl- $\beta$ -amino alcohols (*rac*)-**I-48a-c** leading to esters (*1S,2R*)-**I-49a-c** as major products and (*1R,2S*)-**I-48a-c** in very high *ee* (Scheme 16).<sup>3i</sup> Thus, at relatively high conversions, excellent enantioselectivities were obtained for recovered five-, six- and seven-membered *cis-N*-acyl- $\beta$ -amino alcohols (*1R,2S*)-**I-48a-c**, respectively. Although the selectivity observed for acyclic  $\beta$ -amino alcohols was generally poor, *anti*- $\beta$ -amino alcohol (*rac*)-**I-50** was shown to be enantioselectively acylated to afford ester (*R,R*)-**I-51**, enabling *N*-acyl- $\beta$ -amino alcohol (*S,S*)-**I-50** to be recovered in 93% *ee* at 70% conversion (Scheme 17).<sup>3j</sup>

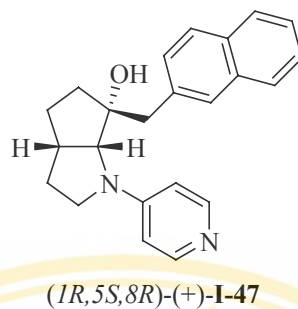
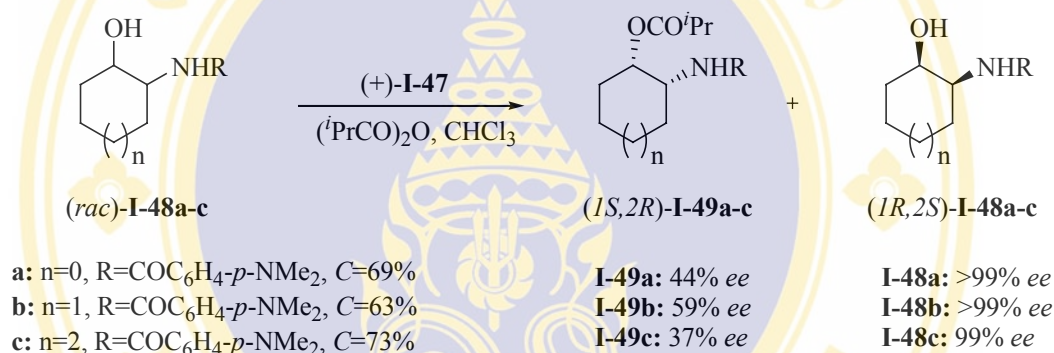
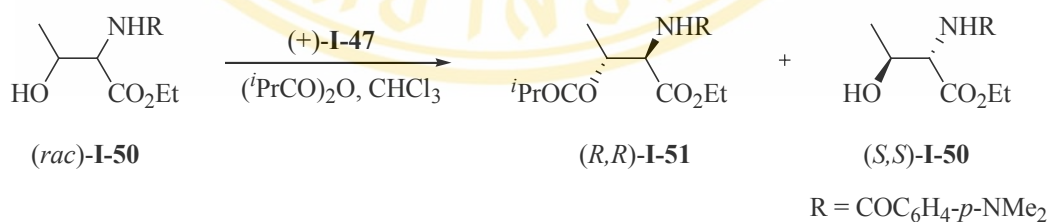


Figure 15



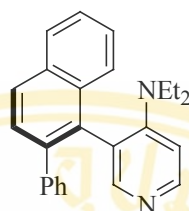
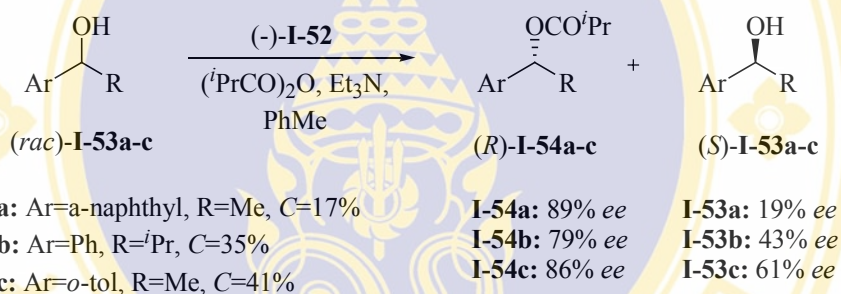
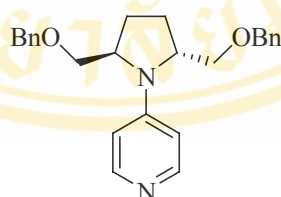
Scheme 16



Scheme 17

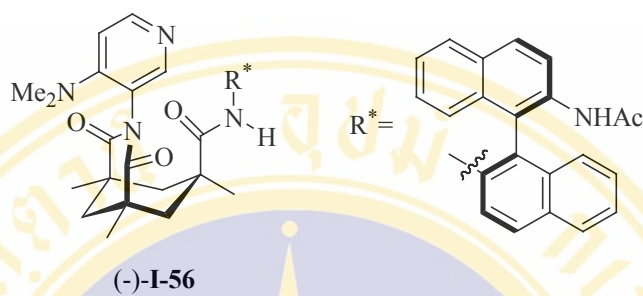
Spivey et al. have explored the use of axially chiral analogues of 4-dimethylaminopyridine, atropisomeric biaryl diamine (-)-**I-52** (Figure 16). It proved to be a successful catalyst for the resolution of aryl alcohols *(rac)*-**I-53a-c** affording esters *(R)*-**I-54a-c** in moderate to good *ee* at low conversion (Scheme 18).<sup>3k</sup> The use

of  $C_2$ -symmetric analogues of 4-(pyrrolidino)-pyridine ( $R,R$ )-**I-55** for related kinetic resolutions proved to be less successful (Figure 17).<sup>31</sup>

(-)-**I-52****Figure 16****Scheme 18** $(R,R)$ -**I-55****Figure 17**

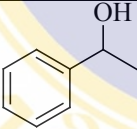
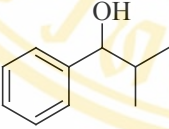
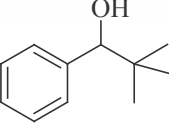
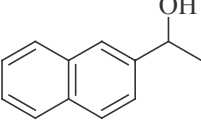
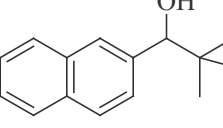
Jeong et al. have reported a new tertiary amine based nucleophilic DMAP analogue (-)-**I-56** (Figure 18) that gives good to excellent results for the resolution of racemic alkylarylcabinols.<sup>3m</sup> It was found that the *s* values for this catalyst increased as the steric bulk of alkyl group of the alcohol substrate increased, with the best result

being obtained for acylation of racemic *trans*-2-phenylcyclohexanol (Table 1, entry 6) which proceeded with  $s = 21$  giving recovered (*1S,2R*)-alcohol in 99% *ee* and the (*1R,2S*)-ester product in 62% *ee*.

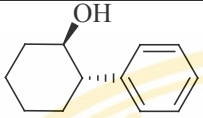


**Figure 18**

**Table 1** Kinetic resolution of racemic secondary alcohols with catalyst (-)-I-56.

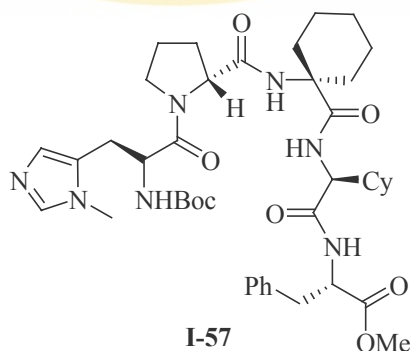
Entry	Substrate	<i>C</i> (%)	<i>ee</i> (%)		<i>s</i>
			( <i>S</i> )-Alcohol	( <i>R</i> )-Ester	
1		70	79	34	4.4
2		77	99	31	8.1
3		59	90	64	13.3
4		72	98	38	8.3
5		63	95	57	12.4

**Table 1.** Kinetic resolution of racemic secondary alcohols with catalyst (-)-**I-56**.  
(Cont.)

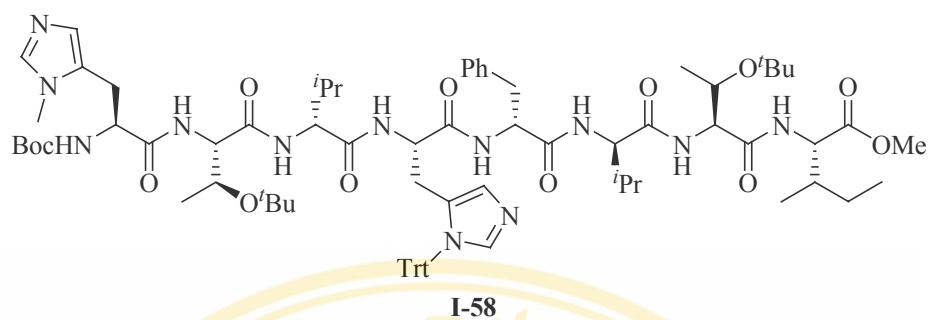
Entry	Substrate	C (%)	ee (%)		s
			(S)-Alcohol	(R)-Ester	
6	 (trans)	62	99 (1S,2R)	62 (1R,2S)	21.0

$s$  = the selectivity factor which was calculated from the equation:  $s = k_{rel(fast/slow)} = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)]$ , where  $C$  = conversion.

Miller et al. have employed an alternative biomimetic approach to the identification of enantioselective *O*-acylation catalysts based on  $\beta$ -turn peptide fragments with defined secondary structures that contain nucleophilic *N*-alkyl-imidazole residues.<sup>21</sup> Initial work was directed towards the kinetic resolution of racemic *N*-acyl-1,2-aminoalcohols which were chosen due to their ability to hydrogen bond to a chiral peptide catalyst **I-57** (Figure 19) that contained a D-Pro residue known to induce  $\beta$ -turns into peptide backbones.<sup>22</sup> Subsequent application of the full power of combinatorial synthesis for the preparation of 1<sup>st</sup> and 2<sup>nd</sup> generation libraries that contained over 100,000 and 600 peptide catalysts, respectively, resulted in the identification of octapeptide **I-58** (Figure 20) that catalyzed the resolution of more conventional secondary alcohol substrates in excellent *ee* (Table 2).<sup>3n</sup>



**Figure 19**

**Figure 20****Table 2** Kinetic resolutions of racemic secondary alcohols catalyzed by peptide I-58.

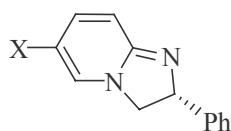
Entry	( <i>rac</i> )-Substrate	Acylated product	$k_{rel}$
1			20
2			>50
3			16
4			11
5			>50
6			30



**Table 3** Kinetic resolution of secondary alcohols (*rac*)-**I-18**, **I-60a-d** catalyzed by (*S,S*)-**I-59** via acylation with isopropenyl acetate.

Alcohol	C (%)	<i>ee</i> (%) of recovered alcohol
<b>I-18</b>	65	23 ( <i>S</i> )
<b>I-60a</b>	39	14 ( <i>R</i> )
<b>I-60b</b>	76	91 ( <i>R</i> )
<b>I-60c</b>	61	36 ( <i>S</i> )
<b>I-60d</b>	42	13 ( <i>S</i> )

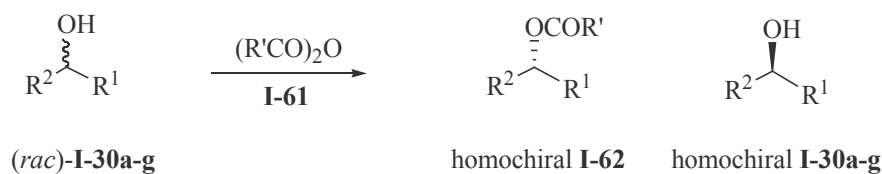
A number of nonenzymatic chiral catalysts were developed which, in some cases, exhibit practically useful levels of enantioselectivity. However, their preparation is typically difficult, often requiring multistep sequences and resolution of racemates. Recently, Birman et al. have set out to develop a new class of asymmetric acyl transfer catalysts, (*R*)-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridines (PIP, **I-61a-d**) (Figure 22), that would be both effective and easily accessible, to use in the kinetic resolution of secondary alcohols (Scheme 18).<sup>3p</sup>



PIP derivatives

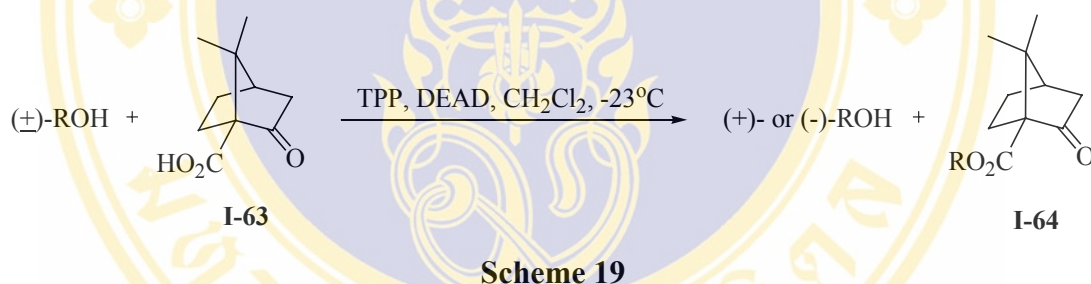
- I-61a**, X = H
- I-61b**, X = Br
- I-61c**, X = NO<sub>2</sub>
- I-61d**, X = CF<sub>3</sub>

**Figure 22**

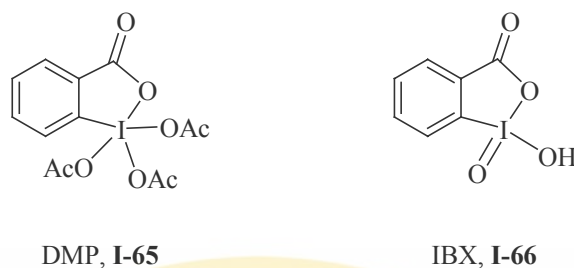


**Scheme 18** Kinetic resolution of secondary alcohols catalyzed by PIP derivatives.

Recently, there is a new process of kinetic resolution with concomitant chirality inversion which has been designed and demonstrated by Chandrasekhar and Kulkarni. The process defines a chiral version of the well-known Mitsunobu reaction, employing the readily accessible (*1S*)-(+)-ketopinonic acid (**I-63**) as a chiral auxiliary, and affords various secondary alcohols in excellent yields and enantiomeric excesses (Scheme 19).<sup>4</sup>

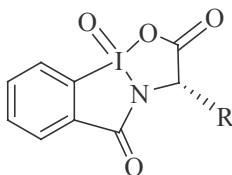


Hypervalent iodine reagents<sup>23</sup> have attracted increasing interest during the last decade because of their selective, mild and environmentally friendly properties as oxidizing agents in organic synthesis. The Dess-Martin periodinane (DMP, **I-65**)<sup>24</sup> as well as its precursor, 2-iodoxybenzoic acid (IBX, **I-66**)<sup>25</sup>, have emerged as the reagents of choice for the oxidation of alcohols to carbonyl compounds and for other synthetically useful oxidative transformations.

**Figure 23**

Dess-Martin reagent **I-65** is particularly useful in natural product synthesis as a mild, selective oxidizer soluble in dichloromethane, chloroform or acetonitrile. Reagent **I-66** is a cheaper alternative to Dess-Martin reagent, however, its practical application is limited due to the potentially explosive nature and insolubility in common solvents. Despite these limitations, IBX **I-66** was shown to be particularly useful as the reagent for a highly selective oxidation of alcohols to carbonyl compound in DMSO.<sup>26</sup>

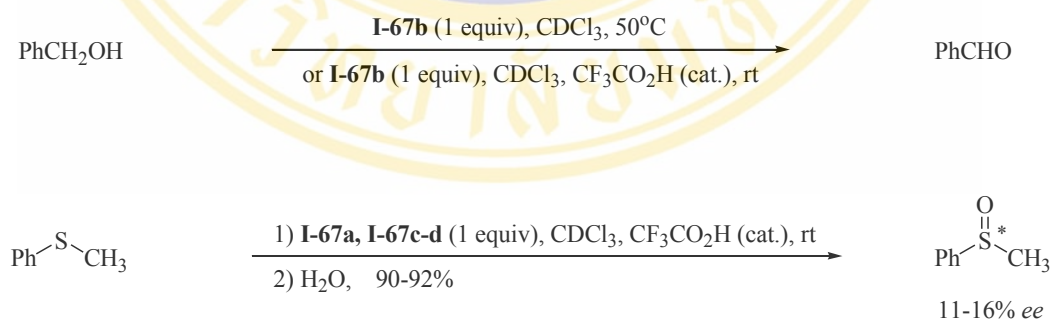
In 2000, Zhdankin et al. reported the preparation of chiral non-racemic amino acid-derived benziodazole oxides (**I-67a-d**) (Figure 24).<sup>27</sup> In contrast to the analogous benziodoxole oxide (IBX, **I-66**), benziodazole oxides **I-67** are non-explosive and are soluble in dichloromethane and other common non-polar organic solvents. These benziodazole oxides **I-67** can be conveniently prepared by oxidation of the readily available *N*-(2-iodobenzoyl)- $\alpha$ -amino acids or esters with potassium bromate or OXONE<sup>®</sup> (2KHSO<sub>5</sub>/KHSO<sub>4</sub>/K<sub>2</sub>SO<sub>4</sub>). They demonstrated that benziodazole oxides and their derivatives could find practical application as selective, chiral oxidizing reagents in organic synthesis.



**I-67a-d;** a, R = CH<sub>3</sub>  
 b, R = CH<sub>2</sub>Ph  
 c, R = CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>  
 d, R = CH<sub>2</sub>(CH<sub>3</sub>)<sub>2</sub>

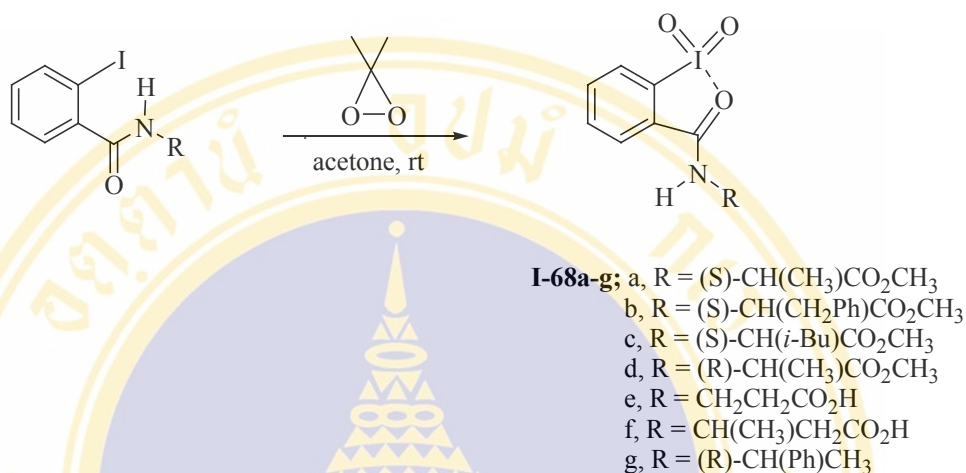
**Figure 24**

Preliminary results indicated that compounds **I-67a-d** can selectively oxidize primary alcohols to aldehydes. For example, compound **I-67b** can react with benzyl alcohol in chloroform at 50 °C or at room temperature in the presence of a catalytic amount of trifluoroacetic acid affording benzaldehyde as the only product detected by <sup>1</sup>H NMR.<sup>27</sup> Moreover, compounds **I-67a** and **I-67d-c** can oxidize methyl phenyl sulfide to give enantiomerically enriched methyl phenyl sulfoxide (90-92%, 11-16% *ee*) in deuteriochloroform at room temperature in the presence of a catalytic amount of trifluoroacetic acid (Scheme 20).<sup>27</sup>



**Scheme 20**

Recently, chiral non-racemic 2-iodoxybenzamides or IBX-amides (**I-68a-g**) have been prepared by dioxirane oxidation of the readily available 2-iodobenzamides (Scheme 21).<sup>28</sup>



**Scheme 21** The preparation of chiral non-racemic 2-iodoxybenzamides (IBX-amides, **I-68a-g**).

Preliminary experiments demonstrated that 2-iodoxybenzamides show aspects of reactivity similar to both IBX and DMP. Benzyl alcohol, cyclohexanol and 3-pentanol can be oxidized by compound **I-68b** into benzaldehyde, cyclohexanone and 3-pentanone, respectively. The oxidative kinetic resolution of racemic 1-phenyl-1-ethanol was also investigated using 0.5 equivalents of reagents **I-68a-b** and **I-68d**. Whereas analysis of the reactions with **I-68a** and **I-68d** indicated no enantiomeric enrichment of the unreacted alcohol, the reaction of **I-68b** showed quite a modest 9% *ee*.<sup>28</sup>

## CHAPTER II

### RESULTS AND DISCUSSION

Recently, new hypervalent iodine derivatives, amino acid-derived benziodazole oxides (**I-67**) and 2-iodoxybenzamides (IBX-amides, **I-68**) were prepared by Zhdankin and co-workers and they were briefly demonstrated as potentially useful reagents for oxidative kinetic resolution of secondary alcohols. In order to probe the scope of their synthetic utilities as chiral oxidizing reagents, we are interested to further investigate on the oxidation of various secondary alcohols using a collection of amino acid-derived benziodazole oxide and IBX-amide derivatives (Scheme 22).

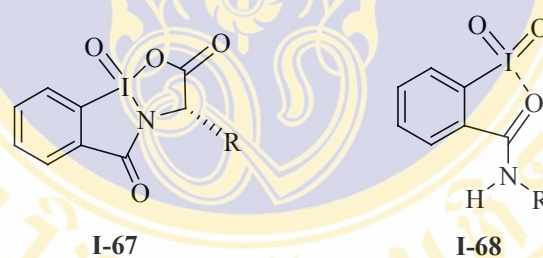
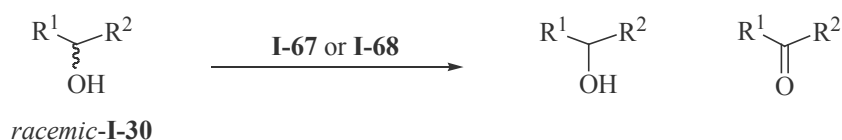


Figure 25

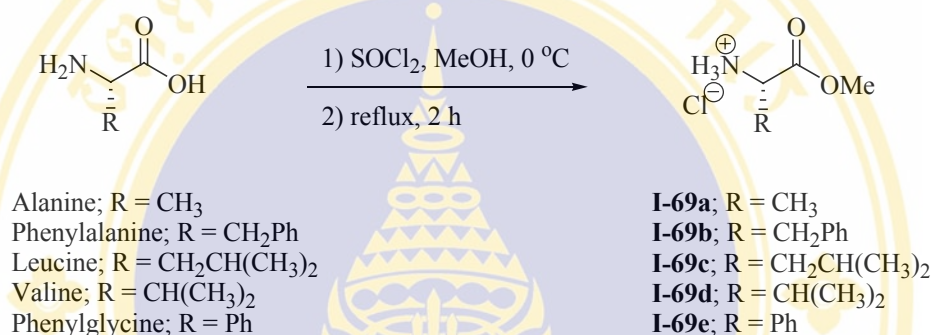


Scheme 22

## Preparation of oxidizing reagents.

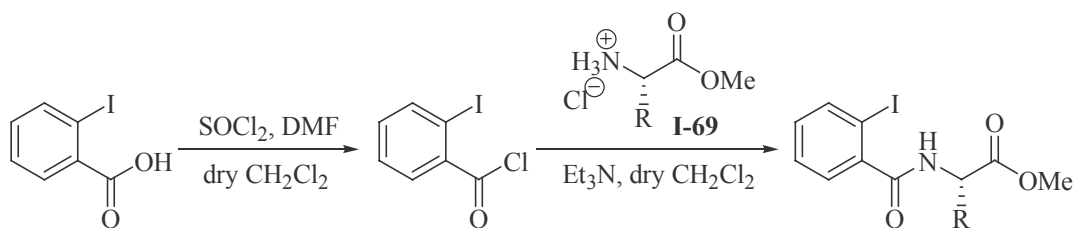
### 1. Amino acid-derived benziodazole oxides (I-67)

Initially, amino acid methyl ester hydrochloride salts (**I-69a-e**) were synthesized from five amino acids as shown in Scheme 23. The reaction of amino acids with thionyl chloride in methanol provided amino acid methyl ester hydrochloride salts (**I-69a-e**), which were used without further purification in the following step.



Scheme 23

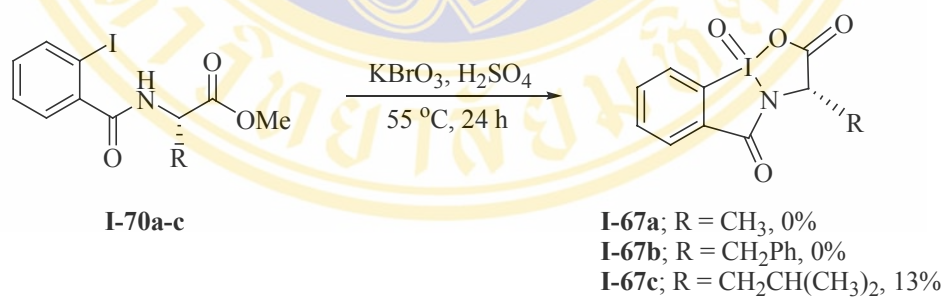
Afterwards, the amino acid methyl ester hydrochloride salts (**I-69a-e**) were coupled with 2-iodobenzoyl chloride, which was prepared from 2-iodobenzoic acid using thionyl chloride and a catalytic amount of dimethylformamide in dry dichloromethane to yield *N*-(2-iodobenzoyl) amino acid methyl ester (**I-70a-e**) in good yields as shown in Scheme 24.



**I-70a**; R = CH<sub>3</sub>, 73%  
**I-70b**; R = CH<sub>2</sub>Ph, 76%  
**I-70c**; R = CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, 85%  
**I-70d**; R = CH(CH<sub>3</sub>)<sub>2</sub>, 92%  
**I-70e**; R = Ph, 89%

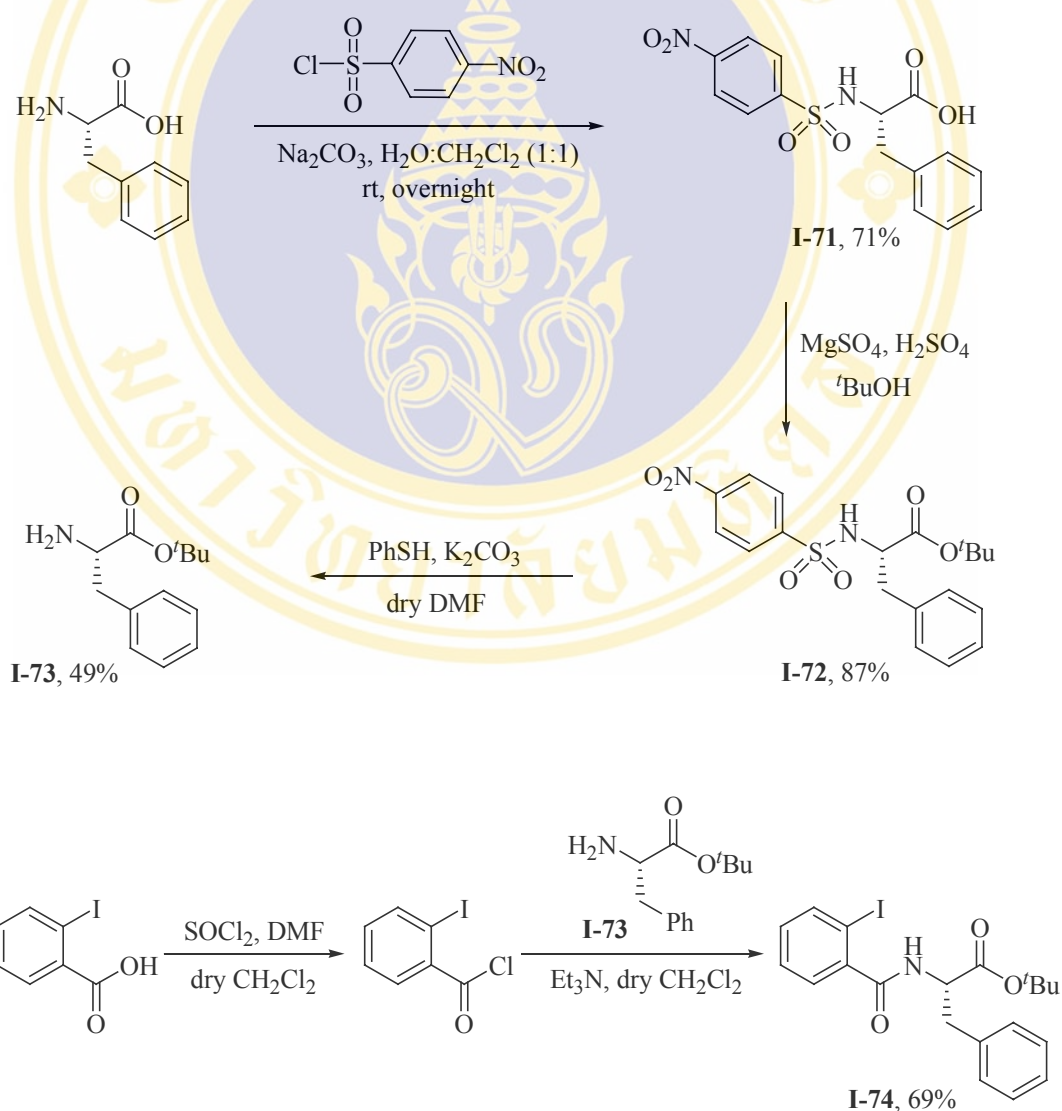
Scheme 24

The chiral amino acid-derived benziodazole oxides were prepared by following the previously reported method.<sup>27</sup> Accordingly, *N*-(2-iodobenzoyl) amino acid methyl esters derived from alanine, phenylalanine and leucine (**I-70a-c**, respectively) were oxidized using potassium bromate (KBrO<sub>3</sub>) in aqueous sulfuric acid. Unexpectedly, only benziodazole oxide derived from leucine was obtained in low yield (13%) while the oxidation of **I-70a-b** was not successful (Scheme 25).



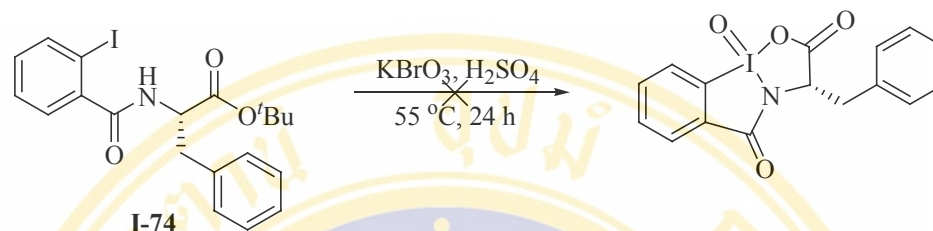
Scheme 25

It was presumed that the acid sensitive ester group is easier to leave when the oxidation occurs. Therefore, *N*-(2-iodobenzoyl)-(*S*)-phenylalanine *tert*-butyl ester was prepared starting from *N*-protection of (*S*)-phenylalanine using 4-nitrobenzene sulfonyl chloride to give compound **I-71** in 71% yield. Esterification of compound **I-71** using magnesium sulfate and sulfuric acid in *tert*-butanol afforded ester **I-72** in 87% yield. Deprotection of ester **I-72** by thiophenol and potassium carbonate in dry DMF gave compound **I-73** which was then coupled with 2-iodobenzoyl chloride to give *N*-(2-iodobenzoyl) (*S*)-phenylalanine *tert*-butyl ester **I-74** in 69% yield (Scheme 26).



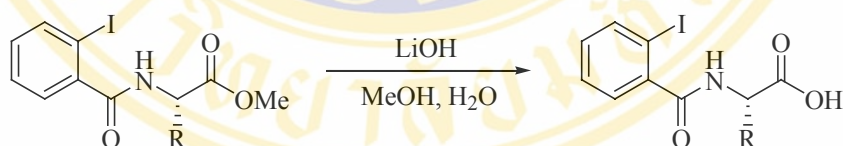
Scheme 26

Unfortunately, oxidation of *N*-(2-iodobenzoyl) (*S*)-phenylalanine *tert*-butyl ester **I-74** by potassium bromate (KBrO<sub>3</sub>), failed to yield the corresponding benziodazole oxide (Scheme 27).

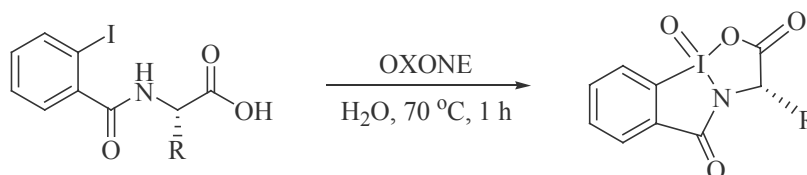


Scheme 27

From the unsatisfactory oxidation using potassium bromate, we then attempted to use commercially available OXONE<sup>®</sup> instead of potassium bromate as an oxidant to oxidize *N*-(2-iodobenzoyl) amino acids, **I-75a-b**, which prepared from treatment of *N*-(2-iodobenzoyl) amino acid methyl ester with methanolic aqueous lithium hydroxide (Scheme 28). Again, the oxidation proved to be ineffective. Benziodazole oxide **I-67b** was not observed while alanine-derived benziodazole oxide **I-67a** was obtained in very low yield (11%).

**I-70a-b**

**I-75a**; R = CH<sub>3</sub>, 93%  
**I-75b**; R = CH<sub>2</sub>Ph, 98%

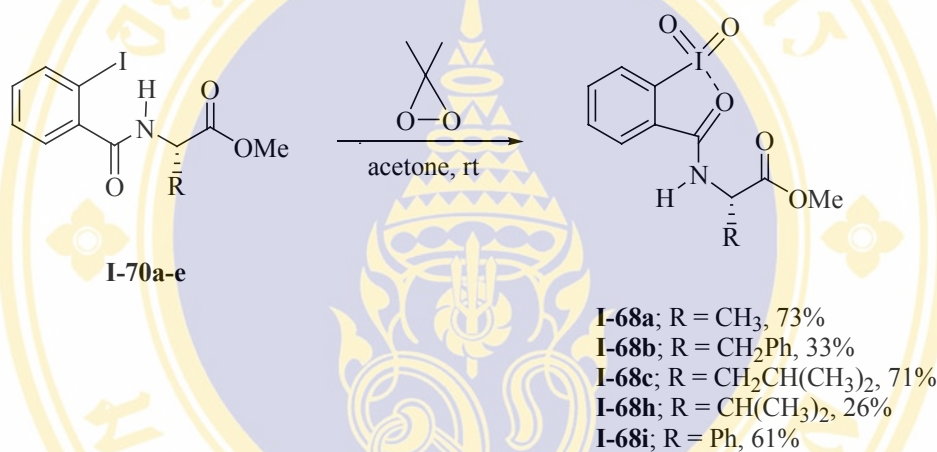
**I-75a-b**

**I-67a**; R = CH<sub>3</sub>, 11%  
**I-67b**; R = CH<sub>2</sub>Ph, 0%

Scheme 28

## 2. Amino acid-derived 2-iodoxybenzamides or IBX amides (**I-68a-c**, **I-68h-i**).

The chiral amino acid-derived IBX amides were prepared from readily available *N*-(2-iodobenzoyl) amino acid methyl esters (**I-70a-e**) according to the previously reported procedure using dimethyldioxirane oxidation.<sup>28</sup> The amino acid-derived IBX amides were obtained in low to good yields (30-70%) (Scheme 29). It should be noted that the amino acid-derived IBX amides, **I-68a-c**, **I-68h-i** were previously synthesized.



Scheme 29

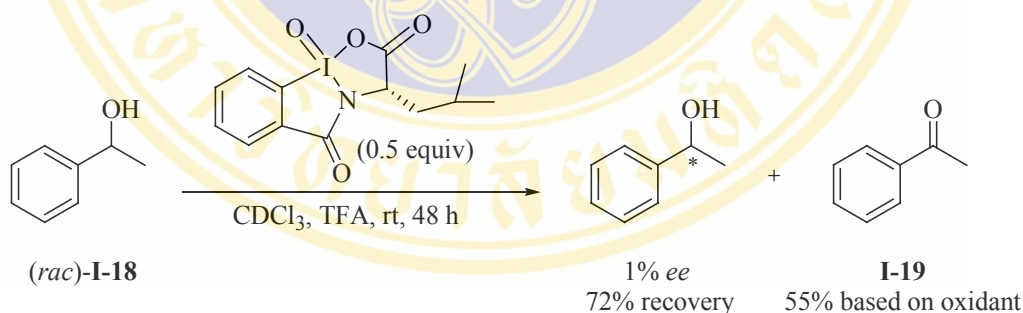
The structure of amino acid-derived IBX amides (**I-68a-c**, **I-68h-i**) was elucidated from their spectral data (<sup>1</sup>H, <sup>13</sup>C NMR, IR) in comparison with the previously reported.<sup>28</sup>

### Oxidation of racemic secondary alcohols using chiral amino acid-derivatived IBX derivatives.

The oxidation of racemic secondary alcohols was allowed to proceed to the maximum of 50% conversion by using 0.5 equivalent of the respective oxidant. The reaction mixture was purified by column chromatography on silica gel and the enantiomeric excesses of the unreacted alcohols were determined by analytical HPLC on a chiral column.

#### 1. Leucine-derived benziodazole oxide (I-67c)

Due to the irreproducible preparation of amino acid-derived benziodazole oxide, oxidation of 1-phenyl-1-ethanol using (*S*)-leucine-derived benziodazole oxide (**I-67c**) was exclusively studied. It was found that leucine-derived benziodazole oxide could oxidize 1-phenyl-1-ethanol in deuteriochloroform in the presence of a catalytic amount of trifluoroacetic acid (TFA) at room temperature to give acetophenone in moderate yield (55%) with lack of selectivity (1% *ee* of the unreacted 1-phenyl-1-ethanol was observed as determined by HPLC assay) (Scheme 30).



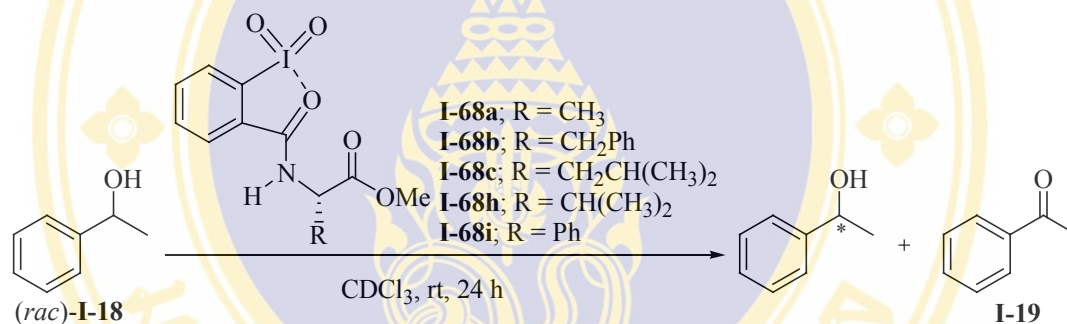
**Scheme 30**

The lack of enantioselection in kinetic resolution of (*rac*)-**I-18** could be probably as a result of the equal interactions of both (*R*)- and (*S*)-isomers of alcohol substrate to the iodine moiety. Even though, the isobutyl group shields on one face of the planar molecule but the interactions on the other face are still available for both (*R*)- and (*S*)-alcohols leading to low enantiomeric excess of the unreacted alcohol **I-18**.

## 2. Amino acid-derived 2-iodoxybenzamides or IBX amides (I-68a-c, I-68h-i).

In initial investigation, oxidation of racemic 1-phenyl-1-ethanol with five amino acid-derived 2-iodoxybenzamides (**I-68a-c**, **I-68h-i**) was studied. The results are summarized in Table 4. 1-Phenyl-1-ethanol was efficiently converted to acetophenone, after 24 h at room temperature, in good yields. Of the various chiral amino acid-derived 2-iodoxybenzamides (**I-68a-c**, **I-68h-i**) tested, low selectivities were obtained. An attempt to optimize the reaction conditions by lowering the reaction temperature to 0 °C (Table 4, entry 4) resulted in significantly lower yield of the ketone and no improvement in enantioselectivity was observed.

**Table 4** Oxidation of racemic 1-Phenyl-1-ethanol.



Entry	Oxidant	Ketone (%) <sup>a</sup>	Unreacted alcohol	
			<i>ee</i> (%)	% recovery <sup>b</sup>
1	<b>I-68a</b>	96	6	47
2	<b>I-68b</b>	Quant.	5 <sup>c</sup>	39
3	<b>I-68c</b>	Quant.	1	31
4	<b>I-68c</b>	42	0 <sup>d</sup>	33
5	<b>I-68h</b>	Quant.	2	41
6	<b>I-68i</b>	ND	2	ND

ND = not determined due to the presence of inseparable side product.

<sup>a</sup>The yields of ketone were calculated based on the amount of oxidant employed.

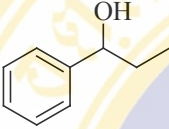
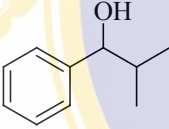
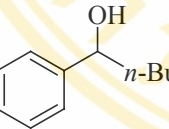
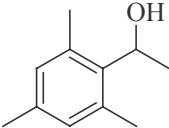
<sup>b</sup>The recoveries of unreacted alcohol were calculated based on the amount of starting material employed.

<sup>c</sup>According to the previously reported data, 9% *ee* was observed as determined by GC.<sup>28</sup>

<sup>d</sup>Reaction was carried out at 0 °C for 9 h.

The substrate-selectivity pattern of the oxidation using chiral amino acid-derived 2-iodoxybenzamides was evaluated (Table 5). The results indicated that 2-iodoxybenzamides **I-68a-c**, **I-68h-i** readily oxidized benzylic secondary alcohols to the corresponding ketones in variable yields as a function of oxidizing reagent or alcohol substrate employed. The oxidation of the substrates carrying a group larger than methyl group at the carbinol carbon was found to be sluggish and required longer reaction time (48 h) in order to achieve good conversion. Even though, all the chiral 2-iodoxybenzamides attempted led to satisfying yields of ketones (50-98%), the remaining alcohols, in all cases, are nearly racemic. As far as the instrumental error is concerned, the enantiomeric purities in the range 1-7 could be a consequence of experimental errors from analytical chiral HPLC analysis. The selectivity was found to be insensitive to the increase in steric encumbrance of either the alcohol substrates or chiral reagents employed. The 2-iodoxybenzamides **I-68a**, **I-68c** and **I-68h** derived from amino acid containing aliphatic  $\alpha$ -substituent gave no to low selectivity (Table 5, entries 1, 3, 4). Modest selectivities were obtained, in some cases, when (*S*)-phenylalanine- or (*S*)-phenylglycine-derived 2-iodoxybenzamide was used as oxidizing reagent (Table 5, entries 2, 5, 7 and 17).

**Table 5** Oxidation of racemic secondary benzylic alcohols with chiral amino acid derived 2-iodoxybenzamides.
$$\begin{array}{c}
 \text{R}^2 \text{---} \text{C} \text{---} \text{R}^1 \\
 | \\
 \text{OH}
 \end{array}
 \xrightarrow[\text{CDCl}_3, \text{rt, 48 h}]{0.5 \text{ equiv I-68a-c, I-68h-i}}
 \begin{array}{c}
 \text{R}^2 \text{---} \text{C} \text{---} \text{R}^1 \\
 | \\
 \text{OH}
 \end{array}
 +
 \begin{array}{c}
 \text{R}^2 \text{---} \text{C} \text{---} \text{R}^1 \\
 || \\
 \text{O}
 \end{array}$$

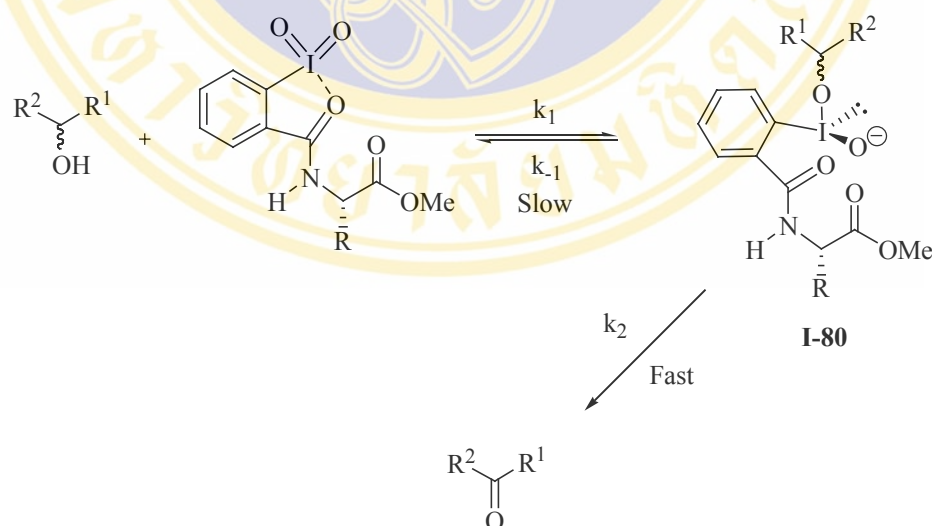
Entry	Alcohol	Oxidant	Ketone (%) <sup>a</sup>	Unreacted alcohol	
				<i>ee</i> (%)	% recovery <sup>b</sup>
1	 I-76	I-68a	54	0	36
2		I-68b	78	5	46
3		I-68c	88	1	55
4		I-68h	56	2	64
5		I-68i	ND	7	ND
6	 I-77	I-68a	50	1	67
7		I-68b	91	7	48
8		I-68c	91	2	58
9		I-68h	74	1.5	51
10		I-68i	ND	1	ND
11	 I-78	I-68a	75	1	44
12		I-68b	98	3	38
13		I-68c	71	2	56
14		I-68h	74	0	45
15		I-68i	ND	2	ND
16	 I-79	I-68a	89	4	60
17		I-68b	89	5	30
18		I-68c	71	1.5	39
19		I-68h	87	2	43
20		I-68i	76	3	47

ND = not determined due to the presence of inseparable side-product.

<sup>a</sup>The yields of ketone were calculated based on the amount oxidant employed.

<sup>b</sup>The recoveries of unreacted alcohol were calculated based on the amount of starting material employed.

The relatively low enantioselectivity observed in the oxidation of *rac-sec*-alcohols with amino acid-derived 2-iodoxybenzamides presumably due to far distance between the chiral position and hypervalent iodine when the oxidation took place and this is in agreement with previously reported data on asymmetric reactions of other hypervalent iodine reagents. A number of chiral hypervalent iodines compounds, particularly organo-iodine (III) compounds, have been previously synthesized.<sup>29a-j</sup> Some of these reagents have been used in an effort to effect a variety of asymmetric oxidations with variable enantioselectivities (none to moderate % *ee*), i.e. phenolic oxidation,<sup>29j</sup> sulfide oxidation<sup>29d</sup> and oxygenation of olefins.<sup>29i</sup> The lack of chirality induction was arisen from a fast conversion to achiral reactive species.<sup>29j</sup> In our oxidation, low enantioselection was believed to stem from a pre-equilibrium step between alcohol and 2-iodoxybenzamide derivative, leading to alkoxyiodinane oxide **I-80**, followed by a fast disproportionation to produce carbonyl compound and IBA derivative through a reductive elimination of the intermediate **I-80**.<sup>30</sup> Thus, once the intermediate **I-80** was formed from either enantiomer of the alcohol substrate, it rapidly collapses to the corresponding carbonyl compound (Scheme 31).



Scheme 31

### CHAPTER III

## CONCLUSIONS

In conclusion, the preliminary study on the oxidation of *rac-sec*-alcohols employing a structurally diverse set of chiral amino acid-derived oxidants (leucine-derived benziodazole oxide, **I-67c** and 2-iodoxybenzamides, **I-68a-c**, **I-68h-i**) indicated that all oxidants attempted led to satisfying yields of ketones (50-98%), but the remaining alcohols, were found to show very low enantiomeric excesses. The (*S*)-phenylglycine- and (*S*)-phenylalanine-derived iodoxybenzamides **I-68i** and **I-68b** exhibited promising results in that the modified structures of these reagents may find practical use as selective oxidizing agents. The oxidation was proposed to take place *via* the mechanism previously described by Santagostino and coworkers.<sup>30</sup>

## CHAPTER IV

### EXPERIMENTAL

#### General Methods.

Unless otherwise noted, all reactions were performed under argon atmosphere in oven-dried glassware cooled in a dessiccator before use. Solvents and reagents were purified as follows: tetrahydrofuran (THF) was distilled from sodium/benzophenone; dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) and acetone were distilled from  $\text{P}_2\text{O}_5$  and were stored over activated molecular sieves (4 Å). Flash column chromatography was performed with Merck silica gel 60 (Art. 7734). Preparatory layer chromatography (PLC) was performed using Merck silica gel 60 PF<sub>254</sub> (Art. 7747). Analytical TLC was performed with Merck silica gel 60 PF<sub>254</sub> (Art. 5554) with 0.2 mm thickness. All chemicals were purchased from Fluka, Aldrich and Acros organics and were used without prior purification

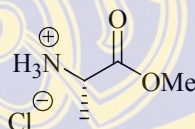
$^1\text{H}$  NMR spectra were recorded on a Bruker DPX-300 (300 MHz) spectrometer.  $^{13}\text{C}$  NMR spectra were obtained from a Bruker Advance-300 (75 MHz) spectrometer. NMR data are reported as follow:  $^1\text{H}$  NMR chemical shifts, measured in parts per million (ppm) down field from TMS ( $\delta$ ), proton count, multiplicity, observed coupling constant (J) in Hertz (Hz). Multiplicities are reported as singlet (s), broad singlet (br s), doublet (d), broad doublet (br d), triplet (t), quartet (q), and multiplet (m).  $^{13}\text{C}$  NMR chemical shifts are reported in ppm with residual non-deuterated solvent peak as the internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. HPLC was performed on an Agilent system using chiral stationary phases with detection by UV. Microanalyses were carried out with Perkin Elmer Elemental Analyzer 2400 CHN. Mass spectrometric analyses were recorded on a Bruker Esquire or a Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on HR-TOF-MS Micromass model VQ-TOF2 at Department of Chemistry, Chiangmai

University. Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected.

**General procedure A for preparation of amino acid methyl ester hydrochloride salts.**

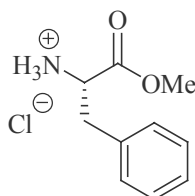
Thionyl chloride (1.5 equiv) was added dropwise to a stirred 0 °C suspension of amino acid in methanol (ca. 2.0 M) at such a rate that the reaction mixture slightly refluxed. After the refluxing ceased, the mixture was brought to reflux (oil bath at 70 °C) for an additional 2 h. Methanol was removed (aspirator followed by vacuum) to give a crude amino acid methyl ester hydrochloride salt, which was used without further purification in the following *N*-acylation reaction. This general procedure was used to prepare amino acid methyl ester hydrochloride salts of amino acids as listed below.

**(*S*)-Alanine methyl ester hydrochloride salt (I-69a).**

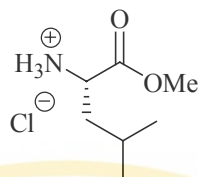


Following the general procedure A, (*S*)-alanine (0.89 g, 10.0 mmol) was employed to give (*S*)-alanine methyl ester hydrochloride salt.

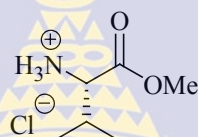
**(*S*)-Phenylalanine methyl ester hydrochloride salt (I-69b).**



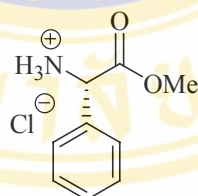
Following the general procedure A, (*S*)-phenylalanine (3.30 g, 20.0 mmol) was employed to give (*S*)-phenylalanine methyl ester hydrochloride salt.

**(S)-Leucine methyl ester hydrochloride salt (I-69c).**

Following the general procedure A, (*S*)-leucine (2.62 g, 20.0 mmol) was employed to give (*S*)-leucine methyl ester hydrochloride salt.

**(S)-Valine methyl ester hydrochloride salt (I-69d).**

Following the general procedure A, (*S*)-valine (2.34 g, 20.0 mmol) was employed to give (*S*)-valine methyl ester hydrochloride salt.

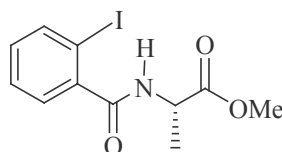
**(S)-Phenylglycine methyl ester hydrochloride salt (I-69e).**

Following the general procedure A, (*S*)-phenylglycine (4.53 g, 30.0 mmol) was employed to give (*S*)-phenylglycine methyl ester hydrochloride salt.

**General procedure B for preparation of *N*-2-iodobenzoyl amino acid methyl ester.**<sup>28</sup>

To a stirred mixture of 2-iodobenzoic acid (1.0 equiv) and a catalytic amount of *N,N*-dimethylformamide in dry CH<sub>2</sub>Cl<sub>2</sub> (ca. 2.0 M), thionyl chloride (4.0 equiv) was added at room temperature and the reaction mixture was brought to reflux (oil bath at 50 °C) for 2 h. After cooling to room temperature, the CH<sub>2</sub>Cl<sub>2</sub> was removed (aspirator). The resulting residue was dissolved in dry toluene (2-3 mL) and the toluene and residual thionyl chloride were removed (aspirator) to give 2-iodobenzoyl chloride, which was used without further purification in the next step.

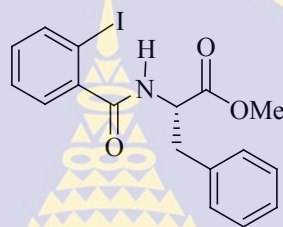
To a stirred mixture of amino acid methyl ester hydrochloride salt and triethylamine (5.0 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (ca. 0.33 M) at 0 °C, the 2-iodobenzoyl chloride in dry CH<sub>2</sub>Cl<sub>2</sub> (ca. 2.0 M) was added dropwise using a pasture pipet. The reaction mixture was stirred at room temperature for an additional 2 h before the mixture was quenched with water (20 mL). Layers were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x10 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with 2.0 M HCl (20 mL), 5% NaOH (20 mL), brine (20 mL), and were then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was removed (aspirator) to give a crude *N*-2-iodobenzoyl amino acid methyl ester, which was further purified by column chromatography or crystallization. This general procedure was used to prepare *N*-2-iodobenzoyl amino acid methyl esters of amino acids as listed below.

***N*-(2-Iodobenzoyl)-(S)-alanine-OMe (I-70a).**

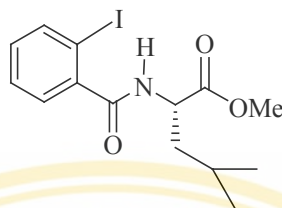
Following the general procedure B, 2-iodobenzoic acid (2.48 g, 10.0 mmol) was coupled with (*S*)-alanine methyl ester hydrochloride salt (10.0 mmol) to produce crude *N*-2-iodobenzoyl-(*S*)-alanine-OMe. After column chromatography on silica gel (15x3.5 cm, 7:3 *n*-hexane/ethyl acetate eluent), *N*-(2-iodobenzoyl)-(*S*)-alanine-OMe (2.39 g, 72%) was obtained as a pale yellow solid: analytical TLC on silica gel, 1:1 *n*-hexane/ethyl acetate, R<sub>f</sub> = 0.30, mp 129.9-130.3 °C (Lit<sup>28</sup> 130-131 °C). IR (KBr):

3271, N-H; 1740, C=O (ester); 1649, C=O(amide). 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.88 (1H, d,  $J = 7.9$  Hz) 7.45-7.36 (2H, m) 7.14-7.09 (1H, m) 6.41 (1H, br d,  $J = 7.2$  Hz) 4.82 (1H, dq,  $J = 7.2, 7.1$  Hz) 3.80 (3H, s) 1.56 (3H, d,  $J = 7.1$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  173.1, 168.5, 141.4, 139.9, 131.2, 128.3, 128.1, 92.3, 52.5, 48.5, 18.3. Anal. calcd for  $\text{C}_{11}\text{H}_{12}\text{INO}_3$ : C, 39.66; H, 3.63; N, 4.20. Found: C, 40.00; H, 3.70; N, 4.25.

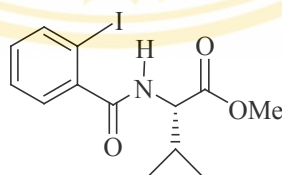
***N*-(2-Iodobenzoyl)-(*S*)-phenylalanine-OMe (I-70b).**



Following the general procedure B, 2-iodobenzoic acid (4.96 g, 20.0 mmol) was coupled with (*S*)-phenylalanine methyl ester hydrochloride salt (20.0 mmol) to produce crude *N*-(2-iodobenzoyl)-(*S*)-phenylalanine-OMe. After crystallization from ethyl acetate/*n*-hexane, *N*-(2-iodobenzoyl)-(*S*)-phenylalanine-OMe (6.21 g, 76%) was obtained as a pale yellow needle: analytical TLC on silica gel, 1:1 *n*-hexane/ethyl acetate,  $R_f = 0.38$ , mp 98.8-99.2 °C (Lit<sup>28</sup> 98-99 °C). IR (KBr): 3293, N-H; 1745, C=O(ester); 1644, C=O(amide). 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.88 (1H, d,  $J = 7.9$  Hz) 7.39-7.20 (7H, m) 7.11 (1H, t,  $J = 7.4$  Hz) 6.32 (1H, br d,  $J = 7.0$  Hz) 5.11 (1H, ddd,  $J = 7.0, 5.8, 5.7$  Hz) 3.79 (3H, s) 3.35 (1H, dd, ABX,  $J = 13.9, 5.8$  Hz) 3.25 (1H, dd, ABX,  $J = 13.9, 5.7$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  171.6, 168.6, 141.2, 140.0, 135.7, 131.3, 129.4, 128.6, 128.2, 127.2, 92.3, 53.6, 52.4, 37.8. Anal. calcd for  $\text{C}_{17}\text{H}_{16}\text{INO}_3$ : C, 49.90; H, 3.94; N, 3.42. Found: C, 50.08; H, 3.86; N, 3.53.

***N*-(2-Iodobenzoyl)-(*S*)-leucine-OMe (I-70c).**

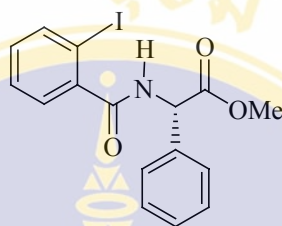
Following the general procedure B, 2-iodobenzoic acid (4.96 g, 20.0 mmol) was coupled with (*S*)-leucine methyl ester hydrochloride salt (20.0 mmol) to produce crude *N*-(2-iodobenzoyl)-(*S*)-leucine-OMe. After column chromatography on silica gel (18x4.5 cm, 8:2 to 7:3 *n*-hexane/ethyl acetate as eluent), *N*-(2-iodobenzoyl)-(*S*)-leucine-OMe (6.40 g, 85%) was obtained as a white solid: analytical TLC on silica gel, 1:1 *n*-hexane/ethyl acetate,  $R_f = 0.45$ , mp 73.8-74.6 °C (Lit<sup>28</sup> 71-73 °C). IR (KBr): 3258, N-H; 1730, C=O(ester); 1646, C=O(amide). 300 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm)  $\delta$  7.87 (1H, d,  $J = 8.0$  Hz) 7.43-7.35 (2H, m) 7.13-7.07 (1H, m) 6.25 (1H, br d,  $J = 8.5$  Hz) 4.86 (1H, ddd,  $J = 8.5, 8.5, 5.4$  Hz) 3.77 (3H, s) 1.91-1.62 (3H, m) 1.02 (3H, d,  $J = 6.3$  Hz) 0.98 (3H, d,  $J = 6.4$  Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, ppm)  $\delta$  173.1, 168.7, 141.6, 139.9, 131.2, 128.3, 128.1, 92.2, 52.4, 51.1, 41.6, 24.9, 22.8, 22.0. Anal. calcd for C<sub>14</sub>H<sub>18</sub>INO<sub>3</sub>: C, 44.82; H, 4.84; N, 3.73. Found: C, 45.18; H, 4.90; N, 3.80.

***N*-(2-Iodobenzoyl)-(*S*)-valine-OMe (I-70d).**

Following the general procedure B, 2-iodobenzoic acid (4.96 g, 20.0 mmol) was coupled with (*S*)-valine methyl ester hydrochloride salt (20.0 mmol) to produce crude *N*-(2-iodobenzoyl)-(*S*)-valine-OMe. After crystallization from ethyl acetate/*n*-hexane, *N*-(2-iodobenzoyl)-(*S*)-valine-OMe (6.65 g, 92%) was obtained as a white solid: analytical TLC on silica gel, 1:1 *n*-hexane/ethyl acetate,  $R_f = 0.45$ , mp 112.7-113.2 °C. IR (KBr): 3276, N-H; 1737, C=O(ester); 1644, C=O(amide). 300 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm)  $\delta$  7.89 (1H, d,  $J = 7.9$  Hz) 7.44-7.37 (2H, m) 7.15-7.09 (1H, m)

6.30 (1H, br d,  $J = 8.9$  Hz) 4.78 (1H, dd,  $J = 8.9, 4.1$  Hz) 3.79 (3H, s) 2.38-2.99 (1H, m) 1.08 (3H, d,  $J = 6.6$  Hz) 1.00 (3H, d,  $J = 6.7$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  172.0, 168.9, 141.7, 139.9, 131.2, 128.3, 128.1, 92.2, 57.5, 52.2, 31.5, 19.1, 17.9. Anal. calcd for  $\text{C}_{13}\text{H}_{16}\text{INO}_3$ : C, 43.23; H, 4.47; N, 3.88. Found: C, 43.63; H, 4.16; N, 3.93.

***N*-(2-Iodobenzoyl)-(*S*)-phenylglycine-OMe (I-70e).**



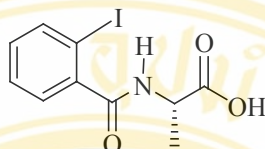
Following the general procedure B, 2-iodobenzoic acid (2.67 g, 10.0 mmol) was coupled with (*S*)-phenylglycine methyl ester hydrochloride salt (10.0 mmol) to produce crude *N*-(2-iodobenzoyl)-(*S*)-phenylglycine-OMe. After crystallization from ethyl acetate/*n*-hexane, *N*-(2-iodobenzoyl)-(*S*)-phenylglycine-OMe (3.50 g, 89%) was obtained as a white needle: analytical TLC on silica gel, 1:1 *n*-hexane/ethyl acetate,  $R_f = 0.55$ , mp 155.4-155.9 °C. IR (KBr): 3308, N-H; 1749, C=O(ester); 1647, C=O (amide). 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.80 (1H, d,  $J = 7.6$  Hz) 7.41-7.29 (7H, m) 7.06-7.02 (1H, m) 6.75 (1H, br d,  $J = 7.2$  Hz) 5.17 (1H, d,  $J = 7.2$  Hz) 3.70 (3H, s) 2.38-2.99 (1H, m) 1.08 (3H, d,  $J = 6.6$  Hz) 1.00 (3H, d,  $J = 6.7$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  171.0, 168.2, 141.0, 140.0, 136.0, 131.4, 128.9, 128.6, 128.5, 128.1, 127.4, 92.3, 56.8, 52.9. Anal. calcd for  $\text{C}_{16}\text{H}_{14}\text{INO}_3$ : C, 48.63; H, 3.57; N, 3.54. Found: C, 48.92; H, 3.57; N, 3.51.

**General procedure C for preparation of *N*-2-iodobenzoyl amino acid.**

To a stirred solution of *N*-2-iodobenzoyl amino acid methyl ester in 2:1 methanol and water was added a 1.0 M aqueous solution of lithium hydroxide (9 equiv) at room temperature. The reaction mixture was further stirred at room temperature for 1 h then water (10 mL) was added. The resulting mixture was acidified to pH 3 using 2.0 M aqueous HCl and was extracted with  $\text{CH}_2\text{Cl}_2$  (3x20 mL).

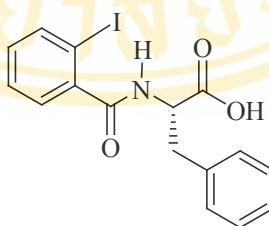
The combined  $\text{CH}_2\text{Cl}_2$  extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated (aspirator) to give analytically pure *N*-2-iodobenzoyl amino acid.

***N*-(2-Iodobenzoyl)-(S)-alanine-OH (I-75a).**



Following the general procedure C, *N*-(2-iodobenzoyl)-(S)-alanine-OMe (1.67 g, 5.0 mmol) in MeOH (100 mL) and water (50 mL) was employed to produce *N*-(2-iodobenzoyl)-(S)-alanine-OH (1.49 g, 93%) as a white solid: analytical TLC on silica gel, 10:20:0.5 *n*-hexane/ethyl acetate/acetic acid,  $R_f = 0.25$ , mp 141.2-141.4 °C. IR (KBr): 3412, O-H; 3266, N-H; 1711, C=O(acid); 1654, C=O(amide). 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.82 (1H, d,  $J = 7.8$  Hz) 7.42-7.31 (2H, m) 7.09-7.01 (1H, m) 6.35 (1H, br d,  $J = 7.0$  Hz) 4.77 (1H, qd,  $J = 7.1, 7.0$  Hz) 2.53 (1H, br s) 1.55 (3H, d,  $J = 7.1$  Hz).  $m/z$  (ESI):  $[(M+\text{Na})^+]$  342.

***N*-(2-Iodobenzoyl)-(S)-phenylalanine-OH (I-75b).**

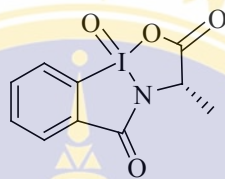


Following the general procedure C, *N*-(2-iodobenzoyl)-(S)-phenylalanine-OMe (0.85 g, 2.07 mmol) in MeOH (40 mL) and water (20 mL) was employed to produce *N*-(2-iodobenzoyl)-(S)-phenylalanine-OH (0.80 g, 98%) as a white solid: analytical TLC on silica gel, 10:20:0.5 *n*-hexane/ethyl acetate/acetic acid,  $R_f = 0.20$ , mp 151.5-151.7 °C. IR (KBr): 3451, O-H; 3278, N-H; 1734, C=O(acid); 1699, C=O(amide). 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.88 (1H, d,  $J = 8.0$  Hz) 7.30 (7H, m) 7.10 (1H, t,  $J = 7.5$  Hz) 6.30 (1H, br d,  $J = 7.5$  Hz) 5.10 (1H, ddd,  $J = 7.5, 6.0,$

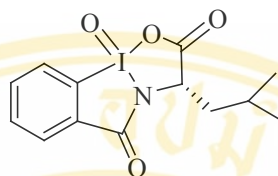
5.6 Hz) 3.77 (3H, s) 3.48 (1H, dd, ABX,  $J = 14.0, 5.6$  Hz) 3.20 (1H, dd, ABX,  $J = 14.0, 6.0$  Hz).  $m/z$  (ESI):  $[(M+Na)^+]$  418.

### Preparation of benziodazole oxide by OXONE<sup>®</sup> oxidation.<sup>27</sup>

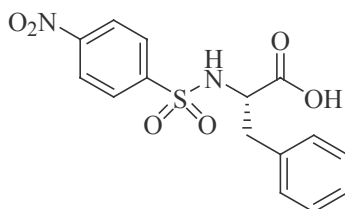
#### (*S*)-Alanine-benziodazole oxide (I-67a).



To a stirred mixture of *N*-(2-iodobenzoyl)-(*S*)-alanine-OH (1.03 g, 3.22 mmol) in 80 mL of distilled water, OXONE<sup>®</sup> (5.94 g, 9.67 mmol) was added all at once. The reaction mixture was warmed to 70-75 °C for 20 minutes and then stirred at this temperature for 1 h. The finely dispersed suspension was then cooled to 5 °C and left at this temperature for 1.5 h with slow stirring. The white precipitate was then filtered, washed with distilled water (100 mL), and dried in a vacuum to give (*S*)-alanine-benziodazole oxide (0.12 g, 11%): mp 150.2-150.4 °C dec (Lit<sup>27</sup> 151 °C dec). IR (KBr): 1734, C=O(lactone); 1635, C=O(amide). 300 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm)  $\delta$  8.30 (1H, d,  $J = 8.0$  Hz) 8.19 (1H, d,  $J = 7.7$  Hz) 7.81 (1H, t,  $J = 7.6$  Hz) 7.68 (1H, t,  $J = 7.4$  Hz) 5.00 (1H, q,  $J = 6.6$  Hz) 1.68 (3H, d,  $J = 6.6$  Hz). 75 MHz <sup>13</sup>C NMR (CDCl<sub>3</sub>, ppm)  $\delta$  180.7, 167.1, 134.5, 132.9, 130.7, 130.4, 130.0, 119.9, 54.4, 19.5.

**Preparation of benziodazole oxide by  $\text{KBrO}_3$  oxidation.<sup>27</sup>****(*S*)-Leucine-benziodazole oxide (I-67c).**

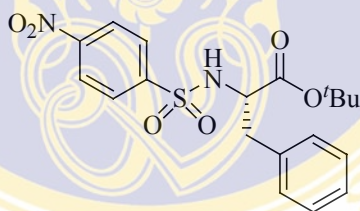
To a stirred mixture of *N*-(2-iodobenzoyl)-(*S*)-leucine-OMe (1.87 g, 5 mmol) in 0.75 M  $\text{H}_2\text{SO}_4$  (75 mL) at 55 °C,  $\text{KBrO}_3$  (1.08 g, 6.5 mmol) was added over 30 minutes. The reaction mixture was stirred for 24 h at 55 °C. The resulting solution was then cooled to 0 °C. The white precipitate was filtered, washed with water (50 mL), acetone (40 mL), diethyl ether (25 mL) and dried under reduced pressure to give (*S*)-leucine-benziodazole oxide (0.25 g, 13%): mp 129.4-129.6 °C. IR (KBr): 1733, C=O(lactone); 1634, C=O(amide). 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  8.21 (1H, d,  $J = 7.9$  Hz) 8.13 (1H, d,  $J = 6.9$  Hz) 7.75 (1H, t,  $J = 7.0$  Hz) 7.62 (1H, t,  $J = 7.3$  Hz) 5.09-4.96 (1H, m) 1.82 (1H, m) 1.83-1.46 (3H, m) 1.08 (3H, d,  $J = 5.7$  Hz) 0.91 (3H, d,  $J = 5.9$  Hz). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  180.5, 166.8, 134.5, 133.3, 130.9, 130.5, 129.9, 119.7, 57.4, 43.2, 25.2, 23.5, 2.0.

**Preparation of *N*-(4-nitrobenzenesulfonyl)-(*S*)-phenylalanine-OH (I-71).**

To a stirred suspension of (*S*)-phenylalanine (3.30 g, 20.0 mmol) in water (30 mL), was added sodium carbonate (4.66 g, 44.0 mmol). When the suspension became a clear solution, a solution of 4-nitrobenzenesulfonyl chloride (4.87 g, 22.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (25 mL) was added dropwise. The resulting mixture was stirred at

room temperature for overnight (16 h) before water (15 mL) was added. Layers were separated and the aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub> (25 mL). The aqueous layer was acidified to pH 2 using 2.0 M aqueous HCl, and was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x20 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated (aspirator) to give crude product. After crystallization from ethyl acetate/*n*-hexane, *N*-(4-nitrobenzenesulfonyl)-(*S*)-phenylalanine-OH (4.99 g, 71%) was obtained as a pale yellow solid: analytical TLC on silica gel, 10:20:0.5 *n*-hexane/ethyl acetate/acetic acid, R<sub>f</sub> = 0.20, mp 166.4-166.5 °C. IR (KBr): 3503, O-H; 3417, N-H; 1678, C=O(acid); 1529, NO<sub>2</sub>; 1353, 1169, SO<sub>2</sub>. 300 MHz <sup>1</sup>H NMR (CD<sub>3</sub>OD, ppm) δ 8.18 (2H, d, J = 8.8 Hz) 7.80 (2H, d, J = 8.8 Hz) 7.12 (5H, br s) 4.11 (1H, dd, J = 9.6, 4.7 Hz) 3.10 (1H, dd, ABX, J = 13.8, 4.7 Hz) 2.81 (1H, dd, ABX, J = 13.8, 9.6 Hz). *m/z* (ESI): [(M+Na)<sup>+</sup>] 373.

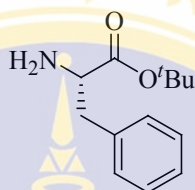
#### Preparation of *N*-(4-nitrobenzenesulfonyl)-(*S*)-phenylalanine-O<sup>t</sup>Bu (I-72).



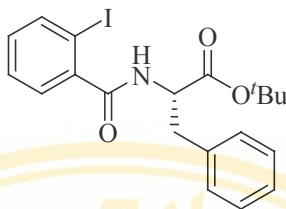
To a vigorously stirred suspension of anhydrous magnesium sulfate (2.40 g, 20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), was added concentrated H<sub>2</sub>SO<sub>4</sub> (0.28 mL, 5 mmol). The mixture was stirred for 15 minutes, after which the *N*-(4-nitrobenzenesulfonyl)-(*S*)-phenylalanine-OH (1.75 g, 5 mmol) was added. Tertiary butanol (2.4 mL, 25 mmol) was added last and the reaction mixture was then stirred at room temperature for 18 h. Saturated aqueous NaHCO<sub>3</sub> (40 mL) was added and the mixture was stirred until all magnesium sulfate has dissolved. Layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x20 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with brine (30 mL), dried over anhydrous MgSO<sub>4</sub> and evaporated (aspirator) to give analytically pure *N*-(4-nitrobenzenesulfonyl)-(*S*)-phenylalanine-O<sup>t</sup>Bu (1.77 g, 87%) was obtained as a pale yellow solid: analytical TLC on silica gel, 1:1 *n*-hexane/ethyl acetate, R<sub>f</sub> = 0.50, mp 53.6-53.8 °C. IR (KBr): 3302, N-H; 1716, C=O

(ester); 1530, NO<sub>2</sub>; 1353, 1173, SO<sub>2</sub>. 300 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm) δ 8.22 (2H, d, J = 8.9 Hz) 7.88 (2H, d, J = 8.8 Hz) 7.25-7.17 (3H, m) 7.14-7.06 (2H, m) 5.49 (1H, d, J = 9.3 Hz) 4.13 (1H, ddd, J = 9.3, 7.1, 5.6 Hz) 3.06 (1H, dd, ABX, J = 13.8, 5.6 Hz) 2.97 (1H, dd, ABX, J = 13.8, 7.1 Hz) 1.28 (9H, s). *m/z* (ESI): [(M+Na)<sup>+</sup>] 429.

### Preparation of (*S*)-phenylalanine-O<sup>t</sup>Bu (I-73).



To a vigorously stirred mixture of *N*-(4-nitrobenzenesulfonyl)-(*S*)-phenylalanine-O<sup>t</sup>Bu (2.74 g, 6.8 mmol) and anhydrous potassium carbonate (2.80, 20.3 mmol) in dry DMF (30 mL) under argon atmosphere, was added thiophenol (1.38 mL, 13.5 mmol) in one portion. The reaction mixture was further stirred at room temperature for an additional 4 h before the mixture was quenched with diethyl ether (20 mL) and water (20 mL). The aqueous phase was extracted with diethyl ether (3x20 mL). The combined diethyl ether extracts were washed with water (3x20 mL) and were then extracted with 1% aqueous HCl (3x20 mL). The combined aqueous HCl extracts were washed with diethyl ether (20 mL) and were then neutralized with a saturated NaHCO<sub>3</sub> solution (20 mL). The resulting aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x20 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with brine (20 mL), and were then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was removed (aspirator) to give a crude, after column chromatography on silica gel (18x3 cm, 8:2 *n*-hexane/ethyl acetate eluent), (*S*)-phenylalanine-O<sup>t</sup>Bu (0.73 g, 49%) was obtained as a pale yellow liquid: analytical TLC on silica gel, 8:2 *n*-hexane/ethyl acetate, R<sub>f</sub> = 0.23. IR (KBr): 3381, N-H; 1719, C=O(ester). 300 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm) δ 7.42-7.18 (5H, m) 3.65-3.51 (1H, m) 3.02 (1H, dd, J = 13.1, 6.0 Hz) 2.82 (1H, dd, J = 13.1, 8.1 Hz) 1.61-1.54 (2H, m) 1.39 (9H, s). *m/z* (ESI): [(M+Na)<sup>+</sup>] 244.

**Preparation of *N*-(2-iodobenzoyl)-phenylalanine-O<sup>t</sup>Bu (I-74).**

To a stirred mixture of 2-iodobenzoic acid (0.82 g, 3.3 mmol) and a catalytic amount of *N,N*-dimethylformamide in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL), thionyl chloride (0.96 mL, 13.2 mmol) was added at room temperature and the reaction mixture was brought to reflux (oil bath at 50 °C) for 2 h. After cooling to room temperature, the CH<sub>2</sub>Cl<sub>2</sub> was removed (aspirator). The resulting residue was dissolved in dry toluene (2-3 mL) and the toluene and residual thionyl chloride were removed (aspirator) to give 2-iodobenzoyl chloride, which was used without further purification in the next step.

To a stirred mixture of (*S*)-phenylalanine-O<sup>t</sup>Bu (0.73 g, 3.3 mmol) and triethylamine (1.38 mL, 9.9 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C, the 2-iodobenzoyl chloride in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added dropwise using a pasture pipet. The reaction mixture was stirred at room temperature for an additional 2 h before the mixture was quenched with water (15 mL). Layers were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x10 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed with 2.0 M HCl (15 mL), 5% NaOH (15 mL), brine (15 mL), and were then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was removed (aspirator) to give a crude product, after column chromatography on silica gel (18x3 cm, 8:2 *n*-hexane/ethyl acetate eluent), *N*-(2-iodobenzoyl)-phenylalanine-O<sup>t</sup>Bu (0.98g, 69%) was obtained as a white solid: analytical TLC on silica gel, 8:2 *n*-hexane/ethyl acetate, R<sub>f</sub> = 0.33, mp 88.8-89.3 °C. IR (KBr): 3235, N-H; 1720, C=O(ester); 1629, C=O(amide). 300 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm) δ 7.86 (1H, d, J = 7.9 Hz) 7.40-7.16 (7H, m) 7.09 (1H, t, J = 7.3 Hz) 6.32 (1H, br d, J = 6.6 Hz) 4.95 (1H, dt, J = 6.6, 6.4 Hz) 3.25 (2H, d, J = 6.4 Hz) 1.43 (9H, s). 75 MHz <sup>13</sup>C NMR (CDCl<sub>3</sub>, ppm) δ 170.3, 168.4, 141.4, 140.1, 136.1, 131.2, 129.7, 128.4, 128.2, 128.1, 127.0, 92.4, 82.7, 54.1, 38.0, 28.0. Anal. calcd for C<sub>20</sub>H<sub>22</sub>INO<sub>3</sub> : C, 53.23; H, 4.91; N, 3.10. Found: C, 53.54; H, 5.20; N, 2.99.

**Preparation of dimethyldioxirane.<sup>31</sup>**

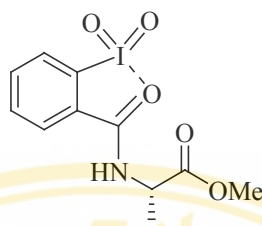
A 500 mL three-necked round-bottomed flask containing a mixture of water (40 mL), acetone (26.0 mL, 0.354 mol), sodium bicarbonate (24.0 g), and a magnetic stirring bar, was equipped with an addition funnel for solid containing potassium monoperoxy sulfate (50.0 g, 0.082 mol), and a receiving flask, cooled by means of dry ice-acetone. While applying a slight vacuum (ca.180 Torr, water aspirator), the potassium monoperoxy sulfate was added in one portion, and vigorous stirring was continued at room temperature until the reaction ceased. The yellow dimethyldioxirane-acetone solution (15 mL, 0.1 M) was collected in the receiving flask.

**Assay for dimethyldioxirane content.<sup>31</sup>**

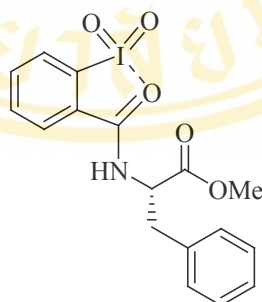
A solution of dimethyldioxirane (1.00 mL) in acetone was mixed with an acetone-*d*<sub>6</sub> solution of phenyl methyl sulfide (0.4 mL, 0.55 M). The solution was allowed to stand at room temperature for 5 min and the <sup>1</sup>H NMR spectrum was taken. Signal integration of sulfoxide phenyl protons ( $\delta$  7.6-7.9) vs. those of the sulfide ( $\delta$  7.1-7.3) gave a 1:1 ratio. Assuming all dioxirane had reacted, the concentration of dioxirane solution in acetone was calculated to be 0.11 M.

**General procedure D for preparation of amino acid derived IBX amide.<sup>28</sup>**

A freshly prepared 0.1 M solution of dimethyldioxirane in acetone (30.0 mL, 3.0 mmol) was added to a stirred solution of *N*-2-iodobenzoyl amino acid methyl ester (1.0 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0 °C. The reaction mixture was further stirred at room temperature for an additional 8 h, then the resulting white microcrystalline precipitate was collected by filtration, washed with ether (2x5 mL) and CH<sub>2</sub>Cl<sub>2</sub> (2x5 mL), and dried in vacuum to afford analytically pure amino acid derived IBX-amide.

**(S)-Alanine-IBX amide (I-68a).**

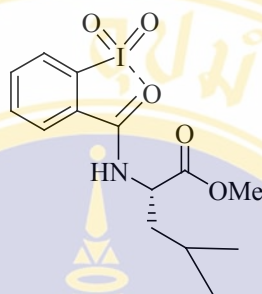
Following the general procedure D, *N*-2-iodobenzoyl-(*S*)-alanine-OMe (0.33 g, 1 mmol) was employed to produce (*S*)-alanine-IBX amide (0.2678 g, 73%): mp 151.6-152.0 °C dec (Lit<sup>28</sup> 153 °C dec).  $[\alpha]_{\text{D}}^{28} = -45^{\circ}$  ( $c = 0.027$ , CH<sub>3</sub>CN), Lit<sup>28</sup>  $[\alpha]_{\text{D}}^{\text{rt}} = -48^{\circ}$  ( $c = 0.0010$ , CH<sub>3</sub>CN). IR (KBr): 3422, 3233, N-H; 1743, C=O(ester); 1618, C=O(amide). 300 MHz <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm)  $\delta$  9.60 (1H, d,  $J = 7.2$  Hz) 8.31 (1H, d,  $J = 7.2$  Hz) 8.30 (1H, d,  $J = 7.4$  Hz) 7.94 (1H, t,  $J = 7.6$  Hz) 7.75 (1H, t,  $J = 7.3$  Hz) 4.64 (1H, qd,  $J = 7.3, 7.2$  Hz) 3.67 (3H, s) 1.47 (3H, d, 7.3 Hz). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, ppm)  $\delta$  172.3, 166.0, 149.2, 133.2, 131.5, 128.0, 127.5, 123.2, 52.3, 48.8, 16.7. Anal. calcd for C<sub>11</sub>H<sub>12</sub>INO<sub>5</sub>: C, 36.18; H, 3.31; N, 3.84. Found: C, 36.38; H, 3.08; N, 3.46.

**(S)-Phenylalanine-IBX amide (I-68b).**

Following the general procedure D, *N*-2-iodobenzoyl-(*S*)-phenylalanine-OMe (0.41 g, 1 mmol) was employed to produce (*S*)-phenylalanine-IBX amide (0.1452 g, 33%): mp 150.1-151.2 °C dec (Lit<sup>28</sup> 156 °C dec).  $[\alpha]_{\text{D}}^{28} = -32^{\circ}$  ( $c = 0.030$ , CH<sub>3</sub>CN), Lit<sup>28</sup>  $[\alpha]_{\text{D}}^{\text{rt}} = -34^{\circ}$  ( $c = 0.0023$ , CH<sub>3</sub>CN). IR (KBr): 3409, 3225, N-H; 1741, C=O(ester); 1619, C=O(amide). 300 MHz <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, ppm)  $\delta$  9.66 (1H, br d,  $J = 7.6$  Hz) 8.27 (1H, d,  $J = 7.6$  Hz) 8.25 (1H, d,  $J = 7.6$  Hz) 7.94 (1H, t,  $J = 7.6$  Hz)

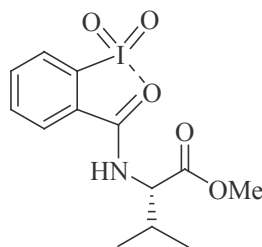
7.75 (1H, dd,  $J = 7.6$  Hz) 7.32-7.15 (5H, m) 4.78-4.68 (1H, br m) 3.66 (3H, s) 3.26-3.11 (2H, m).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , ppm)  $\delta$  171.3, 166.3, 149.2, 137.2, 133.2, 131.4, 129.1, 128.4, 127.9, 127.4, 126.7, 123.2, 54.9, 52.3, 35.9.

**(S)-Leucine-IBX amide (I-68c).**



Following the general procedure D, *N*-2-iodobenzoyl-(*S*)-leucine-OMe (0.3752 g, 1 mmol) was employed to produce (*S*)-leucine-IBX amide (0.2892 g, 71%): mp 160.7-161.1 °C dec (Lit<sup>28</sup> 170 °C dec).  $[\alpha]_{\text{D}}^{28} = -16^\circ$  ( $c = 0.022$ , CH<sub>3</sub>CN). IR (KBr): 3420, 3233, N-H; 1745, C=O(ester); 1615, C=O(amide). 300 MHz  $^1\text{H}$  NMR (DMSO- $d_6$ , ppm)  $\delta$  9.52 (1H, d,  $J = 7.7$  Hz) 8.31 (1H, d,  $J = 7.8$  Hz) 8.29 (1H, d,  $J = 7.3$  Hz) 7.96 (1H, t,  $J = 7.7$  Hz) 7.77 (1H, t,  $J = 7.4$  Hz) 4.63-4.57 (1H, m) 3.67 (3H, s) 1.88-1.82 (1H, m) 1.66-1.63 (2H, m) 0.92 (3H, d,  $J = 5.8$  Hz) 0.88 (3H, d,  $J = 5.9$  Hz).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , ppm)  $\delta$  172.2, 166.3, 149.3, 133.2, 131.4, 128.0, 127.5, 123.2, 52.2, 51.5, 39.1, 24.4, 22.8, 21.2.

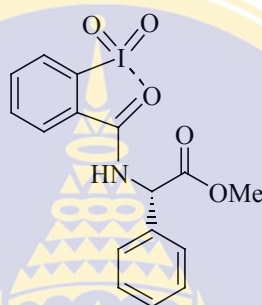
**(S)-Valine-IBX amide (I-68h).**



Following the general procedure D, *N*-2-iodobenzoyl-(*S*)-valine-OMe (0.3622 g, 1 mmol) was employed to produce (*S*)-valine-IBX amide (0.1036 g, 71%): mp 153.8-154.0 °C dec.  $[\alpha]_{\text{D}}^{28} = -41^\circ$  ( $c = 0.021$ , CH<sub>3</sub>CN). IR (KBr): 3422, 3237, N-H; 1746, C=O(ester); 1617, C=O(amide). 300 MHz  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  9.40 (1H,

d,  $J = 7.9$  Hz) 8.40 (1H, d,  $J = 7.6$  Hz) 8.28 (1H, d,  $J = 7.3$  Hz) 7.95 (1H, t,  $J = 7.3$  Hz) 7.76 (1H, t,  $J = 7.5$  Hz) 4.38 (1H, dd,  $J = 7.9, 7.9$  Hz) 3.67 (3H, s) 2.30-2.19 (2H, m) 0.99 (3H, d,  $J = 6.6$  Hz) 0.95 (3H, d,  $J = 6.7$ ).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , ppm)  $\delta$  171.4, 166.6, 149.4, 133.2, 131.4, 128.1, 127.8, 123.2, 59.2, 52.0, 29.6, 19.1. Molecular ion ( $\text{M}^+$ ) calcd. for  $\text{C}_{13}\text{H}_{16}\text{INO}_5$ : 393.0073; found (ESI) 393.0071.

**(S)-Phenylglycine-IBX amide (I-68i).**



Following the general procedure D, *N*-2-iodobenzoyl-(*S*)-phenylglycine-OMe (0.3952 g, 1 mmol) was employed to produce (*S*)-phenylglycine-IBX amide (0.2596 g, 61%): mp 139.7-140.5 °C dec.  $[\alpha]_{\text{D}}^{28} = 56^\circ$  ( $c = 0.018$ ,  $\text{CH}_3\text{CN}$ ). IR (KBr): 3405, 3229, N-H; 1741, C=O(ester); 1618, C=O(amide). 300 MHz  $^1\text{H}$  NMR (DMSO- $d_6$ , ppm)  $\delta$  10.00 (1H, d,  $J = 7.2$  Hz) 8.40 (1H, d,  $J = 7.6$  Hz) 8.29 (1H, d,  $J = 7.7$  Hz) 7.95 (1H, t,  $J = 7.4$  Hz) 7.74 (1H, t,  $J = 7.6$  Hz) 7.50 (2H, d,  $J = 7.2$  Hz) 7.41-7.37 (3H, m) 5.80 (1H, d,  $J = 7.0$  Hz) 3.69 (3H, s).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , ppm)  $\delta$  170.3, 166.2, 149.4, 135.6, 133.4, 131.4, 128.7, 128.5, 128.4, 128.0, 127.9, 123.2, 57.1, 52.6. Molecular ion ( $\text{M}^+$ ) calcd. for  $\text{C}_{16}\text{H}_{14}\text{INO}_5$ : 426.9917; found (ESI) 426.9914.

**General procedure E for oxidation racemic secondary alcohols with amino acid-derived IBX amide.<sup>28</sup>**

Alcohol (2.0 equiv, based on oxidant) was added to a suspension mixture of the respective IBX amide in  $\text{CDCl}_3$  (2.0 mL). The flask was flushed with Ar, sealed with rubber septum and the reaction was stirred at room temperature for the indicated reaction time. The mixture was passed through a pad of silica gel (3 cm) suspended in a pasteur pipet, and eluted with  $\text{CDCl}_3$  (2.5 mL) to remove the spent oxidant. The solvent was removed, and the  $^1\text{H}$  NMR was recorded to determine the conversion

efficiency. The residue was purified by column chromatography on silica gel (3:2 *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> as eluent). The enantiomeric excesses (% *ee*) of the remaining alcohol was determined by analytical HPLC on chiral column.

**Oxidation of 1-phenyl-1-ethanol (I-18).** 1-phenyl-1-ethanol (20 mg, 163.7 μmol) was reacted with reagent **I-68a-c**, **I-68h-i** according to the general procedure D for 24 h.

**Oxidation of 1-phenyl-1-propanol (I-76).** 1-phenyl-1-propanol (20 mg, 146.8 μmol) was reacted with reagent **I-68a-c**, **I-68h-i** according to the general procedure D for 48 h.

**Oxidation of phenyl isopropyl carbinol (I-77).** phenyl isopropyl carbinol (20 mg, 133 μmol) was reacted with reagent **I-68a-c**, **I-68h-i** according to the general procedure D for 48 h.

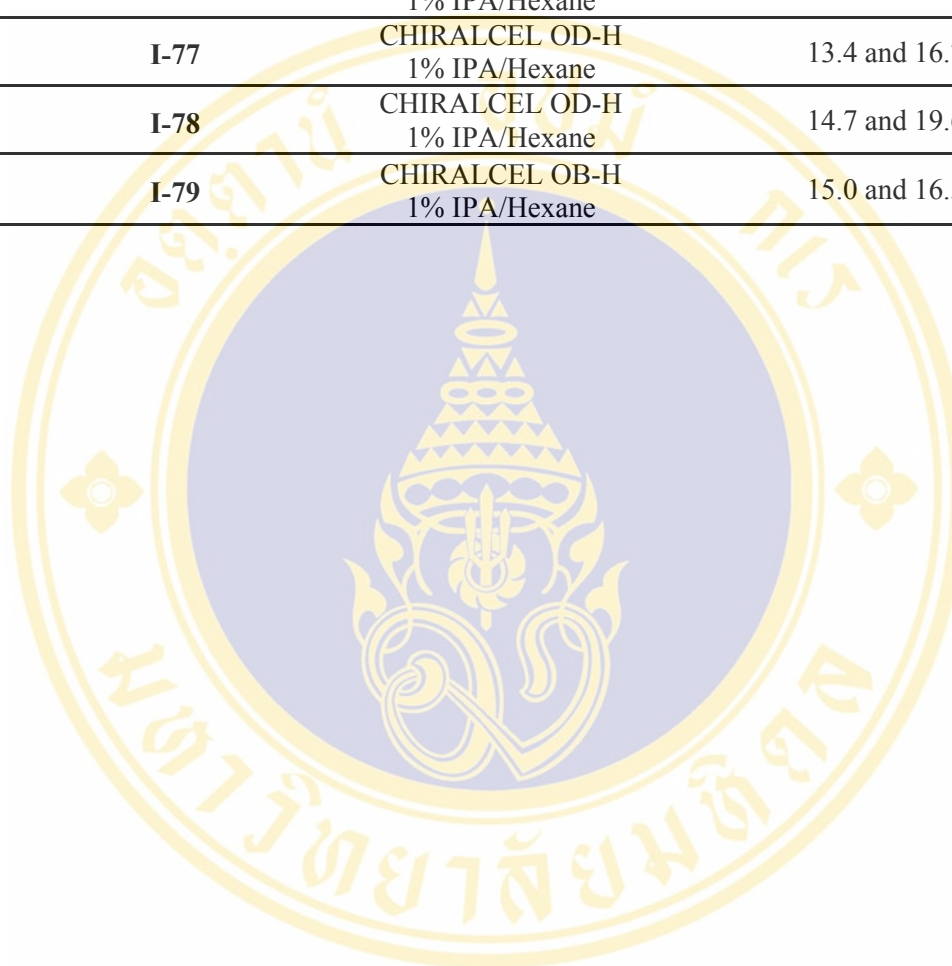
**Oxidation of phenyl *n*-butyl carbinol (I-78).** phenyl *n*-butyl carbinol (20 mg, 121.8 μmol) was reacted with reagent **I-68a-c**, **I-68h-i** according to the general procedure D for 48 h.

**Oxidation of mesityl methyl carbinol (I-79).** mesityl methyl carbinol (20 mg, 121.8 μmol) was reacted with reagent **I-68a-c**, **I-68h-i** according to the general procedure D for 48 h.

**HPLC analysis.** HPLC analysis for enantiomeric excess determination was performed on an Agilent technologies HP-1100 system on chiral column using HPLC grade isopropanol (IPA) and hexane with rate at 1 mL/min.

**Table 6** Methods utilized for the determination of enantiomeric excess.

Alcohol	Column	Retention time (min)
<b>I-18</b>	CHIRALCEL OD-H 3% IPA/Hexane	10.1 and 13.1
<b>I-76</b>	CHIRALCEL OD-H 1% IPA/Hexane	16.0 and 23.5
<b>I-77</b>	CHIRALCEL OD-H 1% IPA/Hexane	13.4 and 16.7
<b>I-78</b>	CHIRALCEL OD-H 1% IPA/Hexane	14.7 and 19.6
<b>I-79</b>	CHIRALCEL OB-H 1% IPA/Hexane	15.0 and 16.5



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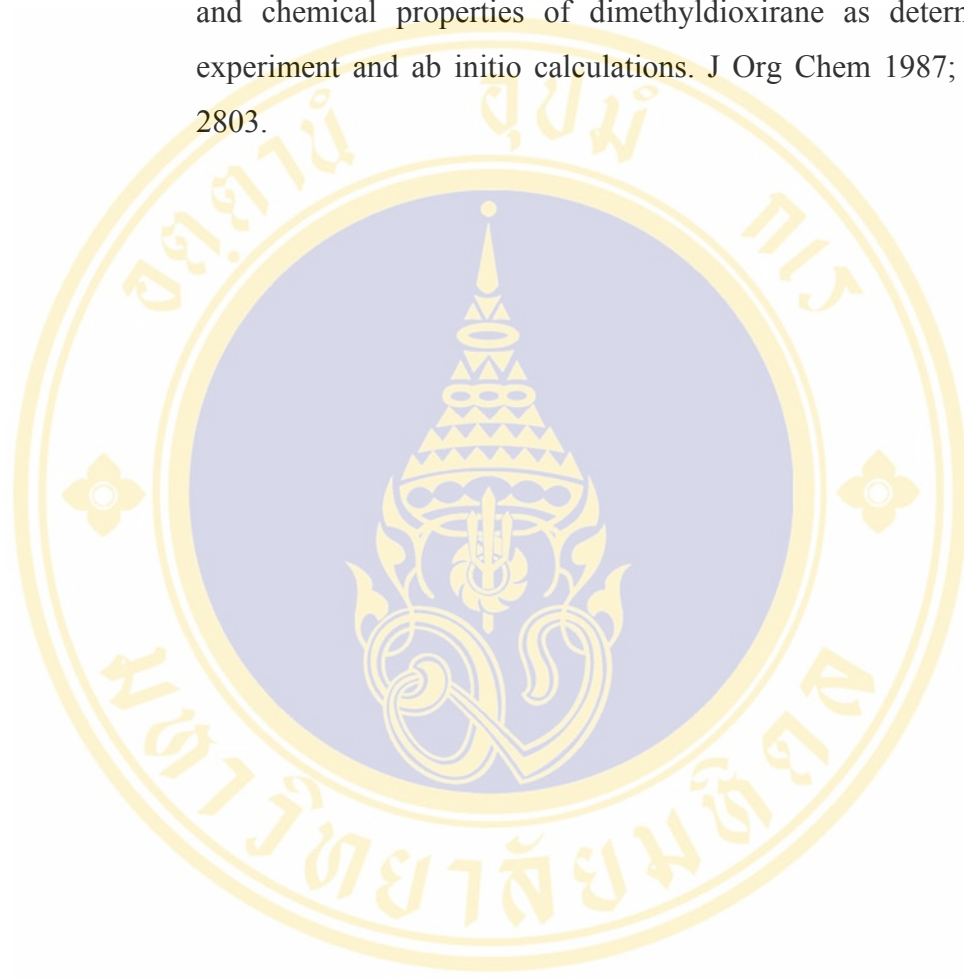
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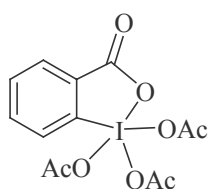
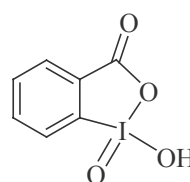


## CHAPTER I

### INTRODUCTION

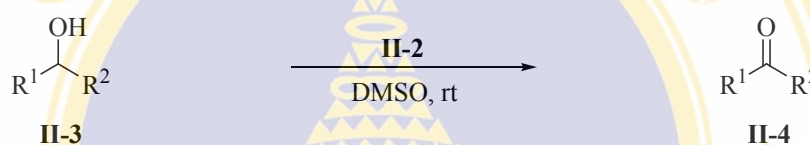
Oxidation of alcohols to carbonyl compounds is a fundamental synthetic transformation and a wide variety of reagents have been developed for this important reaction. Favorable attributes of an alcohol oxidation procedure include high conversions, the absence of side products, the use of available, inexpensive, non-toxic reagents, mild conditions, high chemoselectivity, and compatibility with other functional groups. Some recent methods that have been used extensively in synthesis include hypervalent iodine reagents.

Hypervalent iodine reagents<sup>1</sup> have attracted increasing interest during the past decade because of their selective, mild and environmentally friendly properties as oxidizing reagents in organic synthesis. In 1983, Dess and Martin first introduced the use of hypervalent iodine compounds to facilitate the oxidation of alcohols.<sup>2</sup> They successfully demonstrated that periodinane (Dess Martin periodinane, DMP) **II-1**, prepared in two steps from *o*-iodobenzoic acid, could be used to oxidize primary and secondary alcohols to the corresponding aldehydes and ketones. Subsequently, this reagent found widespread use in synthetic organic chemistry and is renowned for its mild reactivity and chemoselectivity. Unfortunately, periodinane **II-1** is unstable to prolonged storage and is thus best synthesized immediately prior to use.

DMP, **II-1**IBX, **II-2****Figure 1**

Afterwards, *o*-iodoxybenzoic acid (IBX) **II-2**,<sup>3</sup> a precursor of DMP, has come a very popular and convenient oxidizing agent due to its nontoxic nature and ease of preparation. The major drawback, however, is its virtual insolubility in common organic solvents. It is precisely this property, which precluded its applications in organic oxidation reactions for almost a century.

The first demonstration by Frigerio and co-workers on the utilization of IBX in DMSO (the only solvent in which it does dissolve) for the oxidation of alcohols has sparked a revival of interest in IBX-mediated reactions due to its cheap availability and the ease with which the oxidation reactions may be conducted (Scheme 1).<sup>4</sup>



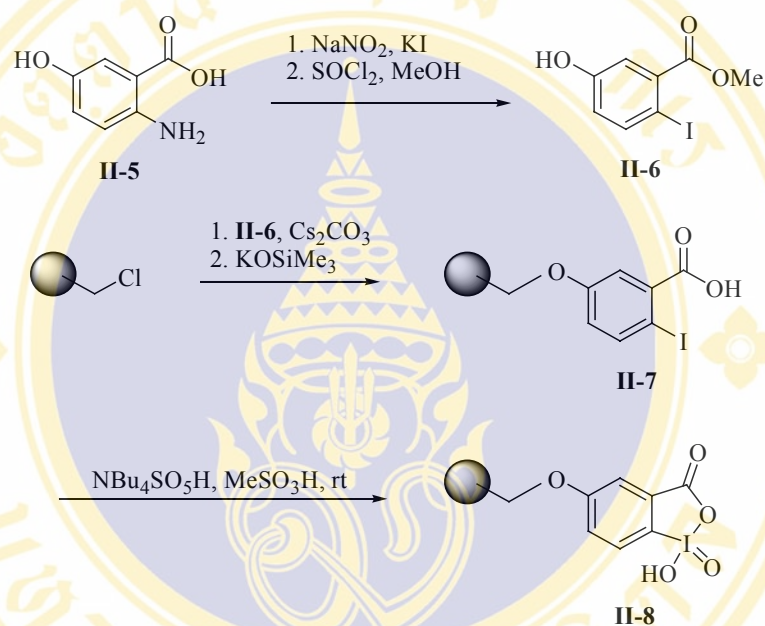
**Scheme 1**

They have found that IBX is a mild and chemoselective reagent; primary alcohols are converted into aldehydes with no over-oxidation to acids, 1,2-diols are converted to  $\alpha$ -ketols or  $\alpha$ -diketones without oxidative cleavage, amino alcohols are oxidized to amino carbonyl without protection of amino group, 1,4-diols are highly selectively oxidized to  $\gamma$ -lactols, sensitive heterocycles are not affected, various other functional groups are compatible with IBX oxidation.

Because of the limitations of DMSO as a solvent in organic synthesis, there are considerable efforts directing toward development of new and varied applications of IBX for convenient use in organic synthesis.

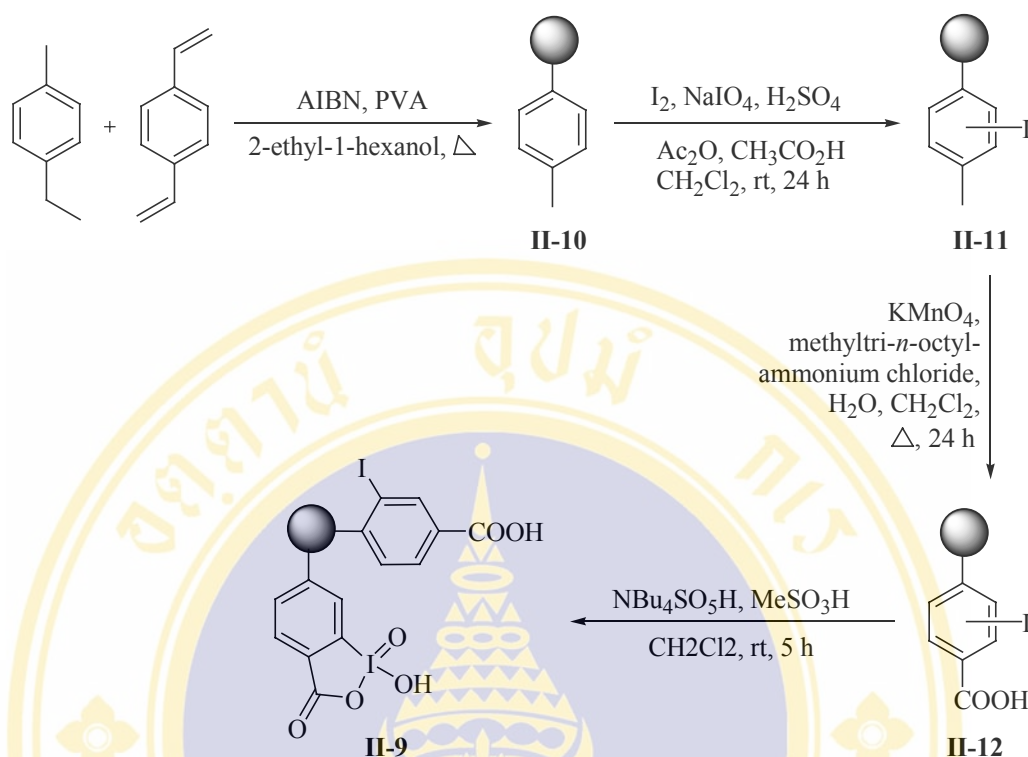
The combination of properties of IBX with the advantage of polymer-supported reagents is an attractive and worthwhile aim. The limitations of DMSO as a solvent are sufficient to have motivated two independent syntheses of solid-phase analogues of IBX (polystyrene- and silica-bound).<sup>5</sup> In each case, the authors correctly noted that these solid-phase reagents expand the range of viable solvents, simplify separation of oxidation byproducts, and facilitate recovery and reuse of the oxidant.

Recently, Rademann and co-workers have developed methodology to utilize IBX. They presented the synthesis of resin **II-8** as the first polymer-supported periodinane reagent (Scheme 2).<sup>5a</sup> This resin was capable of converting a diverse collection of alcohols, including complex and sensitive structure, efficiently and in good to excellent yields, into the respective carbonyl compounds. The novel reagent is likely to find broad application in polymer-assisted solution-phase synthesis.



**Scheme 2** Preparation of polymeric hypervalent iodine reagent **II-8**.

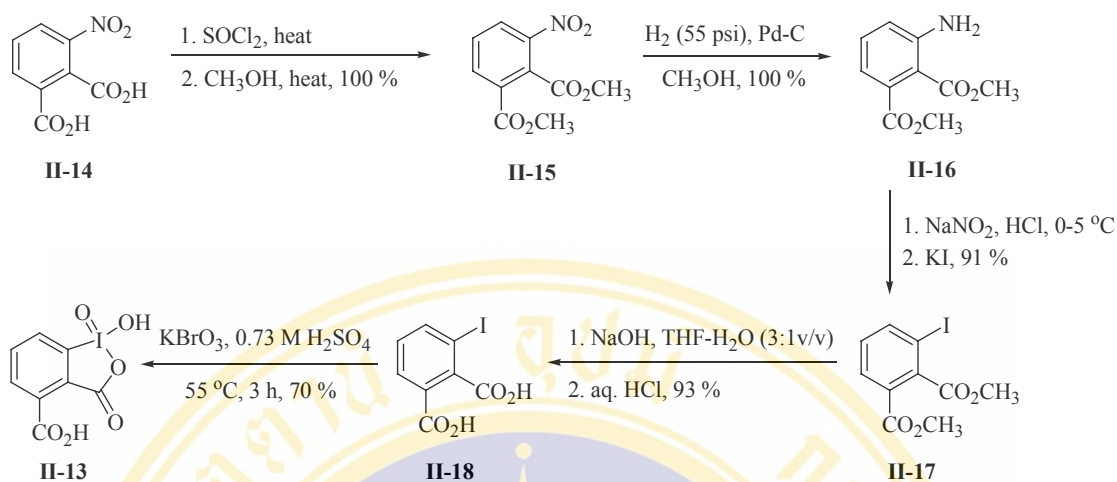
More recently, a short efficient synthesis of a polymer-supported IBX reagent **II-9** has been developed by Lei et al. as shown in Scheme 3. This reagent has been used successfully for the oxidation of a range of alcohols under very mild conditions to furnish the corresponding aldehydes.<sup>5b</sup>



**Scheme 3** Preparation of polymer-supported IBX reagent **II-9**.

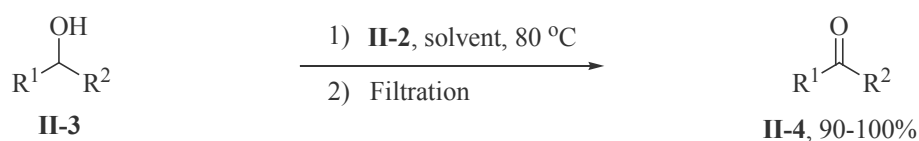
While oxidation reactions using both DMP and IBX tolerate the presence of moisture in the reaction medium, the presence of large amounts of water, when used as a solvent or co-solvent, is detrimental to the outcome of the oxidation reactions using these reagents. This is due to the fact that the mechanisms of oxidation with both the oxidizing agents involve reactive intermediates formed in an equilibrium step that is disfavored with increasing concentration of water.

In 2001, Vinod and Thottumkara reported the synthesis of modified IBX (mIBX, **II-13**) which can be soluble in water as shown in Scheme 4 and oxidation of allylic and benzylic alcohols carried out in water, are eco-friendly solvent, providing good to excellent yields of the carbonyl compounds.<sup>6</sup>

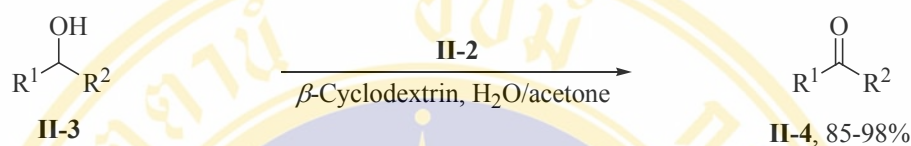


It is obvious that the synthesis of the solid-phase reagents is laborious and time-consuming. Most recently, researchers have turned their attention to carry out the oxidation in common, low boiling point molecular solvents by elevating the reaction temperature or using a suitable catalyst. These two improvements are effective alternatives to classical procedure by avoiding the use of the high boiling point, difficultly removed solvent, DMSO. However, the elevation of reaction temperature may cause decomposition of starting materials and bring about side reaction.

In 2002, Finney et al. have found that, at elevated temperatures, IBX is sufficiently soluble in most organic solvents, to permit clean oxidation of alcohols to the corresponding aldehydes and ketones in excellent yields (Scheme 5).<sup>7</sup> They regarded ethyl acetate and 1,2-dichloroethane as the solvents of choice because they are inert and all byproducts are insoluble at room temperature, such that no purification is required beyond simple filtration.

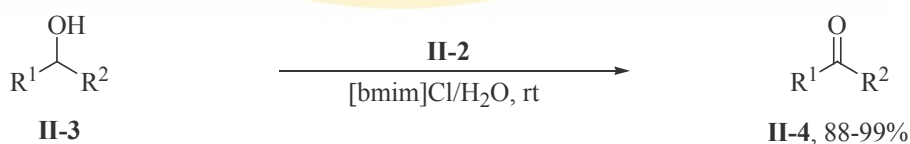


In 2003, a mild and efficient oxidation of alcohols with *o*-iodoxybenzoic acid (IBX) catalyzed by  $\beta$ -cyclodextrin in a water/acetone mixture has been developed by Rao and co-workers. A series of alcohols were oxidized at room temperature in excellent yields. No over-oxidation to acid was observed in the case of aldehyde products (Scheme 6).<sup>8</sup>



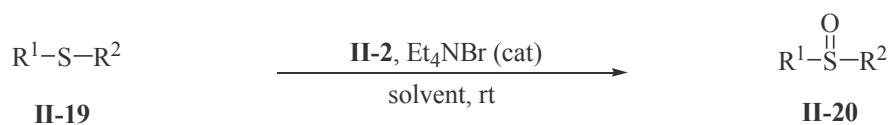
**Scheme 6**

Recently, Chen and co-workers have presented an elegant and simple methodology for the oxidation of a variety of alcohols using IBX at room temperature with [bmim]Cl and water as a solvent compared with the classical procedure in DMSO. The reaction under ambient-temperature ionic liquid [bmim]Cl and water shares the advantage of mild reaction conditions, homogeneous solution, facile recovery of the oxidant, and excellent yields of products and is, to some extent, superior in terms of the easy separation of products, small degree of consumption of the solvent, and recycling of the ionic liquid without decreasing the yields of products (Scheme 7).<sup>9</sup>



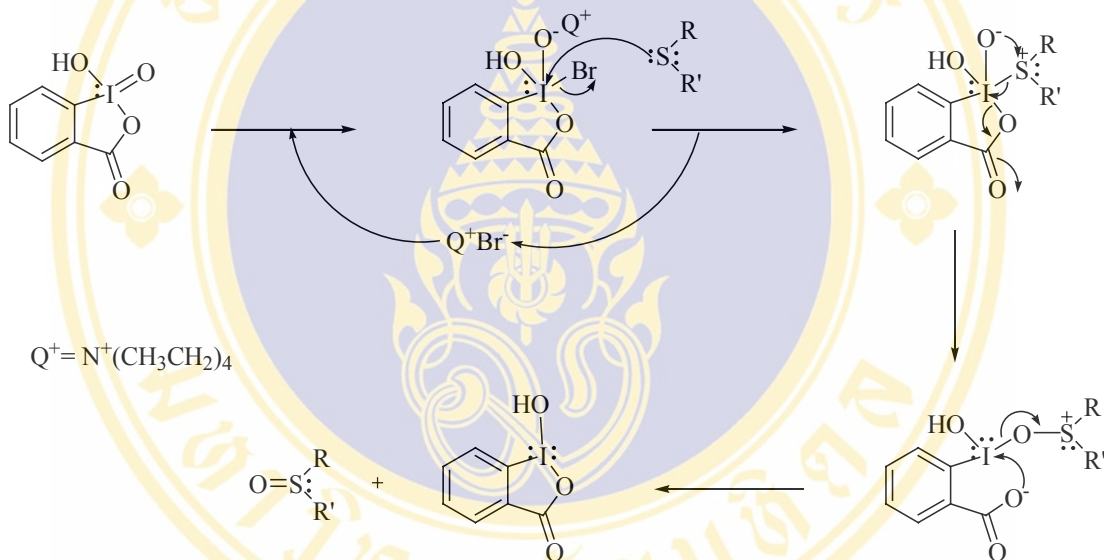
**Scheme 7**

Akamanchi et al. have recently developed a new application of IBX with catalytic amounts of tetraethylammonium bromide (Et<sub>4</sub>NBr) for the oxidation of sulfides to sulfoxides.<sup>10</sup> This method possesses increased compatibility to different functional groups, mild and neutral conditions (Scheme 8).



**Scheme 8**

They suggested the mechanism as depicted in Scheme 9. The oxidation may involve the initial polarization of the I=O bond by Et<sub>4</sub>NBr then a nucleophilic attack of sulfur on the hypervalent iodine(V) center followed by a concerted oxygen transfer to give sulfoxide.



**Scheme 9**

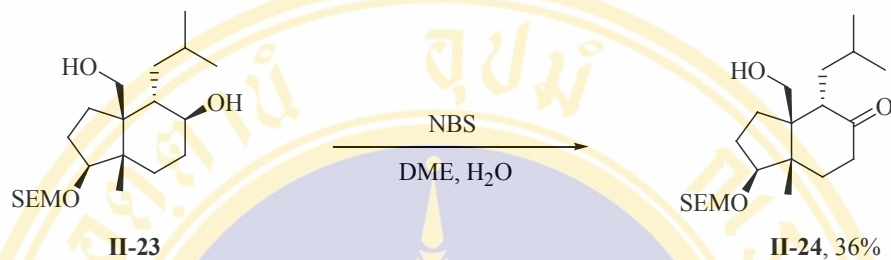
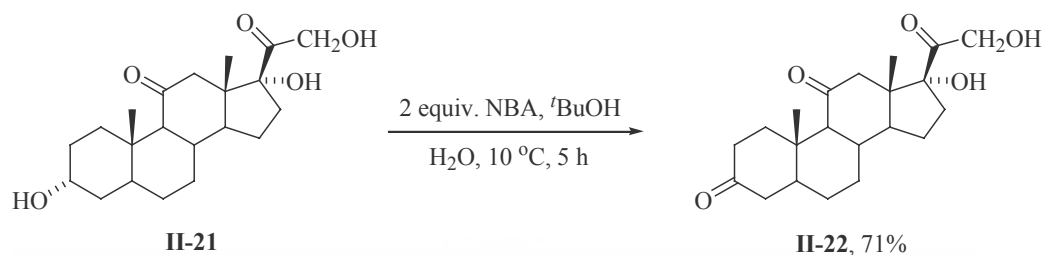
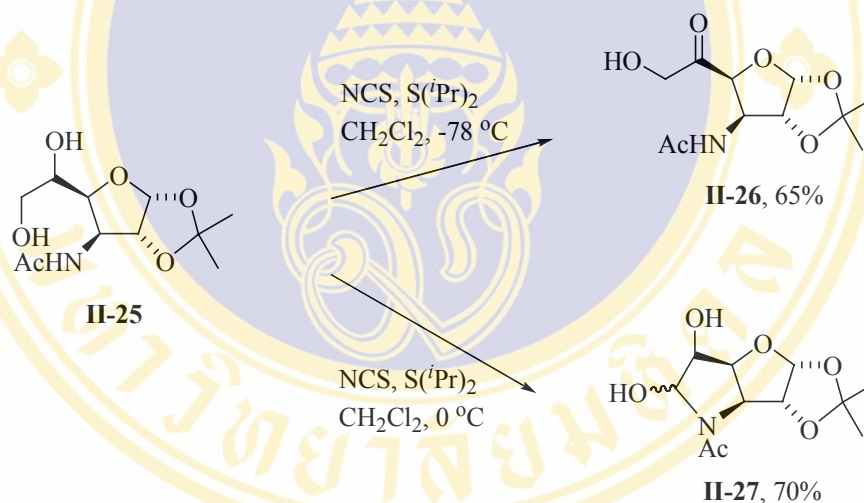
### Selective oxidation of secondary alcohol

The synthesis of natural products frequently involves the manipulation of compounds with multiple oxygen-containing functional groups at different oxidation states, and it is often necessary to selectively oxidize a single secondary or primary alcohol group within the same molecule. Therefore, the development of a new system for selective oxidation of alcohol is still a challenging task to organic chemist particularly when both secondary and primary groups present within the same molecule are present.

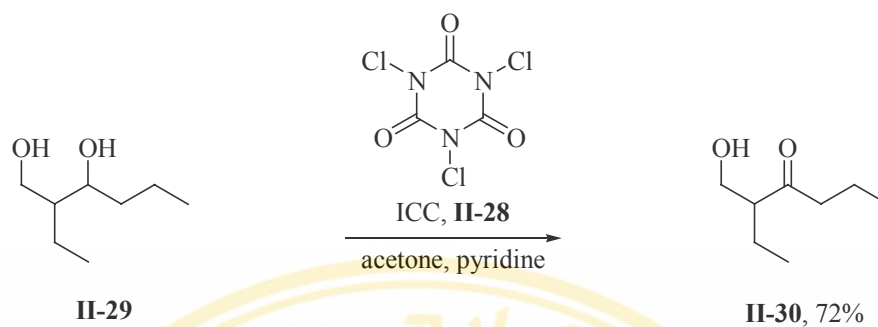
Many reagents for selective oxidation of secondary alcohol to ketone have been reported, including halogen-based oxidant, peroxides, dioxiranes and enzymatic methods.

#### 1. Halogen-based oxidations

A variety of *N*-halogenated reagents have been used for the selective oxidation of secondary alcohols, including *N*-bromoacetamide (NBA), *N*-bromosuccinimide (NBS), *N*-chlorosuccinimide (NCS) as shown in Scheme 10. Selective oxidation of the 3- $\alpha$ -hydroxyl in the trihydroxypregnane derivative **II-21** was achieved with NBA in aqueous *tert*-butanol.<sup>11</sup> The diol **II-23** was oxidized to the ketone using NBS in aqueous dimethoxyethane.<sup>12</sup> The combination of *N*-chlorosuccinimide and diisopropyl sulfide provides a system which exhibits temperature controlled selectivity (Scheme 11).<sup>13</sup> When the oxidation of diol **II-25** was conducted at -78 °C, the ketone **II-26** was obtained, while maintaining the oxidation at 0 °C leading to lactone **II-27**.

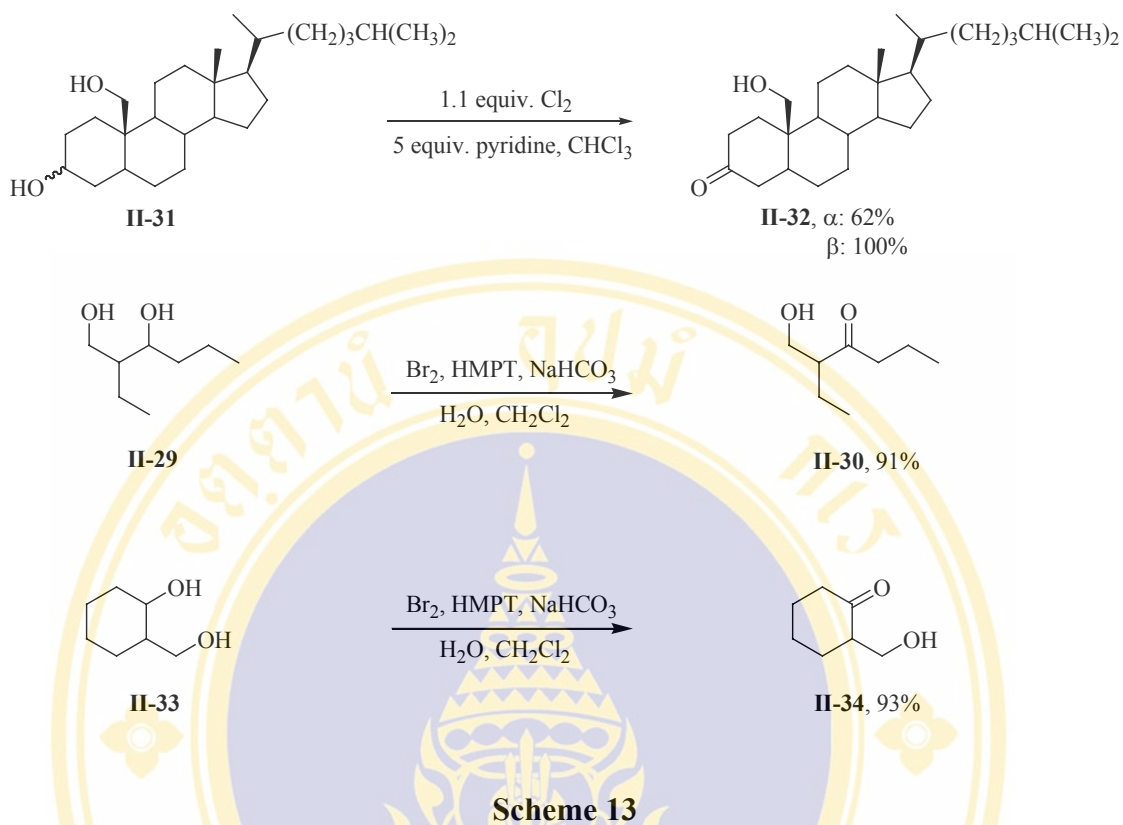
**Scheme 10****Scheme 11**

Trichloroisocyanuric acid (ICC, **II-28**) rapidly oxidizes secondary alcohols in acetone solvent buffered with pyridine. This reagent selectively oxidized the secondary alcohol of 2-ethyl-1,3-hexanediol **II-29** to give the hydroxy ketone **II-30** in high yield (Scheme 12).<sup>14</sup>

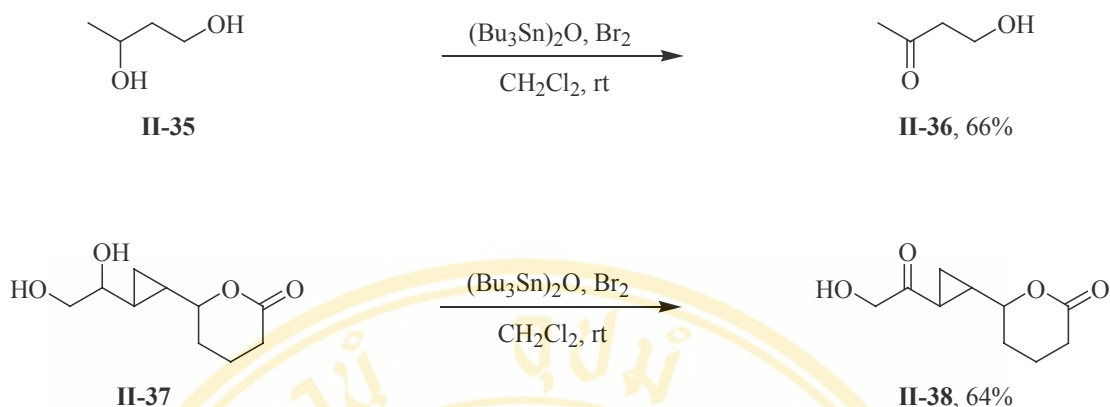


Scheme 12

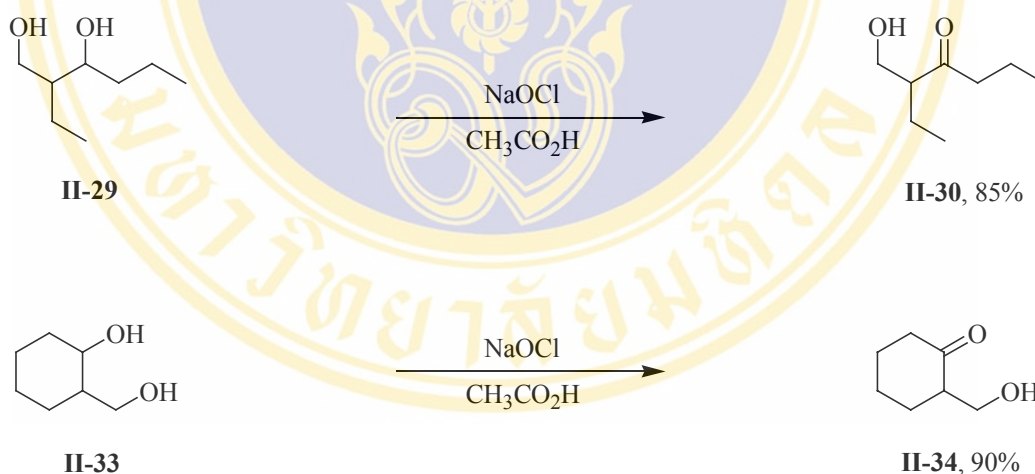
The halogen  $\text{Br}_2$  and  $\text{Cl}_2$  are effective for selective secondary alcohol oxidation under a variety of conditions as shown by the examples in Scheme 13. The secondary alcohol of steroid **II-31** was oxidized to the ketone in the presence of the primary  $\text{C}_{19}$  alcohol with  $\text{Cl}_2$ -pyridine.<sup>15</sup> The addition of hexamethylphosphorotriamide (HMPT) to  $\text{Cl}_2$  or  $\text{Br}_2$  in  $\text{CH}_2\text{Cl}_2$  at  $-40^\circ\text{C}$  results in a reagent that is selective for the oxidation of secondary alcohols in competition experiment with primary alcohol. The 1,3-diol **II-29** was oxidized with  $\text{Br}_2$ /HMPT to give the hydroxy ketone in 91% yield and cyclohexanol **II-33** was similarly oxidized to the hydroxy ketone in excellent yield.<sup>16</sup>



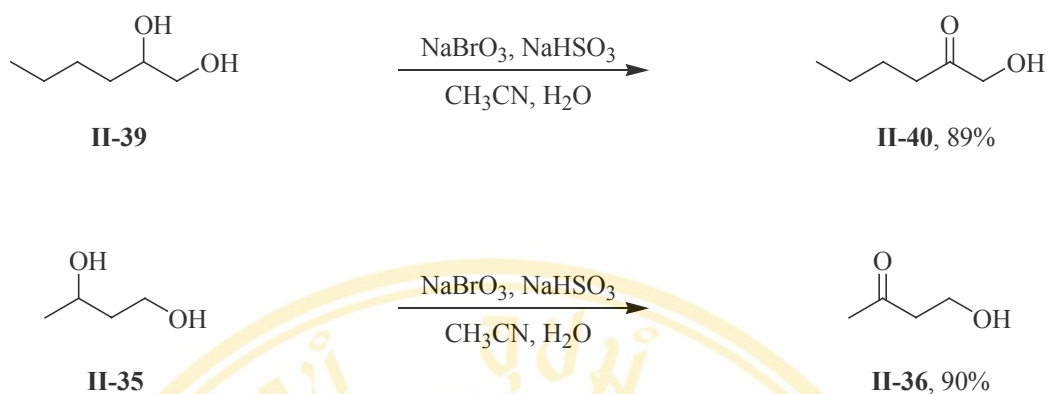
The rapid oxidation of secondary tributyltin alkoxides with  $\text{Br}_2$  has proven to be a synthetically useful method as shown in Scheme 14. The addition of bis(tri-*n*-butyltin) oxide ( $(\text{Bu}_3\text{Sn})_2\text{O}$ ) to secondary, benzylic, and allylic alcohols causes the formation of the corresponding tributyltin alkoxides, which were rapidly oxidized to carbonyls by  $\text{Br}_2$ . Primary alcohols were found to be unreactive with  $(\text{Bu}_3\text{Sn})_2\text{O} + \text{Br}_2$  in  $\text{CH}_2\text{Cl}_2$ , while secondary alcohols were converted to the ketones with high yields.<sup>17</sup> Using this method 1,2- and 1,3- primary-secondary diols were converted to the hydroxy ketones in high yields. This method was used to oxidized a cyclopropyl-substituted-1,2-diol **II-37** to corresponding ketone in good yield.<sup>18</sup>



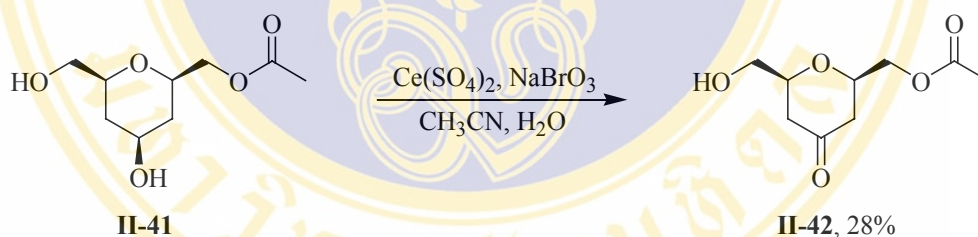
Sodium hypochlorite in acetic acid efficiently oxidizes secondary alcohol to ketone.<sup>19</sup> This procedure is convenient and inexpensive. The secondary alcohol of diol such as **II-29**, **II-33** were selectively oxidized as shown in Scheme 15.<sup>20</sup>



Sodium bromate ( $\text{NaBrO}_3$ ) has been used as a selective alcohol oxidant under a variety of conditions. For example, primary-secondary 1,2- and 1,3-diol **II-39** and **II-35** were oxidized by  $\text{NaBrO}_3$  selectively to hydroxy ketones in the presence of sodium bisulfite ( $\text{NaHSO}_3$ ) in aqueous acetonitrile (Scheme 16).<sup>21</sup>

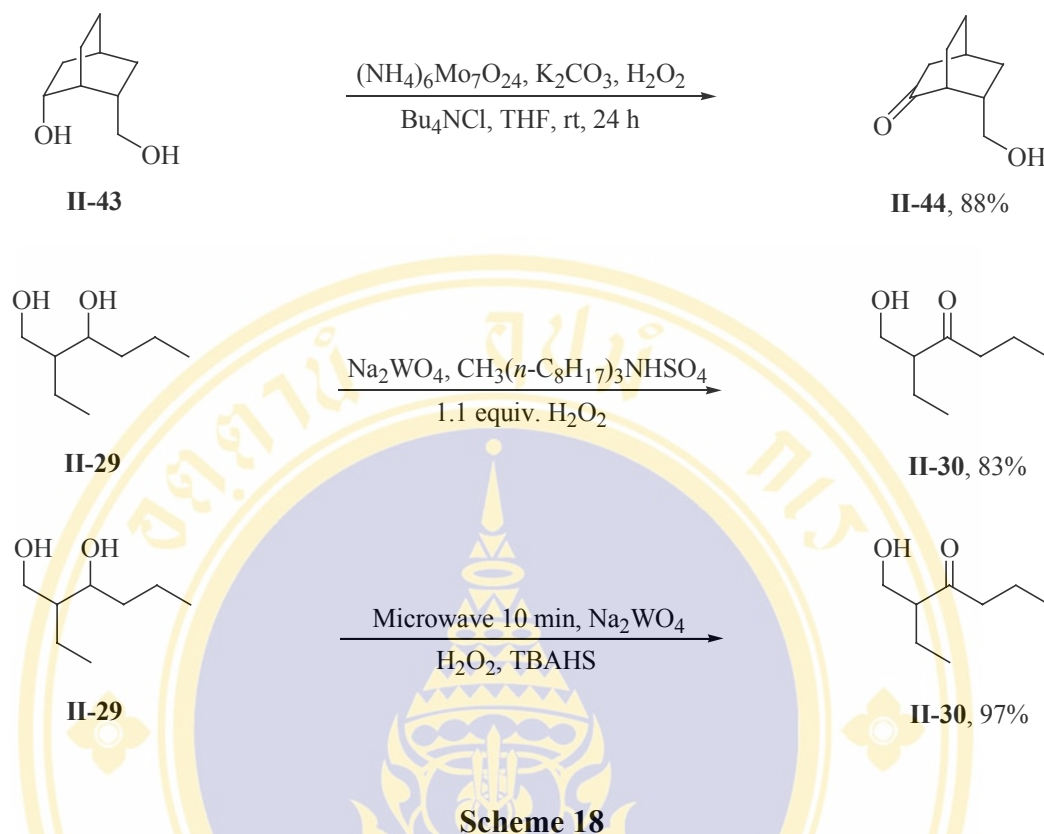


Cerium(IV) was capable of catalyzing the oxidation of secondary alcohols to ketones. For example, the secondary alcohols of diols **II-41** was oxidized using  $\text{NaBrO}_3$  with cerium(IV) sulfate ( $\text{Ce}(\text{SO}_4)_2$ ) as a catalyst to give the ketone **II-42** in 28% yield (Scheme 17).<sup>22</sup>



## 2. Peroxides

Peroxides are readily available, inexpensive and generally considered to be clean oxidants for metal catalyzed oxidations. Metal-catalyzed secondary alcohol oxidations have been reported as shown in Scheme 18.



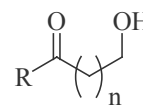
The secondary alcohol of diol **II-43** was selectively oxidized with 30% aqueous  $\text{H}_2\text{O}_2$  in the presence of tetrabutylammonium molybdate in THF at room temperature.<sup>23</sup> The 1,3-diol **II-29** was oxidized to the hydroxy ketone in good yield by using  $\text{H}_2\text{O}_2$  and  $[\text{Na}_2\text{WO}_4][\text{CH}-(n\text{-C}_8\text{H}_{17})_3\text{N}]\text{HSO}_4$  as a catalyst.<sup>24</sup> A microwave-assisted oxidation was also developed for the oxidation of **II-29** to **II-30** in 97% yield.<sup>25</sup>

### 3. Dioxiranes

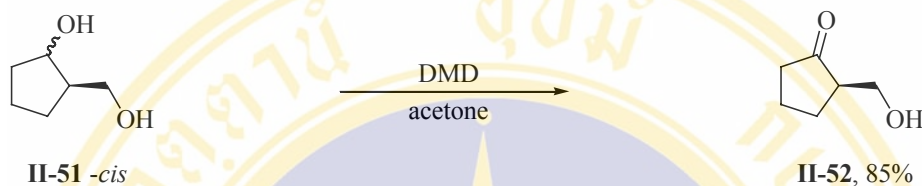
Dimethyldioxirane (DMD) is a versatile electrophilic oxidizing reagent that generally oxidizes secondary faster than primary alcohols. The alcohol oxidation reaction involves insertion into the C-H bond, a transition state that is sensitive to stereoelectronic effects. This feature was shown to be advantageous for the selective oxidation of secondary alcohol as shown in Scheme 19.



**II-45** R = C<sub>3</sub>H<sub>7</sub>, n = 0  
**II-35** R = CH<sub>3</sub>, n = 1  
**II-47** R = CH<sub>3</sub>, n = 2  
**II-49** R = CH<sub>3</sub>, n = 3



**II-46** R = C<sub>3</sub>H<sub>7</sub>, n = 0, 100%  
**II-36** R = CH<sub>3</sub>, n = 1, 90%  
**II-48** R = CH<sub>3</sub>, n = 2, 60%  
**II-50** R = CH<sub>3</sub>, n = 3, 60%



### Scheme 19

Dimethyldioxirane preferentially oxidizes the secondary alcohol of 1,2-, 1,3-, 1,4- and 1,5-diols **II-45**, **II-35**, **II-47**, **II-49** respectively, without further oxidation to diketones.<sup>26</sup> Monooxidation is favored because the strong dipole of the ketone carbonyl destabilizes the transition state for subsequent oxygen insertion.<sup>27</sup> The selectivity for monooxidation of saturated linear diols decreases for 1,4- and 1,5-diols, as the deactivating effect of the carbonyl is reduced. The *cis*-cyclopentanol derivative **II-51** was oxidized to the ketone in very good yield.<sup>26</sup> A complex mixture of oxidation products was obtained from the *trans*-stereoisomer, in which the preferred approach to the secondary C-H bond is blocked by the hydroxymethylene substituent.

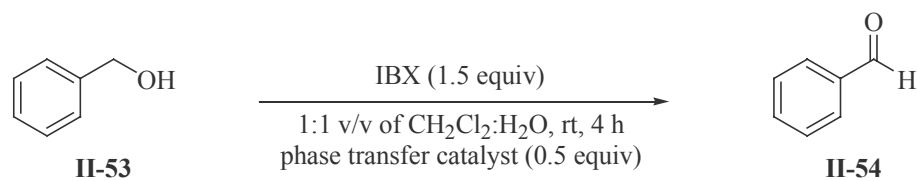
## CHAPTER II

### RESULTS AND DISCUSSION

As a part of our ongoing efforts in development of novel application of hypervalent iodine(V) reagent, we herein report a new application of *o*-iodoxybenzoic acid (IBX) with catalytic amount of tetrabutylammonium bromide (*n*-Bu<sub>4</sub>NBr) for selective oxidation of secondary hydroxyl group. Even though a combination of IBX-Et<sub>4</sub>NBr for chemoselective oxidation of sulfides to sulfoxides was documented,<sup>10</sup> to our knowledge, there is no previous study that was directed toward selective oxidation of secondary hydroxyl group in the presence of primary hydroxyl group within the same molecule using IBX as an oxidizing reagent.

#### 1. Optimization of oxidation conditions.

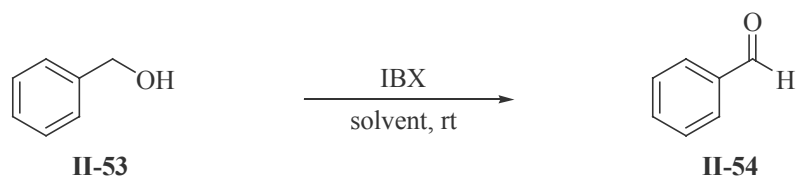
Initially, benzyl alcohol was chosen as a substrate in order to find the reaction conditions. Thus, benzyl alcohol was subjected to oxidation by IBX in a 1:1 v/v of CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O in the presence of 0.5 equivalent of a collection of phase transfer catalysts. The results shown in Table 1 deserved some comments. If the tetraalkylammonium ion is the same, types of halide anion have considerable effect on the oxidation reaction. The tetraethylammonium bromide catalyzed the reaction more effectively than the corresponding iodide and chloride, respectively (Table 1, entries 2-4). The *n*-Bu<sub>4</sub>NBr offers the best conversion of 89% (entry 1).

**Table 1** Effect of types of phase transfer catalysts.

Entry	Catalyst	Conversion (%) <sup>a</sup>
1	<i>n</i> -Bu <sub>4</sub> NBr	89
2	Et <sub>4</sub> NBr	62
3	Et <sub>4</sub> NCl	22
4	Et <sub>4</sub> NI	37
5	BnMe <sub>3</sub> NCl	18
6	BnEt <sub>3</sub> NCl	30

<sup>a</sup>Conversion (%) was calculated from <sup>1</sup>H NMR (300 MHz) integration.

Therefore, *n*-Bu<sub>4</sub>NBr was chosen as a catalyst of choice for further investigating optimum reaction conditions. The results are summarized in Table 2.

**Table 2** Oxidation of benzyl alcohol by IBX under various conditions.

Entry	Solvent (v/v)	IBX (equiv)	<i>n</i> -Bu <sub>4</sub> NBr (equiv)	Time (h)	Conversion (%) <sup>a</sup>
1	acetone	1.5	-	4	81
2	CH <sub>2</sub> Cl <sub>2</sub>	1.5	-	4	45
3	CHCl <sub>3</sub>	1.5	-	4	34
4	acetone	1.5	0.5	2	84
5	CH <sub>2</sub> Cl <sub>2</sub>	1.5	0.5	2	88
6	CHCl <sub>3</sub>	1.5	0.5	2	85
7	CH <sub>2</sub> Cl <sub>2</sub>	1.5	0.5	14	<sup>b</sup>
8	acetone:H <sub>2</sub> O (100:1)	1.5	0.5	4	84
9	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (100:1)	1.5	0.5	4	90
<b>10</b>	<b>acetone:H<sub>2</sub>O (1:1)</b>	<b>1.5</b>	<b>0.5</b>	<b>4</b>	<b>91</b>
<b>11</b>	<b>CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O (1:1)</b>	<b>1.5</b>	<b>0.5</b>	<b>4</b>	<b>89</b>
12	EtOAc:H <sub>2</sub> O (1:1)	1.5	0.5	4	62
13	acetone:H <sub>2</sub> O (1:3)	1.5	0.5	4	45
14	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:3)	1.5	0.5	4	84
15	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (3:1)	1.5	0.5	4	92
16	acetone:H <sub>2</sub> O (1:1)	1.5	-	7	43
17	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:1)	1.5	-	7	31
18	acetone:H <sub>2</sub> O (1:1)	3	1	4	<sup>b</sup>
19	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:1)	3	1	4	<sup>b</sup>
20	acetone:H <sub>2</sub> O (1:1)	2	1	4	<sup>b</sup>
21	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:1)	2	1	4	<sup>b</sup>
22	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:1)	1.5	0.5	6	94
23	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:1)	1.5	0.5	8	93

**Table 2.** Oxidation of benzyl alcohol by IBX under various conditions. (Cont.)

Entry	Solvent (v/v)	IBX (equiv)	<i>n</i> -Bu <sub>4</sub> NBr (equiv)	Time (h)	Conversion (%) <sup>a</sup>
24	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:1)	1.5	0.5	14	<sup>b</sup>
25	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (3:1)	1.5	1	4	53
26	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:1)	1.5	1	4	60
27	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:1)	1.5	1	6	67
28	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:3)	1.5	1	4	55
29	CH <sub>2</sub> Cl <sub>2</sub> :H <sub>2</sub> O (1:1)	1.5	0.1	4	70

<sup>a</sup>Conversion (%) was calculated from <sup>1</sup>H NMR (300 MHz) integration.

<sup>b</sup>The corresponding carboxylic acid formed as well as aldehyde and recovered starting material.

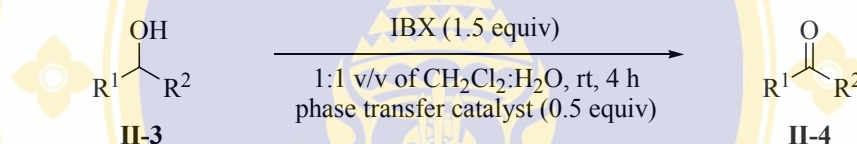
As can be seen in Table 2, the reactions employed 1.5 equivalents of IBX in acetone, dichloromethane and chloroform in the absence of water for 4 h gave benzaldehyde in 81%, 45% and 34%, respectively (entries 1-3). The addition of 0.5 equivalents of tetrabutylammonium bromide (*n*-Bu<sub>4</sub>NBr) provided shorter reaction time (2 h) and better conversion (entries 4-6). The results shown in entries 8-15 suggested that water can be used as a co-solvent and the v/v ratio of organic solvent to water can be as low as 1:3. Even though, the 1:3 CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O solvent system (entry 14) works well with oxidation of benzyl alcohol to benzaldehyde, it failed with other alcohols studied. This might be the result of low solubility of the alcohol substrates in the solvent system with high water content. In addition to obtaining a good conversion, we also like to minimize the amount of organic solvent employed in the reaction. Thus, the reaction conditions shown in entries 10 and 11 are the best conditions so far. The significance of *n*-Bu<sub>4</sub>NBr was studied next. Under the reaction conditions in entries 10 and 11 but in the absence of *n*-Bu<sub>4</sub>NBr, lower conversion was observed even at prolonged reaction time (entries 16 and 17). Over-oxidation to carboxylic acid was observed when the equivalents of IBX were increased (entries 18-21). Although the reaction time was extended from 4 h (in entry 11) to 6 and 8 h (entries 22 and 23), the yield of the product was not significantly higher. When either a stoichiometric or a lesser amount of *n*-Bu<sub>4</sub>NBr was employed, lower conversions

were observed (entries 25-29). Upon utilizing reaction conditions in entry 10 with other alcohols, in some cases, many unidentified side-products formed. Therefore, the reaction conditions in Table 2, entry 11 were chosen as standard conditions.

## 2. Oxidation of alcohols.

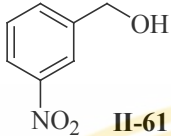
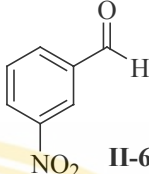
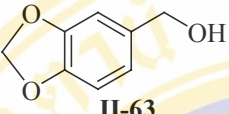
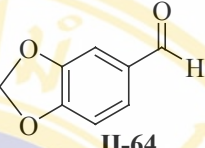
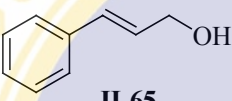
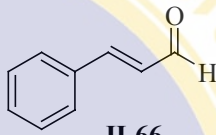
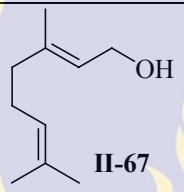
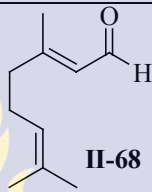
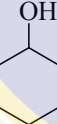
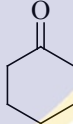
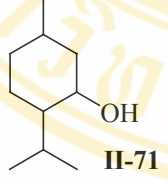
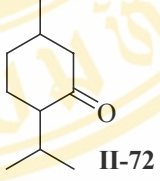
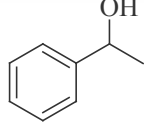
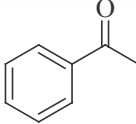
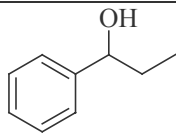
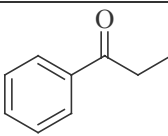
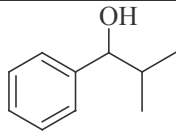
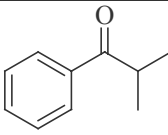
To determine the generality of the oxidation reaction, a variety of alcohols were oxidized by using 1.5 equivalents of IBX at room temperature with 1:1 v/v of dichloromethane and water as a solvent in the presence of 0.5 equivalent *n*-Bu<sub>4</sub>NBr. The reaction was allowed to proceed for 4 h. The results are summarized in Table 3.

**Table 3** Oxidation of alcohols.

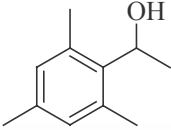
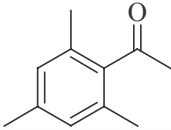
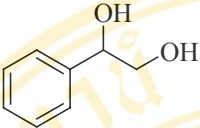
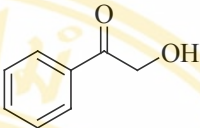


Entry	Alcohol	Product	Yield (%) <sup>a</sup>
1	II-53	II-54	78
2	II-55	II-56	72
3	II-57	II-58	92
4	II-59	II-60	12

**Table 3.** Oxidation of alcohols. (Cont.)

Entry	Alcohol	Product	Yield (%) <sup>a</sup>
5	 II-61	 II-62	19
6	 II-63	 II-64	37
7	 II-65	 II-66	52
8	 II-67	 II-68	72
9	 II-69	 II-70	80
10	 II-71	 II-72	19
11	 II-73	 II-74	71
12	 II-75	 II-76	66
13	 II-77	 II-78	62

**Table 3.** Oxidation of alcohols. (Cont.)

Entry	Alcohol	Product	Yield (%) <sup>a</sup>
14	 II-79	 II-80	94
15	 II-81	 II-82	31

<sup>a</sup>Isolated yields after purification by chromatography.

From Table 3, the yields of products vary from low to excellent (12-94 %). For benzylic alcohols, benzyl alcohol was oxidized to benzaldehyde in good yield (entry 1). The rate as well as the yield of the reactions is dependent on the substituents present on the benzene ring. Electron-donating group such as -OMe (Table 3, entry 3) gave excellent yield of 92%. In contrast, the presence of electron-withdrawing groups such as -Cl, or -NO<sub>2</sub> on the benzene ring resulted in lower yields (entries 2, 4 and 5). Allylic alcohols were readily oxidized to the corresponding carbonyls in moderate to good yields (entries 7 and 8). The aliphatic secondary alcohol, cyclohexanol was oxidized to give cyclohexanone in good yield (80%) (entry 9) while menthol gave very low yield of the corresponding ketone (entry 10). This was hypothesized to stem from the presence of sterically hindered isopropyl substituent at the carbon next to the carbinol carbon. In the case of arylalkylcarbinols, 1-phenyl-1-ethanol was oxidized to acetophenone in good yield (71%) (entry 11). The yields was decreased when steric demanding of the alkyl groups increased (entries 12 and 13). Interestingly, when highly hindered mesityl methyl carbinol was employed as a substrate (entry 14), The corresponding ketone was obtained in excellent yield (94%). In entry 15, with the 1,2-diol substrate, the benzylic secondary alcohol was preferentially oxidized to give  $\alpha$ -hydroxy ketone in moderate yield (31%).

At this point, It is highly interesting to further investigate whether, under the reaction conditions, substrates possess both primary and secondary hydroxyl groups within the same molecule would undergo selective oxidation.

### 3. Selective oxidation of secondary alcohols.

Even though the oxidation of monofunctional alcohols proceeded well as few as 1.5 equivalents of IBX, an increased reaction rate was observed with excess oxidant. For the oxidation of diols, it was found that 3 equivalents of IBX afforded the best results. Therefore, the reaction was carried out by using 3 equivalents of 2-iodoxybenzoic acid (IBX) and 0.5 equivalents of tetrabutylammonium bromide (*n*-Bu<sub>4</sub>NBr) using 1:1 v/v of dichloromethane and water as the solvent at room temperature for 4 h.

Initially, a comparison of the relative selectivity of the oxidation by IBX under some conditions previously used for IBX oxidation of alcohols was studied. The 2,2,4-trimethyl-1,3-pentanediol (**II-83**) was chosen as a diol substrate, the results are shown in Table 4.

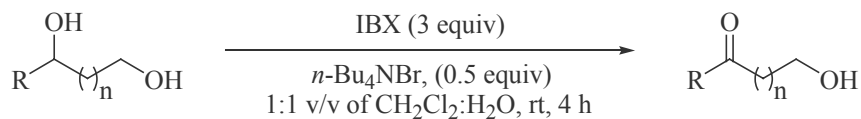


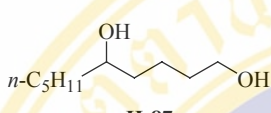
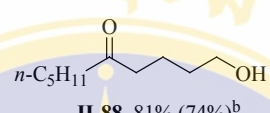
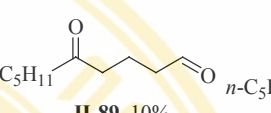
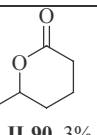
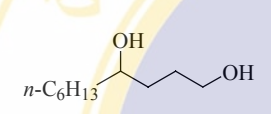
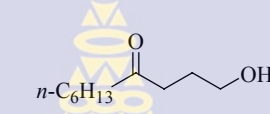
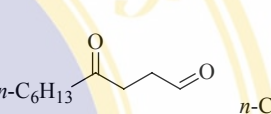
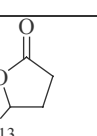
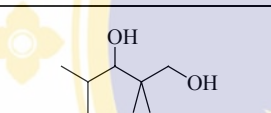
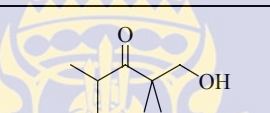
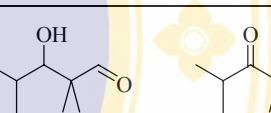
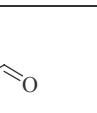
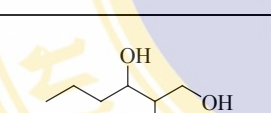
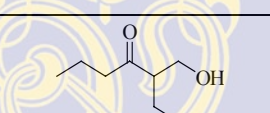
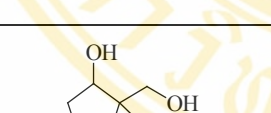
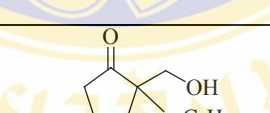
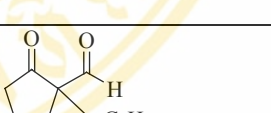
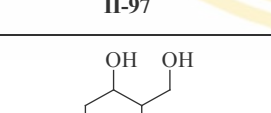
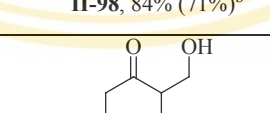
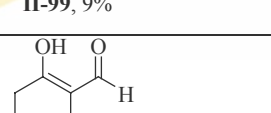
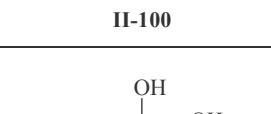
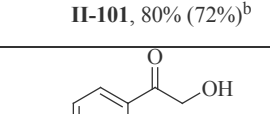
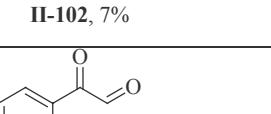
From the results shown in Table 4, when 3 equivalents of IBX were employed, the oxidation of **II-83** lacks of selectivity when the oxidation was carried out at room temperature in DMSO<sup>4</sup> or at 80 °C in EtOAc<sup>7</sup> and the dicarbonyl **II-86** was a single product as detected by GC (entries 1 and 2). Gratifyingly, the reaction under *n*-Bu<sub>4</sub>NBr catalyzed IBX oxidation proceeded well to give product **II-84** (72%) as a major product along with byproducts **II-85** (2%), **II-86** (3%) and recovered **II-83** (20%), entry 3.

When the equivalents of IBX was reduced from 3 equivalents to 1 equivalent (entries 4-6), it demonstrated that under the reaction carried out in DMSO and EtOAc (entries 4 and 5), secondary hydroxyl group was oxidized slightly faster than the primary hydroxyl group. These small multitudes of rate difference are not synthetically useful. In contrast, the reaction carried out using 1 equivalent of IBX under phase transfer catalyzed oxidation gave compound **II-84** (42%) as a major product along with minute amount of byproduct **II-85** (4%), **II-86** (2%) and recovered diol (33%) (entry 6). Therefore, it is an evident that the oxidation of diols by IBX catalyzed by *n*-Bu<sub>4</sub>NBr was chemoselective at secondary hydroxyl group.

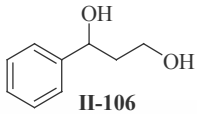
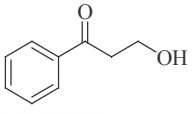
When the oxidation was carried out using 3 equivalents of IBX in 1:1 v/v of CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O but in the absence of *n*-Bu<sub>4</sub>NBr, the chemoselectivity is still preserved (entry 7). The reaction proceeded at slower rate and the compound **II-84** is still obtained as a major product along with significant amount of diol **II-83** was remained (entry 7 vs entry 3). Therefore, the origin of the chemoselectivity of the oxidation was believed to derived from the choice of solvents.

To demonstrate the synthetic utility of the reaction, a variety of diols were subjected to the oxidation under the reaction conditions shown in Table 4, entry 3. The results are summarized in Table 5.

**Table 5** Selective oxidation of secondary alcohols.

Entry	Substrate	Product (% yield) <sup>a</sup>
1	 II-87	 II-88, 81% (74%) <sup>b</sup>  II-89, 10%  II-90, 3%
2	 II-91	 II-92, 87% (70%) <sup>b</sup>  II-93, 2%  II-94, 5%
3	 II-83	 II-84, 72% (70%) <sup>b</sup>  II-85, 7%  II-86, 3%
4	 II-95	 II-96, 62% (56%) <sup>b</sup>
5	 II-97	 II-98, 84% (71%) <sup>b</sup>  II-99, 9%
6	 II-100	 II-101, 80% (72%) <sup>b</sup>  II-102, 7%
7	 II-103	 II-104, 46% (38%) <sup>b</sup>  II-105, 8%

**Table 5.** Selective oxidation of secondary alcohols. (Cont.)

Entry	Substrate	Product (% yield) <sup>a</sup>
8	 <b>II-106</b>	 <b>II-107</b> , 67% (58 %) <sup>b</sup>

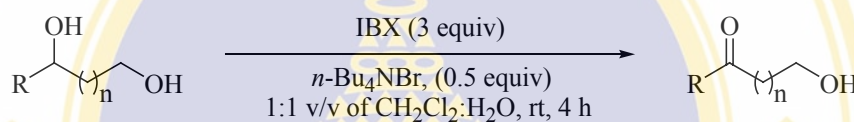
<sup>a</sup>Yield analysed by GC.<sup>b</sup>Yields given in parenthesis are isolated yields after purification by chromatography.

As illustrated in Table 5, 1,5 and 1,4-diols (entries 1-2) were preferentially oxidized at the secondary hydroxyls to give the corresponding keto alcohols in 74% and 70% isolated yields, respectively. The dicarbonyls and lactones were obtained as minor products. 5-Membered and 6-membered lactones were believed to be formed by initial oxidation at the primary hydroxyl to give the aldehyde. Intramolecular hemiacetal formation gave lactol which was then oxidized by IBX to give the observed lactones.<sup>4</sup> 1,3-Diols **II-95** gave  $\beta$ -hydroxy ketone **II-96** in 56% yield (entry 4). In the case of cyclic secondary alcohols, cyclopentanol **II-97** and cyclohexanol **II-100** were similarly selectively oxidized at the secondary hydroxyls to produce hydroxy ketones in high yields (entries 5-6). Secondary benzylic hydroxyls of compound **II-103** and **II-106** were oxidized to hydroxy ketones **II-104** and **II-107**, respectively (entries 7-8). Low yield of compound **II-104** presumably dues to the oxidative cleavage.

### CHAPTER III

### CONCLUSIONS

In conclusion, a selective and efficient alternative method has been developed for the oxidation of secondary hydroxyl groups to ketones in moderate to good yields, in the presence of primary hydroxyl group within the same molecule.



## CHAPTER IV

### EXPERIMENTAL

#### General Methods.

Unless otherwise noted, all reactions were performed under Ar atmosphere in oven-dried glassware cooled in a desiccator before use. Solvents and reagents were purified as follows: tetrahydrofuran (THF) was distilled from sodium/benzophenone; dichloromethane ( $\text{CH}_2\text{Cl}_2$ ) and acetone were distilled from  $\text{P}_2\text{O}_5$  and were stored over activated molecular sieves (4 Å). Flash column chromatography was performed with Merck silica gel 60 (Art. 7734). Preparatory layer chromatography (PLC) was performed using Merck silica gel 60 PF<sub>254</sub> (Art. 7747). Analytical TLC was performed with Merck silica gel 60 PF<sub>254</sub> (Art. 5554) with 0.2 mm thickness. All chemicals were purchased from Fluka, Aldrich and Acros organics and were used without prior purification

<sup>1</sup>H NMR spectra were recorded on a Bruker DPX-300 (300 MHz) spectrometer. <sup>13</sup>C NMR spectra were obtained from a Bruker Advance-300 (75 MHz) spectrometer. NMR data are reported as follow: <sup>1</sup>H NMR chemical shifts, measured in parts per million (ppm) down field from TMS ( $\delta$ ), proton count, multiplicity, observed coupling constant (J) in Hertz (Hz). Multiplicities are reported as singlet (s), broad singlet (br s), doublet (d), broad doublet (br d), triplet (t), quartet (q), and multiplet (m). <sup>13</sup>C NMR chemical shifts are reported in ppm with residual non-deuterated solvent peak as the internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. GC analysis was performed on an Agilent 6890 Series Gas Chromatograph with an HP Chemstation software. Microanalyses were carried out with Perkin Elmer Elemental Analyzer 2400 CHN. Mass spectrometric analyses were recorded on a Bruker Esquire or a Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on HR-TOF-MS Micromass model VQ-TOF2 at the Chulabhorn Research Institute (CRI).

Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected.

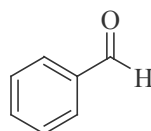
### Preparation of 2-iodoxybenzoic acid (IBX)<sup>3</sup>

2-iodobenzoic acid (2.50 g, 0.01 mmol) was added to an OXONE solution in deionized water (18.60 g, 0.03 mmol, 3 equiv in 100 mL) in a 0.5 L flask. The suspension was set to 70 °C after 1 h at this temperature a clear solution was obtained that delivered analytical grade IBX upon cooling the solution to 0-5 °C for 0.5 h. The mixture was filtered and washed with water and acetone. The white, crystalline solid was left to dry at room temperature for 16 h.

### General procedure A for the oxidation of simple monofunctional alcohols.

To a stirred suspension of IBX (1.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (v/v = 1:1, 0.25 M based on starting alcohol) was added tetrabutylammonium bromide (*n*-Bu<sub>4</sub>NBr) (0.5 equiv) followed by the addition of alcohol (1.0 equiv) in one portion. The mixture was stirred at room temperature for 4 h. The residual solids were filtered off and washed thoroughly with diethyl ether. The combined filtrate was washed successively with 8% sodium thiosulfate (1x15 mL), water (2x15 mL), and brine (1x15 mL). The organic layer was dried over sodium sulfate, filtered and evaporated (aspirator). The crude product was purified by column chromatography (SiO<sub>2</sub>) to provide the isolated yields of aldehydes or ketones as listed below.

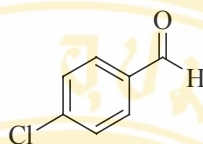
### Benzaldehyde (II-54).



Following the general procedure A, benzyl alcohol (0.1081 g, 1.0 mmol) employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), benzaldehyde (0.0829 g, 78%) was obtained as a pale yellow liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether, R<sub>f</sub> = 0.43. IR (neat, cm<sup>-1</sup>)

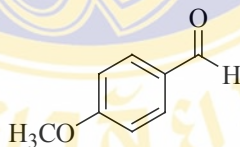
1704, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  10.03 (1H, s) 7.89 (2H, d,  $J = 7.6$  Hz) 7.67-7.62 (1H, m) 7.57-7.52 (2H, m).

#### 4-Chlorobenzaldehyde (II-56).

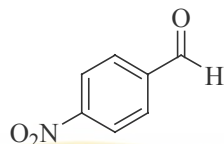


Following the general procedure A, 4-chlorobenzyl alcohol (0.1426 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), 4-chloro benzaldehyde (0.1014 g, 72%) was obtained as a white solid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.27$ . IR (KBr,  $\text{cm}^{-1}$ ) 1702, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  9.91 (1H, s) 7.75 (2H, d,  $J = 8.2$  Hz) 7.44 (2H, d,  $J = 8.2$  Hz).

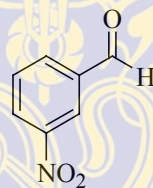
#### 4-Methoxybenzaldehyde (II-58).



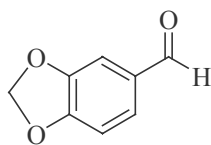
Following the general procedure A, 4-methoxybenzyl alcohol (0.1382 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), 4-methoxy benzaldehyde (0.1268 g, 92%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.25$ . IR (neat,  $\text{cm}^{-1}$ ) 1682, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  9.89 (1H, s) 7.84 (2H, d,  $J = 8.9$  Hz) 7.01 (2H, d,  $J = 8.9$  Hz) 3.89 (3H, s).

**4-Nitrobenzaldehyde (II-60).**

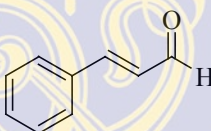
Following the general procedure A, 4-nitrobenzyl alcohol (0.1531 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 8:2 *n*-hexane/diethyl ether eluent), 4-nitro benzaldehyde (0.0185 g, 12%) was obtained as a white solid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.23$ . IR (KBr,  $\text{cm}^{-1}$ ) 1710, C=O; 1538, NO<sub>2</sub>. 300 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm)  $\delta$  10.17 (1H, s) 8.41 (2H, d,  $J = 8.6$  Hz) 8.09 (2H, d,  $J = 8.6$  Hz).

**3-Nitrobenzaldehyde (II-62).**

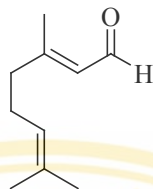
Following the general procedure A, 3-nitrobenzyl alcohol (0.1531 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 8:2 *n*-hexane/diethyl ether eluent), 3-nitro benzaldehyde (0.0289 g, 19%) was obtained as a white crystalline solid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.16$ . IR (KBr,  $\text{cm}^{-1}$ ) 1707, C=O; 1534, NO<sub>2</sub>. 300 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm)  $\delta$  10.14 (1H, s) 8.73 (1H, s) 8.51 (1H, d,  $J = 8.3$  Hz) 8.25 (1H, d,  $J = 7.3$  Hz) 7.78 (1H, t,  $J = 7.8$  Hz).

**3,4-Methylenedioxybenzaldehyde (II-64).**

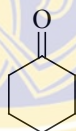
Following the general procedure A, 3,4-methylenedioxybenzyl alcohol (0.1521 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), 3,4-methylenedioxybenzaldehyde (0.0558 g, 37%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.35$ . IR (neat,  $\text{cm}^{-1}$ ) 1687, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  9.82 (1H, s) 7.42 (1H, d,  $J = 8.3$  Hz) 7.34 (1H, s) 6.94 (1H, d,  $J = 8.0$  Hz) 6.09 (2H, s).

**Cinnamaldehyde (II-66).**

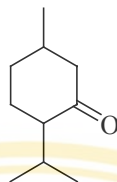
Following the general procedure A, cinnamyl alcohol (0.1349 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), cinnamaldehyde (0.0689 g, 52%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.27$ . IR (neat,  $\text{cm}^{-1}$ ) 1678, C=O; 1626, C=C. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  9.71 (1H, d,  $J = 7.4$  Hz) 7.59-7.40 (6H, m) 6.72 (1H, dd,  $J = 7.4, 15.9$  Hz).

**Citral (II-68).**

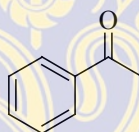
Following the general procedure A, nerol (0.1552 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), citral (0.1068 g, 70%) was obtained as a colorless liquid: analytical TLC on silica gel, 8:2 *n*-hexane/diethyl ether,  $R_f = 0.32$ . IR (neat,  $\text{cm}^{-1}$ ) 1678, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  9.95 (1H, m) 5.88 (1H, d,  $J = 8.2$  Hz) 5.11 (1H, t,  $J = 7.3$  Hz) 2.59 (2H, t,  $J = 7.5$  Hz) 2.24 (2H, q,  $J = 7.4$  Hz) 1.99 (3H, s) 1.69 (3H, s) 1.60 (3H, s).

**Cyclohexanone (II-70).**

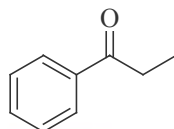
Following the general procedure A, cyclohexanol (0.1002 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), cyclohexanone (0.0866 g, 80%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.28$ . IR (neat,  $\text{cm}^{-1}$ ) 1713, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  2.34 (4H, t,  $J = 6.5$  Hz) 1.87 (4H, m) 1.72 (2H, m).

**(-)-Menthone (II-72).**

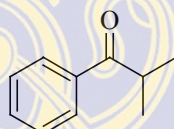
Following the general procedure A, (-)-menthol (0.1563 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), (-)-menthone (0.0295 g, 19%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.48$ . IR (neat,  $\text{cm}^{-1}$ ) 1712, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  2.38-1.78 (7H, m) 1.46-1.26 (2H, m) 1.01 (3H, d,  $J = 6.2$  Hz) 0.91 (3H, d,  $J = 6.5$  Hz) 0.85 (3H, d,  $J = 6.5$  Hz).

**Acetophenone (II-74).**

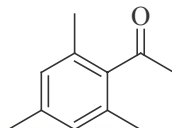
Following the general procedure A, 1-phenyl-1-ethanol (0.1243 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), acetophenone (0.0866 g, 71%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.30$ . IR (neat,  $\text{cm}^{-1}$ ) 1686, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.96 (2H, d,  $J = 7.5$  Hz) 7.57 (1H, t,  $J = 7.3$  Hz) 7.46 (2H, t,  $J = 7.4$  Hz) 2.61 (3H, s).

**Propiophenone (II-76).**

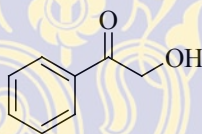
Following the general procedure A, 1-phenyl-1-propanol (0.1362 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), propiophenone (0.0884 g, 66%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.42$ . IR (neat,  $\text{cm}^{-1}$ ) 1688, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.89 (2H, d,  $J = 7.5$  Hz) 7.47 (1H, t,  $J = 7.3$  Hz) 7.37 (2H, t,  $J = 7.5$  Hz) 2.92 (2H, q,  $J = 7.3$  Hz) 1.14 (3H, t,  $J = 7.3$  Hz).

**Isobutyrophenone (II-78).**

Following the general procedure A, 2-methyl-1-phenyl-1-propanol (0.1502 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), isobutyrophenone (0.0917 g, 62%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.52$ . IR (neat,  $\text{cm}^{-1}$ ) 1682, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.96 (2H, d,  $J = 8.0$  Hz) 7.58-7.44 (3H, m) 3.61-3.52 (1H, m) 1.22 (6H, d,  $J = 6.6$  Hz).

**2,4,6-Trimethylacetophenone (II-80).**

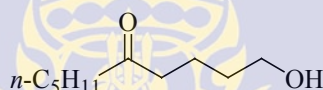
Following the general procedure A, 1-(2,4,6-trimethylphenyl)-1-ethanol (0.1642 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), 2,4,6-trimethylacetophenone (0.1527 g, 94%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.45$ . IR (neat,  $\text{cm}^{-1}$ ) 1699, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  6.82 (2H, s) 2.44 (3H, s) 2.26 (3H, s) 2.20 (6H, s).

**2-Hydroxy-1-phenyl ethanone (II-82).**

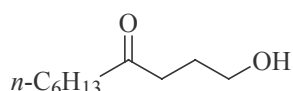
Following the general procedure A, 1-phenyl-1,2-ethanediol (0.1382 g, 1.0 mmol) was employed. After column chromatography on silica gel (12x3 cm, 7:3 *n*-hexane/diethyl ether eluent), 2-hydroxy-1-phenyl ethanone (0.0429 g, 31%) was obtained as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.16$ . IR (neat,  $\text{cm}^{-1}$ ) 3430, O-H; 1683, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.93 (2H, d,  $J = 7.6$  Hz) 7.64 (1H, t,  $J = 7.3$  Hz) 7.51 (2H, t,  $J = 7.7$  Hz) 4.89 (2H, s).

**General procedure B for the oxidation of diols.**

To a stirred suspension of IBX (3.0 equiv) in  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$  ( $v/v = 1:1$ , 0.25 M based on starting alcohol) was added tetrabutylammonium bromide ( $n\text{-Bu}_4\text{NBr}$ ) (0.5 equiv) followed by the addition of diol (1.0 equiv) in one portion. The mixture was stirred at room temperature for 4 h. The residual solids were filtered off and washed thoroughly with diethyl ether. The combined filtrate was washed successively with 8% sodium thiosulfate (1x15 mL), water (2x15 mL), and brine (1x15 mL). The organic layer was dried over sodium sulfate, filtered and evaporated (aspirator). The crude product was purified by column chromatography ( $\text{SiO}_2$ ) to provide the isolated yields of aldehydes or ketones as listed below.

**1-Hydroxy-5-decanone (II-88)**

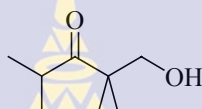
According to the general procedure B, oxidation of 1,5-decanediol (174 mg, 1 mmol) gave 1-hydroxy-5-decanone, after column chromatography on silica gel (18x1.5 cm, 8:2  $n$ -hexane/ethyl acetate as eluent), 127 mg (isolated yield; 74%) as colorless liquid: analytical TLC on silica gel, 7:3  $n$ -hexane/ethyl acetate,  $R_f = 0.17$ . IR (neat,  $\text{cm}^{-1}$ ) 3423, O-H; 1712, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  3.57 (2H, br s) 2.55-2.10 (4H, m) 1.70-1.10 (11H, m) 0.82 (3H, t,  $J = 6.9$  Hz). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  211.6, 62.1, 42.7, 42.1, 32.0, 31.3, 23.5, 22.4, 19.6, 13.8. Molecular ion  $[(\text{M}+\text{H})^+]$  calcd. for  $\text{C}_{10}\text{H}_{21}\text{O}_2$ : 173.1542; found (ESI) 173.1536, error = 3.4 ppm.

**1-Hydroxy-4-decanone (II-92)**

According to the general procedure B, oxidation of 1,4-decanediol (174 mg, 1 mmol) gave 1-hydroxy-4-decanone, after column chromatography on silica gel

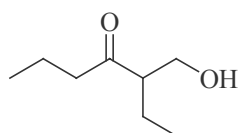
(18x1.5 cm, 8:2 *n*-hexane/ethyl acetate as eluent), 120 mg (isolated yield; 70%) as colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/ethyl acetate,  $R_f = 0.16$ . IR (neat,  $\text{cm}^{-1}$ ) 3422, O-H; 1707, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  3.64 (2H, t,  $J = 6.1$  Hz) 2.55-2.30 (4H, m) 2.00-1.66 (2H, m) 1.65-1.44 (2H, m) 1.40-1.18 (7H, m) 0.88 (3H, t,  $J = 6.6$  Hz). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  212.1, 62.1, 42.9, 39.4, 31.5, 28.8, 26.4, 23.8, 22.4, 14.0.

### 1-Hydroxy-2,2,4-trimethyl-3-pentanone (II-84)



According to the general procedure B, oxidation of 2,2,4-trimethyl-1,3-pentanediol (146 mg, 1 mmol) gave 1-hydroxy-2,2,4-trimethyl-3-pentanone, after column chromatography on silica gel (18x1.5 cm, 8:2 *n*-hexane/diethyl ether as eluent), 101 mg (isolated yield; 70%) as colorless liquid: analytical TLC on silica gel, 8:2 *n*-hexane/diethyl ether,  $R_f = 0.12$ . IR (neat,  $\text{cm}^{-1}$ ) 3479, O-H; 1699, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  3.56 (2H, s) 3.18-3.02 (1H, m) 2.85 (1H, br d,  $J = 7.4$  Hz) 1.18 (6H, s) 1.06 (6H, d,  $J = 6.8$  Hz). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  221.5, 69.3, 49.6, 34.5, 21.0, 19.8.

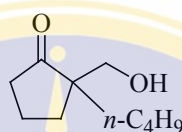
### 3-Hydroxymethyl-4-heptanone (II-96)



According to the general procedure B, oxidation of 2-ethyl-1,3-hexanediol (185 mg, 1.27 mmol) gave 3-hydroxymethyl-4-heptanone, after column chromatography on silica gel (18x1.5 cm, 7:3 *n*-hexane/diethyl ether as eluent), 103 mg (isolated yield; 56%) as colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.05$ . IR (neat,  $\text{cm}^{-1}$ ) 3422, O-H; 1705, C=O. 300 MHz  $^1\text{H}$

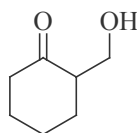
NMR (CDCl<sub>3</sub>, ppm)  $\delta$  3.80 (1H, dd, ABX,  $J = 11.0, 7.4$  Hz) 3.70 (1H, dd, ABX,  $J = 11.0, 4.1$  Hz) 2.70-2.57 (1H, m) 2.48 (2H, t,  $J = 7.3$  Hz) 2.14 (1H, br s) 1.75-1.39 (4H, m) 0.93 (3H, t,  $J = 7.5$  Hz) 0.92 (3H, t,  $J = 7.4$  Hz). 75 MHz <sup>13</sup>C NMR (CDCl<sub>3</sub>, ppm)  $\delta$  215.1, 62.4, 54.9, 44.8, 21.2, 16.8, 13.7, 11.8.

### 2-Butyl-2-hydroxymethylcyclopentanone (II-98)



According to the general procedure B, oxidation of 2-butyl-2-hydroxymethylcyclopentanol (221 mg, 1.28 mmol) gave 2-butyl-2-hydroxymethylcyclopentanone, after column chromatography on silica gel (18x1.5 cm, 8:2 *n*-hexane/ethyl acetate as eluent), 156 mg (isolated yield; 71%) as a pale yellow liquid: analytical TLC on silica gel, 7:3 *n*-hexane/ethyl acetate,  $R_f = 0.32$ . IR (neat, cm<sup>-1</sup>) 3448, O-H; 1731, C=O. 300 MHz <sup>1</sup>H NMR (CDCl<sub>3</sub>, ppm)  $\delta$  3.62 (1H, d,  $J = 11.0$  Hz) 3.47 (1H, d,  $J = 11.0$  Hz) 2.36 (1H, s) 2.31-2.17 (2H, m) 2.01-1.80 (4H, m) 1.55-1.01 (6H, m) 0.88 (3H, t,  $J = 7.0$  Hz). 75 MHz <sup>13</sup>C NMR (CDCl<sub>3</sub>, ppm)  $\delta$  224.7, 65.7, 53.4, 38.8, 32.2, 30.5, 26.2, 23.2, 19.1, 13.8. Anal. Calcd for C<sub>10</sub>H<sub>18</sub>O<sub>2</sub>: C, 70.55; H, 10.66. Found: C, 70.29; H, 10.45.

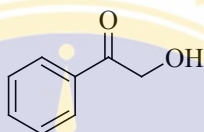
### 2-Hydroxymethylcyclohexanone (II-101)



According to the general procedure B, oxidation of 2-hydroxymethylcyclohexanol (130 mg, 1 mmol) gave 2-hydroxymethylcyclohexanone, after column chromatography on silica gel (18x1.5 cm, 8:2 *n*-hexane/ethyl acetate as eluent), 91.8 mg (isolated yield; 72%) as a colorless liquid: analytical TLC on silica

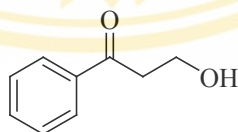
gel, 6:4 *n*-hexane/ethyl acetate,  $R_f = 0.25$ . IR (neat,  $\text{cm}^{-1}$ ) 3421, O-H; 1702, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  3.81-3.68 (1H, m) 3.68-3.54 (1H, m) 2.79 (1H, br s) 2.61-1.36 (9H, m). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  214.6, 62.5, 52.1, 42.1, 30.0, 27.4, 24.6.

### 2-Hydroxy-1-phenylethanone (II-104)



According to the general procedure B, oxidation of 1-phenyl-1,2-ethanediol (138 mg, 1 mmol) gave 2-hydroxy-1-phenylethanone, after column chromatography on silica gel (18x1.5 cm, 8:2 *n*-hexane/ethyl acetate as eluent), 52.4 mg (isolated yield; 38%) as a white solid: analytical TLC on silica gel, 7:3 *n*-hexane/ethyl acetate,  $R_f = 0.31$ . IR (neat,  $\text{cm}^{-1}$ ) 3428, O-H; 1682, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.93 (2H, d,  $J = 7.6$  Hz) 7.63 (1H, t,  $J = 7.4$  Hz) 7.51 (2H, t,  $J = 7.7$  Hz) 4.89 (2H, s) 2.98 (1H, br s). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  198.4, 134.3, 133.4, 128.9, 127.7, 65.4.

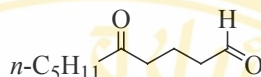
### 3-Hydroxy-1-phenyl-1-propanone (II-107)



According to the general procedure B, oxidation of 1-phenyl-1,3-propanediol (152 mg, 1 mmol) gave 3-hydroxy-1-phenyl-1-propanone, after column chromatography on silica gel (18x1.5 cm, 8.5:1.5 *n*-hexane/ethyl acetate as eluent), 87 mg (isolated yield; 58%) as a colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/ethyl acetate,  $R_f = 0.29$ . IR (neat,  $\text{cm}^{-1}$ ) 3412, O-H; 1681, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  7.97 (2H, d,  $J = 7.3$  Hz) 7.59 (1H, t,  $J = 7.4$  Hz) 7.48 (2H, t,  $J =$

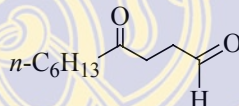
7.5 Hz) 4.05 (2H, t,  $J = 5.4$  Hz) 3.24 (2H, t,  $J = 5.4$  Hz) 2.85 (1H, br s). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  200.4, 136.6, 133.4, 128.6, 128.0, 58.0, 40.3.

### 5-Oxodecanal (II-89)



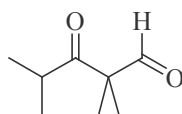
Colorless liquid: analytical TLC on silica gel, 6:4 *n*-hexane/ethyl acetate,  $R_f = 0.52$ . IR (neat,  $\text{cm}^{-1}$ ) 1709, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  9.75 (1H, s) 2.55-2.43 (4H, m) 2.39 (2H, t,  $J = 7.4$  Hz) 1.97-1.80 (2H, m) 1.65-1.47 (2H, m) 1.40-1.16 (4H, m) 0.89 (3H, t,  $J = 6.8$  Hz). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  210.3, 201.8, 42.8, 42.6, 41.1, 31.2, 23.3, 22.2, 15.8, 13.7.

### 4-Oxodecanal (II-93)



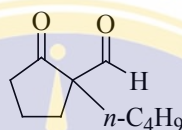
Colorless liquid: analytical TLC on silica gel, 6:4 *n*-hexane/ethyl acetate,  $R_f = 0.47$ . IR (neat,  $\text{cm}^{-1}$ ) 1712, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  9.80 (1H, s) 2.80-2.67 (4H, m) 2.47 (2H, t,  $J = 7.5$  Hz) 1.65-1.50 (2H, m) 1.40-1.18 (6H, m) 0.88 (3H, t,  $J = 6.4$  Hz). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  208.8, 200.4, 42.6, 37.3, 34.5, 31.4, 28.7, 23.7, 22.3, 13.9.

### 2,2,4-Trimethyl-3-oxopentanal (II-86)



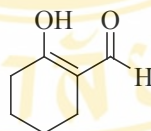
Colorless liquid: analytical TLC on silica gel, 8:2 *n*-hexane/diethyl ether,  $R_f = 0.45$ . IR (neat,  $\text{cm}^{-1}$ ) 1736, 1702, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  9.64 (1H, s) 3.03-2.97 (1H, m) 1.35 (6H, s) 1.06 (6H, d,  $J = 6.7$  Hz). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  213.5, 200.9, 60.7, 36.5, 19.2, 19.0.

### 1-Butyl-2-oxocyclopentanecarbaldehyde (II-99)



Colorless liquid: analytical TLC on silica gel, 7:3 *n*-hexane/diethyl ether,  $R_f = 0.55$ . IR (neat,  $\text{cm}^{-1}$ ) 1745, 1713, C=O. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  9.41 (1H, s) 2.66-1.07 (12H, m) 0.90 (3H, t,  $J = 7.2$  Hz). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  215.3, 199.0, 67.5, 38.6, 32.7, 27.7, 26.6, 22.9, 19.2, 13.7. Molecular ion  $[(M+H)^+]$  calcd. for  $\text{C}_{10}\text{H}_{17}\text{O}_2$ : 169.1229; found (ESI) 169.1223, error = 3.5 ppm.

### 2-Hydroxy-cyclohex-1-enecarbaldehyde (II-102)



Orange liquid: analytical TLC on silica gel, 8:2 *n*-hexane/ethyl acetate,  $R_f = 0.48$ . IR (neat,  $\text{cm}^{-1}$ ) 3421, O-H; 1715, C=O; 1603, C=C. 300 MHz  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  14.40 (1H, br s) 8.64 (1H, s) 2.47-2.25 (4H, m) 1.80-1.59 (4H, m). 75 MHz  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm)  $\delta$  187.5, 184.9, 108.8, 31.2, 23.1, 22.5, 21.2.

**GC analysis:** Analysis for GC yield determination was performed on an Agilent 6890 Series Gas Chromatograph with an HP Chemstation software.

GC conditions:

Column: HP-5 capillary column, 30 m x 0.32 mm I.D., 0.25  $\mu\text{M}$  film thickness

Inlet type: Split mode (split ratio 15:1)

Liner: HP Part No. 5183-4647

Injection mode: Manual injection

Injection Volume: 2  $\mu$ L

Injector temperature: 180  $^{\circ}$ C

Detector temperature: 300  $^{\circ}$ C

Carrier gas: He at constant flow rate 1 ml/min

Temperature program A: Initial 150  $^{\circ}$ C

Increasing at 5  $^{\circ}$ C/min to 200  $^{\circ}$ C

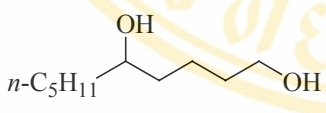
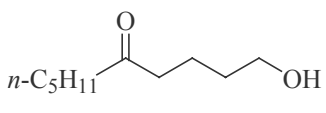
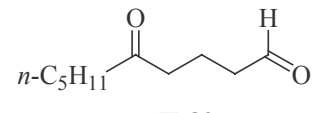
Increasing at 50  $^{\circ}$ C/min to 300  $^{\circ}$ C, hold for 1 min

**B:** Initial 100  $^{\circ}$ C

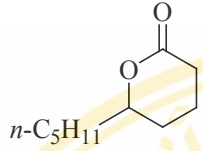
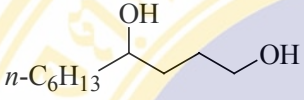
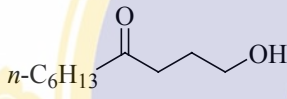
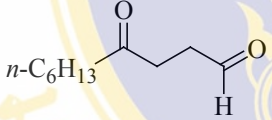
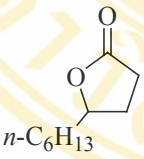
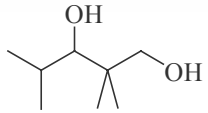
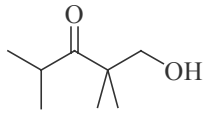
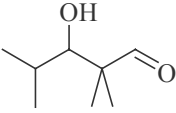
Increasing at 5  $^{\circ}$ C/min to 130  $^{\circ}$ C

Increasing at 50  $^{\circ}$ C/min to 300  $^{\circ}$ C, hold for 1 min

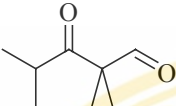
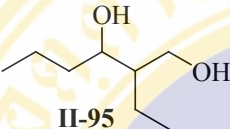
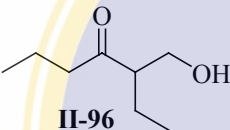
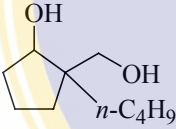
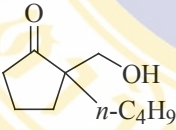
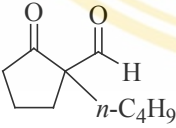
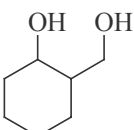
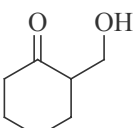
**Table 6** Methods utilized for the yield determination by GC.

Entry	Compounds	Temperature program	Retention time (min)
1	 $n\text{-C}_5\text{H}_{11}$ <b>II-87</b>	A	5.8
2	 $n\text{-C}_5\text{H}_{11}$ <b>II-88</b>	A	5.5
3	 $n\text{-C}_5\text{H}_{11}$ <b>II-89</b>	A	4.7

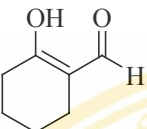
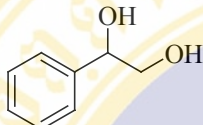
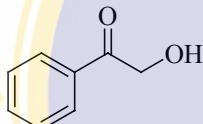
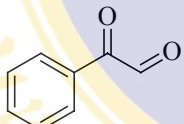
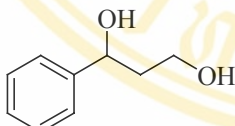
**Table 6.** Methods utilized for the yield determination by GC. (Cont.)

Entry	Compounds	Temperature program	Retention time (min)
4	 $n\text{-C}_5\text{H}_{11}$ <b>II-90</b>	A	6.3
5	 $n\text{-C}_6\text{H}_{13}$ <b>II-91</b>	A	5.8
6	 $n\text{-C}_6\text{H}_{13}$ <b>II-92</b>	A	5.3
7	 $n\text{-C}_6\text{H}_{13}$ <b>II-93</b>	A	4.6
8	 $n\text{-C}_6\text{H}_{13}$ <b>II-94</b>	A	5.9
9	 <b>II-83</b>	B	6.4
10	 <b>II-84</b>	B	5.0
11	 <b>II-85</b>	B	5.2

**Table 6.** Methods utilized for the yield determination by GC. (Cont.)

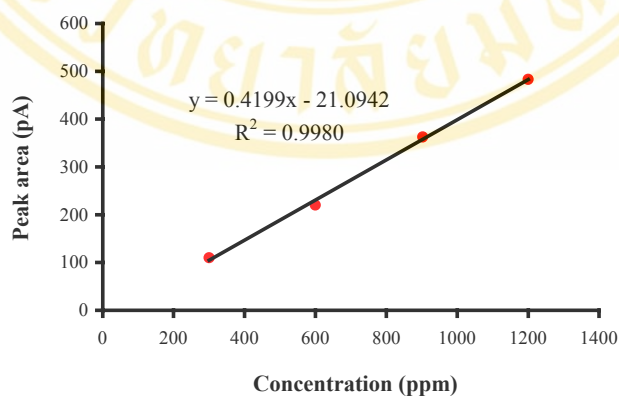
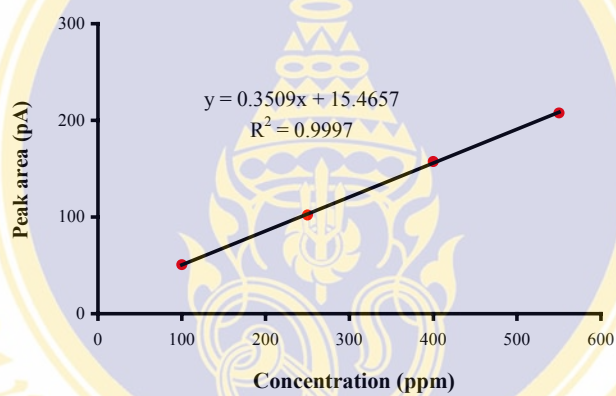
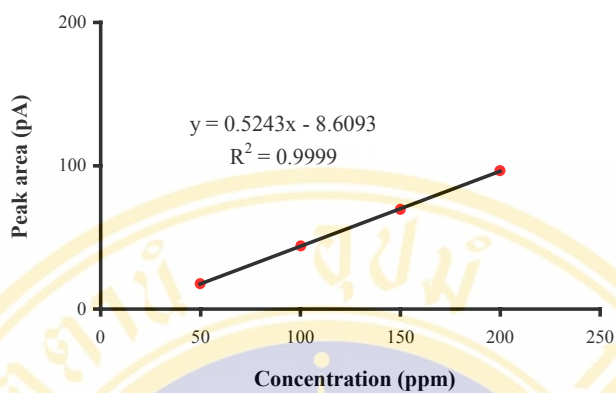
Entry	Compounds	Temperature program	Retention time (min)
12	 II-86	B	4.2
13	 II-95	B	7.1(2 peaks)
14	 II-96	B	6.3
15	 II-97	A	5.6
16	 II-98	A	4.9
17	 II-99	A	4.2
18	 II-100	B	7.2
19	 II-101	B	6.4

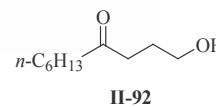
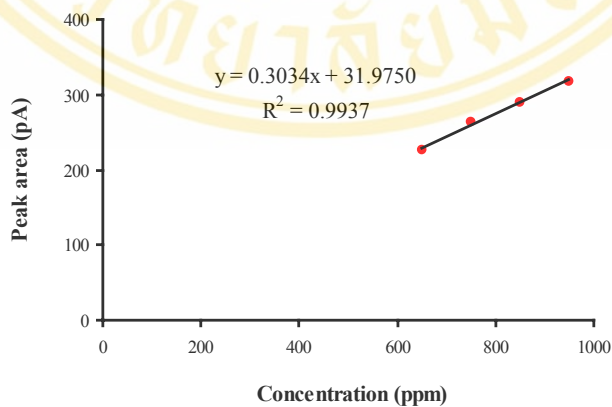
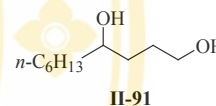
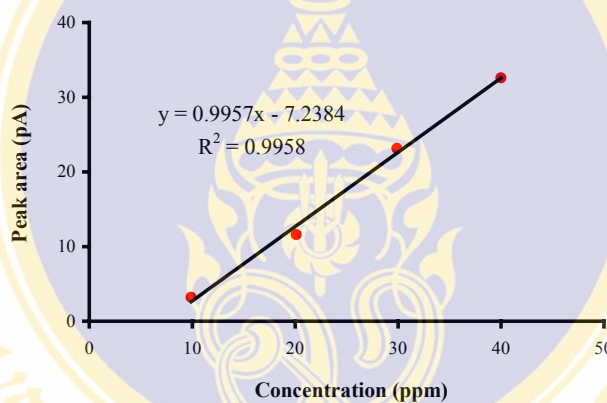
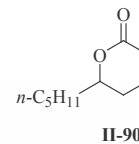
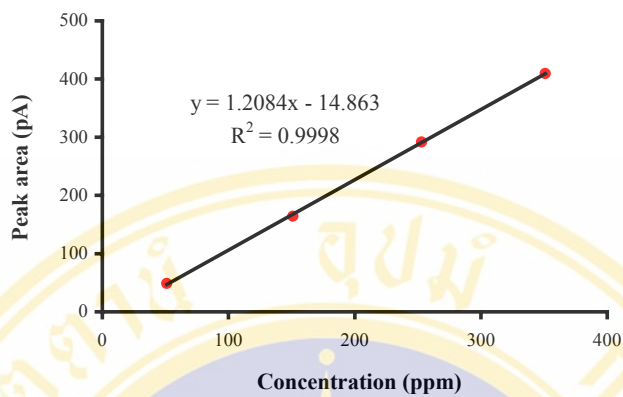
**Table 6.** Methods utilized for the yield determination by GC. (Cont.)

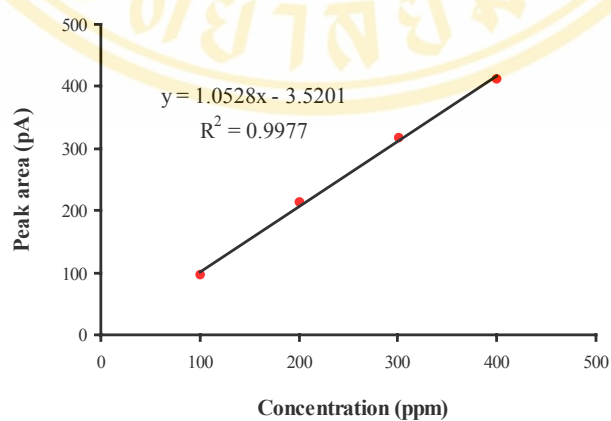
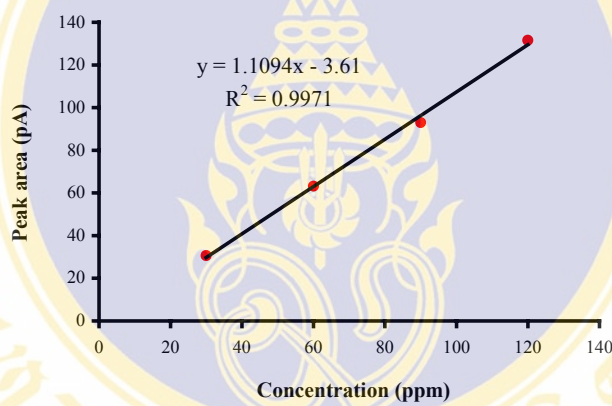
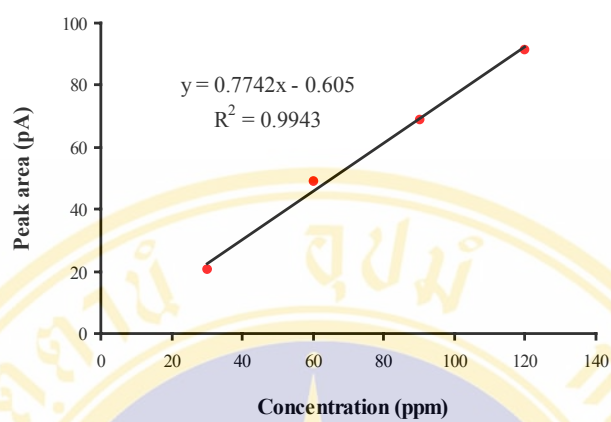
Entry	Compounds	Temperature program	Retention time (min)
20	 II-102	B	5.9
21	 II-103	A	4.4
22	 II-104	A	4.0
23	 II-105	A	3.2
24	 II-106	B	8.7
25	 II-107	B	8.4

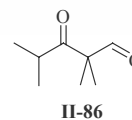
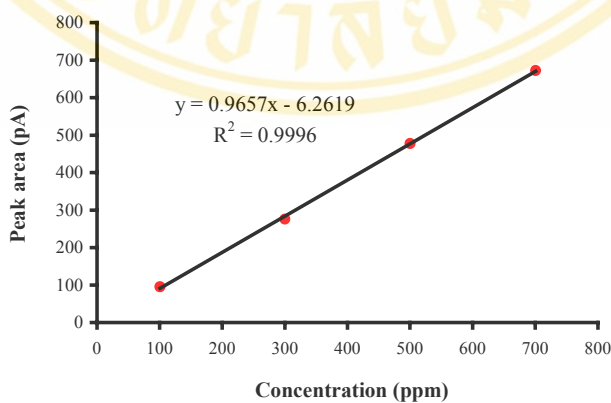
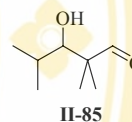
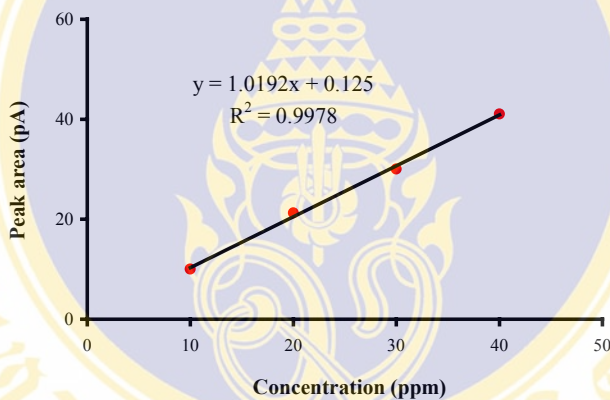
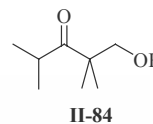
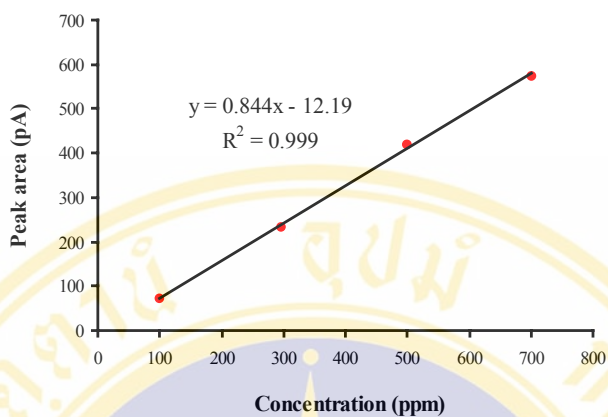
**Calibration curve for GC yield determination.**

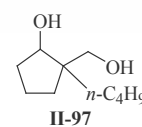
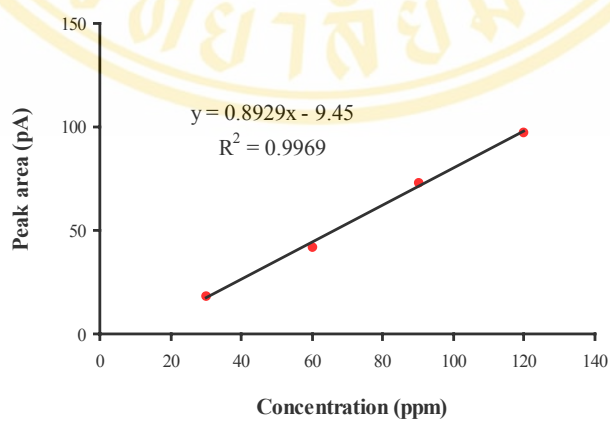
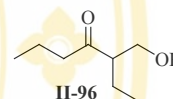
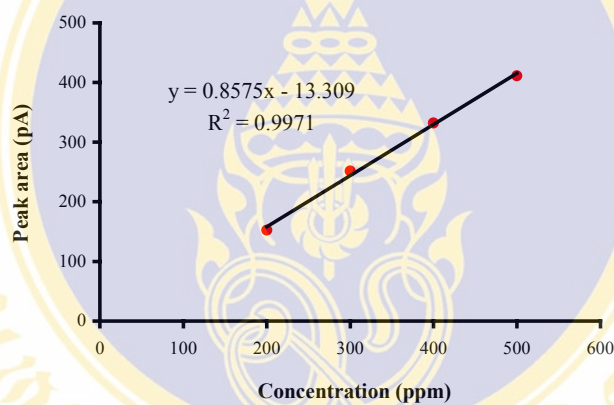
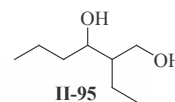
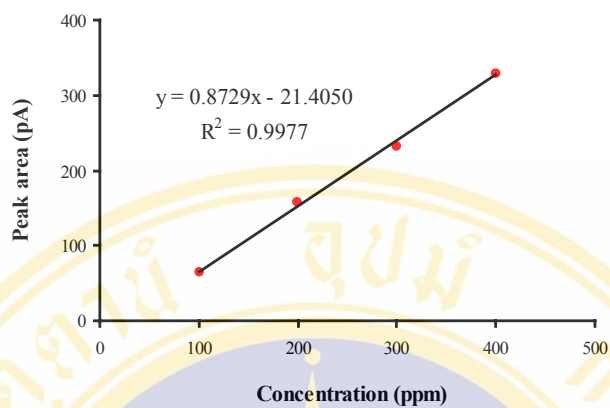
GC yields were calculated from standard curves which are plotted between peak area and concentration of standard.

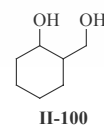
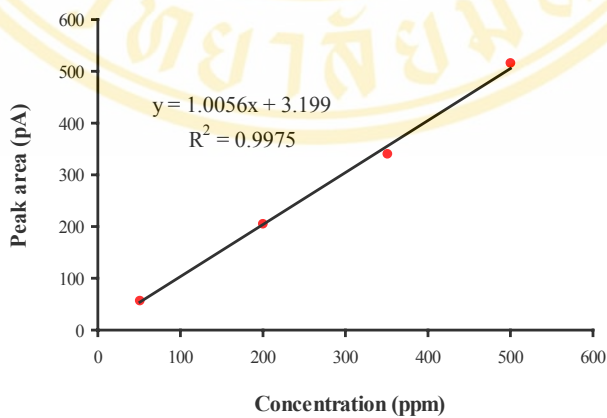
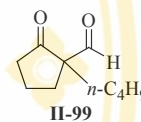
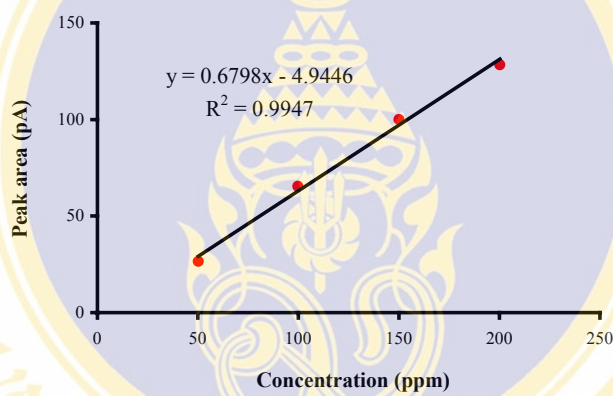
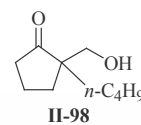
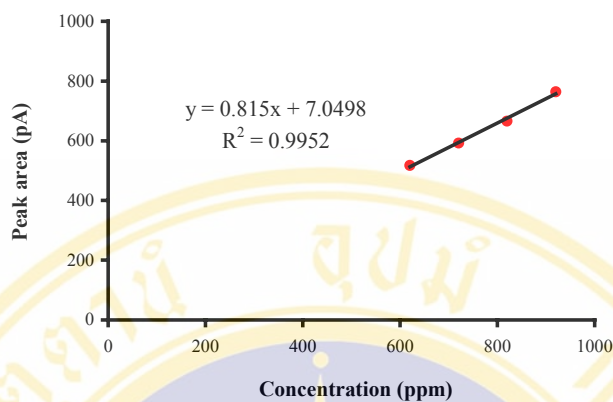


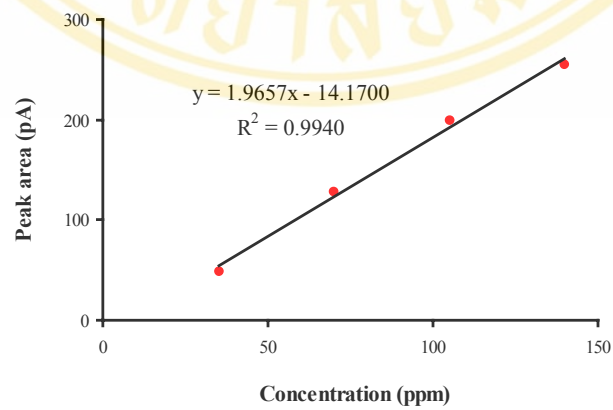
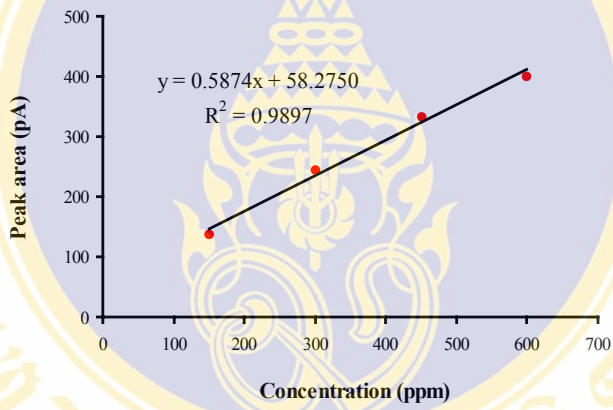
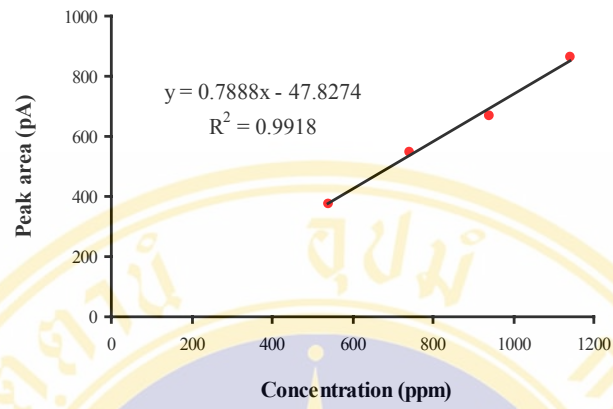


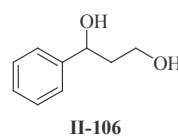
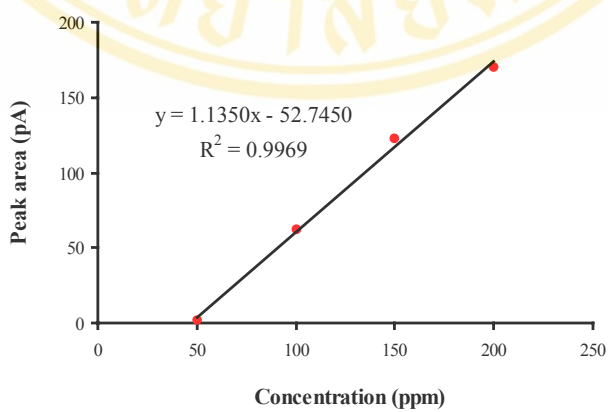
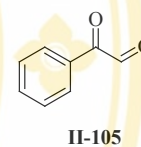
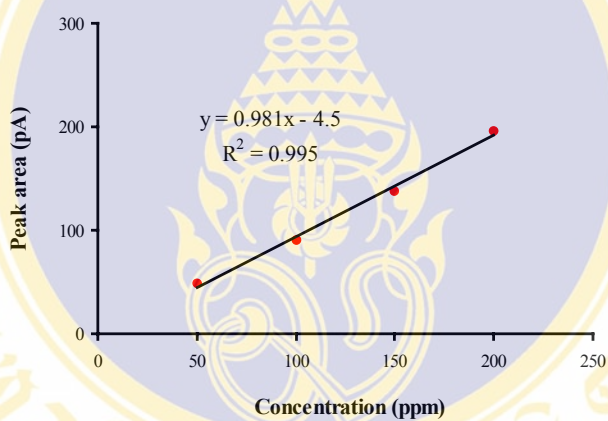
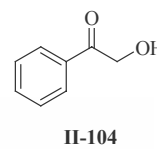
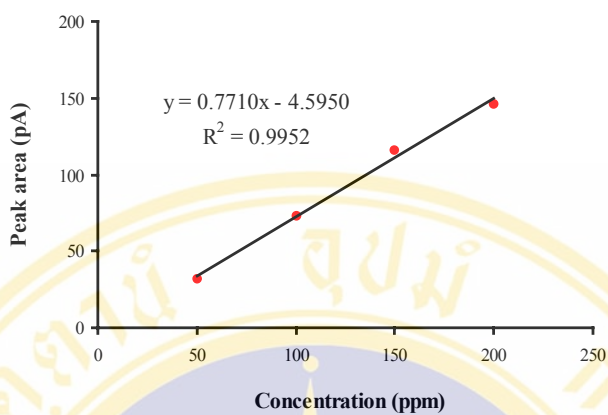


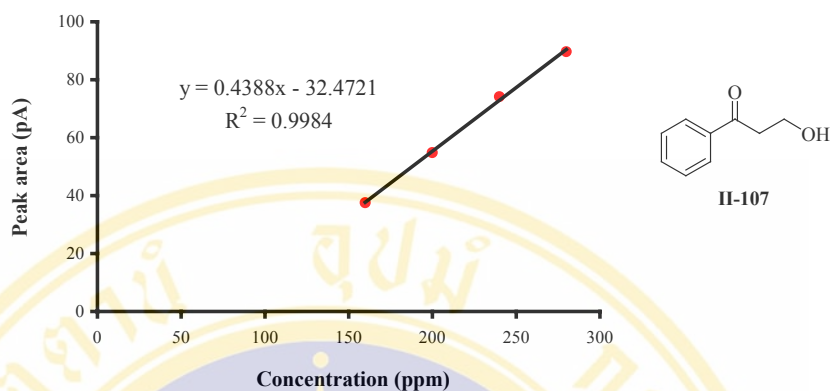






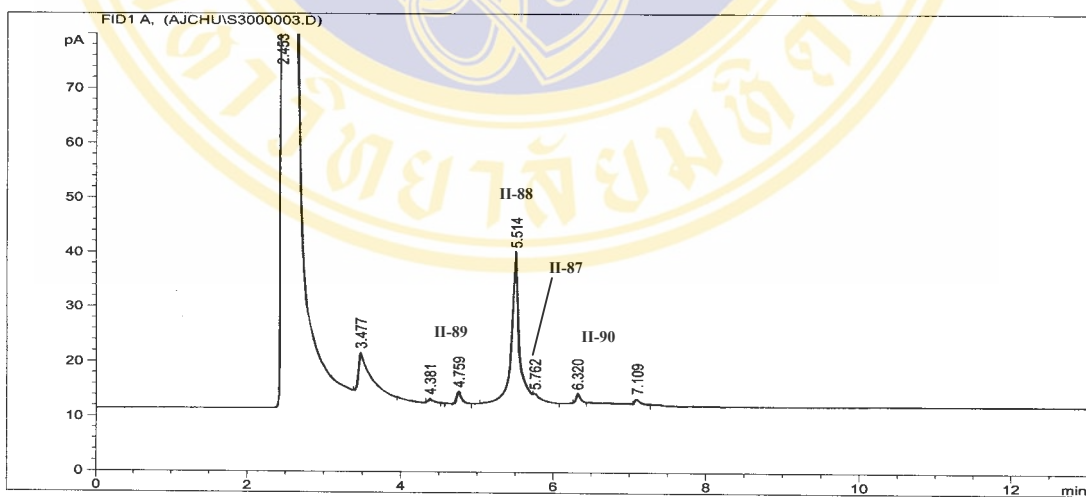
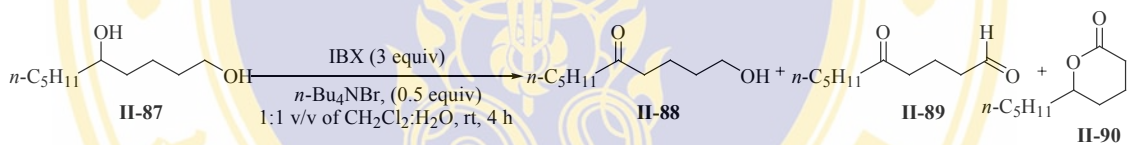


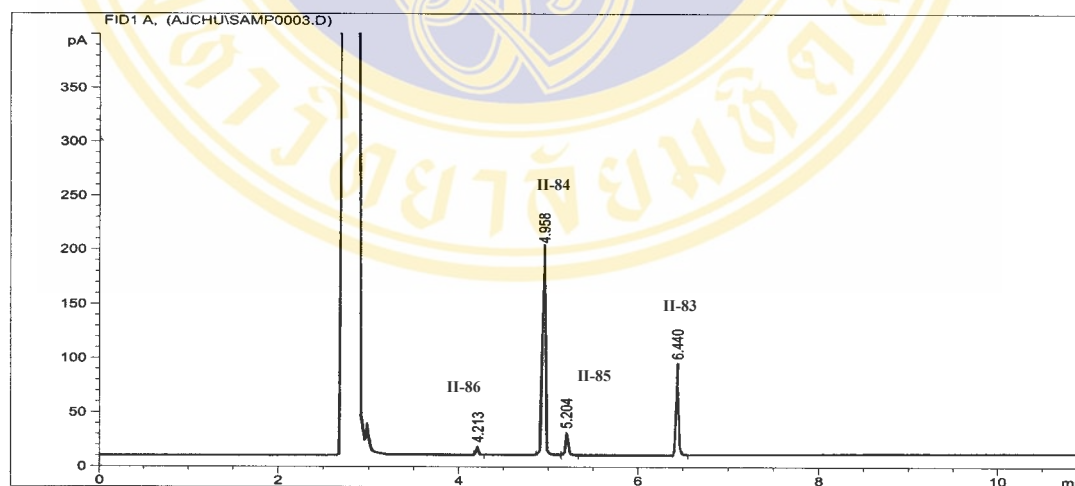
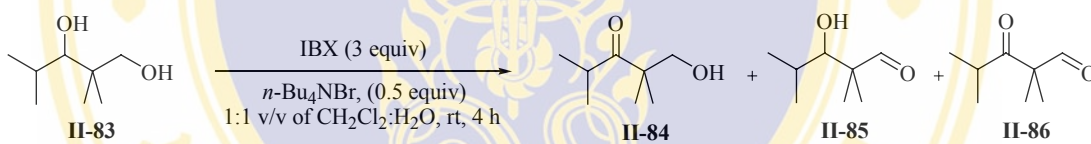
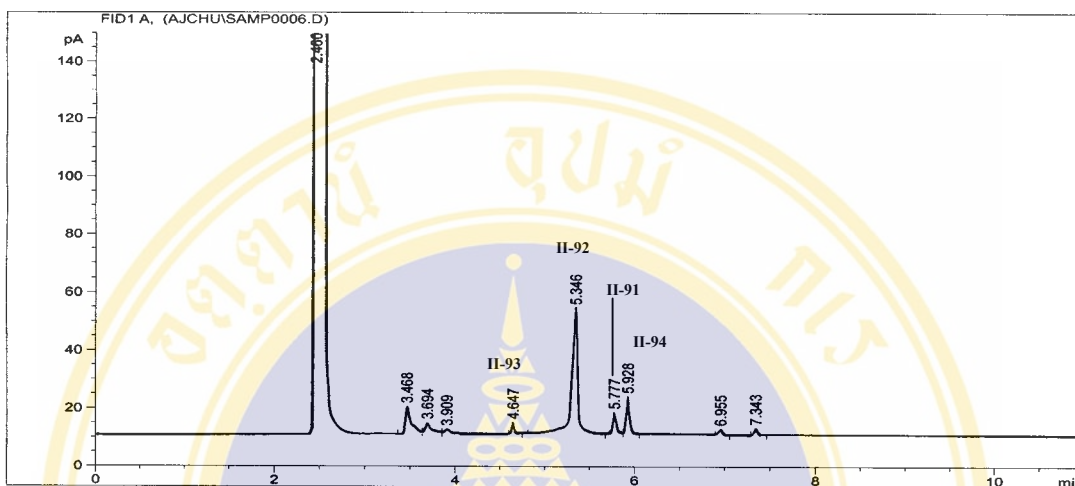
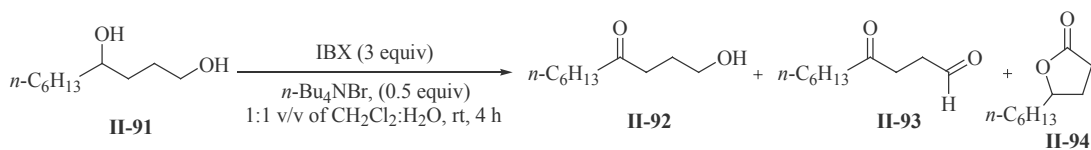


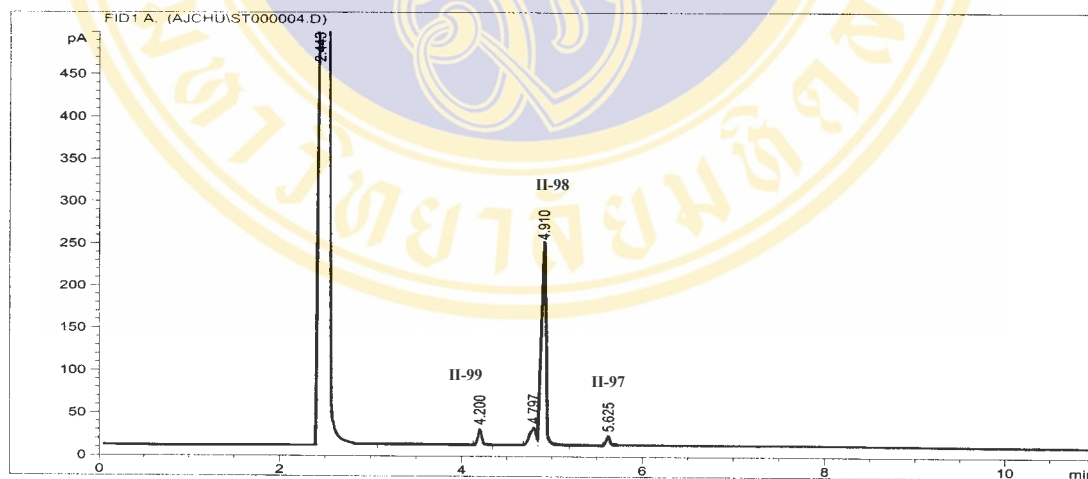
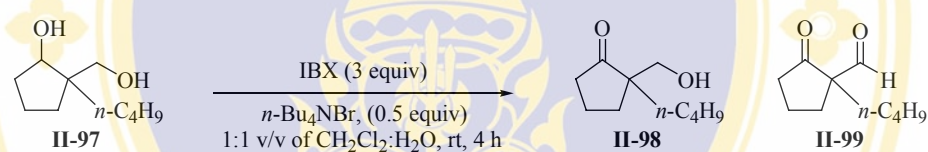
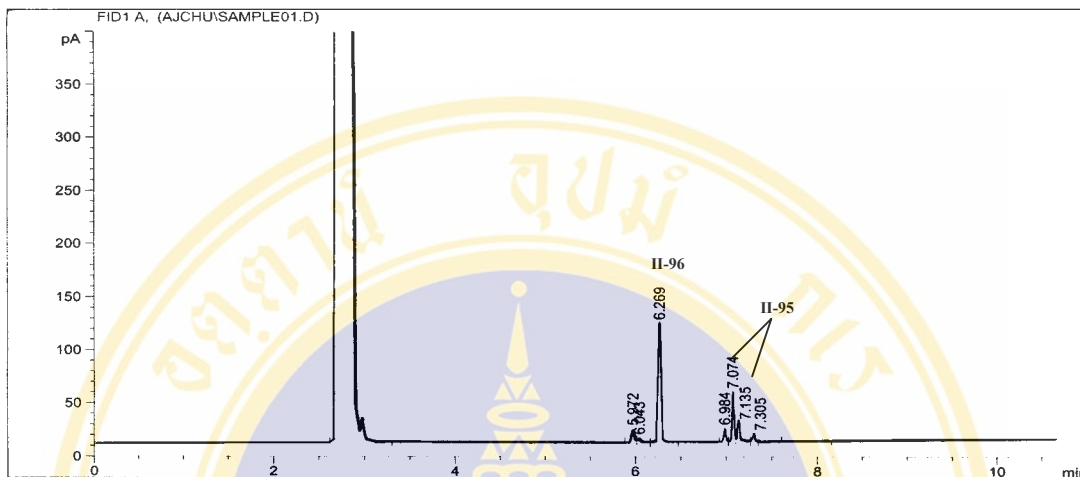
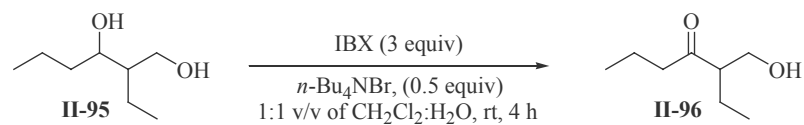


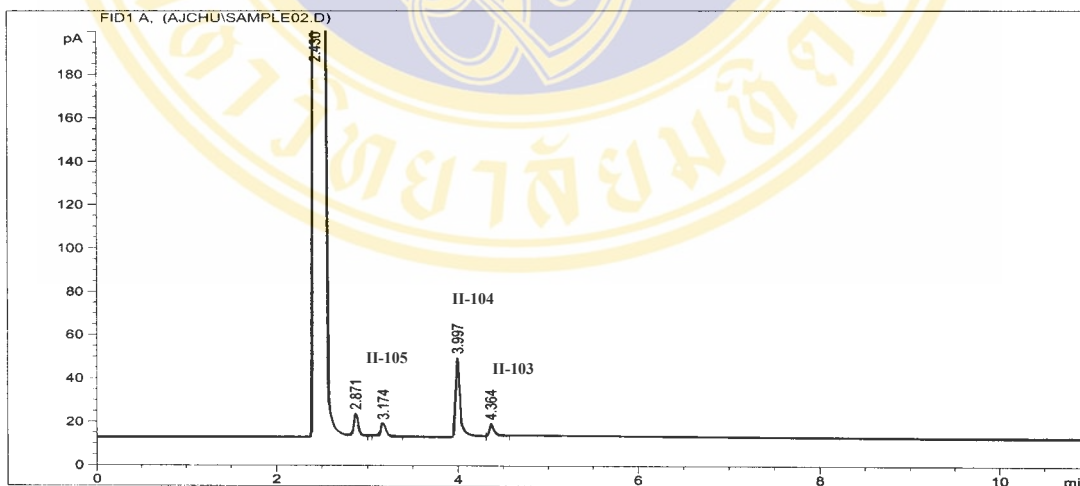
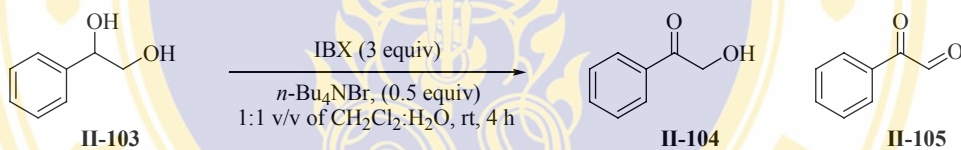
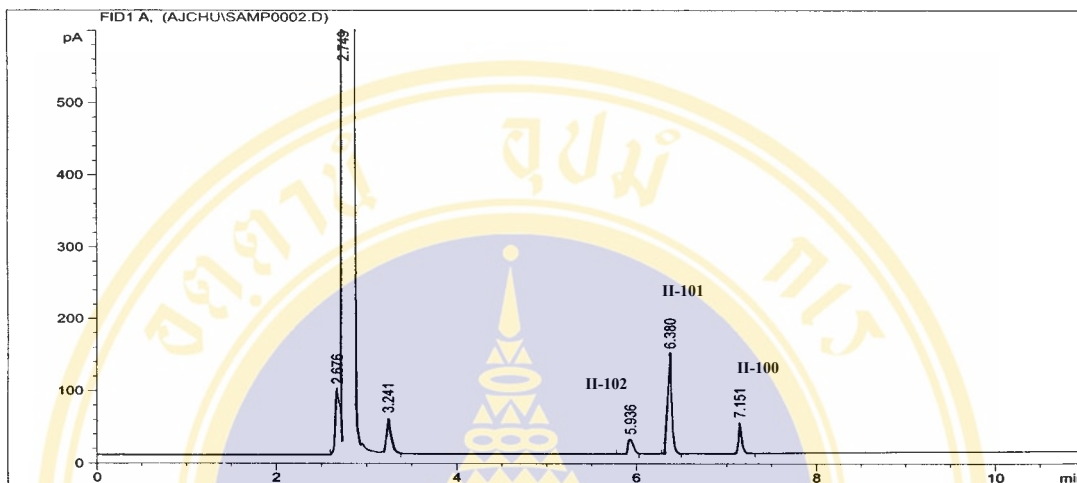
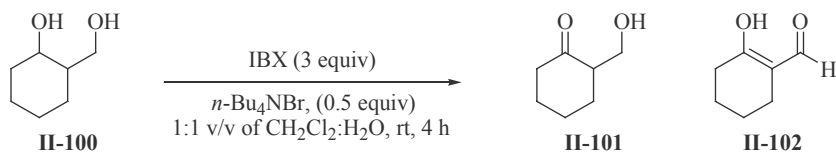
**Figure 2** Standard curves for the determination of the yield

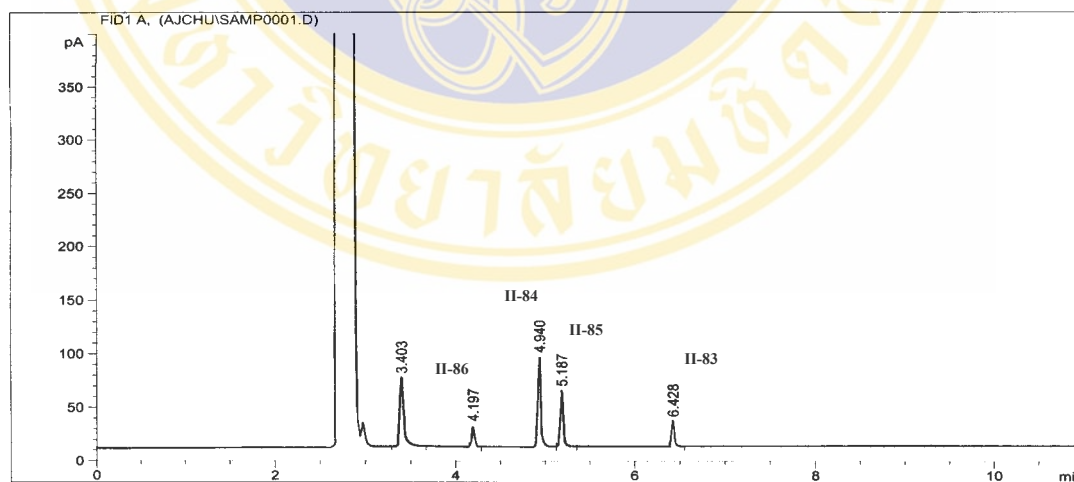
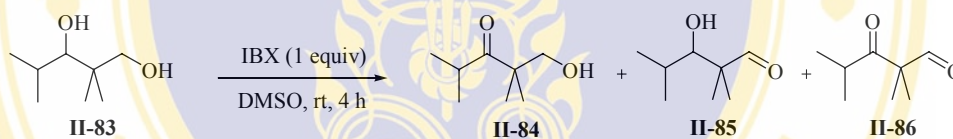
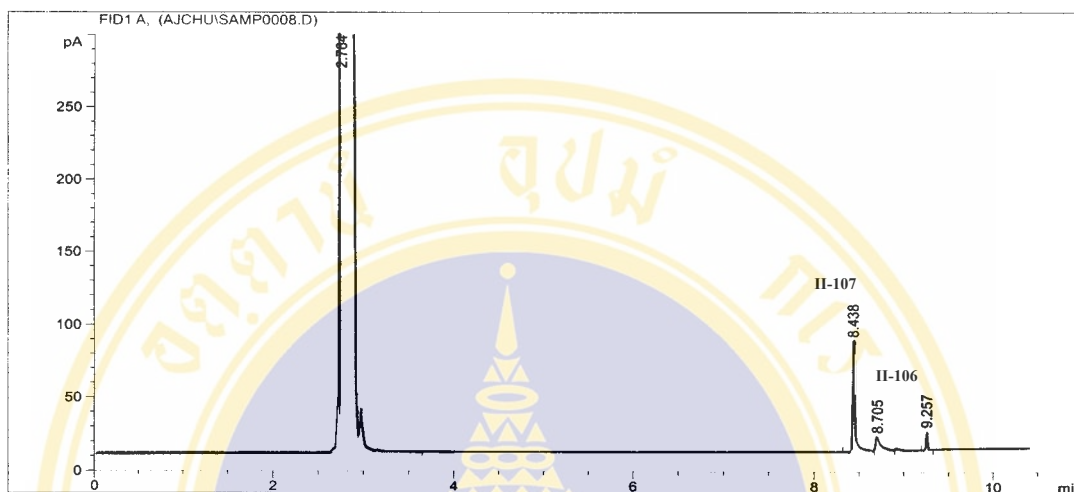
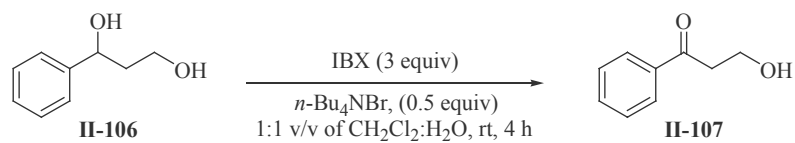
**GC chromatogram:**

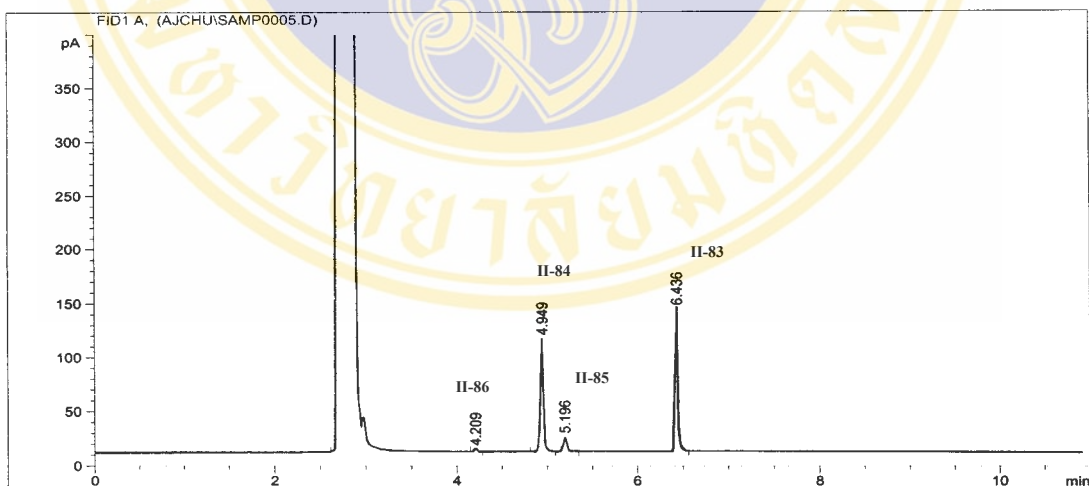
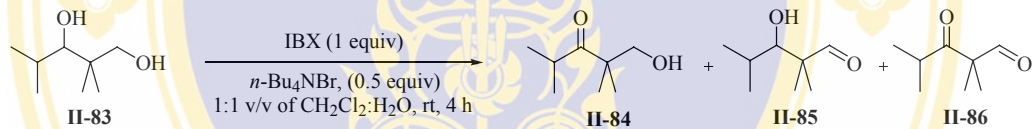
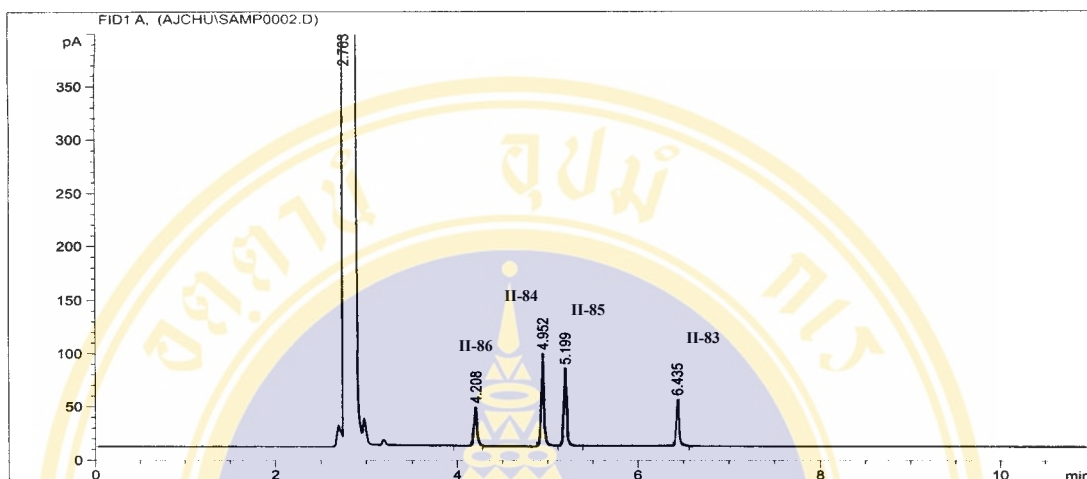
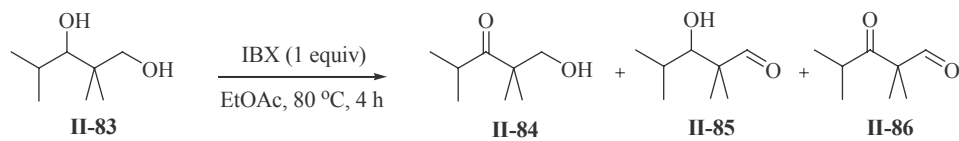


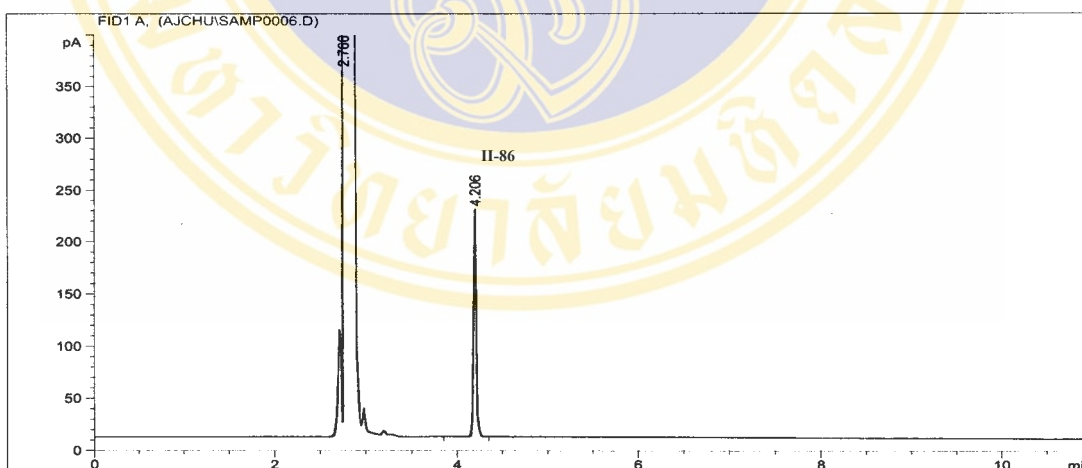
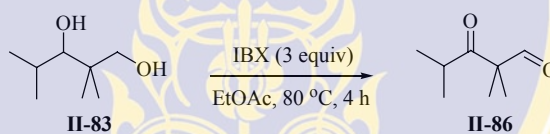
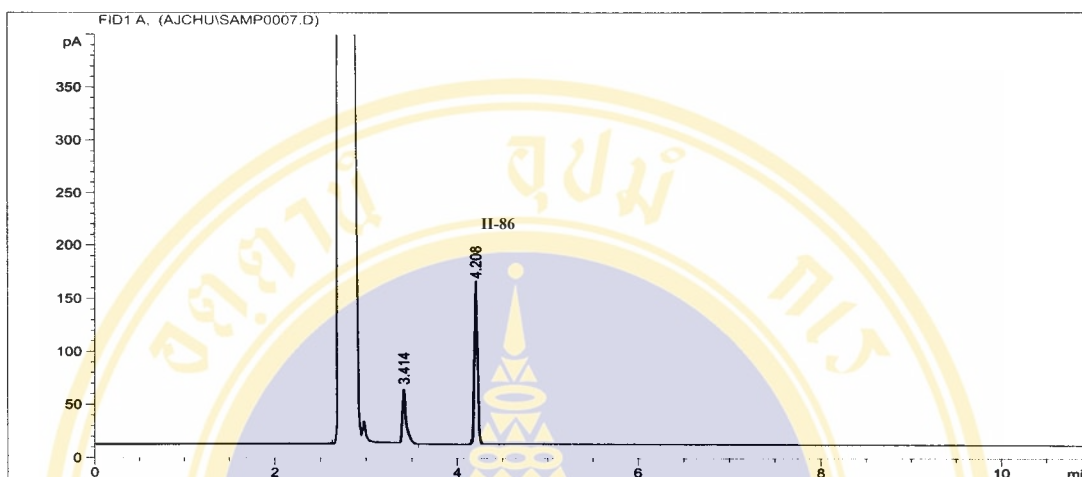
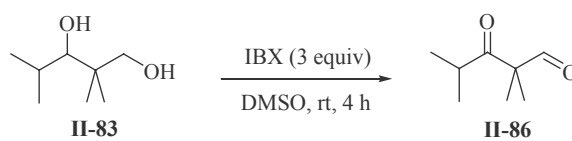


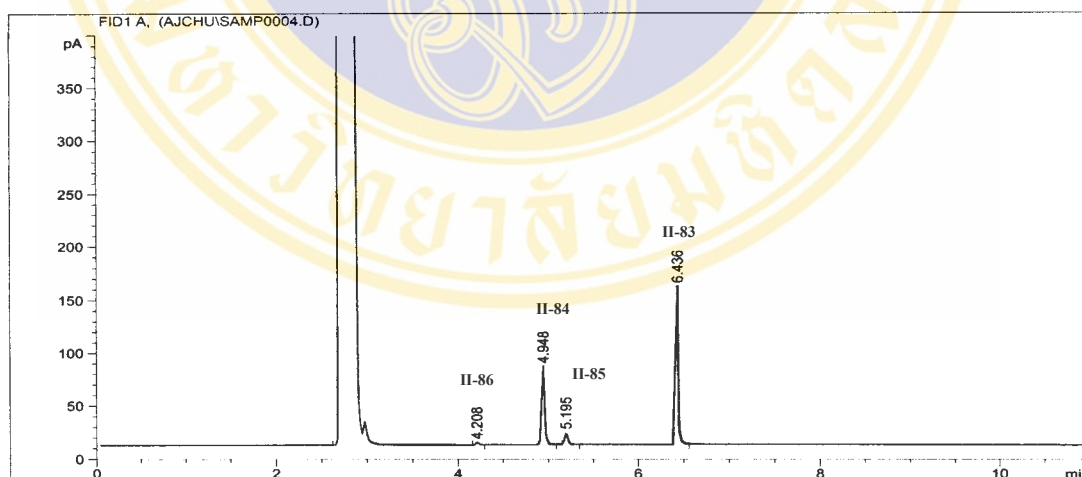
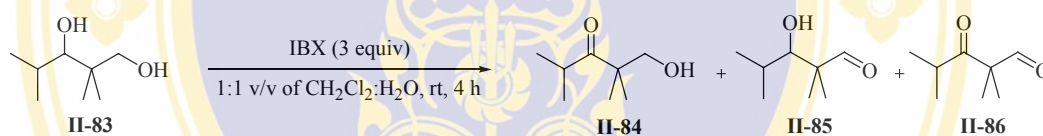
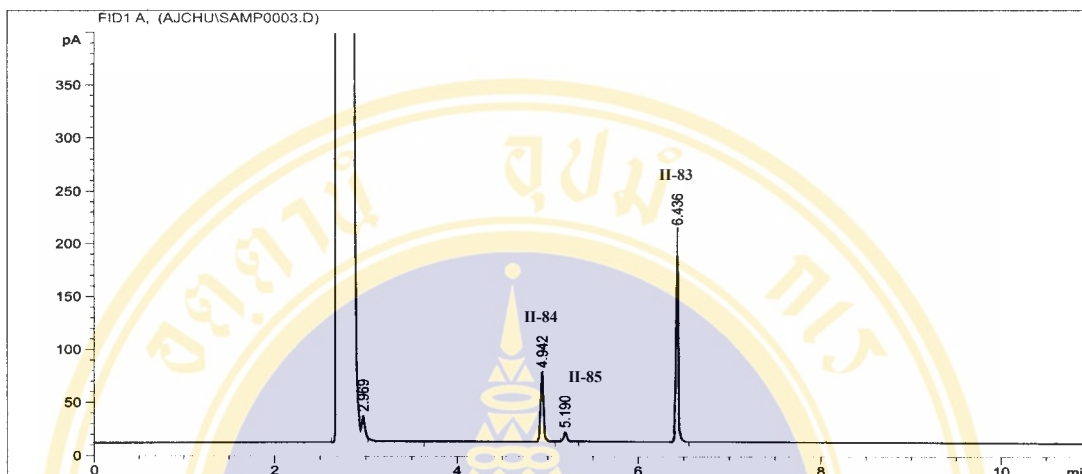
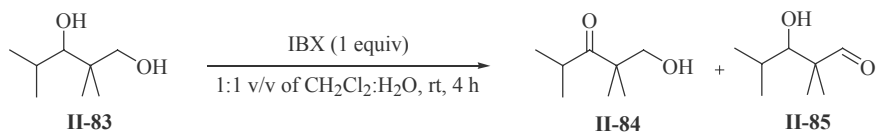












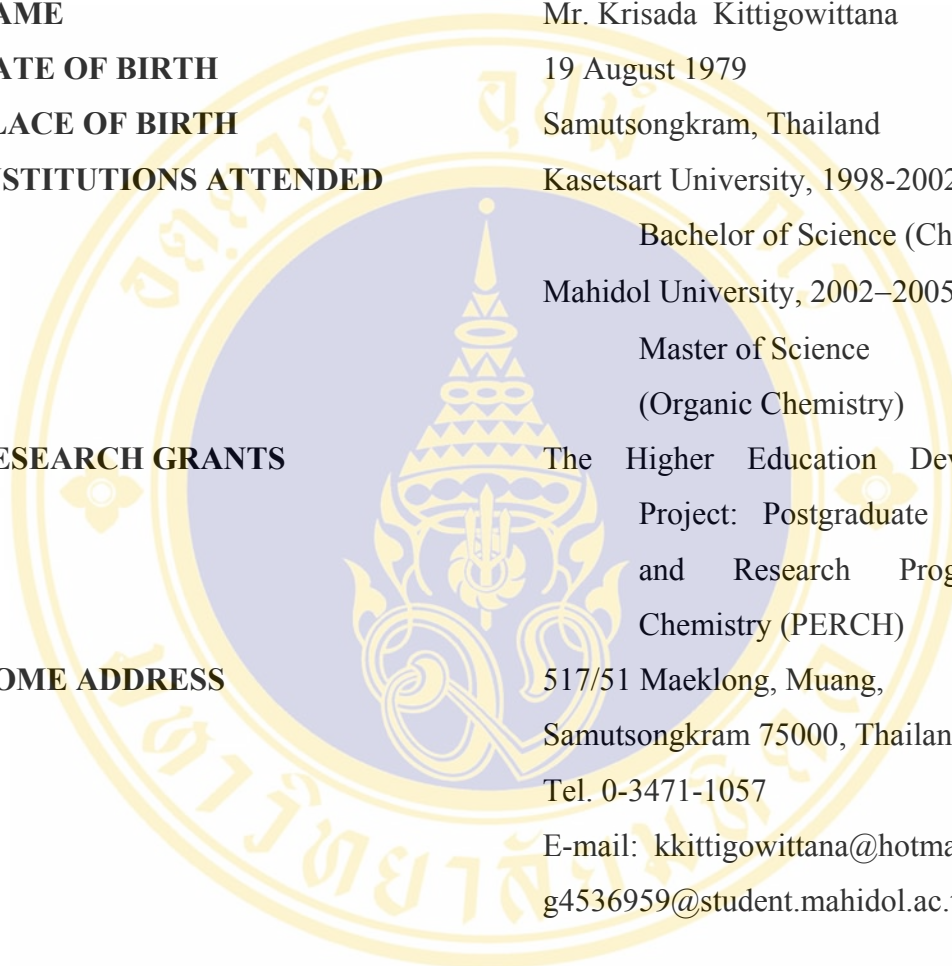
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## BIOGRAPHY



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