Studies on Ruthenium-Catalyzed "Borrowing Hydrogen"-Based Organic Reactions

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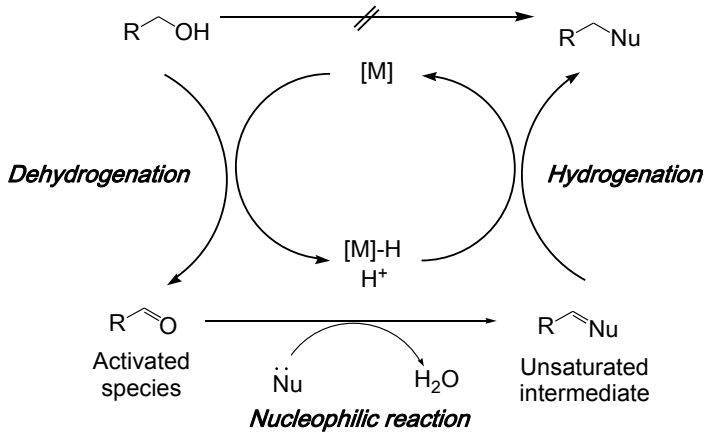
GENERAL INTRODUCTION

I. Introduction

Haloalkanes have been used as a first choice for alkylting reagents because of its high reactivity. Although it shows very good reactivity in reaction with nucleophilic compounds, the haloalkanes have several weak points such as moisture sensitive, usually resulted organic waste in quantitative amount and most of them have high toxicity properties. In addition, over alkylation of the desired product sometime occurred due to its high reactivity.[1]

Alcohols could be considered to replace halogenated alkanes as alkylating reagent. If alcohols can be used instead of halogenated alkanes, it would be an ideal alkylating reagent because it is easy to handle and environmentally benign. However, alcohol has low reactivity for nucleophilic reactions. Therefore, they have to be converted into reactive haloalkanes and related compounds by treating them with halogenated reagents before the reaction with nucleophiles.[2] This activation process would create the same problem as above.

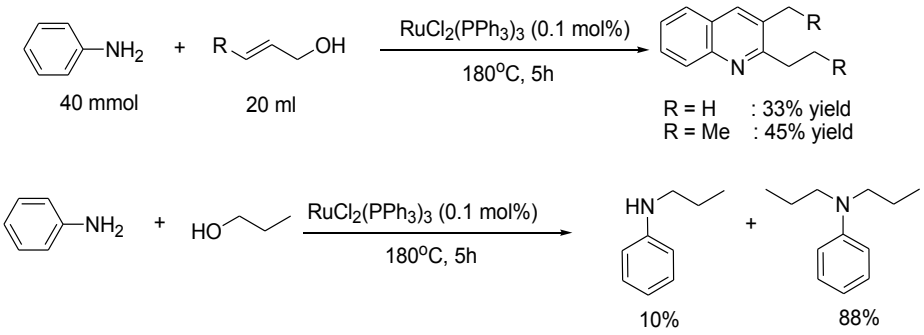
A method so-called "borrowing hydrogen" methodology could be a solution to overcome these problems. Under the "borrowing hydrogen" conditions, alcohols are *in situ* activated by metal catalyst to form aldehydes or ketones which are more reactive in nuclephilic reactions than alcohols are. This activation is *tentatively,* since after the activated species formed (aldehydes or ketones) and react with nucleophile to give the unsaturated intermediate accompanied with H_2O which is hydrogenated by metal hydride species to complete the alkylation of nucleophiles (Scheme 1).[3] During the reaction, H_2O is the only one considerable waste. Therefore, this method is highly atom efficient.



Scheme 1. Concept of tentative activation of alcohol by "borrowing hydrogen"

The use of alcohols as alkylating reagents already known since 1909 when Sabatier and co-worker reported their study on alkylation of amine using alcohol[4] with heterogeneous catalyst ThO_2 and Adkins *et al* reported similar reaction by use of heterogeneous nickel catalyst in 1932.[5] However, these methods required very high temperature (over 200^{o}C), so that the reaction was not suitable for the reactions of temperature labile compounds or the substrates with low boiling point.

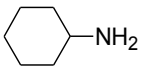
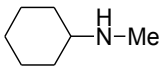
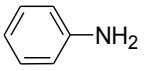
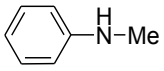
The use of homogenous transition metal catalyst for alkylating reaction by alcohol was reported for the first time in 1981 by Watanabe[6] and Grigg[7] group, independently. Watanabe and his co-worker reported that reaction of aniline with allylic alcohols under $RuCl_2(PPh_3)_3$ catalyst afforded heterocyclization product in moderate yield. They also found that $RuCl_2(PPh_3)_3$ catalyzed the formation of secondary and tertiary amines from aniline and reacted with saturated alcohols (Scheme 2). The improvement and detail of this reaction were reported several years later (1984) in which wider scope of amino arenes and alcohols were shown.[8]



Scheme 2. The first report on homogenous catalyzed alkylation of aniline by use of alcohol reported by Watanabe in 1981

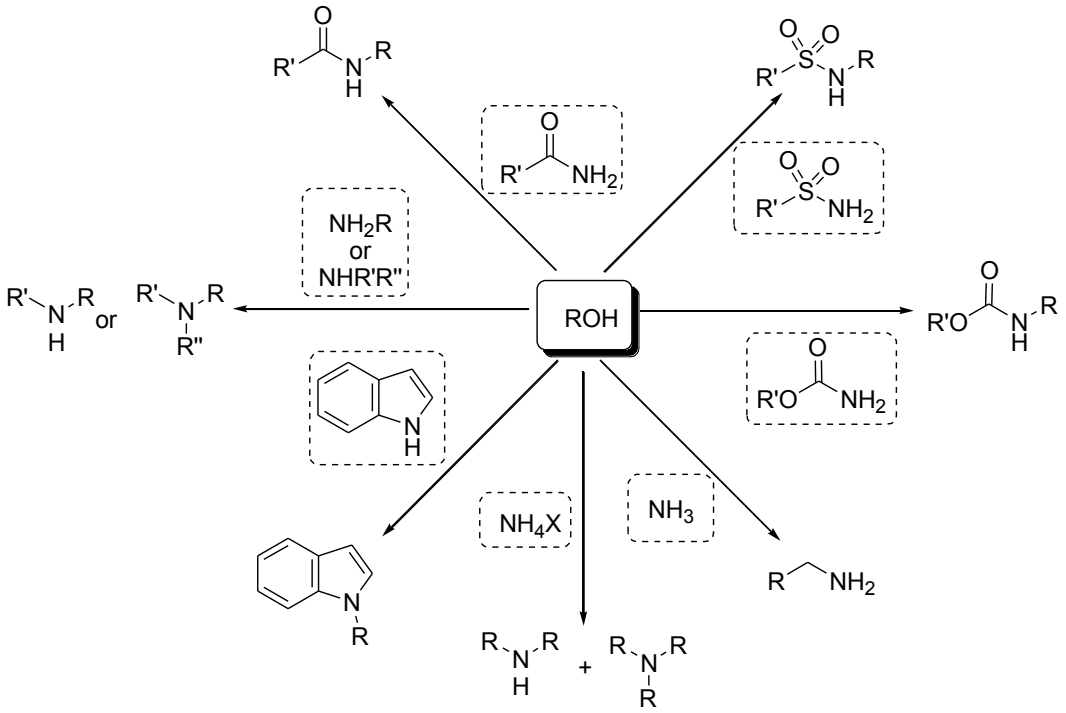
Separately, in the same year Grigg and his co-worker screened several transition metal complex catalysts such as iridium, ruthenium, and rhodium based complexes for alkylation of amines by alcohols. They found that $RhH(PPh_3)_4$ had the best catalytic activity among they tested. Furthermore, this catalyst was successful to catalyze the alkylation of primary and secondary amines with alcohol to give alkylated amines in good to excellent yield (Table 1).

Table 1. $RhH(PPh_3)_4$ catalyzed alkylation of amines with alcohols reported by Grigg *et al* in 1981

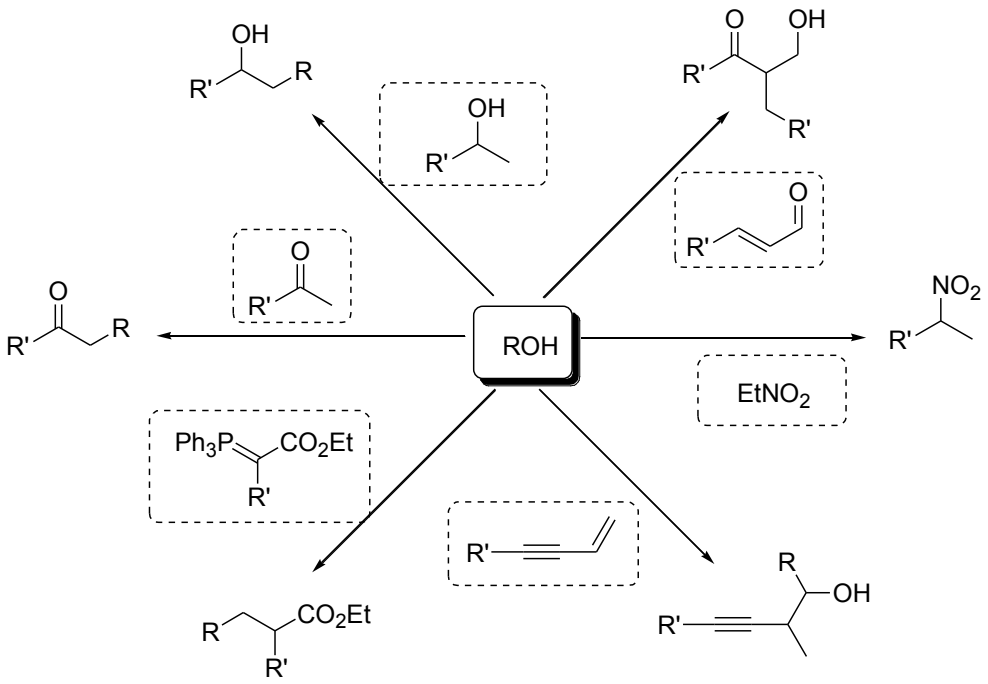
Entry	Amine	Alcohol	Product	Time (h)	Yield (%)
1	H *n*-Bu−N−*n*-Bu	MeOH	Me *n*-Bu−N−*n*-Bu	8	98
2		MeOH		10	99
3		EtOH		6	74
4		BnOH		4	99
5		MeOH		72	39

Reaction condition: Mixture of amine (1 eq.) and $RhH(PPh_3)_4$ (5mol%) was refluxed in corresponding alcohol. Yield was determined by GLC.

After these preliminary reports, the concept of "borrowing hydrogen" started to gain attention of organic chemists. Although Watanabe and Grigg group had great success by alkylation of amines with alcohols, however there were several improvements are needed. For example, both of Grigg and Watanabe's reports need very large excess amount of alcohols because they used the alcohols as solvent. Today, a lot of improvements have been achieved. Various type of transition metal-catalyst such as iridium,[9] ruthenium,[10] iron,[11] copper[12] and others[13] catalyst are reported to be effective catalyst for this type of reaction in lower temperature 80-150^{o}C by using small amount of alcohols (1-5 eq.). It also have been reported that alcohols acted as good alkylating reagents for others nucleophiles to form C-N bonds, for example on alkylation of amides,[14] sulfonamides,[15] carbamates,[16] ammonia,[17] ammonium salts[18] and indoles[10a] (Scheme 3). Alcohols also could be used as alkykating reagent for another type of nucleophiles such as ketone,[19] aldehyde,[20] alcohol[21] and alkene[22] or alkyne[23] to form C-C bond (scheme 4).

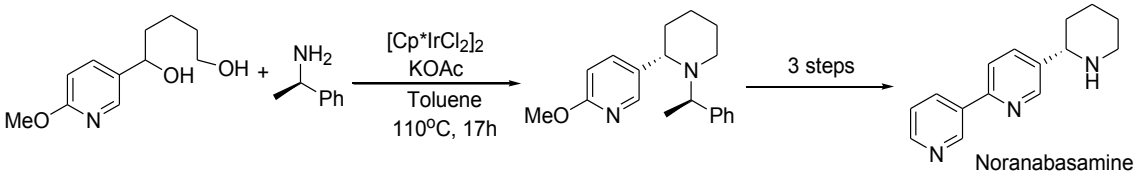


Scheme 3. Several examples of development of "borrowing hydrogen" on C-N bond formation using alcohol as alkylating reagent

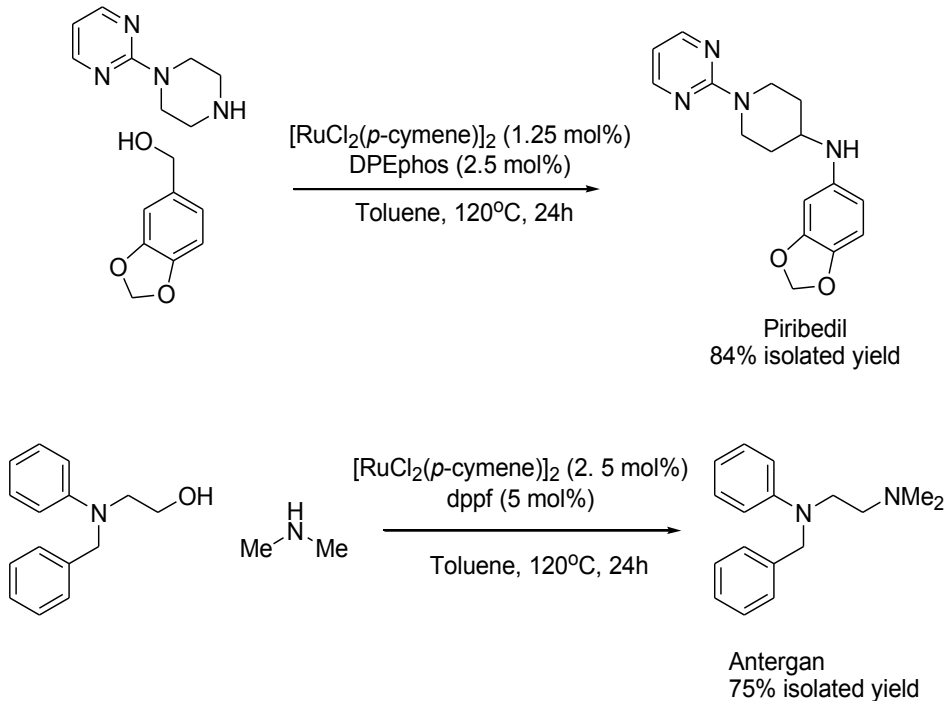


Scheme 4. Several examples of development of "borrowing hydrogen" on formation C-C bond using Alcohols as alkylating reagent

In addition, since the "borrowing hydrogen" methodology allowed substrates with various functional groups, it has been applied on total synthesis. Thus, it acted as key reaction on total synthesis of noranabasamine,[24] an alkaloid which was isolated from Columbian poison-dart frog (Scheme 5). Moreover, it was also applied to synthesis of simple pharmaceuticals such as piribedil, antergan, tripelennamine, pheniramine and choloropheniramine by simple one step reaction of corresponding amines and alcohols substrates[15] (Scheme 6)



Scheme 5. Application of "borrowing hydrogen" on total synthesis of noranabasamine



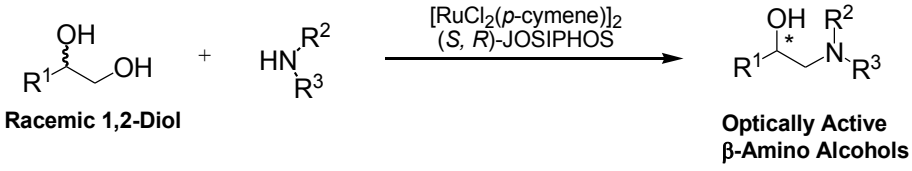
Scheme 6. Application of "borrowing hydrogen" in synthesis of simple pharmaceuticals

However, there still remained many research subjects on this research field. For example, there is no example for the asymmetric synthesis by means of chiral catalysts, though the importances of chiral amines are well known. And also, carbon-carbon bond formation of heteroaromatic rings and alcohols are rare, whereas C-alkylated heterocycles like triptophane is important as bioactive compounds.

In this thesis, the author describes his studies on the ruthenium catalyzed "borrowing hydrogen"-based organic reactions, including: development of a novel ruthenium-catalyzed enantioselective reaction for synthesis of β-amino alcohols by direct reaction of 1,2-diols and amines (chapter 1), followed by its comprehensive mechanistic studies (chapter 2),[26] and development of ruthenium-catalyzed "borrowing hydrogen" reaction for regioselective alkylation of indoles by using alcohol as alkylating reagent (chapter 3).[27]

II. Summary of the Development of Ruthenium-Catalyzed Enantioselective Synthesis of β-amino alcohols with "Borrowing Hydrogen".

In chapter 1, the author described the development of a novel catalytic asymmetric reaction for synthesis of β-amino alcohols from 1,2-diols *via* borrowing hydrogen methodology with of chiral ruthenium catalysis (Scheme 7).



Scheme 7. Enantioselective synthesis of β-amino alcohols from 1,2-diols

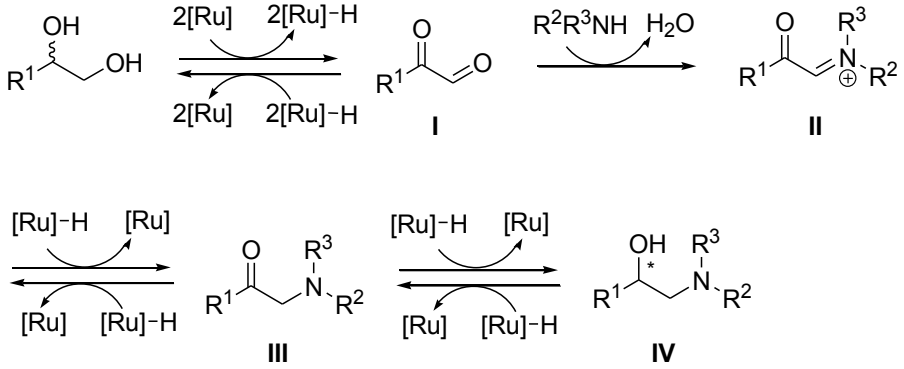
Since the first example of alkylation of amines by using alcohols as alkylating reagents reported by Grigg and Watanabe in early 1980's, there are a lot of reports on the "borrowing hydrogen"-based alkylation of amines. Although the important β-amino alcohols can be synthesized by use of 1,2-diol as alkyl, it has scarcely been reported.[25] On the other hand, the synthetic method for preparation of optically active β-amino alcohol has gaining attention because of its importance in practical applications. The author hypothesized that reaction of 1,2-diols and amines under chiral ruthenium catalysis through the "borrowing hydrogen" process will afford the corresponding optically active β-amino alcohol, if the reaction proceed with the kinetic resolution manner. As a result, the combination of complex $[RuCl_2(p\text{-cymene})]_2$ and (*S, R*)-JOSIPHOS was found to be an effective catalyst for this type of reaction. Various type of 1,2-diols and amines were tested under the optimized reaction condition to give the corresponding β-amino alcohol up to 99% yield and 77% *ee*.

III. Mechanistic Study of Ruthenium-Catalyzed Enantioselective Synthesis of β-Amino Alcohols *via* "Borrowing Hydrogen" Methodology

Chapter 2 describes the mechanistic investigations of the novel ruthenium-catalyzed enantioselective synthesis of β-amino alcohols from 1,2-diols that has been described in chapter 1.

In the beginning of this study, the reaction seemed to proceed through kinetic resolution process. However, several evidences and a series of experimental data lead the author to a different conclusion that the reaction mechanism could be proposed as follow (Scheme 8): the starting diol is converted into oxo aldehyde **I** by ruthenium-catalyzed double dehydrogenation. Oxo aldehyde **I** reacts with the amine to afford

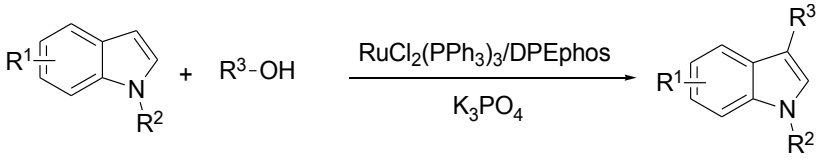
iminium ion intermediate **II**, which is converted into amino ketone **III**. Amino ketone **III** is finally converted into the desired amino alcohol **IV** by a second transfer hydrogenation reaction. Enantioselection occurs in the final step *via* asymmetric reduction reaction.



Scheme 8. Proposed reaction mechanism of enantioselective synthesis of β-amino alcohols from 1,2-diols

IV. Ruthenium-Catalyzed Regioselective Alkylation of Indoles with Alcohols

Chapter 3 describes that the use of $RuCl_2(PPh_3)_3$/DPEphos improved the catalytic efficiency in the regioselective alkylation of indole with alcohols that was previously studied in our laboratory and other group (Scheme 9).



Scheme 9. Ruthenium-catalyzed regioselective alkylation of indoles with alcohols

In our previous of study, it was found that alcohols could be used as alkylating reagent to form 3-substituted indoles by use of heterogenous catalyst Pd/C.[27-a] However, the product yields were strongly dependent on the substrate nature (27-99% yield). Moreover, high catalyst loadings (5 mol%) and a large excess amount of alcohols were required (19 eq.). Griggs group also reported this type of reaction by use of $[Cp^*IrCl_2]_2$ catalyst, however their catalytic reaction was limited to aromatic alcohols, especially benzylic alcohol.[27-b]

In this study, the author found that a combination of homogenous catalyst $RuCl_2(PPh_3)_3$, DPEphos ligand and K_3PO_4 could overcome these problems. Amount of catalyst could be reduced to 1.25 mol% and only 5 molecular equivalents of alcohol were required. This catalysis was not limited to the benzylic alcohols, but was tolerated to almost all types of alcohols such as cyclic and acyclic aliphatic alcohols as well as secondary alcohols and heterocyclic alcohols (up to 99% yield).

The author considered that all findings in this thesis could provide a new and good choice for alkylation of amines and indoles.

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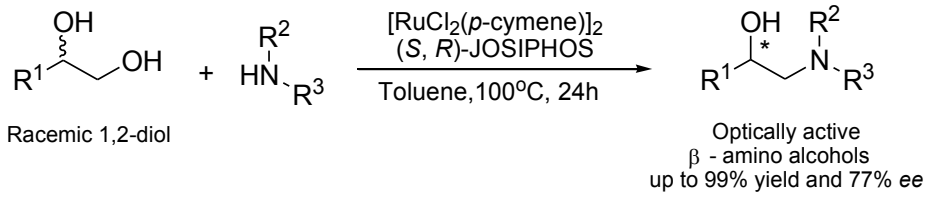
Chapter 1

Ruthenium-Catalyzed Enantioselective Synthesis of β-Amino Alcohols from 1,2-Diols by "Borrowing Hydrogen"

Abstract

The first enantioselective synthesis of β-amino alcohols from 1,2-diols was examined by use of {[$RuCl_2$(*p*-cymene)]$_2$/(*S*, *R*)-JOSIPHOS} catalysis. Several types of 1,2-diols are allowed to react with secondary amines to give corresponding β-amino alcohols up to 99% yield and 77% *ee*.



Introduction

Preparation of enantioenriched compounds has been playing important roles in organic chemistry because of its importance for practical applications.[1] There have been reported a lot of methods for the preparation of these optically active compounds as results of hard work of many scientists since the initial discovery by Luis Pasteur in 1848, in which optically inactive sodium ammonium salt of tartaric acid was found to be able to separate into two optically active salts manually, one of them being identical with natural tartaric acid.[2] This finding was the first report of separation of racemic mixture into its optically active form, and today this method is known as optical resolution. Based on this discovery, the concept of chirality was soon established.[3]

Generally, two main preparation methods of enantioenriched compounds are known. One is the optical resolution explained above and the other is asymmetric synthesis. Unlike optical resolution, the asymmetric synthesis selectively produces one of the enantiomer as a major product through enantioselective reaction. Theoritically, only a half amount of desired stereoisomer can be obtained by optical resolution, but the asymmetric reaction can provide it in perfect yield.[3]

Optically active β-amino alcohols are one of the most popular targets of enantioenriched compounds because of its wide practical application in various fields (Figure 1). In 1962, Black found the first clinically significant effects of β-blocker medicines; propranolol and pronethalol.[4] These medicines were studied by many medical experts and grow up to be one of the most important contributions to clinical medicine and pharmacology of the 20th century.[5] Both propranolol and pronethalol contain an β-amino alcohol skeleton as the backbone of their molecular structures. Not

only two compounds, but most of the β-blocker medicines also have β-amino alcohols backbone. In addition, there are a huge numbers of the other medicines and bioactive compounds containing β-amino alcohol structure. For example, we can find β-amino alcohol moiety in adrenaline (ephineprine) which is well known as an important hormone.[6] Isoprenaline and isoetharine were developed as the next generations of synthetic adrenaline. Both of them contained β-amino alcohol unit in their molecules.[7]

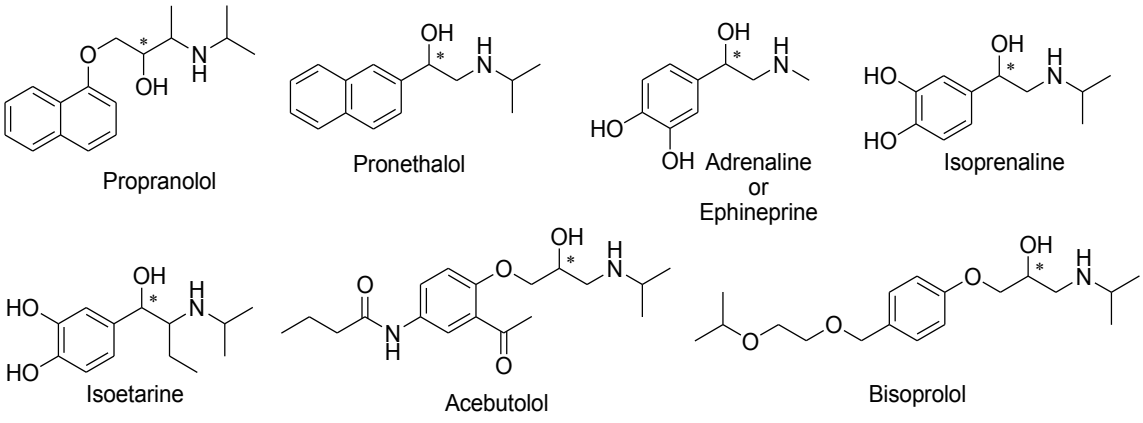


Figure 1. Several examples of medicines with optically active β-amino alcohols backbone

β-Amino alcohols are also found in a lot of natural products (Figure 2). For example, quinine is an alkaloid including β-amino alcohol structure which shows various biological activities such as anti-malarial, analgesic and anti-pyretic (fever reduction).[8] Its enantiomer quinidine, is known as anti-arrhythmic agent.[8-b] Various natural aminoglycosides also have antibiotic activity such as kanamycin[9a] and erythromycin.[9b] Both of these aminoglycosides are containing β-amino alcohol. Beside the examples described above, there are big numbers of natural occurring biologically active compounds are known containing β-amino alcohols moiety.

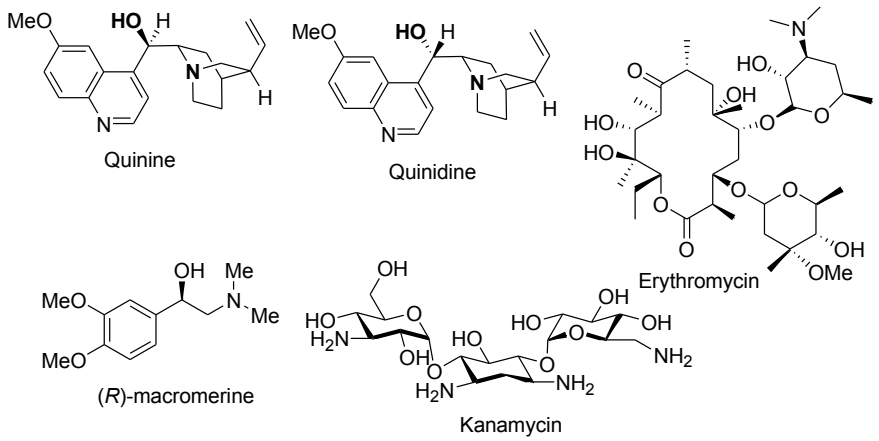


Figure 2. Examples of natural products contain β-amino alcohols

β-Amino alcohols have been used not only as chiral building blocks of medicines, or intermediate of natural product synthesis, but also as chiral sources in asymmetric synthesis. In latter case, they act as organocatalysts, chiral ligands or chiral auxillaries. For example, in 1987, Correy and co-workers introduced one of the famous chiral Lewis acid catalysts that soon known as CBS catalyst which was synthesized from optically active β-amino alcohol. By use of this catalyst, optically active secondary alcohols can be prepared with excellent *ee* from achiral ketones (up to 97%, Figure 3).[10] Chiral ethanolamines derivatives,[11] prolinol,[12] oxazolines[13] and oxazolidinones[14] are also widely used powerful chiral ligands for various asymmetric catalysis (Figure 4).

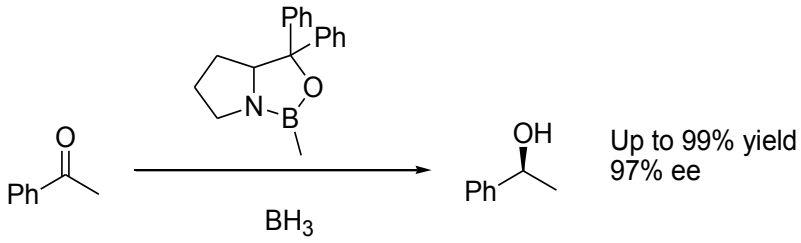


Figure 3. First report of the use of CBS catalyst by Correy and co-workers in 1987

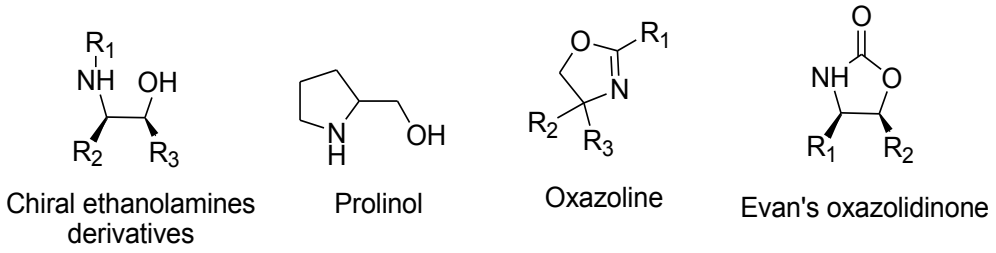
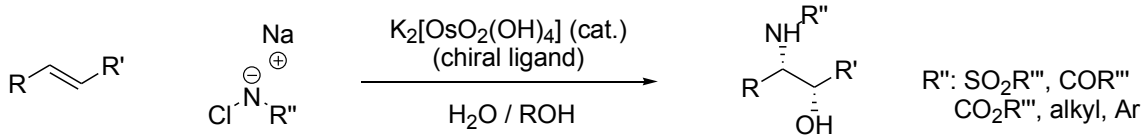


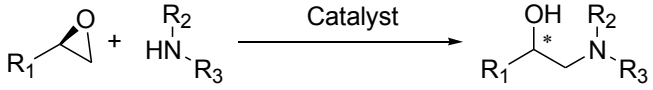
Figure 4. Several ligands with β-amino alcohols backbone

As the consequence of a wide practical use and importance of optically active β-amino alcohols, a lot of new, green, easy and efficient methods have been reported time by time from entire the globe. The Shrapless asymmetric aminohydroxylation reaction, which brought K. B. Sharpless to win the Nobel Prize in 2001, is one of the most famous methods for preparation optically active β-amino alcohols.[15] Asymmetric reduction of aminoketones,[16] ring-opening reaction of enantioenriched epoxides,[17] are also other simplest methods for preparation of optically active β-amino alcohols.

Sharpless asymmetric aminohydroxylation



Ring opening of enantioenriched epoxide



Asymmetric reduction of amino ketone

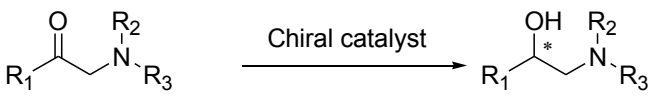


Figure 5. Several common methods for preparation of optically active β-amino alcohols

On the other hand, an environmentally friendly method for activation of alcohol so-called "borrowing hydrogen" methodology, has recently received much attention as a highly atom-efficient synthetic strategy in organic synthesis.[18] Alcohols are usually converted into reactive haloalkanes and related compounds by treating them with halogenated reagents before the reaction with nucleophiles.[19] Under "borrowing hydrogen" methodology conditions, on the other hand, they are *in situ* transformed to aldehydes or ketones which are more reactive in nucleophilic addition reactions than alcohols are. This *in situ* transformation provides a wide range of ways to deal with alcohols as alkylation reagents. The by-product expected is only water, so the reaction proceeds with high atom efficiency. Although there are many reports on the use of ruthenium,[20] iridium,[21] iron,[22] copper[23] and other metal[24] catalysts in the alkylation of amines,[25] ketonitriles,[26] and other targets,[27] the example in which 1,2-diols are used as substrates is so far limited.[28]

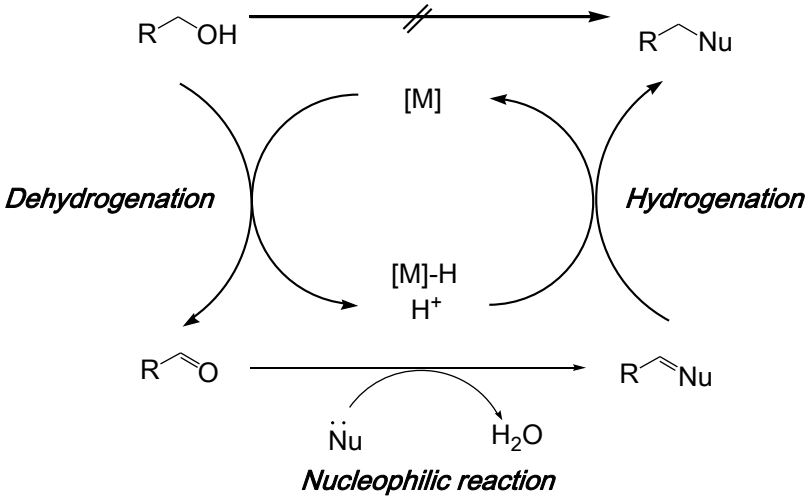


Figure 6. Concept of "borrowing hydrogen" methodology

Two successful applications of the "borrowing hydrogen" methodology for racemic β-amino alcohol preparation from 1,2-diols were reported by Beller and co-workers, who used a $[Ru_3(CO)_{12}]$ catalyst,[22-a] and Williams group by using $[RuCl_2(p\text{-cymene})]_2$/DPPF under microwave irradiation.[22-b] However, to the best of our knowledge, no application of this methodology to the preparation of optically active amino alcohol has been reported in spite that the importance of asymmetric synthesis of β-amino alcohols are well known. The author was interested in investigating the possibility to develop a new method for preparation of optically active β-amino alcohols directly by reaction of racemic 1,2-diol and amine based on "borrowing hydrogen" method. In this chapter, the author shows the use of ruthenium catalyst with chiral ligand provides the enantioselective reaction to afford optically active β-amino alcohols directly from 1,2-diols and amines.

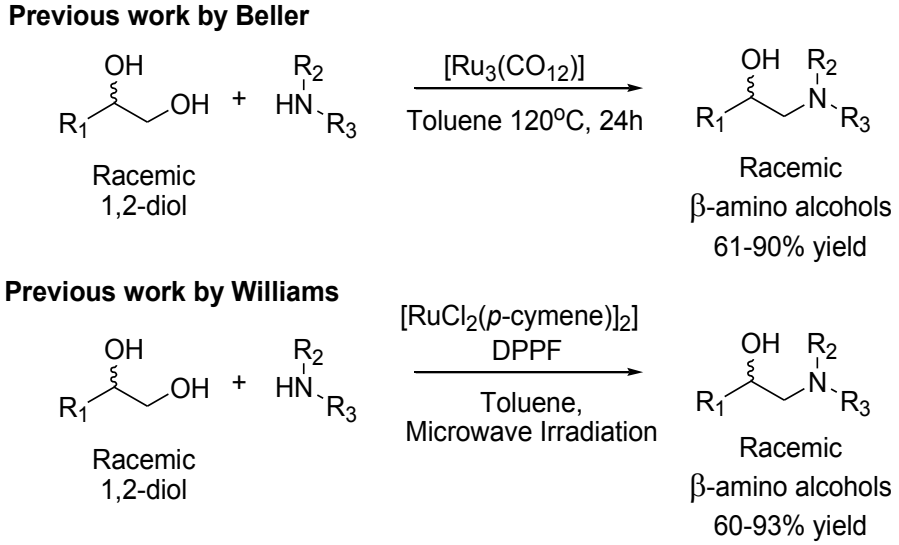


Figure 7. Previous work reported by Beller and Williams group

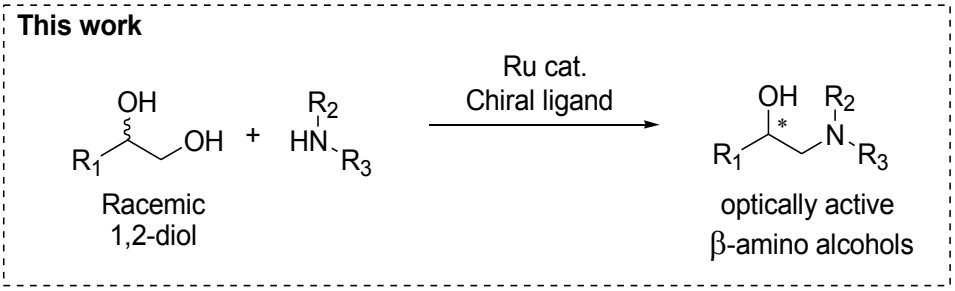


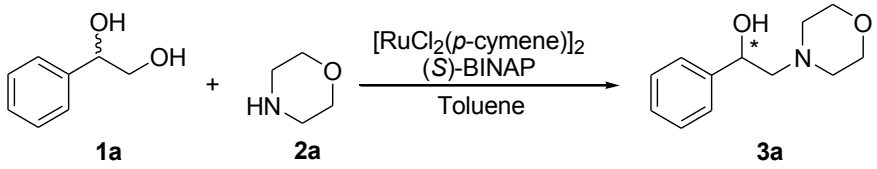
Figure 8. This work: enantioselective synthesis of β-amino alcohols from racemic 1,2-diol

Results and Discussion

Optimization of Reaction Conditions

In the beginning of this study, the author considered that desired chiral β-amino alcohols could be obtained through the kinetic resolution process. Therefore, the reaction of two molecular equivalents of 1-phenyl-1,2-ethanediol (**1a)** and morpholine (**2a)** was initially carried out in the presence of $[RuCl_2(p\text{-cymene})]_2$ and the chiral ligand (*S*)-BINAP at 120°C for 24 hours. The reaction proceeded smoothly to give the desired β-amino alcohol **3a** in 88% yield with 12% *ee* (Table 1, entry 1).

Table 1. Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Ru : Ligand	**1a** : **2a**	Temp. (°C)	Yield (%)[b]	*ee* (%)[c]
1	1 : 1	2 : 1	120	88	12
2	1 : 1.2	2 : 1	120	95	17
3	1 : 1.5	2 : 1	120	95	4
4	1 : 1.2	3 : 1	120	92	21
5	1 : 1.2	5 : 1	120	92	16
6	1 : 1.2	3 : 1	110	23	32

[a] Reaction conditions: 1-phenyl-1,2-ethanediol, morpholine (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), (*S*)-BINAP, under Ar, in toluene (1 mL), heated for 24 hours. [b] Determined by ^{1}H NMR analysis [c] Determined by HPLC analysis.

Although the good enantioselectivity was not obtained, this result encouraged the author to investigate this novel asymmetric reaction. To enhance the enantioselectivity, reaction conditions such as the catalysts, the balance of starting materials, and the temperature effects were examined (Table 1). Increasing the amount of (*S*)-BINAP to 1.2 equivalents of ruthenium improved the chemical yield to 95%. But, amount of (*S*)-BINAP did not influence enantioselectivity (17% *ee*). Further increasing it to 1.5 equivalents of ruthenium, however, resulted in an almost racemic product (entry 3). Addition of further excess amount of **1a** could slightly increase *ee* value (entries 4-5). Reducing of temperature from 120^{o}C to 110^{o}C doubled the *ee*, increasing it to 32%, although the yield was decreased by a factor of 4, from 92% to only 23% yield of corresponding product **3a** (entry 6).

Ligand Effect

Next, the author focused his attention to the effect of the chiral ligand on the enantioselectivity (Figure 8, Table 2). Several types of chiral ligands were screened on the reaction system. Since diphosphine ligands are found to show higher reactivity than other types of chiral ligand, the author initially checked such ligands (entry 1-8). When (*S*)-Tol-BINAP was used, the racemic product was obtained although the reaction proceeded up to 86% yield (entry 1). The SEGPHOS family showed high reactivity (up to 99% yield) however yielded almost racemic products (entries 2–4). Other diphosphine ligands were also tested. (-)-DIOP provided a 99% yield of the desired β-amino alcohol with 18% *ee* (entry 5), and (*S*, *R*)-JOSIPHOS provided a 99% yield of the desire amino alcohol with 25% *ee* (entry 6). Trost ligand yielded almost racemic

β-amino alcohol in 62% yield (entry 7). Monophosphine ferrocene ligand **L1** shows excellent reactivity on this reaction but give only 4% ee (entry 8). The chiral bis(oxazoline) ligand (*R, S*)-IndaBox(Me_2) afforded the desired amino alcohol at a yield of 45% with little enantioselectivity (entry 9). Both the catalytic activity and enantioselectivity were decreased when the phosphoramidite ligand (*S*)-MONOPHOS and bulky ligand **L2** were used (entries 10-11)

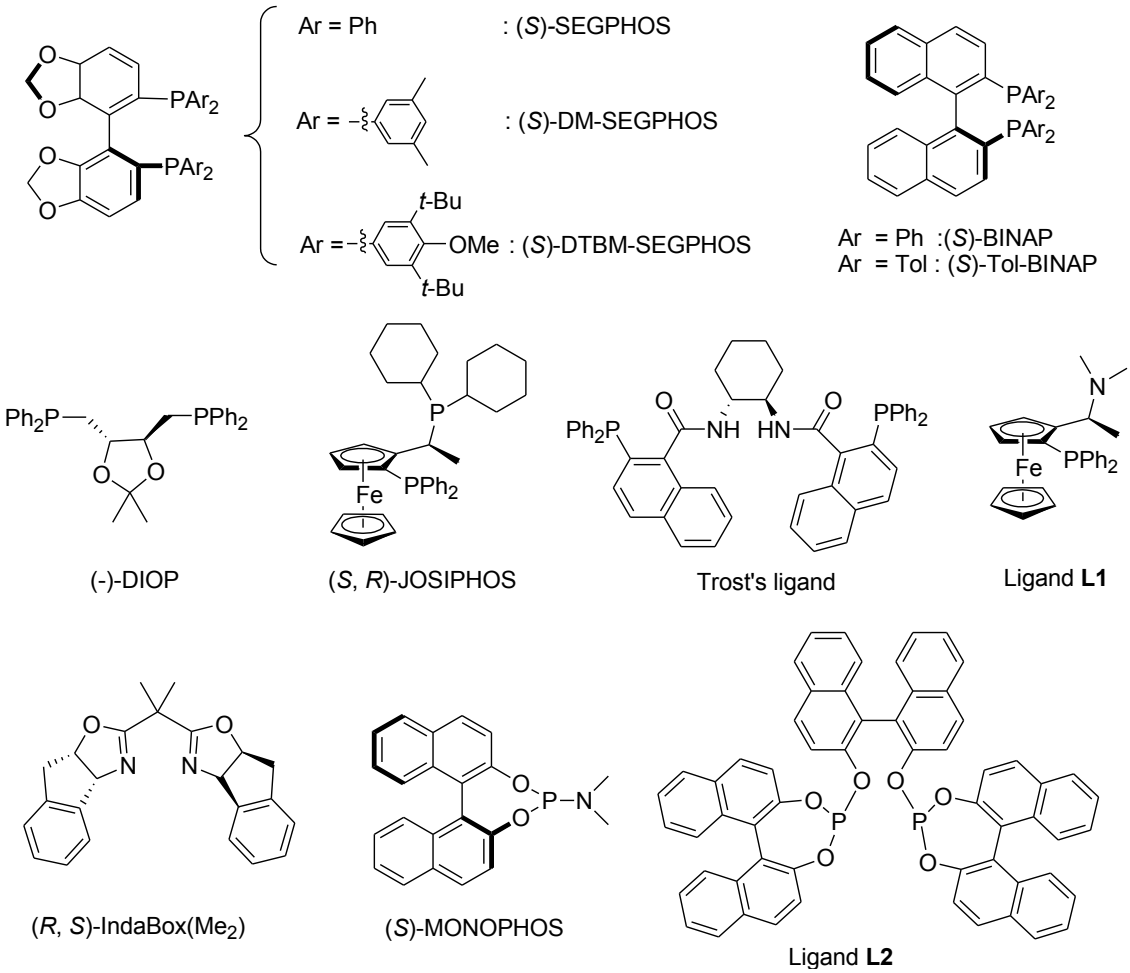
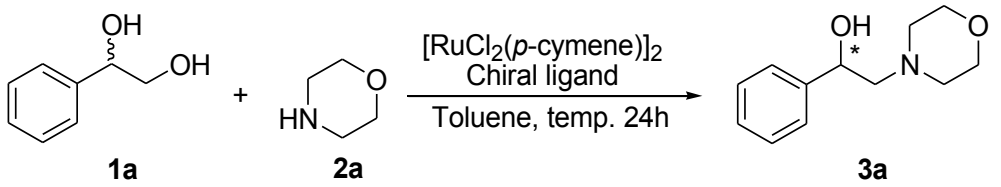


Figure 8. Chiral ligands screened for the asymmetric amination of 1,2-diol

Table 2. Ligand effects[a]



1a **2a** **3a**

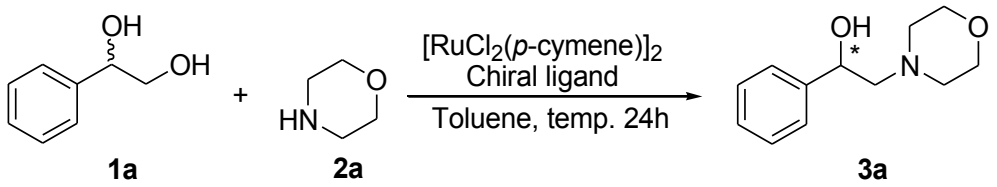
Entry	Ligand	Temp. (°C)	Yield (%)[b]	*ee* (%)[c]
1	(*S*)-Tol-BINAP	110	86	Rac
2	(*S*)-SEGPHOS	110	98	Rac
3	(*S*)-DM-SEGPHOS	110	99	4
4	(*S*)-DTBM-SEGPHOS	110	92	1
5	(-)-DIOP	110	99	18
6	(*S*, *R*)-JOSIPHOS	110	99	25
7	Trost Ligand	110	62	4
8	Ligand **L1**	110	94	4
9	(*R*, *S*)-IndaBox(Me_2)	110	45	5
10	(*S*)-MONOPHOS	110	23	10
11	Ligand **L2**	110	21	13
12	None	110	Nr	-

[a] Reaction conditions: 1-Phenyl-1,2-ethanediol (3 mmol), morpholine (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), chiral ligand (6 mol%), under Ar atmosphere, toluene (1 mL), heated for 24 h. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC analysis.

Temperature Effects

From the results in the optimization of reaction condition section, the author expected that reaction temperature crucially affected the enantioselectivity. Therefore, the author investigated temperature effects on reactions using best three chiral ligands: (*S*)-BINAP, (*S*, *R*)-JOSIPHOS and (-)-DIOP. The author found that lower temperature obtained higher *ee*, however, as a consequence the yield decreased, generally. When the reaction was carried out at 120^{o}C by use of (*S*)-BINAP, the yield was 92% and *ee* was 21%. The yield dropped drastically to 23% when temperature was decreased to 110^{o}C, however *ee* value doubled to 32%. No reaction took place when the reaction temperature was decreased to 100^{o}C. The best *ee* value was obtained when (*S, R*)-JOSIPHOS was used at 100^{o}C without loss of chemical yield (99% yield, 48% *ee*). Unfortunately, (*S, R*)-JOSIPHOS ligand did not work well at the lower temperature (<90^{o}C). When (-)-DIOP was used, the yield was constantly decreased according the decreasing of temperature, otherwise the *ee* value was rising. At 80^{o}C, corresponding β-amino alcohol **3a** was obtained in 80% yield with 40% *ee*.

Table 3. Temperature effect[a]



1a **2a** **3a**

Entry	Ligand	Temp. (^{o}C)	Yield (%)[b]	*ee* (%)[c]
1	(*S*)-BINAP	120	92	16
2	(*S*)-BINAP	110	23	32
3	(*S*)-BINAP	100	Nr	-
4	(*S*, *R*)-JOSIPHOS	110	99	25
5	(*S*, *R*)-JOSIPHOS	100	99	48
6	(*S*, *R*)-JOSIPHOS	90	50	29
7	(*S*, *R*)-JOSIPHOS	80	Nr	-
8	(-)-DIOP	110	99	18
9	(-)-DIOP	100	90	25
10	(-)-DIOP	90	97	28
11	(-)-DIOP	80	80	40
12	(-)-DIOP	60	Nr	-

[a] Reaction conditions: 1-Phenyl-1,2-ethanediol (3 mmol), morpholine (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), chiral ligand (6 mol%), under Ar atmosphere, toluene (1 mL), heated for 24 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis.

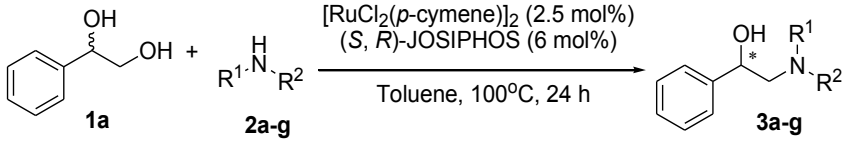
Scope and Limitation of Substrates

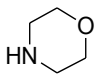
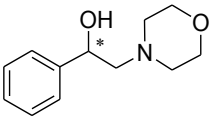
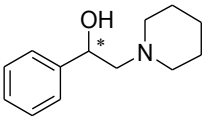
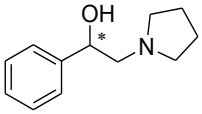
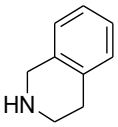
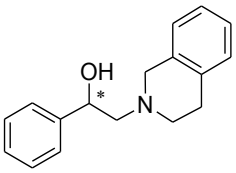
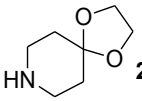
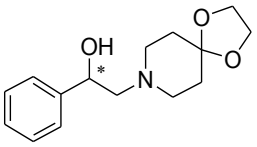
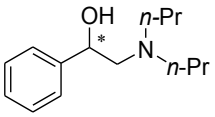
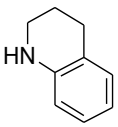
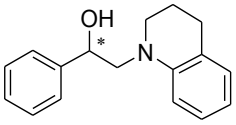
With good enantioselectivity in the reaction of 1-phenyl-1,2-ethanediol (**1a**) with morpholine (**2a**) by use of $[RuCl_2(p\text{-cymene})_2]_2$/(*S*, *R*)-JOSIPHOS catalysis, the author tested various type of 1,2-diols and amines to get information of scope and limitation of the present catalytic reaction.

Amine Substrates

As the first attempt, the investigation was started by testing several secondary amines (Table 4). Five- and six-membered cyclic amines showed good reactivity under the optimized reaction conditions (entries 1–4). Thus, both piperidine (**2b**) and pyrrolidine (**2c**) reacted with 1-phenyl-1,2-ethandiol (**1a**) to afford the corresponding β-amino alcohols in almost quantitative yield with good enantioselectivity (62% and 55% *ee*, respectively). Tetrahydroisoquinoline (**2d**) afforded the desired product in 87% isolated yield with 64% *ee* (entry 4). The present reaction was also used to make a β-amino alcohol having an acetal protecting group **3e** with 48% *ee*, though the chemical yield was only 62% (entry 5). In contrast, an acyclic amine, di-*n*-propylamine (**2f)**, showed low reactivity and gave the product **3f** in only 25% yield as a racemic form (entry 6). The aromatic amine **2g** did not react under the optimized conditions presumably due to the low nucleophilicity of **2g** (entry 7).

Table 4. Amination of 1-phenyl-1,2-ethanediol (**1a**) by secondary amines[a]



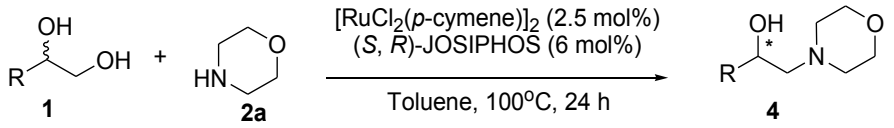
Entry	Amine	Product		Yield (%)[b]	*ee* (%)[c]
1	 **2a**		**3a**	99	48
2	 **2b**		**3b**	99	62
3	 **2c**		**3c**	99	55
4	 **2d**		**3d**	99 (87)[d]	64
5	 **2e**		**3e**	62	48
6	 **2f**		**3f**	25	Rac
7	 **2g**		**3g**	nd	-

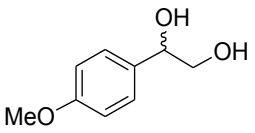
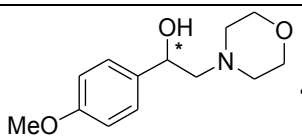
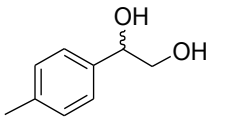
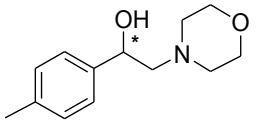
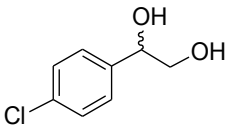
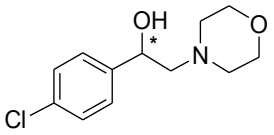
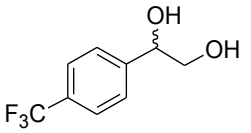
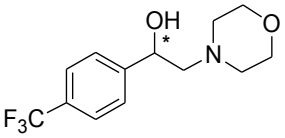
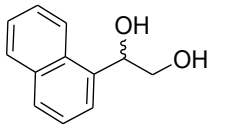
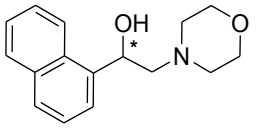
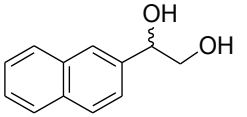
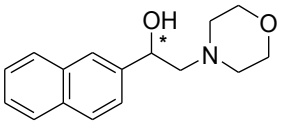
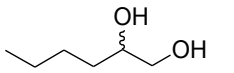
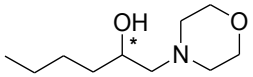
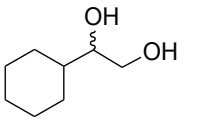
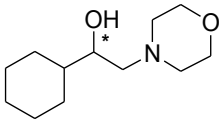
[a] Reaction condition: 1-phenyl-1,2-diol (3 mmol), amine (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), (*S*, *R*)-JOSIPHOS (6 mol%) in toluene (1 mL), 100°C, 24 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis. [d] Isolated yield.

1,2-Diol Substrates

The author moved his attention to investigate the scope of 1,2-diols. Several 1,2-diols were also tested under the optimized reaction conditions (Table 5). First, 1-aryl-1,2-ethanediols (**1b-g**) were examined. A diol with a methyl group at the *para* position gave a 78% yield of β-amino alcohol **5c** with 59% *ee* (entry 2). Other substituents, such as a methoxy group, a chlorine atom, and a trifluoromethyl group, suppressed the reaction progress (entries 1, 3, and 4). 1-(1-naphthyl)-1,2-ethanediol (**1f**) gave only 55% isolated yield with 22% *ee* (entry 5). On the other hand, the author was pleased to find that 1-(2-naphthyl)-1,2-ethanediol (**1g**) afforded the highest *ee* (77%, entry 6). Next, the author examined the use of aliphatic 1,2-diols into the catalytic reaction. It was found that 1,2-hexanediol (**1h)** and **2a** afforded the β-amino alcohol **4h** was obtained in 80% yield with 38% *ee* (entry 7). Found that the reaction was working with acyclic aliphatic 1,2-diol, the author interested to check the reaction by use of cyclic aliphatic 1,2-diol. As a result, β-amino alcohol **4i** was successfully synthesized in 78% yield as an optically active form (48% *ee*) when 1-cyclohexyl-1,2-ethanediol **1i** was used.

Table 5. Amination of various 1,2-diols with morpholine[a]



Entry	1,2-Diol		Product		Yield (%)[b]	ee (%)[c]
1		**1b**		**4b**	28	28
2		**1c**		**4c**	78	59
3		**1d**		**4d**	46	29
4		**1e**		**4e**	nd	-
5		**1f**		**4f**	55[d]	22
6		**1g**		**4g**	76	77
7		**1h**		**4h**	80[d]	38
8		**1i**		**4i**	78	48

[a] Reaction condition: 1,2-diol (3 mmol), morpholine (1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), (*S*, *R*)-JOSIPHOS (6 mol%), under Ar in toluene (1 mL), 100°C, 24 h. [b] Determined by ^{1}H NMR, [c] Determined by HPLC. [d] Isolated yield.

Conclusions

The author achieved the first enantioselective preparation of β-amino alcohols from racemic 1,2-diols by the ruthenium-catalyzed "borrowing hydrogen" reaction. The catalyst {[$RuCl_2$(*p*-cymene)$_2$]$_2$/(*S*,*R*)-JOSIPHOS} was found to be most active catalyst on asymmetric reaction of 1,2-diols and secondary amines among tested to provide the corresponding β-amino alcohols in excellent yield (up to 99%) and up to 77% *ee*.

Experimental Section

General Information

Nuclear magnetic resonance spectra (NMR) were recorded by using Varian Mercury Plus 300-4N spectrometer with TMS at 0 ppm as an internal standard for ^{1}H NMR and $CDCl_3$ at 77 ppm for ^{13}C NMR. Enantiomeric excess (*ee*) was measured by Hitachi L-7100 HPLC with a chiral column (Daicel Chiralcel OD-H or OJ-H) under the conditions described below. All reactions were carried out under argon in a sealed reaction tube. Reagents obtained from commercial sources were used without further purifications. Molecular sieves (4Å) were activated by heating in an oven for 2 hours at 350^{o}C before use.

General procedure for synthesis of β-amino alcohols from 1,2-diols

To an argon-purged reactor tube containing 0.62 g of 4Å molecular sieves was added the representative 1,2-diol (3 mmol), amine (1 mmol), $[RuCl_2(p\text{-cymene})Cl_2]_2$ (0.0154 g, 0.025 mmol), (*S*, *R*)-JOSIPHOS (0.0356 g, 0.060 mmol), and dry toluene (1 ml). The mixture was degassed by three times freeze-pomp-thaw cycles and then purged with argon gas. After the reaction mixture was stirred at 100^{o}C for 24 hours and then filtered. The filtrate was evaporated to remove solvent and volatiles. The inorganic wastes and excess amount of the starting diol were removed by Kugelrohr distillation. The crude product was purified by column chromatography or extracted by using an acidic aqueous solution to give the corresponding β-amino alcohols.

2-Morpholino-1-phenylethanol (3a)

White solid (m.p. = 78-79°C). ^{1}H NMR (ppm): 2.42-2.57 (*m*, 4H), 2.73-2.76 (*m*, 2H), 3.73-3.81 (*m*, 4H), 4.75 (*dd*, 1H, *J*= 10.2, 3.9 Hz), 7.24-7.35 (*m*, 5H). ^{13}C NMR (ppm): 53.4, 66.6, 67.0, 68.5, 125.8, 127.5, 128.3, 141.8. GC-MS (*m*/*z*): 207. FAB-MS (*m*/*z*): 208 [M + H^+]. 48% *ee* by HPLC (column: Daicel Chiralcel OD-H, λ: 225 nm, eluent: *i*-PrOH : Hex = 20 : 80, flow = 0.5mL/min, t_R: 15.86 min (minor) t_R: 17.22 min (major)).

1-Phenyl-2-(piperidin-1-yl)ethanol (3b)

White solid (m.p. = 65-66°C). ^{1}H NMR (ppm): 1.47-1.49 (*m*, 2H), 1.61-1,64 (*m,* 4H), 2.34-2.51 (*m,* 4H), 2.69-2.71 (*m,* 2H), 4.73 (*dd,* 1H *J*= 10.5, 3.6 Hz), 7.24-7.37 (*m*, 5H). ^{13}C NMR (ppm): 24.2, 26.1, 54.4, 66.9, 68.60, 125.8, 127.4, 128.2, 142.4. FAB-MS (*m*/*z*): 206 [M + H^+]. 62% *ee* by HPLC (column: Daicel Chiralcel OJ-H, λ: 225 nm, eluent: EtOH : Hex = 3 : 97, flow = 0.15 mL/min, t_R: 43.20 min (minor) t_R: 46.40 min (major)).

1-Phenyl-2-(pyrrolidin-1-yl)ethanol (3c)

White solid (m.p. = 44-48°C). ^{1}H NMR (ppm): 1.78-1.82 (*m*, 4H), 2.45-2.57 (*m*, 3H), 2.72-2.82 (*m*, 3H), 3.81 (*br*, 1H), 4.70 (*dd*, 1H *J*= 10.6, 3.3 Hz), 7.24-7.41 (*m*, 5H). ^{13}CNMR: 23.6, 53.8, 64.1, 70.7, 125.8, 127.3, 128.2, 142.5. 53% *ee* by HPLC (column: Daicel Chiralcel OJ-H, λ: 225 nm, eluent: *i*-PrOH : Hex = 10 : 90, flow = 0.5mL/min, t_R: 15.82 min (minor) t_R: 16.99 min (major)).

1-Phenyl-2-(tetrahydroisoquinolin-2-yl)ethanol (3d)

Light yellow oil. ^{1}H NMR (ppm): 2.65-2.78 (*m*, 3H), 2.94-3,04 (*m*, 3H), 3.68 (*d*, 1H *J*= 15 Hz), 3.94 (*d*, 1H *J*= 14.7 Hz) 4.86 (*dd*, 1H *J*= 9.8 4.2 Hz), 7.04-7.43 (*m*, 9H). ^{13}C NMR (ppm): 29.2, 50.9, 55.8, 66.0, 69.0, 125.7, 125.8, 126.2, 126.4, 127.4, 128.3, 128.6. FAB-MS (*m*/*z*): 254 [M + H^+]. 28% *ee* by HPLC (column: Daicel Chiralcel OD-H, λ: 225 nm, eluent: *i*-PrOH: Hex = 20 : 80, flow = 0.5 mL/min, t_R: 14.07 min (minor) t_R: 15.19 min (major)).

2-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)-1-phenylethanol (3e)

White Solid (m.p. = 104-107^{o}C). ^{1}H NMR (ppm): 1.75-1.80 (*m*, 4H), 2.42-2.53 (*m*, 4H), 2.82-2.84 (*m*, 2H), 3.95 (*s*, 4H), 4.70 (*dd*, 1H, *J*= 10.3 3.9 Hz), 7.24-7.37 (*m*, 5H). ^{13}C NMR (ppm): 34.9, 51.3, 64.3, 65.7, 68.9, 107.0, 125.8, 127.5, 128.3, 142.1. FAB-MS (*m*/*z*): 264 [M + H^+]. 48% *ee* by HPLC (column: Daicel Chiralcel OJ-H, λ: 225 nm, eluent: EtOH : Hex = 96 : 4, flow = 0.7 mL/min, t_R: 22.38 min (minor) t_R: 23.43 min (major)).

2-Dipropylamino-1-phenylethanol (3f)

Yellow oil. ^{1}H NMR (ppm): 0.92 (*t*, 6H *J* = 7.5 Hz), 1.46-1.56 (*m*, 4H), 2.40-2.53 (*m*, 4H), 2.56-2.63 (*m*, 2H) 4.64 (*dd*, 1H, *J*= 10.5, 3.6 Hz), 7.26-7.39 (*m*, 4H). ^{13}CNMR (ppm): 11.9, 20.4, 56.0, 63.2, 69.3, 125.7, 127.2, 128.2, 142.4. FAB-MS (*m*/*z*): 222 [M + H^+]. Racemic, by HPLC (column: Daicell Chiralcell OJ-H, λ: 225 nm, eluent: EtOH : Hex = 2 : 98, flow : 0.4 mL/min t_R: 12.26 min, t_R: 12,71 min)).

1-(4-Methoxyphenyl)-2-(morpholin-4-yl)ethanol (4b)

White solid (m.p. = 76-77^{o}C). ^{1}H NMR (ppm): 2.41-2.51 (*m*, 4H), 2.70-2.77 (*m*, 2H), 3.69-3.77 (*m*, 4H), 3.79 (*s*, 3H), 4.70 (*dd*, 1H *J*= 8.85 4.8 Hz), 6.85-6.90 (*m*, 2H), 7.27-7.21 (*m*, 2H), ^{13}C NMR (ppm): 53.5, 55.3, 66.7, 67.0, 68.2, 113.8, 127.1, 133.8, 159.1. FAB-MS (*m*/*z*): 238 [M + H^{+}]. 28% *ee* by HPLC(column: Daicel Chiralcel OJ-H, λ: 225 nm, eluent: EtOH : Hex = 20 : 80, flow = 0.5mL/min, t_R: 28.03 min (minor) t_R: 31,74 min (major)).

1-(4-Methylphenyl)-2-(morpholin-4-yl)ethanol (4c)

White solid (m.p. = 75-76^{o}C). ^{1}H NMR (ppm): 2.33 (*s*, 3H), 2.41-2.50 (*m*, 4H), 2.71-2.73 (*m*, 2H), 3.72-3.76 (*m*, 4H), 4.72 (*dd*, 1H *J*= 9.45 4.2 Hz), 7.15 (*d*, 2H *J*= 7.8 Hz), 7.26 (*d*, 2H *J*= 5.1 Hz). ^{13}C NMR (ppm): 21.1, 53.4, 66.7, 67.0, 68.3, 125.8, 129.0, 137.2, 138.8. FAB-MS (*m*/*z*): 222 [M + H^{+}]. 59% *ee* by HPLC (column: Daicel Chiralcel OJ-H, λ: 225 nm, eluent: *i*-PrOH : Hex = 10 : 90, flow = 0.5mL/min, t_R: 45.68 min (minor) t_R: 49.66 min (major)).

1-(4-Chlorophenyl)-2-(morpholin-4-yl)ethanol (4d)

White solid (m.p. = 69-70^{o}C). ^{1}H NMR (ppm): 2.41-2.50 (*m*, 4H), 2.70-2.77 (*m*, 2H), 3.72-3.77 (*m*, 5H), 4.70 (*dd*, 2H *J*= 10.5 3.6 Hz), 7.31 (*m*, 4H). ^{13}C NMR (ppm): 53.4, 66.5, 67.0, 67.9, 127.2, 128.5, 133.2, 140.3. FAB-MS (*m*/*z*): 242 [M + H^{+}]. 29% *ee* by HPLC (column: Daicel Chiralcel OJ-H, λ: 225 nm, eluent : *i*-PrOH: Hex = 20 : 80, flow = 0.5mL/min, t_R: 22.82 min (minor) t_R: 26.80 min (major)).

2-Morpholino-1-(1-naphthyl)ethanol (4f)

White viscous oil. ^{1}H NMR (ppm): 2.50-2.63 (*m*, 3H), 2.81-2.86 (*m*, 3H), 3.75-3.83 (*m*, 4H), 5.60 (*dd*, 1H *J*= 10.5 3.0 Hz), 7.47-7.53 (*m*, 3H), 7.78 (*d*, 2H *J*= 7.8 Hz), 7.87(*d*, 1H *J*= 18.3 Hz), 8.0 (*d*, 1H *J*= 10.2 Hz). ^{13}C NMR (ppm): 53.6, 65.6, 65.7, 67.1, 122.5, 123.1, 123.4, 125.7, 126.0, 127.9, 129.0, 130.4, 133.7, 137.2. FAB-MS (*m*/*z*): 258 [M + H^+]. 22% *ee* by HPLC (column: Daicel Chiralcel OJ-H, λ: 225 nm, eluent: EtOH : Hex = 10 : 90, flow = 0.5mL/min, t_R: 28.51 min (minor) t_R: 30.22 min (major)).

2-Morpholino-1-(2-naphthyl)ethanol (4g)

White solid (m.p. = 92-100^{o}C). ^{1}H NMR (ppm): 2.47-2.65 (*m*, 4H), 2.75-2.79 (*m*, 2H), 3.09-3.82 (*m*, 5H), 4.92 (*dd*, 1H *J*= 10.05 3.6 Hz), 7.45 (*dd*, 3H *J*= 9.3, 6.6 Hz), 7.80-7.84 (*m*, 4H). ^{13}C NMR (ppm): 53.51, 66.56, 67.03, 68.65, 123.76, 124.52, 125.64, 125.97, 127.56, 127.76, 128.01, 132.88, 133.20, 139.16. FAB-MS (*m*/*z*): 258 [M + H^+]. 77% *ee* by HPLC (column: Daicel Chiralcel OJ-H, λ: 225 nm, eluent: *i*-PrOH : Hex = 20 : 80, flow = 0.5mL/min, t_R: 38.70 min (minor) t_R: 44.63 min (major)).

1-Morpholino-2-hexanol (4h)

Colorless oil. ^{1}H NMR (ppm): 0.84 (*t*, 3H *J*= 6.6 Hz), 1.22-1.40 (*m*, 6H), 2.15-2.35 (*m*, 4H), 2.55-2.57 (*m*, 2H), 2.60 (*br*, 1H), 3.62-3.69 (*m*, 5H). ^{13}CNMR (ppm): 14.0, 22.7, 27.7, 34.4, 53.5, 64.7, 65.8, 66.9. FAB-MS (*m*/*z*): 188 [M + H^+]. 38% *ee* by HPLC (column: Daicel Chiralcel OD-H, λ: 225 nm, eluent : *i*-PrOH : Hex = 10 : 90, flow = 1 mL/min, t_R: 10.11 min (minor) t_R: 10.63 min (major)).

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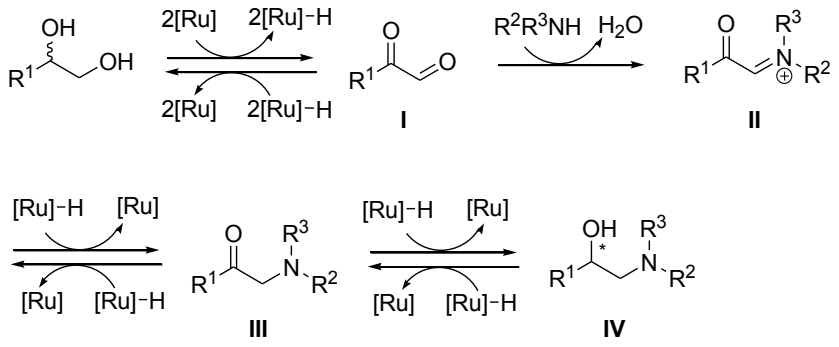
Chapter 2

Mechanistic Studies of Ruthenium-Catalyzed Enantioselective Synthesis of β-Amino Alcohols from 1,2-Diols

Abstract

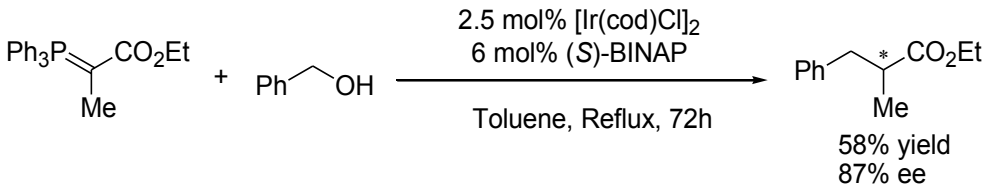
The mechanistic investigations of enantioselective synthesis of β-amino alcohols from 1,2-diols were examined to reveal the asymmetric inducting step on the "borrowing hydrogen"-type reaction. Various possibilities of reaction pathway have been examined, and the asymmetric reduction of β-amino ketone was found as important step to afford optically active β-amino alcohols.



Introduction

The use of "borrowing hydrogen" in such applications has growing so fast since the first application of homogenous catalyst on this reaction was introduced by Watanabe[1] and Grigg.[2] Although there are huge numbers of catalytic C-N[3] and C-C bond[4] forming reactions through this methodology has been reported, there is no example for the asymmetric synthesis of β-amino alcohols by means the use of chiral catalysts are well-known.

In 2007, Williams and co-worker screened several transition metal catalysts including iridium, ruthenium and rhodium-based complexes and various chiral ligands for asymmetric indirect Wittig reaction between ethyl 2-(triphenylphosphoranylidene) propanoate and benzyl alcohol to give the corresponding product in 58% yield and 87% *ee*[5] (Scheme 1). So far, to the best of our knowledge, this is the single example of asymmetric "borrowing hydrogen" reaction that has been reported. Beside no reaction scope was explained, there is no further investigation of mechanistic study has been conducted to explain the reaction detail. Therefore, it seems there is no interest of organic chemists to explore this field in spite of great opportunity to use "borrowing hydrogen" in asymmetric reaction.



Scheme 1. The only one example of "borrowing hydrogen" in asymmetric reaction before our report

In the chapter 1, the author described the example of application of "borrowing hydrogen" methodology on enantioselective synthesis of β-amino alcohols. Since this reaction is very new, the advance understanding how the reaction was taking place is important. In this chapter the author describe the detail of mechanistic investigations that has been conducted to understand the reaction pathway of our asymmetric "borrowing hydrogen" reaction. The author believed that the deep understanding of mechanistic aspect of this reaction will utilize and contribute for further development of asymmetric "borrowing hydrogen", not only for improvement of our novel reaction that has been discussed in chapter 1, but also for another development of potential asymmetric reactions *via* "borrowing hydrogen" methodology.

Result and Discussion

The main question of this chapter is: *how and when did the asymmetric induction occur?* To answer this question, the author suspected several possible reaction pathways. One of the possibilities is *via* the kinetic resolution pathway, because in kinetic resolution process, the racemic substrates react with another chiral source in different reaction rate, resulting that one enantiomer is converted to a major product and another enantiomer recovered as starting material.[6] Therefore, the excess amount of substrate is needed to afford maximum yield of enantioenriched product. As explained in chapter 1, the enantioselective synthesis of β-amino alcohols from 1,2-diols with "borrowing hydrogen" required 3 molecular equivalents of 1,2-diol to give the best result. This condition was match with the characteristic of reaction which runs through kinetic resolution.

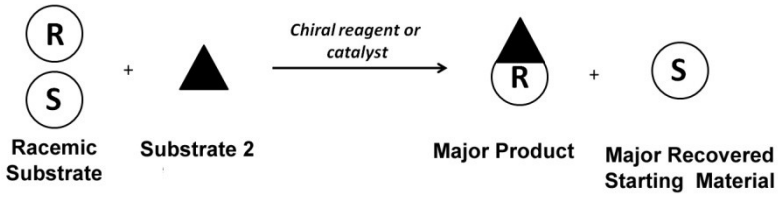
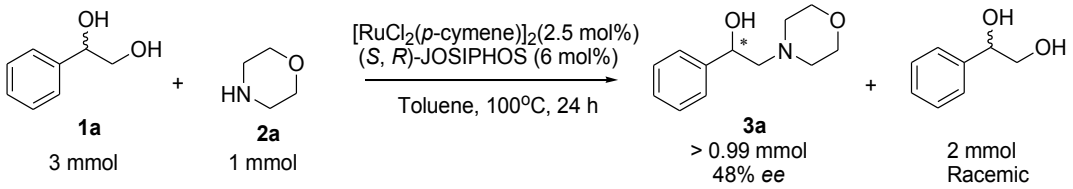


Figure 1. Kinetic resolution process

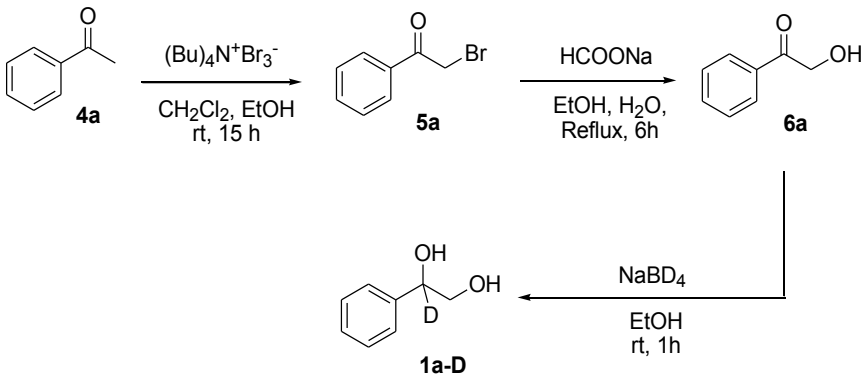
To confirm this possibility, enantiomeric excess of recovered diol was checked. Thus, the reaction of 3 equivalents of 1-phenyl-1,2-ethanediol (**1a**) with morpholine (**2a**) in the present of $[RuCl_2(p\text{-cymene})]_2$/(*S, R*)-JOSIPHOS catalysis according chapter 1 was carried out to give >99% yield of desired amino alcohol **3a** with 48% *ee*. The un-reacted 1,2-diol was recovered and purified, then the *ee* was determined by HPLC

analysis. Surprisingly, the 1,2-diol was found as a racemic mixture. Given this, the author realized that the reaction did not proceed *via* kinetic resolution of the racemic diol by the chiral ruthenium complex as predicted.



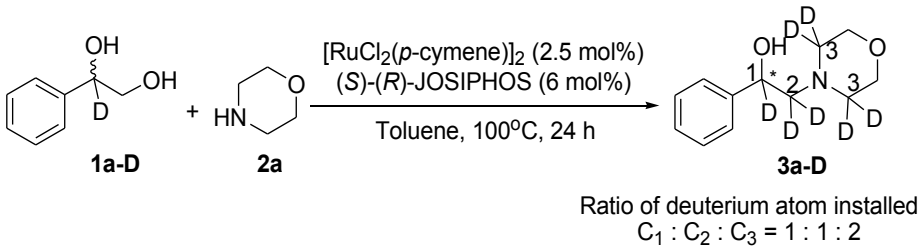
Scheme 2. Recovered 1,2-diol was found as racemic compound

Next, the author hypothesized that the secondary alcohol in diols has high possibility to participate in the "borrowing hydrogen" reaction to give the enentioenriched β-amino alcohols product. That is, the secondary alcohol could be converted into the ketone and then reduced to former alcohol with enantioselectivity. To test this hypothesis, the author prepared the deuterium-labelled diol **1a** to trace the transfer hydrogen possessed at C1 positions. The preparation of deuterium-labelled diol **1a-D** is outlined in Scheme 3. A simple bromination of acetophenone (**4a**) to give 2-bromoacetophenone (**5a**) followed by substitution of bromide to hydroxyl group to give hydroxyketone **6a**. The corresponding deuterium-labelled diol **1a-D** was yielded by reduction of hydroxyketone **6a** with $NaBD_4$.



Scheme 3. Synthetic procedure for preparation of deuterium-labelled diol **1-D**

The diol **1a-D** in hand, the author conducted the reaction of **1a-D** with morpholine (**2a**) in the presence of Ru/(*S*, *R*)-JOSIPHOS catalysis under the optimized reaction conditions in chapter 1 to afford the desired amino alcohol **3a-D** in 99% yield. ^{1}H NMR spectra of **3a-D** suggested that deuterium atoms were found at the C_1 and C_2 positions and even at the α-position of the morpholine ring (Scheme 4). This scrambling of deuterium atoms revealed that the hydrogen transfer reaction from secondary alcohols in **1a** to ruthenium complex possibly occurred to form hydroxyketone **6a**, α-oxo aldehyde **7a,** and/or aminoketone **9a**.



Scheme 4. Reaction of deuterium-labeled 1-phenyl-1,2-ethanediol (**1a-D**) with morpholine

To find out which intermediates was mainly formed under the present reaction conditions, the author checked the GC-MS spectrum of the crude reaction product at an early stage (5 hours). Hydroxyketone **6a** and α-oxo aldehyde **7a** accompanied by the aminoketone **9a** and amino alcohol **3a** were detected, whereas hydroxyl aldehyde **8a** (a possible oxidized product) was not (Figure 2). This result suggested that the double oxidation of diols to α-oxo aldehyde should occur under our catalytic conditions and that the aminoketone is an important intermediate in the process affording enantio-enriched amino alcohols.

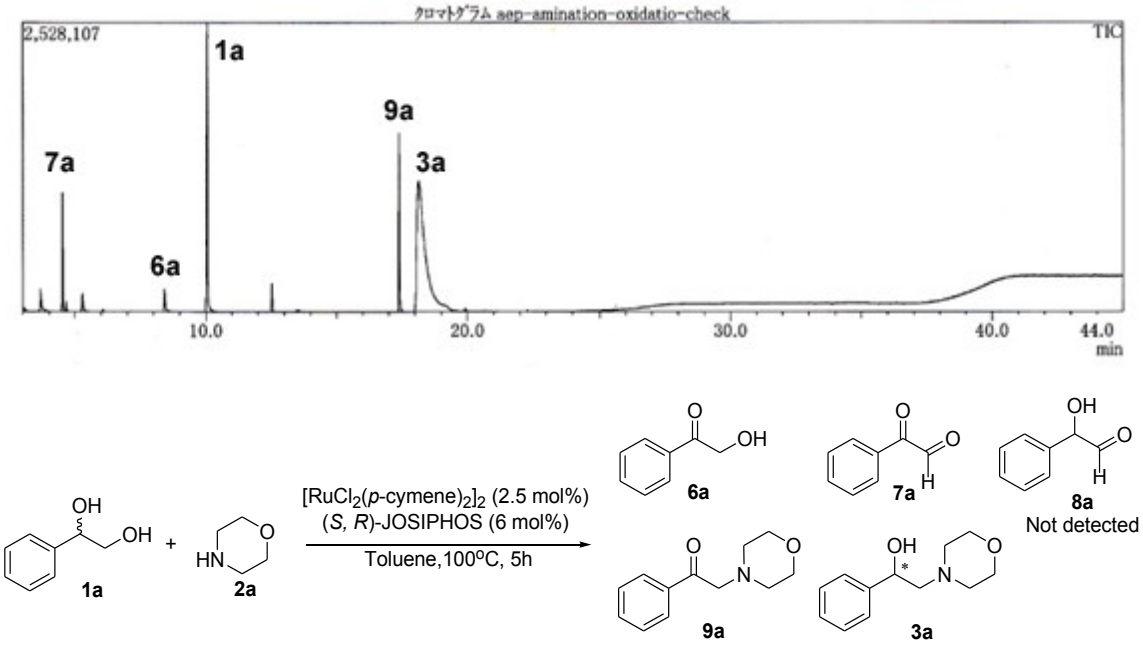
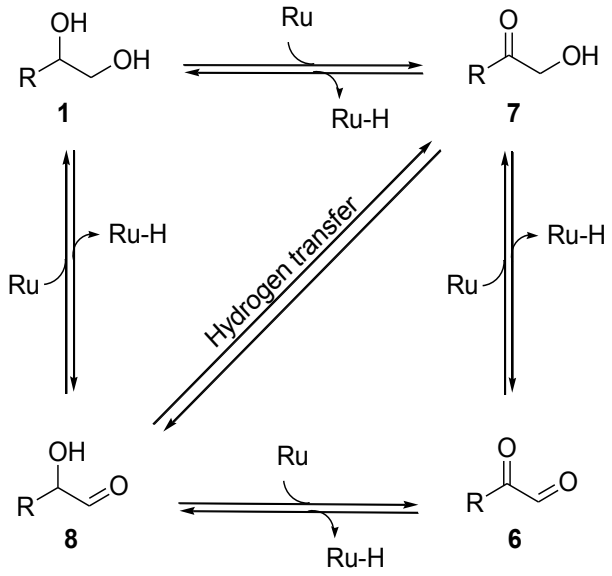


Figure 2. Reaction products at early stage (5 hours) based on GC-MS

To ensure this hypothesis, the author conducted continuing investigation of the reaction intermediates in different reaction time by ^{1}H NMR and GC-MS analysis. As a result, we found that the maximum yield of amino alcohol **9a** has been reached at 18

hours of reaction time. During that time, hydroxyketone **6a** and α-oxo aldehyde **7a** are always detected by GC-MS analysis, but hydroxyl aldehyde **8a** was not. However, at 24 hours we detected the appearance signal of hydroxyl aldehyde **8a**. These results emphasized that double oxidation of 1,2-diol to α-oxo aldehyde occurred, although the major pathway to form α-oxo aldehyde was not clear. The possibilities of α-oxo aldehyde formation by double oxidation of 1,2-diols are outlined in Scheme 5.



Sceme 5. Possibilities of α-oxo aldehydes **6** formation from 1,2 diols **1**

The author also observed the yield of produced amino ketone **9a** and amino alcohol **3a** in different reaction stages (Figure 3). Formation of amino ketone **9a** at early stage was increasing significantly until 6 hours of reaction time to give the maximum 26% yield of amino ketone **9a**. After 6 hour, the yield of **9a** was decreasing gradually according to increasing yield of corresponding amino alcohol **3a**. From the plotted data in figure 3, it was considered that the reaction rate of amino alcohol **3a** formation is faster than amino ketone **9a**.

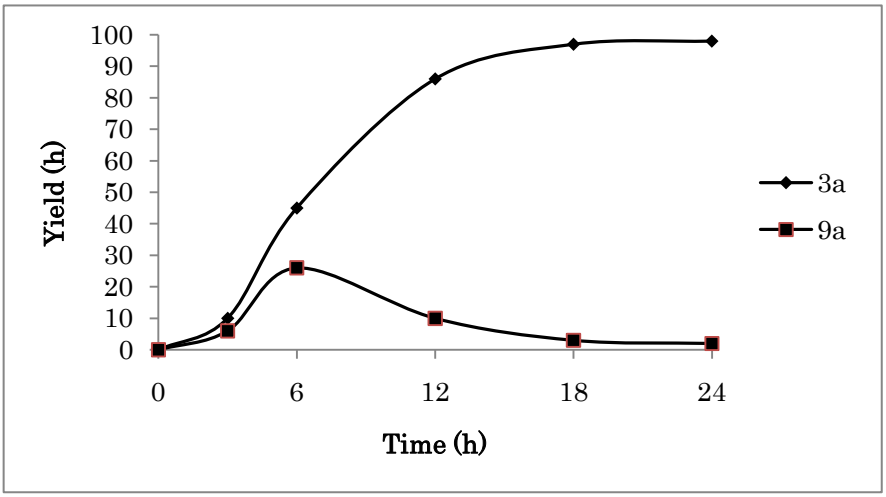
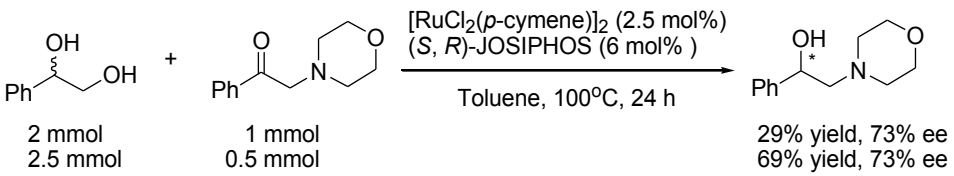


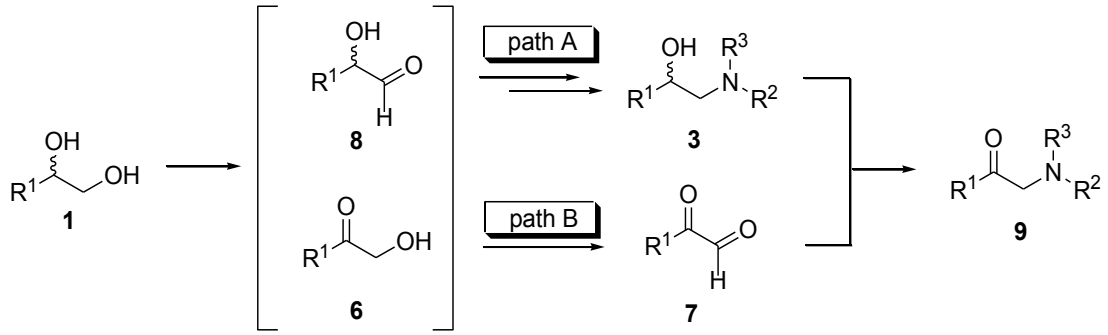
Figure 3. Plots of amino alcohol **3a** and aminoketone **9a** in different reaction stages

The author therefore examined the reduction of aminoketone **9a** by using starting diol **1a** and the present chiral ruthenium catalysis (Scheme 6) to clarify the role of aminoketone **9a** on formation of enantiopure amino alcohol **3a**. Thus, aminoketone **9a** was reacted with 2 equivalent of 1-phenyl-1,2-ethanediol (**1a**) under the optimized reaction conditions to obtain the corresponding amino alcohol **3a** in 29% yield with 73% *ee*. The reaction using 5 equivalents of **1a** also afforded **3a** in 69% yield with 73% *ee*. The formation of amino alcohol **3a** with sufficient optical purity from **1a** is consistent with aminoketone **9a** being a key intermediate at the enantio-determining step. These results gave us strong evidence and emphasized that the aminoketone **9a** is the key intermediate to afford the enantioenriched β-amino alcohol **3a** *via* asymmetric reduction.



Scheme 6. Asymmetric reduction of aminoketone to β-amino alcohol

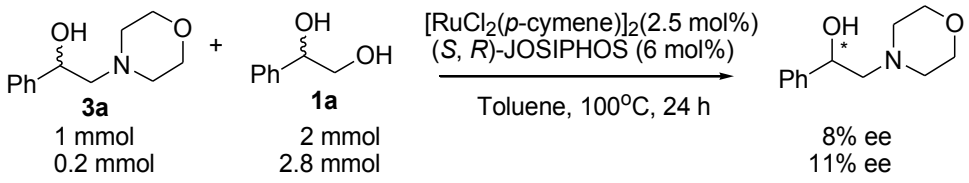
Next, the author examined the possible routes for aminoketone **9a** formation. There are two highly possible routes to form the intermediate aminoketone **9a**, they could be described as shown in scheme 4: (1) oxidation of racemic amino alcohol **3a** that already formed (path A); (2) reaction of morpholine after the double oxidation of the starting diol (path B), which is supported by GC-MS analysis (Scheme 7).



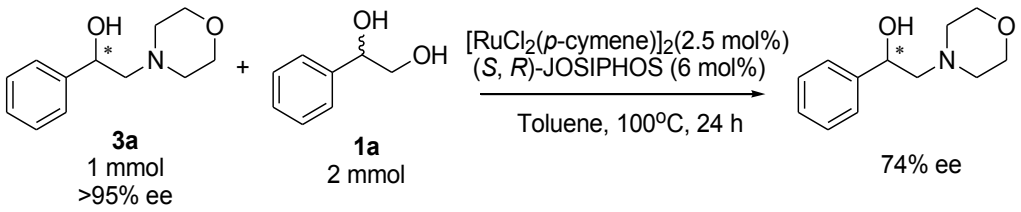
Scheme 7. Possible route of aminoketone **9** formation

To confirm the feasibility of path A, the author first investigated the change of the *ee* value for amino alcohol **3a** under the optimized reaction conditions. When racemic **3a** prepared independently was exposed to the reaction conditions, the *ee* of the recovered **3a** was very low. Even with highly excess amount of 1,2-diol was used, *ee* value was less than 11% (Scheme 8). In addition, almost optically pure amino alcohol **3a** (>95% *ee*) which was prepared by an authentic procedure[7] was slightly racemized

under the optimized reaction conditions to afford **3a** with an *ee* of 74% (Scheme 9). These results suggested that an enantioselective redox reaction took place at the benzylic position of **3a** under the optimized reaction conditions, though the reaction rate is considered to be relatively slow. The author therefore thought that the oxidation of amino alcohol **3a** (path A) is not main route of the formation of aminoketone **9a**. Although the secondary alcohol in aliphatic diols is considered to be oxidized slower than primary one, this trend is also inconsistent with the feasibility of path A. In addition, several selective oxidations of secondary alcohols in diol[8] and isomerization of hydroxyl aldehyde to hydroxyl ketone[9] have been reported, supporting the possibility that the double oxidation could have taken place on the aliphatic diols under the present reaction conditions. Based on these result, the author concludes that the path B is the main route on aminoketone **9a** formation.

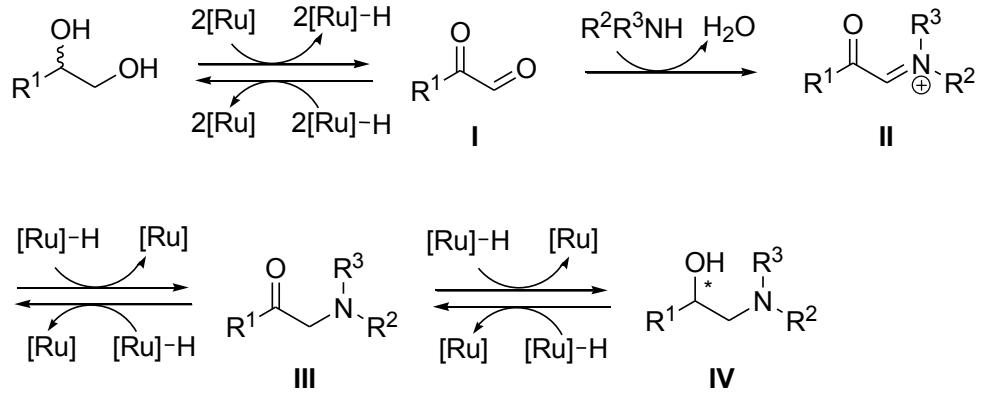


Scheme 8. Treatment of *racemic*-**3a** with **1a** and chiral ruthenium catalysis



Scheme 9. Racemization of enantio-enriched β-amino alcohol **3a**

Given the results of these mechanistic studies, the author proposes the following main reaction pathway (Scheme 10). The starting diol is converted into the α-oxo aldehyde **I** by ruthenium-catalyzed double dehydrogenation. α-oxo aldehyde **I** reacts with the amine to afford the iminium ion intermediate **II**, which is converted into the aminoketone **III**. The aminoketone **III** is finally changed into the desired amino alcohol **IV** by a second transfer hydrogenation reaction. The enantioselection occurs in the final step.



Scheme 10. Proposed reaction mechanism of enantioselective amination of 1,2-diols

Conclusion

In conclusion, the mechanistic investigation of enantioselective synthesis of β-amino alcohols from 1,2-diol *via* "borrowing hydrogen" methodology has been successfully conducted. The asymmetric reduction of corresponding aminoketone was found to be the main reaction step in which asymmetric induction occurred.

Experimental Section

General Information

Nuclear magnetic resonance spectra (NMR) were recorded by using Varian Mercury Plus 300-4N spectrometer with TMS at 0 ppm as an internal standard for ^{1}H NMR and $CDCl_3$ at 77 ppm for ^{13}C NMR. Enantiomeric excess (*ee*) was measured by Hitachi L-7100 HPLC with a chiral column (Daicel Chiralcel OD-H or OJ-H) under the conditions described below. All reactions were carried out under argon in a sealed reaction tube. Reagents obtained from commercial sources were used without further purifications. Molecular sieves (4Å) were activated by heating in an oven for 2 hours at 350^{o}C before use.

Synthesis of 2-bromo acetophenone (5a)

In argon purged 250 mL Schlenk tube, 30 mmol of acetophenone (**4a)** is solved in 20 mL of anhydrous diclorometh**a**ne and 20 mL of dry methanol. In another Schlenk tube, tetrabuthylammonium tribromide was solved in 80 mL of anhydrous dichoromethane. The solution of tetrabuthylammonium tribromide was dropwise transferred to acetophenone (**4a**) solution by using syringe. The solution was stirred for 15 hours in room temperature. After the reaction finished, solvent was evaporated and the mixture was transferred to separation funnel. Ethyl actetate and water was added to the separation funnel. Organic layer was separated and water phase was extracted three times with ethyl acetate. The organic phase was combined and washed by $NaHCO_3$ solution, followed by brine, and dried with Na_2SO_4. Finally the Na_2SO_4 was removed by filtration to give the crude 2-bromoacetophenone **5** in quantitative yield. This crude product was used for next step without further purification. ^{1}HNMR (ppm) δ: 4.5 (*s*,

2H), 7.43-7.78 (*m*, 3H), 8.0-8.1(*m*, 2H),

Synthesis of 2-hydroxy-1-phenylethanone (6a)

To an argon purge 250 mL three neck flask equipped with condenser and bubbler was added 30 mmol of 2-bromoacetophenone **5** from previous step, 180 mmol of sodium formate (ratio of **5** and sodium formate was 1:6), 66 mL of ethanol and 12 mL of water. The mixture was refluxed for 6 h. After the reaction completed (TLC check), the solvent was evaporated. The residue was extracted with diethyl ether followed with washing by water, twice with brine and dried over Na_2SO_4. Finally the Na_2SO_4 was filtered to give the crude product of corresponding hydroxyketone **6a** in quantitative yield. ^{1}H NMR (ppm) δ: 3.1 (*t*, J= 4.2 Hz, 1 H), 4. 89 (*d*, *J* = 4.2 Hz, 2 H), 7. 47-7. 55 (*m*, 2H), 7. 60-7. 69 (*m*, 2H).

Synthesis of deuterium labelled 1-phenyl-1,2-ethanediol (1a-D)

To argon purge 250 mL three necks flask equipped with bubbler was solved the resulting hydroxyketone **6a** from previous step in ethanol. Four equivalents of $NaBD_4$ were added to the solution little by little in 0^{o}C. The solution was allowed to stir at room temperature until completing the reaction (monitoring by TLC). After the reaction finish, the excess of $NaBD_4$ was quenched by water in ice bath. The solution was allowed to stir until no hydrogen gas was observed. Ethanol was evaporated and the crude product was extracted with ethyl acetate, washed with water, followed by brine and dried over Na_2SO_4. After filtration of Na_2SO_4, the crude product was purified with silica gel colomn chromatography to give pure deuterium-labelled diol **1a-D** as white solid. ^{1}H NMR (ppm) δ: 2.42–2.57 (*m*, 4 H), 2.73–2.76 (*m*, 2 H), 3.73–3.81 (*m*, 4 H), 7.24–7.35

(*m*, 5 H).

Synthesis of 2-morpholino-1-phenylethanone (9a)

In a schlenk tube was solved 2-bromo acetophenone or 2-chloro acetophenone in diethyl ether. 10 equivalents of morpholine (**2a**) were slowly added to the solution. The mixture was allowed to react in room temperature. The completion of the reaction was monitored by TLC. After the reaction finish, the reaction mixture was quenched by $NaHCO_3$ solution and water followed by extraction with diethyl ether. The organic layer was dried over Na_2SO_4 and evaporated to give crude product as yellowish oil. Purification by silica gel column chromatography afforded pure 2-morpholino-1-phenyl-ethanone. ^{1}H NMR (ppm) δ: 2.62 (*m*, 4H), 3.79 (*m*, 4H), 3.83 (*s*, 2H), 7.50-7.43 (*m*, 2H), 7.60-7.55 (*m*, 1H), 8.02-7.97 (*m*, 2H)

Synthesis of enantiopure 2-morpholino-1-phenylethanol (1a)

In argon purge schlenk tube was solved 12.5 mmol of (+ or -) DIP-Chloride in 5 mL dry diethyl ether, the solution was stirred for 10 minutes to ensure the DIP-Chloride homogenously solves (solution A). To another argon purge schlenk tube were added 5 mmol of 2-morpholino-1-phenylethanone (**9a**) and 25 mL dry diethyl ether (Solution B). Solution B was cooled to acetone-dry ice bath. The solution A was slowly transferred to solution B by using syringe. The solution mixture was allowed to react until it reached room temperature (12~18h). After the reaction finish, the mixture was quenched by methanol (0.5 mL) followed by concentrated hydrochloric acid (1mL) and allowed to stir for 30 minutes. The mixture was extracted by diethyl ether and water. The water phase was washed by hexane (three times). NaOH was added until the

mixture reach very basic pH. The crude product was collected by extraction with diethyl ether (3 times), dried over Na_2SO_4 and followed by filtration to give crude product as yellowish crystal. The product was easily to purify by recristalization in hexane to give enantiopure 2-morpholino-1-phenyl-1,2-ethanediol **3a** as colourless crystal. 94% *ee* by HPLC [Daicel Chiralcel OD-H; λ = 225 nm; iPrOH/ hexane = 20:80; flow = 0.5 mL/min; tR = 15.86 (minor), 17.22 (major) min]. ^{1}H NMR (ppm) δ: 2.42–2.57 (*m*, 4 H), 2.73–2.76 (*m*, 2 H), 3.73–3.81 (*m*, 4 H), 4.75 (*dd*, *J* = 10.2, 3.9 Hz, 1 H), 7.24–7.35 (*m*, 5 H)

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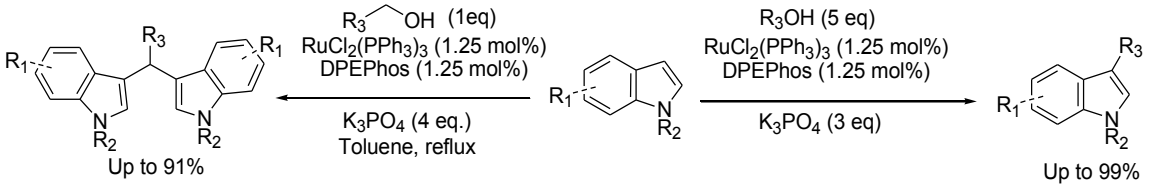
Chapter 3

Ruthenium-Catalyzed Regioselective Alkylation of Indoles with Alcohols

Abstract

The regioselective alkylation of indoles with alcohols as alkylating reagents was developed by using $RuCl_2(PPh_3)_3$/DPEphos as catalysts. Thus, the reaction of indole with benzyl alcohol in the presence of $RuCl_2(PPh_3)_3$/DPEphos catalysis and K_3PO_4 at 165°C for 24 h under argon atmosphere afforded 99% yield of 3-benzylindole. Various types of alcohol were treated with indoles under the optimal reaction conditions to give the corresponding 3-alkylated indoles in high yields (up to 99%). This catalysis was also found to be effective on the formation of bis(3-indolyl)phenylmethanes derivatives refluxed in toluene to give the corresponding bis(3-indolyl)phenylmethanes up to 91% yield.



Introduction

Indole is one of the most abundant heterocyle rings in the nature. It could be found in variety of natural products, and most of them are biologically active compounds. Indole ring is the main skeleton of a class of alkaloid which is known as indole alkaloids. Till date, more than 4.100 indole alkaloid compounds have been identified. It made indole alkaloid become one of the largest classes of alkaloid.[1] These natural products have various biological activities that could be used for various purposes, for example as traditional medicines[2] and pesticides.[3] Not only in alkaloids, indole ring also act as skeleton of indigo, a natural dye that traditionally isolated from several plants to give a color between blue and violet which is known as indigo color.[4] Moreover, various types of medicines contain indole moiety in their molecular structure. Matergine is known as a medicine that usually used for treatment of childbirth bleeding is an example.[5]

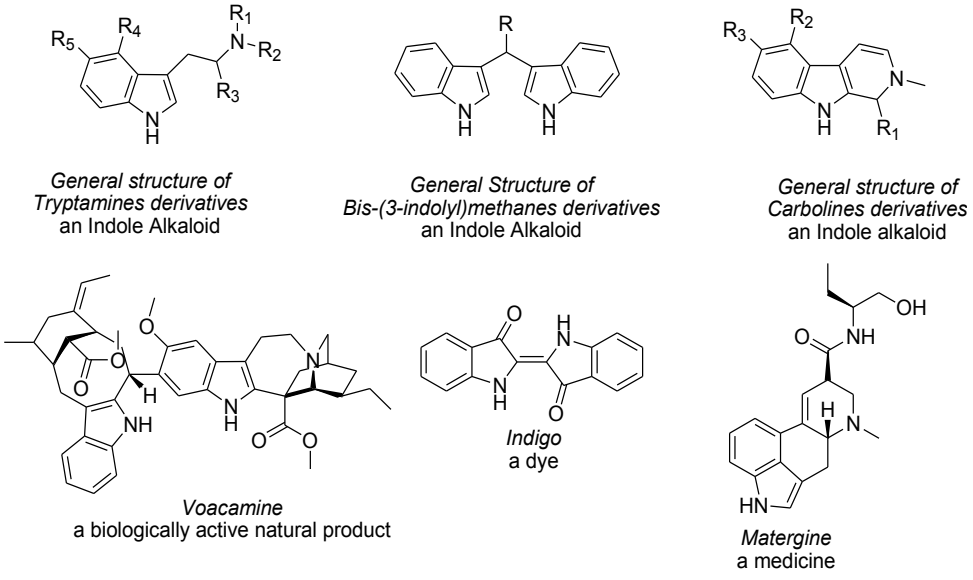
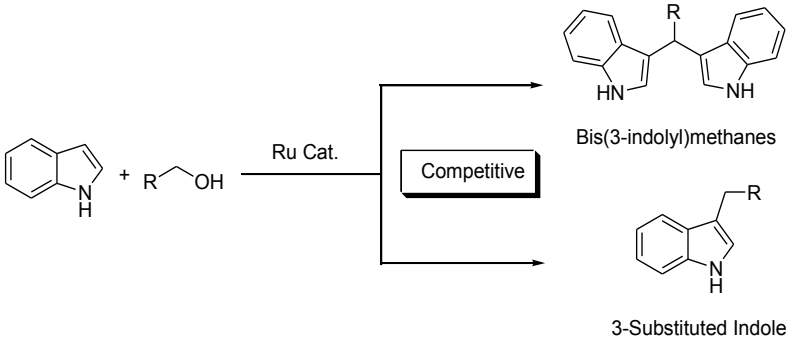


Figure 1. Several examples of compounds containing idole

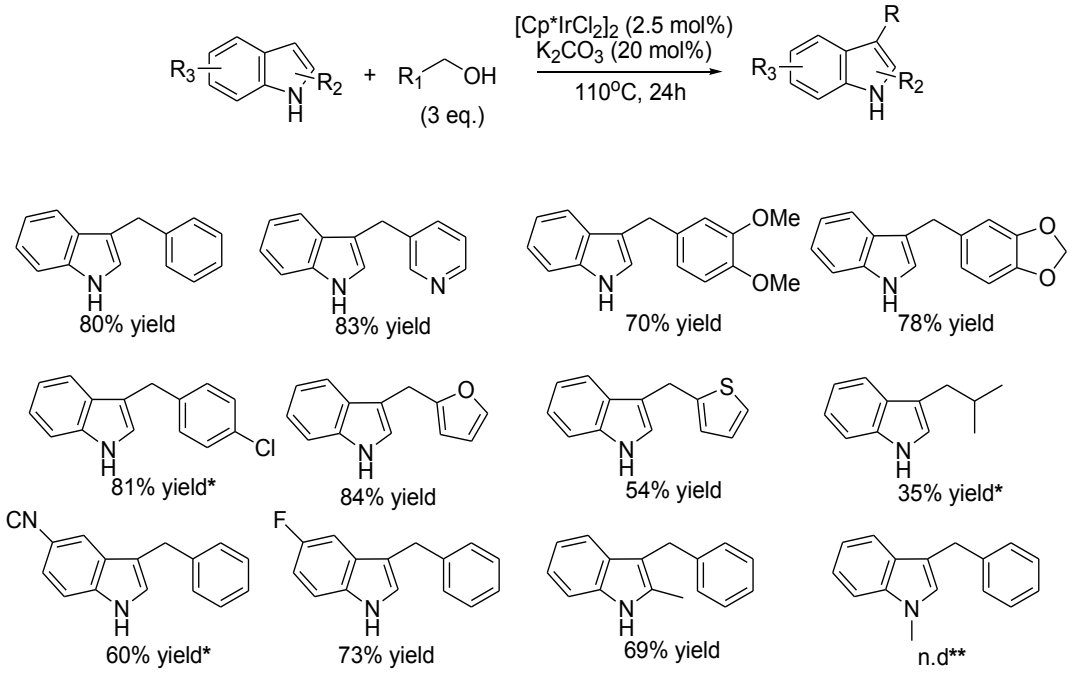
From several examples that outlined in Figure 1, we can clearly see that most of indole derivatives have C-C bonds on C3 position of the ring. This fact emphasize that the methods for preparation of 3-substituted indole is highly important because of its versatility. Therefore, the development of a new, efficient, selective and green synthetic method for the preparation of 3-substituted indole derivatives has attracted much attention. Although alkylation of indoles has traditionally been performed using alkyl halides, this is not an ideal method because of its poor regioselectivity.[6] Regioselective alkylation of indoles has been achieved by reactions with aldehydes,[7] α,β-unsaturated ketones,[8] and other reagents.[9] However, most of these reactions required large amounts of acids and low yields were obtained even for long reaction times. Furthermore, dimerization of the indole sometimes occurred reducing the catalytic efficiency.

The application of "borrowing hydrogen" for preparation of 3-substituted indoles by using alcohol as alkylating reagent is highly possible since the use of aldehyde as alkylating reagent showed very good selectivity to form C-C bond on C3 possition.[10] However, it would be a challenge to turn the selectivity to form 3-substituted indole because a competitive reaction between the formation of 3-substitued indoles and bis(3-indolyl)phenylmethanes possibly occur.



Scheme 1. Hypothesis: alkylation of indoles with alcohols *via* "borrowing hydrogen"

In 2007, Grigg and his co-workers reported the use of alcohols as alkylating reagents for the preparation of 3-substituted indole with $[Cp^*IrCl_2]_2$ catalyst.[11] Several alcohols were allowed to react with indoles to give the corresponding 3 substituted indole (Figure 2). Although it was successful, there are several weak points of this catalysis: 1) The use of alcohol is limited to benzylic or related alcohols, and poor yields were obtained when aliphatic alcohol was used. 2) Yields decreased when substituted indoles substrates were used. 3) No reaction took place when *N*-alkylated indole was used even after 72h.

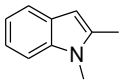
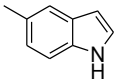
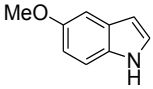
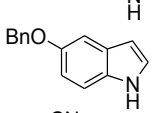
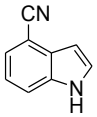


Reaction condition: Indole (1 mmol), Alcohol (3 mmol), $[Cp^*IrCl_2]_2$ (2.5 mol%), K_2CO_3 (20 mol%), under N_2 110°C, 24 h. *Reaction time was 48h. **Reaction time was 72h

Figure 2. Result from Grigg's report

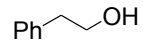
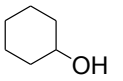
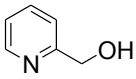
Meanwhile, few years ago our group also interested in this reaction.[12] Several homogenous and heterogenous catalysts were screened for alkylation of indole by using benzyl alcohols. At that time, Pd/C was found to give the best catalytic performance to form 3-benzyl indole in high yield and regioselectivity. After optimization of the reaction condition, the Pd/C catalysis allowed relatively wide substrate scope including aliphatic alcohols and secondary *N*-alkylated indoles (Table 1 and 2). These results showed that Pd/C could afford the 3-substituted indoles in wider scope of indoles and alcohols under air atmosphere. However, the author has several notes on the weak points of this result: 1) Yields were strongly dependent on substrate's nature, that is different substrate required different reaction condition to give the best result, 2) Large amount of catalyst (5 mol%) and alcohol (19 eq.) were required.

Table 1. Scope of Indole in our previous study[a]

Entry	Indole	Base	Temp. (°C)	Time (h)	Yield (%)[b]
1		K_2CO_3	80	24	90
2		K_2CO_3	80	24	0
3		None	150	14	52
4		K_2CO_3	100	24	0
5		None	150	24	99
6		None	150	24	60
7		None	150	24	99
8		K_2CO_3	80	24	60
9		K_2CO_3	100	24	27

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (2 mL), Pd/C (0.05 mmol), K_2CO_3 (4 mmol), under air. [b] Determined by ^{1}H NMR.

Table 2. Scope of alcohol in our previous study[a]

Entry	Alcohol	Base	Temp. (°C)	Yield (%)[b]
1		K_2CO_3	150	90
2[C]		K_2CO_3	150	66
3	$C_{10}H_{21}OH$	KOH	150	74
4		K_2CO_3	150	0
5		KOH	150	99
6		K_2CO_3	150	Trace
7		KOH	100	70
8		KOH	150	88
9		K_2CO_3	80	99

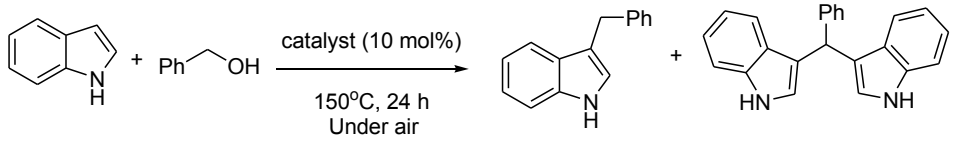
[a] Reaction conditions: indole (1.0 mmol), Pd/C (0.05 mmol), Alcohol (19 mmol), under air, Base (4 mmol), 24h. [b] Determined by ^{1}H NMR. [c] reaction time was 72 h.

In this chapter, the author shows that combination catalysis of $RuCl_2(PPh_3)_3$ and DPEphos ligand nicely catalyzed the formation of 3-substituted indole in the present of K_3PO_4 in excellent yield (up to 99%). The reaction proceeded smoothly in wide scope of substrates, including aliphatic alcohols and *N*-alkylated indole. Moreover, the author achieved to reduce the amount of catalyst (1.25 mol%) and alcohols (5 eq.). In addition, this catalyst system could selectively obtain bis(3-indolyl)phenylmethanes which is also an important indole derivatives selectively (up to 91% yield) under reflux condition in toluene.

Result and Discussion

This study was carried out based on the previous study in our laboratory described above. In the previous investigation, several homogenous and heterogeneous catalysts were screened for preparation of 3-benzylindole (Table 3). In this study, the author was focussing his attention to use homogenous catalyst and $RuCl_2(PPh_3)_3$ was chosen as catalyst.

Table 3. Screening of transition metal catalysts[a]



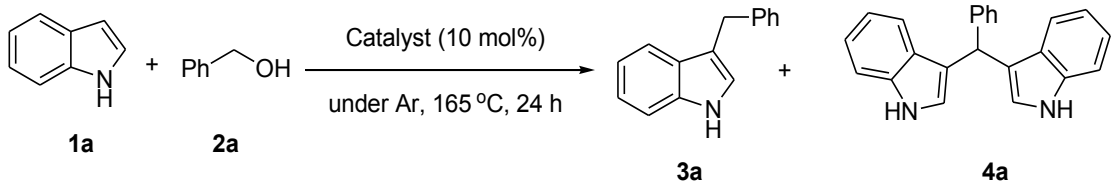
1a **2a** **3a** **4a**

Entry	Catalyst	KOH (mmol)	Conv. (%)[b],[c]	**3a** (%)[c]	**4a** (%)[c]
Homogenous Catalyst					
1	$[Ir(cod)Cl]_2$	0.1	100	41	34
2	$[Ir(cod)Cl]_2$	3.0	100	29	46
3	$[RuCl_2(p\text{-cymene})]_2$	0.2	53	Trace	40
4	$RuCl_2(PPh_3)_3$	0.2	Nr	-	-
5	$RuCl_2(PPh_3)_3$	3.0	100	62	32
6	$[RhCl(cod)]_2$	0.1	24	4	18
7	$[RhCl(cod)]_2$	3.0	100	24	64
8	$RhCl(PPh_3)_3$	0.1	100	35	40
Heterogenous Catalyst					
9	Pd/C	None	72	70	0
10	Ru/C	None	92	68	0
11	Rh/Al_2O_3	None	100	12	61

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (2 mL), catalyst (0.1 mmol), at 150 ºC for 24 h, under air. [b] Based on indole. [c] Determined by ^{1}H NMR.

Although 62% yield of 3-benzylindole **3a** was obtained under air atmosphere, the author believed that the reaction would be better carried out under inert atmosphere since the catalyst complex is known to be air-sensitive. Moreover, an inert atmosphere would provide wider opportunity to improve catalyst performance easily by addition of other ligands. As a result, the author found that the corresponding 3-benzylindole **3a** was afforded in 78% yield catalyzed by the coupling of $RuCl_2(PPh_3)_3$ and a DPEphos ligand accompanied by 12% of bis(3-indolyl)methane **4a**.

Table 4. Preliminary catalyst test[a]



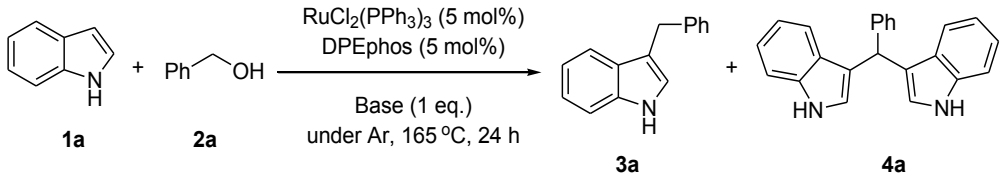
Entry	Catalyst	KOH (mmol)	Conv. (%)[b],[c]	**3a** (%)[c]	**4a** (%)[c]
1	$RuCl_2(PPh_3)_3$	0	100	44	56
2	$RuCl_2(PPh_3)_3$	3	100	52	38
3	$RuCl_2(PPh_3)_3$/DPEphos	3	100	78	12

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (2.0 mL), catalyst (0.1 mmol), KOH, at 165ºC for 24 h, under Ar. [b] Based on indole. [c] Determined by ^{1}H NMR.

Effect of Base

With good catalytic performance of $RuCl_2(PPh_3)_3$/DPEphos in hand, the amount of catalyst, KOH and benzyl alcohol were reduced to 5 mol%, 1 equivalent and 5 equivalents, respectively (Table 5). However, poorer selectivity and lower yield were obtained, affording **3a** in 50% accompanied by 40% of bis(3-indolyl)phenylmethane **4a** (entry 1). Therefore, several bases were screened to tune the catalyst performance (entries 2-9). K_2CO_3 and Cs_2CO_3 exhibited similar activities to yield **3a** in 66% and 65% yields accompanied by ca. 20% of **4a** (entries 2 and 3). A better result was obtained when Na_2CO_3 was used, giving 74% of **3a** and only 7% of **4a** was detected (entry 4). Poor chemoselectivity was resulted when the reaction was carried out in the presence of *t*BuOK to give in almost same yield of **3a** and **4a** (59% and 40%, respectively, entry 5). Finally, K_3PO_4 was found to give the best result to obtain the desired 3-benzylindole (**3a**) in 80% yield. In this case, only 16% of bis(3-indolyl)phenylmethane (**4a)** was detected (entry 7). In contrast, bis(3-indolyl)phenylmethane (**4a)** was the main product and only a trace amount of **3a** was detected when Na_2HPO_4 and K_2SO_4 were used (entries 8 and 9). Based on these results, K_3PO_4 was chosen to use in following investigations.

Table 5. Effect of base on benzylation of indole catalyzed by $RuCl_2(PPh_3)_3$/DPEphos[a]



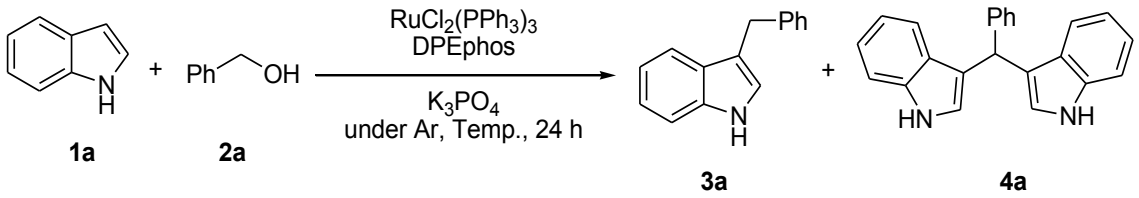
Entry	Base	Conv. (%)[b],[c]	**3a** (%)[c]	**4a** (%)[c]
1	KOH	100	50	40
2	K_2CO_3	94	66	22
3	Cs_2CO_3	100	65	28
4	Na_2CO_3	90	74	7
5	*t*BuOK	100	59	40
6	KF	94	51	24
7	K_3PO_4	100	80	16
8	Na_2HPO_4	78	3	47
9	K_2SO_4	100	1	54

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (5.0 mmol), $RuCl_2(PPh_3)_3$ (0.05 mmol), DPEphos (0.05 mmol), base (1 mmol), at 165ºC for 24 h, under Ar. [b] Based on indole. [c] Determined by ^{1}H NMR

Optimization of Reaction Condition

Next, the effects of catalyst loading, amount of base, and temperature were examined (Table 6). Initially, the amount of K_3PO_4 was reduced to 0.5 mmol. However, the yield of **3a** decreased to 69% (entry 2). The reaction efficiency was enhanced by use of 2 mmol of K_3PO_4 affording **3a** in 89% yield (entry 3). Almost the same result was obtained when 3 mmol K_3PO_4 was used (entry 4). Further optimization reactions employed 2 mmol of K_3PO_4. Reducing the amount of catalyst to 2.5 mol% yielded 99% of the corresponding product **3a** (entry 5), whereas the yield was decreased to 80% when 1.25 mol% of catalyst was loaded (entry 6). On the other hand, increasing K_3PO_4 to 3 equivalents with 1.25 mol% of catalyst increased the catalytic activity to afforded **3a** in 99% yield (entry 7). It is noteworthy that only trace amount of **4a** was detected in the crude product. The author tried to reduce the reaction temperature, however the yield of **3a** decreased upon decreasing the temperature, while formation of bis(3-indolyl)phenylmethane **4a** was increased (entries 8-9).

Table 6. Optimization of reaction condition[a]



Entry	Catalyst (mol%)	K_3PO_4 (mmol)	Temp. (^oC)	Conv. (%)[b]	**3a** (%)[b]	**4a** (%)[b]
1	5	1	165	100	80	16
2	5	0.5	165	100	69	24
3	5	2	165	100	89	4
4	5	3	165	100	87	2
5	2.5	2	165	100	99	Trace
6	1.25	2	165	100	80	20
7	1.25	3	165	100	99	0
8	1.25	3	150	100	91	9
9	1.25	3	120	100	20	66

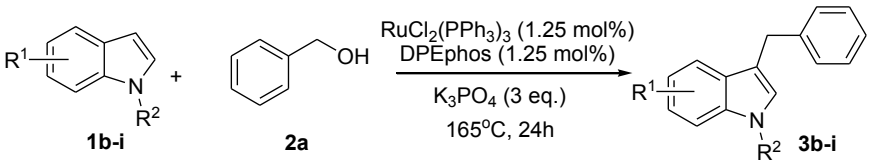
[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (5 mmol), $RuCl_2(PPh_3)_3$ (0.05 mmol), DPEphos (0.05 mmol), K_3PO_4, 24 h, under Ar. [b] Based on indole. [c] Determined by ^1H NMR

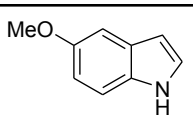
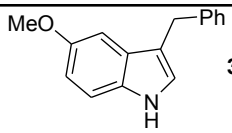
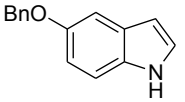
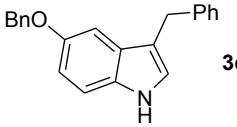
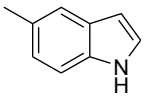
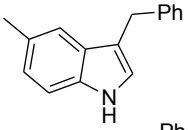
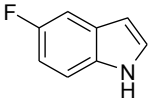
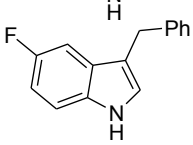
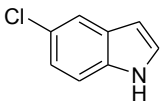
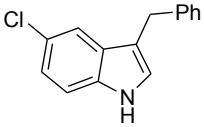
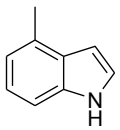
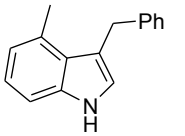
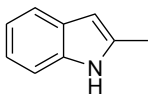
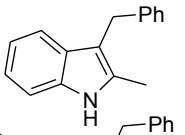
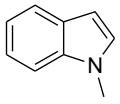
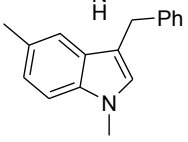
Scope of Substrates

Scope of Indoles

Under the optimized reaction conditions above, the scope of substrates was studied. First, the substrate scope on benzylation of indoles was investigated (Table 7). Various types of indoles including 5-substituted or *N*-alkylated indoles were found to react smoothly with benzyl alcohol under the optimized reaction conditions. Thus, indoles with electron-donating group substituents such as methoxy (**1b**), benzyloxy (**1c**), and methyl (**1d**), as well as electron-withdrawing groups such as fluoro (**1e**) and chloro (**1f**) at 5-position of the rings, gave excellent yields (87-99%) of the desired 3-substituted indoles (entries 1-5). Next, indoles bearing methyl substituent at 1-,2- and 4- position were tested. The reaction proceeded nicely to afford also excellent yields of the corresponding products even when the methyl group was possessed at C4 and C2 positions (entries 6-7). We also glad to find that the reaction also proceeded smoothly by using *N*-alkylated indole as substrate, which is one of the limitation of Grigg's iridium catalyst. Thus, 74% yield of desired 3-substituted indole (**3i**) was observed when 1-methylindole (**1i**) was used (entry 8).

Table 7. Scope of indoles[a]



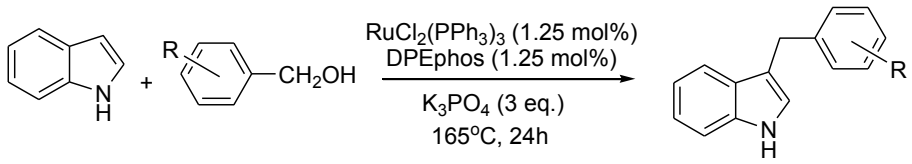
Entry	Indole		Product		Yield (%)[b]
1		**1b**		**3b**	99
2		**1c**		**3c**	92
3		**1d**		**3d**	99
4		**1e**		**3e**	98
5[c]		**1f**		**3f**	87
6		**1g**		**3g**	99
7		**1h**		**3h**	89
8[c]		**1i**		**3i**	74

[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (5.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), K_3PO_4 (3.0 mmol), at 165ºC for 24 h, under Ar. [b] Determined by ^1H NMR. [c] Benzyl alcohol was 7.0 mmol.

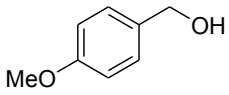
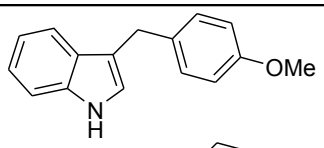
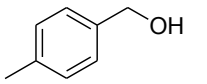
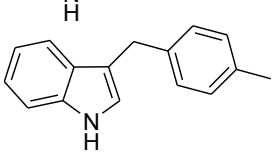
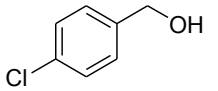
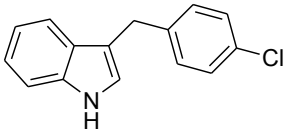
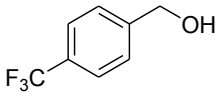
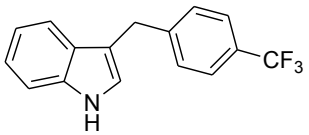
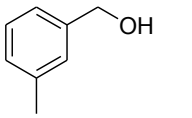
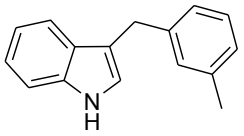
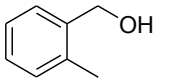
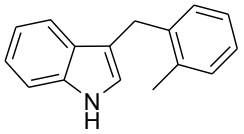
Scope of Benzylic Alcohol

After several types of indoles were tested, the author moved to examine the scope of benzylic alcohols (Table 8). Initially, several substituents with different electronic properties were installed in *para* position of benzyl alcohols. As a result, the corresponding desired 3-substituted indoles were obtained in excellent yields, when 4-methoxy (**2b**) and 4-methylbenzyl alcohol (**2c**) were used (entries 1-2). However, the yield slightly decreased when benzylic alcohols having electron-withdrawing groups at *para* position were used. For example, when chlorine atom was installed, the corresponding product **3l** was obtained in 80% yield (entry 3), and stronger electron-withdrawing group such as $-CF_3$ gave the desired 3-substituted indole **3m** in lower yield (67%, entry 4). This decrease of reaction efficiency was possibly caused by the difficulty of dehydrogenation process on benzyl alcohols with electron withdrawing substituent on *para* position. Next, methyl group was installed at another position on benzene ring of benzyl alcohol. As the result, the desired product **3n** was obtained in 76% yield when 3-methylbenzyl alcohol (**2f**) was used (entry 5). Meanwhile, an excellent yield of desired indole **3o** was obtained by use of *ortho*-methyl benzyl alcohol (**2g**) (entry 6).

Table 8. Scope of benzylic alcohols



1 **2** **3**

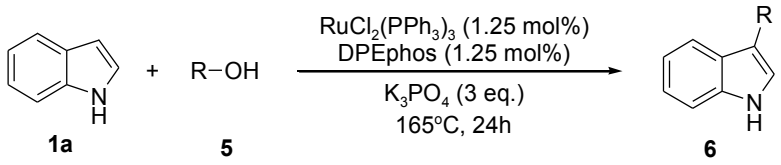
Entry	Benzyl alcohol		Product		Yield (%)[b]
1		**2b**		**3j**	90
2		**2c**		**3k**	99
3		**2d**		**3l**	80
4		**2e**		**3m**	67
5		**2f**		**3n**	76
6		**2g**		**3o**	90

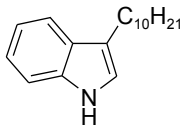
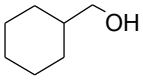
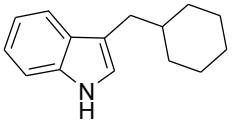
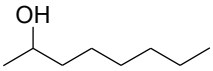
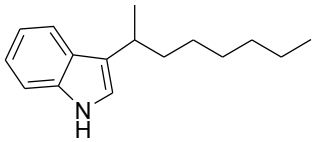
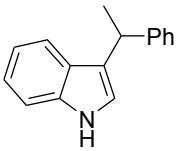
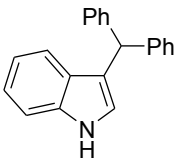
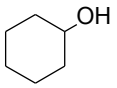
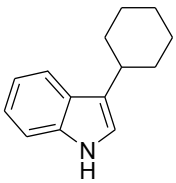
[a] Reaction conditions: indole (1.0 mmol), benzyl alcohol (5.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), K_3PO_4 (3.0 mmol), at 165ºC for 24 h, under Ar. [b] Determined by ^1H NMR.

Scope of Aliphatic and Secondary Alcohols

With excellent results for benzylation of indoles in hand, the author directed his attention to check the scope of the various type of alcohols on this catalytic reaction (Table 9). Firstly, the reactions of indole (**1a**) with primary alcohols were tested. As the result, the reaction of aliphatic primary alcohol, 1-decanol (**5a**) and cyclohexanemethanol (**5b**), afforded the corresponding 3-substituted indoles **6b** and **6c** in excellent yields (94% and 92%, respectively, for entries 1-2). On the other hand, the secondary 2-octanol (**5c**) showed lower reactivity to give the corresponding 3-substituted indole **6c** in 74% yield (entry 3). The steric factor could be considered as the reason of this lower reactivity of the secondary aliphatic alcohol than primary one. The author also found that the reaction of indole with secondary benzylic alcohols afforded the desired 3-substituted indoles **6d** and **6e** in excellent yields (entries 4-5). Interestingly, a cyclic secondary alcohol also acted as a good substrate. Thus, when cyclohexanol (**5f**) was used, 96% of the corresponding product was obtained (entry 6).

Table 9. Effect of alcohol structure on alkylation of indole catalyzed by $RuCl_2(PPh_3)_3$/DPEPhos[a]

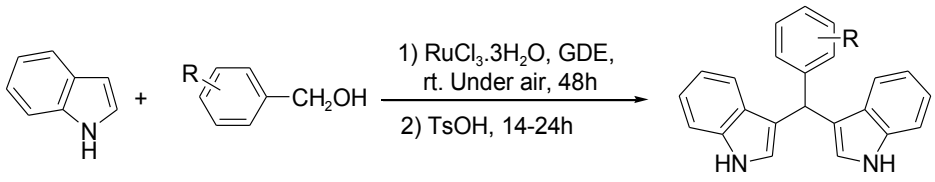


Entry	Alcohol		Product		Yield(%)[b]
1	$C_{10}H_{21}OH$	**5a**		**6a**	94
2		**5b**		**6b**	92
3		**5c**		**6c**	74
4		**5d**		**6d**	93
5[c]		**5e**		**6e**	93
6		**5f**		**6f**	96

[a] Reaction conditions: indole (1 mmol), alcohol (5 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), K_3PO_4 (3.0 mmol), at 165ºC for 24 h, under Ar. [b] Determined by ^1H NMR. [c] Reaction time was 30 h.

Synthesis of Bis(3-indolyl)methanes

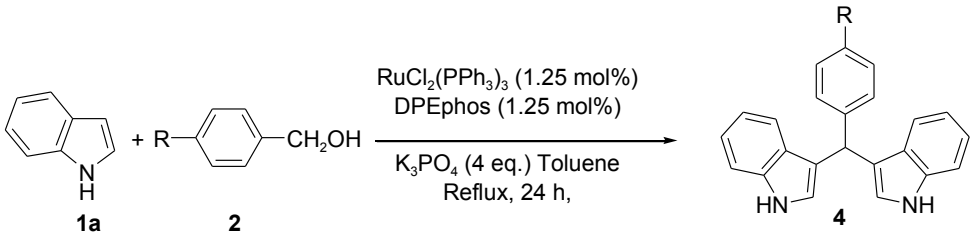
During the course of our investigations on preparation of 3-benzylated indoles, bis(3-indolyl)phenylmethane derivatives were often observed as by-products. Although these compounds were not desirable in that case, bis(3-indolyl)phenylmethanes are also useful materials as backbone of bisindole alkaloids.[13] Therefore, several synthestic methods for this class of compound have been reported. In 2012, Liu and co-workers reported ruthenium-catalyzed preparation of bis(3-indolyl)phenylmethanes by reaction of indoles and benzylic alcohols.[13-b] However, their catalytic reaction was two step reaction and required long reaction time (62-72h). in addition, yields were spread from poor to excellent (30-88%) (Scheme 2)



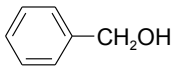
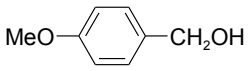
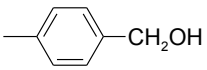
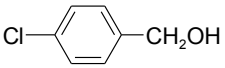
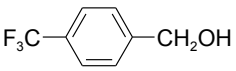
Scheme 2. Synthesis of bis(3-indolyl)phenylmethanes by Liu

When the present reaction was performed under reflux conditions in toluene, the author found that $RuCl_2(PPh_3)_3$/DPEphos catalysis worked well to obtain these compounds. Several types of benzyl alcohols were examined (Table 10). The reaction yielded the corresponding bis(3-indolyl)phenylmethane (**4a**) in 90% yield when benzyl alcohol was used (entry 1). Excellent yields were also observed when electron-donating substituents were installed at the *para*-position of the benzyl alcohol (entries 2-3). Similar to the simple of alkylation of indoles decribed above, the yields were slightly decreased when electron-withdrawing substituents such as chloro and trifluoromethane group were used (entries 4-5).

Table 10. Formation of bis(3-indolyl)phenylmethane derivatives catalyzed by $RuCl_2(PPh_3)_3$/DPEphos[a]



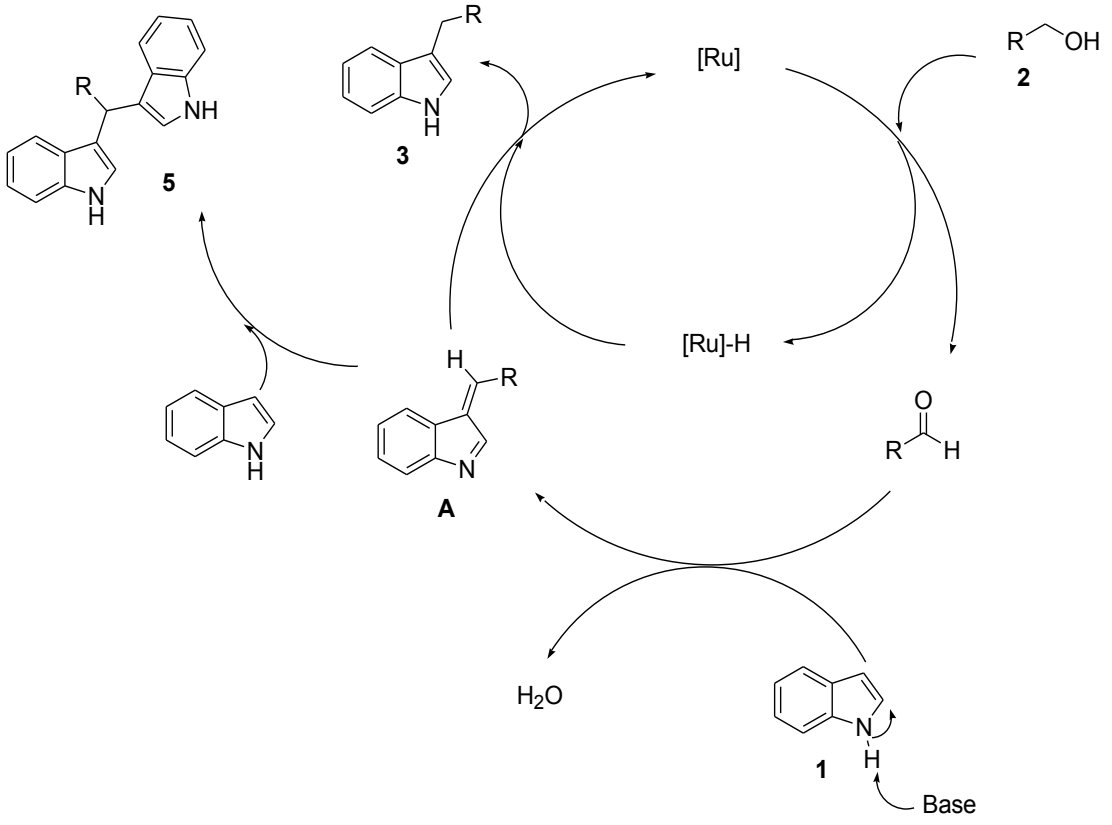
1a **2** **4**

Entry	Alcohol	product	Yield (%)[b]
1		**4a**	90
2		**4b**	91
3		**4c**	87
4		**4d**	70
5		**4e**	70

[a] Reaction conditions: indole (1.0 mmol), benzylic alcohol (2.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol), K_3PO_4 (4.0 mmol), under Ar, reflux in toluene (1 mL) for 24 h. [b] Determined by ^{1}H NMR

Plausible Reaction Mechanism

The plausible reaction mechanism is proposed as follows. Initially, alcohol **2** is dehydrogenated to aldehyde by the catalytically active ruthenium species. Meanwhile, the base activated C3 possition of indole for nucleophilic reaction by abstraction of proton, which attacks the resulting aldehyde to afford intermediate **A** *via* dehydration. The exo carbon-carbon double bond is hydrogenated by ruthenium-hydride species to give 3-substituted indole **3**. When this hydrogenation of **A** is slow, bis(3-indolyl)phenylmethane **4** is formed upon further nucleophilic reaction of indole (Scheme 3). *N*-alkylated products were not detected in our reaction, possibly the effect of base is the reason for this phenomena.



Scheme 3. Plausible reaction mechanism

Conclusions

The author achieved the ruthenium-catalyzed regioselective synthesis of 3-substituted indole by using alcohol as alkylating reagent. The reaction proceeded with high regioselectivity for various type of indole including *N*-substituted indole and almost all type of alcohols to give desired 3-substituted indole in excellent yield (up to 99%). In adition, under reflux condition in toleuene, bis(3-indolyl)phenylmethane was resulted, selectively in excellent yield (up to 91%).

Experimental Section

General Information

Nuclear magnetic resonance (NMR) spectra were measured using Varian MERCURY plus300-4N spectrometer with tetramethylsilane as the internal standard for the ^{1}H NMR and $CDCl_3$ at 77 ppm for the ^{13}C NMR. Mass spectra (GC-MS) data were recorded on a Shimadzu QP5000 instrument. High resolution mass spectra (FAB) were measured using a JEOL JMS-700 with *meta*-nitrobenzyl alcohol as the matrix and PEG-200 as the calibration standard. Commercially available compounds were used without further purification.

Benzyation of indoles catalyzed by $RuCl_2(PPh_3)_3$/DPEphos

To an argon purged 20-mL Schlenk tube was added indole (1.0 mmol), K_3PO_4 (3.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol) and benzyl alcohol (5 mmol). The mixture was degassed by three-cycle of freeze-pomp-thaw method, purged with argon gas and stirred at 165^{o}C for 24 h. The reaction mixture was filtered and solvent was evaporated under reduced pressure. Excess of benzyl alcohol was removed by Kogelrohr distillation. The obtained crude product was purified by column chromatography or recrystalization in hexane to give corresponding 3-benzylated indoles.

Synthesis of bis(3-indolyl)phenylmethane derivatives catalyzed by $RuCl_2(PPh_3)_3$

To an argon purged 20-mL Schlenk tube was added indole (1.0 mmol), benzyl alcohol (2.0 mmol), K_3PO_4 (4.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol) and toluene (1 mL). The mixture was degassed by using three-cycle of freeze-pomp-thaw method, purged with argon gas and stirred at 120 ^oC for 24 h. The reaction mixture was filtered, concentrated *in vacuo* and purified by column chromatography.

Alkylation of indoles catalyzed by $RuCl_2(PPh_3)_3$/DPEphos

To an argon purged 20-mL Schlenk tube was added indole (1.0 mmol), K_3PO_4 (3.0 mmol), $RuCl_2(PPh_3)_3$ (0.0125 mmol), DPEphos (0.0125 mmol) and corresponding alcohol (5 mmol). The mixture was degassed by using three-cycle of freeze-pomp-thaw method, purged with argon gas and stirred at 165 ^oC for 24 h. The reaction mixture was filtered and solvent was evaporated under reduced pressure. Excess of alcohol was removed by Kogelrohr distillation. The obtained crude product was purified by column chromatography or recrystalization in hexane to give corresponding 3-substituted indole.

3-Benzyl-1*H*-indole (3a) [14]

White solid, m. p. = 104-107^oC. ^1H NMR ($CDCl_3$): δ = 4.12 (2H, s, -C<u>H</u>-Ph), 6.91 (1H, d, *J* = 2.4 Hz, -NH-C<u>H</u>=), 7.07 (1H, t, *J* = 6.9 Hz, Ar), 7.15-7.30 (6H, m, Ar), 7.35 (1H, d, *J* = 8.1 Hz, Ar), 7.51 (1H, d, *J* = 7.8 Hz, Ar), 7.94 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 31.5, 110.9, 115.6, 118.9, 119.1, 121.8, 122.1, 125.7, 127.2, 128.1, 128.4, 136.2, 141.0. GC-MS (*m/z*) 207. HRMS (FAB, m-NBA) calcd. for C15H13N: 207.1048,

found: 207.1038.

3-Benzyl-5-methoxy-1*H*-indole (3b)[10]

White solid, m. p. = 61-62°C. ^{1}H NMR ($CDCl_3$): δ = 3.80 (3H, s, -OC<u>H</u>$_3$-), 4.08 (2H, s, Ph-C<u>H</u>$_2$-), 6.82-6.88 (2H, m, Ar), 6.93 (1H, s, -NH-C<u>H</u>=), 7.15-7.37 (6H, m, Ar), 7.85 (1H, s, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$) δ = 31.6, 55.8, 100.9, 111.6, 111.9, 115.3, 123.0, 125.7, 127.7, 128.1, 128.5, 131.5, 140.9, 153.7. GC-MS (*m/z*) 237. HRMS (FAB, m-NBA) calcd. for C16H15NO: 237.1154, found: 237.1136.

3-Benzyl-5-benzyloxy-1*H*-indole (3c)

Brown solid, m. p. = 97.5-101°C. ^{1}H NMR($CDCl_3$): δ = 4.06 (2H, s, -CH-C<u>H</u>$_2$-Ph), 5.03 (2H, s, -O-C<u>H</u>$_2$-Ph), 6.86 (1H, d, *J* = 2.1 Hz, Ar), 6.91 (1H, dd, *J* = 7.8 Hz, 2.4, Ar), 7.02 (1H, s, Ar), 7.16-7.38 (9H, m, Ar), 7.43 (2H, d, *J* = 7.8 Hz, Ar), 7.82 (1H, br, -N<u>H</u>). ^{13}C NMR ($CDCl_3$): δ = 31.6, 70.8, 102.6, 111.6, 112.7, 115.4, 123.0, 125.7, 127.4, 127.5, 128.1, 128.3, 128.4, 131.6, 137.4, 140.5, 140.9, 152.9. GC-MS (*m/z*) 313. HRMS (FAB, m-NBA) calcd. for C22H19NO: 313.1468, found: 313.1474.

3-Benzyl-5-methyl-1*H*-indole (3d)[15]

Brown solid, m. p. = 108.5-113°C. ^{1}H NMR ($CDCl_3$): δ = 2.40 (3H, s, Ar-C<u>H</u>$_3$), 4.06 (2H, s, -C<u>H</u>$_2$-Ph), 6.81 (1H, d, *J* =2.4, -NH-C<u>H</u>=), 7.10-7.51 (8H, m, Ar), 8.05 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 21.6, 31.4, 110.5, 115.1, 118.5, 122.3, 123.4, 125.6, 127.5, 128.1, 128.4, 134.5, 141.1. GC-MS (*m/z*) 221. HRMS (FAB, m-NBA) calcd. for C16H15N: 221.1205, found: 221.1214.

3-benzyl-5-fluoro-1*H*-indole (3e)[10]

Colorless micro-needles, m. p. = 122-126°C. ^{1}H NMR ($CDCl_3$): δ = 4.05 (2H, s, C<u>H</u>$_2$-Ph), 6.88 (1H, dd *J* = 8.85 2.7 Hz, Ar), 6.95 (1H, s, NH-C<u>H</u>), 7.10 (1H, dd, *J* = 9.75 2.7 Hz, Ar), 7.14-7.31 (6H, m, Ar), 7.90 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$) δ = 31.52, 103.89, 104.19, 110.20, 110.56, 111.52, 124.06, 125.99, 128.37, 128.58, 132.90, 140.74, 159.23. HRMS (FAB, m-NBA) calcd. for C15H12FN: 225.0954, found: 225.0969.

3-benzyl-5-chloro-1*H*-indole (3f)[16]

Colorless micro-needles, m. p. = 82-84°C. ^{1}H NMR ($CDCl_3$): δ = 4.05 (2H, s, C<u>H</u>$_2$-Ph), 6.91 (1H, s, NH-C<u>H</u>), 7.13 (1H, dd, *J* = 8.7 1.8 Hz, Ar), 7.13-7.31 (6H, m, Ar), 7.47 (1H, d, *J* = 1.8 Hz, Ar). 7.92 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 31.68, 112.02, 115.62, 118.60, 122.34, 123.68, 125.08, 126.02, 128.40, 128.56, 134.73, 140.65. GC-MS (*m/z*): 241

3-Benzyl-4-methyl-1*H*-indole (3g)[17]

Light yellow solid, m. p. = 84-86°C. ^{1}H NMR ($CDCl_3$): δ = 2.54 (3H, s, -CH_2-C<u>H</u>$_3$), 4.28 (2H, s, C<u>H</u>$_2$-Ph), 6.75 (1H, s, NH-C<u>H</u>-), 6.78 (1H, d, *J* = 8.7 Hz, Ar), 7.02 (1H, t, *J*=8.1 Ar), 7.15-7.29 (6H, m), 7.85 (1H, br, -NH-). ^{13}C NMR ($CDCl_3$): δ = 20.13, 33.30, 108.98, 115.97, 120.92, 122.14, 123.18, 125.79, 126.06, 128.29, 128.56, 131.10, 136.96, 141.93. HRMS (FAB, m-NBA) calcd. for C16H15N: 221.1204, found: 221.1192.

3-Benzyl-2-methyl-1*H*-indole (3h)[10]

Colorless micro-needles, m. p. = 115-118°C. ^{1}H NMR ($CDCl_3$): δ = 2.33 (3H, s,NH-C-C<u>H</u>$_3$), 4.05 (2H, s, -C<u>H</u>$_2$-Ph), 6.98-7.09 (2H, m, Ar), 7.11-7.15 (1H, m, Ar), 7.18-7.25 (5H, m, Ar), 7.36 (1H, d, *J* = 7.5 Hz, Ar), 7.66 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ=11.80, 30.12, 109.98, 110.16, 110.56, 118.39, 119.27, 121.01, 125.68, 128.29, 128.92, 131.67, 135.28, 141.68. HRMS (FAB, m-NBA) calcd. for C16H15N: 221.1204, found: 221.1214.

3-Benzyl-1-methy-1*H*-lindole (3i)[18]

White solid, m. p. = 51-53°C. ^{1}H NMR ($CDCl_3$): δ = 3.80 (3H, s, -NCH_3), 4.11 (2H, s, -CH_2-Ph), 6.75 (1H, s, -NH-CH-), 7.07 (1H, t, *J* = 6.9 Hz, Ar), 7.15-7.30 (6H, m, Ar), 7.35 (1H, d, *J* = 8.1 Hz, Ar), 7.51 (1H, d, *J* = 7.8 Hz, Ar). ^{13}C NMR ($CDCl_3$): δ =31.5, 108.9, 114.1, 118.6, 119.0, 121.4, 125.6, 126.9, 127.6, 128.1, 128.5, 136.9, 141.2. GC-MS (*m/z*) 221. HRMS (FAB, m-NBA) calcd. for C16H15N: 221.1205, found: 221.1192.

3-(4-Methoxybenzyl)-1*H*-indole (3j)[10]

Light yellow solid, m. p. = 80.5-83°C. ^{1}H NMR ($CDCl_3$): δ = 3.77 (3H, s, -C<u>H</u>$_3$), 4.05 (2H, s, -C<u>H</u>$_2$-C_6H_4-), 6.83 (2H, d, *J* = 8.1 Hz, Ar), 6.86 (1H, d, *J* = 2.1 Hz, -NH-C<u>H</u>), 7.07 (1H, t, *J* = 7.5 Hz, Ar), 7.14-7.22 (3H, m, Ar), 7.34 (1H, d, *J* = 8.1 Hz, Ar), 7.51 (1H, d, *J* = 8.1 Hz, Ar), 7.88 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 30.7, 55.2, 110.9, 113.6, 116.1, 119.0, 119.1, 121.8, 122.0, 127.2, 129.4, 133.1, 136.2, 157.5. GC-MS

(*m/z*) 237. HRMS (FAB, m-NBA) calcd. for C16H15NO: 237.1154, found: 237.1172.

3-(4-Methylbenzyl)-1*H*-indole (3k)[17]

Light yellow solid, m. p. = 89.5-91°C. ^{1}H NMR ($CDCl_3$): δ = 2.31 (3H, s, -C<u>H</u>$_3$), 4.07 (2H, s, -C<u>H</u>$_2$-C_6H_4-), 6.89 (1H, d, *J* = 2.1 Hz, -NH-C<u>H</u>=), 7.03-7.08 (3H, m, Ar), 7.14-7.19 (3H, m, Ar), 7.34 (1H, d, *J* = 8.1 Hz, Ar), 7.51 (1H, d, *J* = 8.1 Hz, Ar), 7.94 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 21.0, 31.1, 110.8, 115.9, 119.0, 119.1, 121.8, 122.0, 128.3, 128.4, 128.8, 128.9, 135.0, 137.9. GC-MS (m/z) 221. HRMS (FAB, m-NBA) calcd. for C16H15N: 221.1205, found: 221.1192.

3-(4-chlorobenzyl)-1*H*-indole (3l)[10]

White solid, m. p. = 101-102°C. ^{1}H NMR ($CDCl_3$): δ = 4.07 (2H, s, -C<u>H</u>$_2$-C_6H_4-), 6.91 (1H, s, NH-C<u>H</u>=), 7.04 (1H, t, *J* = 8.1 Hz, Ar), 7.16-7.25 (5H, m, Ar), 7.37 (1H, d, *J* = 7.8 Hz, Ar), 7.47 (1H, d, *J* = 7.8 Hz, Ar), 7.95 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 30.97, 111.12, 115.26, 119.03, 119.53, 122.19, 122.34, 127.24, 128.40, 129.99, 131.58, 136.44, 139.65. HRMS (FAB, m-NBA) calcd. for C16H12ClN: 241.0658, found: 241.0638.

3-(4-Triflouromethylbenzyl)-1*H*-indole (3m)[19]

White solid, m. p. = 95-97°C. ^{1}H NMR ($CDCl_3$): δ = 4.17 (2H, s, -C<u>H</u>$_2$-C_6H_4-), 6.94 (1H, s, NH-C<u>H</u>=), 7.11 (1H, t *J*= 7.8 Hz, Ar), 7.22 (1H, t *J* = 8.1 Hz, Ar), 7.39 (3H, d, *J* = 9.3 Hz, Ar), 7.40-7.54 (3H, m, Ar), 7.99 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 31.44, 111.18, 114.66, 118.95, 119.56, 122.26, 122.44, 125.21, 125.27, 127.19, 128.88, 136.44, 145.35. HRMS (FAB, m-NBA) calcd. for C16H12F3N: 275.0922, found: 275.0924.

3-(3-methylbenzyl)-1*H*-indole (3n)

Light brown solid, m. p. = 48-49°C. ^{1}H NMR($CDCl_3$): δ = 2.29 (3H, s, -C_6H_4-C<u>H</u>$_3$), 4.07 (2H, s, -C<u>H</u>$_2$-C_6H_4-), 6.89 (1H, s, NH-C<u>H</u>=), 6.98 (1H, d, *J* = 9.3 Hz, Ar), 7.04-7.10 (3H, m, Ar), 7.13-7.20 (2H, m, Ar), 7.35 (1H, d, *J* = 8.1 Hz, Ar), 7.54 (1H, d, *J* = 9 Hz, Ar), 7.89 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 21.45, 31.51, 111.03, 115.95, 119.17, 119.34, 122.01, 122.28, 125.73, 126.63, 127.50, 128.22, 129.47, 136.41, 137.86, 141.13. HRMS (FAB, m-NBA) calcd. for C16H15N: 221.1204, found: 221.1192.

3-(2-Methylbenzyl)-1*H*-indole (3o)

Light pink solid, m. p. = 52-53°C. ^{1}H NMR ($CDCl_3$): δ = 2.32 (3H, s, -C_6H_4-C<u>H</u>$_3$), 4.06 (2H, s, -C<u>H</u>$_2$-C_6H_4-), 6.70 (2H, s, NH-C<u>H</u>-), 7.07-7.23 (6H, m, Ar), 7.36 (1H, d *J* = 8.1 Hz, Ar), 7.57 (1H, d, *J* = 8.1 Hz, Ar), 7.88 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 19.47, 29.23, 111.04, 115.18, 119.03, 119.30, 122.02, 122.35, 125.91, 126.14, 127.53, 129.37, 130.09, 136.42, 139,05. HRMS (FAB, m-NBA) calcd. for C16H15N: 221.1204, found: 221.1192.

3,3'-Bis-indolyl phenylmethane (4a)[12-b]

Pink solid. ^{1}H NMR ($CDCl_3$): δ = 5.87 (1H, s, Ph-C<u>H</u>), 6.63 (2H, s, -NH-C<u>H</u>=), 6.99 (2H, t, *J* = 7.8 Hz, Ar), 7.15 (2H, t, *J* = 7.0 Hz, Ar), 7.19-7.39 (9H, m, Ar), 7.90 (2H, s, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 40.1, 110.8, 119.0, 119.5, 119.7, 121.7, 123.4, 125.9, 126.9, 128.0, 128.5, 136.4, 143.8. GC-MS (*m/z*): 322. HRMS (FAB, m-NBA) calcd. for C23H18N2: 322.1470, found: 322.1471.

3,3'-Bis-indolyl-(4-methoxyphenyl)methane (4b)[12-b]

Orange solid. ^{1}H NMR ($CDCl_3$): δ = 3.81 (3H, s, -OC<u>H</u>$_3$), 5.83 (1H, s, Ph-C<u>H</u>), 6.65 (2H, s, -NH-C<u>H</u>=), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 7.02 (2H, t, *J* = 7.2 Hz, Ar), 7.18 (2H, t, *J* = 8.4 Hz, Ar), 7.36 (2H, d, *J* = 8.1 Hz, Ar), 7.40 (2H, d *J* = 9.6 Hz, Ar), 7.89 (2H, s, N<u>H</u>). ^{13}C NMR ($CDCl_3$): δ = 39.3, 55.2, 111.0, 113.5, 119.2, 119.8, 120.1, 121.9, 123.5, 127.0, 129.6, 136.2, 136.7, 157.9.

3,3'-Bis-indolyl-(4-methylphenyl)methane (4c)[9b]

Orange solid.^{1}H NMR ($CDCl_3$): δ = 2.30 (3H, s, -C<u>H</u>$_3$), 5.83 (1H, s, Ph-C<u>H</u>), 6.60 (2H, s, -NH-C<u>H</u>=), 7.01 (2H, t, *J* = 6.9 Hz, Ar), 7.08 (2H, d, *J* = 8.1 Hz, Ar), 7.17 (2H, t, *J* = 8.1 Hz, Ar), 7.22 (2H, d, *J* = 8.4Hz, Ar), 7.32 (2H, d *J* = 9.3 Hz, Ar), 7.39 (2H, d, *J* = 7.8), 7.79 (2H, s, N<u>H</u>). ^{13}C NMR ($CDCl_3$): δ = 21.0, 39.7, 110.9, 119.1, 119.8, 119.9, 121.8, 123.5, 127.0, 128.5, 128.8, 135.4, 136.6, 140.9.

3,3'-Bis-indolyl-(4-cholorophenyl)methane (4d) [12-b]

Orange solid. ^{1}H NMR ($CDCl_3$): δ = 5.85 (1H, s, Ph-C<u>H</u>), 6.64 (2H, s, -NH-C<u>H</u>=), 7.03 (2H, t, *J* = 8.1Hz, Ar), 7.08 (2H, d, *J* = 8.1 Hz, Ar), 7.15-7.218 (4H, m, Ar), 7.37 (4H, d, *J* = 8.7 Hz, Ar), 7.92 (2H, s, N<u>H</u>). ^{13}C NMR ($CDCl_3$): δ = 39.6, 111.1, 119.1, 119.3, 119.8, 122.0, 123.5, 126.8, 128.3, 130.0, 131.7, 136.6, 142.5.

3,3'-Bis-indolyl-(4-trifluoromethylphenyl)methane (4e)[12-b]

Brown solid. ^{1}H NMR ($CDCl_3$): δ = 5.83 (1H, s, Ph-C<u>H</u>), 6.57 (2H, s, -NH-C<u>H</u>=), 7.02

(2H, t, *J* = 8.7Hz, Ar), 7.13-7.22 (4H, m, Ar), 7.35 (4H, t, *J* = 8.4 Hz, Ar), 7.82 (2H, s, N<u>H</u>). ^{13}C NMR ($CDCl_3$) δ = 30.9, 39.5, 111.1, 119.1, 119.2, 119.7, 122.0, 123.5, 126.8, 128.3, 130.0, 131.7, 136.5, 142.5

3-Decyl-1*H*-indole (6a)[20]

Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.86-1.47 (17H, m, -(C<u>H</u>$_2$)$_7$-C<u>H</u>$_3$), 1.70 (2H, quintet, *J* = 7.8 Hz, -C<u>H</u>$_2$-(CH$_2$)$_7$-CH$_3$), 2.74 (2H, t, *J* = 7.8 Hz, -C<u>H</u>$_2$-(CH$_2$)$_8$-CH$_3$), 6.95 (1H, s, -NH-C<u>H</u>=), 7.09 (1H, t, *J* = 7.5 Hz, Ar), 7.16 (1H, t, *J* = 7.5 Hz, Ar), 7.33 (1H, d, *J* = 7.5 Hz, Ar), 7.60 (1H, d, *J* = 7.5 Hz, Ar), 8.00 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.7, 25.1, 29.3, 29.5, 29.7 (x3), 30.1, 31.9, 110.8, 117.0, 118.8 (x2), 120.8, 121.6, 127.4, 136.1. GC-MS (*m/z*): 257. HRMS (FAB, m-NBA) calcd. for C18H27N: 257.2144, found: 257.2125.

3-Cyclohexylmethyl-1*H*-indole (6b)

White solid, m. p. = 64-66^{o}C. ^{1}H NMR ($CDCl_3$): δ = 0.94-1.03 (2H, m, -Cy), 1.15-122 (2H, m, -Cy), 1.56-1.73 (6H, m,-Cy), 2.63(2H, d, *J* = 6.9 Hz, CH-C<u>H</u>$_2$-), 6.93 (1H, s, -NH-C<u>H</u>=), 7.07-7.19 (2H, m, Ar), 7.35 (1H, d, *J* = 1.8 Hz, Ar), 7.61 (1H, d, *J* = 7.8 Hz), 7.85 (1H, s, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 26.3, 26.5, 33.0, 33.5, 38.7, 110.8, 115.4, 118.9, 119.1, 121.6, 121.8, 127.9, 136.1. GC-MS (*m/z*): 213

3-(1-Methyl-heptyl)-1*H*-indole (6c)[10]

Pale yellow oil. ^{1}H NMR($CDCl_3$): δ = 0.83-0.90 (3H, m, -CH$_2$-C<u>H</u>$_3$), 1.25-131 (8H, m, -C$_4$<u>H</u>$_8$-CH$_3$), 1.35 (3H, d, *J* = 6.9, CH-CH$_3$), 1.58-1.62 (1H, m), 1.75-1.80 (1H, m), 3.05

(1H, m, CH_3-C<u>H</u>), 6.94 (1H, s, -NH-C<u>H</u>=), 7.06-7.19 (2H, m, Ar), 7.36 (1H, d, *J* = 6.9 Hz, Ar), 7.66 (1H, d, *J*= 3.8 Hz), 7.86 (1H, s, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 14.1, 21.3, 22.6, 27.6, 29.5, 30,80, 31.87, 37.65, 111.0, 118.9, 119.4, 119.7, 121.7, 122.9, 126.9, 136.4. HRMS (FAB, m-NBA) calcd. for C16H23N: 229.1830, found: 229.1850.

3-(1-Phenylethyl)-1*H*-indole (6d)[20]

White solid, m. p. = 70-71°C. ^{1}H NMR ($CDCl_3$): δ = 1.63 (3H, d, *J* = 7.0 Hz, -CH-C<u>H</u>$_3$), 4.31 (1H, q, *J* = 7.0 Hz, -C<u>H</u>-CH_3), 6.95-7.05 (2H, m, Ar), 7.10-7.36 (8H, m, Ar), 10.86 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 22.4, 36.9, 110.8, 119.0, 119.5, 120.9, 121.3, 121.8, 125.7, 126.7, 127.2, 128.1, 136.4, 146.6. GC-MS (*m/z*): 221. HRMS (FAB, m-NBA) calcd. for C16H15N: 221.1205, found: 221.1214.

3-Benzhydryl-1*H*-indole (6e)[21]

White solid, m. p. = 125-126°C. ^{1}H NMR ($CDCl_3$): δ = 5.66 (1H, s, -C<u>H</u>$(Ph)_2$), 6.53 (1H, s, Ar), 7.01 (1H, t, *J* = 7.0 Hz, Ar), 7.10-7.35 (13H, m, Ar), 7.91 (1H, br, -N<u>H</u>-). ^{13}C NMR ($CDCl_3$): δ = 48.7, 110.9, 119.2, 119.7, 121.9, 123.8, 126.0, 126.8, 128.1, 128.3, 128.8, 136.4, 143.7. GC-MS (*m/z*): 283. HRMS (FAB, m-NBA) calcd. for C21H17N: 283.1361, found: 283.1363.

3-Cyclohexyl-1*H*-indole (6f)[22]

Brown solid, m. p. = 72-77°C. ^{1}H NMR($CDCl_3$): δ = 1.18-2.12 (10H, m, -($C\underline{H}_2$)$_5$-), 2.93 (1H, br, -C<u>H</u>-), 6.92 (1H, s, -NH-C<u>H</u>=), 7.08 (1H, t, *J* = 7.5 Hz, Ar), 7.16 (1H, t, *J* = 7.5 Hz, Ar), 7.33 (1H, d, *J* = 7.5 Hz, Ar), 7.65 (1H, d, *J* = 7.5 Hz, Ar), 7.91 (1H, br, -N<u>H</u>-).

^{13}C NMR ($CDCl_3$): δ = 26.5, 26.9, 34.0, 35.4, 110.9, 118.7, 119.1 (x2), 121.6, 123.0, 126.6, 136.2. GC-MS (*m/z*): 199. HRMS (FAB, m-NBA) calcd. for C14H17N: 199.1361, found: 199.1362.

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Conclusion

The author achieved the first enantioselective preparation of β-amino alcohols from racemic 1,2-diols by the ruthenium-catalyzed "borrowing hydrogen" reaction. The catalyst {[$RuCl_2$(*p*-cymene)$_2$]$_2$/(*S*,*R*)-JOSIPHOS} was found to be most active catalyst on asymmetric reaction of 1,2-diols and secondary amines among tested to provide the corresponding β-amino alcohols in excellent yield (up to 99%) and up to 77% *ee*.

The mechanistic investigations of enantioselective synthesis of β-amino alcohols from 1,2-diols were successfully examined to reveal the asymmetric inducting step on the "borrowing hydrogen"-type reaction. Various possibilities of reaction pathway have been examined, and the asymmetric reduction of β-amino ketone was found as important step to afford optically active β-amino alcohols.

An efficient regioselective alkylation of indoles with alcohol was established by combination of $RuCl_2(PPh_3)_3$ catalyst, DPEphos ligand and K_3PO_4 to afford corresponding 3-substituted indoles from various type of indoles and alcohols substrates in good to excellent yield. This achievement overcomes the weak points of previous methods for C3-alkylation of indole with alcohols that has been reported such as limitation of substrates scope and high catalyst loading. In addition, bis(3-indolyl)phenylmethane derivatives, an indole alkaloid backbone could also be yielded up to 91% by using this catalysis under reflux in toluene.

List of Publication

Ruthenium-Catalyzed Enantioselective Synthesis of β-Amino Alcohols from 1,2-Diols by "Borrowing Hydrogen"

Anggi Eka Putra, Yohei Oe and Tetsuo Ohta.

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(Chapter 1 & 2)

Transition-Metal-Catalyzed Regioselective Alkylation of Indoles with Alcohols.

Anggi Eka Putra, Kei Takigawa, Hatsuki Tanaka, Yoshihiko Ito, Yohei Oe and Tetsuo Ohta.

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(Chapter 3)

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All work in this thesis is totally dedicated to the author's parents and wife.

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