NANYANG TECHNOLOGICAL UNIVERSITY

Atom Economical C-N Bond Formation Catalyzed by *N*-Heterocyclic Carbene Based Ruthenium Complexes

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LIST OF ABBREVIATIONS

δ	chemical shift
°C	degree centigrade
μL	microliter(s)
atm	atmosphere
bs	broad singlet
calcd	calculated
CD_2Cl_2	deuterated dichoromethane
$CDCl_3$	deuterated chloroform
CH_3CN	acetonitrile
cm^{-1}	inverse centimeter
cod	1,5-cyclooctadiene
cot	1,3,5-cyclooctatriene
Cy	cyclohexyl
Cyp	cyclopentyl
d	doublet
DCE	1,2-dicholoroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DFT	density functional theory
dppb	bis(diphenylphosphino)butane
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc or EA	ethyl acetate
g	gram(s)
GC	gas chromatography
Hex	hexanes
HRMS	high resolution mass spectrometry
h or hrs	hours
Hz	hertz

J	coupling constant(s)
KIE	kinetic isotope effect
m	Multiplet
m/z	mass per charge ratio
M^+	parent ion peak (mass spectrum)
Me	Methyl
MeOH	Methanol
mg	milligram(s)
MHz	mega hertz
min	minute(s)
mL	milliliter(s)
mmol	Millimole
mol %	mole percent
MS	mass spectrometry
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
OMS	octahedral molecular sieve(s)
ppm	parts per million
q	Quartet
quint	Quintet
rt	room temperature
s	Singlet
sept	Septet
t	Triplet
*t*Bu	*tert*-butyl
tdd	triplet of doublet of doublets
td	triplet of doublets
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tt	triplet of triplets

LIST OF PUBLICATION

1.	Diffusion Behaviors of Water-Soluble CdSe/ZnS Core/Shell Quantum Dots Investigated by Single-Particle Tracking. **Cheng Chen**, Shu-Lin Liu, Ran Cui, Bi-Hai Huang, Zhi-Quan Tian, Peng Jiang, Dai-Wen Pang, Zhi-Ling Zhang*. *J. Phys. Chem. C.* **2008**, *112,* 18904.
2.	Well-Defined *N*-Heterocyclic Carbene Based Ruthenium Catalysts for Direct Amide Synthesis from Alcohols and Amines. Yao Zhang, **Cheng Chen**, Subhash Chandra Ghosh, Yongxin Li, and Soon Hyeok Hong* *Organometallics* **2010**, *29*, 1374.
3.	Direct Amide Synthesis from Either Alcohols or Aldehydes with Amines: Activity of Ru(II) Hydride and Ru(0) Complexes. Senthilkumar Muthaiah, Subhash Chandra Ghosh, Joo-Eun Jee, **Cheng Chen**, Jian Zhang, and Soon Hyeok Hong*, *J. Org. Chem.* **2010**, *75*, 3002.
4.	Oxidative Amide Synthesis Directly from Alcohols with Amines. **Cheng Chen** and Soon Hyeok Hong*. *Org. Biomol. Chem.* **2011**, *9*, 20.
5.	*N*-Heterocyclic Carbene Based Ruthenium-Catalyzed Direct Amide Synthesis from Alcohols and Secondary Amines: Involvement of Esters. **Cheng Chen**, Yao Zhang, and Soon Hyeok Hong*. *J. Org. Chem.* **2011**, *76*, 10005.
6.	Selective Catalytic sp^3 C-O Bond Cleavage with C-N Bond Formation in 3-Alkoxy-1-propanols. **Cheng Chen** and Soon Hyeok Hong*. *Org. Lett.* **2012**, *14*, 2992.
7.	Copper-Catalyzed Aerobic Spirocyclization of Biaryl-*N*-H-imines via 1,4-Aminooxygenation of Benzene Rings.” Ya Lin Tnay, **Cheng Chen**, Yi Yuan Chua, Line Zhang and Shunsuke Chiba*. *Org. Lett.* **2012**, *14*, 3550.

Abstract

Direct amide synthesis from alcohols and amines is a highly environmentally friendly process with high atom economy. It was reported that *in situ* generated NHC-based Ru catalytic systems, active for alcohol amidation with amines, did not show good activity in the amide formation of aldehydes with amines, forming imines as major products, even though aldehydes were proposed as intermediates formed by dehydrogenation of alcohols. Based on our previous catalytic system using a commercially available ruthenium complex [Ru(*p*-cymene)Cl_2]$_2$, an *N*-heterocyclic carbene ligand, a base and pyridine, we demonstrated an improved method for the direct amide synthesis from aldehydes and amines. Various amides were synthesized from aldehydes and amines in moderate to good yields using this method. For alcohol amidation reactions with amines, previous catalysts showed excellent activity for amidation reactions between alcohols and primary amines, but limited activity for those between alcohols and secondary amines. The direct amidation of alcohols with challenging secondary amines was achieved with a well-defined *N*-heterocyclic carbene based ruthenium complex. Involvement of ester intermediates was suggested unlike the previous amidation with less sterically hindered alcohols and amines. During investigation of the substrate scope for the direct amide synthesis from alcohols and amines, selective sp^3 C-O bond cleavage with amide formation was observed in reactions of 3-alkoxy-1-propanol derivatives and amines. This is the first catalytic C-N bond formation via sp^3 C-O cleavage. The cleavage only occurs at the C3-O position even with 3-benzyloxy-1-propanol. 3-alkoxy-1-propanol derivatives reacted smoothly with benzyl amine to give two amide products. Treatment of different amines with 3-benzyloxy-1-propanol also resulted in the selective C-O cleavage with C-N

bond formation. Based on experimental results, O-bound and C-bound Ru enolate complexes were proposed as key intermediates in the reaction. Moreover, kinetic isotope experiments demonstrated two independent processes from the whole reaction and identified the respective rate-determining steps. Deuterium-labeling experiments showed that acrolein or Ru-bound acrolein species was another important intermediate.

CHAPTER 1

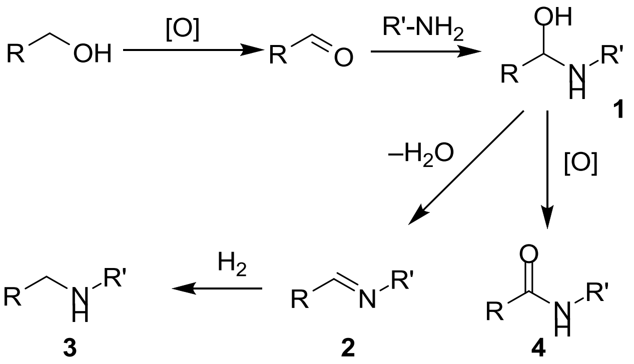
INTRODUCTION

(This chapter has been published in *Organic and Biomolecular Chemistry* **2011**, *9*, 20.)

1.1 Direct amide synthesis from alcohols

The amide bond plays a key role in organic and biological chemistries.[1,2] Traditionally, amides are synthesized from activated carboxylic acid derivatives and amines.[2,3] Numerous alternative strategies such as the Staudinger reaction,[4] the Schmidt reaction,[5] and the Beckmann rearrangement[6] have been developed. However, in most of these methods, stoichiometric amounts of various reagents are required and equimolar amounts of by-products are produced as waste. Recently, a highly atom economical and environmentally benign method, transition metal catalyzed amide synthesis directly from alcohols and amines, was highlighted.[7,8,9] The strategy is demonstrated in Scheme 1.1. An alcohol is initially oxidized to the corresponding aldehyde that reacts with an amine to produce a hemiaminal intermediate (**1**). There are two possible further pathways of the hemiaminal-either it would form an imine (**2**), which could be subsequently hydrogenated to an amine (**3**), or would be further oxidized to the corresponding amide (**4**). The pathway of the dehydration and the hydrogenation of **1**, overall alkylation of the amine, has been extensively reported.[7,10,11] Recent examples have shown that further oxidation of **1** producing amides can be achieved instead, depending on the nature of catalysts, ligands, and substrates. It is currently unexplored what properties of the catalytic systems affect an intermediate toward the alkylation or the amidation, therefore more mechanistic investigations will be necessary.[7] In this chapter, recent catalyst development of the direct amide synthesis and current challenges in this area are presented.

Scheme 1.1 Proposed pathway for amide synthesis from alcohols and amines.



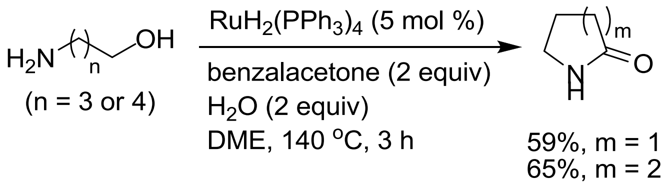
1.2 Catalyst development for the direct amide synthesis from alcohols and amines

Oxidative amide synthesis from alcohols and amines is mainly promoted through homogeneous catalysts using Ru- and Rh-based complexes. Ag-, Au- and Mn-based heterogeneous catalysts have also been reported.

1.2.1 Ru-based homogeneous catalytic systems

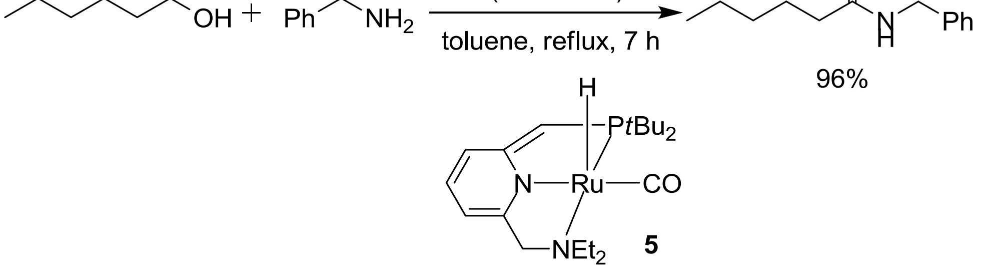
In 1991, Murahashi and Naota reported the first example of the reaction by synthesizing lactams with 1,4- and 1,5-amino alcohols in an intramolecular amidation process (Scheme 1.2).[12] Using $RuH_2(PPh_3)_4$ as a catalyst and a hydrogen acceptor such as benzalacetone, lactams were formed with good yields. When the reaction was run without the hydrogen acceptor, only cyclic amines were obtained. Two equivalents of water had to be added so as to avoid the formation of cyclic amines if there was a primary amine group in the amino alcohols, while addition of water was not required in the case of amino alcohols bearing a secondary amine group.

Scheme 1.2 The first example for amide synthesis from alcohols and amines.



Recently, the Milstein group employed a Ru PNN pincer complex **5** for the direct amide synthesis from alcohols and primary amines without any base, acid promoter, or hydrogen acceptor (Scheme 1.3).[13] It was the first example of allowing the direct amidation of alcohols with amines in an intermolecular fashion. To facilitate the removal of hydrogen gas, the reactions were carried out under a flow of argon. Excellent yields for sterically non-hindered substrates and slightly reduced yields for moderately hindered substrates were obtained. Treatment of primary diamines with alcohols yielded bis-amides in high yields. This catalyst showed a moderate activity for the amidation of aniline, and no activity for the amidation of a secondary amine, dibenzylamine. The essential structure in this catalyst was suggested as being the dearomatized ring which plays an active role in the hydrogen abstraction and liberation process. Complex **5** has been commercialized.

Scheme 1.3 Amide synthesis from alcohols and amines catalyzed by **5**.

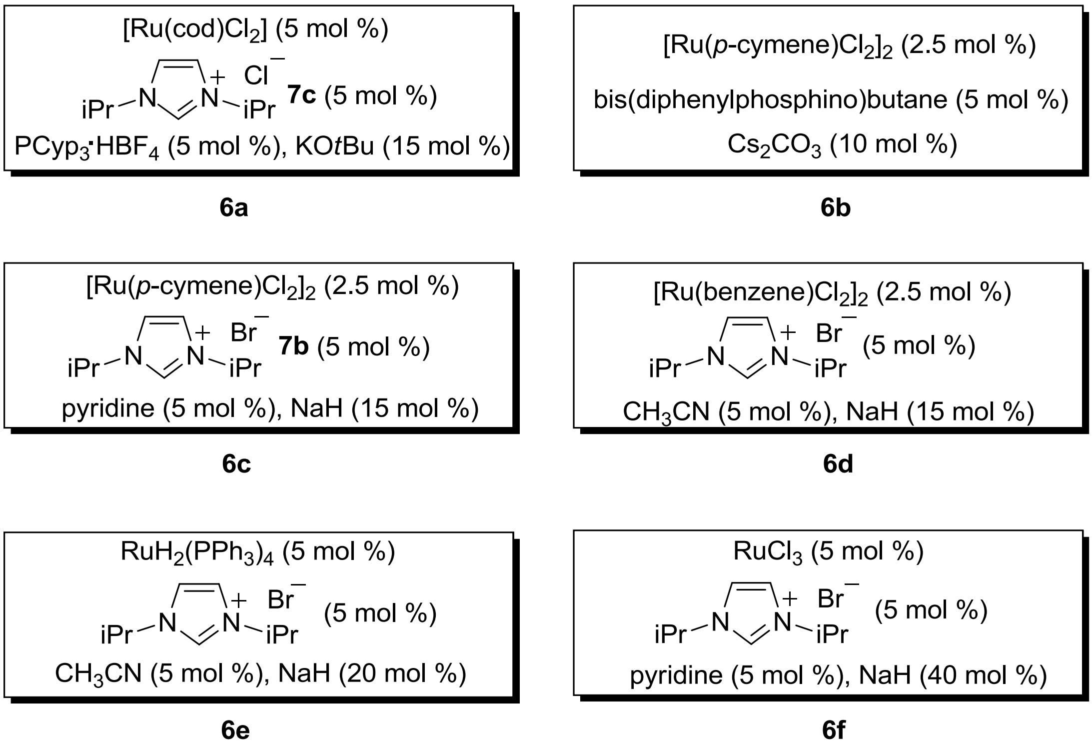


Several *in situ* ruthenium catalytic systems for the intermolecular amidation reactions have been developed since the Milstein's report (Figure 1.1). Madsen and co-workers reported an *in situ* *N*-heterocyclic carbene (NHC) based ruthenium catalyst.[14] This catalytic system (**6a**), consisting of [Ru(cod)Cl_2] (cod = 1, 5-cyclooctadiene), an NHC precursor (1,3-diisopropylimidazolium chloride, **7c**), a phosphine ligand such as $PCyp_3{\cdot}HBF_4$ ($PCyp_3$ = tricyclopentylphosphine), and KO*t*Bu, catalyzed reactions efficiently with non-sterically hindered alcohols and primary amines. Notably, optically pure 1-phenylethylamine was converted to the corresponding amine in 70% yield with no observation of racemization (Scheme 1.4). However, this system exhibited limited activity with aniline and secondary amines.

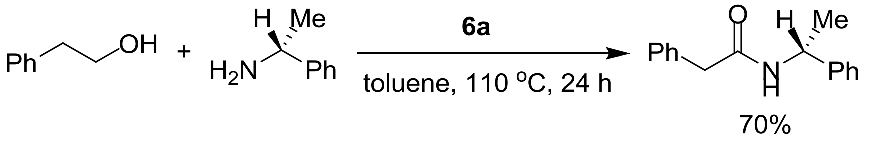
It has been logically proposed that the direct alcohol amidation goes through aldehydes from the oxidation of alcohols (Scheme 1.1). However, when it was tested the amidation of benzaldehyde with benzylamine, only the corresponding imine was formed without any observation of either the amide or the amine. The imine does not react under the catalytic condition of **6a** nor has been detected during the reaction of an alcohol and an amine. Based on the results, it was proposed that these reactions do not go through a free aldehyde but a Ru-bound aldehyde-like species.

Williams and coworkers reported the formation of secondary amides in moderate to good yields using [Ru(*p*-cymene)Cl_2]$_2$, bis(diphenylphosphino)butane (dppb), and Cs_2CO_3 as the catalytic system (**6b**) in refluxing *t*-butanol.[15] A hydrogen acceptor such as 3-methyl-2-butanone (2.5 equiv vs the alcohol substrate) was required to promote the catalysis (Scheme 1.5). Secondary amines were poor substrates, and in the case of morpholine, a 31% yield of the tertiary amide was obtained with the reaction with 3-phenylpropan-1-ol.

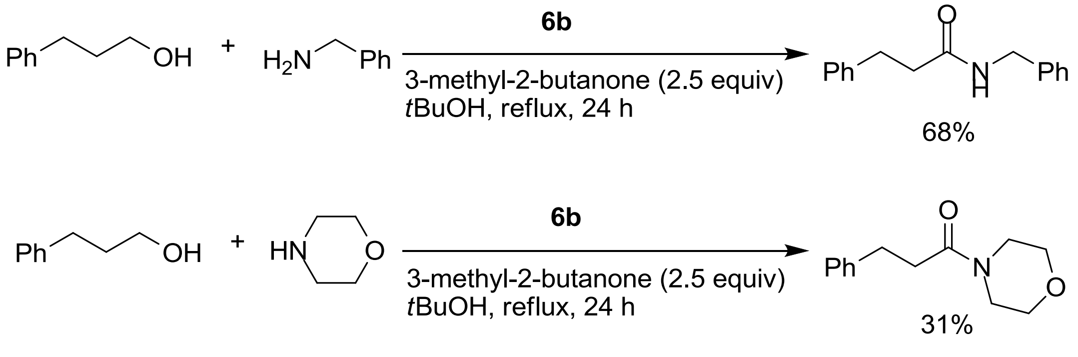
Figure 1.1 *In situ* generated ruthenium catalytic systems.



Scheme 1.4 Amide synthesis from alcohols and amines catalyzed by **6a**.

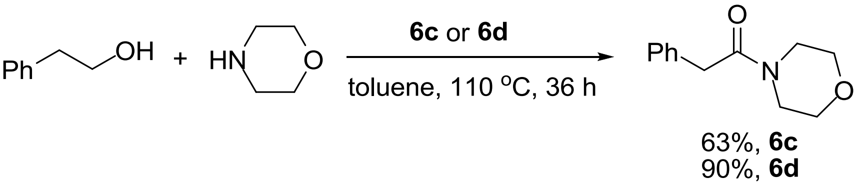


Scheme 1.5 Amide synthesis from alcohols and amines catalyzed by **6b**.



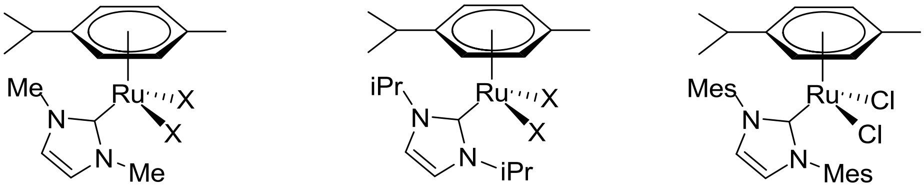
Phosphine-free ruthenium catalytic systems (**6c** and **6d**) for effective amide synthesis from alcohols and amines were also reported by our group.[16] The catalytic systems consist of [Ru(*p*-cymene)Cl_2]$_2$ or [Ru(benzene)Cl_2]$_2$, an NHC precursor (**7b**), pyridine or acetonitrile, and NaH as a base (**6c** and **6d**). Sterically nonhindered substrates worked smoothly, and moderately hindered ones reacted reasonably well. Limited yields were found for the sterically bulky substrates such as neopentyl alcohol. A few secondary amines were also tested, and good to excellent yields were obtained with less hindered secondary amines such as piperidine, morpholine, and *N*-benzylmethylamine (Scheme 1.6). However, no amide was formed from the more sterically hindered dibenzylamine in agreement with the Milstein's observations.[13] Interestingly, for the reaction between benzaldehyde and benzyl amine with **6c**, the corresponding amide (48%) was observed with the concurrent formation of the imine (14%), unlike Madsen's observation that only imine was formed with **6a**.[14]

Scheme 1.6 Amide synthesis from alcohols and amines catalyzed by **6c and 6d**.



Based on the reported phosphine-free *in situ* NHC-based Ru catalysts, our group investigated complexes **8a-e** (Figure 1.2) as precatalysts for the direct amide synthesis.[17] When the activity was screened only with the NHC-Ru complexes, there was no formation of the amide from 2-phenylethanol and benzylamine (Scheme 1.7). It was found out that at least 2 equiv of a strong base *versus* the precatalyst is necessary for the catalytic cycle to proceed. Higher amounts of the base were detrimental to the catalytic activity, suggesting the role of the base is related to the activation of the precatalyst. Among the NHC Ru complexes, **8a** and **8c** showed better activities, similar to the *in situ* NHC-based Ru catalysts using **7b** or **7c** as an NHC precursor.[14,16] The amount of the base was optimized as 15-20 mol % when 5 mol % of **8a** was used for the reaction. Complex **8a** showed comparable activity under basic conditions with the previous NHC-based *in situ* catalytic systems by Madsen[14] and our group.[16]

Figure 1.2 Well-defined NHC based ruthenium complexes.

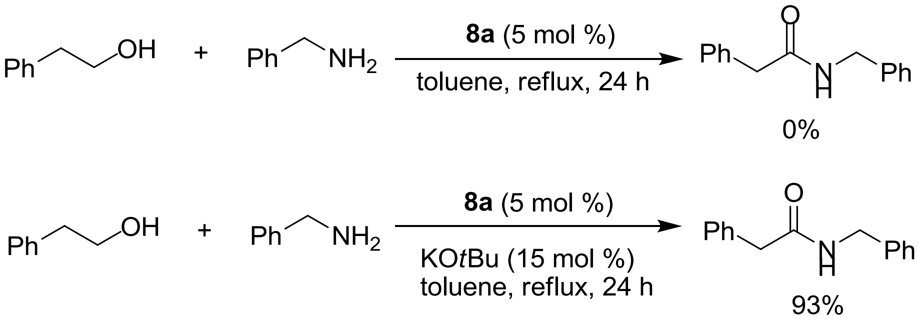


8a X = Cl
8b X = I

8c X = Cl
8d X = I

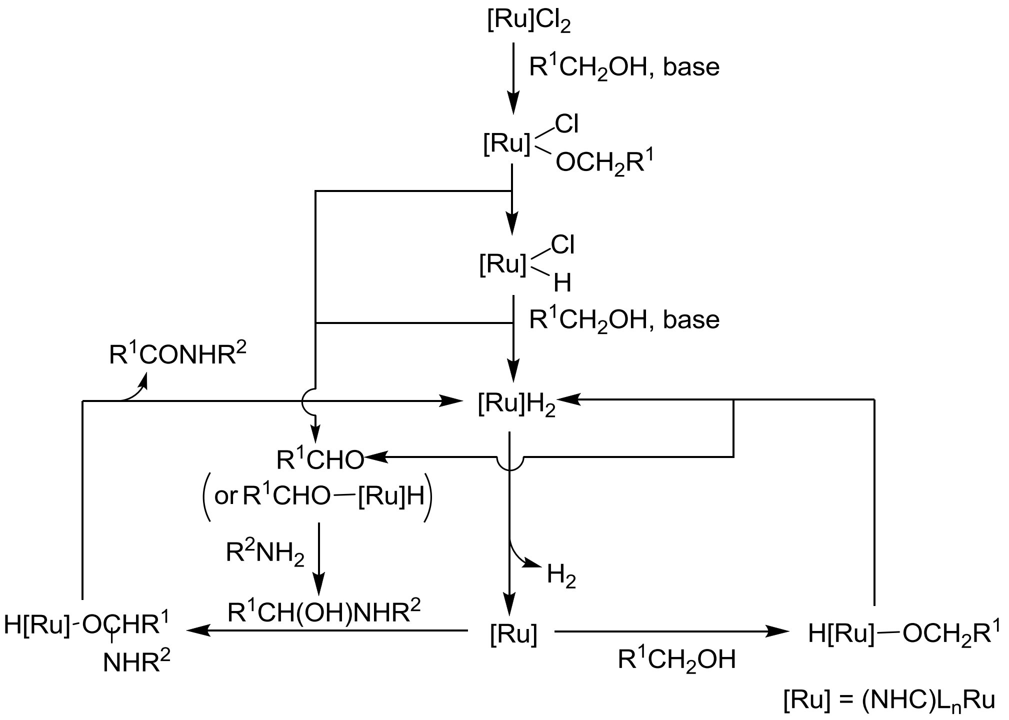
8e

Scheme 1.7 Amide synthesis from alcohols and amines catalyzed by **8a**.

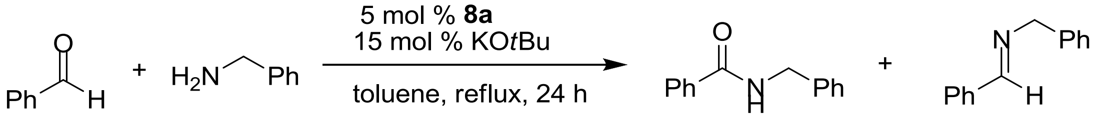


The nature of the active catalyst was investigated with complex **8a** under similar catalytic conditions by ^{1}H NMR spectroscopy.[17] It was reported that a Ru hydride complex, firstly generated by β-hydrogen elimination of Ru alkoxides formed from the precatalyst and an alkoxide, could be an active catalytic intermediate.[17] A mechanism involving a Ru(0)/Ru(II) cycle was proposed on the basis of the investigation (Scheme 1.8), especially elucidating the reason why free aldehyde was not so active under the reported catalytic systems-less efficient formation of active [Ru]H_2 from [Ru]Cl_2 and an aldehyde without the help of a primary alcohol. When 10 mol % of a primary alcohol was added, the amidation of benzaldehyde with benzylamine proceeded well demonstrating that formation of a catalytically active species by an alcohol is necessary for the amidation of aldehydes (Scheme 1.9). However, reduced yields from aldehydes and no observation of free aldehyde during the reaction implied that the amide formation from an alcohol might occur through a transition metal bound aldehyde-like species.

Scheme 1.8 The proposed mechanism.



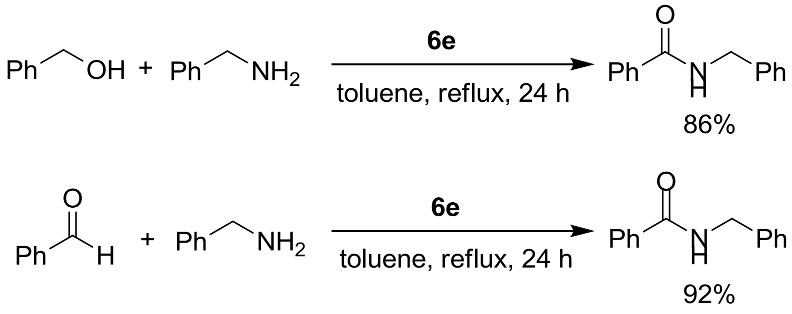
Scheme 1.9 Amidation of an aldehyde with an amine catalyzed by **8a**.



no alcohol	:	24%	70%
10 mol % 2-phenylethanol	:	78%	9%

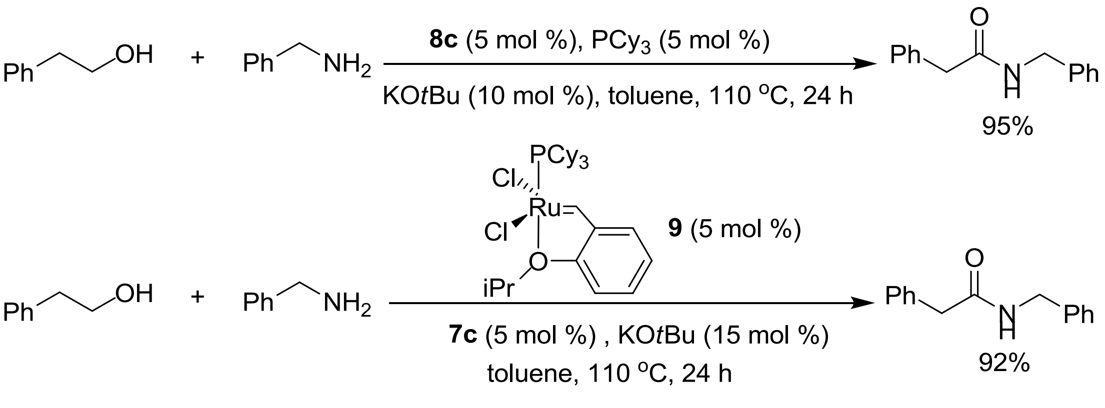
Based on the study on the Ru hydride catalytic intermediates and the requirement of Ru chloride precatalyst activation for aldehyde amidation, an *in situ* catalytic system which can transform either alcohols or aldehydes to amides with amines was developed by our group.[18] The catalytic system (**6e**) was generated from readily available $RuH_2(PPh_3)_4$, an NHC precursor (**7b**), NaH, and acetonitrile. Both alcohols and aldehydes were efficiently transformed into the amides with **6e** (Scheme 1.10). The previously proposed Ru(0)/Ru(II) cycle was supported by the observation of elimination of hydrogen from a reaction among $RuH_2(PPh_3)_4$, **7b**, and NaH at the reaction temperature of 110 °C. Homogeneous Ru(0) complexes such as $Ru_3(CO)_{12}$ and (η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene)ruthenium [Ru(cod)(cot)] were also active for the synthesis of amides from alcohols and amines in the presence of **7b** and NaH.

Scheme 1.10 Amide synthesis from alcohols and amines catalyzed by **6e**.

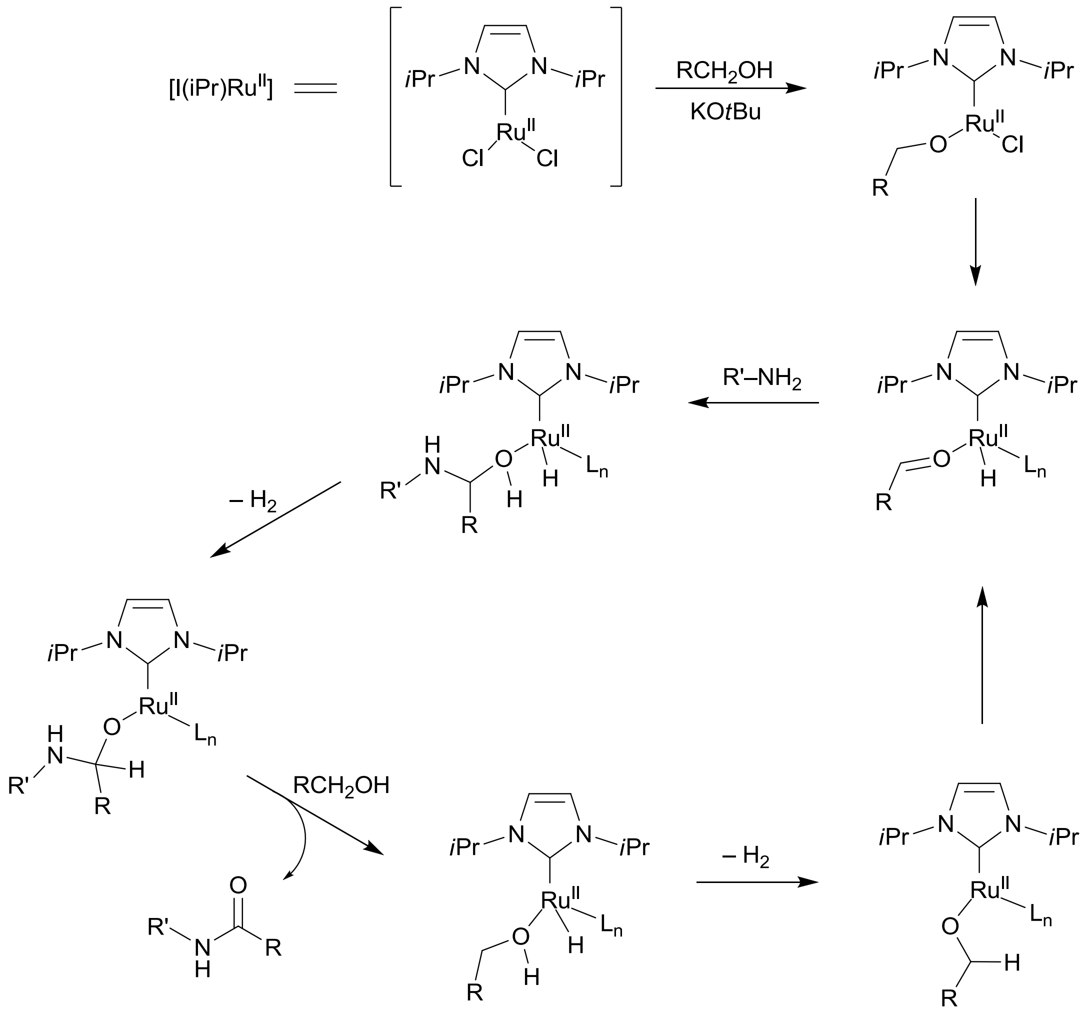


The Madsen group also reported catalytic systems based on the well-defined Ru-NHC complex **8c** shortly after the publication of **8a-e** as the precatalysts by our group.[19] Compared with the reported system,[17] they optimized the conditions of **8c** with tricyclohexylphosphine (PCy_3) as a supporting ligand and less amount of KO*t*Bu (10 mol % vs 15 mol %, for 5 mol % of **8c**, Scheme 1.11). Moderate to excellent yields for the direct amide synthesis from alcohols and amines were demonstrated. The authors proposed a Ru-bound aldehyde and a Ru-bound hemiaminal as intermediates. It was also pointed out the oxidation state (+2) of all Ru species remained same in the whole catalytic cycle (Scheme 1.12) in contrast to the previous proposition of a Ru(0)/Ru(II) cycle as a possible pathway. The mechanistic question should be investigated further as there is not solid experimental evidence. With the proposition of [(I*i*Pr)Ru^{II}] as the catalytically active components, Ru olefin metathesis catalysts were screened for the direct amidation of primary alcohols. The best results were obtained with Hoveyda-Grubbs 1st-generation metathesis catalyst **9** with **7c** and KO*t*Bu (Scheme 1.11). The three catalytic systems based on **6a**, **8c**, and **9**, do not show significant differences in reactivity supporting that the same catalytically active species, [(I*i*Pr)Ru^{II}], is operating under the NHC-based Ru catalytic systems.

Scheme 1.11 Amide synthesis from alcohols and amines catalyzed by **8c** and **9**.

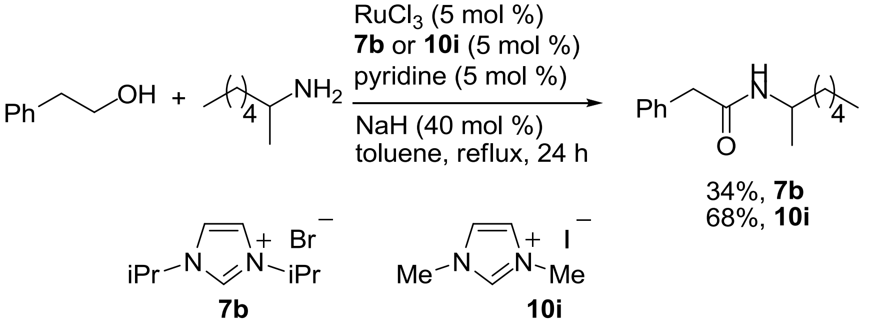


Scheme 1.12 The proposed mechanism.



With the similar hypothesis of [(NHC)Ru] as a catalytically active species, another *in situ* catalytic system (**6f**) using the more economical $RuCl_3$, an NHC precursor, and pyridine in the presence of NaH was reported.[20] Moderately hindered substrates are more reactive when the less bulky NHC precursor **10i** was used instead of **7b** (Scheme 1.13). The optimal condition was achieved with 40 mol % NaH and it was claimed that NaH in this system might not only be used to generate NHCs from the corresponding imidazolium salts but also used as a reducing agent that reduces Ru(III) to Ru(II) or Ru(0). The authors also found NHC-based olefin metathesis catalysts active for the alcohol amidation with amines, which also demonstrated that the oxidative amide formation can be catalyzed by a Ru complex with an NHC ligand under basic conditions.

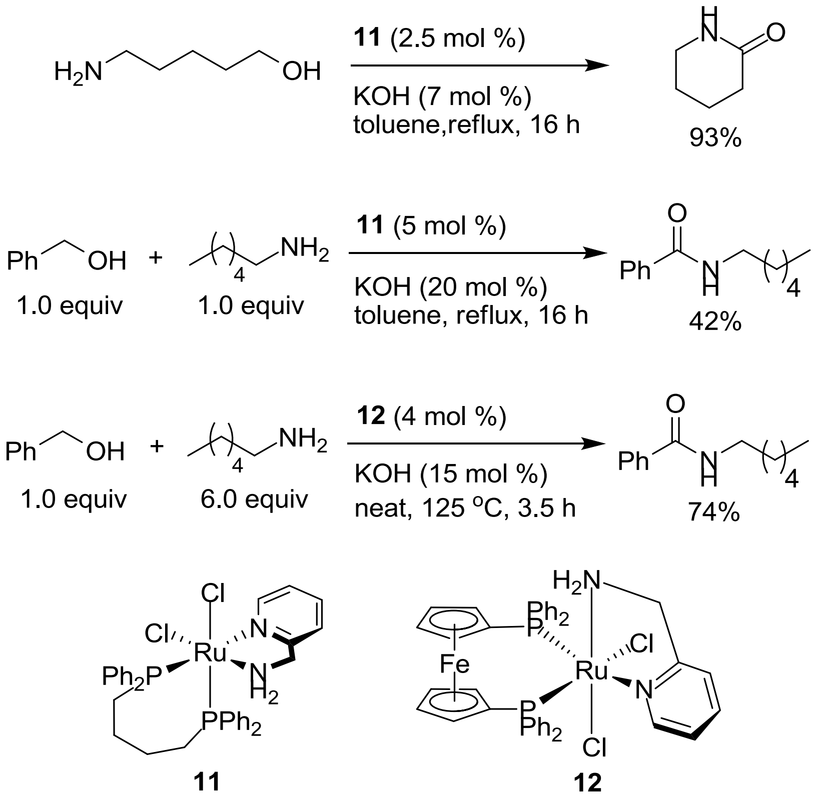
Scheme 1.13 Amide synthesis from alcohols and amines catalyzed by a $RuCl_3$ system.



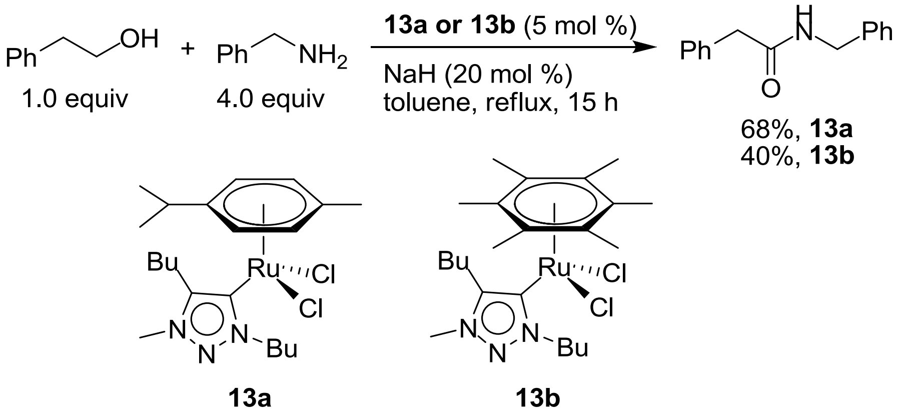
Very recently, The Crabtree group reported a ruthenium diphosphine diamine complex **11** for the alcohol amidation with amines.[21] Using **11** as the catalyst, amide synthesis can be performed smoothly in an intramolecular pattern, while intermolecular amide formation was not efficient (Scheme 1.14). The DFT calculations indicate that the Ru-bound hemiaminal intermediate should be generated, and liberation of H_2 from it must occur to provide a vacant site for β-hydrogen elimination for the efficient intramolecular amide formation.[21] Later, the same group developed a series of ruthenium complexes for both intramolecular and intermolecular amidation reactions.[22] They found that **11** and **12**, which bear both diphosphine and primary aminomethylpyridine ligands, showed better catalytic activities than other complexes tested. In the case of intermolecular amide formation, 74% of *N*-hexylbenzamide can be yielded catalyzed by **12** under neat condition (Scheme 1.14), and excess amount of an amine substrate (6.0 equiv vs an alcohol substrate) is crucial for the high yield.

The Albrecht group also reported 1,2,3-triazolium-derived carbene based ruthenium complexes **13a** and **13b** for the amide synthesis (Scheme 1.15).[23] Although only moderate yields have been obtained, potential application of 1,2,3-triazolidene ligands in the design of highly active homogeneous catalysts can be illustrated.

Scheme 1.14 Amide synthesis from alcohols and amines catalyzed by **11** and **12**.



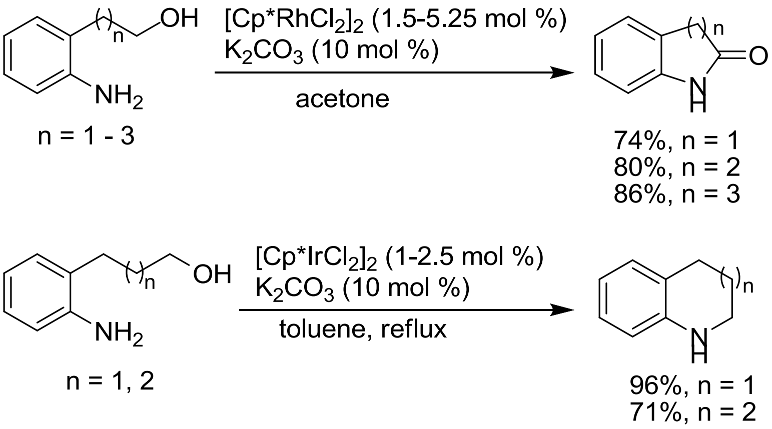
Scheme 1.15 Amide synthesis from alcohols and amines catalyzed by **13a** and **13b**.



1.2.2 Rh-based homogeneous catalyst systems

Fujita, Yamaguchi and coworkers reported the first Rh-based catalytic system, using $[Cp^*RhCl_2]_2$ and K_2CO_3 in acetone, for the lactamization of amino alcohols.[24] This catalytic system is active for the synthesis of five-, six-, and seven-membered benzo-fused lactams. Acetone was used as a hydrogen acceptor as well as the solvent. A rhodium hydride species generated by the β-hydrogen elimination of an alkoxide was also proposed as an active catalytic intermediate similarly to the Ru catalysts. It was noted that selective synthesis of *N*-alkylated or lactamized products from the same amino alcohols can be achieved by altering catalytic systems-$[Cp^*IrCl_2]_2$ in toluene for *N*-alkylation[25] or $[Cp^*RhCl_2]_2$ in acetone for lactamization (Scheme 1.16).

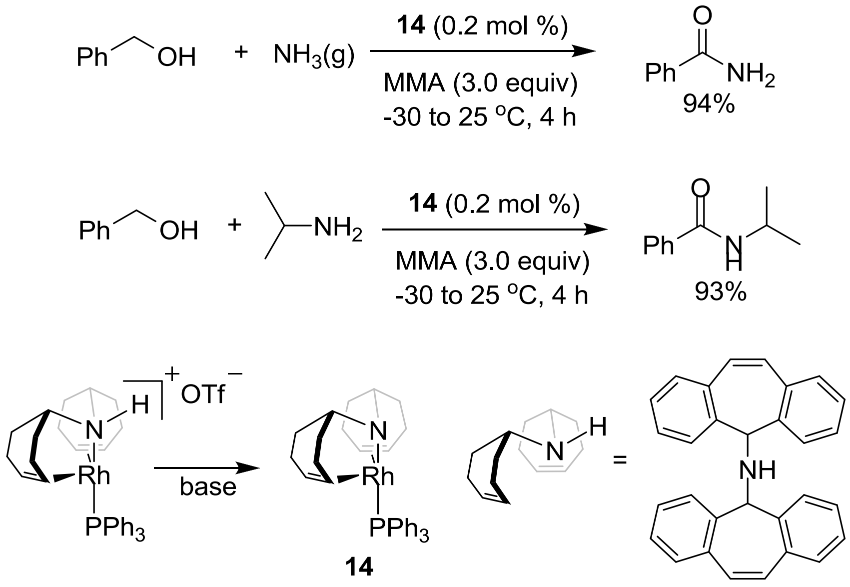
Scheme 1.16 Amide formation versus amine formation.



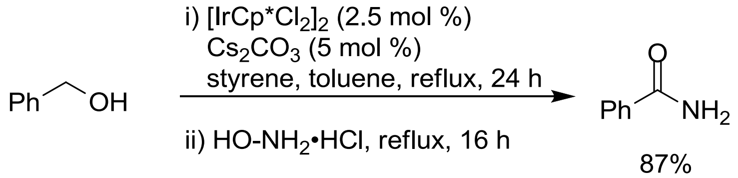
A Rh-based catalyst **14** for the intermolecular amide synthesis was developed by Grützmacher and co-workers (Scheme 1.17).[26] A hydrogen acceptor such as methylmethacrylate (MMA) was required to generate primary and secondary amides in excellent yields. The reaction occurs under much milder conditions than with the

Ru-based catalyst systems, even at room temperature. This method has good functional group tolerance and chemoselectivity with low catalyst loadings. The amido function in **14** is the Lewis basic site which may be crucial for the catalytic cycle. A computational study illustrated that the rhodium monohydride species is an important intermediate in the whole cycle. Notably, this was the first example of the synthesis of primary amides directly from primary alcohols and ammonia gas. The Williams group previously reported the primary amide synthesis from alcohols with hydroxylamine in one pot as two step processes, based on the oxidation of an alcohol followed by the Beckmann rearrangement of the oxime intermediate generated from the aldehyde and hydroxylamine, which is catalyzed by $[Cp^*IrCl_2]_2$ and Cs_2CO_3 (Scheme 1.18).[27]

Scheme 1.17 Amide synthesis from alcohols and amines catalyzed by **14**.



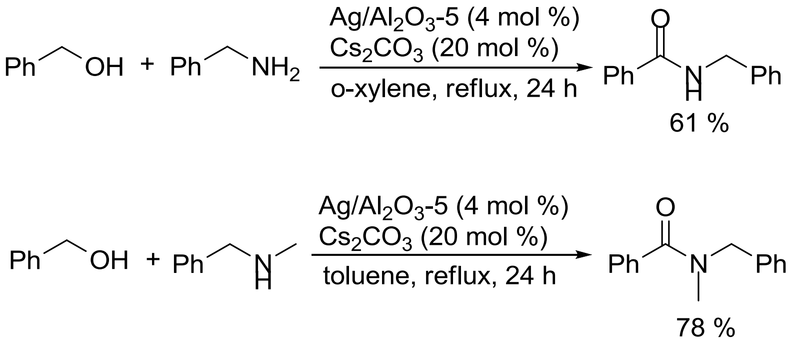
Scheme 1.18 Synthesis of primary amides from an Ir catalyst.



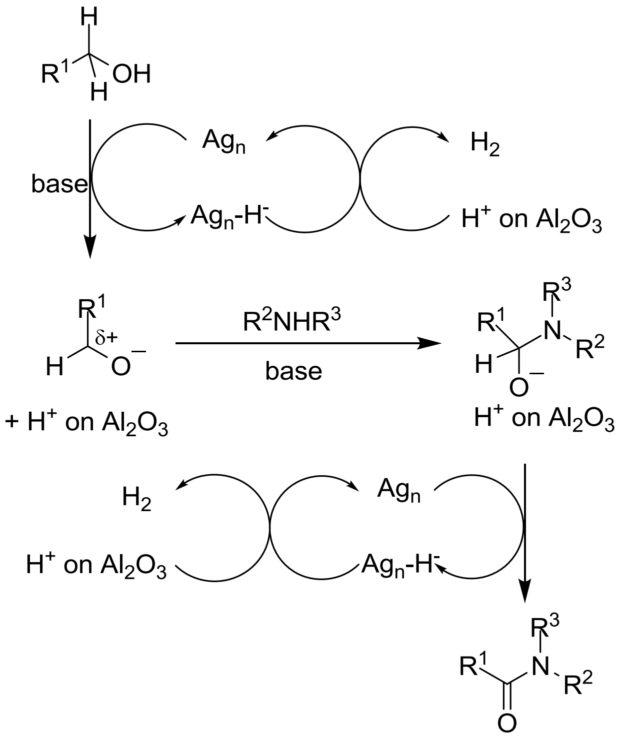
1.2.3 Ag-, Au-, and Mn-based heterogeneous catalysts

A heterogeneous Ag-based catalyst for the direct amidation of alcohols with amines was reported by Shimizu and coworkers (Scheme 1.19).[28] The alumina-supported silver cluster with Cs_2CO_3 was active for the amide synthesis with primary amines, cyclic secondary amines, and less sterically hindered non-cyclic secondary amines such as *N*-benzylmethylamine. Mechanistic investigations suggested that the reaction goes through an aldehyde-like species that was adsorbed on the catalyst, as there was no amide formation from an ester, a free aldehyde, or imine. Subsequent attack to the aldehyde-like species by an amine afforded the hemiaminal, and then the amide was formed after hydride elimination by the silver cluster (Scheme 1.20). Based on the kinetic studies, C–H cleavage of the alkoxide or hemiaminal by silver cluster was proposed as the rate-determining step. A cooperation of coordinatively unsaturated silver site and acid-base site of Al_2O_3 support was suggested from the studies on the structure-activity relationship.

Scheme 1.19 Amide synthesis from alcohols and amines catalyzed by a Ag catalyst.

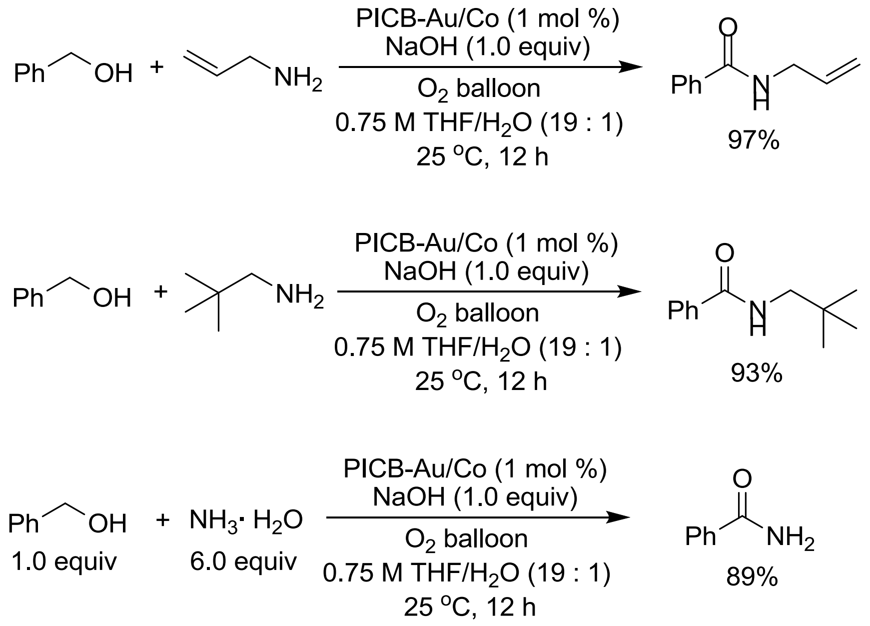


Scheme 1.20 The proposed mechanism.

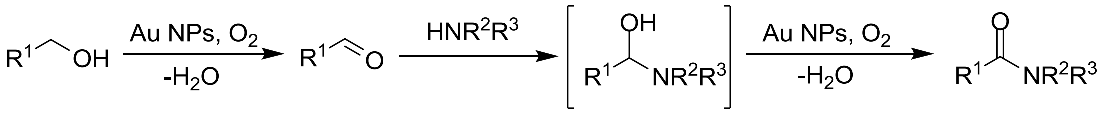


The Kobayashi Group reported the first alcohol amidation with amines using a tandem oxidative process (TOP) catalyzed by PICB-Au (PICB = polymer-incarcerated carbon black) nanoparticle or PICB-Au/Co bimetallic nanoparticle heterogeneous catalysts with molecular oxygen as terminal oxidant and NaOH as a base under mild conditions (Scheme 1.21).[29] In TOP, O_2 is used as the external oxidant and water is the only by-product, which is totally different from the dehydrogenative pathway (Scheme 1.22). Various secondary amides, and sterically less hindered tertiary amides were synthesized. Reaction of benzyl alcohol and allylamine proceeded smoothly to give *N*-allylbenzamide in 97% yield. Notably, the C=C double bond was retained in the current reaction system. Moreover, sterically hindered neopentylamine reacted well with benzyl alcohol. Benzamide was also effectively synthesized using aqueous ammonia, which is the first time to synthesize primary amides from an alcohol and aqueous ammonia.

Scheme 1.21 Amide synthesis from alcohols using a Au catalyst.

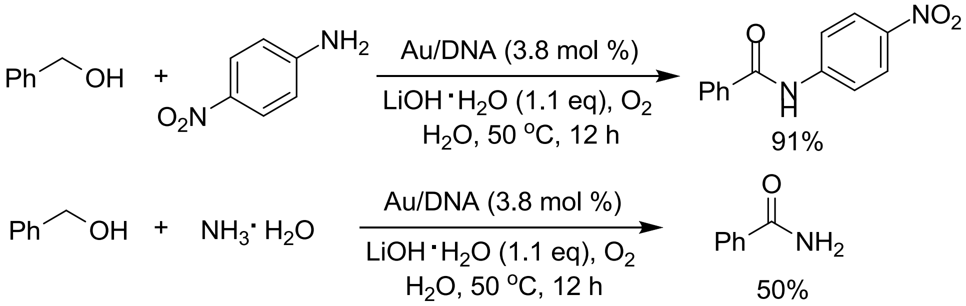


Scheme 1.22 Tandem oxidative process from alcohols.

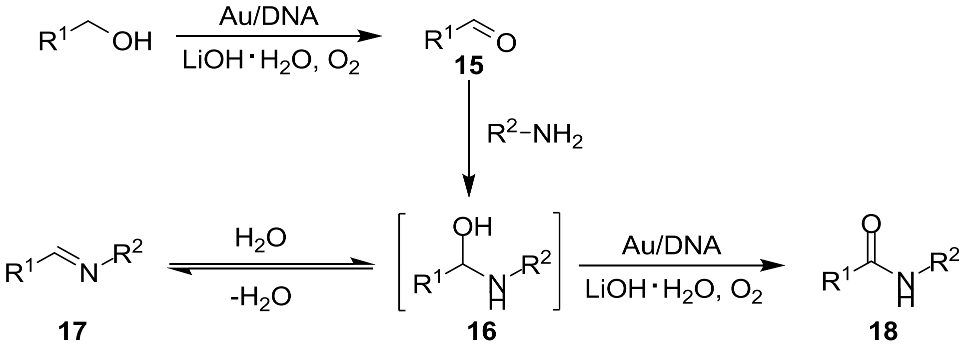


The Wang Group reported a water-soluble heterogeneous gold catalyst immobilized on DNA for the direct amide synthesis from alcohols and amines, and the reaction was conducted in pure water with the reaction temperature of 50 °C (Scheme 1.23).[30] Since limited activity was observed with less basic aromatic amines in previous reports, this study focused on the reactivity of aromatic amines. Various aromatic amines could be employed with high efficiency, and one primary amide was also synthesized with moderate yield. Recyclibility experiments were also performed, and 80% of the desired product was obtained even after five cycles. The reaction pathway was depicted in Scheme 1.24. After the generation of the hemiaminal **16** from the aldehyde **15**. Either the major byproduct imine **17** will be formed by elimination of water, or the product amide **18** will be generated through oxidation. The authors claimed that the oxygen atmosphere and high pH values are of vital importance for the amidation. Besides, the presence of water may promote the equilibrium towards **16** in the process of **17** to **16**, so most of **16** undergoes oxidation to form the amide product **18** (Scheme 1.24).

Scheme 1.23 Amide synthesis from alcohols catalyzed by Au/DNA.

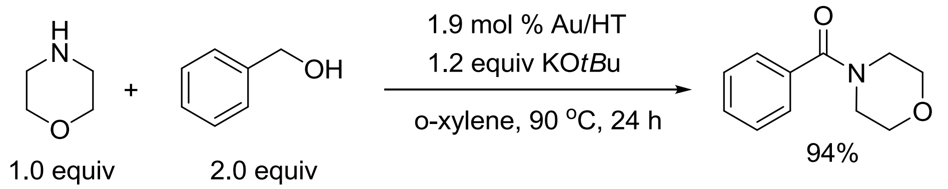


Scheme 1.24 The proposed mechanism.



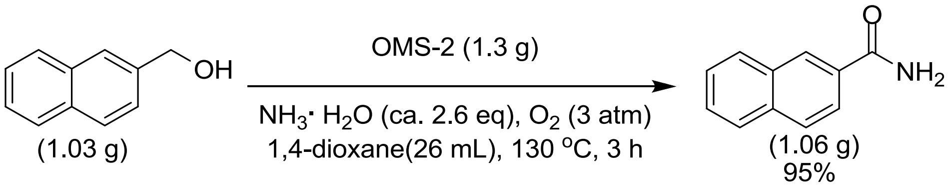
Shi and co-workers also reported hydrotalcite supported nano-gold (Au/HT) catalyzed amide synthesis from alcohols and amines under basic conditions in the absence of hydrogen acceptors (Scheme 1.25).[31] Cyclic secondary amines reacted smoothly with benzyl alcohol, while a moderate yield was observed for the reaction of benzyl alcohol and benzyl amine. Besides, treatment of various alcohols with morpholine afforded good to exellent yields of the corresponding amides.

Scheme 1.25 Amide synthesis from alcohols and amines catalyzed by Au/HT.

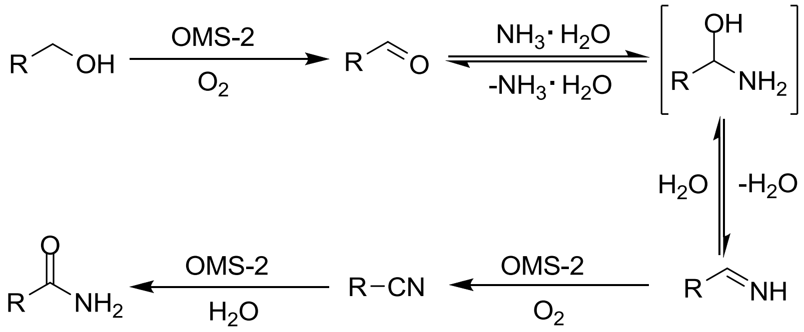


Very recently, the Mizuno Group reported a heterogenous catalyst, manganese oxide based octahedral molecular sieves (OMS-2), for the synthesis of primary amides directly from primary alcohols and aqueous ammonia under 3 atm oxygen atmosphere (Scheme 1.26).[32] This is the first report to synthesize various primary amides from alcohols and aqueous ammonia under a neutral condition without any additive, and even gram-scale transformation proceeded effeciently without any decrease in the yield of the product (Scheme 1.26). The OMS-2 catalyst is recyclable and can be used for eleven cycles without significant loss of its high catalytic activity. Experimental evidences illustrate that the hemiaiminal is firstly generated, the same as previous reports. However, different pathways have been proposed after the formation of the hemiaminal. Dehydration of it affords the corresponding imine, which is then oxidized to the nitrile. Finally, hydration of the nitrile gives the desired amide product (Scheme 1.27).

Scheme 1.26 Amide synthesis from alcohols and aqueous ammonia catalyzed by OMS-2.



Scheme 1.27 The proposed mechanism.



1.3 Conclusion and future challenges

In recent years, Ru-, Rh- based homogeneous and Ag-, Au-, Mn- based heterogeneous catalysts have been developed for the direct amide synthesis from alcohols and amines. Although it is an atom economical transformation producing hydrogen or water as the sole by-product, there are challenges in this area to widely apply the emerged methodology to the important amide bond formation in organic synthesis instead of the traditional amide syntheses. Most of the developed catalysts showed excellent activity with alcohols and primary amines, however, limited activity was observed with alcohols and secondary amines. Also, necessity of special handling of expensive metal complexes and ligands in many cases should be overcome from the environmental and economic point of view. Mechanistic investigation along with the understanding of the exact nature of the catalysts is highly desired for further development of more active and practical catalytic systems.

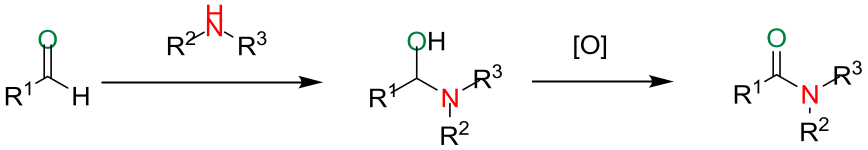
CHAPTER 2

N-HETEROCYCLIC CARBENE BASED RUTHENIUM CATALYZED DIRECT AMIDATION OF ALDEHYDES WITH AMINES

2.1 Introduction

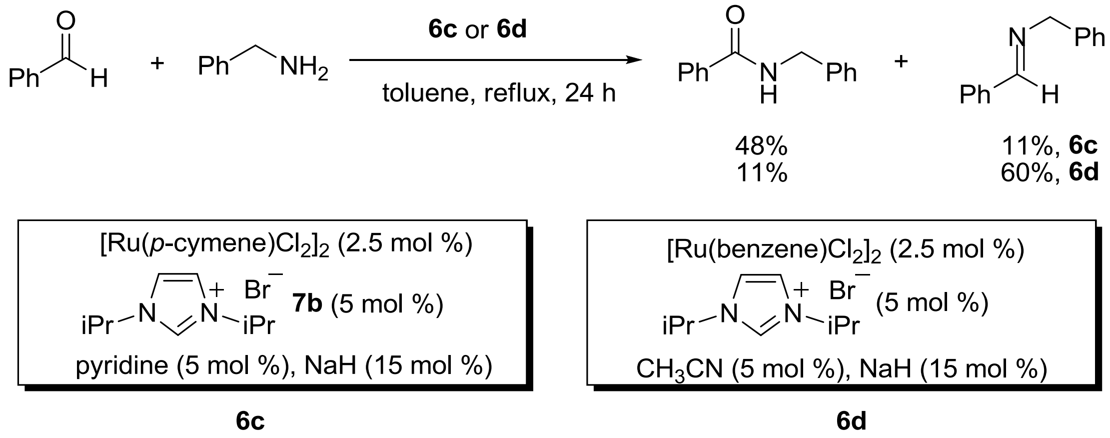
The amide group, one of the most important functional groups, plays a pivotal role in both organic and biological chemistries.[1-2] Aldehydes are desirable starting materials due to their ready availability and non-toxicity. Transition-metal catalyzed direct amidation of aldehydes with amines or amine hydrochlorides, a highly desired atom economical transformation, has been highlighted as an attractive alternative to traditional amide synthesis.[33] Several groups have reported the direct amide synthesis from aldehydes and amines using Ru-,[12,18] Pd-,[34] Cu-,[35] Rh-,[36] Au-,[37] and Lanthanide-based[38] catalytic systems. The general mechanism of this reaction is shown in Scheme 2.1. An aldehyde reacts with an amine or amine hydrochloride to produce a hemiaminal intermediate, which would be further oxidized to the corresponding amide. A major advantage of this approach is that it provides efficient and fast access to amides without isolation of carboxylic acid intermediates. Therefore, it is especially useful for synthesizing compounds containing functional groups which are either unstable in the presence of carboxylic acids or incompatible with reaction conditions used in classical amide formation.[33a]

Scheme 2.1 Amide synthesis from aldehydes and amines.



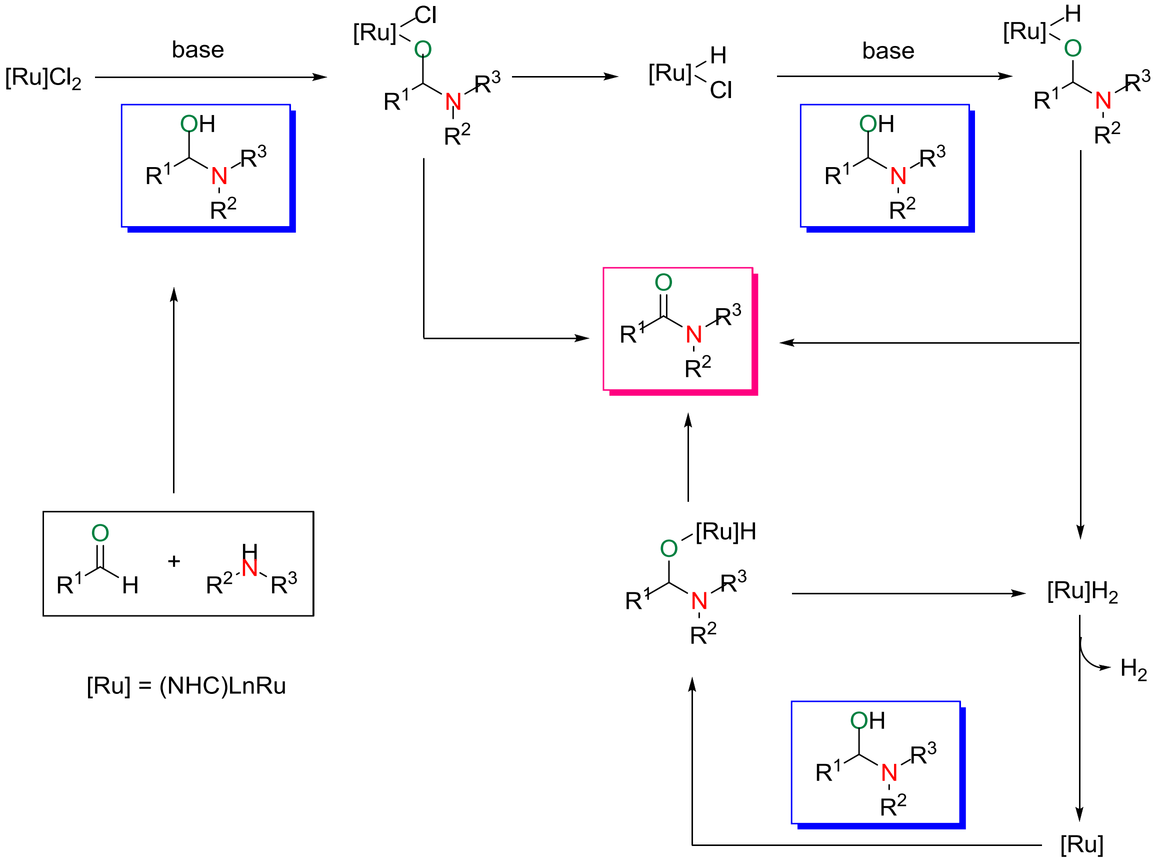
Recently, transition metal catalyzed direct amide synthesis from alcohols and amides has been highlighted as an attractive protocol to construct the amide bond.[7] Ru-,[12-23,39] Rh-,[24,26] Ag-,[28] Au-,[29-30] and Mn[32] based catalytic systems have been reported for this tranformation. In our previous work, we tested the catalytic systems **6c** and **6d** for the reaction of benzaldehyde and benzyl amine, but only 48% and 11% of the amide product were obtained, respectively, with the corresponding imine as the major by-product (Scheme 2.2).[16] Our group also reported a well-defined NHC based ruthenium catalyst for alcohol amidation with amines, and it also showed low activity for the direct amide synthesis from aldehydes and amines.[17] However, efficient amidation of aldehydes can be realized by addition of a catalytic amount of a primary alcohol (Scheme 1.9). It was demonstrated that formation of an active catalytic species by an alcohol is essential for the formation of aldehyde amidation with amines, and it would be less efficient to form active $[Ru]H_2$ from $[Ru]Cl_2$ and an aldehyde without help of a primary alcohol. Therefore, the effective formation of $[Ru]H_2$ is crucial for the amide synthesis from either alcohols or aldehydes.[17]

Scheme 2.2 Reaction between benzaldehyde and benzylamine catalyzed by **6c** and **6d**



The catalyst system **6c**, which is highly active for amidation of alcohols, only showed moderate activity for that of aldehydes. However, a hemiaminal, an important intermediate for amide formation from aldehydes and amines, is also an alcohol. So we hypothesized that the hemiaminal could be used to activate [Ru]Cl$_2$ to generate the key Ru[H]$_2$ species. Dehydrogenation of [Ru]H$_2$ affords [Ru]. Oxidative addition of [Ru] with the hemiaminal, followed by β-hydrogen elimination could give the amide product and regenerate the [Ru]H$_2$ species (Scheme 2.3). With this hypothesis in mind, we believe that satisfactory results could be obtained for the direct amide synthesis from aldehydes and amines by modifying reaction conditions based on **6c**. Herein, we have made a conscious effort to develop our catalytic system using [Ru(*p*-cymene)Cl$_2$]$_2$ with an *N*-heterocyclic carbene ligand and readily available pyridine as an additive for aldehyde amidation with amines.

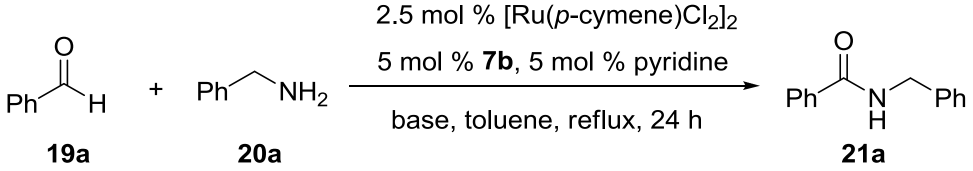
Scheme 2.3 Proposed mechanism on Ru catalyzed aldehyde amidation with amines.



2.2 Results and discussion

The reaction between benzaldehyde and benzylamine was selected as the model reaction for optimization of reaction conditions (Table 2.1). During our previous study, when the catalytic system **6c** was used for the reference reaction, only limited yield was obtained (48%, entry 1) with the corresponding imine as the major by-product. Inspired by our another work which used alcohols to activate aldehyde amidation with a well-defined Ru-NHC complex as a catalyst, we performed our experiments by adding a catalytic amount of a few primary and secondary alcohols as additives. Disappointingly, comparable or even lower yields were given (entries 2-4), and imine is still the dominant by-product. Therefore, precatalyst activation by adding external alcohols was not effective for this catalytic system. Then we tried to screen the amount of NaH used in this reaction. Interestingly, dramatic improvement of this catalytic system was achieved only by changing the amount of NaH used from 15 mol % to 40 mol % (48% for entry 1 vs 87% for entry 7). Further increase of the amount of NaH resulted in reduced yields of the amide product (entries 7-10). Replacement of NaH with KO*t*Bu was not successful, and only low to moderate yields were yielded with 20-100 mol % KO*t*Bu (entries 11-16). So the optimal catalytic system was identified as [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), NHC precursor **7b** (5 mol %), pyridine (5 mol %), NaH (40 mol %) and used for further study.

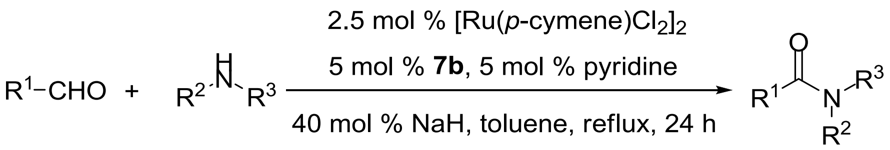
Table 2.1 Optimization of reaction conditions.[a]

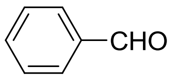
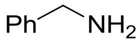
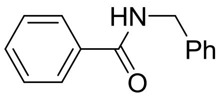
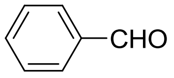
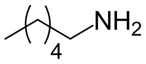
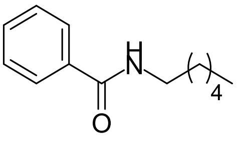
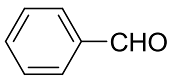
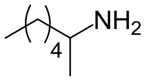
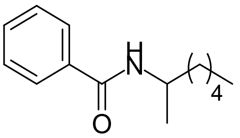
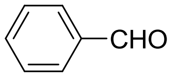
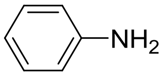
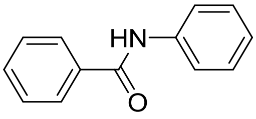
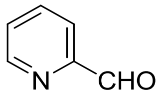
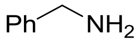
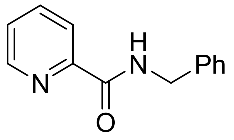
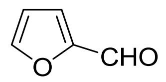
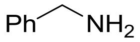
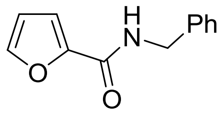
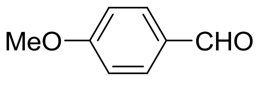
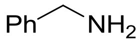
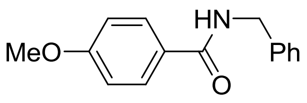
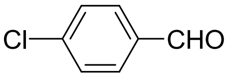
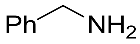
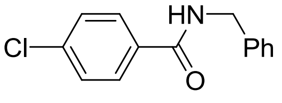


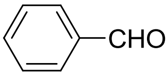
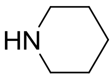
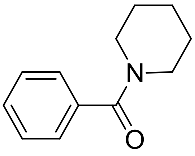
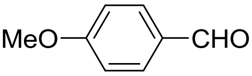
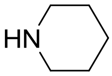
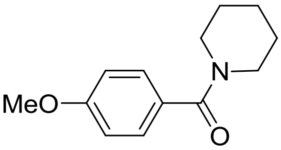
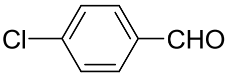
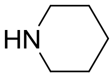
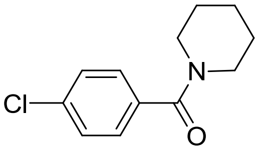
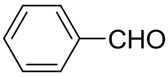
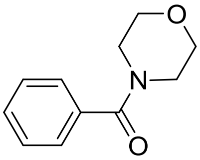
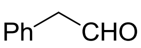
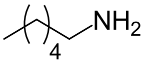
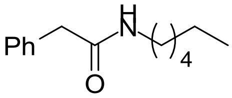
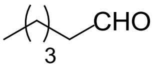
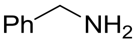
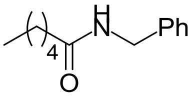
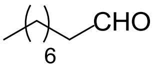
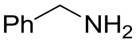
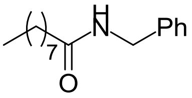
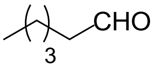
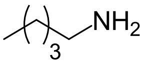
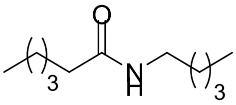
Entry	Base (mol %)	Additive (10 mol %)	Yield [%][b]
1	NaH (15)	-	48
2	NaH (15)	MeOH	35
3	NaH (15)	iPrOH	25
4	NaH (15)	$PhCH_2CH_2OH$	40
5	NaH (20)	-	51
6	NaH (30)	-	63
7	NaH (40)	-	87
8	NaH (50)	-	80
9	NaH (60)	-	62
10	NaH (100)	-	50
11	KO*t*Bu (20)	-	25
12	KO*t*Bu (30)	-	29
13	KO*t*Bu (40)	-	42
14	KO*t*Bu (50)	-	42
15	KO*t*Bu (60)	-	54
16	KO*t*Bu (100)	-	53

[a] [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol %), NHC precursor **7b** (5 mol %), pyridine (5 mol %). [b] GC yields using dodecane as an internal standard.

Table 2.2 Direct amide synthesis from aldehydes and amines.[a]



Entry	Aldehyde	Amine	Amide	Yield [%][b]
1	 **19a**	 **20a**	 **21a**	75
2		 **20b**	 **21b**	80
3		 **20c**	 **21c**	41
4		 **20d**	 **21d**	31[c]
5	 **19b**		 **21e**	36
6	 **19c**		 **21f**	60
7	 **19d**		 **21g**	81
8	 **19e**		 **21h**	64

9		 **20e**	 **21i**	67
10			 **21j**	77
11			 **21k**	70
12		 **20f**	 **21l**	32
13	 **19f**		 **21m**	25
14	 **19g**		 **21n**	42
15	 **19h**		 **21o**	51
16		 **20g**	 **21p**	35

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[a]Isolated yields. [b][Ru(*p*-cymene)Cl$_2$]$_2$ (2.5 mol %), NHC precursor **7b** (5 mol %), NaH (40 mol %), pyridine (5 mol %) in toluene at reflux for 24 h. [c]In mesitylene at reflux for 24 h.

With the optimized reaction conditions in hand, the substrate scope and limitation of this method was investigated. A range of amides were afforded in moderate to good yields (Table 2.2). Aromatic aldehydes are good substrates for this reaction. Benzaldehyde reacted smoothly with sterically non-hindered primary amines (entries 1-2). A reduced yield was observed for a moderately hindered amine **20c** (entry 3). Less basic aniline was converted to the corresponding amide in only 31% yield even at elevated temperature with mesitylene as the solvent (entry 4). Heteroatom-containing aromatic aldehydes can also be tolerated with moderate yields (entries 5-6). Electronic effect on aldehydes was explored with benzaldehyde derivatives and benzyl amine, and slightly lower yields were obtained for electron-deficient substrates (entries 1, 7-8). In the case of cyclic secondary amines, piperidine showed good reactivity with both electron-deficient and electron-rich aromatic aldehydes (entry 9-11), while morpholine didn’t react well with benzaldehyde (entry 12). A low yield was obtained when benzaldehyde was replaced with phenylacetaldehyde (entry 13). Aliphatic aldehydes could also be employed, giving the desired amide products in moderate yields (entries 14-16).

2.3 Conclusion

Our previous catalytic system using commercially available [Ru(*p*-cymene)Cl_2]$_2$, an *N*-heterocyclic carbene ligand and the economical pyridine as an additive is highly active for direct amide synthesis from alcohols and amines, but much less active for that from aldehydes and amines. With the proposition of using hemiaminal intermediate as an alcohol to generate the active [Ru]H_2 species for aldehyde amidation, a catalytic condition for aldehyde amidation with amines was identified. A range of amides were synthesized directly from aldehydes and amines in moderate to good yields. Aromatic aldehydes including heteroatom-containing ones reacted smoothly, and aliphatic aldehydes afforded the corresponding amides in moderate yields.

2.4 Experimental section

2.4.1 General considerations

All reactions were carried out using standard Schlenk techniques or in an argon-filled glove box unless otherwise mentioned. All aldehydes and amines were obtained from Aldrich or Alfa Aesar and used as received. $CDCl_3$ was purchased from Cambridge Isotope Laboratories (CIL) and used as received. NHC precursor **7b** was synthesized by the literature procedure.[25] Toluene was dried over Pure Solv solvent purification system. Analytical TLC was performed on Merck 60 F254 silica gel plates (0.25mm thickness). Column chromatography was performed on Merck 60 silica gel (230-400 mesh). NMR spectra were recorded in $CDCl_3$, using Bruker Bruker AVANCE300, AVANCE400, AVANCE^{III}400 or JEOL ECA400 spectrometers, and TMS (tetramethylsilane) was used as a reference. Chemical shifts were reported in ppm and coupling constants in Hz. GC analyses were carried out with 7980A GC system from Agilent Technologies, equipped with an HP-5 column using dodecane as an internal standard. High resolution mass spectra were recorded by Waters Q-Tof Premier Micromass instrument, using the electro spray ionization (ESI) mode.

2.4.2 Materials

1,3-Diisopropylimdazolium bromide was prepared by the literature procedure.[40] Aldehydes and amines were purchased from commercial suppliers and used as received without further purification. Toluene was dried over a solvent purification system.

2.4.3 General procedure for amide synthesis

Inside an argon-filled glovebox, $[Ru(p\text{-cymene})Cl_2]_2$ (7.7 mg, 0.0125 mmol), 1,3-diisopropylimidazolium bromide (**7b**, 5.8 mg, 0.025 mmol), NaH (4.8 mg, 0.2 mmol), pyridine (2 μL, 0.025 mmol) and toluene (0.6 mL) were added to an oven-dried Schlenk tube. The Schlenk tube was taken out of the glovebox and placed in an oil bath at reflux under argon atmosphere for 30 min. The flask was removed from the oil bath before the aldehyde (0.5 mmol) and the amine (0.55 mmol) were added. Then the mixture was heated to reflux under argon atmosphere for 24 h. The reaction mixture was cooled down to room temperature and the solvent was removed *in vacuo*. The residue was purified by silica gel flash column chromatography to afford the amide.

***N*-Benzylbenzamide (21a).**[16] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 75%. ^{1}H NMR ($CDCl_3$): δ 7.80-7.78 (m, 2H), 7.50-7.30 (m, 8H), 6.48 (bs, 1H), 4.64 (d, 2H, J = 5.9 Hz).

***N*-Hexylbenzamide (21b).**[41] Purified by silica gel chromatography (Hex : EA = 5 : 1) to afford the desired product as a white solid. Isolated yield: 80%. ^{1}H NMR ($CDCl_3$): δ 7.77 (dd, 2H, J = 7.2, 1.3 Hz), 7.49 (t, 1H, J = 7.3 Hz), 7.40 (t, 2H, J = 7.3 Hz), 6.44 (bs, 1H), 3.42 (td, 2H, J = 7.1, 6.0 Hz), 1.62-1.57 (m, 2H), 1.37-1.29 (m, 6H), 0.89 (t, 2H, J =

6.8 Hz).

***N*-(Heptan-2-yl)benzamide (21c).** Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 41%. ^{1}H NMR ($CDCl_3$): δ 7.75 (d, 2H, *J* = 7.2 Hz), 7.49 (t, 1H, *J* = 7.2 Hz), 7.42 (t, 2H, *J* = 7.2 Hz), 5.92 (br, 1H), 4.24-4.14 (m, 1H), 1.60-1.45 (m, 2H), 1.41-1.22 (m, 9H), 0.90-0.87 (m, 3H); ^{13}C NMR ($CDCl_3$): 167.0, 135.3, 131.4, 128.7, 127.0, 46.0, 37.3, 31.9, 26.0, 22.8, 21.3, 14.2; HR-MS (ESI): m/z = 220.1704 [MH^+], calcd. for $C_{14}H_{22}NO$: 220.1701.

***N*-Phenylbenzamide (21d).** Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 31%. ^{1}H NMR ($CDCl_3$): δ 7.88 (bs, 1H), 7.85-7.82 (m, 2H), 7.64-7.61 (m, 2H), 7.55-7.60 (m, 1H), 7.47-7.43 (m, 2H), 7.36-7.32 (m, 2H), 7.15-7.12 (m, 1H); ^{13}C NMR ($CDCl_3$): 166.0, 138.1, 135.2, 132.0, 129.3, 129.0, 127.2, 124.8, 120.4; HR-MS (ESI): m/z = 198.0925 [MH^+], calcd. for $C_{13}H_{12}NO$: 198.0919.

***N*-Benzylpicolinamide (21e).** Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 36%. ^{1}H NMR ($CDCl_3$): δ 8.52 (d, 1H, *J* = 5.0 Hz), 8.39 (bs, 1H), 8.24 (d, 1H, *J* = 8.2 Hz), 7.90-7.75 (m, 1H), 7.50-7.20 (m, 6H), 4.67 (d, 2H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$): 164.4, 150.0, 148.2, 138.4, 137.5, 128.9, 128.0, 127.6, 126.4, 122.5, 43.6; HR-MS (ESI): m/z = 213.1028 [MH^+], calcd. for $C_{13}H_{13}N_2O$: 213.1028.

***N*-Benzylfuran-2-carboxamide (21f).** Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 60%. ^{1}H NMR ($CDCl_3$): δ 7.40 (s, 1H), 7.38-7.20 (m, 5H), 7.15-7.11 (m, 1H), 6.74 (bs, 1H), 6.51-6.47 (m, 1H), 4.60 (d, 2H, *J* = 5.9 Hz); ^{13}C NMR ($CDCl_3$): 158.4, 148.0, 144.1, 138.2, 128.9, 128.0, 127.8, 114.5, 112.3, 43.3; HR-MS (ESI): m/z = 202.0872 [MH^+], calcd. for $C_{12}H_{12}NO_2$: 202.0868.

***N*-Benzyl-4-methoxybenzamide (21g).**[42] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 81%. ^{1}H NMR ($CDCl_3$): δ 7.79-7.75 (m, 2H), 7.36-7.27 (m, 5H), 6.93-6.90 (m, 2H), 6.51 (bs, 1H), 4.63 (d, 2H, *J* = 5.7 Hz), 3.84 (s, 3H).

***N*-Benzyl-4-chlorobenzamide (21h).**[43] Purified by silica gel chromatography (Hex : EA = 5 : 1) to afford the desired product as a white solid. Isolated yield: 64%. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, 2H, *J* = 8.7 Hz), 7.37-7.29 (m, 7H), 6.38 (bs, 1H), 4.61 (d, 2H, *J* = 6.0 Hz).

Phenyl(piperidin-1-yl)methanone(21i).[16] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a colorless oil. Isolated yield: 67%. ^{1}H NMR ($CDCl_3$): δ 7.37 (bs, 5H), 3.70 (bs, 2H), 3.33 (bs, 2H), 1.66-1.50 (m, 6H).

(4-Methoxyphenyl)(piperidin-1-yl)methanone (21j).[38b] Purified by silica gel chromatography (Hex: EA = 1 : 1) to afford the desired product as a colorless oil. Isolated yield: 77%. ^{1}H NMR ($CDCl_3$): δ 7.38-7.36 (m, 2H), 6.91-6.89 (m, 2H), 3.82 (s, 3H), 3.64 (bs, 2H), 3.45 (bs, 2H), 1.67 (bs, 4H), 1.60 (bs, 2H).

(4-Chlorophenyl)(piperidin-1-yl)methanone (21k).[38b] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 70%. ^{1}H NMR ($CDCl_3$): δ 7.39-7.28 (m, 4H), 3.69 (bs, 2H), 3.33 (bs, 2H), 1.68 (bs, 4H), 1.52 (bs, 2H).

Morpholino(phenyl)methanone (21l).[38b] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford it as a white solid. Isolated yield: 32%. ^{1}H NMR ($CDCl_3$): δ 7.41-7.39 (m, 5H), 3.74-3.46 (m, 8H).

***N*-Hexyl-2-phenylacetamide (21m).**[16] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 25%. ^{1}H NMR ($CDCl_3$): δ 7.35-7.26 (m, 5H), 5.35 (bs, 1H), 3.56 (s, 2H), 3.19 (q, 2H, *J* = 6.8 Hz), 1.43-1.37 (m, 2H), 1.29-1.17 (m, 6H), 0.85 (t, 3H, *J* = 6.8 Hz).

***N*-Benzylhexanamide (21n).**[16] Purified by silica gel chromatography (Hex : EA = 4 : 1) to afford the desired product as a white solid. Isolated yield: 42%. ^{1}H NMR ($CDCl_3$): δ 7.30-7.26 (m, 5H), 5.99 (bs, 1H), 4.41 (d, 2H, *J* = 5.9 Hz), 2.19 (t, 2H, *J* = 7.4 Hz), 1.69-1.64 (m, 2H), 1.32-1.28 (m, 4H), 0.88 (t, 3H, *J* = 6.8 Hz).

***N*-Benzylnonanamide (21o).** Purified by silica gel chromatography (Hex : EA = 4 : 1) to afford the desired product as a white solid. Isolated yield: 51%. ^{1}H NMR ($CDCl_3$): δ 7.40-7.24 (m, 5H), 5.75 (bs, 1H), 4.44 (d, 2H, *J* = 5.5 Hz), 2.21 (t, 2H, *J* = 7.8 Hz), 1.65 (quint, 2H, *J* = 7.3 Hz), 1.40-1.10 (m, 10H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$): 173.2, 138.6, 128.9, 128.0, 127.7, 43.8, 37.0, 32.0, 29.5, 29.4, 26.0, 22.9, 14.3; HR-MS (ESI): m/z = 248.2020 [MH^+], calcd. for $C_{16}H_{26}NO$: 248.2014.

***N*-Pentylhexanamide (21p).**[16] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 35%. ^{1}H NMR ($CDCl_3$): δ 5.86 (bs, 1H), 3.20-3.15 (m, 2H), 2.11 (t, 2H, *J* = 7.7 Hz), 1.58 (quint, 2H, *J* = 8.2 Hz), 1.45 (quint, 2H, *J* = 7.2 Hz), 1.27-1.23 (m, 8H), 0.86-0.82 (m, 6H).

CHAPTER 3

N-HETEROCYCLIC CARBENE BASED RUTHENIUM CATALYZED DIRECT AMIDE SYNTHESIS FROM ALCOHOLS AND SECONDARY AMINES – INVOLVEMENT OF ESTERS

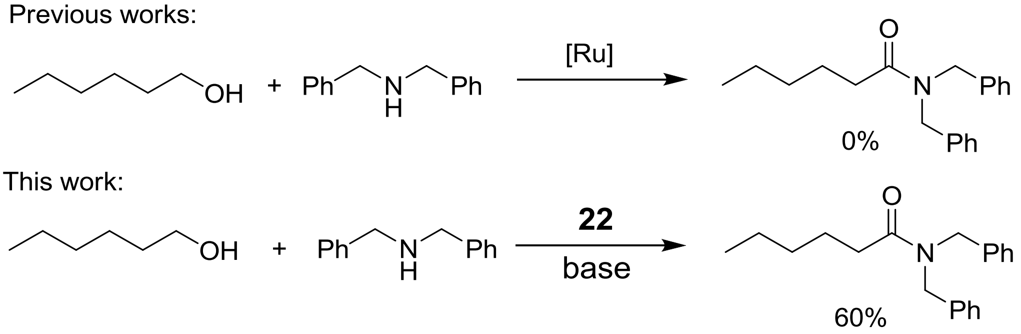
(This chapter has been published in *The Journal of Organic Chemistry* **2011**, *76*, 10005.)

3.1 Introduction

Compared with traditional amide synthesis that often produces toxic chemical waste with tedious procedures, the direct amide synthesis from alcohols and amines is a highly atom economical transformation that generates hydrogen gas as the sole byproduct. This attractive transformation has been recently highlighted.[7-9] Among the reported catalytic systems, ruthenium complexes have been most extensively studied.[12-23,39]

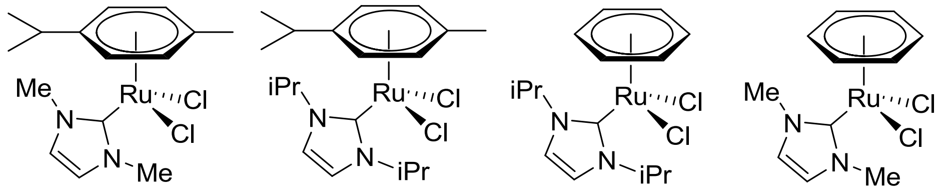
Although the direct amide synthesis has attractive advantages over traditional amide syntheses, there are many challenges for this emerged method to be widely used for the synthesis of ubiquitous amides, such as limited substrate scope and harsh reaction conditions.[7-9] One of the challenges is the amidation of secondary amines.[7-9] The reported Ru catalysts showed limited activity for the reactions between alcohols and linear secondary amines, especially with sterically hindered ones, while they showed excellent activity for less hindered primary amines.[12-23] For example, no desired product has been observed with the previous catalytic systems when dibenzylamine was used for the amidation reaction (Scheme 3.1).[13,16] In this chapter, we wish to address the issue by employing an NHC-based Ru complex as an active precatalyst for the amide synthesis from alcohols and secondary amines.

Scheme 3.1 Reaction of 1-hexanol and dibenzylamine.



Our group reported (*p*-cymene)(NHC)RuX_2 complexes such as **8a** and **8c** as precatalysts for the direct amide synthesis (Figure 3.1).[17] When we attempted less sterically bulky NHC-based **8a** for the transformation of sterically hindered substrates including secondary amines, no improvement was observed. Although it was postulated that the arene group would be dissociated during the catalysis,[17,19,23] it was reported that improvements could be achieved by changing a Ru precursor [Ru(*p*-cymene)Cl_2]$_2$ with [Ru(benzene)Cl_2]$_2$ for less hindered cyclic secondary amines such as piperidine and morpholine.[16] As an example, the [Ru(benzene)Cl_2]$_2$ based catalytic system showed 90% yield on the amidation of morpholine with 2-phenylethanol (vs 63% with [Ru(*p*-cymene)Cl_2]$_2$), although it still showed limitations on other sterically more congested secondary amines such as dibenzylamine.[16] These observations led us to explore the catalytic activity of Ru complex **22** for the amidation of challenging secondary amines with alcohols.

Figure 3.1 Ru complexes for the direct amide synthesis from alcohols and amines.

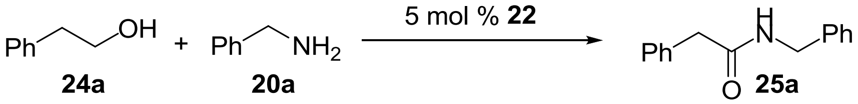


8a **8c** **22** **23**

3.2 Results and discussion

An NHC-Ag carbene complex was first made, which then reacted with [Ru(benzene)Cl_2]$_2$ to give complex **22.** The structure of **22** was confirmed by X-ray crystallography (see **3.5 Appendix**). Attempts to synthesize less sterically conjested **23** by the same procedure were not successful presumably due to less stability. Since no improvement was previously reported on sterically bulky substrates with **8a** over **8c**, we decided to pursue the amidation reaction only with **22**.[17,20] It has been consistently reported that 1,3-diisopropylimidazoline showed the best activities on the NHC-promoted Ru catalyzed amide synthesis among the other NHCs.[14,16-20]

Table 3.1 Optimization of conditions.[a]



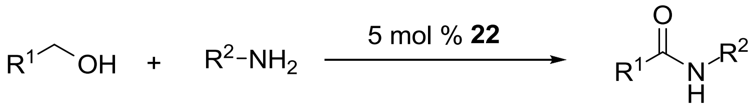
Entry	Base		Additive		Yield[b] [%]
	Base	mol %	Additive	mol %	
1	-	-	-	-	0
2	NaH	10	-	-	38
3	NaH	15	-	-	93
4	NaH	20	-	-	91
5	NaH	30	-	-	78
6	NaH	40	-	-	66
7	NaH	60	-	-	53
8	NaH	100	-	-	46
9	KO*t*Bu	10	-	-	59
10	KO*t*Bu	15	-	-	96
11	KO*t*Bu	20	-	-	93
12	KO*t*Bu	30	-	-	77
13	KO*t*Bu	40	-	-	68
14	KO*t*Bu	60	-	-	60
15	KO*t*Bu	100	-	-	46
16	KO*t*Bu	20	-	-	56[c]
17	KO*t*Bu	20	NaBr	20	53[c]
18	KO*t*Bu	20	NaI	20	55[c]
19	KO*t*Bu	20	KBr	20	60[c]
20	KO*t*Bu	20	KI	20	57[c]
21	KO*t*Bu	20	$AgBF_4$	20	0[c]
22	KO*t*Bu	20	$AgSbF_6$	20	0[c]
23	KO*t*Bu	20	AgOAc	20	0[c]

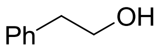
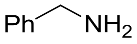
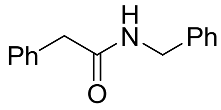
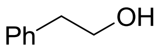
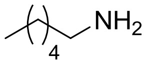
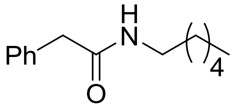
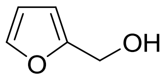
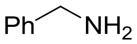
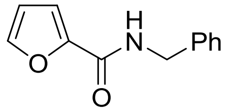
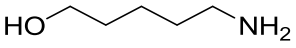
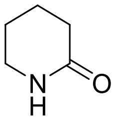
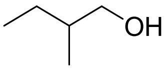
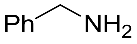
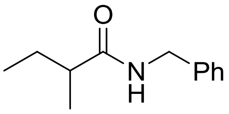
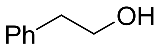
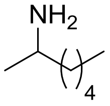
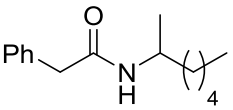
[a] 5 mol % catalyst, toluene, reflux, 24 h unless otherwise noted. [b] Determined by GC using dodecane as an internal standard. [c] 80 °C, 24 h.

The optimization of the catalytic conditions was conducted with a reaction of **24a** and **20a** (Table 3.1). Bases such as NaH and KO*t*Bu were found necessary for catalytic activity. Further optimization demonstrated that only a catalytic amount of a base, 15-20 mol %, is ideal for the catalysis (entries 1-15). Decrease of the reaction temperature to 80 ^{o}C resulted in a reduced yield (entry 16). To improve the activity, we tried to exchange the chloride ligands with bromide and iodide, but only comparable yields were obtained (entries 17-20). Use of silver salts to abstract chloride ligands did not provide the desired product (entries 21-23). So 15-20 mol % KO*t*Bu or NaH and 5 mol % of **22** are required for the catalysis, consistent with the previous report.[17] It was suggested that the role of the strong base is to stimulate the formation of Ru alkoxide species, which are further transformed to an active Ru hydride catalytic intermediate.[17-18]

With the optimized reaction conditions in hand, reactions of alcohols and primary amines were explored first (Table 3.2). Good to excellent yields were obtained for both intermolecular and intramolecular processes with precatalyst **22** (Table 3.2). Catalytic activities of **22** on the amidation of less hindered primary amines with alcohols were generally comparable with **8a** and **8c**.[17] No ester was observed in the reactions in Table 3.2, consistent with other NHC-Ru catalyzed amidation of less hindered primary amines with alcohols.[14,16]

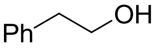
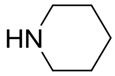
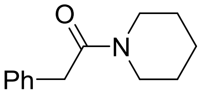
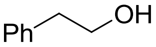
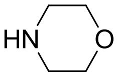
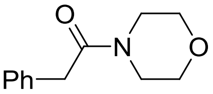
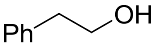
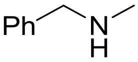
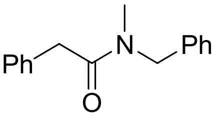
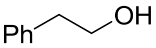
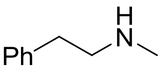
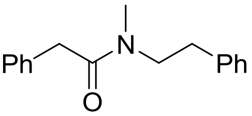
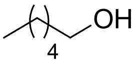
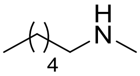
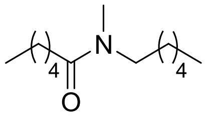
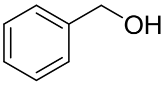
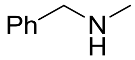
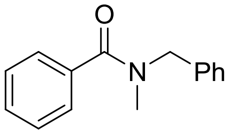
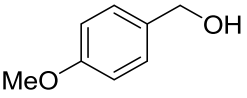
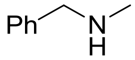
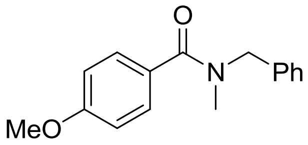
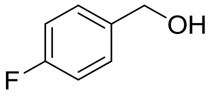
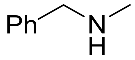
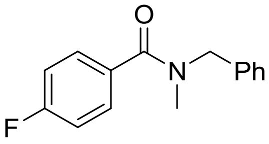
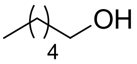
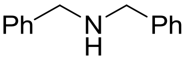
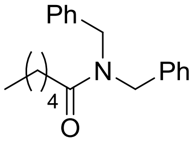
Table 3.2 Amide synthesis from alcohols and primary amines catalyzed by **22**.[a]



Entry	Alcohol	Amine	Amide	Yield [%][b]
1	 **24a**	 **20a**	 **25a**	92
2		 **20b**	 **21m**	90
3	 **24b**		 **21f**	80
4	 **24c**		 **25b**	90
5	 **24d**		 **25c**	66
6		 **20c**	 **25d**	70[c]

[a]Complex **22** (5 mol %), KO*t*Bu (15 mol %), toluene, reflux, 24 h unless otherwise noted. [b]Isolated yields. No ester formation was observed. [c]20 mol % KO*t*Bu.

Table 3.3 Amide synthesis from alcohols and secondary amines catalyzed by **22**.[a]

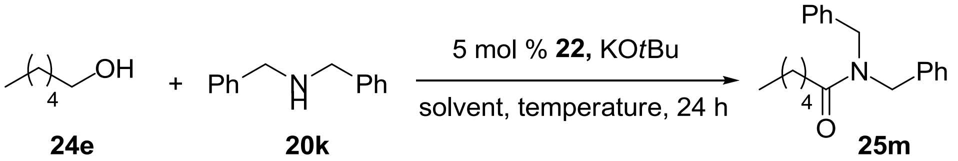
Entry	Alcohol	Amine	Amide	Yield [%][b]
1		 **20e**	 **25e**	92(<1)
2		 **20f**	 **25f**	86(<5)
3		 **20h**	 **25g**	90(<1)
4		 **20i**	 **25h**	87(<5)
5	 **24e**	 **20j**	 **25i**	81(9)
6	 **24f**		 **25j**	54(<1)
7	 **24g**		 **25k**	52(<1)
8	 **24h**		 **25l**	42(<1)
9		 **20k**	 **25m**	34(50)

[a] Complex **22** (5 mol %), KO*t*Bu (20 mol %), 1.0 equiv alcohol and 1.1 equiv amine, toluene, reflux, 24 h unless otherwise noted. [b] Isolated yields. Yields in parentheses represent the yields of the corresponding esters from alcohols **24**.

Next, various secondary amines were tested for the amidation reactions (Table 3.3). Cyclic secondary amines and less bulky noncyclic ones yielded excellent yields (entries 1-5). The previously reported yields for the reaction between a primary alcohol and *N*-benzylmethylamine are 40-70%.[14,16,19] In contrast, **22** can catalyze the same reaction in 90% yield (entry 3). We studied the electronic effect on alcohols using benzyl alcohol derivatives. Slightly lower yields were obtained for electron-deficient substrates as observed with complex **8a** and **8c** (entries 6-8).[17] For these less sterically hindered secondary amines, only small amount of the corresponding esters were observed. Interestingly, the more bulky secondary amine, dibenzylamine (**20k**), reacted with 1-hexanol (**24e**) to give 34% of the amide product (entry 9), while previously reported catalysts were not active for the reaction of a primary alcohol and dibenzylamine.[13,16] Inspired by this interesting result, we focused on improving the reactivity of more bulky secondary amines by screening different reaction conditions.

The reaction of 1-hexanol (**24e**) and dibenzylamine (**20k**) was selected as the reference reaction, and various conditions were screened (Table 3.4). The amount of KO*t*Bu was screened again, and 35% was found to be optimal with the formation of the product in 60% isolated yield (entries 1-7). Different solvents were also tested. DCE didn't provide any product (entry 8), and a moderate yield was obtained in refluxing benzene (entry 9). With benzene as the solvent, when the reaction was performed in a sealed tube with increase of the reaction temperature to 110 °C, an improved yield was observed (59% in entry 10 vs 44% in entry 9). The ruthenium catalyzed amide formation directly from alcohols and amines have been reported to perform in an open condition under inert atmosphere to facilitate removal of H_2.[12-23,39] This result demonstrated that either an open condition or a closed system doesn't considerably affect the efficiency of the amide synthesis from alcohols and secondary amines. This reaction was also done in refluxing mesitylene, with the expectation that higher temperature may result in more efficiency of this reaction. Surprisingly, only 25% of the product was yielded (entry 11), while lowering the temperature to 110 °C led to a much higher yield (entry 12). Probably high temperature promoted ligand exchange between benzene in the catalyst and the bulky solvent molecule-mesitylene, which may delay the reaction progress or decrease the reaction efficiency. Therefore, the optimized condition was selected to be 5 mol % **22**, 35 mol % KO*t*Bu in refluxing toluene for 24 h.

Table 3.4 Optimization of conditions for reaction of 1-hexanol and dibenzylamine.

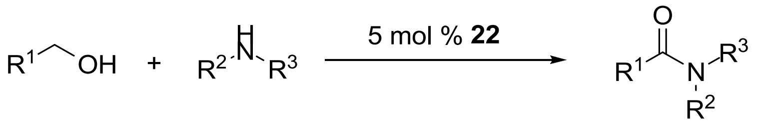


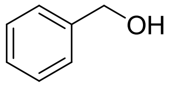
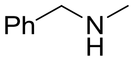
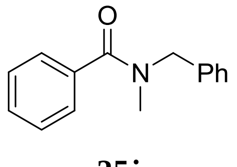
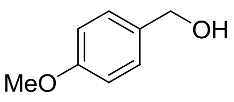
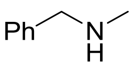
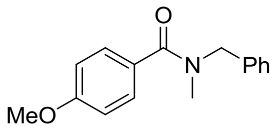
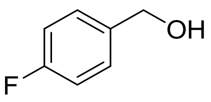
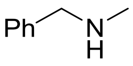
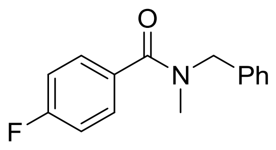
Entry	KO*t*Bu (mol %)	Solvent	Temperature	Yield [%][a]
1	15	toluene	110 °C	33
2	20	toluene	110 °C	34
3	30	toluene	110 °C	51
4	35	toluene	110 °C	60
5	40	toluene	110 °C	44
6	60	toluene	110 °C	30
7	100	toluene	110 °C	11
8	35	DCE	84 °C	0
9	35	benzene	80 °C	44
10	35	benzene	110 °C	59[b]
11	35	mesitylene	163 °C	25
12	35	mesitylene	110 °C	53

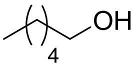
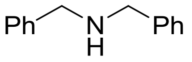
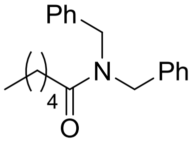
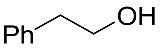
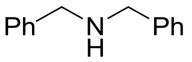
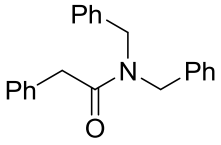
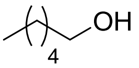
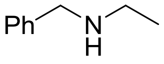
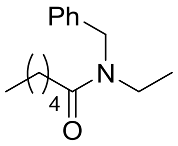
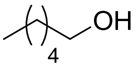
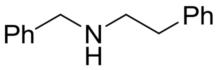
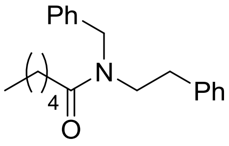
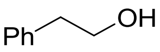
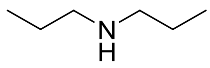
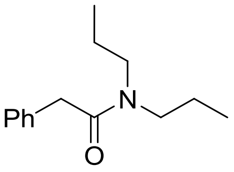
[a]Isolated yields. [b]In a sealed tube.

The optimized reaction condition was applied to different secondary amines (Table 3.5). To our delight, **22** showed good activity for secondary amines, especially sterically hindered ones, with the updated condition using a increased amount of KO*t*Bu. Substrates **24f-h** were tested again with *N*-benzylmethylamine (**20h**) since only moderate yields were given under the previous condition (entries 6-8, Table 3.3). Considerable improvements were observed for **24f** (80% in entry 1, Table 3.5 vs 54% in entry 6 , Table 3.3) and **24g** (75% in entry 2, Table 3.5 vs 52% in entry 7, Table 3.3), and comparable result was found for the electron-deficient substrate **24h** (47% in entry 3, Table 3.5 vs 42% in entry 8, Table 3.3). A few bulky secondary amines were tested, and moderate to good yields were obtained (entries 4–8). We observed esters, formed by oxidative esterification of alcohols **24**, as by-products in some cases, especially when the reaction was performed with sterically bulky secondary amines (Table 3.5).[10f,44]

Table 3.5 Amide synthesis from alcohols and secondary amines catalyzed by **22**.[a]



Entry	Alcohol	Amine	Amide	Yield [%][b]
1	 **24f**	 **20h**	 **25j**	80(<1)
2	 **24g**		 **25k**	75(2)
3	 **24h**		 **25l**	47(<1)

4	 **24e**	 **20k**	 **25m**	60(<3)
5	 **24a**		 **25n**	40(19)
6		 **20l**	 **25o**	60(13)
7		 **20m**	 **25p**	43(18)
8		 **20n**	 **25q**	44(21)[c]

[a]Complex **22** (5 mol %), KO*t*Bu (35 mol %), 1.0 equiv alcohol and 1.1 equiv amine, toluene, reflux, 24 h unless otherwise noted. [b]Isolated yields. Yields in parentheses represent the yields of the corresponding esters from alcohols **24**. [c]1.0 equiv alcohol and 2.0 equiv amine.

To understand the rationale for the improvement on the secondary amine, we first investigated the effect of arene ring of precatalysts **8c** and **22**. Initially, we suspected that less hindered benzene than *p*-cymene would result in the improvement for more hindered secondary amines. Noyori, Ikariya, and coworkers discussed the arene effect in [Ru(arene)Cl_2]$_2$ complexes for asymmetric transfer hydrogenation.[45] Noels and coworkers also reported the effect of the arene on the RuCl_2(arene)(PR_3) catalyzed ring-opening metathesis polymerization.[46] It has been reported in different cases that dissociation of the arene ligand is necessary for catalytic activity of 18-electron $RuCl_2$(arene)(L)-type complexes (L = PR_3 or NHC).[46-47] In the case of the direct amidation catalyzed by **8a** and **8c**, it has been also suggested that arene ligand is fully dissociated especially at the required reaction temperature of 110 °C.[14,16-20] Indeed, free benzene or *p*-cymene was observed during catalysis when the reaction was monitored by ^{1}H NMR spectroscopy in toluene-d_8 indicating the full dissociation of arene rings. Therefore, we believe that the reduced steric effect of benzene ring of **22** should not be the reason. Next, we focused on the less electron rich nature of benzene than *p*-cymene. If the full dissociation of arene ring should occur to generate the active catalytic intermediate, **22** can generate the active catalytic intermediate, *i.e.* initiate the catalytic cycle faster than **8c** due to more electron deficient arene ring. The reaction progress was monitored by GC with the reaction of 1-hexanol (**24e**) and 1-pentylamine (**20g**) catalyzed by **8c** and **22**, respectively (Figure 3.2). The reaction catalyzed by **22** was only slightly faster than that by **8c**. However, when reaction of 1-hexanol (**24e**) and a bulky secondary amine-dibenzylamine (**20k**) was monitored, the reaction catalyzed by **22** were obviously faster than that by **8c (**23% by **8c** vs 31% by **22** for the reaction of entry 4 in Table 3.5, after 3 h, Figure 3.3), suggesting faster dissociation of benzene ring could be one of the reasons of the improvement. However, the undramatic reaction rate acceleration with **22** implied that there might be another reason for the improvement.

Figure 3.2 Comparison of reaction progress for reaction of 1-hexanol and 1-pentylamine.

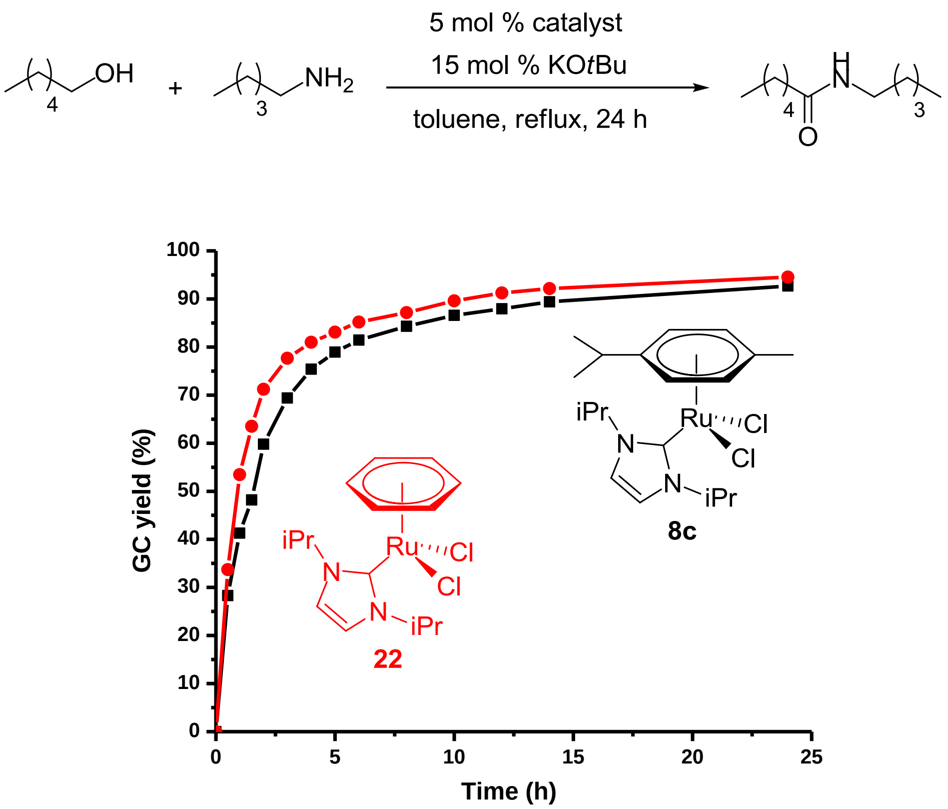


Figure 3.3 Comparison of reaction progress monitored by GC (entry 4 in Table 3.5).

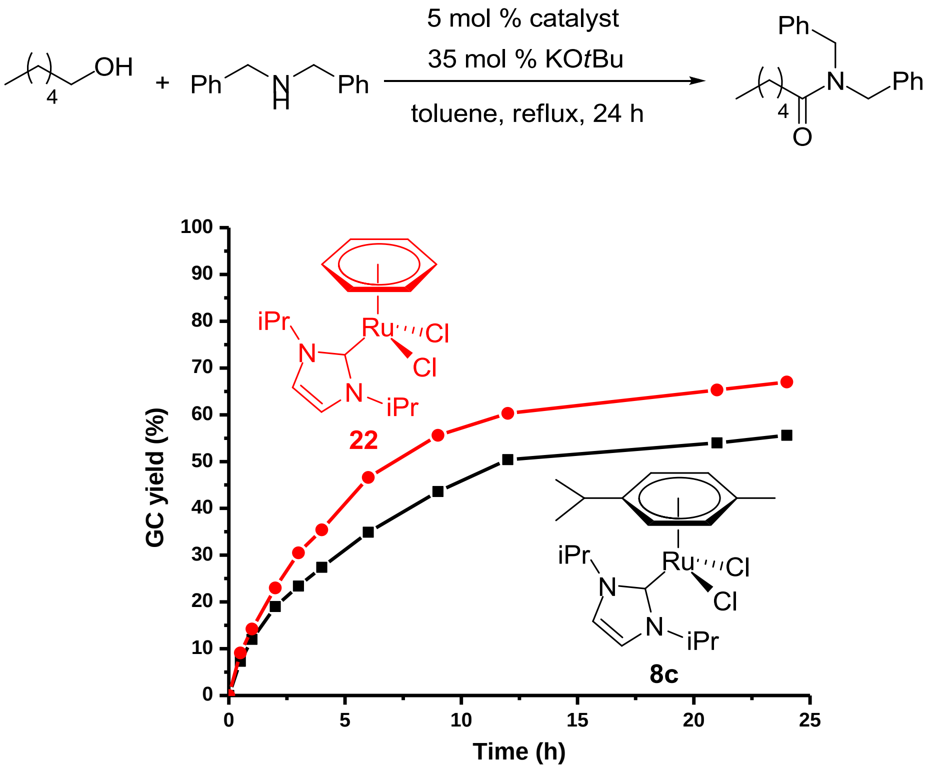
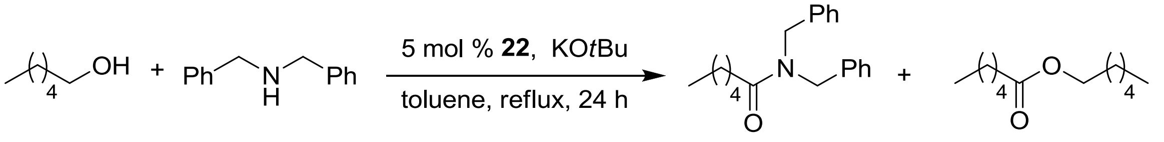


Table 3.6 Reaction of 1-hexanol and dibenzylamine catalyzed by **22** with different amount of KO*t*Bu.



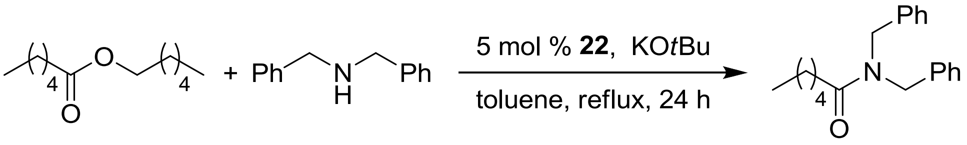
24e **20k** **25m** **26**

Entry	KO*t*Bu (equiv)	**25m** [%][a]	**26** [%][a]
1	0.15	33	61
2	0.20	34	50
3	0.25	50	10
4	0.30	51	8
5	0.35	60	< 3
6	0.40	44	< 1
7	0.60	30	< 1
8	1.00	11	< 1

[a] Isolated yields.

Next, we noticed that the increased amount of KO*t*Bu was required. Previously, there was no significant formation of **25m** with 5 mol % complex **8a** or **8c** and 15-20 mol % of KO*t*Bu. The improved conversion in Figure 3.3, even with **8c**, strongly implied that the increased amount of the strong base might be the key of the improvement. The role of a catalytic amount of a strong base was suggested to activate [Ru]Cl_2-type precatalysts by generating [Ru]H_2 species from alkoxides and the precatalysts.[17] However, the increased amounts of the base in this study, compared to those used in the primary amine amidations, implied that there might be another role of the base. Product distribution depending on the amount of the base was thoroughly investigated with the reaction between **24e** and **20k** catalyzed by **22** (Table 3.6). It was found that as the amount of KO*t*Bu increased up to 35 mol %, the yield of the desired product **25m** increased while that of the major by-product **26** decreased, which means the increased amount of KO*t*Bu either decreased the formation of **26** or promoted the reaction between **26** and **20k** to give **25m** (Table 3.6). The Ru catalyzed formation of esters from alcohols has been well documented.[10f,44] It was also reported as one of side reactions on the Ru catalyzed amide and cyclic imide syntheses from alcohols.[13,19,39]

Table 3.7 Reaction of an ester and dibenzylamine catalyzed by **22** with different amount of KO*t*Bu.



26 **20k** **25m**

Entry	Precatalyst	KO*t*Bu (equiv)	Yield of **25m** (%)[a]
1	**22**	0.00	<1
2	**22**	0.10	<1
3	**22**	0.20	6
4	**22**	0.30	39
5	**22**	0.35	46
6	**22**	0.40	59
7	**22**	0.45	44
8	**22**	0.50	40
9	**22**	0.60	31
10	**22**	1.0	10
11	-	0.40	<1

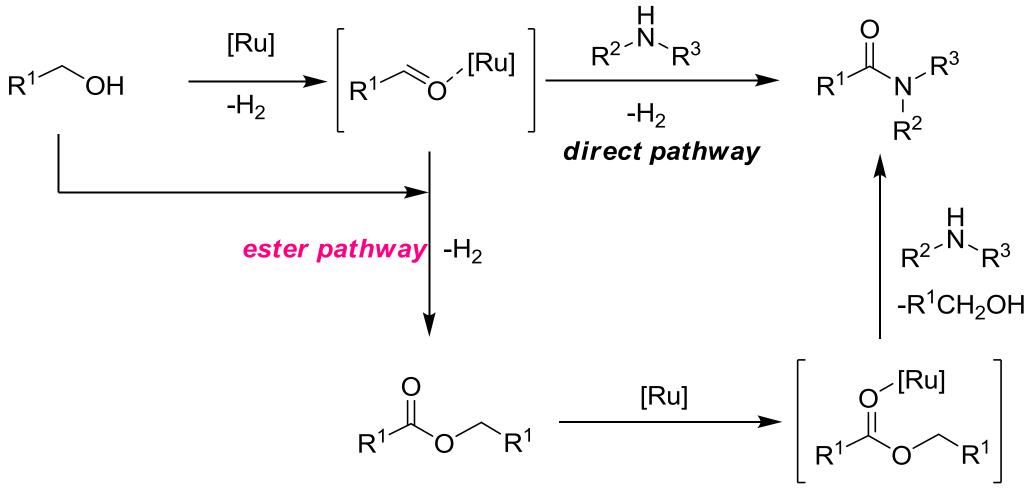
[a] Isolated yields.

Amide synthesis from esters usually requires stoichiometric amount of promoters or metal mediators.[48] Recently, a few catalytic amide formation reactions from esters and amines have also been reported including the very recent report using dearomatized

Ru-pincer complexes by Milstein and co-workers.[49] NHC-based Ru catalytic systems developed for the amide synthesis from alcohols and amines were reported not to be efficient for the amide formation from esters and amines.[13-14,16] The less efficient amidation of esters under the reported catalytic conditions using 15-20 mol % of a strong base were confirmed again by entry 3 in Table 3.7.[16] However, when an increased amount of KO*t*Bu was used, the amidation from esters worked with moderate yields (entries 4-8, Table 3.7). The optimal amount of the base, 0.3-0.5 equiv, was close to our current conditions for the secondary amine amidation.

Therefore, we believe that in the case of sterically hindered secondary amine amidation where direct amidation is less efficient, involvement of an ester intermediate and its conversion to the amide product with help of a catalytic intermediate, presumably generated by a Ru-NHC complex and an increased amount of a base, is essential for the improvement. The exact nature of the catalytic intermediate and the precise role of the increased amount of the base are currently unclear. Revised pathways for the amidation of alcohols with amines were suggested in Scheme 3.2.[50] Investigation of the amidation of esters with the NHC-based Ru catalytic systems is in progress.

Scheme 3.2 Proposed pathways for the direct amidation of alcohols with amines.



3.3 Conclusion

The direct amidation of alcohols with challenging secondary amines were achieved with a well-defined *N*-heterocyclic carbene based ruthenium complex. Involvement of ester intermediates was suggested unlike the previous amidation with less sterically hindered alcohols and amines. The scope and the nature of catalysts for NHC-Ru catalyzed conversion from esters to amides is in progress.

3.4 Experimental section

3.4.1 General considerations

All reactions were carried out using standard Schlenk techniques or in an argon-filled glove box unless otherwise mentioned. ^{1}H and ^{13}C NMR spectra at 400 and 100 MHz, respectively, were recorded in $CDCl_3$ using tetramethylsilane as a reference. Chemical shifts were reported in ppm and coupling constants in Hz. GC analyses were carried out using dodecane as an internal standard. High resolution mass spectra were recorded using the electro spray ionization (ESI) mode.

3.4.2 Materials

1,3-Diisopropylimdazolium bromide,[16] hexyl hexanoate (**26**),[51] and compound **8c**[17] were prepared by the literature procedures. Alcohols and amines were purchased from commercial suppliers and used as received without further purification. Toluene was dried over a solvent purification system.

Synthesis of 22. A suspension of 1,3-diisopropylimdazolium bromide (106.4 mg, 0.46 mmol) and Ag_2O (64.0 mg, 0.28 mmol) in CH_2Cl_2 was stirred at room temperature in dark for 2 h. The mixture was then filtered through a plug of Celite, followed by the addition of $[RuCl_2(benzene)]_2$ (115.0 mg, 0.23 mmol). The reaction mixture was stirred at room temperature for 4 h and then filtered through Celite. The solvent was removed under vacuum. Washing the crude product with diethyl ether (3×5 mL) afforded **22** as an orange powder. Yield: 85% (156.8 mg, 0.39 mmol). Mp 219 °C dec; ^1H NMR (CD_2Cl_2): δ 7.17 (s, 2H), 5.53 (s, 6H), 5.50-5.35 (m, 2H), 1.55-1.25 (m, 12H); ^{13}C NMR (CD_2Cl_2): *δ* 170.1, 119.7, 86.5, 52.8, 25.5, 24.6. Anal. Calcd for $C_{15}H_{22}Cl_2N_2Ru$ (**3**): C, 44.78; H, 5.51; N, 6.96. Found: C, 44.65; H, 5.12; N, 6.64.

3.4.3 General procedure for amide synthesis

Inside an argon-filled glovebox, compound **22** (10.0 mg, 0.025 mmol), KO*t*Bu (15-35 mol %) and toluene (0.6 mL) were added to an oven-dried Schlenk tube. The Schlenk tube was taken out of the glovebox before the alcohol (0.50 mmol) and the amine (0.55 mmol) were added. Then the mixture was heated to reflux under argon atmosphere for 24 h. The reaction mixture was cooled down to room temperature and the solvent was removed *in vacuo*. The residue was purified by silica gel flash column chromatography to afford the amide.

***N*-Benzyl-2-phenylacetamide (25a).**[16] Purified by silica gel chromatography (Hex :

EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 92%. ^{1}H NMR ($CDCl_3$): δ 7.39-7.26 (m, 10H), 5.78 (bs, 1H), 4.41 (d, 2H, *J* = 5.9Hz), 3.62 (s, 2H).

***N*-Hexyl-2-phenylacetamide (21m).**[16] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 90%. ^{1}H NMR ($CDCl_3$): δ 7.35-7.26 (m, 5H), 5.35 (bs, 1H), 3.56 (s, 2H), 3.19 (q, 2H, *J* = 6.8 Hz), 1.43-1.37 (m, 2H), 1.29-1.17 (m, 6H), 0.85 (t, 3H, *J* = 6.8 Hz).

***N*-Benzylfuran-2-carboxamide (21f).** Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 80%. m.p.: 112–113 °C. ^{1}H NMR ($CDCl_3$): δ 7.40 (s, 1H), 7.38-7.20 (m, 5H), 7.14-7.12 (m, 1H), 6.74 (s, 1H), 6.51-6.47 (m, 1H), 4.60 (d, 2H, *J* = 5.9 Hz). ^{13}C NMR ($CDCl_3$): 158.4, 148.0, 144.1, 138.2, 128.9, 128.0, 127.8, 114.5, 112.3, 43.3; HRMS-ESI (m/z): [M + H^+] calcd for $C_{12}H_{12}NO_2$, 202.0868; found, 202.0872.

Piperidin-2-one (25b).[16] Purified by silica gel chromatography (CH_2Cl_2 : MeOH = 20 : 1) to afford the desired product as a white solid. Isolated yield: 90%. ^{1}H NMR ($CDCl_3$): δ 7.52 (bs, 1H), 3.19-3.16 (m, 2H), 2.21 (t, 2H, *J* = 6.4 Hz), 1.72-1.56 (m, 4H).

***N*-Benzyl-2-methylbutanamide (25c).**[16] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 66%. ^{1}H NMR ($CDCl_3$): δ 7.30-7.25 (m, 5H), 5.67 (bs, 1H), 4.51-4.41 (m, 2H), 2.16-2.08 (m, 1H), 1.76-1.64 (m, 1H), 1.51-1.40 (m, 1H), 1.17 (d, 3H, *J* = 6.8 Hz), 0.91 (t, 3H, *J* = 7.2 Hz).

***N*-(Heptan-2-yl)-2-phenylacetamide (25d).**[20] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 70%. ^{1}H NMR ($CDCl_3$): δ 7.32-7.20 (m, 5H), 5.38 (d, 1H, *J* = 7.8 Hz), 3.95-3.87 (m, 1H), 3.50 (s, 2H), 1.29-1.17 (m, 8H), 1.01 (d, 3H, *J* = 6.9 Hz), 0.82 (t, 3H, *J* = 6.8 Hz).

2-Phenyl-1-(piperidin-1-yl)ethanone (25e).[20] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a colorless viscous liquid. Isolated yield: 92%. ^{1}H NMR (CDCl$_3$): δ 7.26-7.19 (m, 5H), 3.68 (s, 2H), 3.52 (t, 2H, J = 5.9 Hz), 3.31 (t, 2H, J = 5.5 Hz), 1.52-1.46 (m, 4H), 1.30-1.26 (m, 2H).

1-Morpholino-2-phenylethanone (25f).[16] Purified by silica gel chromatography (Hex : EA = 1 : 2) to afford the desired product as a white solid. Isolated yield: 86%. ^{1}H NMR (CDCl$_3$): δ 7.34-7.22 (m, 5H), 3.73 (s, 2H), 3.63 (s, 4H), 3.48-3.41 (m, 4H).

***N*-Benzyl-*N*-methyl-2-phenylacetamide (25g).**[16] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a colorless clear oil. Isolated yield: 90%. 1 : 1.1 mixture of rotamers. ^{1}H NMR (CDCl$_3$) (major rotamer): δ 7.31-7.21 (m, 9H), 7.10-7.08 (m, 1H), 4.60 (s, 2H), 3.78 (s, 2H), 2.88 (s, 3H); ^{1}H NMR (CDCl$_3$) (minor rotamer): δ 7.31-7.21 (m, 9H), 7.10-7.08 (m, 1H), 4.51 (s, 2H), 3.75 (s, 2H), 2.94 (s, 3H).

***N*-Methyl-*N*-phenethyl-2-phenylacetamide (25h).** Purified by silica gel column chromatography (Hex : EA = 3 : 1) to afford the desired product as a pale yellow clear oil. Yield: 87%. 1 : 1.1 mixture of rotamers. ^{1}H NMR (CDCl$_3$) (major rotamer): δ 7.38-7.02 (m, 10H), 3.68 (s, 2H), 3.60 (t, 2H, J = 7.6 Hz), 2.84 (s, 3H), 2.83 (t, 2H, J = 7.6 Hz); ^{1}H NMR (CDCl$_3$) (minor rotamer): δ 7.38-7.02 (m, 10H), 3.49 (t, 2H, J = 7.3 Hz), 3.44 (s, 2H), 2.98 (s, 3H), 2.72 (t, 2H, J = 7.3 Hz). ^{13}C NMR (CDCl$_3$): δ 171.1, 171.0, 139.2, 138.3, 135.4, 135.1, 129.0, 128.9, 128.8, 128.6, 127.0, 126.9, 126.8, 126.4, 52.2, 50.3, 41.5, 40.8, 36.7, 34.9, 33.8, 33.7. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{17}H_{20}NO$, 254.1545; found, 254.1547.

***N*-Hexyl-*N*-methylhexanamide (25i).** Purified by silica gel column chromatography (Hex : EA = 5 : 1) to afford the desired product as a colorless clear oil. Yield: 81%. 1: 1.05 mixture of rotamers. ^{1}H NMR (CDCl$_3$) (major rotamer): δ 3.25 (t, 2H, J = 7.6 Hz), 2.91 (s, 3H), 2.40-2.20 (m, 2H), 1.75-1.42 (m, 4H), 1.40-1.20 (m, 10H), 1.00-0.80 (m, 6H); ^{1}H NMR (CDCl$_3$) (minor rotamer): δ 3.35 (t, 2H, J = 7.5 Hz), 2.97 (s, 3H), 2.40-2.20

(m, 2H), 1.75-1.42 (m, 4H), 1.40-1.20 (m, 10H), 1.00-0.80 (m, 6H). ^{13}C NMR (CDCl$_3$): δ 173.2, 173.1, 50.2, 47.8, 35.5, 33.7, 33.5, 33.1, 31.9, 31.8, 31.7, 31.6, 28.6, 27.4, 26.6, 26.5, 25.3, 25.0, 22.7, 22.6, 14.2, 14.1. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{13}H_{28}NO$, 214.2171; found, 214.2178.

***N*-Benzyl-*N*-methylbenzamide (25j).**[38d] Purified by silica gel column chromatography (Hex : EA = 4 : 1) to afford the desired product as a colorless clear oil. Yield: 80%. ^{1}H NMR (CDCl$_3$): δ 7.47-7.16 (m, 10H), 4.76 (s, 1H), 4.51 (s, 1H), 3.02 (s, 1.5H), 2.85 (s, 1.5H).

***N*-Benzyl-*N*-methyl-4-methoxybenzamide (25k).**[38d] Purified by silica gel column chromatography (Hex : EA = 3 : 1) to afford the desired product as a colorless clear oil. Yield: 75%. ^{1}H NMR (CDCl$_3$): δ 7.46-6.88 (m, 9H), 4.73 (s, 1H), 4.59 (s, 1H), 3.81 (s, 3H), 2.97 (s, 3H).

***N*-Benzyl-*N*-methyl-4-fluorobenzamide (25l).**[38d] Purified by silica gel column chromatography (Hex : EA = 3 : 1) to afford the desired product as a colorless clear oil. Yield: 47%. ^{1}H NMR (CDCl$_3$): δ 7.49-7.08 (m, 9H), 4.75 (s, 1H), 4.52 (s, 1H), 3.04 (s, 1.5H), 2.88 (s, 1.5H).

***N,N*-Dibenzylhexanamide (25m).** Purified by silica gel column chromatography (Hex : EA = 10 : 1) to afford the desired product as a pale yellow clear oil. Yield: 60%. ^{1}H NMR (CDCl$_3$): δ 7.45-7.02 (m, 10 H), 4.60 (s, 2H), 4.44 (s, 2H), 2.41 (t, 2H, J = 7.6 Hz), 1.72 (quint, 2H, J = 7.6 Hz), 1.40-1.20 (m, 4H), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR (CDCl$_3$): δ 173.9, 137.7, 136.8, 129.1, 128.7, 128.4, 127.7, 127.5, 126.5, 50.1, 48.2, 33.4, 31.8, 25.3, 22.7, 14.1. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{20}H_{26}NO$, 296.2014; found, 296.2015.

***N,N*-Dibenzyl-2-phenylacetamide (25n).** Purified by silica gel column chromatography (Hex : EA = 7 : 1) to afford the desired product as a pale yellow clear oil. Yield: 40%. ^{1}H NMR (CDCl$_3$): δ 7.45-7.02 (m, 15 H), 4.61 (s, 2H), 4.43 (s, 2H), 3.79 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 171.8, 137.5, 136.6, 135.2, 129.2, 129.0, 128.9, 128.8, 128.5, 127.9, 127.6, 127.1, 126.6, 50.4, 48.4, 41.2. HRMS-ESI (m/z): [M + H^+] calcd for $C_{22}H_{22}NO$: 316.1701, found, 316.1702.

***N*-Benzyl-*N*-ethylhexanamide (25o).** Purified by silica gel column chromatography (Hex : EA = 7 : 1) to afford the desired product as a pale yellow clear oil. Yield: 60%. 1 : 1.3 mixture of rotamers. ^{1}H NMR ($CDCl_3$) (major rotamer): δ 7.38-7.02 (m, 5H), 4.56 (s, 2H), 3.23 (q, 2H, *J* = 7.2 Hz), 2.34 (t, 2H, *J* = 7.8 Hz), 1.80-1.50 (m, 2H), 1.42-1.16 (m, 4H), 1.15-1.02 (m, 3H), 1.00-0.75 (m, 3H); ^{1}H NMR ($CDCl_3$) (minor rotamer): δ 7.38-7.02 (m, 5H), 4.48 (s, 2H), 3.38 (q, 2H, *J* = 7.2 Hz), 2.27 (t, 2H, *J* = 7.8 Hz), 1.80-1.50 (m, 2H), 1.42-1.16 (m, 4H), 1.15-1.02 (m, 3H), 1.00-0.75 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 173.4, 173.2, 138.3, 137.4, 129.0, 128.6, 128.1, 127.6, 127.3, 126.4, 50.7, 47.8, 41.7, 41.0, 33.5, 33.2, 31.9, 31.8, 25.4, 25.2, 22.7, 22.6, 14.2, 14.1, 13.9, 12.9. HRMS-ESI (m/z): [M + H^+] calcd for $C_{15}H_{24}NO$, 234.1858; found, 234.1858.

***N*-Benzyl-*N*-phenethylhexanamide (25p).** Purified by silica gel column chromatography (Hex : EA = 7 : 1) to afford the desired product as a pale yellow clear oil. Yield: 43%. 1 : 1.05 mixture of rotamers. ^{1}H NMR ($CDCl_3$) (major rotamer): δ 7.40-7.02 (m, 10H), 4.35 (s, 2H), 3.56 (t, 2H, *J* = 7.6 Hz), 2.85 (t, 2H, *J* = 7.6 Hz), 2.31 (t, 2H, *J* = 7.5 Hz), 1.75-1.55 (m, 2H), 1.40-1.20 (m, 4H), 1.00-0.80 (m, 3H); ^{1}H NMR ($CDCl_3$) (minor rotamer): δ 7.40–7.02 (m, 10 H), 4.61 (s, 2H), 3.43 (t, 2H, *J* = 7.6 Hz), 2.79 (t, 2H, *J* = 7.6 Hz), 2.22 (t, 2H, *J* = 7.8 Hz), 1.75-1.55 (m, 2H), 1.40-1.20 (m, 4H), 1.00-0.80 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 173.7, 173.5, 139.5, 138.4, 138.0, 137.2, 129.0, 129.0, 128.9, 128.9, 128.7, 128.6, 128.3, 127.7, 127.5, 126.9, 126.5, 52.0, 48.7, 48.5, 48.3, 35.2, 34.2, 33.5, 33.1, 31.8, 31.7, 25.3, 25.2, 22.7, 14.2, 14.1. HRMS-ESI (m/z): [M + H^+] calcd for $C_{21}H_{28}NO$, 310.2171; found, 310.2173.

2-Phenyl-*N,N*-dipropylacetamide (25q). Purified by silica gel column chromatography (Hex : EA = 7 : 1) to afford the desired product as a colorless clear oil. Yield: 44%. ^{1}H NMR (CDCl$_3$): δ 7.40-7.15 (m, 5H), 3.70 (s, 2H), 3.29 (t, 2H, J = 7.5 Hz), 3.18 (t, 2H, J = 7.8 Hz), 1.69-1.41 (m, 4H), 0.95-0.75 (m, 6H); ^{13}C NMR (CDCl$_3$): δ 170.7, 135.7, 128.8, 128.7, 126.8, 50.1, 47.7, 41.1, 22.3, 21.0, 11.6, 11.4. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{14}H_{22}NO$, 220.1701; found, 220.1696.

Phenethyl 2-phenylacetate (27).[14] Purified by silica gel column chromatography (Hex : EA = 10 : 1) to afford the desired product as a colorless clear oil. ^{1}H NMR (CDCl$_3$): δ 7.33-7.14 (m, 10H), 4.30 (t, 2H, J = 7.0 Hz), 3.60 (s, 2H), 2.91 (t, 2H, J = 7.0 Hz).

4-Methoxybenzyl 4-methoxybenzoate (28).[52] Purified by silica gel column chromatography (Hex : EA = 10 : 1) to afford the desired product as a colorless clear oil. ^{1}H NMR (CDCl$_3$): δ 8.01 (dd, 2H, J = 7.0, 1.9 Hz), 7.38 (dd, 2H, J = 6.7, 1.8 Hz), 6.92-6.88 (m, 4H), 5.27 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H).

3.5 Appendices

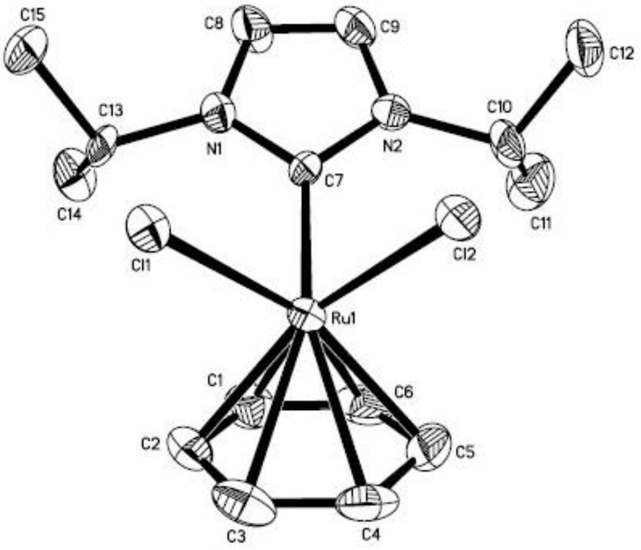


Table 3.5.1 Crystal data and structure refinement for **22**·$CHCl_3$.

Identification code	**22**·$CHCl_3$	
Empirical formula	C16 H23 Cl5 N2 Ru	
Formula weight	521.68	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.9375(3) Å	= 90°.
	b = 15.2834(4) Å	= 95.8110(10)°.
	c = 15.6299(5) Å	= 90°.
Volume	2124.00(11) Å^3	
Z	4	
Density (calculated)	1.631 Mg/m^3	

Absorption coefficient	1.369 mm^{-1}
F(000)	1048
Crystal size	0.34 x 0.32 x 0.20 mm^3
Theta range for data collection	2.52 to 33.28°.
Index ranges	-13<=h<=13, -15<=k<=23, -23<=l<=23
Reflections collected	41142
Independent reflections	8152 [R(int) = 0.0270]
Completeness to theta = 33.28°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7714 and 0.6533
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8152 / 23 / 264
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0251, wR2 = 0.0662
R indices (all data)	R1 = 0.0309, wR2 = 0.0691
Largest diff. peak and hole	1.263 and -0.796 e.Å^{-3}

Table 3.5.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **22** CHCl$_3$. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Ru(1)	9834(1)	8933(1)	8470(1)	12(1)
C(1)	9010(2)	7949(1)	7635(1)	13(1)
C(2)	11050(2)	6807(1)	7971(1)	22(1)
C(3)	12167(2)	6701(1)	7304(2)	35(1)
C(4)	10806(3)	5962(1)	8444(1)	36(1)
C(5)	8774(2)	6665(1)	6908(1)	18(1)
C(6)	7651(2)	7192(1)	6579(1)	17(1)
C(7)	6814(2)	8728(1)	6802(1)	17(1)
C(8)	6958(2)	9021(1)	5883(1)	24(1)
C(9)	5204(2)	8476(1)	6932(1)	26(1)
C(10)	10385(2)	9764(1)	7421(1)	20(1)
C(11)	11582(2)	9165(1)	7632(1)	21(1)
C(12)	12264(2)	9108(1)	8484(1)	26(1)
C(13)	11806(2)	9681(1)	9124(1)	29(1)
C(14)	10654(2)	10271(1)	8930(1)	27(1)
C(15)	9889(2)	10286(1)	8079(1)	24(1)
Cl(1)	7292(1)	9184(1)	8876(1)	16(1)
Cl(2)	10039(1)	7890(1)	9645(1)	18(1)
C(1S)	6349(13)	7058(7)	9591(5)	23(2)
Cl(3)	4511(3)	7401(1)	9697(3)	47(1)
Cl(4)	6436(2)	6646(2)	8559(2)	28(1)
Cl(5)	6963(6)	6259(4)	10359(3)	49(1)
C(1SA)	6533(16)	7057(9)	9649(6)	25(2)
Cl(3A)	4977(7)	7499(2)	10090(5)	64(2)
Cl(4A)	6114(10)	6734(4)	8590(3)	84(1)
Cl(5A)	7113(9)	6134(5)	10263(4)	58(1)
N(1)	9609(1)	7135(1)	7546(1)	15(1)
N(2)	7815(1)	7975(1)	7023(1)	14(1)

Table 3.5.3 Bond lengths [Å] and angles [°] for **22** ·CHCl$_3$.

Ru(1)-C(1)	2.0765(13)
Ru(1)-C(15)	2.1585(16)
Ru(1)-C(11)	2.1665(15)
Ru(1)-C(10)	2.1699(15)
Ru(1)-C(12)	2.1860(16)
Ru(1)-C(13)	2.2575(17)
Ru(1)-C(14)	2.2651(16)
Ru(1)-Cl(2)	2.4249(4)
Ru(1)-Cl(1)	2.4501(4)
C(1)-N(2)	1.3601(17)
C(1)-N(1)	1.3660(18)
C(2)-N(1)	1.4761(19)
C(2)-C(4)	1.514(3)
C(2)-C(3)	1.523(3)
C(2)-H(2)	1.0000
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(5)-C(6)	1.347(2)
C(5)-N(1)	1.3843(18)
C(5)-H(5)	0.9500
C(6)-N(2)	1.3846(18)
C(6)-H(6)	0.9500
C(7)-N(2)	1.4769(18)
C(7)-C(8)	1.522(2)
C(7)-C(9)	1.523(2)
C(7)-H(7)	1.0000
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(15)	1.409(2)

C(10)-C(11)	1.422(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.410(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.420(3)
C(12)-H(12)	0.9500
C(13)-C(14)	1.379(3)
C(13)-H(13)	0.9500
C(14)-C(15)	1.433(3)
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(1S)-Cl(4)	1.741(9)
C(1S)-Cl(3)	1.748(10)
C(1S)-Cl(5)	1.761(8)
C(1S)-H(1X)	0.894(19)
C(1S)-H(1Y)	1.00(4)
C(1SA)-Cl(4A)	1.732(11)
C(1SA)-Cl(3A)	1.749(10)
C(1SA)-Cl(5A)	1.755(11)
C(1SA)-H(1X)	0.80(4)
C(1SA)-H(1Y)	0.89(2)
C(1)-Ru(1)-C(15)	122.24(6)
C(1)-Ru(1)-C(11)	88.33(6)
C(15)-Ru(1)-C(11)	68.52(6)
C(1)-Ru(1)-C(10)	92.46(6)
C(15)-Ru(1)-C(10)	37.99(6)
C(11)-Ru(1)-C(10)	38.28(6)
C(1)-Ru(1)-C(12)	112.57(6)
C(15)-Ru(1)-C(12)	80.48(7)
C(11)-Ru(1)-C(12)	37.79(7)
C(10)-Ru(1)-C(12)	68.59(7)
C(1)-Ru(1)-C(13)	149.59(6)
C(15)-Ru(1)-C(13)	66.62(7)
C(11)-Ru(1)-C(13)	67.20(6)
C(10)-Ru(1)-C(13)	79.56(6)
C(12)-Ru(1)-C(13)	37.23(7)
C(1)-Ru(1)-C(14)	159.47(6)
C(15)-Ru(1)-C(14)	37.70(7)

C(11)-Ru(1)-C(14)	79.30(6)
C(10)-Ru(1)-C(14)	67.71(6)
C(12)-Ru(1)-C(14)	66.25(7)
C(13)-Ru(1)-C(14)	35.51(7)
C(1)-Ru(1)-Cl(2)	89.70(4)
C(15)-Ru(1)-Cl(2)	147.32(5)
C(11)-Ru(1)-Cl(2)	124.15(5)
C(10)-Ru(1)-Cl(2)	162.11(5)
C(12)-Ru(1)-Cl(2)	94.21(5)
C(13)-Ru(1)-Cl(2)	89.66(5)
C(14)-Ru(1)-Cl(2)	110.80(5)
C(1)-Ru(1)-Cl(1)	89.83(4)
C(15)-Ru(1)-Cl(1)	88.39(5)
C(11)-Ru(1)-Cl(1)	151.08(5)
C(10)-Ru(1)-Cl(1)	113.06(5)
C(12)-Ru(1)-Cl(1)	157.58(5)
C(13)-Ru(1)-Cl(1)	120.36(5)
C(14)-Ru(1)-Cl(1)	93.15(5)
Cl(2)-Ru(1)-Cl(1)	84.687(13)
N(2)-C(1)-N(1)	104.09(11)
N(2)-C(1)-Ru(1)	128.56(10)
N(1)-C(1)-Ru(1)	127.26(10)
N(1)-C(2)-C(4)	110.28(15)
N(1)-C(2)-C(3)	109.37(14)
C(4)-C(2)-C(3)	112.31(16)
N(1)-C(2)-H(2)	108.3
C(4)-C(2)-H(2)	108.3
C(3)-C(2)-H(2)	108.3
C(2)-C(3)-H(3A)	109.5
C(2)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(2)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
C(2)-C(4)-H(4A)	109.5
C(2)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
C(2)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5

H(4B)-C(4)-H(4C)	109.5
C(6)-C(5)-N(1)	106.96(13)
C(6)-C(5)-H(5)	126.5
N(1)-C(5)-H(5)	126.5
C(5)-C(6)-N(2)	106.73(13)
C(5)-C(6)-H(6)	126.6
N(2)-C(6)-H(6)	126.6
N(2)-C(7)-C(8)	110.04(12)
N(2)-C(7)-C(9)	109.26(13)
C(8)-C(7)-C(9)	111.83(13)
N(2)-C(7)-H(7)	108.5
C(8)-C(7)-H(7)	108.5
C(9)-C(7)-H(7)	108.5
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(15)-C(10)-C(11)	118.67(15)
C(15)-C(10)-Ru(1)	70.57(9)
C(11)-C(10)-Ru(1)	70.73(9)
C(15)-C(10)-H(10)	120.7
C(11)-C(10)-H(10)	120.7
Ru(1)-C(10)-H(10)	130.5
C(12)-C(11)-C(10)	120.19(15)
C(12)-C(11)-Ru(1)	71.86(9)
C(10)-C(11)-Ru(1)	70.99(8)
C(12)-C(11)-H(11)	119.9
C(10)-C(11)-H(11)	119.9
Ru(1)-C(11)-H(11)	129.7
C(11)-C(12)-C(13)	119.90(17)
C(11)-C(12)-Ru(1)	70.35(9)

C(13)-C(12)-Ru(1)	74.12(10)
C(11)-C(12)-H(12)	120.0
C(13)-C(12)-H(12)	120.0
Ru(1)-C(12)-H(12)	127.5
C(14)-C(13)-C(12)	120.74(16)
C(14)-C(13)-Ru(1)	72.55(10)
C(12)-C(13)-Ru(1)	68.65(9)
C(14)-C(13)-H(13)	119.6
C(12)-C(13)-H(13)	119.6
Ru(1)-C(13)-H(13)	132.2
C(13)-C(14)-C(15)	119.31(15)
C(13)-C(14)-Ru(1)	71.94(10)
C(15)-C(14)-Ru(1)	67.12(9)
C(13)-C(14)-H(14)	120.3
C(15)-C(14)-H(14)	120.3
Ru(1)-C(14)-H(14)	133.8
C(10)-C(15)-C(14)	120.89(16)
C(10)-C(15)-Ru(1)	71.44(9)
C(14)-C(15)-Ru(1)	75.19(10)
C(10)-C(15)-H(15)	119.6
C(14)-C(15)-H(15)	119.6
Ru(1)-C(15)-H(15)	125.6
Cl(4)-C(1S)-Cl(3)	109.1(6)
Cl(4)-C(1S)-Cl(5)	109.9(5)
Cl(3)-C(1S)-Cl(5)	112.0(6)
Cl(4)-C(1S)-H(1X)	112(5)
Cl(3)-C(1S)-H(1X)	106(4)
Cl(5)-C(1S)-H(1X)	107(6)
Cl(4)-C(1S)-H(1Y)	100(5)
Cl(3)-C(1S)-H(1Y)	121(5)
Cl(5)-C(1S)-H(1Y)	104(6)
H(1X)-C(1S)-H(1Y)	15(7)
Cl(4A)-C(1SA)-Cl(3A)	112.6(8)
Cl(4A)-C(1SA)-Cl(5A)	108.4(7)
Cl(3A)-C(1SA)-Cl(5A)	107.3(7)
Cl(4A)-C(1SA)-H(1X)	113(6)
Cl(3A)-C(1SA)-H(1X)	89(4)
Cl(5A)-C(1SA)-H(1X)	124(6)
Cl(4A)-C(1SA)-H(1Y)	104(6)

Cl(3A)-C(1SA)-H(1Y)	107(5)
Cl(5A)-C(1SA)-H(1Y)	117(7)
H(1X)-C(1SA)-H(1Y)	18(8)
C(1)-N(1)-C(5)	110.94(12)
C(1)-N(1)-C(2)	126.64(12)
C(5)-N(1)-C(2)	121.98(12)
C(1)-N(2)-C(6)	111.26(12)
C(1)-N(2)-C(7)	126.98(12)
C(6)-N(2)-C(7)	121.72(12)

Symmetry transformations used to generate equivalent atoms:

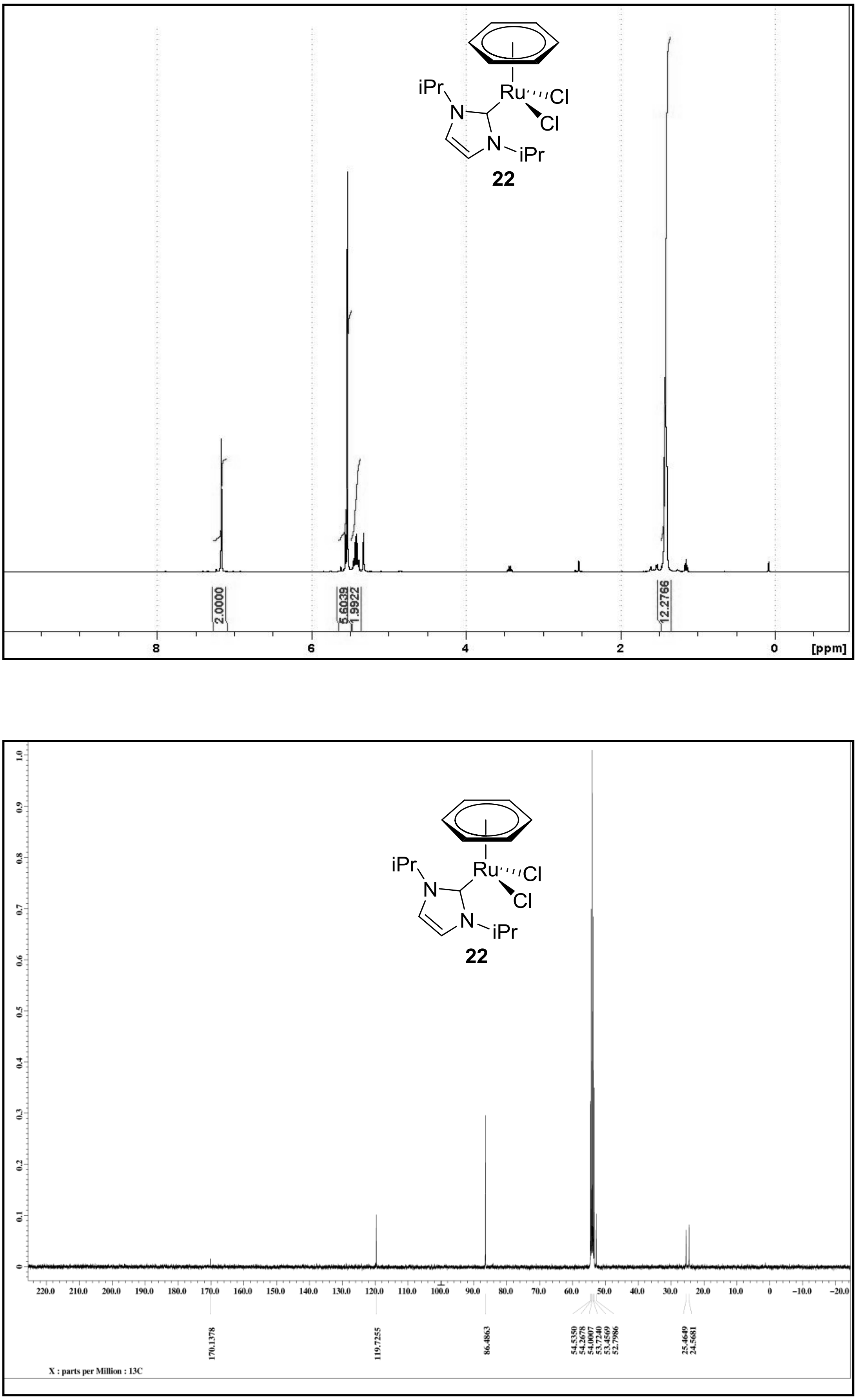
Table 3.5.4 Anisotropic displacement parameters ($Å^2$x 10^3) for **22**·$CHCl_3$. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[h^2 $a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}].

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ru(1)	14(1)	10(1)	12(1)	-2(1)	2(1)	-1(1)
C(1)	13(1)	12(1)	13(1)	-1(1)	2(1)	0(1)
C(2)	21(1)	17(1)	27(1)	-5(1)	-5(1)	7(1)
C(3)	22(1)	34(1)	49(1)	-12(1)	3(1)	11(1)
C(4)	53(1)	19(1)	33(1)	1(1)	-11(1)	10(1)
C(5)	22(1)	14(1)	17(1)	-5(1)	2(1)	-1(1)
C(6)	20(1)	17(1)	15(1)	-4(1)	1(1)	-3(1)
C(7)	16(1)	16(1)	18(1)	0(1)	-1(1)	3(1)
C(8)	33(1)	21(1)	18(1)	4(1)	-2(1)	2(1)
C(9)	15(1)	27(1)	35(1)	1(1)	1(1)	3(1)
C(10)	24(1)	20(1)	18(1)	4(1)	6(1)	-7(1)
C(11)	20(1)	22(1)	22(1)	-5(1)	9(1)	-5(1)
C(12)	16(1)	30(1)	31(1)	1(1)	1(1)	-5(1)
C(13)	30(1)	36(1)	20(1)	-3(1)	0(1)	-18(1)
C(14)	40(1)	18(1)	26(1)	-9(1)	16(1)	-14(1)
C(15)	28(1)	12(1)	33(1)	3(1)	13(1)	-1(1)
Cl(1)	18(1)	16(1)	15(1)	-3(1)	5(1)	-1(1)
Cl(2)	26(1)	15(1)	12(1)	2(1)	-2(1)	0(1)
C(1S)	27(3)	23(3)	20(3)	2(2)	2(2)	-7(2)
Cl(3)	40(1)	45(1)	59(1)	9(1)	25(1)	6(1)
Cl(4)	39(1)	31(1)	15(1)	-4(1)	6(1)	-15(1)
Cl(5)	67(1)	55(2)	23(1)	19(1)	-14(1)	-9(1)
C(1SA)	26(4)	31(5)	18(3)	-9(3)	8(3)	-5(3)
Cl(3A)	62(2)	50(1)	91(3)	14(1)	55(2)	15(1)
Cl(4A)	153(4)	69(2)	24(1)	-1(1)	-17(2)	-53(2)
Cl(5A)	82(2)	43(1)	47(2)	9(1)	-2(1)	10(1)
N(1)	16(1)	12(1)	17(1)	-3(1)	0(1)	1(1)
N(2)	14(1)	13(1)	14(1)	0(1)	1(1)	0(1)

Table 3.5.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **22**·$CHCl_3$.

	x	y	z	U(eq)
H(2)	11459	7253	8401	27
H(3A)	11842	6221	6913	52
H(3B)	13165	6568	7595	52
H(3C)	12215	7244	6976	52
H(4A)	10061	6058	8853	54
H(4B)	11758	5772	8754	54
H(4C)	10440	5511	8029	54
H(5)	8958	6082	6736	21
H(6)	6893	7052	6129	21
H(7)	7129	9223	7199	20
H(8A)	8017	9141	5815	36
H(8B)	6363	9553	5760	36
H(8C)	6588	8557	5484	36
H(9A)	4877	7995	6544	39
H(9B)	4543	8982	6809	39
H(9C)	5156	8290	7529	39
H(10)	9929	9812	6847	24
H(11)	11924	8802	7199	25
H(12)	13028	8686	8630	31
H(13)	12300	9659	9691	35
H(14)	10369	10663	9357	33
H(15)	9037	10654	7957	29
H(1X)	6940(60)	7530(30)	9700(50)	35
H(1Y)	7200(80)	7490(40)	9620(60)	37

Figure 3.5.1 ^{1}H NMR and ^{13}C NMR of **22**.



CHAPTER 4

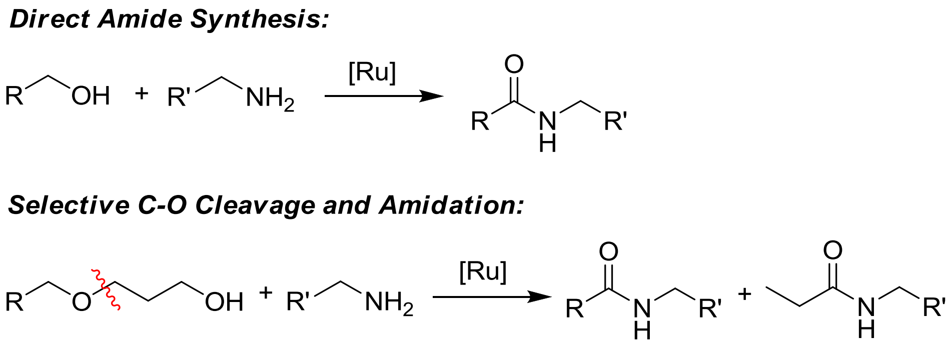
SELECTIVE CATALYTIC SP^3C-O BOND CLEAVAGE WITH C-N BOND FORMATION IN 3-ALKOXY-1-PROPANOLS

(This chapter has been published in *Organic Letters* **2012**, *14*, 2992.)

4.1 Introduction

Selective C–O bond activation in ethers is scientifically challenging and has great potential in organic synthesis. Since the pioneering Ni-catalyzed arylation of aryl or vinyl ethers by Wenkert and coworkers,[53] much attention has been paid to catalytic sp^2 C–O bond activation of aryl ethers for the potential substitution of aryl halides in the C–C and C–N bond formation reactions.[54,55] Compared to sp^2 C–O bond activation, not many cases of catalytic activation of etheric sp^3 C–O bonds have been reported.[55c,56-58] Most examples are with strained cyclic ethers,[57] alkyl C–O bonds with good leaving groups such as OTs and OMs,[58] or relatively reactive sp^3 C–O bond of allyl or benzyl ethers.[59] The challenges for sp^3 C-O cleavage in alkyl ethers lie in (1) the bond dissociation energy for an sp^3 C-O bond is relatively high; (2) it is difficult to distinguish two different sp^3 C-O bonds of in the ether; (3) Constructing C-C bonds after the C-O cleavage is hard to control.[59d]

Scheme 4.1 Observation of selective C-O cleavage with C-N bond formation.

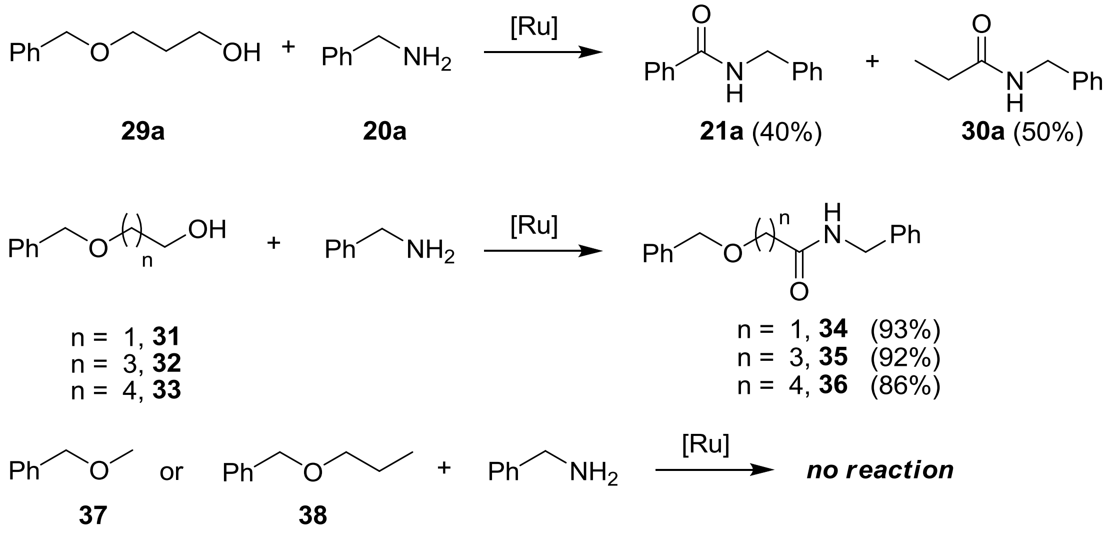


Direct amide synthesis from alcohols and amines catalyzed by transition metal complexes, an environmentally friendly and highly atom economical transformation which generates hydrogen gas as the sole by-product, has been recently highlighted.[7-9] Our group has been involved in the area by developing *N*-heterocyclic carbene (NHC) based Ru catalytic systems.[16-18,20,39] While investigating the scope of the reaction, we found that sp^3 C–O cleavage in alkyl ethers occurred in the reactions of 3-alkoxy-1-propanol derivatives and an amine with concurrent formation of C–N bonds (Scheme 4.1). To the best of our knowledge, this is the first catalytic C–N bond formation via sp^3 C–O bond cleavage. Interestingly, the cleavage occurred selectively in the C3–O position in 3-alkoxy-1-propanols even with 3-benzyloxy-1-propanol.

4.2 Results and discussion

When 3-benzyloxy-1-propanol (**29a**) was reacted with benzyl amine (**20a**) using an NHC Ru hydride-based catalytic system for the oxidative amide synthesis from alcohols and amines,[16] to our surprise, *N*-benzylbenzamide (**21a**) and *N*-benzylpropionamide (**30a)** were isolated in 40% and 50% yields, respectively, instead of the expected amide (Scheme 4.2). Noticeably, the C3–O bond was selectively cleaved with concurrent C–N bond formation instead of the more activated benzylic C–O bond. Inspired by the result, we focused on identifying the key structure for this unique C–O bond cleavage. 2-Benzyloxy-1-ethanol (**31**), 4-benzyloxy-1-butanol (**32**), and 5-benzyloxy-1-pentanol (**33**) were also tested under the same conditions, but only the uncleaved corresponding amides **34–36** were obtained in excellent yields (Scheme 4.2). In the cases of benzyl methyl ether (**37**) and benzyl propyl ether (**38**), no reaction happened (Scheme 4.2). These results indicated that a 3-alkoxy-1-propanol skeleton is necessary to result in the C–O bond cleavage.

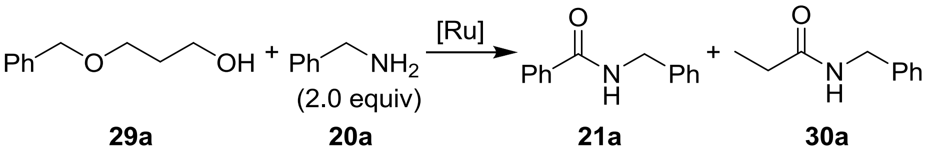
Scheme 4.2 Selective C–O bond cleavage in 3-alkoxy-1-propanol.[a]



[a]Reaction conditions: 1.0 equiv of alcohol or ether and 1.1 equiv of amine were used. [Ru] = 2.5 mol % [Ru(*p*-cymene)Cl_2]$_2$, 5 mol % *N*,*N*-diisopropylimidazolium bromide (**7b**), 5 mol % pyridine, and 15 mol % NaH, toluene, reflux, 24 h.

This catalytic C–O bond cleavage and amidation reaction of 3-benzyloxy-1-propanol (**29a**) with benzyl amine (**20a**) was further optimized (Table 4.1). The amount of NaH was important for the reaction, and 45 mol % of NaH showed the best productivity (entries 1-5). The reaction did not proceed without a Ru complex (entries 6-7). Different Ru sources were screened. The reported $RuCl_3$-based system[20] gave **21a** and **30a** in 76% and 60% yields, respectively, with the increased amount of NaH (entry 8). Although the reported $RuH_2(PPh_3)_4$ system worked more efficiently in the Ru-catalyzed oxidative amide and imide syntheses,[18,39] only low yields were given for the current amide formation via sp^3 C–O bond cleavage reaction (entry 9). [Ru(benzene)Cl_2]$_2$ with 45 mol % NaH was found to be the best combination for the Ru source and the amount of NaH (entry 10). The absence of acetonitrile resulted in slightly reduced activity (entry 11). Also, use of KO*t*Bu instead of NaH exhibited only moderate yields (entry 12). Replacement of the *N*-heterocyclic carbene (NHC) precursor (1,3-diisopropylimidazolium bromide, **7b**) with some phosphine ligands only provided limited yields (entries 13-15). The requirement of these ligands and a strong base has been well studied in the previous reports on the NHC-Ru catalyzed direct amidation.[14,16-18,20,39] The optimized catalytic system was identified as 5 mol % [Ru(benzene)Cl_2]$_2$, 5 mol % **7b**, 5 mol % acetonitrile, and 45 mol % NaH and used for the following study.

Table 4.1 Optimization of reaction conditions.[a]



Entry	Catalyst[b]	Ligand[b]	Ligand[b]	Base (mol %)	**21a** [%][c]	**30a** [%][c]
1	[Ru(*p*-cymene)Cl_2]$_2$	**7b**	pyridine	NaH (15)	43	49
2	[Ru(*p*-cymene)Cl_2]$_2$	**7b**	pyridine	NaH (30)	74	65
3	[Ru(*p*-cymene)Cl_2]$_2$	**7b**	pyridine	NaH (45)	93	75
4	[Ru(*p*-cymene)Cl_2]$_2$	**7b**	pyridine	NaH (60)	87	59
5	[Ru(*p*-cymene)Cl_2]$_2$	**7b**	pyridine	NaH (100)	30	25
6	None	**7b**		NaH (45)	0	0
7	None			NaH (45)	0	0
8	$RuCl_3$	**7b**	pyridine	NaH (45)	76	60
9	$RuH_2(PPh_3)_4$	**7b**	CH_3CN	NaH (45)	20	19
10	[Ru(benzene)Cl_2]$_2$	**7b**	CH_3CN	NaH (45)	99	87
11	[Ru(benzene)Cl_2]$_2$	**7b**		NaH (45)	83	76
12	[Ru(benzene)Cl_2]$_2$	**7b**	CH_3CN	KO*t*Bu (45)	44	45
13	[Ru(benzene)Cl_2]$_2$	PPh_3		NaH (45)	14	12
14	[Ru(benzene)Cl_2]$_2$	PCy_3		NaH (45)	25	11
15	[Ru(benzene)Cl_2]$_2$	dppb		NaH (45)	12	12

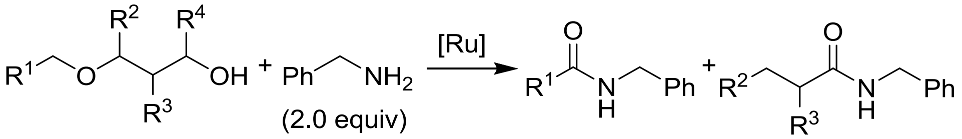
[a]Reaction conditions: 1.0 equiv of **29a** and 2.0 equiv of **20a**, toluene, reflux, 24 h. [b]5 mol %. [c]Determined by GC using dodecane as an internal standard.

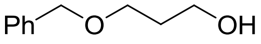
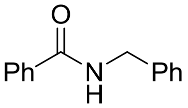
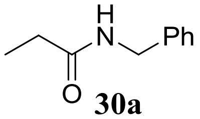
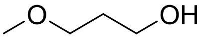
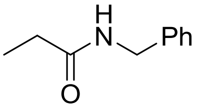
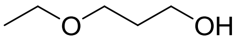
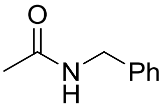
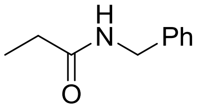
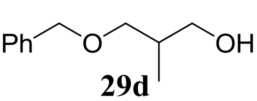
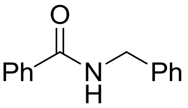
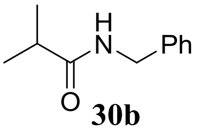
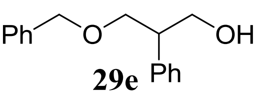
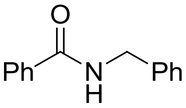
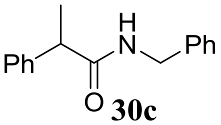
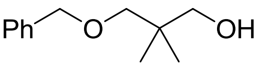
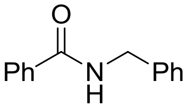
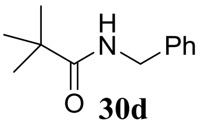
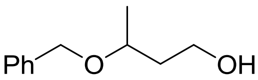
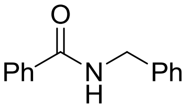
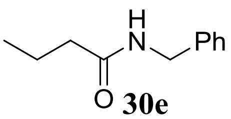
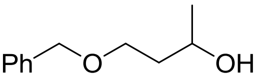
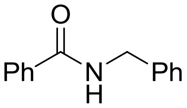
With the optimized condition in hand, the substrate scope of the reaction was studied (Table 4.2). 3-Benzyloxy-1-propanol (**29a**) reacted smoothly with **20a** to give **21a** and **30a** in 88% and 78% isolated yields, respectively (entry 1). 3-Methoxy-1-propanol (**29b**) gave **30a** in 71% yield and the other possible product, *N*-benzylformamide, was not observed (entry 2). (NHC)Ru-catalyzed formamide formation with methanol and amines has not been successful until now.[16-18,20,39] 3-Ethoxy-1-propanol (**29c**) yielded 51% of **39a** and 70% of **30a** in an open reaction condition under Ar flow (entry 3). The Ru catalyzed direct amide syntheses have been reported to perform in an open condition under Ar flow to facilitate removal of H_2.[12-23,39] As the boiling point of *in situ* generated ethanol, a likely C–O bond cleavage product, is low, the reaction was run in a sealed tube. Considerable improvement was achieved for the yield of **39a** (75% in a closed system vs 51% in an open system) and a comparable result was obtained for the yield of **30a** (70% in a closed system vs 71% in an open system (entry 3). These results suggested that either an open condition or a closed condition does not considerably affect the efficiency of the C–O bond cleavage. Substrates **29d-h** were selected to evaluate the effect of substituents on the C1-C3 positions. Comparable yield of **21a** with **29a** was obtained if 3-benzyloxy-2-methyl-1-propanol (**29d**) was used (entry 4), while slightly lower yield was observed in the case of 3-benzyloxy-2-phenyl-1-propanol (**29e**) (entry 5). However, C2-disubstituted 3-benzyloxy-2, 2-dimethyl-1-propanol (**29f**) was not reactive for the C-O cleavage (entry 6). Only 5% of the corresponding amide *N*-benzyl-3-benzyloxy-2, 2-dimethyl-1-propionamide was isolated. These results demonstrated that at least one hydrogen should exist at the C2 carbon of 3-alkoxy-1-propanol. A methyl substituent on the C3 position (**29g**) was effective for the C-O bond cleavage (entry 7). Substrate **29h** with a methyl group on the C1 position worked well to generate **21a**. However, the other part, likely, a cleaved secondary alcohol, 2-butanol (or ketone, 2-butanone), cannot participate in the amidation reaction. We could not detect 2-butanol, 2-butanone, or any C_4-related compound, presumably due to low boiling points of the possible products. Later in Scheme 4.5, we identified cleaved alcohols and an ester product from **29e**.

Only alkoxy groups are efficient for this transformation. Other groups such as 3-phenoxy-, 3-mesyloxy-, and 3-acetoxy- were not effective. Since those electron deficient groups were not reactive, electronic effect on the alkoxy group was investigated with **29a** derivatives with different substituents on the phenyl group (Table 4.3). Both electron-donating and electron-withdrawing substituents can afford the product **30a** in 60-83% yields. Substrates with more electron-rich alkoxy groups showed better reactivity (entries 2-5, Table 4.3). Therefore, electronic properties affected this reaction and electron-deficient alkoxy groups are less favored for the C–O cleavage.

Different amines were also screened (Table 4.4). Sterically less hindered primary aliphatic and benzyl amines worked effectively. Electronically different benzylamines did not significantly affect the yields, unlike electronically different 3-benzyloxy-1-propanols (entry 1 in Table 4.3 and entries 1-2 in Table 4.4). Sterically hindered primary amines and secondary amines gave lower yields as previously reported in the oxidative amidation from alcohols and amines.[7-9,12-23,39]

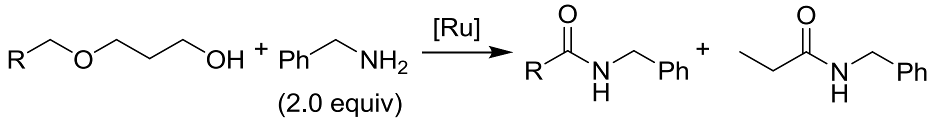
Table 4.2 Selective sp^3 C–O bond cleavage with C–N bond formation.[a]

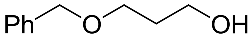
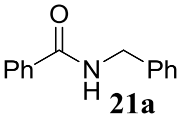
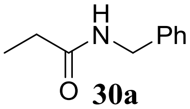
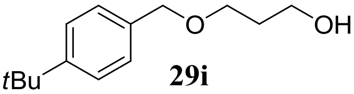
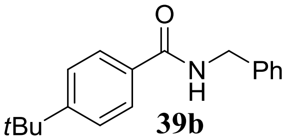
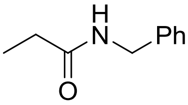
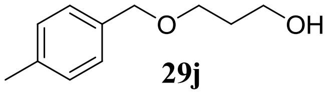
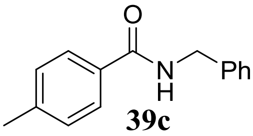
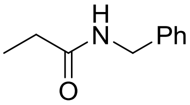
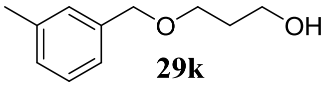
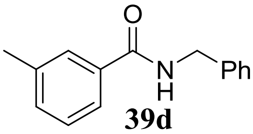
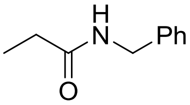
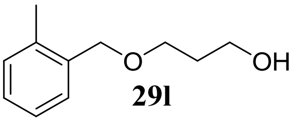
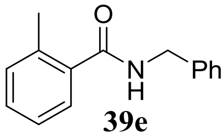
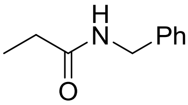
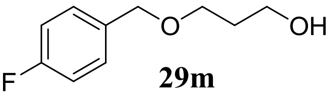
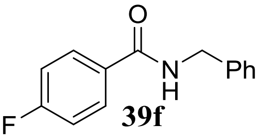
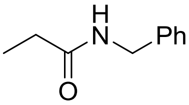
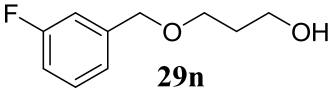
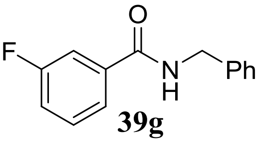
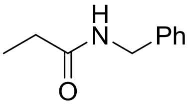
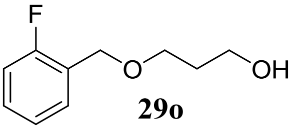
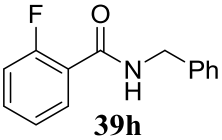
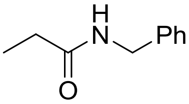
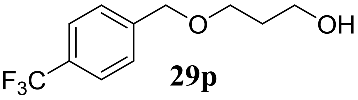
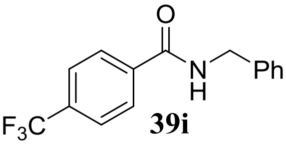
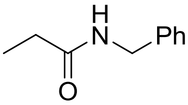


Entry	Alcohol	Amide[b]		Amide[b]	
1	 **29a**	 **21a**	88	 **30a**	78
2	 **29b**				71
3	 **29c**	 **39a**	51 (75[c])		70 (71[c])
4	 **29d**		86	 **30b**	65
5	 **29e**		77	 **30c**	56
6	 **29f**		0	 **30d**	0
7	 **29g**		69	 **30e**	80
8	 **29h**		82		

[a]Reaction conditions: **29** (1.0 equiv), **20a** (2.0 equiv), 2.5 mol % $[Ru(benzene)Cl_2]_2$, 5 mol % **7b**, 5 mol % acetonitrile, and 45 mol % NaH, toluene, reflux, 24 h. [b]Isolated yields. [c]The reaction was carried out in a sealed tube at 115 °C.

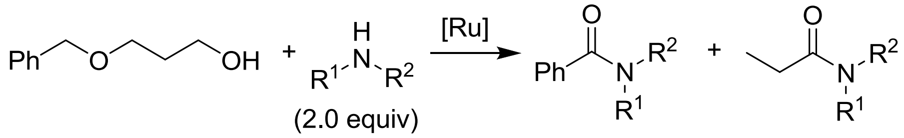
Table 4.3 Investigation of the electronic effect.[a]

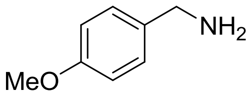
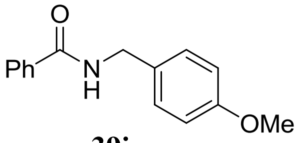
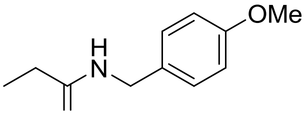
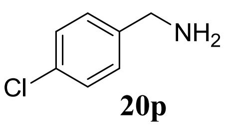
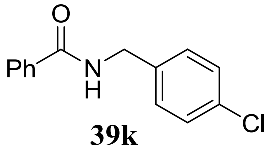
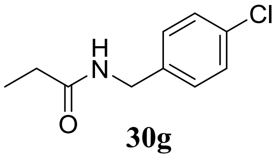
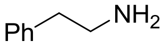
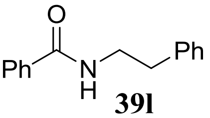
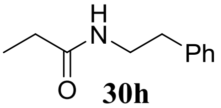
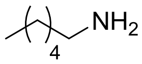
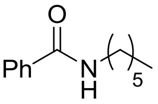
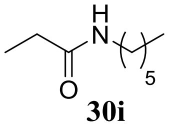
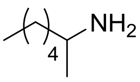
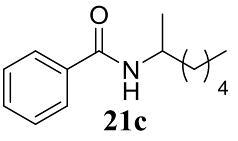
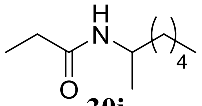
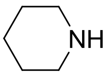
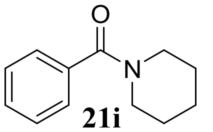
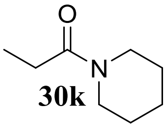
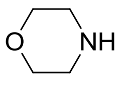
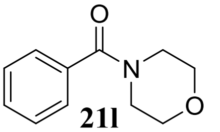
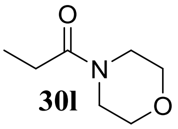
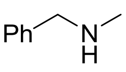
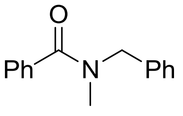
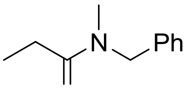


entry	alcohol	amide[b]		amide[b]	
1	 **29a**	 **21a**	88	 **30a**	78
2	 **29i**	 **39b**	92		83
3	 **29j**	 **39c**	88		79
4	 **29k**	 **39d**	89		77
5	 **29l**	 **39e**	60		80
6	 **29m**	 **39f**	68		68
7	 **29n**	 **39g**	62		60
8	 **29o**	 **39h**	20		66
9	 **29p**	 **39i**	41		60

[a]Reaction conditions: **29** (1.0 equiv), **20a** (2.0 equiv), 2.5 mol % [Ru(benzene)Cl_2]$_2$, 5 mol % **7b**, 5 mol % acetonitrile, and 45 mol % NaH, toluene, reflux, 24 h. [b]Isolated yields.

Table 4.4 Reactivity with different amines.^{a}

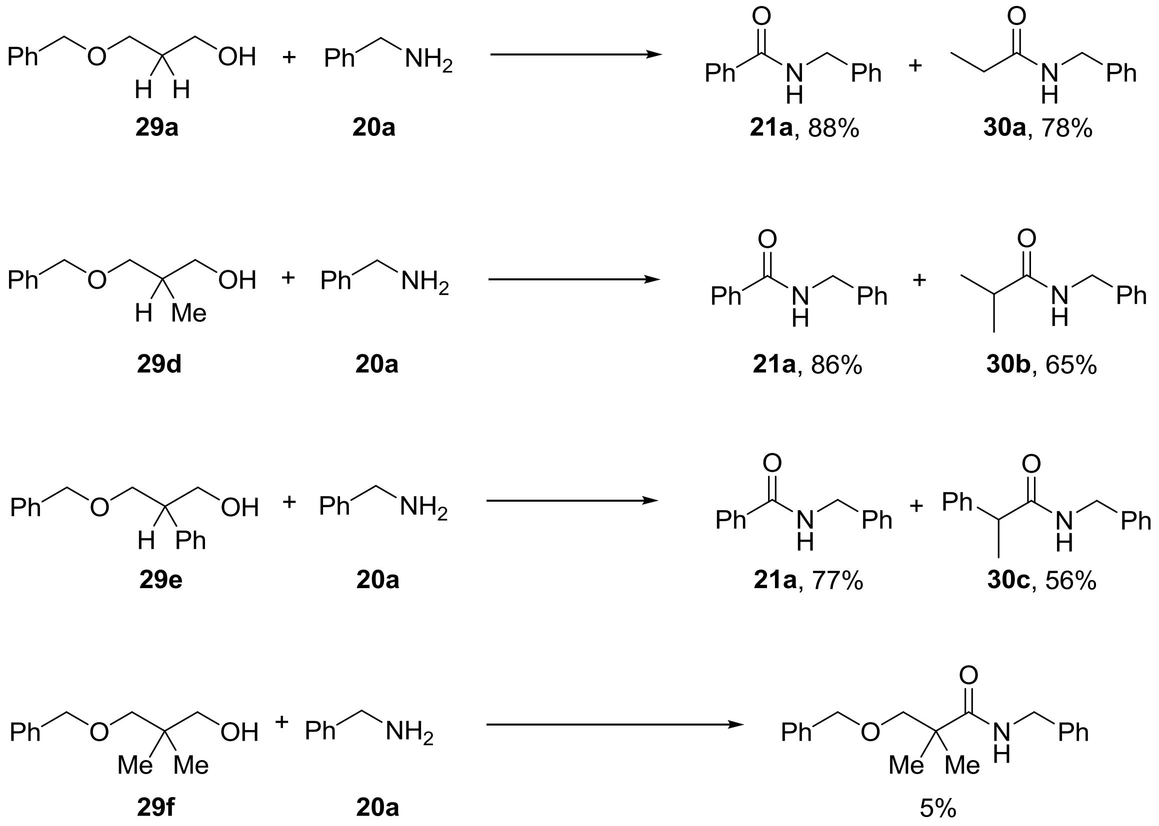


Entry	Alcohol	Amide^{b}		Amide^{b}	
1	 **20o**	 **39j**	76	 **30f**	66
2	 **20p**	 **39k**	71	 **30g**	52
3	 **20q**	 **39l**	70	 **30h**	65
4	 **20b**	 **21b**	81	 **30i**	73
5	 **20c**	 **21c**	21	 **30j**	21
6	 **20e**	 **21i**	60	 **30k**	45
7	 **20f**	 **21l**	61	 **30l**	50
8	 **20h**	 **25j**	58	 **30m**	66

^{a}Reaction conditions: **29a** (1.0 equiv), **20** (2.0 equiv), 2.5 mol % [Ru(benzene)Cl$_2$]$_2$, 5 mol % **7b**, 5 mol % acetonitrile, and 45 mol % NaH, toluene, reflux, 24 h. ^{b}Isolated yields.

Then we focused on studying deeply into the mechanism of this interesting sp^3 C-O bond cleavage. We observed the difference in reactivity of substrates with different substituents on the β-carbon of the OH group (Scheme 4.3). Replacement of one hydrogen on C2 position with a more bulky group such as a methyl (**29d**) and a phenyl group (**29e**) can still promote this transformation effectively although the yields were slightly lower. However, if both hydrogens were substituted with methyl groups (**29f**), no C-O bond cleavage happened and only the uncleavaged amide product was isolated in 5% yield. Therefore, at least one hydrogen should be on the β-carbon of the OH group and C-H cleavage must be involved in this transformation.

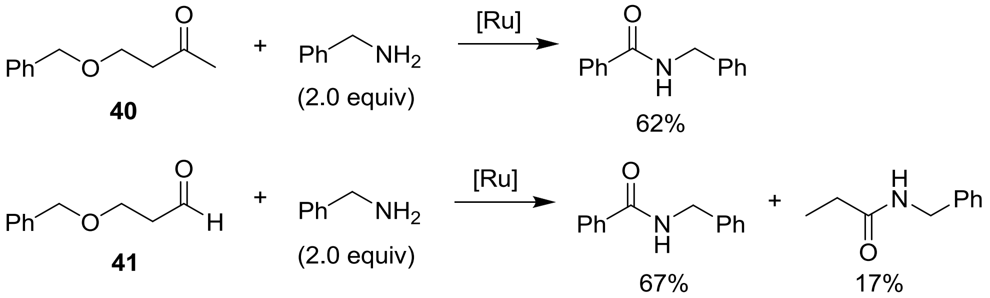
Scheme 4.3 Effect of substituents on C2 position.[a]



[a]Reaction conditions: **29** (1.0 equiv), **20a** (2.0 equiv), 2.5 mol % $[Ru(benzene)Cl_2]_2$, 5 mol % **7b**, 5 mol % acetonitrile, 45 mol % NaH, toluene, reflux, 24 h.

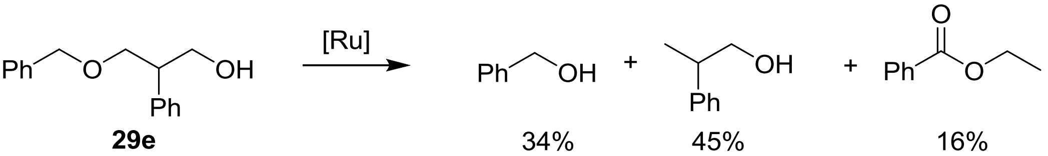
For further investigation, substrates **40** and **41** having a carbonyl group instead of an OH group were subjected to the reaction conditions. The two substrates also showed the selective C–O bond activation leading to the formation of the cleaved amides in good, but less yields than 3-alkoxy-1-propanols, presumably due to the more facile Ru-binding to oxygen when starting from alcohols (Scheme 4.4).[16-18,20,39]

Scheme 4.4 C–O bond cleavage with a ketone or an aldehyde.[a]



[a]Reaction conditions: **40** or **41** (1.0 equiv), **20a** (2.0 equiv), 2.5 mol % [Ru(benzene)Cl$_2$]$_2$, 5 mol % **7b**, 5 mol % acetonitrile, and 45 mol % NaH, toluene, reflux, 24 h.

Scheme 4.5 C–O bond cleavage without an amine.[a]



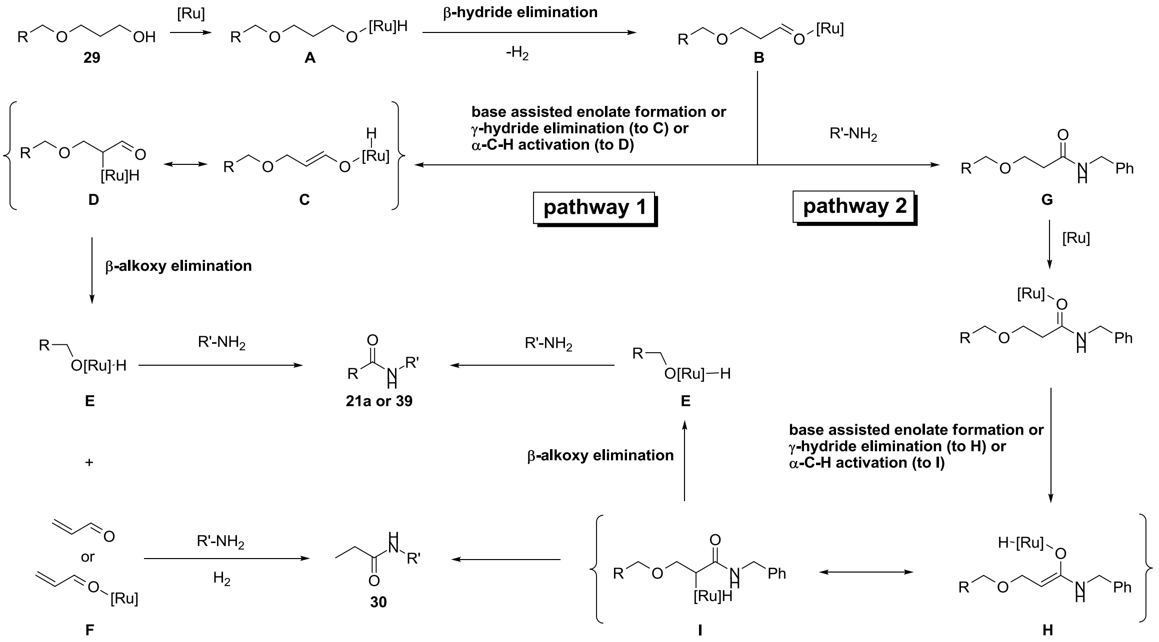
[a]Reaction conditions: **29e** (1.0 equiv), 2.5 mol % [Ru(benzene)Cl$_2$]$_2$, 5 mol % **7b**, 5 mol % acetonitrile, and 45 mol % NaH, toluene, reflux, 24 h.

Next, we tested the reaction of **29e** without amines under the same reaction conditions to check whether an amine is necessary for the C–O bond cleavage (Scheme 4.5). C–O bond cleavage occurred as we expected from the proposed mechanism. Esterification of benzyl alcohol was observed as well reported in other

Ru-catalyzed esterification of primary alcohols.[7,10f,44] For 2-phenyl-1-propanol, the corresponding ester product was not observed, presumably due to steric hindrance of the substrate and transfer hydrogenations between alcohols.

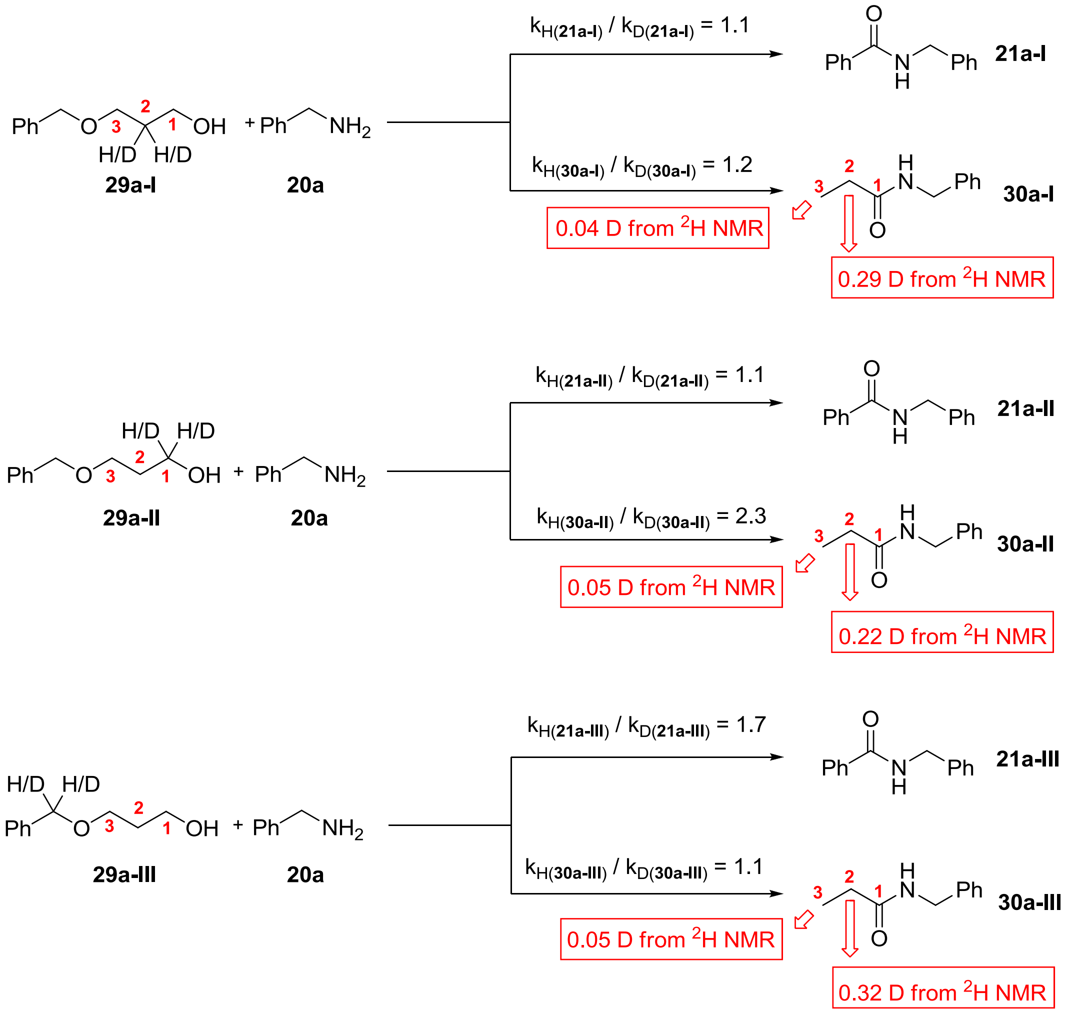
By the reasons of the unique reactivity of 3-alkoxy-1-propanols, requirement of at least one hydrogen on the β-carbon of the OH group, and well-reported dehydrogenation of alcohols to carbonyl compounds by Ru complexes, we proposed involvement of a Ru enolate complex in the process. Bergman and coworkers isolated Ru enolate complexes of both O-bound and C-bound forms.[60] It is proposed that subsequent β-alkoxy elimination, after generation of a C-bound Ru enolate complex, could explain the selective sp^3 C–O bond cleavage. Two possible pathways were presented in Scheme 4.6 based on the above investigations. The first step is the generation of the Ru alkoxide complex **A**, followed by β-alkoxy elimination to give the Ru-bound aldehyde species **B**. There are two possiblities after the formation of **B**. Pathway 1 is treatment of **B** with NaH to give O-bound Ru enolate **C**, which further isomerized to C-bound Ru enolate **D**. Alternatively, **C** could be formed by γ-hydride elimination **B**. **D** could be also directly generated by α-C–H activation of **B**.[61] The role of NaH is not clear. We think that it is related to generation of an active catalytic intermediate or/and assitance to formation of Ru enolate complexes. It was previously reported that an active catalytic intermediate for the direct amide synthesis, $[Ru]H_2$ or [Ru], could be formed from $[Ru]Cl_2$ and alkoxide generated by a strong base and a primary alcohol.[17] β-alkoxy elimination occurred to yield **E** and acrolein (or Ru-bound acrolein), which reacted with an amine to give the respective amides **39 (or 21a)** and **30**. Pathway 2 is the generation of the uncleavage amide **G**, which could be further transformed to Ru enolate **I**. β-alkoxy elimination of **I** afforded the amide **30** and the Ru alkoxide **E** which further reacted with benzyl amine to yield **39 (or 21a).**

Scheme 4.6 Two possible pathways of the sp^3 C-O cleavage reaction.



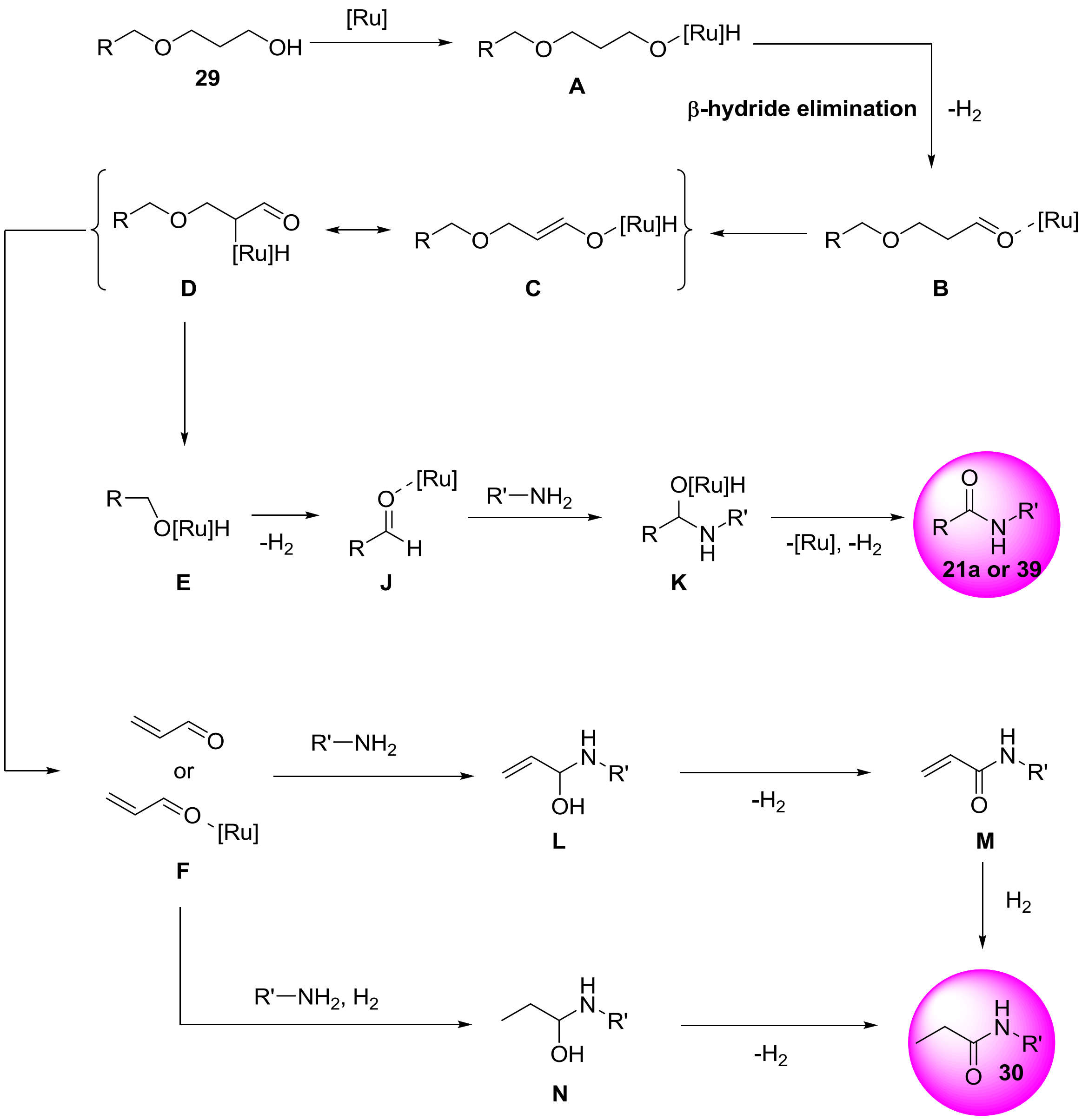
The major difference between the two pathways lies in whether C-O cleavage occurred before amide formation, so more experiments were performed to have a better understanding of the reaction mechanism. Firstly, kinetic isotope effect (KIE) experiments were performed (Scheme 4.7). No KIE was observed when the substrate **29a-I** was introduced, while different KIEs were observed for the formation of **21a-II** ($k_{H(\mathbf{21a\text{-}II})}/k_{D(\mathbf{21a\text{-}II})}$ = 1.1) and that of **30a-II** ($k_{H(\mathbf{30a\text{-}II})}/k_{D(\mathbf{30a\text{-}II})}$ = 2.3) in the case of **29a-II**. Different KIEs between **21a-II** and **30a-II** ruled out the possibility of pathway 2, so the plausible mechanism can be described in Scheme 4.8. The above KIE experiments also indicated that oxidation of the hemiaminal to the amide (either **L** to **M** or **N** to **30a**) not formation of the Ru bound aldehyde **B** from the Ru alkoxide **A** is the rate-determining step for the formation of **30a**. The substrate **29a-III** was also used for KIE experiments. KIE was found for formation of **21a-III** ($k_{H(\mathbf{21a\text{-}III})}/k_{D(\mathbf{21a\text{-}III})}$ = 1.7) and there was no KIE for formation of **30a-III** ($k_{H(\mathbf{30a\text{-}III})}/k_{D(\mathbf{30a\text{-}III})}$ = 1.1), which demonstrated that either transformation of **E** to the Ru-bound aldehyde **J** or the oxidation of the hemiaminal **K** to the amide product **21a** is the rate-determining step for the formation of **21a**. Deuterium-labeling experiments were also done (Scheme 4.7). There were 0.22 D (0.32 D) on C2 and 0.05 D (0.05 D) on C3 of the product **30a-II (30a-III**) if **29a-II** (**29a-III**) was employed from ^{2}H NMR, which proved that **F** was an intermediate and reduction of it by H_2 or HD gave the product **30a-II** (**30a-III**). Besides, 0.29 D on C2 and 0.04 D on C3 of **30a-I** was also measured by ^{2}H NMR. However, at least 1D should be on C2 if **F** was formed as an intermediate. The reason why only 0.29 D was found is probably due to the H-D exchange between the deuterium in a Ru intermediate and the proton in **29** or **20a**.

Scheme 4.7 KIE and deterium-labeling experiments.^{a}



^{a}Reaction conditions: **32a-I, 32a-II** or **32a-III** (1.0 equiv), **20a** (2.0 equiv), 2.5 mol % [Ru(benzene)Cl_2]$_2$, 5 mol % **7b**, 5 mol % acetonitrile, 45 mol % NaH, toluene, reflux, 24 h.

Scheme 4.8 The proposed mechanism of the sp^3 C-O cleavage reaction.



4.3 Conclusion

A novel and effective ruthenium catalyzed selective sp^3 C3–O cleavage was reported for the reaction of 3-alkoxy-1-propanol derivatives and primary or secondary amines. 3-Alkoxy-1-propanol C_3 scaffolds are required for the C–O bond cleavage. The cleavage only occurs at the C3–O position even with 3-benzyloxy-1-propanol.

O-bound and C-bound Ru enolates were proposed as key intermediates to realize the selective sp^3 C3–O bond cleavage in 3-alkoxy-1-propanols. Mechanistic investigation demonstrated that the whole reaction consists of two independent processes and the respective rate-determining step was confirmed by KIE experiments. Deuterium-labeling experiments showed that acrolein or Ru-bound acrolein species was another important intermediate. More detailed mechanistic invesitigation is still in progress.

4.4 Exerimental section

4.4.1 General considerations

All reactions were carried out using standard Schlenk techniques, in sealed tubes or in an argon-filled glove box unless otherwise mentioned. Most substrates were obtained from Aldrich, Alfa Aesar or Tokyo Chemical Industry (TCI) and used as received. $CDCl_3$ was purchased from Cambridge Isotope Laboratories (CIL) and used as received. Toluene, THF, and dichloromethane were dried over Pure Solv solvent purification system. Analytical TLC was performed on Merck 60 F254 silica gel plates (0.25 mm thickness). Column chromatography was performed on Merck 60 silica gel (230-400 mesh). NMR spectra were recorded using Bruker AVANCE300, AVANCE400, AVANCE^{III}400 or JEOL ECA400 spectrometers, and TMS (tetramethylsilane) was used as a reference. Chemical shifts were reported in ppm and coupling constants in Hz. GC analyses were carried out with 7980A GC system from

Agilent Technologies, equipped with an HP-5 column using dodecane as an internal standard. High resolution mass spectra were recorded by Waters Q-Tof Premier Micromass instrument, using the electro spray ionization (ESI) mode.

4.4.2 Materials

1,3-Diisopropylimidazolium bromide (**7b**),[40] 3-(benzyloxy)-2-methylpropan-1-ol (**29d**),[62] 3-(benzyloxy)-2,2-dimethylpropan-1-ol (**29f**),[62] 3-(benzyloxy)butan-1-ol (**29g**),[63] 4-(benzyloxy)butan-2-ol (**29h**),[64] 3-(benzyloxy)propanal (**41**),[65] 3-phenoxy-1-propanol,[66] 3-(benzyloxy)propan-1-ol-2,2-d_2 (**29a-I**),[67] and 3-(benzyloxy)propan-1-ol-1,1-d_2 (**29a-II**),[68] 1,1-d^2-benzyl bromide[69] were prepared by literature procedures. Other chemicals were purchased from commercial suppliers and used as received without further purification.

Synthesis of benzyl n-propyl ether (38).[70] 1-propanol (0.36 g, 6.0 mmol) was added to a suspension of sodium hydride (0.17 g, 7.0 mmol) in DMF (8 mL). The reaction was stirred for 2 h at room temperature. Benzyl bromide (0.79 ml, 6.6 mmol) was added slowly and the reaction mixture stirred at room temperature for 15 h. Saturated aq. ammonium chloride (5 mL) was added and the mixture extracted with Et_2O (2 × 30 ml). The combined organic extracts were washed with brine (20 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 10 : 1) to afford the pure product (0.82 g, 91%). ^{1}H NMR ($CDCl_3$): δ 7.39-7.25 (m, 5H), 4.50 (s, 2H), 3.43 (t, 2H, J = 6.6 Hz), 1.71-1.62 (m, 2H), 0.94 (t, 3H, J = 7.6 Hz).

Synthesis of 3-(benzyloxy)-2-phenylpropan-1-ol (29e).[71] 2-Phenyl-1,3-propanediol

(0.84 g, 5.5 mmol) in 2 mL of THF was added dropwise to a suspension of NaH (0.13 g, 5.5 mmol) in 8 mL of THF. The reaction mixture was refluxed for 1 h, and then benzyl bromide (0.71 mL, 6.0 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (1 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with Et_2O (3 x 20 ml), washed with water, brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 3 : 1) to afford the pure product (0.75 g, 56%). ^1H NMR ($CDCl_3$): δ 7.39-7.21 (m, 10H), 4.56 (s, 2H), 4.05-3.76 (m, 4H), 3.27-3.18 (m, 1H), 2.42 (bs, 1H).

Synthesis of 3-hydroxypropyl methanesulfonate. MsCl (0.40 mL, 5.3 mmol) was added dropwise to a solution of 1,3-propanediol (0.36 mL, 5.0 mmol), Et_3N (0.73 mL, 5.3 mmol), and 10 mL dichloromethane at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 2 h and allowed to warm to room temperature for additional 2 h. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 20 : 1) to afford the pure product (0.25 g, 32%) as a colorless liquid. ^1H NMR ($CDCl_3$): δ 4.40 (t, 2H, J = 6.0 Hz), 3.79 (t, 2H, J = 5.8 Hz), 3.04 (s, 3H), 1.99 (tt, 2H, J = 6.0, 5.8 Hz). ^{13}C NMR ($CDCl_3$): δ 67.1, 58.3, 37.5, 32.0. HR-MS (ESI): m/z = 155.0372 [MH^+], calcd. for $C_4H_{11}O_4S$: 155.0378.

Synthesis of 3-hydroxypropyl acetate. A solution of 1,3-propanediol (0.36 mL, 5.0 mmol) in anhydrous THF (3 mL) was added dropwise to a suspension of NaH (120 mg, 5.0 mmol) in anhydrous THF (15 mL). The suspension was refluxed and stirred under argon for 1 h. Acetic anhydride (0.47 mL, 5.0 mmol) was added dropwise and the mixture was stirred for 3 h, followed by careful addition of water and extraction with ethyl acetate (50 mL). The organic layer was washed with 5% Na_2CO_3 (2 x 25 mL) and brine (2 x 25 mL), and dried with $MgSO_4$. The solvent was evaporated and the residue was purified by flash chromatography (Hex : EA = 3 : 2) to afford the desired product (230 mg, 39%) as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 4.23 (t, 2H, *J* = 6.2 Hz), 3.70 (t, 2H, *J* = 6.1 Hz), 2.29 (bs, 1H), 2.07 (s, 3H), 1.88 (tt, 2H, *J* = 6.2, 6.1 Hz). ^{13}C NMR ($CDCl_3$): δ 171.8, 61.6, 59.3, 31.8, 21.1. HR-MS (ESI): m/z = 119.0704 [MH^+], calcd. for $C_5H_{11}O_3$: 119.0708.

Synthesis of 3-(4-tert-butylbenzyloxy)propan-1-ol (29i). 1,3-propanediol (0.73 mL, 10 mmol) in 2 mL of THF was added dropwise to a suspension of NaH (0.24 g, 10 mmol) in 18 mL of THF. The reaction mixture was stirred at room temperature for 1 h, and then 4-(tert-butyl)benzyl bromide (1.8 mL, 10 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (1 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with ether (3 x 20 ml), washed with water, brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (eluent hexanes : ethyl acetate = 3 : 1) to afford the pure product (1.2 g, 54%) as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.38 (dd, 2H, *J* = 6.4, 1.8 Hz), 7.27-7.25 (m, 2H), 4.49 (s, 2H), 3.79 (t, 2H, *J* = 5.6 Hz), 3.67 (t, 2H, *J* = 5.8 Hz), 2.36 (bs, 1H), 1.87 (tt, 2H, *J* = 5.8, 5.6 Hz), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 150.9, 135.2, 127.7, 125.6, 73.3, 69.7, 62.3, 34.7, 32.3, 31.6. HR-MS (ESI): m/z = 223.1704 [MH^+], calcd. for $C_{14}H_{23}O_2$: 223.1698.

Synthesis of 3-(4-methylbenzyloxy)propan-1-ol (29j). 1,3-propanediol (0.73 mL, 10 mmol) in 2 mL of THF was added dropwise to a suspension of NaH (0.24 g, 10 mmol) in 18 mL of THF. The reaction mixture was stirred at room temperature for 1 h, and then 4-methylbenzyl bromide (1.4 mL, 10 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (1 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with ether (3 x 20 ml), washed with water, brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 3 : 1) to afford the pure product (1.1 g, 61%) as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.22 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz), 4.48 (s, 2H), 3.78 (t, 2H, *J* = 5.5 Hz), 3.64 (t, 2H, *J* = 5.8 Hz), 2.34 (s, 3H), 2.33 (bs, 1H), 1.86 (tt, 2H, *J* = 5.8, 5.5 Hz). ^{13}C NMR ($CDCl_3$): δ 137.7, 135.2, 129.3, 128.0, 73.4, 69.5, 62.3, 32.3, 21.4. HR-MS (ESI): m/z = 181.1231 [MH^+], calcd. for $C_{11}H_{17}O_2$: 181.1229.

Synthesis of 3-(3-methylbenzyloxy)propan-1-ol (29k). 1,3-propanediol (0.73 mL, 10 mmol) in 2 mL of THF was added dropwise to a suspension of NaH (0.24 g, 10 mmol) in 18 mL of THF. The reaction mixture was stirred at room temperature for 1 h, and then 3-methylbenzyl bromide (1.4 mL, 10 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (1 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with ether (3 x 20 ml), washed with water, brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 3 : 1) to afford the pure product (1.1 g, 61%) as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.23 (dd, 1H, *J* = 8.3, 7.5 Hz), 7.14-7.09 (m, 3H), 4.48 (s, 2H), 3.78 (t, 2H, *J* = 5.6 Hz), 3.66 (t, 2H, *J* = 5.8 Hz), 2.35 (s, 3H), 2.32 (bs, 1H), 1.87 (tt, 2H, *J* = 5.8, 5.6 Hz). ^{13}C NMR ($CDCl_3$): δ 138.3, 138.2, 128.7, 128.6, 128.5, 125.0, 73.5, 69.6, 62.1, 32.3, 21.6. HR-MS (ESI): m/z = 181.1232 [MH^+], calcd. for $C_{11}H_{17}O_2$: 181.1229.

Synthesis of 3-(2-methylbenzyloxy)propan-1-ol (29l). 1,3-propanediol (0.73 mL, 10 mmol) in 2 mL of THF was added dropwise to a suspension of NaH (0.24 g, 10 mmol) in 18 mL of THF. The reaction mixture was stirred at room temperature for 1 h, and then 2-methylbenzyl bromide (1.3 mL, 10 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (1 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with ether (3 x 20 ml), washed with water, brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 3 : 1) to afford the pure product (1.2 g, 67%) as a colorless liquid. ^1H NMR ($CDCl_3$): δ 7.30-7.28 (m, 1H), 7.23-7.15 (m, 3H), 4.51 (s, 2H), 3.77 (t, 2H, *J* = 5.7 Hz), 3.67 (t, 2H, *J* = 5.8 Hz), 2.33 (s, 3H), 2.31 (bs, 1H), 1.87 (tt, 2H, *J* = 5.8, 5.7 Hz). ^{13}C NMR ($CDCl_3$): δ 136.8, 136.2, 130.5, 128.7, 128.1, 126.0, 71.9, 69.6, 62.0, 32.4, 18.9. HR-MS (ESI): m/z = 181.1235 [MH^+], calcd. for $C_{11}H_{17}O_2$: 181.1229.

Synthesis of 3-(4-fluorobenzyloxy)propan-1-ol (29m). 1,3-propanediol (0.73 mL, 10 mmol) in 2 mL of THF was added dropwise to a suspension of NaH (0.24 g, 10 mmol) in 18 mL of THF. The reaction mixture was stirred at room temperature for 1 h, and then 4-fluorobenzyl bromide (1.2 mL, 10 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (1 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with ether (3 x 20 ml), washed with water, brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 3 : 1) to afford the pure product (1.0 g, 54%) as a colorless liquid. ^1H NMR ($CDCl_3$): δ 7.32-7.26 (m, 2H), 7.06-6.98 (m, 2H), 4.48 (s, 2H), 3.77 (t, 2H, *J* = 5.7 Hz), 3.64 (t, 2H, *J* = 5.8 Hz), 2.37 (bs, 1H), 1.86 (tt, 2H, *J* = 5.8, 5.7 Hz). ^{13}C NMR ($CDCl_3$): δ 163.8, 161.3, 134.2, 134.1, 129.6, 129.5, 115.6, 115.4, 72.7, 69.3, 61.8, 32.3. HR-MS (ESI): m/z = 185.0973 [MH^+], calcd. for $C_{10}H_{14}O_2F$: 185.0978.

Synthesis of 3-(3-fluorobenzyloxy)propan-1-ol (29n). 1,3-propanediol (0.73 mL, 10 mmol) in 2 mL of THF was added dropwise to a suspension of NaH (0.24 g, 10 mmol) in 18 mL of THF. The reaction mixture was stirred at room temperature for 1 h, and then 3-fluorobenzyl bromide (1.2 mL, 10 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (1 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with ether (3 x 20 ml), washed with water, brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 3 : 1) to afford the pure product (1.1 g, 60%) as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.33-7.28 (m, 1H), 7.09 (d, 1H, *J* = 7.6 Hz), 7.06-7.03 (m, 1H), 6.97 (td, 1H, *J* = 8.4, 2.5 Hz), 4.51 (s, 2H), 3.79 (t, 2H, *J* = 5.7 Hz), 3.67 (t, 2H, *J* = 5.8 Hz), 2.24 (bs, 1H), 1.88 (tt, 2H, *J* = 5.8, 5.7 Hz). ^{13}C NMR ($CDCl_3$): δ 164.4, 162.0, 141.1, 141.0, 130.2, 130.1, 123.1, 123.0, 114.8, 114.6, 114.4, 72.7, 69.5, 61.8, 32.4. HR-MS (ESI): m/z = 185.0978 [MH^+], calcd. for $C_{10}H_{14}O_2F$: 185.0978.

Synthesis of 3-(2-fluorobenzyloxy)propan-1-ol (29o). 1,3-propanediol (0.73 mL, 10 mmol) in 2 mL of THF was added dropwise to a suspension of NaH (0.24 g, 10 mmol) in 18 mL of THF. The reaction mixture was stirred at room temperature for 1 h, and then 2-fluorobenzyl bromide (1.2 mL, 10 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (1 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with ether (3 x 20 ml), washed with water, brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 3 : 1) to afford the pure product (1.1 g, 60%) as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.39 (ddd, 1H, *J* = 7.5, 7.4, 1.6 Hz), 7.30-7.24 (m, 1H), 7.13 (td, *J* = 7.5, 0.8 Hz), 7.03 (dd, 1H, *J* = 9.6, 8.6 Hz), 4.48 (s, 2 H), 3.77 (t, 2 H, *J* = 5.6 Hz), 3.69 (t, 2 H, *J* = 5.8 Hz), 2.36 (bs, 1 H), 1.87 (tt, 2H, *J* = 5.8, 5.6 Hz). ^{13}C NMR ($CDCl_3$): δ 162.2, 159.7, 130.2, 130.1, 129.7, 129.6, 125.4, 125.3, 124.3, 124.2, 115.6, 115.3, 69.6, 66.9, 61.8, 32.3. HR-MS (ESI): m/z = 185.0984 [MH^+], calcd. for $C_{10}H_{14}O_2F$: 185.0978.

Synthesis of 3-(4-(trifluoromethyl)benzyloxy)propan-1-ol (29p). 1,3-propanediol (0.73 mL, 10 mmol) in 2 mL of THF was added dropwise to a suspension of NaH (0.24

g, 10 mmol) in 18 mL of THF. The reaction mixture was stirred at room temperature for 1 h, and then 4-(trifluoromethyl)benzyl bromide (1.5 mL, 10 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (1 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with ether (3 x 20 ml), washed with water, brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 3 : 1) to afford the pure product (1.3 g, 56%) as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.61 (d, 2H, *J* = 8.1 Hz), 7.45 (d, 2H, *J* = 8.0 Hz), 4.58 (s, 2H), 3.81 (t, 2H, *J* = 5.2 Hz), 3.69 (t, 2H, *J* = 5.8 Hz), 2.41 (bs, 1H), 1.88 (tt, 2H, *J* = 5.8, 5.2 Hz). ^{13}C NMR ($CDCl_3$): δ 142.5, 130.5, 130.2, 129.9, 129.6, 128.4, 127.7, 125.7–125.5, 123.0, 120.3, 72.6, 69.5, 61.5, 32.4. HR-MS (ESI): m/z = 235.0948 [MH^+], calcd. for $C_{11}H_{16}O_2$: 235.0946.

Synthesis of 29a-III.. 1,3-propanediol (1.45 mL, 20 mmol) in 4 mL of THF was added dropwise to a suspension of NaH (0.48 g, 20 mmol) in 36 mL of THF. The reaction mixture was stirred at room temperature for 1 h, and then 1,1-d^2-benzyl bromide (3.46 g, 20 mmol) was added and refluxing continued for 16 h. After the reaction mixture was cooled down to room temperature, water (2 mL) was added followed by removal of THF at reduced pressure. The residue was extracted with ether (3 x 40 ml), washed with water, brine and water, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hex : EA = 3 : 1) to afford the pure product (2.1 g, 63%). ^{1}H NMR ($CDCl_3$): δ 7.37-7.27 (m, 5H), 3.77 (t, 2H, *J* = 5.7 Hz), 3.65 (t, 2H, *J* = 5.8 Hz), 2.44 (bs, 1H), 1.86 (quint, 2H, *J* = 5.8 Hz).

4.4.3 General procedure for the sp^3 C-O cleavage

Inside an argon-filled glovebox, [Ru(benzene)Cl$_2$]$_2$ (6.3 mg, 0.0125 mmol), NHC precursor **7b** (5.8 mg, 0.025 mmol), acetonitrile (2 μl, 0.025 mmol), NaH (5.4 mg, 0.225 mmol) and toluene (0.6 mL) were added to an oven-dried Schlenk tube (or a sealed tube). The Schlenk tube (or the sealed tube) was taken out of the glovebox and was heated at reflux for 30 min. After the Schlenk tube (the sealed tube) was cooled down to room temperature, **29** (0.5 mmol) and **20** (1.0 mmol) were added. Then the mixture was heated to reflux under argon atmosphere for 24 h. The reaction mixture was cooled down to room temperature and the solvent was removed *in vacuo*. The residue was purified by silica gel flash column chromatography to afford the products **39(or 21a)** and **30**.

***N*-Benzyl-2-(benzyloxy)acetamide (34).** Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 93%. ^{1}H NMR (CDCl$_3$): δ 7.37-7.26 (m, 10H), 6.94 (bs, 1H), 4.56 (s, 2H), 4.49 (d, 2H, J = 6.0 Hz), 4.05 (s, 2H); ^{13}C NMR (CDCl$_3$): 169.6, 138.2, 136.9, 128.9, 128.8, 128.4, 128.2, 127.9, 127.7, 73.8, 69.7, 43.0; HR-MS (ESI): m/z = 256.1335 [MH$^+$], calcd. for $C_{16}H_{18}NO_2$: 256.1338.

***N*-Benzyl-4-(benzyloxy)butanamide (35).** Purified by silica gel chromatography (Hex : EA = 3 : 2) to afford the desired product as a white solid. Isolated yield: 92%. ^{1}H NMR (CDCl$_3$): δ 7.33-7.22 (m, 10H), 6.06 (bs, 1H), 4.44 (s, 2H), 4.37 (d, 2H, J = 5.8 Hz), 3.51 (t, 2H, J = 6.2 Hz), 2.32 (t, 2H, J = 7.3 Hz), 2.01-1.95 (m, 2H); ^{13}C NMR (CDCl$_3$): 172.8, 138.6, 138.4, 128.8, 128.6, 128.0, 127.9, 127.8, 127.6, 73.1, 69.6, 43.7, 33.7, 25.9; HR-MS (ESI): m/z = 284.1658 [MH$^+$], calcd. for $C_{18}H_{22}NO_2$: 284.1651.

***N*-Benzyl-5-(benzyloxy)pentanamide (36).** Purified by silica gel chromatography (Hex : EA = 1 : 1) to afford the desired product as a white solid. Isolated yield: 86%. ^{1}H NMR (CDCl$_3$): δ 7.37-7.20 (m, 10H), 5.89 (bs, 1H), 4.47 (s, 2H), 4.40 (d, 2H, J = 6.0 Hz), 3.49 (t, 2H, *J* = 6.2 Hz), 2.23 (t, 2H, *J* = 7.6 Hz), 1.84-1.72 (m, 2H), 1.68-1.62 (m, 2H); ^{13}C NMR ($CDCl_3$): 172.9, 138.6, 128.9, 128.6, 128.0, 127.9, 127.8, 127.6, 73.2, 70.3, 43.7, 36.5, 29.3, 22.9; HR-MS (ESI): m/z = 298.1813 [MH^+], calcd. for $C_{19}H_{24}NO_2$: 298.1807.

***N*-Benzylbenzamide (21a).**[16] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.80-7.78 (m, 2H), 7.50-7.30 (m, 8H), 6.48 (bs, 1H), 4.64 (d, 2H, *J* = 5.9 Hz).

***N*-Benzylacetamide (39a).**[72] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 51% (in an open condition) and 75% (in a sealed tube). ^{1}H NMR ($CDCl_3$): δ 7.34-7.25 (m, 5H), 6.08 (bs, 1H), 4.40 (d, 2H, *J* = 5.5 Hz), 2.01 (s, 3H).

***N*-Benzyl-4-tert-butylbenzamide (39b).** Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 92%. ^{1}H NMR ($CDCl_3$): δ 7.75-7.72 (m, 2H), 7.44-7.41 (m, 2H), 7.34-7.26 (m, 5H), 6.53 (bs, 1H), 4.63 (d, 2H, *J* = 5.7 Hz), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$): 167.5, 155.2, 138.6, 131.7, 128.9, 128.0, 127.7, 127.0, 125.7, 44.2, 35.1, 31.3; HR-MS (ESI): m/z = 268.1703 [MH^+], calcd. for $C_{18}H_{22}NO$: 268.1701.

***N*-Benzyl-4-methylbenzamide (39c).**[18] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 88%. ^{1}H NMR ($CDCl_3$): δ 7.69 (d, 2H, *J* = 8.1 Hz), 7.37-7.14 (m, 7H), 6.45 (bs, 1H), 4.62 (d, 2H, *J* = 5.6 Hz), 2.38 (s, 3H).

***N*-Benzyl-3-methylbenzamide (39d).**[73] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 89%. ^{1}H NMR ($CDCl_3$): δ 7.61 (s, 1H), 7.57-7.55 (m, 1H), 7.39-7.27 (m, 7H), 6.43 (bs, 1H), 4.63 (d, 2H, *J* = 5.6 Hz), 2.38 (s, 3H).

***N*-Benzyl-2-methylbenzamide** (**39e).**[74] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 60%. ^{1}H NMR ($CDCl_3$): δ 7.36-7.26 (m, 7H), 7.19-7.13 (m, 2H), 6.06 (bs, 1H), 4.57 (d, 2H, *J* = 5.8 Hz), 2.43 (s, 3H).

***N*-Benzyl-4-fluorobenzamide** (**39f).**[18] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 68%. ^{1}H NMR ($CDCl_3$): δ 7.86-7.72 (m, 2H), 7.35-7.26 (m, 5H), 7.07-7.01 (m, 2H), 6.36 (bs, 1H), 4.57 (d, 2H, *J* = 5.7 Hz).

***N*-Benzyl-3-fluorobenzamide (39g)** Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 62%. ^{1}H NMR ($CDCl_3$): δ 7.54-7.50 (m, 2H), 7.41-7.27 (m, 6H), 7.19 (tdd, 1H, *J* = 8.3, 2.7, 1.0 Hz), 6.51 (bs, 1H), 4.62 (d, 2H, *J* = 5.7 Hz); ^{13}C NMR ($CDCl_3$): 166.3, 164.2, 161.8, 138.1, 137.0, 136.9, 130.5, 130.4, 129.1, 128.1, 128.0, 122.6, 118.9, 118.6, 114.8, 114.5, 44.5; HR-MS (ESI): m/z = 230.0984 [MH^+], calcd. for $C_{14}H_{13}NOF$: 230.0981.

***N*-Benzyl-2-fluorobenzamide (39h).** Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 20%. ^{1}H NMR ($CDCl_3$): δ 8.12 (td, 1H, *J* = 7.9, 2.3 Hz), 7.48-7.43 (m, 1H), 7.37-7.23 (m, 6H), 7.11 (dd, 1H, *J* = 8.3, 1.0 Hz), 7.08 (dd, 1H, *J* = 8.3, 1.0 Hz), 4.67 (dd, 2H, *J* = 5.7, 1.4 Hz); ^{13}C NMR ($CDCl_3$): 163.4, 162.0, 159.5, 138.2, 133.5, 133.4, 132.3, 128.9, 127.9, 127.7, 125.0, 121.2, 121.1, 116.3, 116.0, 44.2; HR-MS (ESI): m/z = 230.0985 [MH^+], calcd. for $C_{14}H_{13}NOF$: 230.0981.

***N*-Benzyl-4-(trifluoromethyl)benzamide** (**39i).**[75] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 41%. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 2H, *J* = 8.2 Hz), 7.67 (d, 2H, *J* = 8.3 Hz), 7.38-7.29 (m, 5H), 6.61 (bs, 1H), 4.64 (d, 2H, *J* = 5.7 Hz).

***N*-Benzylpropionamide** (**30a).**[76] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. ^{1}H NMR (CDCl$_3$): δ 7.32-7.24 (m, 5H), 6.08 (bs, 1H), 4.40 (d, 2H, *J* = 5.5 Hz), 2.21 (q, 2H, *J* = 7.5 Hz), 1.14 (t, 3H, *J* = 7.6 Hz).

***N*-Benzylisobutyramide** (**30b).**[77] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 65%. ^{1}H NMR (CDCl$_3$): δ 7.34-7.24 (m, 5H), 6.01 (bs, 1H), 4.40 (d, 2H, *J* = 5.7 Hz), 2.40 (sept, 1H, *J* = 6.9 Hz), 1.18 (d, 6H, *J* = 6.9 Hz).

***N*-Benzyl-2-phenylpropanamide** (**30c).**[78] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 56%. ^{1}H NMR (CDCl$_3$): δ 7.34-7.20 (m, 8H), 7.12 (d, 2H, *J* = 7.0 Hz), 5.81 (bs, 1H), 4.41-4.31 (m, 2H), 3.59 (q, 1H, *J* = 7.1 Hz), 1.25 (d, 3H, *J* = 7.2 Hz).

***N*-Benzylbutyramide** (**30e).**[79] Purified by silica gel chromatography (Hex : EA = 2 : 1) to afford the desired product as a white solid. Isolated yield: 80%. ^{1}H NMR (CDCl$_3$): δ 7.33-7.24 (m, 5H), 6.16 (bs, 1H), 4.39 (d, 2H, *J* = 5.7 Hz), 2.17 (t, 2H, *J* = 7.4 Hz), 1.70-1.64 (m, 2H), 0.93 (t, 3H, *J* = 7.4 Hz).

***N*-(4-Methoxybenzyl)benzamide** (**39j).**[80] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 76%. ^{1}H NMR (CDCl$_3$): δ 7.77 (d, 2H, *J* = 8.0 Hz), 7.49-7.45 (m, 1H), 7.40-7.36 (m, 2H), 7.25 (d, 2H, *J* = 8.0 Hz), 6.85 (d, 2H, *J* = 8.0 Hz), 6.63 (bs, 1H), 4.53 (d, 2H, *J* = 5.6 Hz), 3.78 (s, 1H).

***N*-(4-Chlorobenzyl)benzamide** (**39k).**[11j] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 71%. ^{1}H NMR (CDCl$_3$): δ 7.77 (d, 2H, *J* = 7.8 Hz), 7.51-7.47 (m, 1H), 7.41-7.38 (m, 2H), 7.31-7.22 (m, 4H), 6.78 (bs, 1H), 4.55 (d, 2H, *J* = 5.6 Hz).

***N*-Phenethylbenzamide** (**39l).**[35] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 70%. ^{1}H NMR (CDCl$_3$): δ

7.69 (dd, 2H, *J* = 7.0, 1.5 Hz), 7.49-7.21 (m, 8H), 6.31 (bs, 1H), 3.70 (td, 2H, *J* = 6.9, 6.0 Hz), 2.92 (t, 2H, *J* = 6.9 Hz).

***N*-Hexylbenzamide (21b).**[41] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 81%. ^{1}H NMR (CDCl$_3$): δ 7.77 (dd, 2H, *J* = 7.2, 1.3 Hz), 7.49 (t, 1H, *J* = 7.3 Hz), 7.40 (t, 2H, *J* = 7.3 Hz), 6.44 (bs, 1H), 3.42 (td, 2H, *J* = 7.1, 6.0 Hz), 1.62-1.57 (m, 2H), 1.37-1.29 (m, 6H), 0.89 (t, 2H, *J* = 6.8 Hz).

***N*-(Heptan-2-yl)benzamide (21c).** Purified by silica gel chromatography (Hex : EA = 7 : 1) to afford the desired product as a white solid. Isolated yield: 21%. ^{1}H NMR (CDCl$_3$): δ 7.75 (d, 2H, *J* = 7.2 Hz), 7.49 (t, 1H, *J* = 7.2 Hz), 7.42 (t, 2H, *J* = 7.2 Hz), 5.92 (br, 1H), 4.24-4.14 (m, 1H), 1.60-1.45 (m, 2H), 1.41-1.22 (m, 9H), 0.90-0.87 (m, 3H); ^{13}C NMR (CDCl$_3$): 167.0, 135.3, 131.4, 128.7, 127.0, 46.0, 37.3, 31.9, 26.0, 22.8, 21.3, 14.2; HR-MS (ESI): m/z = 220.1704 [MH$^+$], calcd. for $C_{14}H_{22}NO$: 220.1701.

Phenyl(piperidin-1-yl)methanone (21i).[16] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a colorless oil. Isolated yield: 60%. ^{1}H NMR (CDCl$_3$): δ 7.37 (bs, 5H), 3.70 (bs, 2H), 3.33 (bs, 2H), 1.66-1.50 (m, 6H).

Morpholino(phenyl)methanone (21l).[41] Purified by silica gel chromatography (Hex : EA = 3 : 1) to afford the desired product as a white solid. Isolated yield: 61%. ^{1}H NMR (CDCl$_3$): δ 7.41-7.39 (m, 5H), 3.74-3.46 (m, 8H).

***N*-Benzyl-*N*-methylbenzamide (25j).**[38d] Purified by silica gel chromatography (Hex : EA = 4 : 1) to afford the desired product as a colorless clear oil. Yield: 58%. ^{1}H NMR (CDCl$_3$): δ 7.47-7.16 (m, 10H), 4.76 (s, 1H), 4.51 (s, 1 H), 3.02 (s, 1.5 H), 2.85 (s, 1.5H).

***N*-(4-Methoxybenzyl)propionamide (30f).**[81] Purified by silica gel column chromatography (Hex : EA = 1 : 1) to afford the desired product as a colorless clear oil. Yield: 66%. ^{1}H NMR (CDCl$_3$): δ 7.20 (d, 2H, *J* = 8.4 Hz), 6.85 (d, 2H, *J* = 8.4 Hz), 5.83

(bs, 1H), 4.35 (d, 2H, *J* = 5.6 Hz), 3.79 (s, 3H), 2.22 (q, 2H, *J* = 7.6 Hz), 1.16 (t, 3H, *J* = 7.6 Hz).

***N*-(4-Chlorobenzyl)propionamide (30g).**[81] Purified by silica gel column chromatography (Hex : EA = 1 : 1) to afford the desired product as a colorless clear oil. Yield: 52%. ^{1}H NMR ($CDCl_3$): δ 7.28 (d, 2H, *J* = 8.4 Hz), 7.19 (d, 2H, *J* = 8.4 Hz), 5.98 (bs, 1H), 4.38 (d, 2H, *J* = 5.6 Hz), 2.24 (q, 2H, *J* = 7.6 Hz), 1.17 (t, 3H, *J* = 7.6 Hz).

***N*-Phenethylpropionamide (30h).**[82] Purified by silica gel column chromatography (Hex : EA = 1:1) to afford the desired product as a colorless clear oil. Yield: 65%. ^{1}H NMR ($CDCl_3$): δ 7.33-7.17 (m, 5H), 5.61 (bs, 1H), 3.51 (td, 2 H, *J* = 6.9, 6.1 Hz), 2.81 (t, 2H, *J* = 5.6 Hz), 2.16 (q, 2H, *J* = 7.6 Hz), 1.13 (t, 3H, *J* = 7.6 Hz).

***N*-Hexylpropionamide (30i).**[83] Purified by silica gel column chromatography (Hex : EA = 1:1) to afford the desired product as a colorless clear oil. Yield: 73%. ^{1}H NMR ($CDCl_3$): δ 5.63 (bs, 1H), 3.21 (td, 2H, *J* = 6.8, 6.4 Hz), 2.20 (q, 2H, *J* = 7.5 Hz), 1.48-1.44 (m, 2H), 1.32-1.27 (m, 6H), 1.13 (t, 3H, *J* = 7.6 Hz), 0.87-0.85 (m, 3H).

***N*-(Heptan-2-yl)propionamide (30j).** Purified by silica gel chromatography (Hex : EA = 3:1) to afford the desired product as a white solid. Isolated yield: 21%. ^{1}H NMR ($CDCl_3$): δ 5.21 (br, 1H), 4.02-3.90 (m, 1H), 2.22-2.15 (m, 2H), 1.41-1.28 (m, 8H), 1.17-1.10 (m, 6H), 0.87 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$): 173.2, 45.2, 37.2, 31.9, 30.2, 25.9, 22.8, 21.2, 14.2, 10.2; HR-MS (ESI): m/z = 172.1700 [MH^+], calcd. for $C_{10}H_{22}NO$: 172.1701.

1-(Piperidin-1-yl)propan-1-one (30k).[84] Purified by silica gel chromatography (Hex : EA = 3:1) to afford the desired product as a white solid. Isolated yield: 45%. ^{1}H NMR ($CDCl_3$): δ 3.55 (t, 2H, *J* = 5.6 Hz), 3.39 (t, 2H, *J* = 5.6 Hz), 2.33 (q, 2H, *J* = 7.6 Hz), 1.66-1.50 (m, 6H), 1.14 (t, 3H, *J* = 7.6 Hz).

1-Morpholinopropan-1-one (30l).[85] Purified by silica gel chromatography (Hex : EA

= 3:1) to afford the desired product as a white solid. Isolated yield: 50%. ^{1}H NMR (CDCl$_3$): δ 3.68-3.62 (m, 6H), 3.49 (t, 2H, *J* = 4.6 Hz), 2.38 (q, 2H, *J* = 7.6 Hz), 1.19 (t, 3H, *J* = 7.6 Hz).

***N*-Benzyl-*N*-methylpropionamide (30m).**[86] Purified by silica gel chromatography (Hex : EA = 3:1) to afford the desired product as a white solid. Isolated yield: 66%. ^{1}H NMR (CDCl$_3$): δ 7.38-7.14 (m, 5H), 4.59-4.53 (m, 2H), 2.95-2.91 (m, 3H), 2.40 (q, 2H, *J* = 7.6 Hz), 1.22-1.14 (m, 3H).

***N*-Benzyl-3-(benzyloxy)-2,2-dimethylpropanamide.** Purified by silica gel chromatography (Hex : EA = 4:1) to afford the desired product as a white solid. Isolated yield: 5%. ^{1}H NMR (CDCl$_3$): δ 7.36-7.05 (m, 10H), 7.03 (bs, 1H), 4.50 (s, 2H), 4.41 (d, 2 H, *J* = 6.0 Hz), 3.44 (s, 2H), 1,21 (s, 6H); ^{13}C NMR (CDCl$_3$): 176.8, 138.9, 137.7, 128.8, 128.7, 128.0, 127.8, 127.7, 127.4, 77.1, 73.8, 43.6, 42.9, 23.4; HR-MS (ESI): m/z = 298.1804 [MH$^+$], calcd. for $C_{19}H_{24}NO_2$: 298.1807.

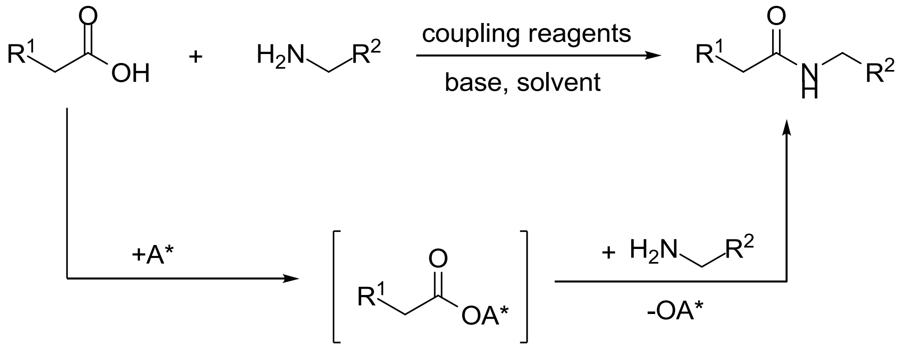
CHAPTER 5

SUMMARY AND PERSPECTIVE

5.1 Conventional methods for amide synthesis.

The amide bond is a key functional group in organic and biological chemistries. It plays a major role in elaboration and composition of biological and chemical systems. Amides are typically synthesized by coupling of activated carboxylic acid derivatives with amines (Scheme 5.1). However, this traditional method requires a stiochiometric amount of various reagents and generates large amounts of by-products as waste, so it is necessary to develop new methods for the amide bond formation.[2b]

Scheme 5.1 Conventional method for the amide bond formation.

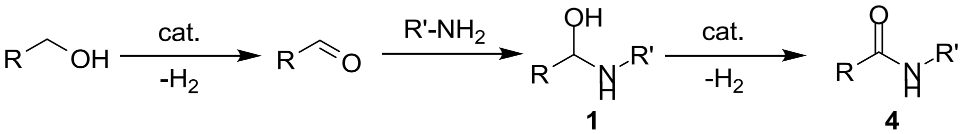


5.2 Amide synthesis from alcohols and amines

5.2.1 Dehydrogenative pathway

In 1991, Murahashi and co-workers reported the synthesis of lactams from 1.4- and 1,5-aminoalcohols in the presence of a hydrogen acceptor using $RuH_2(PPh_3)_4$ as a catalyst. This is the first time to synthsize amides from alcohols in an intramolecular pattern.[12] The breakthrough in the area was the development of the Mistein catalyst, which can catalyze the amide synthesis from alcohols and amines under netrual condition without any additive. Notably, this is the first time to allow alcohol amidation with amines in an intermolecular manner.[13] The generally accepted reaction mechnism is a dehydregenative pathway (Scheme 5.2). An alcohol is initially oxidized to the corresponding aldehyde via releasing one molecule of hydrogen gas, and the aldehyde reacts with an amine to produce a hemiaminal intermediate (**1**). **1** would be further dehydrogenated to the corresponding amide (**4**). This dehydrogenative process has high atom economy that generates two molecules of hydrogen gas as the sole by-products. However, there are still many challenges with this strategy. Limited activity was observed with sterically hindered alcohols or amines, less basic aryl amines, and secondary amines. In addition, primary amides can be generated only with ammonia gas. Moreover, since the reactions were always under reduced conditions, unsaturated bonds such as C=C and C≡C bonds were reduced to the corresponding C-C bonds without hydrogen acceptors.[14,16,18-20]

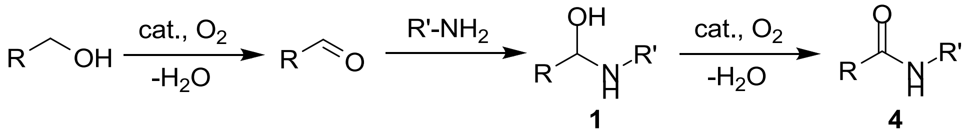
Scheme 5.2 Dehydrgenative pathway for alcohol amidation with amines.



5.2.2 Tandem oxidative process

Recently, Kobayashi and co-workers introduced an alternative way for the direct amide synthesis from alcohols and amines, namely via a tandem oxidative process in which the reaction proceeds under oxidative conditions and the only by-product is water instead of H_2.[29] The reaction pathway is depicted in Scheme 5.3. An alcohol is initially oxidized by O_2 to the corresponding aldehyde with elimination of water, and the aldehyde then reacts with an amine to produce a hemiaminal intermediate (**1**). **1** would be further oxidized to the corresponding amide (**4**) with generation of water. Using this process, sterically hindered substrates[29] and less basic aryl amines[30] can be employed to give the corresponding amides in excellent yields. Besides, substrates containing unsaturated bonds can be tolerated, and primary amides were produced using aqueous ammonia instead of ammonia gas.[29]

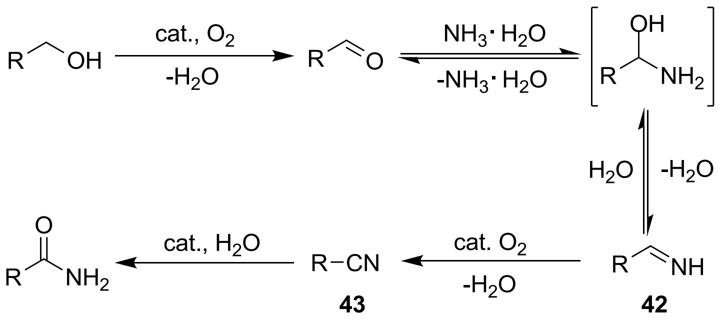
Scheme 5.3 Tandem oxidative process for alcohol amidation with amines.



5.2.3 An oxidative process involving imine and nitrile intermediates

Very recently, Mizuno and co-workers reported amide synthesis from alcohols and aqueous ammonia through a new reaction pathway (Scheme 5.4).[32] An alcohol is initially oxidized to the corresponding aldehyde, which then reacts with the amine to give the hemiaminal. Dehydration of it afforded the corresponding imine (**42**). **42** was then oxidized to the nitrile (**43**), which goes through hydration to give the desired product. For this pathway, this is the first report to synthesize various primary amides by reactions of alcohols and aqueous ammonia without any additive.

Scheme 5.4 An oxidative process involving imine and nitrile intermediates.

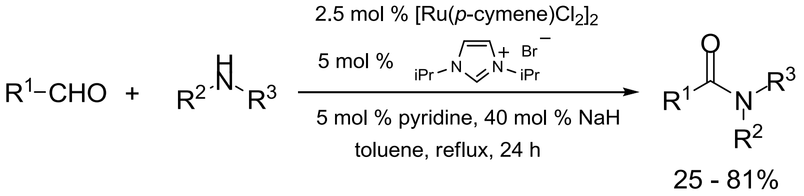


5.3 Summary of the thesis

5.3.1 *N*-Heterocyclic carbene based Ru catalyzed direct amidation of aldehydes with amines

Our previously reported *in situ* Ru-NHC catalytic systems showed excellent activity for alcohol amidation with amines, but only limited activity for direct amidation of aldehydes. Another study with the well-defined Ru-NHC catalysts demonstrated that aldehyde amidation can be achieved by precatalyst activation by an alcohol. Therefore, we believed efficient amide formation from aldehydes with amines could be obtained by using hemiaminal as an activator based on the *in situ* Ru-NHC catalytic systems. We screened and obtained the optimizied reaction conditions, and various secondary and tertiary amides were synthesized directly from aldehydes and amines in 25-81% yields (Scheme 5.5).

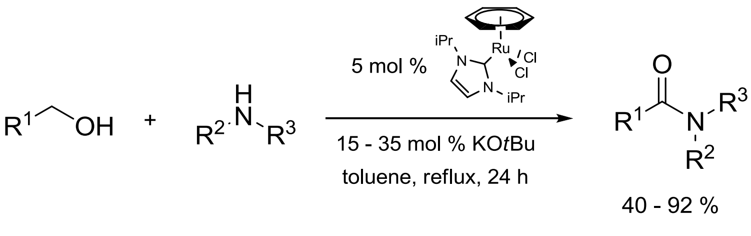
Scheme 5.5 Direct aldehyde amidation with amines.



5.3.2 *N*-Heterocyclic carbene based Ru catalyzed direct amide synthesis from alcohols and secondary amines: Involvement of esters

Amide synthesis directly from alcohols and amines is a highly desirable transformation. Previous catalyst showed exellent activities for reactions of alcohols and primary amines, but limited activities for those of alcohols and secondary amines, especially sterically hindered secondary amines. A well-defined Ru-NHC complex was developed. It exhibited excellent activities for cyclic secondary amines and sterically nonhindered linear secondary amines, and moderate to high activities for sterically hindered linear secondary amines, which demonstrated considerable improvement over previous systems (Scheme 5.6). Interestingly, ester intermediates were observed to be involved in the reaction with secondary amines.

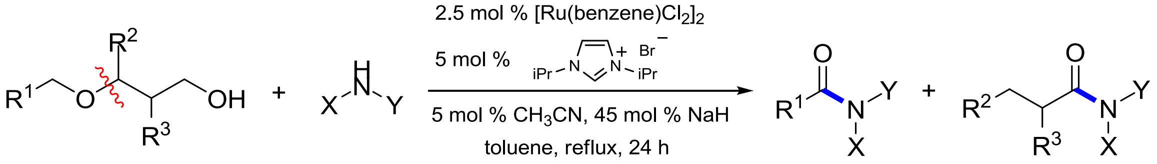
Scheme 5.6 Direct amide synthesis from alcohols and secondary amines.



5.3.3 Selective catalytic sp^3 C-O bond cleavage with C-N bond formation in 3-alkoxy-1-propanols

Amide synthesis from alcohols and amines have been well documented. During the substrate scope investigation of the reaction with our reported *in situ* Ru-NHC catalytic systems, sp^3 C-O cleavage in alkyl ethers occurred in the reactions of 3-alkoxy-1-propanol derivatives and an amine with the concurrent formation of C-N bonds (Scheme 5.7). As far as we know, this is the first example of catalytic C-N bond formation via sp^3 C-O bond cleavage. Since selective activation of unstrained and unactivated etheric sp^3 C-O bonds is highly challenging, we are interested in this reaction and tried to gain more mechanistic insight with experiments. KIE experiments demonstrated that the whole reaction consists of two independent processes and the respective rate-determining step was recognized. Deuterium-labeling experiments showed that acrolein or Ru-bound acrolein species was another important intermediate.

Scheme 5.7 Selective C-O bond cleavage with concurrent C-N bond formation.



5.4 Perspective

Direct amide synthesis from alcohols and amines, an attractive methodology for creating the important amide bonds, has been well reported. However, more efforts should be made in order for this strategy to be widely applied to amide bond formation in organic synthesis. Developing improved strategies that can tolerate unprotected functional groups is challenging but of great importance for organic chemists. Moreover, it is of vital value to synthesize complex, highly functionalized amide-based structures using this strategy without the need for various protecting groups and generation of a large amount of toxic waste. Necessity of special handling of expensive metal complexes and ligands in many cases should be overcome from the environmental and economic point of view. Mechanistic investigation along with the understanding of the exact nature of the catalysts is highly desired for further development of more active and practical catalytic systems.

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