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**TRANSITION METAL-CATALYZED C-C/C-N BOND
FORMATION**

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**SCHOOL OF PHYSICAL AND MATHEMATICAL
SCIENCES**

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TRANSITION METAL-CATALYZED C-C/C-N BOND FORMATION

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LIST OF ABBREVIATIONS

δ	chemical shift
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
Ar	aryl
aq	Aqueous
bipy	2,2'-bipyridine
Bn	benzyl
Bz	benzoyl
calcd	calculated
CH_2Cl_2	dichloromethane
CDCl_3	deuterated chloroform
cm^{-1}	inverse centimeter
d	doublet
DIBAL-H	diisobutylaluminium hydride
dd	doublet of doublets
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DCE	1,2-dichloroethane
dt	doublet of triplets
equiv.	equivalent(s)

ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
FTIR	fourier transform infrared spectrometry
g	gram
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared
<i>i</i> -Pr	isopropyl
M	molar concentration
m	multiplet
m/z	mass per charge ratio
M ⁺	parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	mega hertz
min	minute(s)
mL	milliliter(s)
mmol	millimole
mol%	mole percent
MS	mass spectrometry
<i>n</i> -Bu	<i>n</i> -butyl

NCS	<i>N</i> -chlorosuccinimide
NMR	nuclear magnetic resonance
NMP	<i>N</i> -methyl pyrrolidone
NOESY	nuclear overhauser enhancement spectroscopy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
Ph	phenyl
1,10-Phen	1,10-phenanthroline
PivOH	pivalic acid
ppm	parts per million
PPTS	pyridium <i>p</i> -toluenesulfonate
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
Py	pyridine
q	quartet
R_f	retention factor
rt	room temperature
s	singlet
sat	saturated
t	triplet
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
^{<i>t</i>} Bu	<i>tert</i> -butyl
THF	tetrahydrofuran
TLC	thin layer chromatography

TMEDA	Tetramethylethylenediamine
TsCl	<i>p</i> -toluenesulfonyl chloride
UV	ultraviolet
vol	volume

SUMMARY

Imide derivatives are widely used organic compounds with numerous applications in biological, medicinal, synthetic and polymer chemistry. Traditional methods are not atom economical, usually generating stoichiometric amount of by-products. To address the challenge of atom-economical synthesis of imide derivatives, **chapter 1** describes the first synthesis of cyclic imides from linear diols using a NHC-based ruthenium catalyst, with the liberation of hydrogen as the sole by-product. In **chapter 2**, the dehydrogenation methodology is expanded to direct *N*-acylation of lactams, oxazolidinones, and imidazolidinones with aldehydes using Shvo's catalyst, a cyclopentadienone-ligated ruthenium complex. The reactions are performed without using any other stoichiometric reagent, and the *N*-acylations with α,β -unsaturated aldehydes are achieved with excellent yields.

1,3-Butadiene is an important structural motif in organic chemistry. They also present in a large class of pharmaceutically active molecules and complex natural products. Thus, development of efficient, selective and practical synthetic methodology would be highly desirable. **Chapter 3** describes a ruthenium-catalyzed direct cross-coupling reaction between acrylamides and electrondeficient alkenes to produce (*Z,E*)-dienamides in high efficiency. The same transformation also could be achieved by using rhodium catalyst. Both of two catalytic systems allowed oxidative olefination of a wide range of alkenes bearing different functional groups, such as

CO₂R, SO₂Ph, aryl, CONHBn, CN, PO(OEt)₂, as well as Weinreb amide, which opens up new possibilities for the synthesis of a series of complex natural products and drugs.

With the possible depletion of fossil fuels in near future, lignocellulosic biomass has recently emerged as a possible alternative for the renewable source of energy. In this context, chemical conversion of cellulose and hemicellulose has extensively been studied, while that of lignin remains scarce albeit lignin is the second most abundant biopolymer. The most abundant unit of lignin is the β -O-4 linkage. **Chapter 4** describes simple and efficient methods for conversion of the lignin β -O-4 models into amide derivatives and phenols. The conversion is achieved via chemo-selective oxidation of the secondary benzylic alcohol and subsequent Cu-catalyzed aerobic amide bond formation.

Imidazoheterocycles represent an important class of heterocycles that have numerous applications in medicinal and biological chemistry. In particular, imidazo[1,2-a]pyridine is the key structural moiety in pharmacologically important molecules. **Chapter 5** discloses a method for the aerobic oxidative synthesis of imidazo[1,2-a]pyridines from 2-oxo ketones and 2-aminopyridines. The method is proved to be mild, efficient, operational simple and using a widely available and cheap catalyst CuI.

CHAPTER 1

Ruthenium-Catalyzed Cyclic Imide Synthesis from Simple Diols

1.1 Introduction

The imide moiety represents a very important functional group which has a very broad application in medicinal and synthetic chemistry.¹ Notably, cyclic imides are of particular importance appearing in many natural products and drugs, such as phensuximide¹, palasimide,² salfredins,³ thalidomide,⁴ julocrotine,⁵ lamprolobine,⁶ and migrastatin.⁷ (Figure 1.1).

Figure 1.1 Cyclic imide-based bioactive molecules.

¹ (a) Hargreaves, M. K.; Pritchard, J. G.; Dave, H. R. *Chem. Rev.* **1970**, 70, 439; b) Kamitori, Y.; Hojo, M.; Masuda, R.; Kimura, T.; Yoshida, T. *J. Org. Chem.* **1986**, 51, 1427; c) Rad-Moghadam, K.; Kheyrkhah, L.; *Synth. Commun.* **2009**, 39, 2108; d) Abell, A. D.; Oldham, M. D. *J. Org. Chem.* **1997**, 62, 1509; e) Barker, D.; Lin, D. H. S.; Carland, J. E.; Chu, C. P. Y.; Chebib, M.; Brimble, M. A.; Savage, G. P.; McLeod, M. D. *Bioorg. Med. Chem.* **2005**, 13, 4565; f) de Figueiredo, R. M.; Voith, M.; Fröhlich, R.; Christmann, M. *Synlett* **2007**, 391; g) Luzzio, F. A. *Sci. Synth.* **2005**, 21, 259; h) Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, 62, 2652.

² (a) Peter, M. G.; Snatzke, G.; Snatzke, F.; Nagarajan, K. N.; Schmid, H. *Helv. Chim. Acta* **1974**, 57, 32. (b) Bochi, R. J.; Fisher, M. H. *Tetrahedron Lett.* **1968**, 9, 1971.

³ Matsumoto, K.; Nagashima, K.; Kamiguchi, T.; Kawamura, Y.; Yasuda, Y.; Ishii, K.; Uotani, N.; Sato, T.; Nakai, H.; Terui, Y.; Kikuchi, J.; Ikenisi, Y.; Yoshida, T.; Kato, T.; Itazaki, H. *J. Antibiot.* **1995**, 48, 439.

⁴ (a) Shoji, A.; Kuwahara, M.; Ozaki, H.; Sawai, H. *J. Am. Chem. Soc.* **2007**, 129, 1456; (b) Luzzio, F. A.; Duveau, D. Y.; Lepper, E. R.; Figg, W. D. *J. Org. Chem.* **2005**, 70, 10117; c) Franks, M. E.; Macpherson, G. R.; Figg, W. D. *Lancet* **2004**, 363, 1802.

Although cyclic imide derivatives have numerous applications, available synthetic methods from simple substrates are very limited. Traditionally, the general approaches are the dehydrative condensation of anhydrides with amines at high temperature, or in the presence of Lewis acids,^{1,8} and the dehydrative cyclization of an amic acid with help of acidic reagents.^{1,9} However, neither of the methods are atom economical and they always generate stoichiometric amount of by-products (Scheme 1.1).¹⁰

Scheme 1.1

Recently, several novel and efficient approaches have been developed for the synthesis of cyclic imides. In 2003, Murahashi and co-worker reported an iridium-catalyzed

⁵ Nakano, T.; Djerassi, C.; Corral, R. A.; Orazi, O. O. *J. Org. Chem.* **1961**, 26, 1184.

⁶ Hart, N. K.; Johns, S. R.; Lamberton, J. A. *J. Chem. Soc. Chem. Commun.* **1968**, 302.

⁷ Gaul, C.; Njardarson, J. T.; Shan, D.; Dorn, D. C.; Wu, K. D.; Tong, W. P.; Huang, X. Y.; Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, 126, 11326.

⁸ Da Settimo, A.; Primofiore, G.; Da Settimo, F.; Simorini, F.; La Motta, C.; Martinelli, A.; Boldrini, E. *Eur. J. Med. Chem.* **1996**, 31, 49.

⁹ Mehta, N. B.; Phillips, A. P.; Lui, F. F.; Brooks, R.E. *J. Org. Chem.* **1960**, 25, 1012.

¹⁰ (a) Li, C. J.; Trost, B. M. *Proc. Natl. Acad. Sci. USA* **2008**, 105, 13197. (b) Trost, B. M. *Science* **1991**, 254, 1471.

multicomponent synthesis of glutarimides. This novel three-component reaction of nitriles, olefins, and water occurs in the presence of $[\text{IrH}_5(\text{P}^i\text{Pr}_3)_2]$ to provide glutarimides in high efficiency (Scheme 1.2).¹¹

Scheme 1.2

Succinimide derivatives could be synthesized from 4-formyl- β -lactam by ring expansion. For example, You and co-workers developed a *N*-heterocyclic carbene (NHC)-catalyzed ring expansion of 4-formyl- β -lactam to form succinimides (Scheme 1.3).¹²

Scheme 1.3

In 2009, Beller and co-workers also reported an iron-catalyzed synthesis of succinimides by carbonylation of alkynes with ammonia or amines. Based on the double carbonylation of

¹¹ Takaya, H.; Yoshida, K.; Isozaki, K.; Terai, H.; Murahashi, S.-I. *Angew. Chem.* **2003**, 115, 3424; *Angew. Chem. Int. Ed.* **2003**, 42, 3302.

¹² (a) Domingo, L. R.; Aurell, M. M. J.; Arno, M. *Tetrahedron* **2009**, 65, 3432. (b) Li, G. Q.; Li, Y.; Dai, L. X.; You, S. L. *Adv. Synth. Catal.* **2008**, 350, 1258. (c) Li, G. Q.; Li, Y.; Dai, X. L.; You, S. L. *Org. Lett.* **2007**, 9, 3519. (d) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Chem. Commun.* **2007**, 4788.

¹³ Driller, K. M.; Klein, H.; Jackstell, R.; Beller, M. *Angew. Chem.* **2009**, 121, 6157; *Angew. Chem. Int. Ed.* **2009**, 48, 6041.

alkynes and intra-molecular nucleophilic attack, this convenient method afforded a range of substituted succinimides in high efficiency and good selectivity (Scheme 1.4).¹³

Scheme 1.4

Phthalimides are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. Recently, Larock reported a palladium-catalyzed aminocarbonylation of *o*-halobenzoates producing 2-substituted isoindole-1,3-diones in good yields. This methodology tolerates a variety of functional groups, including methoxy, alcohol, ketone, and nitro groups (Scheme 1.5).^{14a}

Scheme 1.5

Besides, Chatani and co-workers have reported a ruthenium-catalyzed carbonylation of aromatic amides having a pyridine-2-ylmethylamine moiety affording phthalimides by C-H bond activation (Scheme 1.6).^{14b}

Scheme 1.6

Chiral 3-substituted succinimide derivatives could be produced by rhodium-catalysed 1,4-addition of aryl boronic acids to maleimides, and this 1,4-adducts containing a quaternary stereocenter can be synthesized with high region- and enantioselectivity.¹⁵

However, all of these synthetic methodologies have their disadvantages such as limited availability of precursors when used to produce a broad range of functionalized cyclic imides. Therefore, new synthetic methodologies for the cyclic imide synthesis are of great importance, especially when the atom-economical synthetic method from widely used starting materials could be achieved.

In 2007, Milstein reported the first environmentally friendly protocol for the amide synthesis from amines and alcohols using a ruthenium pincer complex, where two molecules of dihydrogen are liberated. It is proposed that the reaction proceeds through a hemiaminal intermediate generating from aldehyde and amine, and it is subsequently dehydrogenated to

¹⁴ (a) Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2008**, 73, 7175. (b) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, 131, 6898.

give the amide as the product. The hemiaminal may also eliminate water to generate an imine which can undergo hydrogenation to form a secondary amine (Scheme 1.7).^{16d}

Scheme 1.7

After this breakthrough, many groups have reported the synthesis of amides from alcohols and amines using ruthenium-,^{16,17} rhodium-,¹⁸ and silver-based catalysts¹⁹. Hong and co-workers have also developed several efficient ruthenium-based catalytic systems for the amide formation by dehydrogenation.¹⁷

To address the challenge of atom-economical synthesis of cyclic imide, it is proposed that direct synthesis of cyclic imides could be achieved from the reaction of alcohols with amides with the liberation of hydrogen. The strategy was similar to the reported amide synthesis

¹⁵ (a) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem.* **2005**, 117, 4687; *Angew. Chem. Int. Ed.* **2005**, 44, 4611. (b) Shintani, R.; Duan, W. L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, 128, 5628. (c) Iyer, P. S.; O'Malley, M. M.; Lucas, M. C. *Tetrahedron Lett.* **2007**, 48, 4413.

¹⁶ (a) Naota, T.; Murahashi, S.-I. *Synlett* **1991**, 693; (b) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, 11, 2667. (c) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, 130, 17 672. (d) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, 317, 790.

from alcohols and amines. So, an efficient catalytic system was of great importance to realize the reaction of aldehyde with the inactive amide containing a less nucleophilic nitrogen atom.

Herein, we reported a direct synthesis of cyclic imides from amines and 1,4-butandiol or 1,5-pentadiols using an ruthenium-hydride-based catalytic system (Scheme 1.8).

1. High atom economy
2. Librating H_2 as the sole by-product
3. No stoichiometric activating reagents
4. Precursors are readily available

Scheme 1.8

¹⁷ (a) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, 351, 2643. (b) Zhang, Y.; Chen, C.; Ghosh, S. C.; Li, Y.; Hong, S. H. *Organometallics* **2010**, 29, 1374. (c) Muthaiah, S.; Ghosh, S. C.; Jee, J.-E.; Chen, C.; Zhang, J.; Hong, S. H. *J. Org. Chem.* **2010**, 75, 3002.

¹⁸ (a) Fujita, K.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, 6, 2785. (b) Zweifel, T.; Naubron, J. V.; Grützmaier, H. *Angew. Chem.* **2009**, 121, 567; *Angew. Chem. Int. Ed.* **2009**, 48, 559.

¹⁹ Shimizu, K.; Ohshima, K.; Satsuma, A. *Chem. Eur. J.* **2009**, 15, 9977.

²⁰ For a recent review, see: Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, 110, 681.

1.2 Results and discussion

At the outset of our research, the reaction of 1,4-butanediol (**3a**) and benzylamine (**4a**) providing *N*-benzylsuccinimide (**5a**) was explored to screen the catalytic systems (Table 1.1) by employing the reported ruthenium catalytic systems used in amide formation from alcohols and amines.^{16,17}

Table 1.1 Catalyst screening ^a

Reaction scheme: 1,4-butanediol (**3a**) + benzylamine (**4a**) $\xrightarrow[\text{i-Pr-N}^+\text{C}_2\text{N}^+\text{i-Pr Br}^- \text{ (NHC)}]{[\text{Ru}] \text{ (5 mol\%)}}$ *N*-benzylsuccinimide (**5a**)

Entry	Catalyst	Ligand	Yield (%) ^b
1	[Ru(<i>p</i> -cymene)Cl ₂] ₂	dppb	0
2	RuH ₂ (PPh ₃) ₄	-	0
3	[Ru(benzene)Cl ₂] ₂	NHC, MeCN	14
4	[Ru(<i>p</i> -cymene)Cl ₂] ₂	NHC, pyridine	28
5	RuH₂(PPh₃)₄	NHC, MeCN	70
6	Ru(COD)Cl ₂	NHC, PCy ₃	41
7	Milstein catalyst	-	52

Milstein catalyst

^a Reaction conditions: diol (0.5 mmol), amine (0.55 mmol), 5 mol% catalyst, 5 mol% ligand, toluene (0.80 mL), reflux, under argon atmosphere, 24h. ^b Isolated yield.

Both of ruthenium complexes [{Ru(benzene)Cl₂}]₂^{17a} and [{Ru(*p*-cymene) Cl₂}]₂^{17b} exhibited limited activities, even in the presence of an *N*-heterocyclic carbene (NHC) ligand generating from 1,3-diisopropylimidazolium bromide (**2**) (Table 1.1, entries 1 and 2). Complex [{Ru(*p*-cymene)Cl₂}]₂ also exhibited no activity for the cyclic imide formation with

the help of diphenylphosphinobutane (dppb) ligand (Table 1.1, entry 3).^{16b} While $[\text{RuH}_2(\text{PPh}_3)_4]$ alone exhibited no catalytic activity toward this transformation, it showed good activity with NHC precursor **2**, and the corresponding cyclic imide was obtained in 70% yield (Table 1.1, entry 5).²¹ This ruthenium-hydride-based catalytic system was previously proved to be efficient for the amide synthesis from amines with alcohols or aldehydes.^{17c} Other catalytic systems using $\text{Ru}(\text{COD})\text{Cl}_2$ ^{16c} and Milstein catalyst^{16d} showed lower activities (Table 1, entries 6 and 7).

With identified catalytic system in hand, we examined various of amines with 1,4-butanediol to obtain *N*-functionalized succinimides (Table 1.2). Both of alkyl and benzyl amines exhibited excellent activities toward **3a** (Table 1.2, **5a-5f**). Notably, electron-rich benzyl amines performed much better than electron-deficient ones (Table 1.2, **5e-5f**). Both of pyridine and ether functionalities were tolerant in this transformation (Table 1.2, **5g-5i**). While 2-aminomethylpyridine showed a lower activity, presumably due to prevention of ruthenium binding to **3a**, 3-aminomethylpyridine and 4-aminomethylpyridine exhibited good reactivity (Table 1.2, **5h-5i**). *tert*-Butylamine was totally inactive showing that this transformation was sensitive to steric hindrance. However, moderately steric hindered amines reacted well affording succinimide derivatives in 36-68% yields, and it is in accordance with previously reported amide syntheses (Table 1.2, **5k**, **5l** and **5m**).¹⁶⁻¹⁷

²¹ Some different NHC precursors were also tested; however, the reported conditions using NHC **2** was the most efficient. See Ref. 17c for more details.

Table 1.2 Synthesis of cyclic imide from 1,4-butanediol^a

^a Reaction conditions: Diol (0.5 mmol, 1.0 equiv), amine (1.1 equiv), RuH₂(PPh₃)₄ (5 mol %), NHC (5 mol %), NaH (20 mol %), MeCN (5 mol %), toluene, reflux, 24 h. All yields are of isolated yield.

²² (a) Murahashi, S.-I.; Ito, K. I.; Naota, T.; Maeda, Y. *Tetrahedron Lett.* **1981**, 22, 5327. (b) Murahashi, S.-I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, 52, 4319. (c) Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, 51, 2034. (d) Blum, Y.; Shvo, Y. *J. Organomet. Chem.* **1984**, 263, 93. (e) Zhao, J.; Hartwig, J. F. *Organometallics* **2005**, 24, 2441. (f) Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* **2007**, 9, 1821. (g) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, 23, 229. (h) Abbenhuis, R. A. T. M.; Boersma, J.; van Koten, G. *J. Org. Chem.* **1998**, 63, 4282.

²³ It has been reported that cyclic amines can be formed from diols and primary amines by ruthenium catalysis. However, we did not observe any cyclic amine by-products. For representative examples of cyclic-amine formation, see Refs. 22g-h.

Aryl amines such as aniline showed no reactivity as previously reported results in the amide formation.^{16c,17} γ -Butyrolactone was usually detected in the reactions, especially with low yielding substrates.²² Some other unknown by-products were also observed presumably generating from inter- and intra-molecular amide bond formation and esterification reactions.^{22, 23}

Table 1.3 Synthesis of cyclic imide from various diols ^a

^a Reaction conditions: Diol (0.5 mmol, 1.0 equiv), amine (1.1 equiv), $\text{RuH}_2(\text{PPh}_3)_4$ (5 mol %), NHC (5 mol %), NaH (20 mol %), MeCN (5 mol %), toluene (0.5 mL), reflux, 24 h. All are isolated yields. ^b With 0.3 M concentration.

Encouraged by the efficient synthesis of succinimides from 1,4-butanediol (**3a**), a series of diols were also tested to obtain a broad range of functionalized cyclic imides (Table 1.3). Both of 2-aryl- and alkyl- substituted 1,4-butanediols provided desired products in good yields (Table 1.3, **5n** and **5o**). *cis*-1,2-Cyclohexanedimethanol was also smoothly converted to a bicyclic succinimides in 80% yield (Table 1.3, **5p**). Phthalimide derivatives were efficiently synthesized from 1, 2-benzenedimethanol in moderate to good yields (Table 1.3, **5q-5t**). At a lower concentration of 0.3M, imide **5q** was obtained in decreased yield (21% yield) along with phthalide (61% yield). The efficient synthesis of phthalides from 1,2-benzenedimethanol was previously reported with Cp*-ligated ruthenium(II)-based catalytic systems.²² Six-membered glutarimides derivatives were also obtained from 1,5-pentadiol in moderate yields (Table 1.3, **5u** and **5v**). Unfortunately, reaction of 1,6-hexanediol with amine failed to produce a seven-membered cyclic imide. Phensuximide, an anticonvulsant drug, was smoothly obtained from 2-phenyl-1,4-butanediol and methylamine in 63% yield (Table 1.3, **5w**).

Linear imide synthesis was also tested from the inter-molecular reaction of amides with alcohols (Scheme 1.9). Unfortunately, neither amide **6** nor amine **4e** afforded linear imide in the presence of alcohol. Amide **6** was recovered totally, and the reaction of **4e** and alcohol **7** only produced amide **9** in 82% yield. The intra-molecular reaction of **10** provided corresponding cyclic imide in 70% yield suggesting that the imide bond formation may form *via* a stepwise process which favored 5- or 6-membered ring formation.

Scheme 1.9

Based on the observations in our study and previously reported mechanisms for amide bond formation from amines and alcohols, we proposed a possible mechanism based on Ru(0)/Ru(II) cycle from the previous study (Figure 1.2).^{17c} Reaction of diol and amine provided an amide intermediate **A**, and further cyclization occurred to afford a cyclic imide. Existence of a lactone intermediate in the formation of a cyclic imide was ruled out, as only a trace amount (< 5%) of succinimide **5e** was observed in the reaction of γ -butyrolactone with amine (Scheme 1.20).

Scheme 1.20

Figure 1.2 Proposed mechanism

1.3 Conclusion

In conclusion, we have developed a direct cyclic imide synthesis from simple diols and amines using an in-situ-generated ruthenium hydride catalytic system. This atom economical method will provide an alternative approach for the synthesis of succinimides, phthalimides, and glutarimides. However, this ruthenium-hydride-based catalytic system is inactive for the formation of linear imide.

1.4 Experimental section

1.4.1 General Considerations

All reactions were carried out in oven-dried glassware under an inert atmosphere of dry argon or nitrogen. All alcohols and amines were obtained from Aldrich or Alfa Aesar and used as received. Toluene was dried over a Pure Solv solvent purification system. Analytical TLC was performed on a Merck 60 F254 silica gel (0.25 mm thickness). Column chromatography was performed on Merck 60 silica gel (230-400 mesh). NMR spectra were recorded on a Bruker 300MHz spectrometer. Tetramethylsilane was used as reference, and the chemical shifts were reported in ppm and the coupling constants in Hz. GC yields were obtained on an Agilent 7890A instrument equipped with an HP-5 column using dodecane as an internal standard. Mass spectrometry was performed by Waters Q-ToF Premier Micromass instrument, using Electro Spray Ionization (ESI) mode. 1,3-diisopropylimidazolium bromide,²⁴ $\text{RuH}_2(\text{PPh}_3)_4$,²⁵ were prepared according to the reported procedures.

²⁴ Starikova, O. V.; Dolgushin, G. V.; Larina, L. I. *Russ. J. Org. Chem.* **2003**, 39, 1467.

²⁵ Levison, J. J.; Robinson, S. D. *J. Chem. Soc. (A)* **1970**, 2947-2954.

1.4.2 General Procedure for the Synthesis of Imides

$\text{RuH}_2(\text{PPh}_3)_4$ (28 mg, 0.025 mmol), 1,3-diisopropylimidazolium bromide (5.8 mg, 0.025 mmol), NaH (2.4 mg, 0.10 mmol) and acetonitrile (1.2 μL , 0.025 mmol) were placed in an oven dried Schlenk tube inside the glove box; toluene (0.8 mL) was added to the mixture over there. The Schlenk tube was taken out and heated to reflux in an oil bath under an argon atmosphere. The flask was removed from the oil bath after 20 min and the 1,4-butanediol (0.5 mmol) and benzylamine (0.55 mmol) were added. The mixture was heated to reflux under an argon atmosphere for 24 h. The reaction mixture was cooled to room temperature; the solvent was removed under vacuum and the residue was purified by silica gel flash column chromatography to afford *N*-benzyl pyrrolidine-2,5-dione (**5a**) (66 mg, yield = 70%).

1.4.3 Characterization data of imides 5a-5x

White solid, isolated yield: 70%. ^1H NMR (CDCl_3): δ = 7.23–7.38 (m, 5H), 4.63 (s, 2H),

2.68 (s, 4H).

Colorless oil, isolated yield: 81%. ¹H NMR (CDCl₃): δ = 3.46 (t, 2H, *J* = 7.5Hz), 2.66 (s, 4H), 1.52 (m, 2H), 1.22-1.25 (b, 6H), 0.84 (t, 3H, *J* = 6.9Hz). ¹³CNMR (CDCl₃): δ = 177.3, 38.9, 31.3, 28.1, 27.6, 26.5, 22.5, 14.0. HRMS (ESI): *m/z* calcd. for C₁₀H₁₇NO₂ [MH⁺]: 184.1338; found 184.1341.

Colorless oil, isolated yield: 76%. ¹H NMR (CDCl₃): δ = 7.17-7.28 (m, 5H), 3.69-3.74 (m, 2H), 2.82-2.87 (m, 2H), 2.61 (s, 4H). ¹³CNMR (CDCl₃): δ = 177.0, 137.8, 128.8, 128.5, 126.7, 39.9, 35.5, 28.1. HRMS (ESI): *m/z* calcd. for C₁₂H₁₃NO₂ [MH⁺]: 204.1025; found 204.1028.

White solid, isolated yield: 88%. ¹H NMR (CDCl₃): δ = 7.11-7.26 (m, 5H), 3.53 (t, 2H, *J*

²⁶ Reddy, P.Y.; Kondo, S.; Toru, T. *J. Org. Chem.* **1997**, 62, 2652-2654

²⁷ Rice, L.M.; E.; Reid, E.E. Grogan C.H. *J. Org. Chem.*, **1954**, 19 (6), 884-893

= 7.2 Hz), 2.61(t, 2H, J = 7.5 Hz), 2.53 (s, 4H), 1.91 (m, 2H). ^{13}C NMR (CDCl_3): δ = 177.3, 141.0, 128.41, 128.2, 126.0, 38.7, 33.2, 28.4, 28.1. HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_2$ [MH^+]: 218.1181; found 218.1185.

1-(4-methoxybenzyl)-pyrrolidine-2, 5-dione (**5e**)²⁸

White solid, isolated yield: 87%. ^1H NMR (CDCl_3): δ = 7.31 (d, 2H, J = 8.7 Hz), 6.79 (d, 2H, J = 8.7Hz), 4.57 (s, 2H), 3.75 (s, 3H), 2.65 (s, 4H). ^{13}C NMR (CDCl_3): δ = 176.9, 159.3, 130.4, 128.1, 113.9, 55.3, 41.8, 28.2.

1-(4-fluorobenzyl)-pyrrolidine-2, 5-dione (**5f**)²⁹

Brown oil, isolated yield: 61%. ^1H NMR (CDCl_3): δ = 7.33-7.37 (m, 2H), 6.93-6.98 (m, 2H), 4.59 (s, 2H), 2.68 (s, 4H). ^{13}C NMR (CDCl_3): δ = 176.8, 130.9, 130.8, 115.6, 115.4, 41.6, 28.2. HRMS (ESI): m/z calcd. for $\text{C}_{11}\text{H}_{10}\text{FNO}_2$ [MH^+]: 208.0774; found 208.0773.

1-(2-Pyridinylmethyl)-2, 5-pyrrolidinedione (**5g**) (New Compound)

Colorless oil, isolated yield: 44%. ^1H NMR (CDCl_3): δ = 8.47 (d, 1H, J = 4.2 Hz), 7.57-7.63 (m, 1H), 7.22(b, 1H), 7.11-7.15 (m, 1H), 4.79 (s, 2H), 2.77 (s, 4H). ^{13}C NMR (CDCl_3): δ = 177.1, 154.5, 149.6, 136.7, 122.6, 122.0, 43.5, 28.3. HRMS (ESI): m/z calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$ [MH^+]: 190.0821; found 191.0816.

1-(3-Pyridinylmethyl)-2, 5-pyrrolidinedione (**5h**)³⁰

Colorless oil, isolated yield: 73%. ^1H NMR (CDCl_3): δ = 8.60 (s, 1H), 8.48 (d, 1H, J = 4.8), 7.68(d, 1H, J = 7.8), 7.17-7.23 (m, 1H), 4.61 (s, 2H), 2.68 (s, 4H). ^{13}C NMR (CDCl_3): δ = 176.6, 150.3, 149.4, 136.7, 131.4, 123.5, 39.9, 28.2. HRMS (ESI): m/z calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$ [MH^+]: 191.0821; found 191.0823.

1-(4-Pyridinylmethyl)-2, 5-pyrrolidinedione (**5i**)²⁹

White solid, isolated yield: 59%. ^1H NMR (CDCl_3): δ = 8.51 (dd, 2H, J = 1.8 Hz, J = 4.5 Hz), 7.21 (dd, 2H, J = 1.8 Hz, J = 4.5 Hz), 4.61(s, 2H), 2.72 (s, 4H). ^{13}C NMR (CDCl_3): δ = 176.6, 150.2, 144.1, 123.3, 41.3, 28.2. HRMS (ESI): m/z calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$ [MH^+]: 191.0821; found 191.0824.

1-(2,2-dimethoxyethyl)-2,5-pyrrolidinedione (**5j**) (New Compound):

White solid, isolated yield: 73%. ^1H NMR (CDCl_3): δ = 4.64 (t, 1H, J = 5.7Hz), 3.60 (d, 2H, J = 5.7Hz), 3.29 (s, 6H), 2.68 (s, 4H). ^{13}C NMR (CDCl_3): δ = 176.9, 99.1, 52.9, 39.4, 28.1. HRMS (ESI): m/z calcd. for $\text{C}_8\text{H}_{13}\text{NO}_4$ [MH^+]: 188.0923; found 188.0927.

1-cyclopentylpyrrolidine-2,5-dione (**5k**)²⁹

White solid, isolated yield: 68%. ^1H NMR (CDCl_3): δ = 4.43 (m, 1H), 2.60 (s, 4H), 1.69-1.99 (m, 6H), 1.53-1.58 (m, 2H). ^{13}C NMR (CDCl_3): δ = 177.4, 51.6, 28.5, 28.1, 25.1.

N-cyclohexylsuccinimide (**5l**)³¹

Colorless oil, isolated yield: 57%. ^1H NMR (CDCl_3): δ = 3.87-3.97 (m, 1H), 2.59 (s, 4H), 2.03-2.16 (m, 2H), 1.69-1.79 (m, 2H), 1.50-1.62 (m, 3H), 1.20-1.33 (m, 3H). ^{13}C NMR (CDCl_3): δ = 177.4, 51.7, 28.7, 28.1, 25.9, 25.0.

³⁰ Sattler, H.J.; Schmitz, H.; Schunack, W. *Pharmaceutica Acta Helvetica*, **1975**, 50, 298-303.

³¹ Bikash, P.; Prasun, K.P.; Parasuraman, J. *Synthesis*, **2003**, 10, 1549-1552.

³² Far, A.R.; Tidwell, T. T. *J. Org. Chem.* **1998**, 63, 8636-8637.

1-(1-phenylethyl) pyrrolidine-2, 5-dione (**5m**)³²

Colorless oil, isolated yield: 36%. ¹H NMR (CDCl₃): δ = 7.23-7.44 (m, 5H), 5.39 (m, 1H), 2.61 (s, 4H), 2.78 (d, 3H, *J* = 7.5H). ¹³CNMR (CDCl₃): δ = 177.0, 139.6, 128.4, 127.8, 127.6, 50.3, 28.1, 16.5.

1-(4-methoxybenzyl)-3-phenyl-pyrrolidine-2,5-dione (**5n**) (New

Compound)

Colorless oil, isolated yield: 78%. ¹H NMR (CDCl₃): δ = 7.23-7.34 (m, 5H), 7.10-7.13 (m, 2H), 6.81(d, 2H, *J* = 8.7Hz), 4.65 (d, 1H, *J* = 13.8 Hz), 4.58 (d, 1H, *J* = 13.8Hz), 3.95 (dd, 1H, *J* = 4.8 Hz, *J* = 6.6 Hz), 3.75 (s, 3H), 3.14 (dd, 1H, *J* = 18.6 Hz, *J* = 6.6 Hz), 2.75 (dd, 1H, *J* = 18.6 Hz, *J* = 4.8 Hz). ¹³CNMR (CDCl₃): δ = 177.5, 175.8, 159.4, 137.2, 130.4, 129.2, 128.1, 127.9, 127.4, 114.0, 55.3, 45.9, 42.2, 37.2. HRMS (ESI): *m/z* calcd. for C₁₈H₁₇NO₃ [MH⁺]: 296.1287; found 296.1284.

1-(4-methoxybenzyl)-3-methyl-3-phenyl-pyrrolidine-2,5-dione

(**5o**) (New Compound)

Colorless oil, isolated yield: 45%. ¹H NMR (CDCl₃): δ = 7.19-7.40 (m, 7H), 6.84-6.87 (m,

2H), 4.68 (s, 2H), 3.80 (s, 3H), 3.10 (d, 1H, $J = 18$ Hz), 2.85 (d, 2H, $J = 18.0$ Hz), 1.70 (s, 3H). ^{13}C NMR (CDCl_3): $\delta = 180.7, 175.2, 159.3, 141.9, 130.1, 129.0, 128.9, 128.1, 127.5, 125.6, 125.2, 114.0, 55.3, 47.8, 45.3, 42.1, 42.0, 25.5$. HRMS (ESI): m/z calcd. for $\text{C}_{19}\text{H}_{19}\text{NO}_3$ [MH^+]: 310.1443; found 310.1443.

N-(4-methoxybenzyl)-*cis*-hexahydrophthalimide (**5p**) (New

Compound)

Colorless oil, isolated yield: 80%. ^1H NMR (CDCl_3): $\delta = 7.25$ (d, 2H, $J = 8.7$ Hz), 6.78 (d, 2H, $J = 8.7$ Hz), 4.52 (s, 2H), 3.73 (s, 3H), 2.7 (m, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.35 (m, 4H). ^{13}C NMR (CDCl_3): $\delta = 179.4, 159.2, 130.1, 128.4, 113.9, 55.2, 41.5, 39.8, 23.6, 21.5$. HRMS (ESI): m/z calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_3$ [MH^+]: 274.1443; found 274.1443.

N-(4-methoxybenzyl)-phthalimide (**5q**)³³

White solid, isolated yield: 45%. ^1H NMR (CDCl_3): $\delta = 7.80$ (m, 2H), 7.65 (m, 2H), 7.36 (d, 2H, $J = 8.7$ Hz), 6.78 (d, 2H, $J = 8.7$ Hz), 4.75 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (CDCl_3): $\delta = 168.1, 159.2, 133.9, 132.2, 130.2, 128.7, 123.3, 114.0, 55.3, 41.1$. HRMS (ESI): m/z calcd.

for $C_{16}H_{13}NO_3$ $[MH^+]$: 268.0974; found 268.0977.

Colorless oil, isolated yield: 66%. 1H NMR ($CDCl_3$): δ = 7.65-7.81 (m, 4H), 7.08-7.24 (m, 5H), 3.72 (t, 2H, J = 7.2 Hz), 2.66 (t, 2H, J = 7.5 Hz), 1.96-2.06 (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 168.4, 141.0, 133.9, 132.1, 128.4, 128.3, 125.9, 123.2, 37.8, 33.2, 29.9. HRMS (ESI): m/z calcd. for $C_{17}H_{15}NO_2$ $[MH^+]$: 266.1181; found 266.1180.

Colorless oil, isolated yield: 60%. 1H NMR ($CDCl_3$): δ = 7.62-7.80 (m, 4H), 3.62 (t, 2H, J = 7.5 Hz), 1.57-1.67 (m, 2H), 1.24-1.33 (m, 4H), 0.83 (t, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ = 168.4, 133.8, 132.2, 123.1, 38.0, 29.0, 28.3, 22.3, 13.9. HRMS (ESI): m/z calcd. for $C_{13}H_{15}NO_2$ $[MH^+]$: 218.1181; found 218.1180.

Colorless oil, isolated yield: 51%. 1H NMR ($CDCl_3$): δ = 8.67 (d, 1H, J = 2.1 Hz), 8.49 (dd, 1H, J = 1.5 Hz, J = 4.8 Hz), 7.67-7.84 (m, 5H), 7.19-7.22 (m, 2H), 4.82 (s, 2H).

^{13}C NMR (CDCl_3): $\delta = 167.8, 150.1, 149.3, 136.4, 134.2, 132.0, 123.6, 123.5, 39.1$.

1-(4-methoxybenzyl)-2,6-dione (**5u**)³⁰

Colorless oil, isolated yield: 44%. ^1H NMR (CDCl_3): $\delta = 7.31$ (d, 2H, $J = 8.7$ Hz), 6.78 (d, 2H, $J = 8.7$ Hz), 4.85 (s, 2H), 3.74 (s, 3H), 2.62 (t, 4H, $J = 5.4$ Hz), 1.88 (m, 2H). ^{13}C NMR (CDCl_3): $\delta = 172.4, 158.9, 130.5, 129.6, 113.7, 55.2, 42.1, 32.9, 17.1$. HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_3$ [MH^+]: 234.1130; found 234.1134.

1-benzylpiperidine-2,6-dione (**5v**)²⁶

Colorless oil, isolated yield: 48%. ^1H NMR (CDCl_3): $\delta = 7.17$ -7.34 (m, 5H), 4.92 (s, 2H), 2.63 (t, 4H, $J = 6.6$ Hz), 1.85-1.94 (m, 2H). ^{13}C NMR (CDCl_3): $\delta = 172.4, 137.3, 128.8, 128.4, 127.4, 42.7, 32.9, 17.1$.

1-methyl-3-phenyl-pyrrolidine-2,5-dione (**5w**)³⁷

Colorless oil, isolated yield: 63%. ^1H NMR (CDCl_3): $\delta = 7.18$ -7.36 (m, 5H), 4.00 (dd, 1H, $J = 3.6$ Hz, $J = 6.9$ Hz), 3.17 (dd, 1H, $J = 7.2$ Hz, $J = 13.8$ Hz), 3.04 (s, 3H), 2.79 (dd, 1H, $J = 3.6$ Hz, $J = 13.8$ Hz). ^{13}C NMR (CDCl_3): $\delta = 177.8, 176.3, 137.1, 129.2, 128.0, 127.4, 46.0, 37.1, 25.2$.

Preparation of diol **3n**³⁸

To a cooled (-78°C) solution of LDA (0.011 mol) in dry THF (30 ml) was added phenylacetic acid ethyl ester (1.6 g, 0.01 mol) in dropwise. After addition, the solution was allowed to stir at -78°C for 30 min. Then a solution of bromoacetic acid methyl ester (1.84 g, 0.011 mol) in THF (5 ml) was added in portions and the mixture was allowed to warm to -10°C gradually before quenched by aqueous Sat. ammonia chloride solution (5 ml). Then water (30 ml) was added and the mixture was extracted with DCM (30 ml×3). The organic layer was combined and dried over anhydrous sodium sulfate. After filtration, the solution was concentrated and the residue obtained was purified by silica gel flash column chromatography (Hex\EA=10:1) to afford the product as a colorless oil (2.1 g, yield = 91%). ¹H NMR (CDCl₃): δ = 7.23-7.30 (m, 5H), 4.02-4.18 (m, 3H), 3.64 (s, 3H), 3.17 (dd, 1H, *J* = 10.2 Hz, *J* = 16.8 Hz), 2.65 (dd, 1H, *J* = 5.4 Hz, *J* = 16.8 Hz), 1.17 (t, 3H, *J* = 7.2 Hz). The above obtained product (2.1 g, 0.0091 mol) was dissolved in dry ethyl ether (5ml) and the solution was added dropwise to a suspension of LAH (690 mg, 0.0182mol) in dry ethyl ether (40 ml) at -78°C. The mixture was allowed to warm to -10°C gradually with stirring. Then the mixture was quenched by aqueous Sat. ammonia chloride solution (5 ml). More water (30 ml) was added to the mixture and it was extracted with DCM (30 ml×3). The organic layer was combined and dried over anhydrous sodium sulfate. After filtration, the solution was concentrated and the residue obtained was purified by silica gel flash column chromatography (Hex\EA=1:1) to afford 2-

phenyl- 1,4-butanediol as a colorless oil (1.2 g, yield = 82%). ^1H NMR (CDCl_3): δ = 7.17-7.32 (m, 5H), 3.72 (d, 2H, J = 6.6 Hz), 3.55-3.68 (m, 2H), 2.87-2.96 (m, 1H), 2.26 (b, 2H), 1.82-2.01 (m, 2H).

Preparation of diol **3o**³⁹

To a solution of LDA (0.018 mol) in dry THF (30ml) was added phenylacetic acid ethyl ester (2.46 g, 0.015 mol) in dropwise at -78°C . After addition, the mixture was allowed to stirred at same temperature for 20min. Then methyl iodine (2.6 g, 0.018 mol) was added and the mixture was allowed to stir at -78°C for 3 h. The solution was quenched by Sat. ammonia chloride (3ml) and water was added (20ml). The mixture was extracted with ethyl acetate (20ml $\times$ 3). The organic layer was combined and dried over anhydrous sodium sulfate. After filtration, the solution was concentrated to afford the crude product, which was purified by silica gel flash column chromatography (Hex\EA=1:1) to afford 2-methyl-phenylacetic acid ethyl ester as a colorless oil (2.5 g, yield = 94%). ^1H NMR (CDCl_3): δ = 7.22-7.30 (m, 5H), 4.05-4.14 (m, 2H), 3.70 (q, 1H, J = 7.2 Hz), 1.48 (d, 3H, J = 7.2 Hz), 1.18 (t, 3H, J = 7.2 Hz). The above obtained product (2.5g, 0.014 mol) was dissolved in dry THF (5ml) and the solution was added to a pre-cooled solution of LDA (0.0167 mol) in THF (25ml) at -78°C . After mixture was stirred at -78°C for 20min, bromoacetic acid methyl ester (2.2g, 0.014 mol) in THF (5 ml) was added in portions and the mixture was allowed to warm to -10°C gradually before quenched by aqueous Sat. ammonia chloride solution (5 ml). Then water (30 ml) was

added and the mixture was extracted with DCM (30 ml×3). The organic layer was combined and dried over anhydrous sodium sulfate. After filtration, the solution was concentrated and the residue obtained was purified by silica gel flash column chromatography (Hex/EA=10:1) to afford the product as a colorless oil (3.2 g, yield = 91%). ^1H NMR (CDCl_3): δ = 7.20-7.30 (m, 5H), 4.14 (q, 2H, J = 7.2 Hz), 3.62 (s, 3H), 3.24 (d, 1H, J = 16.2 Hz), 2.75 (d, 1H, J = 16.2Hz), 1.67 (s, 3H), 1.17 (t, 3H, J = 7.2 Hz). The above obtained product (2.9g, 0.0116mol) was dissolved in dry ethyl ether (5ml) and the solution was added dropwise to a suspension of LAH (900 mg, 0.024mol) in dry ethyl ether (40 ml) at -78°C . The mixture was allowed to warm to -10°C gradually with stirring. Then the mixture was quenched by aqueous Sat. ammonia chloride solution (5 ml). More water (30 ml) was added to the mixture and it was extracted with DCM (30 ml×3). The organic layer was combined and dried over anhydrous sodium sulfate. After filtration, the solution was concentrated and the residue obtained was purified by silica gel flash column chromatography (Hex/EA=1:1) to afford 2-phenyl-2-methyl-1,4-butanediol as a colorless oil (1.93 g, yield = 93%). ^1H NMR (CDCl_3): δ = 7.16-7.37 (m, 5H), 3.62-3.77 (m, 3H), 3.50-3.57 (m, 1H), 2.36 (b, 1H), 1.96-2.00 (m, 3H), 1.32 (s, 3H).

Preparation of Compound **10**⁴⁰:

To a solution of γ -lacton (1.03 g, 0.012 mol) in dry toluene (10ml) was added amine

(1.37g, 0.01mol). The solution was heated to reflux under nitrogen for 24h. After cooling and filtration, the white solid was washed with hexane and dried to afford the pure product (1.8g, Yield = 78%). ^1H NMR (CDCl_3): δ = 7.22-7.32 (m, 5H), 7.27 (d, 2H, J = 8.6 Hz), 6.82 (d, 2H, J = 8.6 Hz), 5.98 (b, 1H), 4.42 (s, 2H), 4.27 (d, 2H, J = 5.6 Hz), 3.75 (s, 3H), 3.47 (t, 2H, J = 6.0 Hz), 2.28 (t, 2H, J = 7.2 Hz), 1.87-1.96 (m, 2H).

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CHAPTER 2

*Direct N-Acylation of Lactams, Oxazolidinones, and
Imidazolidinones with Aldehydes by Shvo's Catalyst*

2.1 Introduction

N-acylated lactams are very important organic compounds exhibiting a broad range of biological activity, thus have numerous applications in pharmaceutical chemistry. Meanwhile, *N*-acylated oxazolidinone and imidazolidinone derivatives also have shown a quite broad range of biological activity and antibacterial activity. They also appear in some drugs and natural products, such as variotin,¹ janolusimide, isobengamide E, aniracetam,² pipartine, piperlotine G,³ and imidapril⁴ (Figure 2.1). Furthermore, chiral oxazolidinone derivatives are widely used in asymmetric synthesis as chiral auxiliaries and ligands.⁵

Figure 2.1. Examples of bioactive compounds containing an imide moiety

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³ Li, C. Y.; Tsai, W.; Damu, A. G.; Lee, E. J.; Wu, T. S.; Dung, N. X.; Thang, T. D.; Thanh, L. *J. Agric. Food Chem.* **2007**, 55, 9436.

⁴ (a) Hayashi, K.; Nunami, K.; Kato, J.; Yoneda, N.; Kubo, M.; Ochiai, T.; Ishida, R. *J. Med. Chem.* **1989**, 32, 289. (b) Robinson, D. M.; Curran, M. P.; Lyseng-Williamson, K. A. *Drugs* **2007**, 67, 1359.

⁵ (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, 96, 835. (b) Banks, M. R.; Blake, A. J.; Brown, A. R.; Cadogan, J. I. G.; Gaur, S.; Gosney, I.; Hodgson, P. K. G.; Thorburn, P. *Tetrahedron Lett.* **1994**, 35, 489. (c) Banks, M. R.; Blake, A. J.; Cadogan, J. I. G.; Dawson, I. M.; Gosney, I.; Grant, K. J.; Gaur, S.; Hodgson, P. K. G.; Knight, K. S.; Smith, G. W.; Stevenson, D. E. *Tetrahedron* **1992**, 48, 7979.

In general, acyl chlorides or anhydrides are used for acylation of lactams, oxazolidinones, and imidazolidinones with a strong base (Scheme 2.1).⁶

Scheme 2.1

Also, a reaction of thioamides and silver carboxylates in an aprotic media was previously reported providing imides, amides, and nitriles (Scheme 2.2).⁷

Scheme 2.2

In 2005, Nicolaou and co-workers reported a synthesis of imides by one-step oxidation of secondary amides with Dess-Martin periodinane (DMP) (Scheme 2.3).⁸

Scheme 2.3

In 2006, Evans' group provided a ceric ammonium nitrate (CAN) promoted oxidations of 4,5-diphenyloxazoles and oxazoles. This transformation resulted in the formation of the

⁶ (a) Giovannini, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, 54, 228. (b) Savoia, D.; Concialini, V.; Roffia, S.; Tarsi, L. *J. Org. Chem.* **1991**, 56, 1822. (c) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, 68, 83.

⁷ Avalos, M.; Babiano, R.; Durán, C.J.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron Letters*, **1994**, 35, 477-480.

⁸ Nicolaou, K.C.; Nathison, C.J.N. *Angew. Chem., Int. Ed.* **2005**, 44, 5992-5997.

corresponding imides in good yields and a wide variety of functional groups and substituents were tolerated (Scheme 2.4).⁹

R¹, R², R³ = Aryl, Alkyl, Alkenyl.

Scheme 2.4

Recently, Fu and co-workers developed a copper-catalyzed coupling reaction of aldehydes with amides in the presence of *N*-bromosuccinimide (NBS) (1.5 equiv.) leading to imides in good yields. Also, FeCl₂/NBS mediated coupling of thioesters with carboxamides provided another good method for the imide synthesis (Scheme 2.5).¹⁰

Scheme 2.5

In 2010, Carreira and co-workers presented a mild method for the synthesis of *N*-acylated oxazolidinones in high yields employing acid fluorides and mild bases, such as *i*Pr₂NEt and NEt₃ (Scheme 2.6).¹¹

⁹ Evans, D.A.; Nagorny, P.; Xu, R. *Org. Lett.*, **2006**, 8, 5669-5671.

¹⁰ Wang, L.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Chem. Eur. J.* **2008**, 14, 10722.

¹¹ Schindler, C. S.; Forster, P. M.; Carreira, E. M. *Org. Lett.* **2010**, 12, 4102.

Scheme 2.6

However, these synthetic methods are not atom economical with the generation of halide and other wasters.

Although a series of methods have been reported on amide formation from amines and aldehydes, synthesis of imide from the acylation of amides has not been well studied. Amide, which has a less nucleophilic nitrogen atom, exhibits limited activity towards aldehyde. So, it is highly desirable to explore more efficient and environmentally friendly method to obtain *N*-acylation products of the amides from simple starting materials without using any stoichiometric reagents.

2.2 Results and discussion

We envisioned that the acylation of amide could be realized directly by using aldehydes with the generation of hydrogen as the sole by-product, which is achieved by activation of the amide moiety and by following dehydrogenation of hemiaminals intermediate by using a transition-metal catalyst. Formation of *N*-benzoylpyrrolidone (**3aa**) from 2-pyrrolidinone (**1a**) and benzaldehyde (**2a**) was chosen to screen the catalytic conditions. A series of transition-metal-based catalyst proved to be efficient for alcohol dehydrogenation were examined. As a result, ruthenium-based Shvo's catalyst (**4a**) (2.5 mol%) provided **3aa** with 21% yield when 1.5 equiv. of **2a** was used. Other Ir or Rh catalysts were also tested but none of them exhibited any significant activity. Further efforts hoping to optimize the catalytic conditions by using certain additives and ligands, such as bases, Lewis acids, phosphine ligands, or by changing different solvents were unsuccessful (Table S1). Then we tried to add more amount of aldehyde to optimize the reaction, as we always observed the formation of benzyl alcohol and benzyl benzoate. To our delight, the reaction proceeded more efficiently yielding **3aa** in 52% yield when 5 equivalence of **2a** was used (Scheme 2.7).

Scheme 2.7

Encouraged by the above results, we screened some other aldehydes and tried to find more

active ones for the acylation of 2-pyrrolidinone (**1a**). To our delight, cinnamaldehyde (**2b**) reacted much better with **1a** to afford acylation products with excellent yields (93%, overall yields) using a less amount (1.5 equiv.) of **2b**. In this acylation process, as hydrogen transfer process was involved, concurrent reduction of C-C double bond occurred, thus generating two products, **3ab-d** and **3ab-s** (scheme 2.8).

Scheme 2.8. *N*-acylation of 2-pyrrolidinone with cinnamaldehyde

For synthetic considerations, we explored a few conditions to selectively get only one product, either **3ab-d** or **3ad-s** (Scheme 2.9). First of all, if hydrogen gas (1 atm.) was applied to the reaction mixture after the catalytic acylation process (condition **A**), ruthenium-catalyzed hydrogenation also proceeded well providing **3ad-s** as the only product in 81% yield. Alternative transfer hydrogenation transformation was achieved by using excess amount of isopropyl alcohol affording **3ad-s** as the sole product in 76% yield (condition **B**). Both of hydrogenation processes were done in one-pot fashion without any isolation job. Next goal was to obtain **3ab-d** selectively. When 2 equiv of benzoquinone was used as an hydrogen acceptor, concurrent transfer hydrogenation of the C-C double bond failed to occur with the generation of **3ab-d** as the only product in good yield (77%) (Condition **C**).

Scheme 2.9. Selectivity synthetic methods

Encouraged by the direct acylation of 2-pyrrolidinone (**1a**) with aldehyde **2a** and **2b**, we examined the substrate scope of this acylation process (Table 2.1). Aldehydes with a broad range of functional groups, such as furan and thiophene were converted smoothly. However, both of aliphatic and aromatic aldehydes exhibited lower activity than α,β -unsaturated aldehydes providing acylation products in moderate yields. Notably, aldehyde containing a conjugated diene moiety, such as (2*E*,4*E*)-2,4-hexadienal (**2d**), was also proved to be a good acylation substrate, and no concurrent transfer hydrogenation of double bond was observed, which was different from the examples using **2b** (Table 2.1, entries 5, 17, 20 and 23). Similarly, no hydrogenation of C-C double bond was observed when α -methyl-trans-cinnamaldehyde (**2e**) was used, but the acylation product **3ae** was obtained in a significantly lowered yield (20%) and most of the starting materials were recovered indicating that steric

hindrance of aldehydes be sensitive to reactivity (Table 2.1, entry 6). Two possible reasons are proposed for the higher reactivity of cinnamaldehyde. One reason is that cinnamaldehyde has a relieved steric hindrance compared to aliphatic or aromatic aldehyde. Another reason could be the activation of the carbonyl group caused by *bis*-coordination of ruthenium to olefin and carbonyl group as proposed in the Yi's report.¹³

2-Azetidinone (**1b**) containing a more nucleophilic nitrogen than 2-pyrrolidinone (**1a**) performed much better in this acylation process (Table 2.1, entries 12-18). Corresponding acylation products were synthesized in good to excellent yields using aliphatic and aromatic aldehydes, as well as using α -enals. It is reported that a broad range of 2-azetidinone derivatives have been used as antibiotics.¹⁴ Herein, a broad range of *N*-acylated 2-azetidinones were smoothly synthesized with aldehydes by dehydrogenation. It is worthy to note that even *N*-formyl azetidinone could be synthesized in 53% yield using paraformaldehyde (Table 2.1, entry 18).

¹³ Kwon, K. H.; Lee, D. W.; Yi, C. S. *Angew. Chem., Int. Ed.* **2011**, 50, 1692.

¹⁴ (a) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, 105, 395. (b) Elander, R. P. *Appl. Microbiol. Biotechnol.* **2003**, 61, 385.

Table 2.1 *N*-acylation of lactams with aldehydes by Shvo's catalyst^a

Entry	Lactam	Aldehyde	Product	Yield % (condition)
1	1a	2a	3aa	51 ^c
2	1a	2b	3ab-s	81 ^d (A) 76 ^d (B)
3	1a	2b	3ab-d	77 (C)
4	1a	2c	3ac-s	92 (A)
5	1a	2d	3ad	75
6	1a	2e	3ae	20
7	1a	2f	3af	65 ^c
8	1a	2g	3ag	40 ^c
9	1a	2h	3ah	39 ^c

Table 2.1 *N*-acylation of lactams with aldehydes by Shvo's catalyst^a

Entry	Lactam	Aldehyde	Product	Yield % (condition)
10		2i	3ai	55 ^c
11		2j	3aj	49 ^c
12	1b	2i	3ba	62 ^d
13		2i	3bi	55 ^d
14		2j	3bj	93 ^c
15		2k	3bf	99 ^c 69 ^d
16		2l	3bk	96 ^c 60 ^d
17		2m	3bd	85
18		2n	3bl	53 ^e
19		2o	3cb-s	98 (A)
20		2m	3cd	47

Table 2.1 *N*-acylation of lactams with aldehydes by Shvo's catalyst^a

Entry	Lactam	Aldehyde	Product	Yield % (condition)
21				36 (A)
22				80 (C)
23				75
24				61 ^c
25				49 ^c

^aReaction conditions: Lactam **1** (0.25 mmol, 1.0 equiv), aldehyde **2** (3.0 equiv), Shvo's catalyst **4a** (2.5 mol %), toluene (0.5 mL), 100 °C, 24 h. ^bYields are of the isolated product, and hydrogenation or hydrogen acceptor conditions applied after the reaction were noted in parentheses. ^c5.0 equiv of aldehyde were used. ^d1.5 equiv of aldehyde were used. ^eReaction was performed in a sealed Schlenk tube using 10 equiv of **2i** at 120 °C for 24 h.

Even six-membered 4-piperidinone (**1c**) reacted well with **2b** providing acylation product in excellent yield (Table 2.1, entry 19). In contrast, reaction of **1c** and **2d** afforded **3cd** in a reduced yield of 47% (Table 2.1, entry 20). However, when a seven-membered lactam (**1d**) was used, the product yield decreased greatly indicating that the reaction activity be affected by the nucleophilicity of the *N*-atom of lactams (Table 2.1, entry 21).

Table 2.2. *N*-acylation of oxazolidinones and imidazolidinones with aldehydes^a

Entry	Lactam	Aldehyde	Product	Yield % (condition)
1	1f		3fb-s	77 ^d (A)
2	1f		3fd	86
3	1f		3fk	51 ^c
4	1g		3gb-d	86 (C)
5	1g		3gd	61
6	1g		3gk	63 ^c
7	1h		3ha	35
8	1h		3hb-d	46 ^c (C)

^aReaction conditions: oxazolidinone or imidazolidinone (0.25 mmol, 1.0 equiv), aldehyde (3.0 equiv), **4a** (2.5 mol %), toluene (0.5 mL), 100 °C, 24 h. ^bYields are of the isolated product, and hydrogenation or hydrogen acceptor conditions applied after the reaction were noted in parentheses. ^c 5.0 equiv of aldehyde were used. ^d1.5 equiv of aldehyde was used.

To our delight, dihydro-isoindol-1-one (**1e**) also reacted smoothly with aldehydes (Table 2.1, entries 22-25).

Next, we extended the substrate scope to the reaction of oxazolidinones and imidazolidinones, both of which exhibited numerous applications in synthetic and medicinal chemistry (Table 2.2). Very recently, Carreira's group disclosed a synthetic method of *N*-acyl oxazolidinones using acid fluorides as an acylation reagent.^[7] Herein, oxazolidinones reacted well with aldehydes affording corresponding acylation products in moderate to good yields. Notably, imidazolidine-2-one (**1h**) reacted with **2a** affording mono-substituted *N*-benzoyl imidazolidine-2-one (**3ha**) in 35% yield, while **2b** provided *bis*-substituted product **3hb-d** (Table 2.2, entries 7 and 8). We attributed this to the differences of solubility and reactivity. Precipitation of product **3ha** was observed as the acylation proceeded.

Based on the reported working mechanism of Shvo's catalyst and our experimental results,¹² we proposed a possible mechanism for this transformation (Scheme 2.4). It is well known that Shvo's catalyst dissociate into 18-electron species **4c** and 16-electron complex **4b** under thermal conditions, which can be inter-converted into each other by hydrogen transfer. Nucleophilic attack of lactam to the activated carbonyl group of aldehyde with the help of ruthenium species **4b** could afford a hemiaminal intermediate, and the following β -hydride elimination occurs to provide acylation product.¹⁵

Scheme 2.4. Proposed mechanism

2.3 Conclusion

In conclusion, we have developed an operatively simple and efficient method for *N*-acylation of lactams, oxazolidinones, and imidazolidinones with aldehydes by Shvo's catalyst without using any activation reagent. The acylation with α,β -unsaturated aldehydes were achieved with excellent yields. This transformation provided a realizing of atom-economical and environmentally benign *N*-acylation of amide moiety using aldehydes with the generation of hydrogen, which has numerous applications in organic synthesis.

¹⁵ (a) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, 123, 1090. (b) Casey, C. P.; Johnson, J. B.; Singer, S. W.; Cui, Q. *J. Am. Chem. Soc.* **2005**, 127, 3100. (c) Johnson, J. B.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, 68, 7681. (d) Conley, B. L.; Pennington-Boggio, M. K.; Boz, E.; Williams, T. J. *Chem. Rev.* **2010**, 110, 2294.

2.4 Experimental Section

General methods

All reactions were carried out in oven-dried glassware under an inert atmosphere of argon gas. All lactams and aldehydes were obtained from Aldrich or Alfa Aesar and used as received. Shvo's catalyst was purchased from Strem. Toluene was dried over a Pure Solv solvent purification system. Analytical TLC was performed on a Merck 60 F254 silica gel (0.25 mm thickness). Column chromatography was performed on Merck 60 silica gel (230-400 mesh). NMR spectra were recorded on a Bruker 400MHz spectrometer. Tetramethylsilane was used as reference, and the chemical shifts were reported in ppm and the coupling constants in Hz. GC yields were obtained on an Agilent 7890A instrument equipped with an HP-5 column using dodecane as an internal standard. Mass spectrometry was performed by Waters Q-ToF Premier Micromass instrument, using Electro Spray Ionization (ESI) mode. IR spectra were recorded as thin films on NaCl plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}).

Table S1. Optimization of reaction conditions ^a

Catalyst	Ligand	Additive	Solvent	Yield [%] ^b
[Ru(<i>p</i> -cymene)Cl ₂] ₂	D , pyridine	NaH	Toluene	< 5
[Ru(<i>p</i> -cymene)Cl ₂] ₂	-	-	Toluene	0
[Ru(benzene)Cl ₂] ₂	D , MeCN	NaH	Toluene	0
[Ru(benzene)Cl ₂] ₂	-	-	Toluene	0
RuH ₂ (PPh ₃) ₄	-	-	Toluene	< 5
RuH ₂ (PPh ₃) ₄	D , MeCN	NaH	Toluene	< 5
[Ru(cod)Cl ₂] _m	D , PCy ₃	KO ^t Bu	Toluene	0
[Ru(<i>p</i> -cymene)Cl ₂] ₂	dppb	K ₂ CO ₃	^t BuOH	0
Milstein's catalyst	-	-	Toluene	0
Shvo's catalyst	-	-	Toluene	21
Shvo's catalyst	-	-	DCE	< 5
Shvo's catalyst	-	-	DMF	< 5
Shvo's catalyst	-	-	EtOH	0
Shvo's catalyst	-	-	Dioxane	12
Shvo's catalyst	-	-	DME	0
Shvo's catalyst	PPh ₃	-	Toluene	0
Shvo's catalyst	dppf	-	Toluene	0
Shvo's catalyst	-	ZnBr ₂	Toluene	< 5
Shvo's catalyst	-	CuCl ₂	Toluene	0
Shvo's catalyst	-	Yb(OTf) ₃	Toluene	12
Shvo's catalyst	-	NaCO ₃	Toluene	11
Shvo's catalyst	-	NaH	Toluene	9
Shvo's catalyst ^c	-	-	Toluene	52
Shvo's catalyst ^d	-	-	Toluene	49

[Ru(COD)(met) ₂]	-	-	Toluene	< 5
RuCl ₂ (PPh ₃) ₃	-	-	Toluene	< 5
Ru ₃ (CO) ₈	-	-	Toluene	0
RuCl ₃	-	-	Toluene	0
[RhCl(COD)] ₂	-	-	Toluene	0
IrH(CO)PPh ₃	-	-	Toluene	0
IrCl ₃	-	-	Toluene	0
[Ir(Cp*) Cl ₂] ₂	-	-	Toluene	0

^aTypical reaction conditions: **1a** (0.25 mmol, 1.0 eq), **2a** (0.25 mmol, 1.5 eq), catalyst (5 mol% calculated by per metal atom), ligand (5 mol%, if applicable), additive (20 mol%, if applicable), solvent (0.5 ml), under Ar atmosphere, 100°C, 24 h. ^bYields are of isolated products. ^c 5.0 equiv **2a** used. ^d 1.0 equiv of water added.

General procedure for direct *N*-acylation of lactams, oxazolidinones, and imidazolidinones with aldehydes

Heterocycle (0.25 mmol, 1.0 equiv), aldehyde (1.5~5.0 equiv), Shvo's catalyst (6.8 mg, 2.5 mol%), and toluene (0.5 mL) were placed in an oven dried Schlenk tube inside a glove box under argon atmosphere. The Schlenk tube was taken out and heated to 100 °C in an oil bath under argon atmosphere. After 24h, the reaction mixture was cooled to room temperature. All volatiles were removed under vacuum and the residue was purified by silica gel flash column chromatography to afford the desired product. All of the acylation products were identified by spectral comparison with literature data or with analogous literature data.

Selectivity control by sequential hydrogenation or a hydrogen acceptor

Condition A: After the catalytic process of *N*-acylation described above, the Schlenk tube was cooled to room temperature. The reaction tube was charged with atmospheric pressure of hydrogen, and heated to reflux for 5 h (using a hydrogen gas balloon). After cooling down,

all volatiles were evaporated under vacuum and the residue was purified by silica gel flash column chromatography to afford the hydrogenation product.

Condition B: After the catalytic process of *N*-acylation described above, the Schlenk tube was cooled to room temperature. After adding 2-propanol (3 equiv), the Schlenk tube was sealed and heated to reflux for 5 h. After cooling down, all volatiles were removed under vacuum and the residue was purified by silica gel flash column chromatography to afford the hydrogenation product.

Condition C: Heterocycle (0.25 mmol, 1.0 equiv), aldehyde (1.5equiv), Shvo's catalyst (6.8 mg, 2.5 mol%), 1,4-benzoquinone (2.0 equiv) and toluene (0.5 mL) were placed in an oven dried Schlenk tube inside the glove box under argon atmosphere. The Schlenk tube was taken out and heated to 100 °C in an oil bath for 24 h. The Schlenk tube was taken out of the heating bath and cooled to room temperature. All volatiles were removed under vacuum and the residue was purified by silica gel flash column chromatography to afford the product.

Characterization data

White solid, yield = 51%. ¹H NMR (CDCl₃): δ = 7.35-7.58 (m, 5H), 3.92 (t, 2H, *J* = 7.2 Hz), 2.56 (t, 2H, *J* = 8.0 Hz), 2.06-2.13 (m, 2H). ¹³C NMR (CDCl₃): δ = 174.6, 170.7, 134.4, 131.9, 128.9, 127.8, 46.6, 33.3, 17.7.

Colourless oil, yield = 81%. ¹H NMR (CDCl₃): δ = 7.17-7.30 (m, 5H), 3.79 (t, 2H, *J* = 7.2 Hz), 3.23 (t, 2H, *J* = 7.6 Hz), 2.97 (t, 2H, *J* = 7.6 Hz), 2.57 (t, 2H, *J* = 8.0 Hz), 1.97-2.05 (m, 2H).

White solid, yield = 77%. ¹H NMR (CDCl₃): δ = 7.90 (d, 1H, *J* = 15.6 Hz), 7.79 (d, 1H, *J* = 15.6 Hz), 7.57-7.59 (m, 2H), 7.23-7.36 (m, 3H), 3.89 (t, 2H, *J* = 6.4 Hz), 2.61 (t, 2H, 8.0 Hz), 1.99-2.07 (m, 2H). ¹³C NMR (CDCl₃): δ = 175.7, 166.4, 145.6, 134.9, 130.4, 128.8, 128.5, 119.0, 45.9, 34.0, 17.2.

¹⁶ (a) Sasaki, H.; Mori, Y.; Nakamura, J.; Shibasaki, J. *J. Med. Chem.* **1991**, *34*, 628. (b) Kaname, M.; Yoshifuji, S.; Sashida, H. *Tetrahedron Lett.* **2008**, *49*, 2786.

1-hexanoyl-pyrrolidin-2-one (3ac-s)¹⁷

Colourless oil, yield = 49%. ¹H NMR (CDCl₃): δ = 3.78 (t, 2H, *J* = 7.2 Hz), 2.86 (t, 2H, *J* = 7.6 Hz), 2.56 (t, 2H, *J* = 8.0 Hz), 1.96-2.04 (m, 2H), 1.57-1.65 (m, 2H), 1.29-1.32 (m, 4H), 0.88 (t, 3H, *J* = 6.8 Hz). ¹³C NMR (CDCl₃): δ = 175.3, 174.5, 45.5, 36.8, 33.8, 31.4, 23.9, 22.5, 17.2, 13.9.

1-[(2*E*, 4*E*)-hexadienoyl] pyrrolidin-2-one (3ad)^{22a}

White solid, yield = 75%. ¹H NMR (CDCl₃): δ = 7.38 (dd, 1H, *J* = 15.2 Hz, *J* = 10.8 Hz), 7.18 (d, 1H, *J* = 14.8 Hz), 6.10-6.30 (m, 2H), 3.82 (t, 2H, *J* = 7.2 Hz), 2.57 (t, 2H, *J* = 8.0 Hz), 1.95-2.02 (m, 2H), 1.82 (d, 3H, *J* = 6.4 Hz). ¹³C NMR (CDCl₃): δ = 175.5, 166.6, 146.1, 140.2, 130.6, 119.9, 45.8, 34.0, 18.7, 17.2.

1-[2*E*-(3-phenyl)-(2-methyl)-acryloyl] pyrrolidin-2-one (3ae)

Colorless oil, yield = 20 %. ¹H NMR (CDCl₃): δ = 7.32-7.39 (m, 4H), 7.23-7.27 (m, 1H), 6.82 (s, 1H), 3.83 (t, 2H, *J* = 7.2 Hz), 2.56 (t, 2H, *J* = 8.0 Hz), 2.10 (d, 3H, *J* = 1.2 Hz), 1.98-2.11 (m, 2H). ¹³C NMR (CDCl₃): δ = 174.5, 173.0, 135.9, 134.3, 133.4, 129.5, 128.3, 127.9,

¹⁷ Sebenda, J.; Mikulova, B. *Collect. Czech. Chem. Commun.* **1964**, 29, 738.

46.0, 33.2, 17.7, 15.5. HRMS (ESI): m/z calcd. for $C_{14}H_{16}NO_2$ $[MH^+]$: 230.1187; found 230.1181. FTIR (NaCl, cm^{-1}): 3073, 3008, 1734, 1670, 1647, 1629, 1421, 1262, 895, 740, 705.

1-(thiophene-2-carbonyl)-2-pyrrolidinone (3af)

Yellow oil, yield = 96%. 1H NMR ($CDCl_3$): δ = 7.85 (d, 1H, J = 4.0 Hz), 7.59 (d, 1H, J = 5.2 Hz), 7.07 (t, 1H, J = 4.4 Hz), 3.93 (t, 2H, J = 7.2 Hz), 2.63 (t, 2H, 8.0 Hz), 2.07-2.14 (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 174.3, 163.2, 136.7, 134.9, 133.3, 127.3, 47.3, 33.6, 17.8. HRMS (ESI): m/z calcd. for $C_9H_{10}NO_2S$ $[MH^+]$: 196.0432; found 196.0438. FTIR (NaCl, cm^{-1}): 3050, 1644, 1632, 1621, 1422, 1264, 756, 706.

1-(4-methoxybenzoyl)-2-pyrrolidinone (3ag)¹⁸

Light yellow oil, yield = 40%. 1H NMR ($CDCl_3$): δ = 7.61 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 3.90 (t, 2H, J = 7.2 Hz), 3.82 (s, 3H), 2.58 (t, 2H, J = 8.0 Hz), 2.06-2.14 (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 174.7, 170.1, 162.9, 131.7, 126.2, 113.1, 55.4, 46.9, 33.4, 17.8.

1-(4-fluorobenzoyl)-2-pyrrolidinone (3ah)³¹

White solid, mp: 139 °C, yield = 39%. 1H NMR ($CDCl_3$): δ = 7.63-7.66 (m, 2H), 7.08 (t,

2H, $J = 8.8$ Hz), 3.95 (t, 2H, $J = 7.2$ Hz), 2.61 (t, 2H, $J = 8.0$ Hz), 2.11-2.18 (m, 2H). ^{13}C NMR (CDCl_3): $\delta = 174.6, 169.5, 131.8, 131.7, 115.1, 114.9, 46.7, 33.3, 17.7$. HRMS (ESI): m/z calcd. for $\text{C}_{11}\text{H}_{11}\text{FNO}_2$ [MH^+]: 208.0762; found 208.0767. FTIR (NaCl, cm^{-1}): 3059, 1746, 1671, 1649, 1511, 1311, 1268, 745, 713.

1-phenylacetyl-pyrrolidin-2-one (3ai) ^{16a}

Colourless oil, yield = 51%. ^1H NMR (CDCl_3): $\delta = 7.24\text{--}7.33$ (m, 5H), 4.27 (s, 2H), 3.82 (t, 2H, 7.2 Hz), 2.61 (t, 2H, $J = 8.0$ Hz), 1.99-2.06 (m, 2H). ^{13}C NMR (CDCl_3): $\delta = 175.4, 172.1, 134.1, 129.7, 128.4, 127.0, 45.7, 42.8, 33.7, 17.1$.

1-benzoyl-azetidin-2-one (3ba) ¹⁹

White solid, yield = 62%. ^1H NMR (CDCl_3): $\delta = 7.99$ (d, $J = 7.6$ Hz, 2H), 7.58-7.62 (m, 1H), 7.47-7.51 (m, 2H), 3.80 (t, 2H, $J = 5.6$ Hz), 3.13 (t, 2H, $J = 5.6$ Hz). ^{13}C NMR (CDCl_3): $\delta = 166.3, 164.0, 133.2, 131.9, 129.7, 128.2, 36.8, 35.1$.

¹⁸ Karimi, F.; Kihlberg, T.; Langstrom, B. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1528.

¹⁹ (a) Wing, T.; Naveed, A.; Karl, H.; Michael, P. *Can. J. Chem.* **2005**, 83, 1432. (b) Xu, H.; Li, J. *Org. Lett.* **2003**, 5, 1575.

1-phenylacetyl-azatedin-2-one (3bi) ³²

Colourless oil, yield = 55%. ¹H NMR (CDCl₃): δ = 7.24 -7.35 (m, 5H), 4.01 (s, 2H), 3.56 (t, 2H, *J* = 5.6 Hz), 3.04 (t, 2H, *J* = 5.6 Hz). ¹³C NMR (CDCl₃): δ = 168.6, 165.2, 133.3, 129.6, 128.6, 127.3, 42.8, 36.8, 36.0. HRMS (ESI): *m/z* calcd. for C₁₁H₁₂NO₂ [MH⁺]: 190.0868; found 190.0866. FTIR (NaCl, cm⁻¹): 3051, 1787, 1697, 1649, 1376, 1311, 1264, 1201, 894, 737, 703.⁸

1-hexanoyl-azatedin-2-one (3bj) ³²

Yellow oil, yield = 93%. ¹H NMR (CDCl₃): δ = 3.54 (t, 2H, *J* = 5.6 Hz), 3.01 (t, 2H, *J* = 5.6 Hz), 2.65 (t, 2H, 7.6 Hz), 1.59-1.67 (m, 2H), 1.26-1.32 (m, 4H), 0.87 (t, 3H, *J* = 6.8 Hz). ¹³C NMR (CDCl₃): δ = 171.3, 165.0, 36.4, 36.3, 35.7, 31.3, 23.7, 22.3, 13.9. HRMS (ESI): *m/z* calcd. for C₉H₁₆NO₂ [MH⁺]: 170.1181; found 170.1181. FTIR (NaCl, cm⁻¹): 3048, 2961, 1784, 1697, 1388, 1307, 1261, 1203, 1153, 890, 748, 719.

1-(thiophene-2-carbonyl)-azatedin-2-one (3bf)

²⁰ Villa, M. V. J.; Targett, S. M.; Barnes, J. C.; Whittingham, W. G.; Marquez, R. *Org. Lett.* **2007**, 9, 1631.

²¹ Borboa, L. G.; Nunez, S. *J. Phy. Org. Chem.* **2006**, 19, 737.

²² (a) Pineschi, M.; Del Moro, F.; Di Bussolo, V.; Macchia, F. *Adv. Syn. Cat.* **2006**, 348, 301. (b) Soloshonok, V. A.; Cai, C. Z.; Hruby, V. J.; Van Meervelt, L.; Yamazaki, T. *J. Org. Chem.* **2000**, 65, 6688.

²³ Ishida, A.; Bando, T.; Mukaiyama, T. *Chem. Lett.* **1976**, 711.

White solid, mp: 90-91 °C, yield = 99%. ^1H NMR (CDCl_3): δ = 8.50 (dd, 1H, J = 1.6 Hz, J = 5.2 Hz), 7.65 (dd, 1H, J = 1.2 Hz, J = 6.4 Hz), 7.15 (dd, 1H, J = 5.2 Hz, J = 6.4 Hz), 3.75 (t, 2H, J = 7.2 Hz), 3.08 (2H, J = 7.2 Hz). ^{13}C NMR (CDCl_3): δ = 163.5, 159.2, 136.2, 134.3, 134.1, 128.2, 36.8, 34.5. HRMS (ESI): m/z calcd. for $\text{C}_8\text{H}_8\text{NO}_2\text{S}$ [MH^+]: 182.0276; found 182.0276. FTIR (NaCl, cm^{-1}): 3057, 1668, 1634, 1608, 1426, 1265, 895, 752.

White solid, mp: 108-109 °C, yield = 96%. ^1H NMR (CDCl_3): δ = 7.93 (d, 1H, J = 3.6 Hz), 7.64 (d, 1H, J = 1.2 Hz), 6.54 (dd, 1H, J = 3.6 Hz, J = 1.2 Hz), 3.77 (t, 2H, J = 5.6 Hz), 3.08 (t, 2H, J = 5.6 Hz). ^{13}C NMR (CDCl_3): δ = 163.3, 154.6, 147.4, 145.5, 120.4, 112.1, 36.9, 35.0. HRMS (ESI): m/z calcd. for $\text{C}_8\text{H}_8\text{NO}_3$ [MH^+]: 166.0504; found 166.0501. FTIR (NaCl, cm^{-1}): 3064, 3016, 1784, 1673, 1657, 1472, 1402, 1337, 1302, 1252, 1223, 1201, 748.

Yellow solid, mp: 117-118 °C, yield = 85 %. ^1H NMR (CDCl_3): δ = 7.39 (dd, 1H, J = 10.4 Hz, J = 15.2 Hz), 6.62 (d, 1H, J = 15.2 Hz), 6.15-6.28 (m, 2H), 3.58 (t, 2H, J = 5.6 Hz), 3.01 (t, 2H, J = 5.6 Hz), 1.83 (d, 3H, J = 5.6 Hz). ^{13}C NMR (CDCl_3): δ = 165.1, 163.5, 146.1, 141.4, 130.1, 119.5, 36.4, 35.8, 18.8. HRMS (ESI): m/z calcd. for $\text{C}_9\text{H}_{12}\text{NO}_2$ [MH^+]: 166.0868; found 166.0872. FTIR (NaCl, cm^{-1}): 3061, 3005, 1780, 1675, 1627, 1608, 1357, 1310, 1265, 1032, 1012, 894, 741, 706.

N-formyl azetidin-2-one (3bl)²⁰

Colourless oil, yield = 53%. ¹H NMR (CDCl₃): δ = 8.78 (s, 1H), 3.64 (t, 2H, *J* = 5.2 Hz), 3.13 (t, 2H, *J* = 5.2 Hz). ¹³C NMR (CDCl₃): δ = 165.8, 156.2, 37.1, 36.7.

1-(3-phenylpropionyl)-2-piperidone (3cb-s)²³

Colourless oil, yield = 98%. ¹H NMR (CDCl₃): δ = 7.16-7.29 (m, 5H), 3.70 (t, 2H, *J* = 5.6 Hz), 3.24 (t, 2H, *J* = 7.6 Hz), 2.97 (t, 2H, *J* = 7.6 Hz), 2.53 (t, 2H, *J* = 6.8 Hz), 1.79-1.81 (m, 4H). ¹³C NMR (CDCl₃): δ = 176.2, 173.4, 141.2, 128.6, 128.4, 126.0, 44.0, 41.2, 34.9, 31.1, 22.4, 20.3.⁹

1-[(2*E*, 4*E*)-hexadienoyl]-2-piperidon (3cd)

Colourless oil, yield = 47%. ¹H NMR (CDCl₃): δ = 7.66 (dd, 1H, *J* = 10.4 Hz, *J* = 14.8 Hz), 7.14 (d, 1H, *J* = 15.2 Hz), 6.47-6.64 (m, 2H), 4.08-4.11 (m, 2H), 2.90-2.93 (m, 2H), 2.18-2.21 (m, 5H). ¹³C NMR (CDCl₃): δ = 174.1, 170.3, 144.5, 139.6, 130.9, 123.3, 44.8,

²⁴ Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, 111, 5340.

²⁵ Wan, J.; Wu, B.; Pan, Y. *Tetrahedron*, **2007**, 63, 9338.

²⁶ (a) Liptrot, D.; Alcaraz, L.; Roberts, B. *Adv. Syn. Cat.* **2010**, 352, 2183. (b) Olsen, R. K.; Hennen, W. J.; Wardle, R. B. *J. Org. Chem.* **1982**, 47, 4605.

35.3, 23.0, 21.0, 19.1. HRMS (ESI): m/z calcd. for $C_{11}H_{15}NO_2$ $[MH^+]$: 194.1181; found 194.1181. FTIR (NaCl, cm^{-1}): 3058, 2991, 1678, 1617, 1589, 1419, 1339, 1275, 1202, 1153, 891, 744, 705.

***N*-(3-phenylpropionyl)-caprolactam (3db-s)** ²⁸

Light yellow oil, yield = 36%. 1H NMR ($CDCl_3$): δ = 7.15-7.26 (m, 5H), 3.85 (t, 2H, J = 4.8 Hz), 3.16 (t, 2H, J = 8.0 Hz), 2.94 (t, 2H, J = 8.0 Hz), 2.66-2.68 (m, 2H), 1.67-1.71 (m, 4H), 1.60-1.62 (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 177.7, 175.5, 141.2, 128.6, 128.4, 126.0, 43.3, 40.8, 39.8, 31.3, 29.2, 28.5, 23.7. HRMS (ESI): m/z calcd. for $C_{15}H_{19}NO_2$ $[MH^+]$: 246.1494; found 246.1497. FTIR (NaCl, cm^{-1}): 3042, 2311, 1661, 1647, 1639, 1429, 1263, 901, 744, 699.

2-[2*E*-(3-phenyl)-acryloyl]-2,3-dihydro-isoindol-1-one (3eb-d)

White solid, mp: 176-177 °C, yield = 80%. 1H NMR ($CDCl_3$): δ = 8.19 (d, 1H, J = 16.0 Hz), 7.88-7.92 (m, 2H), 7.62-7.65 (m, 3H), 7.46-7.50 (m, 2H), 7.35-7.38 (m, 3H), 4.89 (s, 2H). ^{13}C NMR ($CDCl_3$): δ = 167.9, 166.2, 145.9, 141.3, 134.9, 134.1, 131.5, 130.5, 128.9, 128.64, 128.62, 125.2, 123.4, 119.1, 48.6. HRMS (ESI): m/z calcd. for $C_{17}H_{14}NO_2$ $[MH^+]$: 264.1025; found 264.1020. FTIR (NaCl, cm^{-1}): 3045, 3018, 1724, 1670, 1657, 1616, 1442, 1420, 1345, 1258, 1231, 1151, 895, 748, 709.

2-[(2E, 4E)-hexadienoyl]-2, 3-dihydro-isoindol-1-one (3ed)

Yellow solid, mp: 169-170 °C, yield = 75%. ^1H NMR (CDCl_3): δ = 7.87 (d, 1H, J = 7.6 Hz), 7.60-7.64 (m, 1H), 7.45-7.50 (m, 4H), 6.31-6.38 (m, 1H), 6.15-6.24 (m, 1H), 4.84 (s, 2H), 1.86 (d, 3H, J = 6.4 Hz). ^{13}C NMR (CDCl_3): δ = 167.7, 166.6, 146.5, 141.2, 140.6, 134.0, 131.6, 130.7, 128.5, 125.2, 123.4, 120.0, 48.5, 18.8. HRMS (ESI): m/z calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_2$ [MH^+]: 228.1025; found 228.1031. FTIR (NaCl, cm^{-1}): 3053, 3005, 2306, 1727, 1666, 1645, 1602, 1422, 1346, 1265, 1146, 895, 749, 712.

2-(2-furoyl)-2, 3-dihydro-isoindol-1-one (3ek)

White solid, mp: 130-131 °C, yield = 61%. ^1H NMR (CDCl_3): δ = 7.88 (d, 1H, J = 7.6 Hz), 7.63-7.67 (m, 3H), 7.48-7.51 (m, 2H), 6.55 (t, 1H, J = 2.0 Hz), 5.00 (s, 2H). ^{13}C NMR (CDCl_3): δ = 166.4, 158.4, 146.7, 146.4, 141.4, 134.1, 131.0, 128.7, 125.3, 123.4, 120.7, 111.9, 49.1. HRMS (ESI): m/z calcd. for $\text{C}_{13}\text{H}_{10}\text{NO}_3$ [MH^+]: 228.0661; found 228.0658. FTIR (NaCl, cm^{-1}): 3062, 2959, 1739, 1661, 1641, 1616, 1422, 1336, 1305, 1271, 1149, 894, 758, 716.

²⁷ (a) Hanai, K.; Maki, Y.; Kuwae, A. *Bull. Chem. Soc. Jpn.* **1985**, 58, 1367. (b) Duffield, A. M.; Djerassi, C.; Budzikiewicz, H. *J. Am. Chem. Soc.* **1964**, 86, 5536.

White solid, yield = 49%. ¹H NMR (CDCl₃): δ = 7.90 (d, 1H, *J* = 8Hz), 7.64-7.68 (m, 1H), 7.49-7.52 (m, 2H), 4.81 (s, 2H), 3.09 (t, 2H, *J* = 7.2 Hz), 1.70-1.78 (m, 2H), 1.35-1.42 (m, 4H), 0.90-0.93 (m, 3H). ¹³C NMR (CDCl₃): δ = 174.5, 167.6, 141.2, 134.0, 131.5, 128.6, 125.2, 123.4, 48.2, 36.9, 31.5, 24.1, 22.5, 14.0.

White solid, mp: 102-103°C (Lit. 100-101°C), yield = 99%. ¹H NMR (CDCl₃): δ = 7.15-7.28 (m, 5H), 4.34 (t, 2H, *J* = 8.0 Hz), 3.96 (t, 2H, *J* = 7.6 Hz), 3.23 (t, 2H, *J* = 8.0 Hz), 2.96 (t, 2H, *J* = 7.6 Hz). ¹³C NMR (CDCl₃): δ = 172.6, 153.5, 140.5, 128.6, 128.5, 126.3, 62.1, 42.5, 36.8, 30.2. HRMS (ESI): *m/z* calcd. for C₁₂H₁₃NO₃ [MH⁺]: 220.0974; found 220.0973. FTIR (NaCl, cm⁻¹): 3048, 2996, 1779, 1703, 1383, 1263, 1231, 1102, 1042, 911, 739, 704.

White solid, yield = 86%. ¹H NMR (CDCl₃): δ = 7.40 (dd, 1H, *J* = 12.0 Hz, *J* = 15.2 Hz), 7.24 (d, 1H, *J* = 15.2 Hz), 6.14-6.31 (m, 2H), 4.37 (t, 2H, *J* = 8.0 Hz), 4.04 (t, 2H, 8.0 Hz), 1.83 (d, 3H, *J* = 6.8 Hz). ¹³C NMR (CDCl₃): δ = 165.7, 153.6, 146.7, 141.1, 130.4, 117.5, 62.0, 42.8, 18.8.

3-(2-furoyl) oxazolidin-2-one (3fk)

Yellow solid, mp: 121-122 °C, yield = 51%. ^1H NMR (CDCl_3): δ = 7.60 (d, 1H, J = 0.8 Hz), 7.45 (d, 1H, J = 3.6 Hz), 6.5 (dd, 1H, J = 1.6 Hz, J = 3.6 Hz), 4.46 (t, 2H, J = 8.0 Hz), 4.13 (t, 2H, J = 8.0 Hz). ^{13}C NMR (CDCl_3): δ = 157.8, 152.8, 146.9, 145.1, 121.1, 112.1, 62.6, 43.9. HRMS (ESI): m/z calcd. for $\text{C}_8\text{H}_8\text{NO}_4$ [MH^+]: 182.0453; found 182.0452. FTIR (NaCl, cm^{-1}): 2967, 1746, 1649, 1637, 1412, 1350, 1297, 1271, 896, 1189, 764, 701.

1-[(*E*)-(3-phenyl)acryloyl]-3-benzyl-imidazolidin-2-one (3gb-d)

Yellow solid, mp: 139-140 °C, yield = 86%. ^1H NMR (CDCl_3): δ = 8.15 (d, 1H, J = 16.0 Hz), 7.80 (d, 1H, J = 16.0 Hz), 7.63-7.65 (m, 2H), 7.26-7.40 (m, 8H), 4.49 (s, 2H), 3.93 (t, 2H, J = 7.6 Hz), 3.35 (t, 2H, J = 7.6 Hz). ^{13}C NMR (CDCl_3): δ = 166.0, 154.9, 144.0, 135.7, 135.2, 130.1, 128.9, 128.8, 128.5, 128.3, 128.0, 118.5, 47.9, 40.4, 39.8. HRMS (ESI): m/z calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$ [MH^+]: 307.1447; found 307.1445. FTIR (NaCl, cm^{-1}): 3061, 2984, 2307, 1721, 1667, 1616, 1471, 1422, 1381, 1365, 1262, 984, 899, 740, 722, 594.

1-[(2*E*,4*E*)-hexadienoyl]-3-benzyl-imidazolidin-2-one (3gd)

Yellow solid, mp: 119-120 °C, yield = 61%. ^1H NMR (CDCl_3): δ = 7.23-7.38 (m, 7H), 6.25-6.31 (m, 1H), 6.08-6.17 (m, 1H), 4.42 (s, 2H), 3.84 (t, 2H, J = 8.0 Hz), 3.27 (t, 2H, J =

8.0 Hz), 1.82 (d, 3H, $J = 6.8$ Hz). ^{13}C NMR (CDCl_3): $\delta = 166.3, 154.8, 144.6, 139.3, 135.8, 130.7, 128.9, 128.2, 128.0, 119.3, 47.9, 40.4, 39.7, 18.7$. HRMS (ESI): m/z calcd. for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2$ [MH^+]: 271.1447; found 271.1444. FTIR (NaCl , cm^{-1}): 3054, 2986, 2304, 1725, 1661, 1652, 1632, 1609, 1427, 1351, 1269, 891, 766, 709.

1-(2-furoyl)-3-benzyl-imidazolidin-2-one (3gk)

Colorless oil, yield = 63%. ^1H NMR (CDCl_3): $\delta = 7.60$ (d, 1H, $J = 0.8\text{Hz}$), 7.47 (dd, 1H, $J = 0.8$ Hz, $J = 3.6$ Hz), 7.26-7.38 (m, 5H), 6.53 (dd, 1H, $J = 1.6$ Hz, $J = 3.6$ Hz), 4.46 (s, 2H), 3.95 (t, 2H, $J = 7.6\text{Hz}$), 3.37 (t, 2H, $J = 7.6$ Hz). ^{13}C NMR (CDCl_3): $\delta = 158.7, 153.9, 146.1, 145.9, 135.7, 128.9, 128.2, 128.0, 119.7, 111.6, 47.9, 40.9, 40.7$. HRMS (ESI): m/z calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$ [MH^+]: 271.1083; found 271.1081. FTIR (NaCl , cm^{-1}): 2979, 1731, 1652, 1637, 1619, 1341, 1269, 894, 755, 706.

1-benzoyl-imidazolidin-2-one (3ha) ²⁶

White solid, yield = 35%. ^1H NMR (CDCl_3): $\delta = 7.34$ -7.59 (m, 5H), 5.57 (b, 1H), 4.06 (t, 2H, $J = 8.0$ Hz), 3.49 (t, 2H, $J = 8.0$ Hz). ^{13}C NMR (CDCl_3): $\delta = 170.3, 156.1, 134.3, 131.5, 128.9, 127.6, 43.5, 36.8$. HRMS (ESI): m/z calcd. for $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_2$ [MH^+]: 191.0821; found 191.0824.

Yellow solid, mp: 250-252 °C, yield = 46%. ¹H NMR (CDCl₃): δ = 7.93 (d, 1H, *J* = 16 Hz), 7.85 (d, 1H, *J* = 16 Hz), 7.61-7.64 (m, 2H), 7.37-7.39 (m, 3H), 3.96 (s, 2H). ¹³C NMR (CDCl₃): δ = 166.1, 152.0, 145.9, 134.7, 130.6, 128.9, 128.6, 117.8, 39.1. HRMS (ESI): *m/z* calcd. for C₂₁H₁₉N₂O₃ [MH⁺]: 347.1396; found: 347.1397. FTIR (NaCl, cm⁻¹): 3041, 3004, 2321, 1745, 1669, 1641, 1627, 1617, 1428, 1331, 1262, 906, 737, 704.

CHAPTER 3

*Ruthenium- and Rhodium-catalyzed Cross-coupling
Reaction of Acrylamides with Alkenes: Efficient Access
to (Z,E)-Dienamides*

3.1 Introduction

Butadiene is an important structural motif in organic chemistry. For example, they serve as useful precursors for further transformations in Diels-Alder reaction and polymerization.¹ 1,3-Butadiene also present in a large class of pharmaceutically active molecules and complex natural products, such as naphthomycin A,² rifabutine,³ (+)-dactylolide,⁴ etc (Figure 3.1).

Figure 3.1 Examples of natural products containing (Z,E)-butadiene moiety.

Thus, development of efficient, selective and practical synthetic methodology would be highly desirable. To our knowledge, carbonyl olefination⁵ such as Wittig reaction and cross-

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² (a) Keller-Schierlein, W.; Meyer, M.; Cellai, L.; Cerrini, S.; Lamba, D.; Segre, A.; Fedeli, W.; Brufani, M. *J. Antibiot.*, **1984**, 37, 1357-1361. (b) Kuttruff, C. A.; Geiger, S.; Cakmak, M.; Mayer, P.; Trauner, D. *Org. Lett.*, **2012**, 14, 1070-1073.

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⁴ (a) Tanaka, J.; Higa, T. *Tetrahedron Lett.*, **1996**, 37, 5535. (b) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.*, **2001**, 775.

⁵ (a) Mukaiyama, T. *Org. React.*, 1982, 28, 203. (b) Still, W. C.; Gennari, C. *Tetrahedron Lett.*, **1983**, 24, 4405. (c) Maryanoff, B.E.; Reitz, A.B. *Chem. Rev.*, **1989**, 89, 863. (d) Dong, D. J.; Li, H. H.; Tian, S. K. *J. Am. Soc. Chem.*, **2010**, 132, 5018.

coupling reactions⁶ such as Heck coupling reactions represents two general approaches for the synthesis of butadienes. In 2010, Tian *et al.* reported a modification of the Wittig reaction. This simple and efficient protocol improves the stereoselectivity significantly by replacing the aldehydes with *N*-sulfonyl imines, which possess distinct electronic and steric properties relative to aldehydes (Scheme 3.1).⁷

Scheme 3.1

In the same year, Helquist developed a modified HWE reaction using unsaturated phosphonate as a vinylogous reagent (scheme 3.2).⁸

Scheme 3.2

However, direct alkenylation via vinylic C-H bond activation remains highly desirable as it minimizes waste formation and obviates pre-functionalization steps. Unfortunately, although

⁶ (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.*, **2001**, 34, 633. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.*, **2002**, 102, 1731. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.*, **2010**, 110, 1147. (d) Le Bras J.; Muzart, J. *Chem. Rev.*, **2011**, 111, 1170. (e) Negishi, E.-I.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.*, **2008**, 41, 1474..

⁷ Dong, D. J.; Li, H. H.; Tian, S. K. *J. Am. Chem. Soc.* **2010**, 132, 5018

⁸ Markiewicz, J. T.; Schauer, D. J.; Löffstedt, J.; Corden, S. J.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, 75, 2061

the directed oxidative olefination of aromatic C-H bonds have been well studied, applying these methods to alkenes is challenging, because of the increased reactivity and lability of olefins. Consequently, the oxidative olefination of vinylic C-H bonds, leading to valuable butadiene products, has remained underdeveloped. To date, only several research groups reported that certain classes of butadienes can be synthesized by Pd- or Rh-catalyzed olefination between simple alkenes, although the substrate scope is often limited.

The directed oxidative olefination of olefinic C-H bonds, as pioneered by Ishii, was successfully achieved by the use of a $\text{Pd}(\text{OAc})_2/\text{HPMoV}/\text{O}_2$ system (Scheme 3.3).⁹

Scheme 3.3

Recently, our group have developed an efficient method for the Pd(II)-catalyzed direct cross-coupling reaction of simple olefins with acrylates under very mild reaction conditions. The reaction proceeded smoothly in the presence of 20 mol% $\text{Pd}(\text{OAc})_2$ and $\text{Cu}(\text{OAc})_2$ under O_2 at 60 °C in a specific mixed solvent system consisting of DMSO/HOAc (v/v =1:1) (Scheme 3.4).¹⁰

Scheme 3.4

⁹ Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2004**, 6, 4623.

¹⁰ (a) Xu, Y. H.; Lu, J.; Loh, T.P. *J. Am. Soc. Chem.* **2009**, 131, 1372. (b) Xu, Y. H.; Wang, W. J.; Wen, Z. K.; Hartley, J. J.; Loh, T. P. *Tetrahedron Lett.* **2010**, 51, 3504-3507.

A further study revealed that employment of enamide instead of α -methylstyrene with acrylate under similar conditions also provided the butadiene in good yields and excellent stereoselectivities (Scheme 3.5). A six-membered cyclic vinylpalladium intermediate was isolated as a single crystal and characterized by X-ray analysis.¹¹

Scheme 3.5

In 2010, Yu and co-workers developed the palladium (II)-catalyzed direct cross-coupling of α -oxoketene dithioacetals with terminal alkenes. This functionalized 1,3-butadienes can react with diamines efficiently providing potentially bioactive bicyclic pyridines (Scheme 3.6).¹²

Scheme 3.6

In 2011, Glorius and co-workers have reported the first Rh(III)-catalyzed cross-coupling of functionalized alkenes leading to 1,3-butadienes. This methodology could be applied to the formation of $\alpha,\beta,\gamma,\delta$ -unsaturated amino acids, an important class of products in the life science (Scheme 3.7).¹³

¹¹ Xu, Y. H.; Chok, Y. K.; Loh, T. P. *Chem. Sci.* **2011**, 2, 1822.

¹² Yu, H.; Jin, W.; Sun, C.; Chen, J.; Du, W.; He, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2010**, 49, 5792

¹³ Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem. Eur. J.* **2011**, 17, 7167.

Scheme 3.7

Recently, ruthenium has emerged as an efficient catalyst for C-H bond activation, olefination and alkynylation reaction.¹⁴ However, to the best of our knowledge, the use of inexpensive ruthenium catalyst¹⁵ for direct cross-coupling reaction of olefins to form butadienes has not been reported.

During our studies on oxidative olefination of vinylic C-H bond, we developed a ruthenium-catalyzed direct cross-coupling reaction between acrylamides and electron-deficient alkenes to produce (Z,E)-dienamides in high efficiency. The same transformation also could be achieved by using rhodium catalyst (Scheme 3.8). The two catalytic systems allowed oxidative olefination of a wide range of alkenes bearing different functional groups, such as CO_2R , SO_2Ph , aryl, CONHBn , CN , $\text{PO}(\text{OEt})_2$, as well as Weinreb amide, which opens up new possibilities for the synthesis of a series of complex natural products and drugs.

¹⁴ (a) Ackermann, L. *Chem. Rev.*, **2011**, 111, 1315–1345. (b) Ackermann, L.; Vicente, R. *Top. Curr. Chem.*, **2010**, 292, 211–229. (c) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem. Int. Ed.*, **2011**, 50, 6379–6382.

¹⁵ Ruthenium complex $[\text{RuCl}_2(p\text{-cymene})]_2$ has emerged as an efficient catalyst for C-H bond activation, see selected references: (a) Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett.*, **2012**, 14, 728–731. (b) Padala, K.; Jeganmohan, M. *Org. Lett.*, **2011**, 13, 6144–6147. (c) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.*, **2012**, 14, 930–933. (d) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.*, **2011**, 13, 3278–3281.

Scheme 3.8

3.2 Results and discussion

At the outset of our studies, the reaction of methacrylamide with *n*-butyl acrylate was explored to screen the catalytic conditions, employing $[\text{RuCl}_2(p\text{-cymene})]_2$ as the catalyst (Table 3.1). When *t*-AmOH was selected as solvent in the absence of additive, the cross-coupling reaction exhibited low conversion, and the desired product was obtained in only 28% yield (Table 3.1, entry 1). Usage of KPF_6 or AgSbF_6 as an additive¹⁶ led to the corresponding product in moderate yield, and KPF_6 proved to be a little more efficient than AgSbF_6 (Table 3.1, entries 2 and 3). To optimize the catalytic conditions, the effect of solvents was subsequently examined (Table 3.1, entries 4, 5 and 6). To our delight, a mixed solvent system of dioxane/ H_2O / AcOH (v/v/v = 8/4/1) dramatically improved the reaction, and the yield was increased to 83% with good stereoselectivity ($Z/E = 96/4$) (Table 3.1, entry 6). However, the intra-molecular cyclization reaction towards unsaturated lactam was not observed.^{13,15a} If less amount of acetic acid (2.0 equiv) was used, the yield of the product decreased to 57% yield (Table 3.1, entry 7). It is also found that the reaction performed at 100 °C provided the best results, and either higher or lower temperatures resulted in reduced yields (Table 3.1, entries 8 and 9). Other oxidant, such as AgOAc , was also tested, and the desired dienamide was formed in only 21% yield (Table 3.1, entry 10). The catalytic process was inhibited under air atmosphere, and only trace amount of the product was detected (Table 3.1, entry 11). Simple ruthenium salts such as RuCl_3 was also examined but it was ineffective (Table 3.1, entry 12).

¹⁶ (a) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.*, **1974**, 233-241. (b) Fernández, S.; Pfeffer, M.; Ritleng, V.; Sirlin, C. *Organometallics*, **1999**, 18, 2390-2394.

Table 3.1. Optimization of the Ru-catalytic conditions ^a

$\text{1a} + \text{2a} \xrightarrow[\text{100 } ^\circ\text{C, 18 h}]{\text{Cat. [RuCl}_2(\text{p-cymene})]_2 \text{ (5 mol\%)} \text{ Additive (20 mol\%)} \text{ Oxidant (2.0 equiv)}}$
 3aa

Entry	Catalyst	Additive	Oxidant	Solvent	Yield (%)
1	[RuCl ₂ (p-cymene)] ₂	-	Cu(OAc) ₂ ·H ₂ O	t-AmOH	28
2	[RuCl ₂ (p-cymene)] ₂	KPF ₆	Cu(OAc) ₂ ·H ₂ O	Dioxane	50
3	[RuCl ₂ (p-cymene)] ₂	AgSbF ₆	Cu(OAc) ₂ ·H ₂ O	Dioxane	44
4	[RuCl ₂ (p-cymene)] ₂	KPF ₆	Cu(OAc) ₂ ·H ₂ O	t-AmOH	45
5 ^b	[RuCl ₂ (p-cymene)] ₂	KPF ₆	Cu(OAc) ₂ ·H ₂ O	Dioxane/H ₂ O	55
6^c	[RuCl₂(p-cymene)]₂	KPF₆	Cu(OAc)₂·H₂O	Dioxane/H₂O/AcOH	83
7 ^d	[RuCl ₂ (p-cymene)] ₂	KPF ₆	Cu(OAc) ₂ ·H ₂ O	Dioxane/H ₂ O	57
8 ^e	[RuCl ₂ (p-cymene)] ₂	KPF ₆	Cu(OAc) ₂ ·H ₂ O	Dioxane/H ₂ O/AcOH	77
9 ^f	[RuCl ₂ (p-cymene)] ₂	KPF ₆	Cu(OAc) ₂ ·H ₂ O	Dioxane/H ₂ O/AcOH	53
10	[RuCl ₂ (p-cymene)] ₂	KPF ₆	AgOAc	Dioxane/H ₂ O/AcOH	21
11 ^g	[RuCl ₂ (p-cymene)] ₂	KPF ₆	Cu(OAc) ₂ ·H ₂ O	Dioxane/H ₂ O/AcOH	< 5
12	RuCl ₃	KPF ₆	Cu(OAc) ₂ ·H ₂ O	Dioxane/H ₂ O/AcOH	0

^aReaction conditions unless otherwise specified: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.2 mmol, 2.0 equiv), Ru (5 mol%), additive (20 mol%) and an oxidant (2.0 equiv) in a specific solvent (0.6 mL), at 100 °C, under nitrogen, 18 h. The yields indicated in the table are isolated yields. ^bDioxane/H₂O/ = 2/1. ^cDioxane/H₂O/AcOH = 8/4/1. ^d2.0 equiv AcOH added. ^eThe reaction was performed at 120 °C. ^fThe reaction was performed at 80 °C. ^gThe reaction was performed under air.

Table 3.2. Optimization of the Rh-catalytic conditions ^a

$\text{1a} + \text{2a} \xrightarrow[\text{100 } ^\circ\text{C, 18 h}]{[\text{Rh}]/[\text{Pd}] (5 \text{ mol\%}), \text{Oxidant (2.0 equiv)}} \text{3a}$

Entry	Catalyst	Oxidant	Solvent	Yield (%)
1	[RhCp*Cl ₂] ₂	Ag ₂ CO ₃	MeCN	0
2 ^b	[RhCp*Cl ₂] ₂	Cu(OAc) ₂ ·H ₂ O	DME	63
3	[RhCp*Cl ₂] ₂	Cu(OAc) ₂ ·H ₂ O	t-AmOH	68
4	[RhCp*Cl ₂] ₂	Cu(OAc) ₂ ·H ₂ O	DCE	78
5	[RhCp*Cl₂]₂	Cu(OAc)₂·H₂O	Acetone	85
6 ^c	[RhCp*Cl ₂] ₂	Cu(OAc) ₂ ·H ₂ O	Acetone	80
7 ^d	[RhCp*Cl ₂] ₂	Cu(OAc) ₂ ·H ₂ O	Acetone	57
8 ^e	[RhCp*Cl ₂] ₂	Cu(OAc) ₂ ·H ₂ O	Acetone	76
9 ^f	[RhCp*Cl ₂] ₂	Cu(OAc) ₂ ·H ₂ O	Acetone	75
10 ^g	[RhCp*Cl ₂] ₂	Cu(OAc) ₂ ·H ₂ O	Acetone/H ₂ O	83
11	[RhCp*Cl ₂] ₂	O ₂	Acetone	0
12	RhCl ₃	Cu(OAc) ₂ ·H ₂ O	Acetone	Trace
13	Rh ₂ (OAc) ₄	Cu(OAc) ₂ ·H ₂ O	Acetone	0
14 ^h	Pd(OAc) ₂	Cu(OAc) ₂ ·H ₂ O	DMSO/AcOH	9

^a Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), Pd or Rh (5 mol%), and an oxidant (2.0 equiv) in a specific solvent (0.6 mL), under nitrogen, at 100 °C, 18 h. The yields indicated in the table are isolated yields. ^b 10 mol% AgSbF₆ added. ^c 1.0 equiv acrylate used. ^d The reaction was performed at 70 °C. ^e The reaction was performed under air. ^f 2.5 mol% Rh(III) used. ^g Acetone/H₂O = 2/1 (v/v) was used as solvent. ^h The reaction was carried out under oxygen at 60 °C for 24 h, and 1.0 equiv oxidant used.

We also explored the Rh(III)-catalyzed conditions for the same transformation (Table 3.2). Usage of $[\text{RhCp}^*\text{Cl}_2]_2$ and Ag_2CO_3 did not exhibit any catalytic activity (Table 3.2, entry 1). However, when we turned to another published catalytic conditions, using $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as an oxidant along with AgSbF_6 as an additive, reaction yielded the (Z,E)-cross-coupling product in 63% yield as the sole geometrical isomer (Table 3.2, entry 2). To optimize the catalytic conditions, a series of solvents, such as DME, DCE, *t*-AmOH and acetone were screened. Acetone was found to be the best solvent, and the yield was increased to 85%, even without the help of any additive (Table 3.2, entry 5). The results also showed that reducing the amount of acrylate by half had slightly effect on the reaction yield (Table 3.2, entry 6). But when the temperature was lowered, the reaction rate decreased and the yield dropped to a moderate level (Table 3.2, entry 7). Interestingly, the reaction proceeded smoothly under an atmosphere of air (Table 3.2, entry 8). Furthermore, lowering the catalyst load by half had little influence on the cross-coupling reaction (Table 3.2, entry 9). It is worthy to note that the reaction went smoothly in the presence of water (Table 3.2, entry 10). If the reaction was performed under oxygen without copper salt, the cross-coupling failed to occur (Table 3.2, entry 11). Other rhodium salts, such as $\text{Rh}_2(\text{OAc})_4$ and RhCl_3 , were examined, but none of them showed catalytic activity (Table 3.2, entries 11 and 12). $\text{Pd}(\text{OAc})_2$ was also tested as a catalyst but it was ineffective (Table 3.2, entry 13).

With the two optimized catalytic systems in hand, we firstly explored the scope of Ru-catalyzed oxidative olefination by employing differently substituted acrylamides and alkenes (Table 3.3).

Acrylamides **1** bearing different alkyl groups on the nitrogen atom, such as *N*-benzyl, *N*-cyclo

hexyl, or *N*-isopropyl, was smoothly reacted to provide dienamides in good yields (Table 3.3, **3aa**, **3ba** and **3ca**). Methacrylamide also proved to be efficient in the cross-coupling with acrylate affording product **3da** with good stereoselectivity (*Z/E* = 92/8). In contrast, *N,N*-diethyl methacrylamide exhibited much lower reactivity, and the yield of the product dropped to moderate level (Table 3.3, **3ea**). Likewise, the cross-coupling reaction between *N*-aryl methacrylamides with acrylate showed low conversion even at elevated temperature, and the desired products were isolated in 31-39% yield (Table 3.3, **3fa-3ja**). Further structural modifications of the acrylamides, such as introduction of a phenyl and hexyl group, at the α -position slightly influenced the catalytic process, providing 2-functionalized (*Z,E*)-dienamides in excellent yields (Table 3.3, **3ka** and **3la**). On the contrary, benzyloxymethyl acrylamide resulted in a significant decrease in conversion of this transformation, providing the desired functionalized dienamide in only 41% yield (Table 3.3, **3ma**). So, we can conclude that the electron-rich acrylamide was easier to be reacted, thus revealed an electrophilic activation manifold. This result is in agreement with intermolecular competition experiments (see details in experimental section). It is worthy to note that *N*-benzyl-2,3-dimethylpropenamide also led to the *tetra*-substituted diene product in somewhat low yield (Table 3.3, **3na**). This is probably caused by the degradation of the starting material under the catalytic conditions, and no acrylamide could be recovered after the reaction. If the methyl group was switch to the β -position of the acrylamide, the reaction was sluggish and the corresponding product was isolated in 23% yield (Table 3.3, **3oa**). Also, acrylamide with an un-substituted olefin unit reacted with low conversion, and a mixture of isomers (*Z/E* = 1/1) was obtained in only 31% yield (Table 3.3, **3pa**). Although *tert*-butyl acrylate gave messy

Table 3.3. Exploration of the scope of various acrylamides towards direct cross-coupling with alkenes by ruthenium catalyst^a

^aThe reactions were carried out as follows: acrylamide **1** (0.1 mmol), acrylate **2a** (0.15 mmol), [RuCl₂(*p*-cymene)]₂ (2.5 mol %), KPF₆ (20 mol %), Cu(OAc)₂·H₂O (0.2 mmol) in Dioxane/H₂O/AcOH = 8/4/1 (0.6 mL) at 100 °C, 18 h. ^bThe yields indicated in the table are isolated yields. ^cThe reaction was performed at 120 °C. ^d5.0 equiv acrylonitrile used. ^e1.2 equiv alkene used.

results, methyl acrylate **2b** reacted smoothly to give (*Z,E*)-dienamide in 71% yield (Table 3.3, **3ab**). However, α -methyl acrylate provided the desired product in only 21% yield, and most of the acrylamide was recovered. It is noteworthy that a by-product (Table 3.3, **3ac'**) was formed in 22% yield during the catalytic process. The catalytic system was not only restricted to the usage of acrylates, but also allowed for cross-coupling of a series of differently functionalized alkenes, and the functional groups could be CONHBn (Table 3.3, **3ad**), PO(OEt)₂ (Table 3.3, **3ae**), CN (Table 3.3, **3af**), SO₂Ph (Table 3.3, **3ag**) and 4-Cl phenyl (Table 3.3, **3ah**).¹⁷ To our delight, Weinreb acrylamide was converted to desired product with high catalytic efficiency as well (Table 3.3, **3ai** and **3ki**). This catalytic system exhibits wide functional group compatibility and substrate flexibility, and thus would have potential broad application in synthetic organic chemistry.

Next, we examined the scope of Rh-catalyzed cross-coupling reaction of acrylamides with alkenes (Table 3.4). The alkyl acrylates, and even *tert*-butyl acrylates reacted with *N*-benzyl methacrylamide smoothly to afford the corresponding (*Z,E*)-dienamides in excellent yields (Table 3.4, **3aa**, **3ab** and **3aj**). Moderately bulky isopropyl methacrylamide also proceeded well to generate the corresponding dienes in high yields (Table 3.4, **3cj**). However, *N*-aryl methacrylamides exhibited moderate reactivity toward acrylates (Table 3.4, **3fj**). Methacrylamide and *N,N*-diethyl methacrylamide were also good substrates for the coupling reaction (Table 3.4, **3dj** and **3ea**), although higher temperature was necessary for the latter reaction. Further structural modifications of the acrylamides, such as introduction of a phenyl or hexyl group at the α -position slightly influenced the catalytic process, providing 2-

Table 3.4 Exploration of the scope of acrylamides towards direct cross-coupling with various functionalized alkenes by rhodium ^a

^aThe reactions were carried out as follows: acrylamide **1** (0.2 mmol), acrylate **2** (0.3 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.4 mmol) in acetone (0.6 mL) at 100 °C, 18 h. ^bThe yields indicated in the table are isolated yields. ^cThe reaction was performed at 120 °C, 12 h. ^dThe reactions were performed at 80 °C for 6 h. ^e5.0 equiv acrylonitrile used.

functionalized (*Z,E*)-dienamides in excellent yields (Table 3.4, **3lj** and **3kj**). In contrast, introduction of benzyloxymethyl group to the α -position led to low conversion, and the corresponding product was formed in only 52% yield (Table 3.4, **3mj**). It is worthy to note that even a bulky acrylamide such as *N*-benzyl-2,3-dimethylpropenamide reacted smoothly to give corresponding *tetra*-substituted dienamide in high yield (Table 3.4, **3nj**). If a methyl group was introduced into the β -position of the acrylamide, the reaction showed much lower conversion (Table 3.4, **3oj**). Also, acrylamide with an un-substituted olefin unit was not a good coupling partner (Table 3.4, **3pa**). The reaction proceeded smoothly even with more active vinyl methyl ketone (Table 3.4, **3ak**). Less reactive coupling partners, such as chlorostyrene, also reacted with methacrylamide to generate dienes in good yields (Table 3.4, **3ah**).¹² Other functionalized alkenes, such as phenyl vinyl sulfone, acrylamide, acrylonitrile, diethyl vinyl phosphonate, were also competent substrates for the cross-coupling reaction, providing the corresponding highly functionalized dienamides in good to excellent yields (Table 3.4, **3ag**, **3ad**, **3af** and **3ae**). To our delight, coupling with Weinreb acrylamide proceeded smoothly to generate the corresponding functionalized dienamides in good yields (Table 3.4, **3ai**).

For the two catalytic conditions, styrene and 4-methoxy styrene were also tested, but both of them led to low conversion, and the desired dienamide was obtained in ~20% yield. Also, alkyl olefin, such as, 5-methoxy pentene, couldn't be well reacted, and only trace product was observed. These results indicated that electron-deficient alkene was reacted preferentially with acrylamides (See competition experiment). Moreover, alkene with an internal olefin unit, such as methyl trans-2-hexenoate, was totally inactive, and the starting materials were mostly

recovered. Homo-coupling by-product originated from acrylamide could be detected (~10% yield) when less reactive substrates were utilized.

In addition, competition experiments between differently substituted styrenes with acrylamide as limiting reagent was performed, showing that electron-deficient styrene reacted preferentially.¹³ In contrast, intermolecular competition experiments between differently *N*-substituted and α -substituted acrylamides revealed that the electron-rich substrate was more efficiently converted, hence indicating an electrophilic C-H bond activation (see experimental section).

Scheme 3.9. Isotopically labeled experiment.

To obtain some further mechanistic insight, we performed some control experiments with isotopically labelled solvents. Both of the catalytic conditions led to *Z*-selective olefinic H/D

exchange¹⁷ on methacrylamide **1a** in the absence of acrylate, thus indicating reversible cyclometallation modes (Scheme 3.9a). In contrast, if the same reaction is performed in the presence of acrylate **2a**, no deuterium incorporation is observed in recovered **1a**, and no H/D scrambling between the β -olefinic proton of the product **3aa** and the solvent was observed (Scheme 3.9b). These results showed that the following alkene-insertion and β -elimination step is much faster, and reversible cyclometallation should be the rate-determining step.

Based on the experiments and previous reported works, we proposed the possible mechanism (Scheme 3.10).

Scheme 3.10. Proposed mechanism

The reaction is presumably initiated by cyclometallation of acrylamide by amide-directing C-H bond activation. Coordination of alkene to the metal center, and followed by insertion of

¹⁷ A related references about Z-selective vinylic C-H bond activation see: Wencel-Delord, J.; Nimphius, C.; Patureau, F. W.; Glorius, F. *Chem. Asian J.*, **2012**, 7, 1208-1212.

the carbon-carbon double bond forms a seven-membered ruthacycle or rhodacycle species. Subsequent β -elimination occurs to afford the desired (*Z,E*)-dienamide.

3.3 Conclusion

In summary, we have developed Ru- and Rh-catalytic systems for the direct cross-coupling of acrylamides with electron-deficient alkenes forming (*Z,E*)-dienamides. Both of the two transformations exhibit wide functional group compatibility and substrate flexibility, and thus would have potential broad application in organic synthesis.

3.4 Experimental Section

General Methods

All commercially available reagents for the cross-coupling reaction were used as received: AR grade acetone, 1,2-dichloroethane, 1,2-dimethoxyethane and acetonitrile were obtained from Sigma-Aldrich and used as received. $[\text{RhCp}^*\text{Cl}_2]_2$ and $[\text{RuCl}_2(p\text{-cymene})]_2$ were obtained from Strem Chemicals Inc. $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was purchased from Alfa Aesar. The starting materials of acrylamides were prepared according to the reported method. All cross-coupling reactions were run in vials under sealed nitrogen atmosphere. Thin-layer chromatography (TLC) was conducted with Merck 60 F254 pre-coated silica *gel* plate (0.2 mm thickness) and visualized with UV and potassium permanganate staining, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. ^1H NMR spectra were performed on a Bruker 400 NMR spectrometer and are reported in ppm downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ = 7.26 ppm, singlet). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a 400 (100 MHz) or ECA-400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl_3 at 77.23 ppm). IR spectra were recorded as thin films on NaCl plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral analysis (HRMS) was performed on Waters Q-ToF Premier Mass Spectrometer.

General Procedure for the Synthesis of Acrylamides

Representative Procedure A: Synthesis of Acrylamides from Acid Chlorides and Anilines

Acid chloride (5.00 mmol) was added dropwise at 0 °C to a solution of aniline (5.00 mmol) and NEt₃ (0.73 mL, 5.25 mmol) in dry ethyl acetate (20.0 mL). The temperature was allowed to rise to ambient temperature, and then the mixture was stirred at room temperature for 2-6 h. After dilution with ethyl acetate and washing with water, the organic phase was dried over anhydrous Na₂SO₄, filtered. After removal of the solvents in reduced pressure, the crude product was purified by column chromatography on silica gel (EtOAc/Hexane) to yield corresponding acrylamide.

Representative Procedure B: Synthesis of Acrylamides from Acid Chlorides and Amines

Acid chloride (5.00 mmol) was added dropwise at 0 °C to a solution of amine (5.00 mmol) and NEt₃ (0.73 mL, 5.25 mmol) in dry DCM (20.0 mL). The temperature was allowed to rise to ambient temperature, and then the mixture was stirred at the same temperature for 2-6 h. After dilution with DCM and washing with water, the organic phase was dried over anhydrous Na₂SO₄, filtrated. After removal of the solvents in reduced pressure, the crude product was purified by column chromatography on silica gel (EtOAc/Hexane) to yield corresponding acrylamide.

Representative Procedure C: Synthesis of Acrylamides from Acids

EDC HCl (1.15 g, 6.00 mmol) was added at ambient temperature to a stirred mixture of acid (5.00 mmol), HOBt H₂O (230 mg, 1.50 mmol) and amine (5.25 mmol) in anhydrous MeCN (6.00 mL). After 5 min, Et₃N (0.73 mL, 5.25 mmol) was added, and the reaction mixture was allowed to stir for several hours at the same temperature. Thereafter, water was added, and the mixture was extracted with EtOAc. The combined organic phase was washed with brine (30.0 mL) and dried over anhydrous Na₂SO₄. After removal of the solvents in reduced pressure, the crude product was purified by column chromatography on silica gel (EtOAc/Hexane) to yield corresponding acrylamide.²

N-Benzyl methacrylamide¹⁸: This compound was prepared by Procedure **B** and was obtained as a white solid, yield = 61 %. ¹H NMR (400 MHz, CDCl₃): δ = 7.27-7.37 (m, 5H), 6.30 (b, 1H), 5.73 (s, 1H), 5.35 (s, 1H), 4.50 (d, *J* = 5.6 Hz, 2H), 1.99(s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 168.3, 140.0, 138.3, 128.7, 127.8, 127.5, 119.7, 43.7, 18.7.

N-Cyclohexyl methacrylamide¹⁹: This compound was prepared by Procedure **B** and was obtained as a white solid, yield = 67 %. ¹H NMR (400 MHz, CDCl₃): δ = 5.72 (b, 1H), 5.64

¹⁸ Ronald, G.; Monteith, M.; Visuvanathar, S.; Catherine, T. *Tetrahedron* **1998**, 54, 3885-3894.

¹⁹ Ackermann, L.; Lygin, A.V.; Hofmann, N. *Org. Lett.* **2011**, 13, 3278-3281

(s, 1H), 5.28 (s, 1H), 3.80 (m, 1H), 1.93-2.02 (m, 5H), 1.61-1.74 (m, 3H), 1.33-1.43 (m, 2H), 1.11-1.24 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 167.6, 140.5, 118.9, 48.2, 33.1, 25.6, 24.9, 18.7.

***N*-isopropyl methacrylamide¹⁹:** This compound was prepared by Procedure **B** and was obtained as a white solid, yield = 71 %. ^1H NMR (400 MHz, CDCl_3): δ = 5.64 (b, 1H), 5.64 (s, 1H), 5.29 (s, 1H), 4.12 (m, 1H), 1.95 (s, 3H), 1.18 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ = 167.6, 140.4, 118.9, 41.4, 22.7, 18.7.

***N*-Phenyl methacrylamide¹⁹:** This compound was prepared by Procedure **A** and was obtained as a yellow solid, yield = 81 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.67 (b, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.14 (t, J = 7.2 Hz, 1H), 5.81 (s, 1H), 5.46 (s, 1H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.7, 140.9, 137.8, 129.0, 124.4, 120.1, 119.8, 18.8.

***N*-(*o*-Tolyl) methacrylamide¹⁹:** This compound was prepared by Procedure **A** and was obtained as a white solid, yield = 91 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.89 (d, J = 8.0 Hz, 1H), 7.45 (b, 1H), 7.20-7.26 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 5.84 (s, 1H), 5.48 (s, 1H), 2.29 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.5, 140.9, 135.7, 130.5, 128.9, 126.8, 125.2, 122.9, 119.9, 18.8, 17.7.

N-(4-Methoxy phenyl) methacrylamide¹⁹: This compound was prepared by Procedure **A** and was obtained as a white solid, yield = 89 %. ¹H NMR (400 MHz, CDCl₃): δ = 7.61 (brs, 1H), 7.47 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.79 (s, 1H), 5.43 (s, 1H), 3.80 (s, 3H), 2.06 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.6, 156.5, 140.8, 130.9, 122.0, 119.7, 114.1, 55.5, 18.8.

N-(4-Fluoro phenyl) methacrylamide¹⁹: This compound was prepared by Procedure **A** and was obtained as a white solid, yield = 76 %. ¹H NMR (400 MHz, CDCl₃): δ = 7.63 (b, 1H), 7.52-7.55 (m, 2H), 7.03 (t, J = 8.4 Hz, 2H), 5.80 (s, 1H), 5.47 (s, 1H), 2.07 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.7, 159.4 (J = 243 Hz), 140.7, 133.8, 122.0 (J = 8 Hz), 120.0, 115.6 (J = 22 Hz), 18.7.

N,N-Diethyl methacrylamide²⁰: This compound was prepared by Procedure **B** and was obtained as a colourless oil, yield = 69 %. ¹H NMR (400 MHz, CDCl₃): δ = 5.08 (s, 1H), 4.98 (s, 1H), 3.37 (b, 4H), 1.94 (s, 3H), 1.13 (t, J = 7.2 Hz, 6H).

Preparation of N-Benzyl-2-benzyloxymethyl-propenamide

²⁰ Kollar, L.; Consiglio, G.; Pino, P. *J. Organomet. Chem.* **1990**, 386, 389-394.

A solution of formaldehyde (10 mmol) and methyl acrylate (3 mmol) in 10 mL of 1, 4-dioxane-water (1:1, v/v) was stirred at room temperature in the presence of 1.0 equiv DABCO, and the reaction progress was monitored by TLC. Upon completion, the reaction mixture was diluted with water (80 mL) and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, using ethyl acetate and hexane as the eluting solvents to give the **1n-1**, methyl 2-hydroxymethylpropenoate^[6], as a colourless liquid (0.226 g, 65 %). ^1H NMR (CDCl_3): δ = 6.21 (m, 1H), 5.81 (m, 1H), 4.27 (m, 2H), 3.73 (s, 3H), 2.82 (br, 1H). ^{13}C NMR (CDCl_3): δ = 166.6, 139.3, 125.5, 62.0, 51.7. To a mixture of methyl 2-hydroxymethylpropenoate (0.226 g, 1.95 mmol) and imidazole (2.14 mmol) in dry DCM (10 mL) was added TBDPSCl (2.14 mmol) in dropwise at 0 °C. Then the mixture was allowed to warm to room temperature and stirred for additional 1 hours. After that, the reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous MgSO_4 ,

filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, using ethyl acetate and hexane as the eluting solvents to give the **1n-2**, 2-(tert-butyl-diphenyl-silanyloxymethyl)-acrylic acid methyl ester, as a white solid (670 mg, 97%). ^1H NMR (CDCl_3): δ = 7.69-7.71 (m, 4H), 7.39-7.48 (m, 6H), 6.36-6.38 (dd, J = 2.0 Hz, J = 3.6 Hz, 1H), 6.15 (d, J = 2.4 Hz, 1H), 4.46 (t, J = 2.0 Hz, 2H), 3.73 (s, 3H), 1.10 (s, 9H). ^{13}C NMR (CDCl_3): δ = 166.3, 139.4, 135.5, 133.3, 129.8, 127.8, 124.1, 62.2, 51.6, 26.8, 19.3. To a solution of ester obtained above (670 mg, 1.89 mmol) in THF/ H_2O (v/v = 1/1, 10 mL) was treated with aq. LiOH (4.6 N, 2 mL). The mixture was stirred at room temperature for overnight. The reaction was acidified (pH = 1.0) with 1.0 N aq. HCl and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated to afford 2-(tert-butyl-diphenyl-silanyloxymethyl)-acrylic acid (**1n-3**) for further usage (610 mg, 95 %). Compound **1n-4**, *N*-Benzyl-2-(tert-butyl-diphenyl-silanyloxymethyl)-propenamide, was prepared by Procedure C and was obtained as a white solid (517 mg, 67%). ^1H NMR (CDCl_3): δ = 7.62-7.64 (m, 4H), 7.27-7.48 (m, 12H), 6.08 (s, 1H), 5.40 (d, J = 0.8 Hz, 1H), 4.57 (d, J = 5.6 Hz, 2 H), 4.43 (s, 2 H), 0.98 (s, 9H). ^{13}C NMR (CDCl_3): δ = 166.6, 141.1, 138.1, 135.5, 132.5, 130.0, 128.8, 128.1, 127.8, 127.6, 122.7, 64.8, 43.7, 26.7, 19.1. To a solution of compound **1n-4** (517 mg, 1.2 mmol) in dry THF was added TBAF (1.0 M sol. In THF, 1.3 mL) in dropwise at 0°C . After 0.5 h, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried over MgSO_4 and concentrated under reduced pressure. Purification by flash-chromatography (eluent, ethyl acetate and hexane) afforded *N*-Benzyl-2-hydroxymethyl propenamide (**1n-5**) (209 mg, 91 %). ^1H NMR (CDCl_3): δ = 7.29-7.39 (m, 5H), 6.92 (b, 1H), 5.94 (s, 1H), 5.57 (s,

1H), 4.54 (d, $J = 6.0$ Hz, 2H), 4.40 (d, $J = 4.8$ Hz, 2H), 2.78 (b, 1H). ^{13}C NMR (CDCl_3): $\delta = 167.2, 142.2, 138.0, 128.8, 127.8, 127.6, 121.7, 63.9, 43.6$. To a suspension of NaH (60 wt% in mineral oil, 48 mg, 1.2 mmol) and TBAI (cat.) in dry THF (5 mL) was added a solution of methyl 2-hydroxymethylpropenate (209 mg, 1.09 mmol) in THF (5 mL) at 0 °C. After 5 min., benzyl bromide (204 mg, 1.2 mmol) was added and the mixture was allowed to stir at room temperature for 2 hours. Then the reaction was quenched with water and extracted with dichloromethane. The organic layer was dried over MgSO_4 and concentrated under reduced pressure. Purification by flash-chromatography (eluent, ethyl acetate and hexane) afforded *N*-Benzyl-2-benzyloxymethylpropenamide (**1n**) as a white solid, mp: 71-72 °C, yield = 76 %. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.23\text{-}7.34$ (m, 10H), 6.29 (s, 1H), 5.62 (s, 1H), 4.54 (s, 2H), 4.52 (s, 2H), 4.32 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 166.3, 138.8, 138.2, 137.1, 128.7, 128.6, 128.1, 128.0, 127.8, 127.4, 125.4, 72.1, 70.4, 43.5$. HRMS (ESI): m/z calcd. for $\text{C}_{18}\text{H}_{20}\text{NO}_2$ [MH^+]: 282.1494; found: 282.1491. FTIR (NaCl, cm^{-1}): 3053, 2985, 2628, 2304, 1701, 1648, 1561, 1419, 1265, 895, 738, 704.

***N*-Benzyl-2-phenylpropenamide**²¹: This compound was prepared by Procedure C and was obtained as a white solid, yield = 67 %. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.27\text{-}7.41$ (m, 10H), 6.21 (d, $J = 1.2$ Hz, 1H), 6.08 (brs, 1H), 5.67(d, $J = 1.2$ Hz, 1H), 4.56 (d, $J = 6.0$ Hz, 2H).

²¹ Suleiman, R.; Tijani, J.; El Ali, B. *Appl. Organomet. Chem.* **2010**, 24, 38-46.

Preparation of 2-hexylpropenoic acid (for synthesis of *N*-Benzyl-2-hexylpropenamide)

To a suspension of NaH (60 wt% in mineral oil, 5.5mmol) in dry DMSO (5mL) was added triethyl phosphonoacetate (0.99mL, 5.0mmol). After the mixture was stirred at room temperature for 30 min., hexyl iodide (5.0 mmol) was added in dropwise. The mixture was heated to 60 °C and stirred for 2 hours. After cooling, the reaction was quenched with water and extracted with ethyl acetate. The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated. To a solution of the residue in THF (5 mL) were added aqueous potassium carbonate (1 g dissolved in 2.5 mL of H₂O) and aqueous formaldehyde (37 wt%, 5 mL) and the mixture was heated at 80 °C for 2 h. The mixture was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel to give ethyl 2-hexylpropenate (**1k-2**)²² as a colourless oil (561 mg, 61 %). ¹H NMR (400 MHz, CDCl₃): δ = 6.11 (s, 1H), 5.49 (s, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.41-1.46 (m, 2H), 1.26-1.34 (m, 9H), 0.87 (t, *J* = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.4, 141.2, 124.1, 60.5, 31.9, 31.6, 28.9, 28.4, 22.6, 14.2, 14.1. To a solution of ester obtained above (561 mg, 3.0 mmol) in THF (9 mL) was treated

²² Yajima, T.; Saito, C.; Nagano, H. *Tetrahedron*, **2005**, 61, 10203-10215.

with an aq. solution of LiOH (4.6 N, 5 mL). The mixture was stirred at r.t. for hours. After the reaction was complete, the aqueous solution was acidified (pH = 1.0) with 1.0 N aq. HCl and extracted with diethyl ether. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to afford the 2-hexylpropenoic acid (**1k-3**) for further usage (0.464 g, 99 %).

N-Benzyl-2-hexylpropenamide²³: This compound was prepared by

Procedure **C** and was obtained as a white solid, yield = 81 %. ¹H NMR (400 MHz, CDCl₃): δ = 7.28-7.39 (m, 5H), 6.11(b, 1H), 5.62 (s, 1H), 5.29 (s, 1H), 4.53 (d, *J* = 5.6 Hz, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 1.45-1.51 (m, 2H), 1.28-1.36 (m, 6H), 0.90 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 168.9, 145.8, 138.3, 128.8, 127.8, 127.5, 117.3, 43.7, 32.4, 31.7, 28.9, 28.1, 22.6, 14.1.

N-Benzyl-2,3-dimethylpropenamide²⁴: This compound was prepared

by Procedure **C** and was obtained as a colourless oil, yield = 85 %. ¹H NMR (400 MHz, CDCl₃): δ = 7.28-7.38 (m, 5H), 6.47-6.52 (m, 1H), 6.02 (b, 1H), 4.52 (d, *J* = 6.0 Hz, 2H), 1.88 (s, 3H), 1.77 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 169.2, 138.6, 131.7, 130.9, 128.7, 127.9, 127.5, 43.8, 13.9, 12.5.

²³ Park, J.-H.; Kim, S.-Y.; Kim, S.-M.; Chung, Y.-K. *Org. Lett.* **2007**, 9, 2465-2468.

²⁴ (a) Sakamoto, M.; Ishida, T.; Fujita, T.; Watanabe, S. *J. Org. Chem.*, **1992**, 57, 2419-2422. (b) Ihara, M.; Haga, Y.; Yonekura, M.; Ohsawa, T.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1983**, 105, 7345-7352.

N-Benzyl propenamide²⁵: This compound was prepared by Procedure **B** and was obtained as a white solid, yield = 89 %. ¹H NMR (400 MHz, CDCl₃): δ = 7.28-7.38 (m, 5H), 6.33 (dd, *J* = 1.6 Hz, *J* = 17.2 Hz, 1H), 6.14 (dd, *J* = 10.4 Hz, *J* = 17.2 Hz, 1H), 6.01 (b, 1H), 5.68 (dd, *J* = 1.2 Hz, *J* = 10.4 Hz, 1H), 4.53 (d, *J* = 5.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 165.4, 138.1, 130.7, 128.8, 127.9, 127.6, 126.8, 43.7.

N-Benzyl-3-methylpropenamide²⁶: This compound was prepared by Procedure **C** and was obtained as a white solid, yield = 79 %. ¹H NMR (400 MHz, CDCl₃): δ = 7.24-7.33 (m, 5H), 6.78-6.87 (m, 1H), 6.45 (b, 1H), 5.85-5.89 (m, 1H), 4.44 (d, *J* = 5.6 Hz, 2H), 1.81 (d, *J* = 1.6 Hz, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 166.1, 140.0, 138.5, 128.6, 127.8, 127.3, 125.0, 43.4, 17.7.

N-Methyl-N-methoxypropenamide²⁷: This compound was prepared by reported method ¹³ and was obtained as a colourless oil, yield = 79 %. ¹H NMR (400 MHz, CDCl₃): δ = 6.73 (dd, *J* = 10.4 Hz, *J* = 17.2 Hz, 1H), 6.41 (dd, *J* = 1.8 Hz, *J* = 17.2 Hz, 1H), 5.73 (dd, *J* = 1.8 Hz, *J* = 10.4 Hz, 1H), 3.70 (s, 3H), 3.25 (s, 3H). ¹³C NMR (100 MHz,

²⁵ Soule, J.-F.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2011**, 133, 18550-18553.

²⁶ Shintani, R.; Kimura, T.; Hayashi, T. *Chem. Commun.* **2005**, 25, 3213-3214.

²⁷ (a) O'Brien, J.-M.; Kingsbury, J. S. *J. Org. Chem.* **2011**, 76, 1662-1672. (b) Smith, N. D.; Goodman, M. *Org. Lett.* **2003**, 5, 1035-1038.

CDCl₃): δ = 165.2, 129.0, 125.9, 61.8, 31.2.

General Procedure for Cross-Coupling of Acrylamides with Alkenes

[Ru]-catalyzed conditions:

A screw-cap vial was charged with [RuCl₂(p-cymene)]₂ (2.5-5.0 mol%, 0.0025-0.0050 mmol), Cu(OAc)₂·H₂O (2.0 equiv, 0.2 mmol), KPF₆ (20-40 mol%) and dioxane/H₂O/AcOH = 8/4/1(v/v/v) (0.6 ml). Then, acrylamide **1** (1.0 equiv, 0.1 mmol) and acrylate **2** (1.5-2.0 equiv, 0.15-0.20 mmol) were added into the solution in sequence. The vial was sealed under nitrogen and heated to 100 °C with stirring for 18 hours. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated to give the crude product which was directly applied to a flash column chromatography (EtOAc/Hexanes mixtures).

[Rh]-catalyzed conditions:

An oven-dried screw-cap vial was charged with $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%, 0.005 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv, 0.4 mmol) and acetone (0.6 ml). Then, acrylamide **1** (1.0 equiv, 0.2 mmol) and acrylate **2** (1.5 equiv, 0.3 mmol) were added into the solution in sequence. The vial was sealed under nitrogen and heated to 100 °C with stirring for 18 hours. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous MgSO_4 , filtered and concentrated to give the crude product which was directly applied to a flash column chromatography (EtOAc/Hexanes mixtures).

Characterization Data for the Dienamides

(2E,4Z)-n-Butyl 6-benzylamino-5-methyl-6-oxohexa-2,4-dienoate

(3aa): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 83 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.67 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 7.26-7.38 (m, 5H), 6.21 (d, J = 11.6 Hz, 1H), 5.88 (d, J = 15.2 Hz, 1H), 5.94 (b, 1H), 4.55 (d, J = 5.6 Hz, 2H), 4.14 (t, J = 6.8 Hz, 2H), 2.08 (s, 3H), 1.60-1.67 (m, 2H), 1.34-1.43 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 168.4, 166.6, 141.5, 139.5, 137.7, 129.1, 128.9, 128.0, 127.8, 123.8, 64.4, 43.9, 30.7, 21.5, 19.2, 13.8. HR-MS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{23}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 324.1576; found 324.1578. FTIR (NaCl, cm^{-1}): 3056, 2985, 2304, 1705, 1663, 1645, 1632, 1502, 1421, 1265, 1152, 895, 738, 704.

(2E,4Z)-*n*-Butyl 6-cyclohexylamino-5-methyl-6-oxohexa-2,4-dienoate

(3ba): This compound was prepared by the General Procedure described above and was obtained as a yellow oil. Yield = 70 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.60 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 6.18 (d, J = 11.6 Hz, 1H), 5.89 (d, J = 15.6 Hz, 1H), 5.53 (b, 1H), 4.16 (t, J = 6.4 Hz, 2H), 3.91-3.93 (m, 1H), 2.07 (s, 3H), 2.01-2.05 (m, 2H), 1.74-1.79 (m, 2H), 1.62-1.69 (m, 3H), 1.41-1.48 (m, 5H), 1.16-1.39 (m, 4H), 0.96 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 167.7, 166.7, 143.0, 139.6, 127.8, 123.1, 64.4, 48.5, 33.1, 30.7, 25.5, 24.9, 21.3, 19.2, 13.7. HR-MS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{28}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 294.2069; found 294.2068. FTIR (NaCl, cm^{-1}): 3420, 3059, 2961, 2938, 2857, 2309, 1705, 1659, 1648, 1635, 1508, 1450, 1421, 1308, 1266, 1198, 1150, 1123, 984, 890, 747, 709.

(2E,4Z)-*n*-Butyl 6-*iso*-propylamino-5-methyl-6-oxohexa-2,4-dienoate

(3ca): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 75 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.60 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 6.18 (d, J = 11.6 Hz, 1H), 5.89 (d, J = 15.2 Hz, 1H), 5.48 (b, 1H), 4.18-4.27 (m, 1H), 4.15 (t, J = 6.4 Hz, 2H), 2.06 (s, 3H), 1.61-1.68 (m, 2H), 1.36-1.45 (m, 2H), 1.25 (d, J = 6.4 Hz, 6H), 0.95 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 167.8, 166.7, 142.8, 139.5, 127.9, 123.1, 64.4, 41.7, 30.7, 22.7, 21.3, 19.2, 13.7. HR-MS (ESI): m/z

calculated for $C_{14}H_{24}NO_3$ $[M+H]^+$: 254.1756; found 254.1761. FTIR (NaCl, cm^{-1}): 3420, 3053, 2965, 2309, 2054, 1702, 1654, 1633, 1512, 1458, 1420, 1387, 1304, 1262, 1198, 1148, 983, 891, 752, 711.

(2E,4Z)-n-Butyl 6-amino-5-methyl-6-oxohexa-2,4-dienoate (3da):

This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 82 %. 1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 6.25 (d, J = 11.6 Hz, 1H), 6.18 (b, 1H), 5.94 (d, J = 15.2 Hz, 1H), 5.79 (b, 1H), 4.17 (t, J = 6.8 Hz, 2H), 2.10 (s, 3H), 1.63-1.70 (m, 2H), 1.37-1.46 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 166.8, 140.2, 139.6, 129.8, 124.0, 64.5, 30.7, 21.4, 19.2, 13.7. HR-MS (ESI): m/z calculated for $C_{11}H_{18}NO_3$ $[M+H]^+$: 212.1287; found 212.1288. FTIR (NaCl, cm^{-1}): 3469, 3397, 3051, 2971, 2963, 2309, 1708, 1675, 1637, 1609, 1423, 1315, 1271, 1202, 1152, 986, 895, 744, 706.

(2E,4Z)-n-Butyl 6-diethylamino-5-methyl-6-oxohexa-2,4-dienoate (3ea):

This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 54 %. 1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 6.08 (dd, J = 0.8 Hz, J = 11.6 Hz, 1H), 5.83 (d, J = 15.2 Hz, 1H), 4.11

(t, $J = 6.4$ Hz, 2H), 3.48-3.50 (m, 2H), 3.28-3.33 (q, $J = 7.2$ Hz, 2H), 2.05 (s, 3H), 1.58-1.60 (m, 2H), 1.32-1.42 (m, 2H), 1.20 (t, $J = 7.2$ Hz, 3H), 1.12 (t, $J = 7.2$ Hz, 3H), 0.93 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 169.7, 166.7, 143.3, 139.9, 125.3, 121.9, 64.3, 42.5, 38.5, 30.7, 21.3, 19.2, 14.2, 13.7, 12.8$. HR-MS (ESI): m/z calculated for $\text{C}_{15}\text{H}_{26}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 268.1913; found 268.1918. FTIR (NaCl, cm^{-1}): 3439, 3053, 2985, 2304, 1705, 1653, 1638, 1625, 1474, 1435, 1421, 1306, 1269, 1206, 1161, 1142, 1101, 1036, 982, 908, 894, 744, 701.

(2E,4Z)-n-Butyl 6-phenylamino-5-methyl-6-oxohexa-2,4-dienoate

(3fa): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield= 39 %. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.71$ (dd, $J = 11.6$ Hz, $J = 15.2$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.35-7.41 (m, 3H), 7.18 (t, $J = 7.2$ Hz, 1H), 6.31 (d, $J = 11.6$ Hz, 1H), 5.97 (d, $J = 15.2$ Hz, 1H), 4.15 (t, $J = 6.4$ Hz, 2H), 2.18 (s, 3H), 1.60-1.67 (m, 2H), 1.34-1.40 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 166.6, 166.5, 141.6, 139.1, 137.2, 129.4, 129.1, 125.0, 124.3, 120.3, 64.5, 30.7, 21.4, 19.2, 13.7$. HR-MS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 310.1419; found 310.1414. FTIR (NaCl, cm^{-1}): 3412, 3055, 2963, 2949, 2874, 2309, 1708, 1671, 1636, 1599, 1519, 1500, 1440, 1311, 1266, 1185, 1149, 1063, 1030, 983, 907, 897, 749, 709.

(2E,4Z)-n-Butyl 6-p-fluorophenylamino-5-methyl-6-oxohexa-2,4-

dienoate (3ga): This compound was prepared by the General Procedure described above and was obtained as a yellow liquid. Yield = 34 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.69 (dd, J = 12.0 Hz, J = 15.2 Hz, 1H), 7.55-7.58 (m, 2H), 7.39 (b, 1H), 7.05-7.09 (m, 2H), 6.32 (d, J = 11.6 Hz, 1H), 5.99 (d, J = 15.2 Hz, 1H), 4.16 (t, J = 6.4 Hz, 2H), 2.19 (s, 3H), 1.61-1.68 (m, 2H), 1.36-1.43 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.6, 166.5, 159.8 (d, J = 243 Hz), 141.4, 139.1, 133.2, 129.5, 124.3, 122.1 (d, J = 8 Hz), 115.8 (d, J = 23 Hz), 64.6, 30.7, 21.4, 19.2, 13.7. HR-MS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{F}$ $[\text{M}+\text{H}]^+$: 306.1505; found 306.1509. FTIR (NaCl, cm^{-1}): 3412, 3059, 2960, 2301, 1705, 1668, 1643, 1636, 1614, 1508, 1407, 1308, 1259, 1213, 1183, 1149, 981, 897, 836, 755, 701.

(2E,4Z)-n-Butyl 6-(p-methoxyphenylamino)-5-methyl-6-

oxohexa-2,4-dienoate (3ha): This compound was prepared by the General Procedure described above and was obtained as a yellow oil. Yield = 38 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.73 (dd, J = 12.0 Hz, J = 15.6 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.29 (b, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.31 (d, J = 11.6 Hz, 1H), 5.97 (d, J = 15.6 Hz, 1H), 4.16 (t, J = 6.8 Hz, 2H), 3.84 (s, 3H), 2.18 (s, 3H), 1.61-1.68 (m, 2H), 1.36-1.43 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C

NMR (100 MHz, CDCl_3): δ = 166.6, 166.5, 156.9, 141.8, 139.3, 130.2, 129.2, 124.1, 122.2, 114.3, 64.5, 55.5, 30.7, 21.4, 19.2, 13.7. HR-MS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{24}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 318.1705; found 318.1707. FTIR (NaCl, cm^{-1}): 3306, 3057, 2960, 2933, 1714, 1697, 1659, 1634, 1605, 1510, 1466, 1414, 1302, 1273, 1246, 1180, 1147, 1036, 983, 908, 829, 735, 705.

(2E,4Z)-n-Butyl 6-p-chlorophenylamino-5-methyl-6-oxohexa-2,4-

dienoate (3ia): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 31 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.68 (dd, J = 15.2 Hz, J = 12.0 Hz 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.44 (b, 1H), 7.33 (d, J = 8.8 Hz, 2H), 6.33 (d, J = 12.0 Hz, 1H), 5.99 (d, J = 15.2 Hz, 1H), 4.16 (t, J = 6.4 Hz, 2H), 2.18 (s, 3H), 1.61-1.66 (m, 2H), 1.36-1.43 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.6, 141.3, 139.0, 135.8, 130.0, 129.6, 129.2, 124.4, 121.4, 64.6, 30.7, 21.4, 19.2, 13.7. HR-MS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{Cl}$ $[\text{M}+\text{H}]^+$: 322.1210; found 322.1209. FTIR (NaCl, cm^{-1}): 3412, 3061, 2978, 2305, 1701, 1670, 1659, 1635, 1595, 1508, 1493, 1420, 1398, 1306, 1267, 1184, 1146, 1092, 982, 897, 828, 719, 706.

(2E,4Z)-n-Butyl 6-o-tolylamino-5-methyl-6-oxohexa-2,4-dienoate

(3ja): This compound was prepared by the General Procedure described above and was

obtained as a yellow oil. Yield = 37 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.91 (d, J = 8.0 Hz, 1H), 7.82 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 7.14-7.29 (m, 4H), 6.36 (d, J = 11.6 Hz, 1H), 6.00 (d, J = 15.2 Hz, 1H), 4.17 (t, J = 6.8 Hz, 2H), 2.33 (s, 3H), 2.22 (s, 3H), 1.62-1.69 (m, 2H), 1.37-1.43 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.6, 166.5, 141.8, 139.1, 135.0, 130.7, 129.3, 126.9, 125.8, 124.3, 123.3, 64.5, 30.7, 21.5, 19.2, 17.9, 13.7. HR-MS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{24}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 302.1756; found 302.1754. FTIR (NaCl, cm^{-1}): 3409, 3056, 2963, 1705, 1659, 1643, 1636, 1516, 1454, 1265, 1182, 1145, 984, 908, 895, 717, 704.

(2E,4Z)-*n*-Butyl 6-benzylamino-5-hexyl-6-oxohexa-2,4-dienoate

(3ka): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 91 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.57 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 7.28-7.40 (m, 5H), 6.17 (d, J = 12.0 Hz, 1H), 5.97 (b, 1H), 5.91 (d, J = 15.2 Hz, 1H), 4.58 (d, J = 5.6 Hz, 2H), 4.16 (t, J = 6.4 Hz, 2H), 2.40 (t, J = 7.2 Hz, 2H), 1.61-1.67 (m, 2H), 1.29-1.50 (m, 10H), 0.98 (t, J = 7.6 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 168.5, 166.6, 147.6, 139.5, 137.7, 128.8, 128.0, 127.7, 126.9, 123.4, 64.4, 43.8, 35.4, 31.6, 30.7, 28.9, 27.9, 22.5, 19.2, 14.1, 13.8. HR-MS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{30}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 344.2226; found 344.2224. FTIR (NaCl, cm^{-1}): 3420, 3055, 2959, 2930, 2872, 2867, 1705, 1651, 1647, 1634, 1518, 1454, 1423, 1308, 1263, 1204, 1148, 1028, 984, 908, 741, 702.

(2E,4Z)-n-Butyl 6-benzylamino-5-phenyl-6-oxohexa-2,4-dienoate

(3la): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 90 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.74 (dd, J = 12.0 Hz, J = 15.2 Hz, 1H), 7.46-7.49 (m, 2H), 7.23-7.40 (m, 8H), 6.68 (d, J = 11.6 Hz, 1H), 6.07 (d, J = 15.2 Hz, 1H), 5.98 (b, 1H), 4.63 (d, J = 6.0 Hz, 2H), 4.18 (t, J = 6.8 Hz, 2H), 1.64-1.68 (m, 2H), 1.38-1.44 (m, 2H), 0.95 (t, J = 7.6 Hz). ^{13}C NMR (100 MHz, CDCl_3): δ = 167.5, 166.5, 144.6, 139.8, 137.6, 135.7, 129.4, 128.9, 128.9, 128.3, 128.0, 127.9, 127.7, 127.3, 127.2, 126.9, 125.2, 64.5, 44.0, 30.8, 19.2, 13.8. HR-MS (ESI): m/z calculated for $\text{C}_{23}\text{H}_{25}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 386.1732; found 386.1733. FTIR (NaCl, cm^{-1}): 3424, 3051, 2986, 2303, 1701, 1661, 1647, 1626, 1514, 1423, 1309, 1264, 1141, 983, 891, 738, 706.

(2E,4Z)-n-Butyl 6-benzylamino-5-benzyloxymethyl-6-oxohexa-

2,4-dienoate (3ma): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 41 %. ^1H NMR (400 MHz, CDCl_3): δ = 8.09 (dd, J = 11.6 Hz, J = 15.6 Hz, 1H), 7.22-7.36 (m, 10H), 6.98 (b, 1H), 6.45 (d, J = 11.2 Hz, 1H), 6.05 (d, J = 15.6 Hz, 1H), 4.55 (d, J = 6.0 Hz, 2H), 4.54 (s, 2H), 4.26 (s, 2H), 4.19 (t, J = 6.8 Hz, 2H), 1.68-1.72 (m, 2H), 1.40-1.45 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.4, 166.3, 139.1, 137.9, 136.9, 134.6, 128.8, 128.6, 128.1, 128.0, 127.8, 127.6,

127.2, 72.6, 72.3, 64.6, 43.5, 30.7, 19.2, 13.8. HR-MS (ESI): m/z calculated for $C_{25}H_{30}NO_4$ $[M+H]^+$: 408.2175; found 408.2177. FTIR (NaCl, cm^{-1}): 3412, 3056, 2959, 1708, 1678, 1669, 1638, 1522, 1454, 1419, 1308, 1266, 1196, 1153, 1126, 1063, 988, 908, 734, 702.

(2E,4Z)-*n*-Butyl 6-benzylamino-4,5-dimethyl-6-oxohexa-2,4-dienoate

(3na): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 39 %. 1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 15.6 Hz, 1H), 7.28-7.36 (m, 5H), 5.92 (d, J = 15.6 Hz, 1H), 5.73 (b, 1H), 4.56 (d, J = 5.6 Hz, 2H), 4.16 (t, J = 6.8 Hz, 2H), 2.06 (s, 3H), 1.90 (d, J = 0.8 Hz, 3H), 1.61-1.68 (m, 2H), 1.38-1.45 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 166.9, 142.8, 139.8, 137.6, 130.9, 128.9, 128.0, 127.7, 119.4, 64.4, 44.0, 30.8, 19.2, 17.7, 13.8, 13.7. HR-MS (ESI): m/z calculated for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1913; found 316.1915. FTIR (NaCl, cm^{-1}): 3429, 3054, 2986, 2978, 2300, 1700, 1654, 1647, 1624, 1509, 1454, 1425, 1289, 1269, 1176, 1144, 979, 896, 748, 701.

(2E,4Z)-*n*-Butyl 6-benzylamino-4-methyl-6-oxohexa-2,4-dienoate

(3oa): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 23 %. 1H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, J = 16.0

Hz, 1H), 7.28-7.39 (m, 5H), 6.12 (d, $J = 16.0$ Hz, 1H), 5.90 (s, 1H), 5.83 (b, 1H), 4.55 (d, $J = 5.6$ Hz, 2H), 4.22 (t, $J = 6.8$ Hz, 2H), 2.02 (d, $J = 1.2$ Hz, 3H), 1.67-1.74 (m, 2H), 1.42-1.47 (m, 2H), 0.98 (t, $J = 3.6$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 166.7, 165.1, 143.4, 140.6, 138.0, 128.8, 128.0, 127.7, 126.4, 123.5, 64.6, 43.7, 30.7, 20.4, 19.2, 13.8$. HR-MS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{24}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 302.1756; found 302.1755. FTIR (NaCl, cm^{-1}): 3435, 3090, 3055, 1707, 1647, 1637, 1631, 1604, 1508, 1454, 1421, 1306, 1262, 1170, 895, 748, 704.

(2E,4Z)-Methyl 6-benzylamino-5-methyl-6-oxohexa-2,4-dienoate (3ab):

This compound was prepared by the General Procedure described above and was obtained as a white solid, mp: 67-68 °C. Yield = 71 %. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.72$ (dd, $J = 11.6$ Hz, $J = 15.6$ Hz, 1H), 7.29-7.41 (m, 5H), 6.24 (dd, $J = 11.6$ Hz, $J = 0.8$ Hz, 1H), 6.00 (b, 1H), 5.90 (d, $J = 15.6$ Hz, 1H), 4.58 (d, $J = 5.6$ Hz, 2H), 3.76 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 168.3, 167.0, 141.6, 139.8, 137.7, 129.1, 128.9, 128.0, 127.8, 123.2, 51.7, 43.8, 21.5$. HR-MS (ESI): m/z calculated for $\text{C}_{15}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 260.1287; found 260.1282. FTIR (NaCl, cm^{-1}): 3439, 3053, 2986, 2304, 1705, 1662, 1645, 1615, 1510, 1436, 1421, 1265, 1149, 895, 733, 709.

(2*E*,4*Z*)-Methyl 6-benzylamino-2,5-dimethyl-6-oxohexa-2,4-dienoate

(3ac): This compound was prepared by the General Procedure described above and was obtained as a white solid, mp: 71-73 °C. Yield = 21 %. ¹H NMR (400 MHz, CDCl₃): δ = 7.56 (dd, *J* = 12.0 Hz, *J* = 0.8 Hz, 1H), 7.26-7.36 (m, 5H), 6.42 (dd, *J* = 1.6 Hz, *J* = 11.6 Hz, 1H), 5.88 (b, 1H), 4.57 (d, *J* = 6.0 Hz, 2H), 3.73 (s, 3H), 2.11 (s, 3H), 1.95 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 168.8, 168.5, 140.1, 137.8, 133.1, 129.3, 128.8, 128.0, 127.7, 126.2, 52.0, 43.8, 21.7, 12.6. HR-MS (ESI): *m/z* calculated for C₁₆H₂₀NO₃ [M+H]⁺: 274.1443; found 274.1443. FTIR (NaCl, cm⁻¹): 3439, 3053, 2980, 2301, 1705, 1662, 1632, 1627, 1510, 1421, 1265, 895, 754, 733, 723, 706.

Methyl 6-benzylamino-6-oxo-2-methylene-5-methyl-hexa-(*Z*)-4-enoate

(3ac'): This compound was prepared by the General Procedure described above and was obtained as an colourless oil. Yield = 22 %. ¹H NMR (400 MHz, CDCl₃): δ = 7.47 (b, 1H), 7.28-7.38 (m, 5H), 6.20 (d, *J* = 0.4 Hz, 1H), 5.68 (d, *J* = 0.8 Hz, 1H), 5.41-5.45 (m, 1H), 4.56 (d, *J* = 6.0 Hz, 2H), 3.74 (s, 3H), 3.19 (d, *J* = 8.0 Hz, 2H), 1.97 (d, *J* = 1.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 169.5, 167.7, 138.5, 138.2, 134.6, 128.6, 128.1, 127.9, 127.3, 127.0, 52.1, 43.4, 33.1, 21.2. HR-MS (ESI): *m/z* calculated for C₁₆H₂₀NO₃ [M+H]⁺: 274.1443; found 274.1443. FTIR (NaCl, cm⁻¹): 3429, 3053, 2981, 2300, 1707, 1667, 1638, 1619, 1541, 1512,

1440, 1422, 1339, 1247, 1222, 1166, 1134, 955, 893, 722, 701.

***N,N'*-bis-Benzyl-2-methyl-hexa-2*Z*,4*E*-diendiamide (3ad):** This

compound was prepared by the General Procedure described above and was obtained as a yellow oil. Yield = 87 %. ^1H NMR (400 MHz, MeOD): δ = 7.53 (dd, J = 11.6 Hz, J = 14.8 Hz, 1H), 7.24-7.37 (m, 10H), 6.28 (dd, J = 0.8 Hz, J = 11.6 Hz, 1H), 6.11 (d, J = 14.8 Hz, 1H), 4.50 (s, 2H), 4.44 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, MeOD): δ = 170.4, 166.9, 140.8, 138.5, 138.3, 136.3, 128.3, 128.2, 128.19, 128.17, 127.3, 127.3, 126.9, 125.3, 42.9, 42.9, 20.0. HR-MS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 335.1760; found 335.1761. FTIR (NaCl, cm^{-1}): 3419, 3053, 2985, 2301, 1701, 1635, 1611, 1603, 1512, 1421, 1265, 1163, 1143, 895, 736, 706.

Diethyl (5-benzylamino-4-methyl-5-oxopenta-1,3-dienyl) phosphonate

(3ae): This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 65 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.46 (ddd, J = 11.2 Hz, J = 16.8 Hz, J = 20.8 Hz, 1H), 7.28-7.38 (m, 5H), 6.17 (d, J = 11.6 Hz, 1H), 6.16 (b, 1H), 5.74 (dd, J = 16.8 Hz, J = 18.8 Hz, 1H), 4.55 (d, J = 6.0 Hz, 2H), 4.01-4.09 (m, 4H), 2.08 (s, 3H), 1.31 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ = 168.3, 143.3 (d, J = 7

Hz), 140.9, 137.8, 130.0 (d, $J = 27$ Hz), 128.8, 127.8 (d, $J = 27$ Hz), 120.8, 118.9, 61.9 (d, $J = 6$ Hz), 43.8, 21.4, 16.4 (d, $J = 7$ Hz). HR-MS (ESI): m/z calculated for $C_{17}H_{25}NO_4P [M+H]^+$: 338.1521; found 338.1521. FTIR (NaCl, cm^{-1}): 3439, 3053, 2985, 2304, 1658, 1631, 1614, 1513, 1421, 1265, 1157, 1051, 1026, 966, 895, 750, 729, 704.

(2Z,4E)-N-benzyl-2-methyl-5-cyano-2,4-dienamide (3af): This compound

was prepared by the General Procedure described above and was obtained as a white solid, mp: 106-108 °C. Yield = 59 %. 1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (dd, $J = 11.2$ Hz, $J = 16.0$ Hz, 1H), 7.30-7.40 (m, 5H), 6.19 (d, $J = 10.8$ Hz, 1H), 5.91 (b, 1H), 5.37 (d, $J = 16.0$ Hz, 1H), 4.54 (d, $J = 5.6$ Hz, 2H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 146.1, 141.5, 137.5, 129.6, 129.0, 128.0, 127.9, 117.7, 101.1, 43.8, 21.4. HR-MS (ESI): m/z calculated for $C_{14}H_{14}N_2ONa [M+Na]^+$: 249.1004; found 249.1005. FTIR (NaCl, cm^{-1}): 3421, 3053, 2966, 2689, 2301, 2218, 1660, 1651, 1627, 1611, 1509, 1439, 1421, 1265, 895, 750, 729, 704.

(2Z,4E)-N-benzyl-2-methyl-5-(phenylsulfonyl)-2,4-dienamide (3ag):

This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 50 %. 1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (m, 2H), 7.68 (dd, $J = 11.6$ Hz, $J = 14.8$ Hz, 1H), 7.48-7.61 (m, 3H), 7.27-7.40 (m, 5H), 6.34 (d, $J = 14.8$ Hz, 1H),

6.11 (dd, $J = 11.6$ Hz, $J = 0.8$ Hz, 1H), 6.25 (b, 1H), 4.54 (d, $J = 5.6$ Hz, 2H), 2.07 (d, $J = 1.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 167.8, 144.6, 140.4, 137.7, 137.5, 133.4, 131.9, 129.3, 129.0, 128.1, 127.9, 127.7, 126.4, 44.0, 21.6$. HR-MS (ESI): m/z calculated for $\text{C}_{19}\text{H}_{20}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$: 342.1164; found 342.1166. FTIR (NaCl, cm^{-1}): 3439, 3052, 2984, 2701, 2304, 2126, 1662, 1655, 1641, 1631, 1511, 1433, 1421, 1265.3, 1147, 1086, 895, 754, 732, 704.

(2Z,4E)-N-benzyl-2-methyl-5-(4-chloro-phenyl)-penta-2,4-

dienamide (3ah): This compound was prepared by the General Procedure described above and was obtained as a yellow solid, mp: 95-97 °C. Yield = 60 %. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.18\text{-}7.40$ (m, 10H), 6.51 (d, $J = 15.6$ Hz, 1H), 6.32 (d, $J = 11.2$ Hz, 1H), 6.04 (b, 1H), 4.59 (d, $J = 5.6$ Hz, 2H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 168.9, 138.4, 135.4, 133.9, 133.6, 133.5, 132.6, 128.9, 128.8, 128.1, 127.9, 127.7, 125.7, 43.6, 21.1$. HR-MS (ESI): m/z calculated for $\text{C}_{19}\text{H}_{19}\text{NOCl}$ $[\text{M}+\text{H}]^+$: 312.1155; found 312.1161. FTIR (NaCl, cm^{-1}): 3445, 3053, 2985, 2304, 1658, 1511, 1491, 1421, 1265, 1157, 1095, 895, 738, 706.

N-Methoxyl-N-methyl-N'-benzyl-5-methyl-hexa-2E,4Z-diendiamide

(3ai): This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 80 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.69 (dd, J = 12.0 Hz, J = 15.6 Hz, 1H), 7.29-7.40 (m, 5H), 6.52 (d, J = 15.2 Hz, 1H), 6.30 (dd, J = 11.6 Hz, J = 0.4 Hz, 1H), 6.04 (b, 1H), 4.58 (d, J = 5.6 Hz, 2H), 3.71 (s, 3H), 3.26 (s, 3H), 2.10 (d, J = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 168.7, 166.7, 141.3, 138.3, 137.7, 129.1, 128.9, 128.0, 127.7, 121.4, 61.9, 43.8, 32.5, 21.5. HR-MS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 289.1552; found 289.1553. FTIR (NaCl, cm^{-1}): 3439, 3419, 3050, 2987, 2304, 1666, 1653, 1648, 1637, 1513, 1447, 1421, 1265, 895, 736, 704.

***N*-Methoxyl-*N*-methyl-*N'*-benzyl-5-hexyl-hexa-2*E*,4*Z*-**

diendiamide (3ki): This compound was prepared by the General Procedure described above and was obtained as a colourless oil. Yield = 71 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.63 (dd, J = 12.0 Hz, J = 15.2 Hz, 1H), 7.28-7.40 (m, 5H), 6.53 (d, J = 15.2 Hz, 1H), 6.25 (d, J = 11.6 Hz, 1H), 5.92 (b, 1H), 4.60 (d, J = 6.0 Hz, 2H), 3.72 (s, 3H), 3.27 (s, 3H), 2.42 (t, J = 7.6 Hz, 2H), 1.47-1.51 (m, 2H), 1.29-1.34 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 168.6, 166.7, 147.0, 138.3, 137.8, 128.8, 128.0, 127.7, 127.2, 121.2, 61.9, 43.8, 35.4, 32.5, 31.6, 28.9, 28.0, 22.5, 14.1. HR-MS (ESI): m/z calculated for $\text{C}_{19}\text{H}_{27}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 331.2022; found 331.2018. FTIR (NaCl, cm^{-1}): 3421, 3053, 2985, 2675, 2304, 1653, 1645, 1633, 1617, 1438, 1421, 1265, 895, 752, 744, 706.

(2E,4Z)-tert-Butyl 6-benzylamino-5-methyl-6-oxohexa-2,4-dienoate

(3aj): This compound was prepared by the General Procedure described above and was obtained as a yellow oil. Yield = 90 %. δ = 7.55 (dd, J = 12.0 Hz, J = 15.2 Hz, 1H), 7.26-7.36 (m, 5H), 6.15 (d, J = 12.0 Hz, 1H), 6.07 (b, 1H), 5.80 (d, J = 15.2 Hz, 1H), 4.52 (d, J = 5.6 Hz, 2H), 2.05 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ = 168.6, 165.9, 141.1, 138.6, 137.8, 128.9, 128.8, 127.9, 127.7, 125.6, 80.5, 43.8, 28.1, 21.4. HR-MS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{24}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 302.1756; found 302.1756. FTIR (NaCl, cm^{-1}): 3439, 3050, 2988, 2304, 1700, 1662, 1641, 1617, 1510, 1421, 1266, 1143, 895, 733, 711, 703.

(2E,4Z)-tert-Butyl 6-iso-propylamino-5-methyl-6-oxohexa-2,4-dienoate

(3cj): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 91 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.48 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 6.16 (dd, J = 11.6 Hz, J = 0.8 Hz, 1H), 5.82 (d, J = 15.2 Hz, 1H), 5.44 (b, 1H), 4.19-4.27 (m, 1H), 2.06 (d, J = 0.8 Hz, 3H), 1.47 (s, 9H), 1.26 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ = 167.9, 165.8, 142.3, 138.5, 127.8, 125.1, 80.5, 41.6, 28.1, 22.7, 21.2. HR-MS (ESI): m/z calculated for $\text{C}_{14}\text{H}_{23}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 276.1576; found 276.1574. FTIR (NaCl, cm^{-1}): 3440, 3050, 2987, 2304, 1696, 1662, 1645, 1632, 1510, 1421, 1379, 1265, 1176, 1143, 895, 733, 711.

(2E,4Z)-tert-Butyl 6-phenylamino-5-methyl-6-oxohexa-2,4-dienoate

(3fj): This compound was prepared by the General Procedure and was obtained as a white solid, mp: 109-111 °C. Yield = 66 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.59 (m, 3H), 7.33-7.37 (m, 2H), 7.16 (t, J = 7.2 Hz, 1H), 6.28 (d, J = 11.6 Hz, 1H), 5.89 (d, J = 15.2 Hz, 1H), 2.15 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.8, 165.9, 141.3, 138.3, 137.3, 129.2, 129.1, 126.0, 124.9, 120.3, 80.7, 28.1, 21.4. HR-MS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 310.1419; found 310.1414. FTIR (NaCl, cm^{-1}): 3439, 3051, 2985, 2304, 1706, 1662, 1650, 1643, 1421, 1265, 1142, 895, 754, 739, 704.

(2E,4Z)-tert-Butyl 6-amino-5-methyl-6-oxohexa-2,4-dienoate (3dj):

This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 67 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.66 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 6.22 (d, J = 11.6 Hz, 1H), 6.22 (b, 1H), 5.85 (d, J = 15.6 Hz, 1H), 5.80 (b, 1H), 2.07 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ = 170.6, 166.0, 139.7, 138.6, 129.8, 125.9, 80.7, 28.1, 21.4. HR-MS (ESI): m/z calculated for $\text{C}_{11}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 212.1287; found 212.1293. FTIR (NaCl, cm^{-1}): 3427, 3044, 2980, 2669, 2304, 1701, 1687, 1662, 1639, 1441, 1421, 1265, 1149, 895, 740, 732, 704.

(2E,4Z)-tert-Butyl 6-benzylamino-5-benzyloxymethyl-6-oxohexa-2,4-dienoate (3mj): This compound was prepared by the General Procedure and was obtained as an orange oil. Yield = 57 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.94 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 7.19-7.33 (m, 10H), 6.93 (b, 1H), 6.40 (d, J = 11.6 Hz, 1H), 5.94 (d, J = 15.6 Hz, 1H), 4.51 (d, J = 6.0 Hz, 2H), 4.50 (s, 2H), 4.23 (s, 2H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ = 166.5, 165.6, 138.1, 137.9, 137.6, 137.0, 134.6, 129.1, 128.8, 128.6, 128.1, 128.0, 127.8, 127.5, 80.8, 72.5, 72.3, 43.5, 28.1. HR-MS (ESI): m/z calculated for $\text{C}_{25}\text{H}_{30}\text{NO}_4$ $[\text{M}+\text{H}]^+$: 408.2175; found 408.2172. FTIR (NaCl, cm^{-1}): 3053, 2985, 2300, 1719, 1705, 1662, 1641, 1511, 1449, 1421, 1265, 1144, 895, 740, 706.

(2E,4Z)-tert-Butyl 6-benzylamino-5-phenyl-6-oxohexa-2,4-dienoate (3lj): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 90 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.64 (dd, J = 11.6 Hz, J = 15.2 Hz, 1H), 7.45-7.47 (m, 2H), 7.28-7.39 (m, 8H), 6.64 (d, J = 12.0 Hz, 1H), 6.20 (b, 1H), 6.00 (d, J = 15.2 Hz, 1H), 4.62 (d, J = 5.6 Hz, 2H), 1.53 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ = 167.6, 165.7, 144.2, 138.9, 137.6, 135.7, 129.3, 128.9, 128.8, 128.0, 127.7, 127.2, 127.2, 126.8, 80.7, 43.9, 28.2. HR-MS (ESI): m/z calculated for $\text{C}_{23}\text{H}_{26}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 364.1913; found 364.1910. FTIR (NaCl, cm^{-1}): 3427, 3058, 2989, 2302, 1692, 1662, 1620,

1611, 1510, 1465, 1422, 1265, 1178, 1159, 1143, 981, 895, 746, 711.

(3kj): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 80 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.46 (dd, J = 15.2 Hz, J = 11.6 Hz, 1H), 7.27-7.37 (m, 5H), 6.12 (d, J = 11.6 Hz, 1H), 5.98 (brs, 1H), 5.82 (d, J = 15.2 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H), 2.37 (t, J = 7.6 Hz, 2H), 1.42-1.50 (m, 11H), 1.26-1.31 (m, 6H), 0.87 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 168.6, 165.9, 146.9, 138.6, 137.7, 128.8, 127.9, 127.7, 126.9, 125.3, 80.5, 43.8, 35.3, 31.5, 28.8, 28.1, 27.9, 22.5, 14.0. HR-MS (ESI): m/z calculated for $\text{C}_{23}\text{H}_{33}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 394.2358; found 394.2359. FTIR (NaCl, cm^{-1}): 3431, 3042, 2980, 2307, 1700, 1662, 1655, 1620, 1587, 1515, 1421, 1265, 1187, 1143, 981, 895, 740, 730, 707.

(3nj): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 81 %. ^1H NMR (400 MHz, CDCl_3): δ = 7.60 (d, J = 15.6 Hz, 1H), 7.28-7.36 (m, 5H), 5.89 (b, 1H), 5.86 (d, J = 15.6 Hz, 1H), 4.56 (d, J = 5.6 Hz, 2H), 2.05 (s, 3H), 1.84 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ = 170.7, 166.2, 142.0,

139.2, 137.7, 130.9, 128.8, 128.0, 127.7, 121.1, 80.4, 43.9, 28.2, 17.6, 13.8. HR-MS (ESI): m/z calculated for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1913; found 316.1916. FTIR (NaCl, cm^{-1}): 3431, 3048, 2978, 2300, 1700, 1658, 1648, 1629, 1510, 1418, 1265, 1156, 981, 899, 740, 737, 704.

(2E,4Z)-tert-Butyl 6-benzylamino-4-methyl-6-oxohexa-2,4-dienoate

(30j): This compound was prepared by the General Procedure described above and was obtained as a white solid, mp: 124-126 °C. Yield = 27 %. 1H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, J = 16.0 Hz, 1H), 7.29-7.39 (m, 5H), 6.05 (d, J = 16.0 Hz, 1H), 5.89 (s, 1H), 5.87 (b, 1H), 4.54 (d, J = 5.2 Hz, 2H), 2.00 (d, J = 1.2 Hz, 3H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 165.2, 143.4, 139.7, 138.0, 128.8, 128.0, 127.6, 126.2, 125.4, 80.7, 43.7, 28.1, 20.4. HR-MS (ESI): m/z calculated for $C_{18}H_{23}NO_3Na$ $[M+Na]^+$: 324.1576; found 324.1580. FTIR (NaCl, cm^{-1}): 3439, 3050, 2989, 2307, 1696, 1662, 1645, 1633, 1510, 1421, 1265, 1158, 895, 748, 731, 706.

(2E,4Z)-Butyl 6-benzylamino-6-oxohexa-2,4-dienoate and (2E,4E)-Butyl

6-benzylamino-6-oxohexa-2,4-dienoate mixture (ratio: 50/50) (3pa): This compound was prepared by the General Procedure described above and was obtained as an orange oil. Yield = 31 %. 1H NMR (400 MHz, MeOD): δ = 8.55 (ddd, J = 1.2 Hz, J = 11.6 Hz, J = 15.6 Hz,

1H), 7.26-7.41 (m, 12H), 6.63 (t, $J = 11.6$ Hz, 1H), 6.44 (d, $J = 14.0$ Hz, 1H), 6.27 (d, $J = 15.2$ Hz, 1H), 6.14 (d, $J = 11.6$ Hz, 1H), 6.13 (d, $J = 15.2$ Hz, 1H), 4.49 (s, 2H), 4.46 (s, 2H), 4.18-4.22 (m, 4H), 1.66-1.73 (m, 4H), 1.42-1.48 (m, 4H), 0.99 (t, $J = 7.2$ Hz, 6H). ^{13}C NMR (100 MHz, MeOD): $\delta = 166.7, 166.4, 166.1, 165.9, 141.4, 139.6, 138.3, 138.2, 137.0, 136.8, 131.1, 128.2, 127.3, 127.3, 127.2, 127.0, 126.9, 126.8, 126.7, 64.3, 64.2, 43.0, 42.7, 30.5, 30.4, 18.8, 12.6, 12.6$. HR-MS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{22}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 288.1600; found 288.1606. FTIR (NaCl, cm^{-1}): 3439.1, 3053.3, 2985.8, 2304.9, 1705.1, 1662.6, 1610.0, 1510.3, 1421.5, 1265.3, 1160.1, 895.0, 738.7, 704.0.

(2Z,4E)-N-benzyl-2-methyl-6-oxohepta-2,4-dienamide (3ak): This

compound was prepared by the General Procedure described above and was obtained as a white solid, mp: 66-68 °C. Yield = 79 %. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.59$ (dd, $J = 11.6$ Hz, $J = 16.0$ Hz, 1H), 7.29-7.40 (m, 5H), 6.25 (d, $J = 11.6$ Hz, 1H), 6.14 (b, 1H), 6.08 (d, $J = 16.0$ Hz, 1H), 4.57 (d, $J = 6.0$ Hz, 2H), 2.18 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 199.0, 168.1, 141.4, 138.9, 137.9, 132.9, 130.5, 128.9, 128.0, 127.8, 43.7, 26.7, 21.5$. HR-MS (ESI): m/z calculated for $\text{C}_{15}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 244.1338; found 244.1335. FTIR (NaCl, cm^{-1}): 3439, 3053, 2985, 2304, 1705, 1662, 1643, 1601, 1510, 1436, 1421, 1351, 1265, 981, 895, 746, 734, 704.

Competition Experiments with alkenes **2h** and **2j**.

[Ru] Cond.: A screw-cap vial was charged with $[\text{RuCl}_2(p\text{-cymene})]_2$ (2.5 mol%, 0.005 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv, 0.2 mmol), KPF_6 (20 mol%) and dioxane/ H_2O / AcOH = 8/4/1(v/v/v) (0.6 ml). Then, acrylamide **1a** (1.0 equiv, 0.1 mmol), alkenes **2h** (1.0 equiv, 0.1 mmol), and **2j** (1.0 equiv, 0.1 mmol) were added into the solution in sequence. The vial was sealed under nitrogen and heated to 100°C with stirring for 18 hours. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated to give the crude product which was purified by flash column chromatography on silica gel to give dienamide **3ah** (8 mg, 26%) and **3aj** (3 mg, 11%). The ratio of **3ah/3aj** thus was determined to be 71/29.

[Rh] Cond.: An oven-dried screw-cap vial was charged with $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%, 0.0025 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv, 0.4 mmol) and acetone (0.6 ml). Then, acrylamides (0.2 mmol), styrene **2h** (0.1 mmol) and **2j** (0.1 mmol) were added into the solution in sequence. The vial was sealed under nitrogen and heated to 100°C with stirring for 18 hours. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous MgSO_4 , filtered

and concentrated to give the crude product which was directly applied to a flash column chromatography, affording corresponding product **3ah** (9 mg, 29%) and **3aj** (6 mg, 23%).

Competition Experiments with acrylamides **1g** and **1h**.

[Ru] Cond.: A screw-cap vial was charged with $[\text{RuCl}_2(p\text{-cymene})]_2$ (2.5 mol%, 0.005 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv, 0.1 mmol), KPF_6 (20 mol%) and dioxane/ H_2O / AcOH = 8/4/1(v/v/v) (0.6 ml). Then, acrylamide **1g** (2.0 equiv, 0.1 mmol), acrylamide **1h** (2.0 equiv, 0.1 mmol), and acrylate **2a** (1.0 equiv, 0.05 mmol) were added into the solution in sequence. The vial was sealed under nitrogen and heated to 100 °C with stirring for 18 hours. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated to give the crude product which was purified by flash column chromatography on silica gel to give dienamide **3ga** (6.5 mg, 41%) and **3ha** (1.7 mg, 11%). The ratio of **3ga/3ha** thus was determined to be 79/21.

[Rh] Cond.: An oven-dried screw-cap vial was charged with $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%, 0.0025 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv, 0.4 mmol) and acetone (0.6 ml). Then, acrylamides (0.2 mmol) and acrylate (0.1 mmol) were added into the solution in sequence. The vial was sealed under nitrogen and heated to 100 °C with stirring for 18 hours. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous MgSO_4 , filtered and concentrated to give the crude product which was directly applied to a flash column chromatography, affording corresponding product **3i** (7 mg, 23%) and **3j** (5 mg, 16%).

Competition Experiments with acrylamides **1a** and **1m**.

[Ru] Cond.: A screw-cap vial was charged with $[\text{RuCl}_2(p\text{-cymene})]_2$ (2.5 mol%, 0.005 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv, 0.1 mmol), KPF_6 (20 mol%) and dioxane/ H_2O / AcOH = 8/4/1(v/v/v) (0.6 ml). Then, acrylamide **1a** (2.0 equiv, 0.1 mmol), acrylamide **1m** (2.0 equiv, 0.1 mmol), and acrylate **2a** (1.0 equiv, 0.05 mmol) were added into the solution in sequence. The vial was sealed under nitrogen and heated to 100 °C with stirring for 18 hours. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and

brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated to give the crude product. The ratio of **3aa/3ma** in the crude mixture of product was determined to be 82/18 by ^1H NMR.

[Rh] Cond.: An oven-dried screw-cap vial was charged with $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%, 0.0025 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv, 0.4 mmol) and acetone (0.6 ml). Then, acrylamides (0.2 mmol) and acrylate (0.1 mmol) were added into the solution in sequence. The vial was sealed under nitrogen and heated to 100°C with stirring for 18 hours. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous MgSO_4 , filtered and concentrated to give the crude product, the ratio of product **3aa** and **3ma** was calculated as **3aa/3ma** = 76/24 by HNMR.

Ru-Catalyzed H/D Exchange in **1a**.

A screw-cap vial was charged with $[\text{RuCl}_2(\text{p-cymene})]_2$ (2.5 mol%, 0.0025 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv, 0.2 mmol), KPF_6 (20 mol%) and dioxane/ D_2O /AcOD = 8/4/1(v/v/v) (0.6 ml). Then, acrylamide (1.0 equiv, 0.1 mmol) were added into the solution. The vial was sealed under nitrogen and heated to 100°C with stirring for 1 hour. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and

brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated to give the crude product which was purified by flash column chromatography on silica gel (17 mg, 95 % recovered). The D % of **1a**-[D] was estimated by ^1H NMR.

Rh-Catalyzed H/D Exchange in **1a**.

An oven-dried screw-cap vial was charged with $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol%, 0.0025 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv, 0.4 mmol) and acetone/ D_2O (V/V = 2/1) (0.6 ml). Then, acrylamides (0.2 mmol) was added into the solution. The vial was sealed under nitrogen and heated to 100°C with stirring for 1 hour. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated to give the crude product which was purified by flash column chromatography on silica gel (34 mg, 89 % recovered). The D % of **1a**-[D] was estimated by ^1H NMR.

CHAPTER 4

*Chemical Conversion of β -O-4 Lignin Linkage Models
through Cu-Catalyzed Aerobic Amide Bond Formation*

4.1 Introduction

With the possible depletion of fossil fuels in the very near future, lignocellulosic biomass has recently emerged as a possible alternative renewable source of energy. Therefore, many efforts have been directed to fully convert all the components in biomass into useful chemicals, drugs, fuel, materials, etc.¹ While the conversion of cellulose and hemicellulose to useful compounds has been extensively studied, methods for the degradation of lignin to useful chemicals remain scarce albeit lignin constitutes up to 30% of the weight and 40% of the energy content of lignocellulosic biomass.² This is probably because lignin has a complex cross-linked chemical structure formed by oxidative coupling biosynthesis, and the most abundant linkage in lignin is the β -O-4 linkage (Figure 4.1). 2-Aryloxy-1-arylethanol (**1**) and 1-aryl-2-aryloxy propane-1,3-diol (**2**) are often used as lignin model compounds to mimicking the β -O-4 linkage for the purpose of reaction development.²

Figure 4.1 Lignin model compounds **1** and **2** mimicking the β -O-4 linkage.

¹ (a) Corma, A.; Iborra, S.; Velty, A. *Chem Rev.* **2007**, *107*, 2411. (b) Dodds, D. R.; Gross, R. A. *Science* **2007**, *318*, 1250.

² (a) Zakzeski, J.; Bruijninx, P. C. A.; Jongerius, A. L.; Weckhuysen, B. M. *Chem. Rev.* **2010**, *110*, 3552. (b) Lignin and Lignans: Advances in Chemistry; Heitner, C., Dimmel, D., Schmidt, J. A., Eds.; CRC Press: Boca Raton, FL, 2010.

The robust nature of this biopolymer hinders the development of efficient processes to convert them to useful platform chemicals. However, a number of recent reports suggest that catalysis could be a key enabling technology for lignin conversion in general.³

In 2010, Ellman and co-worker reported a ruthenium-catalyzed, redox neutral C-O bond cleavage of 2-aryloxy-1-arylethanol that yielded cleavage products ketones and phenols. This reaction proceeds by a tandem dehydrogenation/reductive ether cleavage, which is applicable to breaking the key ethereal bond found in lignin-related polymers (scheme 4.1).⁴

Scheme 4.1

In 2011, Hartwig reported hydrogenolyses of aromatic C-O bonds in alkyl aryl and diaryl ethers forming exclusively arenes and alcohols.⁵ This process is catalyzed by a soluble nickel carbene complex under just 1 bar of hydrogen at temperatures ranging from 80 to 120 °C.

³ For a recent review, see: Collinson, S. R.; Thielemans, W. *Coord. Chem. Rev.* 2010, **254**, 1854.

⁴ Nichols, J. M.; Bishop, L. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 12554.

⁵ Sergeev, A. G.; Hartwig, J. F. *Science*, **2011**, *332*, 439.

Hydrogenolysis of lignin model compounds highlights the potential of this approach for the conversion of refractory aryl ether biopolymers to hydrocarbons (Scheme 4.2).

Scheme 4.2

In 2010, Toste and co-worker demonstrated a vanadium-catalyzed C-O bond cleavage reaction, which is proposed to proceed through a ketyl radical generated by hydrogen atom transfer to a vanadium (V) complex.⁶ This novel transformation has been applied to a vanadium-catalyzed non-oxidative C-O bond cleavage reaction of dimeric lignin model compounds that produces aryl enones as unprecedented degradation products (Scheme 4.3).

Scheme 4.3

In 2012, Silks presented reactivity studies of a phenolic lignin model compound with vanadium catalysts. It is reported that vanadium catalyst can mediate a new type of reaction in which the C-C bond between the aryl ring and the adjacent alcohol group is broken to give

⁶ Son, S.; Toste, F. D. *Angew. Chem. Int. Ed.* **2010**, 49, 3791.

2,6-dimethoxybenzoquinone and acrolein derivative (Scheme 4.4).⁷

Scheme 4.4

Although these methods are efficient in selective degradations of lignin models, all of them suffer from some drawbacks such as harsh conditions and limited synthetic applications, and they resulted in only C-C/C-O bond cleavage and don't include formation of any new bonds except for C-H and C-O bond formation in hydrogenation and oxidation reactions. As a result, new processes to convert lignin models to useful platform chemicals are highly desirable. In the course of our study in aerobic oxidation to mimic the amino group migration reaction,⁸ we consistently observe a by-product resulted from the oxidative C-C bond cleavage of the intermediate enamine. Coupled with the recent reported oxidative synthesis of ketoamides from ketones,⁹ we proposed that this oxidative method could be applicable to the C-O/C-C bond cleavage of lignin model (Figure 4.2). Our tactics for conversion of the lignin β -O-4 models would commenced with selective 2°-alcohol oxidation

⁷ (a) Zhang, G.; Scott, B. L.; Wu, R.; Silks, L. A.; Hanson, S. A. *Inorg. Chem.* **2012**, *51*, 7354. (b) Hanson, S. K.; Wu, R.; Silks, L. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3410. (c) Hanson, S. K.; Baker, R. T.; Gordon, J. C.; Scott, B. L.; Thorn, D. L. *Inorg. Chem.* **2010**, *49*, 5611.

⁸ (a) Toh, K. K.; Wang, Y.-F.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942. (b) Tian, J.-S.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2010**, *49*, 8417.

⁹ For recent report on transition-metal-catalyzed aerobic synthesis of α -keto amides, see (a) Zhang, C.; Zong, X.; Zhang, L.; Jiao, N. *Org. Lett.* **2012**, *14*, 3280. (b) Du, F.-T.; Ji, J.-X. *Chem. Sci.* **2012**, *3*, 460. (c) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Angew. Chem., Int. Ed.* **2011**, *50*, 11088. (d) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (e) Couty, S.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2819. (f) Al-Rashid, Z. F.; Johnson, W. L.; Hsung, R. P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* **2008**, *73*, 8780.

of the secondary benzylic alcohol to form β -hydroxy ketones **2**, which might undergo the *retro*-aldol reaction to provide ketone **3**. The corresponding enamine derived from ketones and secondary amines may undergo oxidative transformation under transition-metal catalysed aerobic reaction conditions to form new amide bonds.¹⁰

Figure 4.2. Proposal for the oxidative synthesis of ketoamide or amide from lignin model **1**.

In this chapter, we report our success in the conversion of lignin model compounds **1** to useful α -ketoamides, amides and phenols by Cu-catalyzed aerobic C-N bond formation. As we know, α -ketoamide and amide represent a key structural moiety of many natural products, pharmaceuticals and useful precursors for a variety of functional group transformations¹¹.

¹⁰ For recent reviews on transition-metal catalyzed aerobic molecular transformation, see: (a) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (b) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (c) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (d) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (e) Dekorver, K.A.; Li, H.; Lohse, A.G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, P.R., *Chem. Rev.* **2010**, *110*, 5064.

For green and sustainable chemistry, this catalytic aerobic oxidation is appealing for the lignin conversion to fine chemicals since water is the only by-product. Moreover, usage of an inexpensive copper catalyst and readily available oxygen gas as an oxidant could provide additional benefits.

4.2 Results and discussion

Our research commenced with the reaction of 2-phenoxyacetophenone (**3a**) and piperidine (**4a**) under Cu-catalyzed aerobic reaction conditions (Table 4.1). It was found that treatment of **3aa** with **4a** in the presence of CuCl (10 mol%) under an oxygen atmosphere in toluene at 70 °C delivered α -ketoamide and phenol in 69% and 54% yields (Table 4.1, entry 1). Other copper catalysts, such as CuBr and CuI were also screened, and it is showed that CuI performed best in this transformation (Table 4.1, entries 2 and 4). If the reaction was performed with double amount of amine in the absence of solvent, α -ketoamide and phenol in 91% and 61% yields (Table 4.1, entry 3). Higher or lower temperature resulted in reduced yields of the products (Table 4.1, entries 5-6). It is worthy to note that this reaction also proceeded smoothly under an air atmosphere (0.21 atm of O₂) (Table 4.1, entry 7). The reaction with 1,2-dichloroethane (DCE) as well as polar solvents such as MeCN, DMF, DMSO, and THF also resulted in good yields of the products (Table 4.1, entries 9-13), while polar protic solvents such as MeOH rendered the process sluggish (Table 4.1, entry 14). Various nitrogen ligands was tested, and no remarkable effect was observed (Table 4.1, entries 15-19). Usage less amount (3.0 equiv.) of **4a** resulted in decreased yields (Table 4.1, entry 20). Other metal complex such as RuCl₃, FeCl₃ and Pd(OAc)₂ exhibited lower catalytic activities (Table 4.1, entries 21-23). If the reaction was carried out in the absence of copper salt under oxygen, only trace amount of product was detected (Table 4.1, entry 24).

Table 4.1 Optimization of catalytic conditions.^a

Entry	Catalyst 10 mol%	Oxidant	Ligand 10 mol%	Solvent	Temperature °C	Yield (%)	
						6a	7a
1	CuCl	O ₂	-	Toluene	70	69	54
2	CuBr	O ₂	-	Toluene	70	78	56
3 ^b	CuI	O ₂	-	-	70	91	61
4	CuI	O₂	-	Toluene	70	88	63
5	CuI	O ₂	-	Toluene	50	60	62
6	CuI	O ₂	-	Toluene	90	68	63
7	CuI	air	-	Toluene	70	84	71
8 ^c	CuI	O ₂	-	Toluene	70	71	75
9	CuI	O ₂	-	DCE	70	85	70
10	CuI	O ₂	-	MeCN	70	81	65
11	CuI	O ₂	-	DMF	70	67	60
12	CuI	O ₂	-	DMSO	70	71	55
13	CuI	O ₂	-	THF	70	65	55
14	CuI	O ₂	-	MeOH	70	9	-
15	CuI	O ₂	1,10-Phen	Toluene	70	84	57
16	CuI	O ₂	bipy	Toluene	70	75	67
17 ^d	CuI	O ₂	Py	Toluene	70	84	65
18	CuI	O ₂	TMDP	Toluene	70	71	66
19	CuI	O ₂	L-proline	Toluene	70	59	45
20 ^e	CuI	O ₂	-	Toluene	70	76	74
21	RuCl ₃	O ₂	-	Toluene	70	29	14
22	FeCl ₃	O ₂	-	Toluene	70	21	12
23	Pd(OAc) ₂	O ₂	-	Toluene	70	19	16
24	-	O ₂	-	Toluene	70	< 5	< 5

TMDP: 4,4'-trimethylene dipyridine

^aThe reaction scheme is shown above the table. Unless otherwise described, the reaction conditions were as follows: 2-phenoxyacetophenone **3a** (0.1 mmol), piperidine **5a** (0.5 mmol), catalyst (10 mol%), toluene (0.4 ml), 70 °C, 16 h, under oxygen (1 atm.). The isolated yield was obtained by silica gel column chromatography. ^b10 equiv. piperidine was used and the reaction was performed without solvent. ^cThe reaction lasted for 6 hours. ^dDCE was used as solvent. ^e3.0 equiv. piperidine was used.

Table 4.2 Oxidative synthesis of ketoamides from lignin-model **2aa** with amines (**4**)

entry	amine 4	products, yields
1		+
2		+
3		+
4		+
5		+

^aUnless otherwise described, the reaction conditions were as follows: ketone **3** (0.1 mmol), amine **5** (0.5 mmol), CuI (10 mol%), toluene (0.4 ml), 70 °C, under oxygen (1 atm.), 16h. ^bThe isolated yields were obtained by silica gel column chromatography and are the average of the two runs

With the newly established oxidative synthesis of α -ketoamides procedure in hand, the reaction of lignin model compounds **3aa** with various secondary amines **4** were next investigated (Table 4.2). All cyclic, acyclic and alkyl secondary amines reacted efficiently

toward 2-phenyloxyacetophenone **3aa**, and generated differently *N*-substituted α -ketoamides in moderate to good yields, although acyclic amines showed somewhat lower reactivity (Table 4.2, entries 3-5).

Then we examined the compatibility of the methoxy substituent on aryloxyacetophenones **3** for the reactions with piperidine **4a** (Table 4.3). While methoxylation of the O-terminus phenyl ring showed comparatively little effect on reactivity, installation of methoxyl group to the C-terminus phenyl ring resulted in the concurrent formation of amides **7**¹¹ except for the reaction of **3dd** (Table 4.3, entry 5). Chloro-substituted compound **3fa** was also tested to study the electronic influence (Table 4.3, entry 7). Similarly, amide was obtained in 36% yield, indicating that installation of both electro-donating and electro-withdrawing group to the C-terminus phenyl ring led to increased amount of amide.

Next, we turned to the transformation of another lignin model **2**, 1-aryl-3-hydroxy-2-aryloxy propan-1-one (Table 4.4). Interestingly, the present CuI-catalyzed aerobic oxidative conditions allowed direct reactions of **2** with amines to provide α -ketoamides and phenols in good yields. Similarly, the reaction of model **2ec** bearing methoxy groups onto the C-terminus benzene ring also resulted in the formation of not only α -ketoamide **5ea** and phenol **6c** but also amide **7ea** (Table 4.4, entry 6).

¹¹ For Cu-catalyzed aerobic synthesis of amides from enamines, see: (a) Kaneda, K.; Itoh, T.; Kii, N.; Jitsukawa, K.; Teranishi, S. *J. Mol. Catal.* **1982**, *15*, 349. (b) Rheenen, V. V. *Chem. Commun.* **1969**, 314.

Table 4.3. Oxidative synthesis of amides from lignin-model **3** with piperidine (**4a**).^a

entry	model 3	products, yields
1	3ab	5aa , 70% + 5b , 36%
2	3ca	5ca , 73% + 7ca , 18% + 6a , 70%
3	3ba	5ba , 68% + 7ba , 17% + 6a , 72%
4	3cc	5ca , 71% + 7ca , 21% + 6c , 52%
5	3dd	5da , 60% + 6d , 54%
6	3ec	5ea , 58% + 7ea , 27% + 6c , 51%
7	3fa	5fa , 52% + 7fa , 36% + 6c , 50%

^aUnless otherwise described, the reaction conditions were as follows: ketone **3** (0.1 mmol), amine **4** (0.5 mmol), CuI (10 mol%), toluene (0.4 ml), 70 °C, under oxygen (1 atm.), 6 h. ^bThe isolated yields were obtained by silica gel column chromatography and are the average of the two runs.

Table 4.4 Oxidative synthesis of ketoamides from lignin-model compound **2**.

$ \begin{array}{c} \text{R}^1\text{-C}_6\text{H}_4\text{-C(=O)-CH(OH)-CH}_2\text{-O-C}_6\text{H}_4\text{-R}^2 \\ \mathbf{2} \end{array} + \begin{array}{c} \text{R}^3\text{-NH-R}^4 \\ \mathbf{4} \end{array} \xrightarrow[\text{under O}_2]{\text{CuI (10 mol\%), Toluene, 70 }^\circ\text{C}} \begin{array}{c} \text{R}^1\text{-C}_6\text{H}_4\text{-C(=O)-C(=O)-N(R}^3\text{)-R}^4 \\ \mathbf{5} \end{array} + \begin{array}{c} \text{R}^1\text{-C}_6\text{H}_4\text{-C(=O)-N(R}^3\text{)-R}^3 \\ \mathbf{7} \end{array} + \begin{array}{c} \text{HO-C}_6\text{H}_4\text{-R}^2 \\ \mathbf{6} \end{array} $			
entry	model 3	amine 4	products, yields
1	2aa	4a	5aa , 81% + 5b , 65%
2	2aa	4b	5ab , 76% + 6a , 69%
3	2aa	4e	5ae , 61% + 6a , 58%
4	2cc	4b	5cb , 68% + 7cb , 17% + 6c , 55%
5	2dd	4a	5da , 56% + 6d , 59%
6	2ec	4a	5ea , 58% + 7ea , 24% + 6c , 56%

The reaction conditions were as follows: **3** (0.1 mmol), amine **4** (0.5 mmol), CuI (10 mol%), toluene (0.4 ml), 70 °C, under oxygen (1 atm.), 6 h. The isolated yields were average of the two runs.

To investigate the mechanism for this oxidative C-O bond cleavage reaction, we performed reactions using various analogues of lignin model **8** (Table 4.5). When 2-methoxyl acetophenone (**8a**) was reacted with piperidine (**5a**), it also afforded α -ketoamide in 79%

yield (Table 4.5, entry 1). Additionally, 2-phenoxy-1-phenylpropan-1-one (**8b**) showed no reactivity toward piperidine (**5a**) under the same conditions (Table 4.5, entry 2). Moreover, both of phenylglyoxal monohydrate (**8c**)¹² and phenylglyoxylic acid phenyl ester (**8d**) led to α -ketoamide in very good yields (Table 4.5, entry 3 and 4). It is worthy to note that the reaction of 2-phenoxy-1-phenyl-propenone (**8e**) and piperidine also delivered α -ketoamide and phenol in 81% and 76% yields, respectively (Table 4.5, entry 5).

Table 4.5 Reactivity study of analogues of lignin **8**.

Entry	Model 8	6a / Yield (%)	7 / Yield (%)
1	8a	79	-
2	8b	0	0
3	8c	83	0
4	8d	99	98
5	8e	81	76

The reaction conditions were as follows: **8** (0.1 mmol), piperidine **4a** (0.5 mmol), CuI (10 mol%), toluene (0.4 ml), 70 °C, under oxygen (1 atm.), 8 h. The yields are isolated yield.

¹² Zhang, C.; Zong, X.; Zhang, L.; Jiao, N. *Org. Lett.*, **2012**, 14, 3280-3283.

On the basis of the above observations and previous studies, we proposed a possible reaction mechanism illustrated in Figure 4.3. The reaction of lignin model **2** with secondary amine **4** under Cu-catalysed aerobic conditions results to enamine **B** presumably generated from the corresponding iminium cation **A** by retro-aldol reaction. The same intermediate **B** is also generated from model **3** and amine **4**. Subsequently, single-electron-oxidation of enamine **B** with the transient high valent Cu(II)-oxygen species¹³ followed by trapping the resulting cation-radicals of **B** with oxygen provide α -imino copper peroxides **C**. Copper peroxides **C** would cyclize to afford aminodioxetanes **D**. Fragmentation of aminodioxetanes **D** leads to arylglyoxylic acid aryl ester **E**^{9b-d} via O-O bond cleavage, which further reacts with amine **4** to provide α -ketoamide **5** and phenol **6** (*path-I*). On the other hand, concurrent C-C and O-O bond cleavages of aminodioxetane **D** lead to the formation of amide **7** and formyl ester **I**, and **I** is hydrolysed to give phenol **6** (*path-III*). Another possible pathway resulting α -ketoamide **5** includes Fenton-like fragmentation of α -imino copper peroxides **C** to form hemiacetal **F**, which eliminate phenol to afford arylglyoxal **G** (*path-II*). Arylglyoxal **G** is converted into α -ketoamide **5** under the present reaction conditions with amine **4**, and this could be demonstrated experimentally.^{9a}

¹³ For recent reviews of dioxygen-copper systems, see: (a) Rolff, M.; Tucek, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2344. (b) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047. (c) Gamez, P.; Aubel, P. G.; Driessen, W. L.; Reedijk, J. *Chem. Soc. Rev.* **2001**, *30*, 376.

Figure 4.3 Proposed reaction mechanisms.

Oxygen labeling experiments were performed under the standard conditions (Scheme 4.5). The reaction of **3aa** and **4a** in the presence of $^{18}\text{O}_2$ (1 atm) generated **5aa** in 85% yield (^{18}O , ^{18}O -**5aa**: ^{18}O , ^{16}O -**5aa**: ^{16}O , ^{16}O -**5aa** = 54:46:0). The reaction of **2aa** and **4a** in the presence of $^{18}\text{O}_2$ (1 atm) generated **5aa** in 79% yield (^{18}O , ^{18}O -**5aa**: ^{18}O , ^{16}O -**5aa**: ^{16}O , ^{16}O -**5aa** = 72:28:0). Considering the keto-carbonyl oxygen could be easily exchanged with present H_2O , combined with the observation of amide formation, path **I** should be involved. However, there still remains possibility of Path **II** (Figure 4.5).

Scheme 4.5 Oxygen labeling experiments of **3aa** and **2aa**.

The next challenge came in applying the oxidative C-O bond cleavage chemistry into more actual β -O-4 lignin-model compounds, 1-aryl-2-aryloxy propane-1,3-diol (**2**). However, it showed no reactivity toward piperidine **4a** under the standard catalytic system, and no desired products α -ketoamide was obtained. So we need to explore methods for chem-selective oxidation of the secondary benzylic alcohol of lignin model (Table 4.6). Our interests in Cu-catalyzed conversion of lignin model in one-pot fashion prompts us to test previously reported Cu-catalyzed oxidative conditions (Table 4.6, entries 1-4). To our delight, Cu-catalyzed aerobic oxidation with DEAD developed by Markó¹⁴ worked efficiently for the desired 2° alcohol oxidation to afford **3aa** in 89% yield. However, applying this condition to model **1ec** resulted in β -hydroxy ketone **2ec** along with its dehydrated form **8ec** in 65% and 26% yields, respectively (Table 4.6, entry 5).

¹⁴ (a) Maskó, I. E.; Tsukazaki, M.; Giles, P. R.; Brown, S. M.; Urch, C. J. *Angew. Chem., Int. Ed.* **1997**, *36*, 2208.
 (b) Maskó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044.

Table 4.6 Aerobic 2°-alcohol oxidation of lignin models^{a,b}

entry	substrate	conditions	products (isolated yields)
1		CuCl ₂ (10 mol%) TBAB (5 mol%) TBHP (1.2 equiv) DCM, 25 °C, 14 h	 3aa , 57%
2		Cu ₂ (phen) ₂ Cl ₄ (5 mol%) TEMPO (10 mol%) K ₃ PO ₄ (0.5 equiv) MeCN, 25 °C, under O ₂ , 12h	 3aa , 64%
3		CuCl (10 mol%) 1,10-phen (10 mol%) K ₂ CO ₃ (2 equiv) DBADH ₂ (10 mol%) toluene, 90 °C, under O ₂ , 5 h	 3aa , 78%
4		CuBr (10mol%) 1,10-Phen (10mol%) DEAD (1.1 equiv) K ₂ CO ₃ (2.2 equiv) Toluene, 90 °C, under O ₂ , 1.5 h	 3aa , 89%
5		CuBr (10mol%) 1,10-Phen (10mol%) DEAD (1.1 equiv) K ₂ CO ₃ (2.2 equiv) Toluene, 90 °C, under O ₂ , 1.5 h	 2ec , 59% ^c + 8ec , 31% ^c

^aAll reactions were performed in 0.1 mmol scale (cal. from **12** or **1aa**). ^bThe yields are isolated yield.

^c0.36 mmol of **1ec** was used.

Finally, one-pot direct conversion of β-O-4 lignin model was challenged (Figure 4.4). It was of remarkable significance that combination of the Markó-oxidation (Table 4, entry 5) and the Cu-catalyzed aerobic reaction with piperidine (**4a**) delivered α-ketoamide **5ea**, amide **7ea**, and phenol **6c** in 48%, 28% and 41% yields, respectively (Figure 4.4a). It is worthy to note that this one-pot strategy was also applicable to a more complex trimeric lignin β-O-4 model **11ec**, affording α-keto amide **5ea**, amide **7ea**, and phenol **6c** in 43%, 22% and 55% yields, respectively (Figure 4.4b), although the formation of amide derivatives derived from the middle benzene ring fragment could not be detected.

Figure 4.4. One-pot conversion of lignin β -O-4 models.

4.3 Conclusion

In summary, we have developed a method for the oxidative synthesis of α -ketoamide from lignin model compounds and amines. The method was proved to be mild, efficient, operational simple and using a widely available and cheap catalyst CuI. Although there are still challenges for the real applications, this research opens a new path realizing the production of valuable chemicals from lignin substrates, thus offers attractive academic and industrial prospects.

4.4 Experimental Section

General Methods

All commercially available reagents for the catalytic reaction were used as received: toluene, 1,2-dichloroethane were obtained from Sigma-Aldrich. CuI were obtained from Strem Chemicals Inc. Amines was purchased from Alfa Aesar. Thin-layer chromatography (TLC) was conducted with Merck 60 F254 pre-coated silica *gel* plate (0.2 mm thickness) and visualized with UV and potassium permanganate staining. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. ^1H NMR spectra were performed on a Bruker 400 NMR spectrometer and are reported in ppm downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d*. Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a 400 (100 MHz) or ECA-400 (100 MHz) spectrometer and are reported in ppm using CDCl_3 as an internal standard. IR spectra were recorded as thin films on NaCl plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral analysis (HRMS) was performed on Waters Q-Tof Premier Mass Spectrometer.

General Procedure for the Synthesis of Substrates

2-Aryloxy-1-acetophenones were prepared from the corresponding phenols and 2-bromoacetophenones according to the reported method ¹.

Representative Procedure: A round bottom flask equipped with a reflux condenser was charged with 2-bromoacetophenone (1.99 g, 10 mmol), phenol (1.13 g, 12 mmol), potassium carbonate (2.07 g, 15 mmol), and acetone (50 mL). The resulting suspension was heated to reflux for 5 h under nitrogen. After cooling down, the mixture was filtered through Celite and concentrated in vacuo. The obtained solid was crystallized from ethanol to give 1.42 g of 2-phenyloxy-acetophenone as a white solid (67%). ¹H NMR (400 MHz, CDCl₃): δ = 8.03 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.28-7.34 (m, 2H), 6.97-7.03 (m, 3H), 5.30 (s, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 194.6, 158.0, 134.6, 133.9, 129.6, 128.9, 128.2, 121.7, 114.8, 70.8.

Prepared by using the representative procedure, white amorphous solid, yield = 60%. ¹H NMR (400 MHz, CDCl₃): δ = 7.60 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.25-7.34 (m, 2H), 7.17-7.20 (dd, *J* = 2.8 Hz, *J* = 8.4 Hz, 1H), 6.95-7.03 (m, 3H), 5.30 (s, 2H), 3.89 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 194.4, 160.0, 129.8, 129.7, 129.6, 121.7, 120.6, 120.4, 115.3, 114.8, 112.4, 70.9, 55.5.

¹⁵ Nichols, J. M.; Bishop, L. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2010**, 132, 12554.

¹⁶ Mathivanan, N.; Johnston, L. J.; Wayner, D.D.M. *J. Phys. Chem.* **1995**, 99, 8190.

Prepared by using the representative procedure, orange oil, yield = 55%. ^1H NMR (400 MHz, CDCl_3): δ = 7.96-7.98 (m, 2H), 7.57-7.60 (m, 1H), 7.47 (t, J = 8.0 Hz, 2H), 6.72 (d, J = 8.8 Hz, 1H), 6.23 (d, J = 2.8 Hz, 1H), 6.36-6.39 (dd, J = 2.8 Hz, J = 8.8 Hz, 1H), 5.20 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 194.7, 152.6, 149.9, 144.1, 134.6, 133.8, 128.8, 128.1, 111.6, 104.0, 101.5, 71.4, 56.3, 55.9. HR-MS (ESI): m/z calculated for $\text{C}_{16}\text{H}_{16}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 295.0946; found 295.0945. FTIR (NaCl, cm^{-1}): 3421.7, 3053.3, 2985.8, 2304.9, 1690.1, 1641.1, 1500.2, 1421.5, 1265.3, 1028.1, 138.4.

Prepared by using the representative procedure, white solid, yield = 69%. ^1H NMR (400 MHz, CDCl_3): δ = 8.01-8.04 (dd, J = 2.0 Hz, J = 7.2 Hz, 2H), 6.93-6.98 (m, 4H), 6.85 (d, J = 3.6 Hz, 2H), 5.29 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 193.1, 164.0, 149.8, 147.7, 130.5, 127.7, 122.3, 120.8, 114.7, 114.0, 112.2, 72.0, 55.9, 55.5.

¹⁷ Thomas, K. K.; Bokadia, M. M. *J. Indian. Chem. Soc.* **1968**, *45*, 265.

Prepared by using the representative procedure, yellow solid, yield = 76%. ^1H NMR (400 MHz, CDCl_3): δ = 7.45 (d, J = 3.2 Hz, 1H), 7.07-7.11 (dd, J = 3.6 Hz, J = 9.2 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 9.2 Hz, 2H), 6.82 (d, J = 9.6 Hz, 2H), 5.19 (s, 2H), 3.90 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 195.4, 154.2, 153.9, 153.8, 152.6, 125.1, 121.7, 115.9, 114.6, 113.8, 113.1, 75.2, 56.1, 55.9, 55.7. HR-MS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{18}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 325.1052; found 325.1052. FTIR (NaCl, cm^{-1}): 3053.3, 2988.0, 1689.0, 1500.1, 1420.5, 1265.3, 1220.9, 1169.2, 1056.3, 891.0, 766.0, 742.6.

2-Phenyloxy-3'-fluoroacetophenone¹⁸

White solid. ^1H NMR (400 MHz, CDCl_3): δ = 7.96-7.99 (m, 2H), 7.47-7.50 (m, 2H), 7.29-7.33 (m, 2H), 6.95-7.29 (m, 3H), 5.23 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ = 193.8, 157.9, 140.3, 132.9, 129.7, 129.6, 129.2, 121.8, 114.8, 70.9.

1-phenyl-3-hydroxy-2-phenoxy propan-1-one

Representative Procedure: A solution of 1-phenyl-2-phenoxy ethanone (1.0 mmol) and HCHO (aq. solution, 36 wt%, 1.5 mmol) in EtOH/acetone (1:1, 10 mL) was treated with K_2CO_3 (1.0 mmol) for 1.5 h at room temperature. Then the solvent was evaporated, the

¹⁸ Huang, K.; Wang, H.; Stepanenko, V.; De Jesus, M.; Torruellas, C.; Correa, W.; Ortiz-Marciales, M. *J. Org. Chem.* **2011**, 76, 1883-1886.

residue was dissolved in EA, washed with water and brine. The organic phase was concentrated and purified by column chromatography with hexanes/EtOAc to give the product as a white solid. Yield: 61%. ^1H NMR (400 MHz, CDCl_3): δ = 8.07 (d, J = 8.0 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 7.27 (t, J = 8.0 Hz, 2H), 6.91-7.01 (m, 3H), 5.58-5.61 (m, 1H), 4.11-4.22 (m, 2H), 2.65 (b, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 196.7, 157.3, 134.7, 134.0, 129.7, 128.9, 128.8, 122.0, 115.3, 81.1, 63.3.

1-(4-methoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)-propan-1-one

Prepared from 2-(2-methoxyphenyl)oxy-4'-methoxyacetophenone by using the representative procedure, yellow oil, yield = 76%. ^1H NMR (400 MHz, CDCl_3): δ = 8.07 (d, J = 9.2 Hz, 2H), 6.78-6.97 (m, 6H), 5.42 (t, J = 5.2 Hz, 1H), 4.07 (d, J = 5.2 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.33 (b, 1H). HR-MS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{18}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 325.1052; found 325.1049. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 2684.9, 2304.9, 1687.7, 1600.9, 1504.5, 1421.5, 1265.3, 1172.7, 1128.4, 1028.1, 895.0, 754.2, 704.0.

1-(2,5-dimethoxyphenyl)-3-hydroxy-2-(4-methoxyphenoxy)propan-1-one

Prepared from 2-(4-methoxyphenyl)oxy-2',5'-dimethoxyacetophenone by using the

representative procedure, pale yellow oil, yield = 63%. ^1H NMR (400 MHz, CDCl_3): δ = 7.29 (d, J = 3.2 Hz, 1H), 7.06-7.09 (dd, J = 3.2 Hz, J = 9.2 Hz, 1H), 6.91 (d, J = 9.2 Hz, 1H), 6.85 (d, J = 9.2 Hz, 2H), 6.77 (d, J = 9.2 Hz, 2H), 5.72-5.74 (m, 1H), 4.08-4.12 (dd, J = 3.6 Hz, J = 12.0 Hz, 1H), 3.92-3.97 (dd, J = 5.2 Hz, J = 12.0 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 2.32 (b, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 197.6, 154.3, 153.8, 152.9, 152.1, 126.0, 121.4, 116.5, 114.6, 114.3, 113.0, 84.2, 62.8, 56.0, 55.8, 55.7. HR-MS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{20}\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$: 355.1158; found 355.1163. FTIR (NaCl, cm^{-1}): 3480.2, 3053.3, 2985.8, 2305.9, 1680.1, 1500.2, 1422.3, 1267.6, 1221.1, 1038.2, 896.2, 755.4.

^1H NMR (400 MHz, CDCl_3): δ = 7.29-7.50 (m, 7H), 6.95-7.02 (m, 3H), 5.14-5.18 (m, 1H), 4.13-4.16 (dd, J = 3.2 Hz, J = 9.6 Hz, 1H), 4.02-4.07 (dd, J = 8.8 Hz, J = 9.6 Hz, 1H), 2.80 (d, J = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 158.4, 139.6, 129.6, 128.6, 128.2, 126.3, 121.3, 114.7, 73.3, 72.6.

1-(3,4-Dimethoxyphenyl)-2-(2-methoxyphenoxy)propane-1,3-diol (1ec)

This compound (dr = 98:2) was prepared by the literature procedure.⁶ ^1H NMR (400 MHz, CDCl_3) δ 7.07-6.82 (m, 7H), 4.98 (d, J = 4.8 Hz, 1H), 4.18-4.14 (m, 1H), 3.94-3.86 (m, 10H),

3.69-3.65 (m, 2H), 2.93 (s br, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ = 151.49, 148.96, 148.41, 146.87, 132.54, 124.10, 121.58, 120.80, 118.41, 112.13, 110.97, 109.22, 87.22, 72.66, 60.73, 55.87, 55.83.

Trimeric Model 11ec

This compound was prepared by the literature procedure.⁶ ^1H NMR (400 MHz, CDCl_3) δ 7.08-6.82 (m, 10H), 5.02-4.96 (m, 2H), 4.17-4.12 (m, 2H), 3.91-3.87 (m, 14H), 3.68-3.65 (m, 3H), 3.53-3.45 (m, 1H), 2.83-2.70 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.60, 149.06, 148.52, 146.76, 146.27, 146.23, 136.12, 136.09, 132.40, 124.38, 121.67, 121.02, 120.69, 119.23, 118.40, 112.24, 111.06, 110.09, 109.23, 87.42, 87.23, 72.75, 72.70, 72.60, 60.79, 60.73, 56.01, 55.94.

2-phenoxy-1-phenylpropan-1-one¹⁹

^1H NMR (400 MHz, CDCl_3): δ = 8.12 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 7.26 (t, J = 8.0 Hz, 2H), 6.96 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 8.4 Hz, 2H), 5.51 (q, J = 6.8 Hz, 1H), 1.74 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 199.0, 157.4, 134.2, 133.7, 129.6, 128.9, 128.8, 121.5, 115.2, 76.6, 18.8.

¹⁹ Fabbri, C.; Bietti, M.; Lanzalunga, O. *J. Org. Chem.* **2005**, *70*, 2720.

¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H), 7.36 (t, J = 8.4 Hz, 2H), 7.10-7.16 (m, 3H), 5.42 (d, J = 2.4 Hz, 1H), 5.14 (d, J = 2.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ = 190.9, 157.3, 155.3, 136.5, 132.9, 129.9, 129.6, 128.3, 124.3, 119.4, 105.2.

¹H NMR (400 MHz, CDCl₃): δ = 7.93 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 4.71 (s, 2H), 3.51 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 196.2, 134.8, 133.6, 128.7, 127.8, 75.3, 59.4.

General Procedure for the Synthesis of α -ketoamides from ligin model compounds 3 and 4

Copper-catalyzed conditions: An oven dried vial was charged with CuI (3.8 mg, 0.0199 mmol, 10 mmol%), **3aa** (42.4 mg, 0.198 mmol), amine **4a** (98.8 μ L, 1.0 mmol, 5.0 equiv)

²⁰ Wright, J. B. *J. Org. Chem.* **1960**, 25, 1867-1872.

²¹ Katritzky, A. R.; Xie, L.; Serdyuk, L. *J. Org. Chem.* **1996**, 61, 7564.

and dry toluene (0.8 mL). The vial was then sealed under an oxygen atmosphere, and the reaction was heated to 70 °C with stirring for 6 h. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude product, which was purified through a flash column chromatography (eluent: 10 % to 25 % ethyl acetate in hexane solution) to afford **5aa** (38.2 mg, 0.176 mmol, 88% yield) and phenol **6a** (11.8 mg, 0.126 mmol, 63% yield).

Procedure for the Synthesis of α -ketoamides from ligin model compounds 1 and 2

Copper-catalyzed conditions: An oven dried vial was charged with CuBr (5 mol%, 0.01 mmol), 1,10-phenanthroline (5 mol%, 0.01 mol), K₂CO₃ (0.2 mmol, 2.0 equiv.), compound **1** or **2** (0.1 mmol) and toluene (0.7 ml). The mixture was stirred at room temperature for 15 min. DEAD (1.2 equiv.) was added, and the mixture was heated to 90°C with stirring for 1.5 hours while oxygen was bubbled through the reaction mixture. After cooling to room temperature, amine (5.0 equiv.) was added, and the reaction mixture was heated to 70 °C with stirring under oxygen for 12h. The mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude product which was directly applied to a flash column chromatography (EtOAc/Hexanes mixtures).

Characterization Data for the α -ketoamides

1-phenyl-2-(piperidin-1-yl) ethane-1,2-dione (3aa)^{9b}

This compound was prepared by the General Procedure described above and was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 3.72 (b, 2H), 3.31 (t, *J* = 5.6 Hz, 2H), 1.71-1.72 (m, 4H), 1.56-1.63 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 192.0, 165.5, 134.7, 133.3, 129.6, 129.0, 47.1, 42.2, 26.2, 25.5, 24.4.

1-phenyl-2-(pyrrolidine-1-yl) ethane-1,2-dione (3aa)^{9a}

¹H NMR (400 MHz, CDCl₃): δ = 8.02 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 3.68 (t, *J* = 6.4 Hz, 2H), 3.45 (t, *J* = 6.8 Hz, 2H), 1.95-2.00 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ = 191.6, 164.9, 134.6, 133.0, 129.9, 128.9, 46.7, 45.3, 25.9, 24.0.

1-morpholino-2-phenylethane-1,2-dione^{9b}

¹H NMR (400 MHz, CDCl₃): δ = 7.98 (d, *J* = 7.8 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 3.82 (s, 4H), 3.68 (t, *J* = 4.8 Hz, 2H), 3.41 (t, *J* = 4.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 191.2, 165.5, 135.0, 133.1, 129.7, 129.1, 66.8, 66.7, 46.3, 41.6.

1-phenyl-2-(dibutyl amino) ethane-1,2-dione^{9a}

¹H NMR (400 MHz, CDCl₃): δ = 7.94 (d, J = 8.4 Hz, 2H), 7.63-7.65 (m, 1H), 7.53 (t, J = 8.4 Hz, J = 8.0 Hz, 2H), 3.52 (t, J = 8.0 Hz, 2H), 3.17 (t, J = 7.6 Hz, 2H), 1.66-1.71 (m, 2H), 1.54-1.58 (m, 2H), 1.41-1.47 (m, 2H), 1.18-1.24 (m, 2H), 1.02 (t, J = 7.6 Hz, 3H), 0.88 (t, J = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 191.6, 167.1, 134.5, 133.4, 129.6, 128.9, 47.5, 44.1, 30.6, 29.5, 20.3, 19.8, 13.9, 13.6.

***N*-benzyl-*N*-methyl-2-oxo-2-phenylacetamide (a mixture of *s*-cis and *s*-trans isomers)**^{9a-b}

¹H NMR (400 MHz, CDCl₃): δ = 7.99-8.03 (m, 4H), 7.67 (t, J = 7.6 Hz, 2H), 7.54 (t, J = 7.6 Hz, 4H), 7.27-7.42 (m, 10H), 4.77 (s, 2H), 4.43 (s, 2H), 3.02 (s, 3H), 2.88 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 191.5, 167.2, 135.8, 135.0, 134.8, 133.3, 133.1, 129.8, 129.7, 129.1, 129.0, 128.9, 128.8, 128.8, 128.4, 127.9, 127.8, 53.6, 49.9, 34.5, 31.4;

1-phenyl-2-(diallyl amino) ethane-1,2-dione²²

¹H NMR (400 MHz, CDCl₃): δ = 7.97 (d, J = 7.2 Hz, 2H), 7.64-7.68 (m, 1H), 7.51-7.55

²² Cossy, J., Madaci, A.; Pete, J. P. *Tetrahedron Letters* **35**, 154-1544 (1994).

(m, 2H), 5.84-5.93 (m, 1H), 5.68-5.76 (m, 1H), 5.23-5.33 (m, 2H), 5.16-5.23 (m, 2H), 4.17 (d, $J = 6.0$ Hz, 2H), 3.83 (d, $J = 6.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 191.2, 167.0, 134.7, 133.2, 132.1, 131.8, 129.8, 129.0, 119.4, 118.7, 49.5, 45.9$.

1-(4-methoxyphenyl)-2-(piperidin-1-yl)ethane-1,2-dione ^{9b}

^1H NMR (400 MHz, CDCl_3): $\delta = 7.93$ (d, $J = 8.8$ Hz, 2H), 6.99 (d, $J = 8.8$ Hz, 2H), 3.90 (s, 3H), 3.71-3.72 (m, 2H), 3.30 (t, $J = 5.6$ Hz, 2H), 1.70-1.71 (m, 4H), 1.55 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 190.7, 165.8, 164.8, 132.0, 126.4, 114.3, 55.6, 47.1, 42.1, 26.3, 25.5, 24.4$.

1-(3-methoxyphenyl)-2-(piperidin-1-yl)ethane-1,2-dione

^1H NMR (400 MHz, CDCl_3): $\delta = 7.50$ -7.51 (m, 2H), 7.42 (t, $J = 8.0$ Hz, 1H), 7.18-7.21 (m, 1H), 3.88 (s, 3H), 3.71 (m, 2H), 3.28-3.31 (m, 2H), 1.70-1.72 (m, 4H), 1.56-1.58 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 191.9, 165.4, 160.1, 134.6, 130.0, 122.8, 121.6, 112.6, 55.5, 47.1, 42.2, 26.2, 25.5, 24.4$. HR-MS (ESI): m/z calculated for $\text{C}_{14}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 248.1287; found 248.1290. FTIR (NaCl, cm^{-1}): 2961.0, 2302.0, 1679.0, 1639.2, 1592.0, 1444.2, 1201.6, 1233.6, 1005.9, 897.3, 744.9, 633.5.

1-(4-methoxyphenyl)-2-morpholino ethane-1,2-dione²³

¹H NMR (400 MHz, CDCl₃): δ = 7.94-7.96 (dd, J = 2.0 Hz, J = 7.2 Hz, 2H), 6.99-7.02 (dd, J = 2.0 Hz, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.80 (s, 4H), 3.67 (t, J = 4.8 Hz, 2H), 3.40 (t, J = 4.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 189.8, 165.8, 165.0, 132.2, 126.2, 114.4, 66.8, 66.7, 55.7, 46.3, 41.6.

1-(2,5-dimethoxyphenyl)-2-(piperidin-1-yl) ethane-1,2-dione

¹H NMR (400 MHz, CDCl₃): δ = 7.43 (d, J = 3.2 Hz, 1H), 7.11-7.14 (dd, J = 3.2 Hz, J = 9.2 Hz, 1H), 6.93 (d, J = 9.2 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.62 (t, J = 6.0 Hz, 2H), 3.30 (t, J = 5.6 Hz, 2H), 1.65-1.69 (m, 4H), 1.56-1.59 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 190.5, 167.1, 155.0, 154.1, 124.0, 123.7, 114.3, 113.0, 56.8, 55.9, 46.7, 41.9, 25.5, 25.3, 24.5. HR-MS (ESI): m/z calculated for C₁₅H₂₀NO₄ [M+H]⁺: 278.1392; found 278.1391. FTIR (NaCl, cm⁻¹): 3053.3, 2985.8, 2899.3, 2304.9, 1651.2, 1500.2, 1487.2, 1415.2, 1272.2, 1232.2, 1172.7, 1042.4, 998.4, 895.0, 755.2.

1-(3,4-dimethoxyphenyl)-2-(piperidin-1-yl) ethane-1,2-dione²⁴

²³ Liu, J.; Zhang, R.; Wang, S.; Sun, W.; Xia, C. *Org. Lett.* **2009**, 11, 1321-1324.

^1H NMR (400 MHz, CDCl_3): δ = 7.54 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.71-3.73 (m, 2H), 3.30 (t, J = 5.6 Hz, 2H), 1.70-1.72 (m, 4H), 1.55-1.60 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ = 190.8, 165.7, 154.7, 149.6, 126.6, 125.7, 110.4, 110.2, 56.2, 56.1, 47.1, 42.1, 26.2, 25.5, 24.4.

1-(4-Fluorophenyl)-2-(piperidin-1-yl) ethane-1,2-dione^{9a}

^1H NMR (400 MHz, CDCl_3): δ = 7.91 (dd, J = 2.0 Hz, J = 6.8 Hz, 2H), 7.51 (dd, J = 2.0 Hz, J = 6.8 Hz, 2H), 3.72 (t, J = 4.8 Hz, 2H), 3.31 (t, J = 5.6 Hz, 2H), 1.71-1.73 (m, 4H), 1.57-1.59 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ = 190.5, 165.0, 141.3, 131.7, 130.9, 129.4, 47.1, 42.3, 26.3, 25.5, 24.4.

Chemo-Selective Oxidation:

Procedure of oxidation

An oven dried vial was charged with CuBr (6.0 mg, 0.042 mmol, 10 mmol%), 1,10-

²⁴ Palasz, P.D.; Utlej, J. H. P.; Hardstone, J. D. *Acta Chemica Scandinavica, Series B: Org. Chem. BioChem.*, **1984**, 4, 281-292.

phenanthroline (7.6 mg, 0.042 mmol, 10 mmol%), K₂CO₃ (127.7 mg, 0.924 mmol, 2.2 equiv), lignin model compound **1ec** (140.4 mg, 0.420 mmol) and toluene (1.5 mL). The mixture was at first stirred at room temperature for 15 min before adding DEAD (72.5 μ L, 0.462 mmol, 1.1 equiv). The reaction mixture was then heated to 90 °C. With stirring, O₂ gas was bubbled through the needle attached with an O₂ balloon to the reaction mixture, and the reaction was monitored by TLC. After 1.5 h stirring, the reaction mixture was cooled down, diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give the crude material, which was purified through flash column chromatography (eluent: 10 % to 50 % ethyl acetate solution in hexane) to afford **2ec** (82.4 mg, 0.248 mmol, 59% yield) and **8ec** (40.9 mg, 0.130 mmol, 31% yield).

1-(3,4-dimethoxyphenyl)-3-hydroxy-2-(2-methoxyphenoxy)propan-1-one (2ec)²⁵

¹H NMR (400 MHz, CDCl₃) δ 7.76 (dd, J = 8.4, 2.0 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.02-6.98 (m, 1H), 6.92-6.88 (m, 3H), 6.84-6.80 (m, 1H), 5.41 (t, J = 5.4 Hz, 1H), 4.08 (d, J = 5.2 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 3.20 (s br, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 195.00, 153.95, 150.42, 149.21, 146.95, 128.06, 123.65, 123.59, 121.18, 118.35, 112.29, 110.97, 110.12, 84.49, 63.74, 56.12, 55.98, 55.81.

²⁵ Cho, D. W.; Parthasarathi, R.; Pimentel, A. S.; Maestas, G. D.; Park, H. J.; Yoon, U. C.; Dunaway-Mariano, D.; Gnanakaran, S.; Langan, P.; Mariano, P. S. *J. Org. Chem.* **2010**, 75, 6549.

2-(2-methoxy)phenoxy-1-(3,4-dimethoxy) phenyl-propenone (8ec)

Colourless oil. ^1H NMR (400 MHz, CDCl_3): δ = 7.84-7.86 (dd, J = 2.0 Hz, J = 8.4 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.14-7.18 (m, 1H), 7.08-7.11 (dd, J = 1.6 Hz, J = 8.0 Hz, 1H), 6.91-7.01 (m, 3H), 5.22 (d, J = 2.4 Hz, 1H), 4.72 (d, J = 2.4 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 189.1, 158.0, 153.3, 151.0, 148.7, 143.3, 129.1, 125.7, 125.0, 121.6, 121.2, 112.8, 112.3, 109.9, 99.9, 56.1, 56.0, 55.8. HRMS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{18}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$: 337.1052; found 337.1051. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 2304.9, 1803.4, 1770.7, 1595.1, 1500.6, 1440.8, 1419.6, 1271.5, 1141.8, 1111.0, 908.5, 895.0, 706.

Procedure for the One-pot Conversion of Ligin Model 1ec

An oven dried vial was charged with CuBr (6.0 mg, 0.0420 mmol, 10 mmol%), 1,10-phenanthroline (7.6 mg, 0.0420 mmol, 10 mmol%), K_2CO_3 (127.7 mg, 0.924 mmol, 2.2

equiv), model **1ec** (140.4 mg, 0.420 mmol) and toluene (1.5 mL). The mixture was stirred at room temperature for 15 min before adding DEAD (72.5 μ L, 0.462 mmol, 1.1 equiv), and the mixture was then heated to 90 $^{\circ}$ C. To the reaction mixture, O₂ gas was bubbled through the needle attached with an O₂ balloon, and the reaction was monitored by TLC. After stirring 1.5 h, the reaction mixture was cooling down to room temperature. Piperidine (**4a**) (207.4 μ L, 2.10 mmol, 5.0 equiv) was then added directly, and the reaction mixture was heated again to 70 $^{\circ}$ C and stirred for 6 h. The mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude products, which were purified by flash column chromatography (eluent: 10 % to 50 % ethyl acetate solution in hexane) to afford **5ea** (55.9 mg, 0.202 mmol, 48% yield), **7ea** (29.3 mg, 0.118 mmol, 28% yield) and **6c** (21.4 mg, 0.172 mmol, 41% yield).

Procedure for the One-pot Conversion of Ligin Model 11ec

An oven dried vial was charged with CuBr (1.4 mg, 0.010 mmol, 10 mmol%), 1,10-phenanthroline (1.8 mg, 0.010 mmol, 10 mmol%), K₂CO₃ (60.8 mg, 0.440 mmol, 4.4 equiv),

trimeric model **1ec** (53.1 mg, 0.10 mmol) and toluene (0.4 mL). The mixture was stirred at room temperature for 15 min before adding DEAD (34.6 μ L, 0.22 mmol, 2.2 equiv), and the mixture was then heated to 90 $^{\circ}$ C. With stirring, O₂ gas was bubbled through the needle attached with an O₂ balloon to the reaction mixture, and the reaction was monitored by TLC. After being stirred for 1.5 h, the reaction mixture was cooled down, and piperidine (**4a**) (98.8 μ L, 1.00 mmol, 10 equiv) was added directly. The reaction mixture was heated to 70 $^{\circ}$ C for 6 h. The mixture was then diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude products, which were directly applied to a flash column chromatography (eluent: 10 % to 60 % ethyl acetate solution in hexane) to afford **5ea** (11.9 mg, 0.0430 mmol, 43% yield), **6c** (6.8 mg, 0.0550 mmol, 55% yield) and **7ea** (5.5 mg, 0.0220 mmol, 22% yield).

Isotope Labelling Experiments for Scheme 2 (reference 13)

To investigate the possible reaction mechanism, isotope-labeling experiments using ¹⁸O₂ were conducted under the standard reaction conditions (Scheme S-2). The reaction of **3aa** with **4a** under ¹⁸O₂ provided **5aa** in 85% yield, that constituted with (¹⁸O-¹⁸O)-**5aa**, (¹⁸O-¹⁶O)-**5aa**, and (¹⁶O/¹⁶O)-**5aa** in the ratio of 54:46:0 (see Figure S-1 for the mass spectrum). Similarly, the reaction of **2aa** with **4a** afforded (¹⁸O-¹⁸O)-**5aa**, (¹⁸O-¹⁶O)-**5aa**, and (¹⁶O/¹⁶O)-**5aa** in the ratio of 72:28:0 (in 79% yield) (see Figure S-2 for the mass spectrum). Considering the keto-carbonyl oxygen of **5aa** could be easily exchanged with present H₂O, there still remain both possibilities of **Path I** and **II** described in Scheme 2.

Scheme S-2. Isotope Labeling Experiments of **3aa** and **2aa**.

Figure S-1. Spectrum of ESI (LRMS)

Figure S-2. Spectrum of ESI (LRMS)

CHAPTER 5

*Oxidative Synthesis of Imidazoheterocycles from
2-Aminopyridines and Aryloxyacetophenones by Copper
Catalyst*

5.1 Introduction

Imidazoheterocycles represent an important class of heterocycles that have numerous applications in medicinal and biological chemistry.¹ In particular, imidazo[1,2-a]pyridine is the key structural moiety in certain pharmacologically important molecules, such as alpidem,² saripidem,³ and DS-2.⁴ (Figure 5.1)

Figure 5.1 Imidazo[1,2-a]pyridine-based drugs

Consequently, many synthetic methods have been reported for the preparation of imidazo[1,2-a]pyridines framework for their numerous presence in biologically active compounds.⁵ Recently, some novel synthetic approaches have been developed to produce imidazo[1,2-a]pyridine derivatives.

¹ Couty, F.; Evano, G. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, **2008**; Vol. 11, pp 409-499.

² (a) Berson, A.; Descatoire, V.; Sutton, A.; Fau, D.; Maulny, B.; Vadrot, N.; Feldmann, G.; Berthon, B.; Tordjmann, T.; Pessayre, D. J. *Pharmacol. Exp. Ther.* **2001**, 299, 793–800. (b) Saletu, J.; Grunberger, B.; Linzmayer, L. *Int. Clin. Psychopharmacol.* **1986**, 1, 145-164.

³ (a) Boerner, R. J.; Moller, H. J. *Psychopharmakotherapie* 1997, 4, 145-148. (b) Sanger, D. J. *Behav. Pharmacol.* 1995, 6, 116-126.

⁴ Wafford, K.A., *Neuropharmacology*, **2009**, 56, 182-189.

⁵ For select recent examples, see: (a) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, 47, 11333–11335. (b) Wang, X. P.; Ma, L. J.; Yu, W. *Synthesis* **2011**, 2445–2453. (c) Husinec, S.; Markovic, R.; Petkovic, M.; Nasufovic, V.; Savic, V. *Org. Lett.* **2011**, 13, 2286-2289. (d) Chunavala, K. C.; Joshi, G.; Suresh, E.; Adimurthy, S. *Synthesis* **2011**, 1319-1319. (e) Wen, L. R.; Jiang, C. Y.; Li, M.; Wang, L. J. *Tetrahedron* **2011**, 67, 293-302. (f) Sucunza, D.; Samadi, A.; Chioua, M.; Silva, D. B.; Yunta, C.; Infantes, L.; Carreiras, M. C.; Soriano, E.; Marco-Contelles, J. *Chem. Commun.* **2011**, 47, 5043-5045.

In 2010, Gevorgyan and co-worker reported a general and efficient method for the synthesis of imidazopyridine derivatives by a copper-catalyzed three-component coupling reaction of aldehyde, terminal alkynes and 2-aminopyridines (Scheme 5.1).⁶ The synthetic utility of this reaction has been demonstrated in a high efficient one-pot synthesis of alpidem and zolpidem.

Scheme 5.1

In the same year, Zhu reported a novel and efficient synthesis of pyrido[1,2-*a*]benzimidazoles through direct intra-molecular aromatic C-H amination of *N*-aryl-2-aminopyridines (Scheme 5.2).⁷ The reaction, co-catalyzed by Cu(OAc)₂ and Fe(NO₃)₃·9H₂O, is carried out in DMF under an oxygen atmosphere.

Scheme 5.2

One year later, Zhu and co-workers discovered an unexpected and novel intramolecular dehydrogenative aminooxygenation (IDA) reaction affording imidazo[1,2-*a*]pyridine-3-

⁶ Chernyak, N.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, 49, 2743-2746.

⁷ Wang, H. G.; Wang, Y.; Peng, C. L.; Zhang, J. C.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, 132, 13217-13219.

carbaldehydes and 1,2-disubstituted imidazole-4-carbaldehydes from readily available *N*-allyl-2-aminopyridines and substituted *N*-allylamidines, respectively (Scheme 5.3).⁸ The reaction, carried out by using 20 mol% of Cu(II) catalyst in DMF or DMA under dioxygen, is efficient and environmentally benign.

Scheme 5.3

In 2012, Liu and co-workers disclosed a facile synthesis of imidazo[1,2-a] achieved by copper(II) and iron(III) co-catalyzed C-N bond formation (Scheme 5.4).⁹ This reaction involves an intermolecular oxidative diamination of alkynes with high chemoselectivity and regioselectivity.

Scheme 5.4

In the same year, Lei also reported a novel silver-mediated highly selective C-H/N-H oxidative cross-coupling/cyclization between 2-aminopyridines and terminal alkynes.¹⁰ This approach provided a simple and efficient approach to construct heteroaromatic imidazo[1,2-

⁸ Wang, H. G.; Wang, Y.; Liang, D. D.; Liu, L. Y.; Zhang, J. C.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, 50, 5678-5681.

⁹ Zeng, J.; Tan, Y. J.; Leow, M. L.; Liu, X.-W. *Org. Lett.*, **2012**, 14, 4386-4389.

¹⁰ He, C.; Hao, J.; Xu, H.; Mo, Y.; Liu, H.; Han, J.; Lei, A. *Chem. Comm.*, **2012**, 48, 11073-11075.

a]pyridines (Scheme 5.5).

Scheme 5.5

Huang and co-workers have also developed a direct Cu(I)-catalyzed method for the synthesis of imidazo[1,2-a]pyridines with aminopyridines and nitroolefins in one-pot fashion using air as oxidant (Scheme 5.6).¹¹

Scheme 5.6

Although a number of synthetic methods for the synthesis of this kind of important heterocycle have been reported, most of them are limited to narrow substrate scope and require multistep for the preparation of starting materials. Accordingly, the development of further diverse methods to construct various imidazo[1,2-a]pyridines from widely used precursors is still desirable.

¹¹ Yan, R.-L.; Yan, H.; Ma, C.; Ren, Z.-Y.; Gao, X.-A.; Huang, G.-S., Liang, Y.-M. *J. Org. Chem.* **2012**, 77, 2024-2028.

5.2 Results and discussion

Our research commenced with the aerobic oxidative reaction of acetophenone (**4**) and 2-aminopyridine (**1a**) in the hoping that C-H bond activation occur to afford 2-phenyl-3-phenoxyimidazo[1,2-a]pyridine (**3a**). However, the reaction provided only trace amount of desired product, and the major by-product is *N*-(pyridin-2-yl)benzamide, which is generated *via* C-C bond cleavage under the oxidation conditions (Scheme 5.7a).¹²

Scheme 5.7

Then we turned to examine the reaction of 2-phenoxyacetophenone (**2a**) and 2-aminopyridine (**1a**) in toluene in the presence of catalytic amount of CuI at 100 °C under oxygen atmosphere (1 atm) for 16 h (Scheme 5.7b). To our delight, 2-phenyl-3-phenoxyimidazo[1,2-a]pyridines (**3a**) was obtained in 59% yields, and the formation of by-product **5** was not observed (Table 5.1, entry 1). To optimize the catalytic conditions, the effect of

¹² (a) Kaneda, K.; Itoh, T.; Kii, N.; Jitsukawa, K.; Teranishi, S. *J. Mol. Catal.* **1982**, *15*, 349. (b) Rheenen, V. V. *Chem. Commun.* **1969**, 314.

Table 5.1. Optimization of catalytic conditions.^a

Nc1ccccn1 + CC(=O)c1ccccc1O
 $\xrightarrow[\text{Solvent, 100 } ^\circ\text{C, under O}_2]{\text{Catalyst (10 mol\%), Ligand (10 mol\%)}}$
c1ccc(cc1)c2nc3ccccc3n2c1

1a, 3.0 equiv. **2a** **3a**

Entry	Catalyst	Ligand	Solvent	Temperature/ $^{\circ}\text{C}$	Yield/%
1	CuI	-	Toluene	100	59
2	CuI	-	DCE	100	77
3	CuI	-	THF	100	65
4	CuI	-	Dioxane	100	71
5	CuI	-	DMSO	100	23
6	CuI	-	DMF	100	25
7	CuI	-	DME	100	49
8	CuI	-	MeCN	100	27
9	CuI	-	EtOH	100	42
10	CuI	-	DCE	80	70
11	CuI	-	DCE	120	66
12	CuI	bipy	DCE	100	28
13	CuI	Py	DCE	100	21
14	CuI	1,10-Phen	DCE	100	42
15	CuI	TMEDA	DCE	100	45
16	CuBr	-	DCE	100	56
17	CuBr ₂	-	DCE	100	70
18 ^b	CuBr ₂	-	DCE	100	81
19 ^c	CuI	-	DCE	100	55
20	Pd(OAc) ₂	-	DCE	100	5
21	FeCl ₃	-	DCE	100	11
22	RuCl ₃	-	DCE	100	24

^aUnless otherwise described, the reaction conditions were as follows: 2-amino pyridine **1a** (0.6 mmol), 2-phenoxyacetophenone **2a** (0.2 mmol), catalyst (10 mol%), ligand (10 mol%), solvent (0.6 ml), 100 $^{\circ}\text{C}$, 16 h, under oxygen (1 atm.). The isolated yield was obtained by silica gel column chromatography.

^b2.2 equiv. CuBr₂ was used and the reaction was performed under N₂. ^c1.5 equiv. **1a** used.

solvents was subsequently examined. Replacement of toluene with DCE (1,2-dichloroethane) afforded imidazoheterocycle in highest yield (Table 5.1, entry 2). The reaction also proceeded well in other solvents, such as THF, 1,4-dioxane, DME and even ethanol, albeit in somewhat decreased yield (Table 5.1, entry 3, 4, 7 and 9). When polar aprotic solvents, such as DMSO, DMF and acetonitrile were used, the reactions didn't proceed well and only 20-30% yields were obtained (Table 5.1, entries 5, 6 and 8). When the reaction temperature was lowered or elevated, the yield was dropped to a moderate level (Table 5.1, entry 10 and 11). A series of nitrogen ligands were also screened although no remarkable effort was observed (Table 5.1, entries 12-15). Employment of other copper salts, such as CuBr and CuBr₂ could not improve the yield (Table 5.1, entries 16-17). Interestingly, the reaction provided imidazopyridine in 81% yield when 2.2 equivalent amount of CuBr₂ was used under nitrogen atmosphere (Table 5.1, entry 18). The result also showed that reducing the amount of 2-aminopyridine by half made the yield drop to a moderate level (Table 5.1, entry 19). Other transition-metal salts, such as Pd(OAc)₂, FeCl₃ and RuCl₃ were also examined, but all of them showed limited catalytic activity (Table 5.1, entry 20-22).

With this optimized catalytic conditions in hand, we next examined the scope of the substituted 2-aminopyridines and ketones (Table 5.2). It was observed that installing electron-donating functional group such as methoxyl group to C-terminus phenyl ring resulted in corresponding imidazo[1,2-a]pyridines in higher yield (Table 5.2, **3b**), while installing electron-deficient functional group led to the product with reduced yield (Table 5.2, **3c**). The result also applied to O-terminus phenyl ring with I- and Cl- substituents (Table 5.2, **3d** and **3e**). Both electron-rich and electron-deficient aminopyridines could be smoothly

converted into the desired products in good yields (Table 5.2, **3f-3i**).

Table 5.2. Exploration of the substrate scope^a

^aUnless otherwise described, the reaction conditions were as follows: 2-amino pyridine **1** (0.6 mmol), ketone **2** (0.2 mmol), CuI (10 mol%), DCE (0.6 ml), 100 °C, 12 h, under oxygen (1 atm.). The isolated yield was obtained by silica gel column chromatography.

Furthermore, 2-aminoisoquinoline reacted well in this transformation, thus affording imidazoisquinoline **3o** in 49% yield (Table 5.2, **3o**). It is worthy to note that 1-alkoxyphenyl-2-one and 1-(4-Methoxyphenyl)-alkyl-2-one also reacted smoothly and provided corresponding heterocyclic products in good yields (Table 5.2, **3q** and **3p**).

On the basis of the results obtained above and previous reports¹¹, a plausible mechanism of this reaction is illustrated in Figure 5.3. The reaction may undergo the following steps. The first step involves a coupling of the substrates **1** and **2** to produce the imine **4** with the elimination of water. The imine **4** is then equilibrates to enamine **5**. A one-electron oxidation of intermediate **5** by copper(II) catalyst leads to nitrenium ion **7** by hydride abstraction with oxidation. Finally, intermediate **7** undergoes intra-molecular nucleophilic addition to give intermediate **8**, and the subsequent proton elimination occurs to afford product **3**.

Figure 5.3 Plausible mechanism.

5.3 Conclusion

In summary, we have developed a method for the aerobic oxidative synthesis of imidazo[1,2-a]pyridines from aryloxyacetophenone and 2-aminopyridines. The method was proved to be mild, efficient, operational simple and using a widely available and cheap catalyst CuI.

5.4 Experimental Section

General Methods

All commercially available reagents for the catalytic reaction were used as received: toluene, 1,2-dichloroethane were obtained from Sigma-Aldrich. CuI were obtained from Strem Chemicals Inc. Amines was purchased from Alfa Aesar. Thin-layer chromatography (TLC) was conducted with Merck 60 F254 pre-coated silica *gel* plate (0.2 mm thickness) and visualized with UV and potassium permanganate staining. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. ^1H NMR spectra were performed on a Bruker 400 NMR spectrometer and are reported in ppm downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d*. Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a 400 (100 MHz) or ECA-400 (100 MHz) spectrometer and are reported in ppm using CDCl_3 as an internal standard. IR spectra were recorded as thin films on NaCl plates on a Bio-Rad FTS 165 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectral analysis (HRMS) was performed on Waters Q-Tof Premier Mass Spectrometer.

General Procedure for the Synthesis of Substrates

2-Aryloxy-1-acetophenones were prepared from the corresponding phenols and 2-bromoacetophenones according to the reported method.¹³

Representative Procedure: A round bottom flask equipped with a reflux condenser was charged with 2-bromoacetophenone (1.99 g, 10 mmol), phenol (1.13 g, 12 mmol), potassium carbonate (2.07 g, 15 mmol), and acetone (50 mL). The resulting suspension was heated to reflux for 5 h under nitrogen. After cooling down, the mixture was filtered through Celite and concentrated in vacuo. The obtained solid was crystallized from ethanol to give 1.42 g of 2-phenyloxy-acetophenone as a white solid (67%). ¹H NMR (400 MHz, CDCl₃): δ = 8.03 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.28-7.34 (m, 2H), 6.97-7.03 (m, 3H), 5.30 (s, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 194.6, 158.0, 134.6, 133.9, 129.6, 128.9, 128.2, 121.7, 114.8, 70.8.

Prepared by using the representative procedure, white amorphous solid, yield = 60%. ¹H NMR (400 MHz, CDCl₃): δ = 7.60 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.25-7.34 (m, 2H), 7.17-7.20 (dd, *J* = 2.8 Hz, *J* = 8.4 Hz, 1H), 6.95-7.03 (m, 3H), 5.30 (s, 2H), 3.89 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 194.4, 160.0, 129.8, 129.7, 129.6, 121.7, 120.6, 120.4, 115.3, 114.8, 112.4, 70.9, 55.5.

¹³ Nichols, J. M.; Bishop, L. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2010**, 132, 12554-12555.

¹⁴ Mathivanan, N.; Johnston, L. J.; Wayner, D.D.M. *J. Phys. Chem.*, **1995**, 99, 8190-8195.

Prepared by using the representative procedure, white solid, yield = 69%. ¹H NMR (400 MHz, CDCl₃): δ = 8.01-8.04 (dd, *J* = 2.0 Hz, *J* = 7.2 Hz, 2H), 6.93-6.98 (m, 4H), 6.85 (d, *J* = 3.6 Hz, 2H), 5.29 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 193.1, 164.0, 149.8, 147.7, 130.5, 127.7, 122.3, 120.8, 114.7, 114.0, 112.2, 72.0, 55.9, 55.5.

¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.24 (s, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 194.0, 157.2, 134.4, 134.1, 132.4, 128.9, 128.1, 116.7, 113.9, 70.9.

White solid. ¹H NMR (400 MHz, CDCl₃): δ = 7.95-7.97 (dd, *J* = 2.8 Hz, *J* = 7.2 Hz, 2H), 7.47-7.61 (m, 5H), 6.69-6.71 (dd, *J* = 2.0 Hz, *J* = 6.8 Hz, 2H), 5.24 (s, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 194.0, 158.0, 138.4, 134.4, 134.1, 128.9, 128.1, 117.2, 84.0, 70.7.

¹⁵ Thomas, K. K.; Bokadia, M. M. *J. Indian. Chem. Soc.* **1968**, 45, 265-267.

¹⁶ Leadbeater, N.E.; Schmink, J.R. *Tetrahedron*, **2007**, 63, 6764-6773.

¹⁷ Palmer, M.V. *J. Chem. Soc. B: Phy. Org.Chem.*, **1968**, 742.

2-Phenyloxy-3'-fluoroacetophenone¹⁸

White solid. ¹H NMR (400 MHz, CDCl₃): δ = 8.02-8.06 (m, 2H), 7.26-7.30 (dd, J = 7.6 Hz, J = 8.8 Hz, 2H), 7.13-7.17 (m, 2H), 6.92-7.00 (m, 3H), 5.20 (s, 3H).

2-(4-methoxyphenyl)oxy-2',5'-dimethoxyacetophenone

Prepared by using the representative procedure, yellow solid, yield = 76%. ¹H NMR (400 MHz, CDCl₃): δ = 7.45 (d, J = 3.2 Hz, 1H), 7.07-7.11 (dd, J = 3.6 Hz, J = 9.2 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 9.2 Hz, 2H), 6.82 (d, J = 9.6 Hz, 2H), 5.19 (s, 2H), 3.90 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 195.4, 154.2, 153.9, 153.8, 152.6, 125.1, 121.7, 115.9, 114.6, 113.8, 113.1, 75.2, 56.1, 55.9, 55.7. HR-MS (ESI): Calculated for C₁₇H₁₈O₅Na: [M+Na]⁺ 325.1052. Found: m/z 325.1052. FTIR (NaCl, cm⁻¹): 3053.3, 2988.0, 1689.0, 1500.1, 1420.5, 1265.3, 1220.9, 1169.2, 1056.3, 891.0, 766.0, 742.6.

1-(4-Methoxyphenyl)-5-methyl-hexan-2-one¹⁸

¹H NMR (400 MHz, CDCl₃): δ = 6.85 (s, 4H), 4.52 (s, 2H), 3.78 (s, 3H), 2.60 (t, J = 7.6 Hz,

¹⁸ Huang, K.; Wang, H.; Stepanenko, V.; De Jesus, M.; Torruellas, C.; Correa, W.; Ortiz-Marciales, M. *J. Org. Chem.* **2011**, 76, 1883-1886.

2H), 1.52-1.57 (m, 3H), 0.91 (d, $J = 6.4$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 208.4$, 154.5, 152.1, 115.6, 114.8, 73.6, 55.7, 37.1, 32.0, 27.7, 22.3.

2-methoxyacetophenone¹⁹

^1H NMR (400 MHz, CDCl_3): $\delta = 7.93$ (d, $J = 7.2$ Hz, 2H), 7.59 (t, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 4.71 (s, 2H), 3.51 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 196.2$, 134.8, 133.6, 128.7, 127.8, 75.3, 59.4.

General Procedure for the Synthesis of 3-phenoxy-2-phenylimidazo[1,2-a]pyridine

An oven dried vial was charged with CuI (3.8 mg, 0.0199 mmol, 10 mmol%), 2-aminopyridine **1a** (0.6 mmol), ketone **2a** (0.2 mmol) and dry 1,2-dichloroethane (0.8 mL). The vial was then sealed under an oxygen atmosphere, and the reaction was heated to 100 °C with stirring for 12 h. After cooling down, the mixture was diluted with ethyl acetate, filtered and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated to give the crude product, which was purified through a flash column chromatography (eluent: 10 % to 25 % ethyl acetate in hexane solution) to afford **3a** (38.2 mg, 0.176 mmol, 88% yield) as a white solid.

¹⁹ Katritzky, A. R.; Xie, L.; Serdyuk, L. *J. Org. Chem.* **1996**, 61, 7564-7570.

Characterization Data for the α -ketoamides

3-Phenoxy-2-phenylimidazo[1,2-a]pyridine:

This compound was prepared by the General Procedure described above and was obtained as a white solid, mp: 145-146 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.07 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 6.8 Hz, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.28-7.35 (m, 3H), 7.20 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 6.97 (d, J = 8.0 Hz, 2H), 6.77 (t, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 156.1, 139.9, 132.5, 131.1, 130.2, 128.7, 127.8, 126.5, 124.4, 123.7, 121.6, 117.9, 115.0, 112.3. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1647.2, 1495.6, 1421.5, 1390.1, 1362.2, 1265.3, 1201.7, 895.0, 738.7, 706.0. HR-MS (ESI): m/z calculated for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 287.1184; found 287.1184.

3-Phenoxy-2-(4-methoxyphenyl)imidazo[1,2-a]pyridine

White solid, mp: 145-147 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.99-8.01 (m, 2H), 7.71-7.74 (dt, J = 1.2 Hz, J = 6.8 Hz, 1H), 7.61-7.64 (dt, J = 1.2 Hz, J = 9.2 Hz, 1H), 7.28-7.33 (m, 2H), 7.09-7.19 (m, 2H), 6.93-6.97 (m, 4H), 6.72-6.75 (td, J = 6.8 Hz, J = 0.8 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 159.3, 156.2, 139.8, 131.2, 130.2, 129.3, 127.8, 125.2, 124.1, 123.6, 121.5, 117.6, 115.0, 114.1, 112.1, 55.2. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1707.0, 1568.1, 1506.4, 1421.5, 1359.8, 1265.3, 1201.7, 1032.0, 895.0, 837.1, 738.7, 706.0.

HR-MS (ESI): m/z calculated for $C_{20}H_{16}N_2O_2$ $[M+H]^+$: 317.1290; found 317.1188.

3-Phenoxy-2-(4-fluorophenyl)imidazo[1,2-a]pyridine

White solid, mp: 114-115 °C. 1H NMR (400 MHz, $CDCl_3$): δ = 8.02-8.05 (m, 2H), 7.74-7.76 (dt, J = 6.8 Hz, J = 1.2 Hz, 1H), 7.62-7.64 (dt, J = 9.2 Hz, J = 1.2 Hz, 1H), 7.28-7.35 (m, 2H), 7.18-7.22 (qd, J = 6.8 Hz, J = 1.2 Hz, 1H), 7.07-7.15 (m, 3H), 6.95-6.97 (m, 2H), 6.75-6.79 (td, J = 6.8 Hz, J = 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4 (J = 246 Hz), 156.0, 139.9, 130.3 (J = 16 Hz), 128.8, 128.7, 128.2 (J = 8 Hz), 124.4, 123.8, 121.6, 117.8, 115.6 (J = 21 Hz), 115.0, 112.4. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1574.2, 1504.5, 1489.1, 1421.5, 1392.6, 1359.8, 1265.3, 1201.7, 1159.2, 895.0, 842.5, 738.7, 704.5. HR-MS (ESI): m/z calculated for $C_{19}H_{13}FN_2O$ $[M+H]^+$: 305.1090; found 305.1088.

3-(4-bromophenoxy)-2-phenylimidazo[1,2-a]pyridine

Pink oil. 1H NMR (400 MHz, $CDCl_3$): δ = 7.98-8.00 (m, 2H), 7.69 (d, J = 6.8 Hz, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.35-7.40 (m, 4H), 7.25-7.29 (m, 1H), 7.16-7.20 (m, 1H), 6.81-6.84 (m, 2H), 6.74-6.78 (td, J = 0.8 Hz, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 140.0, 133.1, 132.2, 131.3, 128.7, 127.9, 126.5, 124.5, 121.4, 118.0, 116.8, 116.2, 112.5. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1481.3, 1421.5, 1362.6, 1265.3, 1201.7, 1159.2, 895.0,

738.7, 706.2. HR-MS (ESI): m/z calculated for $C_{19}H_{13}BrN_2O$ $[M+H]^+$: 365.0290, 367.0271; found 365.0288, 368.0302.

3-(4-Iodophenoxy)-2-phenylimidazo[1,2-a]pyridine

White solid, mp: 138-140 °C. 1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 6.8 Hz, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.56-7.58 (dd, J = 2.4 Hz, J = 6.8 Hz, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.25-7.29 (dd, J = 7.6 Hz, J = 10.8 Hz, 2H), 7.16-7.20 (m, 1H), 6.70-6.77 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 139.1, 132.2, 128.9, 128.7, 127.9, 127.2, 126.5, 124.5, 121.4, 118.0, 117.3, 112.5, 86.5. FTIR (NaCl, cm^{-1}): 3942.5, 3689.8, 3053.3, 2985.8, 2684.9, 1684.2, 1645.2, 1577.8, 1562.3, 1506.4, 1479.4, 1433.1, 1421.5, 1390.7, 1363.7, 1265.3, 1203.6, 1161.2, 1149.6, 1004.9, 895.0, 823.6, 752.2, 727.2, 706.0. HR-MS (ESI): m/z calculated for $C_{19}H_{13}IN_2O$ $[M+H]^+$: 413.0151; found 413.0153.

3-Phenoxy-2-phenyl-7-cyanoimidazo[1,2-a]pyridine

White solid, mp: 204-206 °C. 1H NMR (400 MHz, $CDCl_3$): δ = 7.98-8.03 (m, 3H), 7.78-7.80 (dd, J = 1.2 Hz, J = 7.2 Hz, 1H), 7.29-7.41 (m, 5H), 7.12 (t, J = 7.2 Hz, 1H), 6.90-6.92 (m, 2H), 6.86-6.88 (dd, J = 1.6 Hz, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 137.4, 135.0, 131.7, 131.4, 130.4, 128.9, 128.7, 126.8, 124.3, 124.0, 122.2, 117.7, 115.0,

112.6, 106.7. FTIR (NaCl, cm^{-1}): 3053.3, 3009.1, 2304.9, 2227.8, 1556.6, 1485.2, 1421.5, 1361.7, 1265.3, 1203.6, 1159.2, 895.0, 746.5, 704.0. HR-MS (ESI): m/z calculated for $\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 312.1137; found 312.1138.

3-Phenoxy-2-phenyl-7-methylimidazo[1,2-a]pyridine

White solid, mp: 158-160 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.03-8.06 (m, 2H), 7.63 (d, J = 6.8 Hz, 1H), 7.26-7.41 (m, 6H), 7.09-7.13 (t, J = 7.6 Hz, 1H), 6.96-6.98 (m, 2H), 6.58-6.60 (dd, J = 1.2 Hz, J = 6.8 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 156.3, 140.4, 135.2, 132.7, 130.7, 130.2, 128.9, 128.6, 127.5, 126.4, 123.6, 120.9, 116.2, 115.0, 114.9, 21.4. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 2924.1, 1643.4, 1583.6, 1568.1, 1489.1, 1446.6, 1421.5, 1394.5, 1363.7, 1265.3, 1201.7, 1159.2, 1072.4, 1026.1, 895.0, 731.0, 704.0. HR-MS (ESI): m/z calculated for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 301.1341; found 301.1345.

3-Phenoxy-2-phenyl-imidazo[1,2-a]pyridine-7-carboxylic acid methyl ester

White solid, mp: 132-134 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.35-8.36 (dd, J = 0.8 Hz, J = 1.6 Hz, 1H), 8.03-8.05 (m, 2H), 7.73-7.75 (dd, J = 0.8 Hz, J = 7.2 Hz, 1H), 7.25-7.40 (m, 6H), 7.08-7.12 (td, J = 8.0 Hz, J = 0.8 Hz, 1H), 6.90-6.93 (m, 2H), 3.94 (s, 3H). ^{13}C NMR

(100 MHz, CDCl_3): δ = 165.7, 155.8, 138.6, 134.2, 132.0, 131.3, 130.3, 128.7, 128.3, 126.7, 125.6, 124.0, 121.1, 120.7, 115.0, 111.7, 52.6. FTIR (NaCl, cm^{-1}): 3053.3, 3004.5, 2304.9, 1718.6, 1556.6, 1487.1, 1404.2, 1367.5, 1334.7, 1265.3, 1232.5, 1203.6, 1159.2, 1091.7, 895.0, 738.7, 704.0. HR-MS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 345.1239; found 345.1238.

3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-imidazo[1,2-a]pyridine

White solid, mp: 121-122 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.02-8.04 (dd, J = 2.0 Hz, J = 6.8 Hz, 2H), 7.79 (d, J = 6.8 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.14-7.18 (m, 1H), 7.05-7.07 (m, 2H), 6.93-6.95 (dd, J = 2.0 Hz, J = 6.8 Hz, 2H), 6.70-6.76 (m, 2H), 6.55 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 159.3, 149.0, 145.1, 139.7, 131.3, 129.7, 127.8, 125.3, 124.2, 124.1, 121.5, 121.1, 117.5, 114.7, 114.1, 112.8, 112.1, 56.2, 55.2. FTIR (NaCl, cm^{-1}): 3053.3, 2986.8, 1701.2, 1614.4, 1568.1, 1498.7, 1456.3, 1421.5, 1394.5, 1361.7, 1265.3, 1251.8, 1199.7, 1174.7, 1114.9, 1030.0, 895.0, 837.2, 738.7, 704.0. HR-MS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 347.1396; found 347.1393.

3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-7-methylimidazo[1,2-a]pyridine

White solid, mp: 154-156 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.95-7.98 (dd, J = 2.0 Hz, J = 6.8 Hz, 2H), 7.63 (d, J = 7.2 Hz, 1H), 7.31 (d, J = 1.2 Hz, 1H), 7.01-7.05 (m, 2H), 6.87-6.90 (m, 2H), 6.66-6.70 (m, 1H), 6.50-6.54 (m, 2H), 4.03 (s, 3H), 3.78 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 159.1, 149.0, 145.3, 140.2, 135.0, 130.7, 129.3, 127.7, 125.5, 124.1, 121.1, 120.8, 115.9, 114.7, 114.6, 114.0, 112.7, 56.2, 55.2, 21.4. FTIR (NaCl, cm^{-1}): 3053.3, 2983.9, 2839.2, 1695.4, 1643.4, 1614.4, 1570.1, 1498.7, 1456.3, 1440.8, 1421.5, 1392.6, 1361.7, 1296.2, 1265.3, 1249.9, 1199.7, 1170.8, 1114.9, 1030.0, 895.0, 837.1, 738.7, 704.0. HR-MS (ESI): m/z calculated for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 361.1552; found 361.1553.

3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-6-fluorolimidazo[1,2-a]pyridine

White solid, mp: 134-136 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.96-7.99 (m, 2H), 7.70-7.72 (m, 1H), 7.51-7.55 (m, 1H), 7.01-7.06 (m, 3H), 6.89-6.93 (m, 2H), 6.69-6.73 (m, 1H), 6.53 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ = 159.4, 155.3 (J = 236 Hz), 149.1, 144.8, 137.2, 133.0, 131.1, 127.8, 125.0, 124.5, 121.1, 118.1 (J = 9 Hz), 116.0 (J = 26 Hz), 114.9, 114.1, 112.9, 108.2 (J = 41 Hz). FTIR (NaCl, cm^{-1}): 3053.3, 2839.2, 2304.9, 1651.1, 1564.3, 1535.3, 1500.6, 1421.5, 1421.5, 1369.5, 1328.9, 1298.1, 1265.3, 1251.8, 1209.4, 1180.4, 1116.8, 1208.1, 839.0, 810.1, 746.5, 704.0. HR-MS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{17}\text{FN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 365.1301; found 365.1302.

3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-6-chlorolimidazo[1,2-a]pyridine

White solid, mp: 130-132 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.96-7.98 (dd, J = 2.0 Hz, J = 6.8 Hz, 2H), 7.82-7.83 (dd, J = 0.8 Hz, J = 2.0 Hz, 1H), 7.49-7.52 (dd, J = 0.8 Hz, J = 9.6 Hz, 1H), 7.05-7.10 (m, 3H), 6.90-6.92 (dd, J = 2.0 Hz, J = 6.8 Hz, 2H), 6.69-6.74 (m, 1H), 6.52 (d, J = 8.0 Hz, 1H), 4.04 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ = 159.5, 149.1, 144.9, 138.0, 132.5, 130.1, 127.9, 125.5, 124.8, 124.5, 121.2, 120.5, 119.4, 117.9, 114.8, 114.2, 112.9, 56.2, 55.3. FTIR (NaCl, cm^{-1}): 3015.6, 2839.2, 1498.7, 1419.6, 1392.6, 1325.1, 1298.1, 1265.3, 1251.8, 1199.7, 1174.7, 1116.7, 1028.1, 895.0, 837.1, 798.5, 738.7, 704.0. HR-MS (ESI): m/z calculated for $\text{C}_{21}\text{H}_{17}\text{ClN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 381.1006; found 381.1003.

3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-6-bromolimidazo[1,2-a]pyridine

White solid, mp: 159-161 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.99-8.01 (m, 2H), 7.86-7.87 (dd, J = 0.8 Hz, J = 1.6 Hz, 1H), 7.49-7.51 (dd, J = 0.8 Hz, J = 9.6 Hz, 1H), 7.20-7.38 (m, 6H), 7.09-7.13 (m, 1H), 6.92-6.95 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ = 155.8, 138.2, 132.2, 132.0, 130.3, 130.1, 128.7, 128.1, 127.9, 126.5, 124.0, 121.6, 118.6, 115.0, 107.3. FTIR (NaCl, cm^{-1}): 3053.3, 3012.2, 1596.3, 1526.3, 1489.1, 1421.5, 1401.3, 1325.1,

1265.3, 1199.7, 1159.2, 895.0, 798.5, 738.7, 704.0. HR-MS (ESI): m/z calculated for $C_{19}H_{13}BrN_2O$ $[M+H]^+$: 367.0251; found 367.0255.

3-(2-Methoxyphenoxy)-2-(4-methoxyphenyl)-imidazo[2,1-a]isoquinoline

White solid, mp: 108-110 °C. 1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.61-7.67 (m, 3H), 7.54 (t, J = 7.2 Hz, 1H), 6.92-7.07 (m, 5H), 6.68-6.72 (m, 1H), 6.58 (d, J = 8.0 Hz, 1H), 4.05 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 149.0, 145.7, 129.3, 128.2, 128.1, 127.6, 127.1, 124.1, 122.9, 121.2, 119.1, 114.8, 114.1, 112.8, 112.7, 56.3, 55.2. FTIR (NaCl, cm^{-1}): 3005.6, 2839.2, 1583.6, 1578.6, 1498.7, 1454.3, 1419.6, 1377.2, 1265.3, 1251.8, 1199.7, 1174.7, 1026.1, 895.0, 792.7, 738.7, 704.0. HR-MS (ESI): m/z calculated for $C_{25}H_{20}N_2O_3$ $[M+H]^+$: 397.1552; found 397.1549.

3-Methoxy-2-phenyl-imidazo[1,2-a]pyridine²⁰

Colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, J = 8.0 Hz, 2H), 7.98 (d, J = 6.8 Hz, 1H), 7.56 (d, J = 9.2 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.12-7.16

²⁰ Alcaide, B.; Perez-Ossorio, R.; Plumet, J.; Sierra, M.A. *Tetrahedron Lett.*, **1986**, 27, 1627-1630.

(m, 1H), 6.83 (t, $J = 6.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 139.0, 133.4, 128.7, 127.4, 126.4, 123.7, 121.3, 117.9, 112.0, 61.1$. FTIR (NaCl, cm^{-1}): 2985.8, 1707.0, 1587.4, 1568.1, 1501.2, 1421.6, 1386.8, 1359.8, 1265.3, 1207.8, 968.3, 896.0, 748.4, 706.0. HR-MS (ESI): m/z calculated for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 225.1028; found 225.1029.

3-(4-Methoxyphenoxy)-2-isopentyl-imidazo[1,2-a]pyridine

Colourless oil. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.69$ (d, $J = 6.8$ Hz, 1H), 7.50 (d, $J = 9.2$ Hz, 1H), 7.06-7.10 (m, 1H), 6.80 (s, 4H), 6.67-6.71 (m, 1H), 3.75 (s, 3H), 2.66 (t, $J = 8.0$ Hz, 2H), 1.53-1.63 (m, 3H), 0.86 (d, $J = 6.4$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3): $\delta = 155.6, 151.1, 139.4, 133.6, 123.2, 121.3, 117.4, 115.7, 114.9, 111.7, 55.7, 37.9, 27.9, 24.6, 22.4$. FTIR (NaCl, cm^{-1}): 3053.3, 2985.8, 1562.2, 1502.6, 1421.5, 1265.3, 1198.05, 1031.9, 895.0, 831.2, 738.7, 706.0. HR-MS (ESI): m/z calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 311.1760; found 311.1756.

Figure 4.2 ORTEP drawing of **3a** with thermal ellipsoids at 50% probability.

The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P 1 21/c 1$, with $Z = 2$ for the formula unit, $C_{19}H_{14}N_2O$.

Crystal data for **3a**:

Chemical formula	$C_{19}H_{14}N_2O$	
Formula weight	286.32	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal size	0.240 x 0.260 x 0.400 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	$P 1 21/c 1$	
Unit cell dimensions	$a = 5.8996(5)$ Å	$\alpha = 90^\circ$
	$b = 8.2125(7)$ Å	$\beta = 92.622(3)^\circ$
	$c = 14.9493(14)$ Å	$\gamma = 90^\circ$
Volume	$723.54(11)$ Å ³	
Z	2	
Density (calculated)	1.314 g/cm ³	
Absorption coefficient	0.083 mm ⁻¹	
$F(000)$	300	

List of Publications

1. "Chemical Conversion of β -O-4 Lignin Linkage Models through Cu-Catalyzed Aerobic Amide Bond Formation" Jian Zhang, Yu Liu, Shunsuke Chiba*, and Teck-Peng Loh*, *Chem. Commun.* 2013, advance article. DOI: 10.1039/C3CC46912C.
2. "Ruthenium- and Rhodium-catalyzed Cross-Coupling Reaction of Acrylamides with Alkenes: Efficient Access to (Z,E)-Dienamides" Jian Zhang and Teck-Peng Loh*, *Chem. Commun.*, **2012**, 48, 11232-11234.
3. "Direct Linear Imide Synthesis from Lactams by Dehydrogenation" Jian Zhang and Soon Hyeok Hong*, *Org. Lett.*, **2012**, 14, 4646-4649.
4. "Synthesis of Cyclic Imides from Simple Diols" Jian Zhang, Senthilkumar Muthaiah, Subhash Chandra Ghosh and Soon Hyeok Hong*, *Angew. Chem. Int. Ed.* **2010**, 49, 6391-6395.

Conferences

- Jian Zhang, and Soon Hyeok Hong, "Synthesis of Cyclic Imides from Simple Diols and Amines", PERCH-CIC Congress VII, Thailand, May, 2011.
- Jian Zhang, and Soon Hyeok Hong, "Synthesis of Cyclic Imides from Simple Diols", 6th Asian-European Symposium, Singapore, June, 2010.