

**NANYANG  
TECHNOLOGICAL  
UNIVERSITY**

**TRANSITION METAL-CATALYZED RADICAL  
FUNCTIONALIZATION OF ALKENES WITH  
ALCOHOLS AND FORMAMIDE DERIVATIVES**

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**SCHOOL OF PHYSICAL AND MATHEMATICAL  
SCIENCES**

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FUNCTIONALIZATION OF ALKENES WITH  
ALCOHOLS AND FORMAMIDE DERIVATIVES**

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A thesis submitted to the Nanyang Technological University  
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Doctor of Philosophy

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## LIST OF ABBREVIATIONS

$\delta$	chemical shift
$^{\circ}\text{C}$	degree centigrade
Ac	acetyl
acac	acetylacetonate
$\text{Ac}_2\text{O}$	acetic anhydride
AcOH	acetic acid
1-Ad	1-adamantane
Ar	aryl
atm	atmosphere
Bn	benzyl
BnBr	benzyl bromide
bs	broad singlet
CFL	compact fluorescent lamp
cod	1,5-cyclooctadiene
Cy	cyclohexane
d	doublet
DABCO	(1,4-diazabicyclo[2.2.2]octane)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
ddt	doublet of doublets of triplets
DIAD	diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
dr	diastereomeric ratio

dt	doublet of triplets
DTBP	di- <i>tert</i> -butyl peroxide
ESI	electrospray ionization
Et	ethyl
Et <sub>2</sub> O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron-withdrawing group
h	hour
HIR	hypervalent iodine reagent
HIV	human immunodeficiency virus
HRMS	high resolution mass spectrometry
<i>hν</i>	photoirradiation
<i>Hz</i>	Hertz
IAd	<i>N,N'</i> -Bis(adamantyl)imidazole-2-ylidene
<i>i</i> Pr	isopropyl
<i>i</i> PrOH	isopropanol
<i>J</i>	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LED	light-emitting diode
MHz	megahertz
<i>n</i> Pr	n-propyl
<i>n</i> Bu	n-butyl
<i>n</i> BuBr	n-butyl bromide
<i>n</i> Hex	n-hexane
NHPI	<i>N</i> -hydroxyphthalimide

pc	phthalocyanine
TMHD	(2,2,6,6-tetramethyl-3,5-heptanedionate)
m	multiplet
MAP	mitogen-activated protein
MeNO <sub>2</sub>	nitromethane
<i>m</i> -NO <sub>2</sub> BzOH	3-nitrobenzoic acid
m.p.	melting point
NMR	nuclear magnetic resonance
NHC	N-heterocyclic carbene
OAc	acetate
OTf	triflate
PCy <sub>3</sub>	tricyclohexylphosphine
PhCF <sub>3</sub>	trifluoromethylbenzene
PhCl	chlorobenzene
Phe	phenylalanine
PIDA	(diacetoxyiodo)benzene
PivOH	pivalic acid
PINO	phthalimide N-Oxyl Radical
PPh <sub>3</sub>	triphenylphosphine
PRE	persistent radical effect
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
Py	pyridine
q	quartet
( <i>rac</i> )-BINAP	(±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
rt	room temperature
rr	regioisomeric ratio

s	singlet
SET	single-electron-transfer
SOMO	singly occupied molecular orbital
t	triplet
td	triplet of doublets
TFAcac	trifluoroacetylacetonate
<i>t</i> -AmOH	2-methyl-2-butyl alcohol
TBHP	<i>tert</i> -butyl hydroperoxide
TBPB	<i>tert</i> -butyl peroxybenzoate
<i>t</i> Bu	<i>tert</i> -butyl
TEA/NEt <sub>3</sub>	triethylamine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetate
THC	transfer hydrogenative coupling
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl

## SUMMARY

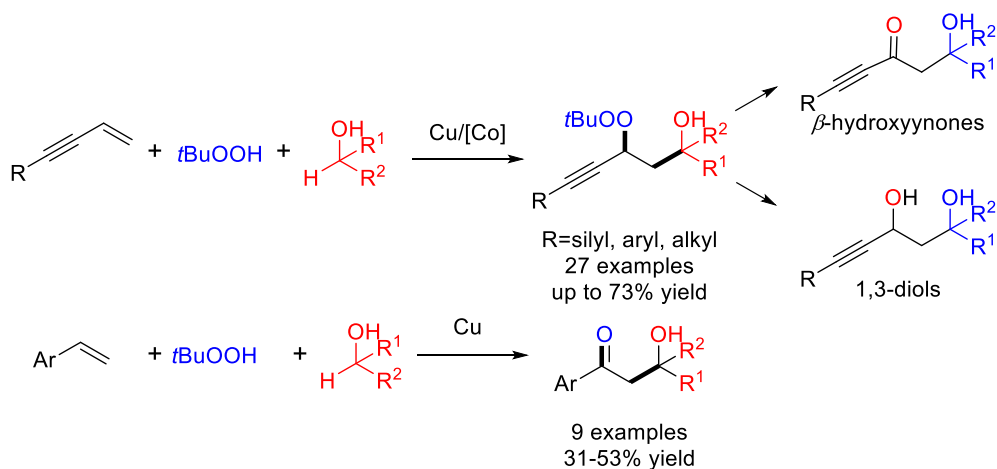
Alkene functionalization is an important class of reaction which builds up molecular complexity in a rapid and efficient manner on the ubiquitous chemical feedstock. In complementary to transition metal-mediated approach, radical-mediated carbofunctionalization of alkene has recently received commendable attention, which features the addition of carbon-centered radical to the alkene double bond, a strategy endowed by high propensity of carbon radical to add to unsaturated system as well as broad functional group tolerance.

This thesis describes the direct functionalization of alkenes with alcohols and formamide derivatives, which proceeds through the addition of radicals derived from respective coupling partner to the alkene acceptor. Following the generation of radical adduct, the latter could couple with an oxygen-centered radical to give carboxygenation product or undergo SET oxidation step. Thereof, the thus-formed carbocation intermediate could trap an oxygen nucleophile or undergo elimination process to restore the alkenyl functionality.

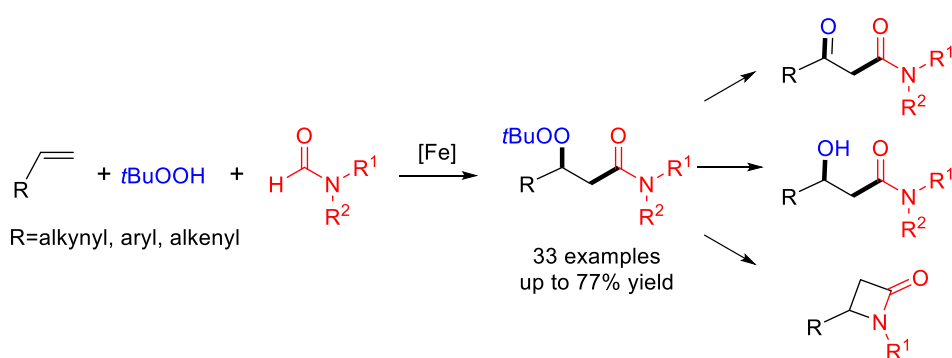
In Chapter 1, recent developments in radical-mediated intermolecular carboxygenation of alkene and the mechanistic details are discussed with highlights on the oxyarylation, oxycarbonylation and oxyalkylation reaction.

In Chapter 2, a novel copper- or cobalt- catalyzed oxyalkylation of 1,3-enynes and arylalkenes with alcohols was introduced. This methodology involves direct addition of  $\alpha$ -hydroxy radical to the C=C double bond, followed by coupling with TBHP to prepare  $\beta$ -peroxy alcohols. The peroxy chemical entity could be facilely transformed to hydroxyl or keto functional group. Remarkably,

this could allow easy access to propargylic 1,3-dioxygenated compounds which is otherwise difficult to achieve using the conventional aldol reaction.

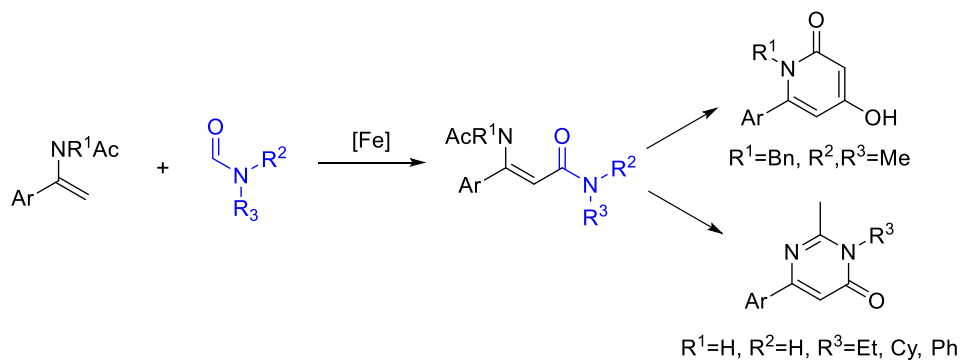


In Chapter 3, an iron-catalyzed three-component coupling of alkene, TBHP and formamides to prepare β-peroxy amides was described. Similarly, the addition of aminocarbonyl/carbamoyl radical to alkene and the ensuing peroxy radical trapping were postulated in the mechanistic pathway. Downstream chemical transformation has demonstrated the versatility of the β-peroxy amide product as synthetic precursor to access β-hydroxy amide, β-keto amide and β-lactam.



In Chapter 4, oxidative coupling of enamides with formamides was successfully realized to furnish *N*-acyl enamine amides through direct formyl C(sp<sup>2</sup>)-H functionalization of formamides. In contrary to the previous works in Chapter 2 and 3 that allow formation of difunctionalized product, the alkene double bond

is restored following the addition of aminocarbonyl radical. Appreciably, the *N*-acyl enamine amide products could undergo cyclodeamination and cyclodehydration to provide 4-hydroxy-2-pyridinones and pyrimidin-4-ones, correspondingly. These heterocyclic frameworks are ubiquitously found in natural products as well as biologically active compounds.



# *CHAPTER 1*

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## **GENERAL INTRODUCTION**

## 1.1 Difunctionalization of alkenes

Alkenes are abundant organic compounds and ubiquitous chemical feedstock, which often serve as building blocks to access chemical compounds of higher molecular complexity. Alkene difunctionalization offers a rapid and efficient entry to building up the structural complexity in a single step. Hence, many research efforts have been devoted to this area and it has advanced to an impactful one in contemporary organic synthesis.<sup>1</sup>

Remarkable progress has been demonstrated in transition metal-catalyzed oxidative difunctionalization of alkenes, which includes dioxygenation,<sup>2</sup> diamination,<sup>3</sup> and aminooxygenation<sup>4</sup> reactions (Scheme 1-1-a). In

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<sup>1</sup> a) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. b) Muniz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412. c) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. d) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. e) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. f) Christie, S. D. R.; Warrington, A. D. *Synthesis* **2008**, 1325.

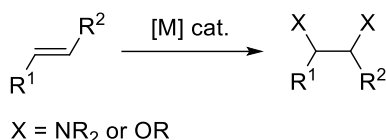
<sup>2</sup> a) Johnson, R.; Sharpless, K. B. *Catalytic Asymmetric Dihydroxylation-Discovery and Developmen*, in *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; John Wiley & Sons, Inc., Hoboken, NJ, USA. **2000**. b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. c) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. d) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076. e) Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846. f) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962. g) Wang, W.; Wang, F.; Shi, M. *Organometallics*, **2010**, *29*, 928. h) Bataille, C. J. R.; Donohoe, T. J. *Chem. Soc. Rev.* **2011**, *40*, 114. i) Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 17074.

<sup>3</sup> a) de Figueiredo, R. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190. b) Muñiz, K. Oxidation: C–N Bond Formation by Oxidation: Dinitrogen Addition to Double Bond (Diamino). In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H, Eds.; Elsevier: Amsterdam, 2012, Vol. 5; p 183–197. c) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi, Y. *Acc. Chem. Res.* **2014**, *47*, 3665. d) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590. e) Iglesias, A.; Perez, E. G.; Muniz, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8109. f) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muniz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. g) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688. h) Yuan, Y.-A.; Lu, D.-F.; Chen, Y.-R.; Xu, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 534.

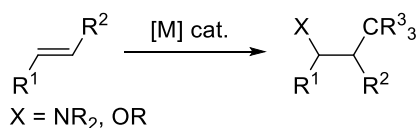
<sup>4</sup> a) Bruncko, M.; Sharpless, K. *Angew. Chem. Int. Ed.* **1997**, *36*, 1483. b) Muñiz, K. *Chem. Soc. Rev.* **2004**, *33*, 166. c) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868. d) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690. e) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. f) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737. g) Haro, T. de; Nevado, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 906. h) Kou, X.; Li, Y.; Wu, L.; Zhang, X.; Yang, G.; Zhang, W. *Org. Lett.* **2015**, *77*, 5566. i) Zhu, C.-L.; Lu, D.-F.; Sears, J. D.; Jia, Z.-X.; Xu, H. *Synthesis*, **2016**, *48*, 3031. j) Lu, D.-F.; Zhu, C. L.; Jia, Z. X.; Xu, H. *J. Am. Chem. Soc.* **2014**, *136*, 13186. k) Liu, G. S.; Zhang, Y. Q.; Yuan, Y. A.; Xu, H. *J. Am. Chem. Soc.* **2013**, *135*, 3343. l) Zhang, Y. Q.; Yuan, Y. A.; Liu, G. S. Xu, H. *Org. Lett.* **2013**, *15*, 3910.

comparison to the flourishing reports on difunctionalization reaction with simultaneous introduction of two heteroatom functionalities, transition metal-catalyzed approaches towards direct carboxygenation of alkenes are relatively lesser (Scheme 1-1-b).<sup>5</sup>

a) Dioxygenation/Diamination of Alkenes (many reports)



b) Carbofunctionalization of Alkenes (fewer reports)



Scheme 1-1: Schematic illustration on alkene difunctionalization

Complementarily, radical-mediated methods for this transformation have received commendable attentions from organic chemists, a strategy made viable by high propensity of radicals to react with unsaturated chemical systems as well as the wide functional group tolerance. In this chapter, the development in radical-mediated approaches towards intermolecular three-component alkene carboxygenation will be highlighted, categorized into oxyarylation, oxycarbonylation and oxyalkylation of alkenes.

## 1.2 Radical carboxygenation of alkenes

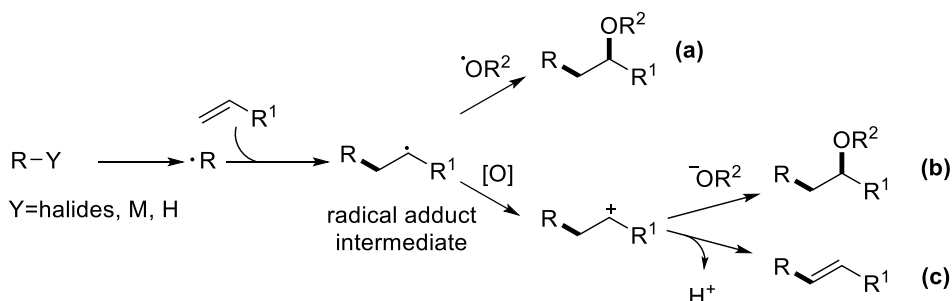
The iterative addition of radical species to unsaturated bond yielding a new radical center, which is susceptible to addition onto another unsaturated bond, illustrates the essence of polymerization, a discipline that is indivisible from radical chemistry. Hence, radical chemistry has traditionally been dominated by

<sup>5</sup> a) Liao, Z.; Yi, H.; Li, Z.; Fan, C.; Zhang, X.; Liu, J.; Deng, Z.; Lei, A. *Chem. Asian J.* **2015**, *10*, 96. b) Quinn, R. K.; Schmidt, V. A.; Alexanian, E. J. *Chem. Sci.* **2013**, *4*, 4030 and the references cited therein.

polymer chemist, which in turn, endows them with an abundant synthetic toolbox.

The development of organic radical chemistry could be traced back to over a hundred years ago. Over the past century, this field constantly revives and remains thriving, thanks to the immigration of researchers with different interests such as those from biology and material sciences. In the past several years, another renaissance of radical chemistry has been witnessed in the field of synthetic organic chemistry.<sup>6</sup>

In realizing multicomponent carbofunctionalization of alkene, radical-mediated methodologies are of high synthetic potentials in view of the high reactivity and propensity possessed by carbon-centered radical intermediates (such as alkyl radical, aryl radical, carbonyl radical) to react with alkene acceptors.<sup>7</sup>



Scheme 1-2: Schematic illustration on radical functionalization of alkenes

Generally, the radical could be generated from different precursors such as SET reduction of halides, SET oxidation of organometallic reagents or preferably

<sup>6</sup> a) Stephenson, C. R. J.; Studer, A.; Curran, D. P. *Beilstein J. Org. Chem.* **2013**, *9*, 2778 and the references cited therein.

<sup>7</sup> a) Giese, B. *Angew. Chem. Int. Ed.* **1983**, *22*, 753. b) Radicals in Synthesis I and II. In *Topics in Current Chemistry*; Gansäuer, A., Ed.; Springer: Berlin, 2006; Vol. 263-264. c) Tojino, M.; Ryu, I. Free-Radical-Mediated Multicomponent Coupling Reactions. In *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany; p 169–198. d) Togo, H. *Advanced Free Radical Reactions for Organic Synthesis*, 1st ed.; Elsevier, Amsterdam, Boston, 2004.

through direct C-H activation.<sup>8</sup> For carboxygenation reaction, the radical adduct intermediate then undergoes selective coupling with oxygen-based radical to give the titled product (Scheme 1-2-a). Alternatively, the radical adduct intermediate could undergo oxidation to form the corresponding carbocation. Thereof, trapping of oxygen nucleophile furnishes the oxyalkylated product (Scheme 1-2-b).

In contrary to the reductive addition of alkene resulting in difunctionalized product, the alkenyl functionality in the substrate could be restored if a judicious choice of elimination protocol is incorporated in the system, which enables the radical adduct intermediate to undergo single-electron oxidation/elimination steps (Scheme 1-2-c).

### 1.3 Oxyarylation of alkenes

#### 1.3.1 Oxyarylation of alkenes with aryl diazonium salts and TEMPO<sub>Na</sub>

Oxyarylation of alkene features the concomitant introduction of aryl or heteroaryl moieties and an oxygen functionality onto alkene double. The method most commonly employed is the Meerwein-type radical oxyarylation that capitalizes on the wealth of well-established aryl radical generation methods from arenediazonium salts, which is seminally reported by Sandmeyer over a century ago.<sup>9,10</sup>

In 2012, Studer's group reported an experimentally simple transition metal-free protocol which uses TEMPO<sub>Na</sub> and aryl diazonium salts as coupling partners

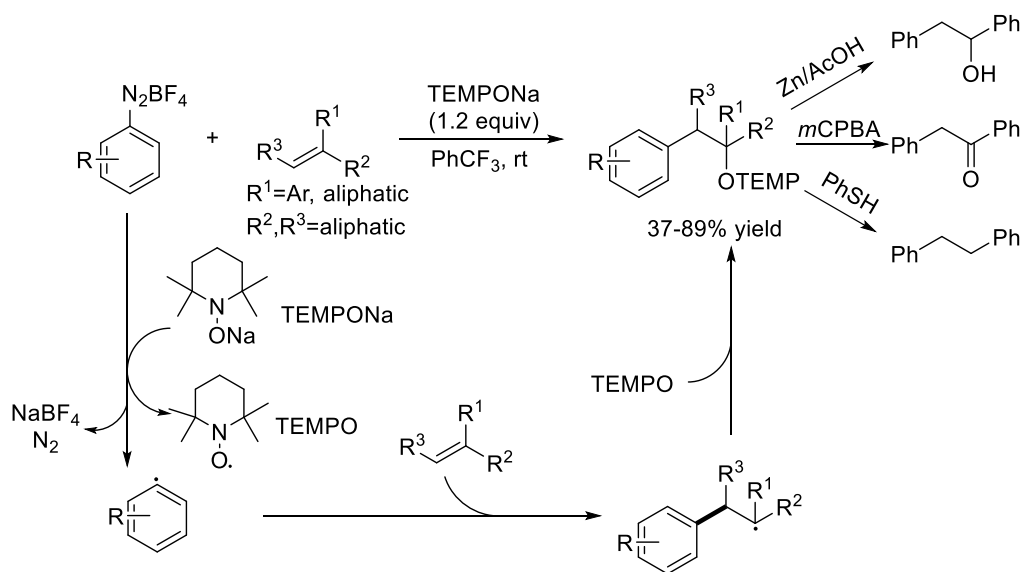
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<sup>8</sup> Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070.

<sup>9</sup> a) Sandmeyer, T. *Chem. Ber.* **1884**, *17*, 1633. b) Sandmeyer, T. *Chem. Ber.* **1884**, *17*, 2650. c) Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251.

<sup>10</sup> a) Meerwein, H.; Buchner, E.; van Emsterk, K. *J. Prakt. Chem.* **1939**, *152*, 237. b) Molinaro, C.; Mowat, J.; Gosselin, F.; O'Shea, P. D.; Marcoux, J.-F. Angelaud, R.; Davies, I. W. *J. Org. Chem. Soc.* **2007**, *72*, 1856.

to prepare oxyarylated alkenes (Scheme 1-3).<sup>11</sup> TEMPONa, which could be prepared conveniently by reduction of TEMPO with sodium, acts as mild SET agent to generate aryl radical from aryl diazonium salt and thus releases the TEMPO radical. Aryl radical will first add to alkene and the resulting radical adduct will couple selectively with TEMPO to give the related oxyarylation product. The persistent radical effect (PRE) underlies this selective cross-coupling reaction of two radicals.<sup>12</sup> In addition to arylalkenes, non-activated aliphatic alkenes including those bearing terminal bromide and epoxide groups provide the respective oxyarylation products albeit in slightly lower yields. Follow-up chemical manipulation such as reduction, oxidation as well as radical deoxygenation was feasible with the TEMPO-based alkoxyamines to afford the corresponding alcohol, ketone and bibenzyl compounds.



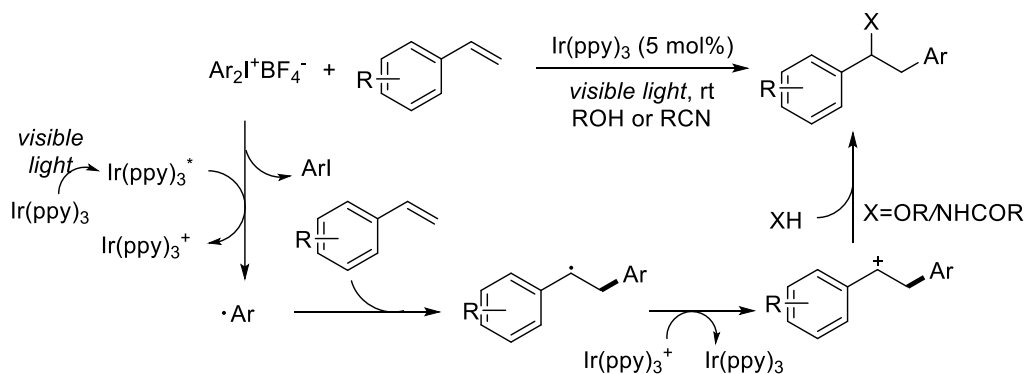
Scheme 1-3: TEMPONa-mediated oxyarylation of alkenes with aryldiazonium salts

<sup>11</sup> Hartmann, M.; Li, Y.; Studer, A. *J. Am. Chem. Soc.* **2012**, *134*, 16516.

<sup>12</sup> Reviews on PRE: a) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581. b) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1976**, *9*, 13. c) Studer, A. *Chem. Eur. J.* **2001**, *7*, 1159. d) Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267. e) Focsaneanu, K.-S.; Scaiano, J. C. *Helv. Chim. Acta* **2006**, *89*, 2473.

### 1.3.2 Oxyarylation of alkenes with photoredox catalysis

In 2013, Greaney *et al.* incorporated photoredox catalysis to bring about simultaneous arylation and C-O or C-N bond formation on vinylarenes, with diaryliodonium or aryldiazonium salts (Scheme 1-4).<sup>13</sup> The proposed mechanism delineates the initial reduction of iodonium salt by the photoexcited iridium(III) complex to generate the aryl radical. The latter then adds to the styrene and forms benzylic radical, which upon oxidation by cationic Ir(IV) complex yields the corresponding cation. Trapping of nucleophile (solvent) thus delivers the oxyarylated product. The intermediacy of benzylic radical is underpinned by radical-trapping experiment in which the reaction was completely shut down in the presence of TEMPO.



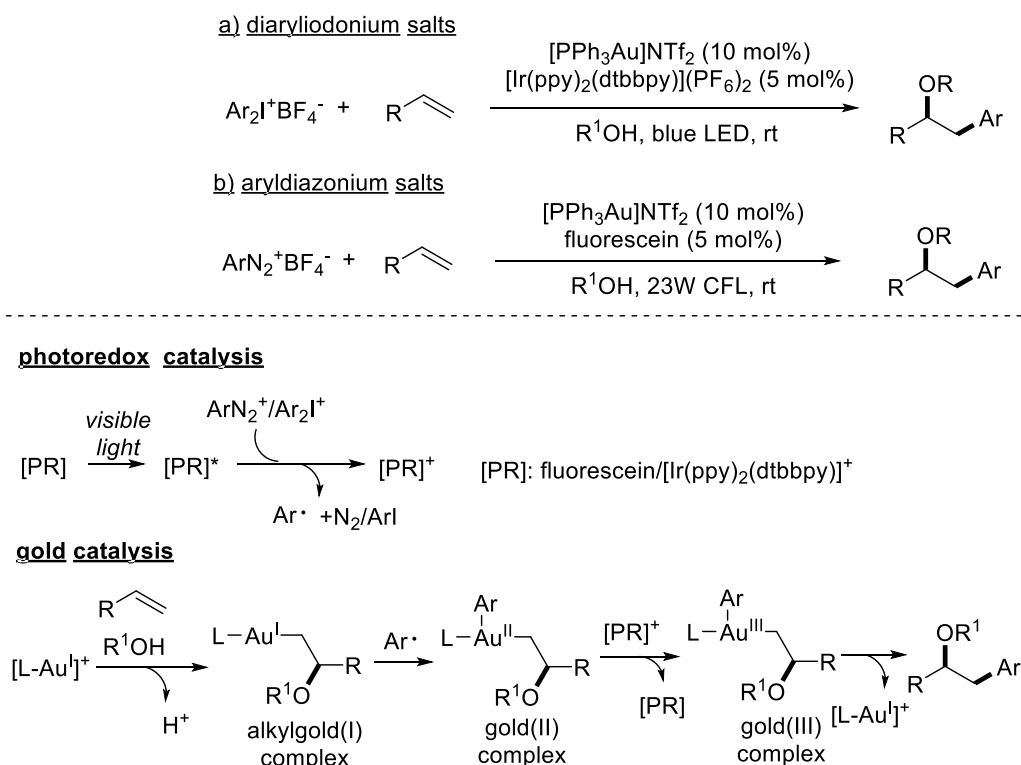
Scheme 1-4: Photoredox catalysis for oxyarylation of styrene derivatives

Glorius and co-workers, on the other hand, developed related work involving a dual gold and photoredox catalytic system to effect the selective intermolecular three-component oxyarylation (Scheme 1-5). Readily accessible diaryliodonium salts serve as compatible coupling partners with gold/iridium complex catalytic system (Scheme 1-5-a). Complementarily, aryldiazonium salts were also effective substrates when inexpensive organic dye, fluorescein is employed

<sup>13</sup> Fumagalli, G.; Boyd, S.; Greaney, M. F. *Org. Lett.* **2013**, *15*, 4398.

together with the gold catalyst (Scheme 1-5-b).<sup>14</sup> These two systems operate at mild conditions and could deliver the oxyarylated products even from non-activated aliphatic alkenes.

In the viewpoint of mechanism, the aryl radical is generated in the photoredox catalytic cycle while the gold catalyst facilitates the alkene activation and nucleophilic attack of the alcoholic solvent. SET by the visible light-excited photocatalyst to diazonium/iodonium salts generates the aryl radical with extrusion of nitrogen or aryl iodide. On the other hand, following alkene activation and trapping of alcohol nucleophile to form alkylgold(I) complex, addition of aryl radical gives the gold(II) complex bringing together the alkyl and aryl groups. SET by the oxidized photocatalyst, [PR]<sup>+</sup> yields the gold(III) complex and regenerates the photocatalyst, [PR]. Reductive elimination then yields the oxyarylation product and completes the gold(I) catalytic cycle.



Scheme 1-5: Dual gold and photoredox catalysis for alkene oxyarylation

<sup>14</sup> Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Adv. Synth. Catal.* **2014**, 356, 2794.

## 1.4 Oxycarbonylation of alkenes

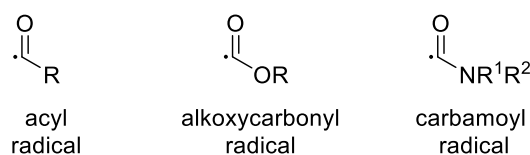


Figure 1-1: Carbonyl radicals

In addition to aryl group, introduction of carbonyl group is another important category of radical alkene carboxygenation reaction. Reactions of carbonyl radicals including acyl, alkoxy carbonyl, and carbamoyl radicals are known and they are regarded as valuable reaction intermediates given the efficient bestowment upon the resulting compounds with carbonyl-containing functional groups such as ketone, ester and amide groups (Figure 1-1).<sup>15,16,17</sup>

### 1.4.1 Oxycarbonylation of alkenes with aldehydes and molecular oxygen

Early in 1991, Iqbal's group reported on oxycarbonylation of electron-deficient alkenes with aldehydes and molecular oxygen to form  $\beta$ -hydroxy ketones.<sup>18</sup> However, only three examples of simple aliphatic aldehyde and two examples of electron-deficient alkenes were accommodated in this reaction (Scheme 1-6). Mechanism wise, the reaction is thought to be initiated by redox reaction of cobalt(II) catalyst and aldehyde which reveals the acyl radical and hydridocobalt(III) species. The Co(II) catalyst is re-generated following

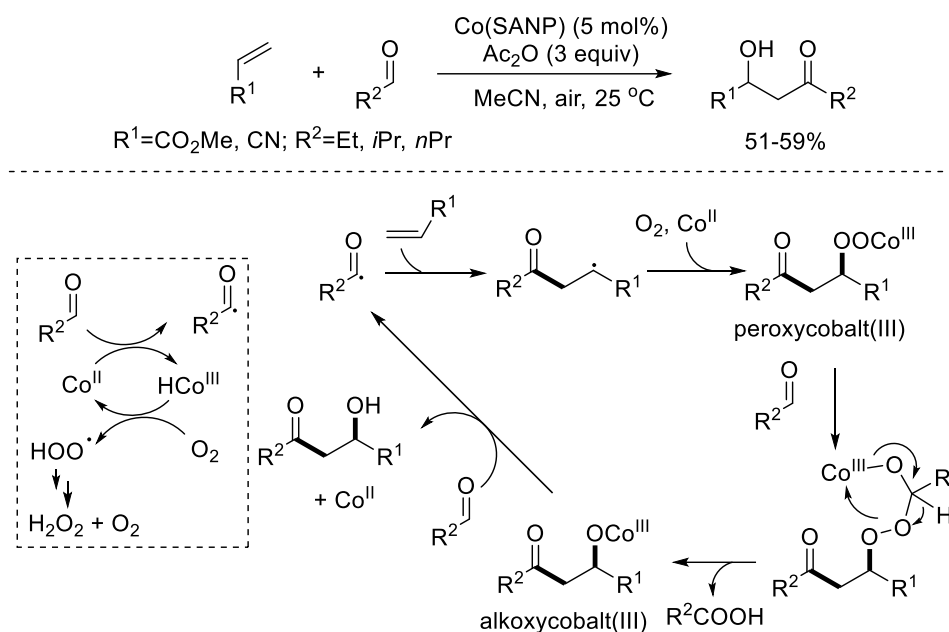
<sup>15</sup> Review on reactions of acyl radicals: Chatgililoglu, C. *Chem. Rev.* **1999**, *99*, 1991.

<sup>16</sup> Selected examples on reactions of alkoxy carbonyl radicals: a) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z. Y.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304. b) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2008**, *130*, 16424. c) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739. d) Baguley, P. A.; Jackson, L. V.; Walton, J. C. *J. Chem. Soc. Perkin Trans. 1* **2002**, 304.

<sup>17</sup> Selected examples on reactions of carbamoyl radicals: a) Herzon, S. B.; Meyer, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342. b) Cannella, R.; Clerici, A.; Panzeri, W.; Pastori, N.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* **2006**, *128*, 5358. c) Yasui, Y.; Takemoto, Y. *Chem. Rec.* **2008**, *8*, 386.

<sup>18</sup> Punniyamurthy, T.; Bhatia, B.; Iqbal, J. *J. Org. Chem.* **1994**, *59*, 850.

reaction with molecular oxygen to give hydroperoxyl radical that disproportionates to hydrogen peroxide and oxygen.



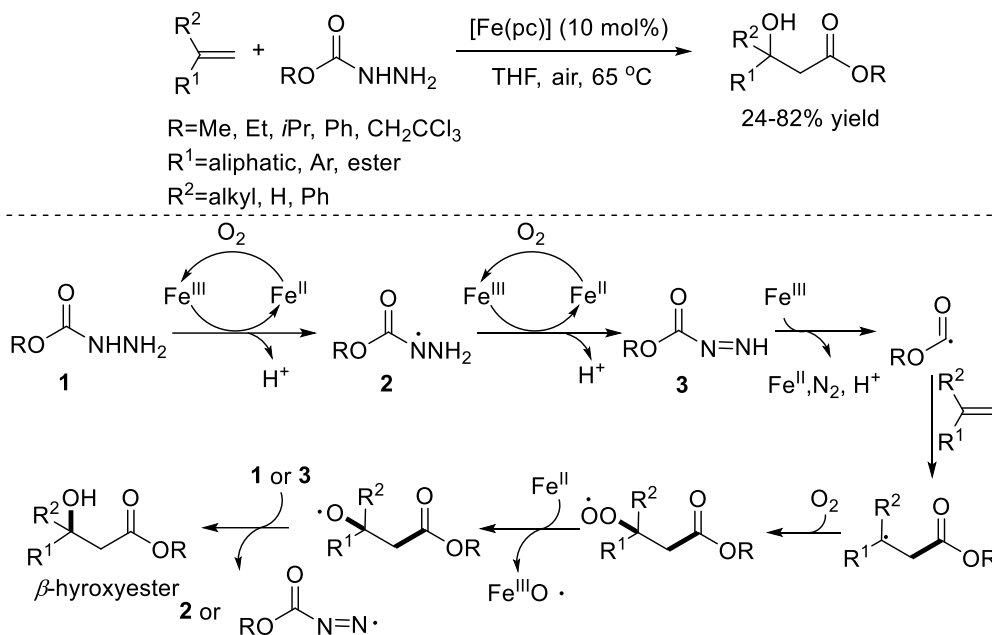
Scheme 1-6: Oxyacylation of alkene with aldehyde and molecular oxygen

Addition of acyl radical to electron-deficient alkene and successive oxygen insertion gives a peroxycobalt(III) species. Following reaction with aldehyde, the intermediate formed readily decomposes to an alkoxy-cobalt(III) complex and carboxylic acid. After hydrogen atom abstraction from another aldehyde molecule, 2-hydroxy-4-oxo ester/nitrile is formed whilst completing the catalytic cycle with acyl radical and Co(II) catalyst. When this reaction condition was tested on non-activated aliphatic alkene and styrene, epoxidation took place on the double bond to give epoxides instead.

### 1.4.2 Oxy-alkoxycarbonylation of alkene with carbazates

Ishibashi's group on the other hand, incorporated carbazate as the precursor of alkoxycarbonyl radical to accomplish oxycarbonylation on wide scope of terminal alkenes (Scheme 1-7).<sup>19</sup>

The initial step of reaction involves generation of alkoxycarbonyl radical with the expulsion of nitrogen molecule from carbazate through synergistic reaction of iron catalyst and molecular oxygen. The alkoxycarbonyl radical reacts with the double bond to form an alkyl radical intermediate trapped by oxygen. Scission of the O-O bond and hydrogen abstraction from **1** or **3** delivers the  $\beta$ -hydroxyester.



Scheme 1-7: Hydroxy-alkoxycarbonylation of alkenes from carbazate precursors and molecular oxygen

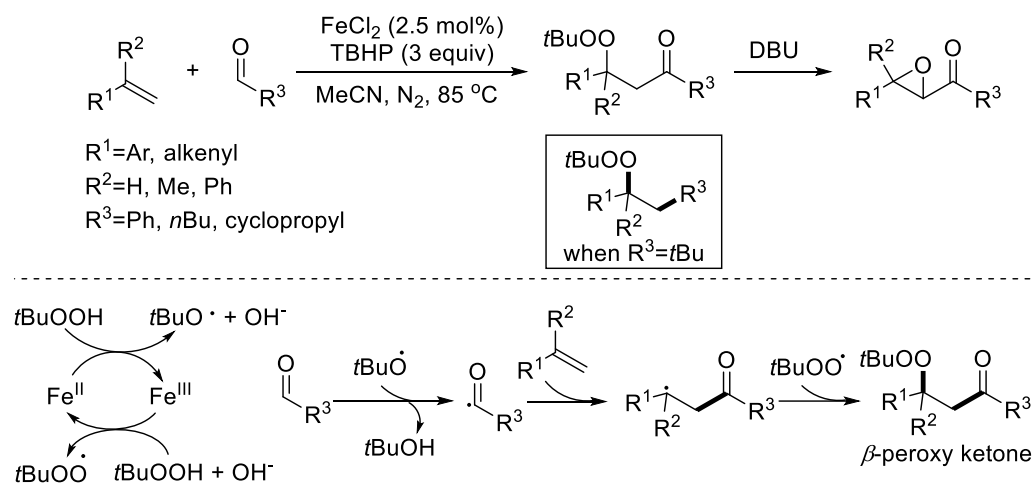
Notably, alkenes with varied electronic properties are effective substrates for this transformation. Aside from the styrenyl substrates and acrylate, non-conjugated alkenes such as  $\beta$ -pinene could yield the respective  $\beta$ -hydroxyester

<sup>19</sup> Taniguchi, T.; Sugiura, Y.; Hisaaki, Z.; Ishibashi, H. *Angew. Chem., Int. Ed.* **2010**, 49, 10154.

albeit in inferior yield and with side-product due to cleavage of cyclobutane ring.

### 1.4.3 Peroxy-carbonylation of alkenes with aldehydes and TBHP

In 2011, Li and co-workers communicated a three-component reaction of alkenes, aldehydes and hydroperoxides for oxycarbonylation of styrene derivatives (Scheme 1-8).<sup>20</sup> This reaction protocol proceeds through iron-catalyzed ( $sp^2$ ) C-H activation of aldehydes to deliver  $\beta$ -peroxy ketones. The iron catalyst in the proposed mechanism is crucial in mediating the generation of *tert*-butoxyl and *tert*-butylperoxyl radicals. Hydrogen abstraction by the oxyl radical reveals the acyl radical which adds to the styrene. Subsequent selective coupling with *tert*-butylperoxyl radical leads to  $\beta$ -peroxy ketone.



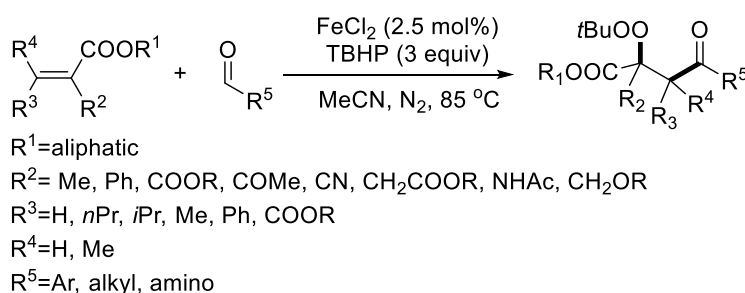
Scheme 1-8: Aldehydes and *tert*-butylhydroperoxide for peroxidation-carbonylation of alkenes

A number of conjugated alkenes together with benzaldehyde, cyclopropanecarboxaldehyde and butyraldehyde could be applied for this transformation successfully. Nonetheless, the substituents on aldehyde could interfere with the kinetics of the competing decarbonylation and carbonylation, as evident in futile incorporation of pivaldehyde for this reaction. This

<sup>20</sup> Liu, W.; Li, Y.; Liu, K.; Li, Z. *J. Am. Chem. Soc.* **2011**, *133*, 10756.

carbonylation-peroxidation procedure also grants facile access to  $\alpha$ -carbonyl ketones through stepwise or one-pot base-induced epoxidation reaction.

Later, they further broadened the substrate scope to  $\alpha,\beta$ -unsaturated esters (Scheme 1-9). The generality of this transformation is attested given  $\alpha$ -substituted, tri- and tetra-substituted acrylates could all be well suited in their protocol to give densely functionalized 2-peroxy-1,4-dicarbonyls.<sup>21</sup> This methodology is also incorporated in the key step reaction for their total synthesis of Clavilactones A, B and D through 3-component carbonylation-peroxidation of a 1,5-diene.<sup>22</sup>



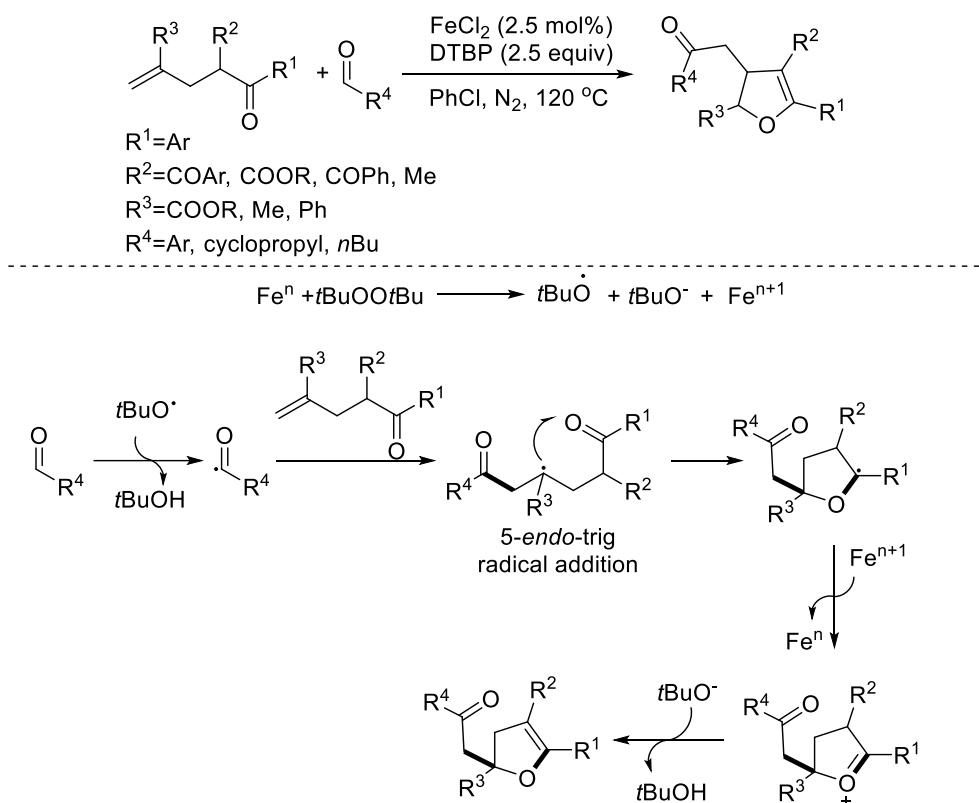
Scheme 1-9: Carbonylation-peroxidation of  $\alpha,\beta$ -unsaturated esters

Aside from the prominent 3-component reaction, the same group achieved a two-component iron-catalyzed tandem acylation-intramolecular oxygenation of terminal alkenes to synthesize 2,3-dihydrofurans (Scheme 1-10).<sup>23</sup> Following addition of acyl radical to the alkene, the adduct undergoes 5-*endo*-trig radical addition to generate  $\alpha$ -oxygen carbon radical intermediate. The ensuing oxidation and deprotonation steps form the dihydrofuran.

<sup>21</sup> Liu, K.; Li, Y.; Zheng, X.; Liu, W.; Li, Z. *Tetrahedron* **2012**, *68*, 10333.

<sup>22</sup> Lv, L.; Shen, B.; Li, Z. *Angew. Chem. Int. Ed.* **2014**, *53*, 4164.

<sup>23</sup> Lv, L.; Lu, S.; Guo, Q.; Shen, B.; Li, Z. *J. Org. Chem.* **2015**, *80*, 698.



Scheme 1-10: Tandem acylation-intramolecular oxygenation of terminal alkenes toward dihydrofurans

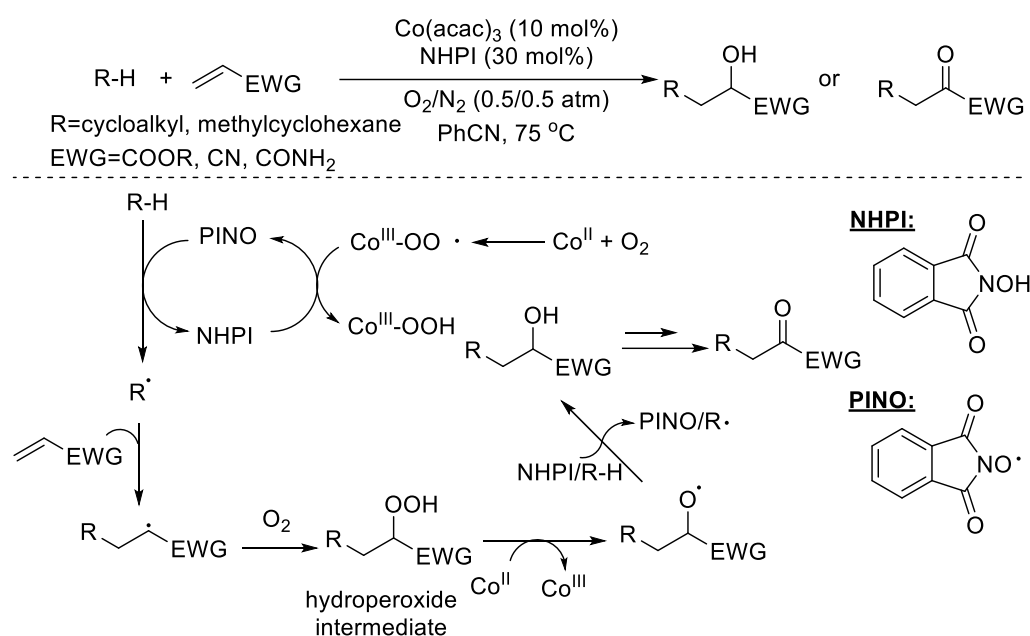
### 1.5 Oxyalkylation of alkenes

Development of transition metal-catalyzed difunctionalization of alkenes with new C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond formation remain difficult, mainly impeded by the reduced rate of oxidative addition of alkyl electrophiles as well as the facile β-hydride elimination of the resulting metal-alkyl species.<sup>24</sup> Radical-mediated approaches therefore serve as attractive alternatives for this transformation.

<sup>24</sup> a) Urkalan, K. B.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 18042. b) Wu, T.; Mu, X.; Liu, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 12578. c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527.

### 1.5.1 Oxyalkylation of alkene with unactivated alkanes and molecular oxygen

In 2001, Ishii's group accomplished oxyalkylation of electron-poor alkenes with simple cyclic alkanes and molecular oxygen (Scheme 1-11).<sup>25</sup> The key step involves addition of alkyl radical which is generated after hydrogen atom abstraction by PINO radical, to the electron-deficient alkene. Subsequent trapping of O<sub>2</sub> gives a hydroperoxide intermediate. Decomposition of hydroperoxide aided by Co(II) species results in introduction of hydroxyl/keto functionalities in the product.



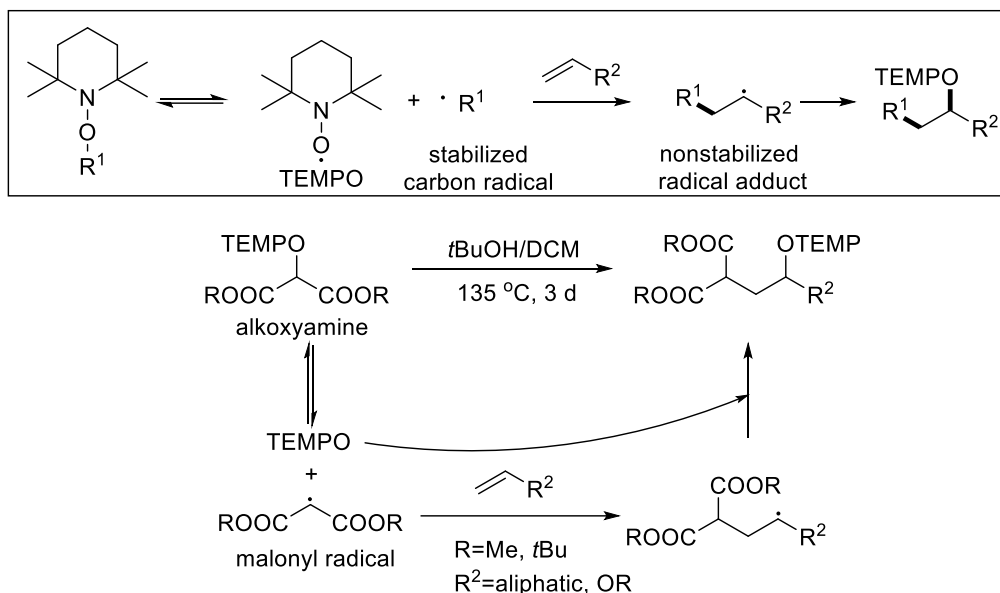
Scheme 1-11: NHPI-assisted catalytic oxyalkylation of alkenes with alkanes and molecular oxygen

### 1.5.2 Oxyalkylation of alkenes with alkoxyamines

Studer's group then disclosed an efficient radical carboaminoxylation of non-activated alkenes with alkoxyamines to give 1,4-functionalized malonates

<sup>25</sup> Hara, T.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2001**, *66*, 6425.

(Scheme 1-12).<sup>26</sup> Alkoxyamines which serve as the precursor for malonyl radical can be readily prepared in high yields from one-step reaction of commercially available TEMPO and dialkyl malonates.



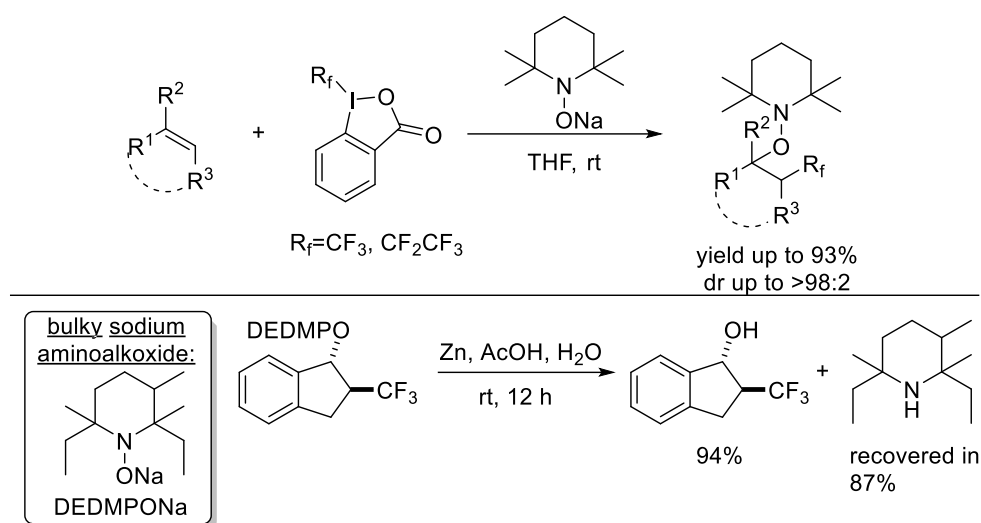
Scheme 1-12: Intermolecular radical addition of alkoxyamines to nonactivated alkenes

The reaction is initiated after reversible thermal homolysis of alkoxyamine that reveals a stabilized malonyl radical which adds to the olefin. Then, irreversible trapping of TEMPO with the radical adduct provides the carboaminoxylation product. Judicious choice of substituents on both coupling partners ( $R^1$ ,  $R^2$ ) is essential to fine-tune the electronic properties of radical intermediates that will allow occurrence of initial homolysis step, rapid intermolecular addition of  $R^1$  radical to alkene and irreversible formation of new C-O bond in product. The strength of C-O bond corresponds to the stability of carbon radical, with the unstabilized one forms a strong C-O bond and vice versa. It is also worth-noting that the combination of electrophilic malonyl radical and electron rich vinyl ether furnished the coupling product in best yield.

<sup>26</sup> Wetter, C.; Jantos, K.; Woihe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899.

### 1.5.3 Oxytrifluoroalkylation of alkenes with TEMPONa and Togni reagent

In addition to generation of aryl radical from aryldiazonium salts (Section 1.3.1), Studer's group has also employed the TEMPONa as the SET reagent for releasing trifluoromethyl or pentafluoroethyl radical from Togni reagent while being oxidized to TEMPO radical itself to realize oxytrifluoromethylation of alkenes at room temperature (Scheme 1-13).<sup>27</sup>



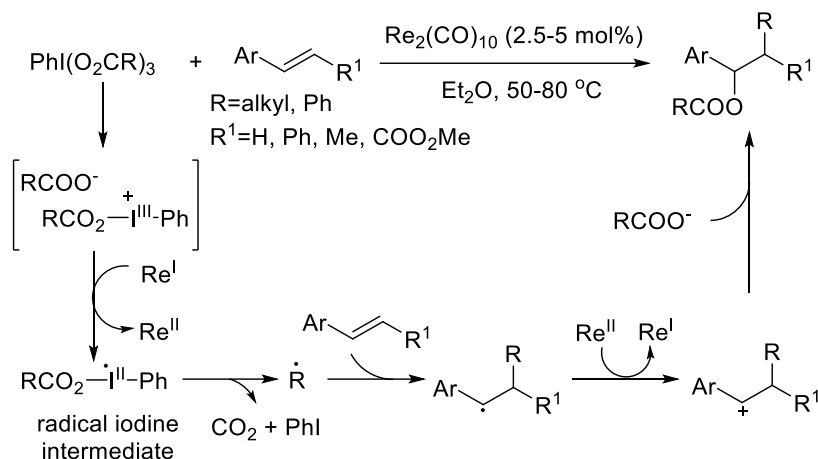
Scheme 1-13: Radical oxytrifluoromethylation of alkenes with TEMPONa and Togni reagent

A similar radical mechanism is involved in this reaction. Instead of generation of aryl radical, TEMPONa performs the single-electron reduction of Togni reagent to reveal the trifluoroalkyl radical, which will add to alkene. Sequential radical coupling driven by 'persistent radical effect' has allowed TEMPO moiety to be installed on the carbon radical (oxidation of the carbon radical). The mild reaction conditions have approved of the amenability of wide-ranged substrates for this reaction. Notwithstandingly, the diastereoselectivity of this reaction was excellent on cyclic substrates. Post-reaction transformation was feasible on the product to give  $\beta$ -trifluoromethylated secondary alcohols with the recovery of piperidine upon treatment with zinc in acetic acid. Aside from

<sup>27</sup> Li, Y.; Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8221.

TEMPO<sub>Na</sub>, the product yields could be improved with the use of a bulkier sodium aminoalkoxide as depicted in Scheme 1-13.

#### 1.5.4 Oxyalkylation of alkene with hypervalent iodine(III) reagents



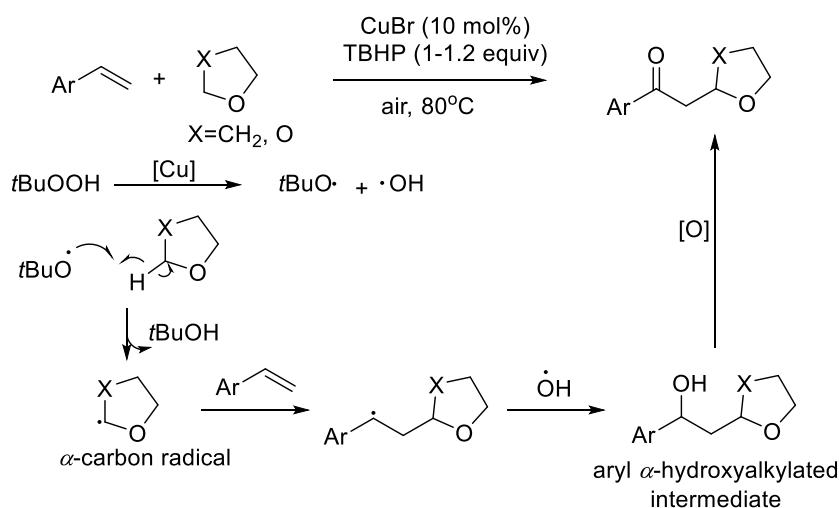
Scheme 1-14: Alkene oxyalkylation with HIR *via* rhenium catalysis

Hypervalent iodine(III) reagents (HIRs) easily derived from aliphatic carboxylic acids could serve as both alkyl and oxygen sources for the oxyalkylation of alkenes, too. This was developed by Wang's group in 2013 using rhenium catalytic system (Scheme 1-14).<sup>28</sup> Prominently, the Re(I) catalyst is thought to first reduce the cationic HIR through SET, giving rise to radical iodine intermediate. The iodine-oxygen bond ruptures homolytically to release iodobenzene and acyloxy radical. The alkyl radical is unmasked following a decarboxylation process. After the cascade radical addition-cation trapping steps, oxyalkylation product is delivered. HIRs derived from various aliphatic carboxylic acids including that from fatty acids (lauric acid and palmitic acid) could form the long-chain oxyalkylation products.

<sup>28</sup> Wang, Y.; Zhang, L.; Yang, Y.; Zhang, P.; Du, Z.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 18048.

### 1.5.5 Oxyalkylation of alkene with cyclic ethers

Direct functionalization of  $\alpha$ -C(sp<sup>3</sup>)-H bond of cyclic ether could be incorporated in oxyalkylation of vinylarenes under aerobic condition, as demonstrated in a protocol developed by Zhang's group in 2009 (Scheme 1-15).<sup>29</sup> The reaction is proposed to proceed through generation of  $\alpha$ -carbon radical on ether which adds to the styrene. The resulting adduct will couple with hydroxyl radical leading to the formation of  $\alpha$ -hydroxyalkylated product, which is then oxidized in-situ to the keto counterpart. The intermediacy of the aryl  $\alpha$ -hydroxyalkylated compound was put forward following its detection in GC-MS analysis.



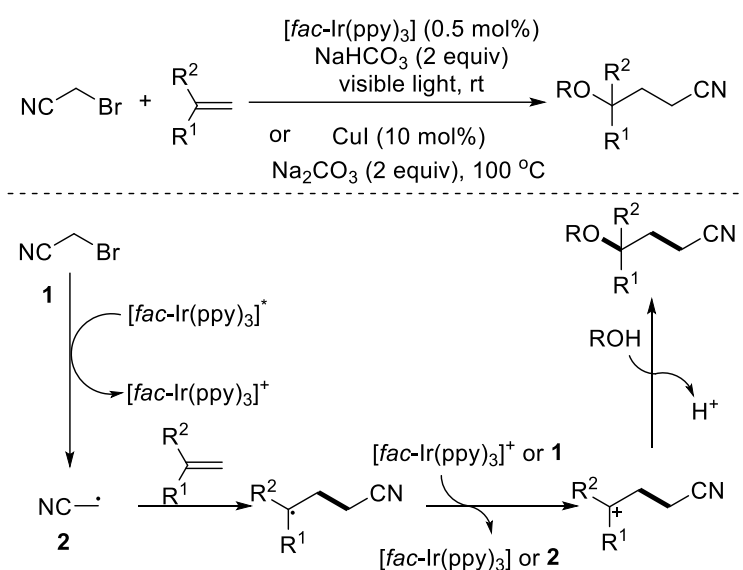
Scheme 1-15: Oxyalkylation of vinylarenes through  $\alpha$ -C(sp<sup>3</sup>)-H functionalization of ether

### 1.5.6 Oxyalkylation of alkene with $\alpha$ -bromoacetonitrile and unactivated alkyl nitriles

Instead of direct C-H activation, generation of alkyl radical from the halide precursor such as alkyl iodide or bromide is extensively employed in many

<sup>29</sup> Kai, C.; Huang, L.; Zhang, Y. *Org. Lett.* **2009**, *11*, 2908.

organic reactions.<sup>30</sup> Organotin hydrides are traditionally used to reveal the carbon-centered radical through halide abstraction. In view of the undesired toxicity issue associated with stannane reagents, chemists have devised alternative approaches such as employing transition metals which could mediate reductive scission of the carbon-halogen bonds<sup>31</sup> and visible light photoredox catalysis<sup>32</sup>.



Scheme 1-16: Visible light-induced alkoxylation of alkenes with bromoacetonitrile

Hereof, Lei *et al.* reported alkoxylation of alkenes induced by visible light using bromoacetonitrile (Scheme 1-16).<sup>33</sup> Mechanism wise, SET occurs between excited Ir(III) and bromoacetonitrile to give cyanomethyl

<sup>30</sup> Jasperse, C. P.; Curran, D. P. Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.

<sup>31</sup> a) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L. Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638. b) Zhang, X.; Yi, H.; Liao, Z.; Zhang, G.; Fan, C.; Qin, C.; Liu, J.; Lei, A. *Org. Biomol. Chem.* **2014**, *12*, 6790. c) Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 19020. d) Bissember, A. C.; Levina, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 14232. e) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068.

<sup>32</sup> a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. b) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 7274. c) Nguyen, J. D. D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854. d) Pirtsch, M.; Paria, S.; Matsuno, T.; Isobe, H.; Reiser, O. *Chem. Eur. J.* **2012**, *18*, 7336. e) Kim, H.; Lee, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 12303. f) Jiang, H.; Cheng, Y.; Wang, R.; Zheng, M.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 13289.

<sup>33</sup> Yi, H.; Zhang, X.; Qin, C.; Liao, Z.; Liu, J. Lei, A. *Adv. Synth. Catal.* **2014**, *356*, 2877.

radical which adds to the alkene. The resulting radical intermediate is oxidized to the carbocation, which upon nucleophilic attack by alcohol, affords the product. Subsequently, they extended the work to using copper catalytic system,<sup>5a</sup> wherein the copper catalyst is thought to mediate the initial generation of alkyl radical and bromide ion in place of the photocatalyst.

A similar work is then disclosed by Zhu's group, in which direct  $\alpha$  C-H functionalization of alkyl nitriles is attained using copper catalyst to perform a three-component oxyalkylation of alkenes, preparing a series of  $\gamma$ -alkoxy alkyl nitriles.<sup>34</sup> This protocol is particularly attractive owing to the atom economical feature as compared to the previous methods.

### **1.5.7 Oxyalkylation of alkenes with activated $\alpha$ -carbonyl compounds toward 1,4-dicarbonyl scaffold**

1,4-Dicarbonyl compounds are a privileged class of synthons toward various carbocyclic and heterocyclic compounds.<sup>35</sup> Alkene oxyalkylation with addition of  $\alpha$ -carbonyl carbon-centered radical to the double bond and successive C-O bond formation through trapping of oxyl radical or oxygen nucleophile thus denotes a departure from the conventional methods that use two carbonyl derivatives to make this class of compounds.<sup>36</sup>  $\alpha$ -Bromo carbonyl compounds and diazo acetates were examined as the precursors for generation of  $\alpha$ -carbonyl carbon-centered radicals in this coupling strategy, which will be discussed below.

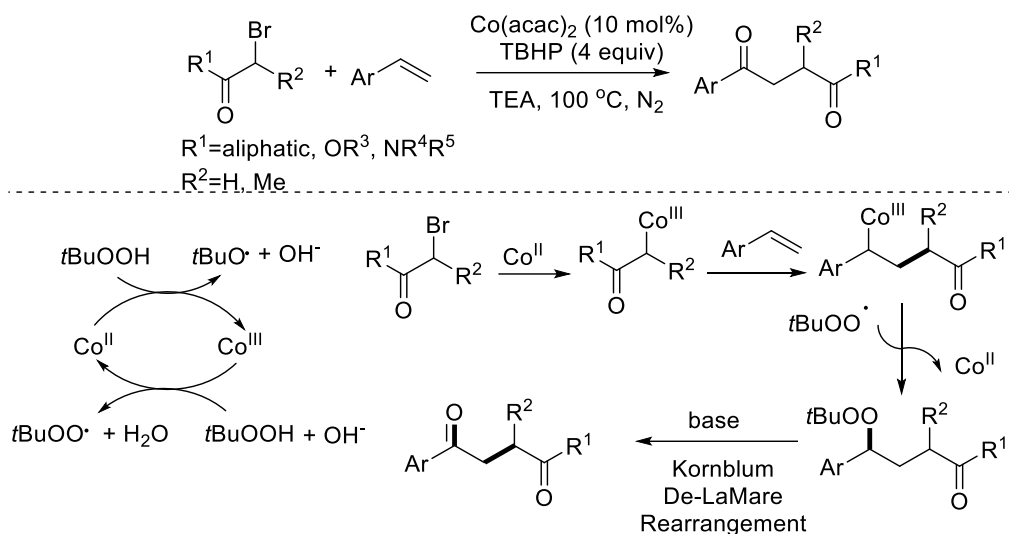
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<sup>34</sup> Chatalova-Sazepin, C.; Wang, Q.; Sammis, G. M. Zhu, *J. Angew. Chem. Int. Ed.* **2015**, *54*, 5443.

<sup>35</sup> Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*; Wiley-VCH: 2003.

<sup>36</sup> Zhang, F.; Du, P.; Chen, J.; Wang, H.; Luo, Q.; Wan, X. *Org. Lett.* **2014**, *16*, 1932 and the references cited therein.

### 1.5.7.1 $\alpha$ -Bromo carbonyl compounds



Scheme 1-17: Oxyalkylation of styrenes with  $\alpha$ -bromo carbonyl compounds

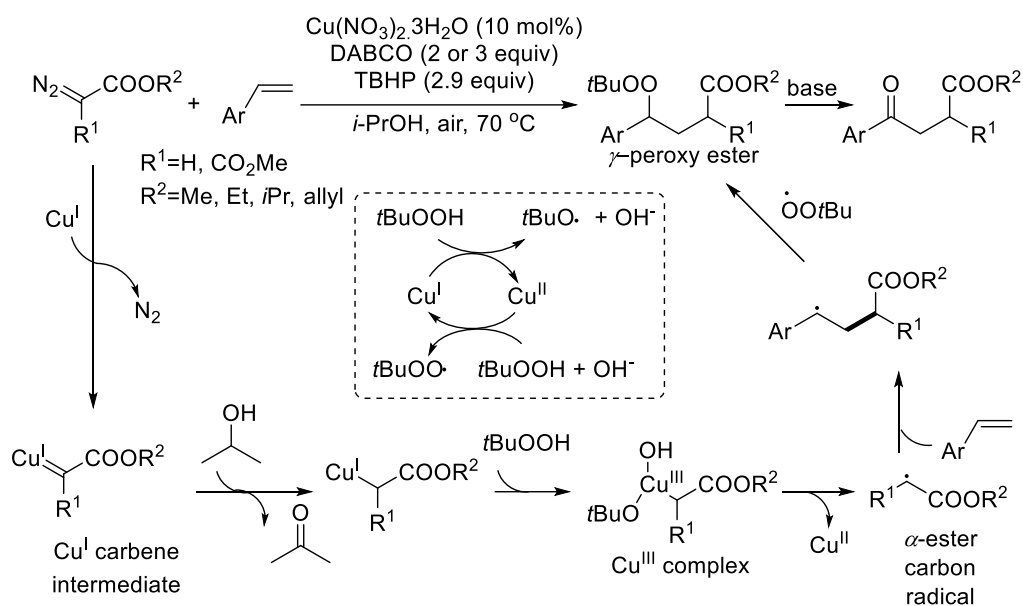
Wan's group uses  $\alpha$ -bromo carbonyl compounds and TBHP to do a 3-component coupling reaction with styrene derivatives to prepare 1,4-dicarbonyls (Scheme 1-17).<sup>35</sup> In this case, cobalt catalyst is postulated to aid in the reductive cleavage of the C-Br bond, giving rise to the  $\alpha$ -carbonyl carbon radical trapped by styrene to generate organocobalt(III) complex. Selective displacement by *tert*-butylperoxyl radical leads to the peroxide intermediate. After which, cleaves readily to the corresponding ketone in the presence of base, a process termed as Kornblum-DeLaMare rearrangement.<sup>37</sup>  $\alpha$ -Bromo esters, amides and ketones are all effective coupling agents to undertake this chemistry.

### 1.5.7.2 Diazo acetates

Diazo compounds could also serve as useful precursor to provide the  $\alpha$ -ester carbon radical in-situ. This work is reported by the same group in 2015 in

<sup>37</sup> a) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880. b) Kelly, D. R.; Bansal, H.; Morgan, J. J. G. *Tetrahedron Lett.* **2002**, *43*, 9331.

which diazoacetates and arylalkenes were successfully coupled to prepare  $\gamma$ -peroxyesters and 1,4-dicarbonyls (Scheme 1-18).<sup>38</sup>



Scheme 1-18: Copper-catalyzed oxyalkylation of styrenes with diazoacetates

On the basis of computational studies and experimental observation, they postulated a plausible mechanism for their reaction which is depicted in the scheme below. An initially-formed Cu(I)-carbene intermediate will lead to an organocopper complex after hydrogen abstraction from *i*-PrOH. The latter is thought to undergo oxidative addition in the presence of TBHP to give Cu(III) complex intermediate, which will cleave homolytically to release the  $\alpha$ -ester carbon radical for the subsequent steps to progress. Prolonged reaction time and additional amount of DABCO could allow for one-pot formation of the  $\beta$ -keto esters. The novel crossover reaction of a Cu-based carbene formed from reaction of diazoacetates and copper with radicals in this reaction represents a milestone in both copper carbene and radical chemistry.

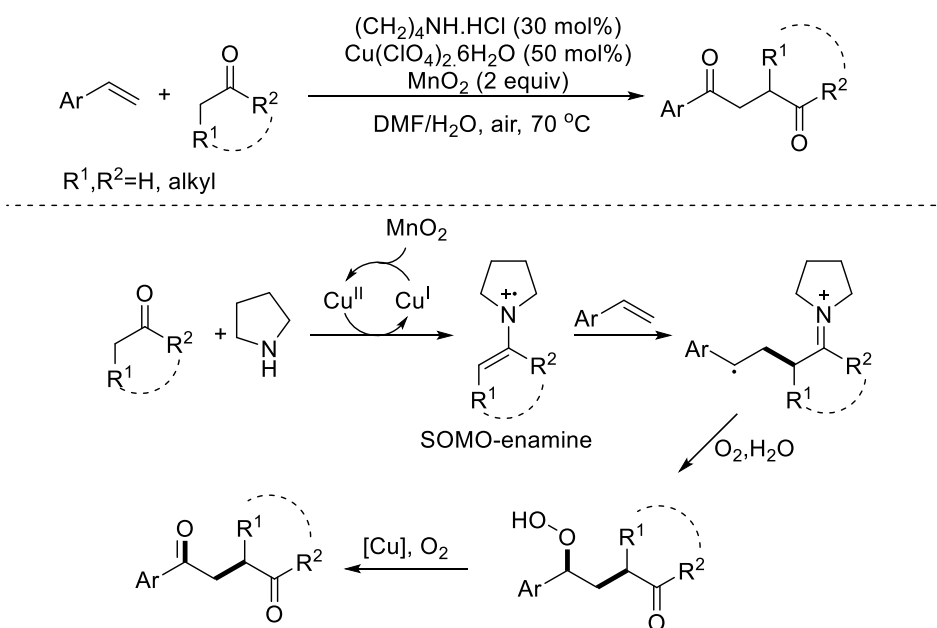
<sup>38</sup> Jiang, J.; Liu, J.; Yang, L.; Shao, Y.; Cheng, J.; Bao, X.; Wan, X. *Chem. Comm.* **2015**, 51, 14728.

## 1.5.8 Oxyalkylation of alkenes with unactivated carbonyl compounds toward 1,4-dicarbonyl scaffold

Aside from activated  $\alpha$ -carbonyl compounds, a number of protocols were developed to incorporate unactivated carbonyl compounds for assembly of 1,4-dicarbonyl scaffold through radical-mediated  $\alpha$ -C(sp<sup>3</sup>)-H activation.

### 1.5.8.1 Simple ketones or aldehydes: dual catalytic system of organocatalyst and copper catalyst

In 2010, Huang and Xie communicated carbo-carbonylation of styrene derivatives using simple ketones or aldehydes, without the need of pre-functionalization to prepare  $\gamma$ -diketones and  $\gamma$ -carbonyl aldehydes (Scheme 1-19).<sup>39</sup>



Scheme 1-19: Oxycarbo-carbonylation of styrenes through SOMO-enamine intermediate

Dual catalytic system involving organocatalyst and copper catalyst is applied in their work which proceeds through a three  $\Pi$ -electron radical cationic enamine (SOMO-enamine) intermediate generated after oxidation of enamine formed

<sup>39</sup> Xie, J.; Huang, Z.-Z. *Chem. Comm.* **2010**, 46, 1947.

from pyrrolidine and ketone/aldehyde. After addition to the styrene double bond, the radical cationic imine intermediate is thought to react with oxygen at the carbon radical center while the hydrolysis of imine takes place. The final step involves the oxidation of the peroxy group to ketone. Interestingly, although oxygen source in the product originates from molecular oxygen in air, pure oxygen atmosphere was found to be deleterious for the product yield.

### **1.5.8.2 Simple ketones: bronsted acid catalyst or copper/manganese dual catalysts**

Later, Klusmann's<sup>40</sup> (Scheme 1-20) and Li's group<sup>41</sup> (Scheme 1-21) independently realized the direct oxidative coupling of simple vinylarenes with unactivated ketones through  $\alpha$ -C(sp<sup>3</sup>)-H functionalization using bronsted acid catalyst and copper/manganese dual catalysts, correspondingly. In both works, the radical pathway is hypothesized with the intermediacy of resonance-stabilized  $\alpha$ -keto carbon radical.

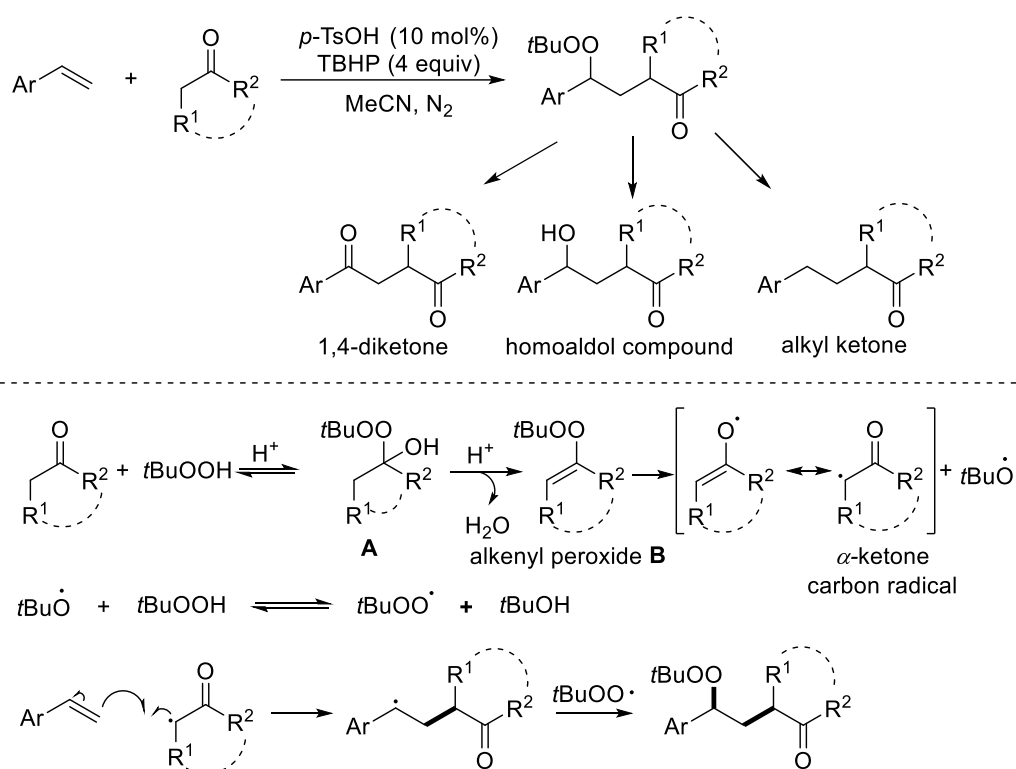
In Klusmann's work, ketone substrate is speculated to give intermediate **A** in the presence of bronsted acid and TBHP, which could decompose homolytically to alkenyl peroxide **B** that in turn gives rise to *tert*-butoxyl radical and  $\alpha$ -ketone carbon radical stabilized by resonance. A prominent feature is the use of bronsted acid in their reaction that mediates the direct generation of the  $\alpha$ -keto carbon radical. Reactions with the use of Fe/Cu salts failed, probably due to the rapid decomposition of TBHP in the presence of these catalysts, thus inhibits the formation of intermediate **A** and **B**. Fast equilibrium is anticipated between *tert*-butoxyl and *tert*-butylperoxyl radicals,

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<sup>40</sup> Schweitzer-Chaput, B.; Demaerel, J.; Engler, H.; Klusmann, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8737.

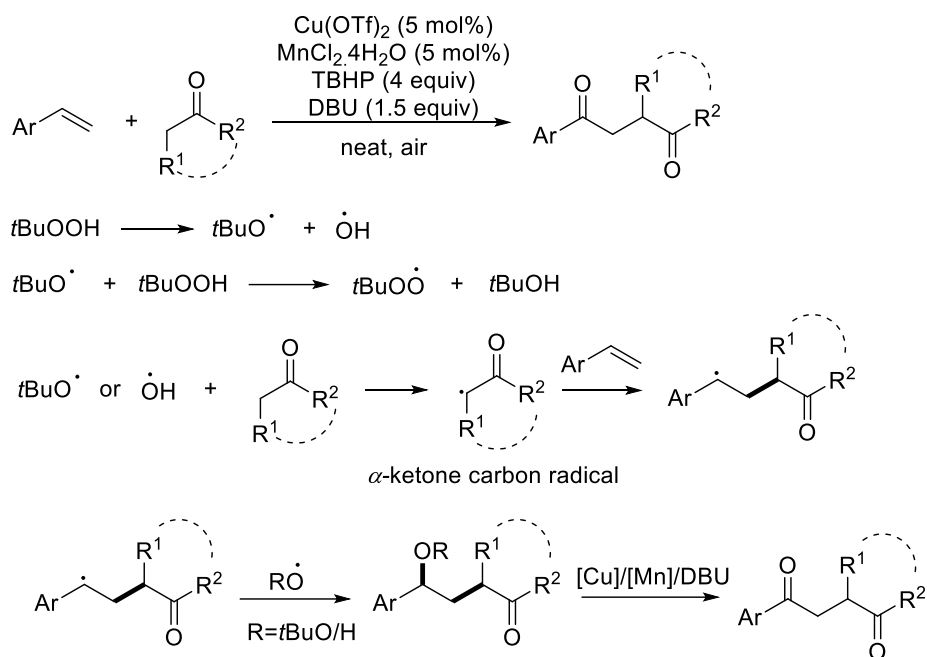
<sup>41</sup> Lan, X.-W.; Wang, N.-X.; Zhang, W.; Wen, J.-L.; Bai, C.-B.; Xing, Y.; Li, Y.-H. *Org. Lett.* **2015**, *17*, 4460.

favouring the latter. Following addition of  $\alpha$ -ketone carbon radical to styrene, the benzylic radical intermediate is speculated to couple selectively with the persistent *tert*-butylperoxyl radical to give  $\gamma$ -peroxy ketones, which upon downstream chemical modification, delivers 1,4-diketones, homoaldol product as well as alkyl ketones (Scheme 1-20).



Scheme 1-20: Oxyalkylation of styrenes with unactivated ketones with bronsted-acid catalyst

On the contrary, copper/manganese catalysts are postulated to mediate the generation of the *tert*-butyloxyl and hydroxyl radicals under Li's conditions (Scheme 1-21). Hydrogen abstraction from ketone by the *tert*-butoxyl and/or hydroxyl radicals forms the  $\alpha$ -ketone radicals. Following addition to alkene, the benzylic radical intermediate is speculated to be trapped by either hydroxyl or *tert*-butylperoxyl radical. The basic medium of reaction or Cu/Mn catalysts renders direct formation of the respective ketone.



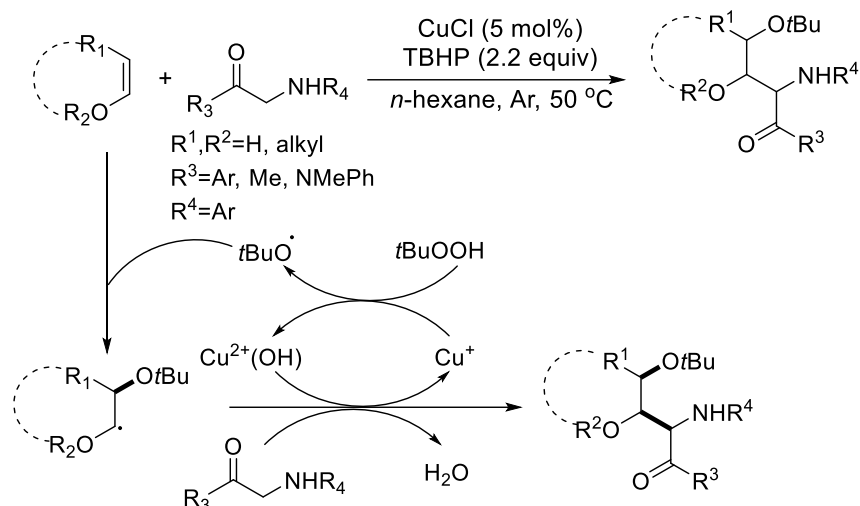
Scheme 1-21: Oxyalkylation of styrenes with unactivated ketones with dual catalytic system

### 1.5.8.3 α-Amino carbonyl compounds

Aside from the simple carbonyl compounds, α-amino carbonyl compounds could be used as the alkylating agent for the alkene acceptor as well. In view of the widespread utilities of this class of building block, this radical-mediated synthetic method have addressed the long-standing issue towards efficient functionalization reaction of the α-CH bond, which include need of stoichiometric amount of strong base and prior protection of the free N-H groups.<sup>42,43,44</sup>

<sup>42</sup> Selected examples discussing chemistry of amino acids: a) Ohfuné, Y. *Acc. Chem. Res.* **1992**, 25, 360. b) Klinger, F. D. *Acc. Chem. Res.* **2007**, 40, 1367. c) Concellon, J. M.; Rodriguez-Solla, *Curr. Org. Chem.* **2008**, 12, 524. d) Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schönholzer, P.; Spiegler, C.; Müller, K. *Helv. Chim. Acta* **1995**, 78, 563. e) Obrecht, D.; Altoefer, M.; Lehmann, C.; Schönholzer, P.; Müller, K. *J. Org. Chem.* **1996**, 61, 4080.

<sup>43</sup> Selected reviews on α-CH functionalization under basic condition: a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, 110, 1082. b) Culkín, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, 36, 234. c) Liu, X.; Hartwig, J. F. *Org. Lett.* **2003**, 5, 1915. d) Hashimoto, T.; Maruoka, K. *Chem. Rev.*



Scheme 1-22: Oxyalkylation of enol ethers with  $\alpha$ -amino carbonyl compounds and TBHP

In this regard, Li's group presented a novel copper-catalyzed difunctionalization reaction of enol ethers with  $\alpha$ -amino carbonyls and hydroperoxides (Scheme 1-22).<sup>45</sup> Distinctively in their proposed mechanism, the *tert*-butyloxy radical generated through mediation of Cu(I) will first add to the enol ether before Cu(II)-assisted coupling with  $\alpha$ -amino carbonyl to give the oxyalkylated product.

## 1.6 Conclusion

By virtue of step economy in building up molecular complexity, 1,2-difunctionalization of alkenes have drawn significant attentions from synthetic chemists. In contrary to the concomitant introduction of two heteroatom-containing functional groups, protocols that feature simultaneous forging of carbon-carbon and carbon-oxygen bonds are lesser. In the above section, radical approaches toward intermolecular carboxygenation of alkenes have

**2007**, 107, 5656. e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, 103, 3013. f) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, 219, 211.

<sup>44</sup> a) Zhao, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2008**, 47, 7075. b) Li, K.; Tan, G.; Huang, J.; Song, F.; You, J. *Angew. Chem. Int. Ed.* **2013**, 52, 12942. c) Wei, W.-T.; Song, R.-J.; Li, J.-H. *Angew. Chem. Int. Ed.* **2014**, 356, 1703. d) Xie, J.; Huang, Z.-Z. *Angew. Chem. Int. Ed.* **2010**, 49, 10181. e) Xie, Y.; Hu, J.; Xie, P.; Qian, B.; Huang, H. *J. Am. Chem. Soc.* **2013**, 135, 18327.

<sup>45</sup> Wei, W.-T.; Li, H.-B.; Song, R.-J.; Li, J.-H. *Chem. Comm.* **2015**, 51, 11325.

been outlined, which have been made viable by the high reactivity and propensity of carbon centered radicals (aryl, carbonyl, alkyl radicals) to add to the alkene double bond. The oxygen functionality is introduced through successive radical coupling with oxygen-centered radical or trapping of oxygen nucleophile by the corresponding carbocation. Despite the impressive progress made over the last decade, reaction protocols that could accommodate broader alkene substrates as well as more oxygen/carbon functionalities are highly desirable to complement current progress.

# *CHAPTER 2*

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***COPPER- OR COBALT- CATALYZED DIRECT  
COUPLING OF  $sp^3$   $\alpha$ -CARBON OF  
ALCOHOLS WITH ALKENES AND  
HYDROPEROXIDES***

## 2.1 Introduction

### 2.1.1 Conventional methods to prepare alcohols

Hydroxyl functional group is ubiquitous in a myriad of natural-occurring compounds with significant biological activities.<sup>46</sup> It is estimated that 65% of known natural products, 40% of drugs, several classes of lipids as well as glycans comprise hydroxyl group, not forgetting the amino acids such as serine, threonine and tyrosine, which make up of approximately 7.5%, 6%, and 3% of amino acids in human protein.<sup>47</sup>

Alcohols could be prepared from alkenes through a couple of fundamental reactions in organic synthesis, including acid-catalyzed hydration, oxymercuration and hydroboration-oxidation reaction.<sup>48</sup> Complementary strategies include reduction or addition of organometallic reagents to carbonyl compounds or the equivalents.<sup>49-50</sup> In addition to the Grignard reagent,<sup>51</sup> organometallic compounds such as organolithium,<sup>52</sup> organozinc,<sup>53</sup> and

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<sup>46</sup> Trader, D.J.; Carlson, E. E. *Mol. Biosyst.* **2012**, *8*, 2484.

<sup>47</sup> a) Henkel, T.; Brunne, R. M.; Muller, H.; Reichel, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 643. b) Doolittle, R. F. In *Prediction of protein structure and the principle of protein conformation*; Fasman, G. D., Ed.; Plenum Press, New York, 1989, p 599. c) Bobbitt, J. M. *Adv. Carbohydr. Chem.* **1956**, *48*, 1.

<sup>48</sup> Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th edition; Wiley: New York, 2001.

<sup>49</sup> Reviews on carbonyl reduction: a) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986. b) Magano, J.; Dunetz, J. R. *Org. Process Res. Dev.* **2012**, *16*, 1156.

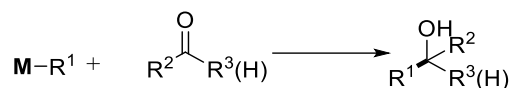
<sup>50</sup> Hatano, M.; Ishihara, K. *Synthesis* **2008**, *11*, 1647.

<sup>51</sup> a) Vidal, C.; García-Álvarez, J.; Hernán-Gómez, A.; Kennedy, A. R.; Hevia, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5969. b) Kadam, A.; Nguyen, M.; Kopach, M.; Richardson, P.; Gallou, F.; Wan, Z.-K.; Zhang, W. *Green Chem.* **2013**, *15*, 1880. c) Hong, Z.; Huang, H.; Liu, J.; Bian, G.; Song, L. *J. Org. Chem.* **2012**, *77*, 4645. d) Wang, X.-J.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D. Senanayake, C. H. *Org. Lett.* **2005**, *7*, 5593. e) Handy, S. T. *J. Org. Chem.* **2006**, *71*, 4659.

<sup>52</sup> a) Luderer, M. R.; Bailey, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.; Sommer, M. B. *Tetrahedron: Asymmetry* **2009**, *20*, 981. b) Fernández-Mateos, E.; Maciá, B.; Yus, M. *Eur. J. Org. Chem.* **2012**, *2012*, 3732. c) Kotani, S.; Kukita, K.; Tanaka, K.; Ichibakase, T.; Nakajima, M. *J. Org. Chem.* **2014**, *79*, 4817.

<sup>53</sup> a) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Org. Lett.* **2012**, *14*, 1816. b) Hatano, M.; Mizuno, T.; Ishihara, K. *Synlett* **2010**, *2010*, 2024. c) Blinder, C. M.; Bautista, A.; Zaidlewicz, M.; Krzemiński, M. P.; Oliver, A.; Singaram, B. *J. Org. Chem.* **2009**, *74*, 2337. d) Song, T.; Zheng, L.-S.; Ye, F.; Deng, W.-H.; Wei, Y.-L.; Jiang, K.-Z.; Xu, L.-W. *Adv. Synth.*

organoaluminium<sup>54</sup> reagents are compatible to synthesize alcohols from carbonyl compounds.



Scheme 2-1: Addition of organometallic reagent to carbonyl compound

Propargylic 1,3-dioxygenated compound are prevalently occurring molecular framework encountered en route to the total synthesis of numerous natural products and heterocyclic compounds.<sup>55-56</sup> The conventional access toward 1,3-dioxygenated compounds is the classical Aldol reaction typically takes place between a carbonyl pro-nucleophile, which is usually enolizable aldehyde, ketone and a carbonyl electrophile (in most cases, an aldehyde) (Scheme 2-2-a).<sup>57</sup>

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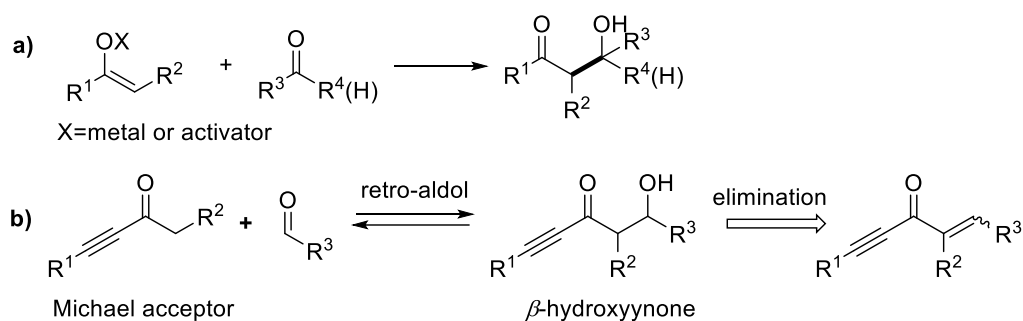
*Catal.* **2014**, 356, 1708. e) Hirose, T.; Kodama, K. Recent Advances in Organozinc Reagents. In *Comprehensive Organic Synthesis*; Knochel, P., Molander, G. A., Eds.; Elsevier, Oxford, 2014; Vol. 1, p 204-266.

<sup>54</sup> Fernández-Mateos, E.; Maciá, B.; Yus, M. *Tetrahedron: Asymmetry* **2012**, 23, 789.

<sup>55</sup> Natural products: a) Evans, D. A.; Starr, J. T. *Angew. Chem. Int. Ed.* **2002**, 41, 1787. b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, 125, 13531. c) Funel, J.-A.; Prunet, J. *J. Org. Chem.* **2004**, 69, 4555. d) Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, 5, 733. e) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, 68, 4215. f) Fang, Z.; Wills, M. *J. Org. Chem.* **2013**, 78, 8594. g) Smith, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1998**, 120, 3935. h) Trost, B. M.; Fredericksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, 127, 3666. i) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc.* **2009**, 131, 15061. j) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2001**, 40, 3667. k) O'Sullivan, P. T.; Buhr, W.; Fuhry, M. A. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, 126, 2194. l) Yao, H.; Song, L.; Tong, R. *J. Org. Chem.* **2014**, 79, 1498.

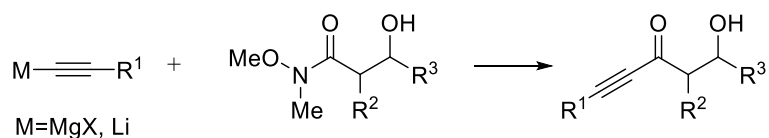
<sup>56</sup> Heterocycles: a) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2003**, 68, 8798. b) Shi, S.-L.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2012**, 51, 3932. c) Fuwa, H.; Matsukida, S.; Sasaki, M. *Synlett* **2010**, 8, 1239. d) O'Neil, G. W.; Fürstner, A. *Chem. Commun.* **2008**, 4294.

<sup>57</sup> a) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, 39, 1600. b) Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2008. c) Mahrwald, R. *Modern Methods in Stereoselective Aldol Reactions*; Wiley-VCH: Weinheim, 2013.



Scheme 2-2: Aldol reactions

Despite the efficient entry Aldol reaction could grant to propargylic 1,3-dioxygenated compounds, examples on such transformation are extremely rare.<sup>58</sup> This owes to the coveted reactivity of ynone substrates as Michael acceptor and the desired product,  $\beta$ -hydroxyynones to undergo retro-aldol or elimination reaction (Scheme 2-2-b). Instead, the  $\beta$ -hydroxyynones are usually prepared through the addition of alkynyllithium or alkynylmagnesium halide to the respective  $\beta$ -hydroxylated Weinreb amides (Scheme 2-3).<sup>55a-f, 56d</sup>



Scheme 2-3: Synthesis of propargylic 1,3-dioxygenated compounds through addition of alkynylmetallic reagent to  $\beta$ -hydroxylated Weinreb amides

This method, though robust, requires additional synthetic steps and the use of organometallic reagents as well as carbonyl compounds. Therefore, an alternative approach to assemble propargylic 1,3-dioxygenated compounds by direct use of alcohol moiety would be particularly attractive.

<sup>58</sup> a) Silva, F.; Sawicki, M.; Gouverneur, V. *Org. Lett.* **2006**, *8*, 5417. b) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660. c) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666. c) Kang, G.; Jiang, J.; Liu, H.; Wu, H. *J. Braz. Chem. Soc.* **2012**, *23*, 5.

### 2.1.2 Direct $\alpha$ C-H functionalization of alcohols: C-C bond formation

Selective functionalization of ubiquitous but inert C(sp<sup>3</sup>)-H bonds has momentous practical applications owing to its step economy feature.<sup>59</sup> The developed synthetic methodologies in this area could be generalized to three categories. C-H functionalization of simple alkane has been constant challenge pertaining to its inertness and the lack of directing group.<sup>60</sup> Other functionalization modes include activation of C(sp<sup>3</sup>)-H bond adjacent to a heteroatom (sulphur, oxygen, nitrogen)<sup>61</sup>, and that adjacent to a  $\pi$ -bond system<sup>62</sup>.

The  $\alpha$ -C-H functionalization of alcohols and amines are synthetically valuable given the efficient C-C bond formation and the direct installment of active alcohol and amine group on final products, which circumvents the protection-deprotection step. However, the inherent higher oxidation potential of the  $\alpha$ -oxygen C-H bond could have posed challenge to its direct functionalization.<sup>59c</sup>

<sup>59</sup> Reviews on functionalization of C(sp<sup>3</sup>)-H bonds: a) Nota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599. b) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. c) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. e) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138.

<sup>60</sup> a) Zhao, J.; Fang, H.; Qian, P.; Han, J.; Pan, Y. *Org. Lett.* **2014**, *16*, 5342. b) Liu, W.; Groves, J. T. *J. Am. Chem. Soc.* **2010**, *132*, 12847. c) Fortman, G. C.; Boaz, N. C.; Munz, D.; Konnick, M. M.; Periana, R. A.; Groves, J. T.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2014**, *136*, 8393. d) Peng, H.; Yu, J.-T.; Jiang, Y.; Yang, H.; Cheng, J. *J. Org. Chem.* **2014**, *79*, 9847. e) Gómez, L.; Canta, M.; Font, D.; Prat, I.; Ribas, X.; Costas, M. *J. Org. Chem.* **2013**, *78*, 1421.

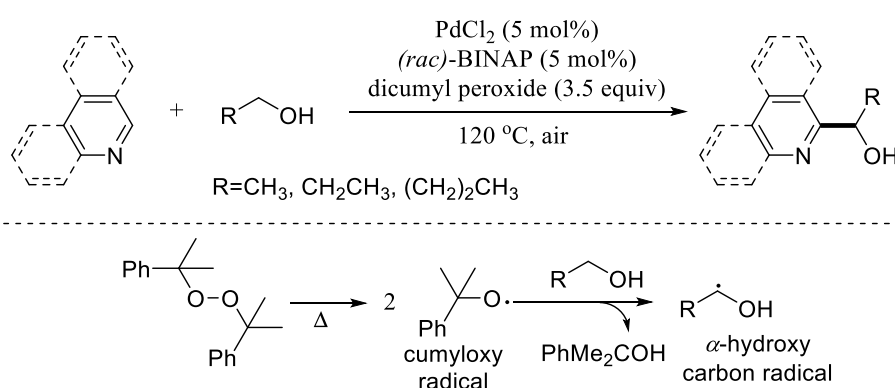
<sup>61</sup> a) Kampos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. b) Roesky, P. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 4892. c) Li, Z.; Yu, R.; Li, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 7497. d) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1937.

<sup>62</sup> Examples on allylic C-H functionalization: a) Wang, P.-S.; Liu, P.; Zhai, Y.-J.; Lin, H.-C.; Han, Z.-T.; Gong, L.-Z. *J. Am. Chem. Soc.* **2015**, *137*, 12732. b) Tao, Z.-L.; Li, X.-H.; Ha, Z.-Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2015**, *137*, 4054. c) Hu, G.; Xu, J.; Li, P. *Org. Lett.* **2014**, *16*, 6036. d) Wang, X.; Ye, Y.; Zhang, S. Feng, J.; Xu, Y.; Zhang, Y. Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410. e) Qin, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 15893. Examples on  $\alpha$ -carbonyl C-H functionalization: f) Tang, S.; Wu, X.; Liao, W.; Liu, K.; Liu, C.; Luo, S.; Lei, A. *Org. Lett.* **2014**, *16*, 3584. g) Gao, Q.; Zhang, J.; Wu, X.; Liu, S.; Wu, A. *Org. Lett.* **2015**, *17*, 134. h) Correia, C. A.; Li, C.-J. *Tetrahedron Lett.* **2010**, *51*, 1172. i) Yip, K.-T.; Nimje, R. Y.; Leskinen, M. V.; Pihko, P. M. *Chem. Eur. J.* **2012**, *18*, 12590. Example on propargylic C-H functionalization: j) Wang, T.; Zhou, W.; Yin, H.; Ma, J.-A.; Jiao, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10823. Examples on benzylic C-H functionalization: k) Vanjari, R.; Singh, K. N. *Chem. Soc. Rev.* **2015**, *44*, 8062. l) Rout, S. K.; Guin, S.; Ghara, K. K.; Banerjee, A.; Patel, B. K. *Org. Lett.* **2012**, *14*, 3982.

It was not until 1990s that this reaction of alcohol received commendable research attention.<sup>61d</sup> In this section, reaction protocols that feature the direct  $\alpha$ -C(sp<sup>3</sup>)-H functionalization of alcohols will be discussed, which mostly involve the intermediacy of a  $\alpha$ -hydroxy carbon radical and its subsequent addition to different acceptors.

### 2.1.2.1 Reactions of alcohols with heterocyclic compounds

Dates back to 1970s, Minisci has seminal reported hydroxymethylation and hydroxyethylation of electron deficient heteroaromatic bases with methanol and ethanol respectively. However, these reactions carry shortcomings include the use of acidic reaction medium, generation of by-products such as acetyl derivatives, dimers as well as poly-hydroxymethylation products.<sup>63</sup>



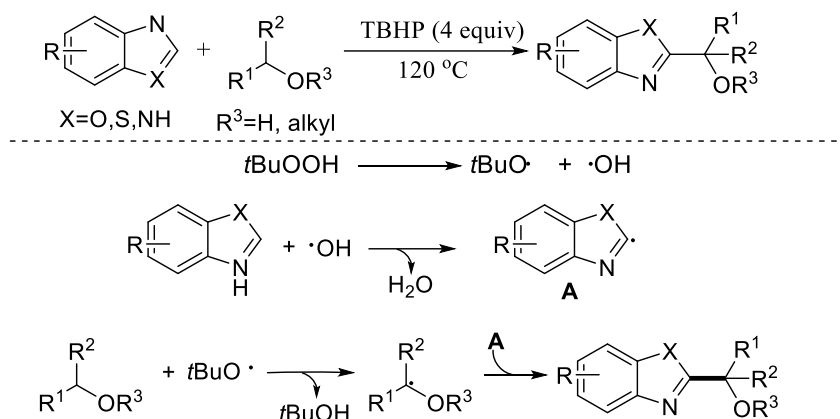
Scheme 2-4: Minisci reaction with alcohols with palladium catalyst

Li's group in 2011 improvised the reaction condition to incorporate palladium catalyst and obviate the use of acids in their protocol (Scheme 2-4).<sup>64</sup> Three primary alkyl alcohols together with quinolones and isoquinolines could be accommodated in this coupling strategy. At high temperature, the hemolytic rupture of O-O bond in cumyl peroxide takes place to release two cumyloxy

<sup>63</sup> Minisci, F.; Buratti, W.; Gardini, G. P.; Bertini, F.; Galli, R.; Perchinummo, M. *Tetrahedron* **1971**, *27*, 3655.

<sup>64</sup> Correia, C. A.; Yang, L.; Li, C.-J. *Org. Lett.* **2011**, *13*, 4581.

radicals. The latter abstracts the  $\alpha$ -hydrogen atom from alcohol to release  $\alpha$ -hydroxy carbon radical which will add to the electron-deficient *N*-heteroaromatics. Ensuing rearomatization steps give the cross-coupled product. Bis-addition products could still be observed in reactions of quinolone substrates where both 2- and 4-position are vacant.



Scheme 2-5: Metal-free direct coupling of alcohols with heterocycles

Around the same time, Wang's group independently described a metal-free C2-direct alkylation of azoles with alcohols and ethers using TBHP (Scheme 2-5).<sup>65</sup> Various fused azoles are effective substrates to undertake this coupling chemistry with primary and secondary alkyl alcohols to afford corresponding products in good yields.

Mechanistically, both protocols proposed intermediacy of the nucleophilic  $\alpha$ -hydroxy carbon centered radical generated from alcohol after hydrogen abstraction. The high reaction temperature would first facilitate the homolytic fragment of weak O-O bond in TBHP to reveal the *tert*-butoxyl radicals. In contrast to Li's proposed pathway, Wang proposed hydrogen abstraction from the azole by hydroxyl radical to form the related C(sp<sup>2</sup>)-carbon radical

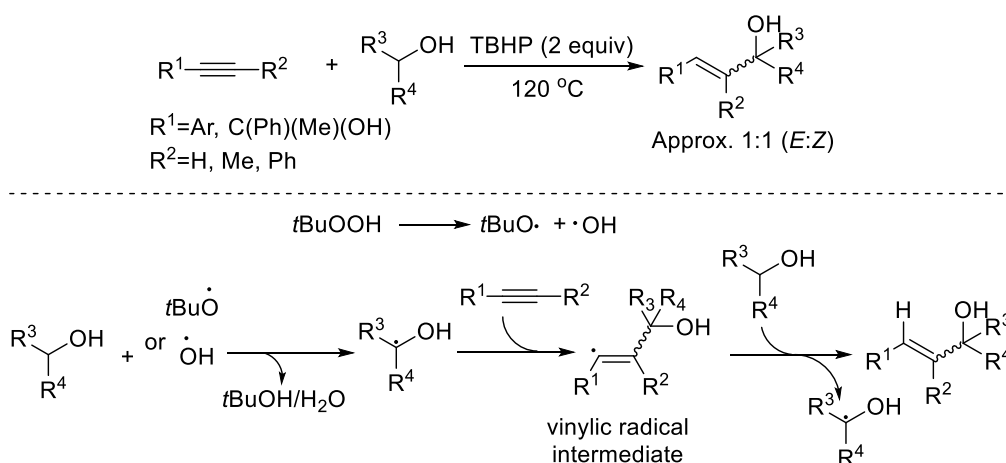
<sup>65</sup> He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. *Org. Lett.*, **2011**, *13*, 5016.

intermediate **A** prior to coupling with the  $\alpha$ -hydroxy carbon radical to give the  $\alpha$ -hydroxyalkylated product. This pathway was put forward based on the observation of homocoupling compound as minor product in their reaction.

### 2.1.2.2 Reactions of alkynes with alcohols

Aside from heterocyclic compounds, alkynes are effective coupling partners with alcohols, too. In 2009, Liu's group reported on preparation of 1:1 mixture of *E:Z* allylic alcohols from electron rich alkynes and alcohols using TBHP (Scheme 2-6).<sup>66</sup>

Mechanism wise, *tert*-butoxyl or hydroxyl radical formed from homolytic rupture of TBHP under high reaction temperature will abstract the  $\alpha$ -C-H bond in a homolytical fashion to reveal the  $\alpha$ -hydroxyalkyl radical. Addition of the latter to alkyne generates a vinylic radical intermediate that will in turn abstract hydrogen homolytically from another molecule of alcohol, thus giving the product as well as  $\alpha$ -hydroxyalkyl radical to propagate the radical chain, which will terminate at the complete consumption of alkyne.

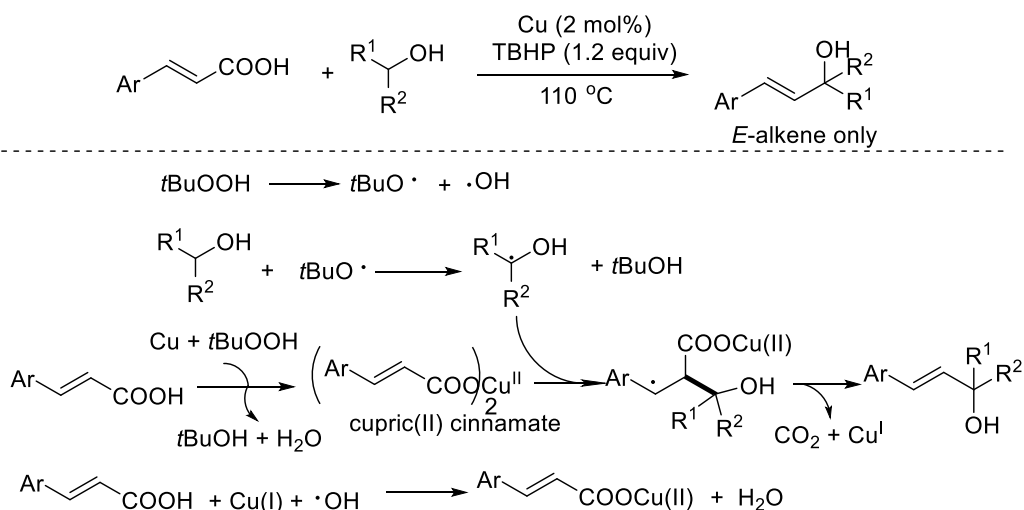


Scheme 2-6: 1:1 Synthesis of (*E:Z*)-allylic alcohols from alcohols and alkynes

<sup>66</sup> Liu, Z.-Q.; Sun, L.; Wang, J.-G.; Han, J.; Zhao, Y.-K.; Zhou, B. *Org. Lett.*, **2009**, *11*, 1437.

### 2.1.2.3 Reactions of cinnamic acids and alcohols

In succession, stereospecific access to *E*-allylic alcohols was realized in a copper-catalyzed decarboxylative coupling reaction of vinylic acids with simple alcohols by the same group (Scheme 2-7).<sup>67</sup>



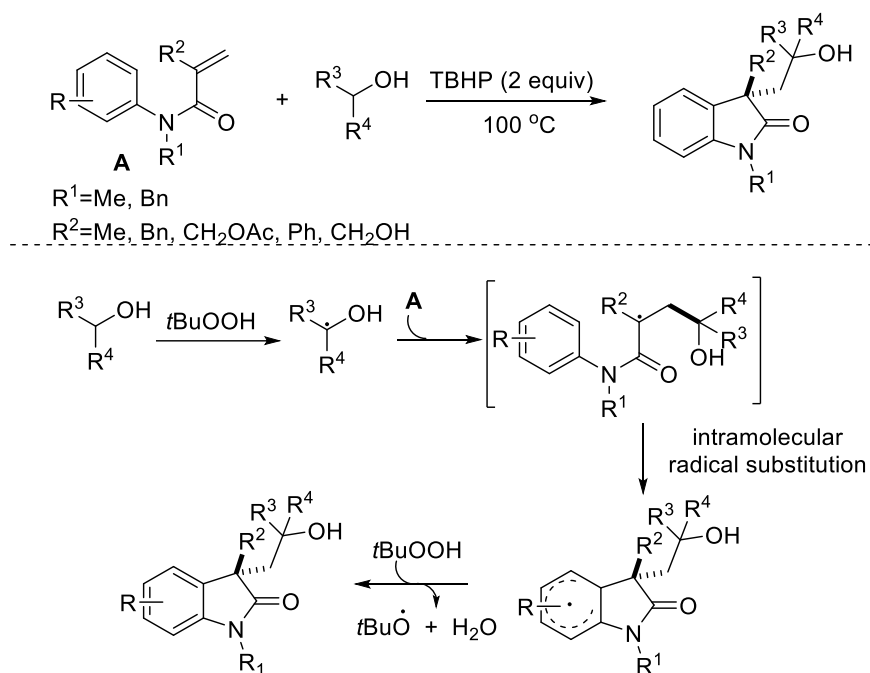
Scheme 2-7: Synthesis of (*E*)-allylic alcohols from cinnamic acids and alcohols

Mechanistic proposal suggested formation of cupric(II) cinnamate from acrylic acid with zerovalent copper and TBHP. The  $\alpha$ -carbon radical formed will add to the  $\alpha$ -position of double bond in Cu(II) cinnamate to give benzylic radical intermediate. Subsequent expulsion of carbon dioxide and Cu(I) species yields the allylic alcohol product. The Cu(II) cinnamate salt is regenerated after oxidation of Cu(I) by hydroxyl radical to complete the catalytic cycle. Aside from primary and secondary aliphatic alcohols, this strategy mediates stereoselective introduction of hydrocarbon and ether moieties onto aryl or heteroaryl-substituted acrylic acids to yield the corresponding (*E*)-alkenyl

<sup>67</sup> Cui, Z.-L.; Shang, X.-J.; Shao, X.-F.; Liu, Z.-Q. *Chem. Sci.*, **2012**, *3*, 2853.

derivatives. Failure of alkyl-substituted acrylic acids to undertake this chemistry was attributed to the instability of the respective radical intermediate.

#### 2.1.2.4 Reactions of acrylamides and alcohols

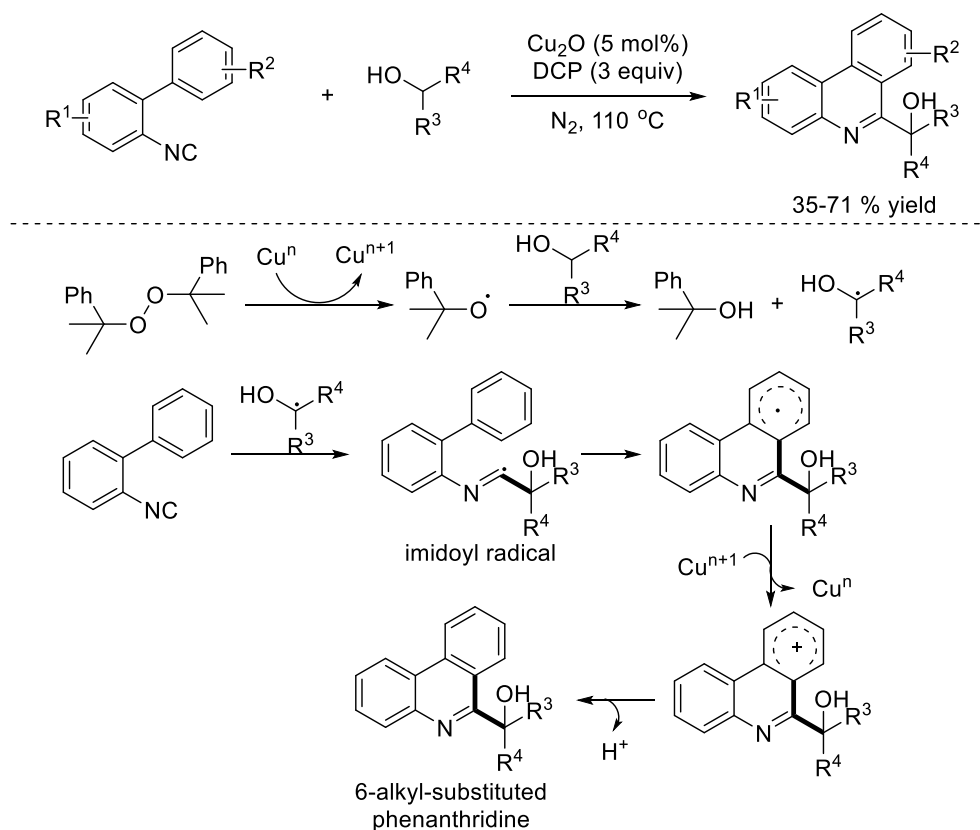


Scheme 2-8: Hydroxyalkylarylation of acrylamides with alcohols

Radical addition of alcohols could also be integrated in tandem-type reaction. A metal-free procedure reported by Duan and co-workers in 2013 demonstrated cascade addition-cyclization of primary and secondary alkyl alcohols with acrylamides to furnish an array of hydroxyl-containing oxindoles, exhibiting high reaction efficiency and atom economy (Scheme 2-8).<sup>68</sup> The radical intermediate generated from addition of  $\alpha$ -hydroxyalkyl radical to the acrylamide will undergo intramolecular radical substitution to produce the oxindole.

<sup>68</sup> Meng, Y.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem. Commun.* **2013**, 49, 7540.

### 2.1.2.5 Reactions of isocyanides with alcohols



Scheme 2-9: Free radical cascade cyclization of isocyanides with alcohols

In 2014, Liu's group has reported on another cascade radical addition/cyclization procedure to access 6-alkyl-substituted phenanthridines from isocyanides and alcohols (Scheme 2-9).<sup>69</sup> With the use of  $\text{Cu}_2\text{O}$  catalyst and dicumyl peroxide, a number of primary as well as, secondary alkyl alcohols could be used to prepare this heterocyclic scaffold, which involves  $\alpha$ - $\text{C}(\text{sp}^3)\text{-H}$  activation and  $\text{C}(\text{sp}^2)\text{-H}$  activation. With the aid of  $\text{Cu}^n$  catalyst, dicumyl peroxide will decompose to cumyloxy radical which abstracts the  $\alpha$ - $\text{C-H}$  bond of alcohol to give the  $\alpha$ -hydroxy carbon-centered radical. Addition of the latter to isocyanide gives rise to an imidoyl radical intermediate. Cyclization of this radical to the neighbouring benzene unit, followed by oxidation by  $\text{Cu}^{\text{n}+1}$

<sup>69</sup> Li, Z.; Fan, F.; Yang, J.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 3396.

species and loss of proton thus generates the phenanthridine product and regenerates the Cu<sup>n</sup> species to complete catalytic cycle. However, alternative mechanistic pathway which involves direct carbocation formation from imidoyl radical and followed by intramolecular electrophilic aromatic substitution to give the phenanthridine product could not be ruled out.

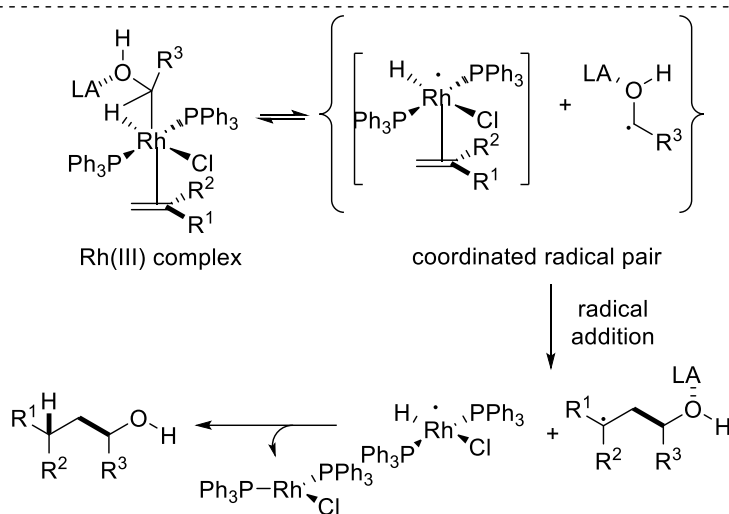
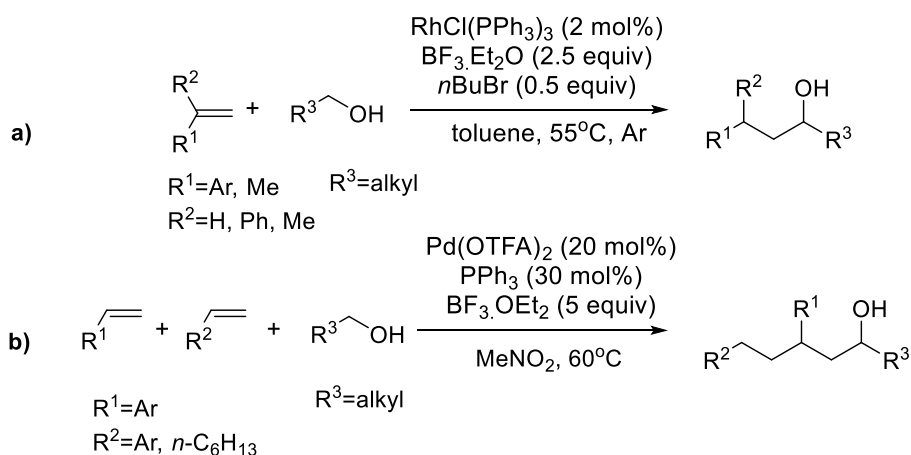
### 2.1.2.6 Hydroalkylation of alkenes with alcohols

Aside from peroxide-mediated  $\alpha$ -C(sp<sup>3</sup>)-H activation of alcohols, Tu and co-workers made exemplary contributions toward transition metal-mediated  $\alpha$ -C(sp<sup>3</sup>)-H activation, wherein the hydroalkylation of alkenes with alcohols through co-promotion of late transition metals and Lewis acids was initially introduced.<sup>70</sup> In 2005, an unprecedented direct coupling of primary unprotected alcohols with alkene was reported on using Rh catalyst and BF<sub>3</sub>.OEt<sub>2</sub> to generate secondary alcohols (Scheme 2-10-a). A mechanistic pathway which also involves radical intermediate is devised. Lewis acid is thought to coordinate with the oxygen in alcohol. Oxidative addition of this complex and alkene coordination to RhCl(PPh<sub>3</sub>)<sub>3</sub> gives Rh(III) complex. A radical pair comprises of alcohol radical and Rh-coordinated alkene is then generated. The secondary alcohol is yielded after Kharasch-like radical addition step.

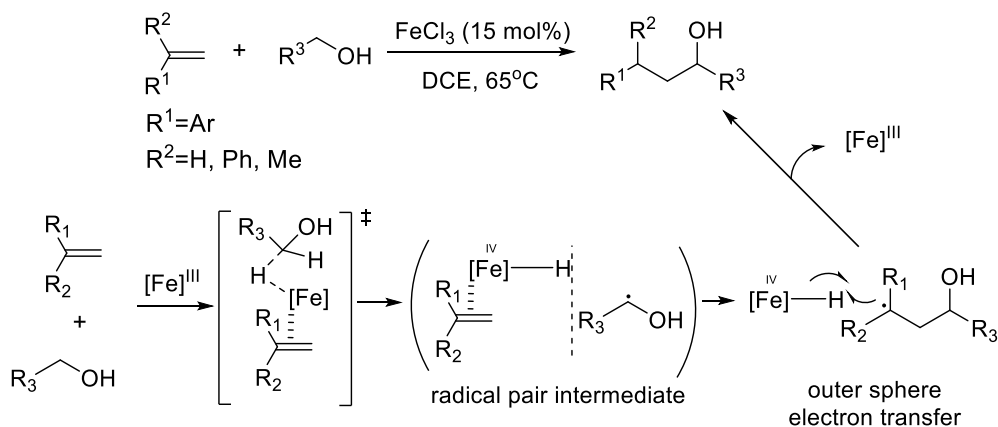
Later, a tandem dimerization of two alkene molecules and coupling with alcohol was effected using palladium catalyst and BF<sub>3</sub>.OEt<sub>2</sub>, constructing secondary alcohols of longer carbon chain (Scheme 2-10-b).

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<sup>70</sup> a) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A.; Zhao, Y.-M.; Xia, W.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10836. b) Jiang, Y.-J.; Tu, Y.-Q.; Zhang, E.; Zhang, S.-Y.; Cao, K.; Shi, L. *Adv. Synth. Catal.* **2008**, *350*, 552. c) Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Shi, L.; Cao, K.; Zhang, E. *Chem. Eur. J.* **2008**, *14*, 10201.



Scheme 2-10: Rhodium- and palladium-catalyzed direct coupling of alkenes with alcohols



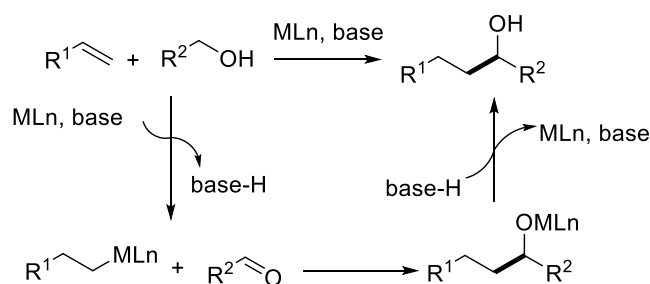
Scheme 2-11: FeCl<sub>3</sub>-catalyzed direct coupling of primary alcohols with aryl alkenes

An impressive advancement was then made by the same group to using environmentally-benign FeCl<sub>3</sub> without the need of co-promoter or additive for

this transformation (Scheme 2-11).<sup>71</sup> The devised mechanism describes the initial role of Fe(III) species to facilitate alkene activation and cleavage of the carbon-hydrogen bond adjacent to oxygen, thus forming the radical pair intermediate. Simultaneous radical addition to alkene and dissociation of Fe<sup>IV</sup> hydride, followed by outer sphere-type hydrogen transfer by Fe<sup>IV</sup> hydride yields the coupling product and Fe<sup>III</sup> species for next catalytic cycle. Notably, these reactions work efficiently for aryl alkenes and primary aliphatic alcohols.

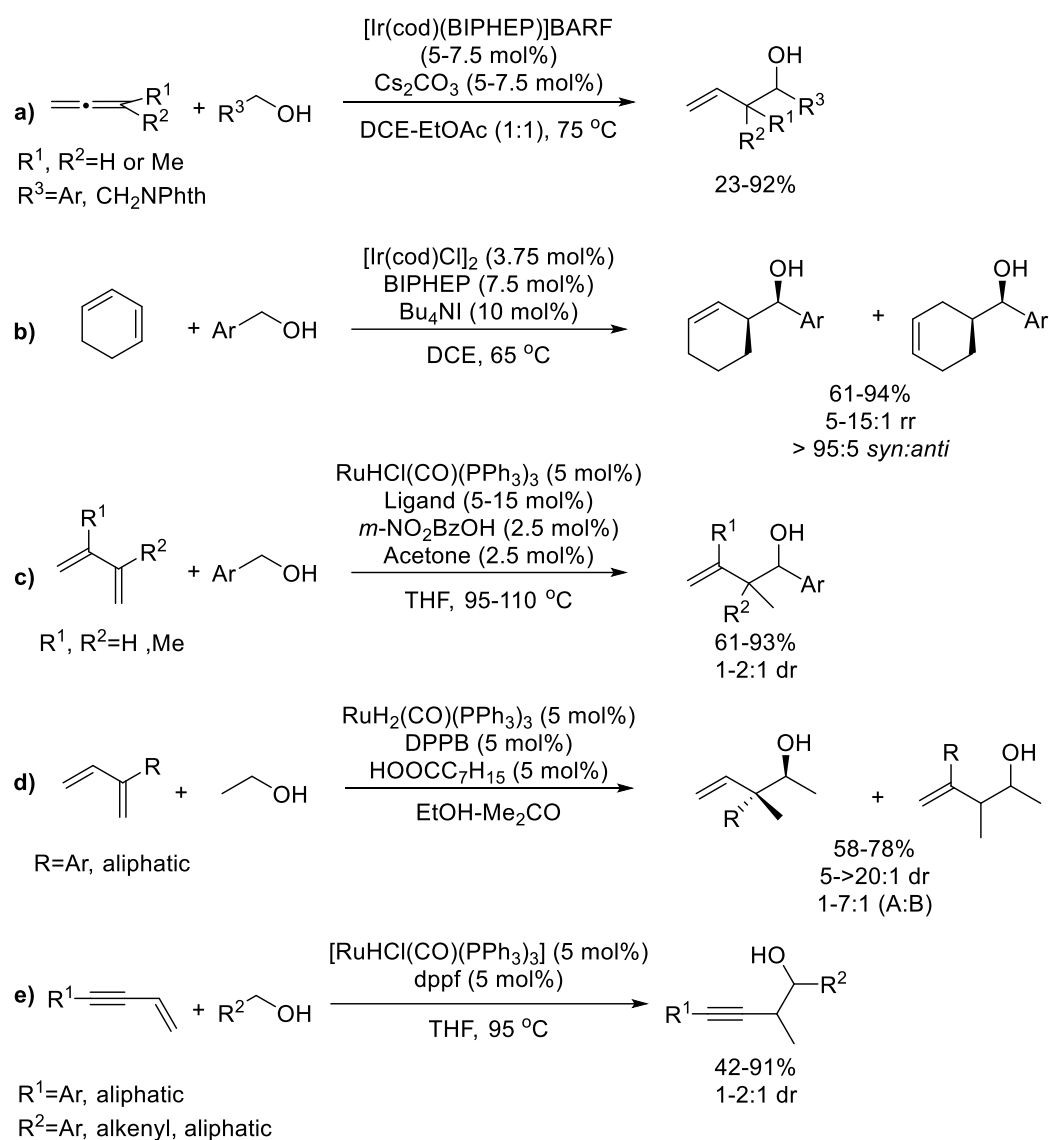
### 2.1.2.7 Transfer hydrogenative coupling (THC) of alcohols with unsaturated system

Another worth-mentioning reaction of alcohols with unsaturated systems is the THC reaction, which involves initial in-situ hydrogen-transfer oxidation of alcohols to aldehydes by a metal (Scheme 2-12). Mechanism wise, the metal hydride will add to the unsaturated bonds to form organometallic intermediate which then reacts with the aldehyde, re-generating the hydroxyl moiety. This strategy denotes departure from the employment of preformed organometallic reagents in carbonyl reduction chemistry.



Scheme 2-12: Schematic representation of THC reactions of alcohols with unsaturated system

<sup>71</sup> Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Zhang, F.-M.; Shi, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 8761.



Scheme 2-13: THC reactions of alcohols

From 2007, Krische and co-workers have developed a series of THC reactions of alcohols with substrates of various unsaturated C-C moieties such as allenes, dienes and enynes, which are representatively depicted in Scheme 2-13.<sup>72</sup> In general, aryl or aliphatic primary alcohols could be effective coupling partner for this chemistry. In the presence of alkynyl group, 1,3-enynes could couple with benzylic, allylic and aliphatic primary alcohols to form homopropargyl

<sup>72</sup> a) Bower, J. F.; Skucas, E.; Patman, TR. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134. b) Bower, J. F.; Patman, R. L.; Krische, M. J. *Org. Lett.* **2008**, *10*, 1033. c) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338. d) Han, H.; Krische, M. J. *Org. Lett.* **2010**, *12*, 2844. e) Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 5220.

alcohols (Scheme 2-13-e). Addition product on the triple bond was not formed, thus highlighting the chemoselectivity of this transformation.

### 2.1.3 Motivation for present work

1,3-Enynes are useful building blocks in synthetic chemistry gifted by the presence of multiple reactive sites, allowing them to demonstrate abundant chemistry in the construction of polysubstituted benzenes,<sup>73</sup> heterocycles,<sup>74</sup> conjugated alkenes<sup>75</sup> and other transformations.<sup>76</sup> To the best of our knowledge, the direct coupling of alcohols with 1,3-enynes and aryl alkenes together with another oxygen source to yield 1,3-dioxygenated compounds is nonetheless yet to be studied. It is envisioned that if the radical oxyalkylation of 1,3-enyne substrates could be assimilated with the direct  $\alpha$ -C(sp<sup>3</sup>)-H activation of alcohol, it will be an unprecedented step-economical approach to prepare propargylic 1,3-dioxygenated compound (Scheme 2-14-b).

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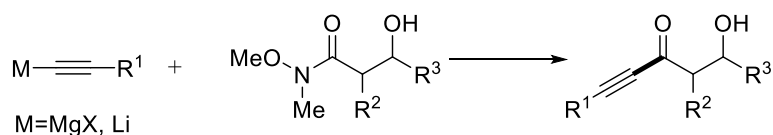
<sup>73</sup> Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.

<sup>74</sup> a) Miki, K.; Yokoi, T.; Nishino, F.; Kato, Y.; Washitaka, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 1557. b) Chen, J. L.; Zheng, F.; Huang, Y. G.; Quing, F. L. *J. Org. Chem.* **2011**, *76*, 652. c) Ackerman, L.; Sandmann, R.; Kaspar, L. *Org. Lett.* **2009**, *11*, 2031. d) Zhang, Y.; Herndon, J. W. *Org. Lett.* **2003**, *5*, 2043. e) Yoshida, M.; Al-Amin, M.; Shishido, K. *Synthesis* **2009**, 2454. f) Lee, C. Y.; Lin, J. L.; Chiu, C. C.; Lu, W. D.; Wu, M. J. *J. Org. Chem.* **2004**, *69*, 2106. g) Li, E.; Yao, W. J.; Xie, X.; Wang, C. Y.; Shao, Y. S.; Li, Y. Z. *Org. Biomol. Chem.* **2012**, *10*, 2960. h) Zhang, W.; Liu, N.; Schienebeck, C. M.; Decloux, K.; Zheng, S.; Werness, J. B.; Tang, W. *Chem. – Eur. J.* **2012**, *18*, 7296.

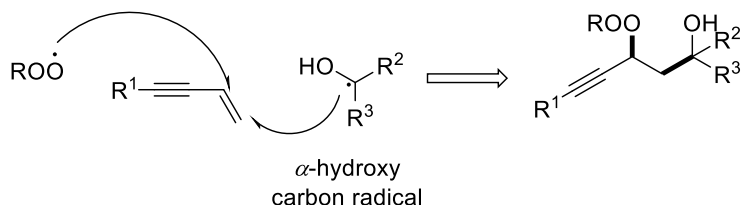
<sup>75</sup> a) Zweifel, G.; Polston, N. L. *J. Am. Chem. Soc.* **1970**, *92*, 4068. b) Betzer, J. F.; Ardisson, J.; Lallemand, J.-Y.; Pancrazi, A. *Tetrahedron Lett.* **1997**, *38*, 2279.

<sup>76</sup> a) Meng, F.; Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 11304. b) Mömming, C. M.; Kehr, G.; Wibbeling, B.; Fröhlich, R.; Schirmer, B.; Grimme, S.; Erker, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2414. c) Arai, S.; Koike, Y.; Hada, H.; Nishida, A. *J. Am. Chem. Soc.* **2010**, *132*, 4522. d) Mori, Y.; Onodera, G.; Kimura, M. *Chem. Lett.* **2014**, *43*, 97.

a) Conventional approach:



b) Our strategy:



Scheme 2-14: Conventional and our hypothesized strategy toward propargylic 1,3-dioxygenated compounds

On the other hand, organic peroxides are important in natural product chemistry and medicinal chemistry due to their ubiquity in naturally-occurring compounds as well as close relation to drug design and cell damage.<sup>77,78</sup> They are also versatile reaction intermediates that can undergo many transformations.<sup>79</sup> Conventional methods toward preparation of organic peroxides from hydroperoxides involve transition metal-catalyzed direct C-H peroxidation (Scheme 2-15-a)<sup>80</sup> or nucleophilic reaction with alkene acceptors or electrophiles (Scheme 2-15-b).<sup>81</sup>

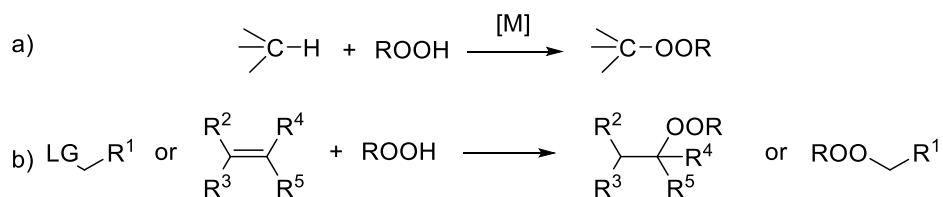
<sup>77</sup> a) Yin, H.; Xu, L.; Porter, N. A. *Chem. Rev.* **2011**, *111*, 5944. b) Posner, G. H.; O'Neill, P. M. *Acc. Chem. Res.* **2004**, *37*, 397.

<sup>78</sup> a) Liu, D.-Z.; Liu, J.-K. *Nat. Prod. Bioprospect.* **2013**, *3*, 161. b) Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55. c) Casteel, D. A. *Nat. Prod. Rep.* **1992**, *9*, 289. d) Rahm, F.; Hayes, P. Y.; Kitching, W. *Heterocycles* **2004**, *64*, 523.

<sup>79</sup> a) Rappoport, Z. In *The Chemistry of Peroxides*; Rappoport, Z., Ed.; Wiley: Chichester, U.K., 2006; Vol. 2. b) *Peroxide Chemistry*; Adam, W., Ed.; Wiley-VCH: Weinheim, Germany, 2000.

<sup>80</sup> a) Kharasch, M. S.; Pauson, P.; Nudenberg, W. *J. Org. Chem.* **1953**, *18*, 322. b) Terent'ev, A. O.; Borisov, D. A.; Semenov, V. V.; Chernyshev, V. V.; Dembitsky, V. M.; Nikishin, G. I. *Synthesis* **2011**, 2091. c) Wei, W.; Zhang, C.; Xu, Y.; Wan, X. *Chem. Commun.* **2011**, 10827. d) Gan, L.; Huang, S.; Zhang, X.; Zhang, A.; Cheng, B.; Cheng, H.; Li, X.; Shang, G. *J. Am. Chem. Soc.* **2002**, *124*, 13384.

<sup>81</sup> a) Zheng, W.; Wojtas, L.; Antilla, J. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6589. b) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134. c) Feng, X.; Yuan, Y.-Q.; Cui, H.-L.; Jiang, K.; Chen, Y. C. *Org. Biomol. Chem.* **2009**, *7*, 3660.



Scheme 2-15: General methods to prepare organic peroxides with hydroperoxides

As previously discussed in section 1.4.3, Li *et al.* has developed peroxidation-carbonylation of alkene using TBHP as the source of peroxy group, which is readily transformed to  $\alpha$ -carbonyl epoxides after post-reaction treatment with base. In the same regard, Klussman also reported the synthesis of  $\gamma$ -peroxyketones through peroxidation-alkylation of alkene with TBHP and ketones (refer to section 1.5.8.2). In their reports, the peroxy group could be chemically modified to a ketone aside from reduction to homoaldol product and alkyl ketones with a switch of solvent system. Thus, in view of the versatile transformation the peroxy group could offer as an oxygen functionality, we embark on the three-component direct coupling reaction of alcohol, hydroperoxide and simple alkenes towards assembly of propargylic 1,3-dioxygenated compounds.

## 2.2 Results and discussion

Table 2-1: Effect of solvents and copper catalysts on the reaction of enyne **1a** with alcohol **3a**<sup>a</sup>

Entry	Solvent	Copper catalysts (10 mol%)	Time (h)	Yield(%) <sup>b</sup>
1 <sup>c</sup>	Neat	Cu	24	23
2	DMF	Cu	6	<5
3	MeCN	Cu	6	38
4	Benzene	Cu	6	-
<b>5</b>	<b>DMSO</b>	<b>Cu</b>	<b>6</b>	<b>48</b>
6	DMSO	CuCl	4	36
7	DMSO	Cu <sub>2</sub> O	6	37
8	DMSO	CuI	4	39
9	DMSO	CuO	24	18
10	DMSO	-	10	28

<sup>a</sup>Unless otherwise noted, typical reaction conditions: **1a** (0.15 mmol), **2** (0.45 mmol, 5.5 M in decane), **3a** (2.10 mmol), copper catalyst (0.015 mmol), solvent (0.9 mL), 65 °C, air. <sup>b</sup>Isolated yields. <sup>c</sup>Reaction conditions: **1a** (0.15 mmol), **2** (0.45 mmol, 5.5 M in decane), **3a** (0.9 mL), Cu (0.015 mmol), 65 °C, air.

Initial studies were focused on investigating the coupling reaction of but-3-en-1-yn-1-yltriphenylsilane **1a**, 3.0 equiv of TBHP and 2-butanol **3a** using 10 mol% of zerovalent copper in neat condition at 65°C. Encouragingly, the attempt yielded 23% of desired peroxyalkylated enyne **4a** after 24 h (Table 2-1, entry 1).

We proceeded on with investigation of solvent effect to this reaction. Switching the solvent to DMSO enhanced the reaction efficiency to furnish 48% of the oxylalkylated enyne **4a** in 6 h (Table 2-1, entry 5). Reactions in DMF and benzene hardly gave any desired product whereas that in acetonitrile proceeded to yield 38% of  $\beta$ -peroxyalcohol (Table 2-1, entries 2-4). Fixing the solvent as DMSO, we turned our attention to examine the efficiency of other copper salts on this transformation. These copper salts did catalyze the reaction but none provided compatible efficiency as that by zerovalent copper (Table 2-1, entries

6-9). Noticeably, sluggish reaction was observed in the absence of any metal catalyst to give 28% of peroxy-alkylated product after 10 h (Table 2-1, entry 10).

Table 2-2: Effect of amount of alcohol and TBHP on the reaction of **1a** and **3a**<sup>a</sup>

Entry	ROH (equiv)	TBHP (equiv)	Time (h)	Yield (%) <sup>b</sup>
1	14	3	6	48
2	12	3	7	49
3	12	4	5	59
4	10	4	7	41
5	12	5	5	58
<b>6<sup>c</sup></b>	<b>12</b>	<b>4</b>	<b>2</b>	<b>68</b>

<sup>a</sup>Unless otherwise noted, reactions were performed with **1a** (0.15 mmol) and Cu (0.015 mmol) in DMSO (0.9 mL), 65 °C, air. <sup>b</sup>Isolated yields. <sup>c</sup>Under nitrogen atmosphere.

The effect of amount of alcohol substrate and TBHP to the model reaction was then studied using 10 mol% of copper powder in DMSO. The chemical yield was not affected when only 12 equiv of alcohol was added (Table 2-2, entries 1-2). Increasing the amount of TBHP to 4 equiv shortened the reaction time and gave the product in 59% (Table 2-2, entry 3). Further decrease in amount of alcohol affected the reaction negatively, resulted in only 41% of product after 7 h (Table 2-2, entry 4). Another equiv of TBHP was added to the model reaction, which resulted in similar outcome as that given by only 4 equiv of TBHP (Table 2-2, entries 3&5). Hence, the optimization study was continued using 4 equiv of TBHP and 12 equiv of alcohol. An inert atmosphere was beneficial to the reaction, as evident from improved chemical yield (68%) and shortened reaction time (2 h) (Table 2-2, entry 6).

Table 2-3: Effect of other metal catalysts on the reaction of **1a** with **3a**<sup>a</sup>

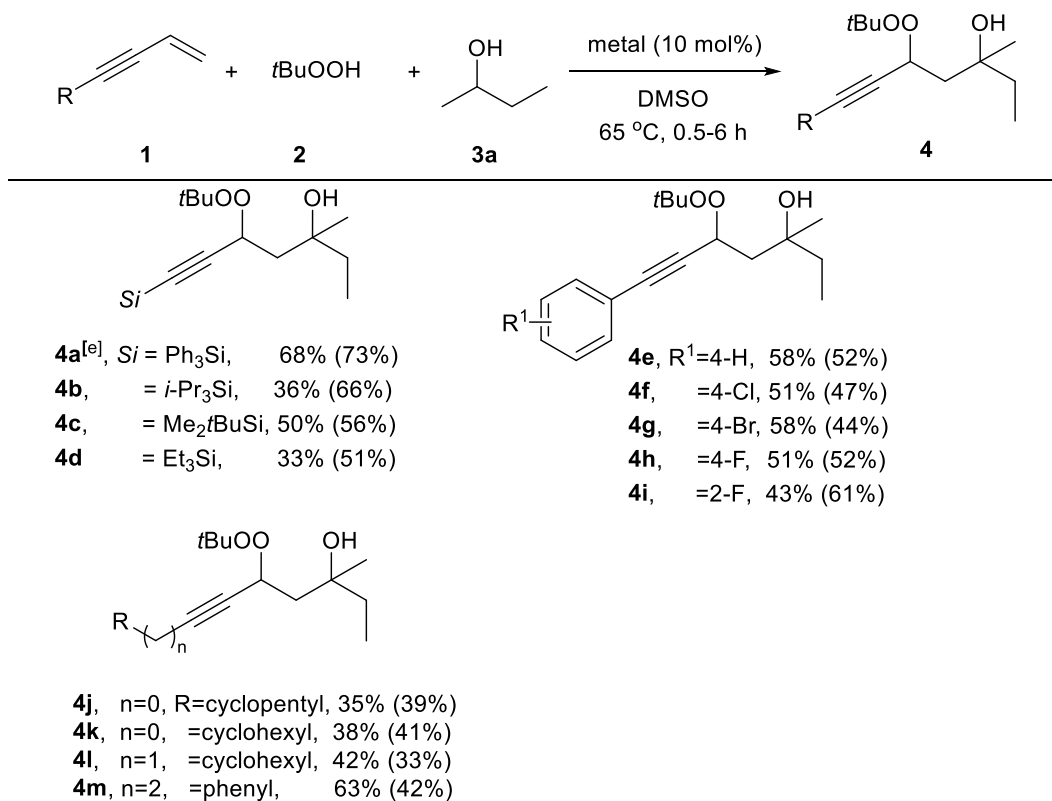
Entry	Catalyt (10 mol%)	Time (h)	Yield (%) <sup>b</sup>
1	FeBr <sub>2</sub>	3	30
2	FeBr <sub>3</sub>	8	<10
3	FeCl <sub>2</sub>	3	38
4	FeCl <sub>3</sub>	8	-
5	Fe(acac) <sub>3</sub>	8	-
6	Fe(TFAcac) <sub>3</sub>	8	trace
7	Fe	24	trace
8	CoCl <sub>2</sub>	8	-
9	Co(acac) <sub>3</sub>	8	-
10	CoBr <sub>2</sub>	8	-
11	Co(C <sub>5</sub> H <sub>5</sub> ) <sub>2</sub>	8	decomposed
12	CoCl <sub>2</sub> ·6H <sub>2</sub> O	8	-
13	Co(OAc) <sub>2</sub>	0.5	73
14	PdCl <sub>2</sub>	8	decomposed
15	Pd(OAc) <sub>2</sub>	8	decomposed

<sup>a</sup>Reaction conditions: **1a** (0.15 mmol), **2** (0.60 mmol, 5.5 M in decane), **3a** (1.80 mmol), catalyst (0.015 mmol), DMSO (0.9 mL), 65 °C, under nitrogen atmosphere. <sup>b</sup>Isolated yields.

With this optimized condition, we continued the search for better catalyst for this reaction. Some iron and palladium salts were also tested for their activities to the model reaction but to futile attempt (Table 2-3, entries 1-7, 14-15). FeBr<sub>2</sub> and FeCl<sub>2</sub> did catalyze the reaction but in lower efficiency (Table 2-3, entries 1&3).

To our delights, cobalt (II) acetate actually improved the efficiency of the reaction to yield 73% of product in 30 mins (Table 2-3, entry 13) while other cobalt salts exhibited no activity (Table 2-3, entries 8-12).

Table 2-4: Reaction scope of enyne **1** with **3a**<sup>a,b,c,d</sup>



<sup>a</sup>Unless otherwise noted, typical reaction conditions: **1** (0.3 mmol), **2** (1.2 mmol, 5.5 M in decane), **3a** (3.6 mmol), Cu (0.03 mmol), DMSO (1.8 mL), 65 °C, under nitrogen atmosphere.

<sup>b</sup>Isolated yields of inseparable diastereomers. <sup>c</sup>dr was approximated as 1:1. <sup>d</sup>Yields in parentheses refer to isolated yields of reactions performed with Co(OAc)<sub>2</sub> instead of Cu.

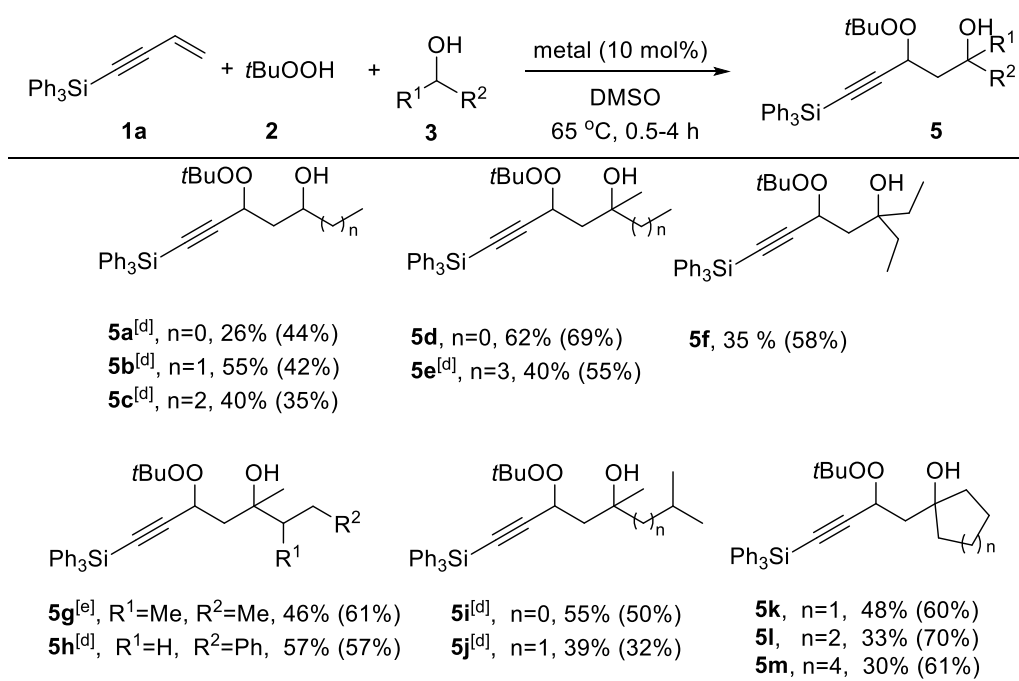
<sup>e</sup>Performed with **1a** (0.15 mmol), **2** (0.6 mmol, 5.5 M in decane), **3a** (1.8 mmol), Cu (0.015 mmol), DMSO (0.9 mL), 65 °C, under nitrogen atmosphere.

The reaction generality of 1,3-enyne substrates with respect to **3a** was studied under the optimized reaction condition using both copper and cobalt catalyst (Table 2-4). To our delight, different silyl protecting group tethered on the triple bond could be tolerated well to afford the respective products in 33-68% isolated yields when zerovalent copper powder was used as the catalyst (**4a-d**). In the presence of Co(OAc)<sub>2</sub> catalyst, these substrates underwent the reaction to give products in augmented chemical yields (51-73%).

Simple phenyl-substituted enynes were also tested for this reaction, giving 58% and 52% of  $\beta$ -peroxy alcohol **4e** in the presence of Cu and Co(OAc)<sub>2</sub>,

correspondingly. Other substituted-aryl enynes furnished the products **4f-i** in moderate yields of 43-61% in reactions with either catalyst. Halogen substituents on the phenyl ring survived the transformation, which approves the amenabilities of **4f-i** for further functionalization. Reactions on cyclic and linear aliphatic enynes could be successfully effected, furnishing the peroxidation-alkylation products **4j-m** in moderate to good yields. In a general trend, both Cu and Co(OAc)<sub>2</sub> demonstrated comparable applicability for these substrates.

Table 2-5: Reaction scope of **1a** with alcohol **3**<sup>a,b,c</sup>



<sup>a</sup>Unless otherwise noted, typical reaction conditions: **1a** (0.15 mmol), **2** (0.75 mmol, 5.5 M in decane), **3** (1.8 mmol), Cu (0.015 mmol), DMSO (0.9 mL), 65 °C, under nitrogen atmosphere. <sup>b</sup>Isolated yields. <sup>c</sup>Yields in parentheses refer to isolated yields of reactions performed with Co(OAc)<sub>2</sub> instead of Cu under typical reaction conditions. <sup>d</sup>dr was approximated as 1:1. <sup>e</sup>dr was approximated as 1:1:1:1.

Using triphenylsilylated-1,3-enyne **1a** as the standard coupling partner, the compatibility of the alcohol substrates was investigated using the optimal reaction condition (Table 2-5). Instead of 4 equiv of TBHP, additional 1 equiv

was utilized for these reactions as it was noted that some alcohol substrates afforded the products in better yields when the amount of TBHP was increased.

Gratefully, primary and secondary alcohols were compatible substrates for this reaction protocol. The linear primary alcohols including ethanol, *n*-propanol and *n*-butanol gave moderate yields of peroxy alcohol products **5a-c** (26%-55%) with either Cu or Co catalyst. *i*-Propanol underwent the transformation efficiently to give 69% of **5d** and other secondary alcohols were found to be equally well accommodated for this reaction. Appreciably, Co(OAc)<sub>2</sub> showed augmented competence for reactions of most substrates, albeit the declined reaction efficiency with increasing chain length on alcohol (**5d** and **5e**, **5i** and **5j**). Analogous trend was observed for cyclic alcohol substrates wherein Co(OAc)<sub>2</sub> catalyst could furnish the respective products, **5k-m** in discernible yields of 60-70%.

In a general trend, the isolated yields of  $\beta$ -peroxy alcohols were hampered due to the instability of the products under the reaction condition, especially with silyl moiety-bearing enyne substrates (**4a-m**, **5a-m**). It was speculated that the homogenous reaction mixture made viable with cobalt (II) acetate has shortened the reaction time (from average of 2-3 h for Cu to average of 0.75 h with Co(OAc)<sub>2</sub>, refer to supporting information for more details), thereby minimize product decomposition due to prolonged stirring.

The study was continued for reactions of simple aryl alkenes (Table 2-6). The reaction condition was slightly modified to accommodate this substrate class using **6a** and **3b** as model substrates. Distinguishably, reaction only worked when zerovalent copper powder was used while none of the cobalt salts exhibited catalytic activity for this transformation (Table 2-6, entries 11-15).

Heightened result was observed when the amount of ethanol and TBHP were reduced to 8 and 3 equivalents only (Table 2-6, entry 3). Also, strict exclusion of oxygen was not mandatory; instead, the reaction proceeded with slightly better yields under ambient air condition (Table 2-6, entry 4).

Table 2-6: The modification of reaction condition of styrene **6a** with alcohol **3b**<sup>a</sup>

Reaction scheme: Styrene (**6a**) + *t*BuOOH (**2**) + Ethanol (**3b**)  $\xrightarrow[80\text{ }^\circ\text{C, 24 h}]{\text{Catalyst (10 mol\%)}}$  1-phenylpropan-2-ol (**7a**)

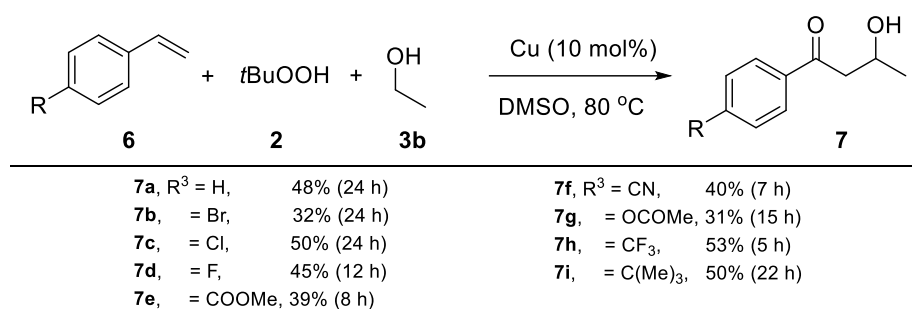
Entry	Catalyst (10 mol%)	<b>2</b> (equiv)	<b>3b</b> (equiv)	Yield (%) <sup>b</sup>
1	Cu	2	8	39
2	-	2	8	-
3	<b>Cu</b>	<b>3</b>	<b>8</b>	<b>48</b>
4 <sup>c</sup>	Cu	3	8	42
5	Cu	4	8	40
6	Cu	3	6	35
7	Cu	3	10	35
8 <sup>d</sup>	Cu	3	8	29
9 <sup>e</sup>	Cu	3	8	32
10 <sup>f</sup>	Cu	3	8	39
11	Co(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	3	8	-
12	CoCl <sub>2</sub>	3	8	-
13	CoBr <sub>2</sub>	3	8	-
14	Co(OAc) <sub>2</sub>	3	8	-
15	Co(acac) <sub>3</sub>	3	8	-

<sup>a</sup>Unless otherwise noted, typical reaction conditions: **6a** (0.50 mmol), **2** (5.5 M in decane), DMSO (3.0 mL), 80 °C, 24 h, air. <sup>b</sup>Isolated yield <sup>c</sup>Under nitrogen atmosphere. <sup>d</sup>TBHP solution, 70% in H<sub>2</sub>O <sup>e</sup>60 °C, 48 h <sup>f</sup>120 °C

Thereafter, reactions of ethanol with different styrene derivatives carrying diversified substituents were examined under this optimal condition (Table 2-7). Halogen bearing styrenes delivered the oxyalkylated product **7b-d** in moderate yields (32-50%). Functionalities including methyl ester, cyano and acetoxy group were well tolerated to furnish **7e**, **7f** and **7g** in moderate yields of 31-40%. It was noted that electronic property of styrenes did not exert observable effect on this reaction. The presence of both electron-rich and electron-deficient functional motifs such as trifluoromethyl as well as *tert*-butyl group on styrene

did not interfere with the efficiency of reaction to give corresponding **7h** and **7i** in 53% and 50% yield. The yields of  $\beta$ -hydroxy ketone **7** derived from aryl alkenes were generally affected by the inherent propensity of the styrenyl substrates to undergo oxidative cleavage, epoxidation as well as wacker oxidation.<sup>82</sup>

Table 2-7: Reaction scope of styrene derivatives **6** with **3b**<sup>a,b</sup>

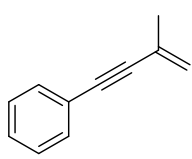
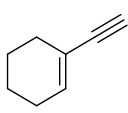
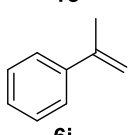
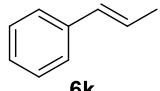

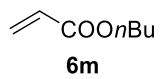


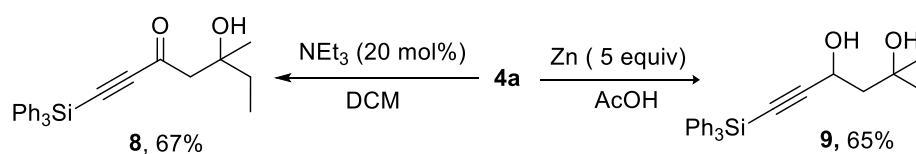
<sup>a</sup>Reaction conditions: **6** (0.50 mmol), **2** (1.5 mmol, 5.5 M in decane), **3b** (4.0 mmol), DMSO (3.0 mL), 80 °C, air. <sup>b</sup>Isolated yields

Moreover, this reaction was tested with several other olefins (Table 2-8) in addition to the terminal 1,3-enynes and aryl alkenes. The reactions of di-substituted terminal enyne **1n** and tri-substituted enyne **1o** were very messy with formation of coupling product in trace amount could be observed in reaction of **1n**. Di-substituted arylalkenes **6j-k** were poised to undergo oxidative side reactions with no formation of coupling product observed. Alkyl-substituted olefin **6l** and acrylate **6m** also gave no desired product but only intractable reaction mixture.

<sup>82</sup> a) Michel, B.; Steffens, L. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 8317. b) Romano, F.; Linden, A.; Mba, M.; Zonta, C.; Licini, G. *Adv. Synth. Catal.* **2010**, *352*, 2937. c) Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.* **2006**, *8*, 693.

Table 2-8: Alkenes failed to give peroxy alcohol products

Entry	Substrates	Results
1	 <b>1n</b>	<ul style="list-style-type: none"> <li>• messy reaction</li> <li>• trace amount of desired product</li> </ul>
2	 <b>1o</b>	<ul style="list-style-type: none"> <li>• intractable reaction mixture</li> </ul>
3	 <b>6j</b>	<ul style="list-style-type: none"> <li>• side reaction (oxidation) occurred</li> </ul>
4	 <b>6k</b>	<ul style="list-style-type: none"> <li>• side reaction (oxidation) occurred</li> </ul>
5	 <b>6l</b>	<ul style="list-style-type: none"> <li>• intractable reaction mixture</li> </ul>
6	 <b>6m</b>	<ul style="list-style-type: none"> <li>• intractable reaction mixture</li> </ul>

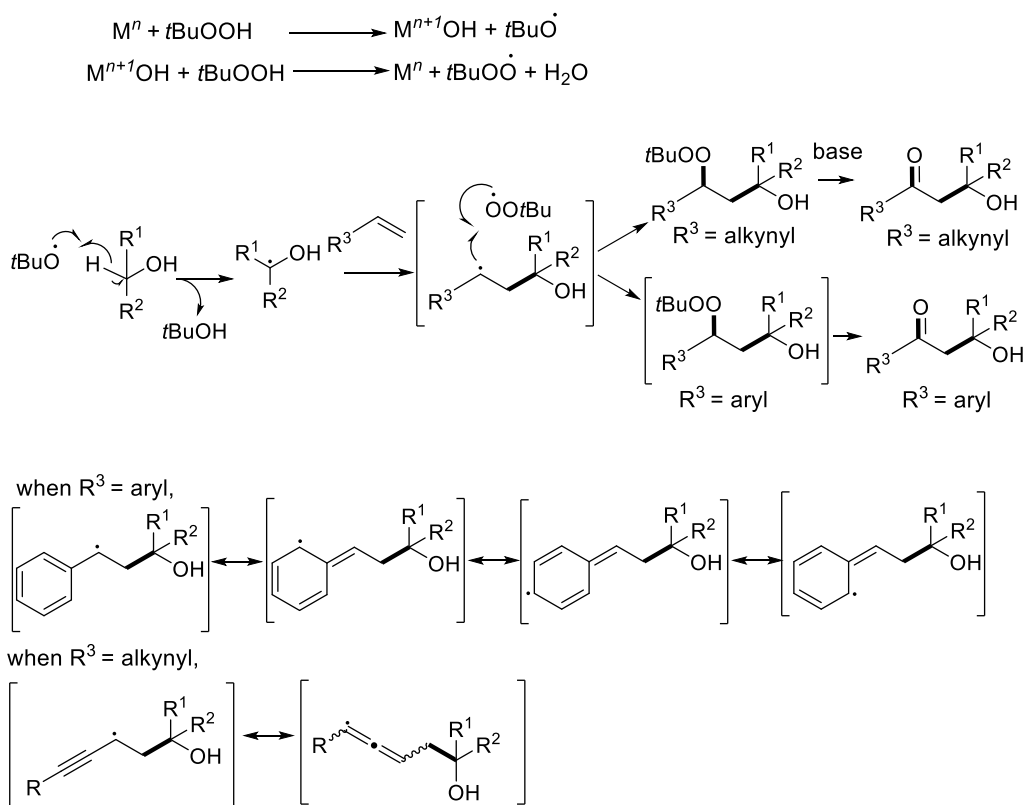


Scheme 2-16: Transformation of **4a**

Subsequently, the chemical modifications of the peroxy group on product were explored using **4a** as model substrate (Scheme 2-16). Under basic condition, Kornblum-DelaMare could be realized to provide the  $\beta$ -hydroxy ynone **8** in 70% yield in the presence of 20 mol% of triethylamine. When subjected under a

reduction condition, **4a** was transformed to the respective propargylic 1,3-diol **9** in 65% yield.<sup>83</sup>

On the basis of precedent reports and experimental observations, a mechanistic pathway has been devised for this reaction (Scheme 2-17).



Scheme 2-17: Proposed mechanism

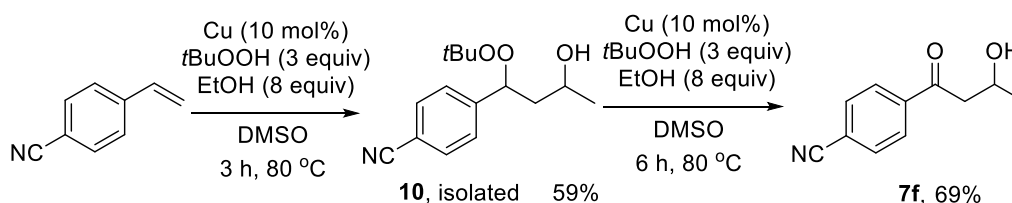
Copper/cobalt is postulated to first mediate the generation of *tert*-butoxyl and *tert*-peroxyl radicals from TBHP.<sup>36,84</sup>  $\alpha$ -Hydroxy carbon radical is formed from alcohol following hydrogen abstraction by *tert*-butoxyl radical, which will add onto the double bond of styrene or enyne. The unpaired electron resides adjacent to a  $\pi$  system (triple bond for enyne substrates and aryl group for

<sup>83</sup> a) Kropf, H. In *Houben-Weyl Methoden der Organischen Chemie, Peroxo-Verbindungen*; Kropf, H., Ed.; Thieme: Stuttgart, 1988; p 1102– 1116. b) Dai, P.; Dussault, P. H.; Trullinger, T. K. *J. Org. Chem.* **2004**, *69*, 2851.

<sup>84</sup> a) Turrà, N.; Neuenschwander, U.; Baiker, A.; Peeters, J.; Hermans, I. *Chem.–Eur. J.* **2010**, *16*, 13226. b) Spier, E.; Neuenschwander, U.; Hermans, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 1581. c) Zhang, J.; Jiang, J.; Xu, D.; Luo, Q.; Wang, H.; Chen, J.; Li, H.; Wang, Y.; Wan, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 1231.

styrene substrates), allowing this radical adduct intermediate to be stabilized by resonance, as depicted in Scheme 2-17.

Ensuing selective radical coupling between *tert*-peroxyl radical and the radical adduct intermediate gives the peroxidation-alkylation product. The peroxy group will undergo in-situ cleavage to the keto group due to the inherent reactivity of benzylic proton. The isolation of peroxy compound **10** is in accord with this speculation (Scheme 2-18). When subjected under the standard reaction condition, **10** transformed facilely to **7f**. It is also worth-noting that isolability of the peroxy intermediate for styrene substrates varied, as some might not be evident on TLC, probability subjective to inherent electronic property.



Scheme 2-18: Mechanistic study

### 2.3 Conclusion

Oxyalkylation of alkene was attained with an unprecedented copper- or cobalt-catalyzed three-component coupling with TBHP and alcohols, which proceeded through  $\alpha$ -C(sp<sup>3</sup>)-H activation of alcohols. 1,3-Enyes substituted with aliphatic, silyl and aryl groups underwent alkylation-peroxidation to give  $\beta$ -peroxy alcohols, which could be facilely transformed to propargylic 1,3-diol and  $\beta$ -hydroxyynone. Aryl alkenes were also effective substrates to give the corresponding  $\beta$ -hydroxyketones owing to the reactive benzylic proton.

## 2.4 Experimental section

### General Information:

Unless otherwise noted, all reagents and solvents were purchased from the commercial sources and used as received.

The *tert*-butyl hydroperoxide solution used was purchased from Sigma-Aldrich (5.5 M in decane, over molecular sieve 4Å).

Thin layer chromatography was used to monitor the reaction on Merck 60 F254 precoated silica gel plate (0.2 mm thickness). TLC spots were visualized by UV-light irradiation on Spectroline Model ENF-24061/F 254 nm. Other visualization method was staining with a basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating.

Flash column chromatography was performed using Merck silica gel 60 with analytical grade solvents as eluents.

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded using Bruker Avance 400 MHz spectrometers. Corresponding chemical shifts are reported in ppm downfield relative to TMS and were referenced to the signal of chloroform-d ( $\delta=7.26$ , singlet). Multiplicities were given as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd=doublets of doublet, td= triplet of doublet. Values of coupling constant are reported as *J* in Hz.

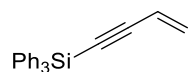
HRMS spectra were recorded on a Waters Q-ToF Premier Spectrometer.

**CAUTION:** We have never encountered any safety issue in working with or handling the compounds described in this work. Nonetheless; extra precaution should be taken when working with peroxides as mixture of peroxides and metal salts or metals will cause explosion. It is noteworthy to avoid exposing neat peroxides with heat, too.

## General procedure for the synthesis of 1,3-enynes (GP1) and their spectral data<sup>1</sup>:

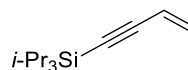
Copper (I) iodide (2.0 mol%) and tetrakis(triphenylphosphin)palladium (0.50 mol%) were dissolved in diethylamine (0.50 mL/1.0 mmol alkyne) under nitrogen which was then cooled to 0 °C. Alkyne (5.0 mmol, 1.0 equiv) and vinyl bromide (6.5 mmol, 1.3 equiv, 1.0 M in THF) were added and the resulting mixture was left to stir and warmed up to room temperature until complete conversion of the starting material was observed from TLC. The reaction mixture was washed with water followed by extraction with *n*-pentane/diethyl ether (1:1). The combined organic layers were washed with 1 M HCl and dried over magnesium sulfate. The crude product was afforded after evaporation of the solvent in vacuo and ready to be purified by column chromatography.

### 1a. but-3-en-1-yn-1-yltriphenylsilane:



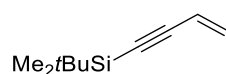
The title compound was prepared according to GP1 using (triphenylsilyl)acetylene (1.42 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.5 equiv) and was obtained after column chromatography with *n*-hexane as white solid (0.993 g, 3.20 mmol, 64%). **m.p.:** 97-99 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.76-7.65 (m, 6H); 7.50-7.35 (m, 9H); 5.98 (dd, *J* = 11.0, 17.6 Hz, 1H); 5.87 (dd, *J* = 2.2, 17.6 Hz, 1H); 5.64 (dd, *J* = 2.2, 11.0 Hz, 1H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 135.6, 133.4, 130.0, 129.3, 128.0, 117.1, 108.1, 90.0 **HRMS (ESI):** C<sub>22</sub>H<sub>19</sub>Si: Calculated: 311.1256; found: 311.1258

### 1b. but-3-en-1-yn-1-yltriisopropylsilane:



The title compound was prepared according to GP1 using (triisopropylsilyl)acetylene (0.912 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as colorless oil (0.938 g, 4.51 mmol, 90%). The analytical data are in accordance with the literature.<sup>2</sup> **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 5.84 (dd, *J* = 11.1, 17.6 Hz, 1H); 5.68 (dd, *J* = 2.4, 17.6 Hz, 1H); 5.48 (dd, *J* = 2.4, 11.1 Hz, 1H); 1.10-1.06 (m, 21H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 127.6, 117.6, 105.7, 91.4, 18.6, 11.3 **HRMS (ESI):** C<sub>13</sub>H<sub>25</sub>Si: Calculated: 209.1726; found: 209.1731

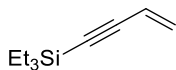
### 1c. but-3-en-1-yn-1-yl(tert-butyl)dimethylsilane:



The title compound was prepared according to GP1 using (*tert*-butyldimethylsilyl)acetylene (0.702 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as colorless oil (0.722g, 4.35 mmol, 87%). The analytical data are in

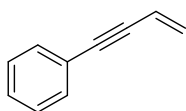
accordance with the literature.<sup>3</sup> **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  5.82 (dd,  $J = 11.2, 17.5$  Hz, 1H); 5.68 (dd,  $J = 2.4, 17.5$  Hz, 1H); 5.49 (dd,  $J = 2.4, 11.2$  Hz, 1H); 0.95 (s, 9H); 0.13 (s, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  127.8, 117.4, 104.4, 93.4, 26.1, 16.7, -4.6 **HRMS (ESI):** C<sub>10</sub>H<sub>19</sub>Si: Calculated: 167.1256; found: 167.1259

#### 1d. but-3-en-1-yn-1-yltriethylsilane:



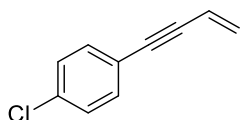
The title compound was prepared according to GP1 using (triethylsilyl)acetylene (0.702 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as colorless oil (0.765g, 4.60 mmol, 92%). **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  5.83 (dd,  $J = 11.1, 17.5$  Hz, 1H); 5.68 (dd,  $J = 2.2, 17.5$  Hz, 1H); 5.49 (dd,  $J = 2.2, 11.1$  Hz, 1H); 1.00 (t,  $J = 8.0$  Hz, 9H); 0.62 (q,  $J = 8.0$  Hz, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  127.8, 117.4, 105.0, 92.6, 7.4, 4.4 **HRMS (ESI):** C<sub>10</sub>H<sub>19</sub>Si: Calculated: 167.1256; found: 167.1261

#### 1e. but-3-en-1-yn-1-ylbenzene:



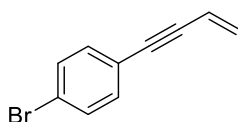
The title compound was prepared according to GP1 using phenylacetylene (0.511 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as colorless oil (0.590 g, 4.61 mmol, 92%). The analytical data are in accordance with the literature.<sup>4</sup> **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.51-7.43 (m, 2H); 7.37-7.29 (m, 3H); 6.03 (dd,  $J = 11.2, 17.5$  Hz, 1H); 5.74 (dd,  $J = 2.1, 17.5$  Hz, 1H); 5.55 (dd,  $J = 2.1, 11.2$  Hz, 1H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  131.6, 128.3, 128.3, 126.9, 123.2, 117.2, 90.0, 88.1 **HRMS (ESI):** C<sub>10</sub>H<sub>9</sub>: Calculated: 129.0704; found: 129.0711

#### 1f. 1-(but-3-en-1-yn-1-yl)-4-chlorobenzene:



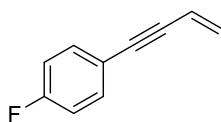
The title compound was prepared according to GP1 using 1-chloro-4-ethynylbenzene (0.683 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as colorless oil (0.574 g, 3.54 mmol, 71%). The analytical data are in accordance with the literature.<sup>1</sup> **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.37 (d,  $J = 8.4$  Hz, 2H); 7.29 (d,  $J = 8.8$  Hz, 2H); 6.00 (dd,  $J = 11.0, 17.4$  Hz, 1H); 5.74 (dd,  $J = 2.0, 17.4$  Hz, 1H); 5.56 (dd,  $J = 2.0, 11.0$  Hz, 1H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  134.3, 132.8, 128.7, 127.4, 121.7, 117.0, 89.0, 88.8 **HRMS (ESI):** C<sub>10</sub>H<sub>8</sub>Cl: Calculated: 163.0315; found: 163.0316

#### 1g. 1-bromo-4-(but-3-en-1-yn-1-yl)benzene:



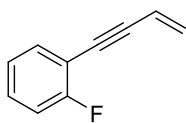
The title compound was prepared according to GP1 using 1-bromo-4-ethynylbenzene (0.905 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as colourless oil (0.671 g, 3.26 mmol, 65%). **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.45 (d, *J* = 8.4 Hz, 2H); 7.30 (d, *J* = 8.4 Hz, 2H); 6.00 (dd, *J* = 11.2, 17.5 Hz, 1H); 5.74 (dd, *J* = 1.7, 17.5 Hz, 1H); 5.57 (dd, *J* = 1.7, 11.2 Hz, 1H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 133.0, 131.6, 127.4, 122.6, 122.1, 117.0, 89.2, 89.0 **HRMS (ESI):** C<sub>10</sub>H<sub>8</sub>Br: Calculated: 206.9809; found: 206.9803

#### 1h. 1-(but-3-en-1-yn-1-yl)-4-fluorobenzene:



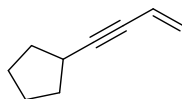
The title compound was prepared according to GP1 using 1-ethynyl-4-fluorobenzene (0.601 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as light yellow oil (0.529 g, 3.62 mmol, 72%). **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.47-7.38 (m, 2H); 7.05-6.97 (m, 2H); 6.00 (dd, *J* = 11.2, 17.5 Hz, 1H); 5.73 (dd, *J* = 2.1, 17.5 Hz, 1H); 5.55 (dd, *J* = 2.1, 11.2 Hz, 1H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 162.5 (d, *J*<sub>C-F</sub> = 248.0 Hz); 133.5 (d, *J*<sub>C-F</sub> = 8.0 Hz); 127.0; 119.3 (d, *J*<sub>C-F</sub> = 4.0 Hz); 117.1; 115.6 (d, *J*<sub>C-F</sub> = 22.0 Hz); 88.9; 87.8 (d, *J*<sub>C-F</sub> = 2.0 Hz) **HRMS (ESI):** C<sub>10</sub>H<sub>8</sub>F: Calculated: 147.0610; found: 147.0607

#### 1i. 1-(but-3-en-1-yn-1-yl)-2-fluorobenzene:



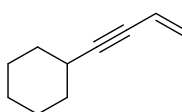
The title compound was prepared according to GP1 using 1-ethynyl-2-fluorobenzene (0.601 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as colourless oil (0.501 g, 3.43 mmol, 69%). **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.49-7.40 (m, 1H); 7.34-7.25 (m, 1H); 7.16-7.04 (m, 2H); 6.05 (dd, *J* = 11.1, 17.5 Hz, 1H); 5.78 (dd, *J* = 1.8, 17.5 Hz, 1H); 5.59 (dd, *J* = 1.8, 11.1 Hz, 1H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 162.6 (d, *J*<sub>C-F</sub> = 250.0 Hz); 133.5; 130.0 (d, *J*<sub>C-F</sub> = 7.0 Hz); 127.7; 124.0 (d, *J*<sub>C-F</sub> = 4.0 Hz); 117.0; 115.5 (d, *J*<sub>C-F</sub> = 20.0 Hz); 111.8 (d, *J*<sub>C-F</sub> = 15.0 Hz); 93.1 (d, *J*<sub>C-F</sub> = 3.0 Hz); 83.2 **HRMS (ESI):** C<sub>10</sub>H<sub>8</sub>F: Calculated: 147.0610; found: 147.0612

#### 1j. but-3-en-1-yn-1-ylcyclopentane:



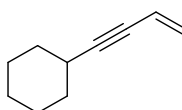
The title compound was prepared according to GP1 using cyclopentylacetylene (0.471 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as colorless oil (0.460 g, 3.83 mmol, 77%). **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 5.77 (ddd, *J* = 2.0, 11.0, 17.5 Hz, 1H); 5.50 (dd, *J* = 2.0, 17.5 Hz, 1H); 5.33 (dd, *J* = 2.0, 11.0 Hz, 1H); 2.78 (m, 1H); 2.00-1.86 (m, 2H); 1.77-1.50 (m, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 125.1, 117.7, 95.2, 78.8, 33.8, 30.7, 25.0 **HRMS (ESI):** C<sub>9</sub>H<sub>13</sub>: Calculated: 121.1017; found: 121.1018

#### 1k. but-3-en-1-yn-1-ylcyclohexane:



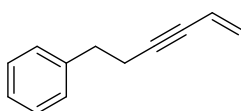
The title compound was prepared according to GP1 using cyclohexylacetylene (0.541 g, 5.0 mmol, 1.0 equiv) and vinyl bromide (1.3 equiv) and was obtained after column chromatography with *n*-hexane as colorless oil (0.578 g, 4.31 mmol, 86%). **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 5.79 (ddd, *J* = 2.0, 11.0, 17.5 Hz, 1H); 5.53 (dd, *J* = 2.0, 17.5 Hz, 1H); 5.36 (dd, *J* = 2.0, 11.0 Hz, 1H); 2.53- 2.41 (m, 1H); 1.85- 1.77 (m, 2H); 1.75- 1.66 (m, 2H); 1.56- 1.40 (m, 3H); 1.37- 1.25 (m, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 125.3, 117.7, 95.2, 79.2, 32.7, 29.7, 25.9, 24.9 **HRMS (ESI):** C<sub>10</sub>H<sub>15</sub>: Calculated: 135.1174; found: 135.1172

#### 1l. pent-4-en-2-yn-1-ylcyclohexane:



The title compound was prepared according to GP1 using 3-cyclohexyl-1-propyne (0.611 g, 5 mmol, 1 equiv) and vinyl bromide (1.30 equiv) and was obtained after column chromatography with *n*-hexane as colorless oil (0.623 g, 4.21 mmol, 84%). **The analytical data are in accordance with the literature.** **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 5.78 (ddt, *J* = 2.0, 11.0, 17.5 Hz, 1H); 5.53 (dd, *J* = 2.0, 17.5 Hz, 1H); 5.36 (dd, *J* = 2.0, 11.0 Hz, 1H); 2.19 (dd, *J* = 2.0, 6.8 Hz, 2H); 1.85-1.77 (m, 2H); 1.76-1.61 (m, 3H); 1.53-1.42 (m, 1H); 1.32-1.11 (m, 3H); 1.06-0.94 (m, 2H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 125.3, 117.7, 90.1, 80.2, 37.4, 32.8, 27.2, 26.3, 26.2 **HRMS (ESI):** C<sub>11</sub>H<sub>17</sub>: Calculated: 149.1330; found: 149.1331

#### 1m. hex-5-en-3-yn-1-ylbenzene:



The title compound was prepared according to GP1 using 4-phenyl-1-butyne (0.651 g, 5 mmol, 1 equiv) and vinyl bromide (1.30 equiv) and was obtained after column chromatography with *n*-hexane as colorless oil

(0.701 g, 4.49 mmol, 90%). **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.38-7.15 (m, 5H); 5.78 (ddt, *J* = 2.0, 10.9, 17.6 Hz, 1H); 5.56 (dd, *J* = 2.0, 17.6 Hz, 1H); 5.39 (dd, *J* = 2.0, 10.9 Hz, 1H); 2.87 (t, *J* = 7.6 Hz, 2H); 2.60 (td, *J* = 1.6, 7.6 Hz) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 140.7, 128.5, 128.4, 126.3, 125.8, 117.5, 90.3, 80.0, 35.1, 21.6 **HRMS (ESI):** C<sub>12</sub>H<sub>13</sub>: Calculated: 157.1017; found: 157.1016

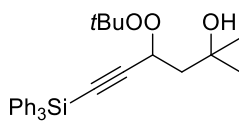
**General Procedure for the Synthesis of β-Peroxy Alcohols (4b-4m) (GP2) and their spectral data:**

To a mixture of copper powder (10 mol%, 1.9 mg) or cobalt(II) acetate (10 mol%, 5.3 mg) in 1.0 mL of DMSO, the enyne (0.3 mmol, 1 equiv.) in 0.8 mL of DMSO and alcohol (3.6 mmol, 12 equiv) were added under nitrogen atmosphere at room temperature. TBHP (5.5 M in decane, 1.2 mmol, 4 equiv) was then added dropwise to the reaction mixture. The reaction mixture was stirred at 65 °C until the starting material spot was observed to disappear from TLC. After cooling to room temperature, the resulting reaction mixture was directly subjected to flash column chromatography and the pure product was isolated as inseparable diastereomers with hexane/ethyl acetate (24:1). <sup>1</sup>H NMR spectra were not well resolved to give a more accurate diastereomeric ratio of the products. The d.r. was approximated as 1:1 judging from the <sup>13</sup>C NMR.

**General Procedure for the Synthesis of β-Peroxy Alcohols (4a, 5a-5m) (GP3) and their spectral data:**

To the mixture of enyne (0.15 mmol, 46.6 mg) and metal catalysts (10 mol%) [metal catalysts: copper (10 mol%, 0.95 mg) or cobalt(II) acetate (10 mol%, 2.7 mg)] in 0.9 mL of DMSO, alcohol (1.8 mmol, 12 equiv) was added under nitrogen atmosphere at room temperature. TBHP (5.5 M in decane, 0.75 mmol, 5 equiv) was then added dropwise to the reaction mixture. The reaction mixture was stirred at 65 °C until the starting material spot was observed to disappear from TLC. After cooling to room temperature, the resulting reaction mixture was directly subjected to flash column chromatography and the pure product was isolated as inseparable diastereomers with hexane/ethyl acetate (24:1). <sup>1</sup>H NMR spectra were not well resolved to give a more accurate diastereomeric ratio of the products. The d.r. was approximated as 1:1 judging from the <sup>13</sup>C NMR.

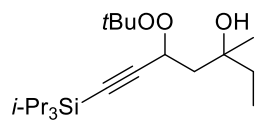
**4a. 5-(tert-butylperoxy)-3-methyl-7-(triphenylsilyl)hept-6-yn-3-ol:**



Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 68%, 2 h; Co(OAc)<sub>2</sub>: 73%, 0.5 h; **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers): δ 7.72-7.66 (m, 6H); 7.48-7.36 (m, 9H); 5.07-4.98 (m, 1H); 2.51 (bs, 1H, 1 diastereomer); 2.35 (bs, 1H, 1 diastereomer); 2.23-2.11 (m, 1H); 2.08-1.94 (m, 1H); 1.70-1.54 (m, 2H); 1.29-1.24 (m, 12H); 0.98-0.91 (2 t, *J* = 7.4 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>,

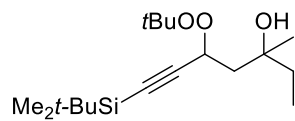
100 MHz, 2 diastereomers):  $\delta$  135.6, 133.3, 130.0, 128.0, 109.7, 109.6, 85.4, 80.8, 80.8, 71.9, 71.9, 71.4, 71.2, 44.3, 44.3, 35.4, 34.4, 26.7, 26.6, 26.0, 8.5, 8.2 **HRMS (ESI)**:  $C_{30}H_{37}O_3Si$ : Calculated: 473.2512; found: 473.2506

#### 4b. 5-(tert-butylperoxy)-3-methyl-7-(triisopropylsilyl)hept-6-yn-3-ol:



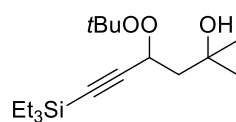
Synthesized according to the GP2 and isolated as colourless oil after purification by flash column chromatography. Cu: 36%, 6 h;  $Co(OAc)_2$ : 66%, 0.5 h;  **$^1H$  NMR**: ( $CDCl_3$ , 400 MHz, 2 diastereomer):  $\delta$  4.88-4.78 (m, 1H); 2.69 (bs, 1H); 2.11-1.99 (m, 1H); 1.95-1.80 (m, 1H); 1.63-1.49 (m, 2H); 1.26 (s, 9H); 1.23 (s, 3H, 1 diastereomer); 1.21 (s, 3H, 1 diastereomer); 1.11-1.03 (m, 21H); 0.95-0.89 (2 t, 3H)  **$^{13}C$  NMR**: ( $CDCl_3$ , 100 MHz, 2 diastereomers):  $\delta$  106.7, 106.6, 87.3, 87.1, 80.6, 80.5, 71.9, 71.8, 71.2, 71.1, 44.4, 44.3, 35.2, 34.6, 26.6, 26.1, 18.6, 11.2, 8.5, 8.3 **HRMS (ESI)**:  $C_{18}H_{43}O_3Si$ : Calculated: 371.2981; found: 371.2978

#### 4c. 7-(tert-butyltrimethylsilyl)-5-(tert-butylperoxy)-3-methylhept-6-yn-3-ol:



Synthesized according to the GP2 and isolated as colourless oil after purification by flash column chromatography. Cu: 50%, 3 h;  $Co(OAc)_2$ : 56%, 0.75 h;  **$^1H$  NMR**: ( $CDCl_3$ , 400 MHz, 2 diastereomers):  $\delta$  4.86-4.76 (m, 1H); 2.66 (bs, 1H, 1 diastereomer); 2.57 (bs, 1H, 1 diastereomer); 2.11-1.98 (m, 1H); 1.96-1.81 (m, 1H); 1.65-1.48 (m, 2H); 1.26 (s, 9H); 1.23 (s, 3H, 1 diastereomer); 1.20 (s, 3H, 1 diastereomer); 1.01-0.80 (m, 12H); 0.11 (s, 6H)  **$^{13}C$  NMR**: ( $CDCl_3$ , 100 MHz, 2 diastereomers):  $\delta$  105.6, 105.5, 89.2, 89.0, 80.68, 80.6, 71.9, 71.8, 71.2, 71.1, 44.3, 44.2, 35.3, 34.6, 26.6, 26.1 (signals of a pair of diastereomers for  $CH_3$  are hidden in the signal of  $\delta$  26.6 and  $\delta$  26.1, see the attached NMR spectrum in  $CD_2Cl_2$ ), 16.5, 8.5, 8.3, -4.7 **HRMS (ESI)**:  $C_{18}H_{37}O_3Si$ : Calculated: 329.2512; found: 329.2514

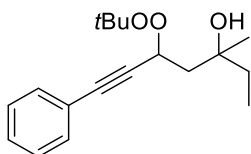
#### 4d. 5-(tert-butylperoxy)-3-methyl-7-(triethylsilyl)hept-6-yn-3-ol:



Synthesized according to the GP2 and isolated as colourless oil after purification by flash column chromatography. Cu: 33%, 3 h;  $Co(OAc)_2$ : 51%, 0.75 h;  **$^1H$  NMR**: ( $CDCl_3$ , 400 MHz, 2 diastereomers):  $\delta$  4.85-4.75 (m, 1H); 2.70 (bs, 1H, 1 diastereomer); 2.61 (bs, 1H, 1 diastereomer); 2.09-1.96 (m, 1H); 1.93-1.79 (m, 1H); 1.62-1.45 (m, 2H); 1.25 (s, 9H); 1.21 (s, 3H, 1

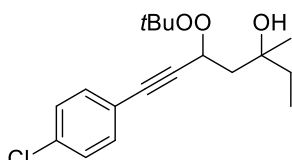
diastereomer); 1.19 (s, 3H, 1 diastereomer); 0.98 (t,  $J = 7.8$  Hz, 9H); 0.93-0.88 (2 t,  $J = 7.4$  Hz, 3H); 0.59 (q,  $J = 7.9$  Hz, 6H)  $^{13}\text{C}$  NMR: ( $\text{CDCl}_3$ , 100 MHz, 2 diastereomers):  $\delta$  106.1, 106.0, 88.4, 88.2, 80.6, 80.6, 71.8, 71.8, 71.2, 71.1, 44.3, 44.2, 35.2, 34.6, 26.5, 26.1, 8.4, 8.3, 7.4, 4.2 **HRMS (ESI)**:  $\text{C}_{18}\text{H}_{37}\text{O}_3\text{Si}$ : Calculated: 329.2512; found: 329.2511

#### 4e. 5-(tert-butylperoxy)-3-methyl-7-phenylhept-6-yn-3-ol:



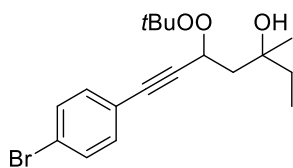
Synthesized according to the GP2 and isolated as colourless oil after purification by flash column chromatography. Cu: 58%, 2 h;  $\text{Co}(\text{OAc})_2$ : 52%, 0.75 h;  $^1\text{H}$  NMR: ( $\text{CDCl}_3$ , 400 MHz, 2 diastereomers):  $\delta$  7.46-7.42 (m, 2H); 7.33-7.28 (m, 3H); 5.10-5.00 (m, 1H); 2.58 (bs, 1H, 1 diastereomer); 2.46 (bs, 1H, 1 diastereomer); 2.20-2.09 (m, 1H); 2.04-1.91 (m, 1H); 1.66-1.55 (m, 2H); 1.31 (s, 9H); 1.28 (s, 3H, 1 diastereomer); 1.25 (s, 3H, 1 diastereomer); 0.95 (t,  $J = 7.6$  Hz, 3H)  $^{13}\text{C}$  NMR: ( $\text{CDCl}_3$ , 100 MHz, 2 diastereomers):  $\delta$  131.7, 128.4, 128.3; 122.7, 88.4, 88.4, 85.7, 85.6, 80.9, 80.8, 71.6, 71.9, 71.4, 71.3, 44.4, 44.4, 35.5, 34.6, 26.7, 26.6, 26.1, 8.5, 8.3 **HRMS (ESI)**:  $\text{C}_{18}\text{H}_{27}\text{O}_3$ : Calculated: 291.1960; found: 291.1969

#### 4f. 5-(tert-butylperoxy)-7-(4-chlorophenyl)-3-methylhept-6-yn-3-ol:



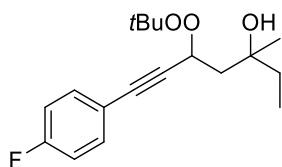
Synthesized according to the GP2 and isolated as light yellow oil after purification by flash column chromatography. Cu: 51%, 2.5 h;  $\text{Co}(\text{OAc})_2$ : 47%, 0.75 h;  $^1\text{H}$  NMR: ( $\text{CDCl}_3$ , 400 MHz, 2 diastereomers):  $\delta$  7.36 (d,  $J = 8.8$  Hz, 2H); 7.28 (d,  $J = 8.4$  Hz, 2H); 5.07-4.99 (m, 1H); 2.47 (bs, 1H, 1 diastereomer); 2.33 (bs, 1H, 1 diastereomer); 2.17-2.06 (m, 1H); 2.04-1.90 (m, 1H); 1.64-1.54 (m, 2H); 1.30 (s, 9H, 1 diastereomer), 1.29 (s, 9H, 1 diastereomer); 1.27 (s, 3H, 1 diastereomer), 1.24 (s, 3H, 1 diastereomer); 0.94 (t,  $J = 7.6$  Hz, 3H)  $^{13}\text{C}$  NMR: ( $\text{CDCl}_3$ , 400 MHz, 2 diastereomers):  $\delta$  134.5, 132.9, 128.7, 121.2, 89.5, 89.5, 84.5, 84.4, 81.0, 80.9, 72.0, 71.9, 71.4, 71.2, 44.4, 44.4, 35.5, 34.6, 26.7, 26.6, 26.7, 8.5, 8.3 **HRMS (ESI)**:  $\text{C}_{18}\text{H}_{26}\text{O}_3\text{Cl}$ : Calculated: 325.1570; found: 325.1574

#### 4g. 7-(4-bromophenyl)-5-(tert-butylperoxy)-3-methylhept-6-yn-3-ol:



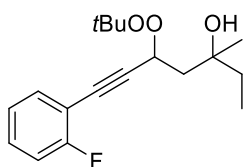
Synthesized according to the GP2 and isolated as light yellow oil after purification by flash column chromatography. Cu: 58%, 2 h; Co(OAc)<sub>2</sub>: 44%, 2 h; <sup>1</sup>H NMR: (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers): δ 7.44 (d, *J* = 8.4 Hz, 2H); 7.29 (d, *J* = 8.4 Hz, 2H); 5.07-4.99 (m, 1H); 2.46 (bs, 1H, 1 diastereomer); 2.33 (bs, 1H, 1 diastereomer); 2.19-2.06 (m, 1H); 2.04-1.89 (m, 1H); 1.64-1.54 (m, 2H); 1.29 (s, 9H); 1.27 (s, 3H, 1 diastereomer); 1.24 (s, 3H, 1 diastereomer); 0.94 (t, *J* = 7.4 Hz, 3H) <sup>13</sup>C NMR: (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers): δ 133.1, 131.6, 122.7, 121.7, 89.7, 89.7, 84.5, 84.5, 81.0, 81.0, 72.0, 71.9, 71.4, 71.2, 44.4, 44.4, 35.5, 34.6, 26.7, 26.6, 26.1, 8.5, 8.3 HRMS (ESI): C<sub>18</sub>H<sub>26</sub>O<sub>3</sub>Br: Calculated: 369.1065; found: 369.1077

#### 4h. 5-(tert-butylperoxy)-7-(4-fluorophenyl)-3-methylhept-6-yn-3-ol:



Synthesized according to the GP2 and isolated as colorless oil after purification by flash column chromatography. Cu: 51%, 3 h; Co(OAc)<sub>2</sub>: 52%, 0.75 h; <sup>1</sup>H NMR: (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers): δ 7.49-7.37 (m, 2H); 7.10-6.96 (m, 2H); 5.09-4.98 (m, 1H); 2.51 (bs, 1H, 1 diastereomer); 2.38 (bs, 1H, 1 diastereomer); 2.20-2.05 (m, 1H); 2.04-1.89 (m, 1H); 1.67-1.53 (m, 2H); 1.30 (s, 9H, 1 diastereomer); 1.29 (s, 9H, 1 diastereomer); 1.27 (s, 3H, 1 diastereomer); 1.24 (s, 3H, 1 diastereomer); 0.94 (t, *J* = 7.4 Hz, 3H) <sup>13</sup>C NMR: (CDCl<sub>3</sub>, 100 MHz, 2 diastereomers): δ 162.61 (d, *J*<sub>C-F</sub> = 248.0 Hz), 133.60 (d, *J*<sub>C-F</sub> = 7.0 Hz), 118.74, 115.59 (d, *J*<sub>C-F</sub> = 22.0 Hz), 88.1, 84.6, 84.5, 81.0, 80.9, 71.9, 71.9, 71.4, 71.23, 44.5, 44.4, 35.5, 34.6, 26.7, 26.6, 26.1, 8.5, 8.3 HRMS (ESI): C<sub>18</sub>H<sub>26</sub>O<sub>3</sub>F: Calculated: 309.1866; found: 309.1866

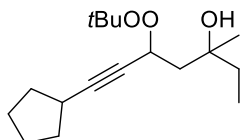
#### 4i. 5-(tert-butylperoxy)-7-(2-fluorophenyl)-3-methylhept-6-yn-3-ol:



Synthesized according to the GP2 and isolated as colorless oil after purification by flash column chromatography. Cu: 43%, 3 h; Co(OAc)<sub>2</sub>: 61%, 0.75 h; <sup>1</sup>H NMR: (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers): δ 7.43 (td, *J* = 1.7, 7.3 Hz, 1H); 7.34-7.23 (m, 1H); 7.12-7.02 (m, 2H); 5.13-5.02 (m, 1H); 2.54 (bs, 1H, 1 diastereomer), 2.42 (bs, 1H, 1 diastereomer); 2.21-2.08 (m, 1H); 2.07-

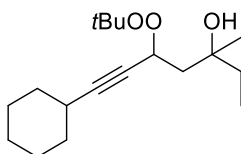
1.92 (m, 1H); 1.70-1.54 (m, 2H); 1.30 (s, 9H); 1.28 (s, 3H, 1 diastereomer); 1.25 (s, 3H, 1 diastereomer); 0.95 (t,  $J = 7.4$  Hz, 3H)  **$^{13}\text{C}$  NMR:** ( $\text{CDCl}_3$ , 100 MHz, 2 diastereomers):  $\delta$  162.9 (d,  $J_{\text{C-F}} = 250.0$  Hz), 133.5, 130.2 (d,  $J_{\text{C-F}} = 8.0$  Hz), 123.9 (d,  $J_{\text{C-F}} = 4.0$  Hz), 115.5 (d,  $J_{\text{C-F}} = 21.0$  Hz), 111.3 (d,  $J_{\text{C-F}} = 17.0$  Hz), 93.7, 81.0, 80.9, 79.1, 79.0, 71.9, 71.9, 71.4, 71.3, 44.3, 44.3, 35.4, 34.6, 26.6, 26.6, 26.06, 8.5, 8.3 **HRMS (ESI):**  $\text{C}_{18}\text{H}_{26}\text{O}_3\text{F}$ : Calculated: 309.1866; found: 309.1867

#### 4j. 5-(tert-butylperoxy)-7-cyclopentyl-3-methylhept-6-yn-3-ol:



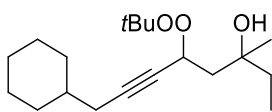
Synthesized according to the GP2 and isolated as colourless oil after purification by flash column chromatography. Cu: 35%, 0.75 h;  $\text{Co}(\text{OAc})_2$ : 39%, 0.75 h;  **$^1\text{H}$  NMR:** ( $\text{CDCl}_3$ , 400 MHz, 2 diastereomers):  $\delta$  4.84-4.74 (m, 1H); 2.76 (bs, 1H, 1 diastereomer); 2.69 (bs, 1H, 1 diastereomer); 2.70-2.60 (m, 1H); 2.07-1.96 (m, 1H); 1.95-1.79 (m, 3H); 1.75-1.66 (m, 2H); 1.65-1.49 (m, 6H); 1.27 (s, 9H); 1.22 (s, 3H, 1 diastereomer); 1.19 (s, 3H, 1 diastereomer); 0.92 (t,  $J = 7.6$  Hz, 3H)  **$^{13}\text{C}$  NMR:** ( $\text{CDCl}_3$ , 100 MHz, 2 diastereomers):  $\delta$  91.3, 91.1, 80.6, 80.6, 78.8, 78.7, 71.8, 71.2, 71.2, 44.5, 44.3, 35.2, 34.7, 33.6, 30.2, 26.6, 26.5, 26.1, 24.9, 8.4, 8.3 **HRMS (ESI):**  $\text{C}_{17}\text{H}_{31}\text{O}_3$ : Calculated: 283.2273; found: 283.2274

#### 4k. 5-(tert-butylperoxy)-7-cyclohexyl-3-methylhept-6-yn-3-ol:



Synthesized according to the GP2 and isolated as colourless oil after purification by flash column chromatography. Cu: 38%, 0.5 h;  $\text{Co}(\text{OAc})_2$ : 41%, 0.75 h;  **$^1\text{H}$  NMR:** ( $\text{CDCl}_3$ , 400 MHz, 2 diastereomers):  $\delta$  4.86-4.76 (m, 1H); 2.78 (bs, 1H, 1 diastereomer); 2.71 (bs, 1H, 1 diastereomer); 2.46-2.36 (m, 1H); 2.08-1.95 (m, 1H); 1.90-1.76 (m, 3H); 1.72-1.65 (m, 2H); 1.61-1.48 (m, 3H); 1.48-1.36 (m, 2H); 1.32-1.17 (m, 15H); 0.91 (t,  $J = 7.6$  Hz, 3H)  **$^{13}\text{C}$  NMR:** ( $\text{CDCl}_3$ , 100 MHz, 2 diastereomers):  $\delta$  91.2, 91.0, 80.6, 80.5, 79.2, 79.1, 71.8, 71.2, 71.1, 44.5, 44.3, 35.2, 34.7, 32.5, 29.1, 26.6, 26.5, 26.1, 25.8, 24.9, 8.4, 8.3 **HRMS (ESI):**  $\text{C}_{18}\text{H}_{33}\text{O}_3$ : Calculated: 297.2430; found: 297.2429

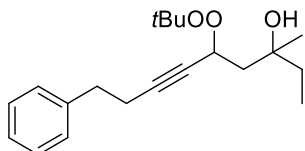
#### 4l. 5-(tert-butylperoxy)-8-cyclohexyl-3-methyloct-6-yn-3-ol:



Synthesized according to the GP2 and isolated as colourless oil after purification by flash column chromatography. Cu: 42%, 0.5 h;  $\text{Co}(\text{OAc})_2$ : 33%, 0.75 h;  **$^1\text{H}$  NMR:** ( $\text{CDCl}_3$ , 400 MHz, 2 diastereomers):  $\delta$

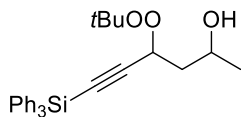
4.93-4.71 (m, 1H); 2.68 (bs, 1H, 1 diastereomer ); 2.61 (bs, 1H, 1 diastereomer ); 2.16-2.08 (m, 2H); 2.05-1.96 (m, 1H); 1.91-1.75 (m, 3H); 1.74-1.61 (m, 3H); 1.60-1.40 (m, 3H); 1.26 (s, 9H); 1.23-1.08 (m, 6H); 1.04-0.94 (m, 2H); 0.91 (t,  $J = 7.6$  Hz, 3H)  **$^{13}\text{C}$  NMR:** (CDCl<sub>3</sub>, 100 MHz, 2 diastereomers):  $\delta$  85.9, 85.7, 80.6, 80.5, 80.1, 80.0, 71.8, 71.2, 71.1, 44.6, 44.4, 37.2, 35.3, 34.6, 32.7, 26.6, 26.5, 26.2, 26.1, 26.0, 8.4, 8.3 **HRMS (ESI):** C<sub>19</sub>H<sub>35</sub>O<sub>3</sub>: Calculated: 311.2586; found: 311.2577

#### 4m. 5-(tert-butylperoxy)-3-methyl-9-phenylnon-6-yn-3-ol:



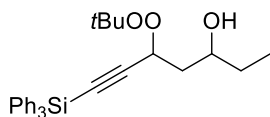
Synthesized according to the GP2 and isolated as colourless oil after purification by flash column chromatography. Cu: 63%, 1 h; Co(OAc)<sub>2</sub>: 42%, 0.75 h;  **$^1\text{H}$  NMR:** (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers):  $\delta$  7.33-7.16 (m, 5H); 4.83-4.73 (m, 1H); 2.83 (t,  $J = 7.6$  Hz, 2H); 2.53 (td,  $J = 7.6$  and 1.6 Hz, 2H); 2.05-1.93 (m, 1H); 1.89-1.75 (m, 1H); 1.58-1.46 (m, 2H); 1.26 (2 s, 9H); 1.20 (s, 3H, 1 diastereomer); 1.17 (s, 3H, 1 diastereomer); 0.95-0.87 (2 t,  $J = 7.6$  Hz, 3H)  **$^{13}\text{C}$  NMR:** (CDCl<sub>3</sub>, 100 MHz, 2 diastereomers):  $\delta$  140.5, 128.5, 128.4, 126.3, 86.0, 85.8, 80.7, 80.7, 80.0, 80.0, 71.8, 71.8, 71.2, 71.1, 44.7, 44.5, 35.3, 34.9, 34.7, 26.5, 26.5, 26.0; 21.0, 8.4, 8.3 **HRMS (ESI):** C<sub>20</sub>H<sub>31</sub>O<sub>3</sub>: Calculated: 319.2273; found: 319.2272

#### 5a. 4-(tert-butylperoxy)-6-(triphenylsilyl)hex-5-yn-2-ol:



Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 26%, 3 h; Co(OAc)<sub>2</sub>: 44%, 0.75 h;  **$^1\text{H}$  NMR:** (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers):  $\delta$  7.69-7.62 (m, 6H); 7.46-7.34 (m, 9H); 4.99-4.94 (m, 1H, 1 diastereomer); 4.93-4.88 (m, 1H, 1 diastereomer); 4.23-4.08 (m, 1H); 2.31-1.89 (m, 3H); 1.28-1.21 (m, 12H)  **$^{13}\text{C}$  NMR:** (CDCl<sub>3</sub>, 100 MHz, 2 diastereomers):  $\delta$  135.6, 133.3, 133.3, 130.0, 128.0, 108.7, 108.7, 85.9, 85.9, 81.0, 80.9, 73.1, 72.0, 66.1, 64.6, 42.7, 26.5, 23.6, 23.4 **HRMS (ESI):** C<sub>28</sub>H<sub>33</sub>O<sub>3</sub>Si: Calculated: 445.2199; found: 445.2191

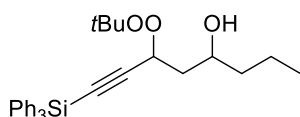
#### 5b. 5-(tert-butylperoxy)-7-(triphenylsilyl)hept-6-yn-3-ol:



Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 55%, 2 h; Co(OAc)<sub>2</sub>: 42%, 0.75 h;  **$^1\text{H}$  NMR:** (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers):  $\delta$  7.71-7.64 (m, 6H); 7.47-7.35 (m, 9H); 5.01 (dd,  $J = 4.4, 7.6$  Hz, 1H, 1 diastereomer); 4.94 (t,  $J = 7.0$  Hz, 1H, 1 diastereomer); 4.00-3.81 (2 m, 1H); 2.27 (d,  $J = 2.8$

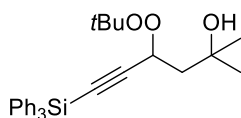
Hz, 1H, 1 diastereomer); 2.17 (d,  $J = 3.6$  Hz, 1H, 1 diastereomer); 2.10-1.91 (m, 2H); 1.59-1.49 (m, 2H); 1.27 (2 s, 9H); 1.00-0.93 (2 t,  $J = 7.6$  Hz, 3H)  $^{13}\text{C}$  NMR: ( $\text{CDCl}_3$ , 100 MHz, 2 diastereomers):  $\delta$  135.6, 133.3, 133.3, 130.0, 130.0, 128.0, 108.9, 108.9, 85.8, 85.8, 81.0, 80.9, 73.2, 72.1, 71.2, 69.6, 40.8, 40.7, 30.4, 30.1, 26.5, 9.9, 9.8 **HRMS (ESI)**:  $\text{C}_{29}\text{H}_{35}\text{O}_3\text{Si}$ : Calculated: 459.2355; found: 459.2352

#### 5c. 6-(tert-butylperoxy)-8-(triphenylsilyl)oct-7-yn-4-ol:



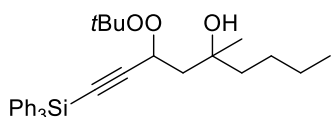
Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 40%, 2 h;  $\text{Co}(\text{OAc})_2$ : 35%, 0.5 h;  $^1\text{H}$  NMR: ( $\text{CDCl}_3$ , 400 MHz, 2 diastereomers):  $\delta$  7.70-7.66 (m, 6H); 7.46-7.36 (m, 9H); 5.00 (dd,  $J = 4.6, 7.4$  Hz, 1H, 1 diastereomer); 4.93 (t,  $J = 7.0$  Hz, 1H, 1 diastereomer); 4.08-3.89 (2 m, 1H); 2.23 (d,  $J = 3.6$  Hz, 1H, 1 diastereomer); 2.15 (d,  $J = 4.0$  Hz, 1H, 1 diastereomer); 2.08-1.92 (m, 2H); 1.56-1.36 (m, 4H); 1.27 (s, 9H, 1 diastereomer); 1.26 (s, 9H, 1 diastereomer); 0.93 (t,  $J = 6.8$  Hz, 3H)  $^{13}\text{C}$  NMR: ( $\text{CDCl}_3$ , 100 MHz, 2 diastereomers):  $\delta$  135.6, 133.3, 133.3, 130.0, 130.0, 128.0, 108.9, 108.8, 85.8, 81.0, 80.9, 73.2, 72.1, 69.5, 68.0, 41.2, 41.1, 39.7, 39.5, 26.5, 26.5, 18.8, 18.7, 14.0, 14.0 **HRMS (ESI)**:  $\text{C}_{30}\text{H}_{37}\text{O}_3\text{Si}$ : Calculated: 473.2512; found: 473.2493

#### 5d. 4-(tert-butylperoxy)-2-methyl-6-(triphenylsilyl)hex-5-yn-2-ol:



Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 62%, 2 h;  $\text{Co}(\text{OAc})_2$ : 69%, 0.5 h;  $^1\text{H}$  NMR: ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.70-7.63 (m, 6H); 7.46-7.35 (m, 9H); 5.00 (dd,  $J = 4.8, 8.8$  Hz, 1H); 2.52 (bs, 1H); 2.19 (dd,  $J = 8.8, 14.8$  Hz, 1H); 1.99 (dd,  $J = 4.8, 14.8$  Hz); 1.32 (s, 3H, diastereotopic proton); 1.29 (s, 3H, diastereotopic proton); 1.25 (s, 9H)  $^{13}\text{C}$  NMR: ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  135.6, 133.3, 130.0, 128.0, 109.5, 85.5, 80.8, 71.5, 69.9, 46.4, 30.1, 29.1, 26.5 **HRMS (ESI)**:  $\text{C}_{29}\text{H}_{35}\text{O}_3\text{Si}$ : Calculated: 459.2355; found: 459.2344

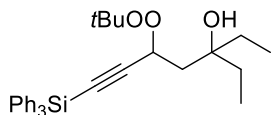
#### 5e. 3-(tert-butylperoxy)-5-methyl-1-(triphenylsilyl)non-1-yn-5-ol:



Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 40%, 2 h;  $\text{Co}(\text{OAc})_2$ : 55%, 0.75 h;  $^1\text{H}$  NMR: ( $\text{CDCl}_3$ , 400 MHz, 2 diastereomers):  $\delta$  7.71-7.64 (m, 6H); 7.46-7.35 (m, 9H); 5.05-4.94 (m, 1H); 2.50 (bs, 1H, 1 diastereomer); 2.35 (bs, 1H, 1 diastereomer); 2.21-2.09 (m, 1H); 2.06-1.92 (m,

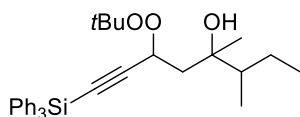
1H); 1.59-1.48 (m, 2H); 1.39-1.23 (m, 16H); 0.94-0.88 (2 t,  $J = 6.9$  Hz, 3H)  $^{13}\text{C}$  NMR: ( $\text{CDCl}_3$ , 100 MHz, 2 diastereomers):  $\delta$  135.6, 133.3, 130.0, 128.0; 109.7, 109.6, 85.4, 80.8, 80.8, 71.8, 71.7, 71.4, 71.2, 44.8, 44.8, 42.8, 41.8, 27.3, 26.6, 26.4, 26.1, 23.3, 14.1, 14.1 HRMS (ESI):  $\text{C}_{32}\text{H}_{41}\text{O}_3\text{Si}$ : Calculated: 501.2825; found: 501.2828

### 5f. 5-(tert-butylperoxy)-3-ethyl-7-(triphenylsilyl)hept-6-yn-3-ol



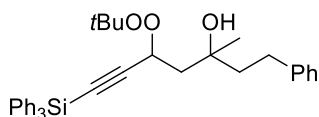
Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 35%, 4 h;  $\text{Co}(\text{OAc})_2$ : 58%, 0.75 h;  $^1\text{H}$  NMR: ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.73-7.63 (m, 6H); 7.48-7.35 (m, 9H); 4.98 (dd,  $J = 4.8, 8.8$  Hz, 1H); 2.29 (bs, 1H); 2.11 (dd,  $J = 8.4, 15.2$  Hz, 1H); 1.97 (dd,  $J = 4.8, 14.8$  Hz); 1.65-1.51 (m, 4H); 1.25 (s, 9H); 0.95-0.85 (m, 6H)  $^{13}\text{C}$  NMR: ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  135.6, 133.3, 130.0, 127.9, 109.7, 85.3, 80.8, 73.8, 71.0, 41.9, 31.3, 30.8, 26.5, 8.1, 7.8 HRMS (ESI):  $\text{C}_{31}\text{H}_{39}\text{O}_3\text{Si}$ : Calculated: 487.2668; found: 487.2666

### 5g. 6-(tert-butylperoxy)-3,4-dimethyl-8-(triphenylsilyl)oct-7-yn-4-ol:



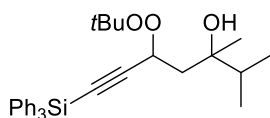
Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography.  $^1\text{H}$  NMR spectrum was not well resolved to give a more accurate diastereomeric ratio of the products. The d. r. was approximated as 1:1:1:1 judging from  $^{13}\text{C}$  NMR. Cu: 46%, 2 h;  $\text{Co}(\text{OAc})_2$ : 61%, 0.75 h;  $^1\text{H}$  NMR: ( $\text{CDCl}_3$ , 400 MHz, 4 diastereomers):  $\delta$  7.70-7.64 (m, 6H); 7.46-7.35 (m, 9H); 5.05-4.95 (m, 1H); 2.63 (bs, 1H, 1 diastereomer); 2.60 (bs, 1H, 1 diastereomer); 2.29 (bs, 2H, 2 diastereomer); 2.20-1.93 (m, 2H); 1.89-1.39 (m, 2H); 1.25 (s, 9H); 1.21 (s, 3H, 1 diastereomer); 1.19 (s, 3H, 1 diastereomer); 1.15 (s, 3H, 1 diastereomer); 1.13 (s, 3H, 1 diastereomer); 0.98-0.86 (m, 7H)  $^{13}\text{C}$  NMR: ( $\text{CDCl}_3$ , 100 MHz, 4 diastereomers):  $\delta$  135.6 (1 signal, 4 diastereomers); 133.3, 133.3, 133.3 (3 signals, 4 diastereomer); 130.0, 130.0 (2 signals, 4 diastereomers); 128.0 (1 signal, 4 diastereomers); 109.9, 109.8, 109.8, 109.7 (4 signals, 4 diastereomer); 85.6, 85.5, 85.4 (3 signals, 4 diastereomers); 80.9, 80.9, 80.8 (3 signals, 4 diastereomers); 74.3, 74.2, 74.1 (3 signals, 4 diastereomers); 71.5, 71.3, 71.1, 71.1 (4 signals, 4 diastereomers); 45.7, 45.5, 44.6, 44.4 (CH, 4 signals, 4 diastereomers); 43.5, 42.8, 42.6, 41.9 (CH2, 4 signals, 4 diastereomers); 26.6 (CH3); 24.6, 24.1, 23.5, 23.4 (CH2, 4 signals, 4 diastereomers); 23.7, 23.6, 23.1, 23.1 (CH3, 4 signals, 4 diastereomers); 14.4, 14.0, 13.2, 13.0, 13.0, 12.9, 12.8 (2 sets of CH3) HRMS (ESI):  $\text{C}_{32}\text{H}_{41}\text{O}_3\text{Si}$ : Calculated: 501.2825; found: 501.2828

### 5h. 5-(tert-butylperoxy)-3-methyl-1-phenyl-7-(triphenylsilyl)hept-6-yn-3-ol:



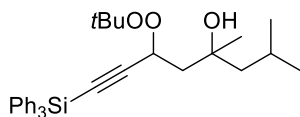
Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 57%, 2 h; Co(OAc)<sub>2</sub>: 57%, 0.75 h; **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers): δ 7.70-7.63 (m, 6H); 7.46-7.35 (m, 9H); 7.30-7.25 (m, 2H); 7.23-7.14 (m, 3H); 5.10-4.98 (m, 1H); 2.78-2.38 (m, 3H); 2.32-2.18 (m, 1H); 2.13-1.97 (m, 1H); 1.95-1.81 (m, 2H); 1.36 (s, 3H, 1 diastereomer), 1.34 (s, 3H, 1 diastereomer); 1.26 (2 s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz, 2 diastereomers): δ 142.5, 142.4, 135.6, 133.2, 130.0, 130.0, 128.4, 128.4, 128.4, 128.3, 128.0, 125.8, 125.7, 109.4, 109.3, 85.7, 85.7, 81.0, 80.9, 71.6, 71.5, 71.3, 71.2, 45.0, 44.9, 44.9, 43.8, 30.4, 30.2, 27.3, 26.6, 26.5 **HRMS (ESI):** C<sub>36</sub>H<sub>41</sub>O<sub>3</sub>Si: Calculated: 549.2825; found: 549.2815

### 5i. 5-(tert-butylperoxy)-2,3-dimethyl-7-(triphenylsilyl)hept-6-yn-3-ol:



Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 55%, 2 h; Co(OAc)<sub>2</sub>: 50%, 0.5 h; **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers): δ 7.70-7.63 (m, 6H); 7.46-7.35 (m, 9H); 5.06-4.95 (m, 1H); 2.57 (bs, 1H, 1 diastereomer); 2.24(bs, 1H, 1 diastereomer); 2.19-1.93 (m, 2H); 1.89-1.72 (m, 1H); 1.25 (2s, 9H); 1.21 (s, 3H, 1 diastereomer), 1.15 (s, 3H, 1 diastereomer); 1.01-0.85 (m, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz, 2 diastereomers): δ 135.6, 133.3, 133.3, 130.0, 130.0, 128.0, 109.9, 109.7, 85.5, 85.4, 80.9, 80.8, 73.9, 73.8, 71.4, 71.1, 43.0, 42.3, 38.1, 37.1, 26.57, 26.6, 23.0, 22.8, 17.9, 17.6, 17.0, 16.9 **HRMS (ESI):** C<sub>31</sub>H<sub>39</sub>O<sub>3</sub>Si: Calculated: 487.2668; found: 487.2654

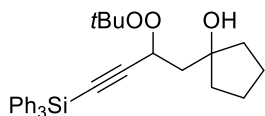
### 5j. 6-(tert-butylperoxy)-2,4-dimethyl-8-(triphenylsilyl)oct-7-yn-4-ol:



Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 39%, 2 h; Co(OAc)<sub>2</sub>: 32%, 1 h; **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers): δ 7.72-7.63 (m, 6H); 7.50-7.33 (m, 9H); 5.07-4.95 (m, 1H); 2.45 (bs, 1H, 1 diastereomer); 2.28 (bs, 1H, 1 diastereomer); 2.24-2.09 (m, 1H); 2.06-1.91 (m, 1H); 1.89-1.77 (m, 1H); 1.54-1.42 (m, 2H); 1.29 (s, 3H, 1 diastereomer); 1.27 (s, 3H, 1 diastereomer); 1.25 (s, 9H); 1.00-0.92 (m, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz, 2 diastereomers): δ 135.6, 133.3, 133.3, 130.0, 128.0, 109.8, 109.6, 85.5, 85.4, 80.9, 80.8; 72.3, 71.4, 71.2, 51.5, 50.5, 46.1, 45.7, 27.6, 26.9, 26.6, 25.0,

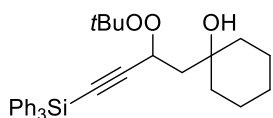
24.9, 24.7, 24.6, 24.3, 24.1 **HRMS (ESI):** C<sub>32</sub>H<sub>39</sub>O<sub>3</sub>Si: Calculated: 499.2668; found: 499.2661

**5k. 1-(2-(tert-butylperoxy)-4-(triphenylsilyl)but-3-yn-1-yl)cyclopentan-1-ol**



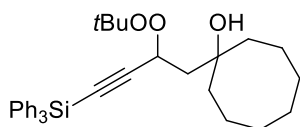
Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 48%, 2 h; Co(OAc)<sub>2</sub>: 60%, 0.5 h; **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.72-7.62 (m, 6H); 7.46-7.34 (m, 9H); 5.02 (dd, *J* = 4.6, 9.0 Hz, 1H); 2.42 (bs, 1H); 2.32 (dd, *J* = 8.8 14.8 Hz, 1H); 2.08 (dd, *J* = 4.6, 14.6 Hz, 1H); 1.87-1.74 (m, 4H); 1.68-1.57 (m, 4H); 1.26 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 135.6, 133.3, 130.0, 128.0, 109.6, 85.5, 80.9, 80.7, 72.2, 44.6, 40.5, 39.6, 26.6, 23.7, 23.5 **HRMS (ESI):** C<sub>31</sub>H<sub>37</sub>O<sub>3</sub>Si: Calculated: 485.2512; found: 485.2509

**5l. 1-(2-(tert-butylperoxy)-4-(triphenylsilyl)but-3-yn-1-yl)cyclohexan-1-ol:**



Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 33%, 3 h; Co(OAc)<sub>2</sub>: 70%, 0.5 h; **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.71-7.63 (m, 6H); 7.46-7.35 (m, 9H); 5.09-4.98 (m, 1H); 2.40 (bs, 1H); 2.13 (dd, *J* = 8.6, 15.0 Hz, 1H); 2.00 (dd, *J* = 4.8, 15.2 Hz, 1H); 1.70-1.22 (m, 19H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 135.6, 133.3, 130.0, 128.0, 109.8, 85.4, 80.8, 70.8, 70.6, 45.0, 38.4, 37.2, 26.6, 25.7, 22.2, 22.2 **HRMS (ESI):** C<sub>32</sub>H<sub>39</sub>O<sub>3</sub>Si: Calculated: 499.2668; found: 499.2661

**5m. 1-(2-(tert-butylperoxy)-4-(triphenylsilyl)but-3-yn-1-yl)cyclooctan-1-ol:**

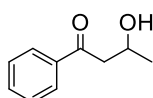


Synthesized according to the GP3 and isolated as colourless oil after purification by flash column chromatography. Cu: 30%, 2 h; Co(OAc)<sub>2</sub>: 61%, 0.5 h; **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.70-7.63 (m, 6H); 7.46-7.35 (m, 9H); 5.06-4.93 (m, 1H); 2.33 (bs, 1H); 2.14-1.98 (m, 2H); 1.91-1.78 (m, 2H); 1.68-1.35 (m, 12H); 1.24 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 135.6, 133.3, 130.0, 128.0, 109.9, 85.3, 80.8, 74.1, 71.1, 44.4, 36.8, 35.6, 28.2, 28.2, 26.6, 25.1, 22.2 **HRMS (ESI):** C<sub>34</sub>H<sub>43</sub>O<sub>3</sub>Si: Calculated: 527.2981; found: 527.2991

## General Procedure for the Reaction of Styrene with Ethanol (GP4) (7a-7i) and their spectral data:

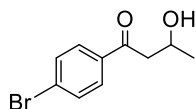
To the mixture of styrene (0.5 mmol, 1 equiv.) and DMSO (3.0 mL) in a screw cap vial, Cu powder (0.05 mmol, 10 mol%) and alcohol (4.0 mmol, 8 equiv) were added sequentially into the reaction mixture. TBHP (5.5 M in decane, 1.5 mmol, 3 equiv) was then added dropwise at room temperature. The vial was heated at 80 °C till the starting material and the peroxy intermediate were fully converted. After cooling to room temperature, the resulting reaction mixture was directly subjected to flash column chromatography and the pure product was isolated with hexane/ethyl acetate (4:1).

### 7a. 3-hydroxy-1-phenylbutan-1-one



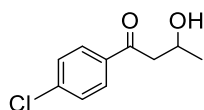
The title compound was prepared according to GP4 and was obtained after flash column chromatography as light yellow oil. Yield: 48% (24 h); The analytical data are in accordance with the literature.<sup>5</sup> **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.95 (d,  $J$  = 7.6 Hz, 2H); 7.58 (t,  $J$  = 7.4 Hz, 1H); 7.47 (t,  $J$  = 7.8 Hz, 2H); 4.46-4.34 (m, 1H); 3.34 (bs, 1H); 3.17 (dd,  $J$  = 2.8, 17.6 Hz, 1H); 3.04 (dd,  $J$  = 8.8, 17.6 Hz, 1H); 1.30 (d,  $J$  = 6.4 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  200.8, 136.7, 133.5, 128.7, 128.1, 64.0, 46.5, 22.4 **HRMS (ESI):** C<sub>10</sub>H<sub>13</sub>O<sub>2</sub>: Calculated: 165.0916; found: 165.0912

### 7b. 1-(4-bromophenyl)-3-hydroxybutan-1-one



The title compound was prepared according to GP4 and was obtained after flash column chromatography as yellow oil. Yield: 32% (24 h); The analytical data are in accordance with the literature.<sup>6</sup> **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.82 (d,  $J$  = 8.8 Hz, 2H); 7.62 (d,  $J$  = 8.8 Hz, 2H); 4.45-4.34 (m, 1H); 3.21-3.07 (m, 2H); 3.02 (dd,  $J$  = 8.6, 17.8 Hz, 1H); 1.30 (d,  $J$  = 6.4 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  199.7, 135.5, 132.1, 129.60, 128.8, 64.0, 46.5, 22.5 **HRMS (ESI):** C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>Br: Calculated: 243.0021; found: 243.0025

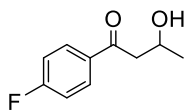
### 7c. 1-(4-chlorophenyl)-3-hydroxybutan-1-one



The title compound was prepared according to GP4 and was obtained after flash column chromatography as yellow oil. Yield: 50% (24 h); **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.94-7.85 (m, 2H); 7.50-7.39 (m, 2H); 4.45-4.35 (m, 1H); 3.22 (bs.H); 3.12 (dd,  $J$  = 2.8, 17.6 Hz, 1H); 3.02 (dd,  $J$  = 8.8, 17.6 Hz, 1H); 1.29 (d,  $J$  = 6.0 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  199.5,

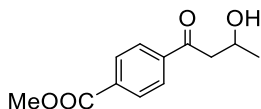
140.1, 135.1, 129.5, 129.0, 64.0, 46.6, 22.5 **HRMS (ESI):** C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>Cl:  
Calculated: 199.0526; found: 199.0529

#### 7d. 1-(4-fluorophenyl)-3-hydroxybutan-1-one



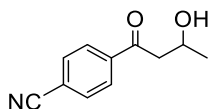
The title compound was prepared according to GP4 and was obtained after flash column chromatography as yellow oil. Yield: 45% (12 h); **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  8.07-7.91 (m, 2H); 7.21-7.09 (m, 2H); 4.47-4.31 (m, 1H); 3.25 (bs, 1H); 3.13 (dd,  $J = 3.0, 17.8$  Hz, 1H); 3.02 (dd,  $J = 8.8, 17.6$  Hz, 1H); 1.30 (d,  $J = 6.4$  Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  199.2, 166.1 (d,  $J_{C-F} = 254.0$  Hz), 133.2 (d,  $J_{C-F} = 3.0$  Hz), 130.8 (d,  $J_{C-F} = 10.0$  Hz), 115.9 (d,  $J_{C-F} = 22.0$  Hz), 64.0, 46.5, 22.5 **HRMS (ESI):** C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>F:  
Calculated: 183.0821; found: 183.0821

#### 7e. methyl 4-(3-hydroxybutanoyl)benzoate



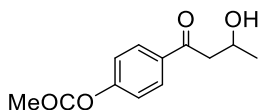
The title compound was prepared according to GP4 and was obtained after flash column chromatography as white solid. Yield: 39% (8 h); **m.p.:** 63-65 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  8.13 (d,  $J = 8.4$  Hz, 2H); 8.00 (d,  $J = 8.4$  Hz, 2H); 4.50-4.36 (m, 1H); 3.95 (s, 3H); 3.22-3.03 (m, 3H); 1.31 (d,  $J = 6.4$  Hz) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  200.2, 166.2, 139.9, 134.3, 129.9, 128.0, 64.0, 52.5, 47.0, 22.5

#### 7f. 4-(3-hydroxybutanoyl)benzonitrile



The title compound was prepared according to GP4 and was obtained after flash column chromatography as colourless oil. Yield: 40% (7 h); **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  8.04 (d,  $J = 8.4$  Hz, 2H); 7.78 (d,  $J = 8.4$  Hz, 2H); 4.49-4.36 (m, 1H); 3.17-3.06 (m, 2H); 3.01 (bs, 1H); 1.31 (d,  $J = 6.4$  Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  199.2, 139.6, 132.6, 128.5, 117.8, 116.8, 63.9, 47.0, 22.5 **HRMS (ESI):** C<sub>11</sub>H<sub>12</sub>NO<sub>2</sub>: Calculated: 190.0868; found: 190.0871

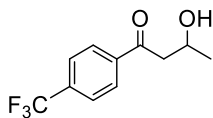
#### 7g. 4-(3-hydroxybutanoyl)phenyl acetate



The title compound was prepared according to GP4 and was obtained after flash column chromatography as white solid. Yield: 31% (15 h); **m.p.:** 57-59 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.98 (d,  $J = 8.8$  Hz, 2H); 7.20 (d,  $J = 8.8$  Hz, 2H); 4.47-4.33 (m, 1H); 3.28 (bs, 1H); 3.13 (dd,  $J = 3.0,$

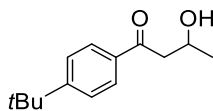
17.8 Hz, 1H); 3.02 (dd,  $J = 8.8, 17.6$  Hz, 1H); 2.32 (s, 3H); 1.29 (d,  $J = 6.4$  Hz, 3H)  **$^{13}\text{C}$  NMR:** ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  199.5, 168.8, 154.7, 134.3, 129.7, 121.9, 64.0, 46.5, 22.4, 21.2 **HRMS (ESI):**  $\text{C}_{12}\text{H}_{15}\text{O}_4$ : Calculated: 233.0970; found: 233.0961

### 7h. 3-hydroxy-1-(4-(trifluoromethyl)phenyl)butan-1-one



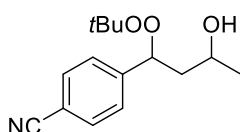
The title compound was prepared according to GP4 and was obtained after flash column chromatography as light yellow oil. Yield: 53% (5 h);  **$^1\text{H}$  NMR:** ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.05 (d,  $J = 8.0$  Hz, 2H); 7.74 (d,  $J = 8.0$  Hz, 2H); 4.49-4.36 (m, 1H); 3.24-3.01 (m, 3H); 1.32 (d,  $J = 6.4$  Hz, 3H)  **$^{13}\text{C}$  NMR:** ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  199.7, 139.4, 134.8 (q,  $J_{\text{C-F}} = 32.3$  Hz); 128.4, 125.8 (q,  $J_{\text{C-F}} = 3.7$  Hz), 123.5 (q,  $J_{\text{C-F}} = 270.7$  Hz), 64.0, 47.0, 22.5 **HRMS (ESI):**  $\text{C}_{11}\text{H}_{12}\text{O}_2\text{F}_3$ : Calculated: 233.0789; found: 233.0785

### 7i. 1-(4-(tert-butyl)phenyl)-3-hydroxybutan-1-one



The title compound was prepared according to GP4 and was obtained after flash column chromatography as yellow oil. Yield: 50% (22 h); The analytical data are in accordance with the literature.<sup>7</sup>  **$^1\text{H}$  NMR:** ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.89 (d,  $J = 8.4$  Hz, 2H); 7.48 (d,  $J = 8.8$  Hz, 2H); 4.47-4.33 (m, 1H); 3.40 (bs, 1H); 3.16 (dd,  $J = 2.8, 17.6$  Hz, 1H); 3.01 (dd,  $J = 8.8, 17.6$  Hz, 1H); 1.34 (s, 9H); 1.30 (d,  $J = 6.4$  Hz, 3H)  **$^{13}\text{C}$  NMR:** ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  200.6, 157.4, 134.2, 128.1, 125.7, 64.1, 46.3, 35.2, 31.1, 22.4 **HRMS (ESI):**  $\text{C}_{14}\text{H}_{21}\text{O}_2$ : Calculated: 221.1542; found: 221.1537

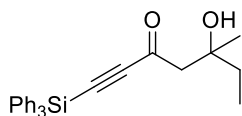
### 10. 4-(1-(tert-butyloxy)-3-hydroxybutyl)benzotrile



The title compound was synthesized according to GP4 when the reaction was terminated after the starting material was consumed, was obtained as colourless oil after flash column chromatography in 1:1.2 dr as determined by  $^1\text{H}$  NMR analysis.  **$^1\text{H}$  NMR:** ( $\text{CDCl}_3$ , 400 MHz, 2 diastereomers):  $\delta$  7.67-7.56 (m, 2H); 7.50-7.42 (m, 2H); 5.24-5.15 (m, 1H, 1 diastereomer, major); 5.14-5.03 (m, 1H, 1 diastereomer, minor) 4.11-4.02 (m, 1H, 1 diastereomer, major); 3.94-3.80 (m, 1H, 1 diastereomer, minor); 2.34-1.79 (m, 2H); 1.76-1.65 (m, 1H); 1.24-1.14 (m, 12H)  **$^{13}\text{C}$  NMR:** ( $\text{CDCl}_3$ , 100 MHz, 2 diastereomers):  $\delta$  147.7, 147.0, 132.1, 132.1, 127.4, 127.1, 118.9, 118.8, 111.5, 111.1, 84.2, 81.8, 80.7, 80.6, 66.0, 64.4, 45.0, 44.4, 26.4, 26.4, 24.0, 23.6 **HRMS (ESI):**  $\text{C}_{15}\text{H}_{22}\text{NO}_3$ : Calculated: 264.1600; found: 264.1607

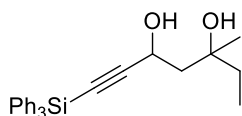
## Transformation of $\beta$ -Peroxy Alcohol **4a**:

### 8. 5-hydroxy-5-methyl-1-(triphenylsilyl)hept-1-yn-3-one:



In a screw cap vial, **4a** (28.4 mg, 0.06 mmol, 1 equiv) was dissolved in 1.0 mL of dichloromethane, to which triethylamine (0.012 mmol, 0.20 equiv) was added. The reaction mixture was allowed to stir at room temperature for 24 h. The reaction mixture was then subjected to flash column chromatography with hexane/ethyl acetate (19:1) to give **8** (16.0 mg, clear oil) in 67% yield.  $^1\text{H}$  NMR: (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.66-7.59 (m, 6H); 7.52-7.38 (m, 9H); 2.97 (s, 1H); 2.95-2.80 (m, 2H); 1.63-1.53 (m, 2H); 1.26 (s, 3H); 0.92 (t,  $J = 7.6$  Hz, 3H)  $^{13}\text{C}$  NMR: (CDCl<sub>3</sub>, 100 MHz):  $\delta$  187.5, 135.6, 131.4, 130.6, 128.3, 105.6, 93.7, 72.4, 54.7, 34.7, 26.3, 8.3 HRMS (ESI): C<sub>26</sub>H<sub>27</sub>O<sub>2</sub>Si: Calculated: 399.1780; found: 399.1776

### 9. 5-methyl-1-(triphenylsilyl)hept-1-yne-3,5-diol:



In a screw cap vial, **4a** (28.4 mg, 0.06 mmol, 1 equiv) was dissolved in 1.0 mL of acetic acid, to which zinc dust (0.30 mmol, 5.0 equiv) was added. The reaction mixture was allowed to stir at 70 °C overnight. The reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, brine and dried over magnesium sulphate. The organic layers were evaporated in vacuo and the residue was purified by flash column chromatography with hexane/ethyl acetate (3:2) to give **9** (15.6 mg, clear oil) in 65% yield.  $^1\text{H}$  NMR spectrum was not well resolved to give a more accurate diastereomeric ratio of the product. The d.r. was approximated as 1:1 judging from  $^{13}\text{C}$  NMR.  $^1\text{H}$  NMR: (CDCl<sub>3</sub>, 400 MHz, 2 diastereomers):  $\delta$  7.68-7.61 (m, 6H); 7.46-7.33 (m, 9H); 4.92 (dd,  $J = 3.0, 10.2$  Hz, 1H, 1 diastereomer) 4.86 (dd,  $J = 3.6, 9.6$  Hz, 1H, 1 diastereomer); 3.46 (bs, 1H, 1 diastereomer); 3.32 (bs, 1H, 1 diastereomer); 2.57 (bs, 1H); 2.15-2.04 (m, 1H); 2.03-1.83 (m, 1H); 1.68-1.53 (m, 2H); 1.27 (s, 3H, 1 diastereomer); 1.24 (s, 3H, 1 diastereomer); 0.92 (t,  $J = 7.6$  Hz, 3H)  $^{13}\text{C}$  NMR: (CDCl<sub>3</sub>, 100 MHz, 2 diastereomers):  $\delta$  135.6, 133.2, 133.2, 130.0, 128.0, 111.2, 111.2, 84.5, 84.4, 73.6, 73.6, 60.8, 60.6, 46.4, 46.2, 36.5, 33.4, 27.5, 25.2, 8.6, 8.0 HRMS (ESI): C<sub>26</sub>H<sub>29</sub>O<sub>2</sub>Si: Calculated: 401.1937; found: 409.1912

References:

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2. Todo, H.; Terao, J.; Watanabe, H.; Kuniyasu, H.; Kambe, N. *Chem. Commun.* **2008**, 1332.
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7. Veeraswamy, S.; Reddy, K. I.; Ragavan, R. V.; Reddy, K. T.; Yennam, S.; Jayashree, A.; *Tetrahedron Lett.* **2012**, 53, 4651.

# *CHAPTER 3*

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***IRON-CATALYZED PEROXIDATION-  
AMINOCARBONYLATION OF ALKENES  
WITH HYDROPEROXIDES AND  
FORMAMIDES VIA FORMYL C(sp<sup>2</sup>)-H  
FUNCTIONALIZATION***

### 3.1 Introduction

#### 3.1.1 Aminocarbonylation with formamide derivatives

In view of the prevalent occurrence of amides linkage in polymers and human proteins, many methods have been devoted to amide synthesis.<sup>85</sup> Amide could be constructed from varied precursors *via* different routes; however the most common method remains to be the acylation of amines with activated acid derivatives (Scheme 3-1-a), despite the undesired accompanying generation of unwanted by-products in large quantities.<sup>86</sup> Aminocarbonylation is an alternative strategy for synthesis of amides in a waste-free manner,<sup>87</sup> through 3-component coupling reaction of aryl halides, alkynes or alkenes with carbon monoxide and amines (Scheme 3-1-b). Another entry for aminocarbonylation involves direct incorporation of carbamoyl derivatives such as carbamoylsilanes, carbamoylstannanes, carbamoyl chlorides or carbamoyl xanthates for the installment of amide group (Scheme 3-1-c).<sup>88</sup> Nonetheless, the wide application of this strategy is impeded by the expensive substrates and the toxicity issue associated with some of these reagents.

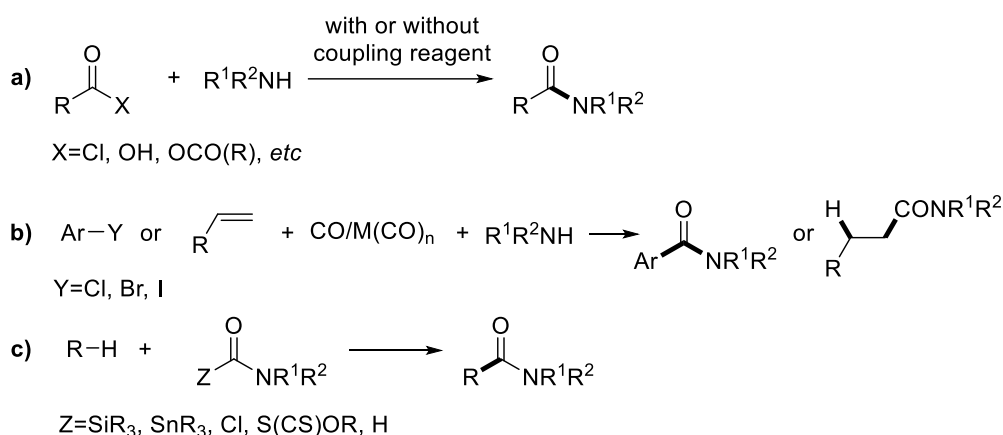
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<sup>85</sup> a) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55. b) *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F. Eds.; Wiley-Interscience, 2000.

<sup>86</sup> a) Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, 7453. b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. c) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.

<sup>87</sup> *Modern Carbonylation Methods*; Kollár, L., Ed.; Wiley-VCH, Weinheim, 2008. b) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405 and the references cited therein.

<sup>88</sup> Examples on reactions with carbomylsilanes: a) Cunico, R. F.; Maity, B. C. *Org. Lett.* **2003**, *5*, 4947. b) Cunico, R. F.; Pandey, R. K. *J. Org. Chem.* **2005**, *70*, 9048. Example on reaction with carbamoylstannanes: c) Lindsay, C. M.; Widdowson, D. A. *J. Chem. Soc. Perkin Trans. 1*, **1988**, 569. Examples on reactions with carbamoylxanthates: d) López-Valdez, G.; Olguín-Urbe, S.; Miranda, L. D. *Tetrahedron Lett.* **2007**, *48*, 8285. e) Grainger, R. S.; Welsh, E. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 5377. Example on reaction with oxime oxalate amides: f) DiLabio, G. A.; Scanlan, E. M.; Walton, J. C. *Org. Lett.* **2005**, *7*, 155. Example on reaction with carbamoyl chlorides: g) Tsukano, C.; Okuno, M.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 2763.



Scheme 3-1: Amidation through acylation of amines and aminocarbonylation  
 Aminocarbonylation reaction *via* direct functionalization of the C(sp<sup>2</sup>)-H bond of formamides has witnessed notable progress in recent decades owing to its atom economy feature (Scheme 3-1-c, Z=H).<sup>89</sup> Remarkably, *N,N*-dimethylformamide (DMF), the structurally simplest formamide, could take on many other roles including ligand,<sup>90</sup> dehydrating agent,<sup>91</sup> reductant<sup>92</sup> and catalyst<sup>93</sup> in addition to the commonly known polar solvent. It is also the versatile reaction partner which acts as masked precursor for a variety of functional groups, such as -CO, -NMe<sub>2</sub>, -CONMe<sub>2</sub>, -Me, -O, and etc, dependent on the reaction conditions.<sup>94</sup>

Aminocarbonylation reaction of formamide involves the introduction of -CONR<sup>1</sup>R<sup>2</sup> moiety with the cleavage of formyl C(sp<sup>2</sup>)-H bond. This pathway could involve transition metal-mediated C(sp<sup>2</sup>)-H activation or generation of carbamoyl radical following homolytic cleavage of the formyl C-H bond and its

<sup>89</sup> Review: Ding, S.; Jiao, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9226.

<sup>90</sup> a) Jutand, A. *Chem. Rev.* **2008**, *108*, 2300. b) Yamaguchi, S.; Shinokubo, H.; Osuka, S. *Inorg. Chem.* **2009**, *48*, 795. c) Arora, H.; Cano, J.; Lloret, F.; Mukherjee, R. *Dalton Trans.* **2011**, *40*, 10055.

<sup>91</sup> Supsana, P.; Liaskopoulos, T.; Tsoungas, P. G.; Varvounis, G. *Synlett* **2007**, 2671.

<sup>92</sup> Teo, J. J.; Chang, Y.; Zeng, H. C. *Langmuir* **2006**, *22*, 7369.

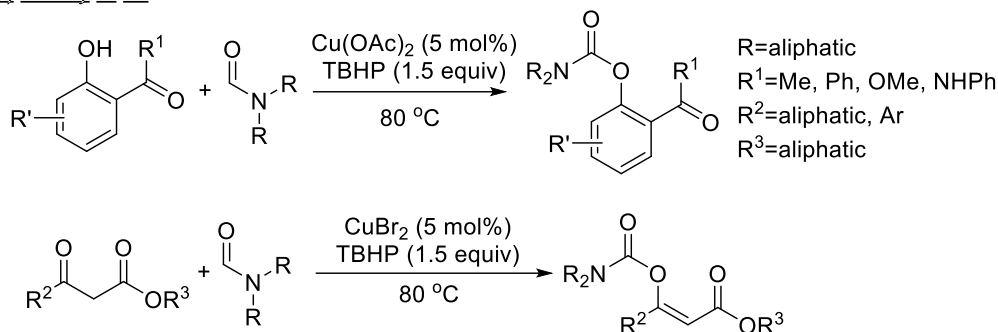
<sup>93</sup> a) Liu, Y.; He, G.; Chen, K.; Jin, Y.; Li, Y.; Zhu, H. *Eur. J. Org. Chem.* **2011**, *2011*, 5323. b) Rai, A.; Rai, V. K.; Singh, A. K.; Yadav, L. D. S. *Eur. J. Org. Chem.* **2011**, *2011*, 4302.

<sup>94</sup> Review: Muzart, J. *Tetrahedron* **2009**, *65*, 8313.

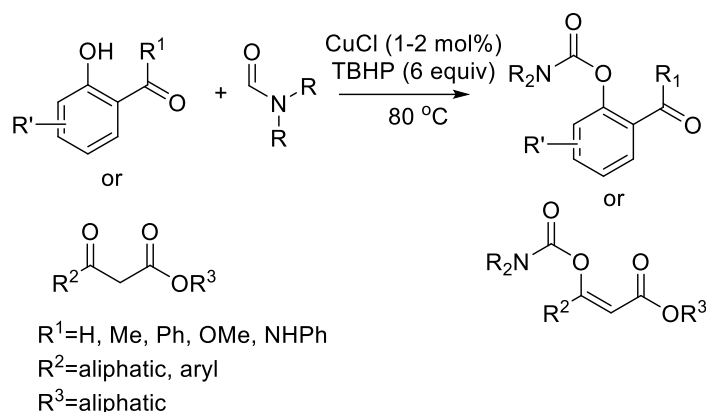
subsequent addition to acceptors, which will be detailed in the following sections for the C-O and C-C bonds formation.

### 3.1.2 C-O bond formation through formyl C (sp<sup>2</sup>)-H functionalization

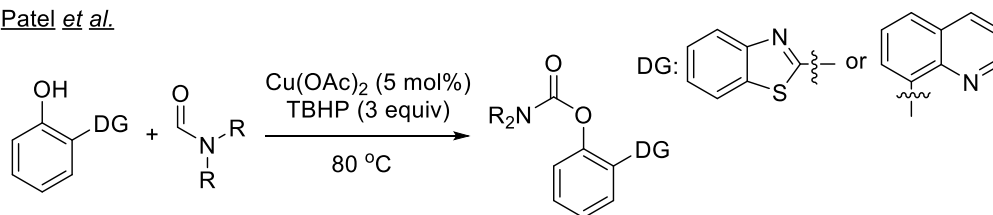
a) *Reddy et al.*



b) *Chang et al.*



c) *Patel et al.*



Scheme 3-2: Copper-catalyzed carbamates formation from phenolic compounds and  $\beta$ -ketoesters with formamides

Formation of C-O bond through direct formyl C(sp<sup>2</sup>)-H functionalization to synthesize carbamates is featured in a series of amidation reaction of phenolic compounds and  $\beta$ -ketoesters, independently developed by Reddy's (Scheme 3-2-a),<sup>95</sup> Chang's (Scheme 3-2-b)<sup>96</sup> and Patel's group (Scheme 3-2-c).<sup>97</sup>

<sup>95</sup> a) Kumar, G. S.; Maheswari, C. U.; Kumar, R. A.; Kantam, M. L.; Reddy, K. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 11748.

<sup>96</sup> a) Barve, B. D.; Wu, Y.-C.; El-Shazly, M.; Chuang, D.-W.; Chung, Y.-M.; Tsai, Y.-H.; Wu, S.-F.; Korinek, M.; Du, Y.-C.; Hsieh, C.-T.; Wang, J.-H.; Chang, F.-R. *Eur. J. Org. Chem.*

Carbamates belong to an important class of organic compounds widely applied in agricultures as pesticides, fungicides and herbicides.<sup>98</sup> This molecular entity is also ubiquitous in many pharmalogically active molecules such as neuroprotective agents, antibiotics and antineoplastic agents.<sup>99</sup> This strategy could complement the conventional synthetic approaches which require the use of phosgenes in the early preparation steps.<sup>100</sup> In general, the desired C-O bond formations are made feasible employing combined system of copper catalyst and TBHP with dialkylformamides under neat conditions (Scheme 3-2).

Mechanistically, these reactions undergo similar mechanistic routes and will be representatively depicted for one example shown below (Scheme 3-3). A distinguished characteristic for this reaction is the coordinating ability of the substrate possessing two binding sites to necessitate the formation of coordination complex with copper, which will successively, facilitate the homolytic rupture of TBHP to *tert*-butoxyl and hydroxyl radicals. The *tert*-butoxyl radical will abstract the hydrogen from formyl C(sp<sup>2</sup>)-H to give the carbamoyl radical. The latter then reacts with the copper complex to give the carbamate product.

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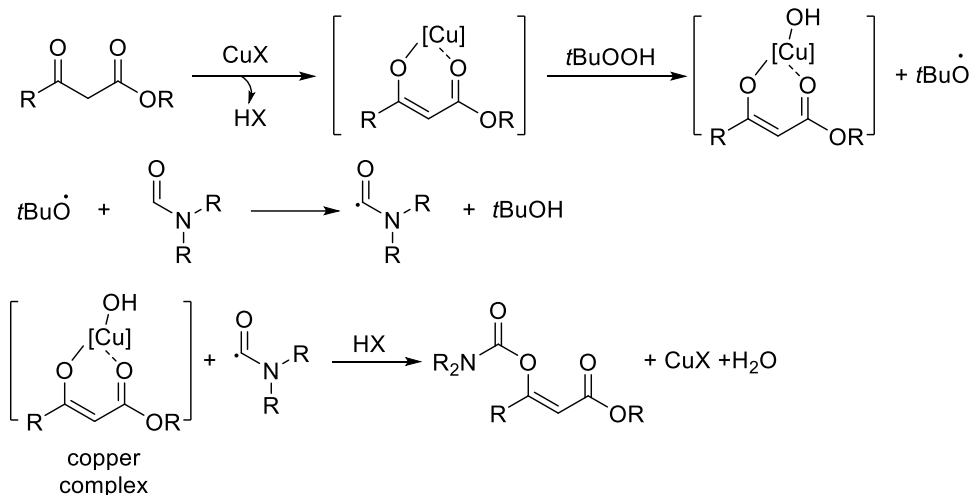
**2012**, 6760. b) Barve, B. D.; Wu, Y.-C.; El-Shazly, M.; Chuang, D.-W.; Cheng, Y.-B.; Wang, J.-J.; Chang, F.-R. *J. Org. Chem.* **2014**, 79, 3206.

<sup>97</sup> Ali, W.; Rout, S. K.; Guin, S.; Modi, A.; Banerjee, A.; Patel, B. K. *Adv. Synth. Catal.* **2015**, 357, 515.

<sup>98</sup> Wu, T. T.; Huang, J.; Arrington, N. D.; Dill, G. M. *J. Agric. Food Chem.* **1987**, 35, 817.

<sup>99</sup> a) Niphakis, M. J.; Johnson, D. S.; Ballard, T. E.; Stiff, C.; Cravatt, B. F. *ACS Chem. Neurosci.* **2012**, 3, 418. b) Fu, L.; Liu, X.; Ling, C.; Cheng, J.; Guo, X.; He, H.; Ding, S.; Yang, Y. *Bioorg. Med. Chem. Lett.* **2012**, 22, 814. c) Wienstock, M.; Bejar, C.; Wang, R. H. *J. Neural Transm. Suppl.* **2000**, 60, 157. d) Ram, S.; Wise, S.; Wotring, L. L.; McCall, J. W.; Townsend, L. B. *J. Med. Chem.* **1992**, 35, 539.

<sup>100</sup> a) Ozaki, S. *Chem. Rev.* 1972, 72, 457. b) Majer, P.; Randad, R. S. *J. Org. Chem.* **1994**, 59, 1937. c) Nowick, J. S.; Powell, N. A.; Nguyen, T. M.; Noronha, G. *J. Org. Chem.* **1992**, 57, 7364.



Scheme 3-3: Mechanistic pathway for amidation of  $\beta$ -ketoesters with C-O bond formation

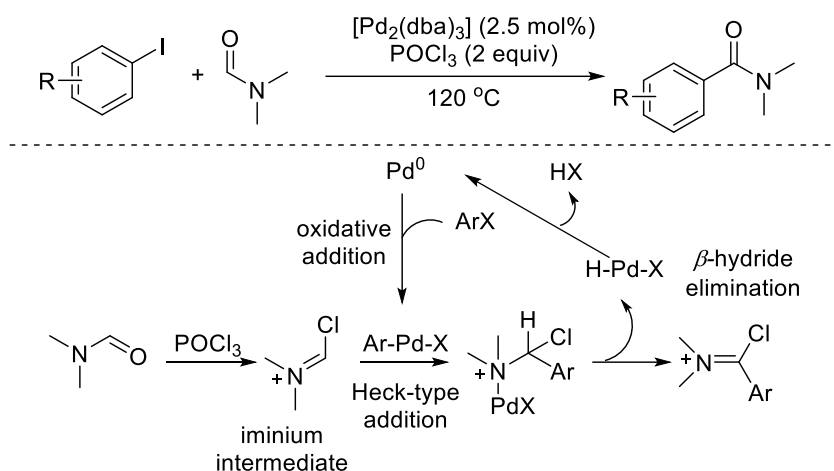
### 3.1.3 C-C bond formation through formyl C(sp<sup>2</sup>)-H functionalization

#### 3.1.3.1 Aminocarbonylation of aryl halides

In term of C-C bond forging, DMF and the derivatives could serve as the amide sources for carbamoylation of aryl halides through direct C(sp<sup>2</sup>)-H activation of the formamides. As early as 2002, the group of Hiyama described an aminocarbonylation protocol of aryl and vinyl iodides with DMF (Scheme 3-4).<sup>101</sup> The intermediacy of iminium species produced from DMF and POCl<sub>3</sub> is postulated for this reaction protocol, while aryl halide forms the arylpalladium halide through oxidative addition. The subsequent Heck-type addition of arylpalladium halide to iminium species and  $\beta$ -hydride elimination gives the carbonylated products. Bhanage's group reported similar transformation using Pd/C catalytic system, and then a Pd(OAc)<sub>2</sub>/Xantphos system which could

<sup>101</sup> Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* **2002**, *4*, 2849.

accommodate wider substrates scope, including aryl bromides and other formamide derivatives.<sup>102</sup>

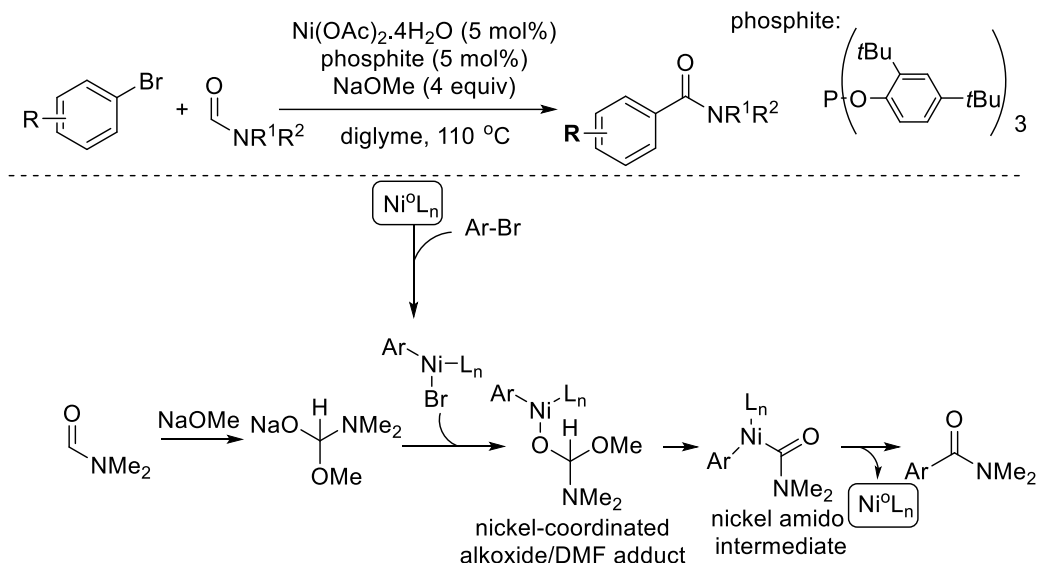


Scheme 3-4: Palladium catalytic system for aminocarbonylation of aryl halides with DMF

Nickel /phosphite catalytic system is also compatible for this transformation, which incorporates the use of methoxide bases instead of the  $\text{POCl}_3$  (Scheme 3-5).<sup>103</sup> The reaction pathway is postulated to proceed through a coordination complex of nickel and alkoxide/DMF adduct, which will convert to a nickel amido species. Reductive elimination affords the amidation product. Remarkably, an improved of reaction generality to include other mono- and di-substituted formamide derivatives in addition to DMF could be attained, albeit the requirement of higher catalyst loading and in lower yields.<sup>103b</sup>

<sup>102</sup> a) Tambade, P. J.; Patil, Y. P.; Bhanushali, M. J.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, 49, 2221. b) Sawant, D. N.; Wagh, Y. S.; Bhatte, K. D.; Bhanage, B. M. *J. Org. Chem.* **2011**, 76, 5489.

<sup>103</sup> a) Ju, J.; Jeong, M.; Moon, J.; Jung, H. M.; Lee, S. *Org. Lett.* **2007**, 9, 4615. b) Jo, Y.; Ju, J.; Choe, J.; Song, K. H.; Lee, S. *J. Org. Chem.* **2009**, 74, 6358.



Scheme 3-5: Nickel/phosphite catalytic system for aminocarbonylation of aryl halides

### 3.1.3.2 Aminocarbonylation of $\alpha$ -oxocarboxylic acids

In recent years, decarboxylative coupling has been explored for C-C bond formation reaction. This class of reaction brought about attractive advantages such as regiospecificity, non-toxicity, low-cost, and easy availability from natural and synthetic sources.<sup>104</sup> This has too been adapted in aminocarbonylation of  $\alpha$ -oxocarboxylic acids to prepare  $\alpha$ -ketoamides (Scheme 3-6).<sup>105</sup>

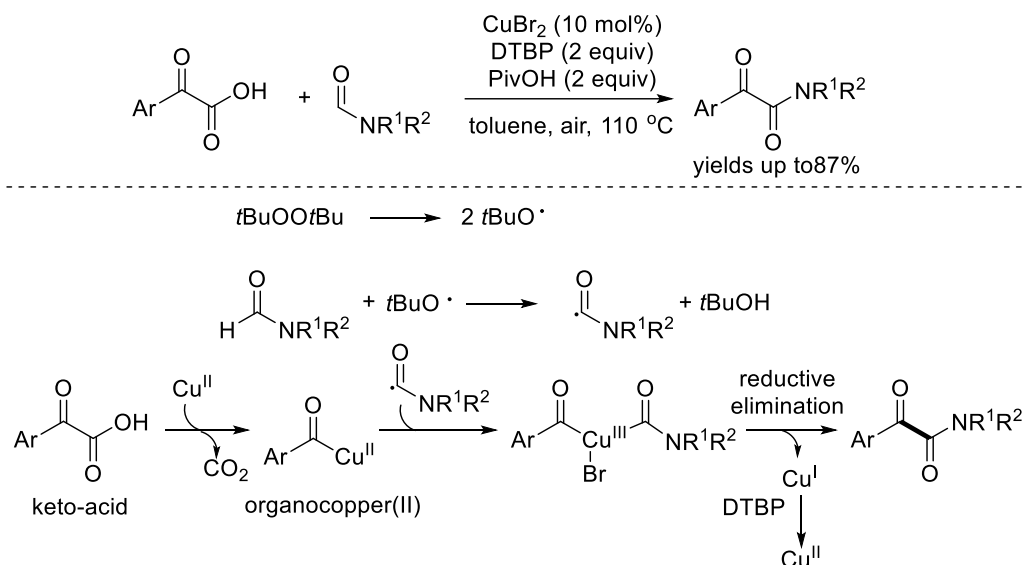
The initiation step requires homolytic decomposition of DTBP to *tert*-butoxyl radicals, which is integral in abstracting formyl C(sp<sup>2</sup>)-H bond to release the carbamoyl radical. On the other hand, Cu(II) will first form a Cu(II) carboxylate salt with the keto-acid before the extrusion of carbon dioxide to give organocopper(II) species. Aminoacyl radical then reacts to form a Cu(III) intermediate, which will then eliminate reductively to give desired product and Cu(I). The Cu(II) is re-formed in the catalytic cycle after oxidation by DTBP.

With 5 equivalents in excess to the 2-oxo-2-phenylacetic acid, both *N*-

<sup>104</sup> Reviews: a) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. b) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846.

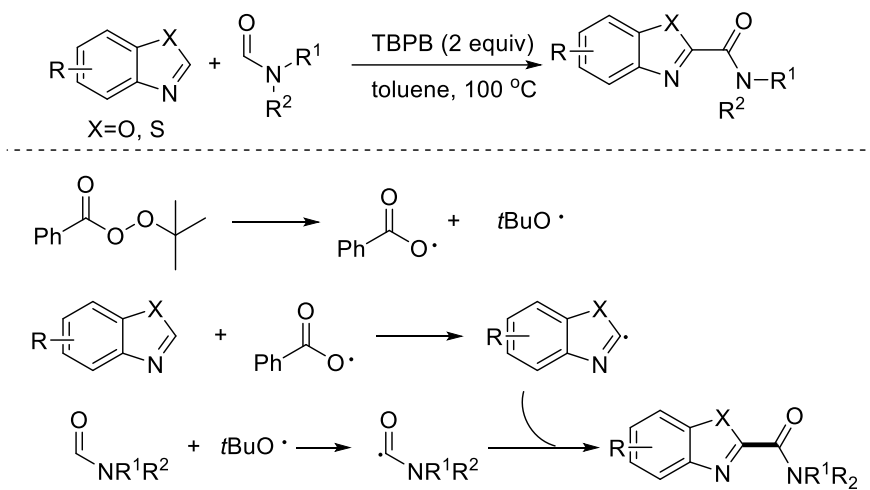
<sup>105</sup> Li, D.; Wang, M.; Liu, J.; Zhao, Q.; Wang, L. *Chem. Commun.* **2013**, *49*, 3640.

monosubstituted and *N,N*-disubstituted formamides could participate in the reactions to give corresponding products in 56-85% yields.



Scheme 3-6: Decarboxylative aminocarbonylation of  $\alpha$ -oxocarboxylic acids

### 3.1.3.3 Aminocarbonylation of heterocycles

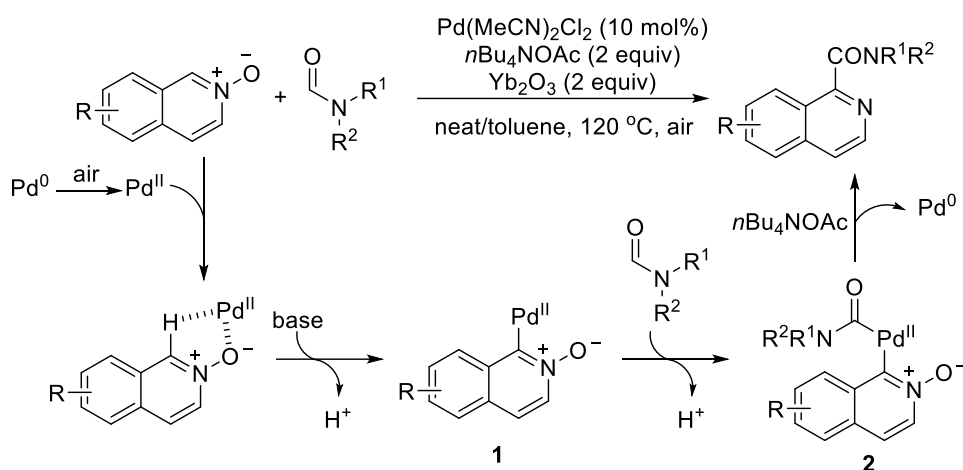


Scheme 3-7: Carbamoylation of azoles with formamides

In term of direct dual C-H bond functionalization, Wang's group reported a metal-free carbamoylation of azoles in the presence of TBPB (for a similar work with alcohol, refer to section 2.1.2.1). A similar radical mechanistic pathway has been postulated for this work; which is initiated by homolytic

cleavage of TBPB to a benzoate and *tert*-butoxyl radical (Scheme 3-7). Related radicals from benzothiazole and formamide are generated following hydrogen atom abstraction steps; cross-coupling of these two radicals gives the product.<sup>106</sup>

Another heterocyclic compound, isoquinoline *N*-oxides are also effective substrates for dual C-H oxidative carbamoylation reaction with formamides using a palladium catalytic system (Scheme 3-8).<sup>107</sup>

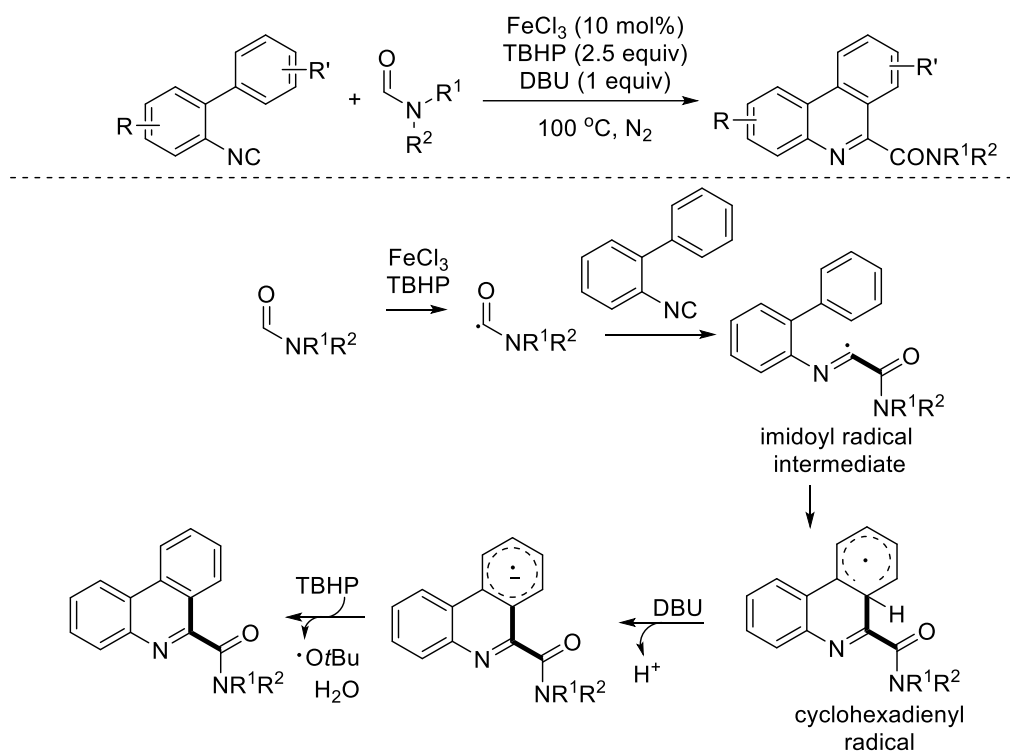


Scheme 3-8: Aminocarbonylation of isoquinoline-*N*-oxides with formamides

Distinctively, the mechanism outlined does not involve the intermediacy of aminoacyl radical. Instead, the Pd(II) generated in-situ is thought to first form a complex with isoquinoline and then inserts into the *ortho*-C(aryl)-H to form **1**. Intermediate **2** is afforded after reaction with amide, which upon reductive elimination and reaction with tetrabutylammonium acetate, gives the desired product and Pd(0).

<sup>106</sup> He, T.; Li, H.; Li, P.; Wang, L. *Chem. Commun.* **2011**, 47, 8946.

<sup>107</sup> Yao, B.; Deng, C.-L.; Liu, Y.; Tang, R.-Y.; Zhang, X.-G.; Li, J.-H. *Chem. Commun.* **2015**, 51, 4097.



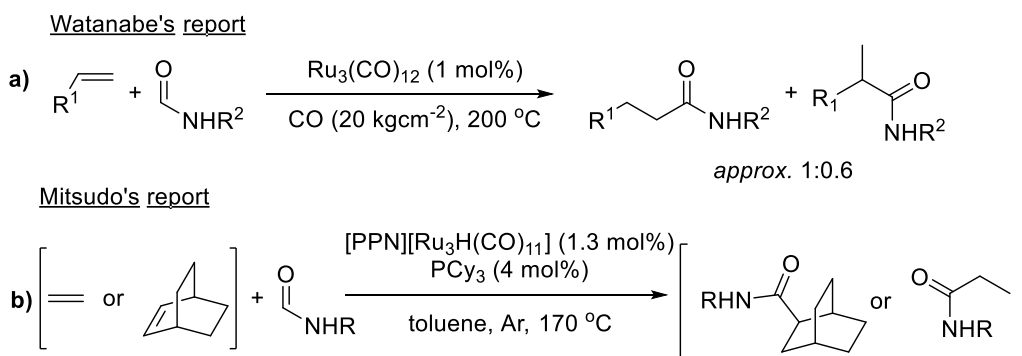
Scheme 3-9: Tandem addition-cyclization of aryl isonitriles with formamides toward phenanthridine-6-carboxamides

In assembling carboxamide-embedded-heterocycles, Zhang *et al.* reported on a synthesis of phenanthridine-6-carboxamides from aryl isonitriles and formamides through iron-promoted tandem carboxamidation-cyclization pathway (Scheme 3-9) (for a similar work with alcohol, refer to section 2.1.2.5).<sup>108</sup> Firstly, the carbamoyl radical generated from in-situ reaction of TBHP and FeCl<sub>3</sub> will add to the isocyanobiphenyl to produce imidoyl radical intermediate. Intramolecular electrophilic attack on the adjacent arene group gives cyclohexadienyl radical which will be deprotonated by DBU to arene radical anion. This radical anion will reduce TBHP by SET to yield the phenanthridine-6-carboxamide and re-generate the *tert*-butoxyl radical back to catalytic cycle.

<sup>108</sup> Tu, H.-Y.; Liu, Y.-R.; Chu, J.-J.; Hu, B.-L.; Zhang, X.-G. *J. Org. Chem.* **2014**, *79*, 9907.

### 3.1.3.4 Hydro-carbonylation of alkenes with formamides

Insertion of alkene into formyl C-H bond offers entry towards longer-chain aliphatic amides. In the late 1980s and late 1990s, Watanabe and Mitsudo independently reported hydrocarbonylation of alkene using ruthenium catalytic system. In Watanabe's report, the aliphatic alkenes reacted with *N*-monosubstituted formamide under harsh reaction condition to afford hydrocarbonylated product that depends upon high reaction temperature (180-200 °C) and high pressure carbon monoxide to suppress decarbonylation (Scheme 3-10-a). Additionally, the regioselectivity of the reaction is poor to generate also branched amide when linear alkenes were used.<sup>109</sup>



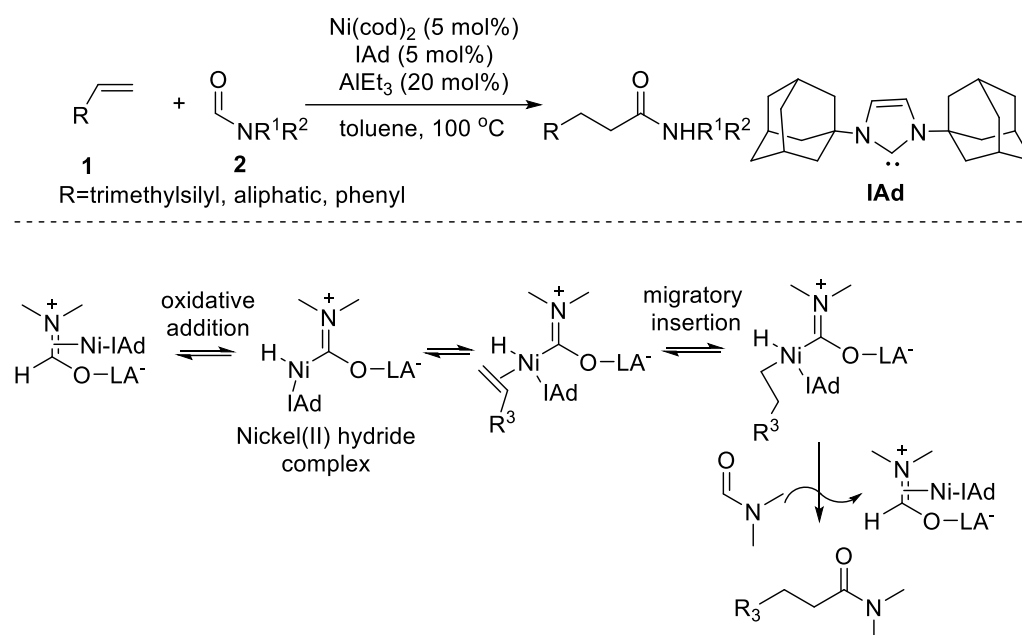
Scheme 3-10: Ruthenium-catalyzed hydroamidation of alkenes

A refined protocol which circumvents the use of poisonous CO is reported by Mitsudo and co-workers (Scheme 3-10-b). Nonetheless, the high reaction temperature is still necessary to facilitate this reaction and steric demand is stringent on the alkene substrate for good coordinating capability with hindered ruthenium center, resulted in only the use of ethylene and norbornene for their

<sup>109</sup> Tsuji, Y.; Yoshii, S.; Ohsumi, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1987**, *331*, 379.



formamides in prominently high regioselectivity. Mechanism wise, Lewis-acid-activated formamide could add oxidatively through C(sp<sup>2</sup>)-H to Ni(0) giving Ni(II) hydride whereas the alkene substrate will first coordinate to the nickel center before migratory insertion to give primary alkylnickel intermediate, which accounts for the regioselective formation of linear alkanamide. Reductive elimination then takes place to yield hydrocarbamoylated product.



Scheme 3-12: Nickel/lewis acid cooperative catalysis in synthesis of alkanamides

### 3.1.3.5 Oxidative coupling of alkenes and formamides

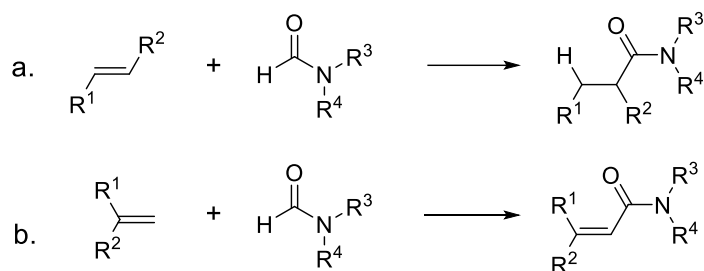
Aside from hydrocarbomylated reaction, Li and co-workers, on the other hand, described a novel radical oxidative coupling of simple alkenes with amides, which retains the double bond functionality.<sup>113</sup>

In their proposed mechanism, DTBP undergoes homolytic cleavage to a *tert*-butoxyl radical and Fe(III)(*Ot*Bu), as facilitated by the Fe(II) species. Carbamoyl radical is delivered following the hydrogen atom abstraction, which will add across the double bond to give a benzylic radical intermediate.

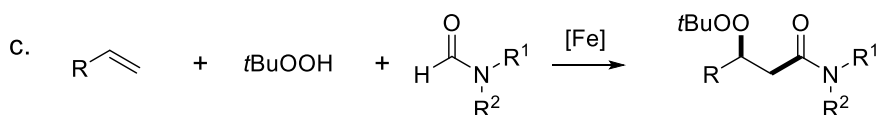
<sup>113</sup> Yang, X.-H.; Wei, W.-T.; Li, H.-B.; Song, R.-J.; Li, J.-H. *Chem. Commun.* **2014**, 50, 12867.



**Previous Work:**



**This Work:**



Scheme 3-14: Previous and current works on coupling reaction of formamides with alkenes

### 3.2 Results and discussion

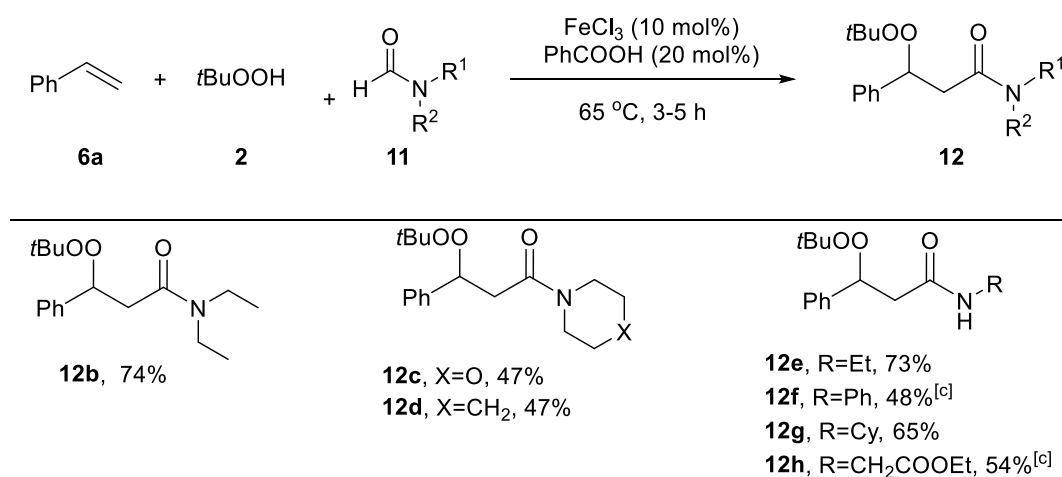
Table 3-1: Optimization of reaction conditions<sup>a</sup>

Entry	Catalyst (10 mol%)	Additive (20 mol%)	Yield [%] <sup>b</sup>
1	FeCl <sub>2</sub>	-	57
2	FeCl <sub>3</sub>	-	61
3	FeBr <sub>3</sub>	-	46
4	Fe(TFA) <sub>3</sub>	-	42
5	Fe(OTf) <sub>2</sub>	-	10
6	Fe <sub>2</sub> O <sub>3</sub>	-	<5
7	CuCl	-	<5
8	CuCl <sub>2</sub>	-	<5
9	Co(OAc) <sub>2</sub>	-	16
10	Co(acac) <sub>3</sub>	-	40
11	-	-	-
12	FeCl <sub>3</sub>	PhCOOH	63
13	-	PhCOOH	-
14	FeCl <sub>3</sub>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COOH	37
15	FeCl <sub>3</sub>	2,4-(OMe) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COOH	57
16	FeCl <sub>3</sub>	(CH <sub>3</sub> ) <sub>3</sub> COOH	52
17 <sup>c</sup>	FeCl <sub>3</sub>	PhCOOH	52
18 <sup>d</sup>	FeCl <sub>3</sub>	PhCOOH	57

<sup>a</sup>Unless otherwise noted, typical reaction conditions: **6a** (0.50 mmol), **2** (2.0 mmol, 5.5 M in decane), catalyst (0.050 mmol), additive (0.10 mmol), **11a** (1.6 mL), 65 °C, air. <sup>b</sup>Isolated yields. <sup>c</sup>**2** (2.5 mmol) <sup>d</sup>Under nitrogen atmosphere.

The investigation was initiated by reacting styrene with DMF in the presence of 10 mol% of FeCl<sub>2</sub> and 4 equiv. of TBHP under neat condition. 57 % of the hypothesized product could be isolated after 5 h at 65 °C (Table 3-1, entry 1). Other metal salts such as that of iron, copper and cobalt tested under same condition could facilitate the reaction (Table 3-1, entries 3-10) but at inferior effectiveness. FeCl<sub>3</sub> exhibited best catalytic activity to yield 61% of peroxy-carbonylated product **12a** (Table 3-1, entry 2). Slight enhancement of product yield to 63% could be achieved when 20 mol% of benzoic acid was added as additive and other acidic additives could not further enhance the reaction (Table 3-1, entries 12, 14-16). In the absence of FeCl<sub>3</sub>, the reaction could not proceed to yield any desired product (Table 3-1, entries 11&13). Reactions with increased amount of TBHP or under inert atmosphere failed to generate the desired product in higher chemical yield (Table 3-1, entries 17-18).

Table 3-2: Reaction scope of **6a** with formamides **11**<sup>a,b</sup>

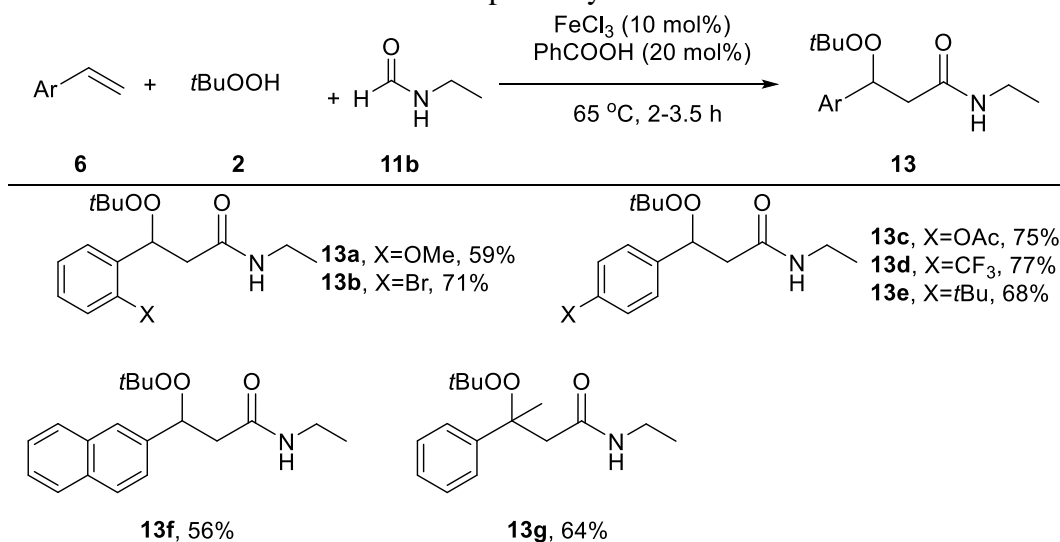


<sup>a</sup>Unless otherwise noted, reaction conditions: **6a** (0.50 mmol), **2** (2.0 mmol, 5.5 M in decane), FeCl<sub>3</sub> (0.050 mmol), PhCOOH (0.10 mmol), **11** (1.6 mL). <sup>b</sup>Isolated yields. <sup>c</sup>**11** (6.0 mmol), DMSO (1.6 mL).

With the optimal reaction condition, the compatibility of different formamides with respect to styrene was probed. In addition to DMF, *N,N*-diethylformamide

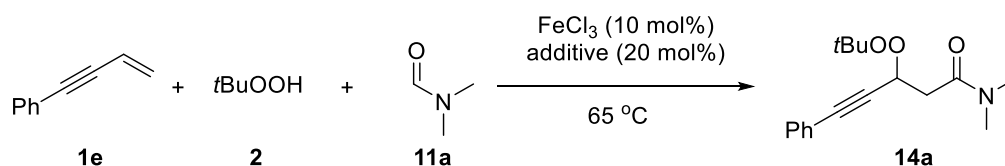
gave the respective peroxy-carbamoylated product **12b** in good yield. Cyclic formamides derived from piperidine and morpholine could assemble the coupling products (**12c&d**) in moderate yield of 47%. The *N*-monosubstituted-formamides bearing linear and cyclic alkyl group as well as phenyl group could be successfully coupled to styrene to give  $\beta$ -peroxy amides **12e-g** in 48-73% yield. Additional functionality on *N*-formyl amino acid ester also sustained the reaction well to give **12h** in demonstrable yield of 54%.

Table 3-3: Reaction scope of aryl alkenes **6** with **11b**<sup>a,b</sup>



<sup>a</sup>Reaction conditions: **1** (0.50 mmol), **2** (2.0 mmol, 5.5 M in decane),  $\text{FeCl}_3$  (0.050 mmol),  $\text{PhCOOH}$  (0.10 mmol), **11b** (1.6 mL). <sup>b</sup>Isolated yield.

With *N*-ethylformamide **11b**, scope of styrene derivatives was explored and all were found to be effective substrates under standard reaction conditions. Styrenes that bear diversified functional groups possessing high synthetic potentials such the methoxy, bromo, acetoxy, trifluoromethyl and *tert*-butyl group could tolerate the reaction well to give **13a-e** in reasonable yields of 59-77%, regardless of the substitution pattern and electronic property. Vinylnaphthalene could also lead to the formation of **13f** albeit at lower yield, whilst  $\alpha$ -methylstyrene could result in the preparation of tertiary peroxides **13g** in 64%.

Table 3-4: Effect of additives on the reaction of **1e** with **11a**<sup>a,b</sup>

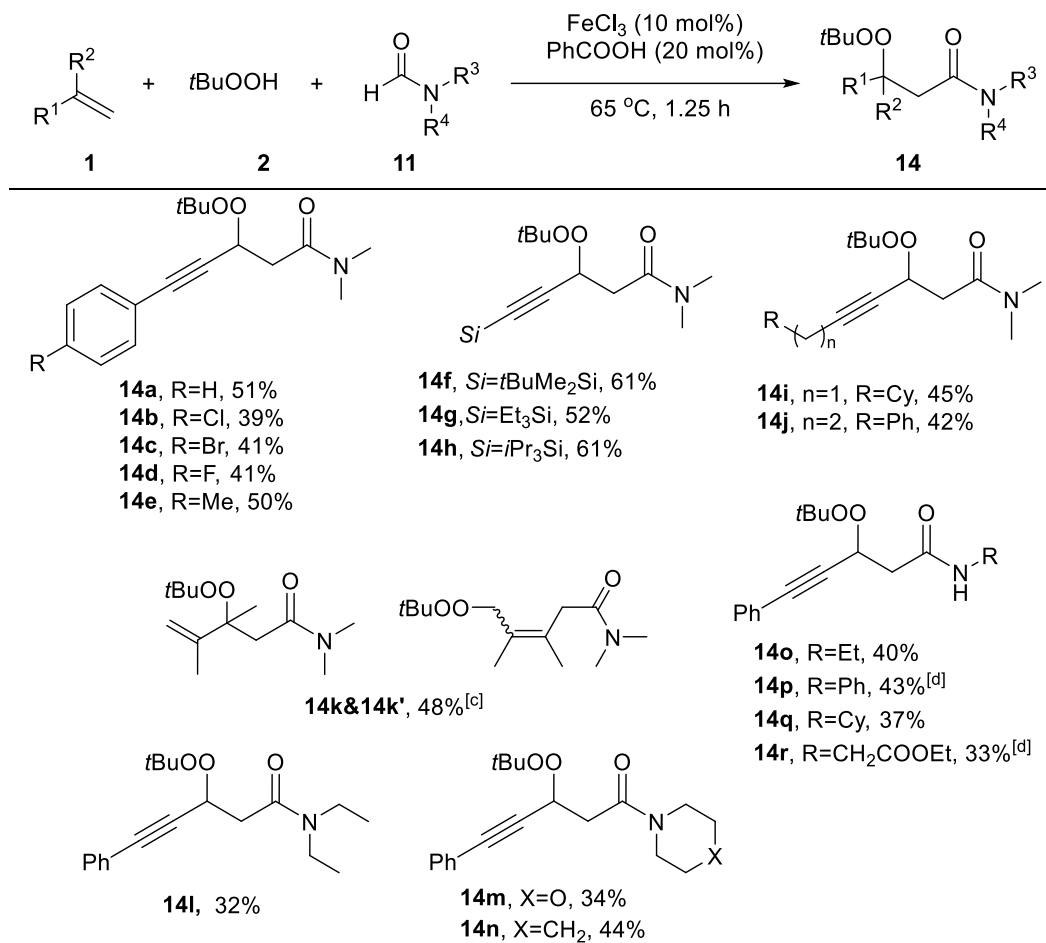
Entry	Additive (20 mol%)	Time (h)	Yield (%)	Entry	Additive (20 mol%)	Time (h)	Yield (%)
1	-	1	42	10	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COOH	1.25	35
<b>2</b>	<b>PhCOOH</b>	<b>1.25</b>	<b>51</b>	11	2,4-(OMe) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COOH	1.25	46
3	Zn(OTf) <sub>2</sub>	3	36	12	(CH <sub>3</sub> ) <sub>3</sub> COOH	8	<10
4	AlCl <sub>3</sub>	3	40	13	CF <sub>3</sub> COOH	16	15
5	InCl <sub>3</sub>	1	38	14	CH <sub>3</sub> COOH	16	16
6	LiOAc	1.5	42	15	Cl <sub>3</sub> CCOOH	16	<10
7	K <sub>2</sub> CO <sub>3</sub>	3	37	16	<i>p</i> TSA	16	<10
8	HNEt <sub>2</sub>	3	38	17	oxalic acid	16	<10
9	DBU	3	34	18	ascorbic acid	1	<10

<sup>a</sup>Reaction conditions: **1e** (0.30 mmol), **2** (1.2 mmol, 5.5 M in decane), FeCl<sub>3</sub> (0.030 mmol), additive (0.060 mmol), **11a** (1.0 mL), 65 °C, air. <sup>b</sup>Isolated yields.

To further improve on the reaction generality, the optimized reaction condition was applied for but-3-en-1-yn-1-ylbenzene **1e**. 51% of the peroxy-amidation **14a** could be formed after 1.25 h. When different acids and bases were tested, none gave compatible amelioration as that by benzoic acid (Table 3-4). The effect of acid additive was notably more profound on the reaction of 1,3-enyne (Table 3-4, entries 1&2).

Good substituent compatibility was demonstrated to accommodate 1,3-enynes tethered with different silyl groups, phenyl substituents as well as aliphatic alkyl groups (Table 3-5).

Table 3-5: Reaction scope of other alkenes **1** and formamides **11**<sup>a,b</sup>



<sup>a</sup> Unless otherwise noted, reaction conditions: **1** (0.30 mmol), **2** (1.2 mmol, 5.5 M in decane), FeCl<sub>3</sub> (0.030 mmol), PhCOOH (0.060 mmol), **11** (1.0 mL).<sup>b</sup> Isolated yields. <sup>c</sup> Performed on 0.5 mmol scale of 2,3-dimethyl-1,3-butadiene **1q**. <sup>d</sup> **11** (3.6 mmol), DMSO (1.0 mL).

Substituents amenable for downstream functionalization such as halogen and alkyl group on aryl enynes afforded **14a-e** in moderate yields. Enynes tethered with silyl protecting moieties and alkyl group prepared the respective desired peroxidation-carbamoylation products **14f-j** in reasonable yields of 42-61%. 2,3-dimethyl-1,3-butadiene **1q** was found to be an effective substrate with current protocol to give the regioisomeric **14k** and **14k'** in 14% and 34% respectively. The *E/Z* isomers of **14k'** were isolable in a ratio of 1.6:1. Facile reaction of phenyl enyne with other formamide derivatives led to corresponding  $\beta$ -peroxy amides **14l-r**, though an overall decline in product

yields could be observed when compared to the reaction of arylalkenes **6**. Increased chain length from dimethylformamide to diethylformamide has depressed the product yield from 51% of **14a** to 32% of **14l**. When cyclic formamides were employed, 34% of **14m** and 44% of **14n** could also be facilely assembled correspondingly. *N*-monosubstituted-formamides also successfully afforded the  $\beta$ -peroxy amides **14o-r** albeit in moderate yields from 33-40%.

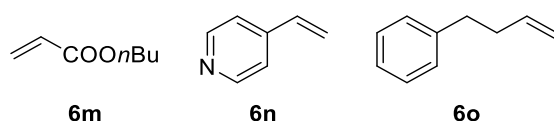
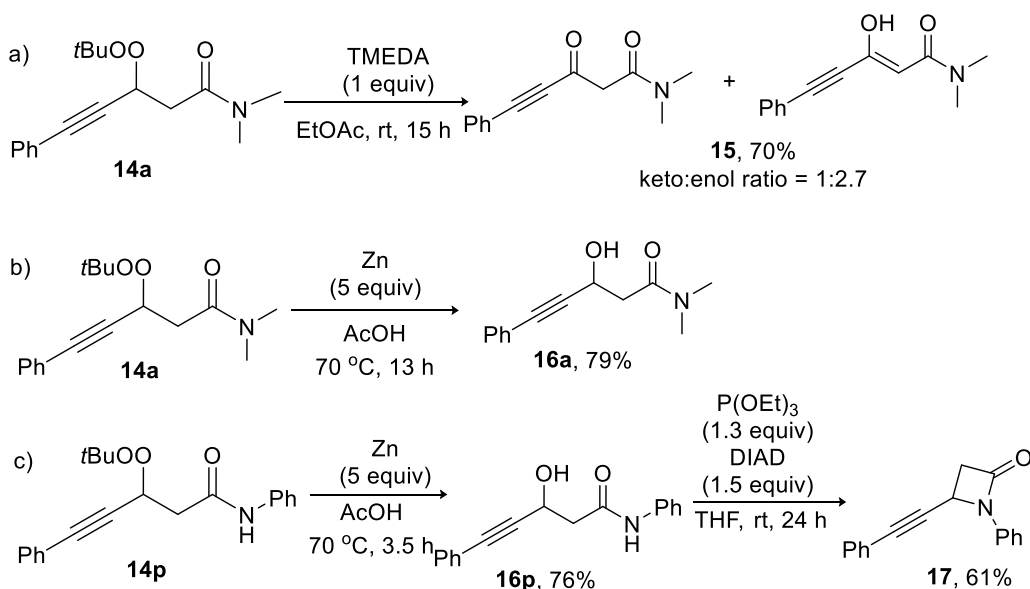


Figure 3-1: Alkenes failed to provide the desired products

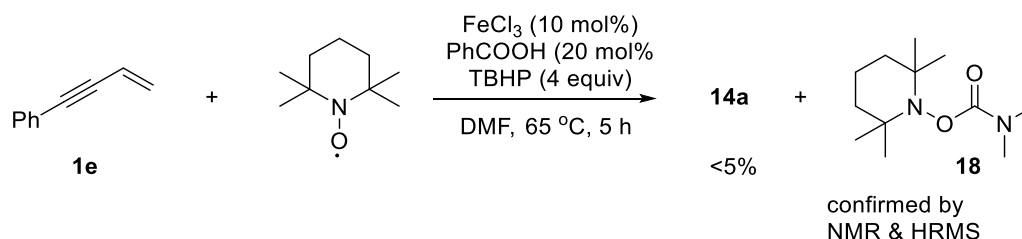
When acrylate **6m** (Figure 3-1) was subjected to the same condition, a messy reaction mixture was obtained though desired coupling product could be observed in trace amount from NMR spectrum. On the other hand, heterocyclic alkene **6n** and aliphatic alkene **6o** could not afford any desired product.



Scheme 3-15: Transformation of peroxyamide **14a** & **14p**

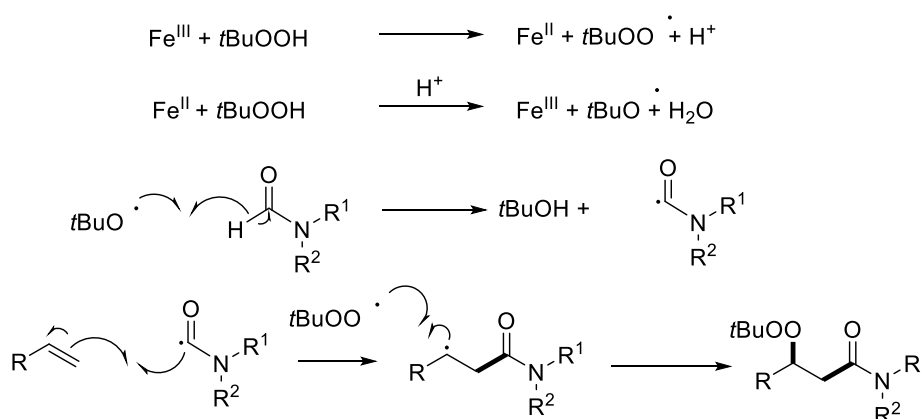
Kornblum-DelaMare rearrangement took place when subjecting peroxyamide **14a** to basic condition to form  $\beta$ -keto amide **15** (Scheme 3-15-

a). On the contrary, treatment of **14a** with zinc under acidic condition gave  $\beta$ -hydroxy amide **16a** in 79% yield (Scheme 3-15-b). It is worth-mentioning that *N*-aryl- $\beta$ -peroxyamide **14p** synthesized from the current reaction protocol could also serve as alternative synthetic precursor for the  $\beta$ -lactam ring **17**, too (Scheme 3-15-c).<sup>114</sup>



Scheme 3-16: Addition of TEMPO to standard reaction of **1e**

When 2.5 equiv of TEMPO was added to the standard reaction for **1e**, the peroxy-carbonylated product **14a** was formed in only trace amount (<5%) (Scheme 3-16). Instead, the TEMPO-DMF adduct (**18**) was isolated and the spectral data corresponds to prior reports.<sup>108, 115</sup> This suggested the functionalization of formyl C(sp<sup>2</sup>)-H could proceed through a radical mechanistic pathway (Scheme 3-17).



Scheme 3-17: Proposed Mechanism

<sup>114</sup> Kern, N.; Hoffmann, M.; Blanc, A.; Weibel, J.-M. *Org. Lett.* **2013**, *15*, 836.

<sup>115</sup> a) Jiang, H.; Lin, A.; Zhu, C.; Cheng, Y. *Chem. Commun.* **2013**, *49*, 819. b) Feng, X.; Zhu, H.; Wang, L.; Jiang, Y.; Cheng, J.; Yu, J.-T. *Org. Biomol. Chem.* **2014**, *12*, 9257.

Based on the literature findings and current observation,<sup>108,116</sup> The aminoacyl radical that adds to the double bond is generated following homolytic rupture of formyl C-H bond. The resulting resonance-stabilized propargylic / benzylic radical intermediate (refer to Scheme 2-17, pg 53) then couples with the *tert*-butylperoxyl radical in a selective fashion to yield the desired product.

### 3.3 Conclusion

A three-component radical coupling reaction which assembled  $\beta$ -peroxy amides from TBHP and formamide derivatives through peroxy-aminocarbonylation of diene, 1,3-enynes as well as styrenes carrying varied functional groups was developed. The  $\beta$ -peroxy amide products serve as versatile synthetic precursor for  $\beta$ -hydroxy amide,  $\beta$ -keto amide and  $\beta$ -lactam.

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<sup>116</sup> a) Barton, D. H. R.; Gloahec, V. N. L.; Patin, H; Launay, F. *New J. Chem.* **1998**, 22, 559. b) Priyadarshini, S.; Joseph, P. J. A.; Kantam, M. L. *RSC Adv.* **2013**, 3, 18283.

### 3.4 Experimental section

#### General Information:

Unless otherwise noted, all reagents and solvents were purchased from the commercial sources and used as received.

The *tert*-butyl hydroperoxide solution (5.5 M in decane, over molecular sieve 4Å) and iron(III) chloride (reagent grade, 97%) were purchased from Sigma-Aldrich.

Thin layer chromatography was used to monitor the reaction on Merck 60 F254 precoated silica gel plate (0.2 mm thickness). TLC spots were visualized by UV-light irradiation on Spectroline Model ENF-24061/F 254 nm. Other visualization method was staining with a basic solution of potassium permanganate, followed by heating.

Flash column chromatography was performed using Merck silica gel 60 with analytical grade solvents as eluents.

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded using Bruker Avance 400 MHz spectrometers. Corresponding chemical shifts are reported in ppm downfield relative to TMS and were referenced to the signal of chloroform-d ( $\delta=7.26$ , singlet). Multiplicities were given as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd=doublets of doublet, td= triplet of doublet. Values of coupling constant are reported as *J* in Hz.

HRMS spectra were recorded on a Waters Q-ToF Premier Spectrometer.

**CAUTION:** No safety issue was encountered in handling the compounds described in this work. However, extra precaution should be taken when working with peroxides as mixture of peroxides and metal salts or metals may cause explosion. Exposure of neat peroxides with heat should be avoided, too.

**General procedure for the synthesis of  $\beta$ -peroxy amides 12a-e, 12g, 13a-g, 14k (GP1):**

To a mixture of the alkene (0.50 mmol, 1 equiv) in 1.6 mL of formamide was added the iron (III) chloride (0.05 mmol, 10 mol%) and PhCOOH (0.10 mmol, 20 mol%). TBHP (5.5 M in decane, 2.0 mmol, 4 equiv) was then added dropwise to the stirring reaction mixture. The reaction mixture was stirred at 65 °C until the starting material spot was observed to disappear from TLC. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine before removal of the solvent under reduced pressure. The crude reaction mixture was subjected to flash column chromatography and the pure product was isolated with hexane / ethyl acetate.

**General procedure for the synthesis of  $\beta$ -peroxy amides 12f, 12h (GP2):**

To a mixture of the styrene (0.5 mmol, 1 equiv) in 1.6 mL of DMSO was added the iron (III) chloride (0.05 mmol, 10 mol%), PhCOOH (0.10 mmol, 20 mol%) and formamide (6.0 mmol, 12 equiv). TBHP (5.5 M in decane, 2.0 mmol, 4 equiv) was then added dropwise to the stirring reaction mixture. The reaction mixture was stirred at 65 °C until the starting material spot was observed to disappear from TLC. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine before removal of the solvent under reduced pressure. The crude reaction mixture was subjected to flash column chromatography and the pure product was isolated with hexane / ethyl acetate.

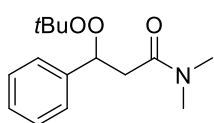
**General procedure for the synthesis of  $\beta$ -peroxy amides 14a-j, 14l-o, 14q (GP3):**

To a mixture of the enyne (0.3 mmol, 1 equiv.) in 1.0 mL of formamide was added the iron (III) chloride (0.03 mmol, 10 mol%) and PhCOOH (0.06 mmol, 20 mol%). TBHP (5.5 M in decane, 1.2 mmol, 4 equiv.) was then added dropwise to the stirring reaction mixture. The reaction mixture was stirred at 65 °C until the starting material spot was observed to disappear from TLC (i.e. 1.25 h). After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine before removal of the solvent under reduced pressure. The crude reaction mixture was subjected to flash column chromatography and the pure product was isolated with hexane / ethyl acetate.

**General procedure for the synthesis of  $\beta$ -peroxy amides 14p, 14r (GP4):**

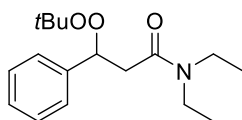
To a mixture of the enyne (0.3 mmol, 1 equiv.) in 1.0 mL of DMSO was added the iron (III) chloride (0.03 mmol, 10 mol%), PhCOOH (0.06 mmol, 20 mol%) and formamide (3.6 mmol, 12 equiv.). TBHP (5.5 M in decane, 1.2 mmol, 4 equiv) was then added dropwise to the stirring reaction mixture. The reaction mixture was stirred at 65 °C until the starting material spot was observed to disappear from TLC (i.e. 1.25 h). After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed with water. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine before removal of the solvent under reduced pressure. The crude reaction mixture was subjected to flash column chromatography and the pure product was isolated with hexane / ethyl acetate.

### 12a. 3-(*tert*-butylperoxy)-*N,N*-dimethyl-3-phenylpropanamide:



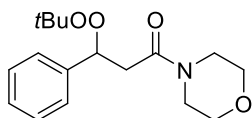
The title compound was prepared according to GP1 and isolated as slowly solidifying colourless oil after purification by flash column chromatography. 63% (5 h)  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.44-7.26 (m, 5H); 5.44 (t,  $J$  = 6.8 Hz, 1H); 3.08 (dd,  $J$  = 7.2, 14.8 Hz, 1H); 3.12-2.90 (2 s, 6H); 2.63 (dd,  $J$  = 6.4, 14.8 Hz, 1H); 1.22 (s, 9H)  $^{13}\text{C NMR}$ : ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  170.2, 140.4, 128.3, 128.0, 127.0, 83.3, 80.8, 38.9, 37.6, 35.5, 26.4 **HRMS (ESI)**:  $\text{C}_{15}\text{H}_{24}\text{NO}_3$ : Calculated: 266.1756; found: 266.1757

### 12b. 3-(*tert*-butylperoxy)-*N,N*-diethyl-3-phenylpropanamide:



The title compound was prepared according to GP1 and was obtained after flash column chromatography as colourless oil. 74% (3 h)  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.42-7.26 (m, 5H); 5.49 (t,  $J$  = 6.8 Hz, 1H); 3.47-3.13 (m, 4H); 3.01 (dd,  $J$  = 7.6, 14.8 Hz, 1H); 2.58 (dd,  $J$  = 6.2, 14.6 Hz, 1H); 1.22 (s, 9H); 1.14-1.05 (m, 6H)  $^{13}\text{C NMR}$ : ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  169.2, 140.6, 128.3, 127.9, 126.9, 83.4, 80.8, 42.2, 40.5, 38.9, 26.4, 14.4, 13.1 **HRMS (ESI)**:  $\text{C}_{17}\text{H}_{28}\text{NO}_3$ : Calculated: 294.2069; found: 294.2068

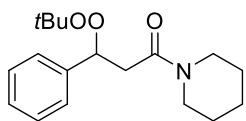
### 12c. 3-(*tert*-butylperoxy)-1-morpholino-3-phenylpropan-1-one:



The title compound was prepared according to GP1 and was obtained after flash column chromatography as colourless oil. 47% (3 h)  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.40-7.26 (m, 5H); 5.42 (t,  $J$  = 6.8 Hz, 1H); 3.73-3.32 (m, 8H); 3.08 (dd,  $J$  = 7.0, 14.6 Hz, 1H); 2.65 (dd,  $J$  = 6.6, 14.6 Hz, 1H); 1.22 (s, 9H)  $^{13}\text{C NMR}$ : ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  168.8, 139.9, 128.4, 128.2, 127.0,

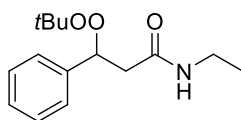
83.3, 80.8, 66.8, 66.5, 46.4, 42.0, 38.3, 26.4 **HRMS (ESI):** C<sub>17</sub>H<sub>26</sub>NO<sub>4</sub>:  
Calculated: 308.1862; found: 308.1860

**12d. 3-(tert-butylperoxy)-3-phenyl-1-(piperidin-1-yl)propan-1-one:**



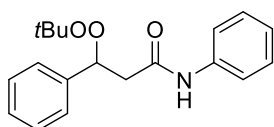
The title compound was prepared according to GP1 and was obtained after flash column chromatography as colourless oil. 47% (4 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.42-7.22 (m, 5H); 5.44 (t, *J* = 6.6 Hz, 1H); 3.61-3.53 (m, 1H); 3.50-3.34 (m, 3H); 3.07 (dd, *J* = 7.2, 14.8 Hz, 1H); 2.65 (dd, *J* = 6.8, 14.8 Hz, 1H); 1.62-1.32 (m, 6H); 1.22 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.1, 140.3, 128.2, 127.9, 127.0, 83.3, 80.6, 47.0, 42.7, 38.4, 26.4, 26.3, 25.4, 24.4 **HRMS (ESI):** C<sub>18</sub>H<sub>28</sub>NO<sub>3</sub>: Calculated: 306.2069; found: 306.2075

**12e. 3-(tert-butylperoxy)-*N*-ethyl-3-phenylpropanamide:**



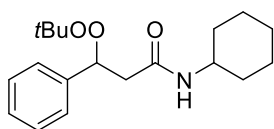
The title compound was prepared according to GP1 and was obtained after flash column chromatography as colourless oil. 73% (4 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.37-7.26 (m, 5H); 5.79 (br, 1H); 5.32 (dd, *J* = 5.0, 8.2 Hz, 1H); 3.33-3.22 (m, 2H); 2.76 (dd, *J* = 8.4, 14.8 Hz, 1H); 2.55 (dd, *J* = 5.0, 14.6 Hz, 1H); 1.21 (s, 9H); 1.08 (t, *J* = 7.2 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.7, 139.8, 128.2, 127.9, 126.6, 82.5, 80.7, 42.4, 34.3, 26.3, 14.6 **HRMS (ESI):** C<sub>15</sub>H<sub>24</sub>NO<sub>3</sub>: Calculated: 266.1756; found: 266.1762

**12f. 3-(tert-butylperoxy)-*N*,3-diphenylpropanamide**



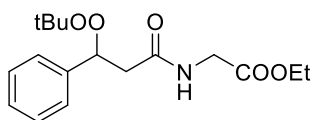
The title compound was prepared according to GP2 and was obtained after flash column chromatography as pale yellow solid. 48% (3 h); m.p.: 92-93°C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.80 (br, 1H); 7.50-7.45 (m, 2H); 7.44-7.26 (m, 7H); 7.15-7.05 (m, 1H); 5.39 (dd, *J* = 4.4, 8.0 Hz, 1H); 2.97 (dd, *J* = 8.0, 14.8 Hz, 1H); 2.82 (dd, *J* = 4.4, 15.2 Hz, 1H); 1.23 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.4, 139.3, 138.0, 128.9, 128.5, 128.3, 126.8, 124.2, 119.9, 82.5, 81.1, 43.2, 26.4 **HRMS (ESI):** C<sub>19</sub>H<sub>24</sub>NO<sub>3</sub>: Calculated: 314.1756; found: 314.1755

**12g. 3-(tert-butylperoxy)-*N*-cyclohexyl-3-phenylpropanamide:**



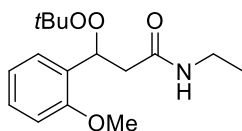
The title compound was prepared according to GP1 and was obtained after flash column chromatography as white solid. 65% (5 h); m.p.: 105-106 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.37-7.24 (m, 5H); 5.73 (br, 1H); 5.30 (dd, *J* = 5.0, 8.2 Hz, 1H); 3.78-3.66 (m, 1H); 2.74 (dd, *J* = 8.2, 14.6 Hz, 1H); 2.53 (dd, *J* = 5.2, 14.8 Hz, 1H); 1.94-1.87 (m, 1H); 1.80-1.54 (m, 4H); 1.40-0.94 (m, 14 H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.7, 139.9, 128.3, 128.0, 126.7, 82.5, 80.7, 48.0, 42.7, 33.0, 32.9, 26.4, 25.5, 24.7, 24.7 **HRMS (ESI):** C<sub>19</sub>H<sub>30</sub>NO<sub>3</sub>; Calculated: 320.2226; found: 320.2223

### 12h. ethyl (3-(*tert*-butylperoxy)-3-phenylpropanoyl)glycinate



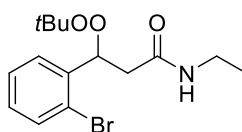
The title compound was prepared according to GP2 and was obtained after flash column chromatography as colourless oil. 54% (5 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.37-7.26 (m, 5H); 6.39 (br, 1H); 5.33 (dd, *J* = 5.2, 8.0 Hz, 1H); 4.20 (q, *J* = 7.1 Hz, 2H); 4.01 (d, *J* = 4.8 Hz, 2H); 2.89 (dd, *J* = 8.0, 14.8 Hz, 1H); 2.66 (dd, *J* = 5.0, 15.0 Hz, 1H); 1.27 (t, *J* = 7.2 Hz, 3H); 1.20 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 170.1, 169.8, 139.6, 128.41, 128.2, 126.9, 82.2, 80.8, 61.5, 42.0, 41.5, 26.4, 14.1 **HRMS (ESI):** C<sub>17</sub>H<sub>26</sub>NO<sub>5</sub>; Calculated: 324.1811; found: 324.1818

### 13a. 3-(*tert*-butylperoxy)-*N*-ethyl-3-(2-methoxyphenyl)propanamide:



The title compound was prepared according to GP1 and was obtained after flash column chromatography as white solid. 59% (3.5 h); m.p.: 116-117 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.39 (dd, *J* = 1.4, 7.4 Hz, 1H); 7.25 (td, *J* = 1.5, 7.8 Hz, 1H); 6.96 (t, *J* = 7.6 Hz, 1H); 6.86 (d, *J* = 8.0 Hz, 1H); 6.03 (br, 1H); 5.69 (dd, *J* = 5.0, 8.2 Hz, 1H); 3.82 (s, 3H); 3.32-3.25 (m, 2H); 2.68 (dd, *J* = 4.2, 15.0 Hz, 1H); 2.61 (dd, *J* = 8.6, 15.0 Hz, 1H); 1.23 (s, 9H); 1.12 (t, *J* = 7.2 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 170.1, 156.4, 128.8, 128.3, 127.08, 120.4, 110.5, 80.7, 55.3, 41.4, 34.3, 26.4, 14.8 **HRMS (ESI):** C<sub>16</sub>H<sub>26</sub>NO<sub>4</sub>; Calculated: 296.1862; found: 296.1859

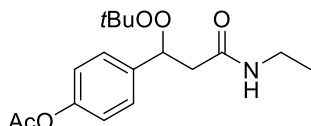
### 13b. 3-(2-bromophenyl)-3-(*tert*-butylperoxy)-*N*-ethylpropanamide:



The title compound was prepared according to GP1 and was obtained after flash column chromatography as white solid. 71% (2.5 h); m.p.: 104-105 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.52-7.46 (m, 2H); 7.31 (t, *J* = 7.6

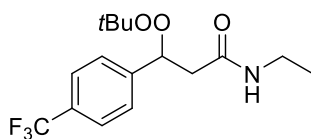
Hz, 1H); 7.13 (dt,  $J = 1.7, 7.7$  Hz, 1H); 5.95 (br, 1H); 5.69 (dd,  $J = 3.6, 9.6$  Hz, 1H); 3.35-3.26 (m, 2H); 2.65 (dd,  $J = 3.6, 15.2$  Hz, 1H); 2.47 (dd,  $J = 9.6, 15.2$  Hz, 1H); 1.22 (s, 9H); 1.13 (t,  $J = 7.2$  Hz, 3H)  $^{13}\text{C}$  NMR: (CDCl<sub>3</sub>, 100 MHz):  $\delta$  169.1, 139.4, 132.8, 129.2, 127.9, 127.5, 122.3, 81.3, 81.1, 41.5, 34.5, 26.4, 14.8 HRMS (ESI): C<sub>15</sub>H<sub>23</sub>NO<sub>3</sub>Br: Calculated: 346.0841; found: 346.0841

### 13c. 4-(1-(*tert*-butylperoxy)-3-(ethylamino)-3-oxopropyl)phenyl acetate:



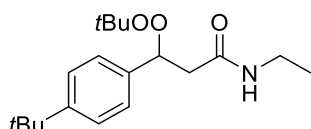
The title compound was prepared according to GP1 and was obtained after flash column chromatography as white solid. 75% (2 h); m.p.: 86-88 °C  $^1\text{H}$  NMR: (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.35 (d,  $J = 8.4$  Hz, 2H); 7.05 (d,  $J = 8.4$  Hz, 2H); 5.78 (br, 1H); 5.33 (dd,  $J = 5.0, 8.2$  Hz, 1H); 3.45-3.21 (m, 2H); 2.72 (dd,  $J = 8.2, 14.6$  Hz, 1H); 2.51 (dd,  $J = 5.0, 14.6$  Hz, 1H); 2.28 (s, 3H); 1.20 (s, 9H); 1.08 (t,  $J = 7.2$  Hz, 3H)  $^{13}\text{C}$  NMR: (CDCl<sub>3</sub>, 100 MHz):  $\delta$  169.5, 169.4, 150.34 137.6, 127.8, 121.5, 82.0, 80.9, 42.7, 34.4, 26.4, 21.1, 14.7 HRMS (ESI): C<sub>17</sub>H<sub>26</sub>NO<sub>5</sub>: Calculated: 324.1811; found: 324.1807

### 13d. 3-(*tert*-butylperoxy)-*N*-ethyl-3-(4-(trifluoromethyl)phenyl)propanamide:



The title compound was prepared according to GP1 and was obtained after flash column chromatography as white solid. 77% (2 h); m.p.: 110-111 °C  $^1\text{H}$  NMR: (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.59 (d,  $J = 8.4$  Hz, 2H); 7.47 (d,  $J = 8.0$  Hz, 2H); 5.80 (br, 1H); 5.40 (dd,  $J = 5.0, 8.4$  Hz, 1H); 3.32-3.22 (m, 2H); 2.68 (dd,  $J = 8.4, 14.8$  Hz, 1H); 2.50 (dd,  $J = 5.0, 14.6$  Hz, 1H); 1.21 (s, 9H); 1.09 (t,  $J = 7.2$  Hz, 3H)  $^{13}\text{C}$  NMR: (CDCl<sub>3</sub>, 100 MHz):  $\delta$  169.0, 144.3, 130.1 (q,  $J_{\text{C-F}} = 32.3$  Hz), 126.9, 125.4 (q,  $J_{\text{C-F}} = 3.7$  Hz), 124.1 (q,  $J_{\text{C-F}} = 270.3$  Hz), 81.8, 81.1, 42.6, 34.5, 26.4, 14.7 HRMS (ESI): C<sub>16</sub>H<sub>23</sub>NO<sub>3</sub>F<sub>3</sub>: Calculated: 334.1630; found: 334.1627

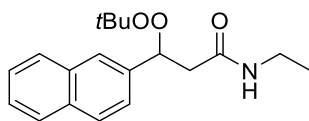
### 13e. 3-(4-(*tert*-butyl)phenyl)-3-(*tert*-butylperoxy)-*N*-ethylpropanamide:



The title compound was prepared according to GP1 and was obtained after flash column chromatography as white solid. 68% (2 h); m.p.: 112-114 °C  $^1\text{H}$  NMR: (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.36 (d,  $J = 8.4$  Hz); 7.27 (d,  $J = 8.0$  Hz); 5.76 (br, 1H); 5.30 (dd,  $J = 4.8, 8.4$  Hz, 1H); 3.28-3.23 (m, 2H); 2.76 (dd,  $J = 8.2, 14.6$  Hz, 1H); 2.57 (dd,  $J = 5.0, 14.6$  Hz, 1H); 1.31 (s, 9H); 1.22 (s, 9H); 1.06 (t,  $J = 7.4$  Hz)  $^{13}\text{C}$  NMR: (CDCl<sub>3</sub>, 100 MHz):  $\delta$  169.9, 150.9,

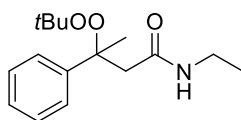
136.6, 126.4, 125.2, 82.4, 80.8, 42.5, 34.5, 34.3, 31.3, 26.4, 14.7 **HRMS (ESI):** C<sub>19</sub>H<sub>32</sub>NO<sub>3</sub>: Calculated: 322.2382; found: 322.2379

**13f. 3-(tert-butylperoxy)-N-ethyl-3-(naphthalen-2-yl)propanamide:**



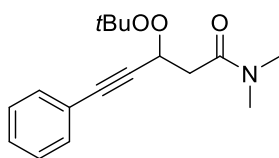
The title compound was prepared according to GP1 and was obtained after flash column chromatography as white solid. 56% (2.5 h); m.p.: 107-109 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.85-7.81 (m, 4H); 7.50-7.44 (m, 3H); 5.89 (br, 1H); 5.51 (dd, *J* = 5.0, 8.2 Hz, 1H); 3.27-3.23 (m, 2H); 2.84 (dd, *J* = 8.2, 14.6 Hz, 1H); 2.62 (dd, *J* = 5.0, 14.6 Hz, 1H); 1.23 (s, 9H); 1.06 (t, *J* = 7.2 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.6, 137.5, 133.2, 133.1, 128.2, 128.1, 127.6, 126.1, 126.0, 125.9, 124.4, 82.7, 80.9, 42.7, 34.4, 26.4, 14.7 **HRMS (ESI):** C<sub>19</sub>H<sub>26</sub>NO<sub>3</sub>: Calculated: 316.1913; found: 316.1905

**13g. 3-(tert-butylperoxy)-N-ethyl-3-phenylbutanamide:**



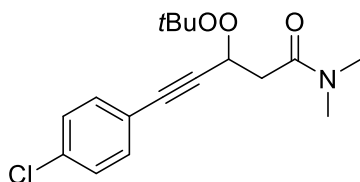
The title compound was prepared according to GP1 and was obtained after flash column chromatography colourless oil. 64% (2 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.45-7.40 (m, 2H); 7.36-7.23 (m, 3H); 6.42 (br, 1H); 3.22-3.14 (m, 1H); 2.97 (d, *J* = 14.8 Hz, 1H); 2.89 (d, *J* = 14.8 Hz, 1H); 1.63 (s, 3H); 1.28 (s, 9H); 0.99 (t, *J* = 7.2 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.9, 143.2, 128.1, 127.4, 125.3, 82.6, 79.9, 44.8, 34.0, 26.6, 26.0, 14.5 **HRMS (ESI):** C<sub>16</sub>H<sub>26</sub>NO<sub>3</sub>: Calculated: 280.1913; found: 280.1913

**14a. 3-(tert-butylperoxy)-N,N-dimethyl-5-phenylpent-4-ynamide:**



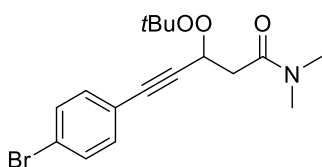
The title compound was prepared according to GP3 and isolated as yellow oil after purification by flash column chromatography. 51% (1.25 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.46-7.42 (m, 2H); 7.30-7.27 (m, 3H); 5.36-5.32 (m, 1H); 3.07-3.02 (m, 4H); 2.97 (s, 3H); 2.77 (dd, *J* = 6.2, 15.0 Hz, 1H); 1.28 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.1, 131.8, 128.4, 128.2, 122.6, 87.1, 85.5, 81.1, 71.7, 37.8, 37.6, 35.6, 26.4 **HRMS (ESI):** C<sub>17</sub>H<sub>24</sub>NO<sub>3</sub>: Calculated: 290.1756; found: 290.1763

**14b. 3-(tert-butylperoxy)-5-(4-chlorophenyl)-N,N-dimethylpent-4-ynamide:**



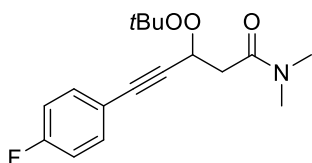
The title compound was prepared according to GP3 and isolated as pale yellow solid after purification by flash column chromatography. 39% (1.25 h); m.p.: 78-79 °C **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 7.36 (d, *J* = 8.4 Hz, 2H); 7.26 (d, *J* = 8.4 Hz, 2H); 5.33 (t, *J* = 6.6 Hz, 1H); 3.07-3.00 (m, 4H); 2.97 (s, 3H); 2.76 (dd, *J* = 6.2, 15.0 Hz, 1H); 1.27 (s, 9H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 169.0, 134.5, 133.1, 128.6, 121.2, 88.1, 84.3, 81.2, 71.6, 37.7, 37.6, 35.6, 26.4 **HRMS (ESI)**: C<sub>17</sub>H<sub>23</sub>NO<sub>3</sub>Cl: Calculated: 324.1366; found: 324.1370

**14c. 5-(4-bromophenyl)-3-(tert-butylperoxy)-N,N-dimethylpent-4-ynamide:**



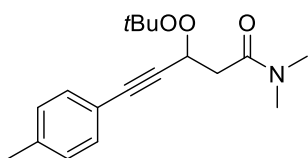
The title compound was prepared according to GP3 and was obtained after flash column chromatography as pale yellow solid. 41% (1.25 h); m.p.: 84-85 °C **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 7.43 (d, *J* = 8.4 Hz, 2H); 7.30 (d, *J* = 8.4 Hz, 2H); 5.35-5.31 (m, 1H); 3.07-3.01 (m, 4H); 2.98 (s, 3H); 2.76 (dd, *J* = 6.0, 15.2 Hz, 1H); 1.27 (s, 9H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 169.0, 133.3, 131.5, 122.7, 121.6, 88.3, 84.4, 81.2, 71.6, 37.7, 37.6, 35.6, 26.4 **HRMS (ESI)**: C<sub>17</sub>H<sub>23</sub>NO<sub>3</sub>Br: Calculated: 368.0861; found: 368.0874

**14d. 3-(tert-butylperoxy)-5-(4-fluorophenyl)-N,N-dimethylpent-4-ynamide:**



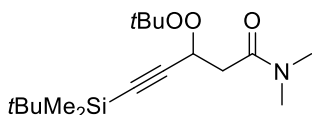
The title compound was prepared according to GP3 and isolated as pale yellow solid after purification by flash column chromatography. 41% (1.25 h); m.p.: 51-53 °C **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 7.44-7.40 (m, 2H); 7.01-6.96 (m, 2H); 5.33 (t, *J* = 6.8 Hz, 1H); 3.07-2.97 (m, 7H); 2.76 (dd, *J* = 6.2, 15.0 Hz, 1H); 1.28 (s, 9H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 169.1, 162.6 (d, *J*<sub>C-F</sub> = 248 Hz), 133.8 (d, *J*<sub>C-F</sub> = 8.0 Hz), 118.7 (d, *J*<sub>C-F</sub> = 3.0 Hz), 115.5 (d, *J*<sub>C-F</sub> = 21.0 Hz), 86.8, 84.4, 81.1, 71.7, 37.7, 37.6, 35.6, 26.4 **HRMS (ESI)**: C<sub>17</sub>H<sub>23</sub>NO<sub>3</sub>F: Calculated: 308.1662; found: 308.1664

**14e. 3-(tert-butylperoxy)-N,N-dimethyl-5-(p-tolyl)pent-4-ynamide:**



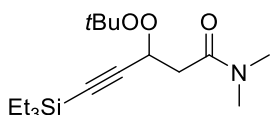
The title compound was prepared according to GP3 and isolated as pale yellow solid after purification by flash column chromatography. 50% (1.25 h); m.p.:93-94 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.33 (d, 2H, *J* = 8.4 Hz); 7.09 (d, 2H, *J* = 8.0 Hz); 5.33 (t, 1H, *J* = 6.6 Hz); 3.08-3.00 (m, 4H); 2.97 (s, 3H); 2.77 (dd, *J* = 6.0, 14.8 Hz, 1H); 2.33 (s, 3H); 1.27 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.2, 138.5, 131.7, 128.9, 119.5, 86.3, 85.7, 81.0, 71.8, 37.8, 37.6, 35.6, 26.4, 21.5 **HRMS (ESI):** C<sub>18</sub>H<sub>26</sub>NO<sub>3</sub>: Calculated: 304.1913; found: 304.1909

**14f. 5-(tert-butyltrimethylsilyl)-3-(tert-butylperoxy)-N,N-dimethylpent-4-ynamide:**



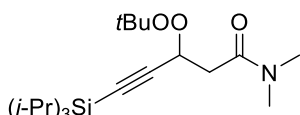
The title compound was prepared according to GP3 and isolated as yellow oil after purification by flash column chromatography. 61% (1.25 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 5.12 (dd, *J* = 6.0, 7.6 Hz, 1H); 3.05 (s, 3H); 2.98-2.91 (m, 4H); 2.66 (dd, *J* = 6.0, 14.8 Hz, 1H); 1.23 (s, 9H); 0.92 (s, 9H); 0.09 (s, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.2, 103.8, 88.8, 80.8, 71.6, 37.7, 37.7, 35.6, 26.4, 26.01 16.6, -4.8 **HRMS (ESI):** C<sub>17</sub>H<sub>34</sub>NO<sub>3</sub>Si: Calculated: 328.2308; found: 328.2309

**14g. 3-(tert-butylperoxy)-N,N-dimethyl-5-(triethylsilyl)pent-4-ynamide:**



The title compound was prepared according to GP3 and isolated as colourless oil after purification by flash column chromatography. 52% (1.25 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 5.12 (dd, *J* = 6.0, 7.6 Hz, 1H); 3.05 (s, 3H); 2.97-2.91 (m, 4H); 2.67 (dd, *J* = 6.0, 14.8 Hz, 1H); 1.23 (s, 9H); 0.97 (t, *J* = 7.8 Hz, 9H); 0.58 (q, *J* = 8.0 Hz, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.1, 104.4, 87.8, 80.7, 71.5, 37.7, 37.7, 35.5, 26.4, 7.3, 4.2 **HRMS (ESI):** C<sub>17</sub>H<sub>34</sub>NO<sub>3</sub>Si: Calculated: 328.2308; found: 328.2310

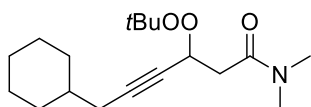
**14h. 3-(tert-butylperoxy)-N,N-dimethyl-5-(triisopropylsilyl)pent-4-ynamide:**



The title compound was prepared according to GP3 and isolated as colourless solid after purification by flash column chromatography. 61% (1.25 h); m.p.: 87-88 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 5.14 (dd, *J* = 6.2, 7.4 Hz, 1H); 3.05 (s, 3H); 2.98-2.91 (m, 4H); 2.68 (dd, *J* = 6.4, 14.8 Hz, 1H); 1.23 (s, 9H); 1.06-1.04 (m, 21H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.2, 105.1,

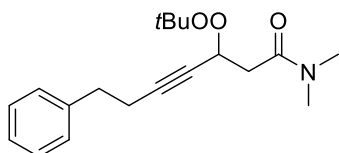
86.7, 80.6, 71.6, 37.8, 37.7, 35.6, 26.4, 18.5, 11.1 **HRMS (ESI):** C<sub>20</sub>H<sub>40</sub>NO<sub>3</sub>Si:  
Calculated: 370.2777; found: 370.2777

**14i. 3-(tert-butylperoxy)-6-cyclohexyl-N,N-dimethylhex-4-ynamide:**



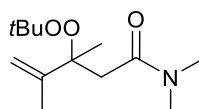
The title compound was prepared according to GP3 and isolated as yellow oil after purification by flash column chromatography. 45% (1.25 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 5.12-5.07 (m, 1H); 3.05 (s, 3H); 2.97-2.90 (m, 4H); 2.64 (dd, *J* = 6.4, 14.4 Hz, 1H); 2.09 (dd, *J* = 2.0, 6.8 Hz, 1H); 1.80-1.74 (m, 2H); 1.70-1.62 (m, 3H); 1.50-1.39 (m, 1H); 1.27-1.18 (m, 12H); 1.02-0.90(m, 2H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.4, 85.5, 80.80, 78.6, 71.7, 38.1, 37.6, 37.2, 35.5, 32.6, 26.6, 26.3, 26.2, 26.1 **HRMS (ESI):** C<sub>18</sub>H<sub>32</sub>NO<sub>3</sub>: Calculated: 310.2382; found: 310.2386

**14j. 3-(tert-butylperoxy)-N,N-dimethyl-7-phenylhept-4-ynamide:**



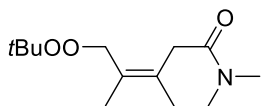
The title compound was prepared according to GP3 and isolated as light yellow oil after purification by flash column chromatography. 42% (1.25 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.30-7.25 (m, 2H); 7.22-7.17 (m, 3H); 5.11-5.06 (m, 1H); 3.01 (s, 3H); 2.97-2.87 (m, 4H); 2.82 (t, *J* = 7.6 Hz, 2H); 2.60 (dd, *J* = 6.4, 14.8 Hz, 1H); 2.51 (td, *J* = 1.6, 7.6 Hz, 2H); 1.24 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 169.2, 140.6, 128.5, 128.3, 126.18, 85.6, 80.9, 78.5, 71.5, 37.9, 37.5, 35.4, 34.8, 26.3, 21.0 **HRMS (ESI):** C<sub>19</sub>H<sub>28</sub>NO<sub>3</sub>: Calculated: 318.2069; found: 318.2062

**14k. 3-(tert-butylperoxy)-N,N,3,4-tetramethylpent-4-enamide compound with methane (1:1)**



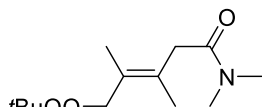
The title compound was prepared according to GP1 with 2,3-dimethyl-1,3-butadiene and isolated as colourless oil together with **14k'** and **14k''** after purification by flash column chromatography. 14% (3 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 4.97-4.91 (m, 2H); 3.09 (s, 3H); 2.93 (s, 3H); 2.82 (d, *J* = 14.0 Hz, 1H); 2.53 (d, *J* = 14.0 Hz, 1H); 1.84 (s, 3H); 1.57 (s, 3H); 1.20 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 170.0, 148.3, 111.8, 83.7, 40.8, 38.4, 35.6, 26.7, 22.1, 19.2 **HRMS (ESI):** C<sub>13</sub>H<sub>26</sub>NO<sub>3</sub>: Calculated: 244.1913; found: 244.1910

**14k'. (Z)-5-(tert-butylperoxy)-N,N,3,4-tetramethylpent-3-enamide**



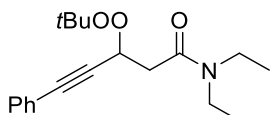
The title compound was prepared according to GP1 with 2,3-dimethyl-1,3-butadiene and isolated as colourless oil together with **14k** and **14k''** after purification by flash column chromatography. The *E*-configuration of this compound was deduced on the basis of the NOESY analysis. 13% (3 h) **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 4.41 (s, 2H); 3.24 (s, 2H); 3.01 (s, 3H); 2.94 (s, 3H); 1.81 (s, 3H); 1.74 (s, 3H); 1.24 (s, 9H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 171.0, 130.6, 126.5, 80.2, 76.0, 39.0, 37.3, 35.6, 26.4, 19.1, 18.1 **HRMS (ESI)**: C<sub>13</sub>H<sub>26</sub>NO<sub>3</sub>: Calculated: 244.1913; found: 244.1914

**14k''.** (*E*)-5-(*tert*-butylperoxy)-*N,N*,3,4-tetramethylpent-3-enamide



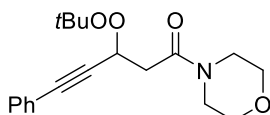
The title compound was prepared according to GP1 with 2,3-dimethyl-1,3-butadiene and isolated as colourless oil together with **14k** and **14k'** after purification by flash column chromatography. 21% (3 h) **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 4.48 (s, 2H); 3.15 (s, 2H); 2.97 (s, 3H); 2.93 (s, 3H); 1.78-1.76 (2s, 6H); 1.24 (s, 9H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 170.9, 130.2, 126.4, 80.2, 76.0, 39.8, 37.3, 35.6, 26.4, 18.3, 17.8 **HRMS (ESI)**: C<sub>13</sub>H<sub>26</sub>NO<sub>3</sub>: Calculated: 244.1913; found: 244.1911

**14l.** 3-(*tert*-butylperoxy)-*N,N*-diethyl-5-phenylpent-4-ynamide:



The title compound was prepared according to GP3 and isolated as yellow oil after purification by flash column chromatography. 32% (1.25 h) **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 7.46-7.42 (m, 2H); 7.32-7.25 (m, 3H); 5.39 (dd, *J* = 6.2, 7.4 Hz, 1H); 3.46-3.36 (m, 4H); 3.02 (dd, *J* = 14.6, 7.6 Hz, 1H); 2.74 (dd, *J* = 14.8, 6.2 Hz, 1H); 1.28 (s, 9H); 1.21 (t, *J* = 7.2 Hz, 3H); 1.13 (t, *J* = 7.2 Hz, 3H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 168.2, 131.8, 128.3, 128.1, 122.6, 87.1, 85.4, 81.1, 71.6, 42.3, 40.5, 37.5, 26.38, 14.5, 13.1 **HRMS (ESI)**: C<sub>19</sub>H<sub>28</sub>NO<sub>3</sub>: Calculated: 318.2069; found: 318.2071

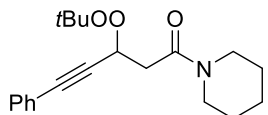
**14m.** 3-(*tert*-butylperoxy)-1-morpholino-5-phenylpent-4-yn-1-one:



The title compound was prepared according to GP3 and isolated as slowly solidifying colourless oil after purification by flash column chromatography. 34% (1.25 h) **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 7.48-7.42 (m, 2H); 7.33-7.25 (m, 3H); 5.34 (dd, *J* = 6.0, 7.2 Hz, 1H); 3.72-3.54 (m, 8H); 3.06 (dd, *J* = 7.4, 15.0 Hz, 1H); 2.78 (dd, *J* = 6.2, 15.0 Hz, 1H); 1.29 (s, 9H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 167.9, 131.8, 128.6, 128.3, 122.5, 86.7, 85.8, 81.2,

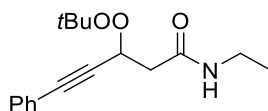
71.7, 66.9, 66.7, 46.5, 42.2, 37.4, 26.5 **HRMS (ESI):** C<sub>19</sub>H<sub>26</sub>NO<sub>4</sub>: Calculated: 332.1862; found: 332.1862

**14n. 3-(tert-butylperoxy)-5-phenyl-1-(piperidin-1-yl)pent-4-yn-1-one:**



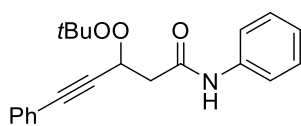
The title compound was prepared according to GP3 and isolated as slowly solidifying colourless oil after purification by flash column chromatography. 44% (1.25 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.46-7.41 (m, 2H); 7.31-7.26 (m, 3H); 5.37-5.33 (m, 1H); 3.65-3.57 (m, 2H); 3.53-3.42 (m, 2H); 3.05 (dd, *J* = 15.2, 7.2 Hz, 1H); 2.77 (dd, *J* = 15.0, 6.2 Hz, 1H); 1.67-1.53 (m, 6H); 1.29 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 167.3, 131.8, 128.4, 128.2, 122.7, 87.3, 85.5, 81.1, 71.8, 47.1, 43.0, 37.5, 26.5, 26.5, 25.6, 24.5 **HRMS (ESI):** C<sub>20</sub>H<sub>28</sub>NO<sub>3</sub>: Calculated: 330.2069; found: 330.2073

**14o. 3-(tert-butylperoxy)-N-ethyl-5-phenylpent-4-ynamide:**



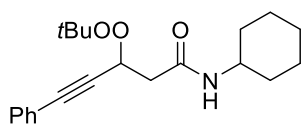
The title compound was prepared according to GP3 and isolated as yellow oil after purification by flash column chromatography. 40% (1.25 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.44- 7.38 (m, 2H); 7.30-7.25 (m, 3H); 6.11 (br, 1H); 5.18 (dd, *J* = 5.4, 7.4 Hz, 1H); 3.35-3.25 (m, 2H); 2.81-2.66 (m, 2H); 1.28 (s, 9H); 1.13 (t, *J* = 7.2 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.7, 131.7, 128.6, 128.2, 122.3, 86.1, 86.1, 81.2, 71.1, 41.2, 34.4, 26.4, 14.8 **HRMS (ESI):** C<sub>17</sub>H<sub>24</sub>NO<sub>3</sub>: Calculated: 290.1756; found: 290.1757

**14p. 3-(tert-butylperoxy)-N,5-diphenylpent-4-ynamide:**



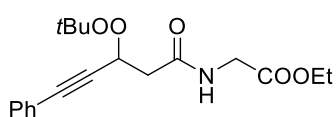
The title compound was prepared according to GP4 and isolated as yellow oil after purification by flash column chromatography. 43% (1.25 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.94 (br, 1H); 7.54-7.50 (m, 2H); 7.45-7.41 (m, 2H); 7.34-7.26 (m, 5H); 7.16-7.07 (m, 1H); 5.27-5.24 (m, 1H); 3.04-2.91 (m, 2H); 1.33 (s, 9H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 167.3, 137.9, 131.8, 129.0, 128.7, 128.3, 124.3, 122.1, 120.0, 86.7, 85.6, 81.5, 71.1, 42.1, 26.5 **HRMS (ESI):** C<sub>21</sub>H<sub>24</sub>NO<sub>3</sub>: Calculated: 338.1756; found: 338.1747

**14q. 3-(tert-butylperoxy)-N-cyclohexyl-5-phenylpent-4-ynamide**



The title compound was prepared according to GP3 and isolated as white solid after purification by flash column chromatography. 37 % (1.25 h); m.p.: 84-85°C  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz): 7.47-7.41 (m, 2H); 7.36-7.26 (m, 3H); 5.95-5.85 (br, 1H); 5.19-5.15 (m, 1H); 3.85-3.78 (m, 1H); 2.75-2.70 (m, 2H); 1.94-1.90 (m, 2H); 1.73-1.64 (m, 2H); 1.61-1.56 (m, 1H); 1.42-1.10 (m, 14H)  $^{13}\text{C NMR}$ : ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  167.9, 131.8, 128.6, 128.3, 122.4, 86.2, 86.2, 81.3, 71.2, 48.1, 41.4, 33.1, 33.0, 26.5, 25.6, 24.7 **HRMS (ESI)**:  $\text{C}_{21}\text{H}_{30}\text{NO}_3$ : Calculated: 344.2226; found: 344.2230

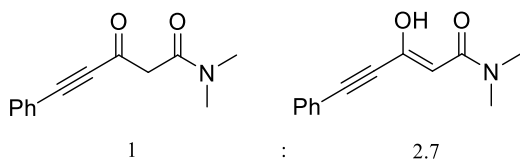
#### 14r. ethyl (3-(tert-butylperoxy)-5-phenylpent-4-ynoyl)glycinate:



The title compound was prepared according to GP4 and isolated as yellow oil after purification by flash column chromatography. 33% (1.25 h)  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.46-7.41 (m, 2H); 7.32-7.26 (m, 3H); 6.54 (br, 1H); 5.20 (dd,  $J = 5.2, 7.2$  Hz, 1H); 4.21 (q,  $J = 7.1$  Hz, 2H); 4.07 (d,  $J = 4.8$  Hz); 2.90 (dd,  $J = 15.0, 7.4$  Hz, 1H); 2.80 (dd,  $J = 5.2, 14.0$  Hz, 1H); 1.30-1.25 (m, 12H)  $^{13}\text{C NMR}$ : ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  169.7, 169.0, 131.9, 128.6, 128.2, 122.3, 86.3, 85.9, 81.3, 70.8, 61.5, 41.6, 40.8, 26.4, 14.1 **HRMS (ESI)**:  $\text{C}_{19}\text{H}_{26}\text{NO}_5$ : Calculated: 348.1811; found: 348.1815

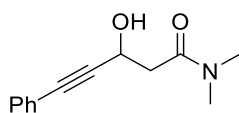
#### Transformation of $\beta$ -Peroxy Amide 14a:

#### 15. *N,N*-dimethyl-3-oxo-5-phenylpent-4-ynamide : (*Z*)-3-hydroxy-*N,N*-dimethyl-5-phenylpent-2-en-4-ynamide:



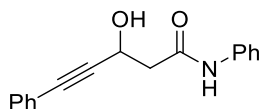
In a screw cap vial, **14a** (63.7mg, 0.22 mmol, 1 equiv) was dissolved in 1.5 mL of ethyl acetate, to which TMEDA (0.22 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 h. The reaction mixture was then subjected to flash column chromatography with hexane/ethyl acetate (5:1) to give **15** (33.1 mg, clear oil) in 70% yield. Analysis of the product showed the keto and the enol form in a 1:2.7 ratio.  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.61-7.31 (m, 5H, both keto and enol form); 5.63 (s, 1H, enol form); 3.80 (s, 2H, keto form); 3.04-2.99 (m, 6H, both keto and enol form)  $^{13}\text{C NMR}$ : ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  180.3 (keto), 171.4 (enol), 165.5 (keto), 155.2 (enol), 133.3 (keto), 132.1 (enol), 131.1 (keto), 129.6 (enol), 128.6 (keto), 128.4 (enol), 121.2 (enol), 119.5 (keto), 94.4 (enol), 92.8 (keto), 91.6 (enol), 87.4 (keto), 84.5 (enol), 51.5 (keto), 37.9, 35.5 **HRMS (ESI)**:  $\text{C}_{13}\text{H}_{14}\text{NO}_2$ : Calculated: 216.1025; found: 216.1025

### 16a. 3-hydroxy-*N,N*-dimethyl-5-phenylpent-4-ynamide



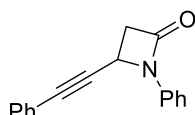
In a screw cap vial, **14a** (49.0 mg, 0.17 mmol, 1 equiv) was dissolved in 1.0 mL of acetic acid, to which zinc dust (0.85 mmol) was added. The reaction mixture was allowed to stir at 70 °C for 13 h. The reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, brine and dried over sodium sulphate. The organic layers were evaporated in vacuo and the residue was purified by flash column chromatography with hexane/ethyl acetate (3:2) to give **16a** (29.0 mg, pale yellow solid) in 79% yield. m.p.: 79-81°C. **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.46-7.42 (m, 2H); 7.34-7.25 (m, 3H); 5.06-5.01 (m, 1H); 4.62 (br, 1H); 3.03-2.94 (2s, 6H); 2.58-2.78 (m, 2H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 171.3, 131.7, 128.4, 128.2, 122.6, 88.6, 84.5, 59.5, 40.0, 37.1, 35.2 **HRMS (ESI):** C<sub>13</sub>H<sub>16</sub>NO<sub>2</sub>: Calculated: 218.1181; found: 218.1177

### 16p. 3-hydroxy-*N*,5-diphenylpent-4-ynamide:



In a screw cap vial, **14p** (30.7 mg, 0.091 mmol) was dissolved in 1.0 mL of acetic acid, to which zinc dust (0.46 mmol) was added. The reaction mixture was allowed to stir at 70 °C for 3.5 hours. The reaction was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution, brine and dried over sodium sulphate. The organic layers were evaporated in vacuo and the residue was purified by flash column chromatography with hexane/ethyl acetate (3:1) to give **16p** (18.3mg, pale yellow solid) in 76% yield. The analytical data are in accordance with the literature.<sup>1</sup> m.p.: 131-132°C. **<sup>1</sup>H NMR:** (CD<sub>3</sub>OD, 400 MHz): δ 7.55 (d, *J* = 8.0 Hz, 2H); 7.40-7.24 (m, 7H); 7.08 (t, *J* = 7.4 Hz, 1H); 5.08 (t, *J* = 6.8 Hz, 1H); 2.88-2.76 (m, 2H) **<sup>13</sup>C NMR:** (CD<sub>3</sub>OD, 100 MHz): δ 170.6, 139.7, 132.6, 129.8, 129.5, 129.4, 125.3, 124.0, 121.4, 90.4, 85.5, 60.4, 46.4 **HRMS (ESI):** C<sub>17</sub>H<sub>16</sub>NO<sub>2</sub>: Calculated: 266.1181; found: 266.1183

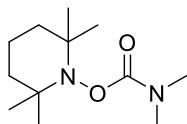
### 17. 1-phenyl-4-(phenylethynyl)azetidin-2-one:



To a stirring solution of **16p** (30.5 mg, 0.11 mmol) in 1.2 mL of THF was added triethylphosphite (0.15 mmol) dropwise, which was then followed by diisopropylazodicarboxylate (0.17 mmol). The resulting yellow solution was stirred for 24 h. The resulting reaction mixture was then evaporated in vacuo, after which the crude residue was purified by flash chromatography (Cyclohexane/EtOAc) to afford **17** (17.3 mg, white solid) in 61%. The analytical data are in accordance with the literature.<sup>1</sup> m.p.: 92-93°C.

**<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.59-7.54 (m, 2H); 7.44-7.28 (m, 7H); 7.12 (t, *J* = 7.4 Hz, 1H); 4.81 (dd, *J* = 2.8, 5.6 Hz, 1H); 3.51 (dd, *J* = 5.8, 15.0 Hz, 1H); 3.29 (dd, *J* = 2.8, 14.8 Hz, 1H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 163.2, 137.6, 131.8, 129.2, 129.0, 128.4, 124.2, 121.8, 116.7, 86.7, 84.7, 44.9, 41.1 **HRMS (ESI):** C<sub>17</sub>H<sub>14</sub>NO: Calculated: 248.1075; found: 248.1080

### 18. 2,2,6,6-tetramethylpiperidin-1-yl dimethylcarbamate:

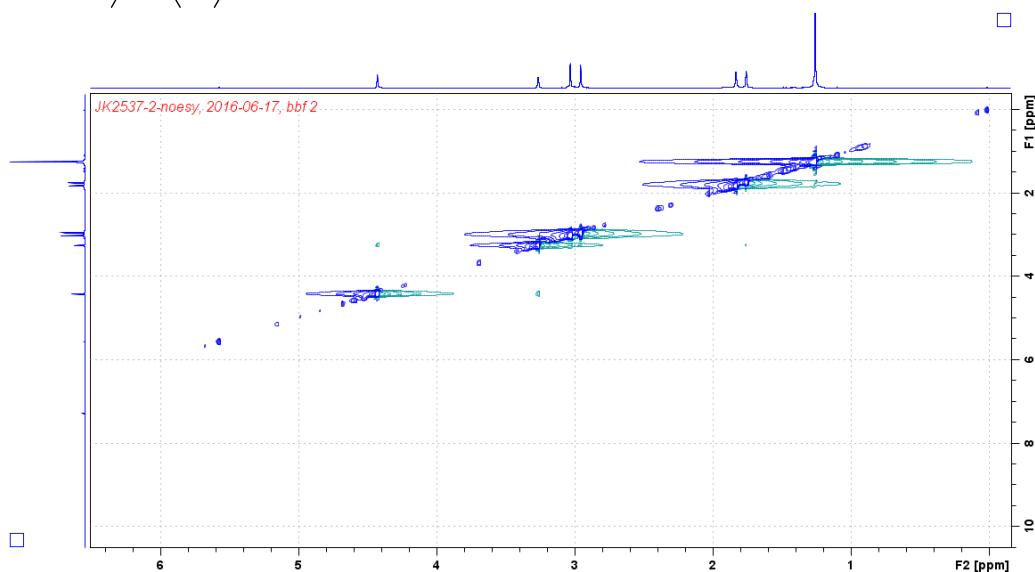
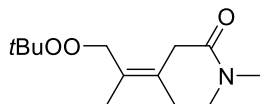


The title compound was prepared according to GP3 with additional 2.5 equiv of TEMPO and isolated as light yellow oil after purification by flash column chromatography. The analytical data are in accordance with the literature.<sup>2</sup> **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 3.00-2.95 (m, 6H); 1.72-1.34 (m, 6H); 1.16-1.12 (m, 6H); 1.10-1.05 (m, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 157.6, 60.0, 39.0, 31.8, 21.0, 17.0 **HRMS (ESI):** C<sub>12</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>: Calculated: 229.1916; found: 229.1919

#### References:

1. Kern, N.; Hoffmann, M.; Blanc, A.; Weibel, J.-M. Pale, P. *Org. Lett.* **2013**, *15*, 836.
2. Tu, H.-Y.; Liu, Y.-R.; Chu, J.-J.; Hu, B.-L.; Zhang, X.-G. *J. Org. Chem.* **2014**, *79*, 9907.

### 14k'. (Z)-5-(tert-butylperoxy)-N,N,3,4-tetramethylpent-3-enamide



# *CHAPTER 4*

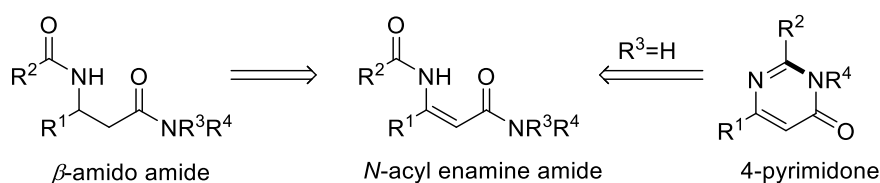
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***IRON-CATALYZED  
AMINOCARBONYLATION OF ENAMIDES  
WITH FORMAMIDES FOR EXPEDIENT  
SYNTHESIS OF N-ACYL ENAMINE AMIDES***

## 4.1 Introduction:

### 4.1.1 Synthesis of *N*-acyl enamine amides

*N*-acyl enamine amides are useful reaction intermediates which can be readily reduced to  $\beta$ -amido amides, a common structural feature in important drugs and  $\beta$ -peptides.<sup>117</sup> Pertaining to the presence of N,O-functionalities in the scaffold, they also represent an integral class of precursors which are poised to undergo cyclodehydration to pyrimidinone, a common structural feature in many compounds with therapeutic values (Scheme 4-1).<sup>118,119</sup>



Scheme 4-1: Access to  $\beta$ -amido amides & 4-pyrimidone from *N*-acyl enamine amide

#### 4.1.1.1 Acylation of $\beta$ -aminocrotonamides

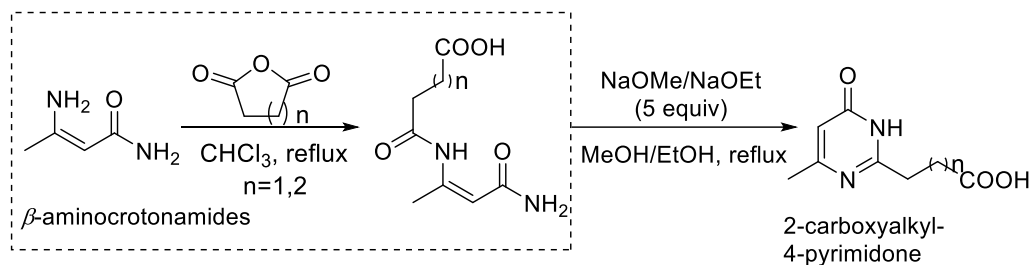
One of the most commonly used strategy to prepare *N*-acyl enamine amides would be acylation of  $\beta$ -aminocrotonamides. In 1983, Kato and co-workers reported preparation of  $\beta$ -acylamidocrotonamide through acylation reaction of

<sup>117</sup> a) *Enantioselective Synthesis of  $\beta$ -Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. Eds.; John Wiley & Sons, Inc.: Hoboken, 2005. b) Weber, A. E.; Thornberry, N. *Annu. Rep. Med. Chem.* **2007**, *42*, 95. c) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.

<sup>118</sup> a) Saxena, A. K., Sinha, S. Pyrimidinones as biodynamic agents. In *Progress in Drug Research*; Jucker, E., Meyer, U. Eds.; Birkhäuser Verlag, Basel, 1987; p 127-160. b) Sarosdy, M. F.; Manyak, M. J.; Sagalowsky, Al.; Belldegrün A.; Benson, M. C.; Bihrlé, W.; Carroll, P. R.; Ellis, W. J.; Hudson, M. A.; Sharkey, F. E. *Urology* **1998**, *51*, 226. c) Balmforth, A. J.; Bryson, S. E.; Aylett, A. J.; Warburton, P.; Ball, S. G.; Pun, K. T.; Middlemiss, D.; Drew, G. M. *Br. J. Pharmacol.* **1994**, *112*, 277.

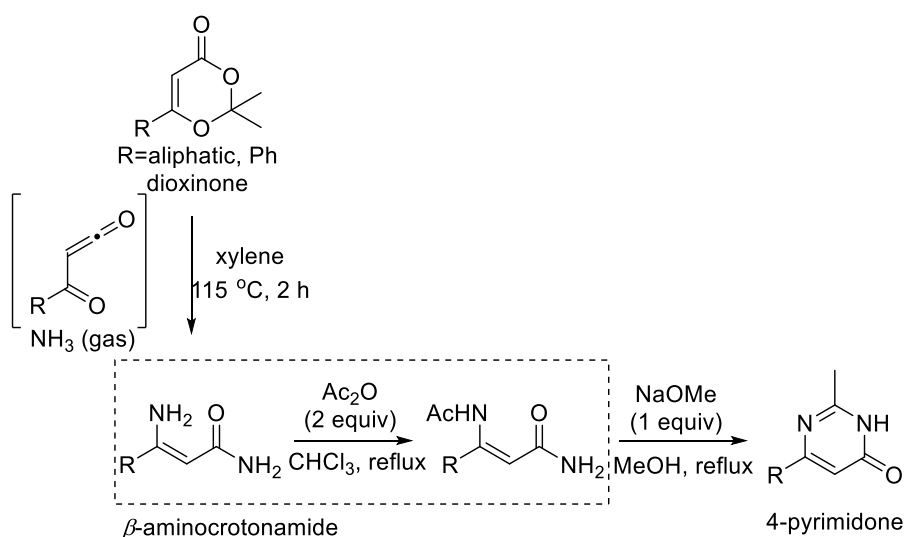
<sup>119</sup> Selected examples of bioactive pyrimidinones synthesis through *N*-acyl enamine amide intermediate: a) Tadiparthi, R.; Aggarwal, P.; Parameswaran, V.; Thirunavukkarasu, S.; Barik, R.; Rajagopal, S.; Reddy, G. O. Novel pyrimidine carboxamides. WO2007031829 A2, 22 Mar 2007. b) Luengo, J. I.; Marquis, R. W.; Xie, J. R., Yamashita, D. S. Calcilytic compounds. WO2005108376 A1, 17 Nov 2005. c) Ku, T. W. F.; Li, H.; Luengo, J. I.; Marquis, R. W. J.; Ramanjulu, J. M.; Trout, R.; Yamashita, D. S. Calcilytic compounds. WO2007062370 A2, 31 May 2007. d) Shcherbakova, I.; Huang, G.; Geoffroy, O. J.; Nair, S. K.; Swierczek, K.; Balandrin, M. F.; Fox, J.; Heaton, W. L.; Conklin, R. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2537.

$\beta$ -aminocrotonamides with saturated diacid anhydrides, which upon treatment of base, cyclizes to yield the respective 2-carboxyalkylpyrimidinone derivative (Scheme 4-2).<sup>120</sup>



Scheme 4-2: Reaction of  $\beta$ -aminocrotonamides with dibasic acid anhydride and base-mediated formation of carboxyalkylpyrimidine

In the foreground, dioxinone could act as the building block towards  $\beta$ -aminocrotonamides which undertakes the role as masked acylketene to react with ammonia to first form the  $\beta$ -ketoamide that further condenses with ammonia to yield  $\beta$ -aminocrotonamide (Scheme 4-3). After *N*-acetylation with acetic anhydride, the 3-amino-2-alkenamamide readily undergoes ring closure to 4-pyrimidinone under basic condition.<sup>121</sup>

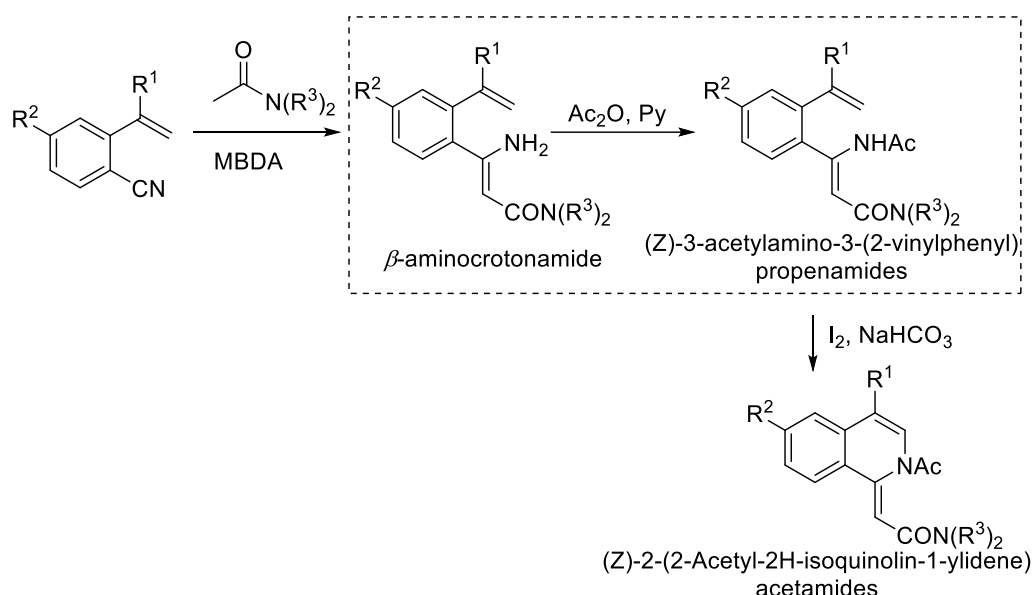


Scheme 4-3: Synthesis of  $\beta$ -ketoamide from dioxinone and ensuing pyrimidinone formation

<sup>120</sup> Sato, M.; Ogasawara, H.; Kato, T. *J. Heterocyclic Chem.* **1983**, 20, 87.

<sup>121</sup> Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull.* **1984**, 32, 3848.

In 2007, Kobayashi and co-workers uncovered the synthetic pathway toward (Z)-2-(2-Acetyl-2H-isoquinolin-1-ylidene)acetamides through 6-endo cyclization of (Z)-3-acetylamino-3-(2-vinylphenyl)propenamides mediated by iodine (Scheme 4-4).<sup>122</sup> Their work involves initial coupling of benzonitriles with tertiary amides using magnesium bis(diisopropylamide) (MBDA) to form the  $\beta$ -aminocrotonamides. Successive *N*-acetylation with acetic anhydride and treatment with stoichiometric amount of iodine/sodium bicarbonate provides the (isoquinolin-1-ylidene)acetamide.



Scheme 4-4: Kobayashi's protocol toward preparation of (isoquinolin-1-ylidene)acetamide from benzonitrile

#### 4.1.1.2 Addition of ammonium ylide to imine

On the other hand, Waser and co-workers came across unexpected formation of  $\alpha,\beta$ -unsaturated  $\beta$ -amino amides during their study of the aziridination reaction from imines using carbonyl-stabilized ammonium ylides (Scheme 4-5).<sup>123</sup> In the presence of more electron-deficient aryl group on imine, the  $\alpha,\beta$ -unsaturated  $\beta$ -amino amides are generated instead of the customary aziridine product. This

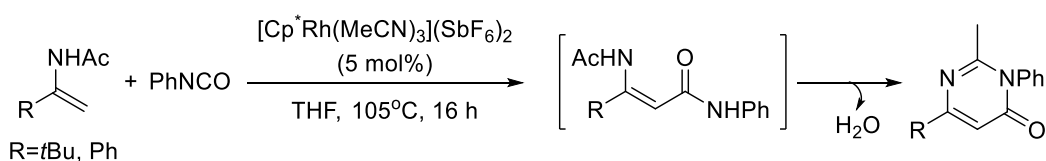
<sup>122</sup> Kobayashi, K.; Hashimoto, K.; Shiokawa, T.; Morikawa, O.; Konishi, H. *Synthesis* **2007**, 6, 824.

<sup>123</sup> Aichhorn, S.; Gururaja, G. N.; Reisinger, M.; Waser, M. *RSC Adv.* **2013**, 3, 4552.



suited for this transformation. This underscores the potential for chiral information delivery to more structurally complex substrates. While the more detailed mechanistic studies are required to elucidate a clearer mechanism, the primary isotope effect suggests the rate-determining direct C(sp<sup>2</sup>)-H bond activation assisted by lewis base directing group, rather than direct  $\pi$ -bond addition to isocyanate.

Additionally, one-pot formation of pyrimidin-4-ones from phenyl and *tert*-butyl enamide is manifested when the reaction was conducted at 105 °C using phenyl isocyanate (Scheme 4-7). Nonetheless, when the alkyl isocyanates were tested, the cyclization for the less acidic *N*-hexyl or *N*-cyclohexyl amides is reported to be sluggish under their condition.

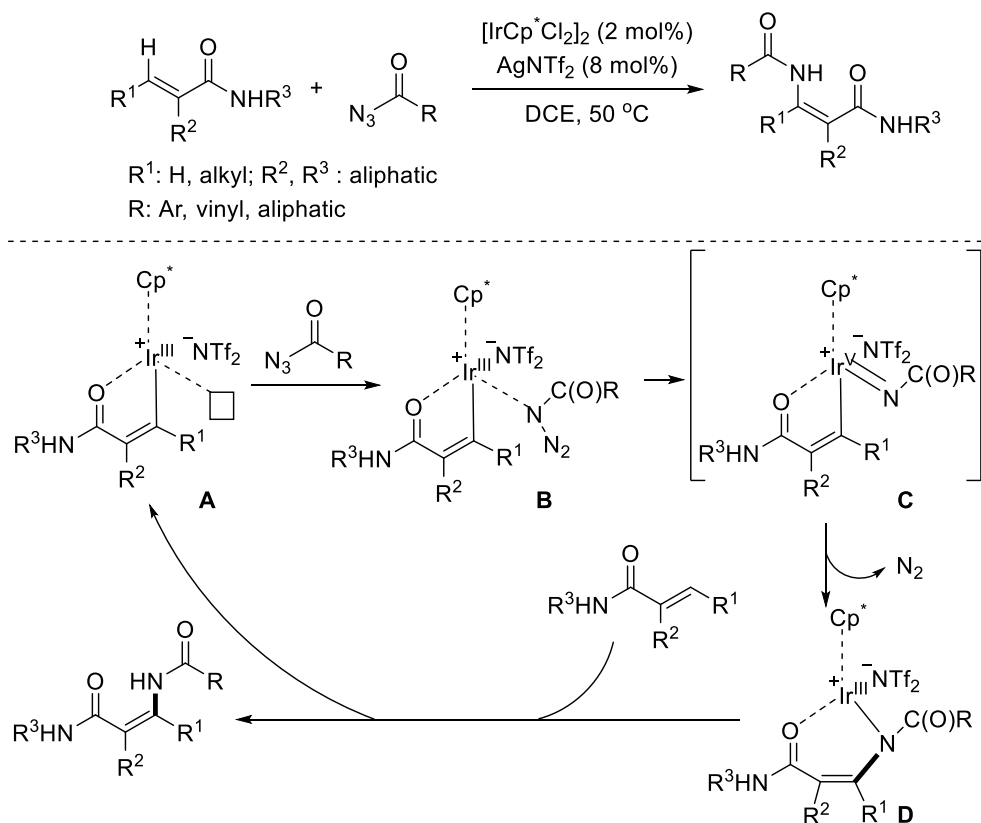


Scheme 4-7: One-pot strategy toward formation of pyrimidin-4-ones

#### 4.1.1.4 Amidation of acrylamides with acyl azides

Alternative retrosynthetic route in constructing *N*-acyl enamine amide involves C(sp<sup>2</sup>)-N bond formation for the installment of amide group onto acrylamide scaffold was also made feasible. In this regard, an iridium-catalyzed direct amidation of the olefinic C-H bond was reported on by Chang's group (Scheme 4-8).<sup>125</sup> In their developed protocol, aryl and aliphatic acyl azides are compatible substrates to introduce the corresponding *N*-monosubstituted amide groups. High functional group tolerance was evident in this protocol on the presence of ester and free hydroxyl groups respectively on the substituents at  $\alpha$ -position (R<sup>2</sup>) and *N*-alkyl amido group (R<sup>3</sup>).

<sup>125</sup> Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. *J. Am. Chem. Soc.* **2013**, *135*, 12861.

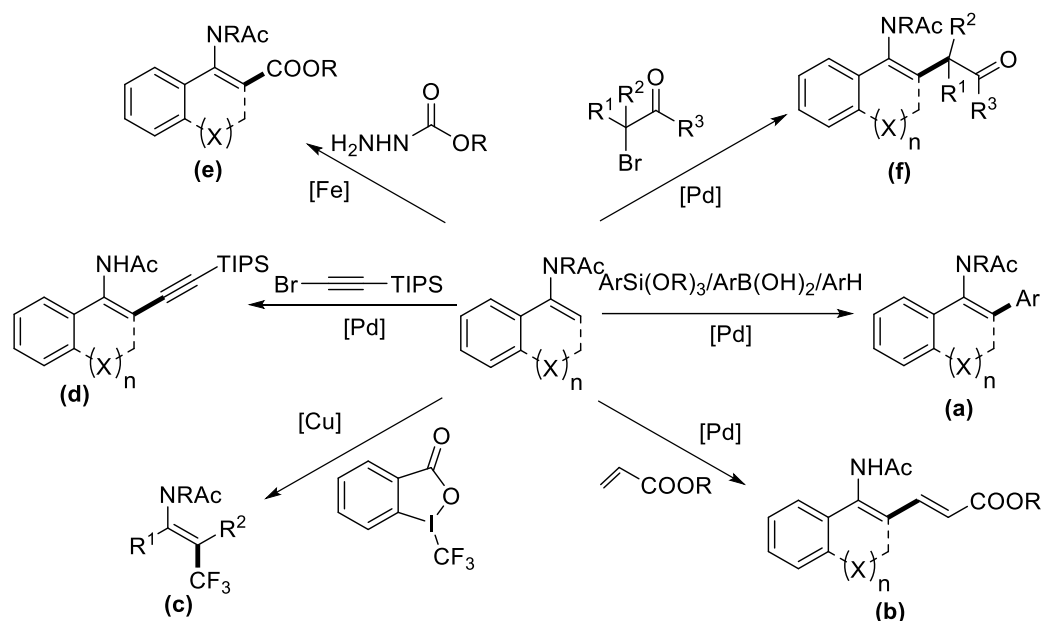


Scheme 4-8: Iridium(III) -catalyzed amidation of acrylamides with acyl azides  
 In the proposed mechanism, azide is considered to interact with the cationic cyclometalated intermediate **A** that possesses one vacant site to give azide-bound complex **B** (Scheme 4-8). Iridium-nitrenoid species **C** is generated from **B** in an oxidative manner with the expulsion of molecular nitrogen. Nitrenoid insertion into iridacycle forges the desired C-N bond formation in complex **D**. Protodemetalation then yields the amidation product and re-introduces **A** ready for next catalytic cycle.

#### 4.1.2 Olefinic functionalization of enamides

The stable enamine variants, enamides possess tempered nucleophilicity by virtue of electron-deficient acyl functionalities on the nitrogen. Their amenability to participate in a wide array of organic transformations as rendered by both characteristics, coupled with recent research progress has

indisputably boosted their synthetic values.<sup>126</sup> Direct olefinic functionalization of enamides would allow alternative access to multisubstituted amines and olefins, the pivotal structural motif in many natural products as well as organic materials.<sup>127,128</sup>



Scheme 4-9:  $\beta$ -C-H functionalization reactions of enamides developed by our group

Our group has been working on development of different strategies toward selective functionalization of  $\beta$ -H of enamides as part of our exploration into the realm of olefinic C-H activation. These reaction protocols include arylation (Scheme 4-9, a),<sup>129</sup> alkenylation (b),<sup>130</sup> trifluoromethylation (c),<sup>131</sup> alkylation

<sup>126</sup> Reviews on chemistry of enamides: a) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455. b) Wang, M.-X. *Chem. Commun.* **2015**, *51*, 6039. c) Gigant, N.; Chausset-Boissarie, L.; Gillaizeau, I. *Chem. Eur. J.* **2014**, *20*, 7548. d) Courant, T.; Dagousset, G.; Masson, G. *Synthesis* **2015**, *47*, 1799.

<sup>127</sup>  $\alpha$ -arylation of enamides: a) Mo, J.; Xu, L. J.; Xiao, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 751. b) Mo, J.; Xiao, J. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4152. c) Hyder, Z.; Ruan, J. W.; Xiao, J. L. *Chem. Eur. J.* **2008**, *14*, 5555. d) Liu, Y.; Li, D.; Park, C. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7333.

<sup>128</sup> a) Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698. b) *Chiral Amine Synthesis: Methods, Developments and Applications*; Nugent, C. T., Ed.; Wiley-VCH, Weinheim, 2010.

<sup>129</sup> a) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2009**, *48*, 5355. b) Zhou, H.; Chung, W.-J.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2009**, 3472. c) Pankajakshan, S.; Xu, Y.-H.; Cheng, J. K.; Low, M. T.; Loh, T.-P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5701.

<sup>130</sup> Xu, Y.-H.; Chok, Y. K.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 1822.

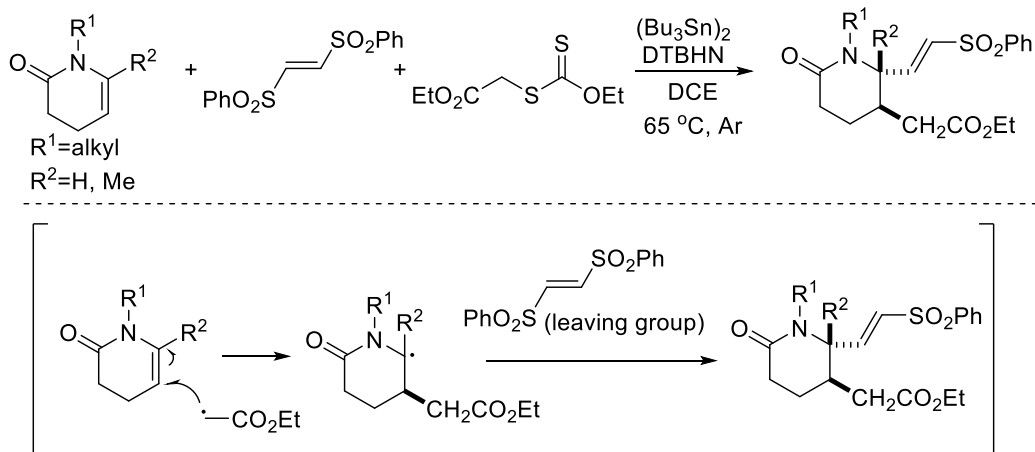
<sup>131</sup> Feng, C.; Loh, T.-P. *Chem. Sci.* **2012**, *3*, 3458.

(d),<sup>132</sup> alkoxyacylation (e),<sup>133</sup> as well as alkylation reaction with sterically bulky  $\alpha$ -bromocarbonyls (f),<sup>134</sup> have featured the introduction of many different molecular entities onto enamide scaffolds.

#### 4.1.3 Radical functionalization of enamides

Addition of radical species to enamides in the intramolecular fashion is also known.<sup>135</sup> These reactions involve halides as the radical precursors and tributylstannane reagents are mandatory to mediate these reactions.

In 2013, Landais *et al.* communicated a radical intermolecular carbonyl-alkenylation of cyclic enamides with xanthates and vinyldisulfones (Scheme 4-10).<sup>136</sup> Radical derived from xanthates will first add to the  $\beta$ -position of enamide, followed by addition of the radical adduct to the vinyldisulfones. Elimination of a sulfonyl group yields the desired 3-component coupling product.



Scheme 4-10: Three-component coupling of enamides with xanthates and vinylsulfones

<sup>132</sup> a) Xu, Y.-H.; Zhang, Q.-C.; He, T.; Meng, F.-F.; Loh, T.-P. *Adv. Synth. Catal.* **2014**, *356*, 1539. b) Feng, C.; Feng, D.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 9865.

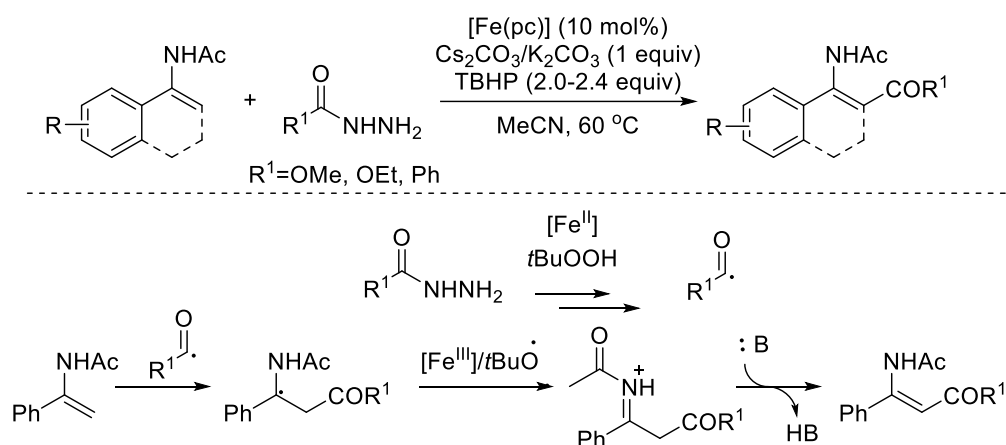
<sup>133</sup> Ding, R.; Zhang, Q.-C.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 11661.

<sup>134</sup> Ding, R.; Huang, Z.-D.; Liu, Z.-L.; Wang, T.-X.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2016**, *52*, 5617.

<sup>135</sup> a) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 84. b) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922. c) Taniguchi, T.; Ishibashi, H. *Tetrahedron* **2008**, *64*, 8773.

<sup>136</sup> Poittevin, C.; Liautard, V.; Beniazza, R.; Robert, F.; Landais, Y. *Org. Lett.* **2013**, *15*, 2814.

In 2014, our group reported on an iron(II)-catalyzed alkoxyacylation of *N*-vinylacetamides using carbazates as the ester group precursor to give ( $\beta$ -acylamino)acrylates (mentioned in section 4.1.2). The plausible mechanism postulated for this reaction involves radical pathway (Scheme 4-11). First, the iron catalyst aids in the generation of alkoxyacyl radical from carbazate (for similar mechanism, refer to Scheme 1-7, section 1.4.2), which will then add to the double bond. Fe(III) species or the *tert*-butoxyl radical could oxidize the more stable iminyl radical intermediate to the corresponding iminium ion. Desired product is formed following hydrogen abstraction by base. This protocol successfully delivers methyl ester, ethyl ester and acetophenyl group onto enamide scaffold.



Scheme 4-11: Iron-catalyzed alkoxyacylation of *N*-vinylacetamides

#### 4.1.4 Motivation for present work

In continuation of our interest in exploring the new reaction pattern for enamides, we envisioned to study the direct coupling of enamides with formamide derivatives to yield *N*-acyl enamine amides, which is of synthetic significance. We have previously developed a direct peroxidation-carbamoylation of alkenes with formamides, *via* radical functionalization of

formamide derivatives (Chapter 3). Building on this work, we wish to explore the viability to integrate the chemistry to prepare the compounds of interest (Scheme 4-13-B).

Furthermore, the cyclodehydration of *N*-acyl enamide amides to pyrimidone is known and have been delineated in the precedent section. However, we wish to explore new reaction mode for this amide product with high density of functionality.

4-Hydroxy-2-pyridinone structural motif represents an integral class of alkaloids possessing broad spectrum biological activities, which could be used as antibiotics, fungicides, insecticides and antineoplastics.<sup>137</sup> This also appears as privileged scaffold in drug discovery.<sup>138</sup> In recent years, medicinal chemists are inspired to explore the therapeutic values associated with 6-substituted 4-hydroxy -2-pyridinones as HIV-1 reverse transcriptase inhibitor<sup>139</sup>, p38 MAP kinase inhibitor<sup>140</sup> as well as antibiotics<sup>141</sup>, evident by a number of publications communicating these recent findings.

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<sup>137</sup> Jessen, H. J.; Gademann, K. *Nat. Prod. Rep.* **2010**, *27*, 1168.

<sup>138</sup> Groutas, W. C.; Stanga, M. A.; Brubaker, M. J. Huang, T. L.; Moi, M. K.; Carroll, R. T. *J. Med. Chem.* **1985**, *28*, 1106. b) Demuner, A. J.; Valente, V. M. M.; Barbosa, L. C. A.; Rath, A. H.; Donohoe, T. J.; Thompson, A. L. *Molecules* **2009**, *14*, 4973.

<sup>139</sup> a) Cao, Y.; Zhang, Y.; Wu, S.; Yang, Q.; Sun, X.; Zhao, J.; Pei, F.; Guo, Y.; Tian, C.; Zhang, Z.; Wang, H.; Ma, L.; Liu, J.; Wang, X. *Bioorg. Med. Chem.* **2015**, *23*, 149. b) Li, A.; Ouyang, Y.; Wang, Z.; Cao, Y.; Liu, X.; Ran, L.; Li, C.; Li, L.; Zhang, L.; Qiao, K.; Xu, W.; Huang, Y.; Zhang, Z.; Tian, C.; Liu, Z.; Jiang, S.; Shao, Y.; Du, Y.; Ma, L.; Wang, X.; Liu, J. *J. Med. Chem.* **2013**, *56*, 3593. c) Wu, S.; Yin, Q.; Zhao, L.; Fan, N.; Tang, X.; Zhao, J.; Sheng, T.; Guo, Y.; Tian, C.; Zhang, Z.; Xu, W.; Liu, Z.; Jiang, S.; Ma, L.; Liu, J.; Wang, X. *Org. Biomol. Chem.* **2016**, *14*, 1413.

<sup>140</sup> a) Selness, S. R.; Devraj, R. V.; Devadas, B.; Walker, J. K.; Boehm, T. L.; Durley, R. C.; Shieh, H.; Xing, L. Rucker, P. V.; Jerome, K. D.; Benson, A. G.; Marrufo, L. D.; Madsen, H. M.; Hitchcock, J.; Owen, T. J.; Christie, L.; Promo, M. A.; Hickory, B. S.; Alvira, E.; Naing, W.; Blevis-Bal, R.; Messing, D.; Yang, J.; Mao, M. K.; Yalamanchili, G.; Embse, R. V.; Hirsch, J.; Saabye, M.; Bonar, S.; Webb, E.; Anderson, G.; Monahan, J. B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4066. b) Selness, S. R.; Devraj, R. V.; Monahan, J. B.; Boehm, T. L.; Walker, J. K.; Devadas, B.; Durley, R. C.; Kurumbail, R.; Shieh, H.; Xing, L.; Hepperle, M.; Rucker, P. V.; Jerome, K. D.; Benson, A. G.; Marrufo, L. D.; Madsem, H. M.; Hitchcock, J.; Owen, T. J.; Christie, L.; Promo, M. A.; Hickory, B. S.; Alvira, E.; Naing, W.; Blevis-Bal, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5851.

<sup>141</sup> a) Vegi, S. R.; Boovanahalli, S. K.; Patro, B.; Mukkanti, K. *Eur. J. Med. Chem.* **2011**, *46*, 1803. b) Shimatani, T.; Hosotani, N.; Ohnishi, M.; Kumagai, K.; Saji, I. *J. Antibiot.* **2006**, *59*, 29.

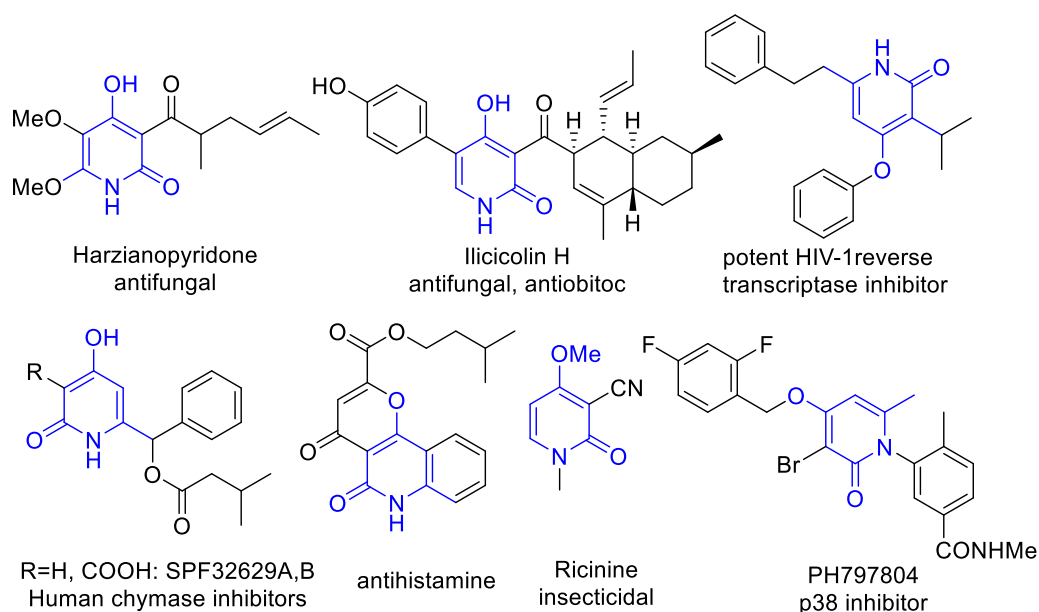


Figure 4-1: Bioactive compounds containing 4-hydroxy-2-pyridinone moiety

The commonly employed methods to assemble 6-substituted-4-hydroxy-2-pyridinones are summarized in Scheme 4-12.

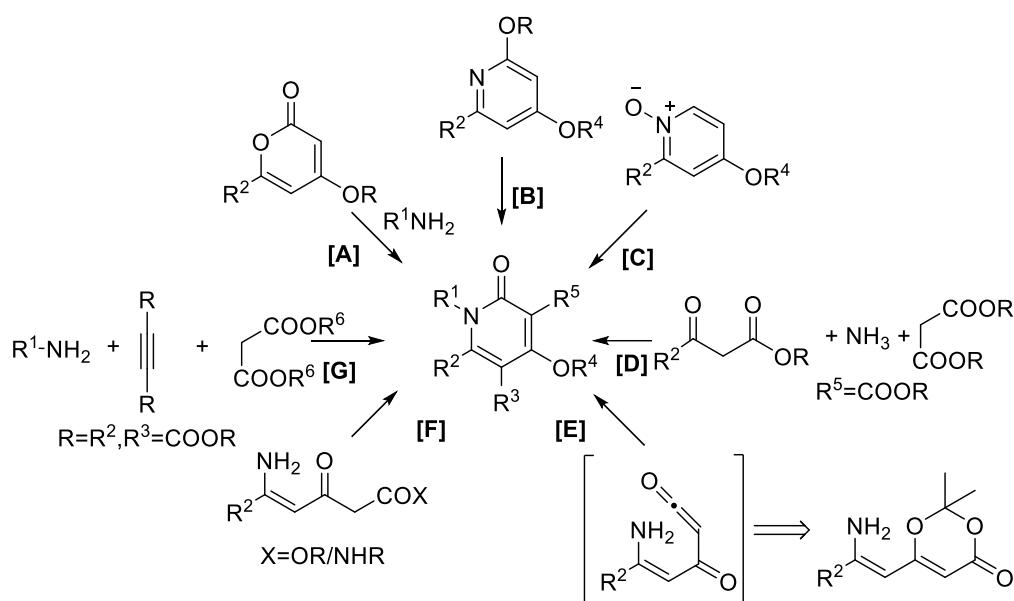
The most prevalent method is through the treatment of the analogous pyrone with ammonia or amines (Pathway A),<sup>138b,140b,142</sup> Other methods that involve the pyridine synthons are through the removal of alkyl ether (pathway B)<sup>139b-c,143</sup> or the rearrangement of pyridine-*N*-oxide with acetic anhydride/hydrolysis (pathway C).<sup>144</sup> Seminally reported by Knoevenagel *et al.*, condensation of  $\beta$ -ketoester with dialkylmalonate in the presence of ammonia, followed by decarboxylation is also a viable route towards this chemical entity (pathway

<sup>142</sup> a) Collie, J. N. *J. Chem. Soc.* **1891**, 59, 607. b) Giddens, A. C.; Nielsen, L.; Boshoff, H. I.; Tasdemir, D.; Perozzo, R.; Kaiser, M.; Wang, F.; Sacchetti, J. C.; Copp, B. R. *Tetrahedron* **2008**, *64*, 1242. c) Kraus, G. A.; Wanninayake, U. K.; Bottoms, J. *Tetrahedron Lett.* **2016**, *57*, 1293.

<sup>143</sup> Kennedy-Smith, J. J.; Arora, N.; Billedeau, J. R.; Fretland, J.; Hang, J. Q.; Heilek, G. M.; Harris, S. F.; Hirschfeld, D.; Javanbakht, H.; Li, Y.; Liang, W.; Roetz, R.; Smith, M.; Su, G.; Suh, J. M.; Villaseñor, A. G.; Wu, J.; Yasuda, D.; Klumpp, K.; Sweeney, Z. K. *Med. Chem. Commun.* **2010**, *1*, 79.

<sup>144</sup> a) Boekelheide, V.; Lehn, W. L. *J. Org. Chem.* **1961**, *26*, 428. b) Vegi, S. R.; Boovanahalli, S. K.; Sharma, A. P.; Mukkanti, K. *Tetrahedron Lett.* **2008**, *49*, 6297.

D).<sup>139a-b,145</sup> Synthesis from linear precursors such as enamine-keto-ketenes<sup>146</sup> (pathway E) or carbamoylated/ alkoxy-carbonylated aminoenones<sup>147</sup> (pathway F) require the intramolecular nucleophilic attack of amine on the carbonyl/ketene group. Three-component coupling reaction of amines, acetylenic esters and malonyl derivatives to construct this scaffold results in the ester functionality at 5- and 6-position ( $R^2, R^3$ ) (pathway G).<sup>148</sup>



Scheme 4-12: Common methods to synthesize 6-substituted-4-hydroxy-2-pyridinones

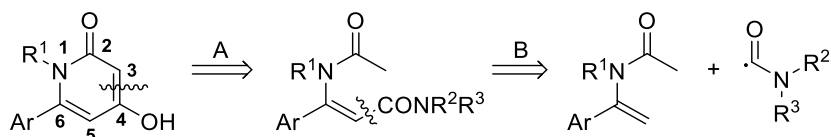
In our strategy, we envisaged to prepare this compound through one-step transformation from our product through disconnection at C3 and C4, wherein the carbanion at C3 is postulated to attack the carbonyl carbon C4. This will thereby further expand the synthetic potentials with *N*-acyl enamine amide products.

<sup>145</sup> Knoevenagel, E.; Fries, A. *Chem. Ber.* **1898**, *31*, 767.

<sup>146</sup> Patel, B. H.; Mason, A. M.; Barrett, A. G. M. *Org. Lett.* **2011**, *13*, 5156.

<sup>147</sup> a) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343. b) Usachev, B. I.; Obydenov, D. L.; Röschenhaler, G.-V.; Sosnovskikh, V. Y. *J. Fluor. Chem.* **2012**, *137*, 22.

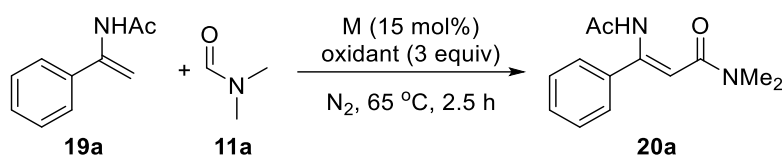
<sup>148</sup> a) Yavari, I. *Synlett* **2007**, *19*, 2969. b) Samzadeh-Kermani, A. *Synlett* **2016**, *27*, 461.



Scheme 4-13: Proposed synthesis of 6-substituted-4-hydroxy-2-pyridinone from *N*-acyl enamine amide

## 4.2 Results and discussions

Table 4-1: Reaction optimization: screening of metal salts and oxidants.<sup>a</sup>

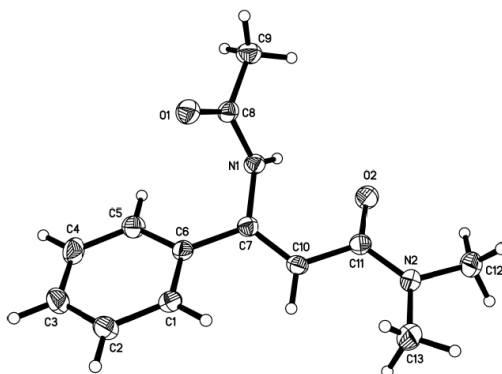


Entry	Metal catalyst (15 mol%)	Oxidant	Yield (%) <sup>b</sup>	Entry	Metal catalyst (15 mol%)	Oxidant	Yield (%) <sup>b</sup>
1	FeCl <sub>3</sub>	TBHP	46	15 <sup>c</sup>	CoBr <sub>2</sub>	TBHP	<10
2	FeBr <sub>3</sub>	TBHP	20	16 <sup>c</sup>	MnCl <sub>2</sub>	TBHP	<10
3	Fe(acac) <sub>3</sub>	TBHP	0	<b>17<sup>d</sup></b>	<b>FeCl<sub>2</sub></b>	<b>DTBP</b>	<b>50</b>
<b>4</b>	<b>FeCl<sub>2</sub></b>	<b>TBHP</b>	<b>48</b>	18 <sup>d</sup>	FeCl <sub>2</sub>	Cumyl hydroperoxide	0
5	FeBr <sub>2</sub>	TBHP	35	19 <sup>d</sup>	FeCl <sub>2</sub>	PIDA	0
6	Fe(OTf) <sub>2</sub>	TBHP	23	20 <sup>d</sup>	FeCl <sub>2</sub>	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	0
7	Fe(OTf) <sub>3</sub>	TBHP	<10	21 <sup>d</sup>	FeBr <sub>2</sub>	DTBP	trace
8	Fe(TFAcac) <sub>3</sub>	TBHP	41	22 <sup>d</sup>	Fe(TFAcac) <sub>3</sub>	DTBP	26
9 <sup>c</sup>	Fe(TMHD) <sub>3</sub>	TBHP	31	23 <sup>d</sup>	FeCl <sub>3</sub>	DTBP	0
10 <sup>c</sup>	FeI <sub>2</sub>	TBHP	0	24 <sup>d</sup>	CuCl <sub>2</sub>	DTBP	0
11 <sup>c</sup>	FePc	TBHP	41	25 <sup>d</sup>	-	DTBP	0
12 <sup>c</sup>	FePcCl	TBHP	38	26 <sup>d,e</sup>	FeCl <sub>2</sub>	DTBP	59
13 <sup>c</sup>	CuCl <sub>2</sub>	TBHP	25	<b>27<sup>d,f</sup></b>	<b>FeCl<sub>2</sub></b>	<b>DTBP</b>	<b>63</b>
14 <sup>c</sup>	CuBr <sub>2</sub>	TBHP	<10	28 <sup>g</sup>	FeCl <sub>2</sub>	DTBP	32

<sup>a</sup>Unless otherwise noted, typical reaction conditions: **19a** (0.20 mmol), metal catalyst (15 mol%, 0.03 mmol), oxidant (3 equiv, 0.60 mmol), **11a** (0.8 mL), 65 °C, 2.5 h, under nitrogen atmosphere. <sup>b</sup>Isolated yields. <sup>c</sup>24 h instead of 2.5 h. <sup>d</sup>80 °C, 5 h instead of 65 °C, 2.5 h. <sup>e</sup>4 equiv of DTBP instead of 3 equiv. <sup>f</sup>5 equiv of DTBP instead of 3 equiv. <sup>g</sup>air, 11 h, 80 °C.

The investigation was begun by choosing *N*-(1-phenylvinyl)acetamide **19a** and DMF as model substrates. The different iron salts were first tested for the catalytic activities using 3 equiv of TBHP as the oxidant at 65°C under inert atmosphere. Delightfully, FeCl<sub>2</sub> catalyzed the reaction to give 48% of *Z*-selective *N*-acetyl enamide amide product **20a** after 2.5 h (Table 4-1, entry 4). The absolute structure of **20a** was unequivocally confirmed by single-crystal X-ray diffraction (Figure 4-2).

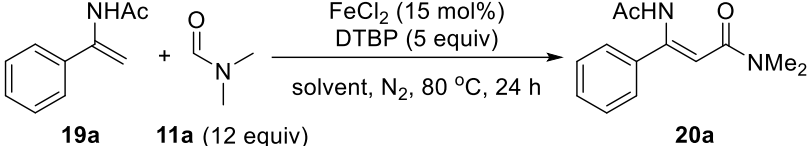
Figure 4-2: X-ray crystallography structure of (*Z*)-3-acetamido-*N,N*-dimethyl-3-phenylacrylamide **20a**



The formation of acetophenone, due to the hydrolysis of enamide was observed when iron(III) salts such as Fe(acac)<sub>3</sub> and Fe(OTf)<sub>3</sub> were employed, resulting in the trace or no product formation. Other iron catalysts including Fe(TMHD)<sub>3</sub>, FePc and FePcCl (Table 4-1, entries 9, 11-12) could not catalyze the reaction in better efficiency despite the longer reaction time needed for complete consumption of starting material. Other metal salts such as that of cobalt, manganese and copper did not exhibit good applicability for this reaction (Table 4-1, entries 13-16). With FeCl<sub>2</sub>, some oxidants were tested for this reaction (Table 4-1, entries 17-20). An elevated reaction temperature (80 °C) and longer reaction time (5 h) have allowed the formation of **20a** in 50% when

DTBP was employed (Table 4-1, entry 17) whereas other oxidants examined could not generate any desired product. It was found that DTBP was more selective with the choice of metal catalysts, wherein the catalysts that have showed moderate activity with TBHP could not form/formed product in lower yields with DTBP. Additionally, we were delighted to realize the formation of **20a** at 63% yield when amount of DTBP was increased to 5 equiv (Table 4-1, entry 27).

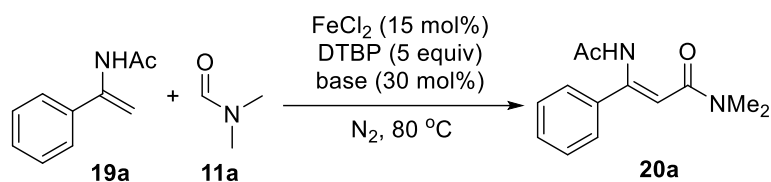
Table 4-2: Reaction optimization: screening of solvents.<sup>a</sup>



Entry	Solvent	Yield (%) <sup>b</sup>	Entry	Solvent	Yield (%) <sup>b</sup>
1	DMSO	6%	6	THF	12%
2	MeCN	0%	7	CHCl <sub>3</sub>	0%
3	DCE	28%	8	PhCN	34%
<b>4</b>	<b>PhCl</b>	<b>44%</b>	9	<i>t</i> -AmOH	24%
5	Toluene	17%	10	benzene	24%

<sup>a</sup>Reaction conditions: **19a** (0.20 mmol), FeCl<sub>2</sub> (15 mol%, 0.03 mmol), DTBP (5 equiv, 1.0 mmol), **11a** (12 equiv, 2.4 mmol), solvent (0.8 mL), 80 °C, 24 h, under nitrogen atmosphere. <sup>b</sup>Isolated yields.

Aiming to obviate the use of formamide in large excess, the next focus was to identify suitable solvent for this coupling reaction (Table 4-2). Satisfyingly, the desired product could be furnished in compromised 44% yield after 24 h when the reaction was performed in chlorobenzene with 12 equiv of formamide (Table 4-2, entry 4).

Table 4-3: Reaction optimization: screening of bases.<sup>a</sup>

Entry	Base (30 mol%)	Yield (%) <sup>b</sup>	Entry	Base (30 mol%)	Yield (%) <sup>b</sup>
<b>1</b>	<b>KOAc</b>	<b>68%</b>	8 <sup>c</sup>	KO <sup>t</sup> Bu	59%
2	NaOAc	66%	9 <sup>d</sup>	K <sub>2</sub> CO <sub>3</sub>	65%
3	LiOAc	64%	10 <sup>d</sup>	K <sub>3</sub> PO <sub>4</sub>	45%
4 <sup>c</sup>	CsOAc	62%	11	LiOH	59%
5	DABCO	55%	<b>12<sup>e</sup></b>	<b>KOAc</b>	<b>68%</b>
6	DBU	62%	13 <sup>f</sup>	KOAc	37%
7	DIPEA	55%	14 <sup>g</sup>	KOAc	51%

<sup>a</sup>Unless otherwise noted, typical reaction conditions: **19a** (0.20 mmol), FeCl<sub>2</sub> (15 mol%, 0.03 mmol), DTBP (5 equiv, 1.0 mmol), base (30 mol%, 0.06 mmol), **11a** (0.8 mL), 80 °C, 5 h, under nitrogen atmosphere. <sup>b</sup>Isolated yields. <sup>c</sup>10 h. <sup>d</sup>24 h. <sup>e</sup>**11a** (12 equiv, 2.4 mmol), PhCl (0.8 mL), 13 h. <sup>f</sup>KOAc (1 equiv, 0.20 mmol), 24 h. <sup>g</sup>**11a** (8 equiv, 1.6 mmol), PhCl (0.8 mL), 24 h.

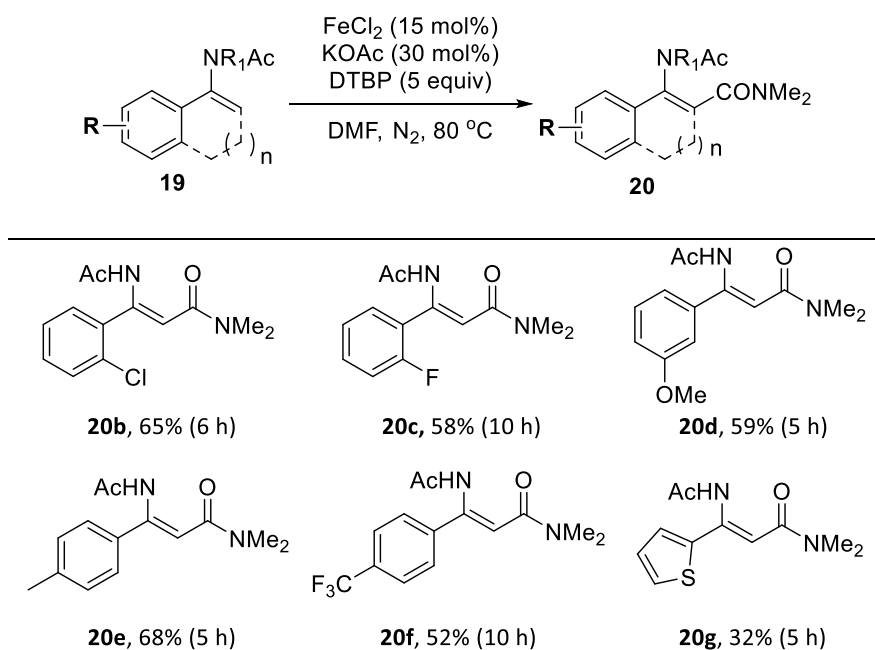
To aid in the proton elimination step, some organic and inorganic bases were then screened for this reaction (Table 4-3). The product yield could indeed be slightly augmented from 63% to 68% (Table 4-1, entry 27 and Table 4-3, entry 1) when 30 mol% of KOAc was employed. When applied to the reaction in chlorobenzene, a remarkable improvement of product yield from 44% to 68% (Table 4-3, entry 12) could be observed. Attempts to increase amount of KOAc (Table 4-3, entry 13) and decrease the stoichiometry of DMF (Table 4-3, entry 14) have affected the product's yield negatively.

To summarize, several comparable reaction conditions have been identified as categorized below:

- FeCl<sub>2</sub> (15 mol%), KOAc (30 mol%), DMF (68%, 5 h)
- FeCl<sub>2</sub> (15 mol%), DMF (63%, 5 h)
- FeCl<sub>2</sub> (15 mol%), KOAc (30 mol%), DMF (12 equiv), PhCl (solvent) (68%, 13 h)

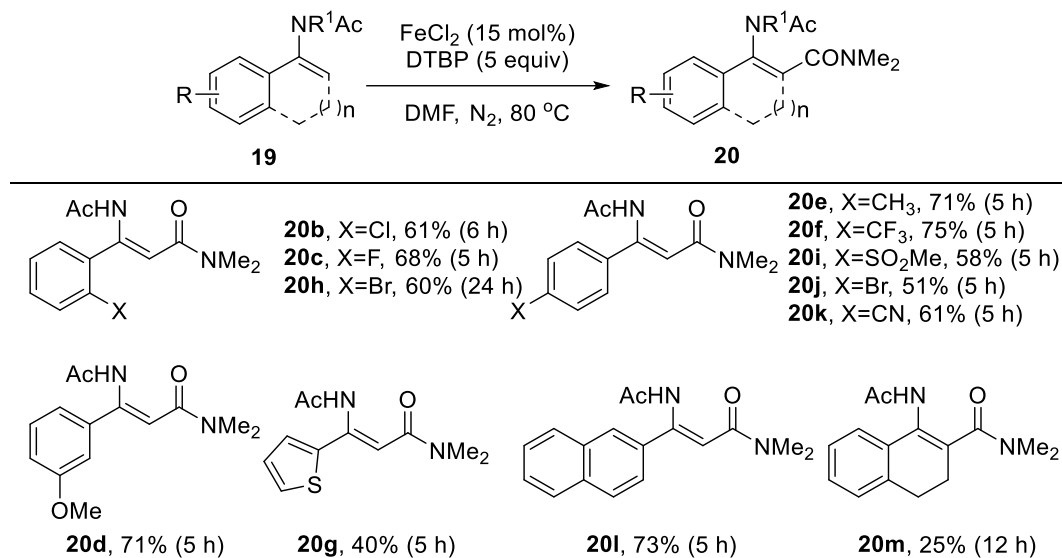
With the optimized conditions in hand, the reaction generality with respect to enamide substrate **19** was examined using DMF as the standard coupling partner. In view of the longer reaction hours needed for reaction conducted in chlorobenzene and easy purification viable with DMF, the reactions with enamides were carried out under neat condition (Table 4-4). However, after initial endeavors with several substrates, it was found that KOAc was not necessary for enhancement of reaction (comparing results of **20b-g** in Table 4-4 & Table 4-5). Thus, the remaining substrate scope was examined with only 15 mol% of FeCl<sub>2</sub> and 5 equiv of DTBP in DMF (Table 4-5).

Table 4-4: Reaction scope with respect to enamide substrates **19** with KOAc in neat condition.<sup>a,b</sup>



<sup>a</sup>Reaction conditions: **19** (0.30 mmol), FeCl<sub>2</sub> (15 mol%, 0.045 mmol), DTBP (5 equiv, 1.5 mmol), KOAc (30 mol%, 0.09 mmol), DMF (1.2 mL), 80 °C, under nitrogen atmosphere. <sup>b</sup>Isolated yields.

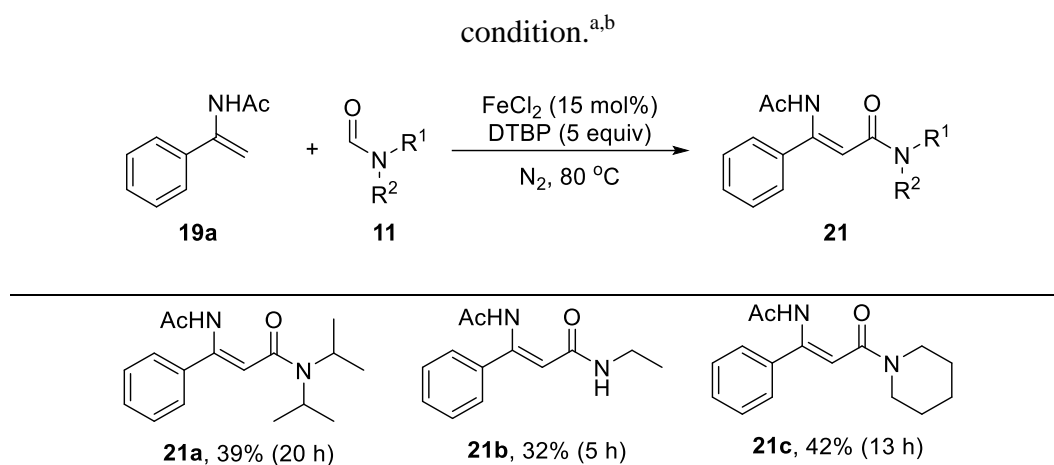
Table 4-5: Reaction scope of enamide substrate **19** with respect to DMF without KOAc in neat condition.<sup>a,b</sup>



<sup>a</sup>Reaction conditions: **19** (0.30 mmol),  $\text{FeCl}_2$  (15 mol%, 0.045 mmol), DTBP (5 equiv, 1.5 mmol), DMF (1.2 mL),  $80^\circ\text{C}$ , under nitrogen atmosphere. <sup>b</sup>Isolated yields.

The acyclic *N*-vinyl acetamides tested demonstrated good compatibility to the current reaction, irrespective of the electronic properties of substituents and substitution pattern. Halogen-substituted aryl enamides that are amenable for downstream chemical modification sustained the reaction to give 51-68% of (**20b,c,h,j**). It was however observed that the reaction proceeded rather sluggishly with bromo substituent at *ortho*-position, and 24 h was needed for formation of product **20h** in 60% yield. Other functional moieties of synthetic potentials such as methoxy (**20d**), trifluoromethyl (**20f**), methyl sulfonyl (**20i**), and cyano groups (**20k**) were well tolerated to form amidation products in good yields. Thiophene- and naphthalene-substituted enamides could also deliver the corresponding products in 40% and 73% yield. Nonetheless, the cyclic enamide was not quite the effective substrate to give only 25% of amidated product **20m**.

Table 4-6: Reaction scope of **19a** with respect to formamide **11** in neat



<sup>a</sup>Reaction conditions: **19a** (0.30 mmol), FeCl<sub>2</sub> (15 mol%, 0.045 mmol), DTBP (5 equiv, 1.5 mmol), **11** (1.2 mL), 80 °C, under nitrogen atmosphere. <sup>b</sup>Isolated yields.

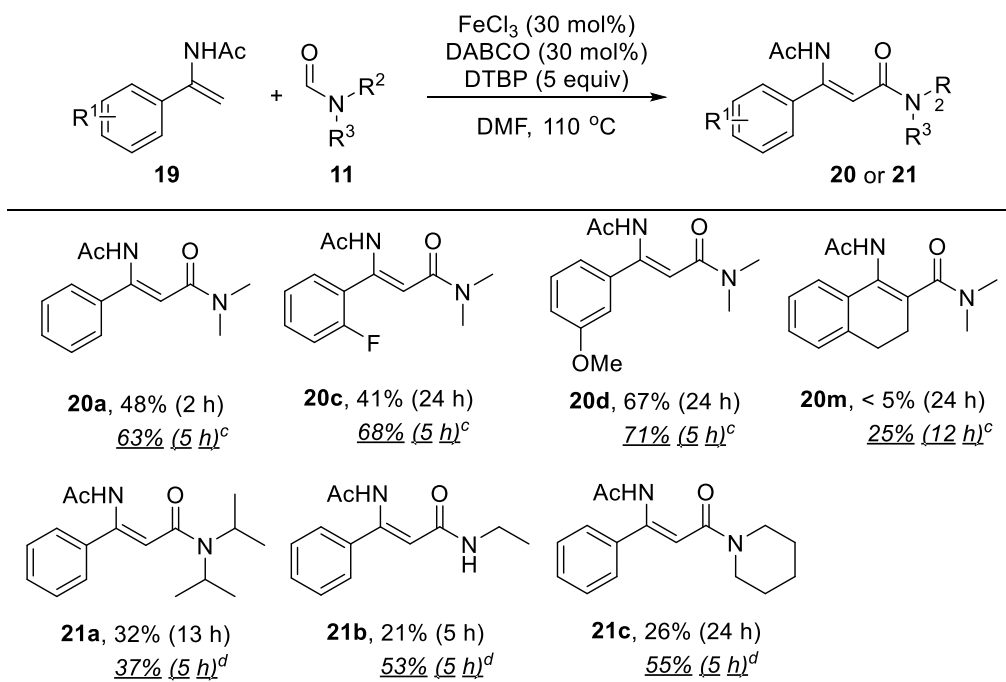
To investigate the compatibility of different formamides with current reaction, the previous condition which used formamide as solvent in Table 4-5 was employed. Despite the moderate yields attained, the high boiling point and viscosity of other formamide derivatives posed hurdles at the purification step; the attention was focused on performing these reactions in chlorobenzene instead.

Delightfully, the products could be isolated at better yields though the amount of formamide was now reduced to only 12 equiv. Additionally, KOAc could actually improve the reaction of *N*-ethyl formamide and 1-formyl piperidine (refer to **21b** & **21c** in Table 4-7). Thus, the addition of KOAc was strategized as the standard condition to study the scope of formamides. Broadly, both mono- and di-substituted formamides could be installed onto β-CH bond of enamide in reasonable yields.



products (refer to section 3.1.3.5). Subjecting enamide substrates under their optimal conditions, the coupling product *N*-acyl enamine amides could also be obtained but in inferior yields generally (Table 4-8). Furthermore, the use of formamides as solvents has posed problems at isolation and purification steps.

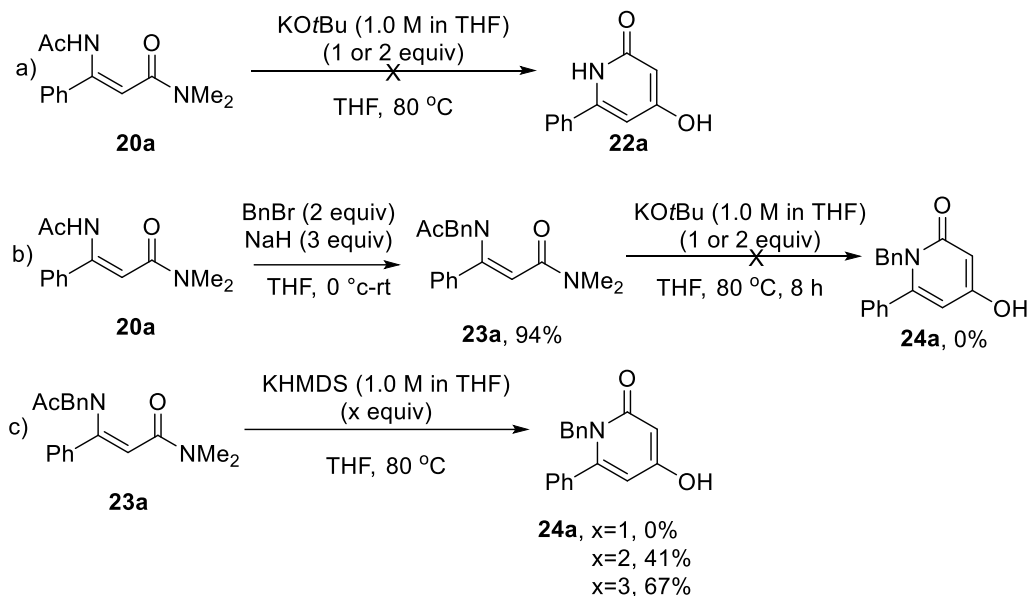
Table 4-8: Substrates scope employing Li's optimal condition.<sup>a,b</sup>



<sup>a</sup>Reaction conditions A: **19** (0.30 mmol), FeCl<sub>3</sub> (30 mol%, 0.090 mmol), DTBP (5 equiv, 1.5 mmol), **11** (1.5 mL), 110 °C. <sup>b</sup>Yields in italic and underlined represents products obtained using our conditions. <sup>c</sup>Reaction conditions: **19** (0.30 mmol), FeCl<sub>2</sub> (15 mol%, 0.045 mmol), DTBP (5 equiv, 1.5 mmol), **11** (1.2 mL), 80 °C. <sup>d</sup>Reaction conditions: **19a** (0.30 mmol), FeCl<sub>2</sub> (15 mol%, 0.045 mmol), DTBP (5 equiv, 1.5 mmol), **11** (12 equiv), PhCl (1.2 mL), 80 °C.

Having established the substrates scopes for current reaction, further functionalization of the amide product was done. The study commenced by reacting the (*Z*)-3-acetamido-*N,N*-dimethyl-3-phenylacrylamide **20a** with 1 or 2 equiv of KO*t*Bu in THF at 80 °C, which only resulted in partial decomposition of **20a** (Scheme 4-14-a). It was speculated that the cyclization step could have been impeded by the interference of the free N-H group. Hence, benzylation was done on **20a** prior to ring-closure attempts. However, **23a** also could not afford any pyridinone product employing 1 or 2 equiv of KO*t*Bu (Scheme 4-14-

b). To our delights, when 2 equiv of KHMDS was used, the reaction led to the formation of a 4-hydroxy-2-pyridinone product **24a** in 41% yield (Scheme 4-14-c).

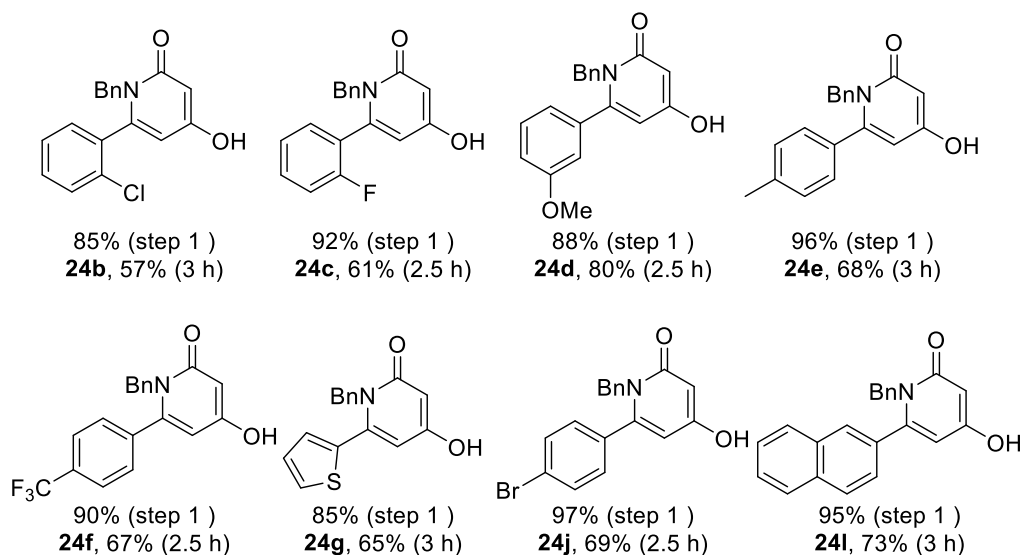
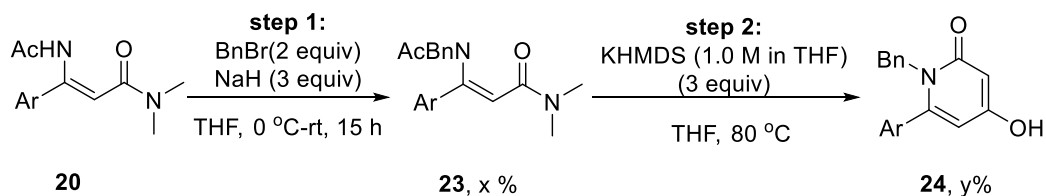


Scheme 4-14: Attempts on cyclodeamination of **20a** and **23a**

Better results were observed when increased amount of KHMDS was added, which eventually led to formation of cyclodeamination product **24a** in 67% yield with 3 equiv of KHMDS (Scheme 4-14-c).

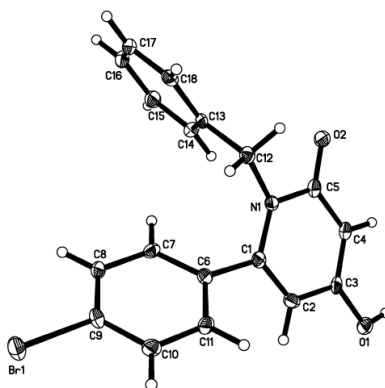
Without further optimization, the breadth of this cyclization protocol was tested on the *N*-acetyl enamine amide products **20** after benzylation step. This cyclodeamination pathway is well-accommodating to prepare 6-aryl-4-hydroxy-2-pyridinones **24** in synthetically useful yields with the results summarized in Table 4-9. Furthermore, the absolute structure of 1-benzyl-6-(4-bromophenyl)-4-hydroxypyridin-2(1H)-one **24j** was unambiguously confirmed by single-crystal X-ray diffraction (Figure 4-4).

Table 4-9: Representative examples on cyclodeamination reaction.

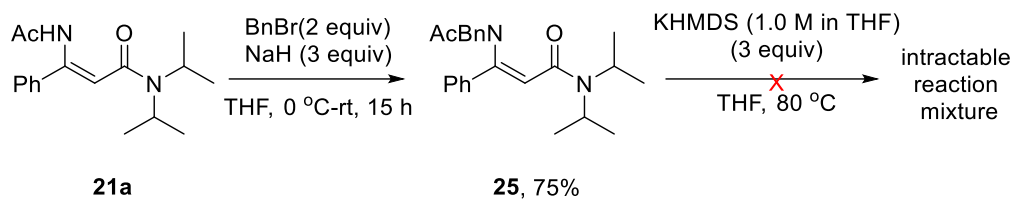


Reaction conditions for step 1: **20** (1 equiv), BnBr (2 equiv), NaH (3 equiv), THF (reaction molarity = 0.10 M), 0 °C-rt, 15 h. Reaction condition for step 2: **23** (1 equiv), KHMDS (1.0 M in THF, 3 equiv), THF (reaction molarity = 0.075 M), 80 °C, 2.5-3 h.

Figure 4-4: X-ray crystallography structure of 1-benzyl-6-(4-bromophenyl)-4-hydroxypyridin-2(1H)-one **24j**

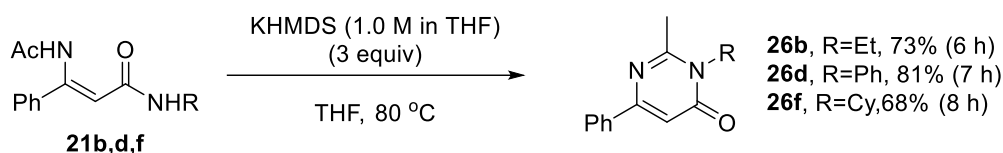


When the *N,N*-dimethylamide group was replaced with *N,N*-diisopropylamide group (**21a**), the postulated cyclization reaction gave only intractable mixture (Scheme 4-15).



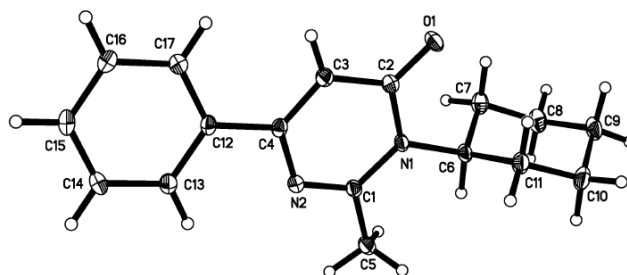
Scheme 4-15: Attempted transformation on **21a**

Remarkably, when *N*-ethyl, *N*-phenyl and *N*-cyclohexyl amides (**21b**, **d**, **f**) prepared from the respective formamides were applied for the same condition, cyclodehydration pathway took place to give the pyrimidin-4-ones (**26b**, **d**, **f**) in synthetically useful yields (Scheme 4-16). The structure of 3-cyclohexyl-2-methyl-6-phenylpyrimidin-4(3H)-one **26f** was unequivocally confirmed by single-crystal X-ray diffraction (Figure 4-5).



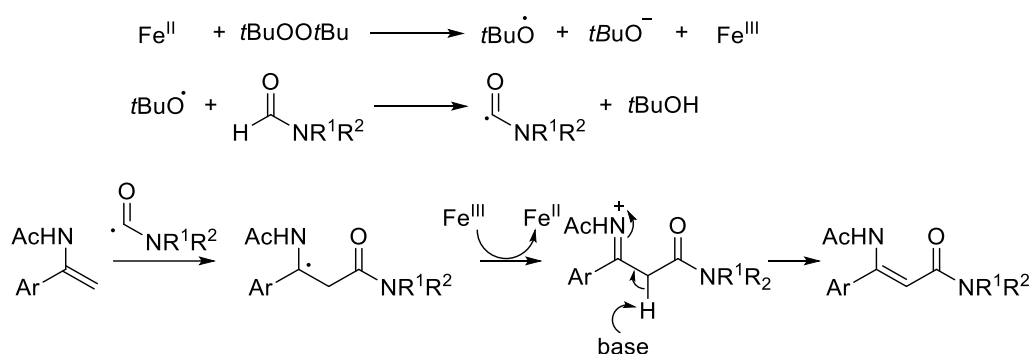
Scheme 4-16: Cyclodehydration of (*Z*)-3-acetamido-*N*-alkyl-3-phenylacrylamide

Figure 4-5: X-ray crystallography structure of 3-cyclohexyl-2-methyl-6-phenylpyrimidin-4(3H)-one **26f**



On the basis of precedent reports and current observation, a plausible mechanism was devised for the current oxidative carbamoylation reaction (Scheme 4-17).<sup>113,133</sup> Similar to previous works reported, a radical process is speculated. The initial step involves iron(II)-mediated decomposition of DTBP

to *tert*-butoxyl radical and *tert*-butoxide anion.<sup>149</sup> The aminocarbonyl radical generated by homolytic cleavage of formyl C(sp<sup>2</sup>)-H bond will add to the  $\beta$ -position of enamide. Iron(III) then oxidizes the iminyl radical to the corresponding iminium ion.<sup>150</sup> The alkenyl functionality is then restored upon deprotonation. Moreover, the current reaction was suppressed in the presence of TEMPO, resulted in no detectable amidation product.



Scheme 4-17: Proposed mechanism.

### 4.3 Conclusion

In conclusion, a novel reaction methodology has been established towards assembly of *N*-acyl enamine amides through direct formyl C-H functionalization of formamides and tandem addition to enamides. Using unoptimized conditions, the densely-functionalized amide products serve as highly versatile building block towards pyrimidin-4-ones and 4-hydroxy-2-pyridinones.

<sup>149</sup> a) Lv, L.; Xi, H.; Bai, X.; Li, Z. *Org. Lett.* **2015**, *17*, 4324. b) Lv, L.; Lu, S.; Guo, Q.; Shen, B.; Li, Z. *J. Org. Chem.* **2015**, *80*, 698. c) Lv, L.; Li, Z. *Org. Lett.* **2016**, *18*, 2264.

<sup>150</sup> a) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2256. b) Lu, D.-F.; Liu, G.-S.; Zhu, C.-L.; Yuan, B.; Xu, H. *Org. Lett.* **2014**, *16*, 2912.

## 4.4 Experimental section

### General Information:

The Luperox® DI, *tert*-Butyl peroxide (98%) and iron(II) chloride (98%) were purchased from Sigma-Aldrich. Unless otherwise noted, all reagents and solvents were purchased from the commercial sources and used as received.

Thin layer chromatography was used to monitor the reaction on Merck 60 F254 precoated silica gel plate (0.2 mm thickness). TLC spots were visualized by UV-light irradiation on Spectroline Model ENF-24061/F 254 nm. Other visualization method was staining with a basic solution of potassium permanganate or acidic solution of ceric molybdate, followed by heating.

Flash column chromatography was performed using Merck silica gel 60 with analytical grade solvents as eluents.

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded using Bruker Avance 400 MHz spectrometers. Corresponding chemical shifts are reported in ppm downfield relative to TMS and were referenced to the signal of chloroform-d ( $\delta=7.26$ , singlet). Multiplicities were given as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd=doublets of doublet, td= triplet of doublet. Values of coupling constant are reported as *J* in Hz.

HRMS spectra were recorded on a Waters Q-ToF Premier Spectrometer.

**CAUTION:** We have never encountered any safety issue in working with or handling the compounds described in this work. Nonetheless; extra precaution should be taken when working with peroxides as mixture of peroxides and metal salts or metals will cause explosion. It is noteworthy to avoid exposing neat peroxides with heat, too.

The enamide substrates were synthesized according to a general procedure adapted from precedent report<sup>1</sup>: Step 1: A mixture of ketone (1 equiv), NaOAc (1.5 equiv) and hydroxylamine hydrochloride (1.5 equiv) in 1:1 mixture of EtOH/H<sub>2</sub>O (0.5M) was stirred for 5 h at 80 °C. The aqueous and organic layers were separated after cooling to room temperature. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate, followed by evaporation in vacuo to afford the ketoxime used directly for the next step. Step 2: To an oven-dried 100 mL two-neck RBF assembled with condenser was added the ketoxime. The flask was vacuumed and back filled with nitrogen for three times. Anhydrous toluene (0.5 M) was added followed by acetic anhydride (3 equiv), acetic acid (3 equiv) and iron powder (2 equiv). The mixture heated at 70 °C under nitrogen atmosphere. Upon completion of reaction and cooling to room temperature, the mixture was filtered through a short pad of celite, washing with ethyl acetate. The filtrate was concentrated in vacuo to crude reaction mixture, which was directly purified by column chromatography to afford the pure enamides.

#### GP1: General procedure for the synthesis of **20a-m**

To an oven-dried schlenk tube charged with stir bar, enamide (0.3 mmol), DMF (1.2 mL) and FeCl<sub>2</sub> (15 mol%, 0.045 mmol, 5.7 mg) were added sequentially. The tube was then evacuated and flushed with nitrogen, a process which was repeated three times. DTBP (5 equiv, 1.5 mmol, 276 µl) was then added dropwise under nitrogen. The reaction mixture was stirred at 80 °C until the enamide was fully consumed, as monitored by TLC. The resulting reaction mixture was cooled before diluted with ethyl acetate and washed with excess amount of water. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine before removal of the solvent under reduced pressure. The crude reaction mixture was subjected to flash column chromatography and the pure product was isolated with hexane / ethyl acetate.

#### GP2: General procedure for the synthesis of **21a-g**

To an oven-dried schlenk tube charged with stir bar, enamide (0.3 mmol), PhCl (1.2 mL), KOAc (30 mol%, 0.09 mmol, 8.8 mg), FeCl<sub>2</sub> (15 mol%, 0.045 mmol, 5.7 mg) and formamide (12 equiv, 3.6 mmol) were added sequentially. The tube was then evacuated and flushed with nitrogen, a process which was repeated three times. DTBP (5 equiv, 1.5 mmol, 276 µl) was then added dropwise under nitrogen. The reaction mixture was stirred at 80 °C until the enamide was fully consumed, as monitored by TLC. The crude reaction mixture was directly subjected to flash column chromatography and the pure product was isolated with hexane / ethyl acetate.

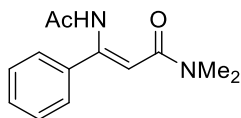
GP3: General procedure for the synthesis of 4-hydroxy-2-pyridinones **24a-g**, **24j**, **24l**

**Step A:** To a stirring mixture of (*Z*)-3-acetamido-*N,N*-dimethyl-3-arylacrylamide **20** in anhydrous THF (reaction molarity: 0.1 M) cooled at 0 °C was added sodium hydride (60% dispersion in mineral oil, 2 equiv). The reaction mixture was left to stir for 15 mins at 0 °C before benzyl bromide (2 equiv) was added dropwise. The resulting mixture was left to stir and warmed up to room temperature until complete conversion of the starting material was observed from TLC. Upon completion, the reaction mixture was directly subjected to flash column chromatography to isolate benzylated product with ethyl acetate used directly for next step. **Step B:** To a stirring mixture of (*Z*)-3-(*N*-benzylacetamido)-3-aryl-*N,N*-dimethylacrylamide in THF (reaction molarity: 0.075M) was added KHMDS (1.0 M in THF, 3 equiv) dropwise at room temperature. The resulting reaction mixture was stirred at 80 °C for 2.5-3 h. Upon completion, the reaction mixture was cooled to room temperature prior to quenching with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were evaporated to dryness before loaded on silica gel for flash column chromatography and the pure product was eluted with 5-10% of methanol in ethyl acetate.

GP4: General procedure for the synthesis of pyrimidin-4-ones **26b**, **26d**, **26f**

To a stirring mixture of (*Z*)-3-acetamido-3-phenyl-*N*-alkylacrylamide in THF (reaction molarity: 0.075M) was added KHMDS (1.0 M in THF, 3 equiv) dropwise. The resulting reaction mixture was stirred at 80 °C for 6-8 h until the complete consumption of starting material was observed from TLC. The reaction mixture was cooled to room temperature prior to quenching with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were evaporated to dryness before loaded on silica gel for flash column chromatography and the pure product was eluted with ethyl acetate/hexane.

#### **20a. (*Z*)-3-acetamido-*N,N*-dimethyl-3-phenylacrylamide**

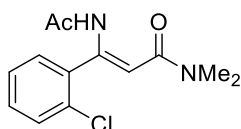


The title compound was prepared according to GP1 and isolated as colourless solid after purification by flash column chromatography. Recrystallization from DCM/hexane afforded single crystals used for X-ray diffraction analysis, which unambiguously confirmed the regio- and stereochemistry of **20a**. 63% (5 h) m.p.: 111-112 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 11.79 (bs, 1H); 7.36 (m, 5H); 5.44 (s, 1H); 3.10 (s, 3H); 3.03 (s, 3H); 2.14 (s, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.6, 168.3, 152.1, 137.1, 129.0,

128.0, 127.0, 100.0, 37.6, 35.4, 24.8 **HRMS (ESI):** C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub>: Calculated: 233.1290; found: 233.1294

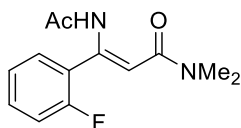
CCDC 1491715 contains the supplementary crystallographic data for **20a**. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

### **20b. (Z)-3-acetamido-3-(2-chlorophenyl)-N,N-dimethylacrylamide**



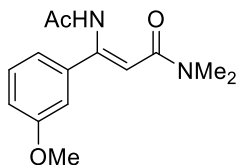
The title compound was prepared according to GP1 and isolated as colourless solid after purification by flash column chromatography. 61% (6 h) m.p.: 111-112 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.36-7.24 (m, 4H); 5.25 (s, 1H); 3.05-3.03 (2s, 6H); 2.09 (s, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.2, 167.4, 149.1, 136.5, 132.1, 129.3, 129.10, 128.9, 126.3, 98.5, 37.4, 35.3, 24.4 **HRMS (ESI):** C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>Cl: Calculated: 267.0900; found: 267.0901

### **20c. (Z)-3-acetamido-3-(2-fluorophenyl)-N,N-dimethylacrylamide**



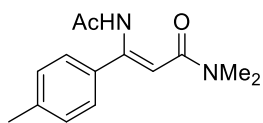
The title compound was prepared according to GP1 and isolated as white solid after purification by flash column chromatography. 68% (5 h) m.p.: 126-127 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 12.07 (bs, 1H); 7.37-7.25 (m, 2H); 7.16-7.11 (m, 1H); 7.06-7.01 (m, 1H); 5.35 (s, 1H); 3.08 (s, 3H); 3.04 (s, 3H); 2.12 (s, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.2, 168.1, 159.5 (d, *J*<sub>C-F</sub> = 247.0 Hz), 146.6, 130.4 (d, *J*<sub>C-F</sub> = 8.0 Hz), 129.1 (d, *J*<sub>C-F</sub> = 3.0 Hz), 125.4 (d, *J*<sub>C-F</sub> = 14.0 Hz), 123.8 (d, *J*<sub>C-F</sub> = 4.0 Hz), 115.1 (d, *J*<sub>C-F</sub> = 21.0 Hz), 99.5, 37.5, 35.4, 24.7 **HRMS (ESI):** C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>F: Calculated: 251.1196; found: 251.1195

### **20d. (Z)-3-acetamido-3-(3-methoxyphenyl)-N,N-dimethylacrylamide**



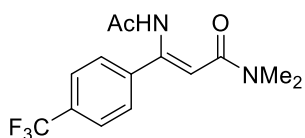
The title compound was prepared according to GP1 and isolated as white solid after purification by flash column chromatography. 71% (5 h) m.p.: 100-101 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 11.73 (bs, 1H); 7.29-7.24 (m, 1H); 6.98-6.95 (m, 1H); .6.91-6.90 (m, 2H); 5.46 (s, 1H); 3.80 (s, 3H); 3.09 (s, 3H); 3.02 (s, 3H); 2.13 (s, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.5, 168.1, 159.1, 151.6, 138.5, 128.9, 119.4, 114.1, 112.9, 100.0, 55.2, 37.5, 35.3, 24.7 **HRMS (ESI):** C<sub>14</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>: Calculated: 263.1396; found: 263.1399

**20e. (Z)-3-acetamido-N,N-dimethyl-3-(p-tolyl)acrylamide**



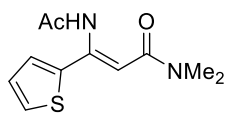
The title compound was prepared according to GP1 and isolated as colourless solid after purification by flash column chromatography. 71% (5 h) m.p.: 158-159 °C  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  11.77 (bs, 1H); 7.27 (d,  $J = 8.0$  Hz, 2H); 7.15 (d,  $J = 8.0$  Hz, 2H); 5.43 (s, 1H); 3.07 (s, 3H); 3.01 (s, 3H); 2.36 (s, 3H); 2.12 (s, 3H)  $^{13}\text{C NMR}$ : ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  168.5, 168.2, 151.9, 139.0, 134.1, 128.6, 126.8, 99.4, 37.4, 35.2, 24.7, 21.2 **HRMS (ESI)**:  $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_2$ : Calculated: 247.1447; found: 247.1447

**20f. (Z)-3-acetamido-N,N-dimethyl-3-(4-(trifluoromethyl)phenyl)acrylamide**



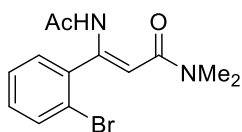
The title compound was prepared according to GP1 and isolated as colourless solid after purification by flash column chromatography. 75% (5 h) m.p.: 130-131 °C  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.59 (d,  $J = 8.2$  Hz, 2H); 7.45 (d,  $J = 8.2$  Hz, 2H); 5.44 (s, 1H); 3.09 (s, 3H); 3.03 (s, 3H); 2.13 (s, 3H)  $^{13}\text{C NMR}$ : ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  168.6, 167.8, 150.5, 140.8, 130.7 (q,  $J_{\text{C-F}} = 32.0$  Hz), 127.3, 124.9 (q,  $J_{\text{C-F}} = 4.0$  Hz), 124.0 (q,  $J_{\text{C-F}} = 270.0$  Hz), 101.0, 37.5, 35.4, 24.6 **HRMS (ESI)**:  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2\text{F}_3$ : Calculated: 301.1164; found: 301.1158

**20g. (Z)-3-acetamido-N,N-dimethyl-3-(thiophen-2-yl)acrylamide**



The title compound was prepared according to GP1 and isolated as yellow oil after purification by flash column chromatography. 40% (5 h)  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  11.48 (bs, 1H); 7.35-7.33 (m, 1H); 7.22-7.20 (m, 1H); 7.02-6.99 (m, 1H); 5.70 (s, 1H); 3.10 (s, 3H); 3.02 (s, 3H); 2.16 (s, 3H)  $^{13}\text{C NMR}$ : ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  169.1, 168.0, 144.6, 139.0, 127.4, 127.1, 126.8, 100.6, 37.6, 35.4, 24.9 **HRMS (ESI)**:  $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}_2\text{S}$ : Calculated: 239.0854; found: 239.0854

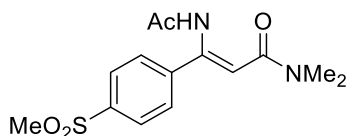
**20h. (Z)-3-acetamido-3-(2-bromophenyl)-N,N-dimethylacrylamide**



The title compound was prepared according to GP1 and isolated as white solid after purification by flash column chromatography. 60% (24 h) m.p.: 102-103 °C  $^1\text{H NMR}$ : ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.56-7.53 (m, 1H); 7.34-7.18 (m, 3H); 5.23 (s, 1H); 3.06-3.04 (2s, 6H); 2.10 (s, 3H)  $^{13}\text{C NMR}$ :

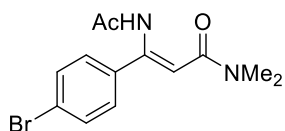
(CDCl<sub>3</sub>, 100 MHz):  $\delta$  168.3, 167.5, 150.5, 138.6, 132.3, 129.5, 129.3, 127.0, 121.7, 98.5, 37.5, 35.4, 24.5 **HRMS (ESI)**: C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub><sup>81</sup>Br: Calculated: 313.0375; found: 313.0375

**20i. (Z)-3-acetamido-N,N-dimethyl-3-(4-(methylsulfonyl)phenyl)acrylamide**



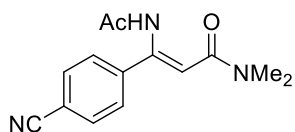
The title compound was prepared according to GP1 and isolated as white solid after purification by flash column chromatography. 58% (5 h) m.p.: 160-161 °C **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz):  $\delta$  11.86 (bs, 1H); 7.88 (d, *J* = 8.2 Hz, 2H); 7.52 (d, *J* = 8.2 Hz, 2H); 5.45 (s, 1H); 3.09 (s, 3H); 3.04 (s, 3H); 3.02 (s, 3H); 2.13 (s, 3H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz):  $\delta$  168.7, 167.6, 149.8, 142.7, 140.4, 127.8, 127.0, 101.6, 44.5, 37.6, 35.4, 24.5 **HRMS (ESI)**: C<sub>14</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub>S: Calculated: 311.1066; found: 311.1061

**20j. (Z)-3-acetamido-3-(4-bromophenyl)-N,N-dimethylacrylamide**



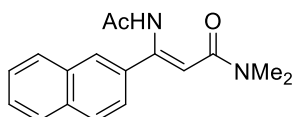
The title compound was prepared according to GP1 and isolated as white solid after purification by flash column chromatography. 51% (5 h) m.p.: 128-129 °C **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz):  $\delta$  11.80 (bs, 1H); 7.46 (d, *J* = 8.4 Hz, 2H); 7.23 (d, *J* = 8.4 Hz, 2H); 5.42 (s, 1H); 3.09 (s, 3H); 3.02 (s, 3H); 2.13 (s, 3H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz):  $\delta$  168.56 167.9, 150.8, 136.0, 131.1, 128.5, 123.1, 100.2, 37.5, 35.3, 24.7 **HRMS (ESI)**: C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>Br: Calculated: 311.0395; found: 311.0401

**20k. (Z)-3-acetamido-3-(4-cyanophenyl)-N,N-dimethylacrylamide**



The title compound was prepared according to GP1 and isolated as white solid after purification by flash column chromatography. 61% (5 h) m.p.: 158-159 °C **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz):  $\delta$  11.83 (bs, 1H); 7.62 (d, *J* = 8.0 Hz, 2H); 7.44 (d, *J* = 8.0 Hz, 2H); 5.44 (s, 1H); 3.10 (s, 3H); 3.03 (s, 3H); 2.13 (s, 3H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz):  $\delta$  168.7, 167.6, 150.0, 141.8, 131.8, 127.6, 118.5, 112.4, 101.3, 37.6, 35.5, 24.6 **HRMS (ESI)**: C<sub>14</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>: Calculated: 258.1243; found: 258.1233

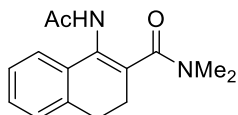
**20l. (Z)-3-acetamido-N,N-dimethyl-3-(naphthalen-2-yl)acrylamide**



The title compound was prepared according to GP1 and isolated as light brown solid after purification by flash column chromatography.

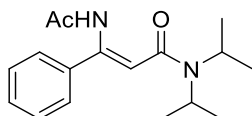
73% (5 h) m.p.: 180-181 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 11.91 (bs, 1H); 7.86-7.78 (m, 4H); 7.49-7.44 (m, 3H); 5.55 (s, 1H); 3.10 (s, 3H); 3.04 (s, 3H); 2.17 (s, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.6, 168.2, 151.9, 134.9, 133.6, 132.9, 128.3, 127.7, 127.2, 126.5, 126.2, 125.8, 125.0, 100.3, 37.6, 35.4, 24.8 **HRMS (ESI):** C<sub>17</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>: Calculated: 283.1447; found: 283.1436

### 20m. 1-acetamido-*N,N*-dimethyl-3,4-dihydronaphthalene-2-carboxamide



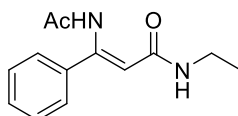
The title compound was prepared according to GP1 and isolated as light brown solid after purification by flash column chromatography. 25% (12 h) m.p.: 150-151 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 8.14 (bs, 1H); 7.18-7.04 (m, 4H); 3.07-3.00 (m, 6H); 2.61 (t, *J* = 8.0 Hz, 2H); 2.39 (t, *J* = 8.0 Hz, 2H); 2.16 (s, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 171.2, 170.0, 135.8, 131.0, 130.9, 128.1, 128.0, 127.2, 126.4, 123.6, 38.2, 34.6, 26.7, 25.2, 23.1 **HRMS (ESI):** C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>: Calculated: 259.1447; found: 259.1451

### 21a. (*Z*)-3-acetamido-*N,N*-diisopropyl-3-phenylacrylamide



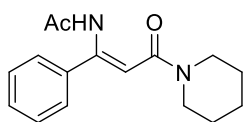
The title compound was prepared according to GP2 and isolated as colourless solid after purification by flash column chromatography. 37% (5 h) m.p.: 114-115 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 11.74 (bs, 1H); 7.39 (m, 5H); 5.45 (s, 1H); 4.12-3.84 (m, 2H); 2.14 (s, 3H); 1.41-1.24 (m, 12H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.8, 167.7, 150.7, 137.6, 128.9, 128.0, 126.9, 103.4, 45.6, 24.9, 21.5, 20.7 **HRMS (ESI):** C<sub>17</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>: Calculated: 289.1916; found: 289.1915

### 21b. (*Z*)-3-acetamido-*N*-ethyl-3-phenylacrylamide



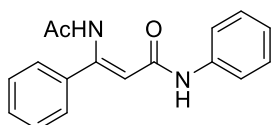
The title compound was prepared according to GP2 and isolated as colourless oil after purification by flash column chromatography. 53% (5 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 11.56 (bs, 1H); 7.33 (m, 5H); 5.59 (bs, 1H); 5.01 (s, 1H); 3.38-3.30 (m, 2H); 2.13 (s, 3H); 1.18 (t, *J* = 7.2 Hz, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.6, 167.9, 151.3, 136.5, 129.0, 127.9, 126.9, 103.5, 34.2, 28.2, 24.8, 14.8 **HRMS (ESI):** C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub>: Calculated: 233.1290; found: 233.1289

### 21c. (*Z*)-*N*-(3-oxo-1-phenyl-3-(piperidin-1-yl)prop-1-en-1-yl)acetamide



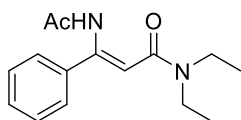
The title compound was prepared according to GP2 and isolated as colourless oil after purification by flash column chromatography. 55% (5 h) **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 11.73 (bs, 1H); 7.36 (m, 5H); 5.48 (s, 1H); 3.62-3.53 (m, 4H); 2.13 (s, 3H); 1.68-1.61 (m, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.6, 166.6, 151.9, 137.3, 129.0, 128.0, 126.9, 100.3, 47.0, 42.7, 26.6, 25.7, 24.8, 24.5 **HRMS (ESI):** C<sub>16</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>: Calculated: 273.1603; found: 273.1602

#### 21d. (Z)-3-acetamido-N,3-diphenylacrylamide



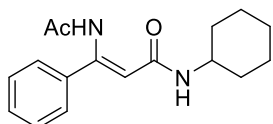
The title compound was prepared according to GP2 and isolated as slowly solidifying white solid after purification by flash column chromatography. 30% (6 h) The analytical data are in accordance with the literature.<sup>2</sup> **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 11.47 (bs, 1H); 7.55-7.45 (m, 5H); 7.40-7.28 (m, 5H); 7.22-7.10 (m, 1H); 5.18 (s, 1H); 2.16 (s, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.8, 166.2, 152.8, 137.5, 136.3, 129.3, 129.1, 128.0, 127.0, 124.6, 120.3, 119.9, 103.7, 24.9 **HRMS (ESI):** C<sub>17</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub>: Calculated: 281.1290; found: 281.1290

#### 21e. (Z)-3-acetamido-N,N-diethyl-3-phenylacrylamide



The title compound was prepared according to GP2 and isolated as colourless solid after purification by flash column chromatography. 60% (13 h) m.p.: 60-61 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 11.89 (bs, 1H); 7.36 (m, 5H); 5.38 (s, 1H); 3.47-3.38 (m, 4H); 2.13 (s, 3H); 1.24-1.17 (m, 6H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.6, 167.3, 152.0, 137.3, 128.9, 127.9, 127.0, 100.2, 42.6, 40.7, 24.8, 14.6, 13.2 **HRMS (ESI):** C<sub>15</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>: Calculated: 261.1603; found: 261.1601

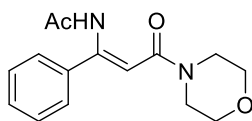
#### 21f. (Z)-3-acetamido-N-cyclohexyl-3-phenylacrylamide



The title compound was prepared according to GP2 and isolated as colourless oil after purification by flash column chromatography. 50% (7.5 h) The analytical data are in accordance with the literature.<sup>2</sup> **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 11.58 (bs, 1H); 7.32 (m, 5H); 5.51 (m, 1H); 5.00 (s, 1H); 3.90-3.75 (m, 1H); 2.13 (s, 3H); 1.99-1.89 (m, 2H); 1.78-1.70 (m, 2H); 1.65-1.59 (m, 1H); 1.47-1.32 (m, 2H); 1.25-1.09 (m, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100

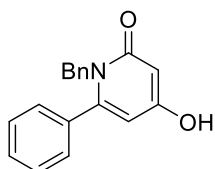
MHz):  $\delta$  168.5, 167.1, 151.3, 136.5, 128.9, 127.6, 126.9, 103.7, 48.2, 33.1, 25.5, 24.9, 24.7 **HRMS (ESI)**:  $C_{17}H_{23}N_2O_2$ : Calculated: 287.1760; found: 287.1761

### 21g. (Z)-N-(3-morpholino-3-oxo-1-phenylprop-1-en-1-yl)acetamide



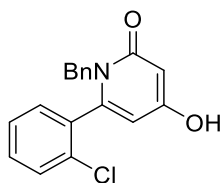
The title compound was prepared according to GP2 and isolated as colourless solid after purification by flash column chromatography. 48% (5 h) m.p.: 119-120 °C  **$^1H$  NMR**: ( $CDCl_3$ , 400 MHz):  $\delta$  11.62 (bs, 1H); 7.36 (m, 5H); 5.40 (s, 1H); 3.71-3.50 (m, 8H); 2.14 (s, 3H)  **$^{13}C$  NMR**: ( $CDCl_3$ , 100 MHz):  $\delta$  168.6, 166.9, 152.9, 137.0, 129.2, 128.0, 126.9, 99.2, 66.8, 66.6, 46.1, 41.7, 24.8 **HRMS (ESI)**:  $C_{15}H_{19}N_2O_3$ : Calculated: 275.1396; found: 275.1396

### 24a. 1-benzyl-4-hydroxy-6-phenylpyridin-2(1H)-one



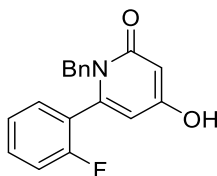
The title compound was prepared according to GP3 on 0.15 mmol scale of **23a** and isolated as colourless solid after purification by flash column chromatography. Step A: 94%; Step B: 67% (2.5 h) m.p.: 215-217 °C  **$^1H$  NMR**: (*d*-DMSO, 400 MHz):  $\delta$  10.93 (bs, 1H); 7.43-7.33 (m, 3H); 7.23-7.15 (m, 5H); 6.82-6.79 (m, 2H); 5.78-5.73 (m, 2H); 4.99 (s, 2H)  **$^{13}C$  NMR**: (*d*-DMSO, 100 MHz):  $\delta$  166.3, 164.0, 150.8, 138.5, 135.6, 129.6, 128.8, 128.6, 127.1, 126.6, 102.7, 97.8, 47.3 **HRMS (ESI)**:  $C_{18}H_{16}NO_2$ : Calculated: 278.1181; found: 278.1172

### 24b. 1-benzyl-6-(2-chlorophenyl)-4-hydroxypyridin-2(1H)-one



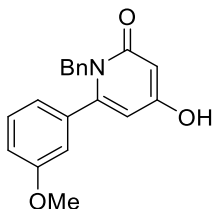
The title compound was prepared according to GP3 on 0.13 mmol scale of **20b** and isolated as white solid after purification by flash column chromatography. Step A: 85%; Step B: 57% (3 h) m.p.: 198-200 °C  **$^1H$  NMR**: (*d*-DMSO, 400 MHz):  $\delta$  7.58-7.55 (m, 1H); 7.49-7.45 (m, 1H); 7.29-7.24 (m, 1H); 7.19-7.12 (m, 4H); 6.79- 6.76 (m, 2H); 5.76-5.75 (m, 2H); 5.17 (d,  $J$  = 15.6 Hz, 1H); 4.41 (d,  $J$  = 15.6 Hz, 1H)  **$^{13}C$  NMR**: (*d*-DMSO, 100 MHz):  $\delta$  166.6, 163.9, 147.3, 137.9, 134.0, 132.6, 131.7, 131.5, 129.9, 128.6, 127.6, 127.3, 126.8, 103.1, 98.4, 47.0 **HRMS (ESI)**:  $C_{18}H_{15}NO_2Cl$ : Calculated: 312.0791; found: 312.0794

### 24c. 1-benzyl-6-(2-fluorophenyl)-4-hydroxypyridin-2(1H)-one



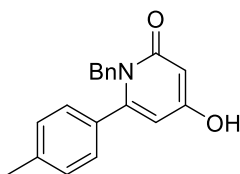
The title compound was prepared according to GP3 on 0.15 mmol scale of **20c** and isolated as white solid after purification by flash column chromatography. Step A: 92%; Step B: 61% (2.5 h) m.p.: 256-258 °C **<sup>1</sup>H NMR:** (*d*-DMSO, 400 MHz):  $\delta$  10.92 (bs, 1H); 7.54-7.48 (m, 1H); 7.29-7.15 (m, 6H); 6.78-6.75 (m, 2H); 5.85 (d,  $J = 2.4$  Hz, 1H); 5.79 (d,  $J = 2.4$  Hz, 1H); 5.19 (d,  $J = 15.4$  Hz, 1H); 4.70 (d,  $J = 15.4$  Hz, 1H) **<sup>13</sup>C NMR:** (*d*-DMSO, 100 MHz):  $\delta$  166.1, 163.9, 159.0 (d,  $J_{C-F} = 245.0$  Hz), 144.5, 137.9, 132.4 (d,  $J_{C-F} = 8.0$  Hz), 131.4, 128.6, 127.3, 126.7, 125.0 (d,  $J_{C-F} = 3.0$  Hz), 123.0 (d,  $J_{C-F} = 16.0$  Hz), 116.2 (d,  $J_{C-F} = 21.0$  Hz), 103.6, 98.5, 47.2 **HRMS (ESI):** C<sub>18</sub>H<sub>15</sub>NO<sub>2</sub>F: Calculated: 296.1087; found: 296.1085

#### 24d. 1-benzyl-4-hydroxy-6-(3-methoxyphenyl)pyridin-2(1H)-one



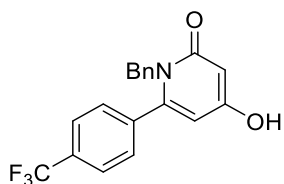
The title compound was prepared according to GP3 on 0.17 mmol scale of **20d** and isolated as light yellow solid after purification by flash column chromatography. Step A: 88%; Step B: 80% (2.5 h) m.p.: 155-156 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.22-7.15 (m, 4H); 7.00-6.85 (m, 3H); 6.74-6.71 (m, 1H); 6.52 (s, 1H); 6.27 (s, 1H); 6.00 (s, 1H); 5.11 (s, 2H); 3.51 (s, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  168.0, 165.9, 159.1, 150.5, 137.6, 136.1, 129.5, 128.4, 126.9, 126.5, 120.8, 115.8, 113.5, 105.3, 98.7, 55.0, 48.8 **HRMS (ESI):** C<sub>19</sub>H<sub>18</sub>NO<sub>3</sub>: Calculated: 308.1287; found: 308.1288

#### 24e. 1-benzyl-4-hydroxy-6-(p-tolyl)pyridin-2(1H)-one



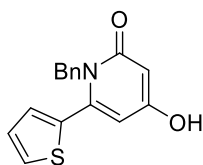
The title compound was prepared according to GP3 on 0.15 mmol scale of **20e** and isolated as white solid after purification by flash column chromatography. Step A: 96%; Step B: 68% (3 h) m.p.: 169-170 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  7.20-6.84 (m, 9H); 6.23 (s, 1H); 5.96 (s, 1H); 5.12 (s, 2H); 2.35 (s, 3H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz):  $\delta$  168.0, 165.9, 150.8, 139.2, 137.5, 132.2, 128.9, 128.5, 128.3, 126.9, 126.5, 105.5, 98.7, 48.6, 21.3 **HRMS (ESI):** C<sub>19</sub>H<sub>18</sub>NO<sub>2</sub>: Calculated: 292.1338; found: 292.1339

#### 24f. 1-benzyl-4-hydroxy-6-(4-(trifluoromethyl)phenyl)pyridin-2(1H)-one



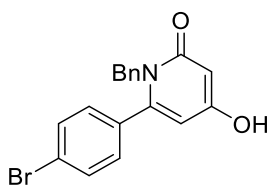
The title compound was prepared according to GP3 on 0.16 mmol scale of **20f** and isolated as white solid after purification by flash column chromatography. Step A: 90%; Step B: 67% (2.5 h) m.p.: 211-212 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 5.98-5.97 (m, 1H); 6.29 (m, 1H); 6.82-6.78 (m, 2H); 7.25-7.12 (m, 5H); 7.54-7.51 (m, 2H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.0, 165.8, 149.0, 138.3, 136.9, 131.4 (q, *J*<sub>C-F</sub> = 33.0 Hz), 129.1, 128.5, 127.4, 127.2, 126.3, 125.3 (d, *J*<sub>C-F</sub> = 3.6 Hz); 123.7 (q, *J*<sub>C-F</sub> = 271.0 Hz), 105.8, 99.1, 48.5 **HRMS (ESI):** C<sub>19</sub>H<sub>15</sub>NO<sub>2</sub>F<sub>3</sub>: Calculated: 346.1055; found: 346.1058

#### 24g. 1-benzyl-4-hydroxy-6-(thiophen-2-yl)pyridin-2(1H)-one



The title compound was prepared according to GP3 on 0.15 mmol scale and isolated as white solid after purification by flash column chromatography. Step A: 85%; Step B: 65% (3 h) m.p.: 236-238 °C **<sup>1</sup>H NMR:** (*d*-DMSO, 400 MHz): δ 10.93 (bs, 1H); 7.67-7.65 (m, 1H); 7.29-7.18 (m, 3H); 7.10-7.05 (m, 2H); 6.91-6.89 (m, 2H); 5.99 (d, *J* = 2.6 Hz, 1H); 5.75 (d, *J* = 2.6 Hz, 1H); 5.13 (s, 2H) **<sup>13</sup>C NMR:** (*d*-DMSO, 100 MHz): δ 165.9, 164.0, 143.4, 138.6, 135.3, 129.5, 128.9, 128.8, 127.8, 127.2, 126.3, 104.5, 98.6, 47.5 **HRMS (ESI):** C<sub>16</sub>H<sub>14</sub>NO<sub>2</sub>S: Calculated: 284.0745; found: 284.0753

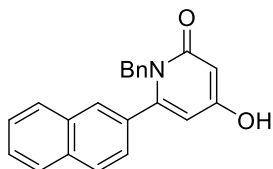
#### 24j. 1-benzyl-6-(4-bromophenyl)-4-hydroxypyridin-2(1H)-one



The title compound was prepared according to GP3 on 0.14 mmol scale of **20j** and isolated as colourless solid after purification by flash column chromatography. Recrystallization from DCM/methanol afforded single crystals used for X-ray diffraction analysis, which unambiguously confirmed the structure of **24j**. Step A: 97% Step B: 69% (2.5 h) m.p.: 197-199 °C **<sup>1</sup>H NMR:** (CDCl<sub>3</sub>, 400 MHz): δ 7.44-7.41 (m, 2H); 7.28-7.14 (m, 3H); 7.04-6.81 (m, 4H); 6.28 (s, 1H); 5.98 (s, 1H); 5.12 (s, 2H) **<sup>13</sup>C NMR:** (CDCl<sub>3</sub>, 100 MHz): δ 168.0, 165.8, 149.4, 137.1, 133.8, 131.5, 130.2, 128.5, 127.1, 126.4, 123.7, 105.7, 98.9, 48.55 **HRMS (ESI):** C<sub>18</sub>H<sub>15</sub>NO<sub>2</sub>Br: Calculated: 356.0286; found: 356.0280

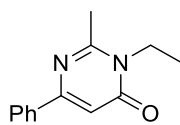
CCDC 1495894 contains the supplementary crystallographic data for **24j**. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

#### 24l. 1-benzyl-4-hydroxy-6-(naphthalen-2-yl)pyridin-2(1H)-one



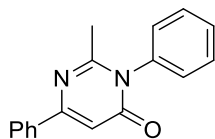
The title compound was prepared according to GP3 on 0.24 mmol scale of **20l** and isolated as light brown solid after purification by flash column chromatography. Step A: 95%; Step B: 73% (3 h) m.p.: 205-206 °C **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 7.82-7.78 (m, 1H); 7.70-7.68 (m, 1H); 7.65-7.59 (m, 1H); 7.57-7.43 (m, 3H); 7.20-7.05 (m, 4H); 6.89-6.80 (m, 2H); 6.35 (d, *J* = 2.4 Hz, 1H); 6.11 (d, *J* = 2.4 Hz, 1H); 5.16 (s, 2H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 168.0, 166.0, 150.6, 137.4, 133.1, 132.5, 132.3, 128.5, 128.3, 128.3, 128.0, 127.7, 127.1, 126.9, 126.8, 126.6, 125.7, 105.9, 99.0, 48.8 **HRMS (ESI)**: C<sub>22</sub>H<sub>18</sub>NO<sub>2</sub>: Calculated: 328.1338; found: 328.1334

#### 26b. 3-ethyl-2-methyl-6-phenylpyrimidin-4(3H)-one



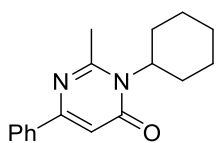
The title compound was prepared according to GP4 on 0.16 mmol scale of **21b** and isolated as white solid after purification by flash column chromatography. 73% (5 h) m.p.: 101-102 °C **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 7.97-7.94 (m, 2H); 7.47-7.45 (m, 3H); 6.78 (s, 1H); 4.14 (q, *J* = 7.2 Hz, 2H); 2.67 (s, 3H); 1.38 (t, *J* = 7.2 Hz, 3H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 162.9, 159.7, 158.4, 136.4, 130.3, 128.7, 126.9, 107.4, 39.5, 22.8, 13.4 **HRMS (ESI)**: C<sub>13</sub>H<sub>15</sub>N<sub>2</sub>O: Calculated: 215.1184; found: 215.1183

#### 26d. 2-methyl-3,6-diphenylpyrimidin-4(3H)-one



The title compound was prepared according to GP4 on 0.08 mmol scale of **21d** and isolated as white solid after purification by flash column chromatography. 81% (7 h) The analytical data are in accordance with the literature.<sup>2</sup> m.p.: 162-163 °C **<sup>1</sup>H NMR**: (CDCl<sub>3</sub>, 400 MHz): δ 8.03-7.98 (m, 2H); 7.60-7.47 (m, 6H); 7.28-7.25 (m, 2H); 6.89 (s, 1H); 2.27 (s, 3H) **<sup>13</sup>C NMR**: (CDCl<sub>3</sub>, 100 MHz): δ 163.3, 160.3, 158.9, 137.4, 136.4, 130.6, 130.12, 129.5, 128.8, 127.6, 127.0, 107.7, 24.3 **HRMS (ESI)**: C<sub>17</sub>H<sub>15</sub>N<sub>2</sub>O: Calculated: 263.1184; found: 263.1190

#### 26f. 3-cyclohexyl-2-methyl-6-phenylpyrimidin-4(3H)-one



The title compound was prepared according to GP4 on 0.08 mmol scale of **21f** and isolated as white solid after purification by flash column chromatography. Recrystallization from hexane/methanol afforded single crystals used for X-ray diffraction analysis, which unambiguously confirmed the structure of **26f**. 68% (8 h) m.p.: 130-131 °C **<sup>1</sup>H NMR:** (CD<sub>3</sub>OD, 400 MHz): δ 8.02-7.94 (m, 2H); 7.50-7.43 (m, 3H); 6.68 (s, 1H); 4.25-4.17 (m, 1H); 2.81-2.60 (m, 5H); 1.96-1.86 (m, 2H); 1.81-1.68 (m, 3H); 1.51-1.38 (m, 2H); 1.36-1.23 (m, 1H) **<sup>13</sup>C NMR:** (CD<sub>3</sub>OD, 100 MHz): δ 164.7, 159.7, 159.7, 135.9, 130.2, 128.4, 126.6, 107.9, 61.2, 27.9, 25.9, 24.9, 22.8 **HRMS (ESI):** C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O: Calculated: 269.1654; found: 269.1653

CCDC 1494987 contains the supplementary crystallographic data for **26f**. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

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1. a) Hu, N.; Zhao, G.; Zhang, Y.; Liu, X.; Li, G.; Tang, W. *J. Am. Chem. Soc.* **2015**, *137*, 6746. b) Feng, C.; Feng, D.; Loh, T.-P. *Chem. Commun.* **2014**, *50*, 9865.
2. Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430.

### List of publications:

1. *Copper- and Cobalt-Catalyzed Direct Coupling of sp<sup>3</sup> α-Carbon of Alcohols with Alkenes and Hydroperoxides*, J. K. Cheng, T. P. Loh, *J. Am. Chem. Soc.* **2015**, *137*, 42-45.
2. *Iron-catalyzed Peroxidation-Aminocarbonylation of Alkenes with Hydroperoxides and Formamides via Formyl C(sp<sup>2</sup>)-H Functionalization*, J. K. Cheng, T. P. Loh (manuscript submitted)