Phosphine catalyzed [3+2] cycloaddition reactions for the synthesis of carbo-and heterocycles

Magesh Sampath

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

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REACTIONS FOR THE SYNTHESIS OF CARBO- AND
HETEROCYCLES

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University in
fulfillment of the requirement for the degree of Doctor of Philosophy

2011

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LIST OF ABBREVIATIONS

δ	chemical shift
$^{\circ}\text{C}$	degree centigrade
Ar	aryl
BINAP	2,2'-diphenylphosphino-1, 1'-binaphthyl
calcd	calculated
CH_2Cl_2	dichloromethane
CDCl_3	deuterated chloroform
cm^{-1}	inverse centimeter
Cy	cyclohexanyl
d	doublet
DIBAL	diisobutylaluminium hydride
DPPE	1,2-bis(diphenylphosphino)ethane
dd	doublet of doublets
DFT	density functional theory
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiomeric excess
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
FTIR	fourier transform infrared spectrometry
g	gram
h or hrs	hour(s)

HRMS	high resolution mass spectrometry
Hz	hertz
m	multiplet
m/z	mass per charge ratio
M ⁺	parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MOM	methoxymethyl
MeOH	methanol
MHz	mega hertz
min	minute(s)
mL	millilitres
mmol	millimole
mol%	mole percent
MS	mass spectrometry
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
q	quartet
R _f	retention factor
rt	room temperature
s	singlet
t	triplet
^t Bu	tert-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TIPS	triisopropylsilyl
α	alpha
β	beta
γ	gamma

ABSTRACT

This thesis describes the development of phosphine as nucleophilic catalyst in cycloaddition reactions and its application in the synthesis of structurally diverged carbo- and hetero cyclic frameworks.

Chapter 1

In chapter 1, the phosphine catalyzed cycloaddition between electron deficient allene/alkyne with various coupling functionalities such as C=C, C=N and C=O in the synthesis of respective carbo- and heterocycles are briefly discussed. Recent advancement in the asymmetric version of this reaction and its application in total synthesis of various natural products were also discussed.

Chapter 2

In chapter 2, the phosphine catalyzed [3+2] cycloaddition reaction between α -trimethylsilyl substituted aryl allenones and electron deficient olefins are described. This new method brings highly functionalized cyclopentenones with a wide substrate scope. The preliminary investigation on asymmetric versions of the reaction gave cyclopentene product with good enantioselectivity.

Chapter 3

In chapter 3, highly functionalized cyclopentenones were synthesized using a phosphine-catalyzed one-pot isomerization and [3+2]-cycloaddition of 3-alkynoates with electron-deficient olefins. Furthermore, the commercially available chiral phosphine DIPAMP was found to promote an asymmetric version of this reaction and produced products in high optical purity.

Chapter 4

In chapter 4, the phosphine catalyzed one-pot isomerization and [3+2]-cycloaddition of 3-

alkynoates with activated imines was described in the synthesis of pyrrolidines. The method was shown to be applicable to the formal synthesis of the bioactive *Securinega* alkaloid ($\pm$)-allosecurinine.

Chapter 5

In chapter 5, an efficient protocol to produce spiro furan-oxindolines *via* phosphine catalyzed [3+2] cycloaddition between carbonyl functionality of oxindolinones and allenolate is described.

CHAPTER 1

Phosphine-Catalyzed Cycloaddition Reactions

Chapter 1 Phosphine-Catalyzed Cycloaddition Reactions

1.1 Introduction

The chemical reaction that focuses on chemo-, regio- and stereoselective synthesis of carbo- and heterocycles is highly sought-after in the field of organic synthesis. Such reactions play a significant role in the synthesis of complex molecular frameworks, which are commonly found in various natural products and pharmaceutical candidates.¹ In this context, the developments of new synthetic methods that make use of metal free catalysis have been actively pursued.² This chapter describes the advances made in the field of phosphine catalysis and also provides a brief preface on the efficient and selective methods for synthesis of highly functionalized carbo- and heterocycles.³

In general, phosphines are highly recognized as a ligand in metal mediated reactions.⁴ Recently, the nucleophilic catalysis using organophosphorus compounds has achieved significant advancement.⁵ The phosphines in organocatalysis, exhibit various beneficial features by simply varying the steric and electronic properties of the substituents on phosphine to suit the reaction type. In addition, enantioselective catalysis can be achieved by using asymmetric variants where the phosphorus center is capable of behaving as a nucleophile as well as a source of stereochemical

¹ (a) Michael, J. P. *Nat. Prod. Rep.* **2004**, *60*, 1701. (b) Hagan, D. O. *Nat. Prod. Rep.* **2000**, *17*, 435. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388.

² (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (b) Ballini, R.; Bosica, G.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933. (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (d) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta*, **2006**, *39*, 79. (e) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (f) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526. (h) Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res.* **2004**, *37*, 580.

³ (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (d) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (e) Marinetti, A.; Voituriez, A. *Synlett*, **2010**, 0174.

⁴ Borner, A. *Phosphorus ligands in Asymmetric Catalysis*; Wiley-VCH: Weinheim, **2008**.

⁵ (a) Quin, L. D. *A Guide to Organophosphorus Chemistry*, Wiley, New York, **2000**. (b) Valentine, D. H.; Hill-house, J. H. *Synthesis*, **2003**, 317.

induction.⁶ The reactivity of the phosphines is centered on the non-bonding lone pair of electrons that can form a chemical bond between phosphines and a variety of electrophiles. The classic reactions in organic synthesis which includes the Wittig reaction⁷ (olefin formation), the Staudinger reaction⁸ (amine derivatives formation) and the Mitsunobu reactions⁹ (replacement of hydroxy with other nucleophiles) were successfully demonstrated with the use of stoichiometric amount of phosphine. Recently, phosphines are also used as a catalyst in a variety of reactions such as intramolecular the Rauhut-Currier reaction,¹⁰ the Morita-Baylis-Hilman reaction¹¹ and the Michael addition reaction.¹² The groups of Trost and Lu have independently reported the first phosphine catalyzed isomerization of ynones **1** to the corresponding dienones **2** (Scheme 1.1). In both synthetic approaches, the reaction were shown to proceeded at catalyst loading of 10 mol% of triphenylphosphine and afforded the corresponding isomerized product **2** in yields of 69-88% (Scheme 1.1). The

⁶ Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, 47, 1560.

⁷ Maercker, A. *Org. React.* **1965**, 14, 270.

⁸ Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron*, **1992**, 48, 1353.

⁹ (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Itô, S.; Tsunoda, T. *Pure Appl. Chem.* **1999**, 71, 1053. (c) Wentworth, P. Jr.; Vandersteen, A. M.; Janda, K. D. *Chem. Commun.* **1997**, 759. (d) Shibata, K.; Mitsunobu, O. *Bull. Chem. Soc. Jpn.* **1992**, 65, 3163. (e) Shibata, K.; Yamaga, H.; Mitsunobu, O. *Heterocycles* **1999**, 50, 947.

¹⁰ (a) Rauhut, M.; Currier, H. (American Cyanamide Co.), *U. S. Patent* 3,074,999, **1963**. (b) McClure, J. D. *U. S. Patent* 3,225,083, **1965**. (c) Baizer, M. M.; Anderson, J. D. *J. Org. Chem.* **1965**, 30, 1357. (d) McClure, J. D. *J. Org. Chem.* **1970**, 35, 3045. (e) Jenner, G. *Tetrahedron Lett.* **2000**, 41, 3091. (f) Amri, H.; Villieras, J. *Tetrahedron Lett.* **1986**, 27, 4307. (g) Basavaiah, D.; Gowriswari, V. V. L.; Bharathi, T. K. *Tetrahedron Lett.* **1987**, 28, 4591. (h) Drewes, S. E.; Emslie, N. D.; Karodia, N. *Synthetic Commun.* **1990**, 20, 1915. For intramolecular version: (i) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, 124, 2402. (j) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, 124, 2404.

¹¹ (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, 41, 2815. (b) Baylis, A. B.; Hillman, M. E. D. *German Patent* 2,155,113, **1972**. (c) Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.* **1991**, 32, 5611. (d) Imagawa, T.; Uemura, K.; Nagai, Z.; Kawanisi, M. *Synth. Commun.* **1984**, 14, 1267. For intramolecular version: (e) Roth, F.; Gygas, P.; Fra'ter, G. *Tetrahedron Lett.* **1992**, 1045. (f) Dinon, F.; Richards, E.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **1999**, 40, 3279. (g) Richards, E.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, 57, 7771. (h) Brown, Kappel, N.; Murphy, P. J. *Tetrahedron Lett.* **2002**, 43, 8707. (i) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, 4, 3687.

¹² (a) White, D. A.; Baizer, M. M. *Tetrahedron Lett.* **1973**, 14, 3597. (b) Gomez-Bengoia, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. *J. Am. Chem. Soc.* **1996**, 118, 8553. (c) Trost, B. M.; Li, C. J. *J. Am. Chem. Soc.* **1994**, 116, 10819. (d) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, 119, 7595. (e) Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W.; *J. Org. Chem.* **2002**, 67, 4595. (f) Lu, C.; Lu, X. *Org. Lett.* **2002**, 4, 4677. (g) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, 129, 12928.

mechanism was proposed to proceed *via* an allenic intermediate which involves nucleophilic addition of phosphine, then underwent a series of prototropic shifts which allows an elimination of phosphine to give conjugated diene **2** (Scheme 1.1).¹³

Scheme 1.1 Phosphine catalyzed isomerization of Ynones to Dienones

This chapter will serve to briefly summarize some recent developments in the field of phosphine catalyzed cycloaddition reactions, which are directly related to this thesis.

¹³ (a) B. M. Trost, U. Kazmaier, *J. Am. Chem. Soc.* 1992, 114, 7933; (b) C. Guo, X. Lu, *Chem. Commun.* **1993**, 394; (c) C. Guo, X. Lu, *Perkin Trans. 1* **1993**, 1921.

1.2 Phosphine-Catalyzed Cycloaddition with Electron Deficient Olefins

1.2.1 Intermolecular Phosphine-Catalyzed Cycloaddition using Electron Deficient Olefins

To broaden the synthetic utility of phosphine catalysis, Lu *et al.* disclosed the first example [3+2]-cycloaddition reaction of electron-deficient allenoates **3a** with electron-deficient olefins **4** catalyzed by 10 mol% of triphenylphosphine (Scheme 1.2).¹⁴ The corresponding cyclopentene **5a** were obtained as a major product in yields up to 81% along with the small amount of **5γ** as a regioisomeric product (yields 55 - 81%; **5a**/**5γ** 63:87 – 87:13; Scheme 1.2). Two regioisomeric products (**5a** and **5γ**) were generated due to the respective addition of the α or γ carbon of the allenoate to the olefin. However, the reaction was found to be ineffective when triethylamine or DABCO was employed as catalyst.

Scheme 1.2 Phosphine catalyzed [3+2]-cycloaddition reaction between allenoate and olefin

The proposed mechanism of the reaction is outlined in Scheme 1.3. Initially, phosphine adds to the β -carbon of the allenoate to form allylic phosphonium intermediates (**3.1a** and **3.1γ**). Next the [3+2]-cycloaddition occurs between the dipolar intermediate and the electron-deficient olefin to form cyclic intermediates

¹⁴ Lu, X.; Zhang, C. *J. Org. Chem.* **1995**, 60, 2906.

3.2 α and **3.2 γ** . Subsequent [1,2]-proton shift and regeneration of phosphine leads to the [3+2]-cyclized products **5 α** and **5 γ** .

Scheme 1.3 Proposed mechanism phosphine catalyzed [3+2]-cycloaddition

The method was found to be limited to activated olefins since, attempted reactions with 1-hexene, methyl (*E* or *Z*)-crotonate or methyl methacrylate was reported to give no reactions. Instead, phosphine catalyzed self condensation of α -allenoate **3a** was observed to obtain **6** (Scheme 1.4).

Scheme 1.4 Phosphine catalyzed self condensation of α -allenoate **1**

Interestingly, the geometrical information of the starting material olefin remains unchanged in the cyclized product. For example, diethyl maleate **7** and

diethyl fumarate **8** reacted with allenoate **3a** to afford single *cis* **9** (eq 1) and *trans* **10** (eq 2) adduct respectively (Scheme 1.5).¹⁵

Scheme 1.5 Stereocontrolled cycloaddition reactions

Lu *et al.* further extended the [3+2] cycloaddition reaction to using ynoates **11**. The reaction initially generates intermediates **1.1 α** and **1.2 γ** similar to those derived from allenoate **3a** (Scheme 1.6). In these reactions the desired cyclized product were obtained in 46-91% yields with up to 93:7 **5 α** /**5 γ** regioselectivity. However, it was found that less nucleophilic triphenylphosphine was not effective in promoting the reaction even after heated at 135 °C for 24 h. It was also suggested that, both diethyl fumarate and maleate affords *trans*-(**10**) product due to the rapid isomerization of starting material diethyl maleate to fumarate in the reaction condition.¹⁶

¹⁵ For the stereochemical determination of *trans* and *cis* adduct, See: (a) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (b) Davies, H. M. L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett.* **1989**, *30*, 5057 and references cited therein.

¹⁶ (a) Ganguly, S.; Roundhill, D. M. *J. Chem. Soc. Chem. Commun.* **1991**, 639. (b) Larpent, C.; Meignan, G. *Tetrahedron Lett.* **1993**, *34*, 4331.

Scheme 1.6 [3+2]-cycloaddition reaction using 2-butynoate

Lu *et al.* further extended this methodology to spirocarbocyclic compounds by using various electron-deficient *exo*-cyclic olefins.¹⁷ The reaction was found to proceed with *tert*-butyl allenoate **3b** and *exo*-methylene **12a** at catalyst loading of 10 mol% of triphenylphosphine affording two regioisomeric products **13α** and **13γ** in 98% yield with the regioselectivity ratio of 91:9 (Scheme 1.7). The other *exo*-methylenes **12b** - **12i** were also tested and each reactant afforded the corresponding spirocycles compounds in yields of 63 - 99% and with good regioselectivities (**13α:13γ** = 74:26 to 95:5; Scheme 1.7).

Scheme 1.7 Spirocarbocycles via phosphine-catalyzed [3+2]-cycloaddition

¹⁷ (a) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, 67, 8901.

This methodology was further extended to the enantioselective total synthesis of (-)-hinesol that relied on chiral *exo*-methylene **12j** (Scheme 1.8).¹⁸ This reaction gave the corresponding **13aj** under room temperature in a good yield of 63% and with an excellent diastereoselectivity ratio of 94:6 (Scheme 1.8). The approach of zwitterionic intermediate from the opposite face of the β -methyl substituent was the probable source of the high diastereoselectivity in this reaction as shown in proposed transition state (Scheme 1.8).

Scheme 1.8 Application of spirocarbocycles in total synthesis of hinesol

As part of the efforts directed toward developing a general method for [3+2] cycloaddition, Ishar and co-worker reported the reaction of formyl chromones **14** with allenolate **3a** at catalyst loading of 10 mol% of triphenylphosphine.¹⁹ In this work, the corresponding cyclized products **15** were obtained in yields of 72 - 74% (Scheme 1.9). The formyl group played a significant role in directing the regioselectivity and it was eliminated after the annulation step.

¹⁸ Du, Y.; Lu, X. *J. Org. Chem.* **2003**, 68, 6463.

¹⁹ Kumar, K.; Kapoor, R.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, 2, 2023.

Scheme 1.9 [3+2]-cycloaddition with *endo*-cyclic double bond

In 2008, Ruano and Martin studied the reaction with chiral *endo*-cyclic double bonds to investigate the stereochemical outcomes of the product.²⁰ The reactions were performed using enantiopure 5-ethoxy-3-sulfinylfuranones **17a** and **17b** with allenoate **3a** in the presence of triphenylphosphine to obtain bicyclic lactones **18a** and **18b** respectively. The products **18a** and **18b** were isolated as single regio and stereoisomer with yields up to 96%. The relative stereochemical outcome is rationalized by the approach of the zwitterionic intermediate *anti* to the 5-ethoxy substituents at C-5 of furanones (**17a** or **17b**; scheme 1.10). Similarly, the reaction between γ -substituted allenoate **16a** with **17a** and **17b** resulted in optically pure products **19a** and **19b** respectively with four stereogenic center in moderate yields with excellent *endo/exo* selectivities (>32:1) (Scheme 1.10). The high stereo and regio chemical outcome of the reaction of **17a/17b** with **3a** was reasoned to be consistent with the sulfinyl group at C-3 position of **17**.

²⁰ Ruano, J. L. G.; Núñez, Jr., A.; Martín, M. R.; Fraile, A. *J. Org. Chem.* **2008**, 73, 9366.

Scheme 1.10 Chiral *endo*-cyclic olefins in [3+2]-cycloaddition reaction

More recently, Krische and co-worker have demonstrated the [3+2]-cycloaddition reaction of allenoate **3a** with the optically pure *endo*-cyclic olefin **17c** at room temperature (Scheme 1.11). This led to the *cis* fused cyclopenta[*c*]pyran **20** in yields of 63% with complete regio and stereoselectivity.²¹ This method was shown to be applicable to the synthesis of the natural product (+)-geniposide (Scheme 1.11).

Scheme 1.11 Application of [3+2]-cycloaddition in total synthesis of geniposide

²¹ Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849.

1.2.2 Intramolecular Phosphine-Catalyzed Cycloaddition

In 2003, Krische and co-worker reported the first intramolecular [3+2]-cycloaddition of 1, 7-enyne as shown in scheme 1.12.²² In these reactions, the desired diquinanes **22** were obtained in 71-86% yields with excellent diastereoselectivities (>95:5 de) (Scheme 1.12).

Scheme 1.12 Intramolecular [3+2]-cycloaddition using 1,7-Enynes

Krische *et al.* further utilized the intramolecular reaction in the total synthesis of ($\pm$) hirsutene.²³ The enyne **E-23** was treated with 10 mol% of tributylphosphine to obtain **24** in 88% yield as a single diastereomer, where the methyl group of quaternary carbon was placed on the concave face of diquinane ring system (Scheme 1.13; eq 1). Further modification of product **24** to hirsutene was achieved in six transformations. It is worth noting that, the reaction of (**Z**)-**23** in the identical reaction condition, afforded

²² Wang, J. C.; Ng, S. S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, 125, 3682.

²³ Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, 42, 5855.

epi-**24** which suggest the stereospecificity of this cycloaddition reaction (Scheme 1.13; eq 2).

Scheme 1.13 Application of intramolecular reaction in total synthesis of Hirsutene

Yet another intramolecular version of the reaction was reported by Kwon and co-workers in 2007.²⁴ In this work, the coumarin derivatives were synthesized by treating 2-styrenyl allenolate **25** with phosphine. Interestingly, the reaction pathways vary depending on the nature of electron withdrawing substituent on **25**. If the substituent is CO₂Et or SO₂Ph, the reaction proceeded smoothly in the presence of PBu₃ to obtain expected [3+2]-cyclized product **26** in good yields with excellent selectivities (Scheme 1.14). On the other hand, the reaction was found to be ineffective for the substrate **25** bearing NO₂ as an electron withdrawing group. However, using less nucleophilic triarylphosphines such as P(*p*-F-C₆H₄)₃, the reaction afforded nitronate **27** as the major product in 62% yield. The resulting **27** was subsequently utilized in 1, 3-dipolar cycloaddition with alkenes to furnish tetracyclic coumarin derivatives **28a** and **28b** in high yield (83-95%) and with good *exo-endo* selectivity (**28a/28b** = 7:1 to 11:1; Scheme 1.14).

²⁴ Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, 9, 3069.

Scheme 1.14 Synthesis of tri- and tetra-cyclic coumarins using [3+2]-cycloaddition

1.2.3 Enantioselective Cycloaddition of Electron Deficient Olefins Using Chiral Phosphines

Zhang and co-workers introduced structurally rigid *P*-chiral 2,5-di-isopropyl-7-phenyl-7-phospha-bicyclo[2.2.1] heptane **29** for enantioselective version of the reaction.²⁵ The reaction was carried out between allenoate **3a** and isobutylacrylate **4a** with catalyst **29** at 0 °C in toluene, afforded the product **5aα** in high yield with excellent enantioselectivity (83% yield and 93% ee) (Scheme 1.15; eq 1). While using diethyl maleate **7** and diethyl fumarate **8** as substrates, *cis* **9** (eq 2) and *trans* **10a** adducts (eq 3) were obtained as single diastereomers. However, a decrease in the product enantioselectivity (36% ee) was observed with diethyl fumarate.

²⁵ Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836.

Scheme 1.15 Enantioselective [3+2]-cycloaddition reaction using **29**

Fu and co-worker elegantly demonstrated the use of chiral binaphthyl derived phosphine **31** in [3+2] cycloaddition reaction.²⁶ Catalyst **31** was found to efficiently mediate the reaction between various β -substituted olefins **30** and allenoate **3a** to afford cyclopentenes with two contiguous chiral centers (Scheme 1.16; eq 1). It is worth mentioning that the regioselectivity of the product was reversed when β -

²⁶ Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, 45, 1426.

substituted olefins **30** were used. The γ -adduct **32 γ** was obtained as the major product instead of expected α -adduct **32 α** . In addition, the optically pure spirocyclic compound containing adjacent quaternary and tertiary chiral centers (**34**) was generated by the reaction of phosphine **31** with *exo*-cyclic dienone **33** (Scheme 1.16; eq 2).

Scheme 1.16 Enantioselective cycloaddition with β -substituted olefins using **31**

In 2007, Wallace *et al.* reported the use of commercially available chiral phosphine (4*S*,5*S*)-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxanone (*S,S*-DIOP) in promoting enantioselective cycloaddition reaction (Scheme 1.17).²⁷ In this work, the allenones **35** and *exo*-methylene enone **36** underwent cycloaddition in

²⁷ Wallace, D. J.; Sidda R. L.; Reamer, R. A. *J. Org. Chem.* **2007**, 72, 1051.

the presence of 10 mol% of DIOP **37** to produce spirocyclic compounds in good yields of 63-80% and high regio- (**38 α** :**38 γ** = 80:20 – 95:5) and enantioselectivities (46-76% ee; Scheme 1.17).

Scheme 1.17 Enantioselective cycloaddition with allenones using **37**

Miller and Cowen introduced the multifunctional phosphine that contain α -amino acid derivative to catalyze [3+2]-annulation reactions (Scheme 1.18).²⁸ In this work, *exo*-cyclic enone **12b** and allenic ester **3c** were reacted in the presence of diphenylphosphinylalanine derived phosphine **38**, affording product **13ba** in high yield (95%) and enantioselectivity (84%; Scheme 1.18; eq 1). More interestingly, using **38** as a catalyst, the process of deracemization of γ -substituted α -allenoate **16b** was observed upon cycloaddition with enones **30**, which led to the *anti-anti* configured cycloadduct **39a** in excellent yields and selectivities (Scheme 1.18; eq 2). However, the reaction using γ -substituted racemic allenoate **16b** require a stoichiometric amount of chiral phosphine **38** to achieve high product yield. The stereochemical outcome was rationalized in the transition state where the

²⁸ Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, 129, 10988.

dipolarophile approaches the zwitterionic intermediate from the bottom face, opposite to the phenyl substituent on catalyst **38** (Scheme 1.18).

Scheme 1.18 Enantioselective [3+2]-cycloaddition reaction using **38**

Another successful chiral phosphine derived from an α -amino acid was reported by Zhao and co-workers.²⁹ Reaction performed between allenoate **3a** and dual activated arylidenemalononitrile **40** in the presence of 10 mol% of aminophosphines **41**, afforded cyclized product **42** in excellent yield and enantioselectivity (Scheme 1.19; eq 1). Notably, this reaction also worked well with γ -substituted racemic allenoate **16a** with 10 mol% of **41** (Scheme 1.19; eq 2). The authors proposed the transition state similar to that of Miller's to account for the stereochemical outcome of this reaction. In the transition state, dipolarophile

²⁹ Xiao, H.; Chai, Z.; Zheng, C.-W.; Yang, Y.-Q.; Liu, W.; Zhang, J.-K.; Zhao, G. *Angew. Chem. Int. Ed.* **2010**, 49, 4467.

approaches the zwitterionic intermediate preferentially from the *Si* face with respect to the phenyl substituent of the catalyst **41** (Scheme 1.19).

Scheme 1.19 Enantioselective [3+2]-cycloaddition reaction using **41**

A chiral phosphine derived from dipeptides was recently disclosed to facilitate enantioselective [3+2]-cycloaddition reactions.³⁰ For example, O-TBDPS-D-Thr-L-*tert*-Leu derived phosphine **44** was used to catalyze the reaction between allenoate **3b** and 2-substituted acrylate **43**, yielding **45a** in high yield with excellent regio and enantioselectivities (Scheme 1.20). The authors proposed a transition state which involved hydrogen bonding interaction between the dipeptidic backbone of the

³⁰ Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, 133, 1726.

catalyst with acrylate. Subsequently, the phosphonium enolate intermediate, generated from the nucleophilic attack of phosphine at the allene, approaches the acrylate from its *Re* face of acrylate to obtain the major stereoisomer (Scheme 1.20).

Scheme 1.20 Enantioselective cycloaddition reaction using **44**

Marinetti and co-workers introduced a chiral phosphine 2-phospha[3]ferrocenophane (*S, S*-FerroPHANE) for catalyzing the cycloaddition reactions.³¹ For example, the reaction was performed between allenolate **3a** and electron-deficient olefins **30** in the presence of 10 mol% of catalyst **46**, it afforded the product **32γ** in excellent yield and enantioselectivity (Scheme 1.21 eq 1). In addition, the catalyst

³¹ Voituriez, A.; Panossian, A.; Fleury-Bre'geot, N.; Retailleau, P.; Marinetti, A. *J. Am. Chem. Soc.* **2008**, *130*, 14030.

also found to work with *exo*-cyclic olefin **47** to afford spirocyclic compound **48 γ** in high yield and selectivity (85% yield; 80% ee; Scheme 1.21, eq 2).

$\text{R}^1 = \text{CO}_2\text{Et}, \text{Ph}, 2\text{-furyl}, 1\text{-naphth}, \text{etc.},$
 $\text{R}^2 = \text{OEt}, \text{Ph}, 4\text{-NO}_2\text{C}_6\text{H}_4$

63-87% yield

87-96% ee

$\gamma:\alpha = 8:1-20:1$

85% yield
80% ee

$\text{R}^1 = \text{Ph}, 1\text{-naphthyl}, 4\text{-NO}_2\text{C}_6\text{H}_4, 3\text{-quinolyl}$
 $\text{R}^2 = \text{Ph}, 4\text{-OMeC}_6\text{H}_4, 2\text{-furyl}$

68-87% yield

85-90% ee

$\text{Ar} = 1\text{-naphthyl},$
 $2\text{-furyl}, 4\text{-PhC}_6\text{H}_4$

56-80% yield
90-92% ee
 $\gamma:\alpha = 77:23 \rightarrow 92:8$

Scheme 1.21 (*S,S*)-FerroPHANE **46** catalyzed enantioselective cycloaddition

Marinetti and co-workers further extended the scope of the catalyst **46** by performing cycloaddition of allenic phosphonates **49** with enones **30** to obtain cyclopentene

product (**50γ**) in high yields and enantioselectivities after prolonged heating at 120 °C (Scheme 1.21, eq 3). Finally, catalyst **46** was found to catalyze the reaction of allenoate **49** with 3-alkylideneindolines-2-ones **51** to generate spirooxindolic cyclopentenones **52γ** in high yields and regio and enantioselectivities (Scheme 1.21, eq 4).

1.2.4 Mechanistic Investigation of Phosphine Catalyzed [3+2] Cycloaddition

In 2007, Yu and co-workers reported the mechanistic investigation of the phosphine catalyzed cycloaddition reaction.³² It was found that, although the reported reaction condition is anhydrous, trace amount of water in the system played a critical role in facilitating the process of intramolecular [1,2]-proton shift. To obtain more information, the deuterium labeled allenoate **3'** and olefin **8'** were reacted with triphenylphosphine in anhydrous benzene and products **5D** and **5H** were produced in a ratio of 75:25. Formation of product **5H** shows that the [1,2]-proton transfer step in the proposed mechanism (Scheme 1.22) is not a simple intramolecular process and the product **5H** could form due to the presence of a trace amount of water in the reaction system. Furthermore, when the reaction was carried out with one equivalent of water, the ratio of **5H** was remarkably increased to 88% (Scheme 1.22).

(i) no additives; **5D:5H** = 75:25

(ii) add 1 equiv. H₂O; **5D:5H** = 12:88

Scheme 1.22 Mechanistic investigation *via* isotope labeling experiments

³² For mechanistic investigation of [3+2]-cycloaddition reactions, see: (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (b) Liang, Y.; Liu, S.; Yu, Z.-X. *Synlett*, **2009**, 0905.

Following this work, Yu and co-workers analyzed these results using DFT calculations [B3LYP/6-31+G(d)] of the reaction of trimethylphosphine catalyzed cycloaddition between allenolate and acrylate.³² The calculated free energies in benzene solution (ΔG ; kcal/mol) for relevant transition state and intermediate were considered. The result revealed that the free energy activation for generally accepted intramolecular [1,2]-proton transfer step was very high (39.6 kcal/mol) for this process; thus, the author proposed an alternative water assisted proton transfer mechanism where the free energy of activation was lowered to 7.4 kcal/mol.³²

1.2.5 [3+2]-Cycloaddition Using Modified Allylic Phosphorus Ylides

In 2003, Lu and co-workers demonstrated the first phosphine catalyzed [3+2]-annulation reaction using allylic derivatives instead of allenolate or 2-butyne.³³ In this work, the reaction between allylic derivatives **53** and dipolarophile **54** in the presence of PPh_3 10 mol% and K_2CO_3 (1.5 equiv.) in toluene at 90 °C, yielded [3+2]-cyclized product **55** in high yield and selectivity (Scheme 1.23). The mechanism was thought to involve a step where by the phosphine trigger the reaction through phosphonium salt 'A' formation. The salt was deprotonated with K_2CO_3 and the resulting phosphonium ylide **B** underwent conjugate addition with olefin **54**. Upon intramolecular cyclization and elimination of phosphine, product **55** was formed to complete the catalytic cycle. It was also found that the reaction using *tert*-butyl carbonate derivative (**53**, X= OBoc) proceeded smoothly without having additional base. In this case, the *in-situ* liberated *tert*-butoxide anion was acting as a base.

³³ (a) Du, Y.; Lu, X.; Zhang, C.; *Angew. Chem. Int. Ed.* **2003**, 42, 1035. (b) Feng, J.; Lu, X.; Kong, A.; Han, X. *Tetrahedron*, **2007**, 63, 6035.

Scheme 1.23 Phosphine catalyzed [3+2]-cycloaddition using allylic derivatives

Lu and co-workers further extended this methodology to synthesize bridged carbocycle *via* the [3+6]-annulation approach.³⁴ The reaction was carried out between allylic compound **53** and tropone **56** in the presence of PPh₃ 10 mol% and K₂CO₃ (1.5 equiv.) in toluene, afforded the [3+6]-adduct **57** in good yield (Scheme 1.24).

Scheme 1.24 Phosphine catalyzed [3+6]-cycloaddition using tropones

Zhou and co-workers first reported the trapping of modified allylic phosphonium intermediate with olefins *via* an intramolecular fashion.³⁵ In this work, allylic carbonate **58** readily underwent intramolecular [3+2] annulation using 10

³⁴ (a) Du, Y.; Feng, J.; Lu, X. *Org. Lett.* **2005**, 7, 1987. (b) Zheng, S.; Lu, X. *Org. Lett.* **2009**, 11, 3978.

³⁵ Wang, Q. G.; Zhu, S.-F.; Ye, L.-W.; Zhou, C.-Y.; Sun, X.-L.; Tang, Y.; Zhou, Q.-L. *Adv. Synth. Catal.* **2010**, 352, 1914.

mol% of chiral phosphine spirobiindane **59** with 20 mol% of $\text{Ti}(i\text{OPr})_4$ to afford benzobicyclo [4.3.0] compounds **60** in excellent yields along with trace amounts of isomerized product **61** (Scheme 1.25). It is worth noting that significant amount of isomerized product **61** was observed when the reaction was performed in the absence of $\text{Ti}(i\text{OPr})_4$ (**60**:**61** = 80:20).

Scheme 1.25 Intramolecular asymmetric cycloaddition using **59**

More recently, Barbas research group demonstrated the intermolecular asymmetric version of the [3+2]-cycloaddition reaction using a commercially available chiral phosphine. In this work, allylic carbonates **63** and methyleneindolinones **62** underwent [3+2]-cycloaddition to produce spirooxindolines **65** in the presence of chiral phosphine (+)-Ph-BPE in excellent yield and selectivity (Scheme 1.26, eq 1).³⁶ It is worthy to mention that the role of the second phosphorus center in **64** had a major impact on the enantioselectivity of the product. Replacing the ester function with a phenyl group resulted in a drastic decrease in the enantioselectivity of product **67** (Scheme 1.26, eq 2).

³⁶ Tan, B.; Candeias, N. R.; Barbas, III, C.-F. *J. Am. Chem. Soc.* **2011**, *133*, 4672.

Scheme 1.26 Intermolecular asymmetric cycloaddition using **64**

1.2.6 Phosphine-Catalyzed [4+2]-Cycloadditions with Olefins

Kwon and co-workers reported the significant variation of [3+2] cycloaddition reaction by utilizing α -methyl substituted allenoates **68** instead of simple α -allenoate.³⁷ The reaction proceeded *via* a phosphine catalyzed [4+2]-annulation pathway to afford functionalized cyclohexene derivatives (Scheme 1.27).

³⁷ Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632.

proposed mechanism:

Scheme 1.27 Phosphine catalyzed [4+2]-cycloaddition using **68**

Further examination revealed that the regioselectivity of the reaction depends on the nucleophilicity of the phosphine. Using a more nucleophilic hexamethylphosphorus triamide (HMPA) the zwitterionic intermediate **68.1 γ** added to the dipolarophile **40**, resulted **69** in excellent yields (86 – 98%; Scheme 1.27). In contrast, less nucleophilic triarylphosphines such as P(4-FC₆H₄) furnished a regioisomeric adduct **70** in excellent yield (80 – 93%; Scheme 1.27).

1.3 Phosphine Catalyzed Cycloadditions with Imines

After a successful examination of various electron deficient olefins, Lu and co-workers extended the reaction to other electrophiles such as imines.³⁸ It was found that, *N*-protected aldimines **71** underwent cycloaddition reaction with allenates **3d** in the presence of triphenylphosphine to afford pyrrolidine **72** in good to excellent yields (26–97%; Scheme 1.28; eq 1). In the case of aliphatic imine, only trace amount of product was detected due to its low reactivity. Interestingly, 2-butyne **11** was also found to react with imine **71** in the presence of tributylphosphine to afford pyrrolidine **72** in good yield (Scheme 1.28, eq 2).

Scheme 1.28 Phosphine catalyzed [3+2]-cycloaddition using imines

A similar approach to synthesize pyrrolidine derivatives using γ -substituted allenates **16** was subsequently reported by Kwon and co-workers. It was found that the reaction of allenates **16** and imine **71** in the presence of tributylphosphine

³⁸ (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, 38, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, 63, 5031.

afforded 2,5-*cis*-disubstituted-3-pyrrolines **74** as a major product along with a trace amount of the corresponding *trans* adduct **74'** (Scheme 1.29).³⁹

Scheme 1.29 Phosphine catalyzed [3+2]-cycloaddition using imines

1.3.1 Enantioselective Cycloadditions with Imine

The enantioselective [3+2]-cycloaddition of allenolate with imine was first reported by Marinetti and co-workers by using commercially available chiral phosphine.⁴⁰ The authors reported that the chiral phosphine (*R, R*)-Et-FerroTANE was able to catalyze the reaction of imine **71** with allenolate **3** to afford pyrrolidine **72** in moderate enantioselectivity (up to 60% ee; Scheme 1.30; eq 1). A year later, using binaphthylphosphine **31** as a catalyst, the same group reported an improved enantioselectivity for the reaction of **3e** and **71** (up to 80% ee; Scheme 1.30; eq 2).⁴¹

³⁹ Zhu, X. -F.; Henry, C. E.; Kwon, O. *Tetrahedron* **2005**, *61*, 6276.

⁴⁰ Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141.

⁴¹ Fleury-Bregeot, N.; Jean, L.; Retaillieu, P.; Marinetti, A. *Tetrahedron*, **2007**, *63*, 11920.

Scheme 1.30 Enantioselective cycloaddition with imines

Until now, the best chiral phosphine known for catalyzing the enantioselective [3+2]-cycloaddition of imine was disclosed by Jacobsen and co-worker.⁴² The bifunctional alanine-derived thiourea phosphine **75** was found to catalyze the reaction of allenolate **3a** with *N*-diphenylphosphinoyl imine (*N*-Dpp) **71** to afford pyrrolidine **72** in excellent yield and enantioselectivity (Scheme 1.31). Although *N*-Dpp imine **71** exhibited greater enantioselectivity than the corresponding *N*-tosyl imine (*N*-Ts), the reaction rate and yield with *N*-Dpp imine was significantly diminished due to its lower electrophilicity compared with *N*-tosylimines. This problem was addressed by adding a substoichiometric amount of polar protic additives such as triethylamine and

⁴² Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660.

H₂O. It was proposed in the transition state that the catalyst formed specific hydrogen bonds with imine prior to the zwitterionic moiety approaching the imine from its *Re* face in an intramolecular fashion (Scheme 1.31).

Scheme 1.31 Enantioselective cycloaddition with imine using **75**

1.3.2 Phosphine-Catalyzed [4+2]-Cycloadditions with Imines

In 2003, Kwon and co-workers reported the synthesis of functionalized tetrahydropyridines *via* phosphine catalyzed [4+2]-cycloaddition of α -substituted allenoate and imine.⁴³ In this work, α -alkyl substituted allenoate **68** reacted with imine **71** *via* a [4+2] annulation pathway to furnish tetrahydropyridine **76** in excellent yield and diastereoselectivity (Scheme 1.32). The authors proposed that the tributylphosphine first reacted with **68** to form a zwitterionic intermediate **68.1**, which was resonance stabilized with **68.2**. The α -substitution enabled the intermediate **68.1** to react with imine to obtain **68.3**. Two consecutive proton transfer steps shuffle the proton from β' -carbon to β carbon leading to the formation of intermediate **68.4**. Ultimately, intermediate **68.4** underwent a 6-*endo* cyclization, followed by expulsion

⁴³ Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, 125, 4716.

of phosphine to afford the desired product **76** (Scheme 1.32). Kwon *et al.* successfully applied this methodology to the formal syntheses of the natural products (±)-alstonerine and (±)-macroline.⁴⁴

proposed mechanism:

Scheme 1.32 Phosphine catalyzed [4+2] annulation with imines

The enantioselective version of this [4+2]-cycloaddition with imine was first published by Fu and co-workers.⁴⁵ In the report, the chiral binaphthyl derived phosphine **31** catalyzed the reaction of allenoate **68** and imine **71** to provide **76a** in excellent yield and enantioselectivity (Scheme 1.33).

⁴⁴ Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, 7, 4289.

⁴⁵ Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, 127, 12234.

Scheme 1.33 Enantioselective phosphine catalyzed [4+2] annulation with imines

1.4 Phosphine Catalyzed Cycloaddition with Aldehydes

As olefins and imines were extensively investigated as coupling partner, Kwon *et al.* also examined other electrophiles such as aldehydes in phosphine catalyzed cycloaddition of allenoates and ynoates.⁴⁶ When the reaction was carried out between allenoate **3f** and aldehyde **77**, and in the presence of trimethylphosphine none of the expected [3+2]-cyclized dihydrofuran adduct **78b** was formed (Scheme 1.34). In contrast, allenoate **3f** cyclized with two equivalents of aldehyde **77** via a [2+2+2] process to afford dioxanylidene **78a** in excellent yield and selectivity (Scheme 1.34). The synthetic utility of dioxanylidene **78a** was demonstrated in the synthesis of δ -hydroxy- β -ketoesters **79** (Scheme 1.34).

⁴⁶ Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, 7, 1387.

Scheme 1.34 Phosphine catalyzed [2+2+2] annulation with aldehyde

In the proposed mechanism, trimethylphosphine reacted with allenate **3f** to form the zwitterionic intermediate **78.1γ** and **78.1α**. Addition of **78.1γ** to an aldehyde should give **78.2**, which should subsequently react with a second equivalent of aldehyde to afford **78.3**. Eventually, 6-*exo*-cyclization and trimethylphosphine dissociation provided the final product dioxanylidene **78a** (Scheme 1.34).

Kwon's research group described a new reaction pathway by tuning the steric bulk of phosphine to synthesize 6-substituted-2-pyrones **80**.⁴⁷ The reaction was performed between allenolate **3** and aldehyde **77** in the presence of a bulky tricyclohexylphosphine to afford 6-substituted pyrones **80** in excellent yield (Scheme 1.35). It was found that the sterically demanding tricyclohexylphosphine shifted the equilibrium from the commonly accepted more stable *Z*-isomers **78.1** to less stable *E*-isomers **80.1** in order to overcome the intramolecular electrostatic interactions.

Scheme 1.35 Phosphine catalyzed [4+2] annulation with aldehyde

⁴⁷ a) Zhu, X. -F.; Schaffner, A. -P.; Li, R. C; Kwon, O. *Org. Lett.* **2005**, 7, 2977. b) Creech, G. S.; Kwon, O. *Org. Lett.* **2008**, 10, 429.

Mechanistically, if the α -carbon (**80.1 α**) was added to an aldehyde, this *E*- or *Z*-geometrical information would be lost in the following steps. Whereas, in this reaction addition of γ -carbon (**80.1 γ**) to an aldehyde would produce the intermediate **80.2** with retention of geometry. Subsequent intramolecular nucleophilic addition of alkoxide to the ester functionality would give lactone intermediate **80.3**, subsequent elimination of phosphine would furnish 6-substituted-2-pyrone **80** (Scheme 1.35).

1.5 Proposed work

The work of this thesis has been directed toward the development of phosphine catalyzed cycloaddition that enables the delivery of regio-, diastereo- and enantioselective five membered carbo- and heterocycles.

It is envisioned that the reactivity of the aryl allenones could be tuned by incorporating a trimethylsilyl substituent at the α -position, which due to its steric bulk should prevent self dimerization of aryl allenones. This change should provide a direct and efficient synthetic route to cyclopentenones (eq 1).

Next it is reasoned that the extension of this approach by using a phosphine catalyzed one-pot isomerization of 3-alkynoates to allenones and [3+2]-cycloaddition with electron deficient olefins could also be developed for synthesis of cyclopentenones (eq 2).

Replacing the electron deficient olefin with an imine functional group, pyrrolidine products can be prepared *via* the phosphine catalyzed [3+2]-cycloaddition of 3-alkynoates. It is also surmised that such compounds can be further extended to synthesis of natural product allosecurinine (eq 3).

Finally, it is envisioned that a synthetic route to spiro[furan-oxindolines] can be developed by using phosphine catalyzed [3+2]-cycloaddition of allenoates and oxindolinones (eq 4).

CHAPTER 2

Silicon as a Directing group in the Phosphine-Catalyzed [3+2]-Cycloaddition of Aryl Allenones with Electron-Deficient Olefins

Chapter 2 Silicon as a Directing Group in the Phosphine-Catalyzed

[3+2]-Cycloaddition of Aryl Allenones with Electron-Deficient Olefins

2.1 Introduction

Functionalized five-membered ring is featured widely in many natural products and drug molecules.⁴⁸ Accordingly, much effort has been directed towards the development of new synthetic methods for the construction of five-member rings.⁴⁹ Among the methods available, Lu's phosphine catalyzed synthesis of functionalized cyclopentenones *via* the [3+2]-cycloaddition between allenones and electron deficient olefins has been shown to be one of the most useful methods.¹⁴

While allenones have been widely used in the [3+2]-cycloaddition, the reaction of allenones was first reported by Wallace and co-workers in 2007.²⁷ It was found that the reaction of allenyl methyl ketone⁵⁰ **35** underwent a [3+2]-cycloaddition reaction with *exo*-cyclic enones⁵¹ **12** in the presence of tributylphosphine. The reaction afforded spirocyclic compound **38α** in good yield and selectivity. A trace amount of a regioisomeric product **38γ** was also formed (Scheme 2.1). It was also found that, the

⁴⁸ (a) Hartley, R. C.; Caldwell, S. T. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 477. (b) Zhao, G.; Wu, H.; Zhang, H. *Tetrahedron* **2007**, 63, 6454. (c) Sannigrahi, M. *Tetrahedron* **1999**, 55, 9007 and references cited therein.

⁴⁹ (a) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, 89, 1467. (b) Trost, B. M. *Angew. Chem. Int. Ed.* **1986**, 25, 1. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, 96, 49 and reference cited therein. (d) Hao, L.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, 133, 7149. (e) Cooks, J. M.; Scott, G.; Ornum, V. *Tetrahedron Lett.* **1997**, 38, 3657. (f) Trost, B. M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* **1989**, 111, 7487. (g) Danheiser, R. L.; Carini, D. J.; Flink, D. M.; Basak, A. *Tetrahedron* **1983**, 39, 935. (h) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, 110, 3300. (i) Tsuiji, J.; Shimizu, I.; Ohashi, Y. *Tetrahedron Lett.* **1984**, 25, 5183. (j) Tsuiji, J.; Shimizu, I.; Ohashi, Y. *Tetrahedron Lett.* **1985**, 26, 3825.

⁵⁰ Allenyl methyl ketone was prepared according to Constantieux, T.; Buono, G. *Organic Synthesis*; Wiley: New York, Coll. Vol. 10, p 595; Vol. 78, p 135.

⁵¹ Gras, J.-L. *Tetrahedron Lett.* **1978**, 24, 2111.

reaction with commercially available chiral phosphine DIOP, provided the cyclized product **38 α** in good yield and moderate enantioselectivity (Scheme 2.1).

Scheme 2.1 Phosphine catalyzed cycloaddition with aliphatic allenones

Like allenates, the reaction of allenones with the β -substituted enone **12k** provides opposite regioselective product **13 γ k** as major product together with a trace amount of the α -adduct **13 α k** (Scheme 2.2).

Scheme 2.2 Phosphine catalyzed cycloaddition of aliphatic allenones with β -substituted enones

Interestingly, the reaction of allenones **35** with other electron deficient olefins such as **4**, **12l** and **12m** failed to afford the desired respective product (Scheme 2.3; eq 1). However, the reaction of allenone **35** with other electrophile such as *N*-tosyl

benzalimine **71** in the presence of PPh_3 or DIOP, afforded pyrrolidine **72** in moderate yield and selectivity (Scheme 2.3; eq 2). In addition, the reaction of allenone **35** with 4-nitrobenzaldehyde afforded a diastereomeric mixture of the [2+2+2] cyclized product dioxanylidenes (**78c** and **78d**) in moderate yields (Scheme 2.3, eq 3).

Scheme 2.3 Cycloaddition of aliphatic allenones with electron deficient double bonds

Although this method has been shown to work with different aliphatic allenones, one of the major limitations of this method is that higher Michael acceptors property such as aromatic allenones afforded the self dimerized [4+2] Diels-Alder product **82** rather than the desired cross cyclized adduct (Scheme 2.4). Dimerization was found to

be the general reaction for a range of aromatic allenones, affording dimerized pyran in moderate yields with typical *E/Z* ratio of 85:15 (Scheme 2.4).

Scheme 2.4 Phosphine catalyzed dimerization of aromatic allenones

The proposed mechanism for the dimerization reaction is outlined in Scheme 2.4.

In the first step where the phosphine reacts with aryl allenones **35b** to form the resonance stabilized zwitterionic intermediates **82.1α** and **82.1γ**. (Scheme 2.4).

Scheme 2.4 Proposed mechanism for dimerization of aryl allenones

Then, **82.1γ** undergoes conjugate addition with a second equivalent of aryl allenone to obtain **82.2**, followed by cyclization and regeneration of triphenylphosphine afforded the [4+2]-dimerized product **82** (Scheme 2.4).

We envisage that the use of trimethylsilyl group at the α -position of aryl allenones may suppress the formation of the dimerized [4+2] adduct due to the steric bulk of trimethylsilyl group thereby producing the desired cross [3+2] cycloaddition adduct. In this chapter, we describe an efficient synthetic route for the synthesis of functionalized cyclopentenes *via* a [3+2]-annulation reaction between α -trimethylsilyl substituted aryl allenones and electron deficient olefins in the presence of triphenylphosphine.⁵²

2.2 Results and Discussion

To examine our hypothesis, 1-phenyl-2-(trimethylsilyl) buta-2, 3-dien-1-one **83a** was treated with *trans*-chalcone **30a** in the presence of 20 mol% of triphenylphosphine (Scheme 2.5). The reaction proceeded smoothly at room temperature to afford the [3+2] cyclized product **84a** in high yield of 84% (Table 1, entry 1).

Scheme 2.5 [3+2]-cycloaddition with aryl allenones

⁵² M. Sampath and T.-P. Loh, *Chem. Commun.*, **2009**, 1568–1570.

Only trace amount (5% yields) of the [4+2] Diels-alder product was isolated (For detailed characterization of [4+2]-adduct, please see ref. 27). The regioselectivity of the [3+2] adduct **84a** was confirmed by X-ray crystal structure determination (Figure 2.1). It is worth noting that the trimethylsilyl group was not retained in the final product.

Figure 2.1 ORTEP drawing of **84a** with thermal ellipsoids at 50% probability levels⁵³

To define the scope of this reaction, we next turned our attention to the reaction of phenyl allenone **83a** with variety of electron deficient olefins **30** in the presence of 20 mol% of triphenylphosphine. In all cases, the cyclized products were obtained in moderate to good yields (Table 2.1; entries 1 - 8). Notably, the reaction of diethyl maleate and diethyl fumarate afforded the cyclized product in good yields with retention of geometry (Table 2.1; entries 4 and 5). The coupling partner included ethyl

⁵³ CCDC 708751 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4, 4, 4-trifluorocrotonoate provided an easy access to biologically important trifluoromethyl substituted cyclopentenoids in moderate yield (entry 7). In the case of β -unsubstituted olefin such as methyl acrylate **30f**, it provided two regioisomeric products (**84f γ** and **84f α**) in the ratio of 80:20 respectively. The cycloaddition reaction with methyl methacrylate **30h** provided product **84h** which contain a quaternary carbon center.

Table 2.1 Trimethylsilyl Directed [3+2] cycloaddition using phenyl allenone ^a

Entry	R ¹	R ²	R ³	Product (84γ) ^b	Yield (%) ^c
1	COC ₆ H ₅	H	C ₆ H ₅	84a	84
2	4-MeCOC ₆ H ₄	H	4-OEtC ₆ H ₄	84b	75
3	4-MeCOC ₆ H ₄	H	4-MeC ₆ H ₄	84c	78
4	H	COOEt	COOEt	84d	72
5	COOEt	H	COOEt	84e	82
6 ^{d,e}	COOMe	H	H	84f	80
7	CF ₃	H	COOEt	84g	63
8 ^e	CH ₃	COOMe	H	84h	52

^a See experimental section for a detailed experimental procedure and relative stereochemistry of the product (**84a**) was identified by X-ray analyses. ^b > 99 % of single isomer (γ) was observed by ¹H NMR analysis. ^c Isolated yield. About 5% of the self-dimerized products were obtained (Please see ref. 27 for characterization of dimerized adduct). ^d Two regioisomeric products (**84 γ** and **84 α**) were observed in the ratio of 80:20 respectively by ¹H-NMR analysis. ^e 10 mol% of enoate was used.

To further explore the synthetic value of this method, we extended this reaction to furan-2-yl allenones **83b**, a more versatile reactant since the furan ring could be readily and chemically manipulated (Table 2.2).⁵⁴

Table 2.2 Trimethylsilyl Directed [3+2] Cycloaddition using Furyl-2-allenone ^a

	83b	30		85γ	85γ
Entry	R ¹	R ²	R ³	Product (85γ)	Yield (%)
1	COC ₆ H ₅	H	C ₆ H ₅	85a	75
2	4-MeCOC ₆ H ₄	H	4-OEtC ₆ H ₄	85b	80
3	4-MeCOC ₆ H ₄	H	4-MeC ₆ H ₄	85c	78
4	H	COOEt	COOEt	85d	83
5	COOEt	H	COOEt	85e	80
6 ^{b,c}	COOMe	H	H	85f	83
7	CF ₃	H	COOEt	85g	72
8 ^c	CH ₃	COOMe	H	85h	55

^a See experimental section for detailed experimental procedure. ^b Two regioisomeric products (**85γ** and **85α**) were observed in the ratio of 5:1 respectively by ¹H-NMR analysis. ^c 10 mol% of enoate was used.

⁵⁴(a) Mukaiyama, T.; Tsuzuki, R.; Kato, J. *Chem. Lett.* **1985**, 837. (b) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, 62, 5497. (c) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, 101, 259. (d) Danishefsky, S.; Maring, C. *J. Am. Chem. Soc.* **1985**, 107, 163. (e) Woodward, R. W.; Ramalingam, K.; Nanjappan, P.; Calvin, D. M. *Tetrahedron* **1988**, 44, 5597.

Next, we focused on the catalytic asymmetric aspect of this method, we did that by screening various commercially available chiral phosphines such as (+)-BINAP (0% yield, 0% ee); (2*S*,3*R*)-CHIRAPHOS (82% yield, 22% ee); (*S,S*)-Et-DUPHOS (30% yield, 60% ee); (*R,R*)-Et-DUPHOS (40% yield, -70% ee); (+)-DIOP (62% yield, 10% ee) and (*S*)-(-)-2-[2-(Diphenylphosphino)-phenyl]-4-isopropyl-2-oxazoline (75% yield, 37% ee). Although (*R,R*)-Et-DUPHOS showed moderate enantioselectivity in this series, the yield was low. In order to increase the yield, different solvents were screened. Among them, dichloromethane was found to be the best solvent providing the desired product in 52% yield and retaining essentially the same ee of 71% (Table 2.3, entry 1). Increasing the amount of catalyst loading and slow addition of catalyst did not affect the yield nor ee of the product. Upon cooling the reaction to -10 °C and using CH₂Cl₂ as the solvent a decline in the rate and yield was observed. With these optimized conditions (20 mol% Et-DUPHOS, rt in CH₂Cl₂), the asymmetric cycloaddition reaction using phenyl allenone **83a** and furan allenone **83b** with a series of electron deficient olefins were carried out and the results are shown in Table 2.3. Interestingly, the reaction of furan allenone **83b** with *trans*-chalcone (Table 3.2, entry 2), afforded the product in high enantioselectivity (92% ee). Although dichloromethane showed good results, isomerization of maleate to fumarate was observed in the reaction conditions. For these cases, toluene was the solvent of choice (Table 2.3, entries 4 and 5). In the proposed transition state, the dipolarophile **30** approaches through the *Re* face of zwitterionic intermediate to form

the major enantiomers **84'**/**85'**, whereas the *Si* face approach of the electrophile is blocked by the ethyl substituents of the catalyst.

Table 2.3 Trimethylsilyl Directed [3+2] Cycloaddition using Et-Duphos^a

Entry	Allene	R ¹	R ²	Yield (%) ^[c]	Ee (%) ^[d]
1	83a	COC ₆ H ₅	C ₆ H ₅	52	71
2	83b	COC ₆ H ₅	C ₆ H ₅	54	92
3	83b	4-MeCOC ₆ H ₄	4-OEtC ₆ H ₄	56	70
4 ^{e,f}	83b	COOC ₂ H ₅	COOC ₂ H ₅	62	74
5 ^{e,f}	83a	COOC ₂ H ₅	COOC ₂ H ₅	48	80

^a See experimental section for detailed experimental procedure. ^b Absolute stereochemistry has not determined. ^c > 99% single isomer (γ) was observed and Isolated yield. ^d ee (%) was determined using chiral HPLC. ^e Diethyl maleate (*Z*) was used as enone. ^f Toluene was used as solvent, when the reaction using CH₂Cl₂ two regio isomeric products were observed.

The possible mechanism of this cycloaddition reaction was proposed on the basis of deuterium labelling experiments. In the controlled experiment of allenone **83a** and *trans*-chalcone **30a** in the presence stoichiometric amount of deuterium oxide, **84D γ** is formed as the major product (Scheme 2.6; eq 1). However, when the reaction was carried out using deuterium labelled allenone **83aD** in the presence of stoichiometric amount of water afforded **84H γ** with no deuterium shuffling (Scheme 2.6; eq 2). These results suggest the presence of water plays a significant role in these reactions.

Scheme 2.6 Deuterium labeling experiments

Previously, Yu's group found that the trace amount of water in the reaction system play a critical role in assisting the process of [1,2]-proton shift.³² On the basis of Yu's conclusion, a possible mechanism for the cycloaddition reaction of α -trimethylsilyl substituted allenones was proposed (Scheme 2.7).

In the proposed mechanism, resonance stabilized 1,3-dipolar intermediates **84.1 α** and **84.1 γ** were formed upon the addition of triphenylphosphine to allenone. The

steric bulk of trimethylsilyl group blocks the addition of α -carbon to the secondary electrophile **30**. Compound **84.1 γ** undergoes cycloaddition with **30** and the resulting intermediate **84.2** could react with water to obtain **84.3**. Finally, the free hydroxyl facilitates the E₂- elimination of phosphine and trimethylsilyl group to afford the final product **84 γ** (Scheme 2.7).

Scheme 2.7 Proposed mechanism for [3+2]-cycloaddition of aryl allenones

2.3 Conclusion

In this chapter, we have demonstrated that introduction of a trimethylsilyl group at the α -position of the allenones is key to producing cross cyclized [3+2] products. This is probably due to a steric effect of the trimethylsilyl group which suppresses the [4+2] self condensation reaction. Interestingly, the reaction of α -silyl substituted allenones with β -unsubstituted olefins like methyl acrylate and methyl methacrylate affords products in reversal of regioselectivity due to the steric bulk of silicon blocks

the α -position. In addition, complete γ adduct products were observed with β -substituted olefins. Preliminary studies on the asymmetric version using (*R,R*)-Et-Duphos, a commercially available chiral phosphine shows that [3+2] products can be synthesized in high enantioselectivities.

2.4 Experimental Section

2.4.1 General

Phosphine includes PPh_3 , BINAP, (*2S, 3R*)-CHIRAPHOS, (*S, S*)-Et-DUPHOS, (*R,R*)-Et-DUPHOS, (+)-DIOP, (*S*)-(-)-2-[2-Diphenylphosphino)phenyl]-4-isopropyl-2-oxazoline were purchased from commercial suppliers. All reactions were carried out under nitrogen atmosphere unless otherwise stated. Commercial solvents and reagents were used without further purification with following exceptions: Toluene and dichloromethane was distilled from calcium hydride prior to use. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible using basic solution of potassium permanganate or acidic solution of ceric molybdate as stain, followed by heating on a hot plate. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. All HPLC chromatograms were recorded using Agilent 1100 and 1200 series. Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR. Liquid samples were examined as film between NaCl salt plates. HRMS spectra were recorded on a Waters Q – Tof Premier Spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded using Bruker

Avance 300, 400 and 500MHz spectrometers. Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.26, singlet). Multiplicities were given as: s (singlet); brs (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dt (doublets of triplet); m (multiplet); ddt (doublet of doublet of triplet). Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.00, triplet).

2.4.2 Experimental procedure for the synthesis of aryl allenones

I.

(3-Bromoprop-1-ynyl)trimethylsilane (1.80 g, 10.0 mmol) was added over 30 minutes to a mixture of indium (1.20 g, 10.4 mmol) and benzaldehyde (1.00 g, 9.43 mmol) in water at 0 °C. After 18 h stirring, the reaction was quenched with 1 M HCl (30 mL) and extracted with ethyl acetate (100 mL). The organic phase was then back washed with water (100 mL), brine (50 mL) and dried over Na_2SO_4 (anhydrous). The allenic alcohol was purified through column chromatography (1% ethyl acetate in hexane) to

give a pale yellow oil of 1-phenyl-2-(trimethylsilyl)buta-2,3-dien-1-one (1.32 g, 80%).

II.

Allenic alcohol **87a** (1.00 g, 4.60 mmol) was added dropwise to the round bottom flask containing Dess-Martin periodinane (2.14 g, 5.0 mmol) in dichloromethane (20 mL) at 0 °C under N₂ atmosphere. After 5 h stirring, the reaction mixture was diluted with dichloromethane (100 mL), washed with 3M NaOH (50 mL) solution followed by water (100 mL) and brine (50 mL). The organic phase was dried over Na₂SO₄ (anhydrous) and concentrated to obtain the crude product. The aryl allenone was purified through column chromatography (1% ethylacetate in hexane) to give a colorless oil of 1-phenyl-2-(trimethylsilyl)buta-2,3-dien-1-one (0.89 g, 90%).

¹H-NMR (CDCl₃, 300MHz): δ 7.80(m, 2H), 7.54(m, 1H), 7.45(m, 2H), 4.7(s, 2H), 0.24(s, 9H). **¹³C-NMR (CDCl₃, 75MHz):** δ 218.4, 195.1, 139.4, 132.0, 128.2 (2C), 127.4 (2C), 100.6, 70.3, 0.1. **HRMS (ESI) *m/z*** calc. for C₁₃H₁₇OSi⁺ [M+H]⁺ 217.1049, found 217.1055. **FTIR (neat) ν** = 1915, 1645, 1263, 1247, 842 cm⁻¹.

The same procedure was followed to synthesize **1-(furan-2-yl)-2-(trimethylsilyl)buta-2, 3-dien-1-one 83b**.

¹H-NMR (CDCl₃, 300MHz): δ 7.58(brs, 1H), 7.27(m, 1H), 6.48(m, 1H), 4.82(s, 2H), 0.23(s, 9H). **¹³C-NMR (CDCl₃, 75MHz):** δ 215.7, 181.4, 152.0, 146.2 (2C), 118.9, 111.6, 100.6, 99.7, -1.2. **HRMS (ESI) *m/z* calc.** for C₁₁H₁₅O₂Si⁺ [M+H]⁺ 207.0841, found 207.0838. **FTIR (neat) ν** = 1917, 1636, 1467, 1290, 1236, 748 cm⁻¹.

2.4.3 General experimental procedure for the [3+2] cycloaddition reaction

To a stirred solution of aryl allenone (50 mg; 0.23 mmol) and enone or enolate (0.25 mmol) in toluene (1.5 mL) was added drop-wise addition a solution of phosphine (5.3 mg; 20 mol %) (pre dissolved in toluene) at 0° C under nitrogen. After 20 h stirring at room temperature under N₂ atmosphere, the reaction mixture was concentrated and purified using flash column chromatography (15-20% ethylacetate in Hexane).

This procedure is common for entries given in Tables 1 and 2, unless otherwise stated.

For Table 3, CH₂Cl₂ (1.5 mL) was used as solvent, unless otherwise stated.

(5-Phenylcyclopent-2-ene-1,2-diyl)bis(phenylmethanone) 84a:

R_f: 0.6 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p.

158-161 °C; **¹H – NMR (CDCl₃, 300MHz)** δ 7.80 (m, 2H), 7.70

(m, 2H), 7.45 (m, 1H), 7.40 (m, 3H), 7.25-7.35(m, 4H), 7.15 (m,

3H), 6.70 (m, 1H), 5.10 (m, 1H), 3.55 (dt, *J* = 8.8, 5.4 Hz, 1H),

3.25 (ddt, *J* = 19.0, 8.8, 2.3 Hz, 1H), 2.75 (m, 1H); **¹³C – NMR (CDCl₃, 75MHz)** δ

200.8, 192.8, 146.1, 144.6, 143.7, 138.2, 136.5, 133.0, 132.2, 129.1 (2C), 128.9 (2C),

128.8 (2C), 128.3 (2C), 128.2 (2C), 127.0, 126.9 (2C), 60.9, 48.3, 43.1; **FTIR (neat)**

ν = 3018, 1674, 1641, 1598, 1251, 756 cm⁻¹; **HRMS (ESI) *m/z* calc. for C₂₅H₂₁O₂⁺**

[M+H]⁺ 353.1542, found 353.1544; HPLC analysis: 71% ee; Daicel CHIRALPAK

AD (0.46 cm ϕ X 25 cm); solvent system: 2% isopropanol/hexane; retention time:

(minor) 15.0 min, (major) 22.4 min. **[α]_D²⁰ = + 130° (c 0.2, CH₂Cl₂).**

(5-(4-Ethoxyphenyl)-2-(furan-2-carbonyl)cyclopent-2-enyl)(p-tolyl)methanone**(85a):**

R_f: 0.6 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p.

162-165 °C; **¹H-NMR (CDCl₃, 300MHz)** δ 7.80 (m, 2H),

7.60 (m, 1H), 7.50 (m, 1H), 7.44 (m, 1H), 7.35-7.15 (m, 8H), 6.55 (dd, *J* = 3.53, 1.69

Hz, 1H), 5.10 (m, 1H), 3.55 (dt, *J* = 8.8, 5.3 Hz, 1H), 3.35 (ddt, *J* = 19.1, 8.9, 2.3 Hz,

1H), 2.88(m, 1H); **¹³C-NMR (CDCl₃, 100MHz)** δ 200.7, 177.7, 152.9, 146.1, 145.8,

144.7, 142.5, 136.4, 132.9, 128.9, 128.8 (2C), 128.3 (2C), 127.0, 126.9 (2C), 118.4,

112.1, 60.9, 53.4, 47.7, 43.4; **FTIR (neat) ν** = 3018, 1629, 1560, 1467, 1215, 748

cm⁻¹; **HRMS (ESI) *m/z* calc. for C₂₃H₁₉O₃⁺ [M+H]⁺ 343.1344, found 343.1436;**

HPLC analysis: 92% ee; Daicel Chiralpak AD-H (0.46 cm ϕ X 25 cm); solvent system: 2% isopropanol/hexane; retention time: (minor) 26.2 min (major) 44.2 min.

$[\alpha]_D^{20} = +55^\circ$ (c 0.2, CH_2Cl_2)

(2-Benzoyl-5-(4-ethoxyphenyl)cyclopent-2-enyl)(p-tolyl)methanone (84b):

R_f: 0.5 (Hexane:Ethyl acetate = 4:1). White solid; m.p. 144-149 °C; **¹H-NMR** (CDCl_3 , 300MHz) δ 7.90 (m, 2H), 7.70 (m, 2H), 7.55 (m, 1H), 7.45 (m, 2H), 7.15 (m, 4H), 6.85 (m, 2H), 6.75 (m, 1H), 5.11 (m, 1H), 4.05 (q, J = 6.9 Hz,

2H), 3.58 (dt, J = 8.8, 5.4 Hz, 1H), 3.3 (ddt, J = 18.9, 8.8, 2.2 Hz, 1H), 2.78 (m, 1H), 2.36 (s, 3H), 1.42 (t, J = 6.9 Hz, 3H); **¹³C-NMR** (CDCl_3 , 75MHz) δ 200.4, 192.8, 157.8, 146.0, 143.7, 143.7, 138.2, 136.7, 133.9, 132.1, 129.2 (2C), 129.1 (2C), 129.0 (2C), 128.1 (2C), 127.8 (2C), 114.7 (2C), 63.4, 61.0, 47.6, 43.2, 21.5, 14.8; **FTIR** (neat) ν = 3018, 1641, 1608, 1512, 1215, 756 cm^{-1} ; **HRMS** (ESI) m/z calc. for $\text{C}_{28}\text{H}_{27}\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 411.1960, found 411.1943.

(5-(4-Ethoxyphenyl)-2-(furan-2-carbonyl)cyclopent-2-enyl)(p-tolyl)methanone (85b):

R_f: 0.6 (Hexane: Ethyl acetate = 4:1). **¹H-NMR** (CDCl_3 , 300Mz) δ 7.70 (m, 2H), 7.58 (brs, 1H), 7.39 (brs, 1H), 7.25 (brs, 1H), 7.13 (m, 4H), 6.84 (m, 2H),

6.53 (dd, J = 3.3, 1.4 Hz, 1H), 5.05 (m, 1H), 4.00 (q, J = 6.9 Hz, 2H), 3.50 (dt, J = 8.8, 5.1 Hz, 1H), 3.30 (ddt, J = 19.2, 9.2, 1.9 Hz, 1H), 2.80 (m, 1H), 2.3(s, 3H), 1.40 (t, J = 6.9 Hz, 3H); **¹³C-NMR** (CDCl_3 , 75MHz) δ 200.3, 177.8, 157.8, 153.0, 146.0,

145.7, 143.7, 142.5, 136.9, 133.9, 129.1 (2C), 129.0 (2C), 127.8, 118.4, 114.7, 112.1, 63.4, 61.0, 47.0, 43.5, 21.6, 14.8; **FTIR (neat)** ν = 3016, 1672, 1631, 1608, 1512, 1467, 1246, 1217, 756 cm^{-1} ; **HRMS (ESI)** m/z calc. for $\text{C}_{26}\text{H}_{25}\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 401.1753, found 401.1751; **HPLC analysis**: 70% ee; Daicel Chiralpak AD-H (0.46 cm ϕ X 25 cm); solvent system: 15% isopropanol/hexane, retention time: (minor) 11.8 min. (major) 60.5 min. $[\alpha]_{\text{D}}^{20} = +62^\circ$ (c 0.2, CH_2Cl_2)

2-Benzoyl-5-p-tolylcyclopent-2-enyl-(p-tolyl)methanone (84c):

R_f: 0.4 (Hexane: Ethyl acetate = 4:1). Pale yellow solid; m.p. 162-165 °C; **¹H-NMR (CDCl₃, 300MHz)** δ 7.80 (m, 2H), 7.70 (m, 2H), 7.55 (m, 1H), 7.45 (m, 2H), 7.15 (brs, 6H), 6.75 (m, 1H), 5.13 (m, 1H), 3.55 (dt, J = 8.8, 5.24 Hz, 1H), 3.3 (ddt J = 19.0, 8.8, 2.3 Hz, 1H), 2.80 (m, 1H), 2.36 (s, 3H), 2.35 (s, 3H); **¹³C-NMR (CDCl₃, 100MHz)** δ 200.5, 192.9, 146.2, 143.9, 143.8, 143.7, 141.9, 138.3, 136.5, 134.0, 132.1, 129.5 (2C), 129.2 (2C), 129.1, 129.0 (2C), 128.2 (2C), 126.8 (2C), 60.8, 47.9, 43.3, 21.6, 21.0; **FTIR (neat)** ν = 3016, 1637, 1606, 1217, 756 cm^{-1} ; **HRMS (ESI)** m/z calc. for $\text{C}_{27}\text{H}_{25}\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 381.1855, found 381.1841.

2-(Furan-2-carbonyl)-5-p-tolylcyclopent-2-enyl-(p-tolyl)methanone (85c):

R_f: 0.4 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 160-163 °C; **¹H-NMR (CDCl₃, 300Hz)** δ 7.70 (m, 2H), 7.50 (m, 1H), 7.40 (m, 1H), 7.25 (m, 1H), 7.13 (m, 6H), 6.53 (dd, J = 3.3, 1.4 Hz, 1H), 5.01 (m, 1H), 3.50 (dt, J = 8.9, 5.0 Hz, 1H), 3.3 (ddt, J = 19.0, 8.9, 2.3 Hz, 1H), 2.83 (m, 1H), 2.35 (s, 3H), 2.33 (s, 3H); **¹³C-NMR (CDCl₃,**

100MHz) δ 200.3, 177.9, 153.0, 146.1, 145.9, 143.8, 142.6, 142.0, 136.5, 133.9, 129.5 (2C), 129.1 (2C), 129.0 (2C), 126.8 (2C), 118.5, 112.1, 60.9, 47.3, 43.6, 21.6, 21.0; **FTIR (neat)** ν = 3018, 2924, 1672, 1606, 1467, 1217, 756 cm^{-1} ; **HRMS (ESI)** m/z calc. for $\text{C}_{25}\text{H}_{23}\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 371.1647, found 371.1644.

Diethyl 3-benzoylcyclopent-3-ene-1,2-dicarboxylate (84d):

R_f: 0.6 (Hexane: Ethyl acetate = 4:1). **¹H-NMR** (CDCl_3 , **300MHz**) δ 7.70 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 6.62 (m, 1H), 4.27 (m, 1H), 4.18-4.08 (m, 4H), 3.53 (q, J =9.0 Hz, 1H), 3.33 (ddt, J = 18.4, 8.7, 2.3 Hz, 1H), 2.85 (ddd, J = 18.6, 8.7, 2.7 Hz, 1H), 1.29-1.20 (m, 6H); **¹³C-NMR** (CDCl_3 , **75MHz**) δ 196.0, 172.0, 171.6, 145.9, 141.6, 137.8, 132.4, 129.0 (2C), 128.3 (2C), 61.0, 52.3, 46.0, 36.1, 30.9, 14.1, 14.0; **FTIR (neat)** ν = 3018, 1734, 1635, 1629, 1215, 756 cm^{-1} ; **HRMS (ESI)** m/z calc. for $\text{C}_{18}\text{H}_{21}\text{O}_5^+$ $[\text{M}+\text{H}]^+$ 317.1389, found 317.1375; **HPLC analysis:** 80%ee [Daicel Chiralpak AD-H (0.46 cm ϕ X 25 cm), solvent system: 2% isopropanol/hexane, retention time: (major) 44.5 min. (minor) 61.0 min. $[\alpha]_{\text{D}}^{20}$ = - 64° (c 0.5, CH_2Cl_2).

Diethyl 3-(furan-2-carbonyl)cyclopent-3-ene-1,2-dicarboxylate (85d):

R_f: 0.5 (Hexane: Ethyl acetate = 4:1). **¹H-NMR** (CDCl_3 , **300MHz**) δ 7.59 (brs, 1H), 7.25 (m, 2H), 6.53 (dd, J = 3.5, 1.6 Hz, 1H), 4.24 (m, 1H), 4.18-4.08 (m, 4H), 3.50 (q, J = 9.0 Hz, 1H), 3.30 (ddt, J = 18.6, 8.7, 2.2 Hz, 1H), 2.90 (ddd, J = 18.6, 8.8, 2.9 Hz, 1H), 1.20 (m, 6H); **¹³C-NMR** (CDCl_3 , **75MHz**) δ 177.4,

171.9, 171.6, 152.6, 146.2, 145.8, 140.6, 118.5, 112.1, 61.0 (2C), 52.1, 45.7, 36.3, 14.1, 14.0; **FTIR (neat)** ν = 3018, 1734, 1635, 1467, 1215, 771 cm^{-1} ; **HRMS (ESI)** m/z calc. for $\text{C}_{16}\text{H}_{19}\text{O}_6^+$ $[\text{M}+\text{H}]^+$ 307.1182, found 307.1173; **HPLC analysis:** 74% ee [Daicel Chiralpak AD-H (0.46 cm ϕ X 25 cm), solvent system: 5% isopropanol/hexane, retention time: (major) 26.9 min. (minor) 43.1 min. $[\alpha]_{\text{D}}^{20}$ = - 48° (c 0.5, CH_2Cl_2).

Diethyl 3-benzoylcyclopent-3-ene-1,2-dicarboxylate (84e):

R_f: 0.6 (Hexane: Ethyl acetate = 4:1). **¹H-NMR** (CDCl_3 , 300MHz) δ 7.76 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 6.51 (m, 1H), 4.3 (m, 1H), 4.26-4.15 (m, 4H), 3.46 (m, 1H), 2.90 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). **¹³C-NMR** (CDCl_3 , 75MHz) δ 192.2, 173.3, 173.0, 144.3, 141.6, 137.9, 132.3, 128.9 (2C), 128.3 (2C), 61.3, 61.2, 53.8, 46.1, 36.7, 14.2, 14.1 **FTIR (neat)** ν = 3020, 2981, 1730, 1647, 1577, 1217, 754 cm^{-1} . **HRMS (ESI)** m/z calc. for $\text{C}_{18}\text{H}_{21}\text{O}_5^+$ $[\text{M}+\text{H}]^+$ 317.1389, found 317.1377.

Diethyl 3-(furan-2-carbonyl)cyclopent-3-ene-1,2-dicarboxylate (85e):

R_f: 0.6 (Hexane: Ethyl acetate = 4:1). **¹H-NMR** (CDCl_3 , 300MHz) δ 7.58 (m, 1H), 7.22 (m, 1H), 7.10 (m, 1H), 6.52 (dd, J = 3.5, 1.7 Hz, 1H), 4.32 (m, 1H), 4.25-4.10 (m, 4H), 3.37 (m, 1H), 3.05 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H); **¹³C-NMR** (CDCl_3 , 75MHz) δ 177.4, 173.2, 173.0, 152.6, 146.2, 144.0, 144.9, 118.4, 112.1, 61.2, 61.1, 53.7, 45.7, 37.0, 14.1, 14.0 **FTIR (neat)** ν =

3020, 2983, 1732, 1635, 1467, 1217, 754 cm^{-1} ; **HRMS (ESI)** m/z calc. for $\text{C}_{16}\text{H}_{19}\text{O}_6^+$ $[\text{M}+\text{H}]^+$ 307.1182, found 307.1194.

Methyl 2-benzoylcyclopent-2-enecarboxylate (84f):

R_f: 0.4 (Hexane: Ethyl acetate = 4:1). Pale yellow solid; m.p. 103-106 °C; **¹H-NMR (CDCl₃, 300MHz)** δ 7.70 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 6.64 (m, 1H), 4.04 (m, 1H), 3.70 (s, 3H), 2.80 (m, 1H), 2.60-2.70 (m, 1H), 2.35-2.45 (m, 1H), 2.10-2.20 (m, 1H); **¹³C-NMR (CDCl₃, 75MHz)** δ 192.9, 175.0, 147.7, 142.8, 138.2, 132.2, 129.0 (2C), 128.2 (2C), 52.1, 49.9, 33.5, 28.0; **FTIR (neat)** ν = 3018, 1732, 1643, 1435, 1215, 167 cm^{-1} ; **HRMS (ESI)** m/z calc. for $\text{C}_{14}\text{H}_{15}\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 231.1021, found 231.1017.

Methyl 2-(furan-2-carbonyl)cyclopent-2-enecarboxylate (85f):

R_f: 0.5 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 106-109 °C; **¹H-NMR (CDCl₃, 300MHz)** δ 7.59 (m, 1H), 7.23 (m, 2H), 6.53 (dd, J = 3.5, 1.7 Hz, 1H), 4.02 (m, 1H), 3.68 (s, 3H), 2.40-2.10 (m, 2H), 2.35 (m, 1H), 2.10 (m, 1H); **¹³C-NMR (CDCl₃, 100MHz)** δ 178.1, 174.9, 152.8, 147.1, 146.1, 141.7, 118.2, 112.0, 52.0, 49.9, 33.8, 27.6; **FTIR (neat)** ν = 3018, 1734, 1629, 1215, 756 cm^{-1} ; **HRMS (EI)** m/z calc. for $\text{C}_{12}\text{H}_{12}\text{O}_4^+$ $[\text{M}]^+$ 220.0730, found 220.0733.

Ethyl 3-benzoyl-2-(trifluoromethyl)cyclopent-3-enecarboxylate (84g):

R_f: 0.6 (Hexane: Ethyl acetate = 4:1). **¹H-NMR (CDCl₃, 400MHz)** δ 7.70 (m, 2H), 7.55 (m, 1H), 7.45 (m, 2H),

6.50 (m, 1H), 4.20 (m, 3H), 3.30 (m, 1H), 3.01 (ddt, $J = 19.0, 9.3, 2.5$ Hz, 1H), 2.80 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 100MHz) δ 191.8, 172.3, 143.2, 141.5, 137.6, 132.5 (2C), 128.9 (2C), 128.4 (2C), 61.6, 51.1 (q), 45.1 (q), 33.9 (q), 14.0; **FTIR** (neat) $\nu = 3018, 1730, 1647, 1215, 1114, 756\text{ cm}^{-1}$. **HRMS** (ESI) m/z calc. for $\text{C}_{16}\text{H}_{16}\text{O}_3\text{F}_3^+ [\text{M}+\text{H}]^+$ 313.1052, found 313.1040.

Ethyl 3-(furan-2-carbonyl)-2-(trifluoromethyl)cyclopent-3-enecarboxylate (85g):

R_f: 0.5 (Hexane: Ethyl acetate = 4:1). $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 7.60 (m, 1H), 7.25 (m, 1H), 7.15 (m, 1H), 6.55 (dd, $J = 3.5, 1.7$ Hz, 1H), 4.20 (m, 3H),

3.25 (m, 1H), 3.05 (ddt, $J = 19.0, 9.3, 2.5$ Hz, 1H), 2.85 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 75MHz) δ 176.9, 172.4, 152.6, 146.3, 143.1, 140.4, 118.6, 112.3 (2C), 61.5, 51.2 (q), 44.6 (q), 34.2 (q), 13.9; **FTIR** (neat) $\nu = 3016, 1633, 1618, 1215, 756\text{ cm}^{-1}$; **HRMS** (ESI) m/z calc. for $\text{C}_{14}\text{H}_{14}\text{O}_4\text{F}_3^+ [\text{M}+\text{H}]^+$ 303.0844, found 303.0862.

Methyl 2-benzoyl-1-methylcyclopent-2-enecarboxylate (84h):

R_f: 0.6 (Hexane: Ethyl acetate = 4:1). $^1\text{H-NMR}$ (CDCl_3 , 300MHz) δ 7.73 (m, 2H), 7.53 (m, 1H), 7.42 (m, 2H), 6.54 (t, $J = 2.5$ Hz, 1H), 3.68 (s, 3H), 2.66 (m, 2H), 2.3-2.4 (m, 1H),

1.9-2.0 (m, 1H), 1.53 (s, 3H); $^{13}\text{C-NMR}$ (CDCl_3 , 100MHz) δ 178.1, 176.5, 153.1, 146.5, 145.9, 145.9, 128.9 (2C), 128.7 (2C), 55.5, 52.1, 37.4, 32.3, 21.9; **FTIR** (neat) $\nu = 3018, 1728, 1622, 1469, 1214, 755\text{ cm}^{-1}$.

Methyl 2-(furan-2-carbonyl)-1-methylcyclopent-2-enecarboxylate (85h):

R_f: 0.6 (Hexane: Ethyl acetate = 4:1). **¹H-NMR** (CDCl₃, 400MHz) δ 7.58 (m, 1H), 7.18 (m, 2H), 6.52 (dd, *J* = 3.4, 1.6 Hz, 1H), 3.60 (s, 3H), 2.70 (m, 2H), 2.30 (m, 1H), 1.95 (m, 1H), 1.47 (s, 3H); **¹³C-NMR** (CDCl₃, 100MHz) δ 178.0, 176.5, 153.1, 146.5, 145.9 (2C), 118.0, 112.0, 55.5, 52.1, 37.3, 32.3, 21.9; **FTIR** (neat) ν = 3020, 1728, 1629, 1467, 1215, 754 cm⁻¹; **HRMS** (ESI) *m/z* calc. for C₁₃H₁₅O₄⁺ [M+1]⁺ 235.0970, found 235.0969.

CHAPTER 3

*Highly Selective One-Pot [3+2]-
Cycloaddition Reaction via
Isomerization of 3-Alkynoates to
Allenoates*

Chapter 3 Highly Selective One-Pot [3+2]-Cycloaddition Reaction via Isomerization of 3-Alkynoates to Allenates

3.1 Introduction

Highly enantio-, regio- and diastereo-selective approaches toward the synthesis of functionalized five-membered rings is highly sought-after, as these are featured widely in many natural products and synthetic building blocks.⁴⁸ Although, there are many methods available for the construction of five-membered ring system, Lu's phosphine-catalyzed [3+2]-cycloaddition reaction between electron-deficient allenates/2-butynoates and electron-deficient alkenes is considered to be one of the most efficient methods.¹⁴ Recently, the asymmetric versions of this method have also been elegantly demonstrated by different groups.²⁵⁻³¹ However, there are still limitations in the reported cases. For example, in some systems, the reported chiral phosphines are difficult to obtain and the scope of substrates is relatively narrow. Another problem associated with this reaction is the need to use allenates or 2-alkynoates, which are difficult to synthesize and have limited substrate scope. Furthermore, the allenes are sometimes contaminated with the corresponding 3-alkyne isomer.⁵⁵ In this sense, usage of 3-alkynoates which can be isomerized⁵⁶ *in situ* to the

⁵⁵ (a) Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 13042. (b) Fu, F.; Hoang, L. M.; Loh, T. P. *Org. Lett.* **2008**, *10*, 3437. (c) Sato, F.; Nakagawa, T.; Kasatkin, A. *Tetrahedron Lett.* **1995**, *36*, 3207. (d) Maeorg, U.; Jogi, A. *Molecules*, **2001**, *6*, 964. (e) Wu, Y.; Wu, X.; Yao, Z.; Li, Y.; Li, J.; Xia, Y. *J. Org. Chem.* **1995**, *60*, 3257. (f) Iyoda, M.; Kanao, Y.; Nishizaki, M.; Oda, M. *Bull. Chem. Soc. Jpn.*, **1989**, *62*, 3380. (g) Suarez, A.; Fu, G. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3580. (h) Takami, K.; Usugi, S.; Yorimitsu, H.; Oshima, K. *Synthesis*, **2005**, 824.

⁵⁶ For base promoted isomerization see: (a) Jung, M. E.; Node, M. R.; Pfluger, W.; Lyster, M. A.; Lowe III, J. A. *J. Org. Chem.* **1982**, *47*, 1150. (b) Ma, D.; Yu, Y.; Lu, X. *J. Org. Chem.* **1989**, *54*, 1105. (c) H. Liu, D. Leow, K. W. Huang, C. H. Tan, *J. Am. Chem. Soc.* **2009**, *131*, 7212.

corresponding allenoates for the [3+2]-cycloaddition reaction is highly desirable (Scheme 3.1). If successful, we speculate that mixtures of alkynoates and allenoates equivalents can be directly employed in this reaction without the need of prior isolation. In this chapter, the use of tributylphosphine which concurrently catalyzes the isomerization of 3-butynoates to allenoates, as well as the subsequent Lu's [3+2]-cyclization reaction of the latter is described. In addition, the first successful use of the commercially available chiral phosphine DIPAMP for this reaction to obtain the cyclopentenones in high optical purity is described.

3.2 Results and Discussion

To examine our speculation, the reaction was performed between ethyl 4-phenylbut-3-ynoate⁵⁷ **87a** and *trans*-chalcone **30a** in the presence of 20 mol% of tributylphosphine. As expected, the reaction proceeded smoothly at room temperature to afford the [3+2] cyclized product **39aα** in high yield of 75% with complete control of regio- and diastereo-selectivity (Scheme 3.1).

Scheme 3.1 Phosphine catalyzed one-pot isomerization and [3+2]-cycloaddition

⁵⁷ Suarez, A.; Fu, G. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3580.

Notably, employing a less nucleophilic triphenylphosphine as catalyst, the reaction failed to afford the product. Moreover, the reaction with triethylamine or 1,4-diazabicyclo [2.2.2] octane (DABCO) instead of tributylphosphine under the same reaction conditions led only to isomerized products (allenoates). No cycloaddition or conjugate addition product was observed.⁵⁸ To define the generality of this method, various electron-deficient olefins (Table 3.1, entries 1-8) were screened. Reaction of both electron-withdrawing and electron-donating substituents on the phenyl ring of enones **30** provided **39** in good yield and excellent selectivity. Interestingly, the reaction with conjugate dienone **30g** afforded the cyclized product **39g** as single product. Cycloaddition with enoate such as diethyl fumarate afforded product **39h** in good yield (Table 3.1, entry 8).

To further extend the synthetic utility of this method, a series of 3-alkynoates were examined using the optimized reaction condition. In particular, the 3-butynoates bearing trifluoromethyl substituent **87e**, thiophene **87f**, naphthalene **87g** and aliphatic substituent **87h** were employed successfully to afford the cyclized products in good yields and excellent selectivities (Table 3.2, entries 4-8).

⁵⁸ Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394.

Table 3.1 Phosphine catalyzed [3+2]-cycloaddition reactions using 3-butynoate and various electron deficient double bonds.^a

<p style="text-align: center;"> $\text{EtO}_2\text{C}-\text{C}\equiv\text{C}-\text{Ph}$ (87a) + $\text{R}^2-\text{CH}=\text{CH}-\text{C}(=\text{O})-\text{R}^1$ (30) $\xrightarrow[\text{toluene, 8 h, rt}]{n\text{Bu}_3\text{P (20 mol\%)}}$ $\text{EtO}_2\text{C}-\text{C}(\text{R}^2)=\text{C}(\text{Ph})-\text{C}(=\text{O})-\text{R}^1$ (39α) </p>				
Entry	R ¹	R ²	Product ^b	Yield (%) ^c
1	C ₆ H ₅	C ₆ H ₅	39a	75
2	4-BrC ₆ H ₄	4-FC ₆ H ₄	39b	72
3	4-MeC ₆ H ₄	4-MeC ₆ H ₄	39c	77
4	4-ClC ₆ H ₄	4-FC ₆ H ₄	39d	70
5	4-OMeC ₆ H ₄	4-FC ₆ H ₄	39e	80
6	C ₆ H ₅	4-FC ₆ H ₄	39f	68
7 ^d	C ₆ H ₅ CH=CH	C ₆ H ₅	39g	70
8 ^{d,e}	OEt	COOEt	39h	78

^a See the experimental section for detailed experimental procedure; 3-butynoates **1a** possesses 2% of the corresponding allenates. ^b Single regio (α)- and diastereoisomers were observed by crude NMR analysis. ^c Isolated yield. ^d Trace amount of minor diastereoisomers were observed in NMR analysis. ^e 10 equiv. of diethyl fumarate was used.

Table 3.2 Phosphine catalyzed [3+2] cycloaddition using various 3-butynoates.^a

Entry	R	Product ^b	Yield (%) ^c
1	4-MeC ₆ H ₄ 87b	39i	77
2	4-OMeC ₆ H ₄ 87c	39j	82
3	(2-Me)(4-OMe)C ₆ H ₃ 87d	39k	88
4	4-CF ₃ C ₆ H ₄ 87e	39l	71
5	2-thienyl 87f	39m	78
6	6-OMe-2-naphthyl 87g	39n	80
7 ^{d,e}	cyclopropyl 87h	39o	85
8	CH ₃ 87i	39p	87

^a See the experimental section for detailed experimental procedure; 3-butynoates **87a** possesses 2% of the corresponding allenates. ^b Single regio (α)- and diastereoisomers were observed by crude NMR analysis. ^c Isolated yield. ^d Trace amount of minor diastereoisomers were observed in NMR analysis. ^e 10 equiv. of diethyl fumarate was used.

The ethyl ester functionality of the product **39o** was transformed to the corresponding carboxylic acid and the structure was confirmed by x-ray crystallographic determination (figure 3.1).

Figure 3.1 Hydrolysis of product **39o**; X-Ray crystallographic structure of hydrolyzed product **39oo**; 50% probability was chosen for the ellipsoids

The mechanism of this reaction is proposed as depicted in scheme 3.2. Tri-*n*-butylphosphine triggers the isomerization of alkynoate **87** to allenoate **16** which in turn reacts with phosphine to obtain 1,3-dipolar phosphonium intermediate **39.1**. The resulting dipolar species **39.1** underwent cycloaddition with **30** via α -addition not γ -addition. Although, both the α and γ carbon of **39.1** are sterically hindered, the α -addition is predominate due to electronic stabilization of anion at the α -carbon which led to α -adduct **39.2**. Subsequent proton transfer and elimination of phosphine afforded the cyclized product **39 α** (Scheme 3.2).

Scheme 3.2 Proposed mechanism for one-pot isomerization and cycloaddition

Next, we focused on the asymmetric version of this reaction. We believed that aliphatic phosphines that contain stereogenic centre in close proximity to the reactive sites will be more promising for asymmetric cycloaddition reactions. With this in mind, various commercially available chiral phosphines were screened using a solution of 3-butynoate **87a** and *trans*-chalcone **30a** (Table 3.3, entries 1-8).

Table 3.3 Screening various commercially available chiral phosphines for asymmetric [3+2] cycloaddition reactions.

87a	30a	39a
<hr/>		
<p>(+)-DIOP; 72% yield 66% ee</p>	<p>(<i>R,R</i>)-Et-BPE; 78% yield; 63% ee</p>	<p>(<i>R,R</i>)-DIPAMP; 87% yield 95% ee</p>
<p>(<i>R,R</i>)-Et-Duphos; 27% yield 33% ee</p>	<p>(<i>S,S</i>)-CHIRAPHOS; 58% yield 34% ee</p>	<p>(<i>R</i>)-Tol-BINAP; <5% yield</p>
<p>(<i>R</i>)-BINAP; <5% yield</p>	<p>(<i>S</i>)-(-)-2-[2-(Diphenylphosphino)phenyl]- 4,5-dihydro-4-isopropyl-1,3-oxazole < 5% yield.</p>	

As expected, the commercially available (*R, R*)-DIPAMP emerged as the best catalyst in terms of both yield and enantioselectivity (Table 3.3; entry 3). Using the best chiral phosphine (*R, R*)-DIPAMP, asymmetric reactions were carried out with a series of electron-deficient enones to explore the synthetic utility of the reaction

(Table 3.4, entries 1-8). In all cases, both excellent enantioselectivities and yields were observed and electronic effects of the enones on the reaction were apparently minimal.

Table 3.4 Asymmetric [3+2]-cycloaddition reaction using (*R, R*) –DIPAMP.^{a, b}

Entry	R ¹	R ²	Product /Yield (%) ^c	Ee (%) ^d
1	C ₆ H ₅	C ₆ H ₅	39a' /87	95
2	4-BrC ₆ H ₄	4-FC ₆ H ₄	39b' /92	95
3	4-MeC ₆ H ₄	4-MeC ₆ H ₄	39c' /95	93
4	4-ClC ₆ H ₄	4-FC ₆ H ₄	39d' /88	95
5	4-OMeC ₆ H ₄	4-FC ₆ H ₄	39e' /82	98
6	C ₆ H ₅	4-FC ₆ H ₄	39f' /85	95
7 ^e	C ₆ H ₅ CH=CH	C ₆ H ₅	39g' /90	99
8 ^{f, g}	OEt	COOEt	39h' /88	81

^a See the experimental section for the detailed experimental procedure; 3-butynoates **87a** possesses 2% of the corresponding allenoates. ^b Single regio (α)- and diastereoisomers were observed by crude NMR analysis. ^c Isolated yield. ^d Trace amount of minor diastereoisomers were observed in NMR analysis. ^e 10 equiv. of diethyl fumarate was used.

To further explore the generality of (*R, R*)-DIPAMP, electronically and sterically diverged 3-alkynoates were screened (Table 3.5, entries 1-8). In all cases, except for entry 4, excellent yield and enantioselectivity were obtained. However, (*R, R*)-DIPAMP failed to yield the desired product with the cyclopropyl substituted 3-alkynoate **87h** even after stirring for 3 days. However, it was gratifying to find that addition of 10 mol% of triethylamine facilitated the isomerization to afford the cyclized product in good yield with high enantioselectivity (Table 3.5, entry 7).

Table 3.5 Asymmetric [3+2]-cycloaddition reaction using (*R, R*)-DIPAMP: Scope with respect to 3-butynoates.

Entry	R	Product/Yield (%)	Ee (%)
1	4-MeC ₆ H ₄ 87b	39i' /82	97
2	4OMeC ₆ H ₄ 87c	39j' /89	95
3	(2-Me)(4-OMe)C ₆ H ₃ 87d	39k' /93	84
4	4-CF ₃ C ₆ H ₄ 87e	39l' /66	94
5	3-thienyl 87f	39m' /90	96
6	6-OMe-2-naphthyl 87g	39n' /77	96
7 ^a	cyclopropyl 87h	39o' /93	90
8 ^b	CH ₃ 87i	39p' /87	99

^a 10 mol% of triethylamine was added and reaction completed in 12 h. ^b Absolute configuration was assigned by comparing with the optical rotation value ref. 28.

The absolute configuration of the product **39p'** was assigned by comparing the optical rotation of the corresponding benzyl ester.²⁸ Product **39p'** was transformed in to the corresponding benzyl ester in two steps as described in scheme 3.3.

Scheme 3.3 Determination of absolute stereochemistry; reagents and conditions: a) $\text{LiOH} \cdot \text{H}_2\text{O}$ (5 equiv.), $\text{THF}:\text{H}_2\text{O}$ (1:1), 60 °C, 5 h, 92%; b) PhCH_2Br , K_2CO_3 , DMF, rt, 12 h, 95%.

A control experiment was carried out by first isolating the intermediate (±)-allenoate **16** intermediate before subjecting it to the asymmetric [3+2]-cycloaddition using *trans*-chalcone and 10 mol% of (*R,R*)-DIPAMP (Scheme 3.4). The above reaction afforded identical results with the one-pot [3+2]-cycloaddition of 3-alkynoate **87a** (Table 3.4, entry 1), indicating that the chirality of the allenoates played no significant role in the asymmetric induction of the reaction.

Scheme 3.4 Controlled experiment

Transition state proposed is inconsistent with the identity of the major enantiomer formed. The second phosphine moiety in the catalyst probably interacts with electropositive γ -carbon of 1,3-dipolar intermediate through a cyclic six-membered conformation. Then, the dipolarophile approaches the zwitterion from the *Re* face of the substituents of the catalyst.

Scheme 3.5 Plausible transition state

3.3 Conclusion

In this chapter, we have demonstrated the direct application of 3-alkynoates in the [3+2]-cycloaddition reaction. This one-pot procedure is an attractive alternative to the usual protocol reported for this type of reaction. In addition, we have identified a more efficient commercially available chiral phosphine (*R, R*)-DIPAMP for this cycloaddition reaction, that enables the synthesis of cyclopentene derivatives in high optical purities.

3.4 Experimental Section

3.4.1 General

Phosphine includes PPh₃, BINAP, (2*S*, 3*S*)-CHIRAPHOS, (*S, S*)-Et-DUPHOS, (*R,R*)-Et-DUPHOS, (*R,R*)-Et-BPE(+)-DIOP, (*S*)-(-)-2-[2-(Diphenylphosphino)-phenyl]-4-isopropyl-2-oxazoline and (*R, R*)-DIPAMP were purchased from commercial suppliers. Alkynes, ethyl diazoacetate, CuI and *trans*-chalcone were purchased from commercial suppliers.

3.4.2 General procedure for the synthesis of 3-butynoates 87a

Ethyl diazoacetate (134 mg, 1.17 mmol) was added to a solution of ethynylbenzene (100 mg, 0.980 mmol) and CuI (20 mg, 0.098 mmol) in MeCN (5 mL). The resulting mixture was stirred for 18 h at 25 °C. At which time, the solvent

was removed and the residue was purified by column chromatography (2% ethyl acetate in hexane) to afford product (**1a**) as colourless oil (135 mg, 0.718 mmol, 72% yield); $R_f = 0.7$ (hexane: ethyl acetate = 4:1). ^1H NMR analysis shows little contamination of product with corresponding allenic ester. This mixture was used in the cycloaddition reaction without purification. Spectroscopic data are in accordance with reported values.

Ethyl 4-*p*-tolylbut-3-ynoate (87b): The product was prepared using the general

procedure but employing

1-ethynyl-4-methylbenzene (100 mg, 0.86 mmol),

ethyl diazoacetate (118 mg, 1.03 mmol) and CuI (16

mg, 0.08 mmol). After 18 h, the solvent was removed and the residue was purified through flash column chromatography (3% ethyl acetate in hexane) to afford the product **87b** as a colorless oil (142 mg, 0.70 mmol, 81% yield); $R_f = 0.7$ (hexane: ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.32 (d, $J=8.04$ Hz, 2H), 7.07-7.09 (d, $J=7.91$ Hz, 2H), 4.18 (q, $J=7.13$ Hz, 2H), 3.50 (s, 2H), 2.32 (s, 3H), 1.28 (t, $J=7.13$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 168.3, 138.2, 131.6 (CH x 2), 128.9 (CH x 2), 119.9, 83.5, 80.5, 61.5, 26.7, 21.4, 14.1 ppm; FTIR (neat): $\nu = 3028$, 2984, 2939, 1737, 1694, 1607, 1511, 1369, 1265, 1177, 1031, 931, 817, 757, 667 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 225.0891, found: 225.0896. ^1H NMR analysis shows 5% of corresponding allenic ester.

Ethyl 4-(4-methoxyphenyl)-but-3-ynoate (87c): The product was prepared using the

general procedure but employing

1-ethynyl-4-methoxybenzene (100 mg, 0.757 mmol),

ethyl diazoacetate (103 mg, 0.909 mmol) and CuI (16

mg, 0.075 mmol). After 15 h, the solvent was removed and the residue was purified

through flash column chromatography (2% ethyl acetate in hexane) to afford product

87c as a colorless oil (145 mg, 0.666 mmol, 88% yield); R_f = 0.7 (hexane: ethyl

acetate = 4:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.37 (d, J =8.8 Hz, 2H), 6.82 (d, J = 8.1

Hz, 2H), 4.22 (q, J =7.13 Hz, 2H), 3.79 (s, 3H), 3.48 (s, 2H), 1.29 (t, J =7.13 Hz, 3H);

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 168.4, 159.5, 133.1 (CH x 2), 115.1, 113.8 (CH x 2),

83.2, 79.7, 61.5, 55.2, 26.7, 14.1 ppm; **FTIR** (neat): ν = 3430, 1734, 1683, 1647,

1606, 1510, 1465, 1370, 1339, 1325, 1290, 1264, 1171, 1130, 1107, 1031, 910, 834,

732 cm^{-1} ; **HRMS** (ESI, m/z): calcd for $\text{C}_{13}\text{H}_{15}\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 219.1021, found:

219.1062. $^1\text{H NMR}$ analysis shows 5% of corresponding allenic ester.

Ethyl 4-(4-methoxy-2-methylphenyl) but-3-ynoate (87d): The product was prepared

using the general procedure but employing

1-ethynyl-4-methoxy-2-methylbenzene (100 mg,

0.685 mmol), ethyl diazoacetate (93 mg, 0.822

mmol) and CuI (13 mg, 0.068 mmol). After 18 h, the solvent was removed and the

residue was purified through flash column chromatography (2% ethyl acetate in

hexane) to afford product **87d** as a colorless oil (103 mg, 0.445 mmol, 65% yield); R_f

= 0.8 (hexane: ethyl acetate = 4:1); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.33 (d, J =8.4

Hz, 1H), 6.65-6.73 (m, 2H), 4.22 (q, $J=7.13$ Hz, 2H), 3.78 (s, 3H), 3.52 (s, 2H), 2.42 (s, 3H), 1.31 (t, $J=7.13$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 168.5, 159.3, 142.1, 133.2 (CH x 2), 114.9, 111.0, 83.3, 82.2, 61.5, 55.1, 26.9, 20.9, 14.1 ppm; **FTIR (neat):** ν = 3018, 2938, 2964, 2909, 1739, 1605, 1568, 1498, 1465, 1456, 1443, 1295, 1236, 1163, 1119, 1050, 1032, 850, 810, 754 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{14}\text{H}_{17}\text{O}_3^+ [\text{M}+\text{H}]^+$ 233.1178, found 233.1170. ^1H NMR analysis shows 5% of corresponding allenic ester.

Ethyl 4-(4-(trifluoromethyl)phenyl)but-3-ynoate (87e): The product was prepared

using the general procedure but employing 1-ethynyl-4-(trifluoromethyl)benzene (100

mg, 0.588 mmol), ethyl diazoacetate (80 mg, 0.705 mmol) and CuI (11 mg, 0.058 mmol). After 16 h solvent was removed and the residue was purified through flash column chromatography (2% ethyl acetate in hexane) to afford product **87e** as a colorless oil (78 mg, 0.305 mmol, 52% yield); R_f = 0.6 (hexane: ethyl acetate = 4:1); ^1H NMR (300 MHz, CDCl_3): δ 7.54-7.59 (m, 2H), 7.39-7.42 (m, 2H), 4.22 (q, $J=7.13$ Hz, 2H), 3.52 (s, 2H), 1.32 (t, $J=7.13$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 214.9, 167.8, 164.6, 132.0 (CH x 2), 127.6 (CH x 2), 125.8, 97.8, 92.4, 61.8, 26.7, 14.1 ppm; **FTIR (neat):** ν = 3025, 1955, 1716, 1615, 1410, 1384, 1326, 1303, 1273, 1216, 1168, 1130, 1111, 1064, 1035, 846, 802, 773 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{13}\text{H}_{12}\text{O}_2\text{F}_3^+ [\text{M}+\text{H}]^+$ 257.0789, found: 257.0786. ^1H NMR analysis shows 35% of corresponding allenic ester.

Ethyl 4-(thiophen-3-yl)-but-3-ynoate (87f): The product was prepared using the

general procedure A but employing 3-ethynylthiophene (100 mg, 0.925 mmol), ethyl diazoacetate (127 mg, 1.111 mmol) and CuI (13 mg,

0.092 mmol). After 18 h solvent was removed and the residue was purified through flash column chromatography (2% ethyl acetate in hexane) to afford product **87f** as a colorless oil (140 mg, 0.722 mmol, 78% yield); R_f = 0.7 (hexane: ethyl acetate = 4:1); ^1H NMR (300 MHz, CDCl_3): δ 7.20-7.23 (m, 2H), 7.05-7.15 (m, 1H), 4.22 (q, J =7.13 Hz, 2H), 3.47 (s, 2H), 1.30 (t, J =7.13 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 168.5, 139.1, 138.7, 133.6 (CH x 2), 83.3, 82.2, 55.1, 26.9, 14.1 ppm; FTIR (neat): ν = 3445, 3018, 2983, 1736, 1392, 1369, 1332, 1301, 1261, 1216, 1176, 1096, 1032, 864, 756, 626 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{SNa}^+$ $[\text{M}+\text{Na}]^+$ 217.0294, found: 217.0299. ^1H NMR analysis shows 5% of corresponding allenic ester.

Ethyl 4-(6-methoxynaphthalen-2-yl) but-3-ynoate (87g): The product was prepared

using the general procedure but employing 2-ethynyl-6-methoxynaphthalene (100 mg, 0.55 mmol), ethyl diazoacetate (75 mg, 0.657 mmol)

and CuI (10 mg, 0.055 mmol). After 12 h, the solvent was removed and the residue was purified through flash column chromatography (4% ethyl acetate in hexane) to afford product **87g** as a colorless oil (108 mg, 0.401 mmol, 73% yield); R_f = 0.6 (hexane: ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 7.87 (s, 1H), 7.61-7.65

(m, 2H), 7.43-7.45 (m, 1H), 7.05-7.13 (m, 2H) 4.23 (q, $J=7.13$ Hz, 2H), 3.87 (s, 3H), 3.53 (s, 2H), 1.31 (t, $J=7.13$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 168.3, 158.2, 134.0, 131.4, 129.2, 129.1, 128.4, 126.7, 119.3, 117.9, 105.7, 83.9, 80.7, 61.6, 55.3, 26.8, 14.1 ppm; FTIR (neat): ν = 3445, 3018, 2983, 1736, 1392, 1369, 1332, 1301, 1261, 1216, 1176, 1096, 1032, 864, 756, 626 cm^{-1} . ^1H NMR analysis shows 5% of corresponding allenic ester.

Ethyl 4-cyclopropylbut-3-ynoate (87h): The product was prepared using the general

procedure but employing ethynylcyclopropane (100 mg, 1.510 mmol), ethyl diazoacetate (207 mg, 1.818

mmol) and CuI (30 mg, 0.151 mmol). After 17 h, the solvent was removed and the residue was purified through flash column chromatography (3% ethyl acetate in hexane) to afford product **87h** as a colorless oil (207 mg, 1.363 mmol, 90% yield); R_f = 0.5 (hexane: ethyl acetate = 4:1); ^1H NMR (400 MHz, CDCl_3): δ 4.18 (q, $J=7.13$ Hz, 2H), 3.19 (s, 2H), 1.27-1.24 (m, 4H), 0.64-0.74 (m, 4H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 168.8, 86.6, 80.6, 66.7, 61.3, 26.0, 14.0, 7.9, -0.48 ppm; FTIR (neat): ν = 3009, 2984, 2906, 1753, 1465, 1446, 1404, 1369, 1333, 1098, 1029, 933, 891, 814, 786 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_9\text{H}_{13}\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 153.0916, found: 153.0916. ^1H NMR analysis shows 5% of corresponding allenic ester.

To a stirred solution of ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol) and *trans*-chalcone (61 mg, 0.292 mmol) in toluene (1.5 mL) was added (*R, R*)-DIPAMP (12 mg, 0.026 mmol) drop-wise at 0 °C under nitrogen. After 8 h stirring at room temperature under N₂ atmosphere, the reaction mixture was concentrated and purified through flash column chromatography (10% ethyl acetate in hexane) to afford pure product (**39a'**) as a colorless oil (89.5 mg, 0.228 mmol, 87% yield, 95% ee); *R_f* = 0.4 (hexane: ethyl acetate = 4:1); **¹H NMR (500 MHz, CDCl₃):** δ 7.40-7.45 (m, 3H), 7.10-7.30 (m, 12H), 6.95 (t, *J*=2.0 Hz, 1H), 4.65 (td, *J*=7.1, 2.3 Hz, 1H), 4.45 (td, *J*=7.1, 2.0 Hz, 1H), 3.92-4.12 (m, 3H), 1.05 (t, *J*=7.1 Hz, 3H) ppm; **¹³C NMR (125 MHz, CDCl₃):** δ 200.4, 164.1, 144.3, 143.3, 142.4, 137.7, 136.4, 133.2, 128.9 (CH x 2), 128.8 (CH x 2), 128.5 (CH x 2), 128.2 (CH x 2), 127.6 (CH x 2), 127.1 (CH x 2), 126.8 (CH x 2), 64.7, 60.2, 55.3, 53.8, 13.9 ppm; **FTIR (neat):** ν = 1716, 1676, 1448, 1249, 1099 cm⁻¹; **HRMS (ESI, m/z):** calcd for C₂₇H₂₅O₃⁺ [M+H]⁺ 397.1804, found: 397.1800; The enantiomeric excess was determined by HPLC analysis employing Daicel CHIRACEL OD & ODH column (each 0.46 cm ϕ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): t₁ = 27.6 min (major), t₂ = 35.6 min (minor); [*α*]_D²⁰ = + 16.9° (*c* = 0.53, CH₂Cl₂).

Ethyl-4-(4-bromobenzoyl)-5-(4-fluorophenyl)-3-phenylcyclopent-1-enecarboxylate

e: The product was prepared using the general procedure but employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol),\

(*E*)-3-(4-bromophenyl)-1-(4-fluorophenyl)prop-2-en-1-one

(96 mg, 0.318 mmol) and (*R,R*)-DIPAMP (12 mg, 0.026

mmol). After 8 h, the solvent was removed and the residue was purified through flash column chromatography (10% ethyl acetate in hexane) to afford product **39b'** as a colorless oil (120 mg, 0.244 mmol, 92% yield, 95% ee); *R_f* = 0.5 (hexane: ethyl acetate = 4:1); ¹H NMR (500 MHz, CDCl₃): δ 7.25-7.35 (m, 7H), 7.10-7.15 (m, 4H), 6.92-6.99 (m, 3H), 4.59 (td, *J*=7.3, 2.4 Hz, 1H), 4.46 (td, *J*=7.2, 2.3 Hz, 1H), 3.95-4.15 (m, 2H), 3.94 (t, *J*=7.3 Hz, 1H), 1.09 (t, *J*=7.1 Hz, 3H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 199.1, 163.8, 162.7, 160.7, 144.3, 142.0, 138.95, 138.92, 137.5, 135.0, 131.5, 130.3, 129.08, 129.02, 128.9 (CH x 2), 128.7, 127.5 (CH x 2), 127.3, 115.5, 115.4, 64.9, 60.4, 54.4, 53.8, 13.9 ppm; FTIR (neat): ν = 1714, 1678, 1585, 1508, 1215, 1101, 669 cm⁻¹; HRMS (ESI, *m/z*): calcd for C₂₇H₂₃O₃BrF⁺ [M+H]⁺ 493.0815, found: 493.0903; The enantiomeric excess was determined by HPLC analysis employing Daicel CHIRACEL OD & ODH column (each 0.46 cm φ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): *t*₁ = 29.0 min (major), *t*₂ = 36.3 min (minor); [α]_D²⁰ = + 10.9° (*c* = 0.55, CH₂Cl₂).

Ethyl 4-(4-methylbenzoyl)-3-phenyl-5-*p*-tolylcyclopent-1-enecarboxylate: The

product was prepared using the general procedure but

employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol), (*E*)-1,3-dip-tolylprop-2-en-1-one (75 mg, 0.318 mmol) and (*R, R*)-DIPAMP (12 mg, 0.026 mmol). After 8 h, the solvent was removed and the residue was purified through flash column chromatography (12% ethyl acetate in hexane) to afford product **39c'** as a colorless oil (107 mg, 0.252 mmol, 95% yield, 93% ee); $R_f = 0.5$ (hexane: ethyl acetate = 4:1); $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.35-7.4 (m, 2H), 7.25-7.30 (m, 2H), 7.20-7.25 (m, 3H), 6.95-7.05 (m, 6H), 6.92 (t, $J=2.3$ Hz, 1H), 4.59-4.62 (td, $J=6.8, 2.3$ Hz, 1H), 4.42-4.45 (td, $J=6.8, 2.2$ Hz, 1H), 3.97-4.15 (m, 3H), 2.30 (brs, 6H), 1.09 (t, $J=7.1$ Hz, 3H) ppm; $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 200.0, 164.1, 144.1, 144.0, 142.6, 140.3, 137.9, 136.2, 133.9, 129.17 (CH x 2), 129.12 (CH x 2), 128.9 (CH x 2), 128.7 (CH x 2), 127.6 (CH x 2), 127.5 (CH x 2), 127.0, 64.3, 60.2, 54.9, 53.9, 21.5, 21.0, 13.9 ppm; **FTIR** (neat): $\nu = 1712, 1670, 1215, 1099 \text{ cm}^{-1}$; **HRMS** (ESI, m/z): calcd for $\text{C}_{29}\text{H}_{28}\text{O}_3\text{Na}^+ [\text{M}+\text{Na}]^+ 447.1936$, found: 447.1931; The enantiomeric excess was determined by HPLC analysis employing Daicel CHIRACEL OD & ODH column (each 0.46 cm ϕ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): $t_1 = 23.5$ min (major), $t_2 = 47.6$ min (minor); $[\alpha]_D^{20} = +11.6^\circ$ ($c = 0.6, \text{CH}_2\text{Cl}_2$).

Ethyl4-(4-chlorobenzoyl)-5-(4-fluorophenyl)-3-phenylcyclopent-1-enecarboxylate

The product was prepared using the general procedure B but employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol), (*E*)-1-(4-chlorophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (83 mg, 0.318 mmol) and (*R, R*)-DIPAMP (12 mg, 0.026

mmol). After 8 h, the solvent was removed and the residue was purified through flash

column chromatography (12% ethyl acetate in hexane) to afford product **39d'** as a colorless oil (104 mg, 0.234 mmol, 88% yield, 95% ee); $R_f = 0.5$ (hexane: ethyl acetate = 4:1); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.25-7.36 (m, 5H), 7.09-7.20 (m, 6H), 6.92-6.96 (m, 3H), 4.57-4.61 (td, $J=7.2, 2.4$ Hz, 1H), 4.44-4.48 (td, $J=7.2, 2.3$ Hz, 1H), 3.92-4.18 (m, 3H), 1.06-1.11 (t, $J = 7.1$ Hz, 3H) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 198.9, 163.8, 163.3, 160.1, 144.3, 142.0, 139.8, 138.97, 138.93, 137.5, 134.7, 130.2 (CH x 2), 129.1, 129.0, 128.9, 128.5 (CH x 2), 127.5, 127.3, 115.6, 115.3, 64.9, 60.3, 54.4, 53.8, 13.9 ppm; **FTIR** (neat): $\nu = 1712, 1676, 1589, 1508, 1215, 1093\text{ cm}^{-1}$; **HRMS** (ESI, m/z): calcd for $\text{C}_{27}\text{H}_{23}\text{O}_3\text{ClF}^+$ $[\text{M}+\text{H}]^+$ 449.1320, found: 449.1331; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): $t_1 = 27.3$ min (major), $t_2 = 34.8$ min (minor); $[\alpha]_D^{20} = +11.5^\circ$ ($c = 0.52, \text{CH}_2\text{Cl}_2$).

Ethyl-5-(4-fluorophenyl)-4-(4-methoxybenzoyl)-3-phenylcyclopent-1-enecarboxylate

ate: The product was prepared using the general procedure but employing

ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol),

(*E*)-3-(4-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-

one (81 mg, 0.318 mmol) and (*R,R*)-DIPAMP (12 mg,

0.026 mmol). After 8 h, the solvent was removed and the residue was purified through

flash column chromatography (10% ethyl acetate in hexane) to afford product **39e'** as

a colorless oil (97 mg, 0.218 mmol, 82% yield, 98% ee); $R_f = 0.4$ (hexane: ethyl

acetate = 4:1); **¹H NMR (400 MHz, CDCl₃)**: δ 7.42-7.44 (m, 2H), 7.15-7.35 (m, 5H), 7.10-7.14 (m, 2H), 6.90-6.95 (m, 3H), 6.65-6.70 (m, 2H), 4.60 (td, *J*=7.2, 2.4 Hz, 1H), 4.45 (td, *J*=7.2, 2.3 Hz, 1H), 3.92-4.15 (m, 3H), 3.76 (s, 3H), 1.08 (t, *J*=7.1 Hz, 3H) ppm; **¹³C NMR (100 MHz, CDCl₃)**: δ 198.4, 163.9, 163.6, 162.8, 160.4, 144.6, 142.3, 139.2, 137.5, 131.2 (CH x 2), 129.3, 129.1, 129.0, 128.8 (CH x 2), 127.5 (CH x 2), 115.4, 115.2, 113.4 (CH x 2), 64.4, 60.3, 55.3, 54.7, 53.9, 13.9 ppm; **FTIR (neat)**: ν = 1712, 1666, 1598, 1508, 1249, 1215, 1170 cm⁻¹; **HRMS (ESI, m/z)**: calcd for C₂₈H₂₆O₄F⁺ [M+H]⁺ 445.1815, found: 445.1813; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 2% isopropanol/hexane, 1.0 mL/min): *t*₁ = 28.3 min (major), *t*₂ = 38.6 min (minor); [α]_D²⁰ = + 16.0° (*c* = 0.56, CH₂Cl₂).

Ethyl 4-benzoyl-5-(4-fluorophenyl)-3-phenylcyclopent-1-enecarboxylate:

The product was prepared using the general procedure but employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol), (*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (72 mg, 0.318 mmol) and (*R, R*)-DIPAMP (12 mg, 0.026 mmol). After 8 h, the solvent was removed and the residue was purified through flash column chromatography (10% ethyl acetate in hexane) to afford product **39f'** as a colorless oil (93 mg, 0.226 mmol, 85% yield, 95% ee); *R_f* = 0.4 (hexane: ethyl acetate = 4:1); **¹H NMR (300 MHz, CDCl₃)** δ 7.42-7.46 (m, 3H), 7.07-7.35 (m, 9H), 6.88-6.96 (m, 3H), 4.63 (td, *J*=7.1, 2.4 Hz, 1H), 4.47 (td, *J*=7.1, 2.3 Hz, 1H), 3.95-4.15 (m, 3H), 1.11 (s, *J*=7.1 Hz, 3H) ppm; **¹³C NMR (75 MHz, CDCl₃)** δ 200.1,

163.9, 163.2, 160.0, 144.5, 142.2, 139.1, 139.0, 137.5, 136.3, 133.2, 129.1, 129.0, 128.85, 128.82, 128.2 (CH x 2), 127.5 (CH x 2), 127.2, 115.5, 115.2, 64.7, 60.3, 54.4, 53.7, 13.9 ppm; **FTIR (neat):** ν = 1712, 1680, 1508, 1215 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{27}\text{H}_{24}\text{O}_3\text{F}^+$ $[\text{M}+\text{H}]^+$ 415.1709, found: 415.1695; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): t_1 = 25.0 min (major), t_2 = 32.3 min (minor); $[\alpha]_{\text{D}}^{20}$ = + 13.4° (c = 0.52, CH_2Cl_2).

Ethyl 4-cinnamoyl-3, 5-diphenylcyclopent-1-enecarboxylate: The product was

prepared using the general procedure but employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol), (1*E*, 4*E*)-1,5-diphenylpenta-1,4-dien-3-one (75 mg, 0.318 mmol) and (*R*, *R*)-DIPAMP (12 mg, 0.026 mmol). After 8 h, the

solvent was removed and the residue was purified through flash column chromatography (10% ethyl acetate in hexane) to afford product **39g'** as a colorless oil (101 mg, 0.239 mmol, 90% yield, 99% ee); R_f = 0.5 (hexane: ethyl acetate = 4:1);

¹H NMR (300 MHz, CDCl₃): δ 7.15-7.40 (m, 15H), 7.05 (d, J =16.2 Hz, 1H), 6.92 (t, J =2.2 Hz, 1H), 6.45 (d, J =16.2 Hz, 1H), 4.57 (td, J =7.7, 2.4 Hz, 1H), 4.46 (td, J =7.7, 2.4 Hz, 1H), 3.92-4.15 (m, 2H), 3.59 (t, J =7.7 Hz, 1H), 1.06 (t, J =7.1 Hz, 3H) ppm;

¹³C NMR (75 MHz, CDCl₃): δ 198.9, 164.1, 144.5, 144.3, 143.8, 142.7, 137.7, 134.1, 130.5, 128.9 (CH x 2), 128.7 (CH x 2), 128.6 (CH x 2), 128.3 (CH x 2), 127.76 (CH x 2), 127.75 (CH x 2), 127.2, 126.8, 125.8, 68.0, 60.2, 54.5, 52.8, 13.9 ppm;

FTIR (neat): ν = 1714, 1608, 1494, 1454, 1247, 1217, 1099 cm^{-1} ; **HRMS (ESI,**

m/z): calcd for $C_{29}H_{27}O_3^+$ $[M+H]^+$ 423.1960, found: 423.1940. The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): t_1 = 48.4 min (major), t_2 = 59.8 min (minor); $[\alpha]_D^{20}$ = + 33.3° (c = 0.51, CH_2Cl_2).

Triethyl-5-phenylcyclopent-3-ene-1, 2, 3-tricarboxylate: The product was prepared

using the general procedure but employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol), diethyl fumarate (456 mg, 2.650 mmol) and (*R, R*)-DIPAMP (12 mg, 0.026 mmol). After 8 h, the solvent was removed and

the residue was purified through flash column chromatography (10% ethyl acetate in hexane) to afford product **39h'** as a colorless oil (84 mg, 0.234 mmol, 88% yield, 81% ee); R_f = 0.4 (hexane: ethyl acetate = 4:1); 1H NMR (300 MHz, $CDCl_3$): δ 7.16-7.27 (m, 5H), 6.73 (t, J =2.2 Hz, 1H), 4.28 (td, J =7.2, 2.3 Hz, 1H), 4.05-4.20 (m, 6H) 4.01 (td, J =7.6, 2.2 Hz, 1H), 3.21 (t, J =7.5 Hz, 1H), 1.15-1.25 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 172.5, 163.3, 145.8, 141.3, 134.3, 128.7 (CH x 2), 127.7 (CH x 2), 127.3, 61.2, 61.1, 60.7, 56.6, 54.1, 53.2, 14.0 (CH_3 x 3) ppm; FTIR (neat): ν = 1860, 1608, 1570, 1414, 1327, 1207, 1199 cm^{-1} ; HRMS (ESI, **m/z**): calcd for $C_{20}H_{25}O_6^+$ $[M+H]^+$ 361.1651, found: 361.1651; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 1.0% isopropanol/hexane, 1.0 mL/min): t_1 = 9.5 min (minor), t_2 = 16.7 min (major).

Ethyl 4-benzoyl-5-phenyl-3-*p*-tolylcyclopent-1-enecarboxylate: The product was

prepared using the general procedure but employing Ethyl 4-*p*-tolylbut-3-ynoate (50 mg, 0.247 mmol), *trans*-chalcone (57 mg, 0.2750 mmol) and (*R*, *R*)-DIPAMP (11 mg, 0.023 mmol). After 8 h, the solvent was removed and the

residue was purified through flash column chromatography (10% ethyl acetate in hexane) to afford product **39i'** as a colorless oil (83 mg, 0.202 mmol, 82% yield, 97% ee); R_f = 0.6 (hexane: ethyl acetate = 4:1); $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 7.32-7.50 (m, 3H), 7.12-7.27 (m, 7H), 7.05 (s, 4H), 6.93 (t, J =2.2 Hz, 1H), 4.60 (td, J =7.0, 2.4 Hz, 1H), 4.47 (td, J =7.0, 2.1 Hz, 1H), 3.90-4.15 (m, 3H), 2.30 (s, 3H), 1.04 (t, J =7.1 Hz, 3H) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 200.4, 164.0, 144.6, 143.3, 139.3, 137.4, 136.6, 136.4, 133.0, 129.4 (CH x 2), 128.8 (CH x 2), 128.4 (CH x 2), 128.1 (CH x 2), 127.6 (CH x 2), 127.4 (CH x 2), 126.7, 64.6, 60.1, 55.2, 53.5, 20.9, 13.8 ppm; **FTIR** (neat): ν = 1712, 1679, 1514, 1448, 1251, 1215, 1099 cm^{-1} ; **HRMS** (ESI, m/z): calcd for $\text{C}_{28}\text{H}_{27}\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 411.1960, found: 411.1956; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): t_1 = 21.0 min (major), t_2 = 36.8 min (minor); $[\alpha]_D^{20}$ = +42.5° (c = 0.54, CH_2Cl_2).

Ethyl 4-benzoyl-3-(4-methoxyphenyl)-5-phenylcyclopent-1-enecarboxylate: The

product was prepared using the general procedure but employing ethyl 4-(4-methoxyphenyl)-but-3-ynoate

(50 mg, 0.229 mmol), *trans*-chalcone (54 mg, 0.258 mmol) and (*R,R*)-DIPAMP (11 mg, 0.021 mmol). After 8 h, the solvent was removed and the residue was purified through flash column chromatography (12% ethyl acetate in hexane) to afford product **39j'** as a colorless oil (87 mg, 0.204 mmol, 89% yield, 95% ee); R_f = 0.4 (hexane: ethyl acetate = 4:1); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.35-7.45 (m, 3H), 7.10-7.28 (m, 9H), 6.91 (t, J =2.2 Hz, 1H), 6.81-6.85 (m, 2H), 4.55 (td, J =7.0, 2.3 Hz, 1H), 4.48-4.50 (m, 1H), 3.90-4.15 (m, 3H), 3.75 (s, 3H), 1.05 (t, J =7.1 Hz, 3H) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 200.4, 164.0, 158.6, 144.6, 143.3, 137.3, 136.4, 134.3, 133.0, 128.8 (CH x 2), 128.6 (CH x 2), 128.4 (CH x 2), 128.1 (CH x 2), 127.5 (CH x 2), 126.6, 114.1 (CH x 2), 64.8, 60.1, 55.1, 55.0, 53.3, 13.8 ppm; **FTIR** (neat): ν = 1712, 1676, 1514, 1251, 1215 cm^{-1} ; **HRMS** (ESI, m/z): calcd for $\text{C}_{28}\text{H}_{27}\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 427.1909, found: 427.1908; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): t_1 = 45.0 min (major), t_2 = 77.5 min (minor); $[\alpha]_{\text{D}}^{20}$ = + 52.0° (c = 0.50, CH_2Cl_2).

Ethyl-4-benzoyl-3-(4-methoxy-2-methylphenyl)-5-phenylcyclopent-1-enecarboxyl

ate: The product was prepared using the general procedure but employing ethyl 4-(4-methoxy-2-methylphenyl)-but-3-ynoate (50 mg,

0.2155 mmol), *trans*-chalcone (54 mg, 0.2586 mmol) and (*R,R*)-DIPAMP (10 mg, 0.023 mmol). After 8 h, the solvent was removed and the residue was purified through flash column chromatography (12% ethyl acetate in hexane) to afford product **39k'** as

a colorless oil (88 mg, 0.200 mmol, 93% yield, 84% ee); R_f = 0.5 (hexane: ethyl acetate = 4:1); ^1H NMR (300 MHz, CDCl_3): δ 7.41-7.51 (m, 3H), 7.10-7.35 (m, 8H), 6.91 (t, J =2.2 Hz, 1H), 6.81 (dd, J =8.4, 2.6 Hz, 1H), 6.62 (d, J =2.5 Hz, 1H), 4.78 (td, J =6.3, 2.3 Hz, 1H), 4.41 (td, J =6.4, 1.9 Hz, 1H), 3.92-4.15 (m, 3H), 3.77 (s, 3H), 2.01 (t, 3H), 1.07 (s, J =7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 200.5, 164.0, 158.3, 145.3, 143.3, 137.4, 137.3, 136.1, 133.2, 128.8 (CH x 2), 128.6 (CH x 2), 128.4 (CH x 2), 128.3 (CH x 2), 127.7 (CH x 2), 126.7, 116.0, 111.6, 63.8, 60.2, 55.5, 55.1, 49.5, 19.9, 13.9 ppm; FTIR (neat): ν = 1712, 1676, 1606, 1502, 1448, 1255, 1215, 1095 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{29}\text{H}_{29}\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 441.2066, found: 441.2068; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 1% isopropanol/hexane, 1.0 mL/min): t_1 = 28.9 min (major), t_2 = 64.7 min (minor); $[\alpha]_D^{20}$ = + 53.3° (c = 0.30, CH_2Cl_2).

Ethyl-4-benzoyl-5-phenyl-3-(4-(trifluoromethyl)phenyl)cyclopent-1-enecarboxylate

te: The product was prepared using the general procedure but employing ethyl

4-(4-(trifluoromethyl)-phenyl)-but-3-ynoate (50 mg, 0.195 mmol), *trans*-chalcone (48.5 mg, 0.234 mmol) and (*R,R*)-DIPAMP (10 mg, 0.023 mmol). After 8 h,

the solvent was removed and the residue was purified through flash column chromatography (12% ethyl acetate in hexane) to afford product **391'** as a colorless oil (60 mg, 0.128 mmol, 66% yield, 94% ee); R_f = 0.5 (hexane: ethyl acetate = 4:1); ^1H

NMR (300 MHz, CDCl_3): δ 7.55-7.57 (m, 2H), 7.41-7.44 (m, 3H), 7.32-7.35 (m,

2H), 7.18-7.26 (m, 5H), 7.09-7.12 (m, 2H), 6.94 (t, $J=2.1$ Hz, 1H), 4.80 (td, $J=7.1$, 2.3 Hz, 1H), 4.42 (td, $J=7.1$, 2.2 Hz, 1H), 3.92-4.15 (m, 3H), 1.06 (t, $J=7.1$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 199.8, 163.8, 146.5, 143.1 (CH x 2), 142.8, 138.5, 136.2, 133.4, 129.0 (CH x 2), 128.6 (CH x 2), 128.3 (CH x 2), 127.9 (CH x 2), 127.6 (CH x 2), 127.0 (CH x 2), 125.87, 125.82, 52.1, 49.9, 33.5, 28.0, 13.8 ppm; FTIR (neat): ν = 1714, 1676, 1325, 1215, 1130, 1066 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{28}\text{H}_{24}\text{O}_3\text{F}_3^+$ $[\text{M}+\text{H}]^+$ 465.1678, found: 465.1655; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 1% isopropanol/hexane, 1.0 mL/min): t_1 = 20.1 min (major), t_2 = 35.6 min (minor); $[\alpha]_{\text{D}}^{20}$ = + 13.7° (c = 0.51, CH_2Cl_2).

Ethyl-4-benzoyl-5-phenyl-3-(thiophen-3-yl)-cyclopent-1-enecarboxylate: The

product was prepared using the general procedure but employing Ethyl 4-(thiophen-3-yl)-but-3-ynoate (50 mg, 0.257 mmol), *trans*-chalcone (64.0 mg, 0.309 mmol) and

(*R, R*)-DIPAMP (12 mg, 0.025 mmol). After 8 h, the solvent was removed and the residue was purified through flash column chromatography (12% ethyl acetate in hexane) to afford product **39m'** as a colorless oil (93 mg, 0.2319 mmol, 90% yield, 96% ee); R_f = 0.4 (hexane: ethyl acetate = 4:1); ^1H NMR (300 MHz, CDCl_3): δ 7.42-7.55 (m, 3H), 7.10-7.30 (m, 8H), 6.93-7.02 (m, 3H), 4.71 (td, $J=6.6$, 2.3 Hz, 1H), 4.46 (td, $J=6.7$, 2.2 Hz, 1H), 3.90-4.10 (m, 3H), 1.06 (t, $J=7.1$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ 200.2, 164.0, 143.9, 143.2, 142.7, 137.3, 136.3, 133.2, 128.9 (CH x 2), 128.5 (CH x 2), 128.2 (CH x 2), 127.6 (CH x 2), 126.9, 126.8, 126.5,

121.2, 63.5, 60.2, 55.0, 49.0, 13.8 ppm; **FTIR (neat):** ν = 1712, 1676, 1215, 1099 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{25}\text{H}_{23}\text{O}_3\text{S}^+$ $[\text{M}+\text{H}]^+$ 403.1368, found: 403.1351; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): t_1 = 37.2 min (major), t_2 = 48.0 min (minor); $[\alpha]_{\text{D}}^{20}$ = + 11.7° (c = 0.51, CH_2Cl_2).

Ethyl 4-benzoyl-3-(6-methoxynaphthalen-2-yl)-5-phenylcyclopent-1-enecarboxylate

te: The product was prepared using the general procedure but employing Ethyl

4-(6-methoxynaphthalen-2-yl)-but-3-ynoate (50 mg, 0.1865 mmol), *trans*-chalcone (47 mg, 0.2238 mmol) and (*R,R*)-DIPAMP (8.5 mg, 0.018 mmol). After 8 h,

the solvent was removed and the residue was purified through flash column chromatography (12% ethyl acetate in hexane) to afford product **39n'** as a colorless oil (68 mg, 0.143 mmol, 77% yield, 96% ee); R_f = 0.6 (hexane: ethyl acetate = 4:1); **^1H NMR (300 MHz, CDCl_3):** δ 7.66 (t, J =9.1 Hz, 2H), 7.55 (brs, 1H), 7.35-7.50 (m, 3H), 7.05-7.30 (m, 10H), 7.02 (t, J =2.2 Hz, 1H), 4.77 (td, J =7.0, 2.3 Hz, 1H), 4.51 (td, J =7.0, 2.2 Hz, 1H), 3.95-4.20 (m, 3H), 3.89 (s, 3H), 1.07 (t, J =7.1 Hz, 3H) ppm; **^{13}C NMR (75 MHz, CDCl_3):** δ 200.5, 164.1, 157.6, 144.5, 143.3, 137.7, 137.4, 136.4, 133.6, 133.1, 129.1, 128.9 (CH x 2), 128.8, 128.5 (CH x 2), 128.1 (CH x 2), 127.6 (CH x 2), 127.5, 126.7, 126.2, 126.0, 119.1, 105.5, 64.6, 60.3, 55.3, 55.2, 53.8, 13.9 ppm; **FTIR (neat):** ν = 1712, 1676, 1606, 1251, 1215, 1099, 1031 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{32}\text{H}_{29}\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 477.2066, found: 477.2075; The enantiomeric

excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 1% isopropanol/hexane, 1.0 mL/min): t_1 = 64.5 min (major), t_2 = 97.4 min (minor); $[\alpha]_D^{20}$ = + 150.0° (c = 0.50, CH₂Cl₂).

Ethyl 4-benzoyl-3-cyclopropyl-5-phenylcyclopent-1-enecarboxylate:

The product was prepared using the general procedure but employing Ethyl 4-cyclopropylbut-3-ynoate (50 mg, 0.3289 mmol), *trans*-chalcone (82 mg, 0.3947 mmol) and (*R*, *R*)-DIPAMP (15 mg, 0.033 mmol). After 8 h, the solvent was removed and the residue was purified through flash column chromatography (12% ethyl acetate in hexane) to afford product **39o'** as a colorless oil (110 mg, 0.3059 mmol, 93% yield, 90% ee); R_f = 0.4 (hexane: ethyl acetate = 4:1); ¹H NMR (500 MHz, CDCl₃): δ 7.72-7.74 (m, 2H), 7.45-7.55 (m, 1H), 7.30-7.38 (m, 2H), 7.10-7.30 (m, 5H), 6.88 (t, J = 2.1 Hz, 1H), 4.32-4.38 (m, 1H), 3.90-4.10 (m, 3H), 2.65-2.75 (m, 1H), 1.05 (t, J = 7.1 Hz, 3H), 0.85-0.98 (m, 1H), 0.55-0.65 (m, 1H), 0.35-0.45 (m, 1H), 0.25-0.33 (m, 1H), 0.01-0.08 (m, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 201.1, 164.1, 145.3, 143.6, 136.4, 136.3, 133.0, 128.8 (CH x 2), 128.4 (CH x 2), 128.2 (CH x 2), 127.5 (CH x 2), 126.6, 61.2, 60.0, 55.0, 54.2, 15.6, 13.8, 4.4, 3.9 ppm; FTIR (neat): ν = 1712, 1678, 1597, 1448, 1255, 1215, 1020, 776, 744, 700, 668 cm⁻¹; HRMS (ESI, *m/z*): calcd for C₂₄H₂₅O₃⁺ [M+H]⁺ 361.1804, found: 361.1802; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD-H & OD-H column (each 0.46 cm ϕ X 25 cm; 1% isopropanol/hexane, 1.0 mL/min): t_1 = 19.4 min (major), t_2 = 33.5 min (minor); $[\alpha]_D^{20}$ = - 92.5° (c = 0.40, CH₂Cl₂).

Ethyl 4-benzoyl-3-methyl-5-phenylcyclopent-1-enecarboxylate:

The product was prepared using the general procedure but employing ethyl penta-2, 3-dienoate (50 mg, 0.3968 mmol), *trans*-chalcone (99 mg, 0.4761 mmol) and (*R, R*)-DIPAMP (18 mg, 0.039 mmol). After 8 h, the solvent was removed and

the residue was purified through flash column chromatography (12% ethyl acetate in hexane) to afford product **39p'** as a colorless oil (115 mg, 0.3452 mmol, 87% yield, 99% ee); R_f = 0.4 (hexane: ethyl acetate = 4:1); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.55-7.65 (m, 2H), 7.30-7.40 (m, 1H), 7.0-7.3 (m, 7H), 6.7 (t, J =2.2 Hz, 1H), 4.35 (td, J =5.9, 1.7 Hz, 1H), 3.8-4.1 (m, 2H), 3.6 (t, J =5.7 Hz, 1H), 3.2-3.3 (m, 1H), 1.2 (d, J =7.2 Hz, 3H), 0.97 (t, J =7.1 Hz, 3H) ppm; $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 200.7, 164.2, 147.2, 143.8, 136.6, 135.9, 133.1, 128.8, 127.7, 128.5, 128.48, 128.42, 128.2, 127.5, 127.2, 126.6, 62.5, 60.1, 54.9, 43.5, 20.1, 13.8 ppm; **FTIR** (neat): ν =1718, 1667, 1597, 1444, 1259, 1215, 1120, 798, 677 cm^{-1} ; **HRMS** (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{23}\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 335.1647, found: 335.1642; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD-H & OD-H column (each 0.46 cm ϕ X 25 cm; 1% isopropanol/hexane, 1.0 mL/min): t_1 = 22.9 min (major), t_2 = 30.1 min (minor).

3.4.4 Determination of Absolute Stereochemistry

4-Benzoyl-3-methyl-5-phenylcyclopent-1-enecarboxylic acid (**39.1p'**)

To a stirred solution of ethyl 4-benzoyl-3-methyl-5-phenylcyclopent-1-ene carboxylate (100 mg, 0.299 mmol) in a mixture of THF (2.5 mL) and water (2.5 mL), was added methanol (0.5 mL) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (63 mg, 1.5 mmol) at $0\text{ }^\circ\text{C}$. After stirring the reaction mixture for 20 h at $60\text{ }^\circ\text{C}$, concentrated to remove the THF, and then acidified to pH 5 using 1M HCl. The pure products (90 mg, 0.294 mmol, 98%) get precipitated as white solid that was filtered and dried over vacuum. **^1H NMR (300 MHz, CDCl_3):** δ 7.70-7.65 (m, 2H), 7.50-7.55 (m, 1H), 7.37-7.30 (m, 2H), 7.25-7.15 (m, 4H), 7.05-7.10 (m, 2H), 6.95 (t, $J=2.2$ Hz, 1H), 4.35-4.45 (m, 1H), 3.65 (t, $J=5.4$ Hz, 1H), 3.30-3.40 (m, 1H), 1.27 (d, $J=7.2$ Hz, 3H) ppm; **^{13}C NMR (100 MHz, CDCl_3):** δ 200.2, 168.8, 150.0 (CH x 2), 144.5 (CH x 2), 135.0 (CH x 2), 134.7, 133.5 (CH x 2), 124.8 (CH x 3), 124.6 (CH x 2), 63.8, 55.2, 42.8, 18.8 ppm.

Benzyl 4-benzoyl-3-methyl-5-phenylcyclopent-1-enecarboxylate (39α):

To a mixture of 4-benzoyl-3-methyl-5-phenylcyclopent-1-enecarboxylic acid (90 mg, 0.29 mmol) and anhydrous K₂CO₃ (61 mg, 0.44 mmol) in DMF (3 mL), was added benzyl bromide (55 mg, 0.32 mmol) drop-wise at 0 °C under nitrogen atmosphere. After 18 h stirring at room temperature, the reaction was quenched with ice-cold water and extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine and then dried over anhydrous sodium sulfate. After filtration and evaporation of solvent in vacuum, the resulting residue was purified by flash column chromatography using 10% ethyl acetate in hexane, which provided the pure product as a colorless oil (111 mg, 0.282 mmol; 96% yield, 97% ee); **¹H NMR (300 MHz, CDCl₃):** δ 7.65-7.75 (m, 2H), 7.45-7.50 (m, 1H), 7.20-7.35 (m, 8H), 7.05-7.15 (m, 2H), 6.95-7.02 (m, 2H), 6.85 (t, *J*=2.1 Hz, 1H), 5.02 (ABq, *J*_{AB}=12.6 Hz, 2H), 4.45 (td, *J*=5.8, 1.7 Hz, 1H), 3.68 (t, *J*=5.7 Hz, 1H), 3.30-3.40 (m, 1H), 1.27 (d, *J*=7.2 Hz, 3H) ppm; **¹³C NMR (100 MHz, CDCl₃):** δ 200.7, 164.1, 148.3, 143.8, 136.7, 135.8, 135.6, 133.2, 128.8, 128.7 (CH x 2), 128.5 (CH x 2), 128.3 (CH x 2), 127.8 (CH x 2), 127.7 (CH x 2), 127.6 (CH x 2), 126.8, 65.9, 62.6, 54.9, 43.7, 20.2 ppm; **FTIR (neat):** ν = 3433, 3063, 2692, 1714, 1675, 1635, 1597, 1493, 1447, 1297, 1229, 1108, 1077, 753, 698, 668 cm⁻¹; **HRMS (ESI, m/z):** calcd for C₂₇H₂₅O₃⁺ [M+H]⁺ 397.1804, found: 397.1805; The enantiomeric excess was determined by HPLC analysis employing Daicel chiracel OD & OD-H column (each 0.46 cm ϕ X 25 cm; 0.8% isopropanol/hexane, 1.0 mL/min): t₁ = 41.9 min (major), t₂ = 73.9 min (minor).

CHAPTER 4

*Phosphine-Catalyzed One-Pot
Isomerization of 3-Alkynoates and
[3+2]-Cycloaddition with Imines:
Application in the Formal Synthesis
of Securinega Alkaloid ($\pm$)-
Allosecurinine*

Chapter 4 Phosphine-Catalyzed One-Pot Isomerization of 3-Alkynoates and [3+2]-Cycloaddition with Imines: Application in the Formal Synthesis of Securinega Alkaloid (±)-Allosecurinine

4.1 Introduction

Heterocycles are important components of biologically active molecules.⁵⁹ Many natural products and drug molecules possess nitrogen containing heterocycles as core structural units. Amongst them, pyrrolines are featured widely in many natural products.⁶⁰ Consistent with their biological importance, various methods have been developed for the synthesis of pyrrolines.

An efficient method to construct such a heterocycle, using metal free catalysis, has been attracting much attention. Amongst the available methods, Lu's phosphine catalyzed [3+2]-cycloaddition between electron-deficient allenoates/2-alkynoates and imine is considered to be an efficient strategy for the construction of pyrrolines.³⁸ In addition, the asymmetric version of this reaction was successfully examined by Jacobsen⁴² and Marinetti.^{40 & 41} Kwon and Fu *et al.* have elegantly demonstrated the usefulness of the [4+2] approach by using α -methyl substituted allenoates in the synthesis of tetrahydropyridine derivatives.⁴³⁻⁴⁵ Although Lu's methodology with

⁵⁹ (a) Fowden, L. *Nature* **1955**, 176, 347. (b) Cheng, Q.; Kiyota, H.; Yamaguchi, M.; Horiguchi, T.; Oritani, T. *Bioorg. Med. Chem. Lett.* **2003**, 13, 1075. (c) Bannon, A. W.; Decker, M. W.; Holladay, M. W.; Curzon, P.; Dickenson, A. H.; Porsolt, R. D.; Williams, M.; Arnerie, S. P. *Science* **1998**, 279, 77. (d) Michael, J. P. *Nat. Prod. Rep.* **2004**, 21, 625. (e) Michael, J. P. *Alkaloids* **2001**, 55, 91. (f) Khalaf, J. K.; Datta, A. *J. Org. Chem.* **2004**, 69, 387. (g) Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, 2, 3039. (h) Poisson, J. -F.; Orellana, A.; Greene, A. E. *J. Org. Chem.* **2005**, 70, 10860-10863. (i) Joo, J. -E.; Lee, K. -Y.; Pham, V. -T.; Tian, Y. -S.; Ham, W. -H. *Org. Lett.* **2007**, 9, 3627.

⁶⁰ (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, 17, 435. (b) Green, M. P.; Prodger, J. C.; Hayes, C. J.; *Tetrahedron Lett.* **2002**, 43, 6609. (c) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, 36, 1621.

activated olefins have been widely utilized in the synthesis of natural products,^{18, 21 & 23} surprisingly, there is no documentation of Lu's reaction with imines in the natural product synthesis. This is probably due to the difficulty of executing this reaction using aliphatic aldimines which contain α -C-H functionality. Another limitation is the difficulty of synthesizing the allenoate/2-alkynoate starting material and their limited substrate scope. In this chapter, we envisioned the phosphine catalyzed *in situ* isomerization of 3-alkynoate **87** to allenoate **16** and [3+2]-cycloaddition with various activated aromatic and aliphatic imines **71** in the synthesis of 2, 5-*syn*-disubstituted pyrrolines **74** (Scheme 4.1).

Scheme 4.1 Proposed synthesis of 2, 5-*syn* substituted pyrrolines and its application in formal synthesis of Allosecurinine

We also envisaged the application of the one-pot isomerization and cycloaddition method in the synthesis of the *Securinega* alkaloid (Scheme 4.1).⁶¹ The most representative examples of this family include securinine (**1**), its C-2 epimer allosecurinine (**2**) and their corresponding enantiomers, virosecurinine (**3**) and viroallosecurinine (**4**) (Scheme 4.2). Due to their interesting structural features and potential biological activities of these alkaloids, many research groups have focused on the synthesis.⁶⁴

Scheme 4.2 Structure of securinega alkaloids

Recently, Barcelona and Kerr research group reported the total synthesis of (-)-Allosecurinine. In 2008, Kerr and coworker have developed Yb(OTf)₂ catalyzed intramolecular addition of cyclopropane diester with tethered oxime ethers to the

⁶¹ For previous studies on securinine alkaloids, see: (a) Weinreb, S. M. *Nat. Prod. Rep.* **2009**, 26, 758. (b) Honda, T.; Namiki, H.; Watanabe, M.; Mizutani, H. *Tetrahedron Lett.* **2004**, 45, 5211. (c) Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, 130, 7562. (d) Alibés, A.; Bayón, P.; de March, P.; Figueredo, M.; Font, J.; Garcia-Garcia, E.; González-Gálvez, D. *Org. Lett.* **2005**, 7, 5107-5109. (e) Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H.; *Org. Lett.* **2004**, 6, 87. (f) Honda, T.; Namiki, H.; Kudoh, M.; Nagase, H.; Mizutani, H. *Heterocycles* **2003**, 59, 169. (g) Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, 130, 7562 and references cited therein.

stereoselective synthesis of *cis*-pyrroloisoxazolidines. In the same year, Kerr and Leduc reported the use of this methodology as a key step in the total synthesis of (-)-allosecurinine.⁶² The key pyrrolidine skeleton of allosecurinine could be synthesized from *cis*-pyrroloisoxazolidines after series of chemical transformation such as reductive N-O bond cleavage, Krapcho decarboxylation of geminal diester and α -hydroxylation of ester using Davis oxaziridine. In 2008, the Barcelona research group reported the total synthesis of (+)-Viroallosecurinine, starting from simple natural product (-)-menisdaurilide. Similarly, its enantiomer (-)-Allosecurinine was synthesized from unnatural (+)-menisdaurilide.

4.2 Results and Discussion

In our initial studies, ethyl-4-phenylbut-3-ynoate **87a** and *N*-tosylimine **71a** were chosen as model substrate and the reactions were attempted with various commercially available phosphines (Table 4.1). The reaction proceeded smoothly with catalytic amount of trimethylphosphine to afford functionalized pyrrolines **74aa** in 84% yield with excellent regio- and diastereoselectivity (Table 4.1, entry 6).

⁶² Leduc, A. B.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 7945.

Table 4.1 Optimization of reaction condition

$\text{Ph}-\text{C}\equiv\text{C}-\text{CH}_2\text{CO}_2\text{Et}$ (87a) + $\text{Ts}-\text{N}=\text{CH}-\text{Ph}$ (71a) $\xrightarrow[\text{solvent, rt}]{\text{phosphine (20 mol\%)}}$ $\text{Ph}-\text{CH}=\text{C}(\text{CO}_2\text{Et})-\text{N}(\text{Ts})-\text{CH}(\text{Ph})-\text{Ph}$ (74aa)

Entry	Phosphines	Solvent	Yield (%)
1	Triphenylphosphine	toluene	0
2	Tricyclohexylphosphine	toluene	51
3	Trimethoxyphosphine	toluene	27
4.	Tri-n-butylphosphine	toluene	71
5	Tri-t-butylphosphine	toluene	69
6	Trimethylphosphine	toluene	84
7	Trimethylphosphine	CH_2Cl_2	77
8	Trimethylphosphine	Diethyl ether	68
9.	Trimethylphosphine	Dimethoxymethane	trace
10.	Trimethylphosphine	THF	81
11.	Trimethylphosphine	DMF	trace
12.	Triethylphosphine	toluene	75
13.	Ethylenebis(diphenylphosphine)	toluene	64
14.	1,3-bis(diphenylphosphino)propane	toluene	69

To examine the generality of this protocol, a series of electron-deficient *N*-tosylimine⁶³ (Table 4.2; entries 1-8) and 3-alkynoates⁵⁷ (Table 4.3, entries 9-15) were screened, in all cases, excellent yields were observed. Both electron withdrawing and releasing substituents on the phenyl ring of *N*-tosylimines **71** and 3-alkynoates **87** provided products in good yields. In addition, the heteroaromatic containing 3-alkynoate **87f** and imine **71h** proceeded smoothly in the reaction condition to afford the cyclized products in good yields (Table 4.2).

Table 4.2 Scope of [3+2] cycloaddition with respect to the various electron deficient 3-alkynoates and imines ^a

Reaction scheme: 3-alkynoate **87** (R¹-C≡C-CO₂Et) reacts with *N*-tosylimine **71** (Ts-N=CH-R²) in the presence of PMe₃ (20 mol%) in toluene at room temperature for 2 hours to yield the cyclized product **74** (a 2,3-disubstituted pyrrole derivative with a Ts group on the nitrogen).

Entry	R ¹	R ²	Product	Yield (%) ^b
1	C ₆ H ₅ 87a	C ₆ H ₅ 71a	74aa	84
2	C ₆ H ₅ 87a	4-Et-C ₆ H ₄ 71b	74ab	76
3	C ₆ H ₅ 87a	4-Me-C ₆ H ₄ 71c	74ac	68
4	C ₆ H ₅ 87a	4-OMe-C ₆ H ₄ 71d	74ad	71
5	C ₆ H ₅ 87a	2-OMe-C ₆ H ₄ 71e	74ae	70
6	C ₆ H ₅ 87a	4-Br-C ₆ H ₄ 71f	74af	54
7	C ₆ H ₅ 87a	4-Cl-C ₆ H ₄ 71g	74ag	89
8	C ₆ H ₅ 87a	2-furyl 71h	74ah	64

⁶³ (a) Jin, T.-S.; Yu, M.-J.; Liu, Y.; Zhao, L.-B.; Li, T.-S. *Synthetic Communications* **2006**, 36, 2339.

Table 4.2 (*continued*)

9	4-Me-C ₆ H ₄ 87b	2-furyl 71h	74bh	77
10	4-OMe-C ₆ H ₄ 87c	2-furyl 71h	74ch	68
11	H 87d	2-furyl 71h	74dh	70
12	4-CF ₃ -C ₆ H ₄ 87e	2-furyl 71h	74eh	83
13	thien-2-yl 87f	2-furyl 71h	74fh	79
14	6-OMe-2-naphthyl 87g	2-furyl 71h	74gh	61
15	CO ₂ Et 87j	C ₆ H ₅ 71a	74ja	55

^a See the experimental section for detailed experimental procedure; 3-alkynoates (**84a-84j**) was contaminated with 2 – 5 % of the corresponding allenates. ^b Isolated yield.

To enhance the synthetic value of this method, a series of N-mesyl protected imines⁶⁴ were subjected to the optimized reaction conditions. In all the cases, the pyrrolidines were obtained in good yields (Table 4.3, entries 1-7).

⁶⁴ Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 1231.

Table 4.3 Scope with respect to the various methanesulfonamide imines ^{a, b}

^a See the experimental section for detailed experimental procedure; 3-butynoate (**87a**) was contaminated with 2 % of corresponding allenoate. ^b Isolated yield.

Pyrrolines with aliphatic substitutions are important building blocks featured widely in many natural products and drug molecules. With this in mind, we next turned our attention to perform the reactions using aliphatic 3-alkynoates and imines.⁶⁵ Surprisingly, to the best of our knowledge, there is just one example using aliphatic imine (*N*-tosylcinnamaldimine) was reported.^{38b} Using previously optimized

⁶⁵ Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75.

reaction condition; the aliphatic imines containing α -H functionality reacted smoothly to afford cyclized products in excellent yields (Table 4.4, entries 1-7). Moreover, THP protected hex-3-ynoates **87k** and imine **71q** provided 2,5-di-alkyl substituted pyrrolidine **74kq** in 70% yield with 1.2:1 diastereomeric mixture.

Table 4.4 Scope of Cycloaddition with respect to the various aliphatic aldimines

The mechanism of the reaction is proposed in scheme 4.2, which is similar to the mechanism proposed by Lu.^{38b} Initially, trimethylphosphine triggers the isomerization of alkynoate **87** to allenoate **16** which in turn reacts with trimethylphosphine to obtain

1,3-dipolar phosphonium intermediate **39.1**. The resulting dipolar species **39.1** underwent nucleophilic addition with imine **71** via a α -carbon to obtain sterically more favoured linear intermediate **39.1A**. Subsequent ring closure, proton transfer and elimination of phosphine afforded 2,5-syn substituted cyclized product **74** (Scheme 4.2).

Scheme 4.2 Proposed mechanism for one-pot isomerization and cycloaddition

Our retrosynthetic approach for the synthesis of allosecurinine is shown in scheme 4.3. The crucial steps involve (i) coupling of alkynoates **87i** and imine **71w** using our

previously developed PMe_3 -catalyzed [3+2]-cyclization to obtain **74lw** and (ii) subsequent reductive opening of the epoxide to give the key intermediate 1, 2-diol **89**.

Scheme 4.4 Proposed synthesis of 2, 5-*syn* substituted pyrrolines and its application in formal synthesis of allosecurinine

To commence our synthetic plan, alkynoate **87l** and *N*-tosylimine **71w** were readily prepared following reported procedures.^{57 & 63} Using a previously optimized condition, [3+2]-cycloaddition reaction of **87l** with **71w** was proceeded smoothly in the presence of 20 mol% of trimethylphosphine to furnish the desired product **74lw** in 82% isolated yields as single *syn*-diastereomers. Reduction of the ester group in **74lw**

with DIBAL-H furnished the primary alcohol **88**, and subsequent epoxidation with *m*-CPBA gave the required product **89**. In the next step, various reducing agents for epoxide opening such as Red-Al, lithium aluminum hydride and sodium hydride were tested. However, only trace amount of products were obtained. With DIBAL-H the required product **90** was isolated in 64% yield. The resulting 1, 2-diol moiety in product **90** was protected using 2, 2'-dimethoxypropane to provide **91** and the remaining primary alcohol was iodinated to give **92** along with a trace amount of di-iodide product **92a** (X-ray; Figure 4.1). The product **92** was treated with sodium hydride to afford the E₂-eliminated product **93**. Although removal of tosyl group failed with various mild protocols, sodium naphthalide in DMSO was found to work smoothly and product **94** was isolated in 69% yields.⁶⁶ Finally, deprotection of the 1, 2-diol and Boc protection were carried out in one-pot to furnish the key intermediate **95** (88% yield from **17**) and the structure was confirmed by comparing with a previous report.⁶²

⁶⁶ Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548.

Scheme 4.5 Synthesis of key intermediate **95**; Reaction condition: a) PMe_3 20 mol%, toluene, 2 h, 25 °C, 82%; b) 2.0 equiv. DIBAL-H (1.0 M in THF), -78 °C, CH_2Cl_2 , 74%; c) *m*-CPBA, CH_2Cl_2 , 12 h, 81%; d) 4.0 equiv. DIBAL-H (1.0 M in THF); -78 °C, -25 °C, CH_2Cl_2 , 24 h, 64%; e) 10 equiv. 2-2'-dimethoxypropane, 0.1 equiv. CSA, CH_2Cl_2 ; 77% yield f) I_2 , PPh_3 , imidazole; THF; 87%; g) NaH (60%), TBAI, THF, 78

°C, 88%; h) Na-naphthalide, DME, 69%; i) 3M HCl, THF-H₂O (1:1) and j) (Boc)₂O, TEA; THF, 88% (over 2 steps).

Figure 4.1 ORTEP drawing of **92a** with thermal ellipsoids at 50% probability levels⁶⁷

4.3 Conclusion

In this chapter, an effective procedure for the synthesis of 2,5-*syn*-di-substituted pyrrolines is described. This one-pot isomerization of 3-alkynoates and cycloaddition

⁶⁷ CCDC 829904 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

sequence with imines provided an efficient alternative to existing protocols for the synthesis of 2,5-*syn*-disubstituted pyrrolines. Moreover, pyrrolines with both aromatic and aliphatic substitutions were synthesized in excellent yields. In addition, the utility of this protocol was demonstrated in the efficient formal synthesis of the natural product allosecurinine. Further investigations on the asymmetric synthesis of optically pure *cis* 2,5-disubstituted pyrrolines, which can be rerouted to the enantioselective synthesis of both allosecurinine and viroallosecurinine are in progress.

4.4 Experimental Section

4.4.1 General procedure for synthesis of **74**:

To a solution of alkynoates and imines in toluene (4 mL), phosphine catalyst in toluene was added dropwise for 10 min at 0 °C. The solution was warmed to room temperature and stirred until then disappearance of alkynoates. Flash column chromatography using hexane and ethyl acetate was done to obtain the pyrrolines **74**.

Ethyl 2,5-diphenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**74aa**):

The product was prepared by the above general procedure employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol), (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (82 mg, 0.318

mmol) and PMe₃ (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate

in hexane) to afford product **74aa** (100 mg, 0.223 mmol, 84% yield); **R_f**: 0.4 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 99-101 °C; **¹H NMR (400 MHz, CDCl₃)**: δ = 7.25 – 7.30 (m, 10H), 7.19 – 7.21 (m, 2H), 6.99 – 7.01 (m, 2H), 6.75 (t, *J* = 2.1 Hz, 1H), 5.95 (t, *J* = 2.5 Hz, 1H), 5.87 (t, *J* = 2.5 Hz, 1H), 3.93 - 4.13 (m, 2H), 2.31 (s, 3H), 1.07 (t, *J* = 7.13 Hz, 3H) ppm; **¹³C NMR (100 MHz, CDCl₃)**: δ = 162.0, 143.1, 139.3, 139.2, 138.2, 136.0, 133.9, 129.1(2), 128.55(2), 128.50(2), 128.1(2), 128.0, 127.7(2), 127.2(2), 69.8, 69.5, 60.8, 29.6, 21.3, 13.8 ppm; **FTIR (neat)**: ν = 3053, 2986, 2926, 2304, 1721, 1454, 1421, 1341, 1265, 1165, 1093 cm⁻¹; **HRMS (ESI, m/z)**: calcd for C₂₆H₂₆NO₄S [M+H]⁺ 448.1583, found: 448.1585.

Ethyl-2-(4-ethylphenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74ab):

The product was prepared by the above general procedure employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol),

(*E*)-*N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide (92 mg, 0.318 mmol) and PMe₃ (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ab** (96 mg, 0.202 mmol, 76% yield); **R_f**: 0.4 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 95-98 °C; **¹H NMR (400 MHz, CDCl₃)**: δ = 7.16 – 7.30 (m, 9H), 6.97 – 7.09 (m, 4H), 6.72 – 6.73 (m, 1H), 5.85 – 5.90 (m, 2H), 3.92 - 4.07 (m, 2H), 2.61 (q, *J* = 7.60 Hz, 2H), 2.30 (s, 3H), 1.22 (t, *J* = 7.60 Hz, 3H), 1.08 (t, *J* =

7.12 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 162.2 (1C), 144.1 (1C), 143.1 (1C), 139.1 (1C), 138.4 (1C), 136.6 (1C), 136.2 (1C), 134.1 (1C), 129.1 (2C), 128.6 (2C), 128.5 (2C), 128.2 (1C), 127.8 (2C), 127.7 (2C), 127.3 (2C), 69.8 (1C), 69.4 (1C), 60.8 (1C), 28.6 (1C), 21.4 (1C), 15.7 (1C), 13.9 (1C) ppm; FTIR (neat): ν = 3055, 2984, 2968, 2932, 1721, 1599, 1454, 1422, 1340, 1265, 1165, 1093 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{28}\text{H}_{30}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 476.1896, found: 476.1896.

Ethyl 5-phenyl-2-p-tolyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74ac):

The product was prepared by the above general procedure, employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol), (*E*)-4-methyl-N-(4-methylbenzylidene)

benzenesulfonamide (87 mg, 0.318 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ac** (83 mg, 0.181 mmol, 68% yield); R_f : 0.4 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 94–98 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ = 7.22 – 7.37 (m, 9H). 7.01 – 7.08 (m, 4H), 6.72 – 6.73 (m, 1H), 5.88 – 5.89 (m, 1H), 5.82 – 5.84 (m, 1H), 3.97 – 4.08 (m, 2H), 2.32 (s, 6H), 1.09 (t, J = 7.12 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ = 162.2 (1C), 143.2 (1C), 139.1 (1C), 138.4 (1C), 137.8 (1C), 136.5 (1C), 136.0 (1C), 134.0 (1C), 129.2 (2C), 128.9 (2C), 128.6 (2C), 128.4 (2C), 128.1 (1C), 127.7 (2C), 127.4 (2C), 69.9 (1C), 69.4 (1C), 60.9 (1C), 21.4 (1C), 21.2 (1C), 13.9 (1C) ppm;

FTIR (neat): ν = 3053, 2986, 2305, 1721, 1454, 1341, 1265, 1165, 1092 cm^{-1} ;

HRMS (ESI, m/z): calcd for $\text{C}_{27}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 462.1705, found: 462.1712.

Ethyl-2-(4-methoxyphenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74ad):

The product was prepared by the above general procedure employing

ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol),

(*E*)-*N*-(4-methoxybenzylidene)-4-methylbenzenesulfona

mide (92 mg, 0.318 mmol) and PMe_3 (5 mg, 0.053

mmol). After 2 h the solvent was removed and the residue was purified through flash

column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ad**

(90 mg, 0.189 mmol, 71% yield); **R_f :** 0.4 (Hexane: Ethyl acetate = 4:1). Yellow solid;

m.p. 99-101 $^{\circ}\text{C}$; **^1H NMR (400 MHz, CDCl_3):** δ = 7.21 – 7.36 (m, 9H), 7.00 – 7.03

(m, 2H), 6.79 – 6.81 (m, 2H), 6.72 – 6.73 (m, 1H), 5.89 – 5.90 (m, 1H), 5.82 – 5.83

(m, 1H), 3.98 - 4.09 (m, 2H), 3.79 (s, 3H), 2.31 (s, 3H), 1.09 (t, J = 7.50 Hz, 3H)

ppm; **^{13}C NMR (100MHz, CDCl_3):** δ = 162.4 (1C), 159.6 (1C), 143.3 (1C), 139.3

(1C), 138.6 (1C), 136.3 (1C), 134.1 (1C), 131.8 (1C), 129.9 (2C), 129.4 (2C), 128.8

(2C), 128.3 (1C), 127.8 (2C), 127.5 (2C), 113.8 (2C), 69.9 (1C), 69.3 (1C), 61.0

(1C), 55.4 (1C), 21.7 (1C), 14.1 (1C) ppm; **FTIR (neat):** ν = 3053, 2986, 2305,

1719, 1512, 1341, 1265, 1165, 1094, 1034 cm^{-1} ; **HRMS (ESI, m/z):** calcd for

$\text{C}_{27}\text{H}_{28}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 478.1688, found: 478.1681.

Ethyl-2-(2-methoxyphenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74ae):

The product was prepared by the above general procedure, employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol), (*E*)-N-(2-methoxybenzylidene)-4-methylbenzenesulfonamide

(92 mg, 0.318 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ae** as a colorless oil (89 mg, 0.186 mmol, 70% yield); ^1H NMR (400 MHz, CDCl_3): δ = 7.47 – 7.53 (m, 4H), 7.30 – 7.38 (m, 3H), 7.12 – 7.21 (m, 4H), 6.83 – 6.85 (m, 2H), 6.71 (m, 1H), 6.33 (m, 1H), 5.82 (m, 1H), 3.89 – 4.09 (m, 2H), 3.85 (s, 3H), 2.34 (s, 3H), 1.01 (t, J = 7.50 Hz, 3H) ppm; ^{13}C NMR (100MHz, CDCl_3): δ = 162.1 (1C), 157.5 (1C), 143.4 (1C), 139.2 (1C), 138.9 (1C), 135.0 (1C), 134.3 (1C), 129.3 (3C), 129.2 (1C), 128.6 (2C), 128.4 (1C), 128.0 (1C), 127.8 (2C), 127.5 (2C), 120.5 (1C), 111.1 (1C), 69.8 (1C), 62.6 (1C), 60.7 (1C), 55.8 (1C), 21.5 (1C), 13.8 (1C) ppm; FTIR (neat): ν = 3055, 2984, 2839, 2305, 1719, 1598, 1493, 1352, 1265, 1167, 1094 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{27}\text{H}_{28}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 478.1688, found: 478.1681.

Ethyl-2-(4-bromophenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate

(**74af**): The product was prepared by the above general procedure, employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol),

(*E*)-*N*-(4-bromobenzylidene)-4-methylbenzenesulfonamide (108 mg, 0.318 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74af** (76 mg, 0.143 mmol, 54% yield); R_f : 0.5 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 96-101 °C; ^1H NMR (400 MHz, CDCl_3): δ = 7.32 – 7.34 (m, 7H), 7.20 – 7.23 (m, 4H), 7.03 – 7.05 (m, 2H), 6.76 (brs, 1H), 5.86 (brs, 2H), 3.99 – 4.10 (m, 2H), 2.34 (s, 3H), 1.11 (t, J = 7.20 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 162.1 (1C), 143.7 (1C), 139.8 (1C), 138.7 (1C), 138.3 (1C), 135.9 (1C), 133.8 (1C), 131.5 (2C), 130.4 (2C), 129.5 (2C), 128.9 (2C), 128.5 (1C), 127.8 (2C), 127.5 (2C), 122.3 (1C), 70.1 (1C), 69.1 (1C), 61.2 (1C), 21.6 (1C), 14.1 (1C) ppm; FTIR (neat): ν = 3053, 2986, 2305, 1719, 1421, 1341, 1265, 1165, 1092 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{26}\text{H}_{25}\text{BrNO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 526.0688, found: 526.0682.

Ethyl-2-(4-chlorophenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate

e (74ag): The product was prepared by the above general procedure, employing

ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol),

(*E*)-*N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide

(94 mg, 0.318 mmol) and PMe_3 (5 mg, 0.053 mmol). After

2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ag** (114 mg, 0.236 mmol, 89% yield); R_f : 0.6 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 98-101 °C; ^1H NMR (400 MHz, CDCl_3): δ = 7.36 – 7.37 (m, 2H), 7.24 – 7.29 (m,

4H), 7.06 – 7.08 (m, 2H), 6.93 – 6.94 (m, 2H), 6.73 (t, $J = 2.18$ Hz, 1H), 6.43 – 6.44 (m, 1H), 6.31 – 6.32 (m, 1H), 6.07 (t, $J = 2.35$ Hz, 1H), 5.79 (t, $J = 2.60$ Hz, 1H), 4.02 – 4.19 (m, 2H), 2.27 (s, 3H), 1.14 (t, $J = 7.13$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 162.0$ (1C), 151.6 (1C), 142.9 (1C), 142.4 (2C), 140.5 (2C), 138.1 (1C), 136.8 (1C), 131.1 (1C), 128.3 (4C), 110.6 (2C), 110.0 (2C), 69.8 (2C), 62.3 (2C), 61.0 (2C), 21.5 (2C) ppm; FTIR (neat): $\nu = 3063, 2982, 2928, 2905, 1715, 1655, 1599, 1495, 1456, 1341, 1258, 1161$ cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{26}\text{H}_{25}\text{ClNO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 482.1193, found: 482.1163.

Ethyl-2-(furan-2-yl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate

(74ah): The product was prepared by the above general procedure, employing ethyl-4-phenylbut-3-ynoate (50 mg, 0.265 mmol),

(*E*)-*N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide (79 mg, 0.318 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ah** (74 mg, 0.170 mmol, 64% yield); R_f : 0.4 (Hexane: Ethyl acetate = 4:1). Orange solid; m.p. 94-97 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.22 - 7.37$ (m, 10H), 7.04 – 7.05 (m, 2H), 6.76 – 6.77 (m, 1H), 5.88 – 5.89 (m, 1H), 5.85 – 5.86 (m, 1H), 3.99 – 4.09 (m, 2H), 2.33 (s, 3H), 1.10 (t, $J = 7.13$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 161.9, 143.4, 139.6, 138.1, 137.9, 135.7, 133.8, 133.6, 129.8$ (2), 129.2 (2), 128.6 (2), 128.3, 128.2, 127.6 (2), 127.2 (2), 69.8, 68.8, 21.4, 13.8 ppm.

FTIR (neat): ν = 3053, 2986, 1719, 1597, 1422, 1341, 1265, 1165, 1092 cm^{-1} ;

HRMS (ESI, m/z): calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 438.1341, found: 438.1345.

Ethyl-2-(furan-2-yl)-5-p-tolyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate

(74bh):

The product was prepared by the above general procedure, employing ethyl 4-p-tolylbut-3-ynoate (50 mg, 0.247 mmol),

(*E*)-*N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide (74 mg, 0.297 mmol) and PMe_3 (5 mg, 0.049 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74bh** (86 mg, 0.190 mmol, 77% yield); **R_f**: 0.6 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 99-101 °C; **¹H NMR (300 MHz, CDCl_3):** δ = 6.90 – 7.30 (m, 9H), 6.76 (t, J = 2.1 Hz, 1H), 6.45 – 6.49 (m, 1H), 6.25 – 6.35 (m, 1H), 6.05 (t, J = 2.5 Hz, 1H), 5.75 (t, J = 2.6 Hz, 1H), 3.99 – 4.09 (m, 2H), 2.33 (s, 3H), 2.28 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H) ppm; **¹³C NMR (100 MHz, CDCl_3):** δ = 162.0 (1C), 151.6 (1C), 142.8 (1C), 142.2 (1C), 140.6 (1C), 138.0 (1C), 136.7 (1C), 135.1 (1C), 130.9 (1C), 129.1 (2C), 128.9 (2C), 128.0 (2C), 127.0 (2C), 110.5 (1C), 109.8 (1C), 69.5 (1C), 62.1 (1C), 60.9 (1C), 21.4 (1C), 21.1 (1C), 13.9 (1C) ppm; **FTIR (neat):** ν = 3055, 2984, 2968, 1721, 1599, 1340, 1265, 1165, 1094 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{25}\text{H}_{26}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 452.1524, found: 452.1521.

Ethyl-2-(furan-2-yl)-5-(4-methoxyphenyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74ch):

The product was prepared by the above general procedure, employing ethyl

4-(4-methoxyphenyl)but-3-ynoate (50 mg, 0.229 mmol),

(*E*)-*N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide (69 mg, 0.275 mmol) and PMe_3 (5 mg, 0.046 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ch** as colorless oil (73 mg, 0.156 mmol, 68% yield); **^1H NMR (400 MHz, CDCl_3):** δ = 7.26 – 7.31 (m, 3H), 7.04 – 7.06 (m, 2H), 6.93 – 6.95 (m, 2H), 6.77 – 6.79 (m, 2H), 6.71 – 6.72 (m, 1H), 6.41 – 6.42 (m, 1H), 6.30 – 6.32 (m, 1H), 6.04 – 6.05 (m, 1H), 5.75 – 5.77 (m, 1H), 4.04 – 4.17 (m, 2H), 3.78 (s, 3H), 2.28 (s, 3H), 1.15 (t, J = 7.20 Hz, 3H) ppm; **^{13}C NMR (125 MHz, CDCl_3):** δ = 162.0 (1C), 159.6 (1C), 151.5 (1C), 142.7 (1C), 142.3 (1C), 140.5 (1C), 136.9 (1C), 130.9 (1C), 130.2 (1C), 129.5 (2C), 128.9 (2C), 127.0 (2C), 113.8 (2C), 110.5 (1C), 109.9 (1C), 69.2 (1C), 62.0 (1C), 60.9 (1C), 55.3 (1C), 21.4 (1C), 14.0 (1C) ppm; **FTIR (neat):** ν = 3055, 2984, 2305, 1719, 1512, 1265, 739 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{25}\text{H}_{26}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$ 468.1481, found: 468.1480.

Ethyl-2-(furan-2-yl)-5-(6-methoxynaphthalen-2-yl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74dh):

The product was prepared by the above general

procedure, employing ethyl

4-(6-methoxynaphthalen-2-yl)but-3-ynoate (50 mg, 0.186 mmol), (*E*)-*N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide (56 mg, 0.224 mmol) and PMe_3 (3 mg, 0.037 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74dh** as colorless oil (59 mg, 0.114 mmol, 61% yield); **^1H NMR (400 MHz, CDCl_3):** δ = 7.58 – 7.68 (m, 3H), 7.34 – 7.45 (m, 2H), 6.98 – 7.14 (m, 4H), 6.76 – 6.80 (m, 3H), 6.47 – 6.48 (m, 1H), 6.35 – 6.36 (m, 1H), 6.13 – 6.14 (m, 1H), 5.93 (t, J = 2.3 Hz, 1H), 4.05 – 4.19 (m, 2H), 3.92 (s, 3H), 2.17 (s, 3H), 1.16 (t, J = 7.20 Hz, 3H) ppm; **^{13}C NMR (75 MHz, CDCl_3):** δ = 162.0 (1C), 158.0 (1C), 151.7 (1C), 142.7 (1C), 142.2 (1C), 140.5 (1C), 136.8 (1C), 134.4 (1C), 132.9 (1C), 131.0 (1C), 129.6 (1C), 128.8 (2C), 128.5 (1C), 127.4 (1C), 127.1 (1C), 126.9 (2C), 125.9 (1C), 118.9 (1C), 110.6 (1C), 110.0 (1C), 105.5 (1C), 69.8 (1C), 62.2 (1C), 60.9 (1C), 55.3 (1C), 21.3 (1C), 14.0 (1C) ppm; **FTIR (neat):** ν = 3053, 2986, 2305, 1719, 1609, 1421, 1341, 1265, 1161, 1094 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{29}\text{H}_{27}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$ 518.1637, found: 518.1636.

Ethyl-2-(furan-2-yl)-1-tosyl-5-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (74eh):

The product was prepared by the above general procedure, employing ethyl 4-(4-(trifluoromethyl) phenyl) but-3-ynoate (50 mg, 0.195 mmol), (*E*)-*N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide (58 mg, 0.234 mmol) and PMe_3 (3 mg, 0.039 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74eh** as colorless oil (82 mg, 0.162 mmol, 83% yield); ^1H NMR (300 MHz, CDCl_3): δ = 7.46 (brs, 4H), 7.35 (m, 1H), 6.90-7.10 (m, 4H), 6.70 (t, J = 2.2 Hz, 1H), 6.50 (m, 1H), 6.40(m, 1H), 6.10 (t, J = 2.6 Hz, 1H), 5.81 (t, J = 2.7 Hz, 1H), 4.00-4.22 (m, 2H), 2.28 (s, 3H), 1.16 (t, J = 7.20 Hz, 3H) ppm. ^{13}C NMR (100MHz, CDCl_3): δ = 162.0 (1C), 159.6 (1C), 151.5 (1C), 142.7 (1C), 142.3 (1C), 140.5 (1C), 136.9 (1C), 130.9 (1C), 130.2 (1C), 129.5 (2C), 128.9 (2C), 127.0 (2C), 113.8 (2C), 110.5 (1C), 109.9 (1C), 69.2 (1C), 62.0 (1C), 60.9 (1C), 55.3 (1C), 21.4 (1C), 14.0 (1C) ppm. FTIR (neat): ν = 3055, 2986, 2305, 1722, 1325, 1265, 1167, 1128, 1067, 1016 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{25}\text{H}_{23}\text{F}_3\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 506.1249, found: 506.1250.

Ethyl-2-(furan-2-yl)-5-(thiophen-2-yl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxy

late(74fh): The product was prepared by the above general procedure, employing ethyl 4-(thiophen-2-yl)but-3-ynoate (50 mg, 0.257 mmol),

(*E*)-*N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide (77 mg, 0.309 mmol) and PMe_3 (5 mg, 0.051 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74fh** (103 mg, 0.203 mmol, 79% yield); **R_f**: 0.5 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 98-101 °C; **¹H NMR (300 MHz, CDCl₃)**: δ = 7.25 – 7.28 (m, 2H), 7.10 – 7.15 (m, 1H), 7.00 – 7.05 (m, 3H), 6.94 – 6.96 (m, 2H), 6.75 – 6.77 (m, 1H), 6.41 – 6.42 (m, 1H), 6.29 – 6.31 (m, 1H), 6.05 – 6.07 (m, 1H), 5.93 – 5.95 (m, 1H), 3.99 – 4.17 (m, 2H), 2.29 (s, 3H), 1.16 (t, J = 7.20 Hz, 3H) ppm; **¹³C NMR (75 MHz, CDCl₃)**: δ = 161.9 (1C), 151.4 (1C), 142.7 (1C), 142.3 (1C), 139.7 (1C), 139.1 (1C), 137.0 (1C), 131.3 (1C), 128.9 (2C), 127.1 (1C), 126.8 (2C), 126.0 (1C), 124.3 (1C), 110.5 (1C), 109.9 (1C), 64.7 (1C), 61.9 (1C), 61.0 (1C), 21.4 (1C), 13.9 (1C) ppm. **FTIR (neat)**: ν = 3055, 2984, 1719, 1340, 1265, 1161, 1094, 1013, 737 cm^{-1} ; **HRMS (ESI, m/z)**: calcd for $\text{C}_{22}\text{H}_{22}\text{NO}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 444.0939, found: 444.0938.

Ethyl 2-(furan-2-yl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74gh):

The product was prepared by the above general procedure, employing ethyl but-3-ynoate (50 mg, 0.446 mmol),

(*E*)-*N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide (77 mg, 0.309 mmol) and PMe_3 (7 mg, 0.089 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74gh** as a colorless oil (158 mg, 0.312 mmol, 70% yield); ^1H NMR (300 MHz, CDCl_3): δ = 7.45 – 7.48 (m, 2H), 7.15 – 7.20 (m, 3H), 6.82 (q, J = 2.0 Hz, 1H), 6.34 – 6.37 (m, 1H), 6.25 – 6.30 (m, 1H), 5.87 (td, J = 5.5, 1.7 Hz, 1H), 4.25 – 4.55 (m, 2H), 4.00 – 4.20 (m, 2H), 2.38 (s, 3H), 1.59 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): δ = 161.6, 151.3, 143.2, 142.1, 136.9, 135.6, 133.0, 129.5 (2), 127.0 (2), 110.4, 109.1, 61.7, 60.8, 54.2, 21.4, 13.9 ppm. FTIR (neat): ν = 3053, 2986, 2305, 1721, 1422, 1265, 1165, 895 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 362.1062, found: 362.1067.

Triethyl 1-tosyl-2, 5-dihydro-1H-pyrrole-2,3,5-tricarboxylate (74ja):

The product was prepared by the above general procedure, employing diethyl pent-2-ynedioate (50 mg, 0.271 mmol), (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (84 mg, 0.326

mmol) and PMe_3 (5 mg, 0.054 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ja** as a colorless oil (75 mg, 0.149 mmol, 55% yield); ^1H NMR (400 MHz, CDCl_3): δ = 7.42 – 7.45 (m, 2H), 7.32 – 7.35 (m, 2H), 7.26 (brs, 3H), 7.15 – 7.17 (m, 2H), 6.70 (t, J = 2.3 Hz, 1H), 5.80 – 5.82 (m, 1H), 5.51 (t, J = 2.7 Hz, 1H), 4.15 – 4.35 (m, 2H), 3.95 – 4.10 (m, 2H), 2.30 (s, 3H), 1.30 (t, J =

7.1 Hz, 3H), 1.10 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): $\delta = 168.3$, 161.4, 143.4, 138.2, 137.2, 135.8, 132.8 (2), 128.9 (2), 128.5 (2), 127.89 (2), 127.83(2), 69.5, 67.9, 62.1, 61.0, 21.4, 14.0, 13.7 ppm.

Ethyl-1-(methylsulfonyl)-2,5-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylate

(74ai):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-*N*-benzylidene methanesulfonamide (58 mg, 0.319 mmol)

and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ai** (113 mg, 0.223 mmol, 84% yield); R_f : 0.6 (Hexane: ethyl acetate = 4:1). Orange solid; m.p. 94-96 °C; ^1H NMR (300 MHz, CDCl_3): $\delta = 7.30 - 7.51$ (m, 10H), 6.83 – 6.84 (m, 1H), 6.03 – 6.04 (m, 1H), 5.96 – 5.98 (m, 1H), 3.99 – 4.17 (m, 2H), 2.04 (s, 3H), 1.10 (t, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 162.1$ (1C), 139.2 (1C), 139.1 (1C), 138.3 (1C), 134.1 (1C), 129.0 (1C), 128.7 (2C), 128.6 (1C), 128.4 (2C), 128.4 (2C), 128.0 (2C), 69.4 (1C), 68.9 (1C), 60.9 (1C), 42.6 (1C), 13.9 (1C) ppm. FTIR (neat): $\nu = 3055$, 2986, 2305, 1719, 1456, 1422, 1334, 1265, 1151 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 372.1270, found: 372.1270.

Ethyl-1-(methanesulfonyl)-5-phenyl-2-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (74aj):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol),

(*E*)-*N*-(4-(trifluoromethyl)benzylidene)methanesulfonamide (80 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74aj** as a colorless oil (102 mg, 0.202 mmol, 76% yield); ^1H NMR (300 MHz, CDCl_3): δ = 7.59 – 7.66 (m, 4H), 7.38 – 7.50 (m, 5H), 6.88 – 6.90 (m, 1H), 6.08 – 6.09 (m, 1H), 5.97 – 5.99 (m, 1H), 4.03 – 4.16 (m, 2H), 2.25 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 161.8 (1C), 143.4 (1C), 139.7 (1C), 138.0 (1C), 133.8 (1C), 129.2 (2C), 129.0 (1C), 128.8 (2C), 128.0 (2C), 125.7 (1C), 125.6 (1C), 125.6 (1C), 125.6 (1C), 69.6 (1C), 68.5 (1C), 61.2 (1C), 42.3 (1C), 13.9 (1C) ppm. FTIR (neat): ν = 3053, 2986, 2305, 1721, 1422, 1325, 1067, 895 cm^{-1} .

Ethyl-1-(methanesulfonyl)-2-(4-nitrophenyl)-5-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74ak):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-*N*-(4-nitrobenzylidene)

methanesulfonamide (73 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ak** (63 mg, 0.125 mmol, 47% yield); R_f : 0.4 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 99-101 °C; ^1H NMR (300 MHz, CDCl_3): δ = 8.23 – 8.26 (m, 2H), 7.67 – 7.69 (m, 2H), 7.40– 7.47 (m, 5H), 6.91 – 6.93 (m, 1H), 6.11 – 6.12 (m, 1H), 5.98 – 6.00 (m, 1H), 4.05 – 4.17 (m, 2H), 2.29 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 161.6 (1C), 147.7 (1C), 146.6 (1C), 140.0 (1C), 137.7 (1C), 133.5 (1C), 129.4 (2C), 129.3 (2C), 129.2 (1C), 127.9 (2C), 123.8 (2C), 69.7 (1C), 68.2 (1C), 129.4 (2C), 129.3 (2C), 129.2 (1C), 127.9 (2C), 123.8 (2C), 69.7 (1C), 68.2 (1C), 42.2 (1C), 13.9 (1C) ppm; FTIR (neat): ν = 3053, 2986, 2305, 1719, 1526, 1348, 1265, 1152, 1074 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$ 417.1127, found: 417.1129.

Ethyl-2-(4-chlorophenyl)-1-(methylsulfonyl)-5-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74al):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-*N*-(4-chlorobenzylidene) methanesulfonamide (69 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74al** (95 mg, 0.189 mmol, 71% yield); R_f : 0.4 (Hexane: Ethyl acetate = 4:1). Pale yellow solid; m.p. 110-113 °C; ^1H NMR (300 MHz,

CDCl₃): δ = 7.34– 7.47 (m, 9H), 6.84 – 6.86 (m, 1H), 6.00 – 6.02 (m, 1H), 5.94 – 5.96 (m, 1H), 4.03 – 4.16 (m, 2H), 2.23 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃)**: δ = 161.9 (1C), 139.5 (1C), 138.1 (1C), 138.0 (1C), 134.3 (1C), 133.8 (1C), 129.8 (2C), 129.1 (2C), 128.9 (3C), 127.9 (2C), 69.5 (1C), 68.3 (1C), 61.1 (1C), 42.5 (1C), 13.9 (1C) ppm. **FTIR (neat)**: ν = 3053, 2986, 2305, 1721, 1491, 1335, 1265, 1152, 1090 cm⁻¹; **HRMS (ESI, m/z)**: calcd for C₂₀H₂₁ClNO₄S [M+H]⁺ 406.0880, found: 406.0723.

Ethyl-2-(4-cyanophenyl)-1-(methanesulfonyl)-5-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74am):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-N-(4-cyanobenzylidene) methanesulfonamide (66 mg, 0.319 mmol) and PMe₃ (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74am** as a colorless oil (86 mg, 0.170 mmol, 64% yield); **¹H NMR (300 MHz, CDCl₃)**: δ = 7.73 – 7.76 (m, 2H), 7.61 – 7.65 (m, 1H), 7.40– 7.52 (m, 6H), 6.90 – 6.91 (m, 1H), 6.03 – 6.05 (m, 1H), 5.95 – 5.97 (m, 1H), 4.04 – 4.18 (m, 2H), 2.27 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H) ppm; **¹³C NMR (125 MHz, CDCl₃)**: δ = 161.6 (1C), 141.2 (1C), 139.9 (1C), 137.7 (1C), 133.5 (1C), 133.0 (1C), 132.1 (1C), 131.8 (1C), 129.5 (1C), 129.3 (2C), 129.2 (1C), 127.9 (2C), 118.4 (1C), 112.8 (1C), 69.6 (1C), 68.2 (1C), 61.3

(1C), 42.2 (1C), 13.9 (1C) ppm; **FTIR (neat):** ν = 3055, 2986, 2305, 1719, 1339, 1265, 1153 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 397.1229, found: 397.1222.

Ethyl-2-(4-methoxyphenyl)-1-(methylsulfonyl)-5-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74an)

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-*N*-(4-methoxybenzylidene) methanesulfonamide (68 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74an** as a colorless oil (94 mg, 0.186 mmol, 70% yield); **^1H NMR (300 MHz, CDCl_3):** δ = 7.33 – 7.49 (m, 7H), 6.91 – 6.92 (m, 1H), 6.89 – 6.90 (m, 1H), 6.80 – 6.81 (m, 1H), 6.00 – 6.01 (m, 1H), 5.93 – 5.95 (m, 1H), 4.02 – 4.15 (m, 2H), 3.81 (s, 3H), 2.20 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H) ppm; **^{13}C NMR (125 MHz, CDCl_3):** δ = 162.5 (1C), 159.8 (1C), 139.1 (1C), 138.7 (1C), 134.3 (1C), 131.5 (1C), 129.8 (2C), 129.1 (2C), 128.8 (1C), 128.1 (2C), 114.2 (2C), 69.5 (1C), 68.6 (1C), 61.2 (1C), 55.5 (1C), 42.9 (1C), 14.2 (1C) ppm; **HRMS (ESI, m/z):** calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 402.1368, found: 402.1371.

Ethyl-2-(furan-2-yl)-1-(methanesulfonyl)-5-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74ao):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-*N*-(furan-2-ylmethylene) methanesulfonamide (55 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ao** as a colorless oil (120 mg, 0.236 mmol, 89% yield); ^1H NMR (300 MHz, CDCl_3): δ = 7.53 – 7.56 (m, 2H), 7.34 – 7.46 (m, 4H), 6.81 – 6.83 (m, 1H), 6.53 – 6.54 (m, 1H), 6.40 – 6.41 (m, 1H), 6.08 – 6.10 (m, 1H), 5.82 – 5.84 (m, 1H), 4.06 – 4.25 (m, 2H), 2.10 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 161.9 (1C), 151.0 (1C), 142.7 (1C), 140.2 (1C), 137.8 (1C), 131.3 (1C), 128.9 (2C), 128.8 (1C), 128.4 (2C), 110.8 (1C), 110.2 (1C), 69.3 (1C), 61.7 (1C), 61.0 (1C), 42.1 (1C), 14.0 (1C) ppm. HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 362.1062, found: 362.1061.

Ethyl-2-(4-(benzyloxy)butyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74ap):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-*N*-(5-(benzyloxy)pentylidene)-4-methylbenzenesulfonamide (110 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the

residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ap** (103 mg, 0.194 mmol, 73% yield); **R_f**: 0.5 (Hexane: Ethyl acetate = 4:1).

White solid; m.p. 99-102 °C; **¹H NMR (300 MHz, CDCl₃)**: δ = 7.63 – 7.65 (m, 2H), 7.38 – 7.39 (m, 2H), 7.22 – 7.34 (m, 10H), 6.59 – 6.61 (m, 1H), 5.58 (s, 1H), 4.82 – 4.86 (m, 1H), 4.46 (s, 2H), 4.12 – 4.19 (m, 2H), 3.39 – 3.43 (m, 2H), 2.38 (s, 3H), 1.88 – 1.97 (m, 1H), 1.72 – 1.82 (m, 1H), 1.45 – 1.64 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H) ppm; **¹³C NMR (500MHz, CDCl₃)**: δ = 162.5 (1C), 143.8(1C), 139.0 (1C), 138.8 (1C), 138.7 (1C), 135.1 (1C), 134.8 (1C), 129.7 (2C), 128.6 (2C), 128.3 (2C), 128.0 (1C), 127.7 (2C), 127.6 (2C), 127.4 (1C), 127.3 (2C), 72.9 (1C), 70.3 (1C), 69.5 (1C), 66.8 (1C), 60.9 (1C), 34.9 (1C), 29.6 (1C), 22.0 (1C), 21.5 (1C), 14.1 (1C) ppm. **FTIR (neat)**: ν = 3053, 2984, 2938, 2864, 1717, 1647, 1599, 1495, 1454, 1350, 1265, 1165, 1090, 1028 cm⁻¹; **HRMS (ESI, m/z)**: calcd for C₃₁H₃₅NO₅S [M+H]⁺ 534.2314, found: 534.2317.

Ethyl-2-(4-(benzyloxy)butyl)-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74aq):

The product was prepared by the above general procedure, employing ethyl 6-(tetrahydro-2H-pyran-2-yloxy)hex-3-ynoate (50 mg, 0.208 mmol), (*E*)-N-(5-(benzyloxy)pentylidene)-4-methylbenzenesulfonamide (86 mg, 0.250

mmol) and PMe_3 (3 mg, 0.042 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74aq** (85 mg, 0.146mmol, 70% yield); **R_f**: 0.5 (Hexane: Ethyl acetate = 4:1). White solid; m.p. 110-114 °C; **¹H NMR (400 MHz, CDCl₃)**: δ = 7.60 – 7.70 (m, 2H), 7.20 – 7.35 (m, 7H), 6.50 – 6.65 (m, 1H), 4.57 – 4.70 (m, 2H), 4.47 (s, 2H), 4.40 – 4.45 (m, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.75 – 3.90 (m, 2H), 3.47 – 3.67 (m, 2H), 3.45 (t, J = 6.6 Hz, 2H), 2.37 (s, 3H), 2.10 – 2.30 (m, 1H), 1.44 – 2.00 (m, 12H), 1.32 – 1.42 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H) ppm; **FTIR (neat)**: ν = 3053, 2941, 2866, 1717, 1346, 1265, 1165, 1092, 1076, 1034 cm^{-1} ; **HRMS (ESI, m/z)**: calcd for $\text{C}_{27}\text{H}_{36}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$ 502.2246, found: 502.2263 (THP cleaved mass).

Ethyl-2-benzyl-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74ar):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-4-methyl-N-(2-phenylethylidene) benzenesulfonamide (87 mg,

0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74ar** (109 mg, 0.236 mmol, 89% yield); **R_f**: 0.4 (Hexane: Ethyl acetate = 4:1). Pale yellow solid; m.p. 110-113 °C; **¹H NMR (300 MHz, CDCl₃)**: δ = 7.67 – 7.69 (m, 2H), 7.14 – 7.29 (m, 6H), 7.02 – 7.08 (m, 4H), 6.54 – 6.57 (m, 2H), 6.40 – 6.41 (m, 1H), 5.36 – 5.38 (m, 1H), 5.05 – 5.08 (m, 1H),

4.14 – 4.25 (m, 2H), 3.30 – 3.48 (m, 2H), 2.44 (s, 3H), 1.30 (t, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 162.8$ (1C), 143.9 (1C), 139.7 (1C), 138.7 (1C), 136.4 (1C), 134.3 (1C), 133.1 (1C), 131.0 (2C), 129.9 (2C), 128.3 (2C), 128.2 (2C), 128.0 (2C), 127.9 (2C), 127.9 (1C), 126.5 (1C), 70.0 (1C), 67.7 (1C), 61.1 (1C), 39.6 (1C), 21.6 (1C), 14.2 (1C) ppm. FTIR (neat): $\nu = 3055, 2984, 1717, 1599, 1350, 1265, 1165, 1092\text{ cm}^{-1}$; HRMS (ESI, m/z): calcd for $\text{C}_{27}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 462.1739, found: 462.1698.

Ethyl-2-isopropyl-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate

(74as):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-4-methyl-*N*-(2-methylpropylidene) benzenesulfonamide (72 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74as** (92 mg, 0.223 mmol, 84% yield); R_f : 0.4 (Hexane: Ethyl acetate = 4:1). White solid; m.p. 95-98 °C; ^1H NMR (300 MHz, CDCl_3): $\delta = 7.70 - 7.72$ (m, 2H), 7.46 – 7.48 (m, 2H), 7.33 – 7.36 (m, 2H), 7.26 – 7.29 (m, 3H), 6.70 – 6.71 (m, 1H), 5.56 – 5.57 (m, 1H), 4.73 (d, $J = 5.0$ Hz, 1H), 4.11 – 4.19 (m, 2H), 2.40 (s, 3H), 1.97 – 2.01 (m, 1H), 1.26 (t, $J = 7.2$ Hz, 3H), 0.93 (d, $J = 7.0$ Hz, 3H), 0.79 (d, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 163.0$ (1C), 143.9 (1C), 139.0 (1C), 138.2 (1C), 136.0 (1C), 134.2 (1C), 129.7 (2C), 128.5

(2C), 127.9 (2C), 127.8 (1C), 127.1 (2C), 72.4 (1C), 68.9 (1C), 60.9 (1C), 33.6 (1C), 21.5 (1C), 19.5 (1C), 19.4 (1C), 14.1 (1C) ppm. **FTIR (neat):** ν = 3057, 2968, 2934, 2907, 1719, 1647, 1599, 1348, 1265, 1165, 1090, 895, 816 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 414.1739, found: 414.1738.

Ethyl-2-cyclohexyl-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate

(74at):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-*N*-(cyclohexylmethylene)-4-methylbenzenesulfonamide (85 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74at** (108 mg, 0.239 mmol, 90% yield); **R_f**: 0.4 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 96-99 °C; **¹H NMR (300 MHz, CDCl₃):** δ = 7.68 – 7.70 (m, 2H), 7.45 – 7.47 (m, 2H), 7.30 – 7.34 (m, 2H), 7.23 – 7.27 (m, 3H), 6.67 (brs, 1H), 5.56 (brs, 1H), 4.70 – 4.71 (m, 1H), 4.12 – 4.17 (m, 2H), 2.37 (s, 3H), 1.61 – 1.69 (m, 6H), 1.26 (t, J = 7.0 Hz, 3H), 0.85 – 1.16 (m, 5H) ppm; **¹³C NMR (125 MHz, CDCl₃):** δ = 163.0 (1C), 143.8 (1C), 139.0 (1C), 138.1 (1C), 136.0 (1C), 134.3 (1C), 129.7 (2C), 128.5 (2C), 127.8 (2C), 127.8 (1C), 127.2 (2C), 71.8 (1C), 68.9 (1C), 60.9 (1C), 43.6 (1C), 29.9 (1C), 29.8 (1C), 26.4 (1C), 26.4 (1C), 26.1 (1C), 21.5 (1C), 14.1 (1C) ppm; **FTIR (neat):** ν = 3055, 2984, 2930,

2853, 1719, 1647, 1599, 1495, 1449, 1348, 1265, 1165, 1092 cm^{-1} ; **HRMS (ESI, m/z)**: calcd for $\text{C}_{26}\text{H}_{32}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 454.2018, found: 454.2029.

Ethyl 5-phenyl-2-propyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74au):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-*N*-butylidene-4-methylbenzenesulfonamide (72 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74au** (85 mg, 0.205 mmol, 77% yield); **R_f**: 0.6 (Hexane: Ethyl acetate = 4:1). Yellow solid; m.p. 99-101 °C; **¹H NMR (300 MHz, CDCl₃)**: δ = 7.60 – 7.70 (m, 2H), 7.20 – 7.40 (m, 7H), 6.55 – 6.60 (m, 1H), 5.55 – 5.60 (m, 1H), 4.80 – 4.85 (m, 1H), 4.10 – 4.25 (m, 2H), 2.40 (s, 3H), 1.65 – 1.75 (m, 2H), 1.35 – 1.50 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H). 5.96 – 5.98 (m, 1H), 3.99 – 4.17 (m, 2H), 2.04 (s, 3H), 1.10 (t, J = 7.0 Hz, 3H) ppm; **¹³C NMR (125 MHz, CDCl₃)**: δ = 162.8 (1C), 144.0 (1C), 139.3 (1C), 138.8 (1C), 135.4 (1C), 135.0 (1C), 129.9 (2C), 128.8 (2C), 128.2 (1C), 127.9 (2C), 127.5 (2C), 69.7 (1C), 67.0 (1C), 61.1 (1C), 37.6 (1C), 21.7 (1C), 18.8 (1C), 14.3 (1C), 14.2 (1C) ppm. **FTIR (neat)**: ν = 3055, 2982, 2963, 2934, 2872, 1719, 1647, 1599, 1350, 1265, 1165, 1092 cm^{-1} ; **HRMS (ESI, m/z)**: calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 414.1739, found: 414.1720.

Ethyl 2-heptyl-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74av):

The product was prepared by the above general procedure, employing ethyl 4-phenylbut-3-ynoate (50 mg, 0.266 mmol), (*E*)-4-methyl-N-octylidenebenzenesulfonamide (90 mg, 0.319 mmol) and PMe_3 (5 mg, 0.053 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (25 – 30% ethyl acetate in hexane) to afford product **74av** as a colorless oil (101 mg, 0.215 mmol, 81% yield); ^1H NMR (300 MHz, CDCl_3): δ = 7.61 – 7.64 (m, 2H), 7.41 – 7.43 (m, 2H), 7.28 – 7.36 (m, 3H), 7.24 – 7.26 (m, 2H), 6.60 (brs, 1H), 5.60 (brs, 1H), 4.84 – 4.86 (m, 1H), 4.13 – 4.22 (m, 2H), 2.40 (s, 3H), 1.84 – 1.91 (m, 1H), 1.70 – 1.77 (m, 1H), 1.29 – 1.43 (m, 2H) 1.26 (m, 5H), 1.20 (s, 6H), 0.86 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 162.6 (1C), 143.7 (1C), 139.0 (1C), 138.7 (1C), 135.2 (1C), 135.0 (1C), 129.7 (2C), 128.6 (2C), 128.0 (1C), 127.7 (2C), 127.4 (2C), 69.4 (1C), 66.9 (1C), 60.9 (1C), 34.9 (1C), 31.7 (1C), 29.4 (1C), 29.0 (1C), 25.1 (1C), 22.7 (1C), 21.5 (1C), 14.1 (2C) ppm; FTIR (neat): ν = 3053, 2986, 2957, 2928, 2857, 1715, 1422, 1350, 1265, 1165, 1092 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{27}\text{H}_{35}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 470.2291, found: 470.2302.

Ethyl-5-(2-hydroxyethyl)-2-(4-(4-methoxybenzyloxy)-butyl)-1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (74lw): **1H-pyrrole-3-carboxylate (74lw):**

The product was prepared by the above general procedure, employing ethyl 6-hydroxyhex-3-ynoate (2

g, 12.0 mmol), (*E*)-*N*-(5-(4-methoxybenzyloxy)pentylidene)-4-methylbenzenesulfonamide (5.76 g, 14.4 mmol) and PMe_3 (200 mg, 2.5 mmol). After 2 h the solvent was removed and the residue was purified through flash column chromatography (30% ethyl acetate in hexane) to afford product **74lw** (5.5 g, 81% yield); R_f : 0.6 (Hexane: Ethyl acetate = 4:1). White solid; m.p. 111-114 °C; ^1H NMR (300 MHz, CDCl_3): δ = 7.66 - 7.69 (m, 2H), 7.24 - 7.27 (m, 4H), 6.85 - 6.88 (m, 2H), 6.48 (brs, 1H), 4.60 - 4.65 (m, 2H), 4.42 (s, 2H), 4.07 - 4.15 (m, 3H), 3.93 - 4.01 (m, 1H), 3.77 (s, 3H), 3.69 - 3.75 (m, 1H), 3.46 (t, J = 6.4 Hz, 2H), 2.38 (s, 3H), 1.48 - 2.00 (m, 9H), 1.18-1.21 (m, 4H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 162.2, 159.0, 144.0, 140.2, 134.5, 133.5, 130.7, 129.8, 127.6, 113.7, 72.5, 69.9, 66.6, 64.2, 60.8, 58.5, 55.2, 39.0, 35.4, 29.5, 21.9, 21.5, 14.0 ppm; FTIR (neat): ν = 3053, 2985, 2304, 1716, 1555, 1344, 1265, 1163, 738 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{20}\text{H}_{30}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$ 412.1794, found: 412.1800 (PMB cleaved mass).

4-(hydroxymethyl)-5-(4-(4-methoxybenzyloxy)-butyl)-1-tosyl-2,5-dihydro-1H-pyrrole-2-yl)ethanol (88):

DIBAL-H (1.0 M in THF, 2.7 g, 18.8 mmol) was added dropwise to a solution of ethyl 5-(2-hydroxyethyl)-2-(4-(4-methoxybenzyloxy)butyl)-

1-tosyl-2,5-dihydro-1H-pyrrole-3-carboxylate (5 g, 9.4 mmol) in dry THF (100 mL) at 0 °C. After 2 h, ethanol (2 mL) was added slowly, and then stirred with aq. solution of sodium potassium tartarate for 5 h. Organic layers were evaporated to get crude

residue, that was purified through flash column chromatography (50% ethyl acetate in hexane) to afford product **88** as a colorless oil (3.4 g, 74% yield); **¹H NMR (300 MHz, CDCl₃)**: δ = 7.68 (d, J = 8.1 Hz, 2H), 7.24 – 7.28 (m, 4H), 6.88 (d, J = 8.5 Hz, 2H), 5.42 (s, 1H), 5.30 (s, 1H), 4.51 (brs, 1H), 4.38 – 4.42 (m, 3H), 3.88 – 4.02 (m, 3H), 3.80 (s, 3H), 3.68 – 3.72 (m, 1H), 3.40 – 3.50 (m, 2H), 2.40 (s, 3H), 1.40–2.00 (m, 11H) ppm; **¹³C NMR (125 MHz, CDCl₃)**: δ = 159.1, 143.8, 141.9, 133.7, 130.5, 129.6, 129.2, 127.6, 124.5, 113.7, 72.5, 69.7, 67.1, 64.0, 58.9(2), 55.2, 39.9, 34.5, 29.4, 21.6, 21.5 ppm. **FTIR (neat)**: ν = 3055, 2933, 2304, 1512, 1421, 1340, 1265, 1161, 1093, 894, 815, 744 cm⁻¹; **HRMS (ESI, m/z)**: calcd for C₁₈H₂₈NO₅S [M+H]⁺ 370.1688, found: 370.1689 (PMB cleaved mass).

2-(5-(hydroxymethyl)-4-(4-(4-methoxybenzyloxy)-butyl)-3-tosyl-6-oxa-3-azabicyclo[3.1.0]hexan-2-yl)ethanol (89):

m-CPBA (2.75 g, 61.3 mmol; 77%) was added to

a solution of

4-(hydroxymethyl)-5-(4-(4-methoxybenzyloxy)butyl)

-1-tosyl-2,5-dihydro-1H-pyrrol-2-yl)ethanol (3 g, 6.1 mmol) in CH₂Cl₂ (50 mL) at 0

°C. After 12 h, saturated NaHCO₃ solution was added, extracted with ethyl acetate.

Organic layers were evaporated to get crude residue, that was purified through flash column chromatography (40% ethyl acetate in hexane) to afford product **89** as a

colorless oil (2.5 g, 81% yield); **¹H NMR (300 MHz, CDCl₃)**: δ = 7.62 (d, J = 8.1,

2H), 7.25 – 7.29 (m, 4H), 6.88 (d, J = 8.5 Hz, 2H), 4.43 (s, 2H), 3.85 – 4.05 (m, 4H),

3.79 (s, 3H), 3.65 – 3.75 (m, 1H), 3.55 – 3.65 (m, 1H), 3.45 – 3.50 (m, 2H), 3.31 (brs, 1H), 2.41 (s, 3H), 1.35 – 1.85 (m, 9H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 159.0, 143.6, 134.7, 130.4, 129.3, 129.2, 127.9, 113.7, 72.5, 69.6, 68.2, 61.5, 61.3, 58.5, 58.1, 57.6, 55.1, 35.6, 32.9, 29.3, 23.0, 21.5 ppm; FTIR (neat): ν = 3053, 2985, 2303, 1512, 1421, 1342, 1265, 1159, 1093, 894, 740 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{28}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$ 386.1657, found: 386.1647 (PMB cleaved mass).

5-(2-hydroxyethyl)-3-(hydroxymethyl)-2-(4-(4-methoxybenzyloxy)butyl)-1-tosyl pyrrolidin-3-ol (90):

DIBAL-H (1.0 M in THF, 2.24 g, 15.8 mmol) was added dropwise to a solution of 5-(hydroxymethyl)-4-(4-(4-methoxybenzyloxy)butyl)-3-tosyl-6-oxa-3-azabicyclo[3.1.0]hexan-2-yl)ethanol (2 g, 3.9 mmol) in dry THF (100 mL) at -78°C then increased the temperature to -25°C . After 24 h, ethanol (2 mL) was added slowly, and then stirred with aq. solution of sodium potassium tartarate for 5 h. Organic layers were evaporated to get crude residue, that was purified through flash column chromatography (80% ethyl acetate in hexane) to afford product **90** as a colorless oil (1.28 g, 64% yield); ^1H NMR (300 MHz, CDCl_3): δ = 7.75 (d, J = 8.2 Hz, 2H), 7.24 – 7.28 (m, 4H), 6.88 (d, J = 8.5 Hz, 2H), 4.41 (s, 2H), 3.95 – 4.05 (m, 1H), 3.79 (s, 3H), 3.73 – 3.78 (m, 1H), 3.58 – 3.66 (m, 2H), 3.38 – 3.53 (m, 4H), 2.42 – 2.52 (brs, 1H), 2.39 (s, 3H), 2.28 – 2.33 (brs, 1H), 2.05 – 2.10 (m, 1H), 1.95 – 2.03 (m, 1H), 1.70 – 1.80 (m, 1H), 1.50 – 1.65 (m, 5H),

1.30 – 1.38 (m, 1H), 1.17 – 1.25 (m, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 159.1, 143.7, 134.9, 130.5, 129.3, 129.2, 128.3, 113.7, 82.0, 72.4, 69.8, 69.3, 64.6, 59.6, 56.4, 55.2, 40.6, 40.5, 33.0, 29.3, 22.6, 21.5 ppm; FTIR (neat): ν = 3053, 2981, 2304, 1421, 1265, 1159, 1091, 1033, 894, 738 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{30}\text{NO}_6\text{S}$ $[\text{M}+\text{H}]^+$ 388.1794, found: 388.1769 (PMB cleaved mass).

6-(4-(4-methoxybenzyloxy)butyl)-2,2-dimethyl-7-tosyl-1,3-dioxo-7-azaspiro[4.4]nonan-8-yl)ethanol (91):

To a solution of 2,2-dimethoxy propane (2.63 g, 25 mmol) and 5-(2-hydroxyethyl)-3-(hydroxymethyl)-2-(4-(4-methoxybenzyloxy)butyl)-1-tosylpyrrolidin-3-ol (1.2 g, 2.5 mmol) in CH_2Cl_2 , camphorsulfonic acid (58 mg, 0.25 mmol) was added and stirred for 1h at 25 $^\circ\text{C}$. Saturated solution of NaHCO_3 (2 mL) was added, extracted with CH_2Cl_2 . Organic layer was concentrated to get crude product that was purified using column chromatography (70% ethyl acetate in hexane) to get pure product **91** as a colorless oil (1.0 g, 77% yield); ^1H NMR (300 MHz, CDCl_3): δ = 7.71 (d, J = 8.2 Hz, 2H), 7.23 – 7.28 (m, 4H), 6.88 (d, J = 8.6 Hz, 2H), 4.44 (s, 2H), 3.80 – 3.85 (m, 2H), 3.79 (s, 3H), 3.77 – 3.78 (m, 1H), 3.62 – 3.70 (m, 2H), 3.57 (dd, J = 9.7, 3.7 Hz, 1H), 3.45 – 3.52 (m, 2H), 2.41 (s, 3H), 2.20 – 2.27 (m, 1H), 2.09 (dd, J = 9.7, 3.7 Hz, 1H), 1.65 – 1.85 (m, 4H), 1.55 – 1.62 (m, 2H), 1.38 – 1.48 (m, 1H), 1.27 – 1.37 (m, 1H), 0.99 (s, 3H), 0.95 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 159.0, 142.8, 134.9,

130.5, 129.2, 128.7, 128.5, 113.6, 109.0, 88.0, 72.4, 69.8, 68.7, 67.3, 59.6, 56.9, 55.1, 42.3, 40.3, 33.5, 29.5, 26.7, 25.5, 22.5, 21.3 ppm; **FTIR (neat):** ν = 3055, 2983, 2968, 1720, 1598, 1454, 1340, 1265, 1165, 1093, 813, 742 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{29}\text{H}_{42}\text{NO}_7\text{S}$ $[\text{M}+\text{H}]^+$ 548.2682, found: 548.2677.

8-(2-iodoethyl)-6-(4-(4-methoxybenzyloxy)-butyl)-2,2-dimethyl-7-tosyl-1,3-dioxaspiro[4.4]nonane (92):

To a solution of 6-(4-(4-methoxybenzyloxy)butyl)-2,2-dimethyl-7-tosyl-1,3-dioxaspiro[4.4]nonan-8-yl)ethanol (1 g, 1.8 mmol), imidazole (375 mg, 5.4 mmol)

and triphenylphosphine (710 mg, 2.7 mmol) in CH_2Cl_2 , was added I_2 (685 mg, 2.7 mmol) at 25 °C then continued stirring for 12 h. Saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL) and NaHCO_3 (2 mL) was added, extracted with ethyl acetate. Organic layer was concentrated to get crude product that was purified using column chromatography (25% ethyl acetate in hexane) to get pure product **92** as a colorless oil (1.0 g, 87% yield); **^1H NMR (300 MHz, CDCl_3):** δ = 7.74 (d, J = 8.2 Hz, 2H), 7.25 – 7.28 (m, 4H), 6.87-6.89 (m, 2H), 4.44 (s, 2H), 3.81 – 3.83 (m, 1H), 3.80 (s, 3H), 3.62 – 3.72 (m, 2H), 3.59 (dd, J = 9.6, 3.4 Hz, 1H), 3.48 (t, J = 5.7 Hz, 2H), 3.21 – 3.31 (m, 1H), 2.98 – 3.05 (m, 1H), 2.69 – 2.79 (m, 1H), 2.42 (s, 3H), 1.95 – 2.10 (m, 2H), 1.50 – 1.70 (m, 6H), 1.38 – 1.48 (m, 1H), 1.02 (s, 3H), 0.98 (s, 3H) ppm; **^{13}C NMR (125 MHz, CDCl_3):** δ = 159.0, 142.9, 134.5, 130.6, 129.2, 128.8, 128.7, 113.7, 109.2,

87.6, 72.5, 69.8, 68.9, 67.2, 59.6, 55.2, 40.9, 40.6, 33.8, 29.5, 26.8, 25.5, 22.6, 21.4, 14.1, 0.92 ppm; **FTIR (neat):** ν = 3444, 2983, 2933, 1512, 1454, 1342, 1247, 1159, 1089, 1004, 815, 738 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{21}\text{H}_{33}\text{NIO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 538.1124, found: 538.1116 (PMB cleaved mass).

6-(4-(4-methoxybenzyloxy)butyl)-2,2-dimethyl-7-tosyl-8-vinyl-1,3-dioxo-7-azaspiro[4.4]nonane (93):

To a slurry of NaH (120 mg, 3.0 mmol, 60%) and TBAI (55.3 mg, 0.15 mmol) in THF (10 mL) was added 8-(2-iodoethyl)-6-(4-(4-methoxybenzyloxy)-butyl)-2,2-dimethyl-7-tosyl-1,3-dioxo-7-azaspiro[4.4]nonane (1 g, 1.5 mmol) in THF (10 mL) at 0 °C then refluxed for 12 h. Ice-cold water was added dropwise, extracted with ethyl acetate. Organic layer was concentrated to get crude product that was purified using column chromatography (20% ethyl acetate in hexane) to get pure product **93** as a colorless oil (0.7 g, 88% yield); **^1H NMR (300 MHz, CDCl_3):** δ = 7.72 (d, J = 8.2 Hz, 2H), 7.22 – 7.28 (m, 4H), 6.89 (d, 2H), 5.88 – 5.97 (m, 1H), 5.24 (d, 1H), 5.12 (d, 1H),) 4.43 (s, 2H), 4.00 – 4.07 (m, 1H), 3.83 – 3.87 (m, 1H), 3.78 (s, 3H), 3.68 – 3.71 (m, 1H), 3.63 – 3.73 (m, 1H), 3.47 (t, J = 5.7 Hz, 2H), 2.4 (s, 3H), 2.00 – 2.07 (m, 1H), 1.75 -1.81 (m, 1H), 1.30 – 1.70 (m, 6H), 1.00 (s, 3H), 1.03 (s, 3H) ppm; **^{13}C NMR (125 MHz, CDCl_3):** δ = 159.0, 142.7, 139.7, 134.9, 130.5, 129.1, 128.7, 128.4, 115.1, 113.6, 109.1, 87.5, 72.4, 69.7, 68.9, 67.0, 61.0, 55.1, 42.3, 33.7, 29.5, 26.7, 25.6, 22.5, 21.3 ppm. **FTIR (neat):** ν = 3053,

2985, 2304, 1421, 1265, 1159, 894, 738, 705 cm^{-1} ; **HRMS (ESI, m/z)**: calcd for $\text{C}_{21}\text{H}_{32}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 410.1942, found: 410.945 (PMB cleaved mass).

6-(4-(4-methoxybenzyloxy)butyl)-2,2-dimethyl-8-vinyl-1,3-dioxo-7-azaspiro[4.4]nonane (94) :

To a solution of naphthalene (1.69 g, 13.2 mmol) in dry DMSO (2 mL), sodium metal (261 mg, 11.8 mmol) was added then stirred at 25 °C. After 2 h, dark green colour was observed. Above mixture was added dropwise to a pre-dissolved solution of 6-(4-(4-methoxybenzyloxy)butyl)-2,2-dimethyl-7-tosyl-8-vinyl-1,3-dioxo-7-azaspiro[4.4]nonane (700 mg; 1.32 mmol) in dry DMSO at -78 °C. After 30 minute, saturated solution of NaHCO_3 (2 mL) was added then stirred with solid K_2CO_3 (6 g) for 5 h. Extracted with CH_2Cl_2 (100 mL, 3 times), combined organic layer was concentrated to get crude product that was purified using column chromatography (80% ethyl acetate in hexane) to get pure product **94** as a colorless oil (340 mg, 69% yield); **^1H NMR (300 MHz, CDCl_3)**: δ = 7.18 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 5.62 – 5.71 (m, 1H), 4.90 -5.11 (m, 2H), 4.34 (s, 2H), 4.02 (d, J = 9.0 Hz, 1H), 3.71 (s, 3H), 3.57 – 3.67 (m, 2H), 3.37 – 3.40 (m, 2H), 2.95 – 2.98 (m, 1H), 2.55 (brs, 1H), 2.13 (dd, J = 13.3, 7.0 Hz, 1H), 1.40 – 1.70 (m, 5H), 1.31 (s, 3H), 1.28 (s, 3H), 1.15 – 1.25 (m, 1H) ppm; **^{13}C NMR (125 MHz, CDCl_3)**: δ = 159.0, 140.3, 130.5, 129.1, 115.1, 113.6, 108.4, 88.0, 72.4, 69.9, 69.8, 66.1, 58.4, 55.1, 44.4, 30.5, 29.7,

26.8, 25.7, 24.2 ppm; **FTIR (neat):** ν = 3053, 2985, 2937, 2862, 2304, 1612, 1512, 1265, 1099, 1056, 1035, 738 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{14}\text{H}_{26}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 256.1913, found: 256.1915 (PMB cleaved mass).

Tert-butyl-3-hydroxy-3-(hydroxymethyl)-2-(4-(4-methoxybenzyloxy)butyl)-5-vinylpyrrolidine-1-carboxylate (95):

To a solution of 6-(4-(4-methoxybenzyloxy)butyl)-2,2-dimethyl-8-vinyl-1,3-dioxo-7-azaspiro[4.4]nonane (300mg; 0.8 mmol) in THF:H₂O (1:1, 10 mL), was added 3 M HCl (3.0 mL) at 0 °C. After 5 h stirring at 25 °C, adjusted the pH to 9.0 using NaHCO₃ then (Boc)₂O (350 mg, 1.6 mmol) in THF was added dropwise at 25 °C. After 2 h, extracted with ethyl acetate, combined organic layer was concentrated to get crude product that was purified by column chromatography (90% ethyl acetate in hexane) to get pure product **95** as a colorless oil (330mg; 88% over 2 step); **¹H NMR (300 MHz, DMSO-*d*₆):** δ = 7.22 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.75 (brs, 1H), 4.90 -5.05 (m, 2H), 4.50 – 4.65 (m, 2H), 4.34 (s, 2H), 4.25 (brs, 1H), 3.73 (s, 3H), 3.65 (brs, 1H), 3.35 – 3.40 (m, 4H), 1.85 -1.90 (m, 1H), 1.40 – 1.60 (m, 6H), 1.35 (s, 9H), 1.00 – 1.10 (brs, 1H) ppm; **¹³C NMR (125 MHz, CDCl₃):** δ = 159.0, 156.4, 140.2, 130.5, 129.1(2), 114.0, 113.6 (2), 81.2, 79.6, 72.4, 70.0(2), 66.3, 64.8, 58.8, 55.1 (2), 39.6, 32.6, 29.6, 28.3 (2) ppm. **FTIR (neat):** ν = 3053, 2980, 1683, 1612, 1512, 1392, 1265, 1033, 738 cm^{-1} ; **HRMS**

(ESI, m/z): calcd for $\text{C}_{16}\text{H}_{30}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 316.2065, found: 316.2066 (PMB cleaved mass).

CHAPTER 5

Synthesis of Spiro Furan- Indolinones via Phosphine Catalyzed [3+2]-Cycloaddition Reactions

Chapter 5 Synthesis of Spiro Furan-Indolinones via Phosphine Catalyzed

[3+2]-Cycloaddition Reactions

5.1 Introduction

Many natural products and drug molecules possess a spiro-oxindoline core structural unit.⁶⁸ In particular, heterocyclic spiro-oxindole frameworks are considered to be a significant structural motif since they are found in a wide range of alkaloids.⁶⁹ Interestingly, the spiro ring fusion at 3-position of oxindolinone greatly enhances the molecular complexity and biological importance.⁷⁰ Consistent with their biological significance, many research groups have focused on the development of diversely functionalized spiro-oxindolines. Even though the synthetic approach of spiro[pyrrolidine-oxindolines] is widely studied,⁷¹ the corresponding furan fused oxindoline analogues have only been scarcely investigated.⁷² Thus, a efficient

⁶⁸ For reviews, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Lin, H.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2003**, 42, 36. (c) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, 126, 16077. (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, 46, 8748. (e) Venkatesan, H.; Davis, M. C.; Altas, Y.; Snyder, D. Liotta, C. J. *J. Org. Chem.* **2001**, 66, 3653. (f) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (g) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, 36, 127. (h) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, 352, 1381–1407; i) S. Kotha, A. C. Deb, K. Lahiri, E. Manivannan, *Synthesis* **2009**, 165–193.

⁶⁹ (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, 36, 127. (b) He, Y.; Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewsky, D. *Bioorg. Med. Chem. Lett.* **2006**, 16, 2109. (c) Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, 31, 7277.

⁷⁰ (a) Booker-Milburn, K. I.; Fedoulo, M. S.; Paknoham, J.; Strachan, J. B.; Melville, J. L.; Voyleb, M. *Tetrahedron Lett.* **2000**, 41, 4657. (b) Wang, L.; Zhang, Y.; Hu, H. Y.; Fun, H. K.; Xu, J.-H. *J. Org. Chem.* **2005**, 70, 3850. (c) Tratat, C.; Giorgi-Renault, S.; Husson, H.-P. *J. Org. Chem.* **2000**, 65, 6773. (d) Xue, J.; Zhang, Y.; Wang, X.; Fun, H. K. Xu, J.-H. *Org. Lett.* **2000**, 2, 2583.

⁷¹ (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Fokas, D.; Ryan, W. J.; Casebier, D. S.; Coffen, D. L. *Tetrahedron Lett.* **1998**, 2235. (c) Rehn, S.; Bergman, J.; Stensland, B. *Eur. J. Org. Chem.* **2004**, 413.

⁷² (a) Smet, M.; Oosterwijck, C. V.; Hecke, K. V.; Meervelt, L. V.; Vandendriessche, A.; Dehaen, W. *Synlett* **2004**, 2388. (b) Savitha, G.; Niveditha, S. K.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2007**, 48, 2943. (c) Shanmugam, P.; Vaithiyanathan, V. *Tetrahedron* **2008**, 64, 3322. (e) Li, J.; Liu, Y.; Li, C.; Jia, X. *Chem. Eur. J.* **2011**, 17, 7409.

protocol to construct such furan fused oxindolines, using metal free catalysis is highly desirable. We envisioned the use of Lu's phosphine catalyzed [3+2]-cycloaddition between oxindolinone and allenates to construct spiro[furan-oxindoles]. However, Lu's reaction with activated olefins ($C=C$)¹⁴ and imines ($C=N$)³⁸ has only been applied to the synthesis of corresponding carbo- and heterocycles. Surprisingly, there has not been any reports on the use of other coupling partner carbonyls ($C=O$) in the [3+2]-cycloaddition process. Kwon and co-workers have pioneered the phosphine catalyzed cycloaddition between aldehydes and electron deficient allenates.^{46 & 47} Unlike olefins and imines, the reaction with aldehydes did not afford the expected [3+2]-cyclized dihydrofuran adduct. However, the reaction followed unprecedented pathways to obtain series of cyclized products includes 1,3-dioxan-4-ylidines **78** (Scheme 2.3), 6-substituted pyrones **80** and 6,4-disubstituted-5,6-dihydro-2-pyrones **81**. Recently, Song Ye reported the formal [3+2]-cycloaddition of allenates with carbonyl compounds in the synthesis of dihydrofuran adduct (Scheme 5.1).⁷³ Mechanistically, all these products were resulted from nucleophilic addition of γ -carbon of zwitterionic intermediate to aldehydes.

⁷³ Wang, T.; Ye, S. *Org. Biomol. Chem.* **2011**, 9, 5260.

Scheme 5.1 Phosphine-catalyzed cycloaddition across C=O

In this chapter, the spiro [furan-oxindoline] derivatives was synthesized by using phosphine catalyzed [3+2] cycloaddition between oxindolinone and allenates.

5.2 Result and discussion

To examine our speculation, ethyl 2, 3-butadienoate **3a** and *N*-benzyloxindolinone **96a** were chosen as model substrates to react with commercially available phosphines (Table 5.1, entries 1-9).

Table 5.1 Screening phosphines

3a	96a		97a
Entry	Phosphine	Time (h)	Yield (%)
1	Triphenylphosphine	24	70
2	Tricyclohexylphosphine	12	51
3	Trimethoxyphosphine	18	58
4	Tri- <i>n</i> -butylphosphine	6	27
5	Tri- <i>t</i> -butylphosphine	6	39
6	Trimethylphosphine	6	trace
7	Ethylenebis(diphenylphosphine)	12	36
8	1,3-bis(diphenylphosphino)propane	12	60
9	1,5-Bis(diphenylphosphino)pentane	12	55

The reaction proceeded smoothly with catalytic amount of triphenylphosphine to afford the spiro furan-oxindoline **97a** in 70% yield (Table 5.1, entry 1). In the case of more nucleophilic phosphines such as aliphatic phosphines, although, the reaction proceeded faster, a noticeable decrease in the product yield was observed. On contrary to the reaction reported with aldehydes in literature,^{46 & 47} the regioselectivity

of the present [3+2]-cyclized product **97a** suggest the α -carbon of 1,3-dipolar zwitterionic intermediate added to an oxindolinones.

Encouraged by this result, a series of nitrogen substituted oxindolinones were screened under the previously optimized reaction condition. In all of the cases, spiro oxindolines were obtained in good yields and excellent regioselectivities (Table 5.2; entries 1-10). Noticeably, the substituents such as allyl **96c** and prop-2-yn **96d** were tested to afford the spirocycles in good yields (Table 5.2, entries 3 and 4). Interestingly, the oxindolinone bearing labile substituents such as TMS **97g** and TIPS **97j** were smoothly proceeded to afford product in 66% and 59% yields respectively. The structure of product **97f** was confirmed by ^1H , ^{13}C and X-ray crystallographic analysis (Figure 5.1).

Figure 5.1 ORTEP drawing of **97f** with thermal ellipsoids at 50% probability level

Table 5.2 Scope of [3+2]-Cycloaddition with respect to the *N*-substituted oxindolinones ^a

Entry	R ¹	Product ^b	Yield (%) ^c
1	Bn	97a	70
2	CH ₃	97b	78
3	allyl	97c	70
4	CH ₂ CCH	97d	81
5	CH ₂ CO ₂ Et	97e	63
6	PMB	97f	76
7	CH ₂ TMS	97g	66
8	CH ₂ OCOPh	97h	58
9	CH ₂ CH ₂ CH=CH ₂	97i	71
10	CH ₂ OTIPS	97j	59

^a See experimental section for detailed experimental procedure. ^b Single regioisomer was observed by ¹H NMR analysis. ^c Isolated yield.

To further explore the scope of this process, various *N*-benzyloxindolinones were examined. As shown in table 5.3, both electron withdrawing and releasing substituents on the phenyl ring of oxindolinones proceeded smoothly to afford the products in good yields (Table 5.3; entries 1-11).

Table 5.3 Scope of [3+2] cycloaddition with respect to the substituted oxindolinones^a

Entry	R ²	Product ^b	Yield (%) ^c
1	5-F	97k	69
2	5-Cl	97l	63
3	5-Br	97m	78
4	5-I	97n	61
5	5-NO ₂	97o	65
6	5-CH ₃	97p	64
7	5-OCF ₃	97q	68
8	5,7-Cl	97r	55
9	7-F	97s	64
10	7-Cl	97t	60
11	7-Br	97u	57

^a See experimental section for a detailed experimental procedure. ^b Single regioisomer was observed by ¹H NMR analysis. ^c Isolated yield.

The proposed mechanism of this cycloaddition is depicted in scheme 5.2. Upon addition of triphenylphosphine to 2,3-butadienoate **3a**, the resonance stabilized zwitterionic intermediates (**A**↔**B**) are formed. The intermediate **B** preferentially undergoes cycloaddition with oxindolinones to form cyclized intermediate **C**, after the subsequent [1,2]-proton transfer and elimination of phosphine yielded final product **97** (Scheme 5.2).

Scheme 5.2 Proposed mechanism

Recently, Lu *et al.* and other research groups have demonstrated the use of a modified Morita-Baylis-Hillman (MBH) adduct as the three carbon precursor in a phosphine catalyzed [3+2] cycloaddition reaction with activated olefins.³³⁻³⁶ Whereas, the reaction of MBH adduct with aldehyde yielded a conjugated diene through Wittig type transformations.⁷⁴ Herein, we describe the employment of oxindolinones instead of aldehydes in this process to obtain tetra-substituted conjugated dienes. Reaction of

⁷⁴ (a) Palmelund, A.; Myers, E. L.; Tai, L. R.; Tisserand, S.; Butts, C. P.; Aggarwal, V. K. *Chem. Commun.* **2007**, 4128. (b) Zhou, R.; Wang, C.; Song, H.; He, Z. *Org. Lett.* **2010**, 12, 976.

allylic carbonates **53** and oxindolinone **96c** in the presence of 10 mol % of triphenylphosphine yielded the product **98** in < 10% yield and no trace of cyclized adduct. Increasing the triphenylphosphine loading to stoichiometric amount, a considerable increase in the yield of **98** was observed (Table 5.4, entry 1).

Table 5.4 Scope of allylic carbonates in salt free Wittig type transformations ^a

Entry	R	Product	Yield (%)
1	Ph	98ac	65
2	2-furyl	98bc	58
3	2-thienyl	98cc	52
4	4-ClC ₆ H ₄	98dc	60
5	4-NO ₂ C ₆ H ₄	98ec	57

^a See experimental section for detailed experimental procedure. ^b Single regioisomer was observed by ¹H NMR analysis. ^c Isolated yield.

To increase the synthetic utility of this reaction, various allylic carbonates were screened and in all the cases, good yields and excellent diastereoselectivities were observed (Table 5.4; entries 1-5). Interestingly, the allylic carbonates bearing heteroaromatic substituents such as furan **53b** and thiophene **53c** proceeded smoothly to afford dienes in good yields. The stereochemistry of **98ac** was conformed from the X-ray crystallographic analysis (Figure 5.2).

Figure 5.2 ORTEP drawing of **98** with thermal ellipsoids at 50% probability level

5.3 Conclusion

In conclusion, an efficient method for preparing spiro furan-oxindolines is described. The reaction involves a phosphine catalyzed [3+2] cycloaddition between oxindolinones and allenates. The enantioselective version of this reaction and its application towards the synthesis of natural products are in progress. In addition, the synthesis of tetra-substituted conjugated dienes by Wittig type transformations of modified Morita-Baylis-Hilman adducts and indolines-2,3-dione is also described.

5.4 Experimental Section

5.4.1 General procedure for the synthesis of products 97a-97u

To a solution of oxindolinone (0.400 mmol) and ethyl buta-2,3-dienoate (0.400 mmol) in toluene (3 mL), a solution of triphenylphosphine (0.080 mmol) in toluene (1 mL) was added dropwise at 0 °C. After the reaction mixture was stirred for 24 h at 25 °C purified through flash column chromatography using hexane and ethyl acetate to obtain **97**.

Ethyl 1'-benzyl-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate (**97a**)

Yellow solid, m.p. 142-144 °C, ^1H NMR (500 MHz, CDCl_3):

$\delta = 7.38 - 7.37$ (m, 2H), $7.33 - 7.29$ (m, 3H), $7.27 - 7.25$ (m, 1H), $7.21 - 7.17$ (m, 2H), $7.01 - 6.97$ (m, 1H), $6.69 - 6.67$ (m,

1H), 5.14 (ABq, $J = 16.0$ Hz, 2H), 4.91 (ABq, $J = 12.0$ Hz, 2H), $4.14 - 4.03$ (m, 2H),

0.96 (t, $J = 6.0$ Hz, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3): $\delta = 174.6$, 161.0 , 143.6 ,

142.6 , 135.5 , 133.7 , 130.4 , 128.7 (2C), 128.3 , 127.6 , 127.4 (2C), 124.3 , 123.0 , 109.5 ,

89.3 , 76.0 , 60.8 , 44.1 , 13.8 ppm; FTIR (neat): $\nu = 3053$, 1724 , 1614 , 1489 , 1467 ,

1421 , 1367 , 1265 , 1180 , 894 , 738 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{20}\text{NO}_4$

$[\text{M}+\text{H}]^+ 350.1392$, found: 350.1392 .

Ethyl 1'-methyl-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate (**97b**)

Pale yellow solid, m.p. 162-165 °C, ^1H NMR (500 MHz,

CDCl_3): $\delta = 7.35 - 7.29$ (m, 2H), $7.19 - 7.18$ (d, $J = 7.9$ Hz,

1H), 7.06 – 7.02 (m, 1H), 6.83 – 6.82 (m, 1H), 5.13 (ABq, $J = 15.0$ Hz, 2H), 4.03 – 3.95 (m, 2H), 3.22 (s, 3H), 1.04 (t, $J = 7.5$ Hz, 3H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 174.4, 161.0, 144.4, 142.2, 133.7, 130.4, 128.2, 124.2, 123.0, 108.3, 89.2, 76.0, 60.7, 26.3, 13.7$ ppm; FTIR (neat): $\nu = 1726, 1614, 1471, 1373, 1265, 1101, 1047, 1020, 738$ cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 274.1079, found: 274.1098.

Ethyl 1'-allyl-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97c)

White solid, m.p. 122-123 °C, ^1H NMR (400 MHz, CDCl_3): $\delta = 7.31 - 7.27$ (m, 2H), 7.21 – 7.19 (m, 1H), 7.04 (t, $J = 8.0$ Hz, 1H), 6.84 – 6.82 (m, 1H), 5.91 – 5.82 (m, 1H), 5.39 – 5.34 (m, 1H), 5.26 – 5.23 (m, 1H), 5.13 (ABq, $J = 16.0$ Hz, 2H), 4.35 (ABq, $J = 16.0$ Hz, 2H), 4.15 – 3.94 (m, 2H), 1.06 (t, $J = 6.0$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 174.1, 161.0, 143.7, 142.4, 133.6, 131.1, 130.3, 128.2, 124.2, 122.9, 117.8, 109.3, 89.2, 76.0, 60.8, 42.6, 13.8$ ppm; FTIR (neat): $\nu = 3055, 2984, 2968, 2932, 1721, 1599, 1454, 1422, 1340, 1265, 1165, 1093$ cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 300.1236, found: 300.1247.

Ethyl 2'-oxo-1'-(prop-2-ynyl)-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97d)

Yellow solid, m.p. 112-114 °C, ^1H NMR (400 MHz, CDCl_3): $\delta = 7.37 - 7.31$ (m, 2H), 7.22 – 7.20 (m, 1H), 7.09 – 7.04 (m, 2H), 5.12 (ABq, $J = 16.0$ Hz, 2H), 4.51 (ABq, $J = 20.0$ Hz, 2H), 4.15 – 3.93 (m, 2H), 2.25 (t, $J=2.0\text{Hz}$, 1H), 1.01 (t, $J = 8.0\text{Hz}$, 3H) ppm. ^{13}C NMR

(100 MHz, CDCl₃): δ = 173.4, 160.9, 142.5, 133.6, 130.4, 128.1, 124.3, 123.3 (2C), 109.4, 89.1, 76.6, 76.1, 72.5, 60.9, 29.4, 13.8 ppm; **FTIR (neat)**: ν = 1730, 1614, 1467, 1375, 1265, 1184, 1109, 1043, 736 cm⁻¹; **HRMS (ESI, m/z)**: calcd for C₁₇H₁₆NO₄ [M+H]⁺ 298.1079, found: 298.1073.

Ethyl-1'-(2-ethoxy-2-oxoethyl)-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97e)

¹H NMR (300 MHz, CDCl₃): δ = 7.33 – 7.27 (m, 2H), 7.22 – 7.20 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.74 – 6.71 (m, 1H), 5.12 (ABq, *J* = 15.0 Hz, 2H), 4.45 (ABq, *J* = 8.0 Hz, 2H), 4.26 – 4.19 (m, 2H), 4.13 – 3.95 (m, 4H), 1.27 (t, *J* = 7.5 Hz, 3H), 1.02 (t, *J* = 7.5 Hz, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃)**: δ = 174.4, 167.3, 160.9, 143.2, 142.5, 133.6, 130.4, 128.0, 124.4, 123.3, 108.5, 89.1, 76.0, 61.7, 60.8, 41.6, 14.1, 13.8 ppm; **FTIR (neat)**: ν = 1732, 1614, 1467, 1375, 1352, 1261, 1207, 1101, 1022, 754 cm⁻¹; **HRMS (ESI, m/z)**: calcd for C₁₈H₂₀NO₆ [M+H]⁺ 346.1291, found: 346.1295.

Ethyl-1'-(4-methoxybenzyl)-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97f)

Yellow solid, m.p. 162–164 °C, **¹H NMR (400 MHz, CDCl₃)**: δ = 7.32 – 7.17 (m, 5H), 7.00 – 6.97 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 4.0 Hz, 1H), 5.13 (ABq, *J* = 12.0 Hz, 2H), 4.84 (ABq, *J* = 16.0 Hz, 2H), 4.10 – 3.86 (m, 2H), 3.76 (s, 3H), 0.96 (t, *J* = 8.0 Hz, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃)**: δ = 174.5, 161.0, 159.1, 143.6, 142.5,

133.7, 130.3, 128.7 (2C), 128.3, 127.6, 124.2, 122.9, 114.1 (2C), 109.5, 89.3, 76.0, 60.8, 55.3, 43.5, 13.7 ppm; **FTIR (neat):** ν = 3053, 1722, 1614, 1514, 1265, 1178, 894, 738 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{22}\text{H}_{22}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 380.1498, found: 380.1501.

Ethyl-2'-oxo-1'-((trimethylsilyl)methyl)-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97g)

^1H NMR (400 MHz, CDCl_3): δ = 7.18 – 7.14 (m, 2H), 7.03 – 7.01 (m, 1H), 6.88 – 6.84 (m, 1H), 6.64 – 6.62 (m, 1H), 4.97 (ABq, J = 16.0 Hz, 2H), 3.94 – 3.79 (m, 2H), 3.03 (s, 2H), 0.92 (t, J = 8.0 Hz, 3H), 0.00 (s, 9H) ppm. **^{13}C NMR (100 MHz, CDCl_3):** δ = 173.9, 160.9, 145.0, 142.3, 133.7, 130.2, 128.7, 108.7, 89.0, 75.9, 60.7, 31.7, 13.9, -1.5 (3C) ppm; **FTIR (neat):** ν = 1720, 1614, 1465, 1373, 1263, 1166, 1105, 1020, 844 cm^{-1} ; **HRMS (ESI, m/z):** calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_4\text{SiNa}$ $[\text{M}+\text{Na}]^+$ 368.1294, found: 368.1307.

Ethyl-1'-(benzoyloxymethyl)-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97h)

^1H NMR (500 MHz, CDCl_3): δ = 8.06 – 8.04 (m, 2H), 7.58 – 7.55 (m, 1H), 7.43 – 7.32 (m, 4H), 7.24 – 7.08 (m, 3H), 6.04 (s, 2H), 5.15 (ABq, J = 15.0 Hz, 2H), 4.03 – 3.89 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR (100 MHz, CDCl_3):** δ = 174.6, 166.0, 160.8, 142.4, 142.1, 133.6, 133.5, 130.8, 129.9, 129.2, 128.4, 127.6, 124.6, 123.8, 109.5, 89.1, 76.2, 64.0, 60.9, 13.7 ppm; **FTIR (neat):** ν = 3053, 2303, 1724, 1616, 1421,

1261, 894, 748 cm^{-1} ; **HRMS (ESI, m/z)**: calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_6$ $[\text{M}+\text{H}]^+$ 394.1291, found: 394.1284.

Ethyl 1'-(but-3-enyl)-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97i)

Pale yellow solid, m.p. 143-145 °C, ^1H NMR (400 MHz, CDCl_3): δ = 7.33 – 7.29 (m, 2H), 7.19 – 7.18 (m, 1H), 7.04 – 7.01 (m, 1H), 6.85 – 6.83 (m, 1H), 5.89 – 5.80 (m, 1H), 5.19 – 5.04 (m, 4H), 4.07 – 3.93 (m, 2H), 3.77 – 3.74 (m, 2H), 2.46 (q, J = 8.0 Hz, 2H), 1.04 (t, J = 6.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 174.2, 160.9, 143.7, 142.3, 134.5, 133.7, 130.4, 128.3, 124.4, 122.8, 117.4, 108.6, 89.1, 76.0, 60.8, 39.7, 31.6, 13.8 ppm; **FTIR (neat)**: ν = 3053, 1724, 1614, 1489, 1467, 1369, 1263, 738 cm^{-1} ; **HRMS (ESI, m/z)**: calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 314.1392, found: 314.1401.

Ethyl-2'-oxo-1'-((triisopropylsilyloxy)methyl)-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97j)

^1H NMR (400 MHz, CDCl_3): δ = 7.35 – 7.29 (m, 2H), 7.20 – 7.18 (m, 1H), 7.09 – 7.03 (m, 2H), 5.39 (ABq, J = 12.0 Hz, 2H), 5.11 (ABq, J = 16.0 Hz, 2H), 4.06 – 3.88 (m, 2H), 1.22 – 1.13 (m, 3H), 1.09 – 1.06 (m, 18H), 0.99 (t, J = 8.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 173.6, 160.9, 143.2, 142.4, 133.8, 130.4, 127.8, 124.2, 123.1, 110.1, 89.5, 76.0, 65.2, 60.7, 53.4, 17.9 (3C), 17.8 (3C), 13.7, 11.9 (2C) ppm; **FTIR**

(neat): $\nu = 1732, 1421, 1265, 1112, 1045, 1020, 738 \text{ cm}^{-1}$; **HRMS (ESI, m/z)**: calcd for $\text{C}_{24}\text{H}_{36}\text{NO}_5\text{Si}$ $[\text{M}+\text{H}]^+$ 446.2363, found: 446.2318.

Ethyl-1'-benzyl-5'-fluoro-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate

(97k)

White solid, m.p. 88-91 °C, **^1H NMR (500 MHz, CDCl_3)**: $\delta = 7.36 - 7.24$ (m, 6H), 6.95 – 6.86 (m, 2H), 6.59 – 6.57 (m, 1H), 5.14 (ABq, $J = 15.0$ Hz, 2H), 4.90

(ABq, $J = 15.0$ Hz, 2H), 4.12 – 3.92 (m, 2H), 1.01 (t, $J = 7.5$ Hz, 3H) ppm. **^{13}C NMR**

(125 MHz, CDCl_3): $\delta = 174.3, 160.8, 160.3, 158.4, 142.8, 139.5$ (2), 135.2, 133.3, 129.8, 129.7, 128.8, 127.7 (2), 116.6, 112.5, 110.0, 89.2, 76.2, 60.9, 44.2, 13.8 ppm;

FTIR (neat): $\nu = 1728, 1608, 1485, 1454, 1427, 1373, 1263, 1178, 1045, 738 \text{ cm}^{-1}$;

HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_4\text{F}$ $[\text{M}+\text{H}]^+$ 368.1299, found: 368.1298.

Ethyl-1'-benzyl-5'-bromo-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate

(97m)

Pale yellow solid, m.p. 87-90 °C, **^1H NMR (500 MHz, CDCl_3)**: $\delta = 7.36 - 7.26$ (m, 8H), 6.55 – 6.53 (m, 1H), 5.14 (ABq, $J = 15.0$ Hz, 2H), 4.89 (ABq, $J = 15.0$ Hz,

2H), 4.11 – 3.95 (m, 2H), 1.03 (t, $J = 7.5$ Hz, 3H) ppm. **^{13}C NMR (125 MHz,**

CDCl_3): $\delta = 174.0, 160.8, 142.8, 142.7, 135.0, 133.3, 133.1, 130.3, 128.8$ (2C), 127.8, 127.6, 127.3 (2C), 115.6, 111.0, 89.0, 76.3, 61.0, 44.2, 13.8 ppm.

Ethyl 1'-benzyl-5'-iodo-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97n)

Yellow solid, m.p. 96-99 °C, ^1H NMR (300 MHz,

CDCl_3): δ = 7.51 – 7.46 (m, 2H), 7.35 – 7.26 (m, 6H),

6.44 (d, J = 8.1 Hz, 1H), 5.13 (ABq, J = 15.0 Hz, 2H),

4.88 (ABq, J = 15.8 Hz, 2H), 4.18 – 3.93 (m, 2H), 1.03 (t, J = 7.2 Hz, 3H) ppm. ^{13}C

NMR (100 MHz, CDCl_3): δ = 173.8, 160.8, 143.4, 142.7, 139.1, 135.0, 133.3, 133.1,

130.6, 128.8 (2C), 127.8, 127.3 (2C), 111.6, 88.9, 85.5, 76.3, 61.0, 44.1, 13.8 ppm;

FTIR (neat): ν = 1728, 1606, 1483, 1421, 1265, 1178, 894, 744 cm^{-1} ; HRMS (ESI,

m/z): calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_4\text{I}$ $[\text{M}+\text{H}]^+$ 476.0359, found: 476.0336.

Ethyl 1'-benzyl-5'-nitro-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97o)

Yellow solid, m.p. 108-109 °C, ^1H NMR (400 MHz,

CDCl_3): δ = 8.18 – 8.15 (m, 1H), 8.08 (d, J = 2.3 Hz,

1H), 7.38 – 7.29 (m, 6H), 6.75 (d, J = 8.0 Hz, 1H), 5.21

(ABq, J = 16.0 Hz, 2H), 4.97 (ABq, J = 16.0 Hz, 2H), 4.13 – 3.97 (m, 2H), 1.08 (t, J =

6.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 174.7, 160.7, 149.3, 143.7,

143.1, 134.3, 132.8, 129.3, 129.0 (2C), 128.1, 127.3, 127.3 (2C), 120.2, 109.2, 88.5,

76.4, 61.3, 44.5, 13.9 ppm; FTIR (neat): ν = 3053, 1707, 1608, 1523, 1421, 1265,

894, 738 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$ 395.1243, found:

395.1239.

Ethyl-1'-benzyl-5'-methyl-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate

(97p)

¹H NMR (300 MHz, CDCl₃): δ = 7.38 – 7.24 (m, 6H), 7.01 – 6.96 (m, 2H), 6.56 (d, J = 7.86 Hz, 1H), 5.12 (ABq, J = 15.7 Hz, 2H), 4.89 (ABq, J = 15.6 Hz, 2H), 4.13 – 3.90 (m,

2H), 2.25 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ = 174.5, 161.1, 142.4, 141.2, 135.6, 133.7, 132.6, 130.6, 128.7 (2C), 128.2, 127.5, 127.3 (2C), 125.0, 109.2, 89.4, 76.0, 60.8, 44.1, 21.0, 13.8 ppm; **FTIR (neat):** ν = 3053, 1718, 1496, 1375, 1265, 1166, 1120, 1045, 738 cm⁻¹; **HRMS (ESI, m/z):** calcd for C₂₂H₂₂NO₄ [M+H]⁺ 364.1549, found: 364.1572.

Ethyl-1'-benzyl-2'-oxo-5'-(trifluoromethoxy)-5H-spiro[furan-2,3'-indoline]-3-carboxylate (97q)

¹H NMR (400 MHz, CDCl₃): δ = 7.37 – 7.26 (m, 6H), 7.07 – 7.05 (m, 2H), 6.66 – 6.64 (m, 1H), 5.16 (ABq, J = 15.8 Hz, 2H), 4.91 (ABq, J = 15.8 Hz, 2H),

4.13 – 3.90 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ = 174.4, 160.7, 145.0, 143.0, 142.3, 135.0, 133.2, 129.8, 128.9 (3C), 127.8, 127.3 (2C), 123.3, 118.2, 109.9, 89.0, 76.3, 61.0, 44.2, 13.7 ppm; **FTIR (neat):** ν = 3053, 1730, 1494, 1421, 1263, 1220, 1176, 894 cm⁻¹; **HRMS (ESI, m/z):** calcd for C₂₂H₁₉NO₅F₃ [M+H]⁺ 434.1215, found: 434.1218.

Ethyl 1'-benzyl-5',7'-dichloro-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate**(97r)** White solid, m.p. 112-114 °C, ^1H NMR (300 MHz, CDCl_3): δ = 7.34 – 7.20 (m, 7H), 7.09 – 7.08 (m, 1H),5.29 (s, 2H), 5.14 (ABq, J = 15.0 Hz, 2H), 4.15 – 3.99(m, 2H), 1.10 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 174.8,

160.7, 143.1, 138.5, 136.9, 133.0, 132.5, 132.2, 128.7, 128.6 (2C), 127.2, 126.5 (2C),

123.6, 116.1, 88.4, 76.4, 61.2, 45.2, 13.9 ppm; FTIR (neat): ν = 3053, 1735, 1579,1456, 1421, 1321, 1265, 1157, 1111, 1020, 894, 750 cm^{-1} ; HRMS (ESI, m/z): calcdfor $\text{C}_{21}\text{H}_{18}\text{NO}_4\text{Cl}_2$ $[\text{M}+\text{H}]^+$ 418.0613, found: 418.0631.**Ethyl-1'-benzyl-7'-fluoro-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate****(97s)** White solid, m.p. 99-101 °C, ^1H NMR (300 MHz, CDCl_3): δ =

7.41 – 7.39 (m, 2H), 7.32 – 7.24 (m, 4H), 7.00 – 6.93 (m, 3H),

5.26 (s, 1H), 5.20 – 5.03 (m, 3H), 4.07 – 3.83 (m, 2H), 0.94 (t,

 J =7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 173.8, 160.8, 143.4, 142.7,

139.1, 135.0, 133.3, 133.1, 130.6, 128.8 (2C), 127.8, 127.3 (2C), 111.6, 88.9, 85.5,

76.3, 61.0, 44.1, 13.8 ppm; FTIR (neat): ν = 3053, 1728, 1631, 1489, 1473, 1352,1265, 1244, 740 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_4\text{F}$ $[\text{M}+\text{H}]^+$ 368.1298,

found: 368.1293.

Ethyl-1'-benzyl-7'-chloro-2'-oxo-5H-spiro[furan-2,3'-indoline]-3-carboxylate**(97t)** Orange solid, m.p. 119-121 °C, **¹H NMR (400 MHz, CDCl₃):** δ = 7.33 – 7.23 (m, 6H), 7.19 – 7.09 (m, 2H), 6.97 – 6.93 (m, 1H), 5.33 (s, 2H) 5.13 (ABq, J = 16.0 Hz, 2H), 4.12 – 3.94 (m,2H), 1.05 (t, J = 7.2 Hz, 3H) ppm. **¹³C NMR (100 MHz,****CDCl₃):** δ = 175.2, 160.8, 142.9, 139.7, 137.3, 133.4, 132.9, 131.3, 128.5 (2C), 127.1,126.6 (2C), 124.0, 123.0, 115.7, 88.5, 76.1, 61.0, 45.2, 13.8 ppm; **FTIR (neat):** ν =1716, 1612, 1454, 1375, 1352, 1325, 1263, 1244, 1166, 1022, 736 cm⁻¹; **HRMS (ESI,****m/z):** calcd for C₂₁H₁₉NO₄Cl [M+H]⁺ 384.1003, found: 384.1003.**5.4.2 General procedure for the synthesis of products 98ac – 98ec**

To a solution of **14c** (0.400 mmol) and Baylis-Hillman carbonate (0.400 mmol) in toluene (4 mL) cooled to 0°C, tributylphosphine catalyst (0.080 mmol) in toluene (1 mL) was added dropwise and the solution was warmed to room temperature and stirred for 24h. Flash column chromatography using hexane and ethyl acetate (15 – 30% ethyl acetate/hexane solution) was done to obtain purified product **23**.

(E)-methyl 2-((E)-(1-allyl-2-oxoindolin-3-ylidene)methyl)-3-phenylacrylate (98ac) Orange solid, m.p. 133-135 °C, **¹H NMR (500 MHz, CDCl₃):** δ =

7.96 (brs, 1H), 7.62 – 7.61 (m, 1H), 7.53 – 7.50 (m, 2H), 7.34 –

7.32 (m, 3H), 7.21 – 7.15 (m, 2H), 6.88 (td, J = 7.5, 0.9 Hz, 1H),

6.80 – 6.78 (m, 1H), 5.92 – 5.85 (m, 1H), 5.28 – 5.23 (m, 2H), 4.42 – 4.40 (m, 2H), 3.75 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ = 167.3, 167.1, 144.1, 143.3, 134.3, 131.7, 130.8 (2C), 130.4, 130.3, 129.9, 129.7, 128.8 (2C), 126.3, 123.9, 122.1, 121.4, 117.6, 108.9, 52.6, 42.4 ppm; **FTIR (neat):** ν = 3053, 1707, 1610, 1467, 1421, 1265, 738 cm⁻¹; **HRMS (ESI, m/z):** calcd for C₂₂H₂₀NO₃ [M+H]⁺ 346.1443, found: 346.1455.

(E)-methyl 2-((E)-(1-allyl-2-oxoindolin-3-ylidene)methyl)-3-(furan-2-yl)acrylate (98bc)

Yellow solid, m.p. 108-111 °C, **¹H NMR (400 MHz, CDCl₃):** δ = 7.75 (brs, 1H), 7.70 (brs, 1H), 7.53 (brs, 1H), 7.20 (t, J = 7.74 Hz, 1H), 7.11 – 7.09 (m, 1H), 6.91 – 6.88 (m, 1H), 6.81 – 6.80 (m, 1H), 6.75 – 6.74 (m, 1H), 6.47 – 6.46 (m, 1H), 5.94 – 5.84 (m, 1H), 5.29 – 5.23 (m, 2H), 4.43 – 4.42 (m, 2H), 3.74 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ = 167.6, 166.8, 150.6, 146.3, 143.3, 131.7, 130.0, 129.9, 129.7, 129.5, 124.0, 122.6, 122.1, 121.6, 118.4, 117.6, 112.9, 108.9, 52.5, 42.4 ppm; **FTIR (neat):** ν = 3055, 2984, 2968, 2932, 1721, 1599, 1454, 1422, 1340, 1265, 1165, 1093 cm⁻¹; **HRMS (ESI, m/z):** calcd for C₂₀H₁₈NO₄ [M+H]⁺ 336.1236, found: 336.1251.

(E)-methyl-2-((E)-(1-allyl-2-oxoindolin-3-ylidene)methyl)-3-(thiophen-2-yl)acrylate (98cc)

Orange solid, m.p. 136-138 °C, **¹H NMR (400 MHz, CDCl₃):** δ = 8.12 (s, 1H), 7.61 (s, 1H), 7.49 – 7.48 (m, 1H), 7.39 – 7.38 (m,

1H), 7.22 – 7.16 (m, 2H), 7.08 – 7.06 (m, 1H), 6.90 – 6.87 (m, 1H), 6.81 – 6.79 (m, 1H), 5.94 – 5.85 (m, 1H), 5.30 – 5.23 (m, 2H), 4.43 – 4.42 (m, 2H), 3.76 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ = 167.1, 166.7, 143.4, 137.9, 136.0, 134.2, 132.4, 131.7, 131.4, 129.8, 129.1, 127.7, 124.0, 122.8, 122.2, 121.5, 117.6, 109.0, 52.5, 42.4 ppm; **FTIR (neat):** ν = 3055, 2984, 2968, 2932, 1721, 1599, 1454, 1422, 1340, 1265, 1165, 1093 cm⁻¹; **HRMS (ESI, m/z):** calcd for C₂₀H₁₈NO₃S [M+H]⁺ 352.1007, found: 352.1005.

(E)-methyl-2-((E)-(1-allyl-2-oxoindolin-3-ylidene)methyl)-3-(4-chlorophenyl)acrylate (98dc)

late (98dc)

Yellow solid, m.p. 130-132 °C, **¹H NMR (400 MHz, CDCl₃):**

δ = 7.89 (brs, 1H), 7.56 (brs, 1H), 7.46 – 7.44 (m, 2H), 7.31 –

7.29 (m, 2H), 7.22 – 7.19 (m, 1H), 7.15 – 7.13 (m, 1H), 6.88

(t, J = 7.8, 1H), 6.80 – 6.79 (m, 1H), 5.93 – 5.83 (m, 1H), 5.29 – 5.23 (m, 2H), 4.42 –

4.40 (m, 2H), 3.76 (s, 3H) ppm. **¹³C NMR (100 MHz, CDCl₃):** δ = 167.1, 166.8,

143.4, 142.5, 136.4, 132.7, 131.8 (2C), 131.6, 130.6, 129.9, 129.2, 129.1 (2C), 126.8,

123.9, 122.2, 121.2, 117.7, 109.0, 52.7, 42.4 ppm; **FTIR (neat):** ν = 3053, 1724,

1614, 1467, 1421, 1367, 1265, 1180, 894, 738 cm⁻¹; **HRMS (ESI, m/z):** calcd for

C₂₂H₁₉NO₃Cl [M+H]⁺ 380.1053, found: 380.1059.

(E)-methyl-2-((E)-(1-allyl-2-oxoindolin-3-ylidene)methyl)-3-(4-nitrophenyl)acrylate (98ec)

Yellow solid, m.p. 139-141 °C, ^1H NMR (400 MHz, CDCl_3): δ = 8.17 – 8.15, (m, 2H), 7.95 (brs, 1H), 7.67 – 7.65 (m, 2H), 7.54 (brs, 1H), 7.23 – 7.19 (m, 1H), 7.14 – 7.12 (m, 1H), 6.89 – 6.85 (m, 1H), 6.80 – 6.79 (m, 1H), 5.91 – 5.83 (m, 1H), 5.28 – 5.24 (m, 2H), 4.41 – 4.39 (m, 2H), 3.80 (s, 3H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 166.8, 166.3, 148.1, 143.6, 140.6, 140.4, 131.4, 131.2, 130.9 (2C), 130.4, 130.3, 128.0, 123.9 (2C), 123.7, 122.2, 120.8, 117.8, 109.3, 53.0, 42.5 ppm; FTIR (neat): ν = 3055, 2984, 2968, 2932, 1721, 1599, 1454, 1422, 1340, 1265, 1165, 1093 cm^{-1} ; HRMS (ESI, m/z): calcd for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 391.1294, found: 391.1291.

LIST OF PUBLICATIONS

1. “Silicon as a directing group in the phosphine catalyzed [2+3]-cycloaddition using aryl allenones and electron-deficient olefins” Magesh Sampath, Teck-Peng Loh, *Chem. Commun.* **2009**, 1568.
2. “Highly Enantioselective One-Pot [2+3]-Cycloaddition reactions using 3-butynoates and Electron Deficient Olefins *via* Isomerization of 3-butynoates to Allenates” Magesh Sampath and Teck-Peng Loh, *Chem. Sci.* **2010**, 739-742.
3. “Phosphine-Catalyzed One-Pot Isomerization and [2+3]-Cycloaddition: Formal Synthesis of *Securinine* alkaloid ($\pm$)-Allosecurinine” Magesh Sampath, Pei-Ying Beatrix Lee and Teck-Peng Loh, *Chem. Sci.* **2011**, DOI: 10.1039/c1sc00311a.
4. “Synthesis of *spiro* furan-indolines *via* phosphine-catalyzed [3+2]-cycloaddition between buta-2,3-dienoate and indoline-2,3-dione” Magesh Sampath, Pei-Ying Beatrix Lee and Teck-Peng Loh, Manuscript in preparation.