DISSERTATION

CATALYTIC ASYMMETRIC STETTER REACTION: INTRAMOLECULAR DESYMMETRIZATION OF CYCLOHEXADIENONE AND INTERMOLECULAR REACTION OF GLYOXAMIDE

Submitted by

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY QIN LIU ENTITLED "CATALYTIC ASYMMETRIC STETTER REACTION: INTRAMOLECULAR DESYMMETRIZATION OF CYCLOHEXADIENONE AND INTERMOLECULAR REACTION OF GLYOXAMIDE" BE ACCEPTED AS FULFILLING IN PART THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Prof. Alan J Kennan

Prof. Robert Williams

Prof. Richard G Finke

Prof. Robert Woody

Prof. Tomislav Rovis, Advisor

Prof. Anthony Rappé, Department Chair

ABSTRACT OF DISSERTATION

CATALYTIC ASYMMETRIC STETTER REACTION: INTRAMOLECULAR DESYMMETRIZATION OF CYCLOHEXADIENONE AND INTERMOLECULAR REACTION OF GLYOXAMIDE

A series of cyclohexadienones were synthesized through dearomatization of phenols. The asymmetric intramolecular desymmetrizations of these substrates via Stetter reactions afford hydrobenzofuranones in good yields and excellent selectivities. Up to three contiguous stereocenters, as well as quaternary stereocenter, have been generated.

An asymmetric intermolecular Stetter reaction of glyoxamides with alkylidenemalonates has been successfully developed. These reactions are catalyzed by a pyrrolidinone-derived carbene catalyst, and proceed in good yields with high asymmetric induction. When alkylidene ketoamides are employed, the reactions afford desired β-ketoamides in good yields, excellent enantioselectivities, and good diastereoselectivities.

A carbene-catalyzed asymmetric redox reaction of ynal has been investigated. Cyclohexadienone-tethered ynal and alkylidenemalonate-tethered ynal were demonstrated as suitable substrates for the redox reaction. The desired products were obtained with moderate yields and modest selectivities.

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I must thank my parents for their support to me; and finally, I want to say "Thank you!" to my wife, Di Xue, for giving me a sweet family.

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LIST OF ABBREVIATIONS

AcOH	acetic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DMAP	4-(dimethylamino)pyridine
DMP	Dess-Martin periodinane
Hunig's base	di-isopropylethyl amine
KHMDS	potassium bis(trimethylsilyl)amide
PIDA	phenyliodine diacetate
PIFA	phenyliodine bis(trifluoroacetate)
Super-Hydride	lithium triethylborohydride
TFA	trifluoroacetic acid
TBAF	tetrabutylammonium fluoride
TsOH	p-toluenesulfonic acid

Chapter 1

Asymmetric Synthesis of Hydrobenzofuranones via Desymmetrization of Cyclohexadienones Using the Intramolecular Stetter Reaction

1.1 Introduction

1.1.1 Stetter Reaction

Introduced by D. Seebach and E. J. Corey, umpolung reactivity [1] is a process in which the normal donor and acceptor reactivity of a functional group is inverted to provide non-obvious, complementary reactivity in organic synthesis. The Stetter reaction[2] is an umpolung process in which an acylanion equivalent, generated from an aldehyde in the presence of a nucleophilic carbene catalyst, is added to a Michael acceptor to form a C-C bond. As shown in Scheme 1, acetaldehyde **1** is converted to a nucleophile by thiazolium carbene generated in-situ from **3**, and the carbene converts the acetaldehyde to a nucleophilic intermediate, which adds to the Michael acceptor **2** to afford the 1,4-dicarbonyl compound **4**. When the Michael acceptor involves a prochiral alkene and a chiral catalyst is used, enantioenriched compound can be obtained.[3]

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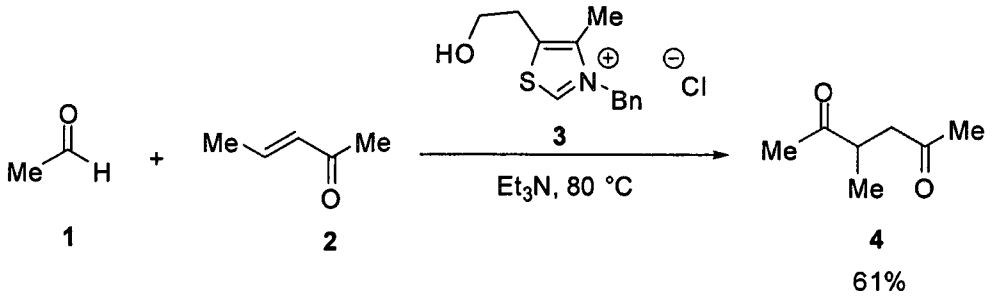
[1] (a) Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1077-1078. (b) Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075-1077. (c) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231-237. (d) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239-258. (e) Barluenga, J.; Mendoza, A.; Dieguez, A.; Rodriguez, F.; Fananas, F. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 4848-50. (f) Brehme, R.; Enders, D.; Fernandez, R.; Lassaletta, J. M. *Eur. J. Org. Chem.* **2007**, *2007*, 5629-5660.

[2] (a) Stetter, H.; Schrecke.M. *Angew. Chem.Int. Edit. Engl.* **1973**, *12*, 81-81. (b) Stetter, H.; Kuhlmann, H. *Tetrahedron Lett.* **1974**, 4505-4508. (c) Stetter, H. *Angew. Chem. Int. Edit. Engl.* **1976**, *15*, 639-647. (d) Stetter, H.; Skobel, H. *Chem. Ber.* **1987**, *120*, 643-645. (e) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407-496.

[3] (a) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899-1902. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534-541. (c) Johnson, J. S. *Angew. Chem. Int. Edit.* **2004**, *43*, 1326-1328. (d) Christmann, M. *Angew. Chem.-Int. Edit.* **2005**, *44*, 2632-2634. (e) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606-5655. (f) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000.

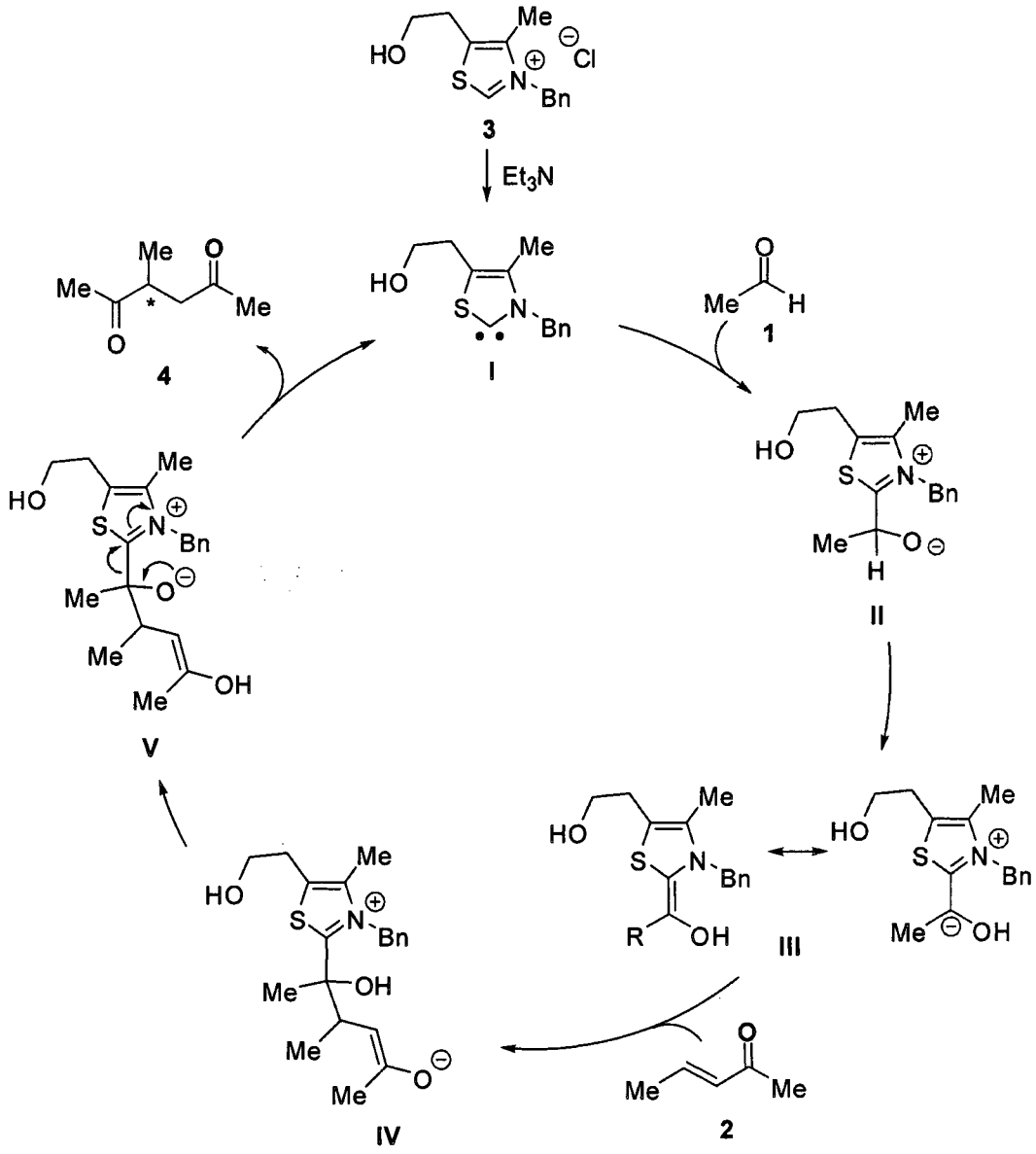
Scheme 1



The mechanism of the Stetter reaction was proposed by Stetter in 1976,[2c] Scheme 2. Carbene **I** is generated in situ from catalyst precursor thiazolium salt **3** by deprotonation with triethylamine. **I** reacts with acetaldehyde **1** to form an alkoxide intermediate **II**. Intermolecular proton transfer occurs to give a nucleophilic alkene **III**, the Breslow intermediate.[4] Nucleophilic addition of **III** to Michael acceptor **2** generates enolate **IV**. Another proton transfer leads to alkoxide intermediate **V**, which collapses to regenerate the carbene **I** and afford the product **4**.

[4] Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726

Scheme 2.



Recently, our group developed a family of triazolium catalysts that promotes the intramolecular Stetter reaction in excellent enantioselectivity and diastereoselectivity.[5] As shown in Scheme 3, our catalyst precursors are derived from either morpholinone (**6** and **12**) or pyrrolidinone (**9** and **15**). By switching the backbone, we can tune the bulkiness of the catalyst. What is more, our catalyst precursor can be tuned from electron-rich (**6**) to electron-deficient (**12**) by changing the stereoelectronic property of the N-substituent. We have applied our catalysts on aromatic substrates such as **5** and aliphatic substrates such as **8** to afforded desired Stetter products in excellent yield and ee (Scheme 3, eqs 1, 2). Products with quaternary stereogenic center can also be obtained in very good yield and ee (Scheme 3, eq 3). Using trisubstituted olefin as Michael acceptor, a product with two contiguous stereocenters such as **16** is obtained in very good selectivities (Scheme 3, eq 4).

As powerful as it may be, any strategy is inherently limited if the requisite substrates are esoteric or difficult to access. In an effort to expand the scope of the asymmetric intramolecular Stetter reaction in order to access more diverse product scaffolds amenable to complex molecule total synthesis, we initiated an effort to provide optically-active Stetter products via dearomatization of phenols followed by carbene-catalyzed asymmetric desymmetrization reactions.

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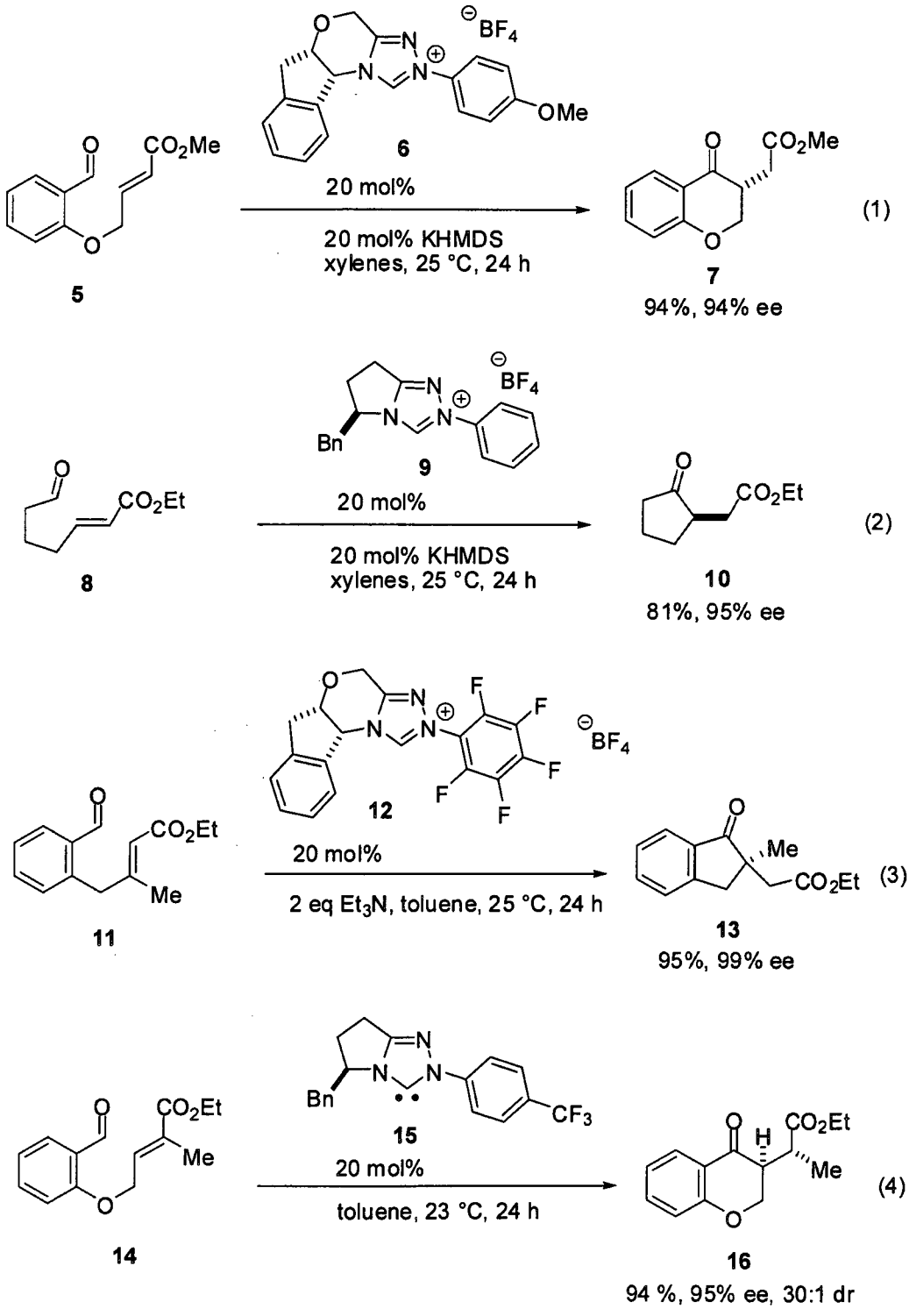
[5] (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298-10299. (b) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934-1936. (c) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876-8877. (d) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284-6289. (e) Kerr, M. S.; Read de Alaniz, J, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725-5728. (f) Reynolds, N. T.; Rovis, T. *Tetrahedron* **2005**, *61*, 6368-6378. (g) Moore, J. L.; Kerr, M. S.; Rovis, T. *Tetrahedron* **2006**, *62*, 11477-11482. (h) Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033-2040. (i) Orellana, A.; Rovis, T. *Chem. Commun.* **2008**, 730-732. (j) Rovis, T. *Chem. Lett.* **2008**, *37*, 2-7.

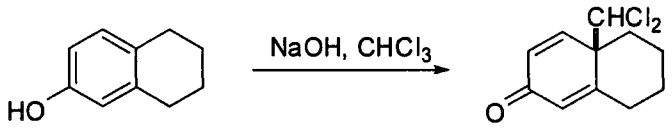
Scheme 3.


BF4
OMe
6
20 mol%
20 mol% KHMDS
xylenes, 25 °C, 24 h
CO2Me
5
7
94%, 94% ee
(1)
Bn
9
20 mol%
20 mol% KHMDS
xylenes, 25 °C, 24 h
CO2Et
8
10
81%, 95% ee
(2)
F
12
20 mol%
2 eq Et3N, toluene, 25 °C, 24 h
Me
11
13
95%, 99% ee
(3)
CF3
15
20 mol%
toluene, 23 °C, 24 h
14
16
94 %, 95% ee, 30:1 dr
(4)

1.1.2 Dearomazation of Aromatic Compounds

Dearomatization is the process of breaking the delocalized π system of benzene or its derivatives, which are widely available at low cost and highly stable. This reaction is a very useful strategy to synthesize alicyclic compounds due to the reaction's high economy and simplicity.[6] An early example of this transformation was reported by Woodward.[7] He investigated the reaction of tetrahydronaphthalene **17** with chloroform and aqueous sodium hydroxide to yield dearomatization product **18** (Scheme 4). This work is consistent with an earlier observation by Auwers and coworkers.[8]

Scheme 4.



17 **18**

15%

Another early utilization of a dearomatization strategy was reported by Corey and coworkers.[9] In a key step of the total synthesis of *dl*-cedrene and *dl*-cedrol, treatment of the phenol derivative **19** with one equivalent of potassium *tert*-butoxide in dry *tert*-butyl alcohol at 60 °C give a mixture of the *cis* and *trans* forms (ratio 53:47) of the cyclohexadienone **20** (Scheme 5). The Birch reduction is also an important dearomatization reaction.[10]

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[6] (a) Waring, A. J. *Advances in Alicyclic Chemistry*; Academic Press: New York, **1966**. (b) Thorsten, B. *Angew. Chem, Int. Ed. Engl.* **1996**, *35*, 729-730. (c) Pape, A. R.; Kaliappan, K. P.; Kundig, E. P. *Chem. Rev.* **2000**, *100*, 2917-2940.

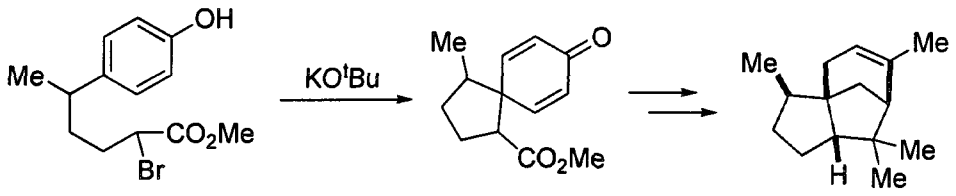
[7] Woodward, R. B. *J. Am. Chem. Soc.* **1940**, *62*, 1208-1214.

[8] Auwers K., Keil G. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 4207 -4217.

[9] Corey, E. J.; Girotra, N. N.; Mathew, C. T. *J. Am. Chem. Soc.* **1969**, *91*, 1557-1559.

[10] (a) Robinson, B. *Chem. Rev.* **1969**, *69*, 785-797. (b) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35-85. (c) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1-334. (d) Schultz, A. G. *Chem.*

Scheme 5.



19 **20** *dl*-cedrene

cis:trans = 53:47

Currently the synthesis of organic molecules via a dearomatization strategy has been intensively studied. Usually this transformation is induced by metal,[11] Lewis acid,[12] and oxidant.[13] Because the strategy of dearomatization is so elegant and versatile in organic synthesis, it has been widely used in total synthesis.[14]

1.1.3 Desymmetrization of Achiral Compounds

In stereochemical terms, desymmetrization is the modification of a molecule which results in the loss of one or more symmetry elements, such as those which give rise to chirality (a mirror plane, center of inversion, rotation-reflection axis), as in the

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Commun. **1999**, 1263-1271. (e) Subba Rao, G. S. R. *Pure Appl. Chem.* **2003**, *75*, 1443-1451

[11] (a) Semmelhack, M. F.; Harrison, J. J.; Thebtaranonth, Y. *J. Org. Chem.* **1979**, *44*, 3275-3277. (b) Pearson, A. J.; Zhu, P. Y.; Youngs, W. J.; Bradshaw, J. D.; McConville, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 10376-10377. (c) Kopach, M. E.; Harman, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 6581-6592. (d) Pearson, A. J.; Milletti, M. C.; Zhu, P. Y. *J. Chem. Soc.-Chem. Commun.* **1995**, 853-854. (e) Bao, M.; Nakamura, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 759-760.

[12] (a) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091-9092.

[13] (a) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175-177. (b) Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett* **2008**, 467-495.

[14] (a) Wiesner, K.; Tsai, T. Y. R.; Nambiar, K. P. *Can. J. Chem.* **1978**, *56*, 1451-1454. (b) Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256-257. (c) Mander, L. N. *Synlett* **1991**, 134-144. (d) Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2843-2846. (e) Jones, S. B.; He, L. W.; Castle, S. L. *Org. Lett.* **2006**, *8*, 3757-3760. (f) Marsini, M. A.; Gowin, K. M.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 3481-3483. (g) Mejorado, L. H.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2006**, *128*, 15625-15631. (h) Zhu, J. L.; Porco, J. A. *Org. Lett.* **2006**, *8*, 5169-5171.

conversion of a prochiral molecular entity into a chiral one.[15] Desymmetrization is a very powerful synthetic tool to prepare highly useful building blocks in one step. In most cases, more than two new stereogenic centers are formed in a single operation. When coupled with chiral reagents or catalysts, desymmetrization has the potential to afford enantioenriched material from commonly available precursors in rapid fashion.[16]

Prochiral cyclohexadienones are very important substrates in desymmetrization processes. For example, Feringa and coworkers reported an intramolecular asymmetric Heck reaction of cyclohexadienone **21**.[17] Product **23** is isolated in 75% yield and 96% ee with a chiral monodentate phosphoramidite ligand **22** (Scheme 6). Hayashi and coworkers synthesized bicyclo[4.3.0]nonene carbon skeleton using a highly enantioselective intramolecular Michael reaction.[18] As shown in Scheme 7, catalyzed by a cysteine-derived organocatalyst **22**, aldehyde **24** is converted to enone **26** in good yield and ee. Recent examples of desymmetrization of cyclohexadienones were also reported by Renaud[19] and Clive.[20]

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[15] Moss, G. P. *Pure Appl. Chem.* **1996**, *68*, 2193-2222

[16] (a) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765-1784. (b) Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131-3134. (c) Spivey, A. C.; Andrews, B. I.; Brown, A. D. *Recent Res. Dev. Org. Chem.* **2002**, *6*, 147-167. (d) Pesti, J. A.; DiCosimo, R. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 884-901. (e) Studer, A.; Schleth, F. *Synlett* **2005**, 3033-3041. (f) Rovis, T. *New Frontiers in Asymmetric Catalysis* **2007**, 275-311.

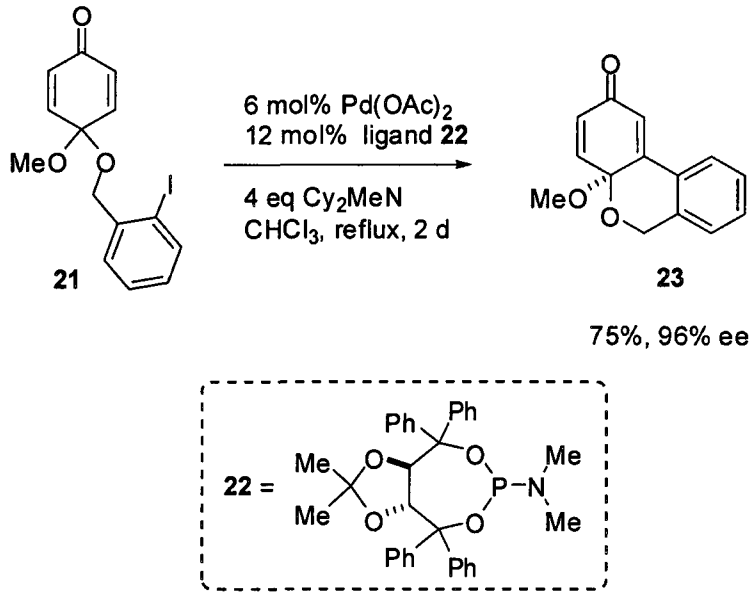
[17] Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184-185.

[18] Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028-16029.

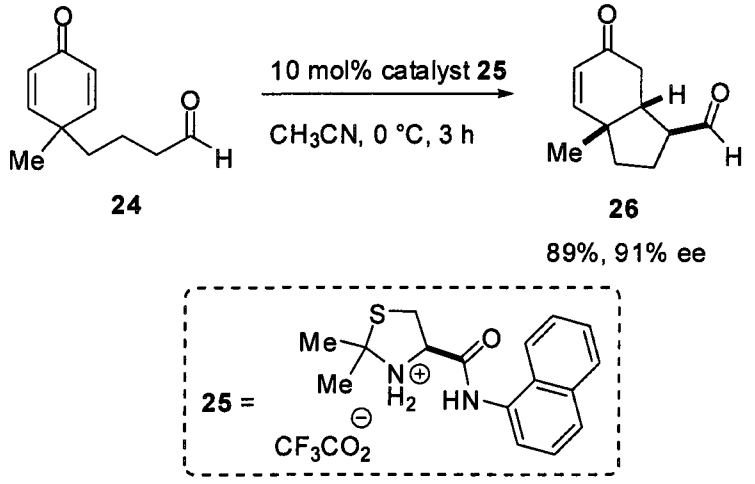
[19] Villar, M.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem.-Eur. J.* **2003**, *9*, 1566-1577.

[20] (a) Clive, D. L. J.; Fletcher, S. P.; Liu, D. Z. *J. Org. Chem.* **2004**, *69*, 3282-3293. (b) Clive, D. L. J.; Sunasee, R. *Org. Lett.* **2007**, *9*, 2677-2680.

Scheme 6.



Scheme 7.

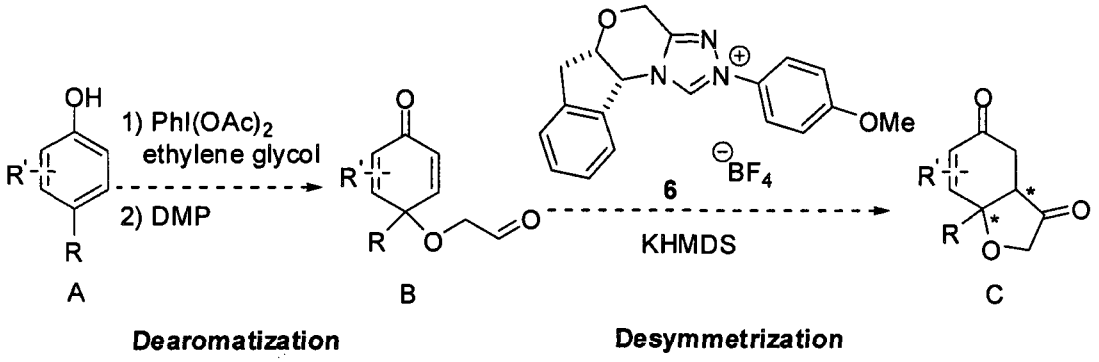


1.1.4 Our Research Goal

Based on the successful development of carbene catalyst in our group, [5] we put our effort into extending their application to the asymmetric intramolecular Stetter reaction. We envisioned that dearomatization of readily available phenols would lead to cyclohexadienones, which could be suitable substrates for an asymmetric desymmetrizing

Stetter reaction. As shown in Scheme 8, oxidative dearomatization of phenol **A**, followed by Dess-Martin oxidation will afford the cyclohexadienone-tethered aldehyde **B**. Desymmetrization of **B** by carbene catalyst will generate a hydrobenzofuranone, which is a common skeleton in natural products. [21] Obviously, this transformation will generate at least two stereogenic centers in only three steps from simple starting materials.

Scheme 8.



1.2 Syntheses of Cyclohexadienones via Dearomatization of Phenols

1.2.1 Initial Screen of Reaction Conditions

PIFA (phenyliodine bis(trifluoroacetate)) and PIDA (phenyliodine diacetate) can serve as oxidants for the dearomatization of phenols, and are less toxic than heavy metal containing reagents. [22] When we originally tried to dearomatize phenols, p-cresol was

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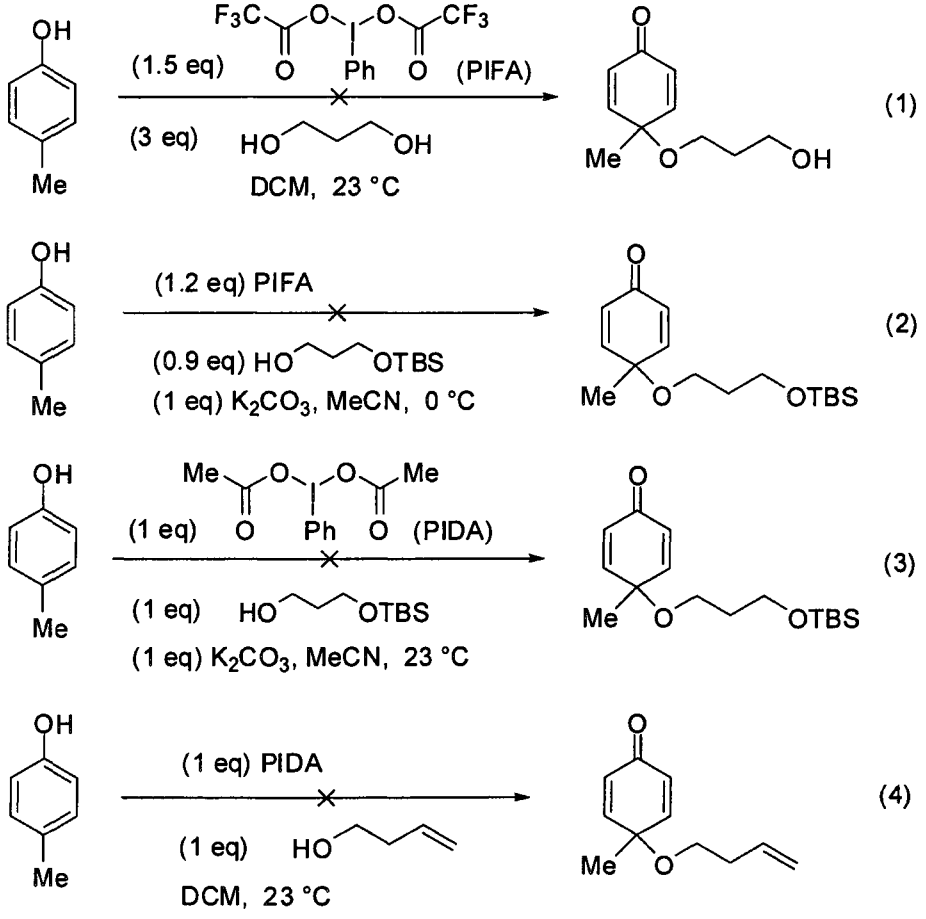
[21] (a) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1985**, *50*, 3420-3421. (b) Chumoyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1994**, *116*, 11213-11228. (c) Guth, H. *Helv. Chim. Acta* **1996**, *79*, 1559-1571.(d) Yao, S. L.; Johannsen, M.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **1998**, *63*, 118-121. (e) Jonasson, C.; Ronn, M.; Backvall, J. E. *J. Org. Chem.* **2000**, *65*, 2122-2126. (f) Germain, J.; Deslongchamps, P. *J. Org. Chem.* **2002**, *67*, 5269-5278. (g) Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 12416-12417. (h) Takao, K.; Tsujita, T.; Hara, M.; Tadano, K. *J. Org. Chem.* **2002**, *67*, 6690-6698. (i) Booker-Milburn, K. I.; Hirst, P.; Charmant, J. P. H.; Taylor, L. H. J. *Angew. Chem.-Int. Edit.* **2003**, *42*, 1642-1644. (j) Clive, D. L. K.; Fletcher, S. P. *Chem. Commun.* **2003**, 2464-2465. (k) Yamashita, M.; Ohta, N.; Shimizu, T.; Matsumoto, K.; Matsuura, Y.; Kawasaki, I.; Tanaka, T.; Maezaki, N.; Ohta, S. *J. Am. Chem. Soc.* **2003**, *68*, 1216-1224.

[22] (a) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc.-Perkin Trans. 1* **1993**, 1891-1896. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123-1178. (c) Georg, P. *J. Prakt. Chem.* **2000**, *342*, 731-734. (d) Moriarty, R. M.; Prakash, O. *Org. React.* **2001**, *57*, 327-415. (e) Tran-Huu-Dau, M. E.; Wartchow, R.;

chosen as the starting material. The initial reaction results are shown in Scheme 9. The mixture of one equivalent of p-cresol and three equivalents of propane-1,3-diol was treated with one and half equivalent of PIFA. Unfortunately the reaction is very messy, and no desired product was isolated after workup (Scheme 9, eq 1). Similar results were observed with mono-protected propane-1,3-diol (Scheme 9, eq 2). We also tried PIDA as an oxidant, however the reaction of p-cresol with mono-protected propane-1,3-diol or but-3-en-1-ol again yield no desired products (Scheme 9, eq 3, 4).

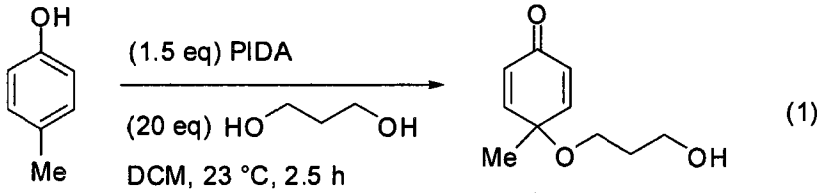
Scheme 9.



Winterfeldt, E.; Wong, Y. S. *Chem.-Eur. J.* **2001**, *7*, 2349-2369. (f) Rodriguez, S.; Wipf, P. *Synthesis* **2004**, 2767-2783. (g) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175-177.

After screening more reaction conditions, we found that increasing the number of equivalents of the diol is the key (Scheme 10). With 20 equivalents of diol and 1.5 equivalent PIDA, the desired product **27** is obtained in 43% yield (Scheme 10, eq 1). With similar conditions, analogues **28** (Scheme 10, eq 2) and **29** (Scheme 10, eq 3) are successfully synthesized in 49% and 70% yield respectively.

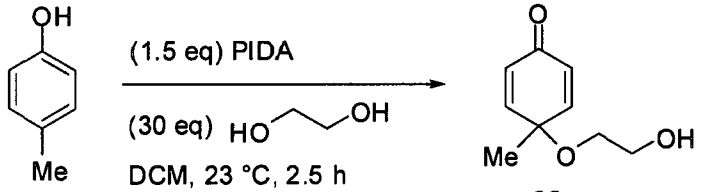
Scheme 10.



27

43%

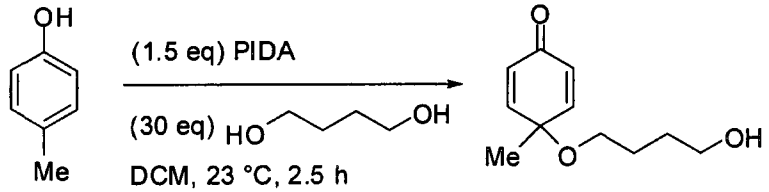
(1)



28

49%

(2)



29

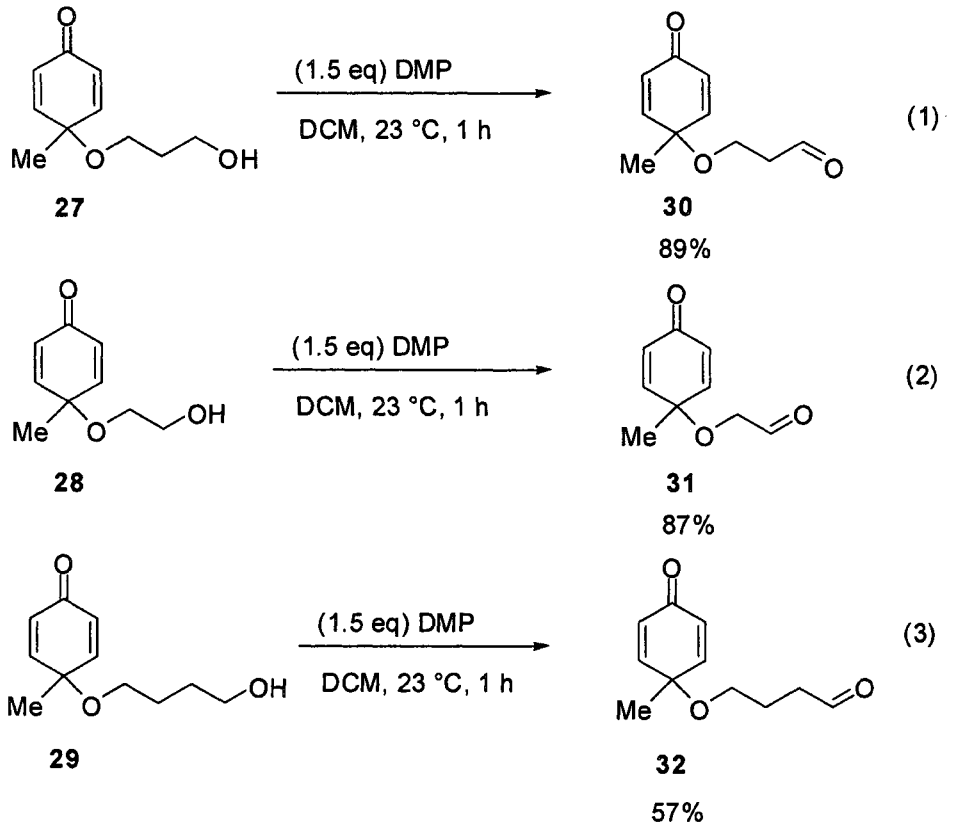
70%

(3)

The Dess-Martin oxidation is found to be the most appropriate for the second step, with fresh batches of reagent providing the highest and most reproducible yields. The intermediate alcohols **27**, **28**, and **29** are then converted to aldehydes **30**, **31**, and **32** respectively using Dess-Martin periodinane (DMP) in good to excellent yields (Scheme

11). As a result, this route was chosen to be the general procedure for the rest of the substrates.

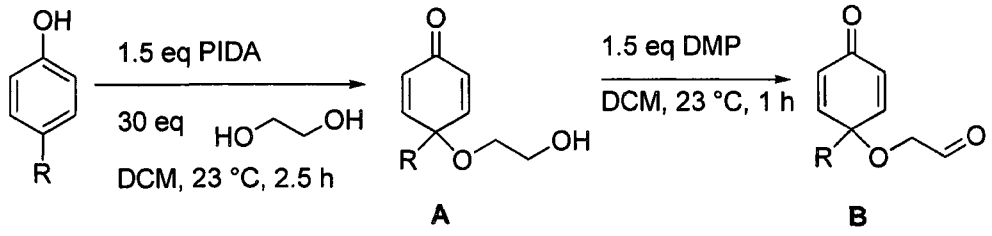
Scheme 11.



1.2.2 Syntheses of a Series of Aldehyde-tethered Cyclohexadienones

Using the general procedure described previously, a series of cyclohexadienones (**31**, **34**, **36**, **38**, **40**, **42**, **44**, **46**, **48**, and **50**) derived from mono-substituted phenols were synthesized successfully (Table 1). As shown in Table 1, this approach is remarkably tolerant of arene substitution. Although yields in the arene oxidation vary, most reactions were conducted only once and as such are unoptimized.

Table 1.



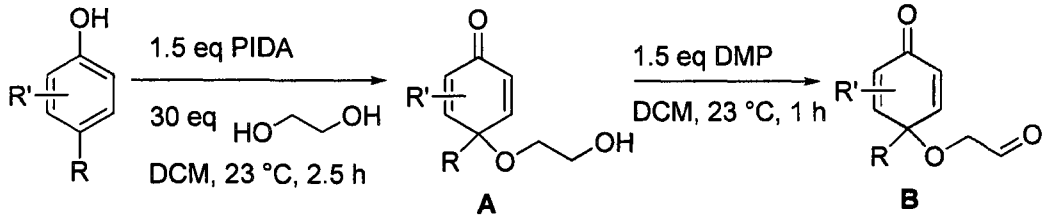
A **B**

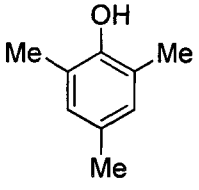
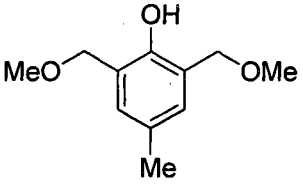
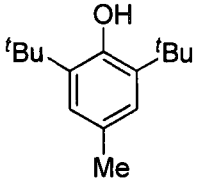
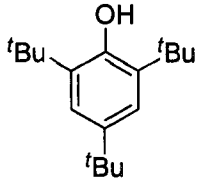
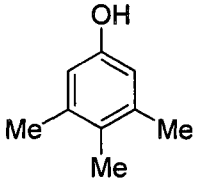
entry	R	A	yield (%)[a]	B	yield (%)[b]
1	Me	**28**	49	**31**	87
2	Et	**33**	42	**34**	78
3	^{i}Pr	**35**	38	**36**	92
4	^{t}Bu	**37**	31	**38**	78
5	Ph	**39**	56	**40**	64
6	4-BrC_6H_4	**41**	26	**42**	75
7	CH_2OAc	**43**	17	**44**	52
8	CH_2CH_2OMe	**45**	39	**46**	59
9	$CH_2CH_2CO_2Me$	**47**	20	**48**	47
10	CH_2CH_2NHBoc	**49**	22	**50**	26

a) All reactions conducted in the presence of 1.5 eq PIDA and 30 eq glycol in DCM.
b) Conducted in the presence of 1.5 eq DMP in DCM, Yields are not optimized.

This general procesure is also tolerant of the use of trisubstituted phenols. As shown in Table 2, a series of multi-substituted cyclohexadienones (**52**, **54**, **56**, **58**, and **60**) were synthesized rapidly. As we will show later, the intramolecular Stetter reaction of these substrates will be able to produce products with up to three stereogenic centers in one step.

Table 2.

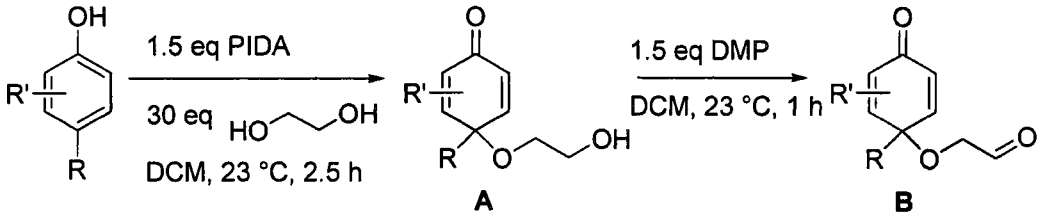


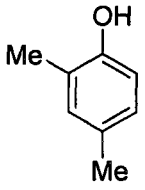
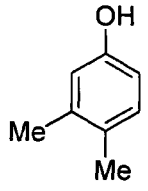
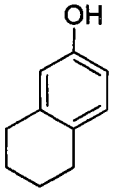
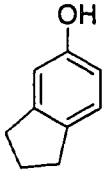
entry	starting material	A	yield (%)[a]	B	yield (%)[b]
1		**51**	93	**52**	56
2		**53**	25	**54**	54
3		**55**	31	**56**	89
4		**57**	70	**58**	74
5		**59**	56	**60**	62

a) All reactions conducted in the presence of 1.5 eq PIDA and 30 eq glycol in DCM.
b) Conducted in the presence of 1.5 eq DMP in DCM, Yields are not optimized.

Interestingly, chiral cyclohexadienones (**62**, **64**, **66**, and **68**) can also be made by using di-substituted phenols and ring fused phenols in good yield (Table 3). These substrates will be suitable for studying the competition between substrate control and catalyst control in the intramolecular Stetter reaction.

Table 3.



entry	starting material	A	yield (%)[a]	B	yield (%)[b]
1		**61**	93	**62**	56
2		**63**	25	**64**	54
3		**65**	31	**66**	89
4		**67**	70	**68**	74

a) All reactions conducted in the presence of 1.5 eq PIDA and 30 eq glycol in DCM.
b) Conducted in the presence of 1.5 eq DMP in DCM, Yields are not optimized.

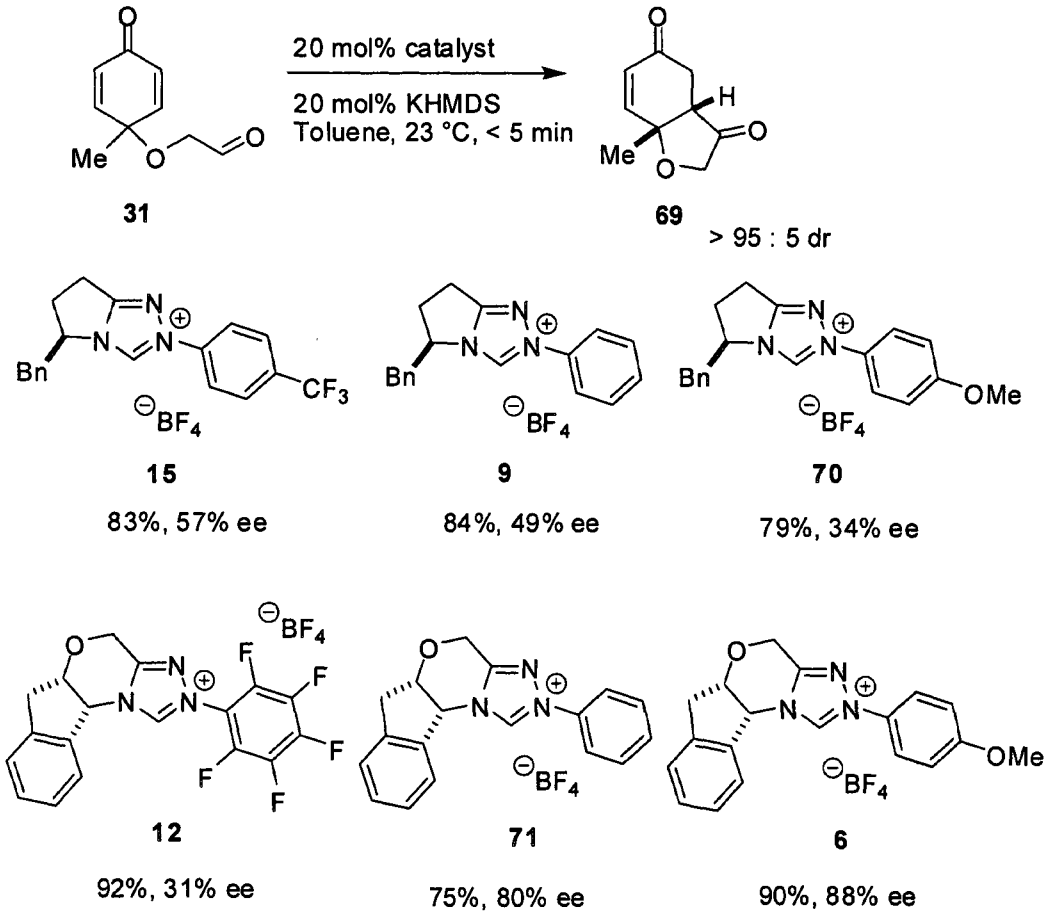
1.3 Desymmetrizing Intramolecular Stetter Reaction of Cyclohexadienones

1.3.1 Optimization of Reaction Conditions

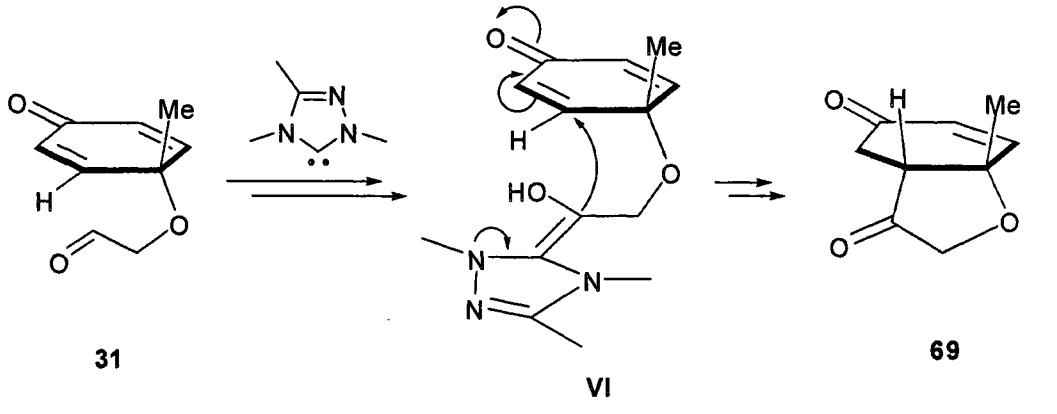
a) Catalyst Screen

The reactivity of a series of catalysts was studied using substrate **31** (Scheme 12). Subjection of **31** to the standard Stetter reaction conditions (20 mol% catalyst and 20 mol% KHMDS in toluene at 23 °C) provides the desired hydrobenzofuranone **69** in good yields within 5 min. The diastereoselectivity of this transformation is excellent (>95:5 by 1H NMR and GC), favoring formation of the cis-fused hydrobenzofuranone. The excellent diastereoselectivities are explained in Scheme 13. Starting material **31** reacts with catalyst carbene to form the Breslow intermediate **VI**, which undergoes a nucleophilic addition to the tethered dienone to form a five-membered ring. The nucleophilic olefin should approach the dienone from the bottom, thus leading to a cis-bicyclic product **69**. Surprisingly, the pyrrolidine-derived catalysts (**15**, **9**, **70**) and morpholine-derived catalysts (**12**, **71**, **6**) show different trends in the reaction's enantioselectivity. For the pyrrolidine-derived catalysts, when the N-aryl substitution changes from electron-deficient to electron-enriched, the enantioselectivity of the reaction decreases. By contrast, for morpholine-derived catalysts, when the N-aryl substitution switches from electron-deficient to electron-enriched, the enantioselectivity of the reaction increases. Although we cannot account for these differences at this time, the tunability of these triazolium salts is a hallmark of their design.[5e] We found the best catalyst to be **6**, providing the product **69** in 90% yield and 88% ee in 5 min.

Scheme 12.



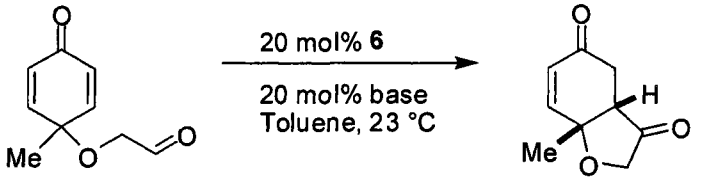
Scheme 13.



b) Base Screen

A screen of different bases revealed that KHMDS is the best base for this reaction (Table 4). KO^{t}Bu is equally effective at inducing asymmetry, but requires a longer reaction time. Amine bases also require longer reactions times, consistent with their reduced basicity, thereby leading to lower concentrations of active carbene catalyst. Somewhat surprising is the reduced selectivity evident when amine bases are used, a situation not generally encountered in other Stetter reactions developed by our group.

Table 4.



31 **69** > 95 : 5 dr

entry	base	reaction time	yield (%)[a]	ee (%)[b]
1	KHMDS	5 min	90	88
2	KOt-Bu	30 min	83	88
3	KH	16 h	76	76
4	$(i\text{-}Pr)_2EtN$	21 h	62	70
5	Et_3N	32 h	68	66

a) Reactions conducted in the presence of 20 mol% **6** and 20 mol% KHMDS in less than 5 min. b) Enantiomeric excess determined by GC analysis

c) Solvent Screen and the Special Effects of Alcohols

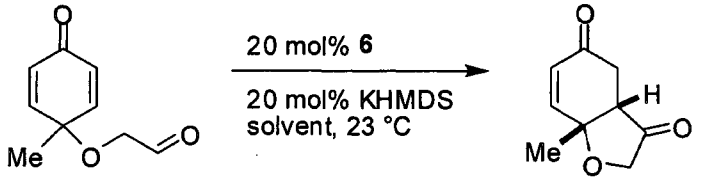
When screening a variety of solvents (Table 5), we observed a large effect on both yield and ee. For example, the reaction results in 16% yield and 67% ee after 3 days when dichloromethane is used as the solvent (Table 5, entry 7). Overall, toluene was found to be the best solvent for this reaction (Table 5, entry 1).

By far the most surprising aspect of this study was the effect of alcoholic solvents on the reaction, which invariably affords the opposite enantiomer using the same series of catalysts (Table 6). There is a clear effect of alcohol size on selectivity with isopropanol providing the highest ee's. Trifluoroethanol shuts down the reaction, presumably because of its increased acidity. The profound difference between polar aprotic solvents such as DMF and the alcoholic solvents cannot be accounted for by polarity alone.

In order to study the effect of the alcohol further, a mixture of toluene and isopropanol was used as the solvent for the reaction. A gradual inversion in selectivity occurs as the volume fraction of isopropanol increases to a plateau of ~60% isopropanol in toluene (Figure 1). We suggest that these effects are most consistent with the involvement of the alcohol in the transition state likely via hydrogen bonding to either the nucleophilic enol or the carbonyl acceptor or both. This hydrogen bonding thus changes the chiral environment, ultimately affecting the stereochemical outcome of the reaction.

A stereochemical rationale to account for the turnover in selectivity is provided in Figure 2. The absolute stereochemistry of **69** is consistent with model **VII** wherein minimization of charge separation is emphasized. We suggest that extensive hydrogen bonding in isopropanol destabilizes this transition state relative to **IX** since the incipient enolate and alkoxide are each hydrogen-bonded to solvent. Solvation and electrostatic effects are likely also playing a role.

Table 5.

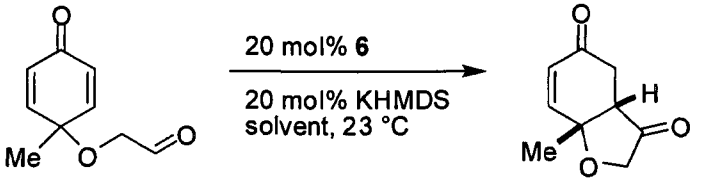


31 **69** > 95 : 5 dr

entry	solvent	reaction time	yield (%)[a]	ee (%)[b]
1	Toluene	< 5 min	90	88
2	Xylene	10 min	81	75
3	Benzene	< 5 min	88	89
4	Ether	10 min	67	87
5	DMF	10 min	71	73
6	THF	< 5 min	77	89
7	DCM	72 h	16	67

a) Reactions conducted in the presence of 20 mol% **6** and 20 mol% KHMDS.
b) See Table 4.

Table 6.



31 **69** > 95 : 5 dr

entry	Solvent	reaction time	yield (%)[a]	ee (%)[b]
1	MeOH	< 5min	29	- 11
2	EtOH	< 5min	63	- 42
3	CF_3CH_2OH	4h	0	N/A
4	$^{i}PrOH$	< 5min	64	- 63
5	$^{t}BuOH$	5h	30	- 57

a) Reactions conducted in the presence of 20 mol% **6** and 20 mol% KHMDS.
b) See Table 4.

Figure 1.

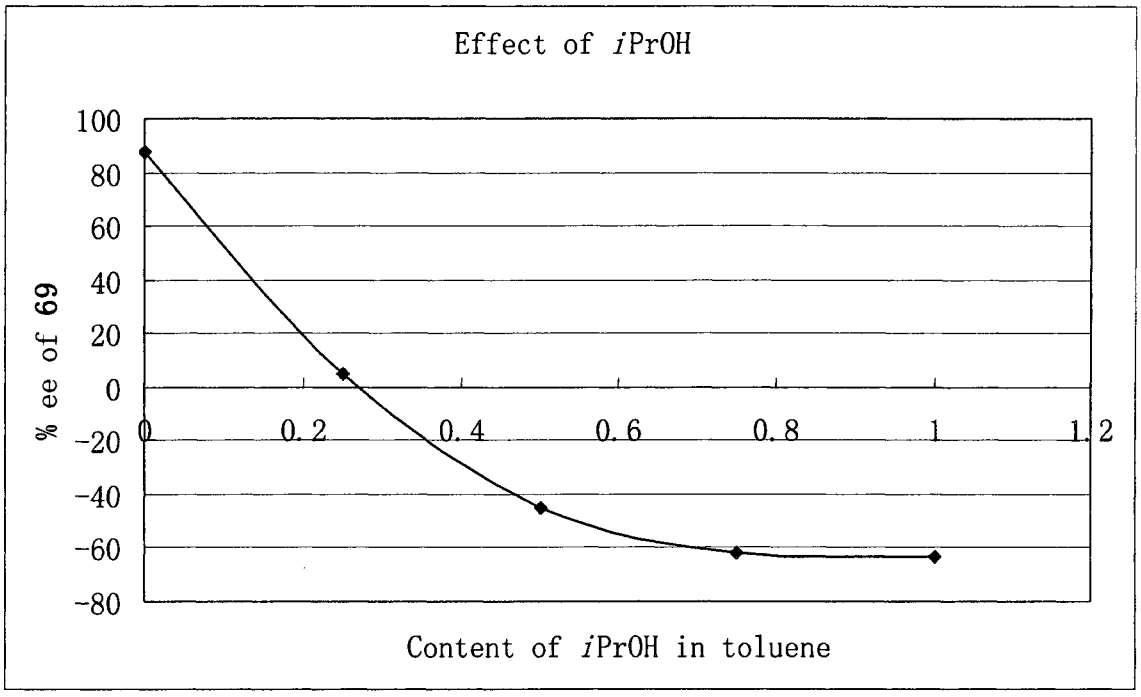
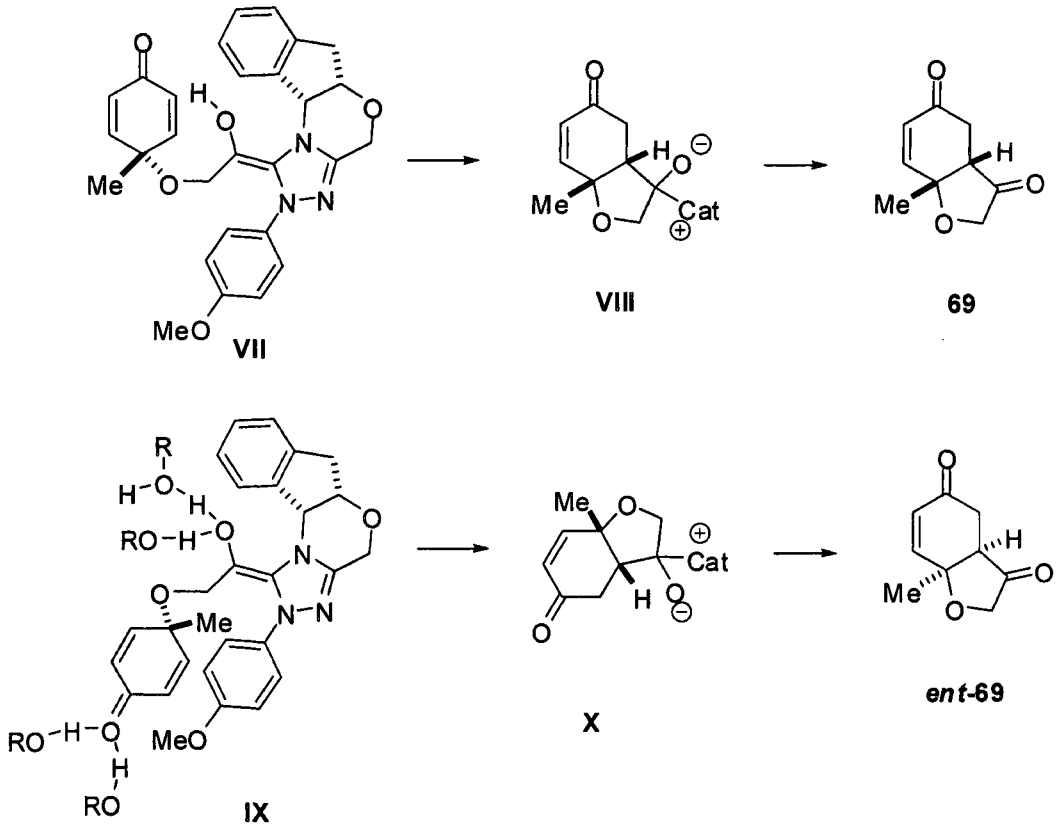


Figure 2.



d) Concentration Screen

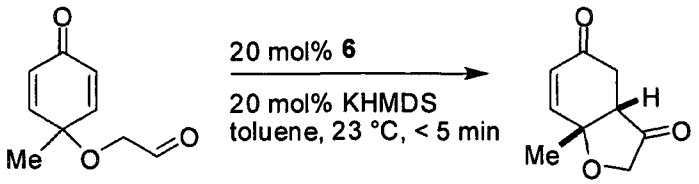
Having evaluated the effect of each component on the reaction, we were faced with a reaction that provided product in 88% ee. A preliminary screen of different substrates (not shown) revealed that the enantioselectivities were invariably <88%. We were particularly intrigued with the effect of alcoholic solvents on enantioselectivity and speculated whether hydrogen-bond donors present as intermediates in the reaction could be interfering. In an effort to minimize the contribution of bimolecular events to the stereoselectivity of the process, we evaluated the impact of reaction concentration, Table 7.

When the concentration of **31** decreased from 0.12 to 0.013 M, the ee increased from 79 to 90%. Selectivities were further improved by a serendipitous discovery that the use of an argon purge through the reaction leads to improved ee's, entries 5 and 7 in Table 7. We suggest that these effects are a consequence of the availability of hydrogen-bond donors under conditions involving higher concentrations or adventitious oxygen-derived byproducts, and these lead to competitive transition states similar to **XIII** in Figure 2 above.

e) Temperature Screen

The effect of temperature was also studied for this reaction (Table 8). It is surprising that the reaction is still complete in five minutes even at -10 °C, although ee decreases. Lowering the temperature further slows down the reaction. The ee of the product was also decreased when the reaction was run at 50°C. Overall, room temperature was found to be the optimal for this reaction.

Table 7.

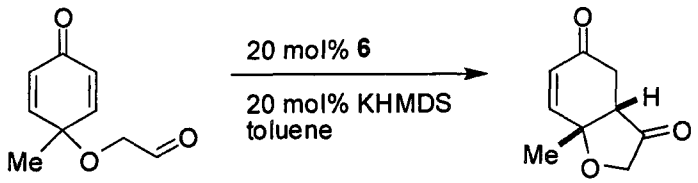


31 **69**

entry	concentration (M)	yield (%)[a]	ee (%)[b]
1	0.12	85	79
2	0.04	90	88
3	0.013	90	90
4	0.008	90	90
5[c]	0.008	90	93
6	0.005	86	90
7[c]	0.005	91	96

a) See Table 4, b) See Table 4, c) Ar bubbling

Table 8.



31 **69** > 95 : 5 dr

entry	temperature	reaction time	yield (%)[a]	ee (%)[b]
1	50 °C	< 5 min	79	90
2	23 °C	< 5min	90	93
3	- 10 °C	< 5 min	90	89
4	- 78 °C	6h then warm to rt	87	77

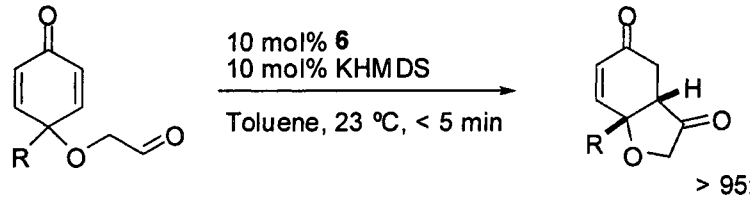
a) See Table 6. b) See Table 4.

1.3.2 Substrate Scope

a) Mono-substituted Substrates

With the optimized reaction conditions in hand, we screened a series of monosubstituted dienone substrates, Table 9. As the steric size of the R group is increased from methyl to *tert*-butyl, the enantioselectivity of the transformation remained largely invariant (Table 9, entries 1-4). Aryl groups result in slightly lower selectivities (Table 9, entries 5-6). Single crystal analysis of **76** (Table 9, entry 6) revealed the absolute configuration of this product, while the rest were assigned by analogy. More functionalized substitutions are also tolerated in the reaction, although with lower ee's (Table 9, entries 7-10). In light of the detrimental effect of groups capable of hydrogen bonding, it is tempting to invoke an intramolecular hydrogen bond that alters selectivities in the case of substrates 7-10. However, this scenario clearly cannot account for depressed selectivities observed with aryl substituents in substrates **40** and **42**. Furthermore, it is difficult to envision an intramolecular hydrogen bond affecting the transition state when cyclization occurs trans to the R group at the 4-position of the dienone. We suggest, therefore, that this effect may best be rationalized as due to electronics. Every group in substrates **40**, **42**, **44**, **46**, **48**, and **50** is sigma withdrawing, and this may have a subtle effect in altering the diastereomeric transition states. Of note is that all the substrates provide products in excellent diastereoselectivities (>95:5 by ^{1}H NMR and GC).

Table 9.



> 95:5 dr

entry	R	substrate	product	yield (%)[a]	ee (%)[b]
1	Me	**31**	**69**	90	92
2	Et	**34**	**72**	86	94
3	^{i}Pr	**36**	**73**	87	94
4	^{t}Bu	**38**	**74**	86	94
5	Ph	**40**	**75**	87	88
6	4-BrC_6H_4	**42**	**76**	78	85
7	CH_2OAc	**44**	**77**	86	83
8	CH_2CH_2OMe	**46**	**78**	86	82
9	$CH_2CH_2CO_2Me$	**48**	**79**	94	87
10	CH_2CH_2NHBoc	**50**	**80**	28	64

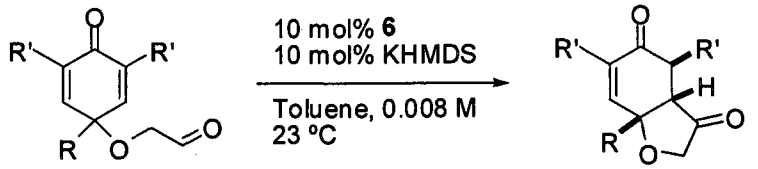
a) Argon purge, [substrate]=0.008M. b) Determined by GC or HPLC.

b) Multi-substituted Substrates

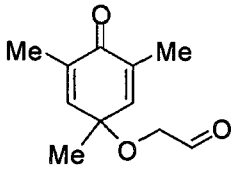
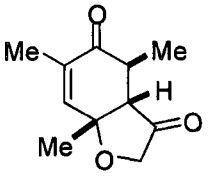
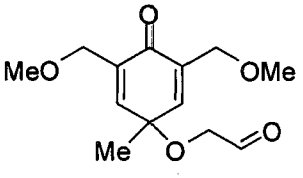
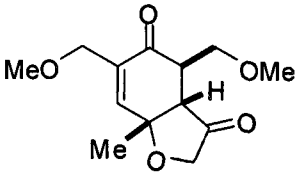
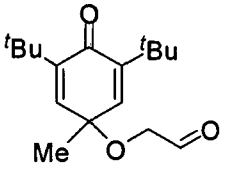
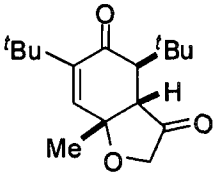
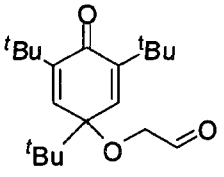
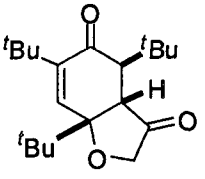
Given our previous success in cyclizing onto trisubstituted Michael acceptors, [5d] we were intrigued to attempt cyclizations onto dienones derived from trisubstituted phenol starting materials. A number of 2,4,6-trisubstituted phenols are readily available. When the derived dienones are subjected to the optimized reaction conditions, hydrobenzofuranones with three contiguous stereocenters are formed in good yield and excellent selectivities (Table 10). No elimination of methoxy group is observed under the basic reaction conditions (Table 10, entry 2). The tolerance of this reaction to steric bulk is particularly noteworthy. Dienone **56**, derived from the ubiquitous and inexpensive antioxidant BHT, provides product **83** in good yield as largely a single enantiomer and diastereomer (Table 10, entry 3) possessing a neopentyl stereocenter. Substrate **58**, derived from 2,4,6-tri-tert-butyl phenol, provides product **84** in excellent ee, having three contiguous stereocenters, two of them being neopentyl. Significantly, for each reaction in Table 10, a single diastereomer is observed (>95:5 by ^{1}H NMR, GC, and HPLC).

Attempted epimerization experiments on products **81** and **83** (Et_3N in PhMe at 110 °C for 24 h) failed to provide noticeable evidence of epimeric products. Preliminary semiempirical calculations (Scheme 14) suggest that the major diastereomers are more thermodynamically stable products. (For example, **81** is ~ 9.9 kJ/mol more stable than the diastereomer ***dt*-81** having the methyl group on the endo face of the bicycle by Spartan calculation, while **83** is ~ 36 kJ/mol more stable than the diastereomer ***dt*-83** having the bulky tert-butyl in that position by Spartan calculation.) The relative configuration of the product was also confirmed by nOe experiments (see chapter 1 experimental).

Table 10.

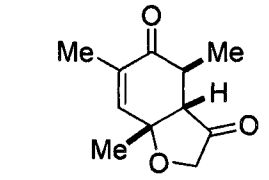


single diastereomer

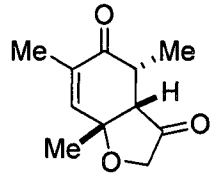
Entry	Substrate	Product	Yield (%)[a]	*ee* (%)[b]
1	 **52**	 **81**	86[c]	>99
2	 **54**	 **82**	71[c]	99
3	 **56**	 **83**	80[d]	>99
4	 **58**	 **84**	62[d]	>99

a) See Table 9. b) See Table 9. c) Reaction time = 5 min. d) Reaction time = 2 h.

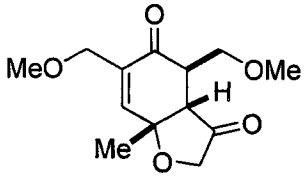
Scheme 14.



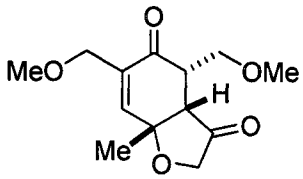
81 - 9.9 kJ/mol



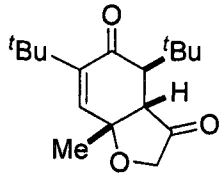
***dt*-81** 0 kJ/mol



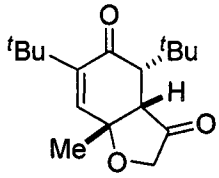
82 - 5.9 kJ/mol



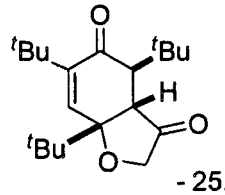
***dt*-82** 0 kJ/mol



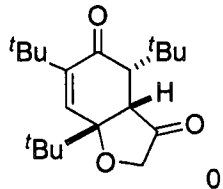
83 - 36.3 kJ/mol



***dt*-83** 0 kJ/mol



84 - 25.0 kJ/mol



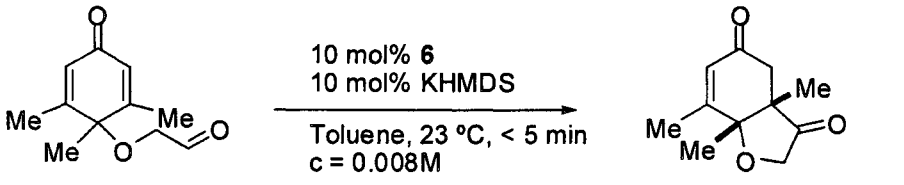
***dt*-84** 0 kJ/mol

* The relative energies were calculated using SPARTAN (PM3)

c) Formation of Quaternary Center

In order to test whether this chemistry is able to generate quaternary stereocenter,[4c,4g] cyclohexadienone **60** was synthesized from commercially available 3,4,5-trimethylphenol. Cyclization of **60** provides the desired product **85** with a quaternary stereocenter adjacent to a tertiary ether in good yield and excellent stereoselectivity (Scheme 15).

Scheme 15.



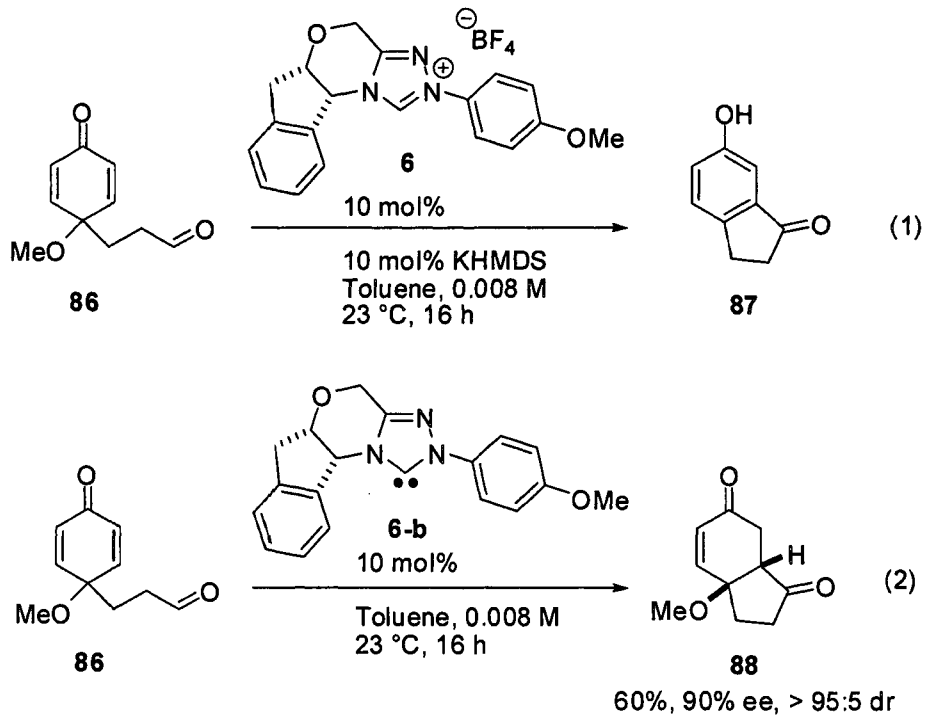
60 → **85**

64%, 99% ee, > 95:5 dr

d) Carbon-tethered Substrate

The above examples all involve the synthesis of hydrobenzofuranones, largely due to the accessibility of the substrate by the above route. In order to test whether the oxygen tether is required, we synthesized substrate **86** starting from 4-(3-hydroxypropyl)-phenol (see chapter 1 experimental). However, when **86** was subjected to the optimized conditions, the only isolated product was 6-hydroxy-1-indanone **87** (Scheme 16, eq 1). We suggest that this product is derived from the elimination of the expected product under the reaction conditions. Fortunately, we found that the elimination may be avoided if the reaction of **86** is conducted using the preformed free carbene,[5d] providing the desired carbocycle **88** in 60% yield and 90% ee (Scheme 16, eq 2).

Scheme 16.



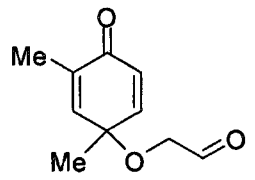
e) Chiral Substrates

The use of several commercially available disubstituted phenols as starting materials in this chemistry would lead to chiral racemic dienones. Previous work in our laboratory has revealed that kinetic resolutions are not practical using this approach; rather, the catalysts override pre-existing stereocenters unless they are alpha to the aldehyde.[5f] However, we were intrigued by the opportunity to investigate the relative propensity of our catalysts to induce cyclization onto disubstituted versus trisubstituted Michael acceptors in an intramolecular competition. As such, chiral substrates **62**, **64**, **66**, and **68** were assembled and subjected to optimized reaction conditions using catalyst **6** along with an achiral catalyst (Scheme 17). Substrates **62**, **64**, and **66** provided the products favoring cyclization onto the less-substituted olefin, consistent with expectations. Reaction of **62** affords **89** in 12:1 selectivity over **90** when using an achiral catalyst. This

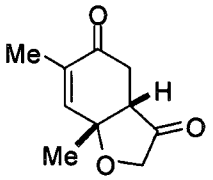
selectivity is greatly degraded when the chiral catalyst is used, as it exerts its influence to provide only 2:1 selectivity, with the minor adduct formed in high ee (Scheme 17, eq 1). Substrates **64** and **66** provide products **91** and **93**, respectively, in nearly exclusive selectivity regardless of catalyst (Scheme 17, eq 2-3). However, when we subject substrate **68** to both catalysts, we observe both constitutional isomers formed in identical amounts (Scheme 17, eq 4), illustrating no selectivity between cyclization onto a di- versus trisubstituted Michael acceptor. When this reaction is conducted using catalyst **6**, both isomers are formed in high ee's, as the chirality of the catalyst exerts its control.

The different behavior of substrates **62**, **64** and **66** versus **68** is not easy to rationalize. We speculate that the dichotomy lies in the product stability. Semi-empirical calculations were carried out, and the results are consistent with our suggestion (Scheme 18). Products **89**, **91** and **93** are correspondingly more thermodynamically stable than **90**, **92**, and **94** by 14-26 kJ/mol. In contrast, **96** is actually very slightly more stable than **95** (but only ~1.5 kJ/mol), implying that the fused five-membered ring has a profound effect on the outcome of the reaction. We suggest this is due to destabilization of **95** having the fused cyclopentane considerably twisted in the angular tricycle, a situation that is alleviated in **96**. We further suggest that this difference in ground-state energy is partially reflected in the transition states leading to each of these constitutional isomers, thereby negating the typical selectivities we observe between di- and tri-substituted Michael acceptors. This situation also allows the chiral catalyst to exert control over the newly formed bond, providing parallel kinetic resolution.

Scheme 17.

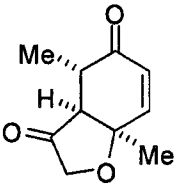


62



89

+

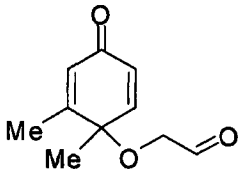


90

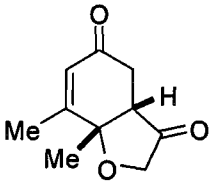
(1)

a 77% yield 12 : 1

b 76% yield 58% ee, > 95:5 dr 2 : 1 > 95% ee, > 95:5 dr

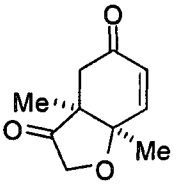


64



91

+

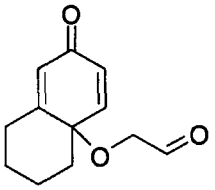


92

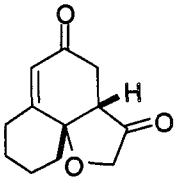
(2)

a 82% yield 130 : 1

b 79% yield 4% ee, > 95:5 dr not observed

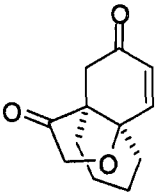


66



93

+

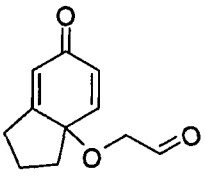


94

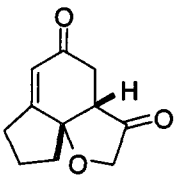
(3)

a 60% yield 105 : 1

b 74% yield 5% ee, > 95:5 dr 34 : 1 > 95% ee, > 95:5 dr

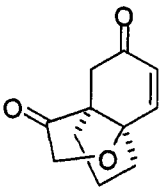


68



95

+



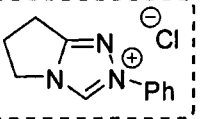
96

(4)

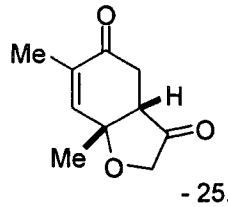
a 74% yield 1 : 1

b 75% yield 87% ee, > 95:5 dr 1 : 1 93% ee, > 95:5 dr

a: 20 mol% **achiral cat**, 20 mol% KHMDS, toluene, 0.04M, 23 °C, < 5 min
b: 10 mol% **6**, 10 mol% KHMDS, toluene, 0.008M, 23°C, < 5 min

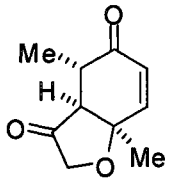
achiral cat = 

Scheme 18.



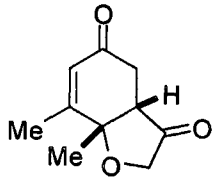
- 25.6 kJ/mol

89



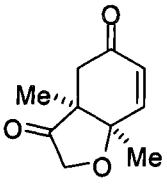
0 kJ/mol

90



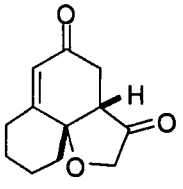
- 16.0 kJ/mol

91



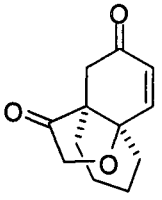
0 kJ/mol

92



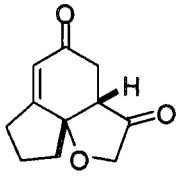
- 13.9 kJ/mol

93



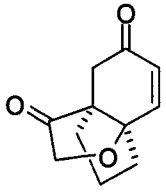
0 kJ/mol

94



0 kJ/mol

95



- 1.5 kJ/mol

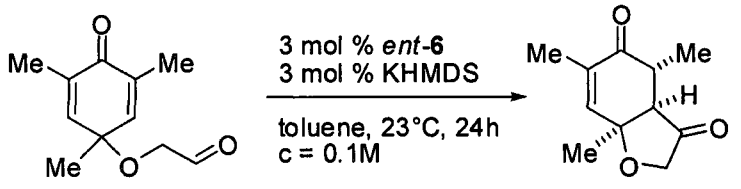
96

* the relative energies were calculated using SPARTAN (PM3)

f) Scale-up experiment

In order to test whether this chemistry could be used on larger scale, we conducted an experiment using one gram of **52** as the starting material. Although the catalyst loading was reduced to 3 mol % and the concentration (0.1 M) is much higher than that in small-scale experiments (0.008 M), the reaction proceeds efficiently, providing *ent*-**81** in 82% yield and 96% ee (Scheme 17).

Scheme 17.



52
1 gram

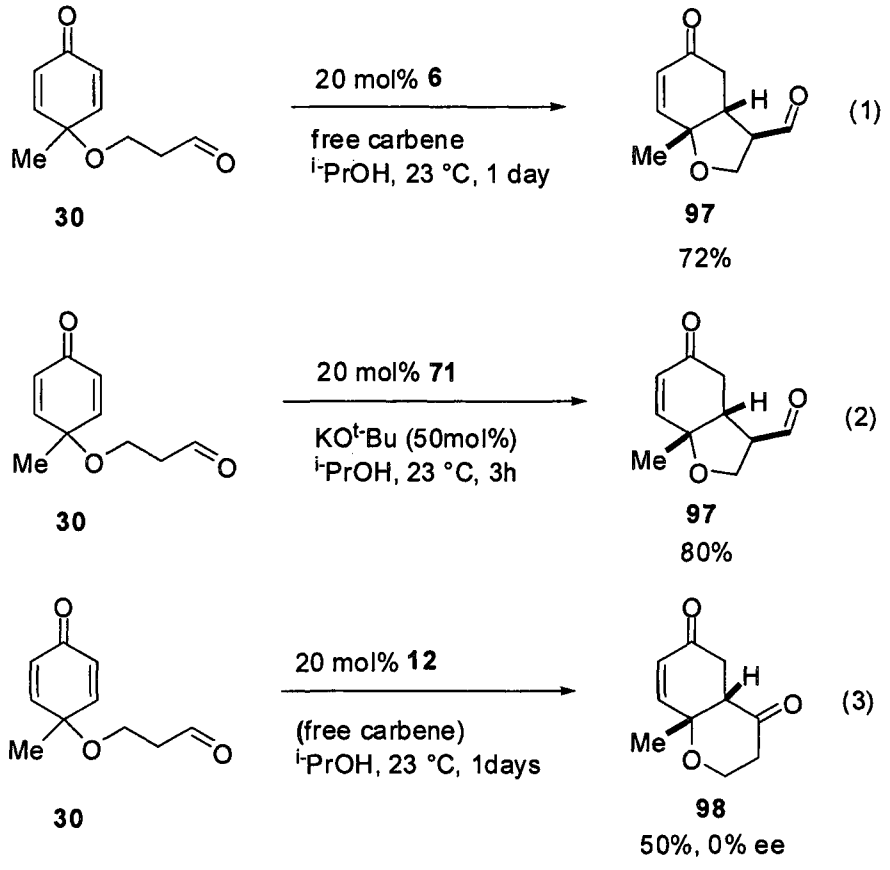
ent-**81**
82%, 96% ee

* enantiomer of **6** was used as catalyst

1.3.3 Substrates that did not Provide the Expected Results

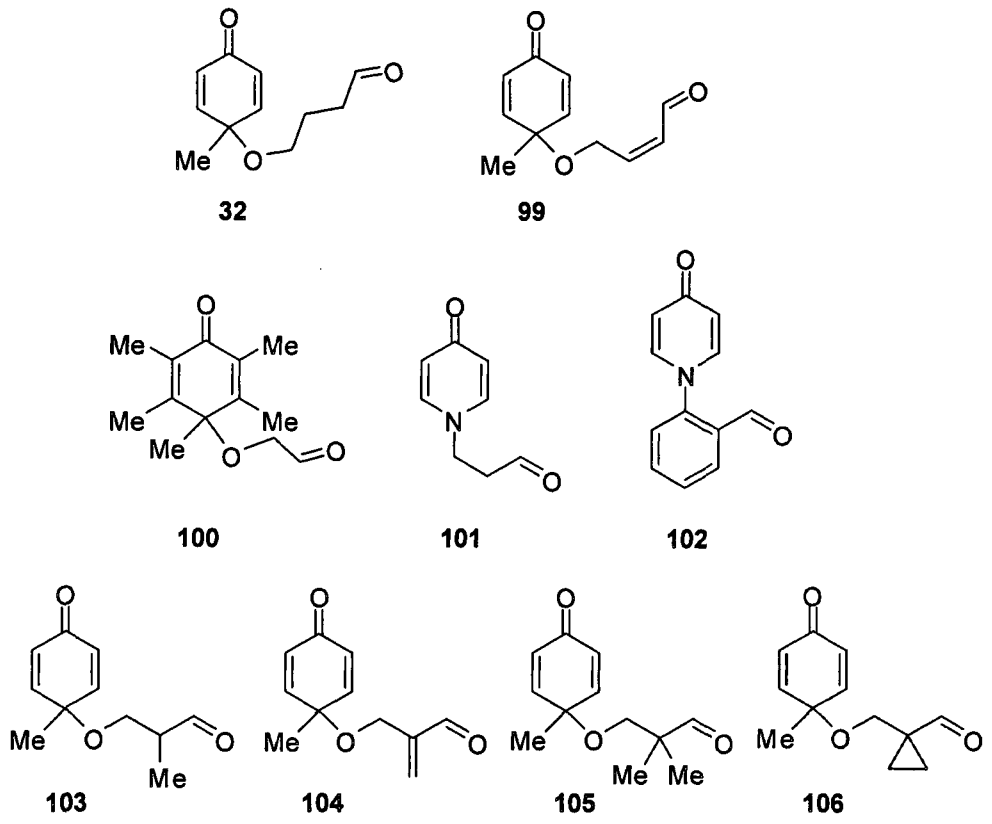
Stetter reaction of substrate **30** was expected to afford a [4.4.0]-bicycle product. However, the reaction with catalysts **6** and **71** in isopropanol generated **97**, which was not expected (Scheme 18, eq 1-2). These results are consistent with the work of Hayashi, [18] which implies that the product is formed through an aldol mechanism. After more conditions were screened, catalyst **12** was found to be able to catalyze the Stetter reaction of **30** to afford the desired product **98**. Unfortunately the enantioselectivity of this reaction is very poor, and the product is racemic.

Scheme 18.



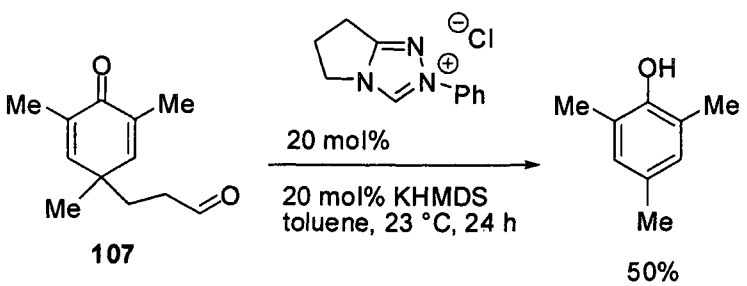
We screened more substrates which are shown in Scheme 19. Under a variety of Stetter reaction conditions, those substrates didn't give the expected product. Basically, substrates **99, 100, 101, 102, 104, 105, 106** were recovered after workup. The reaction of **32** is very messy, but the starting material is consumed. Substrate **103** affords the desired product in very low yield, and the major product is formed via an aldol reaction.

Scheme 19.



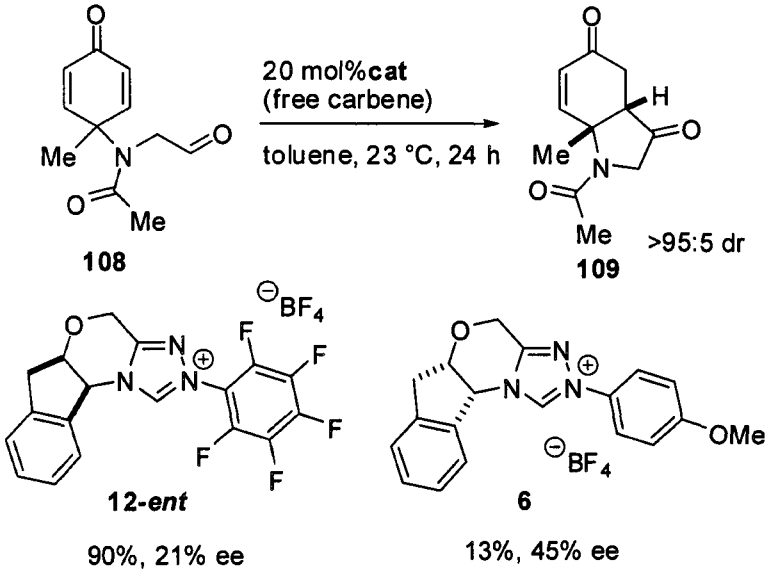
We spent more effort to synthesize another C-tether substrate **107**, an analogue of substrate **86** (see chapter 1 experimental for detailed procedure). However, the reaction of **107** under our standard conditions gives 2,4,6-trimethyl phenol as the major product, and none of the desired product was isolated (Scheme 20). It is possible that the major product is generated through an elimination mechanism.

Scheme 20.



A N-tether analogue **108** was made using a different route (see chapter 1 experimental). The Stetter reaction of this substrate provides desired product, Scheme 21. However the enantioselectivity is not good, and further optimization of the reaction conditions are needed to improve the ee.

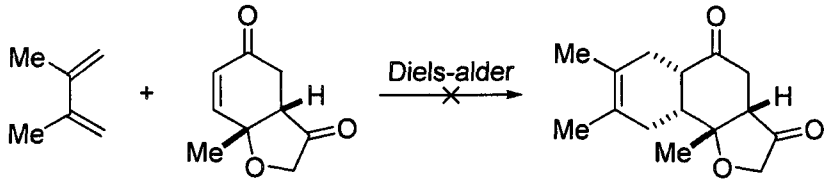
Scheme 21



1.4 Functionalization of Hydrobenzofuranones

In order to show that the obtained Stetter product is a useful building block for organic synthesis, we tried to further manipulate the hydrobenzofuranones. Product **69** was subjected to Diels-alder reaction conditions. Unfortunately the reaction of 2,3-dimethylbuta-1,3-diene with **69** failed to provide any desired product under different conditions (Scheme 22). It is possible that the steric effect of the methyl group and the fused THF ring prevent the approach of the diene to **69**, as shown in Figure 3.

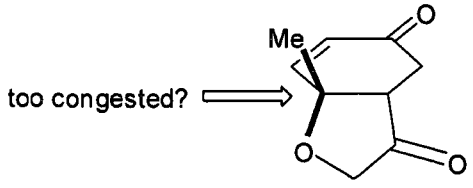
Scheme 22.



69 110

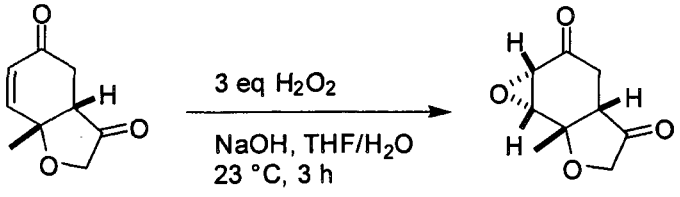
rxn condition	result
0.5eq $EtAlCl_2$ Toluene, 23 °C	No desired product, messy
Toluene, reflux	Starting material

Figure 3.



We were delighted to find the epoxidation of **69** is successful, Scheme 23. Treatment of **69** with hydrogen peroxide in sodium hydroxide solution provides epoxide **111** in quantitative yield and excellent diastereoselectivity. This result is consistent with the work of Meyers in 1999.[23] The configuration of **111** is confirmed by nOe experiment (see chapter 1 experimental).

Scheme 23.



69 **111**

100%, one diastereomer

[23] Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931-8952.

1.5 Conclusion

In a rapid and efficient manner, a series of cyclohexadienones were synthesized through dearomatization of widely available phenols. The asymmetric desymmetrizations of these substrates via Stetter reactions afford hydrobenzofuranones in good yields and excellent selectivities. Up to three contiguous stereocenters as well as quaternary stereocenters can be formed using this transformation. Scalability and functionalization of the product demonstrates the utility of this methodology.

Chapter 2

Catalytic Asymmetric Intermolecular Stetter Reaction of Glyoxamide

2.1 Introductions

The Stetter reaction,[24] the N-heterocyclic Carbene (NHC) catalyzed addition of aldehydes to Michael acceptors, is a prototypical example of the emerging class of catalyzed umpolung reactions. [25] Following the seminal report by Enders,[26] we[27] and others[28] have extensively investigated the asymmetric intramolecular Stetter reaction. On the other hand, the asymmetric intermolecular Stetter has remained a much more significant challenge. Two early reports by Enders and co-workers [29] described asymmetric intermolecular Stetter reactions utilizing chiral thiazolium salt **4** or **5** as catalyst precursor. The reaction of n-butanal **1** and chalcone **2** affords Stetter product **3** with low enantiomeric excess and yields (Scheme 1).

---

[24] (a) Stetter, H.; Schrecke, M. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 81; (b) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407-496. (c) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534-541; (d) Christmann, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2632-2634; (e) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606-5655. f) Rovis, T. *Chem. Lett.* **2008**, *37*, 2-7.

[25] (a) Corey, E. J., Seebach, D. *Angew. Chem. Int. Ed.* **1965**, *4*, 1075-1077; b) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239-258.

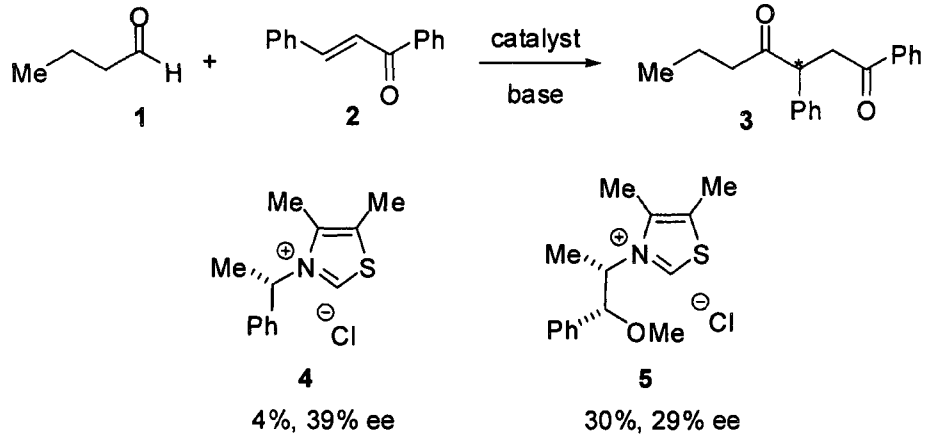
[26] Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899-1902.

[27] (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298-10299. (b) Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934-1936. (c) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876-8877. (d) de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284-6289. (e) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725-5728. (f) Reynolds, N. T.; Rovis, T. *Tetrahedron* **2005**, *61*, 6368-6378. (g) Moore, J. L.; Kerr, M. S.; Rovis, T. *Tetrahedron* **2006**, *62*, 11477-11482. (h) Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033-2040. (i) Orellana, A.; Rovis, T. *Chem. Commun.* **2008**, 730-732. (j) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552-2553; (k) Liu, Q.; Rovis, T. *Org. Process Res. Dev.* **2007**, *11*, 598-604; (l) Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033-2040.

[28] a) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025-2035; b) Mennen, S. M.; Blank, J. T.; Tran-Dube, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195-197; c) Matsumoto, Y.; Tomioka, K. *Tetrahedron Lett.* **2006**, *47*, 5843-5846.

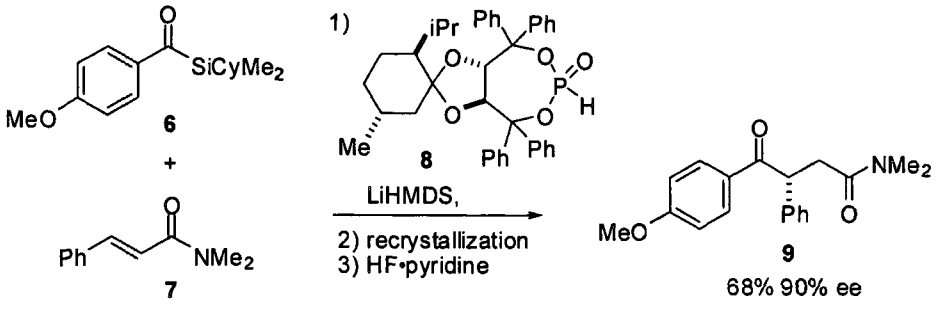
[29] (a) Tiebes, J. Diploma Thesis, RWTH Aachen, Aachen, Germany, **1990**. (b) Enders, D. In *Stereoselective Synthesis*; Springer-Verlag: Heidelberg, Germany, **1993**; p 63. (c) Enders, D.; Bockstiegel, B.; Dyker, H.; Jegelka, U.; Kipphardt, H.; Kownatka, D.; Kuhlmann, H.; Mannes, D.; Tiebes, J.; Papadopoulos, K. In *Dechema-Monographies*; VCH: Weinheim, Germany, **1993**; Vol. *129*, p 209. (d) Enders, D.; Breuer, K. in *Comp Asym Cat*, **1999**; pp 1093-1104.

Scheme 1.



In a related process, Johnson has published an asymmetric metallophosphite-catalyzed Stetter-like reaction of acyl silanes.[30] As shown in Scheme 2, the asymmetric conjugate additions of acyl silanes **6** to N,N-dimethylcinnamide **7** was catalyzed by the lithium salt of a TADDOL phosphite **8**. After enantioenrichment via recrystalization and desilylation with HF•pyridine, a formal Stetter product **9** was obtained in good yield and excellent enantioselectivity.

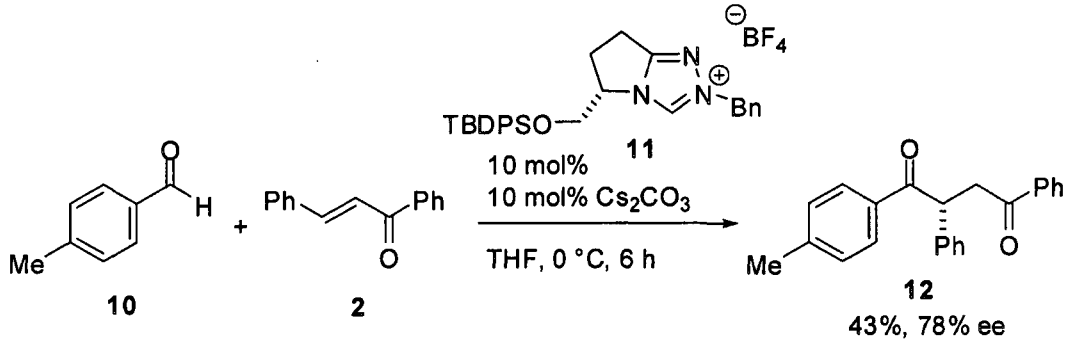
Scheme 2.



[30] (a) Nahm, M. R.; Potnick, J. R.; White, P. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 2751-2756. (b) Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem.-Int. Edit.* **2005**, *44*, 2377-2379.

In 2008, concurrently with our own work, Enders and coworkers reported an asymmetric intermolecular Stetter reaction catalyzed by the carbene derived from a new triazolium salt **11**.[31] The reaction of 4-methylbenzaldehyde **10** and chalcone **2** furnished 1,4-diketone **12** in moderate yield and ee (Scheme 3).

Scheme 3.

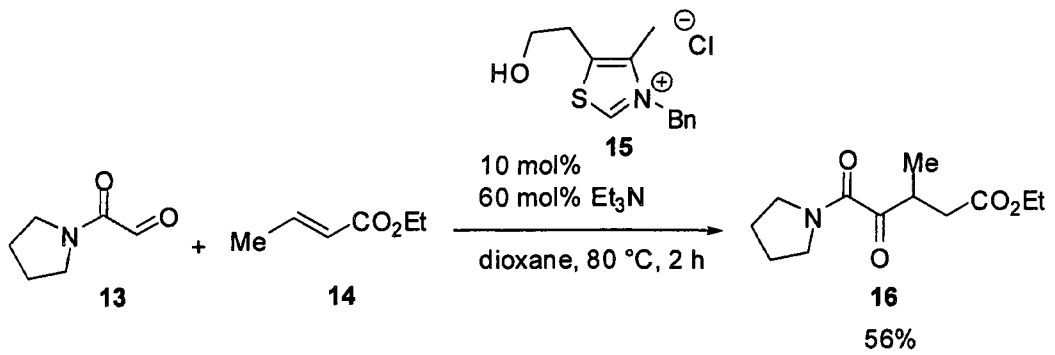


A close examination of Stetter's pioneering work on this reaction reveals that Michael acceptors bearing β-substituents often result in diminished reactivity and are typically restricted to chalcones or other highly activated alkenes such as fumarates.[24b] Interestingly, thiazolylidene-catalyzed addition of glyoxamides to β-substituted Michael acceptors seems to be an exception to this tendency.[32] As shown in Scheme 4, carbene generated from **15** catalyzed the addition of glyoxamide **13** with β-substituted acrylate **14** to afford **16** in good yield. We envisioned that the combination of glyoxamide with the appropriate electrophilic alkene could result in an enantioselective intermolecular Stetter reaction using enantioenriched NHC as catalysts.

---

[31] Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989-3991.
[32] Stetter, H.; Skobel, H. *Chem. Ber.* **1987**, *120*, 643-645.

Scheme 4.



2.2 Enantioselective Intermolecular Stetter Reaction of Glyoxamide

2.2.1 Optimization of Reactants and Reaction Conditions

a) Preliminary Results

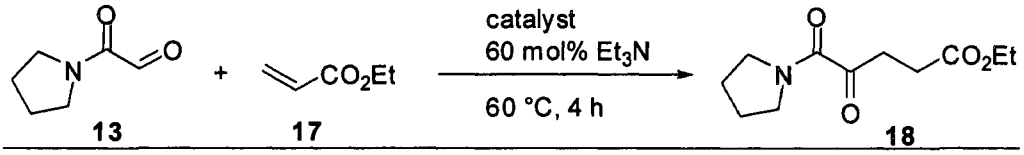
We began by testing whether triazolium salt is a suitable catalyst for the intermolecular Stetter reaction of glyoxamide. A series of catalysts **19-22** were screened in the reaction of glyoxamide **13** and acrylate **17** in various solvents (Table 1). The electron-deficient catalyst **21** shows good reactivity and the best yield (87%) is obtained with tert-butanol as a solvent (Table 1, entries 3-5). However, the reactivity of a similar electron-deficient catalyst **22** is generally low for the reaction in a variety of solvents (Table 1, entries 6-13).

b) Screen of Michael Acceptors and Glyoxamides

As shown in Scheme 5, α- and β-substituted acrylates were tried, but, the desired products **23** or **24** are not obtained. Presumably, the sterics of the Michael acceptors play a role. A range of other Michael acceptors failed to generate the corresponding Stetter products **25-29**. Fortunately, vinyl ketone turns out to be a good Michael acceptor and the reaction furnishes desired product **30** in very good yield. β-substituted vinyl ketones were screened and desired products **31, 32,** and **33** are all obtained. Chalcone was found to be

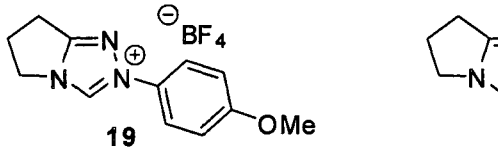
best vinyl ketone with 87% yield of **33**. Finally, the malonate-derived Michael acceptor shows the best activity and the corresponding product **34** is isolated in quantitative yield.

Table 1.

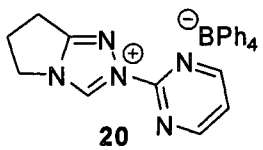


13 **17** **18**

entry	catalyst	mol% catalyst	solvent	yield (%)[a]
1	**19**	10	iso-propanol	<1
2	**20**	10	iso-propanol	<1
3	**21**	10	iso-propanol	50
4		20	iso-propanol	73
5		20	tert-butanol	87
6	**22**	10	toluene	3.5
7		10	DCM	5.7
8		10	ether	4.0
9		10	THF	4.9
10		10	methanol	1.7
11		10	ethanol	1.7
12		10	iso-propanol	9.3
13		20	iso-propanol	13



19



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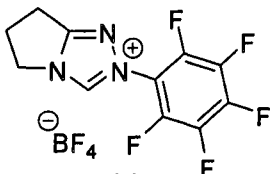
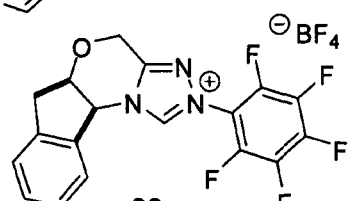


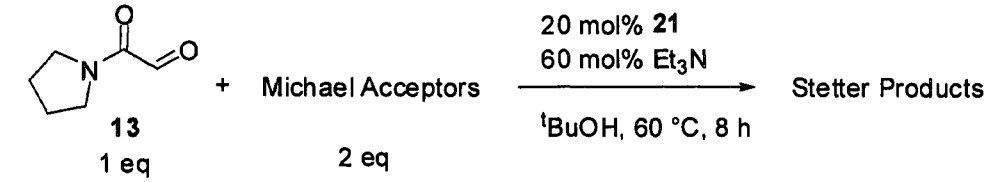
21



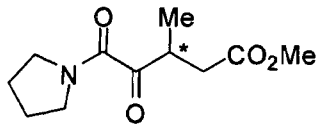
22

a) All reactions conducted with 1 equiv of **13** and 2 equiv of **17** at 23 °C.

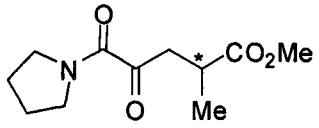
Scheme 5.



13
1 eq



23
0%



24
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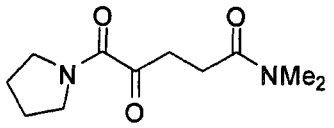
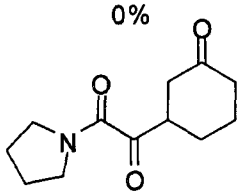


25
0%



26
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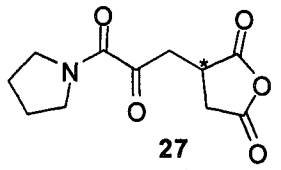

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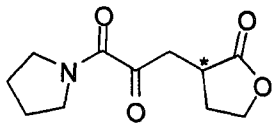

28
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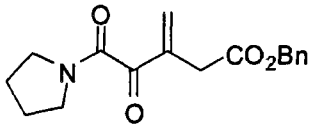
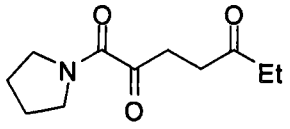
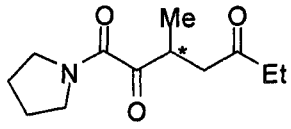


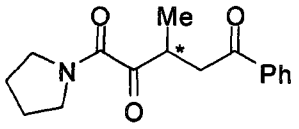
29
0%



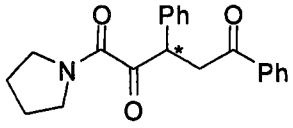
30
99%



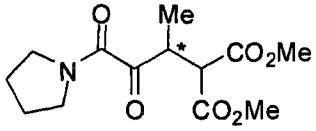
31
12%



32
53%



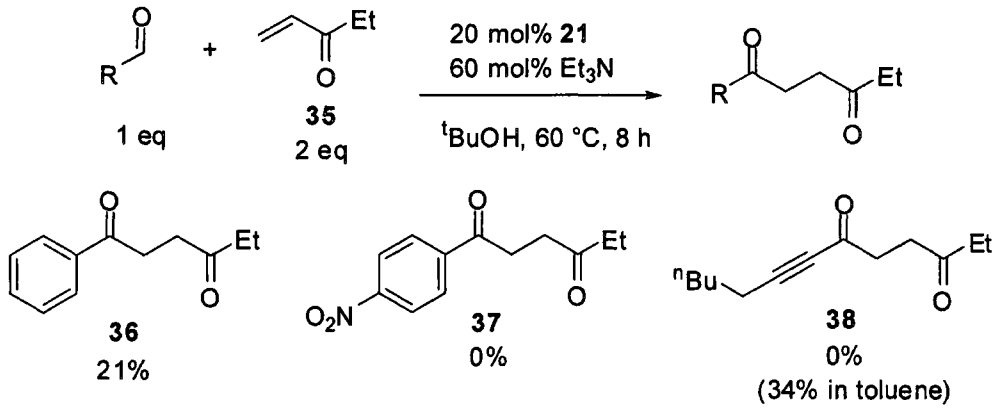
33
87%



34
100%

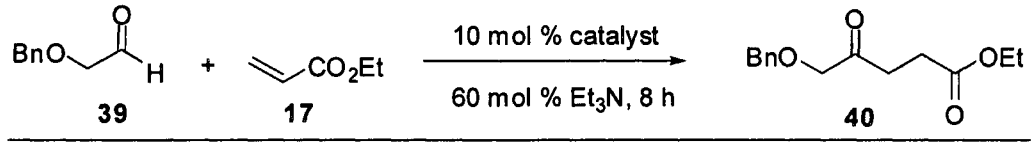
A variety of aldehydes were screened using ethyl vinyl ketone **35** as Michael acceptor and **21** as catalyst (Scheme 6). Benzaldehyde provides product **36** in only 21% yield, and para-nitro-benzaldehyde is inactive in this reaction. Ynal is not active in tert-butanol, but the desired product **38** could be generated in 34% yield with toluene as a solvent.

Scheme 6.



2-(benzyloxy)acetaldehyde **39** was synthesized and subjected to the intermolecular Stetter reaction. Unfortunately, **39** is not a suitable aldehyde and didn't lead to desired product **40** under a variety of conditions (Table 2).

Table 2.



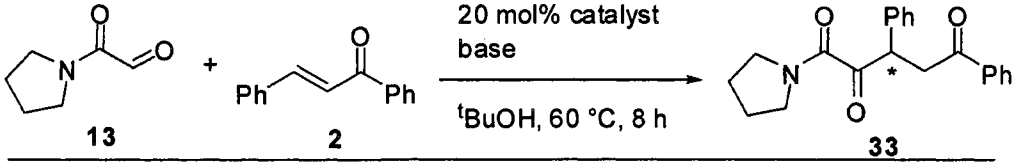
entry	catalyst	solvent	temp (°C)	yield (%)[a]
1	**15**	dioxane	80	0
2	**22**	dioxane	25	0
3		toluene	25	0
4		DCM	25	0

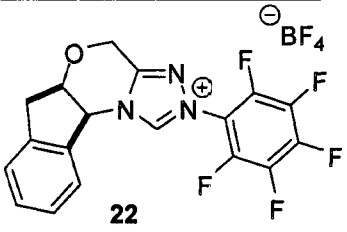
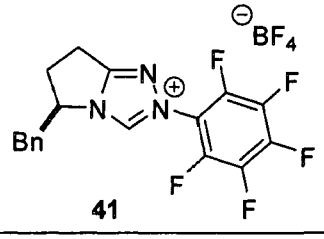
a) All reactions conducted with 1 equiv of **39** and 2 equiv of **17** at 23 °C.

c) α,β-Unsaturated Ketones as Michael Acceptors

Two chiral catalysts **22** and **41** were investigated in the reaction of chalcone with glyoxamide **17**. The less bulky catalyst **41** is more active than **22** (Table 3). However the enantioselectivities of the reaction are generally poor. We took an aliquot from the reaction and determined the ee of product (Table 3, entry 3). We found that the ee of product formed in 3 h is 25% but it drops to 3% in 8 h. This result strongly suggests that the product is epimerized during the reaction. This epimerization can be explained by the increase in acidity of the α-proton in product **33** by the phenyl substituent.

Table 3.

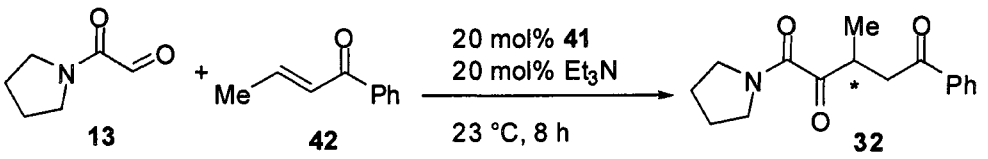


entry	catalyst	base	yield (%)[a]	ee (%)[b]
1	 22	20 mol% Et_3N	2	2.5
2	 41	60 mol% Et_3N	24	2
3		20 mol% Et_3N	30	3 (3h: 25% ee)
4		20 mol% KO^tBu	31	8

a) All reactions conducted with 1 equiv of **13** and 2 equiv of **2** at 23 °C. b) Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

Using **41** as the catalyst and phenyl propenyl ketone **42** as the Michael acceptor, we screened different solvents (Table 4). Despite good yield, the ee remained low due to epimerization.[33]

Table 4.



13 **42** **32**

entry	solvent	yield (%)[a]	ee (%)[b]
1	^{t}BuOH	51	38
2	toluene	47	13
3	dioxane	70	28

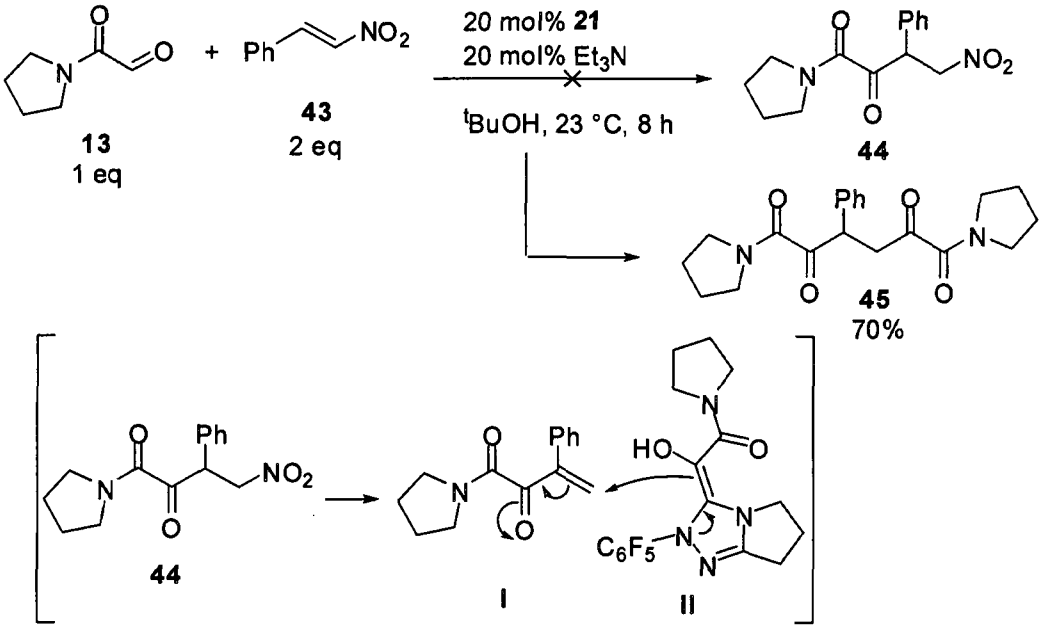
a) All reactions conducted with 1 equiv of **13** and 2 equiv of **42** at 23 °C.
b) See Table 3.

d) Nitro-olefin as Michael Acceptor

An unexpected result was observed when we used (E)-(2-nitrovinyl)benzene **43** as Michael acceptor (Scheme 7). We did not isolate desired product **44**, but obtained **45** in 70% yield. We believe that **44** is formed, but it is converted to the unsaturated ketone **I** by nitro elimination. Then nucleophilic addition of the Breslow intermediate **II** can occur and lead to the observed product **45**. This is an interesting transformation that warrants further investigation.

[33] Dr. Stéphane Perreault did aliquot experiments and found the product was epimerized during the reaction. He also investigated more substituted vinyl ketones that unfortunately did not provide good results.

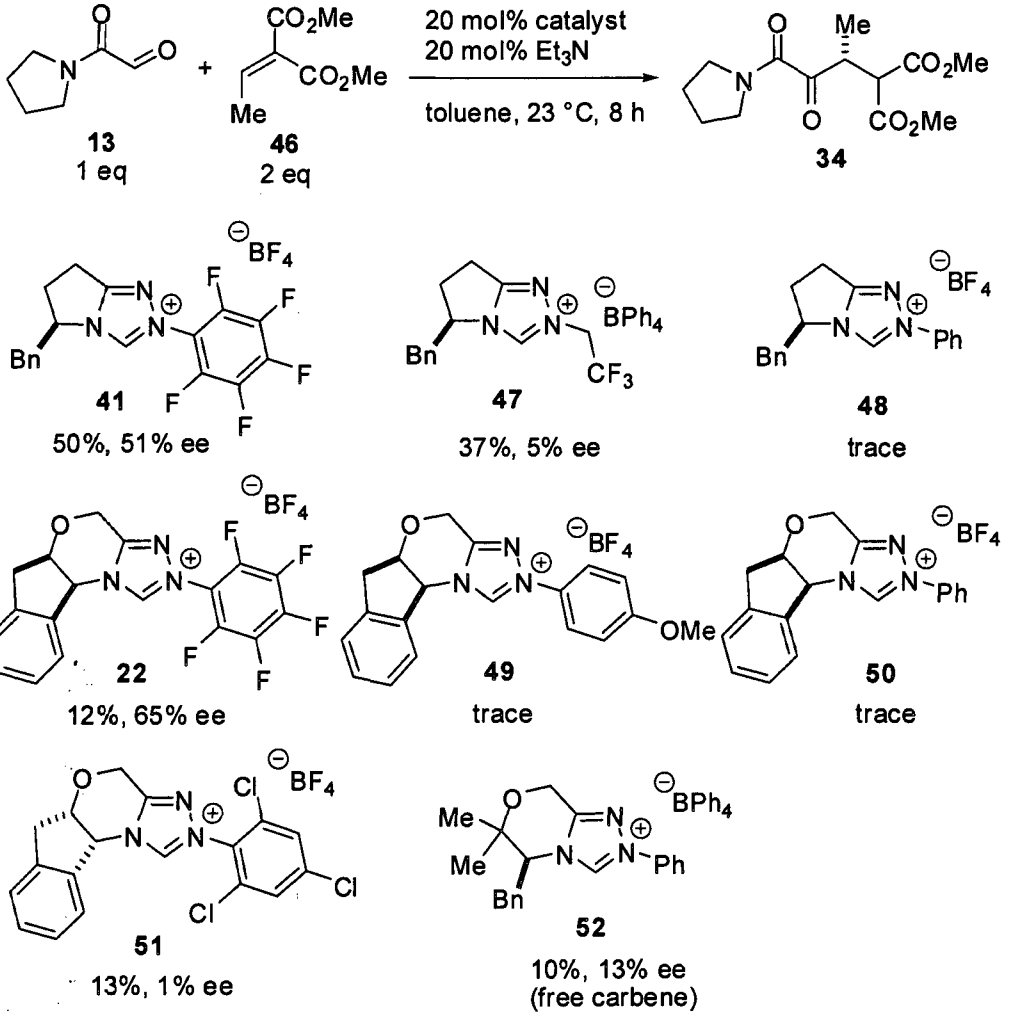
Scheme 7.



e) Catalysts Screen

As the reaction with vinyl ketones does not afford product in sufficient enantioselectivities, we switched our focus to malonate-derived Michael acceptor **46**, which is also very active for intermolecular Stetter reaction (Scheme 5). A series of triazolium salts were screened for the reaction with **46** (Scheme 8). Pyrrolidinone-derived catalysts **41** and **47** were found to be much more active than morpholinone-derived catalysts **22**, **49**, **50**, and **51**. Electron-defficient catalysts **41**, **47**, **22**, and **51** are more active than the others. Catalyst **22** provides the best enantioselectivity, albeit yield is low. We screened different solvents, bases, and temperatures with **22** and could not improve the yield of product. We believe **22** is bulkier than **41** and this negatively affects yields; therefore we chose to optimize conditions with **41** as the catalyst.

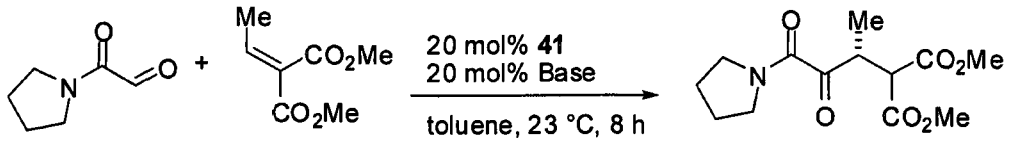
Scheme 8.



f) Base Screen

The effect of base on the reaction was studied using **41** as catalyst (Table 5). Product **34** is sensitive to strong bases so we focused on weak bases such as amines or amine derivatives. Triethylamine provides the best base, which leads to the best ee (Table 5, entry 1), while Hunig's base gives the best yield of product (Table 5, entry 2).

Table 5.



13 **46** **34**

entry	Base	yield (%)[a]	ee (%)[b]
1	Et_3N	50	51
2	$^iPr_2NEt$	61	38
3	$EtNH_2$	33	46
4	imidazole	17	48
5	pyridine	15	49
6	DABCO	46	46
7	Ethanolamine	28	37
8	DMAP	57	30
9	N-Me-morpholine	48	33

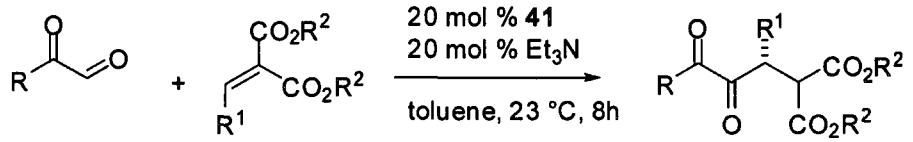
a) All reactions conducted with 1 equiv of **13** and 2 equiv of **46** at 23 °C.
b) See Table 3.

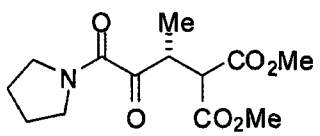
g) Alkylidenemalonates as Michael Acceptors

Using triethylamine as the base and **41** as the catalyst, we again screened a broad range of substrates, including different glyoxamides and Michael acceptors (Scheme 9). When the methyl group was switched to ethyl group on the Michael acceptor, the ee is not improved (see product **53**). Products **54** or **55** were not generated from the corresponding Michael acceptors presumably due to steric effects. Product **56** was not obtained. A diketone-derived product **57** was obtained in better yield, but lower ee. Similar results were observed when the piperidine-derived glyoxamide was used (see product **58**). Product **59** was isolated in 51% yield as a racemate; the reason could be

epimerization during the reaction. Two acyclic glyoxamides were used for the reaction, but the yield and ee are lower. The ethyl glyoxylate was found to be very active for the reaction, although enantioselectivity suffers (see product **62**). Finally, the di-tert-butylmalonate-derived Michael acceptor was found to provide product **63** in 80 % ee.

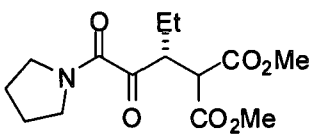
Scheme 9.





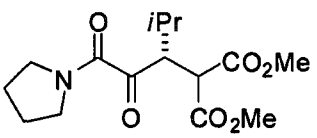
34

50%, 51% ee



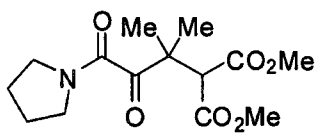
53

52%, 51% ee



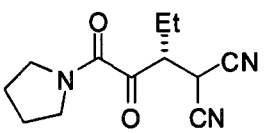
54

0%



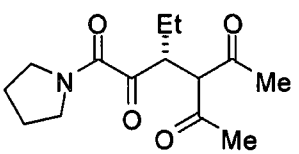
55

0%



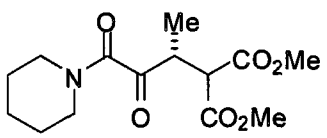
56

0%



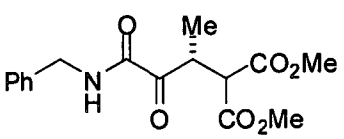
57

70%, 20% ee



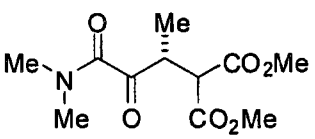
58

63%, 36% ee



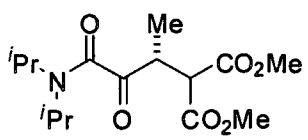
59

51%, 0% ee



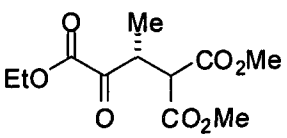
60

24%, 42% ee



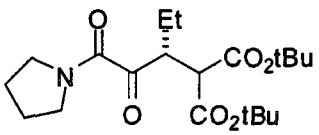
61

30%, 24% ee



62

100%, 23% ee



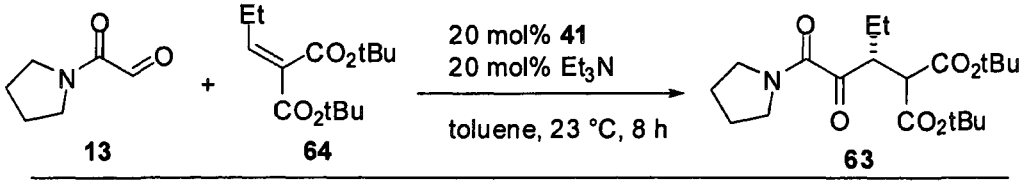
63

39%, 80% ee

h) Effect of Drying Agents

As glyoxamide **13** is very hygroscopic, we envisioned that the yield of reaction could be improved by adding a desicant to remove any possible moisture in the reaction (Table 6). Several desicants were tested and it was found that $MgSO_4$ is able to improve the yield to 47% without sacrificing the enantioselectivity of the reaction.

Table 6.



13 **64** **63**

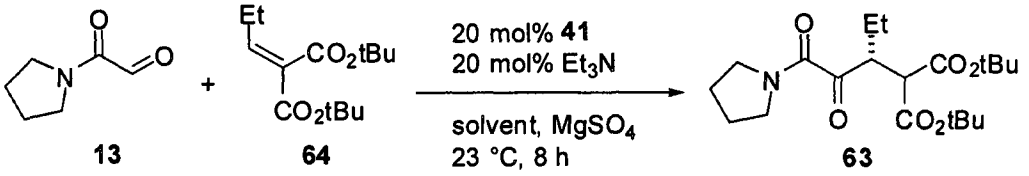
entry	drying agent	yield (%)[a]	ee (%)[b]
1	none	39	80
2	3 Å MS	36	80
3	$MgSO_4$	47	81
4	Na_2SO_4	27	81

a) All reactions conducted with 1 equiv of **13** and 2 equiv of **64** at 23 °C.
b) See Table 3.

i) Screen of Solvents, Bases, and Catalyst Loading

A variety of solvents were screened and we found the enantioselectivities were all around 80% (Table 7). It is not clear why the solvent has little effect on the selectivity of the reaction; it is possible the reaction occurs by a concerted mechanism. However, the yield of the reaction was significantly changed with different solvents. Benzene, toluene, and carbon tetrachloride are all good solvent (Table 7, entries 7, 8, 14). Carbon tetrachloride provides the highest yield and was chosen as the solvent for subsequent reactions.

Table 7.



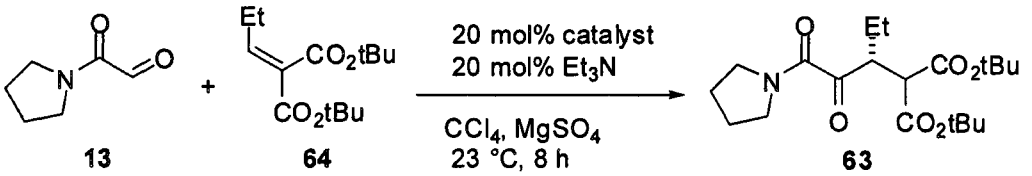
13 64 63

entry	solvent	yield (%)[a]	ee (%)[b]
1	Dioxane	37	79
2	THF	32	77
3	Dimethoxy ethane	34	77
4	^{t}BuOH	24	82
5	^{i}PrOH	23	80
6	DMF	3	69
7	benzene	49	79
8	toluene	47	80
9	xylenes	33	82
10	1,2-dichloroethane	7	78
11	chlorobenzene	20	80
12	methylene chloride	16	77
13	chloroform	20	82
14	carbon tetrachloride	51	81

a) See Table 6. b) See Table 3.

Another brief base screen for the reaction is shown in Table 8. Two pentafluoro-phenyl substituted catalysts **41** and **22** were used in the reactions. Triethylamine leads to the best yield and ee for both catalysts (Table 8, entries 1, 3). Reactions with catalyst **22** provide excellent enantioselectivities, but very poor yields (Table 8, entries 3, 4, 5).

Table 8.



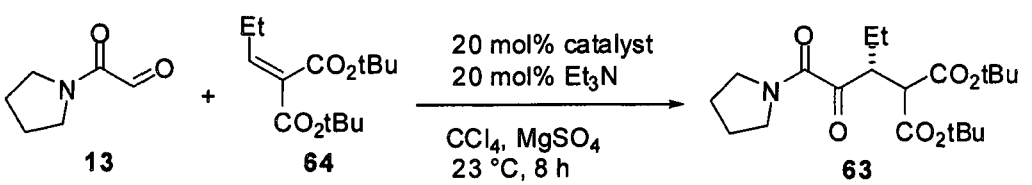
13 64 63

entry	catalyst	base	yield (%)[a]	ee (%)[b]
4	**41**	Et_3N	51	81
4		KO^tBu	11	81
4	**22**	Et_3N	11	92
4		$^iPr_2NEt$	3	92
4		KO^tBu	2	92

a) See Table 6. b) See Table 3.

Table 9 shows the results of reaction with different equivalents of Michael acceptor. The yield was not improved by adding more **64** when catalyst **22** was used (Table 9, entries 3, 4). However, more **64** with catalyst **41** did increase the yield of product **63** (Table 9, entry 2).

Table 9.



13 64 63

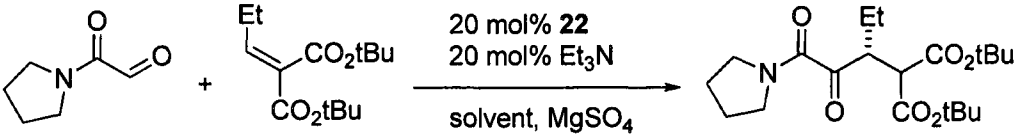
entry	catalyst	eq of **64**	yield (%)[a]	ee (%)[b]
1	**41**	2	51	81
2		4	72	81
3	**22**	2	11	92
4		5	10	92

a) See Table 6. b) See Table 3.

j) Optimization of a Morpholinone-derived Catalyst

Due to catalyst **22** providing excellent enantioselectivity but poor yield, we screened more reaction conditions in order to improve the yield (Table 10). We screened the reaction temperature (Table 10, entry 2) and concentration (Table 10, entries 3-4). Unfortunately, none of them increased the yield of **63**. We examined more solvents, but these were also unfruitful. We believe catalyst **22** is bulkier compared to **41**, so the reaction catalyzed by **22** affords product in excellent ee but very poor yield.

Table 10.



13 **64** **63**

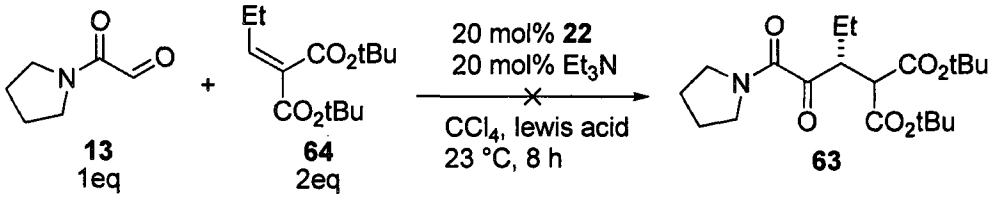
entry	solvent	yield (%)[a]	ee (%)[b]
1	CCl_4	11	92
2		2	95[c]
3		8	93[d]
4		7	92[e]
5	toluene	5	94
6	benzene	5	94
7	MeOH	3	86
8	EtOH	3	90
9	^{i}PrOH	5	87
10	^{t}BuOH	1	90

a) All reactions conducted with 1 equiv of **13** and 2 equiv of **64** at 23 °C, concentration = 0.25 M.
b) See Table 3. c) Reaction temp = - 10 °C. d) Concentration = 1 M. e) Concentration = 0.1 M.

We investigated other methods to improve the yield of reaction with catalyst **22** because of the excellent enantioselectivities. For example, we thought a Lewis acid might

be able to activate Michael acceptor **64** to increase the yield of the reaction. However a variety of Lewis acids were screened and the results were disappointing (Scheme 10).

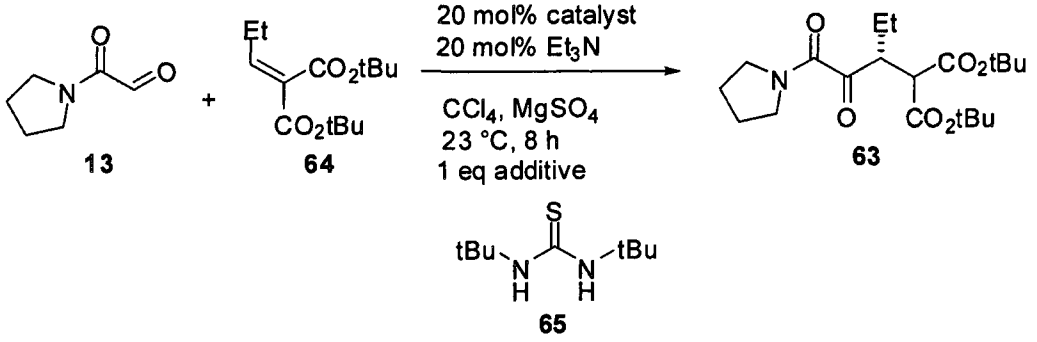
Scheme 10.



Lewis acid tried: $TiCl_4$ BF_3-OEt_2 MgI_2 $MgBr_2$ $ZnCl_2$ $ZnBr_2$ ZnI_2 $Zn(OTf)_2$ $Cu(OTf)_2$

We also tried additives such as 1,3-di-tert-butylthiourea **65** which could possibly activate **64** by forming hydrogen bonds with it. This additive failed to increase the yield or ee with catalyst **22** or **41** (Table 11).

Table 11.



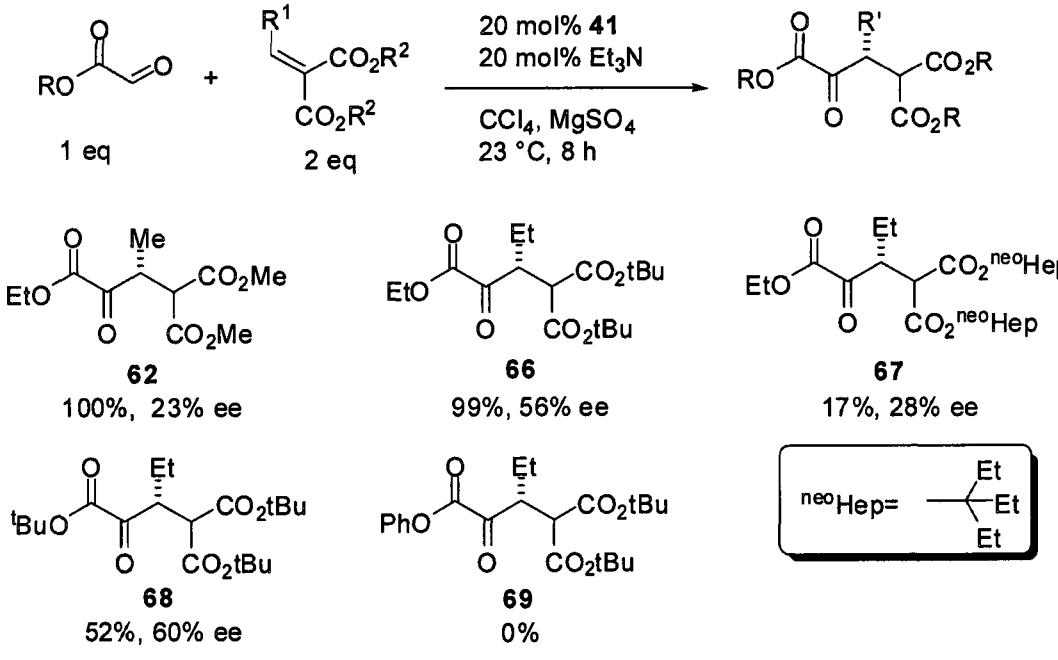
entry	catalyst	yield (%)[a]	ee (%)[b]
1	**22**	0	NA
2	**41**	46	79

a) See Table 6. b) See Table 3.

k) Glyoxylates as Starting Materials

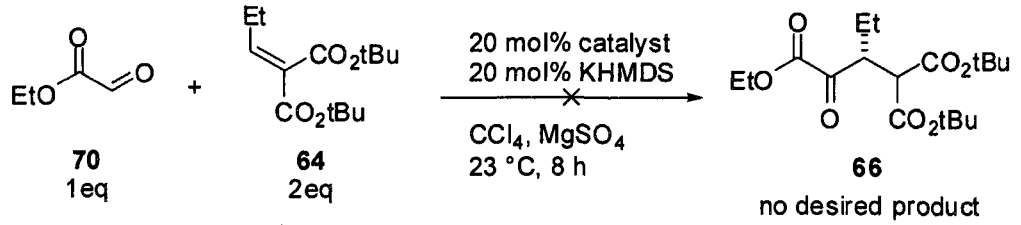
Glyoxylates are also promising substrates for the Stetter reaction because of their high activity (see Scheme 9, compound **62**). Thus a range of substrates was examined and the results are shown in Scheme 11. When **64** was used as Michael acceptor, **66** was isolated in 99% yield and 56% ee, which is much better than that of **62**. However, a bulkier R^2 group decreases the yield and ee (Scheme 11, compound **67**). Glyoxylates with different R groups were synthesized and subjected to the Stetter reactions. A tert-butyl substituted glyoxylate provides **68** in 52% yield, 60% ee. A phenyl glyoxylate didn't give desired product **69** under the same reaction condition; the reason for this is not clear.

Scheme 11.

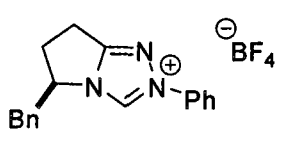


Other catalysts such as **48**, **49**, **50**, and **22** were screened for the intermolecular Stetter reaction of **70** (Scheme 12). Unfortunately, these catalysts failed to provide the desired products.

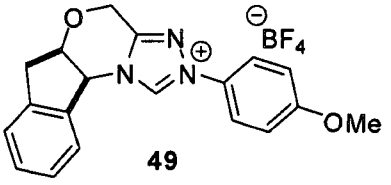
Scheme 12.



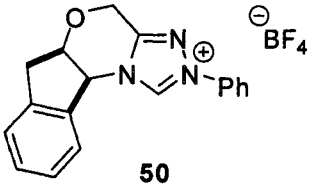
catalysts screened:



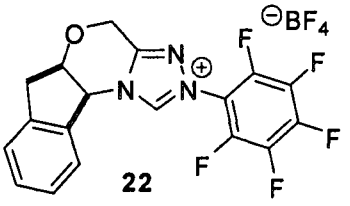
48



49



50



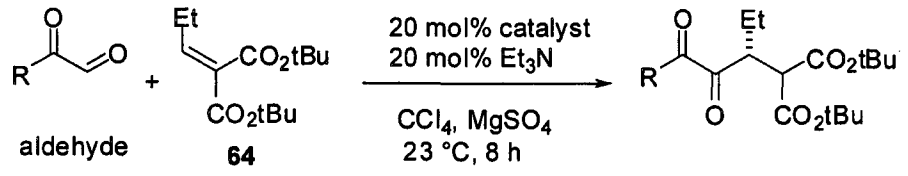
22

l) Test of New Catalysts

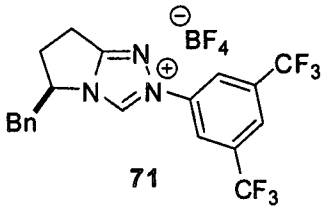
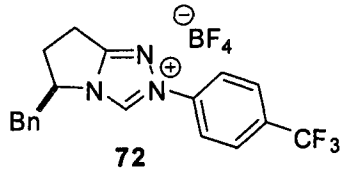
Suzuki and coworkers has reported a series of modified Rovis catalysts, which were used in asymmetric Benzoin cyclization. [34] Because we hypothesized that morpholinone-backbone is too bulky for our intermolecular Stetter reaction, we synthesized two pyrrolidinone-derived catalysts **71** and **72**, similar to Suzuki's catalysts. As shown in Table 12, both glyoxamide **13** and glyoxylate **70** were subjected to the reactions catalyzed with **71** or **72**. Only the reaction of glyoxylate **70** with Michael acceptor **64** gave desired product **66** when **71** were used as catalyst. All of the other reactions just don't afford desired products.

[34] Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 2713-2716.

Table 12.



aldehyde **64**

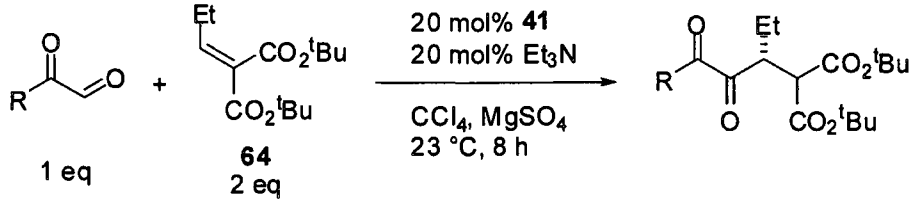
entry[a]	catalyst	aldehyde	product	result[b]
1	 **71**	**13**	**63**	no desired product benzoin observed
2		**70**	**66**	17%, 53%ee
3	 **72**	**13**	**63**	no desired product no benzoin observed
4		**70**	**66**	no desired product no benzoin observed

a) All reactions conducted with 1 equiv of **13** or **70** and 2 equiv of **64** at 23 °C.
b) See Table 3.

m) Further screen of Glyoxamides and Michael Acceptors

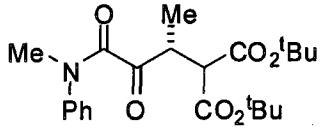
Catalyst **41** has proven the most efficient catalyst, so we decided to screen more glyoxamides in an effort to increase yields and enantioselectivities (Scheme 13). All reactions afford desired products, albeit in low yields and modest enatioselectivities.

Scheme 13.

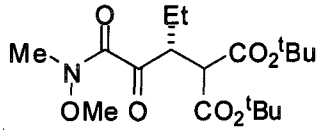


1 eq

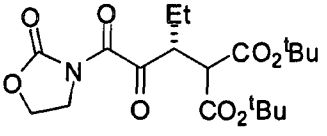
64
2 eq



73
30 %, 65 % ee



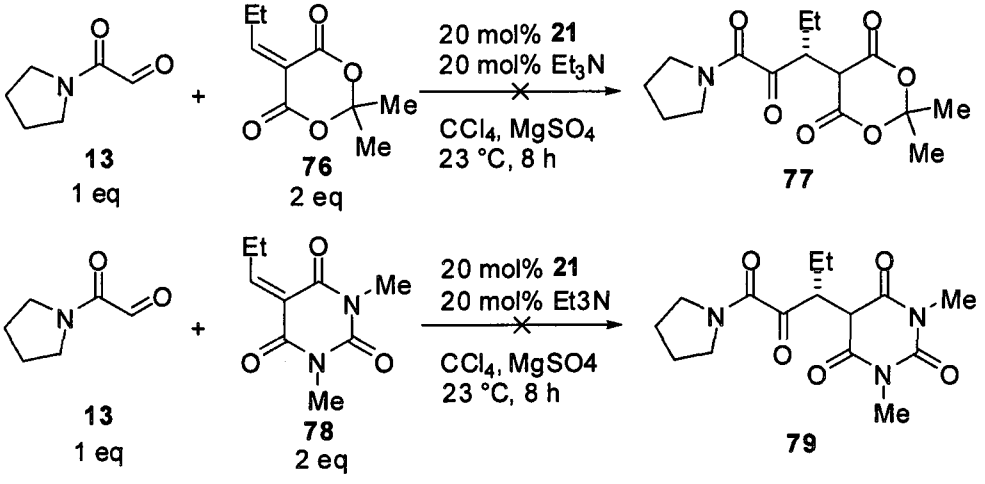
74
12 %, 64 % ee



75
16 %, 52 % ee

Two new Michael acceptors **76** and **78** were synthesized from Meldrum's acid and 1,3-dimethylbarbituric acid, respectively. Under standard intermolecular Stetter reaction condition, neither **76** nor **78** lead to expected products **77** and **79**. The reactions were messy and trace amount of product were isolated but were not characterizable (Scheme 14).

Scheme 14.

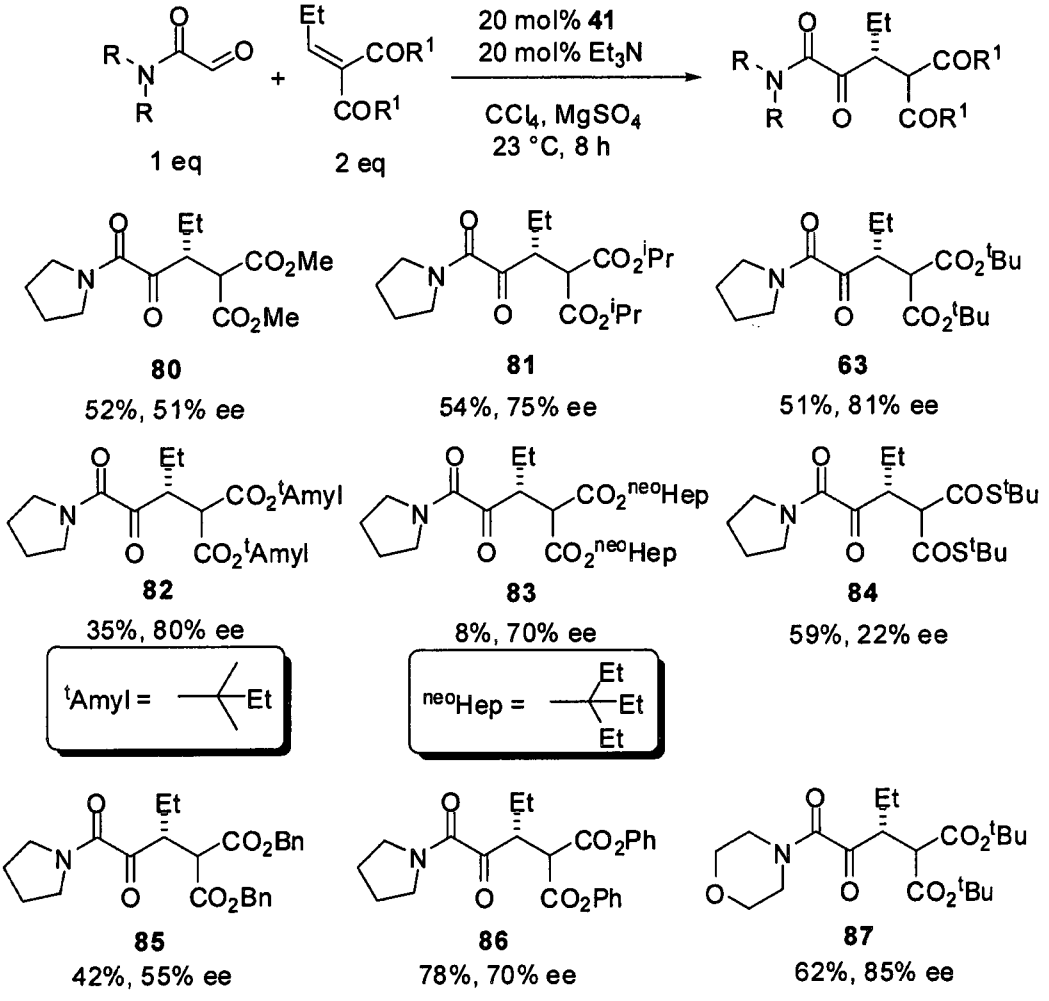


n) Steric Effect Study

We investigated the influence of sterics by changing the bulkiness of the Michael acceptor (Scheme 15). It is very clear that the ee improves from 51% to 75% and then 81% when R^1 is changed from methyl to iso-propyl and then to tert-butyl. Encouraged by these results, we further increased the size of R^1 in the Michael acceptors; however, the ee of product **82** was not improved. The other Michael acceptors with even bulkier R^1 furnished products in a lower yield and ee. The thioester-derived Michael acceptor was synthesized and subjected to the Stetter reaction condition. **84** was afforded in a slightly higher yield but only with 22% ee. Interestingly, we found di-phenyl malonate-derived

Michael acceptors are more active than aliphatic analogues; product **86** was obtained in 78% yield, although the ee is 70%. Finally, we found that the morpholine-derived glyoxamide gives product **87** in good yield and 85% ee, which is the best ee we have obtained to date.

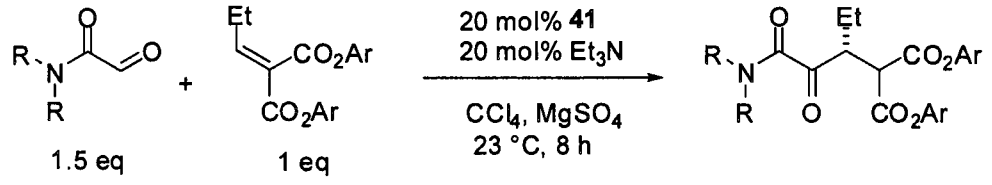
Scheme 15.

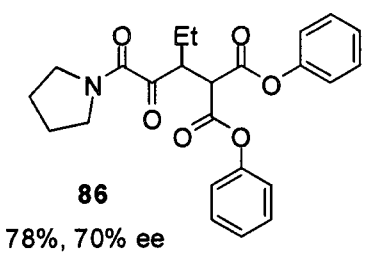


o) Michael Acceptors with Aromatic Substitution

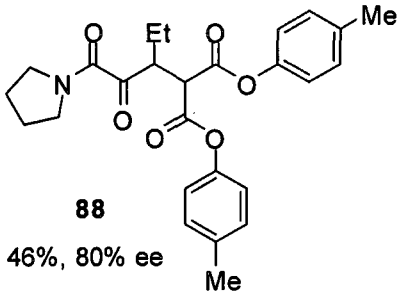
We screened a series of Michael acceptors with different aromatic groups. The results of Stetter reactions with these substrates are shown in Scheme 16. Reaction of glyoxamide **13** leads to product **86** and **88** in good yield and 70% ee. We then focused on the reaction of morpholine-derived glyoxamide. Stetter prodcuts **89**, **90**, **91**, and **92** were obtained in lower yield with around 80% ee, except **90** with 64% yield.

Scheme 16.

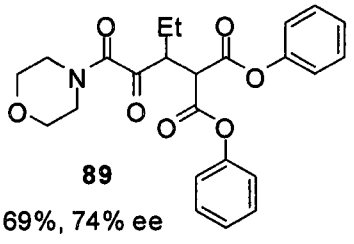




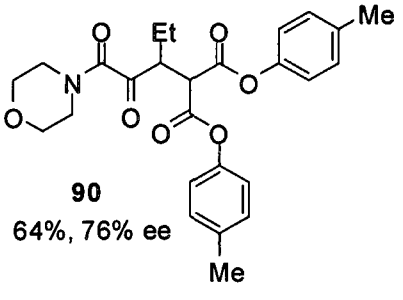
86
78%, 70% ee



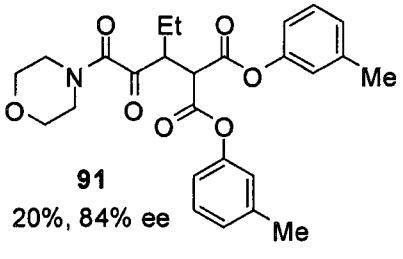
88
46%, 80% ee



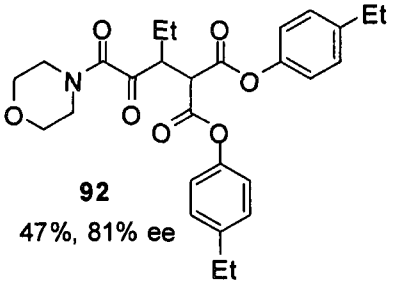
89
69%, 74% ee



90
64%, 76% ee



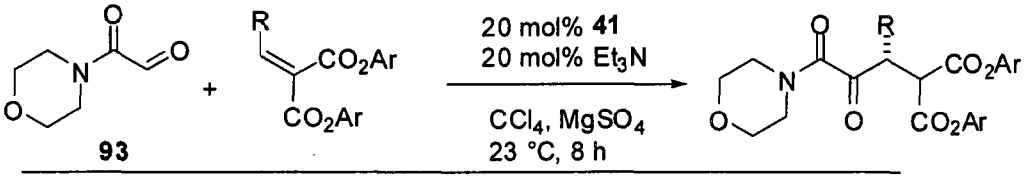
91
20%, 84% ee



92
47%, 81% ee

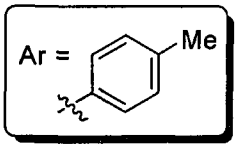
We briefly screened a series of substrates with p-methyl-phenyl substitutions (Table 13). A similar trend was found: the ee of product increased when the size of R group increased from methyl to butyl. Unfortunately, the best ee obtained with these substrates was only 81%.

Table 13.



93

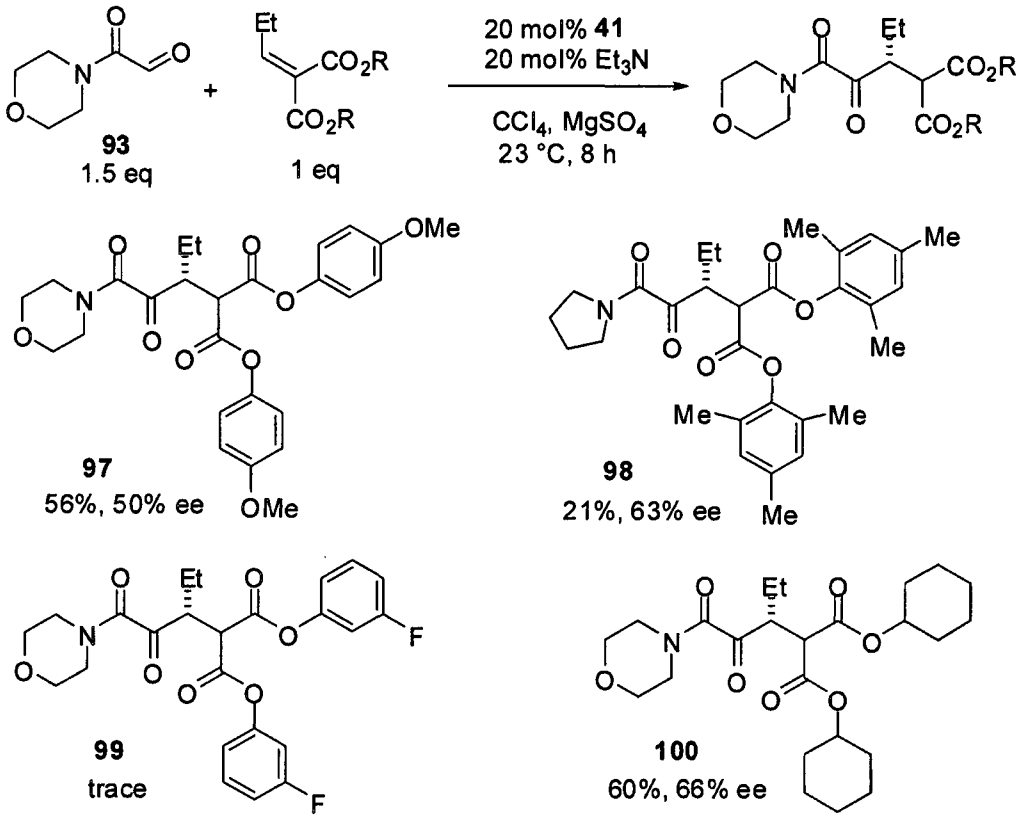
entry	R	product	yield (%)[a]	ee (%)[b]
1	Me	**94**	71	68
2	Et	**90**	64	76
3	Pr	**95**	51	79
4	Bu	**96**	61	81



a) All reactions conducted with 1 equiv of **93** and 2 equiv of Michael acceptor at 23 °C. b) See Table 3.

Scheme 17 shows the results of reaction with additional Michael acceptors. A methoxy-phenyl derived product **97** was obtained in 56% yield and 50% ee. Another bulkier substrate with mesityl groups gives product **98** in very low yield. Interestingly, product **99** is not obtained from a substrate with fluoro-phenyl substitution. A cyclohexyl substituted product is generated in 60% yield and 66% ee, a similar result to product **81** in Scheme 15.

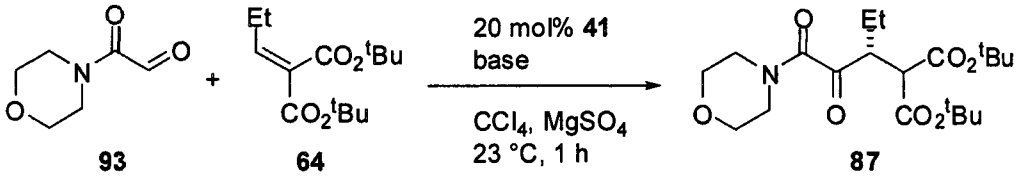
Scheme 17.



p) Influence of Low Temperature

Based on the previous substrate screens shown above, we decided to use **93** as our primary glyoxamide, and the di-tert-butyl malonate-derived Michael acceptor **64** was chosen to optimize the reaction conditions. An investigation on the influence of the number of base equivalents on the reaction is shown in Table 14. When stoichiometric base is used, the yield is dramatically increased (Table 14, entries 2-3). Also, Hunig's base leads to higher yields than triethylamine (Table 14, entry 3). We attempted to lower the concentration to improve ee, but the yield decreased (Table 14, entry 4). Similar results were found when less catalyst was used for the reaction (Table 14, entry 5). An aliquot experiment revealed that the product **87** was epimerized during the reaction at room temperature.

Table 14.



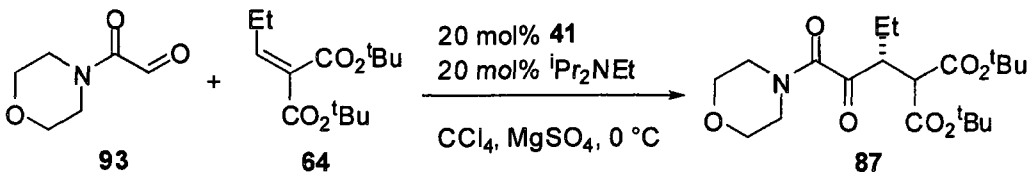
93 64 87

entry	base	yield (%)[a]	ee (%)[b]
1	20 mol% Et_3N	36	86
2	100 mol% Et_3N	86	82
3	100 mol% $^iPr_2NEt$	95	82
4		76	84[c]
5		74	82[d]

a) All reactions conducted with 1 equiv of **93** and 2 equiv of **64** at 23 °C, concentration = 0.25 M. b) See Table 3. c) Concentration = 0.08 M. d) 10 mol% **41**.

Considering that lower temperature may slow down or prevent the epimerization, we did a control experiment at 0 °C (Table 15). We were delighted to find the ee of product **87** increases to 90% when the reaction is done at 0 °C. The ee of product started to decrease a small amount when the reaction time was longer than 12 hours. This result suggested to us to lower the reaction's temperature.

Table 15.



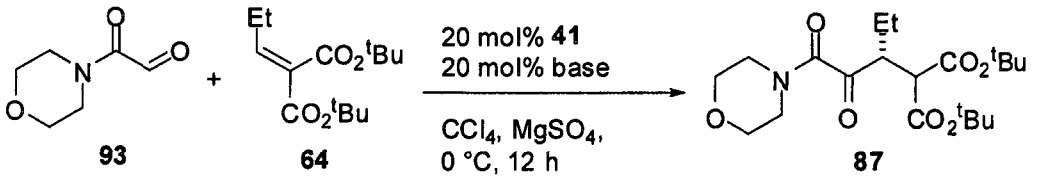
93 64 87

entry[a]	time (h)	ee (%)[b]
1	3	90
2	6	90
3	9	90
4	12	90
5	15	89
6	20	89
7	30	88

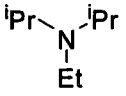
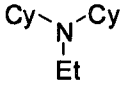
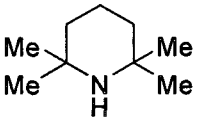
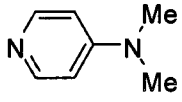
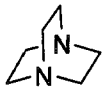
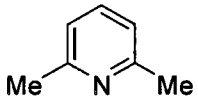
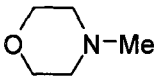
a) Reactions conducted with 1 equiv of **93** and 2 equiv of **64** at 0 °C. b) See Table 3.

We envisioned that using a bulkier base or weaker base might also diminish the epimerization of the product, so we screened a series of bases for the reaction at 0 °C and the results are shown in Table 16. Dicyclohexyl ethyl amine also gave the product in 90% ee (Table 16, entry 2). However, the reaction was slow and only 40% product was isolated in 40 hours. Another promising base is 2,2,6,6-tetramethyl piperidine, which gives product in 66% yield and 87% ee (Table 16, entry 3). DMAP leads to lower yield and ee (Table 16, entry 4), while DABCO gives similar yield, but much lower ee (Table 16, entry 5). 2,6-dimethyl pyridine and N-methyl-morpholine failed to provide any desired product (Table 16, entry 6-7).

Table 16.



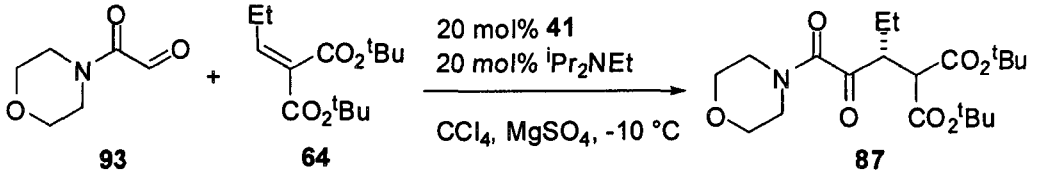
93 64 87

entry		yield (%)[a]	ee (%)[b]
1		41	90
2		40[c]	90
3		66	87
4		55	83
5		53	32
6		0	NA
7		0	NA

a) See Table 15. b) See Table 3. c) Reaction time = 40 h.

Encouraged by the good enantioselectivity obtained at 0 °C, we further lowered the reaction temperature to -10 °C and the conversion and selectivity of the reaction was monitored by checking aliquot samples using HPLC (Table 17). We were happy to observe the expected result; the reaction was finished in 24 hours with excellent enantioselectivity.

Table 17.



93 64 87

entry	time (h)	conversion (%)[a]	ee (%)[b]
1	1	12	90
2	6	58	90
3	12	90	90
4	24	92	90
5	40	92	90

a) Reactions conducted with 1 equiv of **93** and 2 equiv of **64** at - 10°C. b) See Table 3.

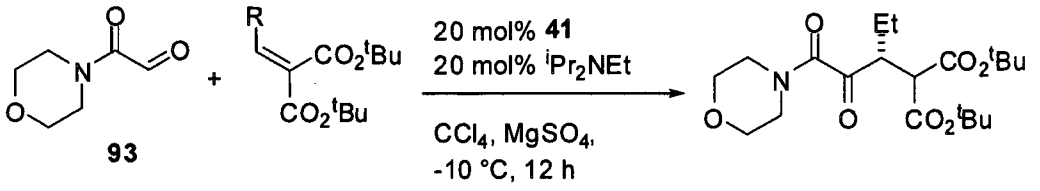
2.2.2 Substrate Scope

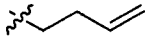
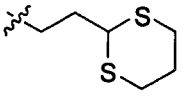
A series of Michael acceptors with different alkyl groups at the β-position were synthesized and subjected to the optimized reaction conditions (Table 18). By lowering the temperature and using 100 mol% Hunig's base, Stetter adduct **87** has been isolated in 84% yield and 90% ee (Table 18, entry 2). Longer alkyl chains offer nearly the same results (Table 18, entries 3, 4). However, a methyl substituent is more vulnerable to epimerization (Table 18, entry 1). A 12 h reaction time led to product **102** in 97% yield with 81% ee. Stopping the reaction after 3 h resulted in 68% yield and 87% ee. The substrate containing a bulkier iso-butyl side-chain requires a longer reaction time (28 h) without any loss of enantioselectivity (Table 18, entry 5).[35] The reaction is also tolerant

[35] A Michael acceptor with an iso-propyl β-substituent was subjected to the same reaction conditions at 23°C but did not afford any Stetter adduct.

of a wide range of functional groups, such as protected alcohol, alkyl chloride, protected amine, alkene, and protected aldehyde (entries 6-12).

Table 18.



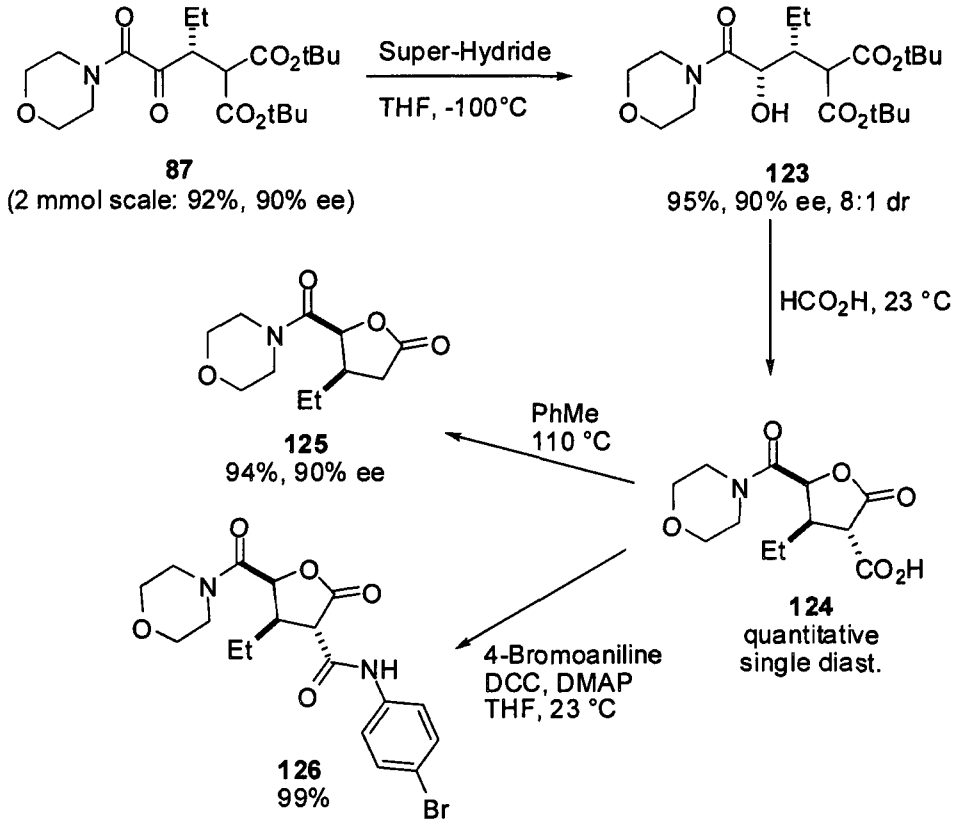
entry	R	substrate	product	yield (%)[a]	ee (%)[b]
1	Me	101	102	68[c]	87
2	Et	64	87	84	90
3	Pr	103	104	83	90
4	Bu	105	106	70	90
5	^{i}Bu	107	108	51[d]	91
6	CH_2CH_2Ph	109	110	81	88
7	CH_2CH_2OBn	111	112	91[e]	80
8	$CH_2CH_2OTBDPS$	113	114	50	80
9	$CH_2CH_2CH_2Cl$	115	116	84	81
10	CH_2CH_2NHTs	117	118	20	64
11		119	120	97	89
12		121	122	88	84

a) All reactions conducted with 1 equiv of **93** and 2 equiv of Michael Acceptor at -10 °C.
b) See Table 3. c) Reaction time = 3 h. d) Reaction time = 28 h. e) Reaction time = 6 h.

2.2.3 Product Derivatization

A 2 mmol-scale experiment allowed us to isolate pure Stetter adduct **87** in 92% yield and 90% ee along with a 100% recovery of excess **64** (Scheme 18).[36] The α-ketoamide product **87** can be further functionalized to afford different useful intermediates. Chemo- and diastereoselective reduction of **87** affords the secondary alcoho **123** in 8:1 dr, favoring the syn diastereomer.[37] Concomitant deprotection of the esters and lactonization can be accomplished in neat formic acid leading to **124**. Finally, thermal decarboxylation was performed to provide disubstituted lactone **125**. Importantly, this sequence of events leads to no epimerization, affording the final material in 90% ee.

Scheme 18.



[36] Dr. Stéphane Perreault did this scale up experiment and the following functionalization of the product **87**.
[37] Absolute configuration and relative stereochemistry were assigned by X-ray structure analysis of **126** and **124**. The opposite diastereomer of **123** is formed in Et_2O at -78°C (3:1 dr).

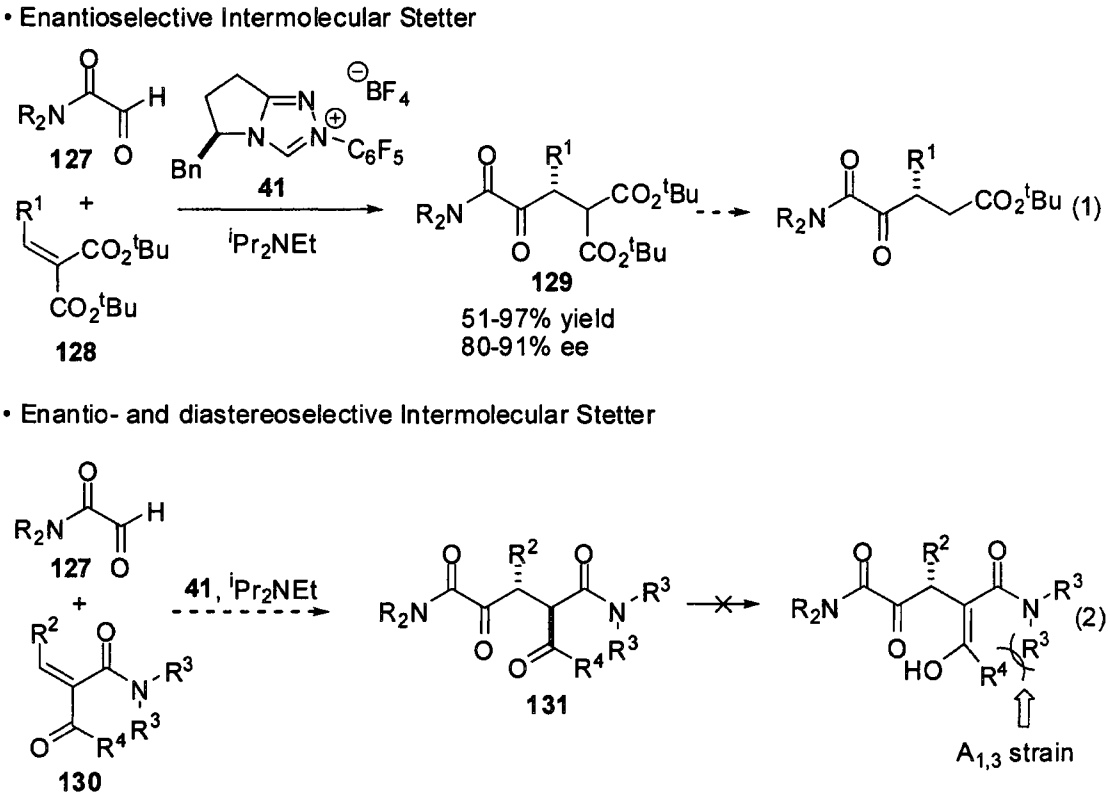
2.3 Diastereoselective Intermolecular Stetter Reaction of Glyoxamide

2.3.1 The Research Goal

A shortcoming of the use of alkylidene malonates is the need for the second ester group (Scheme 19, eq 1). We considered that the use of alkylidene ketoacid derivatives would provide an opportunity to incorporate synthetically useful substitutents on the second carbonyl, with the caveat that substrate synthesis could be a complication (Scheme 19, eq 2). More significantly, the reaction would generate diastereomers, a situation that could be rectified through the use of alkylidene ketoamides. We have already demonstrated that the protonation event in the asymmetric Stetter is highly diastereoselective [4d] and it has been well documented that tertiary β-ketoamides, bearing a stereocenter between the carbonyls, are configurationally stable due to strong $A_{1,3}$ strain in the enolate. Interestingly, catalytic asymmetric transformations that generate ketoamide stereocenters are surprisingly rare. [38]

[38] a) J. Clariana, N. Gálvez, C. Marchi, M. Moreno-Mañas, A. Vallribera, E. Molins, *Tetrahedron* **1999**, *55*, 7331-7344; b) V. K. Aggarwal, A. J. Belfield, *Org. Lett.* **2003**, *5*, 5075-5078; c) D. Yang, Y.-L. Yan, K.-L. Law, N.-Y. Zhu, *Tetrahedron* **2003**, *59*, 10465-10475.

Scheme 19.

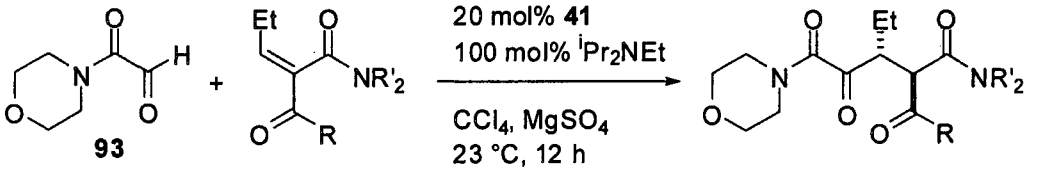


2.3.2 Reaction Condition Optimization

Knoevenagel reaction of various ketoamides and aldehydes generates the requisite substrates **130** as single olefin isomers. Adducts were subjected to our previously developed reaction conditions (Table 19). At ambient temperature, the carbene derived from triazolium salt **41** catalyzes the reaction of glyxoamide **93** with β-keto-amide-derived Michael acceptors in good to excellent yield and high diastereoselectivities. As shown in Table 19, when R = R' = methyl in Michael acceptor, the product **132** is isolated in 68% yield, 82% ee and 6:1 dr (Table 1, entry 1). When the diethylamide was employed, the product **133** is obtained in similar yield, but lower ee (Table 1, entry 2). Interestingly, the dr of **133** increases to 14:1. A Weinreb amide analogue **134** was generated in quantitative yield, but with much lower selectivities (Table 1, entry 3). We

switched the R group from methyl to phenyl while keeping R' as methyl, and observed an almost racemic product **135** (Table 1, entry 4). Finally, with larger ketone substituents, the product **136** was affored in 92% yield, 89% ee and 5:1 dr; lastly we found that optimal conditions involved conducting the reaction at 0 °C.

Table 19.

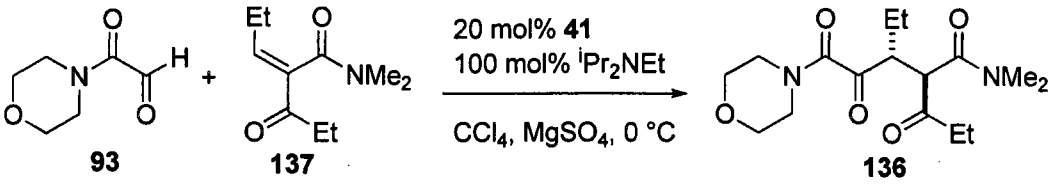


entry	R	R'	product	yield (%)[a]	ee (%)[b]	dr[c]
1	Me	Me	**132**	68	82	6:1
2		Et	**133**	66	77	14:1
3		Me, OMe[d]	**134**	100	15	2:1
4	Ph	Me	**135**	60	7	14:1
5	Et	Me	**136**	92	89	5:1
6			**136**	90[e]	92	12:1

a) Reaction conducted with 1 equiv of 1 and 2 equiv of Michael acceptor at 23 °C. b) See Table 3. c) Diastereomer ratio determined by NMR. d) N-methoxy-N-methylamide was used. e) Reaction conducted at 0 °C.

A primary concern on the outset of this study was the configurational stability of the newly formed stereocenters. A control experiment using 20 mol% precatalyst **41** and one equivalent Hunig's base was performed in carbon tetrachloride at 0 °C, shown in Table 20. It was found the yield of **136** increases almost linearly with reaction time and the reaction was complete in 12 hours (Figure 1). Fortunately, no epimerization was observed during the reaction under basic conditions, which is consistent with our hypothesis.

Table 20.

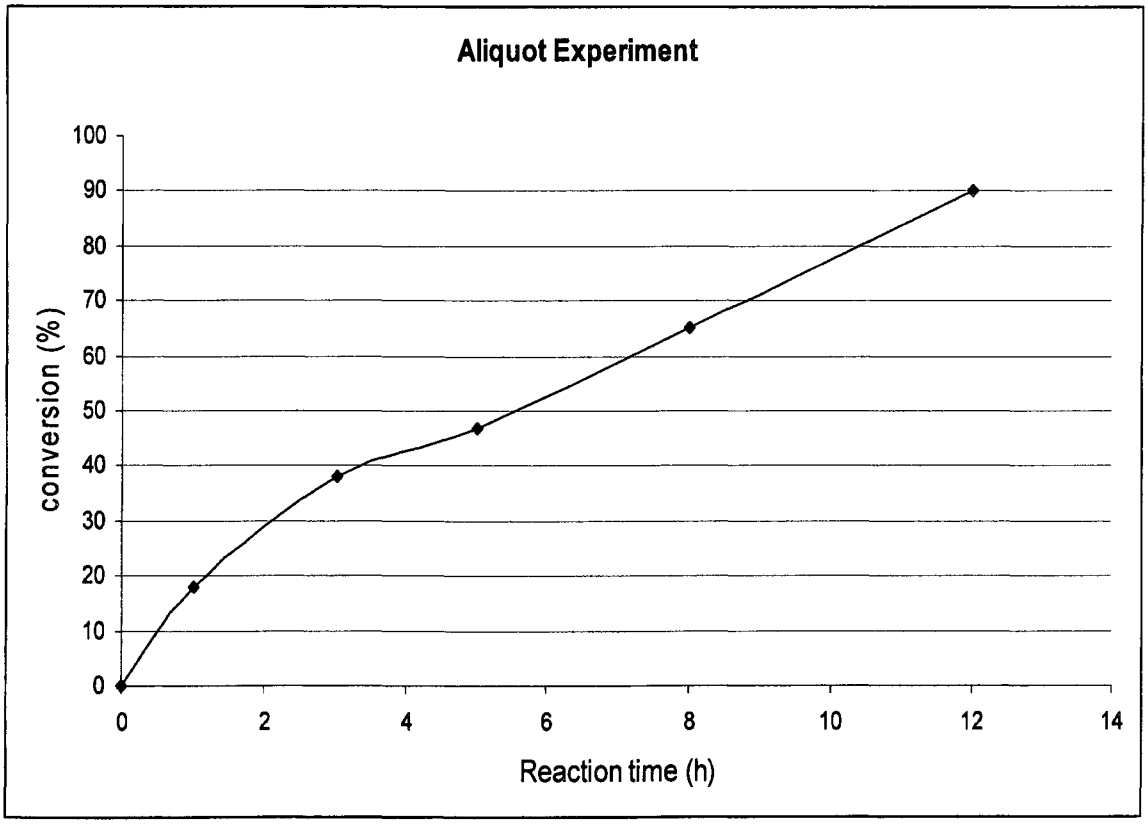


93 137 136

entry	time (h)	conversion (%)[a]	ee (%)[b]
1	1	18	92
2	3	38	92
3	5	47	92
4	8	65	92
5	12	90	92

a) Reactions conducted with 1 equiv of **93** and 2 equiv of **137** at 0 °C. b) See table 3.

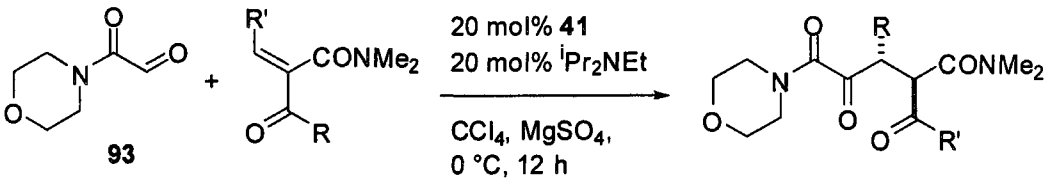
Figure 1.

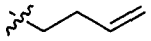
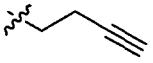
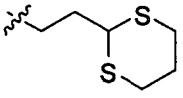
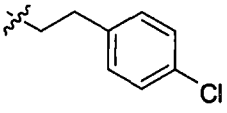
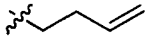


2.3.3 Substrate Scope

A series of Michael acceptors with different substitution were synthesized and tested using the optimized reaction conditions, with the results shown in Table 21. When R' is a methyl group, the product **140** is obtained in excellent yield and good ee, with 7:1 dr (Table 21, entry 1). Similar results are observed with other alkyl substituents (Table 21, entry 3-5). The reaction also tolerates a variety of functional groups; substrates with tethered benzyl ether, olefin, alkyne and phenyl give desired products in excellent enantioselectivities and good diastereoselectivities (Table 21, entry 6, 7, 9, 10). Compounds with tethered halogen or protected aldehyde were also obtained in good yield and good stereoselectivities (Table 21, entry 8, 11). Substrates with different R groups were also made and subjected to the optimized reaction conditions. When R is propyl while R' is ethyl, the Stetter adduct **160** is generated in 92% yield, 92% ee and 11:1 dr (Table 21, entry 12). As R' was changed to a tethered aromatic group, the ee's increased although the yield and dr decreased (Table 21, entry 13). Finally substrate **163** with a tethered olefin R group leads to product **164** with excellent yield and excellent ee and dr.

Table 21.



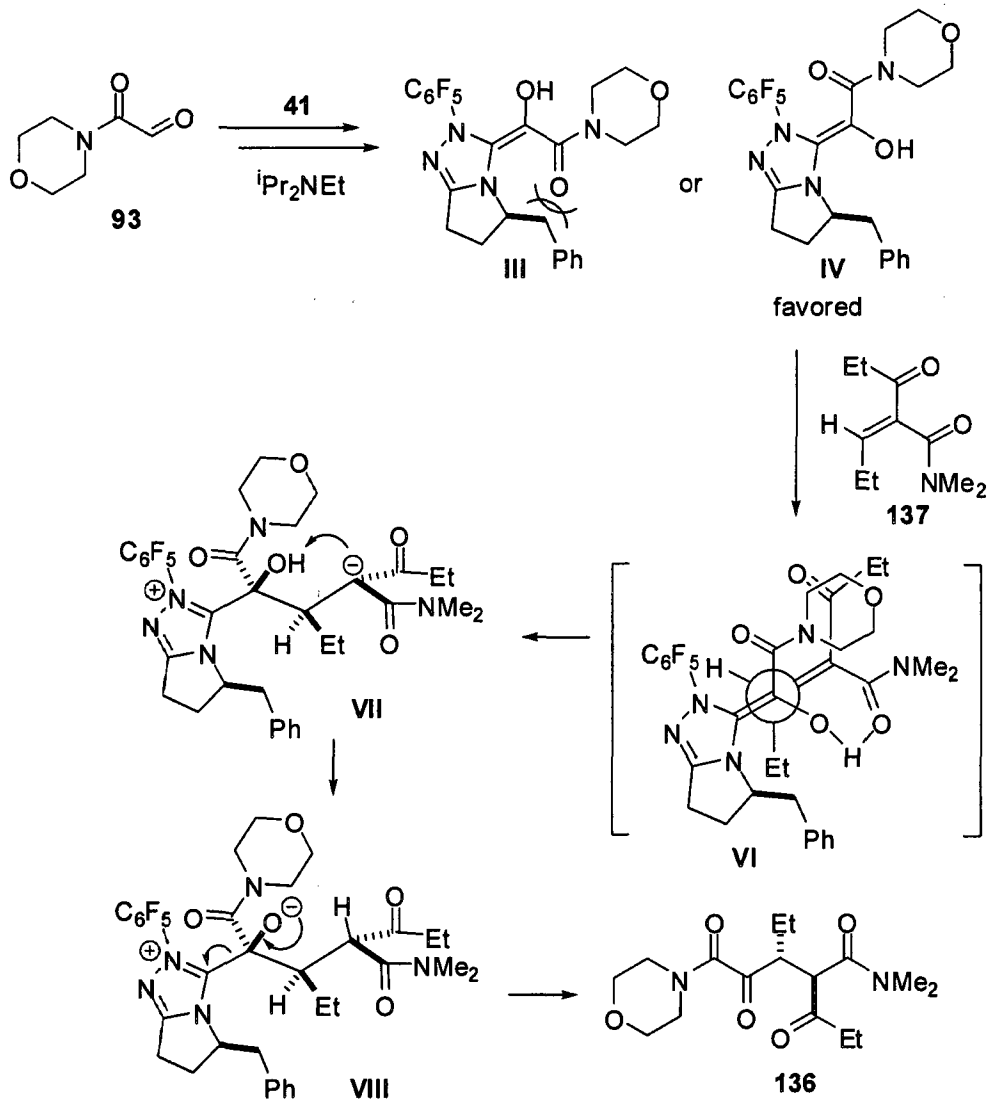
entry	R	R'	substrate	product	yield (%)[a]	ee (%)[b]	dr[c]
1	Et	Me	**138**	**139**	95	89	7:1
2		Et	**137**	**136**	90	92	12:1
3		Pr	**140**	**141**	81	90	6:1
4		Bu	**142**	**143**	71	92	12:1
5		^{i}Bu	**144**	**145**	44[d]	87	11:1
6		CH_2CH_2Ph	**146**	**147**	65	83	19:1
7		CH_2CH_2OBn	**148**	**149**	87	98	11:1
8		$CH_2CH_2CH_2Cl$	**150**	**151**	83	81	10:1
9			**152**	**153**	83	90	14:1
10			**154**	**155**	78	92	4:1
11			**156**	**157**	77	86	9:1
12	Pr	Et	**158**	**159**	92	92	11:1
13			**160**	**161**	64	94	5:1
14		Et	**162**	**163**	94	90	9:1

[a] All reactions conducted with 1 equiv of **93** and 2 equiv of Michael acceptor at 0 °C.
[b] See table 3. [c] See table 19. [d] Reaction time = 20h.

In order to explain the stereochemistry of this transformation, a plausible mechanism is proposed as in Scheme 20. Reaction of glyoxamide **93** with carbene derived from **41** will generate a nucleophilic olefin intermediate, which could have two

different conformers (**III** or **IV**). Nucleophilic 1,4-addition of the favored intermediate **IV** [39] to **137** generates the carbanion **VII**. The Michael acceptor **137** should approach **IV** from the bottom face to avoid interaction with the benzyl group in the catalyst, as shown in **VI**. The hydrogen bond between the enol and the amide could also play a directing role. An intramolecular proton transfer [27d] leads to the alkoxide intermediate **VIII**, which collapses to release the desired product **136**.[40]

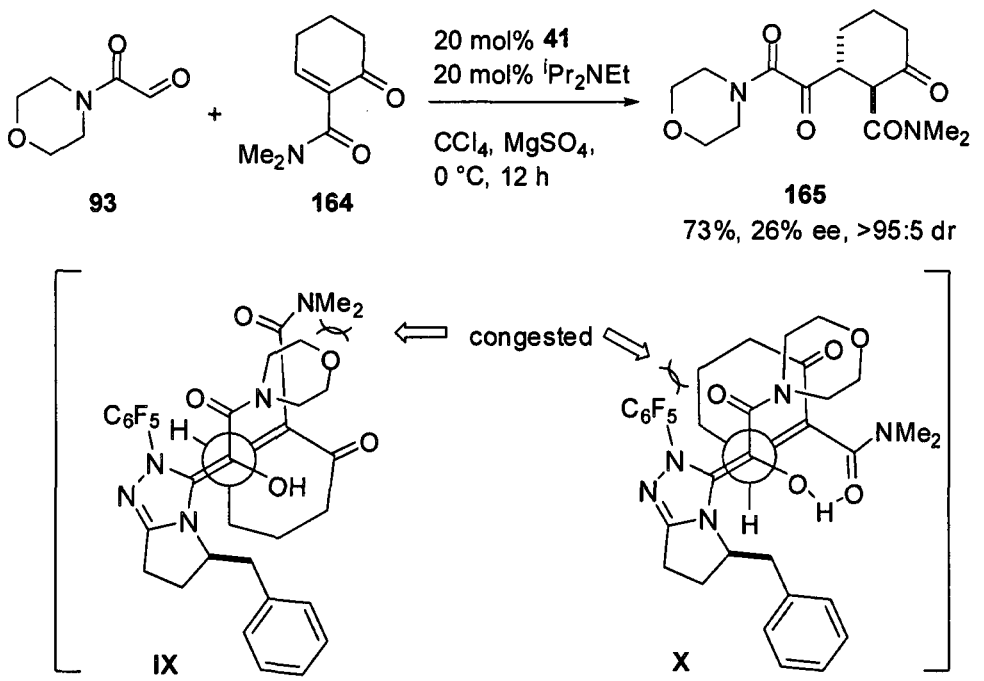
Scheme 20.



[39] T. Dudding, K. N. Houk, *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5770-5775.
[40] The stereochemistry of **136** was confirmed by single crystal XRD.

A cyclic Michael acceptor **164** was synthesized and subjected to the optimized reaction condition, Scheme 21. The desired product **165** was isolated in 73 % yield and excellent dr, but only with 26 % ee. To explain this surprisingly low ee of the product, the possible transition state **IX** and **X** were compared. Steric congestion exists in both **IX** and **X**, so there is no highly favored pathway in this reaction and both enantiomers are generated without good selectivity.

Scheme 21.

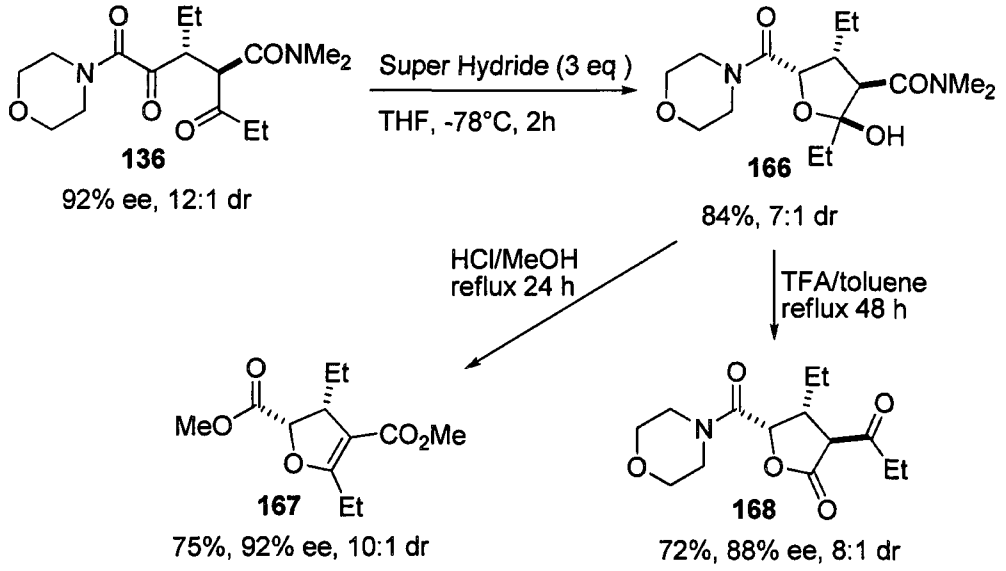


2.3.4 Product Derivatization

The obtained β-ketoamides have been further functionalized to useful building blocks for synthesis, Scheme 22. Reduction of **136** with Super Hydride at -78 °C affords hemiketal **166** in 84 % yield. Treatment of **166** with dry HCl in methanol at 60 °C gives a

tetra-substituted dihydrofuran sketelon **167**, which is a versatile intermediate[41] and also is a common skeleton of many natural products.[42] During this transformation, no epimerization is observed. When **166** is refluxed with TFA in toluene for 24 hours, another synthetically useful compound **168**[43] with three contiguous stereocenters is isolated in 72 % yield with a slightly lower ee.

Scheme 22.



[41] (a) Kawakami, H.; Ebata, T.; Koseki, K.; Okano, K.; Matsumoto, K.; Matsushita, H. *Heterocycles* **1993**, *36*, 665-669; (b) Le Menez, P.; Berque, I.; Fargeas, V. r.; Pancrazi, A.; Dau, M. E. T. H.; Ardisson, J. *Synlett* **1996**, *1996*, 1125-1128; (c) Lee, Y. R.; Kim, N. S.; Kim, B. S. *Tetrahedron Lett.* **1997**, *38*, 5671-5674; (d) Temme, O.; Taj, S.-A.; Andersson, P. G. *The Journal of Organic Chemistry* **1998**, *63*, 6007-6015; (e) Pettigrew, J. D.; Bexrud, J. A.; Freeman, R. P.; Wilson, P. D. *Heterocycles* **2004**, *62*, 445-452; (f) Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 11958-11959; (g) Pettigrew, J. D.; Wilson, P. D. *Org. Lett.* **2006**, *8*, 1427-1429; (h) Toth, F.; Kalaus, G.; Greiner, I.; Kajtar-Peredy, M.; Gomory, A.; Hazai, L.; Szantay, C. *Heterocycles* **2006**, *68*, 2301-2317; (i) Feducia, J. A.; Gagne, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 592-599; (j) Hayakawa, I.; Ueda, M.; Yamaura, M.; Ikeda, Y.; Suzuki, Y.; Yoshizato, K.; Kigoshi, H. *Org. Lett.* **2008**, *10*, 1859-1862.

[42] (a) Boeckman, R. K.; Yoon, S. K.; Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682-9684; (b) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T.; Kobayashi, M.; Kitagawa, I. *The Journal of Organic Chemistry* **1994**, *59*, 6606-6613; (c) Pirrung, M. C.; Lee, Y. R. *J. Am. Chem. Soc.* **1995**, *117*, 4814-4821; (d) Takao, K.-i.; Ochiai, H.; Hashizuka, T.; Koshimura, H.; Tadano, K.-i.; Ogawa, S. *Tetrahedron Lett.* **1995**, *36*, 1487-1490; (e) Aungst, R. A.; Funk, R. L. *J. Am. Chem. Soc.* **2001**, *123*, 9455-9456.

[43] (a) Rainka, M. P.; Milne, J. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6177-6180; (b) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14977-14985; (c) Ramazonov, N. S.; Syrov, V. N. *Chem. Nat. Compd.* **2006**, *42*, 558-561; (d) Akiyama, K.; Maruyama, M.; Yamauchi, S.; Nakashima, Y.; Nakato, T.; Tago, R.; Sugahara, T.; Kishida, T.; Koba, Y. *Biosci., Biotechnol., Biochem.* **2007**, *71*, 1745-1751; (e) Kim, H.; Wooten, C. M.; Park, Y.; Hong, J. *Org. Lett.* **2007**, *9*, 3965-3968; (f) Nakato, T.; Yamauchi, S. *J. Nat. Prod.* **2007**, *70*, 1588-1592; (g) Fillion, E.; Carret, S.; Mercier, L. G.; Trepanier, V. E. *Org. Lett.* **2008**, *10*, 437-440.

2.4 Conclusion

In conclusion, we have developed an asymmetric intermolecular Stetter reaction involving glyoxamides. A variety of β-substituted alkylidenemalonates undergo the enantioselective reaction in good yield with high asymmetric induction in the presence of a phenylalanine-derived carbene catalyst. When alkylidene ketoamides are employed, the reactions afford desired β-ketoamides in good yields, excellent enantioselectivities and good diastereoselectivities. In both cases, the obtained Stetter products were further functionalized to afford useful building blocks for organic synthesis.

Chapter 3

N-Heterocyclic Carbene Catalyzed Redox Reaction of ynal

3.1 Introductions

Catalysis of umpolung reactivity of aldehydes has been extensively studied in the last decade. Among this family of transformations, the most notable reactions are Benzoin[44] and Stetter[45] reactions, which have been developed asymmetrically using chiral N-heterocyclic carbene (NHC) catalysts to a great extent.[46] In Benzoin or Stetter reactions, aldehyde **1** is converted to intermediate **3** catalyzed by NHC **2** (Scheme 1). The nucleophilic intermediate **3** can react with electrophiles such as aldehyde **1** (Benzoin reaction; Scheme 1, eq 1) or Michael acceptor **4** (Stetter reaction; Scheme 1, eq 2). Concurrently, it has been found that if the aldehyde bears an alpha leaving group, such as **7** in Scheme 2, the intermediate **8** can eliminate the leaving group instead of reacting with an electrophile. This elimination results in an enol intermediate **9** which can tautomerize to an activated carboxylate **10**, which is further capable of reacting with a nucleophile to afford product **11** (Scheme 2). This reaction manifold is termed "redox reactivity" because it results in a net oxidation of the aldehyde to an acyl derivative and concomitant reduction at the α position of the aldehyde. α-Haloaldehydes,[47] α,β-epoxy and α,β-

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[44] a)Wohler, F.; Liebig, J. *Ann. Pharm.* **1832**, *3*, 249-282. b) Lapworth, A. *J. Chem. Soc., Trans.* **1903**, *83*, 995-1005. c) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726.

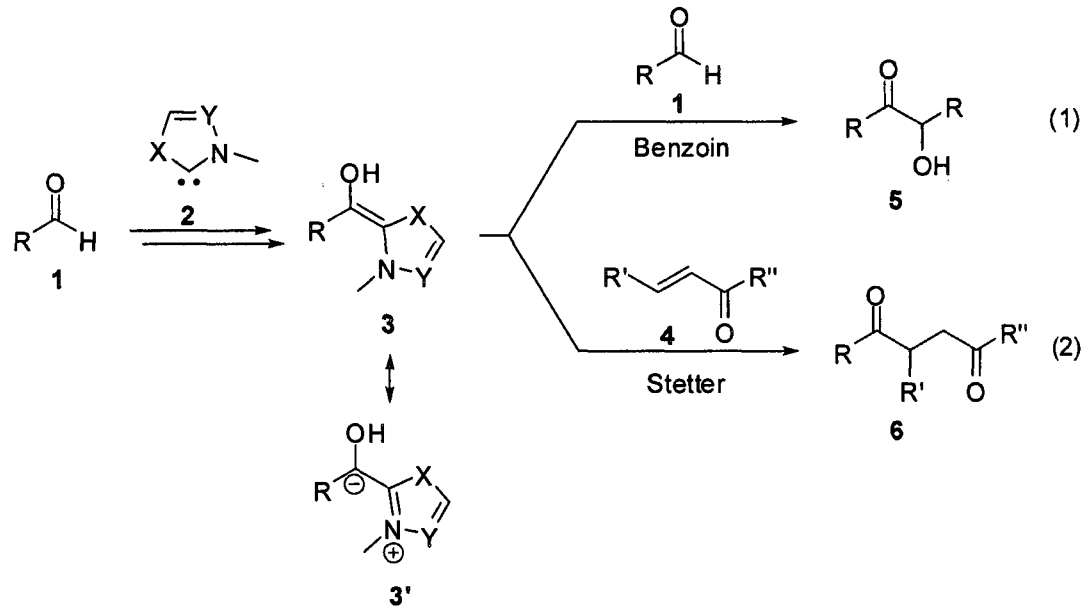
[45] a) Stetter, H.; Schrecke.M *Angew. Chem.-Int. Edit. Engl.* **1973**, *12*, 81-81. b) Stetter, H.; Kuhlmann, H. *Organic Reactions* **1991**, *40*, 407-496.

[46] a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534-541. b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606-5655. c) Rovis, T. *Chem. Lett.* **2008**, *37*, 2-7.

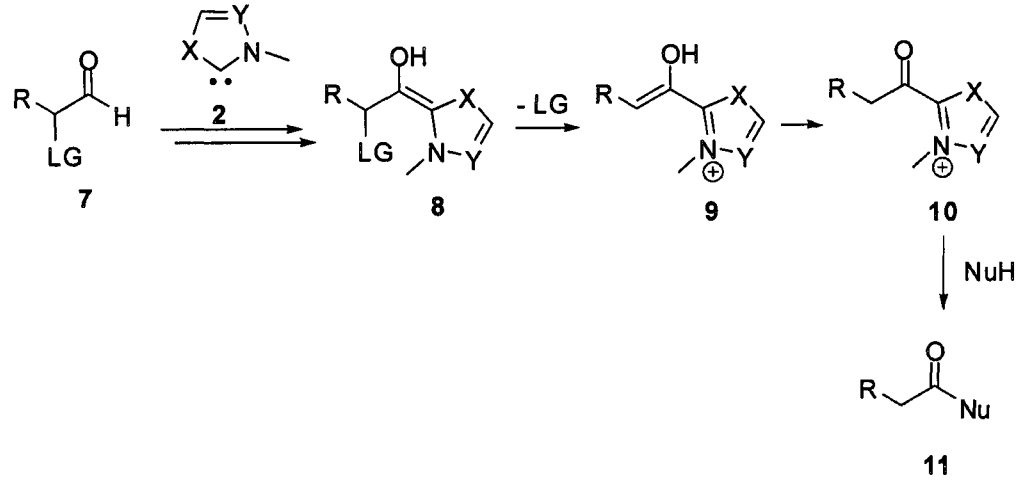
[47] a) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518-9519. b) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406-16407. c) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088-15089.

aziridinyl aldehyde [48] have been employed in this type of reactions, and this represents a growing field in organic synthesis.

Scheme 1.



Scheme 2.

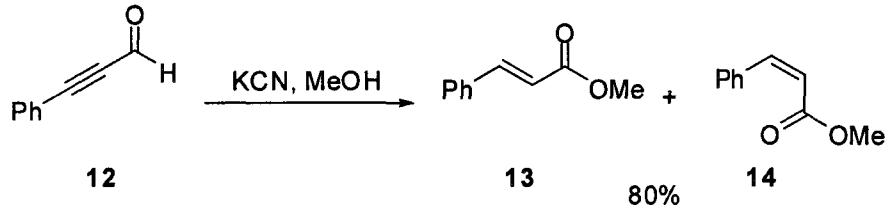


In addition to aldehydes bearing leaving groups, α,β-unsaturated aldehydes can also undergo the redox reaction. An early example of redox reaction of α, β-unsaturated

[48] a) Chow, K. Y.-K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126-8127 b) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796-13797. c) Vora, H. U.; Moncecchi, J. R.; Epstein, O.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 9727-9731.

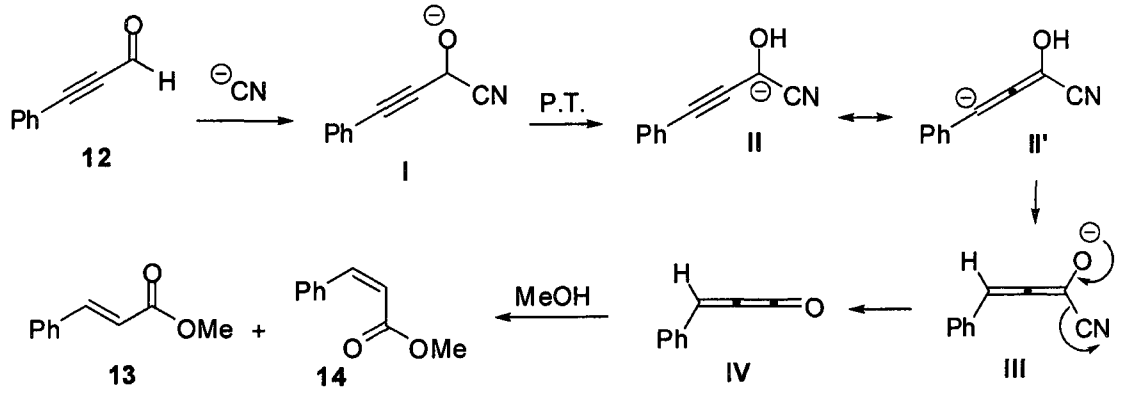
aldehyde was reported by Walia and coworkers in 1969.[49] Treatment of 3-phenylprop-2-ynal (**12**) with one equivalent of potassium cyanide in methanol afforded a 1:1 mixture of methyl esters **13** and **14** in 80% yield (Scheme 3). In this case, a degree of unsaturation is lost at the α position while the aldehyde is oxidized to an ester.

Scheme 3.



The proposed mechanism is shown in Scheme 4. The ynal **12** react with cyanide to generate an alkoxide intermediate **I**, which is converted to a stabilized carbanion **II** after proton transfer. This species protonates through resonance structure **II'** to give allenolate **III**, which releases the cyanide to generate phenylpropadienone (**IV**). Addition of methanol to **IV** then affords the mixture of esters **13** and **14**.

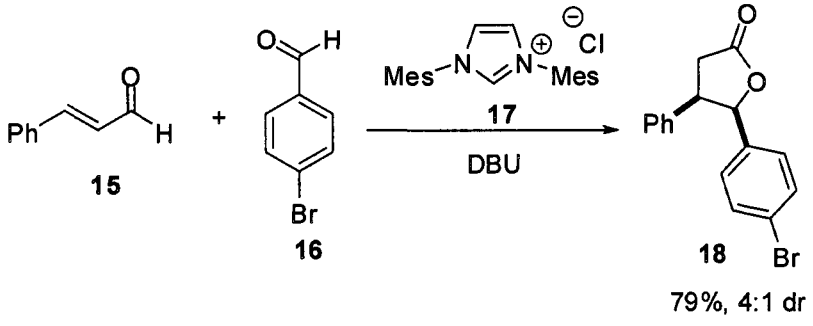
Scheme 4.



[49] Walia, J. S.; Vishwakarma, L. C. *J. Chem. Soc. D: Chem. Comm.* **1969**, 396.

In 2004, Bode[50] published the syntheses of γ-butyrolactones such as **18** from trans-cinamaaldehyde (**15**) through a homoenolate intermediate. When imidazolium salt **17** was used as catalyst precursor for the reaction, the cis-diastereomer **18** was obtained in good yield (Scheme 5). Simultaneously, Glorius and coworkers reported the same approach. [51]

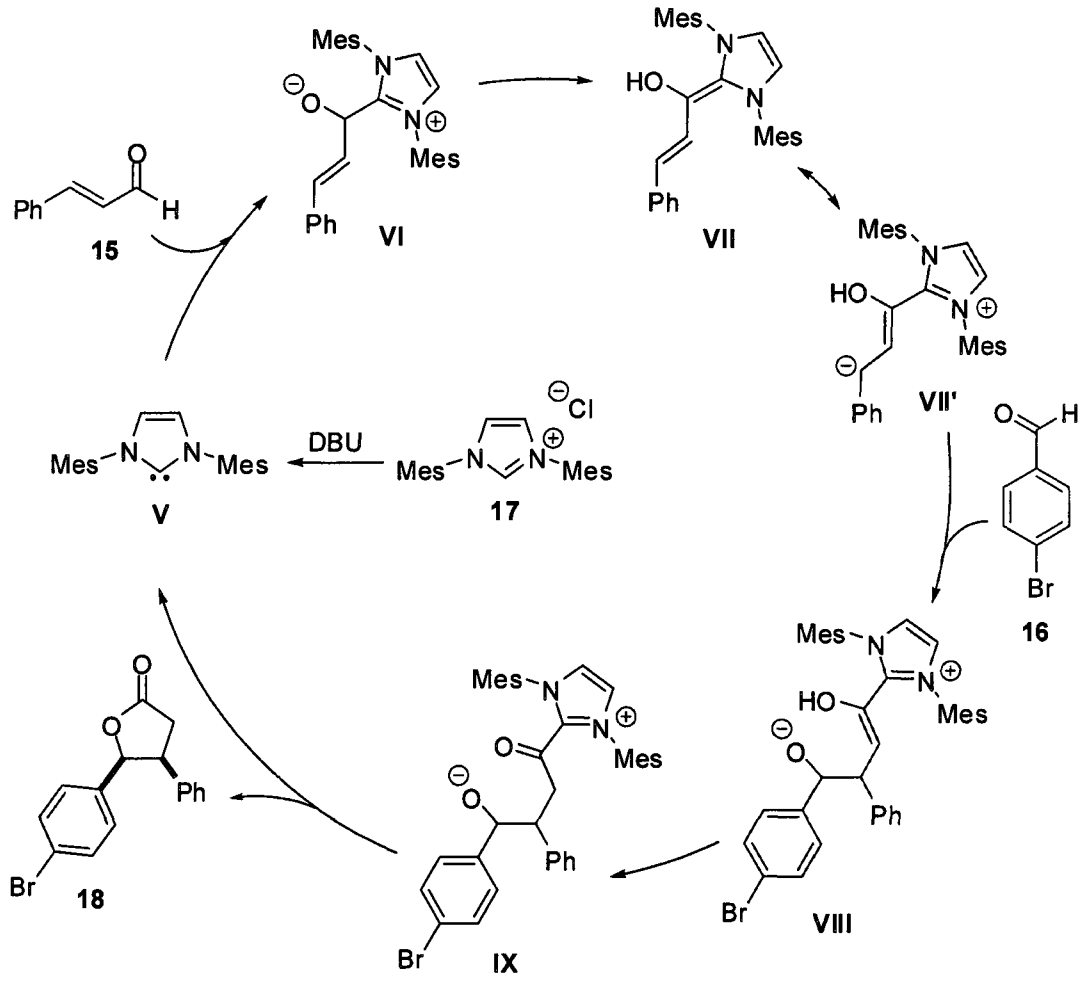
Scheme 5.



The proposed catalytic cycle begins with the reaction of the aldehyde **15** with carbene **V** generated in situ from **17.** The resulting alkoxide intermediate **VI** is then converted to vinylogous enamine **VII** after proton transfer. This intermediate reacts as a "homoenolate" as seen in resonance structure **VII'**, intercepting aldehyde **16** to generate the enol **VIII**. Tautomerization of **VIII** leads to acylimidazolium intermediate **IX**, which is an activated carboxylate. Intramolecular attack of the alkoxide at the carbonyl group regenerates the carbene catalyst **V** and produces the γ-butyrolactone **18** (Scheme 6).

[50] Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370-14371.
[51] Burstein, C.; Glorius, F. *Angew. Chem.-Int. Edit.* **2004**, *43*, 6205-6208.

Scheme 6.



Scheidt and coworkers have reported the conversion of trans-cinamaaldehyde (**15**) into saturated ester **20** catalyzed by carbene generated from **19** (Scheme 7).[52] Homoenolate **X"** is protonated to generate enol **XI**, which is tautomerized to intermediate **XII**. The activated carboxylate **XII** is trapped with benzyl alcohol to afford saturated ester **20**. A similar reaction was also documented concurrently by Bode and coworkers.[53]

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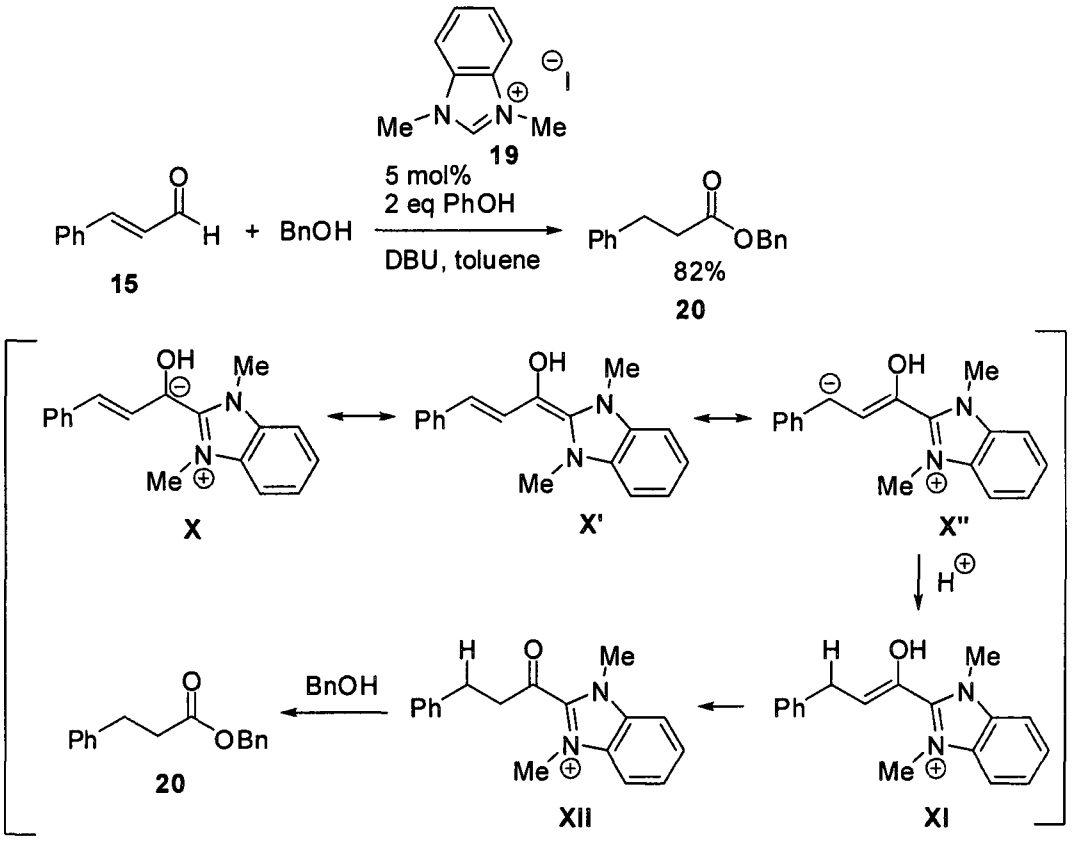
[52] Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905-908.
[53] Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873-3876.

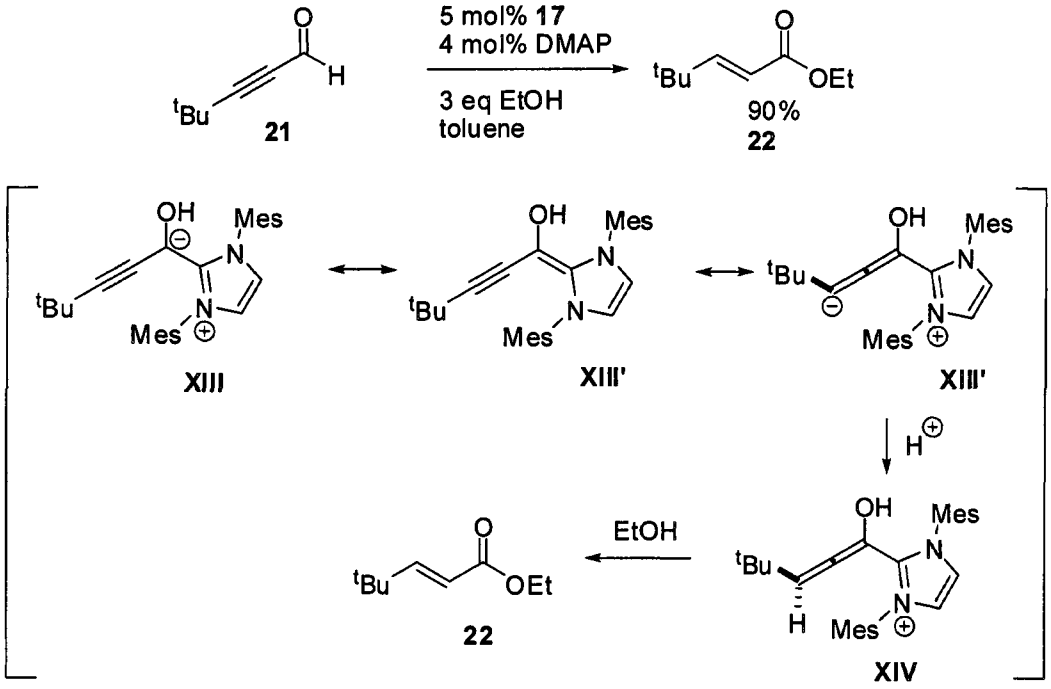
Scheme 7.



In 2006, Zeitler and coworkers reported a carbene catalyzed redox esterification of 4,4-dimethylpent-2-ynal (**21**).[54] Similar to the work of Scheidt and Bode, the proposed catalytic cycle also includes a formation of homoenolate **XIII**. In this case, protonation of **XIII** leads to formation of an α,β-unsaturated ester **22** with a greater than 95:5 E /Z ratio (Scheme 8).

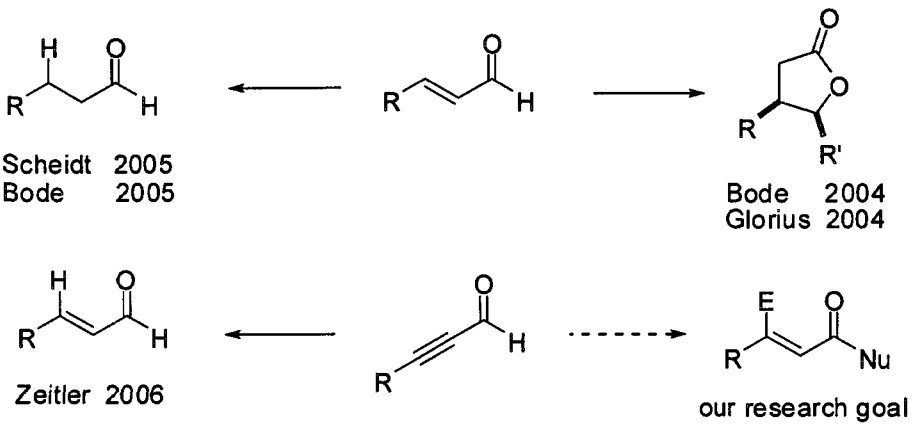
[54] Zeitler, K. *Org. Lett.* **2006**, *8*, 637-640.

Scheme 8.



While enal-derived homoenolates have been quenched with fairly complicated electrophiles, [7, 8] homoenolates generated from ynals have only been trapped with proton sources.[11] We envisioned that an ynal-derived homoenolate could potentially react with electrophiles to generate interesting compounds (Scheme 9). If a chiral catalyst is used, the reaction could be rendered asymmetric. Herein, we report enantio- and diastereoselective redox reactions of ynal-derived homoenolates with Michael acceptors catalyzed by chiral triazolylidene carbenes.

Scheme 9.


H
O
R
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Scheidt 2005
Bode 2005
R
H
O
O
O
R
R'
Bode 2004
Glorius 2004
H
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H
Zeitler 2006
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H
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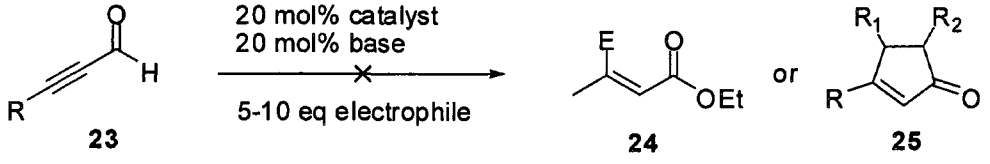
E
O
R
Nu
our research goal

3.2 Experiments and Results

3.2.1 Intermolecular Redox Reaction of Ynal with Michael Acceptors

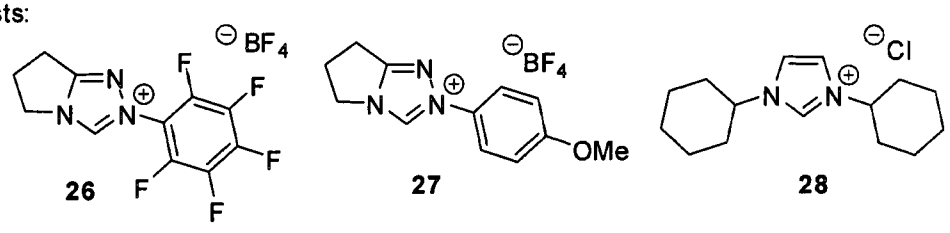
Our investigation started with attempts at trapping the ynal-derived homoenolate with different types of electrophiles (Scheme 10). We screened different ynals, catalysts, electrophiles, bases, solvents and reaction temperatures. While ynal **23** readily reacted with carbene catalysts, the intermediate was never converted to desired products such as α,β-unsaturated ester **24** or lactone **25**.

Scheme 10.

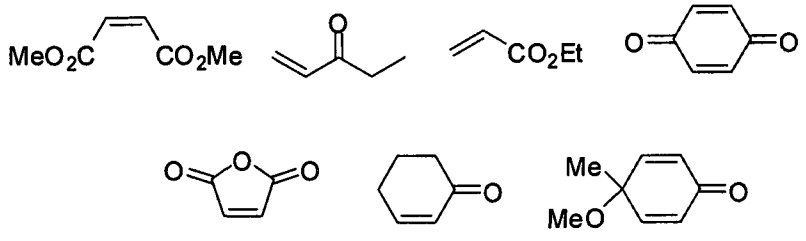


R: n-Pentyl, Phenyl, CH_2OBn

Catalysts:



Electrophiles:



Bases: Et_3N, KHMDS, DMAP

Solvents: toluene, DCM, THF, EtOH

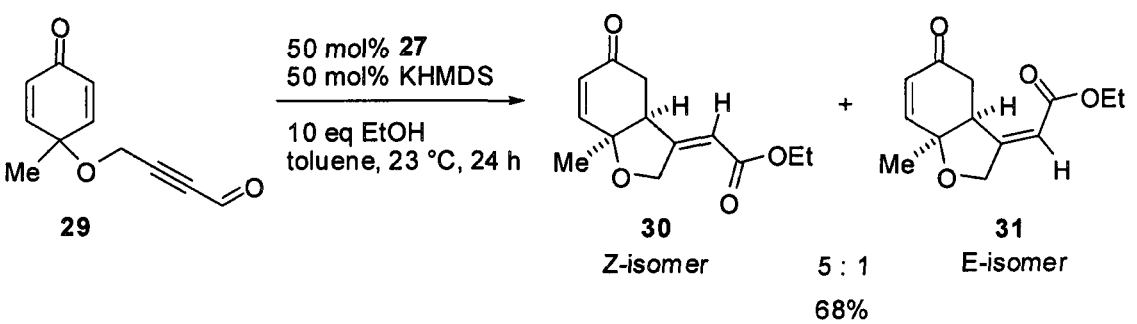
Reaction temperature: 23 °C, 60 °C.

3.2.2 Intramolecular Redox Reaction of Cyclohexadienone -tethered Ynal

a) An Unexpected Result

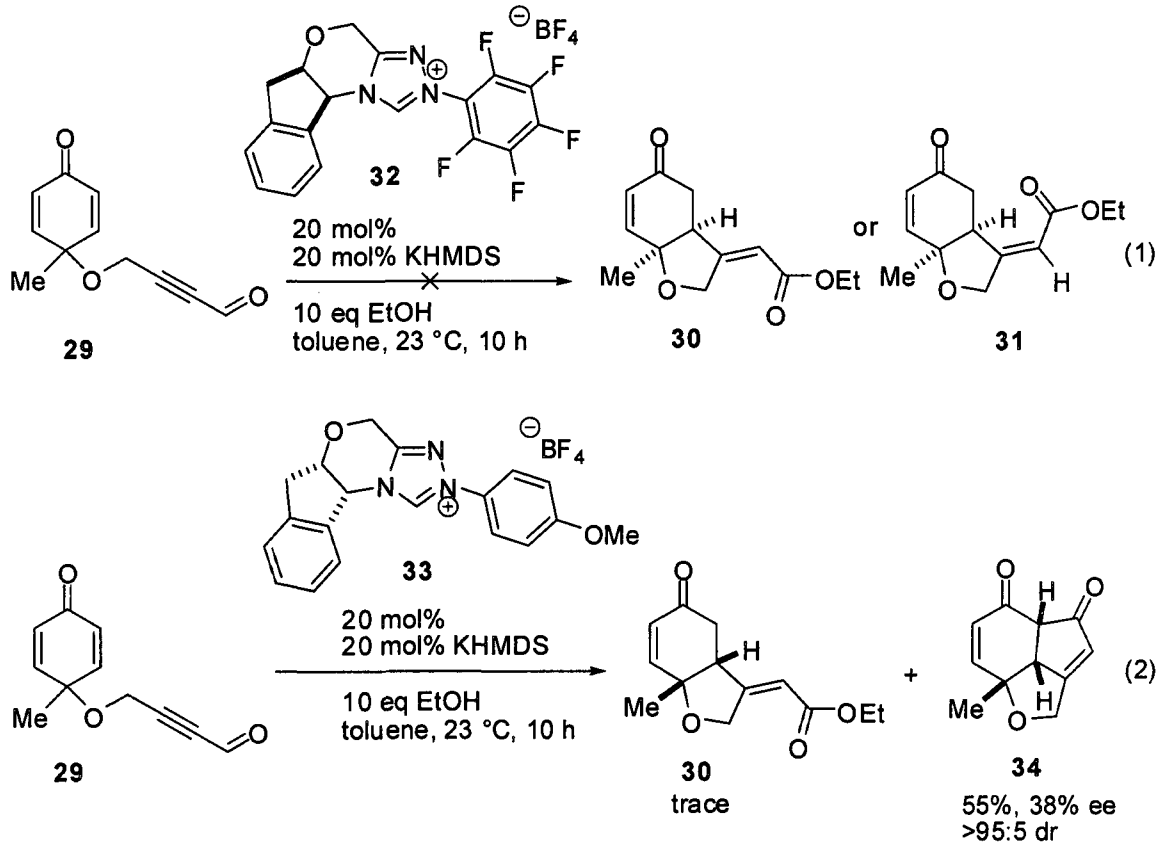
We considered that the intramolecular reaction of an ynal might have a better chance to afford desired product. Therefore, we synthesized cyclohexadienone-tethered ynal **29** using the dearomatization strategy described in chapter 1. Substrate **29** was subjected to 50 mol% **27** and 50 mol% KHMDS with 10 equivalent ethanol, which was used to quench the activated carboxylate and regenerate carbene. Desired products **30** and **31** were isolated in good yield and 5:1 ratio of Z/E isomer (Scheme 11).

Scheme 11.

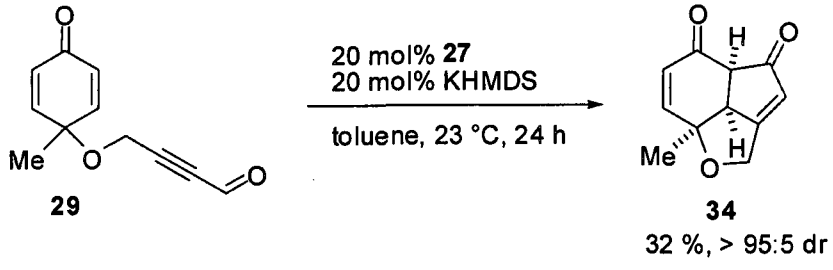


The substrate **29** was then subjected to reactions catalyzed by chiral carbene catalysts, with results shown in Scheme 12. The reaction with catalyst **32** and **33** did not afford expected product (Scheme 11, eq 1, 2). To our surprise, reaction with catalyst **33** led to a new product **34**, which is a tricyclic compound, formed in 38 % ee and >95:5 dr (Scheme 11, eq 2). To repeat this result, we subjected the substrate **29** to the reactions with achiral catalysts in toluene, with result shown in Scheme 13. Reaction catalyzed by **27** afforded **34** in 32 % yield, which confirmed the product could be generated without ethanol.

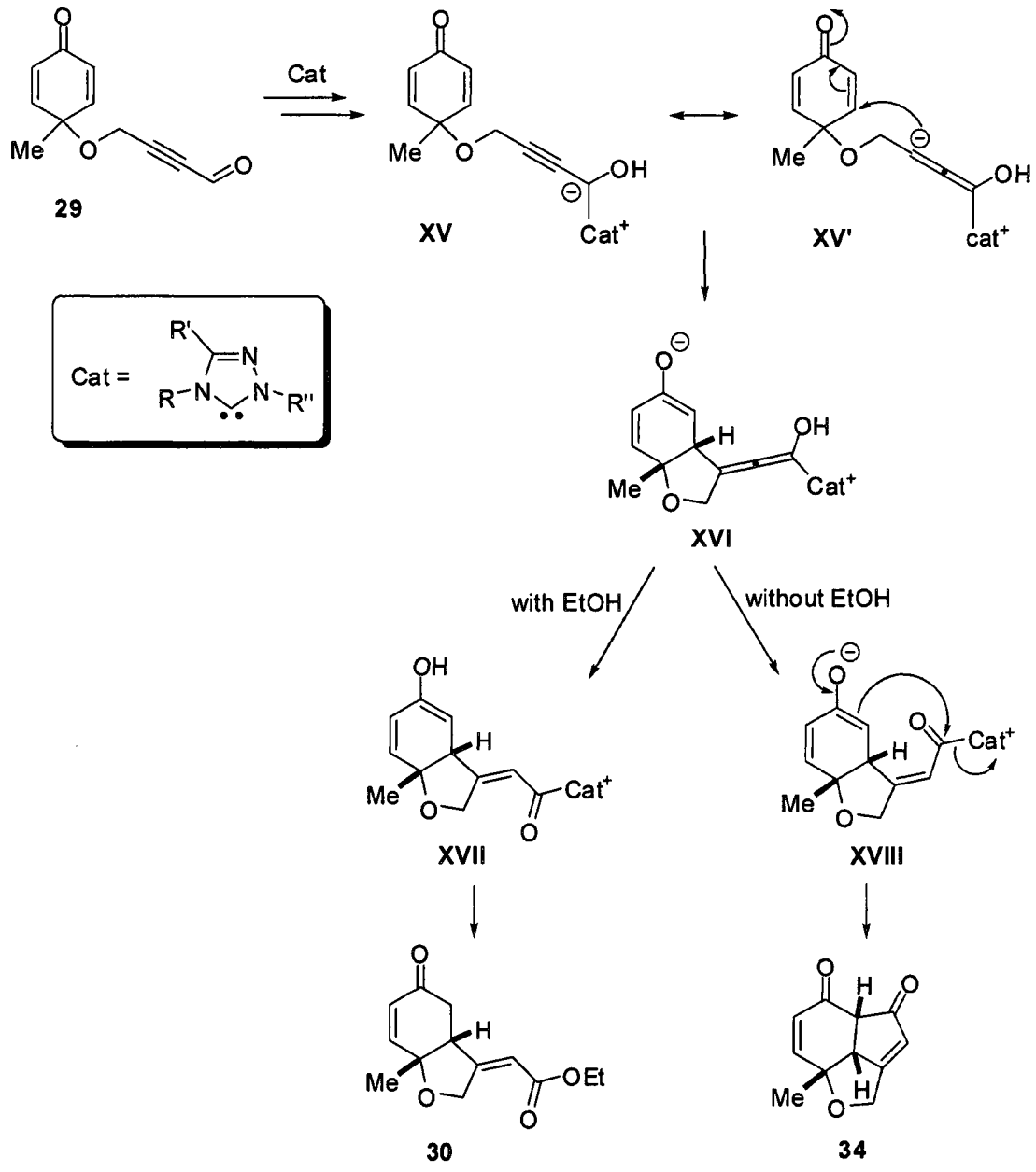
Scheme 12.



Scheme 13.



Scheme 14.



b) Proposed Mechanism

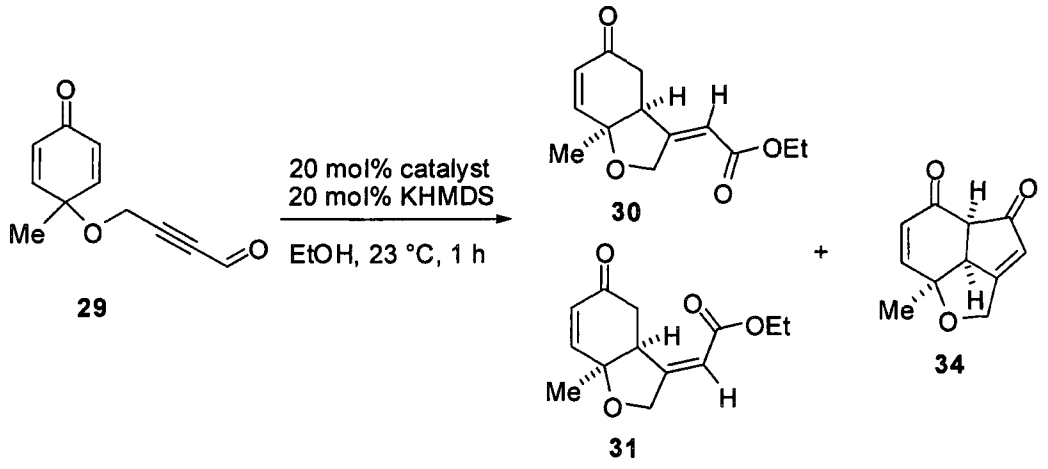
In order to explain the unexpected formation of **37**, we proposed a plausible mechanism shown in Scheme 14. Reaction between **29** and carbene catalyst leads to the carbanion intermediate **XV**. An intramolecular nucleophilic attack generates an allenol intermediate **XVI**. With ethanol in the reaction, **XVI** can protonate and tautomerize to an

activated carboxylate **XVII**, which is quenched by ethanol to form the α,β-unsaturated ester **30**. If there is no ethanol in the reaction, **XVI** can tautomerize to **XVII**, which undergoes intramolecular enolate addition to the activated carboxylate. In this transformation, the tricycle **34** is afforded and the catalyst is regenerated. Currently, the mechanism cannot rule out the possibility of ketene formation (see Scheme 4 in this chapter).

c) Solvent Effect

When ethanol was used as solvent, catalyst **32** led to three products **30**, **31**, and **34** with a ratio of 3:1:12 respectively and around 60% ee for all products (Table 1). Reaction with catalyst **33**, surprisingly, didn't generate the tricyclic product **34**. The major product was **30** formed in 65% ee, and the minor product was **31** formed in 30% ee.

Table 1.

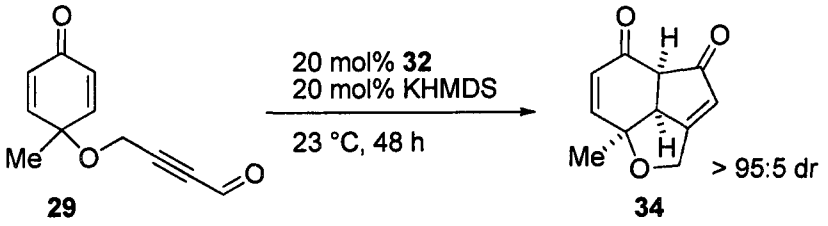


entry[a, b]	catalyst	30	31	34
1	**32**	12%, 60% ee > 95:5 dr	4%, 58% ee > 95:5 dr	50%, 65% ee > 95:5 dr
2	**33**	65%, 68% ee > 95:5 dr	10%, 30% ee > 95:5 dr	0%

a) All reactions conducted with 20 mol % catalyst and 20 mol % KHMDS at 23 °C.
b) Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

An additive was tested in the reaction of **29** catalyzed by **32** (Table 2, entry 1). Ten equivalents of ethylene glycol were mixed with toluene as solvent. The yield of **34** was improved to 60%, but with worse selectivity (30% ee). The reaction using isopropanol as solvent afforded **34** in 36% yield and 63% ee, showing no significant improvement (Table 4, entry 2).

Table 2.



29 **34**

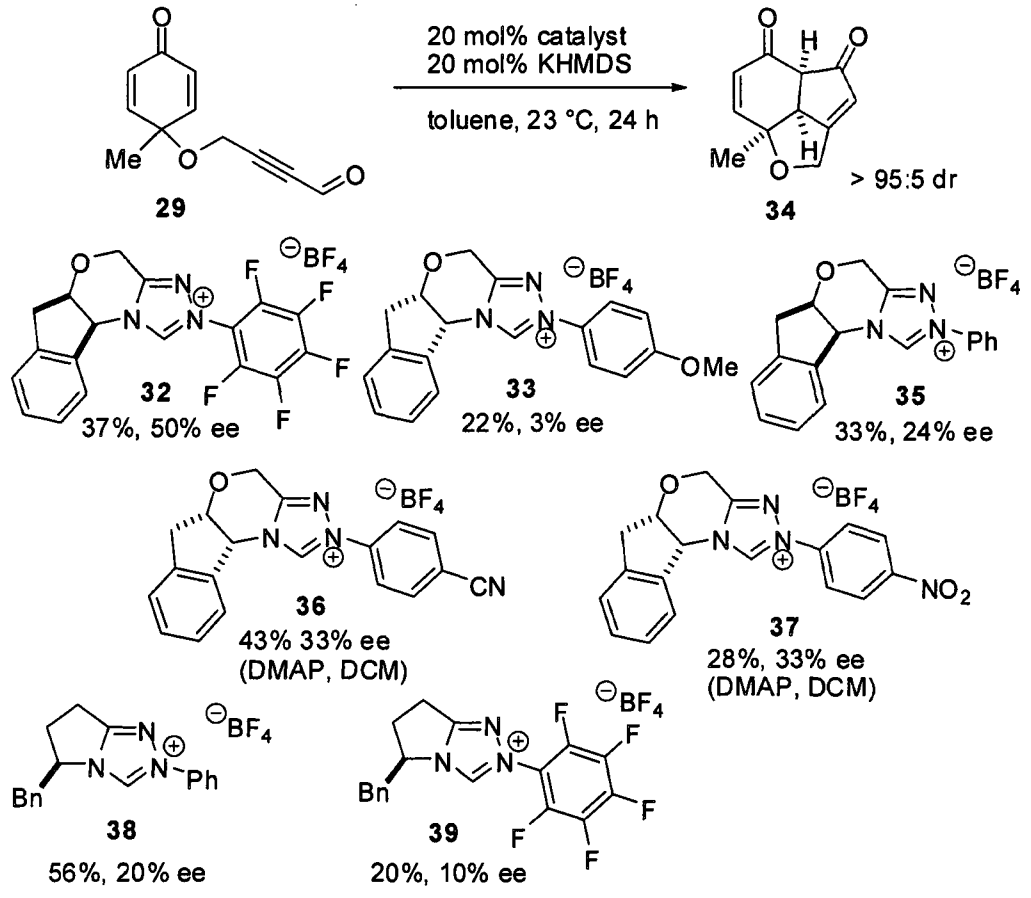
entry	solvent	additive	yield (%)[a]	ee (%)[b]
1	toluene	HO OH 10 eq	60	30
2	^{i}PrOH	–	36	63

a) All reactions conducted with 20 mol % **29** and 20 mol % KHMDS at 23 °C.
b) Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

d) Catalyst Screen

To determine the optimal reaction condition, a variety of catalysts were screened (Scheme 15). It was found catalyst **32** led to product with the best ee, although in moderate yield (37%). Catalyst **38** gave the best yield (56%), but very low enantioselectivity. Therefore **32** was chosen for further optimization experiments.

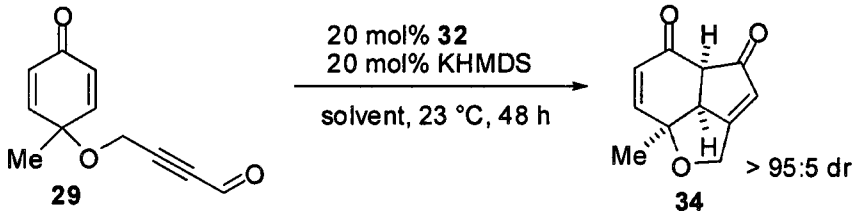
Scheme 15.



e) Base Effect

Using **32** as catalyst, several solvents were screened with two different bases for the reaction, shown in Table 3. Polar solvents such as DMF, DMSO and acetonitrile led to trace product. Dichloromethane was found to be the best solvent for the reaction with both triethylamine and KHMDS as base. The free carbene was tested; however, it led to similar yield and lower ee. We also noticed a significant difference between triethylamine and KHMDS in terms of enantioselectivity and concluded that base may play an important role.

Table 3.

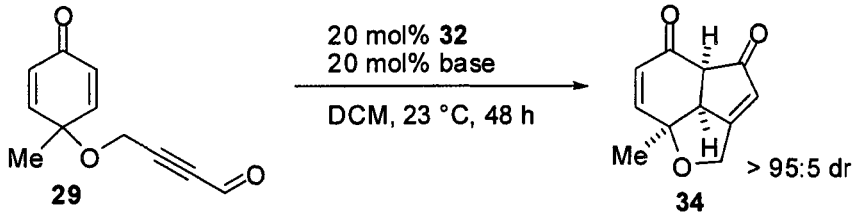


entry	base	solvent	yield (%)[a]	ee (%)[b]
1	Et_3N	DCM	52	72
2		THF	33	56
3		DMF	trace	
4		DMSO	trace	
5	KHMDS	DCM	47	53
6		CH_2Cl_2	44	61
7			47	46 (free carbene)
8		CH_3CN	trace	

a) All reactions conducted with 20 mol % **29** and 20 mol% base at 23 °C. b) see Table 2.

A thorough base screen was then conducted, with results shown in Table 4. To our surprise, very weak bases such as lutidine are also active for the reaction. There is not a clear trend between the result and the conjugate acid pKa of each base. *N*-methyl morpholine gave the best selectivity, but also low yield. At the same time, we found that Hunig's base gave the highest yield but only modest ee. Unfortunately, none of the bases led to both good yield and good selectivity for the reaction.

Table 4.



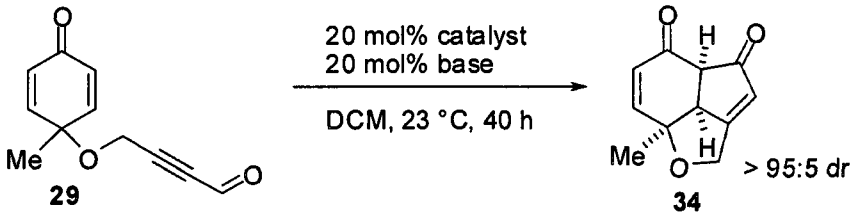
entry	base	pKa (H_2O)	yield (%)[a]	ee (%)[b]
1	Pyridine	5.2	4	80
2	Lutidine	6.8	50	71
3	imidazole	7.0	9	85
4	N-Me morpholine	7.4	37	87
5	DABCO	8.8	36	81
6	Ethanolamine	9.5	10	76
7	DMAP	9.7	56	71
8	Et_3N	10.8	52	72
9	Hunig's base	11.0	91	56
10	Quinuclidine	11.1	29	80
11	DBU	12.0	32	61
12	KOtBu	18.0	15	71
13	KHMDS	26.0 (THF)	44	61

a) All reactions conducted with 20 mol % **32** and 20 mol % base in DCM at 23 °C. b) see Table 2.

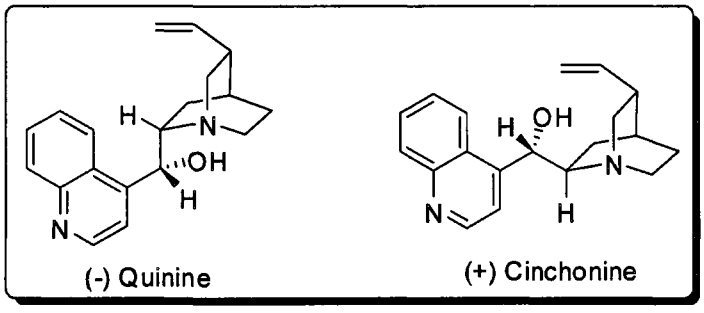
We envisioned that chiral bases with achiral carbene might be able to induce an asymmetric reaction. Two chiral bases, (+) cinchonine and (-) quinine, were investigated with both achiral and chiral catalyst (Table 5). It seems that these chiral bases are not very efficient in this reaction; both gave products with very low yields. The combination of achiral catalyst **27** with (+) cinchonine led to 6 % ee, which is not a convincing sign

that the chirality of the base was transferred to the product (Table 5, entry 1). When chiral catalyst **32** was used with chiral bases, the enantioselectivities of the reaction were not improved (Table 5, entry 2, 3) compared to the previous result (Table 4, entry 4).

Table 5.



entry	catalyst	base	yield (%)[a]	ee (%)[b]
1	**27**	(+) Cinchonine	6	6
2	**32**	(+) Cinchonine	6	86
3		(-) Quinine	6	80

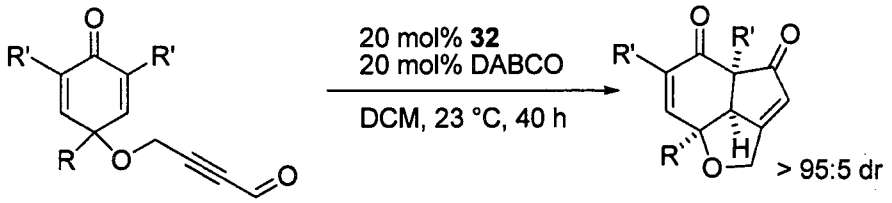


a) All reactions conducted with 20 mol % catalyst and 20 mol % base in DCM at 23 °C.
b) see Table 2

f) Substrate Scope

In order to test the generality of this reaction, dienone substrates with different substitutions were synthesized and subjected to the standard reaction conditions. As shown in Table 6, the ethyl analogue **40** afforded desired product **41** in 23% yield and 90% ee (Table 6, entry 2). Substrate **42** with aromatic substituent gave product **43** in 16% yield and 82% ee. The reaction of α,α-dimethylsubsituted substrate **44** didn't produce desired product **45** (Table 6, entry 4).

Table 6.



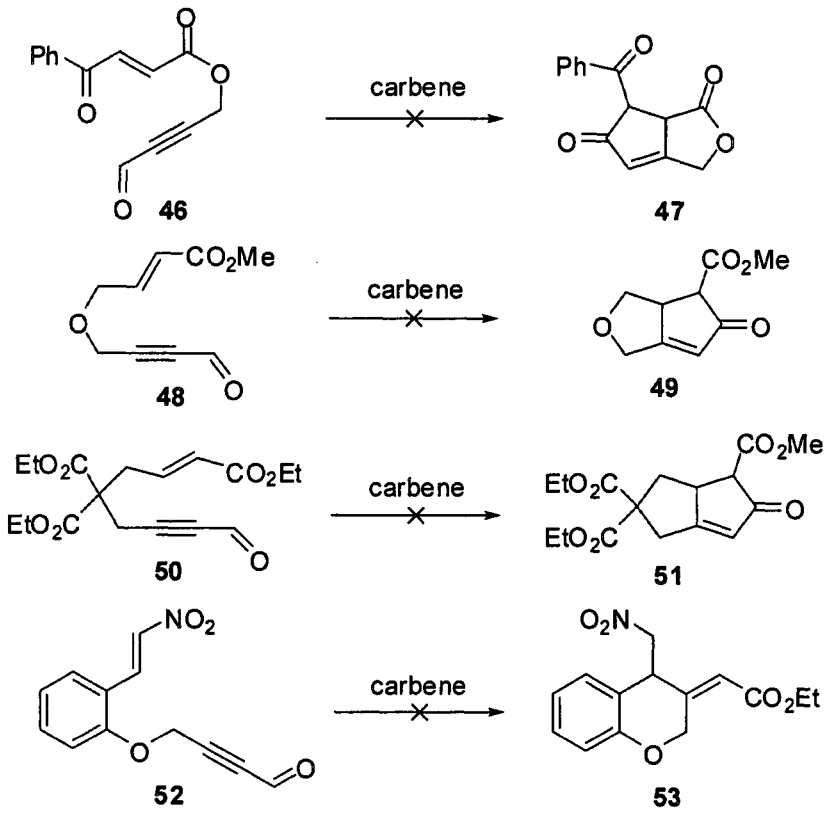
entry	R	R'	substrate	product	yield (%)[a]	ee (%)[b]
1	Me	H	**29**	**34**	36	81
2	Et	H	**40**	**41**	23	90
3	Ph	H	**42**	**43**	16	82
4	Me	Me	**44**	**45**	0	–

a) All reactions conducted with 20 mol % **32** and 20 mol % DABCO in DCM at 23 °C.
b) see Table 2.

3.2.3 Intramolecular Redox Reaction of Other Ynal Substrates

Seeking to expand the scope of the intramolecular ynal-derived homoenolate reaction, we synthesized different types of ynals, including **46**, **48**, **50**, and **52**. Unfortunately, these substrates failed to give desired redox product under the variety of conditions we screened (Scheme 16).

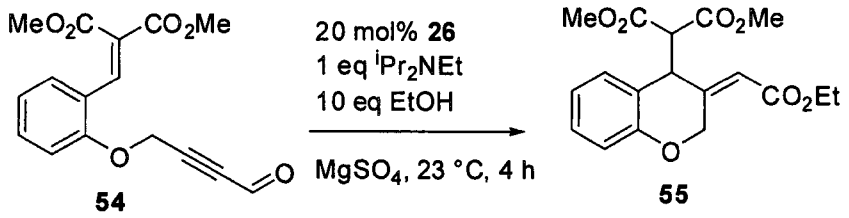
Scheme 16.



Based on our research on the intermolecular Stetter reaction (chapter 2), we envisioned that a doubly activated Michael acceptor might be a good substrate for the redox reaction. The requisite ynal-tethered alkylidenemalonate **54** was synthesized from salicylaldehdye and subjected to standard redox reaction conditions. A solvent screen was performed, and the results are shown in Table 7. Catalyzed by achiral catalyst **26**, the redox reaction of **54** afforded desired product **55** in modest yield and ~ 2:1 Z/E ratio.

Two different chiral catalysts **42** and **35** were tested, with the results shown in Table 8. It was found that solvent has significant influence on the outcome of the reaction. Although the yield, ee and Z/E ratio of the product are not optimal, these types of substrates are still very promising for the redox reactions catalyzed by carbenes.

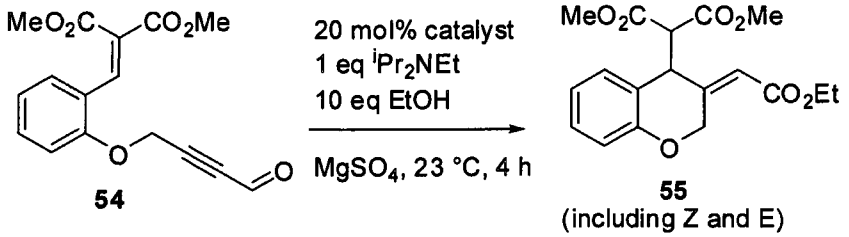
Table 7.



entry	solvent	yield (%)[a]	ratio of Z/E
1	DCM	40	1.5 : 1
2	toluene	29	1.3 : 1
3	Dioxane	39	1.8 : 1
4	THF	52	1.7 : 1
5	CCl_4	61	1.2 : 1
6	EtOH	52	2.3 : 1

a) All reactions conducted with 20 mol % **26** and 20 mol % $^{i}Pr_2NEt$ at 23 °C.

Table 8.



entry	catalyst	solvent	yield (%)[a]	ratio of Z/E (% ee)
1	**39**	DCM	29	3.3 : 1 (57, 31)
2		EtOH	52	1.4 : 1 (61, 27)
3	**32**	DCM	54	1 : 1.9 (40, 25)
4		EtOH	46	1 : 2.2 (12, 14)

a) All reactions conducted with 20 mol% catalyst and 20 mol% $^{i}Pr_2NEt$ at 23 °C.

3.3 Conclusion

A carbene-catalyzed asymmetric redox reaction of ynal-derived homoenolate has been developed. Different types of substrates were synthesized and tested. Cyclohexadienone-tethered ynal and alkylidene-malonate-tethered ynal were found suitable as substrates for the redox reaction. The desired products were obtained with moderate yields and modest selectivities. Further substrate screen and reaction condition optimizations are needed to obtain an optimal yield and selectivity for this reaction.

Chapter 1 Experimental

Asymmetric Synthesis of Hydrobenzofuranones via Desymmetrization of Cyclohexadienones Using the Intramolecular Stetter Reaction

General Methods.

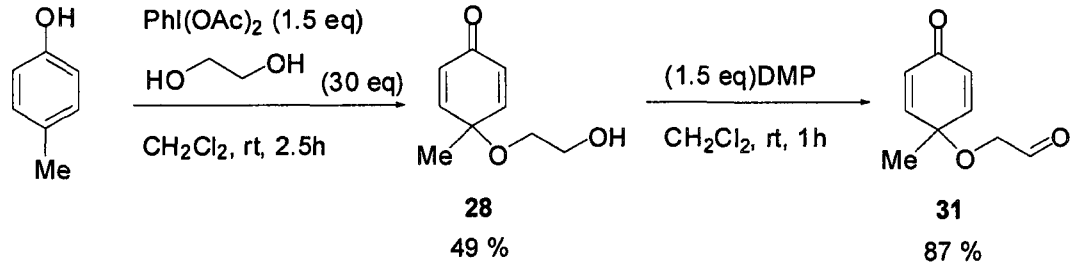
All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Methanol was distilled from CaH_2 prior to use. Methylene chloride was degassed with argon and passed through two column of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate dips followed by heating.

KHMDS (0.5 M solution in toluene), Ethylene glycol (anhydrous, 99.8%) and $PhI(OAc)_2$ (iodobenzene diacetate, 98%) was purchased from Aldrich Chemical Co. and used without purification.

^1H NMR was recorded at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) or deuterated acetone (acetone-D6), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR was recorded at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm or (acetone-D6) taken as 30.8.

General procedure for synthesis of the substrates (parent substrate as example):

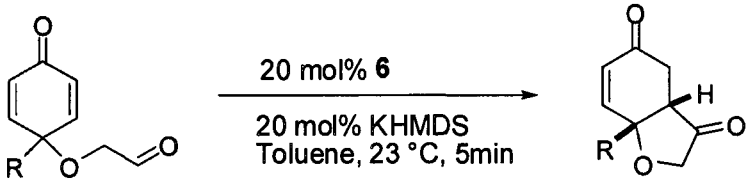
A flame-dried 100 ml round bottom flask was charged with cresol (1.08 g, 10 mmol); the flask was purged under vacuum for 5 mins and then refilled with argon and 2 ml CH_2Cl_2. Ethylene glycol (16.7 ml, 300 mmol) and then $PhI(OAc)_2$ (4.83 g, 15 mmol, dissolved in 40 ml CH_2Cl_2) was added dropwise over 2 hours. The solution was then allowed to stir at ambient temperature for further 30 mins. The solution was concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc : Hexane = 1:1) to provide **28** (823 mg, 49 %) as orange oil.



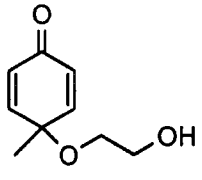
In a flame-dried 50 ml round bottom flask, **28** (556 mg, 3.86 mmol) was dissolved in 36 ml CH_2Cl_2, Dess Martin periodinane (1.80 g, 4.25 mmol) was added to the solution directly and the solution was then allowed to stir at ambient temperature for 1 hour. The solution was filtered through Celite 545 and then concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc : Hexane = 1:3) to provide **31** (556 mg, 87 %) as yellow oil.

This is the general procedure for all other substrates (two-step yields are reported respectively in the following sections). All the phenols were purchased from Aldrich and used without further purification except for further notice.

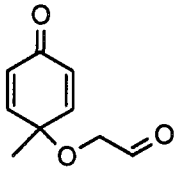
General procedure for the synthesis of Hydrobenzofuranones:



A flame-dried 25 ml round bottom flask was charged with triazolium salt **6** (4.9 mg, 0.012 mmol). The flask was purged under vacuum for 5 mins and then refilled with argon and 12 ml toluene. Argon was bubbled through the solution for 5 mins, and then KHMDS (0.024 ml, 0.012 mmol) was added and the solution was allowed to stir at ambient temperature for 15 minutes. The substrate (around 20 mg, 0.12 mmol) was dissolved in 3 ml toluene and then was added via syringe and the reaction was allowed to stir at ambient temperature. After the reaction was complete (checked by TLC), usually in 5 mins, the reaction mixture was directly purified by flash column chromatography.

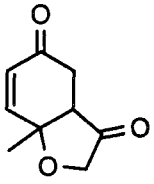


4-(2-Hydroxy-ethoxy)-4-methyl-cyclohexa-2,5-dienone (28): Rf = 0.23 (2:1 EtOAc/Hex); 54 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, 2H, J = 10.2 Hz), 6.27 (d, 2H, J = 10.2 Hz), 3.68 (t, 2H, J = 4.5 Hz), 3.40 (t, 2H, J = 4.5 Hz), 2.26 (s, 1H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 151.4, 130.0, 72.4, 66.6, 62.0, 26.3; IR (NaCl, neat) 3431, 2929, 1665, 1624, 1081, 861 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{12}O_3$, 168.0786. Found 168.0782.

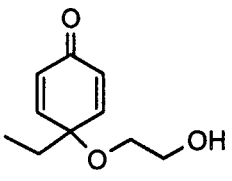


(1-Methyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (31): Rf = 0.30 (2:1 EtOAc/Hex); 87 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H),

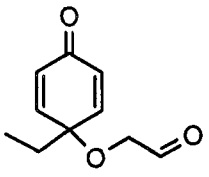
6.75 (d, 2H, J = 10.2 Hz), 6.29 (d, 2H, J = 10.2 Hz), 3.95 (s, 2H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 184.3, 149.6, 130.7, 73.1, 71.1, 26.0; IR (NaCl, neat) 2976, 1736, 1670, 1624, 1086, 861 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{10}O_3$, 166.0630. Found 166.0630.



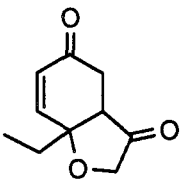
7a-Methyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (69): Rf = 0.48 (2:1 EtOAc/Hex); 90 % yield; $[\alpha]_D^{21}$ = + 69.4 (c = 1.5, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 160 °C oven temperature. Major: 5.8 min, Minor: 6.7 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, 1H, J = 10.2, 1.7 Hz), 6.01 (d, 1H, J = 10.2 Hz), 4.21 (d, 1H, J = 17.4 Hz), 3.83 (d, 1H, J = 17.4 Hz), 3.02 (d, 1H, J = 17.7 Hz), 2.69 (dd, 1H, J = 6.9, 1.2 Hz), 2.57 (dd, 1H, J = 17.7, 6.9 Hz), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4, 193.9, 150.6, 131.1, 78.9, 69.7, 50.8, 33.0, 24.3; IR (NaCl, neat) 2971, 1767, 1680, 1236, 1060, 879 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{10}O_3$, 166.0630. Found 166.0631.



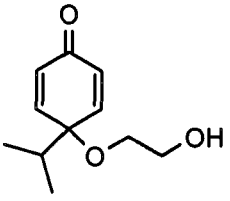
4-Ethyl-4-(2-hydroxy-ethoxy)-cyclohexa-2,5-dienone (33): Rf = 0.24 (2:1 EtOAc/Hex); 42 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, 2H, J = 10.4 Hz), 6.35 (d, 2H, J = 10.0 Hz), 3.67-3.73 (m, 2H), 3.44 (dd, 2H, J = 4.8, 4.4 Hz), 2.02 (s, 1H), 1.80 (q, 2H, J = 7.6 Hz), 0.84 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 150.7, 131.4, 76.1, 66.4, 62.1, 22.2, 7.8; IR (NaCl, neat) 3432, 2934, 1668, 1631, 1066, 854 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{14}O_3$, 182.0943. Found 182.0940.



(1-Ethyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (34): Rf = 0.42 (2:1 EtOAc/Hex); 78 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 6.70 (d, 2H, J = 10.4 Hz), 6.37 (d, 2H, J = 10.0 Hz), 3.98 (s, 2H), 1.89 (q, 2H, J = 7.6 Hz), 0.87 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 184.9, 149.0, 132.1, 76.9, 71.0, 32.0, 7.8; IR (NaCl, neat) 2966, 2878, 1733, 1668, 1095, 861 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0792.

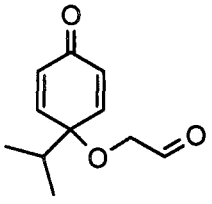


7a-Ethyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (72): Rf = 0.58 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 86.0 (c = 1.7, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 180 °C oven temperature. Major: 4.1 min, Minor: 4.4 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, 1H, J = 10.5, 1.8 Hz), 6.07 (d, 1H, J = 10.2 Hz), 4.20 (dd, 1H, J = 17.4, 1.2 Hz), 3.83 (d, 1H, J = 17.4 Hz), 3.02 (d, 1H, J = 18.0 Hz), 2.71-2.76 (m, 1H), 2.55 (dd, 1H, J = 18.0, 7.2 Hz), 1.87-2.11 (m, 2H), 1.09 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 194.2, 150.1, 131.9, 81.4, 69.5, 48.5, 33.4, 30.9, 7.7; IR (NaCl, neat) 2971, 2914, 1766, 1679, 924, 707 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0790.

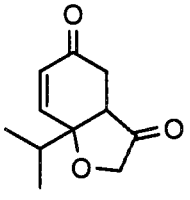


4-(2-Hydroxy-ethoxy)-4-isopropyl-cyclohexa-2,5-dienone (35): Rf = 0.33 (2:1 EtOAc/Hex); 38 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (d, 2H, J = 10.5 Hz), 6.37 (d, 2H, J = 10.2 Hz), 3.69 (t, 2H, J = 4.5 Hz), 3.41 (t, 2H, J = 4.5 Hz), 2.13 (s, 1H), 1.94-2.07 (m, 1H), 0.92 (d, 6H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 149.7, 131.9, 78.0, 66.3, 62.2, 36.6, 17.1; IR (NaCl,

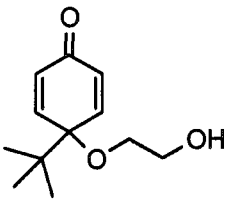
neat) 3432, 2964, 1670, 1626, 1066, 846 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{16}O_3$, 196.1099. Found 196.1092.



(1-Isopropyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (36): Rf = 0.44 (2:1 EtOAc/Hex); 84 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H), 6.70 (d, 2H, J = 10.5 Hz), 6.38 (d, 2H, J = 10.5 Hz), 3.94 (s, 2H), 2.03-2.18 (m, 1H), 0.97 (d, 6H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 184.8, 148.0, 132.5, 78.8, 70.9, 36.5, 17.0; IR (NaCl, neat) 2966, 1736, 1669, 1629, 1079, 856 cm^{-1} ; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0945.

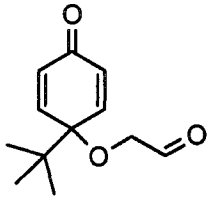


7a-Isopropyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (73): Rf = 0.65 (2:1 EtOAc/Hex); 87 % yield; $[\alpha]_D^{21}$ = + 82.4 (c = 1.5, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 °C oven temperature. Major: 7.0 min, Minor: 7.6 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 (dd, 1H, J = 10.5, 1.5 Hz), 6.14 (d, 1H, J = 10.5 Hz), 4.20 (dd, 1H, J = 17.4, 1.2 Hz), 3.83 (d, 1H, J = 17.4 Hz), 3.04 (d, 1H, J = 18.6 Hz), 2.58 (dd, 1H, J = 18.3, 7.5 Hz), 2.12-2.28 (m, 1H), 1.10 (dd, 6H, J = 7.0, 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.1, 194.4, 149.2, 132.7, 83.6, 69.3, 46.9, 36.1, 34.4, 17.4, 16.7; IR (NaCl, neat) 2966, 2878, 1763, 1684, 1062, 702 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0950.

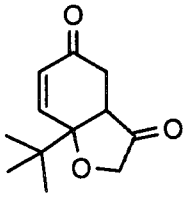


4-tert-Butyl-4-(2-hydroxy-ethoxy)-cyclohexa-2,5-dienone (37): Rf = 0.37 (2:1 EtOAc/Hex); 31 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ

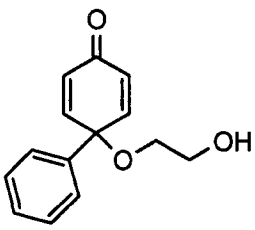
6.89 (d, 2H, J = 10.2 Hz), 6.37 (d, 2H, J = 10.2 Hz), 3.69 (t, 2H, J = 4.7 Hz), 3.39 (t, 2H, J = 4.7 Hz), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7, 150.1, 131.8, 79.2, 66.3, 62.2, 39.5, 25.6; IR (NaCl, neat) 3440, 2965, 2873, 1671, 1073, 857 cm^{-1}.



(1-tert-Butyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (38): Rf = 0.48 (2:1 EtOAc/Hex); 78 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 6.87 (d, 2H, J = 10.5 Hz), 6.40 (d, 2H, J = 10.5 Hz), 3.92 (s, 2H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 184.3, 148.3, 132.6, 80.2, 71.0, 39.5, 25.6; IR (NaCl, neat) 2966, 2873, 1737, 1671, 1079, 861 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{16}O_3$, 208.1099. Found 208.1100.

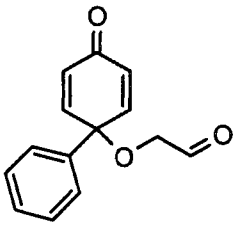


7a-tert-Butyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (74): Rf = 0.69 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 58.0 (c = 2.0, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 °C oven temperature. Major: 8.4 min, Minor: 9.2 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, 1H, J = 10.6, 1.6 Hz), 6.15 (d, 1H, J = 10.5 Hz), 4.20 (d, 1H, J = 17.4), 3.83 (d, 1H, J = 17.7 Hz), 3.05 (d, 1H, J = 18.6 Hz), 2.89 (d, 1H, J = 7.5 Hz), 2.61 (dd, 1H, J = 18.6, 7.5 Hz), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 194.0, 148.9, 132.8, 85.2, 69.3, 45.6, 37.8, 34.8, 25.2; IR (NaCl, neat) 2959, 2873, 1759, 1676, 939, 697 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{16}O_3$, 208.1099. Found 208.1101.

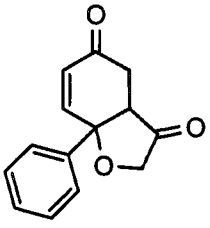


4-(2-Hydroxy-ethoxy)-4-phenyl-cyclohexa-2,5-dienone (39): Rf = 0.38 (2:1 EtOAc/Hex); 56 % yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ

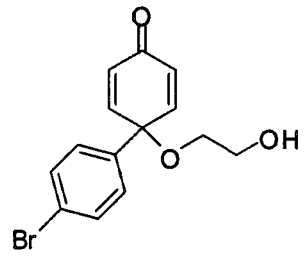
7.44-7.48 (m, 2H), 7.28-7.39 (m, 3H), 6.83 (d, 2H, J = 10.0 Hz), 6.38 (d, 2H, J = 10.4 Hz), 3.83 (t, 2H, J = 4.6 Hz), 3.66 (t, 2H, J = 4.6 Hz), 2.25 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.4, 150.2, 137.9, 129.7, 128.8, 128.4, 125.6, 76.1, 66.3, 62.1; IR (NaCl, neat) 3432, 2925, 1668, 1627, 1060, 699 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{14}O_3$, 230.0943. Found 230.0939.



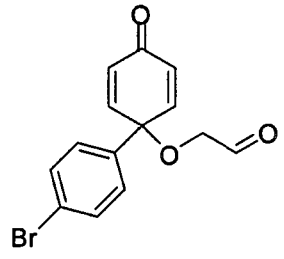
(4-Oxo-1-phenyl-cyclohexa-2,5-dienyloxy)-acetaldehyde (40): Rf = 0.45 (2:1 EtOAc/Hex); 64 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.48-7.53 (m, 2H), 7.30-7.41 (m, 3H), 6.80 (d, 2H, J = 10.2 Hz), 6.39 (d, 2H, J = 10.2 Hz), 4.18 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 184.7, 148.4, 137.2, 130.2, 128.8, 128.5, 76.7, 70.6; IR (NaCl, neat) 2821, 1735, 1670, 1629, 1061, 699 cm^{-1} ; HRMS (FAB+) calcd for $C_{14}H_{12}O_3$, 228.0786. Found 228.0779.



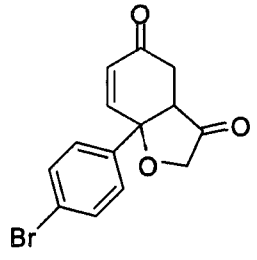
7a-Phenyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (75): Rf = 0.70 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 230.3 (c = 2.2, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 180 °C oven temperature. Major: 23.6 min, Minor: 24.6 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.56 (m, 2H), 7.37-7.48 (m, 3H), 6.78 (dd, 1H, J = 10.4, 1.8 Hz), 6.28 (d, 1H, J = 10.0 Hz), 4.47 (dd, 1H, J = 17.6, 1.2 Hz), 3.04 (d, 1H, J = 17.6 Hz), 2.86-2.91 (m, 1H), 2.62 (dd, 1H, J = 18.0, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 194.1, 148.4, 139.1, 132.4, 129.0, 128.9, 125.0, 82.2, 69.7,52.7, 32.8; IR (NaCl, neat) 2894, 1762, 1685, 1057, 755, 700 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{12}O_3$, 228.0786. Found 228.0784.



4-(4-Bromo-phenyl)-4-(2-hydroxy-ethoxy)-cyclohexa-2,5-dienone (41): Rf = 0.37 (2:1 EtOAc/Hex); 26 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 2H, *J* = 8.7 Hz), 7.33 (d, 3H, *J* = 8.7 Hz), 6.78 (d, 2H, *J* = 10.2 Hz), 6.39 (d, 2H, *J* = 10.2 Hz), 3.84 (t, 2H, J = 4.5 Hz), 3.66 (t, 2H, *J* = 4.5 Hz), 2.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 149.4, 137.0, 131.8, 130.0, 127.4, 122.5, 66.4, 62.1, 31.0; IR (NaCl, neat) 3432, 2930, 1668, 1627, 1073, 728 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{13}BrO_3$, 308.0048. Found 308.0038.



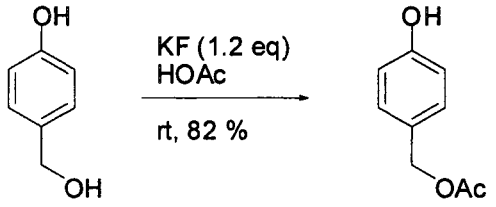
[1-(4-Bromo-phenyl)-4-oxo-cyclohexa-2,5-dienyloxy]-acetaldehyde (42): Rf = 0.38 (2:1 EtOAc/Hex); 75 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.51 (d, 2H, *J* = 8.7 Hz), 7.38 (d, 2H, *J* = 8.7 Hz), 6.76 (d, 2H, *J* = 10.2 Hz), 6.41 (d, 2H, *J* = 10.2 Hz), 4.19 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 184.4, 147.9, 136.4, 130.2, 130.6, 127.3, 122.8, 76.5, 70.6; IR (NaCl, neat) 2822, 1735, 1670, 1074, 1010, 826 cm^{-1} ; HRMS (FAB+) calcd for $C_{14}H_{11}BrO_3$, 305.9892. Found 305.9895.

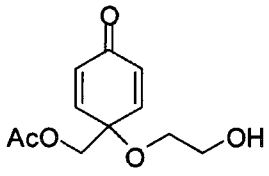


7a-(4-Bromo-phenyl)-3a,7a-dihydro-4H-benzofuran-3,5-dione (76): Rf = 0.68 (2:1 EtOAc/Hex); 78 % yield; $[\alpha]_D^{21}$ = + 212.8 (c = 2.0, $CHCl_3$); HPLC analysis – Chiracel OD-H column 95:5 hexanes : isopropanol 1.0 mL / min. Major: 31.8 minutes, Minor: 41.1 minutes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2H, *J* = 8.4 Hz), 7.42 (d, 2H, *J* = 8.8 Hz), 6.73 (dd, 1H, *J* = 10.4, 1.6 Hz), 6.29 (d, 1H, *J* = 10.0 Hz), 4.47 (dd, 1H, *J* = 17.6, 1.0

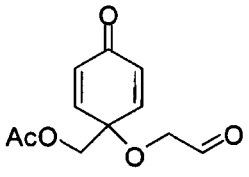
Hz), 3.05 (dd, 1H, J = 18.0, 1.0 Hz), 2.83 (dd, 1H, J = 7.0, 1.4 Hz), 2.58 (dd, 1H, J = 18.0, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 193.7, 147.7, 138.2, 132.7, 132.2, 126.8, 123.1, 81.8, 69.7,52.6, 32.7; IR (NaCl, neat) 2884, 1764, 1683, 1055, 1010, 820 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{11}BrO_3$, 305.9892. Found 305.9892.

4-hydroxybenzyl acetate was synthesized from 4-(hydroxymethyl)-phenol. [55]





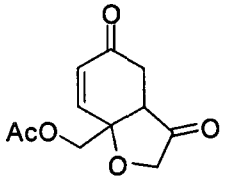
Acetic acid 1-(2-hydroxy-ethoxy)-4-oxo-cyclohexa-2,5-dienylmethyl ester (43): Rf = 0.20 (2:1 EtOAc/Hex); 17 % yield; ^{1}H NMR (400 MHz, acetone-D6) δ 6.92 (d, 2H, J = 10.0 Hz), 6.35 (d, 2H, J = 10.0 Hz), 4.20 (s, 2H), 3.75 (t, 2H, J = 6.0 Hz), 3.61 (dt, 2H, J = 5.6, 5.6 Hz), 3.45 (t, 2H, J = 5.2 Hz), 1.97 (s, 3H); ^{13}C NMR (100 MHz, acetone-D6) δ 186.2, 171.4, 149.9, 133.8, 75.9, 68.8, 68.3, 63.0, 21.6; IR (NaCl, neat) 3442, 2935, 2868, 1747, 1235, 1045 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_5$, 226.0841. Found 226.0833.



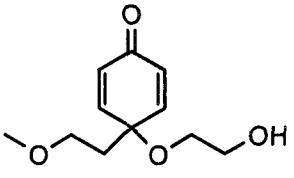
Acetic acid 4-oxo-1-(2-oxo-ethoxy)-cyclohexa-2,5-dienylmethyl ester (44): Rf = 0.23 (2:1 EtOAc/Hex); 52 % yield; ^{1}H NMR (400 MHz, acetone-D6) δ 9.62 (s, 1H), 6.93 (d, 2H, J = 10.0 Hz), 6.37 (d, 2H, J = 10.0 Hz), 4.30 (s, 2H), 4.10 (s, 2H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, acetone-

[55] John, B. J. W.; Rama, R. B.; Anil K, S. *Synthetic Communications*, **2004**, *34*, 2849-2855.

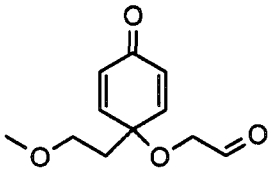
D6) δ 201.1, 185.9, 171.4, 148.0, 134.4, 76.4, 72.4, 68.2, 21.6; IR (NaCl, neat) 2950, 2827, 1731, 1670, 1230, 856 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_5$, 224.0685. Found 224.0682.



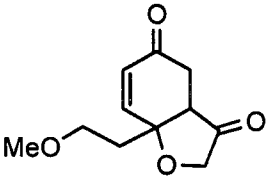
Acetic acid 3,5-dioxo-3,3a,4,5-tetrahydro-2H-benzofuran-7a-ylmethyl ester (77): Rf = 0.5 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 116.1 (c = 1.8, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 °C oven temperature. Major: 16.2 min, Minor: 16.8 minutes; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (dd, 1H, *J* = 10.4, 2.4 Hz), 6.17 (d, 1H, *J* = 10.4 Hz), 4.44 (s, 2H), 4.27 (dd, 1H, *J* = 17.6, 0.8 Hz), 3.89 (d, 1H, *J* = 17.2 Hz), 3.04 (d, 1H, *J* = 18.4 Hz), 2.91 (dd, 1H, *J* = 7.2, 1.2 Hz), 2.62 (dd, 1H, *J* = 18.4, 7.2 Hz), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 193.5, 170.2, 145.8, 133.7, 79.6, 69.4, 65.8, 47.1, 33.0, 20.7; IR (NaCl, neat) 2955, 2899, 1742, 1685, 1229, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_5$, 224.0685. Found 224.0688.



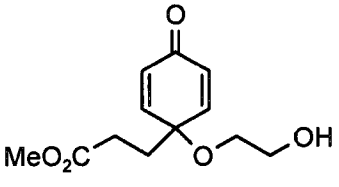
4-(2-Hydroxy-ethoxy)-4-(2-methoxy-ethyl)-cyclohexa-2,5-dienone (45): Rf = 0.13 (2:1 EtOAc/Hex); 39 % yield; ^1H NMR (400 MHz, acetone-D6) δ 6.91 (d, 2H, *J* = 10.0 Hz), 6.24 (d, 2H, *J* = 10.4 Hz), 3.71 (t, 1H, *J* = 5.2 Hz), 3.59 (dt, 2H, *J* = 4.8, 4.8 Hz), 3.42 (t, 2H, *J* = 6.4 Hz), 3.39 (t, 2H, *J* = 5.0 Hz), 3.20 (s, 3H), 1.98 (t, 2H, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 186.4, 153.0, 131.9, 75.7, 69.0, 68.6, 63.1, 59.4, 41.2; IR (NaCl, neat) 3432, 2925, 2863, 1665, 1091, 846 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{14}O_3$, 182.0943. Found 182.0940.



[1-(2-Methoxy-ethyl)-4-oxo-cyclohexa-2,5-dienyloxy]-acetaldehyde (46): Rf = 0.20 (2:1 EtOAc/Hex); 59 % yield; ^{1}H NMR (400 MHz, acetone-D6) δ 9.62 (s, 1H), 6.90 (d, 2H, *J* = 10.0 Hz), 6.26 (d, 2H, *J* = 10.4 Hz), 4.03 (s, 2H), 3.47 (t, 2H, *J* = 6.4 Hz), 3.22 (s, 3H), 2.08 (t, 2H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 201.5, 186.1, 151.2, 132.6, 76.5, 72.4, 68.8, 59.4, 41.0; IR (NaCl, neat) 2925, 2873, 1670, 1624, 1112, 856 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_4$, 210.0892. Found 210.0887.

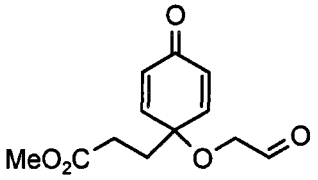


7a-(2-Methoxy-ethyl)-3a,7a-dihydro-4H-benzofuran-3,5-dione (78): Rf = 0.41 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 67.8 (c = 2.0, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 °C oven temperature. Major: 11.1 min, Minor: 11.5 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (dd, 1H, *J* = 10.6, 1.4 Hz), 6.05 (d, 1H, *J* = 10.4 Hz), 4.20 (d, 1H, *J* = 17.2 Hz), 3.82 (d, 1H, *J* = 17.6 Hz), 3.62-3.69 (m, 1H), 3.49-3.55 (m, 1H), 3.30 (s, 3H), 2.92-3.00 (m, 2H), 2.68 (dd, 1H, *J* = 18.8, 7.6 Hz), 2.11-2.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.8, 194.6, 149.8, 131.9, 80.4, 69.2, 67.4, 58.7, 49.3, 37.7, 33.1; IR (NaCl, neat) 2914, 2889, 1757, 1685, 1107, 1050 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_4$, 210.0892. Found 210.0889.

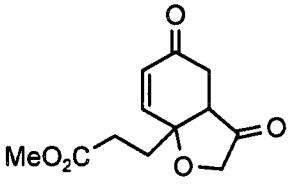


3-[1-(2-Hydroxy-ethoxy)-4-oxo-cyclohexa-2,5-dienyl]-propionic acid methyl ester (47): Rf = 0.18 (2:1 EtOAc/Hex); 20 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, 2H, *J* = 10.2 Hz), 6.34 (d, 2H, *J* = 10.2 Hz), 3.64-3.69 (m, 2H), 3.65 (s, 3H), 3.42 (t,

2H, J = 4.5 Hz), 2.34 (t, 2H, J = 7.6 Hz), 2.11 (t, 2H, J = 7.5 Hz); ^{13}C NMR (75 MHz, acetone-D6) δ 185.9, 174.3, 152.1, 132.6, 76.2, 68.8, 63.1, 52.7, 36.0, 29.8; IR (NaCl, neat) 3452, 2949, 2859, 1734, 1665, 1077 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{16}O_5$, 240.0998. Found 240.0986.



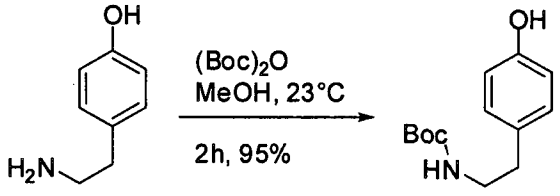
3-[4-Oxo-1-(2-oxo-ethoxy)-cyclohexa-2,5-dienyl]-propionic acid methyl ester (48): Rf = 0.28 (2:1 EtOAc/Hex); 47 % yield; ^{1}H NMR (400 MHz, acetone-D6) δ 9.62 (s, 1H), 6.87 (d, 2H, J = 10.4 Hz), 6.32 (d, 2H, J = 10.0 Hz), 4.05 (s, 2H), 3.60 (s, 3H), 2.39 (t, 2H, J = 7.8 Hz), 2.16 (t, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, acetone-D6) δ 201.4, 185.9, 174.3, 150.5, 133.5, 77.1, 72.7, 52.8, 35.7, 29.7; IR (NaCl, neat) 2945, 2838, 1736, 1665, 1070, 856 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}O_5$, 238.0841. Found 238.0846.

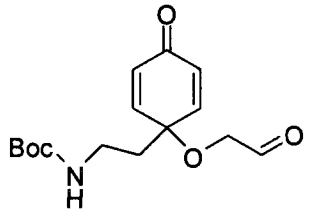


3-(3,5-Dioxo-3,3a,4,5-tetrahydro-2H-benzofuran-7a-yl)-propionic acid methyl ester (79): Rf = 0.50 (2:1 EtOAc/Hex); 94 % yield; $[\alpha]_D^{21}$ = + 88.1 (c = 2.3, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 180 °C oven temperature. Major: 21.7 min, Minor: 22.7 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (dd, 1H, J = 10.5, 1.8 Hz), 6.05 (d, 1H, J = 10.2 Hz), 4.19 (dd, 1H, J = 17.4 Hz), 3.82 (d, 1H, J = 17.4 Hz), 3.69 (s, 3H), 3.01 (d, 1H, J = 18.0 Hz), 2.72 (dd, 1H, J = 6.9, 1.2 Hz), 2.49-2.65 (m, 3H), 2.20-2.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 193.7, 173.0, 132.1, 80.1, 69.4, 52.0, 48.5, 32.9, 32.2, 27.9; IR (NaCl, neat) 2950, 2843,

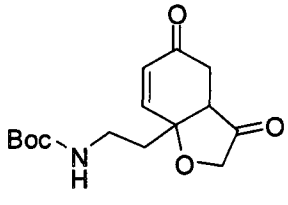
1762, 1726, 1685, 1045 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}O_5$, 238.0841. Found 238.0847.

Synthesis of *tert*-butyl 4-hydroxyphenethylcarbamate



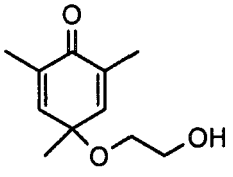


tert-butyl 2-(4-oxo-1-(2-oxoethoxy)cyclohexa-2,5-dienyl)ethylcarbam ate (50): This substrate is somewhat sensitive and could not be satisfactorily purified without extensive decomposition. Rf = 0.23 (2:1 EtOAc/Hex); ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 6.79 (d, 1H, J = 10.2 Hz), 6.37 (d, 1H, J = 10.2 Hz), 4.84 (s, 1H), 3.99 (s, 2H), 3.26 (dd, 2H, J = 6.6, 6.5 Hz), 2.05 (t, 2H, J = 7.1 Hz), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 185.1, 148.4, 132.1, 94.6, 71.0, 53.7, 39.8, 36.1, 28.6; IR (NaCl, neat) 3355, 2971, 2925, 1693, 1669, 1167 cm^{-1}; HRMS (EI+) calcd for $C_{15}H_{21}NO_5$, 295.1420. Found 295.1419.

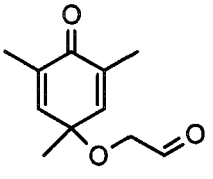


tert-butyl 2-(3,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-7a-yl)ethyl carbamate (80): Rf = 0.49 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 39.6 (c = 0.9, $CHCl_3$); HPLC analysis – Chiracel AD-H

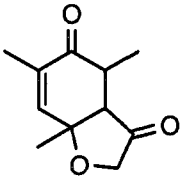
column 93:7 hexanes : isopropanol 1.0 mL / min. Major: 35.8 minutes, Minor: 29.8 minutes.; IR (NaCl, neat) 3360, 2971, 2925, 1766, 1788, 1168 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{21}O_5$, 295.1420. Found 295.1419.



4-(2-Hydroxy-ethoxy)-2,4,6-trimethyl-cyclohexa-2,5-dienone (51): Rf = 0.38 (2:1 EtOAc/Hex); 83 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (s, 2H), 3.61 (dt, 2H, J = 5.7, 4.2 Hz), 3.32 (t, 2H, J = 4.5 Hz), 2.55 (t, 1H, J = 6.0 Hz), 1.83 (s, 6H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.2, 146.5, 136.1, 72.2, 66.0, 62.0, 26.5, 15.9; IR (NaCl, neat) 3457, 2925, 1645, 1368, 1077, 912 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{16}O_3$, 196.1099. Found 196.1101.



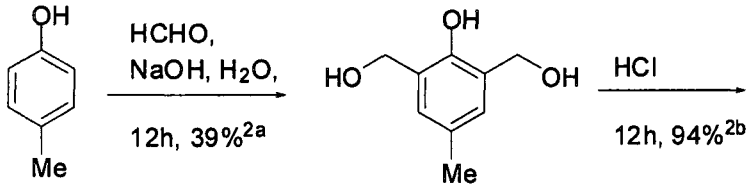
(1,3,5-Trimethyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (52): Rf = 0.55 (2:1 EtOAc/Hex); 51 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 6.46 (s, 2H), 3.88 (s, 2H), 1.87 (s, 6H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 185.8, 144.7, 137.2, 73.1, 70.8, 26.2, 16.0; IR (NaCl, neat) 2924, 1736, 1645, 1372, 1072, 907 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0948.

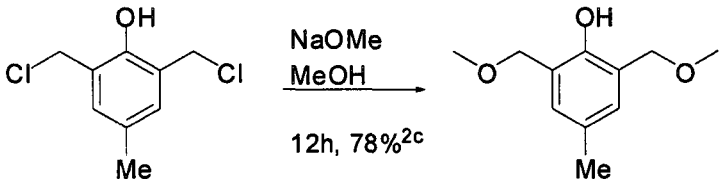


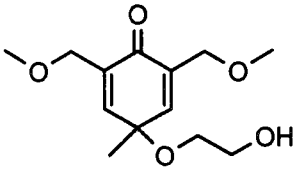
4,6,7a-Trimethyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (81): Rf = 0.63 (2:1 EtOAc/Hex); 86 % yield; $[\alpha]_D^{21}$ = + 135.3 (c = 1.4, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 120 °C oven temperature. Major: 25.9 min, Minor: 27.5 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40-6.44 (m, 1H), 4.15 (d, 1H, J = 17.1 Hz), 3.82 (d, 1H,

J = 17.4 Hz), 3.06 (ddd, 1H, J = 15.6, 7.8, 2.1 Hz), 2.45 (s, 1H), 1.77 (d, 3H, J = 1.2 Hz), 1.67 (s, 3H), 1.31 (d, 3H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 198.1, 144.7, 136.3, 78.7, 69.1, 56.5, 39.2, 26.9, 18.0, 16.3; IR (NaCl, neat) 2971, 1763, 1678, 1434, 1052, 861 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0948.

2,6-bis(methoxymethyl)-4-methylphenol was synthesized from cresol.[56]

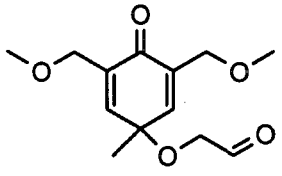




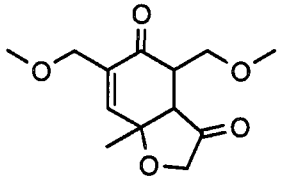


4-(2-Hydroxy-ethoxy)-2,6-bis-methoxymethyl-4-methyl-cyclohexa-2,5-dienone (53): Rf = 0.16 (2:1 EtOAc/Hex); 70 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 2H), 4.18 (s, 4H), 3.67 (dt, 2H, J = 5.4, 4.8 Hz), 3.42 (s, 6H), 3.39 (t, 2H, J = 4.5 Hz), 2.04 (t, 1H, J = 6.0 Hz), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 146.5, 136.6, 72.5, 66.4, 62.2, 58.9, 26.6; IR (NaCl, neat) 3462, 2929, 2858, 1639, 1098, 917 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{20}O_5$, 256.1311. Found 256.1309.

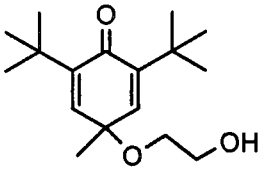
[56] (a) Barry M, T.; Vince S. C, Y.; Hisanako, I.; Nadine, B. *Organic Letters*, **2002**, *4*, 2621-2623. (b) Paine, R. T.; Tan, Y.; Gan, X. *Inorg. Chem.* **2001**, *40*, 7009-7013. (c) Ledovskikh, V. M.; Shapovalova, Yu. P.; Sumlivenko, N. V. *Ukrainskii Khimicheskii Zhurnal (Russian Edition)*, **1989**, *55*, 858-61.



(3,5-Bis-methoxymethyl-1-methyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (54): Rf = 0.28 (2:1 EtOAc/Hex); 74 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 6.76 (s, 2H), 4.18 (s, 4H), 3.90 (s, 2H), 4.18 (s, 4H), 3.90 (s, 2H), 3.42 (s, 6H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 183.4, 144.6, 137.5, 73.3, 71.0, 68.3, 59.0, 26.3; IR (NaCl, neat) 2976, 2821, 1735, 1641, 1190, 1120 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{18}O_5$, 254.1154. Found 254.1150.

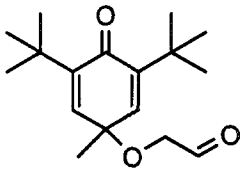


4,6-Bis-methoxymethyl-7a-methyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (82): Rf = 0.53 (2:1 EtOAc/Hex); 71 % yield; $[\alpha]_D^{21}$ = + 98.2 (c = 1.7, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99:1 hexanes : isopropanol 0.7 mL / min. Major: 26.3 minutes, Minor: 22.4 minutes. ^{1}H NMR (300 MHz, acetone-D6) δ 6.64 (dt, 1H, *J* = 1.8, 1.5 Hz), 4.21 (dd, 1H, *J* = 17.4, 1.2 Hz), 3.96 (d, 2H, *J* = 1.5 Hz), 3.69-3.81 (m, 2H), 3.56 (dd, 1H, *J* = 9.6, 4.6 Hz), 3.31 (d, 6H, *J* = 0.9 Hz), 3.06-3.12 (m, 1H), 2.91-2.94 (m, 11H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.2, 195.6, 147.2, 138.9, 80.4, 74.2, 70.6, 69.8, 59.7, 59.6, 54.4, 47.8, 27.5; IR (NaCl, neat) 2981, 2879, 1763, 1118, 1054 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{18}O_5$, 254.1154. Found 254.1166.

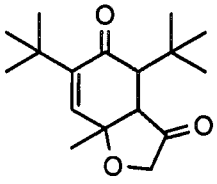


2,6-Di-tert-butyl-4-(2-hydroxy-ethoxy)-4-methyl-cyclohexa-2,5-dienone (55): Rf = 0.60 (2:1 EtOAc/Hex); 25 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 2H), 3.67 (dt, 2H, *J* = 5.7, 4.2 Hz), 3.33 (t, 2H, *J* = 4.5 Hz), 2.06 (t, 1H, *J* = 6.0 Hz), 1.38 (s, 3H), 1.22 (s, 18H); ^{13}C NMR

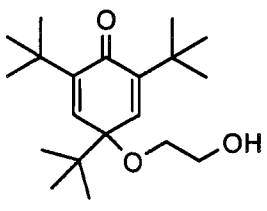
(75 MHz, $CDCl_3$) δ 185.7, 148.4, 142.2, 72.1, 65.6, 62.3, 34.9, 29.6, 27.4; IR (NaCl, neat) 3432, 2958, 1665, 1364, 1364, 880 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{28}O_3$, 280.2038. Found 280.2037.



(3,5-Di-tert-butyl-1-methyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (56): Rf = 0.38 (1:3 EtOAc/Hex); 54 % yield; ^1H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 6.40 (s, 2H), 3.85 (s, 2H), 1.47 (s, 3H), 1.22 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 185.5, 149.5, 140.7, 73.0, 70.5, 34.9, 29.5, 26.9; IR (NaCl, neat) 2959, 2869, 1738, 1646, 1364, 879 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{26}O_3$, 278.1882. Found 278.1887.

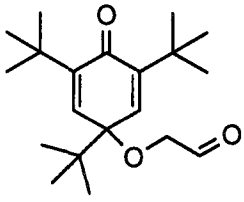


4,6-Di-tert-butyl-7a-methyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (83): Rf = 0.45 (1:3 EtOAc/Hex); 80 % yield; $[\alpha]_D^{21}$ = + 178.8 (c = 1.9, $CHCl_3$); HPLC analysis – Chiracel AD-H column 99:1 hexanes : isopropanol 0.3 mL / min. Major: 18.8 minutes, Minor: 17.8 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (d, 1H, *J* = 1.5 Hz), 4.14 (dd, 1H, *J* = 17.4, 1.2 Hz), 3.76 (d, 1H, *J* = 17.4 Hz), 2.68 (d, 1H, *J* = 2.1 Hz), 2.61-2.63 (m, 1H), 1.70 (s, 3H), 1.15 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 197.9, 150.6, 140.1, 78.7, 68.5, 57.2, 52.4, 35.2, 33.6, 29.5, 29.1, 27.4; IR (NaCl, neat) 2960, 2871, 1765, 1672, 1366, 1058 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{26}O_3$, 278.1882. Found 278.1889.

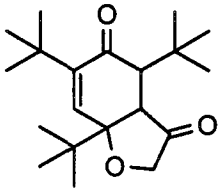


2,4,6-Tri-tert-butyl-4-(2-hydroxy-ethoxy)-cyclohexa-2,5-dienone (57): Rf = 0.73 (2:1 EtOAc/Hex); 31 % yield; ^1H NMR

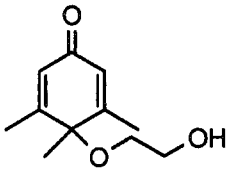
(300 MHz, $CDCl_3$) δ 6.50 (s, 2H), 3.67 (t, 2H, J = 4.8 Hz), 3.32 (t, 2H, J = 4.8 Hz), 2.22 (s, 1H), 1.19 (s, 18H), 0.90 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8, 150.0, 140.8, 78.8, 65.5, 62.4, 40.2, 35.2, 29.6, 25.8; IR (NaCl, neat) 3421, 2958, 2870, 1665, 1363, 1048 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{34}O_3$, 322.2508. Found 322.2495.



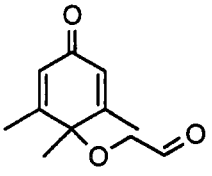
(1,3,5-Tri-tert-butyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (58): Rf = 0.53 (1:3 EtOAc/Hex); 89 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 6.50 (s, 2H), 3.83 (d, 2H, J = 0.6 Hz), 1.20 (s, 18H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 185.4, 151.0, 139.2, 80.0, 70.7, 40.1, 35.3, 29.6, 25.8; IR (NaCl, neat) 2959, 2871, 1739, 1666, 1364, 1085 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{32}O_3$, 320.2351. Found 320.2356.



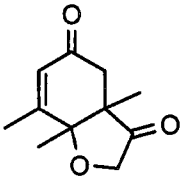
4,6,7a-Tri-tert-butyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (84): Rf = 0.58 (1:3 EtOAc/Hex); $[\alpha]_D^{21}$ = + 160.7 (c = 2.2, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 120 °C oven temperature. Major: 244.7 min, Minor: 248.4 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (s, 1H), 4.20 (d, 1H, J = 17.1 Hz), 3.99 (d, 1H, J = 17.4 Hz), 2.74 (d, 1H, J = 4.2 Hz), 2.37 (d, 1H, J = 4.2 Hz), 1.14 (d, 18H, J = 7.8 Hz), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 200.4, 154.6, 136.1, 85.7, 69.1, 56.5, 45.9, 39.4, 35.5, 33.6, 29.3, 28.7, 25.4; IR (NaCl, neat) 2955, 2868, 1762, 1696, 1358, 1117 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{32}O_3$, 320.2351. Found 320.2351.



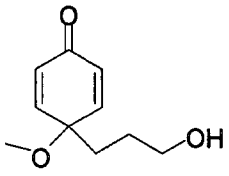
4-(2-Hydroxy-ethoxy)-3,4,5-trimethyl-cyclohexa-2,5-dienone (59): Rf = 0.18 (2:1 EtOAc/Hex); 56 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (s, 2H), 3.58 (t, 2H, *J* = 4.8 Hz), 3.25 (s, 1H), 2.97 (t, 2H, *J* = 4.8 Hz), 1.90 (s, 6H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 160.9, 128.4, 76.0, 65.7, 61.2, 24.7, 17.6; IR (NaCl, neat) 3421, 2919, 1670, 1621, 1094, 892 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{16}O_3$, 196.1099. Found 196.1098.



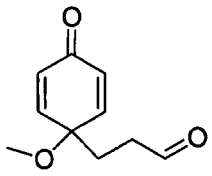
(1,2,6-Trimethyl-4-oxo-cyclohexa-2,5-dienyloxy)-acetaldehyde (60): Rf = 0.24 (2:1 EtOAc/Hex); 61 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 6.08 (s, 2H), 3.59 (s, 2H), 1.92 (s, 6H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 184.3, 158.6, 129.2, 76.8, 70.1, 24.2, 17.6; IR (NaCl, neat) 2991, 1736, 1672, 1634, 1094, 895 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.094.



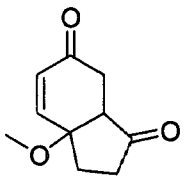
3a,7,7a-Trimethyl-3a,7a-dihydro-4H-benzofuran-3,5-dione (85): Rf = 0.48 (2:1 EtOAc/Hex); 64 % yield; $[\alpha]_D^{21}$ = + 79.6 (c = 1.2, $CHCl_3$); HPLC analysis – Chiracel OD-H column 97:3 hexanes : isopropanol 1.0 mL / min. Major: 27.4 minutes, Minor: 31.4 minutes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.18 (d, 1H, *J* = 17.6 Hz), 3.64 (d, 1H, *J* = 17.6 Hz), 2.90 (d, 1H, *J* = 18.0), 2.26 (d, 1H, *J* = 18.0), 2.01 (s, 3H), 1.49 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 194.2, 162.0, 130.2, 83.1, 68.0, 50.7, 40.5, 19.2, 18.3, 17.9; IR (NaCl, neat) 2971, 1752, 1665, 1265, 1045, 866 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{14}O_3$, 194.0943. Found 194.0946.



4-(3-hydroxypropyl)-4-methoxycyclohexa-2,5-dienone (86a). A flame-dried 25 ml round bottom flask was charged with 4-(3-hydroxypropyl)-phenol (Aldrich) (152 mg, 1.0 mmol) and 5 ml methanol, then $PhI(OAc)_2$ (386 mg, 1.2 mmol, dissolved in 5 ml methanol) was added dropwise. The solution was then allowed to stir at ambient temperature for further 2 hours. The solution was concentrated in *vacuo* and the residue subjected to column chromatography to provide 32a (116 mg, 64 %); Rf = 0.18 (2:1 EtOAc/Hex).

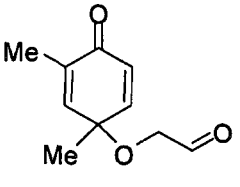


3-(1-methoxy-4-oxocyclohexa-2,5-dienyl)propanal (86): A flame-dried 10 ml round bottom flask was charged with **86a** (110 mg, 0.6 mmol) and 6 ml methylene chloride, then Dess Martin periodinane (380 mg, 0.9 mmol) was added to the solution directly. The solution was then allowed to stir at ambient temperature for further 1.5 hours. The solution was filtered through Celite 545 and then concentrated in *vacuo.* The residue was subjected to column chromatography to provide **32** (74 mg, 68 %). Rf = 0.45 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, 1H, J = 1.2 Hz), 6.73 (d, 2H, J = 10.3 Hz), 6.37 (d, 2H, J = 10.3 Hz), 3.21 (s, 3H), 2.49 (dt, 2H, J = 7.6 Hz, J = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 185.1, 150.3, 132.0, 74.9, 53.4, 38.4, 31.5; IR (NaCl, neat) 2934, 2827, 1722, 1670, 1634, 1082 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0787.



3a-methoxy-3,3a,7,7a-tetrahydro-1H-indene-1,6(2H)-dione (88): A flame-dried 25 ml round bottom flask was charged with triazolium salt **3** (4.9 mg, 0.1 equiv.). The flask was purged under vacuum for 5 mins and

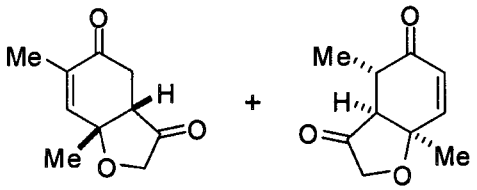
then refilled with argon and 6 ml toluene. Argon was bubbled through the solution for 5 mins, and then 0.1 equiv. KHMDS (0.024 ml) was added and the solution was allowed to stir at ambient temperature for 15 minutes. Toluene and HMDS was removed *in vacuo* by being placed under high vacuum for about 1 hour.[57] 12 ml toluene was then added and argon was bubbled through the solution for 5 mins. **32** (21.6 mg, 1 equiv.) was dissolved in 3 ml toluene and then was added via syringe and the reaction was allowed to stir at ambient temperature for 16 hours. The reaction was quenched by 1ml glacial AcOH and then subjected to column chromatography to provide **33** (13 mg, 60 %). [Pre-elute the column using Hexane (10 % volumn of AcOH in it) and then elute the column with Hexane and ethyl acetate (1 % AcOH in it)][58]; Rf = 0.36 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 200.7 (c = 0.82, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 °C oven temperature. Major: 8.3 min, Minor: 8.6 minutes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, 1H, J = 10.3 Hz, J = 1.2 Hz), 6.21 (d, 1H, J = 10.3 Hz), 3.42 (s, 3H), 2.81-2.95 (m, 2H), 2.58-2.77 (m, 2H), 2.13-2.37 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 195.4, 147.7, 133.3, 78.7, 52.2, 51.4, 36.3, 34.8, 32.8; IR (NaCl, neat) 2917, 2827, 1744, 1683, 1384, 1087 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0787.



2-(1,3-dimethyl-4-oxocyclohexa-2,5-dienyloxy)acetaldehyde (62): Rf = 0.46 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 6.70 (dd, 1H, J = 10.0, 3.0 Hz), 6.48-6.51 (m, 1H), 6.27 (d, 1H, J = 10.0 Hz), 3.91 (s, 2H), 1.88 (d, 3H, J = 1.4 Hz), 1.49 (s, 3H); ^{13}C NMR (75 MHz,

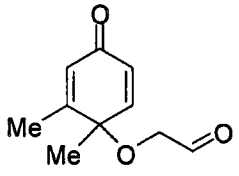
[57] Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284-6289.
[58] We have observed that this product decomposes by methanol elimination and tautomerization to hydroxyindanone on silica gel. These precautions prevent this problem.

$CDCl_3$) δ 199.7, 185.5, 149.8, 145.2, 137.9, 130.8, 73.8, 71.3, 26.5, 16.1; IR (NaCl, neat) 2966, 2919, 1735, 1673, 1644, 1098 cm^{-1}; HRMS (EI+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0786.

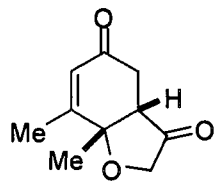


89 **90**

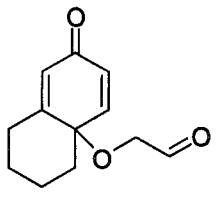
(3aS,7aR)-6,7a-dimethyl-3a,4-dihydrobenzo-furan-3,5(2H, 7aH)-dione (89) and **(3aS,4S,7aR)-4,7a-dimethyl-3a,4-dihydrobenzo-furan-3,5(2H,7aH)-dione (90)**: 43 and 44 cannot be separated. Rf = 0.54 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 61.2 (c = 0.9, $CHCl_3$, mixture of **43** and **44** with 2:1 ratio); Gas chromatography analysis – Chiraldex GTA column, gas flow 3ml/min with constant 130 °C oven temperature. **43**: Major: 9.6 min, Minor: 10.7 minutes; **44**: Major: 10.3 min, Minor: 13.4 minutes; IR (NaCl, neat) 2966, 2919, 2883, 1764, 1682, 1055 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0786.



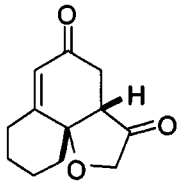
2-(1,2-dimethyl-4-oxocyclohexa-2,5-dienyloxy)acetaldehyde (64): Rf = 0.35 (2:1 EtOAc/Hex); ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 6.74 (d, 1H, J = 10.0 Hz), 6.28 (dd, 1H, J = 10.0, 1.9 Hz), 6.19 (s, 1H), 3.80 (dd, 2H, J = 34.4, 17.7 Hz), 1.98 (d, 3H, J = 1.0 Hz), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 185.2, 158.9, 150.5, 130.7, 129.8, 75.2, 70.9, 25.3, 18.0; IR (NaCl, neat) 2981, 1735, 1670, 1635, 1294, 1093 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0786.



7,7a-dimethyl-3a,4-dihydrobenzofuran-3,5(2H,7aH)-dione (91): Rf = 0.44 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 6.6 (c = 1.5, $CHCl_3$); Gas chromatography analysis – Chiraldex GTA column, gas flow 3ml/min with constant 150 °C oven temperature. Major: 8.5 min, Minor: 8.9 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (s, 1H), 4.17 (dd, 1H, *J* = 17.2, 1.1 Hz), 3.64 (d, 1H, *J* = 17.2 Hz), 3.01 (ddd, 1H, *J* = 17.9, 1.4, 1.0 Hz), 2.69 (d, 1H, *J* = 7.1 Hz), 2.56 (dd, 1H, *J* = 17.9, 7.0 Hz), 1.98 (d, 3H, *J* = 1.3 Hz), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 193.7, 160.9, 130.1, 81.0, 69.5, 52.2, 33.2, 23.8, 18.2; IR (NaCl, neat) 2981, 2914, 1760, 1683, 1270, 1052 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{12}O_3$, 180.0786. Found 180.0786.

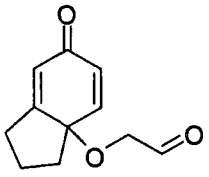


2-(7-oxo-1,2,3,4,4a,7-hexahydronaphthalen-4a-yloxy)acetaldehyde (66): Rf = 0.38 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 6.68 (d, 1H, *J* = 10.0 Hz), 6.31 (dd, 1H, *J* = 10.0, 1.9 Hz), 6.22 (s, 1H), 3.79 (dd, 2H, *J* = 17.8, 2.5 Hz), 2.23-2.44 (m, 3H), 1.92-2.10 (m, 2H), 1.60-1.72 (m, 1H), 1.28-1.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 185.9, 161.6, 149.8, 131.4, 127.3, 74.4, 70.2, 39.2, 32.7, 28.1, 20.5; IR (NaCl, neat) 2939, 2855, 1734, 1664, 1092, 883 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}O_3$, 206.0943. Found 206.0942.

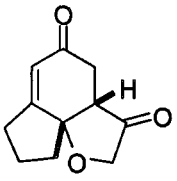


3a,4,7,8,9,10-hexahydro-2H-naphtho[1-b]furan-3,5-dione (93): Rf = 0.56 (2:1 EtOAc/Hex); $[\alpha]_D^{21}$ = + 2.3 (c = 1.5, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 170 °C oven temperature. Major: 22.0 min, Minor: 21.4 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (s, 1H), 4.15 (dd, 1H, *J* = 17.2, 0.7 Hz), 3.69 (d, 1H, *J* = 17.2

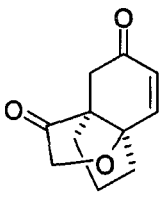
Hz), 2.97 (d, 1H, J = 16.5 Hz), 2.62-2.75 (m, 1H), 2.46-2.60 (m, 2H), 1.90-2.26 (m, 5H), 1.70-1.80 (m, 1H), 1.32-1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 194.6, 163.7, 126.6, 80.9, 68.9, 50.6, 37.9, 34.2, 32.5, 28.1, 21.3; IR (NaCl, neat) 2940, 2858, 1762, 1675, 1245, 1050 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}O_3$, 206.0943. Found 206.0942.



2-(6-oxo-2,3,3a,6-tetrahydro-1H-inden-3a-yloxy)acetaldehyde (68): Rf = 0.4 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 6.80 (d, 1H, J = 10.0 Hz), 6.28 (dd, 1H, J = 9.9, 1.7 Hz), 6.17-6.20 (m, 1H), 3.81 (dd, 2H, J = 24.7, 17.9 Hz), 2.61-2.78 (m, 1H), 2.40-2.54 (m, 1H), 2.18-2.34 (m, 2H), 1.88-2.22 (m, 1H), 1.60-1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 185.9, 165.5, 144.0, 132.2, 125.9, 79.4, 69.9, 35.6, 28.8, 21.8; IR (NaCl, neat) 2955, 2838, 1733, 1668, 1645, 1046 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_3$, 192.0786. Found 192.0786.

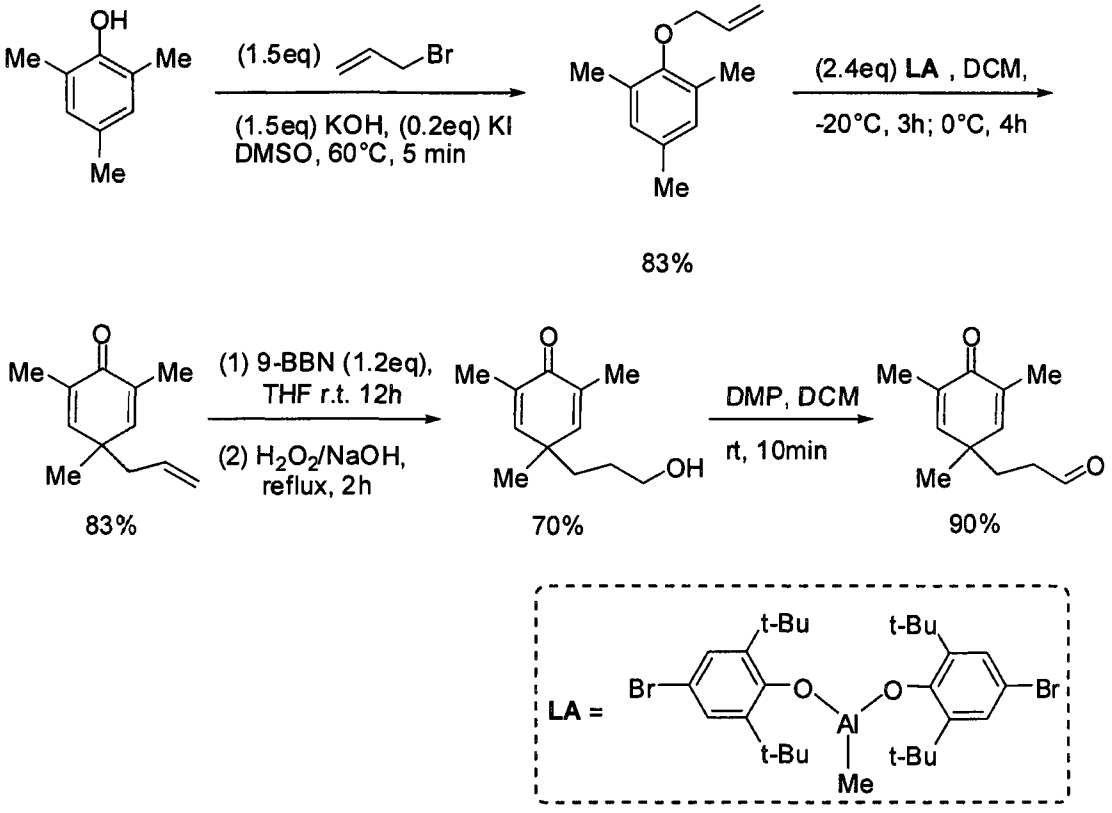


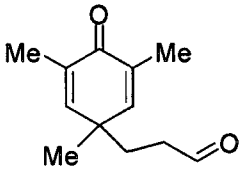
3a,4,8,9-tetrahydroindeno[4-b]furan-3,5(2H,7H)-dione (95): Rf = 0.42 (4:1 Et_2O/Hex); $[\alpha]_D^{21}$ = + 13.2 (c = 0.1, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 150 °C oven temperature. Major: 29.7 min, Minor: 27.0 minutes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (dd, 1H, J = 2.0, 1.9 Hz), 4.20 (dd, 1H, J = 17.5, 0.8 Hz), 4.07 (d, 1H, J = 17.5), 2.76-2.94 (m, 2H), 2.46-2.64 (m, 3H), 2.06-2.24 (m, 2H), 1.84-1.96 (m, 1H), 1.52-1.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 195.2, 164.8, 125.3, 85.4, 69.4, 48.4, 35.0, 34.4, 29.6, 20.8; IR (NaCl, neat) 2955, 2843, 1757, 1675, 1035, 912 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_3$, 192.0786. Found 192.0786.



[4.3.3]oxo-propellenedione (96): Rf = 0.48 (4:1 Et_2O/Hex); $[\alpha]_D^{21}$ = -112.7 (c = 0.36, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM column, gas flow 3ml/min with constant 150 °C oven temperature. Major: 11.6 min, Minor: 13.0 minutes; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, 1H, *J* = 10.3 Hz), 6.02 (d, 1H, *J* = 10.3 Hz), 4.30 (d, 1H, *J* = 17.3 Hz), 3.88 (d, 1H, *J* = 17.3 Hz), 3.06 (d, 1H, *J* = 17.4 Hz), 2.36 (d, 1H, *J* = 17.4 Hz), 2.30-2.40 (m, 1H), 1.94-2.18 (m, 4H), 1.68-1.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 195.4, 147.4, 130.3, 90.7, 69.9, 57.9, 41.2, 37.8, 36.9, 24.4; IR (NaCl, neat) 2955, 2873, 1757, 1670, 1050, 917 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{12}O_3$, 192.0786. Found 192.0786.

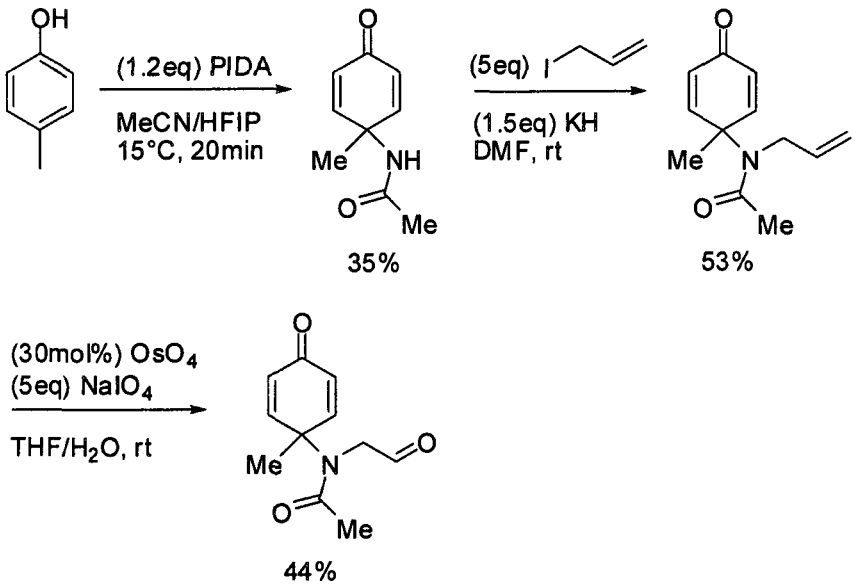
Synthesis of substrate **107**:

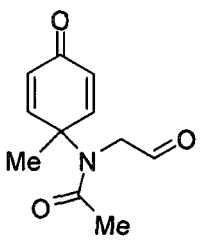




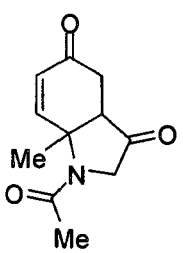
3-(1,3,5-trimethyl-4-oxocyclohexa-2,5-dienyl)propanal (107): Rf = 0.63 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 6.44 (s, 2H), 2.20 (t, 2H, J = 7.8 Hz), 1.90 (t, 2H, J = 7.8 Hz), 1.87 (s, 6H).

Synthesis of **108**:

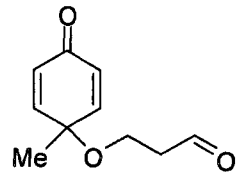




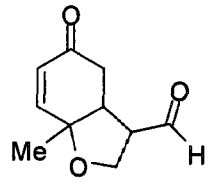
N-(1-methyl-4-oxocyclohexa-2,5-dienyl)-N-(2-oxoethyl)acetamide (108): Rf = 0.50 (9:1 DCM/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.09 (d, 1H, J = 10.0 Hz), 6.25 (d, 2H, J = 10.0 Hz), 4.40 (s, 2H), 2.02 (s, 3H), 1.58 (s, 3H).



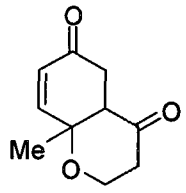
N-(1-methyl-4-oxocyclohexa-2,5-dienyl)-N-(2-oxoethyl)acetamide (109): Rf = 0.56 (9:1 DCM/MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, 1H, J = 11.0 Hz), 5.95 (d, 1H, J = 11.0 Hz), 4.13 (d, 2H, J = 18.2 Hz), 3.79 (d, 1H, J = 18.2 Hz), 3.04 (dd, 1H, J = 17.4, 2.6 Hz), 2.90-2.95 (m, 1H), 2.11 (s, 3H), 2.00 (s, 3H).



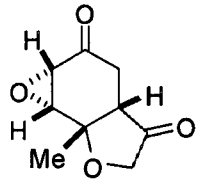
3-(1-methyl-4-oxocyclohexa-2,5-dienyloxy)propanal (30): Rf = 0.51 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74-9.77 (m, 1H), 6.78 (d, 1H, J = 10.2 Hz), 6.30 (d, 2H, J = 10.1 Hz), 3.64 (t, 2H, J = 5.91Hz), 2.60-2.66 (m, 2H), 1.40 (s, 3H).



7a-methyl-5-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carbaldehyde (97): Rf = 0.37 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (d, 1H, J = 2.3 Hz), 6.59 (dd, 1H, J = 10.3, 1.6 Hz), 6.02 (d, 1H, J = 10.3 Hz), 4.12 (dd, 1H, J = 9.6, 5.2 Hz), 3.90 (t, 1H, J = 9.4 Hz), 2.84-2.93 (m, 1H), 2.65-2.74 (m, 3H), 1.52 (s, 3H).

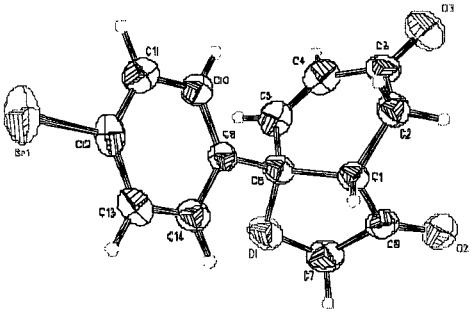


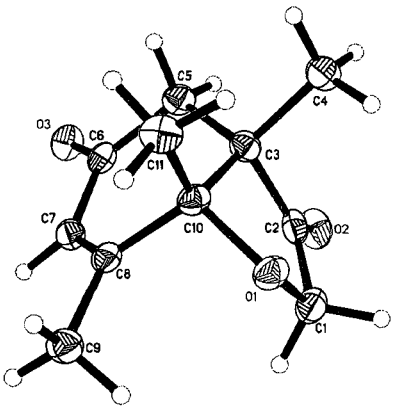
8a-methyl-4a,5-dihydro-2H-chromene-4,6(3H,8aH)-dione (98): Rf = 0.36 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, 1H, J = 10.4 Hz), 5.97 (d, 1H, J = 10.4 Hz), 4.14-4.22 (m, 1H), 3.84 (dt, 1H, J = 12.3, 2.5 Hz), 3.07-3.16 (m, 1H), 2.93-2.98 (m, 1H), 2.66-2.78 (m, 1H), 2.33-2.47 (m, 2H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 195.8, 151.8, 131.5, 77.9, 63.2, 55.4, 41.8, 35.2, 27.2

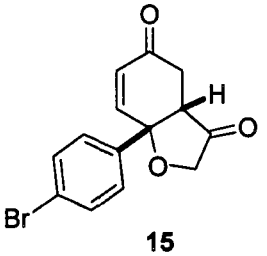


Epoxide (111): Rf = 0.51 (2:1 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (d, 1H, J = 16.7 Hz), 4.24 (d, 1H, J = 16.8 Hz), 3.55 (d, 1H, J = 4.4 Hz), 3.32 (d, 1H, J = 4.5 Hz), 3.04 (d, 1H, J = 18.0 Hz), 2.35-2.53 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 202.1, 79.7, 70.5, 62.2, 55.2, 47.9, 31.3, 22.0

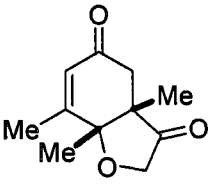
Absolute configurations of 15 and 31[59]:





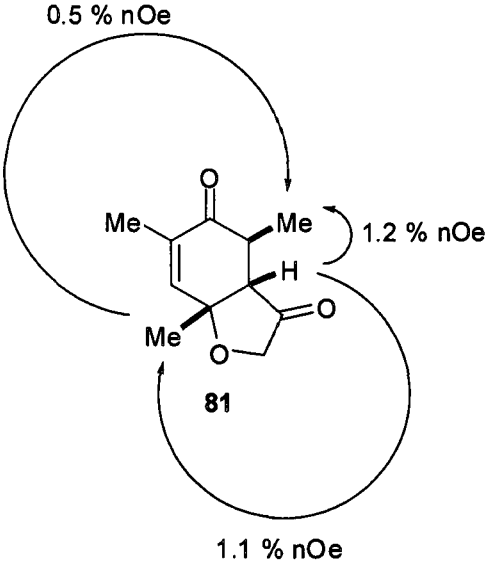


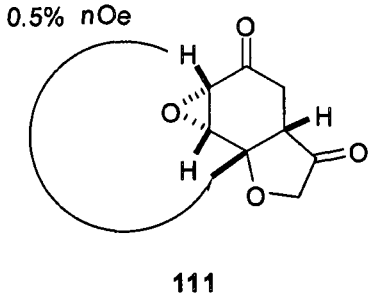
15



31

nOe result of **81** and **111:**





[59] Determined by anomalous dispersion. See: Thiessen, W.; Hope, H. *Acta Cryst.* **1970**, *B26*, 554-62.

Chapter 2

Asymmetric Intermolecular Stetter Reaction of Glyoxylamide

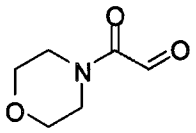
General Methods.

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran and Dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Triethylamine, Hunig's base and methanol were distilled from CaH_2. CCl_4 (99.9%) was purchased from Aldrich and redistilled before use. KHMDS (0.5 M solution in toluene) was purchased from Aldrich Chemical Co. and used without purification.

Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate dips followed by heating.

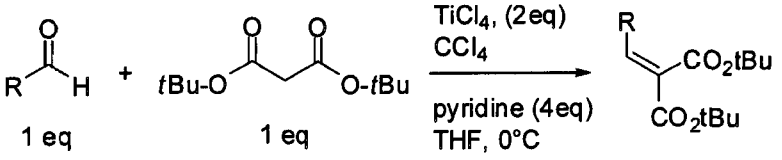
^1H NMR was recorded at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR was recorded at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm.

Synthesis of the glyoxamide 93:



2-morpholino-2-oxoacetaldehyde (93): Acryloyl Morpholine (5.65 g, 40 mmol, Aldrich 97%) was dissolved in a mixture of 80 ml dichloromethane and 20 ml methanol. The solution was purged with O_3 at -78 °C until the solution turned to blue. The excess O_3 in the solution was removed by purging of oxygen at -78 °C. To the mixture was added 4 equivalent of Dimethyl sulfide (160 mmol, 10 g) at -78 °C, and then stirred it at -78 °C to rt under argon atmosphere over night. After all solvent was removed on a rotary evaporator, the crude mixture was distilled *in vacuo* (b.p. 80 °C/1 torr). The product was obtained as yellow liquid (4 g, 70% yield). This compound is sensitive to air and mositure so it was sealed protected under Argon and stored in Freezer. It was melt by heat gun before used. Rf = 0.3 (100% EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 3.65-3.80 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.7, 161.8, 67.1, 66.8, 45.4, 42.8; IR (NaCl, neat) 3360, 2919, 2852, 1648, 1413, 1110 cm^{-1}; HRMS (FAB+) calcd for $C_6H_{10}NO_3$, 143.0582, Found 143.0585.

General procedure for synthesis of Alkylidenemalonates[60]

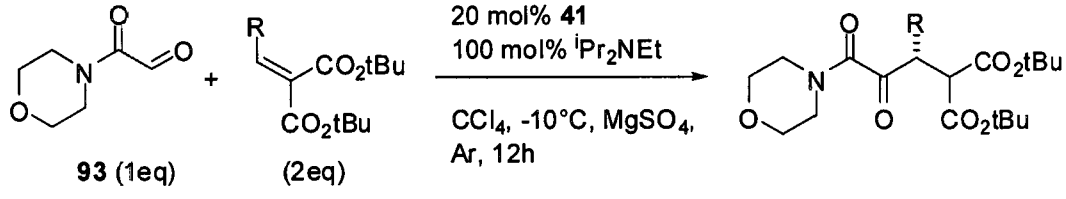


A flame-dried 50 ml round bottom flask with magnetic stir bar was charged with $TiCl_4$ (1.90 g, 10 mmol) and 2.5ml CCl_4 at 0°C; 20ml dry THF was added dropwise to the

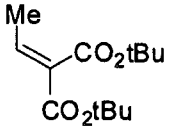
[60] Antonioletti, R.; Bovicelli, P.; Malancona, S. *Tetrahedron* **2002** (*58*) 589-596.

flask and bright yellow precipitate formed; 5mmol aldehyde and 5mmol di-tert-butyl malonate were added. A solution of 1.61ml pyridine in 3ml dry THF was then added dropwise to the stirring mixture in one hour. The reaction was then allowed to warm up to room temperature and stirred overnight. The reaction was quenched with water and extract with EtOAc. The organic layer was washed with brine and then dried with Na_2SO_4, then concentrated *in vacuo* and the residue was subjected to column chromatography (Et_2O : Hexane = 1:40) to provide Alkylidenemalonates.

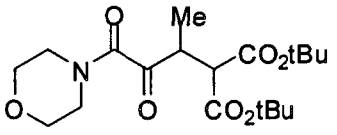
General procedure for the asymmetric intermolecular Stetter reaction:



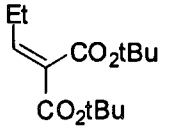
A flame-dried 5 ml test tube was charged with triazolium salt **41** (14.5 mg, 0.032 mmol), Michael acceptor (0.32 mmol) and MgSO4 (20 mg, 0.16 mmol). The test tube was purged under vacuum and then refilled with argon for 3 times. Glyoxamide **93** (23 mg, 0.16 mmol) was then added followed by 0.5 ml of distilled CCl_4. The test tube was put into -12°C cryo-cool bath (temperature of reaction in test tube is -10°C). Then hunig's base (0.028 ml, 0.16 mmol) was added to the solution. The reaction was allowed to stir at -10°C for 12 hours and then quenched by 0.1 ml HOAc and then directly purified by flash column chromatography (EtOAc : Hexane = 1:2) to provide Stetter products.



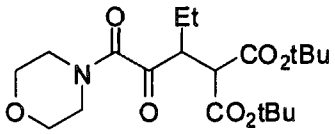
di-tert-butyl 2-ethylidenemalonate (101): Rf = 0.73 (1:2 EtOAc/Hex); 74 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (q, 1H, J = 7.3 Hz), 1.89 (d, 3H, J = 7.3 Hz), 1.52 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 163.4, 141.5, 132.6, 81.7, 81.4, 28.2, 28.1, 15.1; IR (NaCl, neat) 2970, 1720, 1367, 1279, 1171, 845 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{22}O_4$, 242.1518. Found 242.1520.



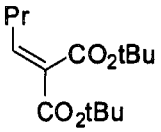
di-tert-butyl 2-(4-morpholino-3,4-dioxobutan-2-yl)malonate (102): Rf = 0.36 (1:2 EtOAc/Hex); 68 % yield (3h); $[\alpha]_D^{21}$ = +14.8 (c = 0.038 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 95:5 hexanes : isopropanol 1.0 mL / min. Major: 8.5 minutes, Minor: 7.8 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45-3.80 (m, 10H), 1.45 (s, 9H), 1.40 (s, 9H), 1.29 (d, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 168.5, 167.3, 164.7, 82.6, 82.2, 67.2, 66.8, 57.5, 46.6, 42.8, 42.1, 28.0, 15.8; IR (NaCl, neat) 2975, 2924, 1718, 1640, 1256, 1142 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{31}NO_7$, 385.2101, Found 385.2106.



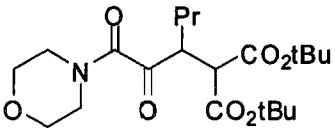
di-tert-butyl 2-propylidenemalonate (64): Rf = 0.75 (1:2 EtOAc/Hex); 95 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (t, 1H, J = 7.8 Hz), 2.26 (m, 2H), 1.52 (s, 9H), 1.48 (s, 9H), 1.08 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 163.6, 147.7, 131.1, 81.8, 81.6, 28.3, 28.2, 23.0, 13.1; IR (NaCl, neat) 2971, 2929, 1724, 1367, 1252, 1141 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{24}O_4$, 256.1675, Found 256.1679.



di-tert-butyl 2-(1-morpholino-1,2-dioxopentan-3-yl)malonate (87): Rf = 0.40 (1:2 EtOAc/Hex); 84 % yield; $[\alpha]_D^{21}$ = +28.6 (c = 0.049 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 5.7 minutes, Minor: 4.9 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 3.45-3.80 (m, 10H), 1.65-1.85 (m, 2H), 1.44 (s, 9H), 1.39 (s, 9H), 0.91 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 168.6, 167.4, 164.7, 82.6, 82.2, 67.1, 66.8, 56.4, 48.3, 46.6, 42.3, 28.0, 23.6, 10.7; IR (NaCl, neat) 2975, 2924, 1720, 1643, 1369, 1116 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{33}NO_7$, 399.2257, Found 399.2251.

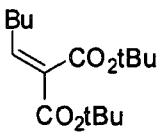


di-tert-butyl 2-butylidenemalonate (103): Rf = 0.77 (1:2 EtOAc/Hex); 92 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (t, 1H, J = 7.8 Hz), 2.22 (q, 2H, J = 7.7 Hz), 1.51 (s, 9H), 1.48 (s, 9H), 0.93 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 163.6, 146.3, 131.8, 81.8, 81.6, 31.5, 28.2, 28.0, 21.9, 14.0; IR (NaCl, neat) 2975, 2929, 1723, 1367, 1170, 840 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{26}O_4$, 270.1831, Found 270.1827.

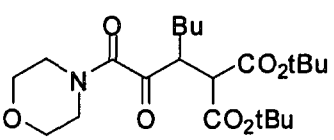


di-tert-butyl 2-(1-morpholino-1,2-dioxohexan-3-yl)malonate (104): Rf = 0.45 (1:2 EtOAc/Hex); 83 % yield; $[\alpha]_D^{21}$ = +23.4 (c = 0.034 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 5.2 minutes, Minor: 4.5 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 3.45-3.80 (m, 10H), 1.55-1.75 (m, 2H), 1.45 (s, 9H), 1.39 (s, 9H), 0.87 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 168.6, 167.4, 164.7, 82.6, 82.2, 67.1, 66.8, 57.1, 47.0, 46.7, 42.3, 32.7, 28.0, 19.8, 14.3; IR (NaCl, neat) 2970, 2924,

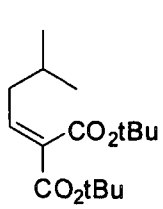
1719, 1643, 1144, 1116 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{35}NO_7$, 413.2414, Found 413.2420.



di-tert-butyl 2-pentylidenemalonate (105): Rf = 0.80 (1:2 EtOAc/Hex); 90 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (t, 1H, J = 7.8 Hz), 2.24 (q, 2H, J = 7.5 Hz), 1.51 (s, 9H), 1.48 (s, 9H), 1.25-1.45 (m, 4H), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 163.6, 146.6, 131.6, 81.8, 81.6, 34.4, 30.6, 29.2, 28.2, 28.0, 25.9, 22.7, 22.6, 14.2, 14.0; IR (NaCl, neat) 2965, 2863, 1723, 1454, 1274, 1050 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{28}O_4$, 284.1988, Found 284.1992.

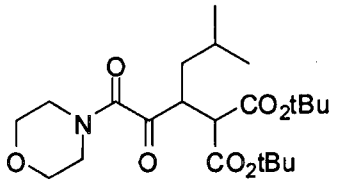


di-tert-butyl 2-(1-morpholino-1,2-dioxoheptan-3-yl)malonate (106): Rf = 0.49 (1:2 EtOAc/Hex); 70 % yield; $[\alpha]_D^{21}$ = +24.6 (c = 0.041 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 5.4 minutes, Minor: 4.4 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 3.50-3.85 (m, 9H), 2.16-2.30 (m, 1H), 1.63-1.74 (m, 2H), 1.46 (s, 9H), 1.41 (s, 9H), 1.22-1.38 (m, 4H), 0.91 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 168.6, 167.4, 164.7, 145.8, 82.7, 82.2, 67.2, 66.9, 57.0, 47.2, 46.7, 42.3, 32.3, 28.6, 23.0, 14.0; IR (NaCl, neat) 2960, 2858, 1719, 1645, 1362, 1145 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{37}NO_7$, 427.2570, Found 427.2575.

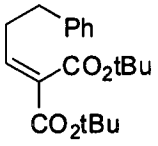


di-tert-butyl 2-(3-methylbutylidene)malonate (107): Rf = 0.73 (1:2 EtOAc/Hex); 74 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (t, 1H, J = 7.9 Hz), 2.12 (dd, 2H, J = 7.9, 6.8 Hz), 1.70-1.83 (m, 1H), 1.50 (s, 9H),

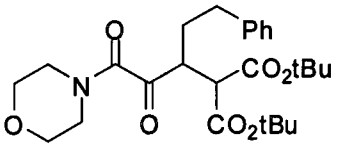
1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 163.6, 145.4, 132.2, 81.6, 38.4, 28.3, 22.7; IR (NaCl, neat) 2971, 2868, 1721, 1460, 1368, 845 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{28}O_4$, 284.1988, Found 284.1992.



di-tert-butyl 2-(5-methyl-1-morpholino-1,2-dioxohexan-3-yl) malonate (108): Rf = 0.49 (1:2 EtOAc/Hex); 51 % yield (28h); $[\alpha]_D^{21}$ = +9.6 (c = 0.032 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 4.7 minutes, Minor: 4.4 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 3.48-3.82 (m, 10H), 1.55-1.76 (m, 2H), 1.45 (s, 9H), 1.40 (s, 9H), 1.20-1.28 (m, 1H), 0.90 (dd, 6H, J = 6.4, 33.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 168.6, 167.3, 164.7, 82.8, 82.2, 67.1, 58.6, 46.8, 45.1, 42.4, 40.3, 28.1, 25.8, 23.7, 22.1; IR (NaCl, neat) 2971, 2873, 1719, 1644, 1363, 1147 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{37}NO_7$, 427.2570, Found 427.2564.

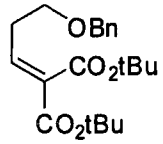


di-tert-butyl 2-(3-phenylpropylidene)malonate (109): Rf = 0.68 (1:2 EtOAc/Hex); 61 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16-7.33 (m, 5H), 6.82 (t, 1H, J = 7.7 Hz), 2.75-2.82 (m, 2H), 2.53-2.62 (m, 2H), 1.52 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 163.5, 145.2, 140.9, 128.7, 128.5, 126.4, 82.0, 81.8, 34.8, 31.3, 28.3, 28.2, 28.1; IR (NaCl, neat) 2971, 2925, 1724, 1368, 117590, 697 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{28}O_4$, 332.1988, Found 332.1997.

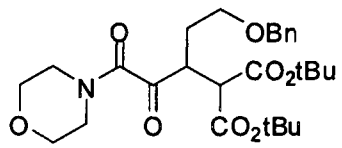


di-tert-butyl 2-(1-morpholino-1,2-dioxo-5-phenylpentan-3-yl) malonate (110): Rf = 0.45 (1:2 EtOAc/Hex); 81 %

yield; $[\alpha]_D^{21}$ = +15.4 (c = 0.056 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 9.1 minutes, Minor: 6.1 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12-7.28 (m, 5H), 3.50-3.85 (m, 10H), 2.58-2.72 (m, 2H), 1.96-2.04 (m, 2H), 1.43 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 168.5, 167.3, 164.7, 141.9, 128.6, 128.5, 126.1, 82.8, 82.4, 67.2, 66.9, 57.0, 47.1, 46.7, 42.3, 32.7, 32.6, 28.0; IR (NaCl, neat) 2971, 2858, 1719, 1643, 1368, 994 cm^{-1}; HRMS (FAB+) calcd for $C_{26}H_{37}NO_7$, 475.2570, Found 475.2569.

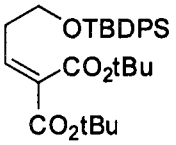


di-tert-butyl 2-(3-(benzyloxy)propylidene)malonate (111): Rf = 0.63 (1:2 EtOAc/Hex); 55 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25-7.34 (m, 5H), 6.87 (t, 1H, J = 7.6 Hz), 4.50 (s, 2H), 3.57 (t, 2H, J = 6.5 Hz), 2.55-2.63 (m, 2H), 1.51 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 163.4, 143.1, 138.3, 133.0, 128.6, 127.9, 82.0, 81.7, 73.1, 68.4, 30.1, 28.2; IR (NaCl, neat) 2980, 2863, 1721, 1367, 1165, 730 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{30}O_5$, 362.2093, Found 362.1962.

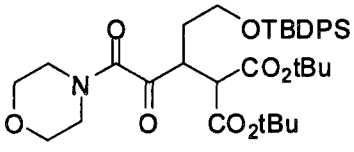


di-tert-butyl 2-(5-(benzyloxy)-1-morpholino-1,2-dioxopentan-3-yl) malonate (112): Rf = 0.34 (1:2 EtOAc/Hex); 91 % yield; $[\alpha]_D^{21}$ = +13.4 (c = 0.067 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 10.6 minutes, Minor: 7.1 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23-7.36 (m, 5H), 4.43 (dd, 2H, J = 14.7, 11.8 Hz), 3.82-3.90 (m, 1H), 3.40-3.70 (m, 11H), 1.97-2.04 (m, 2H), 1.44 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 168.1, 167.5, 164.0, 138.4, 128.5, 127.9, 82.6, 82.3, 73.2, 67.7, 67.1, 66.8, 56.6, 46.6, 44.5, 42.5, 30.2, 28.1; IR (NaCl, neat)

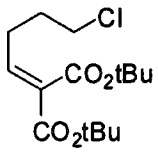
2965, 2852, 1719, 1642, 1460, 1115 cm^{-1}; HRMS (FAB+) calcd for $C_{27}H_{39}NO_8$, 505.2676, Found 505.2598.



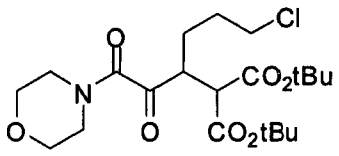
di-tert-butyl 2-(3-(tert-butyldiphenylsilyloxy)propylidene)malonate (113): Rf = 0.74 (1:2 EtOAc/Hex); 87 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64-7.68 (m, 4H), 7.35-7.45 (m, 6H), 6.92 (t, 1H, J = 7.6 Hz), 3.76 (t, 2H, J = 6.4 Hz), 2.55 (q, 2H, J = 6.5 Hz), 1.52 (s, 9H), 1.51 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 163.4, 143.4, 135.7, 133.7, 132.7, 129.8, 127.9, 81.9, 81.6, 62.4, 32.8, 28.2, 28.1, 28.1, 27.0, 19.4; IR (NaCl, neat) 2971, 2848, 1716, 1398, 1163, 697 cm^{-1}; HRMS (FAB+) calcd for $C_{30}H_{42}O_5Si$, 510.2802, Found 510.2807.



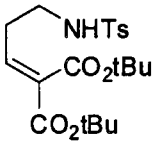
di-tert-butyl 2-(5-(tert-butyldiphenylsilyloxy)-1-morph -olino-1,2-dioxopentan-3-yl)malonate (114): Rf = 0.54 (1:2 EtOAc/Hex); 50 % yield; $[\alpha]_D^{21}$ = +6.1 (c = 0.047 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 4.5 minutes, Minor: 3.9 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.67 (m, 4H), 7.32-7.40 (m, 6H), 3.95-4.06 (m, 1H), 3.45-3.78 (m, 10H), 1.43 (s, 9H), 1.41 (s, 9H), 1.20 (s, 3H), 1.18 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 168.3, 167.5, 164.2, 135.7, 133.8, 133.8, 129.7, 127.8, 82.6, 82.2, 67.1, 66.8, 61.6, 56.8, 46.6, 44.7, 42.3, 33.0, 28.0, 26.9, 25.5, 19.3; IR (NaCl, neat) 2976, 2848, 1720, 1363, 1113, 702 cm^{-1}; HRMS (FAB+) calcd for $C_{36}H_{51}NO_8Si$, 653.3384, Found 653.3385.



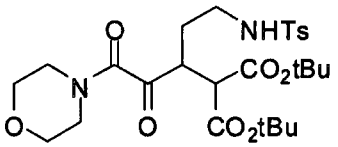
di-tert-butyl 2-(4-chlorobutylidene)malonate (115): Rf = 0.66 (1:2 EtOAc/Hex); 53 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (t, 1H, J = 7.9 Hz), 3.50 (t, 2H, J = 6.5 Hz), 2.34-2.42 (m, 2H), 1.86-1.96 (m, 2H), 1.48 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 163.3, 144.0, 132.8, 82.2, 81.8, 44.2, 31.4, 28.2, 28.1, 26.8; IR (NaCl, neat) 2971, 2930, 1726, 1368, 1152, 846 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{25}ClO_4$, 304.1441, Found 304.1451.



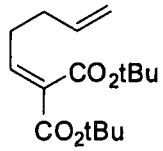
di-tert-butyl 2-(6-chloro-1-morpholino-1,2-dioxohexan-3-yl) malonate (116): Rf = 0.39 (1:2 EtOAc/Hex); 84 % yield; $[\alpha]_D^{21}$ = +15.8 (c = 0.054 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 7.4 minutes, Minor: 5.8 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46-3.83 (m, 12H), 1.75-1.87 (m, 4H), 1.46 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 168.5, 167.1, 164.6, 83.0, 82.5, 67.1, 66.8, 57.6, 46.7, 46.2, 44.9, 42.3, 29.4, 28.0, 27.9; IR (NaCl, neat) 2976, 2868, 1720, 1450, 1260, 1145 cm^{-1}; HRMS (FAB+) calcd for $C_{21}H_{34}ClNO_7$, 447.2024, Found 447.2030.



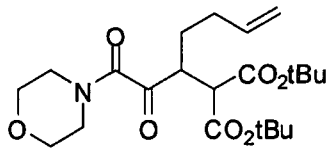
di-tert-butyl 2-(3-(4-methylphenylsulfonamido)propylidene)malonate (117): Rf = 0.41 (1:2 EtOAc/Hex); 20 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.72 (m, 2H), 7.25-7.29 (m, 2H), 6.55 (t, 1H, J = 8.2 Hz), 3.05 (q, 2H, J = 6.2 Hz), 2.35-2.42 (m, 5H), 1.49 (s, 6H), 1.46 (s, 6H), 1.41 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 165.2, 162.9, 143.6, 141.5, 136.9, 136.8, 134.4, 130.2, 129.9, 129.8, 127.3, 126.4, 83.0, 82.3, 82.2, 57.2, 41.4, 29.3, 28.2, 28.0, 21.7.



di-tert-butyl 2-(5-(4-methylphenylsulfonamido)-1-morpho -lino-1,2-dioxopentan-3-yl)malonate (118): Rf = 0.20 (1:2 EtOAc/Hex); 33 % yield; HPLC analysis – Chiracel AD-H column 6:4 hexanes : isopropanol 1.0 mL / min. Major: 8.9 minutes, Minor: 10.6 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.72 (d, 2H, J = 8.3 Hz), 7.25 (d, 2H, J = 8.5 Hz), 6.32 (dd, 1H, J = 5.2, 8.5 Hz), 3.40-3.94 (m, 10H), 3.05-3.14 (m, 1H), 2.61-2.74 (m, 1H), 2.39 (s, 3H), 1.80 (m, 2H), 1.48 (s, 9H), 1.40 (s, 9H).

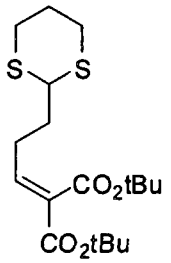


di-tert-butyl 2-(pent-4-enylidene)malonate (119): Rf = 0.74 (1:2 EtOAc/Hex); 78 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (t, 1H, *J* = 7.7 Hz), 5.68-5.84 (m, 1H), 4.93-5.05 (m, 2H), 2.27-2.35 (m, 2H), 2.13-2.22 (m, 2H), 1.47 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 163.5, 145.4, 137.0, 131.9, 115.8, 81.9, 81.6, 32.5, 28.8, 28.2; IR (NaCl, neat) 2976, 2929, 1723, 1644, 1368, 1167 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{26}O_4$, 282.1831, Found 282.1838.

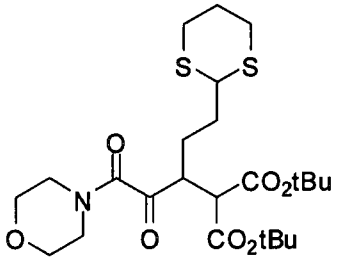


di-tert-butyl 2-(1-morpholino-1,2-dioxohept-6-en-3-yl)malonate (120): Rf = 0.30 (1:2 EtOAc/Hex); 97 % yield; $[\alpha]_D^{21}$ = +23.7 (c = 0.060 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 5.6 minutes, Minor: 4.8 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69-5.84 (m, 1H), 4.91-5.05 (m, 2H), 3.48-3.82 (m, 10H), 2.05-2.15 (m, 2H), 1.72-1.83 (m, 2H), 1.45 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 168.5, 167.4, 164.6, 137.8, 115.4, 82.8, 82.3, 67.1, 66.8,

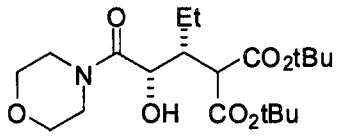
57.0, 46.7, 46.6, 42.3, 30.6, 29.8, 28.0; IR (NaCl, neat) 2981, 2863, 1720, 1643, 1265, 1144 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{35}NO_7$, 425.2414, Found 425.2410.



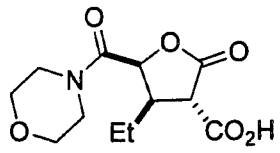
di-tert-butyl 2-(3-(1,3-dithian-2-yl)propylidene)malonate (121): Rf = 0.62 (1:2 EtOAc/Hex); 82 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.70 (t, 1H, J = 7.9 Hz), 5.66-5.72 (m, 1H), 2.76-2.84 (m, 5H), 2.38-2.50 (m, 2H), 1.80-1.90 (m, 2H), 1.48 (s, 9H), 0.93 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 165.0, 163.4, 144.1, 132.6, 131.0, 125.7, 82.1, 81.9, 81.8, 57.7, 47.2, 46.7, 38.6, 34.2, 30.5, 28.2, 26.7; IR (NaCl, neat) 2976, 2899, 1725, 1368, 1250, 1154 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{30}O_4S_2$, 374.1586, Found 374.1597.



di-tert-butyl 2-(5-(1,3-dithian-2-yl)-1-morpholino-1,2-dioxopent an-3-yl) malonate (122): Rf = 0.29 (1:2 EtOAc/Hex); 88 % yield; $[\alpha]_D^{21}$ = + 15.7 (c = 0.066 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 13.1 minutes, Minor: 15.8 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94-4.03 (m, 2H), 3.46-3.78 (m, 9H), 2.76-2.82 (m, 3H), 1.70-2.10 (m, 6H), 1.44 (s, 7H), 1.38 (s, 7H), 1.18 (s, 2H), 1.16 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 168.4, 167.1, 164.5, 82.8, 67.1, 57.0, 47.0, 42.3, 32.2, 30.2, 28.0, 27.6, 26.1, 25.6; IR (NaCl, neat) 2980, 2863, 1716, 1643, 1369, 906 cm^{-1}; HRMS (FAB+) calcd for $C_{24}H_{39}NO_7S_2$, 517.2168, Found 517.2177.

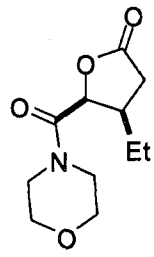


Alcohol **(123)**: A flame-dried round bottom flask was charged with α-ketoamide **14c** (100 mg, 0.25 mmol) in 2.5 mL of THF. Upon cooling to -100 °C, Et_3BHLi (1.0 M in THF, 0.38 mL, 0.38 mmol) was added dropwise via syringe. After stirring for 0.5 h at -100 °C, 4.0 mL of 1 M aq. HCl was added at -100 °C via syringe and the mixture was stirred for 1 h at room temperature. The reaction mixture was then diluted with EtOAc and the layers were separated. The aqueous layer was extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product (8:1 dr) was purified by column chromatography (2:3 EtOAc/Hex) to give pure alcohol **123** (80 mg, 80%) and the minor diastereomer contaminated with **123** (15 mg, 15%), both isolated as colorless oils. Rf (major) = 0.50 and Rf (minor) = 0.45 (3:2 EtOAc/Hex); $[\alpha]_D^{21}$ = +38.8 (c = 0.008 g/ml, $CHCl_3$); HPLC analysis – Chiracel OD-H column, 85:15 hexanes/*iso*-propanol, 1.0 mL/min. Major: 5.3 min, minor: 6.3 min; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.53 (dd, 1H, J_1 = 6.6 Hz, J_2 = 1.5 Hz), 3.83-3.62 (m, 8H), 3.52 (d, 1H, J = 9.9 Hz), 2.19-2.12 (m, 1H), 1.65-1.41 (m, 1H), 1.46 (s, 9H), 1.45 (s, 9H), 1.26-1.15 (m, 1H), 0.86 (t, 3H, J = 7.5 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.5, 168.7, 82.1, 81.9, 68.3, 66.9, 55.8, 45.6, 43.3, 42.6, 28.1, 28.0, 18.8, 13.5; **IR** (NaCl, neat) 3560-3304 (br), 2976, 2930, 2863, 1742, 1721, 1639, 1460 cm^{-1}; **HRMS** (FAB+) calcd for $C_{40}H_{70}N_2NaO_{14}$, 802.4827. Found 802.4829.

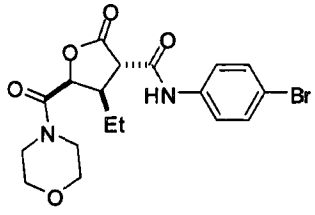


Carboxylic acid **(124)**: A solution of **123** (80 mg, 0.20 mmol) in formic acid (≥ 96%, 2.0 mL) was stirred at room temperature for 5 h. Formic acid was then co-evaporated with EtOAc (3 times) to give lactone **124** (54 mg, quantitative) as a white solid. The crystals were grown by slow

evaporation of an ethanol solution at room temperature. $[\alpha]_D^{21}$ = +92.5 (c = 0.012 g/ml, MeOH); **m.p.** (°C): 148-149; **^{1}H NMR** (300 MHz, acetone-D6) δ 5.72 (d, 1H, *J* = 8.0 Hz), 3.79-3.59 (m, 8H), 3.56 (d, 1H, *J* = 11.4 Hz), 3.21-3.10 (m, 1H), 1.75-1.62 (m, 1H), 1.47-1.30 (m, 1H), 0.94 (t, 3H, *J* = 7.5 Hz); **^{13}C NMR** (75 MHz, acetone-D6) δ 172.7, 169.8, 167.0, 74.2, 66.6, 51.1, 46.2, 45.8, 42.3, 22.6, 11.8; **IR** (NaCl, neat) 3682-2382 (br), 2965, 2930, 2863, 1778, 1731, 1639, 1450 cm^{-1}; **HRMS** (FAB+) calcd for $C_{11}H_{17}NO_4$ (M-CO_2), 227.1158. Found 227.1159.



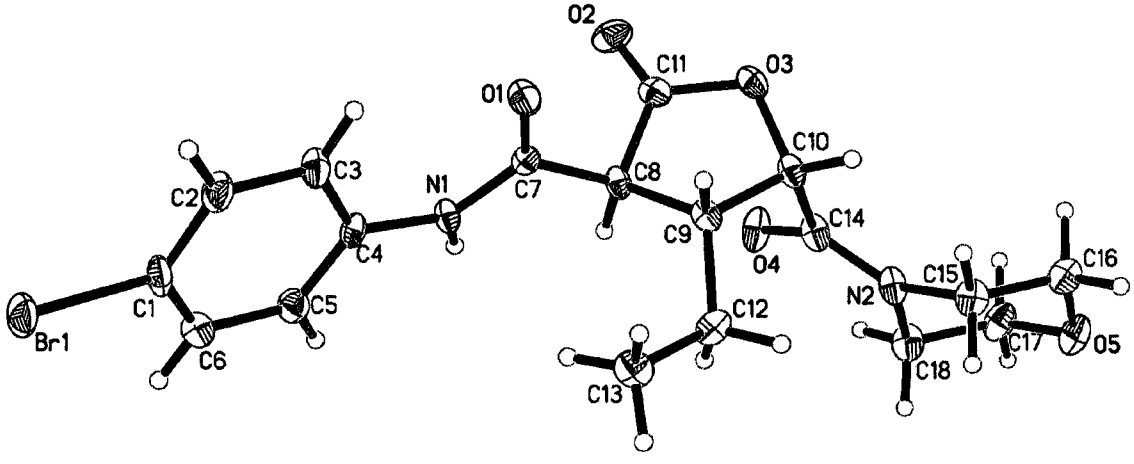
Lactone **(125)**: A solution of acid **124** (54 mg, 0.20 mmol) in toluene (4.0 mL) was stirred at 110 °C for 8 h. After concentration *in vacuo*, the crude product was purified by column chromatography (7:3 EtOAc/Hex) to give lactone **125** (43 mg, 94%) as a white solid. Rf = 0.25 (7:3 EtOAc/Hex); $[\alpha]_D^{21}$ = +66.1 (c = 0.011 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column, 50:50 hexanes/*iso*-propanol, 1.0 mL/min. Major: 6.9 min, minor: 5.5 min; **m.p.** (°C): 139-140; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.29 (d, 1H, *J* = 7.7Hz), 3.78-3.54 (m, 8H), 2.71-2.61 (m, 1H), 2.56 (s, 1H), 2.53 (d, 1H, *J* = 1.5 Hz), 1.57-1.44 (m, 1H), 1.42-1.29 (m, 1H), 0.96 (t, 3H, *J* = 7.5 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.6, 167.0, 75.6, 67.1, 66.7, 46.4, 42.5, 41.6, 32.8, 23.0, 12.8; **IR** (NaCl, neat) 2955, 2929, 2847, 1757, 1634, 1450 cm^{-1}; **HRMS** (FAB+) calcd for $C_{11}H_{17}NO_4$, 227.1158. Found 227.1163.



Amide **(126)**: To a solution of carboxylic acid **124** (25 mg, 0.09 mmol) in THF (1.0 mL) at 0 °C were added 4-bromoaniline (19 mg, 0.11 mmol), DMAP (1.1 mg, 0.009 mmol) and DCC (21 mg, 0.10 mmol). The reaction mixture was warmed to room

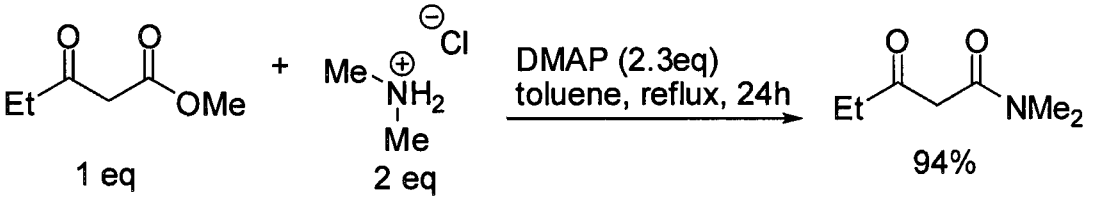
temperature and allowed to stir for 24 hours. After concentration in vaccuo, dichloromethane was added and the suspension was filtrated. Concentration in vacuo followed by column chromatography (3:2 EtOAc/Hex) give amide **126** (39 mg, 99%) as a white solid. The crystals were grown by slow evaporation of an ethanol solution at room temperature. Rf = 0.15 (3:2 AcOEt/Hex); $[a]^{D}_{21}$ = +10.0 (c = 0.092 g/ml, MeOH); m.p. (°C): 110-111; ^{1}H NMR (300 MHz, $CDCl_3$-D_6) δ 8.68 (s, 1H), 7.46-7.26 (m, 4H), 5.43 (d, 1H, *J* = 7.7 Hz), 3.81-3.52 (m, 9H), 3.29-3.18 (m, 1H), 1,81-1.66 (m, 1H), 1.60-1.46 (m, 1H), 0.99 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 166.8, 163.9, 136.7, 132.1, 121.8, 117.5, 74.4, 66.9, 66.7, 50.9, 46.6, 43.2, 42.7, 22.8, 12.5; IR (NaCl, neat) 3313 (br), 3190, 3114, 3067, 2955, 2919, 2852, 1767, 1685, 1634, 1598, 1526 cm-1; HRMS (FAB+) calcd for $C_{18}H_{21}BrN_2O_5$, 424.0634. Found 424.0634.

Absolute configuration of 126:



Diastereoselective Intermolecular Stetter Reaction of Glyoxylamide with alkylideneoxopentanamides

General procedure for synthesis of the β–keto amides: [61]



A toluene solution (10ml) of methyl 3-oxopentanoate (5 mmol, 0.63 ml), dimethylammonium chloride (10 mmol, 815 mg) and DMAP (2.3 mmol, 1.4 g) was stirred under reflux for 24h. The solution was cooled to room temp and then quenched with water and extract with EtOAc. The organic layer was washed with brine and dried with Na2SO4. Concentration in vacuo followed by column chromatography provided N,N-dimethyl-3-oxopentanamide in 94% yield.

Rf = 0.34 (EtOAc); 78 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.48 (s, 2H), 2.94 (s, 3H), 2.90 (s, 3H), 2.53 (q, 2H, J = 7.3 Hz), 1.00 (t, 3H, J =7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 167.0, 49.1, 38.1, 36.5, 35.6, 7.8; IR (NaCl, neat) 2939, 1719, 1647, 1398, 1137, 1050 cm^{-1}; HRMS (FAB+) calcd for $C_7H_{13}NO_2$, 143.0946. Found 143.0946.

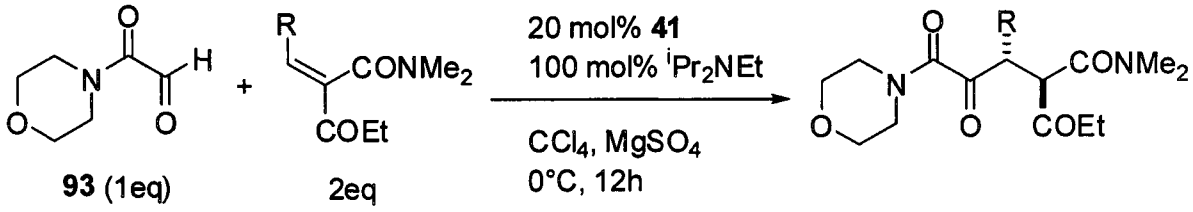
All other non-commerical available β-keto amides were all synthesized using this general procedure.

[61] E. Holtz, U. Albrecht, P. Langer, *Tetrahedron* **2007**, *63*, 3293-3301

General procedure for synthesis of alkylideneoxopentanamides [62]:

A flame-dried 5 ml round bottom flask with magnetic stir bar was charged with β-keto-*N,N*-dimethyl-amide (4.7 mmol), acetic anhydride (14 mmol, 1.4 ml), and lithium bromide (0.94 mmol, 81mg). The reaction was then allowed to heat to 80 °C and allowed to reflux for 4 hours. Then aldehyde (14 mmol) was added and the mixture was refluxing for another 4 hours. The reaction was quenched with water and extract with EtOAc. The organic layer was washed with brine and dried with Na2SO4. Concentration in vacuo followed by column chromatography provides the corresponding Michael acceptors.

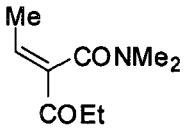
General procedure for the asymmetric intermolecular Stetter reaction:



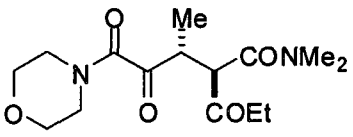
A flame-dried 5 ml test tube was charged with triazolium salt **41** (14.5 mg, 0.032 mmol), Michael acceptor (0.32 mmol) and $MgSO_4$ (20 mg, 0.16 mmol). The test tube was purged under vacuum and then refilled with argon 3 times. Glyoxamide 93 (23 mg, 0.16 mmol) was then added followed by 0.5 ml of distilled CCl_4. The test tube was placed in an ice-water bath and Hünig's base (0.028 ml, 0.16 mmol) was added dropwise to the reaction. The mixture was allowed to stir at 0 °C for 12 hours, quenched with 0.1

[62] Sylla, M.; Joseph, D.; Chevallier, E.; Camara, C.; Dumas, F. *Synthesis-Stuttgart* **2006**, 1045-1049

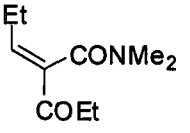
ml AcOH and directly purified by flash column chromatography to provide Stetter products.



(Z)-2-ethylidene-N,N-dimethyl-3-oxopentanamide (138): Rf = 0.18 (EtOAc); 44 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (q, 1H, J = 7.1 Hz), 2.88 (s, 3H), 2.70 (s, 3H), 2.48 (q, 2H, J = 7.2 Hz), 1.67 (d, 3H, J =7.1 Hz), 0.89 (t, 3H, J =7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 167.9, 140.5, 139.0, 37.7, 34.3, 31.4, 15.6, 8.0; IR (NaCl, neat) 2925, 1672, 1638, 1503, 1400, 1144 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{15}NO_2$, 169.1103. Found 169.1103.

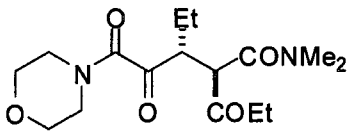


(2R,3R)-N,N,3-trimethyl-5-morpholino-4,5-dioxo-2-propionylpentanamide (139): Rf = 0.25 (EtOAc); $[\alpha]_D^{21}$ = +24.5 (c = 0.020 g/ml, $CHCl_3$); HPLC analysis – Chiracel ASH column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 20.9 minutes, Minor: 17.5 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (d, 1H, J = 9.9 Hz), 3.50-3.84 (m, 9H), 3.22 (s, 3H), 3.06 (s, 3H), 2.32-2.54 (m, 2H), 1.28 (d, 3H, J = 7.2 Hz), 1.02 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 201.3, 168.6, 164.9, 67.3, 66.9, 59.0, 46.6, 43.7, 42.0, 38.6, 36.3, 34.2, 15.9, 7.8; IR (NaCl, neat) 2937, 1710, 1638, 1399, 1114, 999 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{24}N_2O_5$, 312.1685, Found 312.1687.

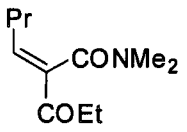


(Z)-N,N-dimethyl-2-propionylpent-2-enamide (137): Rf = 0.34 (EtOAc); 52 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (t, 1H, J = 7.6 Hz), 2.96 (s, 3H), 2.78 (s, 3H), 2.56 (q, 2H, J = 7.2 Hz), 2.10 (dq, 2H, J = 7.5, 7.6 Hz),

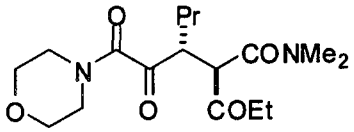
1.00 (t, 3H, J = 7.5 Hz), 0.99 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 168.0, 145.2, 138.9, 37.9, 34.4, 31.6, 23.5, 12.8, 8.1; IR (NaCl, neat) 2939, 1671, 1637, 1458, 1400, 1143 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}NO_2$, 183.1257, Found 183.1261.



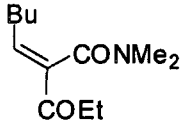
(2R,3R)-3-ethyl-N,N-dimethyl-5-morpholino-4,5-dioxo-2-propionylpentanamide (136): Rf = 0.26 (EtOAc); $[\alpha]_D^{21}$ = +34.0 (c = 0.047 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 16.4 minutes, Minor: 14.4 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (d, 1H, J = 10.0 Hz), 3.50-3.82 (m, 9H), 3.20 (s, 3H), 3.02 (s, 3H), 2.30-2.52 (m, 2H), 1.68 (dq, 2H, J = 7.1, 7.6 Hz), 0.98 (t, 3H, J = 7.2 Hz), 0.89 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 200.2, 168.4, 164.8, 67.2, 66.8, 58.6, 49.6, 46.7, 42.2, 38.6, 36.3, 34.2, 23.6, 11.5, 7.8; IR (NaCl, neat) 2971, 1709, 1640, 1461, 1114, 1000 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{26}N_2O_5$, 326.1842, Found 326.1841.



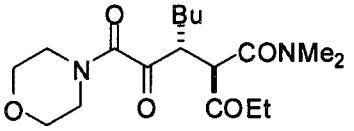
(Z)-N,N-dimethyl-2-propionylhex-2-enamide (140): Rf = 0.44 (EtOAc); 40 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (t, 1H, J = 7.6 Hz), 3.05 (s, 3H), 2.86 (s, 3H), 2.64 (q, 2H, J = 7.2 Hz), 2.15 (q, 2H, J = 7.4 Hz), 1.45-1.57 (m, 2H), 1.08 (t, 3H, J = 7.3 Hz), 0.94 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 168.0, 143.9, 139.5, 37.9, 34.3, 32.0, 31.5, 21.7, 14.1, 8.0; IR (NaCl, neat) 2936, 2873, 1671, 1638, 1400, 1142 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{19}NO_2$, 197.1416, Found 197.1413.



(2R,3R)-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhexanamide (141): Rf = 0.32 (EtOAc); $[\alpha]_D^{21}$ = +70.5 (c = 0.044 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 12.3 minutes, Minor: 11.4 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, 1H, *J* = 9.9 Hz), 3.50-3.82 (m, 9H), 3.20 (s, 3H), 3.02 (s, 3H), 2.28-2.52 (m, 2H), 1.45 -1.72 (m, 2H), 1.20 -1.40 (m, 2H), 0.98 (t, 3H, *J* = 7.2 Hz), 0.86 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 200.2, 168.6, 164.7, 67.1, 66.9, 59.4, 48.2, 46.7, 42.3, 38.5, 36.3, 34.1, 32.8, 20.5, 14.4, 7.8; IR (NaCl, neat) 2960, 1709, 1640, 1461, 1272, 1115 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{28}N_2O_5$, 340.1998, Found 340.2006.

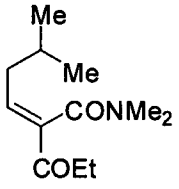


(Z)-N,N-dimethyl-2-propionylhept-2-enamide (142): Rf = 0.49 (EtOAc); 51 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (t, 1H, *J* = 7.6 Hz), 2.86 (s, 3H), 2.69 (s, 3H), 2.58 (q, 2H, *J* = 7.2 Hz), 2.11 (q, 2H, *J* = 7.4 Hz), 1.36-1.44 (m, 2H), 1.23-1.32 (m, 2H), 1.02 (t, 3H, *J* = 7.2 Hz), 0.83 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 168.1, 144.1, 139.4, 37.9, 34.5, 31.7, 30.5, 29.9, 22.7, 14.0, 8.1; IR (NaCl, neat) 2935, 1671, 1640, 1458, 1400, 1142 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{21}NO_2$, 211.1572, Found 211.1571.

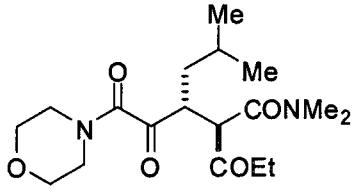


(2R,3R)-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylheptanamide (143): Rf = 0.25 (EtOAc); $[\alpha]_D^{21}$ = +72.5 (c = 0.040 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 98:2 hexanes : isopropanol 1.0 mL / min. Major: 45.7 minutes, Minor: 42.3 minutes; ^1H NMR (300

MHz, $CDCl_3$) δ 4.19 (d, 1H, J = 9.9 Hz), 3.42-3.72 (m, 9H), 3.12 (s, 3H), 2.94 (s, 3H), 2.86-2.93 (m, 2H), 2.20 -2.43 (m, 2H), 1.44 -1.62 (m, 2H), 1.10 -1.25 (m, 4H), 0.89 (t, 3H, J = 7.2 Hz), 0.75 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 200.3, 168.5, 164.7, 67.2, 66.9, 59.2, 48.4, 46.7, 42.3, 38.6, 36.3, 34.2, 30.4, 29.2, 23.0, 14.1, 7.8; IR (NaCl, neat) 2934, 2858, 1709, 1641, 1461, 1115 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{30}N_2O_5$, 354.2155, Found 354.2156.

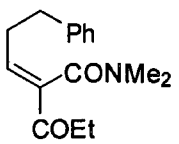


(Z)-N,N,5-trimethyl-2-propionylhex-2-enamide (144): Rf = 0.47 (EtOAc); 28 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (t, 1H, J = 7.5 Hz), 3.04 (s, 3H), 2.85 (s, 3H), 2.64 (q, 2H, J = 7.1 Hz), 2.06 (dd, 2H, J = 7.1, 7.2 Hz), 1.81 (m, 1H), 1.08 (t, 3H, J = 7.2 Hz), 0.92 (d, 6H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 167.9, 143.1, 139.9, 38.9, 37.8, 34.3, 31.5, 28.2, 22.6, 8.0; IR (NaCl, neat) 2956, 2863, 1672, 1637, 1399, 1141 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{21}NO_2$, 211.1572, Found 211.1573.

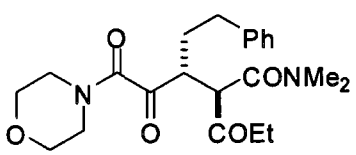


(2R,3R)-N,N,5-trimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhexanamide (145): Rf = 0.26 (EtOAc); $[\alpha]_D^{21}$ = +64.0 (c = 0.025 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 12.5 minutes, Minor: 14.9 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (d, 1H, J = 9.5 Hz), 3.48-3.82 (m, 9H), 3.16 (s, 3H), 3.02 (s, 3H), 2.43-2.57 (m, 1H), 2.24 -2.38 (m, 1H), 1.10 -1.20 (m, 2H), 0.98 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 200.1, 168.6, 164.6, 67.1, 66.8, 60.6, 46.8, 46.2, 42.3, 38.5, 36.3, 34.1, 26.0, 23.7, 22.1, 7.8; IR (NaCl, neat) 2957,

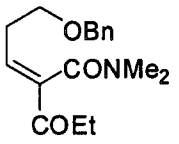
1709, 1640, 1462, 1398, 1114, cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{30}N_2O_5$, 354.2155, Found 354.2157.



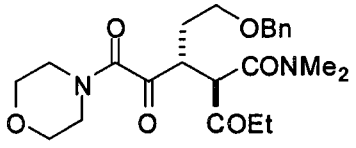
(Z)-N,N-dimethyl-5-phenyl-2-propionylpent-2-enamide (146): Rf = 0.47 (EtOAc); 54 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08-7.24 (m, 5H), 6.68 (t, 1H, J = 7.5 Hz), 2.92 (s, 3H), 2.74 (t, 3H, J = 7.4 Hz), 2.56 (s, 3H), 2.42-2.58 (m, 4H), 1.00 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 167.8, 142.9, 140.7, 140.0, 128.8, 128.5, 126.5, 37.6, 34.5, 34.4, 32.0, 31.6, 8.2; IR (NaCl, neat) 2935, 1671, 1638, 1400, 1142, 701 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{21}NO_2$, 259.1572, Found 259.1575.



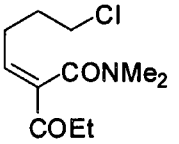
(2R,3R)-N,N-dimethyl-5-morpholino-4,5-dioxo-3-phenethyl-2-propionylpentanamide (147): Rf = 0.41 (EtOAc); $[\alpha]_D^{21}$ = +42.8 (c = 0.042 g/ml, $CHCl_3$); HPLC analysis – Chiracel OD-H column 85:15 hexanes : isopropanol 1.0 mL / min. Major: 19.5 minutes, Minor: 16.2 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12-7.29 (m, 5H), 4.30 (d, 1H, J = 9.6 Hz), 3.54-3.84 (m, 9H), 3.14 (s, 3H), 3.02 (s, 3H), 2.56-2.70 (m, 2H), 2.28 -2.54 (m, 2H), 1.94 -2.10 (m, 1H), 1.76 -1.90 (m, 1H), 1.00 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 199.9, 168.4, 164.7, 141.8, 128.6, 126.2, 67.2, 66.8, 59.6, 47.9, 46.7, 42.3, 38.5, 36.3, 34.2, 33.6, 32.6, 7.8; IR (NaCl, neat) 2935, 1708, 1639, 1454, 1398, 1114 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{30}N_2O_5$, 402.2155, Found 402.2157.



(Z)-5-(benzyloxy)-N,N-dimethyl-2-propionylpent-2-enamide (148): Rf = 0.30 (EtOAc); 35 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.28 (m, 5H), 6.72 (t, 1H, J = 7.4 Hz), 4.40 (s, 2H), 3.51 (t, 2H, J = 6.1 Hz), 2.93 (s, 3H), 2.71 (s, 3H), 2.36-2.60 (m, 4H), 1.00 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 167.8, 140.9, 140.7, 138.1, 128.5, 127.8, 73.2, 68.2, 48.9, 37.9, 34.4, 31.5, 30.8, 8.1; IR (NaCl, neat) 2929, 1672, 1641, 1454, 1399, 1100 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{23}NO_3$, 289.1678, Found 289.1680.

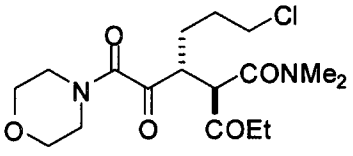


(2R,3R)-3-(2-(benzyloxy)ethyl)-N,N-dimethyl-5-morpholino-4,5-dioxo-2-propionylpentanamide (149): Rf = 0.35 (EtOAc); $[\alpha]_D^{21}$ = +4.8 (c = 0.060 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 12.4 minutes, Minor: 9.1 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.36 (m, 5H), 4.40 (d, 2H, J = 4.6 Hz), 4.33 (d, 1H, J = 9.4 Hz), 3.44-3.72 (m, 9H), 3.01 (s, 3H), 2.94 (s, 3H), 2.38-2.66 (m, 4H), 1.92-2.04 (m, 2H), 0.96 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 199.8, 168.1, 164.4, 140.8, 138.2, 128.6, 128.1, 127.9, 73.4, 68.2, 67.1, 66.8, 58.6, 46.6, 45.9, 42.4, 38.2, 36.3, 34.1, 30.8, 29.8, 7.7; IR (NaCl, neat) 2939, 2847, 1711, 1640, 1398, 1114, cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{32}N_2O_6$, 432.2260, Found 432.2264.

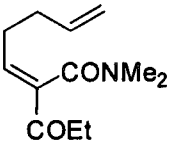


(Z)-6-chloro-N,N-dimethyl-2-propionylhex-2-enamide (150): Rf = 0.26 (EtOAc); 43 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (t, 1H, J = 7.6 Hz), 3.55 (t, 2H, J = 6.3 Hz), 3.05 (s, 3H), 2.88 (s, 3H), 2.64 (q, 2H, J = 7.3 Hz), 2.34 (q, 2H, J = 7.4 Hz), 1.92-2.00 (m, 2H), 1.09 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$)

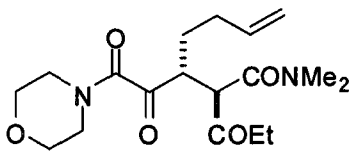
δ 198.0, 167.7, 141.7, 140.4, 44.4, 38.0, 34.6, 31.9, 31.3, 27.4, 8.1; IR (NaCl, neat) 2934, 1673, 1633, 1402, 1229, 1144 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{18}ClNO_2$, 231.1026, Found 231.1028.



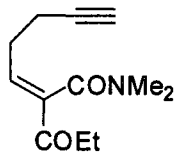
(2R,3R)-6-chloro-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhexanamide (151): Rf = 0.36 (EtOAc); $[\alpha]_D^{21}$ = +33.8 (c = 0.050 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 7.4 minutes, Minor: 9.1 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (d, 1H, J = 9.9 Hz), 3.48-3.84 (m, 9H), 3.23 (s, 3H), 3.04 (s, 3H), 2.94-3.00 (m, 2H), 2.30-2.60 (m, 2H), 1.70-1.88 (m, 4H), 0.98 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 199.7, 168.3, 164.7, 67.1, 66.8, 59.5, 47.3, 46.7, 45.0, 42.3, 38.6, 36.3, 34.1, 30.0, 27.9, 7.7; IR (NaCl, neat) 2936, 1708, 1638, 1444, 1271, 1114, cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{27}ClN_2O_5$, 374.1608, Found 374.1610.



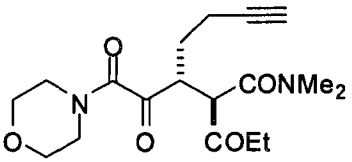
(Z)-N,N-dimethyl-2-propionylhepta-2,6-dienamide (152): Rf = 0.49 (EtOAc); 46 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.59 (t, 1H, J = 7.2 Hz), 5.55-5.69 (m, 1H), 4.82-4.94 (m, 2H), 2.88 (s, 3H), 2.71 (s, 3H), 2.49 (q, 2H, J = 7.2 Hz), 2.05-2.16 (m, 4H), 0.92 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 167.8, 143.0, 139.7, 136.9, 116.0, 37.9, 34.4, 32.2, 31.5, 29.2, 8.0; IR (NaCl, neat) 2929, 1671, 1638, 1400, 1142, 906 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}NO_2$, 209.1416, Found 209.1422.



(2R,3R)-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhept-6-enamide (153): Rf = 0.36 (EtOAc); $[\alpha]_D^{21}$ = +53.3 (c = 0.045 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 13.7 minutes, Minor: 12.5 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66-5.81 (m, 1H), 4.90-5.02 (m, 2H), 4.27 (d, 1H, J = 9.8 Hz), 3.49-3.82 (m, 9H), 3.20 (s, 3H), 3.03 (s, 3H), 2.26-2.56 (m, 2H), 1.96-2.18 (m, 2H), 1.54-1.84 (m, 2H), 0.98 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 199.8, 168.5, 164.7, 137.8, 115.4, 67.1, 66.8, 59.4, 47.7, 46.7, 42.2, 38.5, 36.3, 34.1, 31.3, 29.9, 7.7; IR (NaCl, neat) 2924, 1708, 1639, 1443, 1114, 996 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{28}N_2O_5$, 352.1998, Found 352.2003.

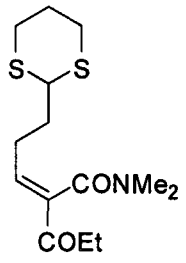


(Z)-N,N-dimethyl-2-propionylhept-2-en-6-ynamide (154): Rf = 0.45 (EtOAc); 53 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (t, 1H, J = 7.2 Hz), 3.06 (s, 3H), 2.88 (s, 3H), 2.68 (q, 2H, J = 7.2 Hz), 2.38-2.42 (m, 4H), 2.01 (t, 1H, J = 2.5 Hz), 1.10 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 167.6, 141.4, 140.5, 82.7, 70.0, 38.1, 34.5, 31.7, 28.9, 17.7, 8.1; IR (NaCl, neat) 2937, 1672, 1633, 1503, 1400, 1143 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{17}NO_2$, 207.1259, Found 207.1258.

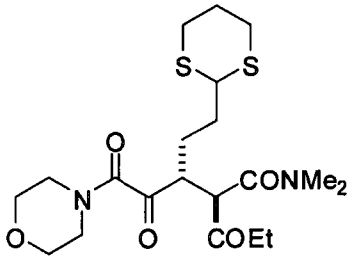


(2R,3R)-N,N-dimethyl-3-(2-morpholino-2-oxoacetyl)-2-propionylhept-6-ynamide (155): Rf = 0.33 (EtOAc); $[\alpha]_D^{21}$ = +54.5 (c = 0.044 g/ml, $CHCl_3$); HPLC analysis – Chiracel AS-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 22.3 minutes,

Minor: 20.2 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (d, 1H, J = 9.2 Hz), 3.48-3.82 (m, 9H), 3.18 (s, 3H), 3.02 (s, 3H), 2.22-2.58 (m, 4H), 1.90-2.04 (m, 2H), 1.66-1.78 (m, 1H), 0.98 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 199.0, 168.3, 164.6, 69.1, 67.1, 66.8, 59.6, 47.1, 46.7, 42.3, 38.5, 36.3, 34.3, 29.5, 16.8, 7.7; IR (NaCl, neat) 2924, 2847, 1707, 1637, 1444, 1113, cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{26}N_2O_5$, 350.1842, Found 350.1845.

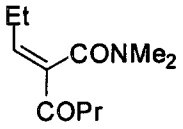


(Z)-5-(1,3-dithian-2-yl)-N,N-dimethyl-2-propionylpent-2-enamide (156): Rf = 0.42 (EtOAc); 52 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (t, 1H, J = 7.6 Hz), 4.01 (t, 1H, J = 6.9 Hz), 3.05 (s, 3H), 2.82-2.88 (m, 5H), 2.64 (q, 2H), 2.40 (q, 2H, J = 7.6 Hz), 1.79-2.15 (m, 4H), 1.08 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 167.6, 141.9, 140.2, 46.7, 38.0, 34.5, 34.0, 31.7, 30.3, 27.2, 25.9, 8.1; IR (NaCl, neat) 2933, 1671, 1634, 1511, 1399, 1143 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{23}NO_2S_2$, 301.1170, Found 301.1174.

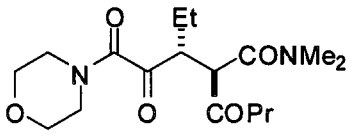


(2R,3R)-3-(2-(1,3-dithian-2-yl)ethyl)-N,N-dimethyl-5-morpholino-4,5-dioxo-2-propionylpentanamide (157): Rf = 0.35 (EtOAc); $[\alpha]_D^{21}$ = +46.7 (c = 0.030 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 30:70 hexanes : isopropanol 1.0 mL / min. Major: 15.1 minutes, Minor: 27.2 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (d, 1H, J = 9.6 Hz), 3.50-3.80 (m, 9H), 3.22 (s, 3H), 2.76-2.84 (m, 4H), 2.30-2.54 (m, 2H), 1.70-1.90 (m, 6H), 0.98 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 199.7, 168.2, 164.6, 67.2, 66.8, 58.8, 47.7, 47.3, 46.7, 42.3, 38.7, 36.4,

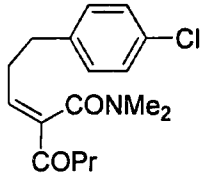
34.2, 32.8, 30.5, 30.4, 27.6, 26.1, 7.8; IR (NaCl, neat) 2924, 1709, 1638, 1444, 1114, 996 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{32}N_2O_5S_2$, 444.1753, Found 444.1756.



(Z)-N,N-dimethyl-3-oxo-2-propylidenehexanamide (158): Rf = 0.47 (EtOAc); 61 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (t, 1H, J = 7.6 Hz), 2.90 (s, 3H), 2.46 (t, 2H, J = 7.2 Hz), 2.00-2.10 (m, 2H), 1.42-1.55 (m, 2H), 0.94 (t, 3H, J = 7.6 Hz), 0.77 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 167.9, 145.2, 139.2, 40.0, 37.8, 34.3, 23.5, 17.5, 13.8, 12.8; IR (NaCl, neat) 2964, 2875, 1638, 1458, 1399, 1130 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{19}NO_2$, 197.1416, Found 197.1417.

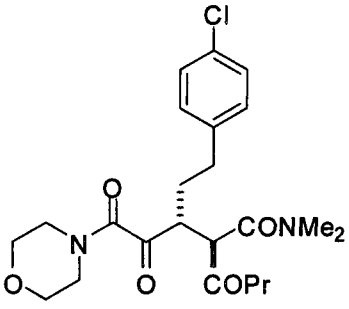


(R)-N,N-dimethyl-2-((R)-1-morpholino-1,2-dioxopentan-3-yl)-3-oxohexanamide (159): Rf = 0.34 (EtOAc); $[\alpha]_D^{21}$ = +82.0 (c = 0.050 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 6.9 minutes, Minor: 6.1 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 4.29 (d, 1H, J = 10.1 Hz), 3.50-3.82 (m, 9H), 3.22 (s, 3H), 3.04 (s, 3H), 2.25-2.48 (m, 2H), 1.64-1.75 (m, 2H), 1.48-1.58 (m, 2H), 0.90 (t, 3H, J = 7.4 Hz), 0.85 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 200.1, 168.4, 164.7, 67.1, 66.8, 59.1, 49.5, 46.6, 42.7, 42.2, 38.6, 36.3, 23.6, 17.1, 13.7, 11.5; IR (NaCl, neat) 2965, 2933, 1708, 1640, 1397, 1114, cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{28}N_2O_5$, 340.1998, Found 340.1998.

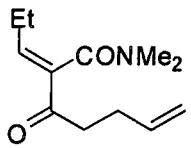


(Z)-2-(3-(4-chlorophenyl)propylidene)-N,N-dimethyl-3-oxohexanamide (160): Rf = 0.39 (EtOAc); 45 % yield; ^1H NMR (300

MHz, $CDCl_3$) δ 7.22-7.27 (m, 2H), 7.07-7.12 (m, 2H), 6.68 (t, 1H, J = 7.5 Hz), 3.00 (s, 3H), 2.77 (t, 3H, J = 7.5 Hz), 2.66 (s, 3H), 2.44-2.57 (m, 4H), 1.54-1.67 (m, 2H), 0.90 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 167.7, 142.4, 140.6, 139.2, 132.3, 130.0, 128.9, 40.4, 37.8, 34.5, 34.0, 31.8, 17.7, 14.0; IR (NaCl, neat) 2933, 1670, 1637, 1491, 1400, 1090 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{22}ClNO_2$, 307.1339, Found 307.1337.

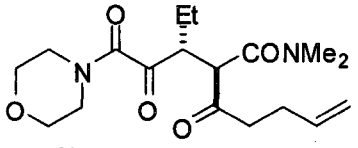


(R)-2-((R)-5-(4-chlorophenyl)-1-morpholino-1,2-dioxopentan-3-yl)-N,N-dimethyl-3-oxohexanamide (161): Rf = 0.37 (EtOAc); $[\alpha]_D^{21}$ = +49.6 (c = 0.046 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 10.8 minutes, Minor: 12.4 minutes; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.23 (m, 2H), 7.04-7.08 (m, 2H), 4.27 (d, 1H, J = 9.8 Hz), 3.50-3.82 (m, 9H), 3.14 (s, 3H), 3.02 (s, 3H), 2.52-2.68 (m, 2H), 2.22 - 2.46 (m, 2H), 1.70-2.00 (m, 2H), 1.48 -1.57 (m, 2H), 0.85 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 199.6, 168.2, 164.7, 140.2, 131.8, 129.9, 128.6, 67.1, 66.8, 60.2, 47.7, 46.7, 42.6, 42.3, 38.5, 36.3, 32.9, 32.6, 17.1, 13.7; IR (NaCl, neat) 2963, 2931, 1708, 1640, 1492, 1114 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{31}ClN_2O_5$, 450.1921, Found 450.1922.



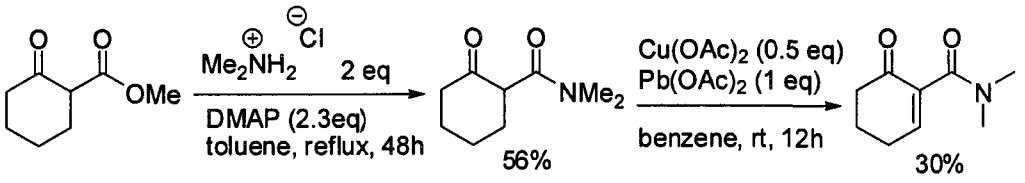
(Z)-N,N-dimethyl-3-oxo-2-propylidenehept-6-enamide (162): Rf = 0.41 (EtOAc); 43 % yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.70 (t, 1H, J = 7.6 Hz), 5.72-5.84 (m, 1H), 4.92-5.40 (m, 2H), 3.20 (s, 3H), 2.84 (s, 3H), 2.62-2.72 (m,

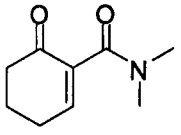
2H), 2.28-2.37 (m, 2H), 2.12-2.22 (m, 2H), 1.07 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 167.9, 145.5, 139.2, 137.3, 115.6, 38.0, 37.6, 34.5, 28.0, 23.6, 12.9; IR (NaCl, neat) 2933, 1639, 1399, 1265, 1137, 912 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}NO_2$, 209.1416, Found 209.1419.



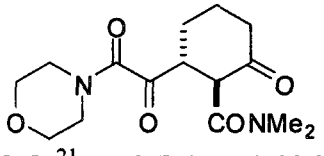
(R)-N,N-dimethyl-2-((R)-1-morpholino-1,2-dioxopentan-3-yl)-3-oxohept-6-enamide (163): Rf = 0.33 (EtOAc); $[\alpha]_D^{21}$ = +68.1 (c = 0.053 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 7.5 minutes, Minor: 6.6 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65-5.79 (m, 1H), 4.93-5.02 (m, 2H), 4.30 (d, 1H, J = 10.1 Hz), 3.48-3.82 (m, 9H), 3.22 (s, 3H), 3.04 (s, 3H), 2.38-2.62 (m, 2H), 2.22-2.30 (m, 2H), 1.64-1.76 (m, 2H), 0.91 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 200.1, 168.3, 164.7, 136.7, 115.8, 67.2, 66.8, 59.0, 49.5, 46.6, 42.2, 39.9, 38.6, 36.3, 27.5, 23.6, 11.5; IR (NaCl, neat) 2924, 2858, 1709, 1639, 1442, 1114 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{28}N_2O_5$, 352.1998, Found 352.2007.

Synthesis of 164:[63]





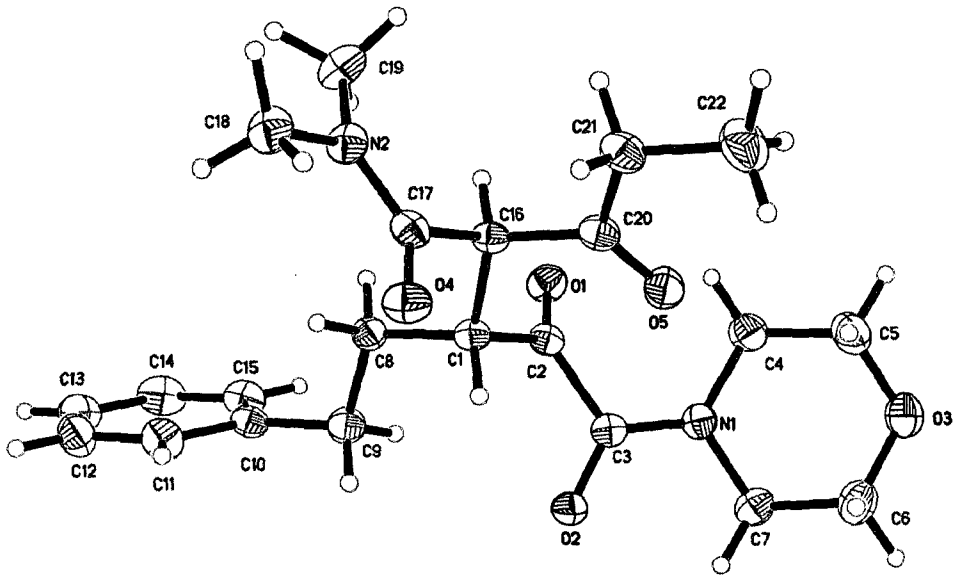
N,N-dimethyl-6-oxocyclohex-1-enecarboxamide (164): Rf = 0.05 (EtOAc); 30 % yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (t, 1H, J = 4.3 Hz), 3.00 (s, 3H), 2.84 (s, 3H), 2.42-2.52 (m, 4H), 2.02-2.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 167.7, 149.8, 139.0, 38.2, 35.0, 25.8, 22.6; IR (NaCl, neat) 2930, 1676, 1636, 1396, 1355, 1039 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{13}NO_2$, 167.0946, Found 167.0950.



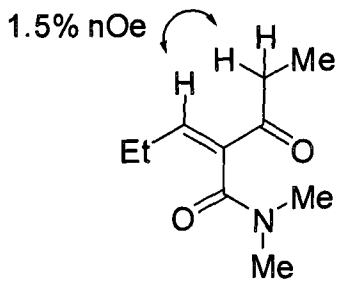
(1S,2R)-N,N-dimethyl-2-(2-morpholino-2-oxoacetyl)-6-oxocyclohexanecarboxamide (165): Rf = 0.20 (EtOAc); $[\alpha]_D^{21}$ = -9.7 (c = 0.036 g/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 60:40 hexanes : isopropanol 1.0 mL / min. Major: 8.9 minutes, Minor: 9.8 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (d, 1H, J = 11.6 Hz), 3.40-3.80 (m, 9H), 2.94 (s, 3H), 2.88 (s, 3H), 2.50-2.66 (m, 2H), 2.36-2.46 (m, 1H), 2.14-2.24 (m, 1H), 1.80-1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 199.8, 168.4, 165.0, 67.2, 66.7, 57.2, 51.7, 46.5, 42.0, 41.9, 37.5, 35.9, 29.9, 26.6; IR (NaCl, neat) 2924, 2852, 1708, 1637, 1446, 1113, cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{22}N_2O_5$, 310.1529, Found 310.1534.

[63] Meyer, C.; Piva, O.; Pete, J.-P. *Tetrahedron* **2000**, *56*, 4479-4489.

Absolute configuration of 147:



nOe of 137:



Chapter 3

N-Heterocyclic Carbene Catalyzed Redox Reaction of ynal

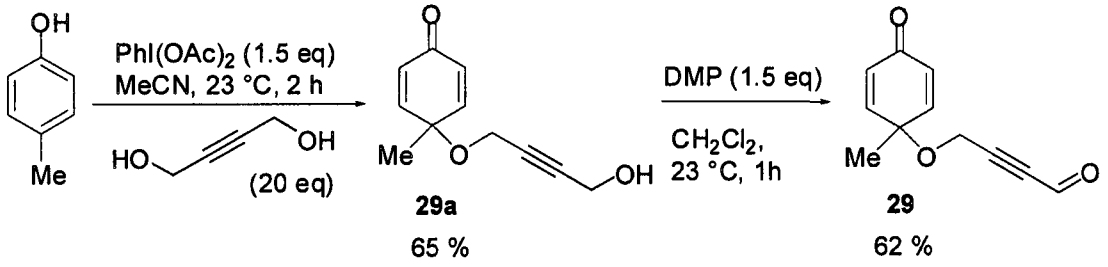
General Methods.

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran and Dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Triethylamine, Hunig's base and methanol were distilled from CaH_2. CCl_4 (99.9%) was purchased from Aldrich and redistilled before use. KHMDS (0.5 M solution in toluene), 2-Butyne-1,4-diol (99%) and $PhI(OAc)_2$ (iodobenzene diacetate, 98%) was purchased from Aldrich Chemical Co. and used without purification.

Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, or aqueous ceric ammonium molybdate dips followed by heating.

^1H NMR was recorded at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR was recorded at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm.

General procedure for synthesis of ynal-tethered cyclohexadienones

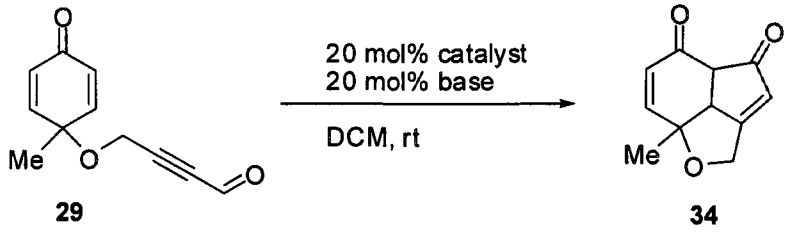


A flame-dried 50 ml round bottom flask was charged with 2-Butyne-1,4-diol (3.44 g ml, 40 mmol) and $PhI(OAc)_2$ (966 mg, 3 mmol) and 20 ml acetonitrile. Cresol (216 mg, 2 mmol) was added dropwise in 1 hour. The solution was then allowed to stir at ambient temperature for further 1 hour. The solution was worked up with DCM/water, dried with Na_2SO_4, concentrated *in vacuo* and the residue was subjected to column chromatography (EtOAc : Hexane = 1:2) to provide **29a** (248 mg, 65 %).

In a flame-dried 50 ml round bottom flask, **29a** (248 mg, 1.3 mmol) was dissolved in 15 ml CH_2Cl_2, Dess Martin periodinane (820 mg, 1.9 mmol) was added to the solution directly and the solution was then allowed to stir at ambient temperature for 1 hour. The solution was diluted with hexanes and filtered through Celite 545. The filtrate was then subjected to column chromatography (EtOAc : Hexane = 1:6) to provide **29** (152 mg, 62 %).

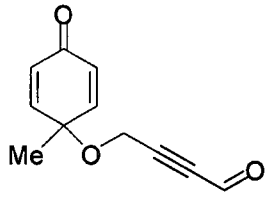
This is the general procedure for all other substrates (two-step yields are reported respectively in the following sections). All the phenols were purchased from Aldrich and used without further purification.

General procedure for redox reaction of ynal-tethered cyclohexadienones.

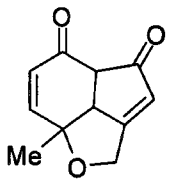


29 **34**

A flame-dried 10 ml round bottom flask was charged with triazolium salt (0.01 mmol) and **29** (10 mg, 0.052 mmol). The flask was purged under vacuum and then refilled with argon for 3 times. 5.0 ml solvent followed by base (0.01 mmol) was added to the solution. The reaction was allowed to stir at ambient for 40 hours and then directly purified by flash column chromatography to provide product **34**.

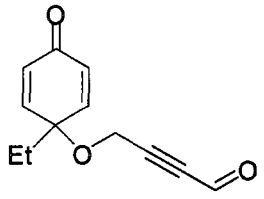


4-(1-methyl-4-oxocyclohexa-2,5-dienyloxy)but-2-ynal (29): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (s, 1H), 6.80 (d, 2H, J = 10.2 Hz), 6.34 (d, 2H, J = 10.2), 4.18 (s, 2H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 176.3, 150.0, 131.1, 92.6, 85.7, 73.8, 53.6, 26.3.

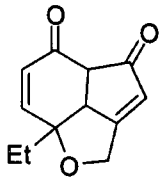


7a-methyl-4a,7a-dihydroindeno[7,1-bc]furan-4,5(2H,2a1H)-dione (34): Rf = 0.45 (EtOAc); $[\alpha]_D^{21}$ = -76.9 (c = 0.005/ml, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM2 column, gas flow 3ml/min with constant 170 °C oven temperature. Major: 25.8 min, Minor: 23.9 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (dd, 1H, J = 10.4, 1.5 Hz), 6.10 (s, 1H), 5.82 (d, 1H, J = 10.4

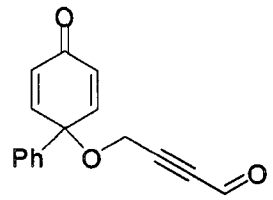
Hz), 4.89 (d, 1H, J = 16.4 Hz), 4.66 (d, 1H, J = 16.3 Hz), 3.68 (d, 1H, J = 5.9 Hz), 3.48-3.54 (m, 1H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 187.1, 184.1, 151.4, 127.0, 124.3, 66.5, 59.5, 52.4, 29.9, 26.6; IR (NaCl, neat) 2914, 1726, 1670, 1647, 1112, 1089 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{10}O_3$, 190.0630, Found 190.0632.



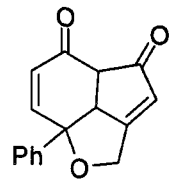
4-(1-ethyl-4-oxocyclohexa-2,5-dienyloxy)but-2-ynal (40): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (s, 1H), 6.71 (d, 2H, J = 10.3 Hz), 6.34 (d, 2H, J = 10.3 Hz), 4.16 (s, 2H), 1.78 (q, 2H, J = 7.6 Hz), 0.79 (t, 3H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 176.3, 149.2, 132.3, 92.8, 85.7, 77.6, 53.5, 32.3, 8.0; HRMS (FAB+) calcd for $C_{12}H_{12}O_3$, 204.0786, Found 204.0786.



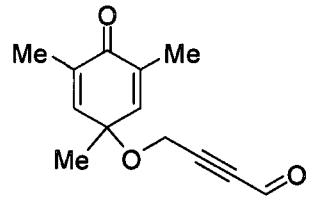
7a-ethyl-4a,7a-dihydroindeno[7,1-bc]furan-4,5(2H,2a1H)-dione (41): Rf = 0.49 (EtOAc); $[\alpha]_D^{21}$ = -84.6 (c = 0.005/ml, $CHCl_3$); Gas chromatography analysis – Chiraldex B-DM2 column, gas flow 3ml/min with constant 170 °C oven temperature. Major: 36.1 min, Minor: 33.6 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (dd, 1H, J = 10.4, 1.6 Hz), 6.05-6.07 (m, 1H), 5.88 (d, 1H, J = 10.4 Hz), 4.84 (d, 1H, J = 16.2 Hz), 4.66 (dq, 1H, J = 16.2, 1.4 Hz), 3.61 (d, 1H, J = 5.9 Hz), 3.44-3.48 (m, 1H), 1.89 (dq, 2H, J = 7.6, 1.6 Hz), 0.93 (t, 3H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 187.3, 183.9, 150.1, 128.3, 124.1, 80.0, 66.4, 60.1, 50.6, 32.5, 8.5; IR (NaCl, neat) 2967, 1726, 1669, 1647, 1114, 1020 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{12}O_3$, 204.0786, Found 204.0786.



4-(4-oxo-1-phenylcyclohexa-2,5-dienyloxy)but-2-ynal (42): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.30-7.46 (m, 5H), 6.85 (d, 2H, J = 10.2 Hz), 6.41 (d, 2H, J = 10.2 Hz), 4.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 176.3, 148.8, 137.3, 130.7, 129.1, 128.9, 125.8, 92.5, 85.9, 77.5, 53.4; HRMS (FAB+) calcd for $C_{16}H_{12}O_3$, 252.0786, Found 252.0786.

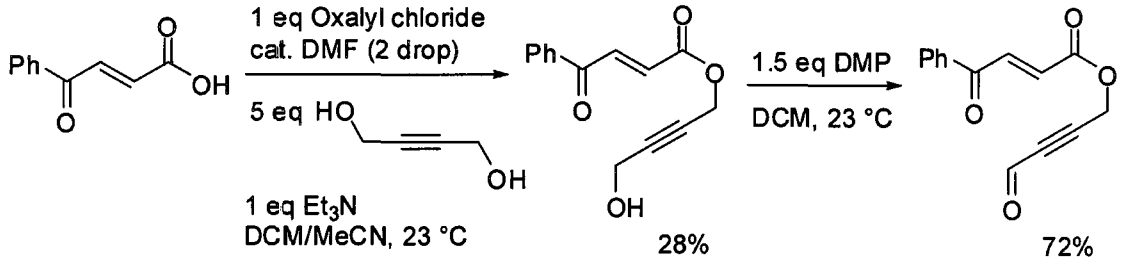


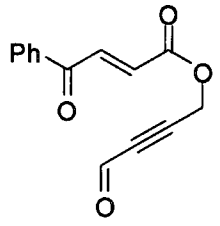
7a-phenyl-4a,7a-dihydroindeno[7,1-bc]furan-4,5(2H,2a1H)-dione (43): Rf = 0.66 (EtOAc); $[\alpha]_D^{21}$ = -50.0 (c = 0.004/ml, $CHCl_3$); HPLC analysis – Chiracel AD-H column 90:10 hexanes : isopropanol 1.0 mL / min. Major: 23.3 minutes, Minor: 20.8 minutes; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.46 (m, 5H), 6.64 (dd, 1H, J = 10.3, 1.1 Hz), 6.16-6.19 (m, 1H), 5.96 (d, 1H, J = 10.3 Hz), 5.06 (dd, 1H, J = 16.3, 1.6 Hz), 4.90 (d, 1H, J = 16.1 Hz), 3.78 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 187.4, 183.1, 149.8, 140.9, 129.2, 128.7, 127.1, 125.3, 124.5, 80.0, 66.7, 59.8, 53.8; IR (NaCl, neat) 2914, 2837, 1728, 1668, 1045, 757 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{12}O_3$, 252.0786, Found 252.0786.



4-(1,3,5-trimethyl-4-oxocyclohexa-2,5-dienyloxy)but-2-ynal (44): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1H), 6.51 (s, 2H), 4.12 (s, 2H), 1.89 (s, 6H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.3, 176.3, 145.0, 137.5, 93.5, 85.7, 73.8, 53.0, 26.5, 16.1; HRMS (FAB+) calcd for $C_{13}H_{14}O_3$, 218.0943, Found 218.0942.

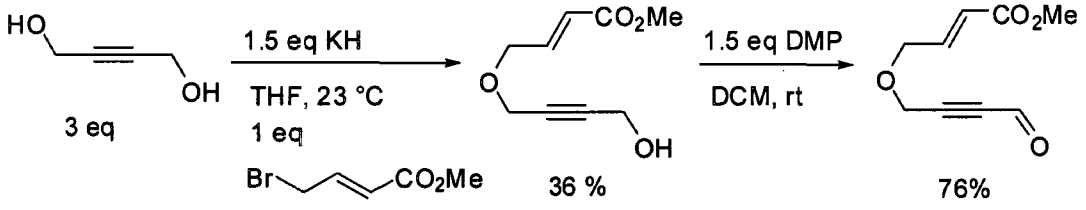
Synthesis of substrate 46

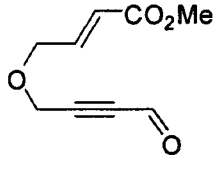




(E)-4-oxobut-2-ynyl 4-oxo-4-phenylbut-2-enoate (46): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H), 7.92-8.03 (m, 3H), 7.58-7.68 (m, 1H), 7.45-7.55 (m, 2H), 6.90 (d, 1H, J = 15.5 Hz), 5.02 (s, 2H).

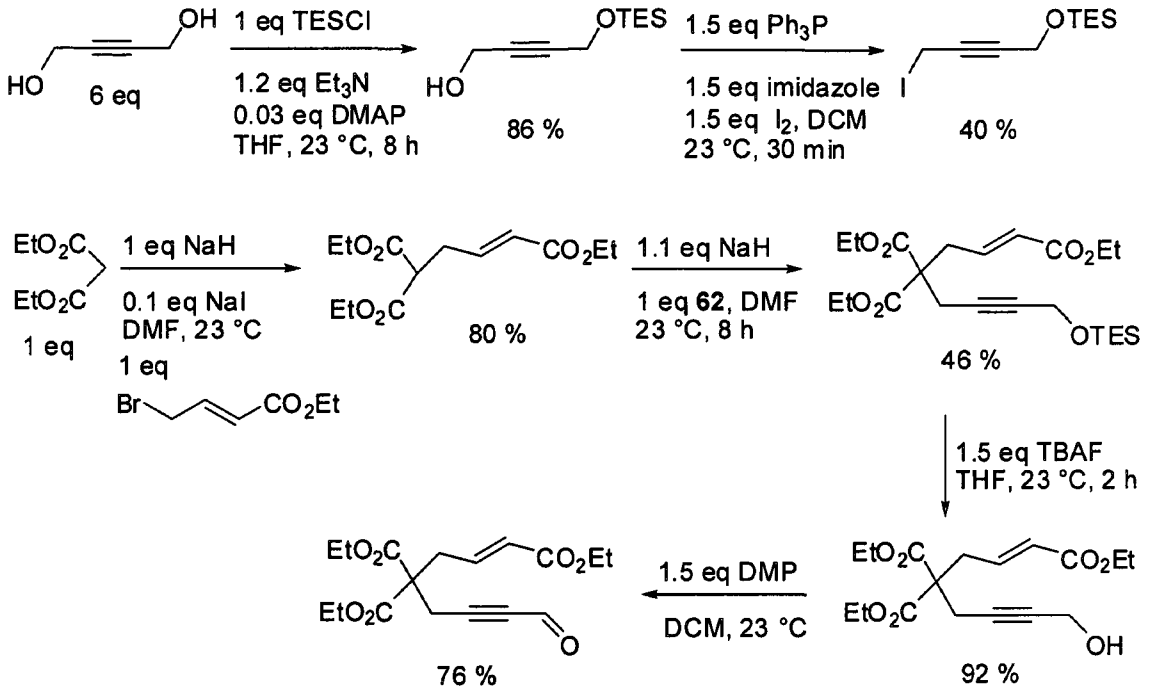
Synthesis of substrate 48

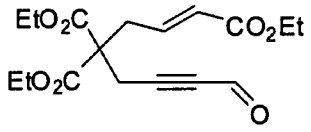




(E)-methyl 4-(4-oxobut-2-ynyloxy)but-2-enoate (48): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (t, 1H, J = 0.53 Hz), 6.94 (dt, 1H, J = 15.8, 4.4 Hz), 6.10 (dt, 1H, J = 15.8, 2.0 Hz), 4.40 (d, 2H, J = 0.53 Hz), 4.26 (dd, 2H, J = 4.4, 2.0 Hz), 3.75 (s, 3H).

Synthesis of substrate 50





(E)-triethyl 8-oxooct-1-en-6-yne-1,4,4-tricarboxylate (50): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 6.72 (dt, 1H, J = 15.5, 7.7 Hz), 5.92 (dt, 1H, J = 15.5, 1.3 Hz), 4.22 (q, 3H, J = 7.1 Hz), 4.15 (q, 3H, J = 7.1 Hz), 3.00 (s, 2H), 2.90 (dd, 2H, J = 7.8, 1.3 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.24 (t, 6H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 168.7, 165.8, 141.1, 126.3, 92.0, 83.8, 62.6, 60.7, 56.2, 35.3, 23.8, 14.4, 14.2.