Distribution Agreement

In presenting this thesis as a partial fulfillment of the requirements for a degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis in whole or in part in all forms of media, now or hereafter know, including display on the World Wide Web. I understand that I may select some access restrictions as part of the online submission of this thesis. I retain all ownership rights to the copyright of the thesis. I also retain the right to use in future works (such as articles or books) all or part of this thesis.

Adam Levinson 03/16/2011

Asymmetric Synthesis of 8-oxabicyclo[3.2.1]octane Derivatives Using a Chiral Dirhodium Catalyst

by

Adam Levinson

Dr. Huw M.L. Davies, Ph.D.
Adviser

Department of Chemistry

Dr. Huw M.L. Davies, Ph.D.

Adviser

Dr. Frank McDonald, Ph.D.

Committee Member

Dr. Darrell Stokes, Ph.D.

Committee Member

03/16/2011

Asymmetric Synthesis of 8-oxabicyclo[3.2.1]octane Derivatives Using a Chiral Dirhodium Catalyst

By

Adam Levinson

Dr. Huw M.L. Davies, Ph.D.

Adviser

An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Sciences with Honors

Department of Chemistry

2011

Abstract

Asymmetric Synthesis of 8-oxabicyclo[3.2.1]octane Derivatives using a Chiral Dirhodium Catalyst

By Adam Levinson

The 8-oxabicyclo[3.2.1]octane molecular structure is a very synthetically useful motif for the construction of several complex natural products. Although it has previously been demonstrated that this structure can be synthesized asymmetrically in high yields using the Rh(II)-catalyzed tandem cyclopropanation/Cope-rearrangement with the aid of a chiral auxiliary, this reaction has not demonstrated high enantioselectivity with the use of a chiral dirhodium catalyst. This study has focused primarily on trying to achieve a highly enantioselective synthesis of 8-oxabicyclo[3.2.1] derivatives using the chiral Rh_2(S-PTAD)$_4$ catalyst. Furthermore, this study gives insight into the discrepancies between the stereochemical outcome for the tandem cyclopropanation/Cope-rearrangement of furan substrates catalyzed by Rh_2(S-DOSP)$_4$ versus Rh_2(S-PTAD)$_4$.

Asymmetric Synthesis of 8-oxabicyclo[3.2.1]octane Derivatives using a Chiral Dirhodium Catalyst

By

Adam Levinson

Dr. Huw M.L. Davies, Ph.D.

Adviser

A thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Sciences with Honors

Department of Chemistry

2011

Acknowledgements

I would like to foremost thank Prof. Huw Davies for the opportunity to work in his research laboratory for the past two years. I have not only gained synthetic chemistry laboratory skills and independence through this experience, but I have also gained a true appreciation and love for the field of synthetic organic chemistry. I plan to pursue graduate work in organic chemistry next year, ultimately due to my experiences in this lab.

I would also like to thank the other two members of my Honors' Thesis committee, Prof. Frank McDonald and Prof. Darrell Stokes. I specifically requested for both of you to sit on my committee as you have been very influential professors in my college career, and I cannot thank you enough for the gifts of knowledge that you have given me.

Thank you also to my graduate student research mentor, Yajing Lian, who has helped me immensely on this project. You have been an incredible teacher and help to me throughout the course of this year. Thank you also to Spandan Chennamadhavuni, who was my graduate student research mentor during my Junior year, and who taught me so many useful laboratory skills that I will take on with me after college.

Thanks to the entire Davies' lab group for your support and for being a great group of co-workers.

Finally, thank you to my family and friends who have supported me throughout my entire life and who have inspired me to pursue my own interests and learning.

Table of Contents

Figures and Tables

Seven-membered rings are important structural motifs found in a variety of pharmaceuticals and complex natural products. However, the ability to rapidly synthesize cycloheptane derivatives, especially in a diastereo- and enantioselective fashion, is quite limited. The Davies group has previously developed a method for the rapid construction of seven-membered rings with high regio- and diastereomeric control using Rh(II) catalysts[1]. This formal [4+3] cycloaddition reaction between vinyl dirhodium carbenoids and dienes proceeds through a cyclopropanation step, followed by a subsequent Cope-rearrangement to afford cycloheptadiene products in high yield with unusually high diastereoselectivity. Furthermore, it was found that the use of the chiral dirhodium catalyt, Rh_2(*S*-DOSP)$_4$ can catalyze [4+3] cycloaddition reactions between vinyl carbenoids and acyclic dienes with very high enantioselectivity (up to 98% ee)[2,3].

The diastereoselectivity of the tandem cyclopropanation/Cope-rearrangement arises because the *cis*-divinylcyclopropane intermediate must undergo a boat transition state in order for a Cope rearrangement to take place[4]. Because the *cis*-divinylcyclopropane can only undergo one transition state, alkene geometry is conserved in the process, lending itself to immense control over three possible stereocenters (**Figure 1**).

---

[1] Davies, H.M.L. Clark, T.J.; Smith, H.D. *J. Org. Chem.* **1991**, *56*(12) 3817-3824.

[2] Davies, H.M.L.; Stafford, D.G.; Doan, B.D.; Houser, J.H. *J. Am. Chem. Soc.* **1998**, *120*, 3326-3331.

[3] Davies, H.M.L.; Doan, B.D. *J. Am. Chem. Soc.* **1999**, *64*(23), 8501-8508.

[4] Piers, E. In *Comprehensive Organic Synthesis*. Trost, B.M., Ed.; Pergamon Press: Oxford, U.K., **1991**, Vol. 3, pp. 971-998.

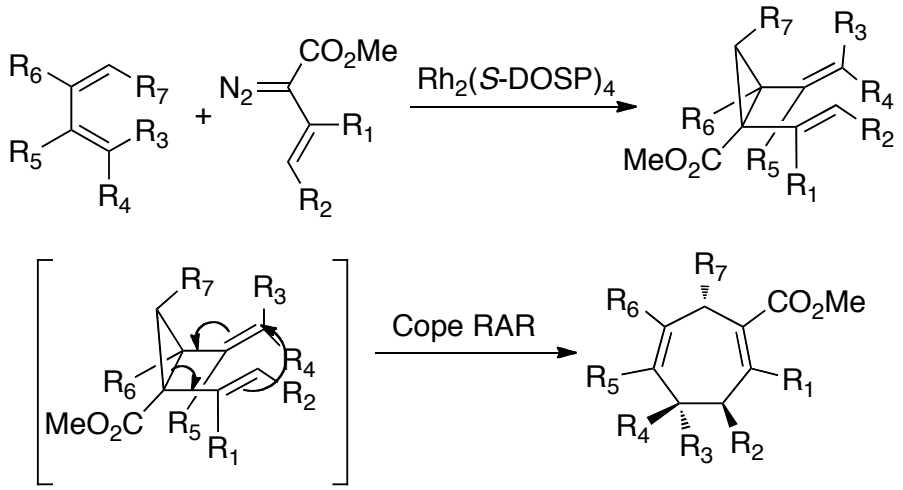
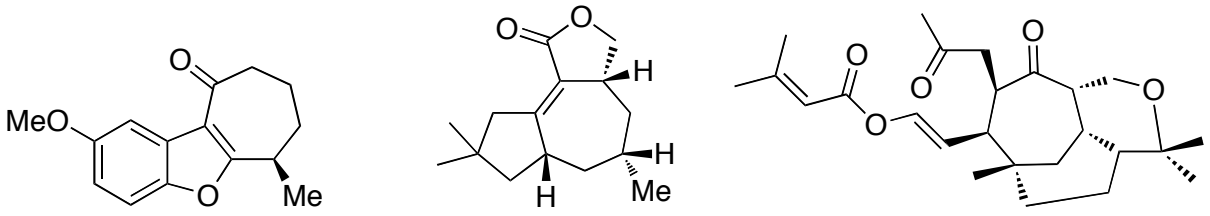
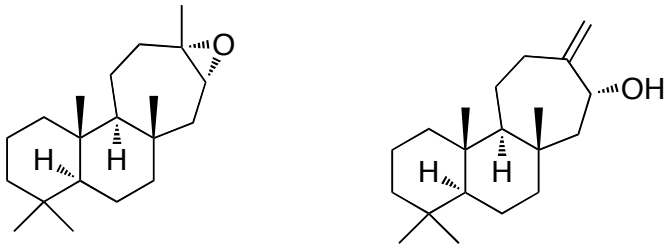


Figure 1: Mechanism of tandem cyclopropanation/Cope-rearrangement

Such reactions have now been demonstrated to allow for easy access to the enantiomerically pure core structures of several natural products containing seven-membered rings (**Figure 2**)[5,3,6,7].



(+)-Frondosin B Precursor | 5-*epi*-tremulenolide | (-)-5-*epi*-vibsanin E



(+)-barekoxide | (-)-barekol

Figure 2: Natural Products Synthesized

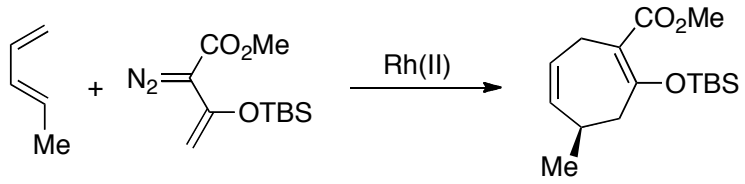
[5] Olson, J.P.; Davies, H.M.L. *Org. Lett.* **2008** *10*(4), 573-576.

[6] Schwartz, B.D.; Denton, J.R.; Lian, Y.; Davies, H.M.L.; Williams, C.M. *J. Am. Chem. Soc.* **2009**, *131*(23) 8329-8332.

[7] Lian, Y., Miller, L.C.; Born, S.; Sarpong, R., Davies, H.M.L. *J. Am. Chem. Soc.* **2010**, *132*, 12422-12425.

More recently, the chiral dirhodium catalyst Rh_2(*S*-PTAD)$_4$ has been shown to provide excellent asymmetric induction in the [4+3] cycloaddition of acyclic dienes and siloxyvinydiazoacetate[6,7]. This was extended in the total synthesis of (-)5-*epi*-vibsanin E, where Rh_2(*S*-DOSP)$_4$ gave poor enantioselectivity in a key step of the synthesis (**Table 1**).

Table 1



Catalyst	Temp (°C)	% yield	%ee
Rh_2(*S*-DOSP)$_4$	23	85	38
Rh_2(*S*-DOSP)$_4$	-26	35	53
Rh_2(*S*-PTAD)$_4$	23	78	86
Rh_2(*S*-PTAD)$_4$	-26	88	95

This project has focused on the asymmetric synthesis of 8-oxabicyclo[3.2.1]octane derivatives using the tandem cyclopropanation/Cope-rearrangement reaction between vinyl carbenoids and furans. The 8-oxabicyclo system is a very synthetically useful molecular structure, as it is a key intermediate in the synthesis of several natural products, including β-C-hexopyranosyl, nonactic acid, furanether B, and norhalichondrin B (**Figure 3**)[8,9,10,11].

[8] Fattori, D.; Vogel, P. *Tetrahedron Lett.* **1993**, *34*, 1017.
[9] Molander, G.A.; Eastwood, P.R. *J. Org. Chem.* **1994**, *59*, 7148.
[10] Molander, G.A.; Carey, J. *J. Org. Chem.* **1995**, *60,* 4845-4849
[11] Jackson, K.L.; Henderson, J.A., Motoyoshi, H.; Phillips, A.J. *Angew Chem Int. Ed.* **2009**, 48(13), 2346-2350.

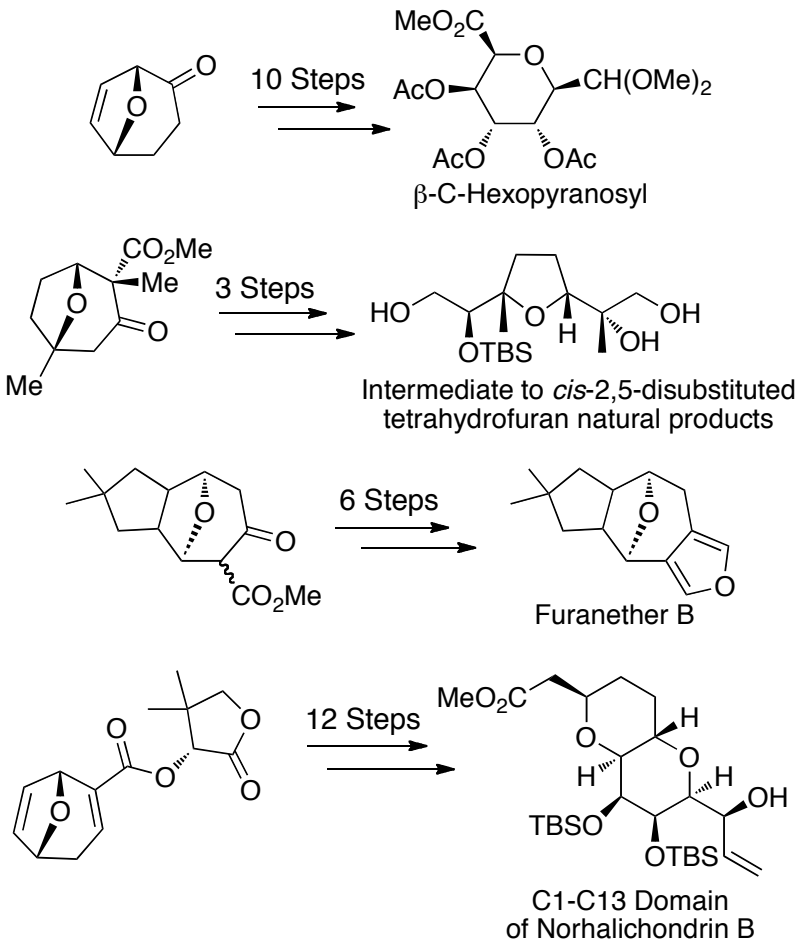


Figure 3: Natural Products Derived From 8-oxabicyclo[3.2.1]octane structures

Aside from the Rhodium(II)-catalyzed [4+3] annulation, there have been other methods developed for the synthesis of the oxabicyclic core structure. One method involves [4+3] coupling between polybromo ketones and furans using an iron carbonyl catalyst[12]. In this reaction, an oxallylic cation is formed *in situ*, which can then undergo a [4+3] cycloaddition with furan (**Figure 4**). This method has drawbacks, however, as it may generate several side products, and it lacks general regioselectivity with non-symmetric substrates.

[12] Noyori, R. *Acc. Chem. Res.* **1979,** *12*, 61.

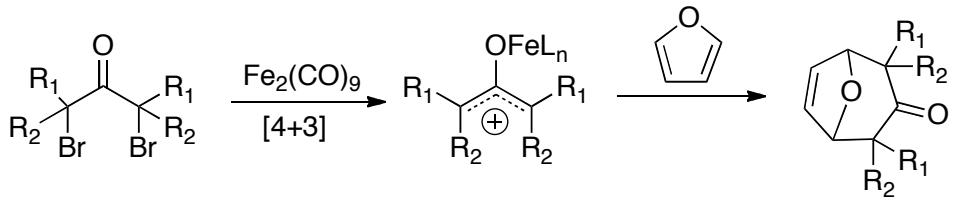


Figure 4: [4+3] cycloaddition of polybromoketones and furan

Another useful method for the construction of oxabicyclic systems is a [4+3] annulation between disilyl enol ethers and 1,4-dicarbonyl compounds[13,14]. The use of trimethylsilyl triflate (as well as Lewis acid catalysts) can catalyze the formation of an oxocarbenium ion from the dicarbonyl compound, which can then undergo nucleophilic addition with the disilyl enol ether (**Figure 5**). This reaction has been demonstrated to give bicyclic products with very high regio- and diastereoselectivity.

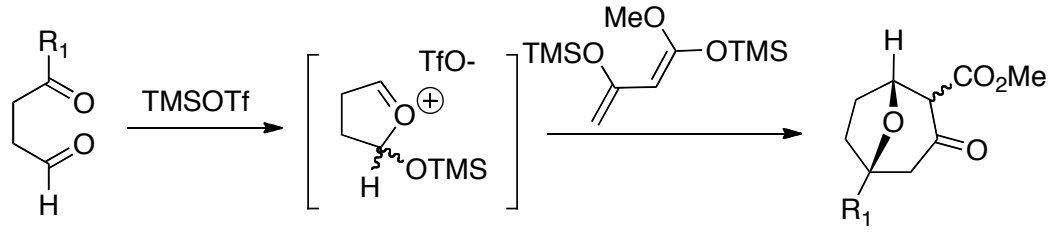


Figure 5: [4+3] annulation of 1,4-dicarbonyls and disilyl enol ethers

This molecular architecture has also been constructed via [5+2] cycloaddition between oxidopyrilium ions with alkenes (**Figure 6**)[15]. With the aid of a chiral auxiliary on the alkene substrate, moderate diastereoselectivity can also be achieved[16]. Although this reaction can be very useful in the synthesis of 8-oxabicyclic[3.2.1] derivatives, it lacks generality, in that modification of substituents can alter the electronics of the oxidopyrilium species generated.

---

[13] Brownbridge, P.; Chan. T. *Tetrahedron Lett.* **1979**, *46*, 4437-4440.

[14] Molander, G.A.; Eastwood, P. R. *J. Org. Chem.* **1995,***60*, 4559-4565

[15] Wender, P.A., Mascarenas, J. *Tetrahedron Lett.*, **1992,** 33(16) 2115-2118.

[16] Nicolaou, K.C.; Kang, Q.; Ng, S.Y.; Chen, D.Y. *J. Am. Chem. Soc.* **2010**, *132,* 8219-8222

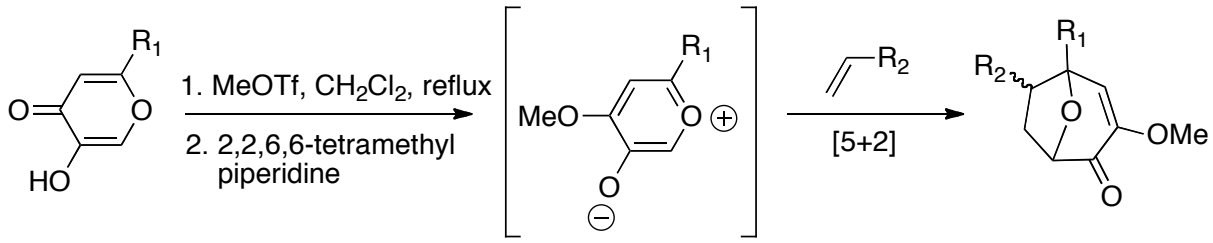


Figure 6 [5+2] cycloaddition of oxidopyrilium ions and alkenes

Using rhodium carbenoid chemistry, Padwa, et al. have demonstrated that rhodium acetate can catalyze the intramolecular formation of carbonyl ylides, which in the presence of alkenes or alkynes will undergo a 1,3-dipolar cycloaddition to form bicyclic products in good yields (**Figure 7**)[17]. Using a *chiral* dirhodium catalyst to initiate the formation of a 1,3-dipole, it has been shown that intramolecular reactions with alkynes can give high enantioselectivity[18].

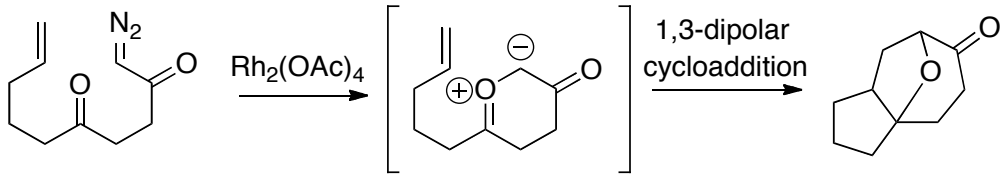


Figure 7 Rh(II) catalyzed 1,3-dipolar cycloaddition

Although vinyldiazoacetate readily undergoes the tandem cyclopropanation/Cope-rearrangement with furans in the presence of a rhodium catalyst to form oxabicyclo[3.2.1]octane structures, one difficulty is the potential formation of triene side products. It was shown, however, that the formation of trienes can be minimized by using a bulky siloxy vinyldiazoacetate, which preferentially undergoes the cyclopropanation step to afford the desired product (**Figure 8**)[19].

---

[17] Padwa, A.; Weingarten, M.D. *Chem Rev.***, 1996,** *96*, 223-269.

[18] Kitagaki, S.; Anaha, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.*, **1999**, *121*(6), 1417.

[19] Davies, H.M.L,; Ahmed, G.; Churchill, M.R. *J. Am. Chem. Soc.* **1996**, *118*, 10774.

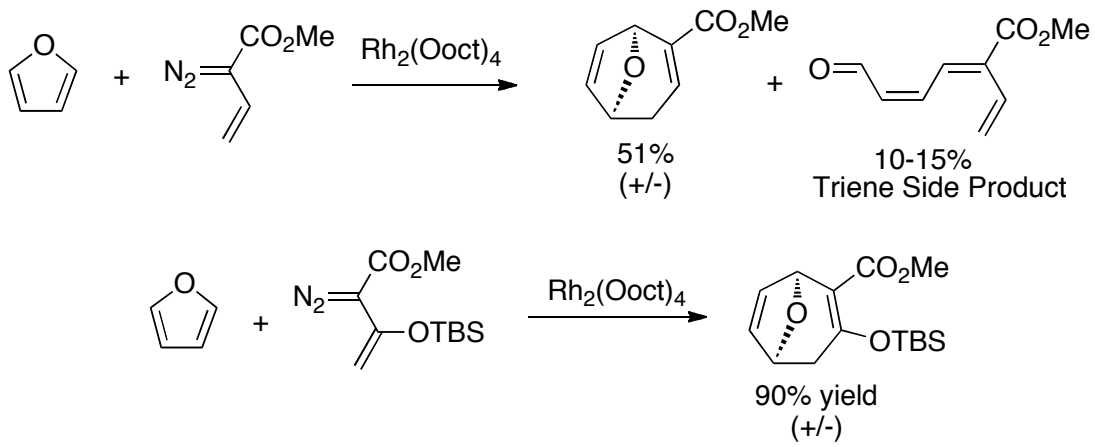


Figure 8 Tandem cyclopropanation/Cope-Rearrangement using siloxyvinyldiazoacetate

Trienes are thought to arise from a zwitterionic transition state in the cyclopropanation step, whereby the rhodium carbenoid undergoes electrophilic addition with furan to form a zwitterionic intermediate[20]. The intermediate then collapses into a more stable triene with conservation of double bond geometry (**Figure 9**). This occurs almost exclusively with furan and 2-substituted furans, although it is not observed with 2,5-disubstituted furans. Furthermore, electron rich furans, such as 2-methoxy furan almost exclusively undergo a rearrangement to the triene as the major product.

[20] Davies, H.M.L; Hedley, S.J. *Chem. Soc. Rev.*, **2007**, *36*. 1109-1119.

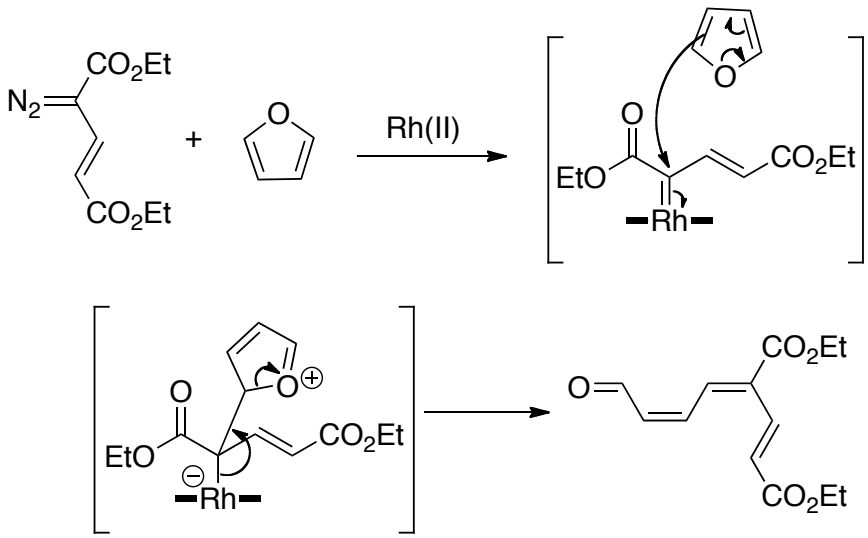
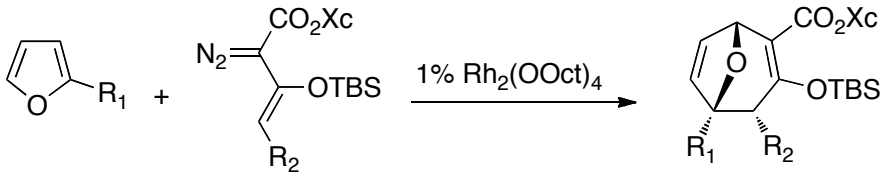


Figure 9 Proposed mechanism for triene formation

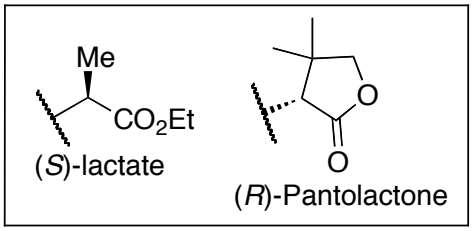
In 1996, the Davies group developed a method for the *asymmetric* synthesis of 8-oxabicyclic systems using siloxy vinyldiazoacetate and furans. This method uses a chiral auxiliary and an achiral rhodium(II) octanoate catalyst to afford [4+3] products in up to 95% diastereomeric excess (de), and >99% de after flash chromatography (**Table 2**)[16]. The chiral auxiliaries that were found to be most useful are (*S*)-lactate, and (*R*)-Pantolactone.

Table 2



Xc[1]	R1	R2	Yield (%)	de(%)
(*R*)-Pantolactone	H	H	82	94
(*S*)-Lactate	H	H	69	79
(*R*)-Pantolactone	H	Me	75	95
(*S*)-Lactate	H	Me	62	90
(*R*)-Pantolactone	Me	H	91	83
(*S*)-Lactate	Me	H	81	75
(*R*)-Pantolactone	Me	Me	69	94
(*S*)-Lactate	Me	Me	91	84
(*R*)-Pantolactone	CO_2Me	H	65	94
(*S*)-Lactate	CO_2Me	H	74	79

1. (*S*)-Lactate yields opposite stereochemistry from picture.



Recently, this method has been applied by Theodorakis, et al. as a key step towards the total synthesis of (-)-Englerin A, a potent inhibitor of renal cell carcinoma. (**Figure 10**)[21].

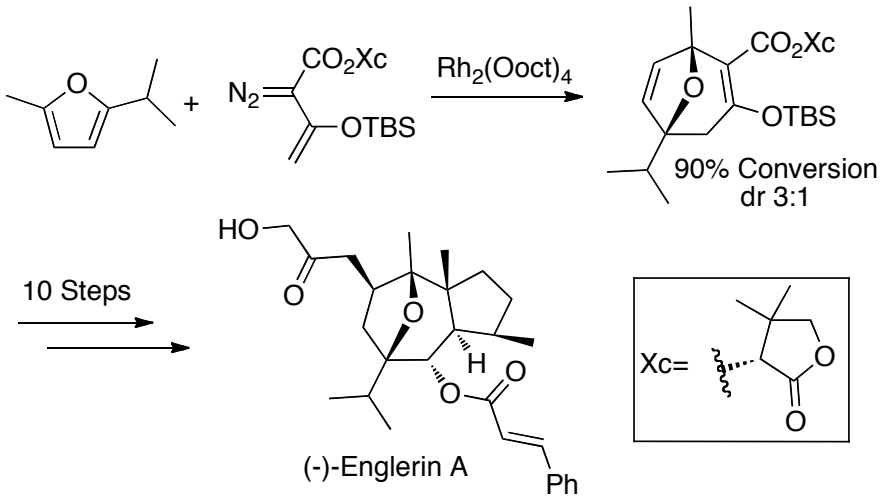


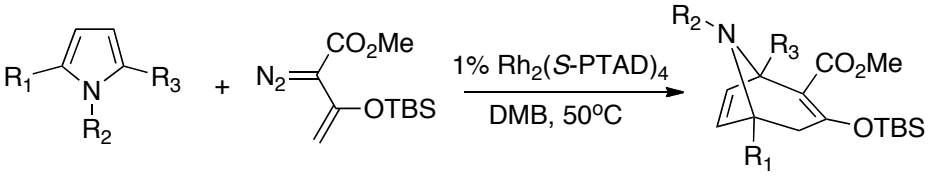
Figure 10 Total Synthesis of (-)-Englerin A

Heterocyclic dienes, such as pyrrole, have been shown to undergo [4+3] cycloadditions with very high enantioselectivity using Rh_2(*S*-PTAD)$_4$. This has proven incredibly useful in the rapid construction of enantiopure tropane molecules (**Table 3**)[22].

[21] Xu, J.; Caro-Diaz, J. E.; Theodorakis, E. *Org. Lett.* **2010**. 12(*16*). 3708-3711.

[22] Reddy, R.; Davies, H.M.L. *J. Am. Chem. Soc.* **2007**. *129*, 10312-10313

Table 3 Enantioselective Synthesis of Tropanes



R1	R2	R3	Yield (%)	ee(%)
Me	Boc	H	69	96
Me	Boc	Me	72	98
CO_2Me	Boc	H	71	89
H	Ph	H	64	97
H	*p*-$C_6H_4CH_3$	H	68	94

Interestingly, the enantioinduction of the Rh_2(*S*-PTAD)$_4$ catalyst with N-boc protected pyrroles to form tropanes is opposite to that of furans, which is a trend observed with the Rh_2(*S*-DOSP)$_4$ catalyst. This is likely due to a difference in the trajectory by which the diene enters the catalyst model. Using the model developed for the D_2-symmetric Rh_2(*S*-DOSP)$_4$ catalyst, furan generally prefers an entry to the carbenoid from a "head-on" approach, whereby a partial positive charge builds up on the more electronically stabilized β-carbon (**Figure 11**). Due to steric interactions with the catalyst ligands, N-boc pyrroles as well as 2,5-disubstituted furans prefer an approach from the opposite direction.[20,22] Although the same predicted compound is formed from both transition states, the *opposite* enantiomer is formed. This dual transition state can make it difficult to achieve high enantioselectivity in cases where the diene substrate can easily enter the catalyst model from both trajectories.

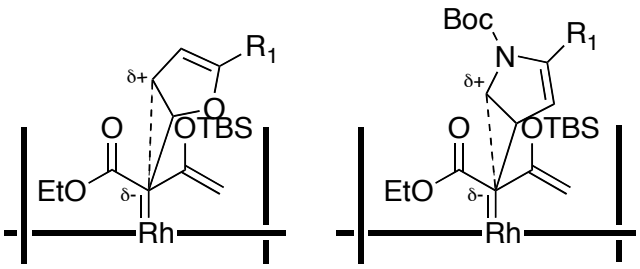
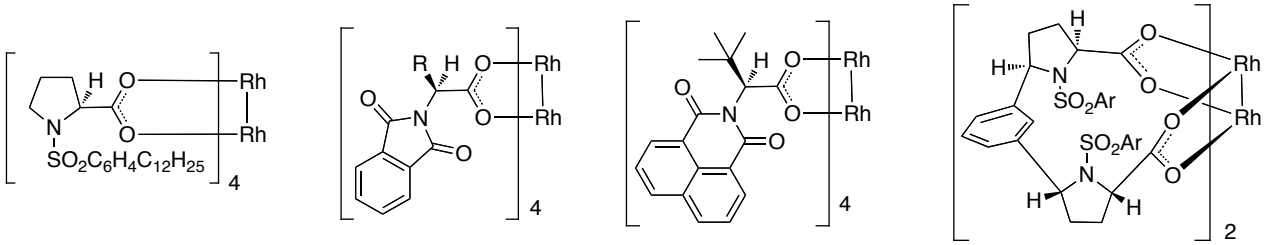


Figure 11: Transition state as dienes enter Rh_2(*S*-DOSP)$_4$ from the side

Although the use of chiral auxiliaries has proven useful in the enantioselective formation of oxabicyclo[3.2.1]octane systems, the use of a chiral catalyst to induce enantioselectivity would be preferable, as it does not require the stoichiometric use of chiral starting materials. Therefore, we sought to better understand whether it was possible to induce high enantioselectivity in the [4+3] cycloaddition between furans and siloxy vinyldiazoacetate using a *chiral* dirhodium catalyst, thus negating the need for a chiral auxiliary to enhance diastereoselectivity.



Rh_2(*S*-DOSP)$_4$

R=Ad Rh_2(*S*-PTAD)$_4$

R=^{t}Bu Rh_2(*S*-PTTL)$_4$

Rh_2(*S*-NTTL)$_4$

Rh_2(*S*-biTISP)$_4$

Ar=2,4,6-tri-^{i}PrC$_6$H$_2$

Figure 12: Example Chiral Dirhodium Catalysts

Synthesis of Diazo Compounds

The donor-acceptor siloxyvinyldiazo compounds used in this study were easily synthesized from an acetyldiazoacetate starting material (**1**). Acetyldiazoacetate was synthesized by means of a diazo-transfer reaction. Diazo-transfer occurs from an enolate attack onto an azide source, followed by a proton extraction to afford a diazo compound and an amine sideproduct. The azide source used in this reaction was P-ABSA (*para*-acetamidobenzenesulfonylazide), which was synthesized on a multigram-scale in one step from *para*-acetamidobenzenesulfonyl chloride in a 1:1 aqueous/acetone solvent (**Figure 13**).

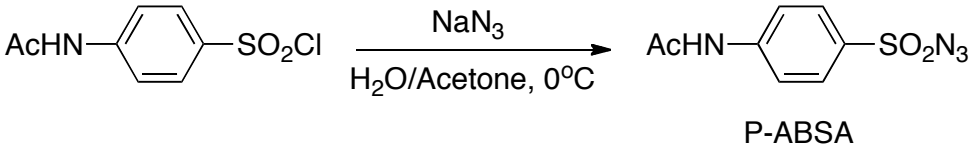


Figure 13 Synthesis of P-ABSA

Treatment of methyl 3-oxobutanoate with triethylamine as a base and P-ABSA afforded the diazo product **1** in good yield. Subsequent treatment of the product with triethylamine and TBSOTf afforded the TBSO-vinyldiazoacetate **2** in good yield (**Figure 14**). Vinyldiazo compounds with TIPS and TMS protecting groups were synthesized in a similar fashion.

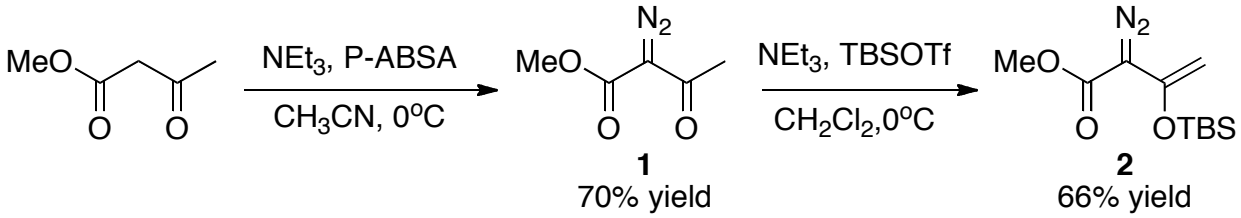


Figure 14 Synthesis of **1** and **2**

TBDPS-protected vinyldiazoacetate (**3**) was synthesized in a similar manner, although TBDPSOTf (not commercially available) was synthesized *in situ* from triphenyl-*tert*-butylsilane and triflic acid according to literature[23]. The resulting mixture was added slowly to a stirring mixture containing acetyldiazoacetate (**1**) and triethylamine to afford the final product **3**.

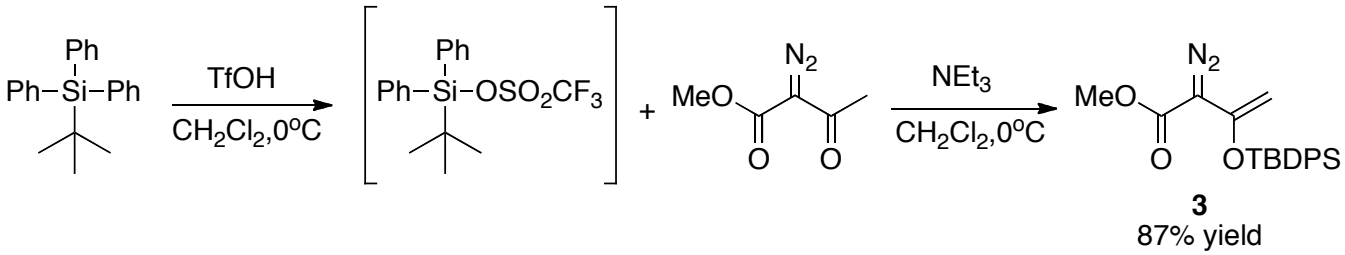


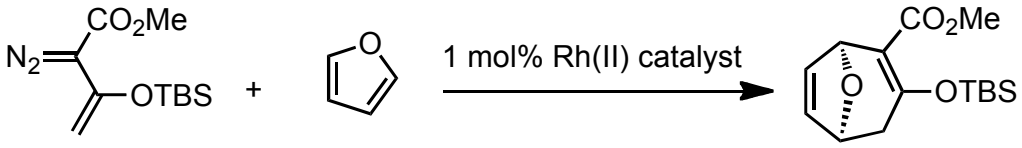
Figure 15 Synthesis of **3**

[23] Bassindal, A.R.; Stout, T. *J. Organometallic Chem*. **1984**, *271*, C1-C3.

Optimization Process:

The reaction between *tert*-butyldimethylsilyl vinyldiazoacetate (**2**) and furan (**4**) was used as a model reaction for the optimization of the tandem cyclopropanation/Cope-rearrangement. A variety of temperatures, solvents, and catalysts were screened in order to find optimum results. Additionally, variation of the siloxy group on the diazo compound was also explored.

Table 4: Screening of Catalysts



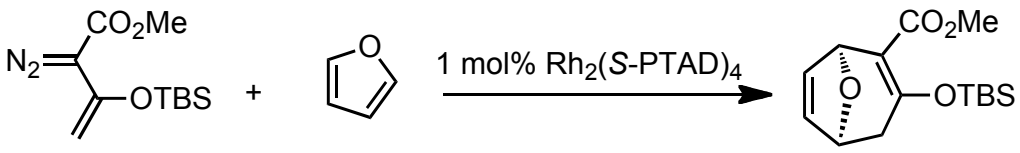
2 **4** **5**

entry	catalyst	ratio (2/4)	temp (°C)	yield (%)[a]	ee (%)[b]
1	*S*-DOSP	1 : 2	23	91	51
2	*S*-NTTL	1 : 2	23	92	62
3	*S*-PTTL	1 : 2	23	94	68
4	*S*-PTAD	1 : 2	23	92	72
5	*S*-biTISP	1 : 5	0	75	39

a. Isolated Yield

b. Determined by Chiral OD-H Column

Table 5: Solvent and Temperature Screening Table



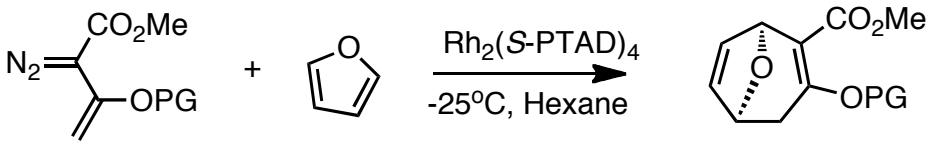
2 **4** **5**

entry	Solvent	ratio (2/4)	temp (°C)	yield (%)	ee (%)
1	Hexane	1 : 5	0	70	73
2	Hexane	1 : 5	-78-rt	98	69
3	Hexane	1 : 5	-25	98	77
4	DMB	1 : 5	-25	98	73
5	Toluene	1 : 5	-78-rt	98	63

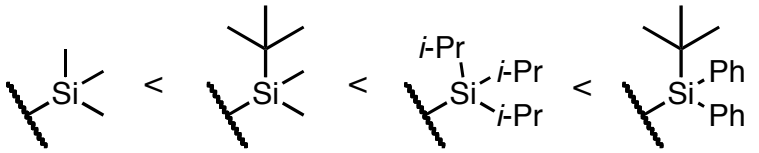
Based on these studies, which screened commonly used chiral dirhodium catalysts as well as various temperatures and solvents, it was found that the optimum catalyst for this study was Rh_2(*S*-PTAD)$_4$, and reactions were subsequently run at -25^{o}C in hexanes for approximately 18 hrs. Reactions were generally run on a 0.5mmol scale in flame-dried glassware, using a 5-fold excess of furan and 1 mol% catalyst, which gave nearly quantitative yields of the desired product.

In addition to catalysts, variation of the siloxy protecting group on the diazo starting material was explored (**Table 6**). It was hypothesized that the steric bulk of the siloxy group could have an effect on the enantioselectivity of this reaction. Screened siloxy groups included TMS, TBS, TIPS, and TBDPS (listed in order of increasing size).

Table 6: Variation of Protecting Groups



Protecting Group	Yield	%ee
TMS	Unstable to silica	NA
TBS	98%	77%
TIPS	96%	83%
TBDPS	79%	48%



TMS TBS (TBDMS) TIPS TBDPS

Interestingly, the steric bulk of the triisopropyl siloxyvinyldiazoacetate gave higher enantioselectivity compared to the TBS-protected diazo compound. When a TBDPS-protected diazo compound was used, however, the enantioselectivity diminished considerably. Although the use of a TMS-protected substrate showed clean conversion to the desired product by ^{1}H NMR in C_6D_6, the product was unstable to silica chromatography, and was therefore not isolated.

Synthesis of Furan Substrates:

A few of the furan substrates used in this study were not commercially available, and were therefore synthesized from commercially available materials. 5-methyl-2-isopropyl furan was synthesized according to literature in a three step sequence[21]: 2-methyl furan was treated with butyllithium, which in the presence of acetone was trapped to form tertiary alcohol **6**. The crude material was then treated with acetic anhydride and potassium acetate to afford the dehydrated product **7**, which was then hydrogenated to afford the final product **8**. Flash chromatography in plain pentane and careful concentration of the product yielded the pure furan in 41% overall yield (**Figure 16**).

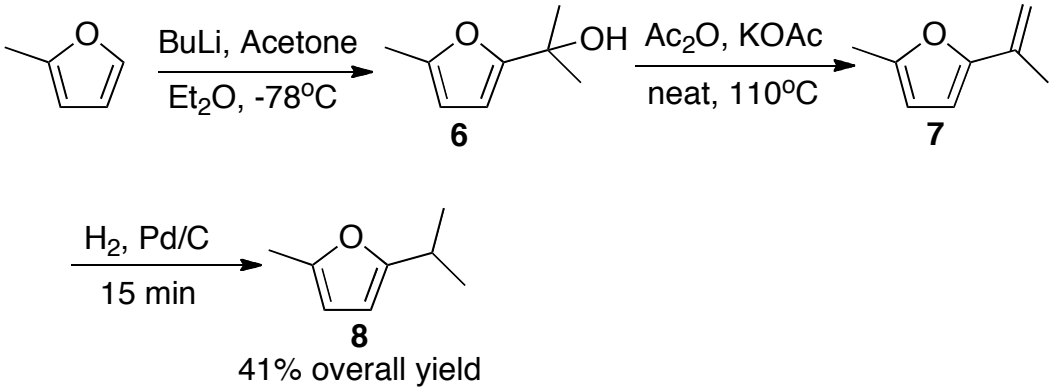


Figure 16: Synthesis of **8**

2-trimethylsilylfuran (**9**) as well as 2-benzylfuran (**10**) were synthesized from furan using a similar lithiation procedure (**Figure 17**). Compound **9** was isolated via distillation to afford 16% yield of the pure product, and compound **10** was isolated via column chromatography to afford a mixture of the compound and benzyl bromide starting material (42 wt% mixture of **10** by ^{1}H NMR).

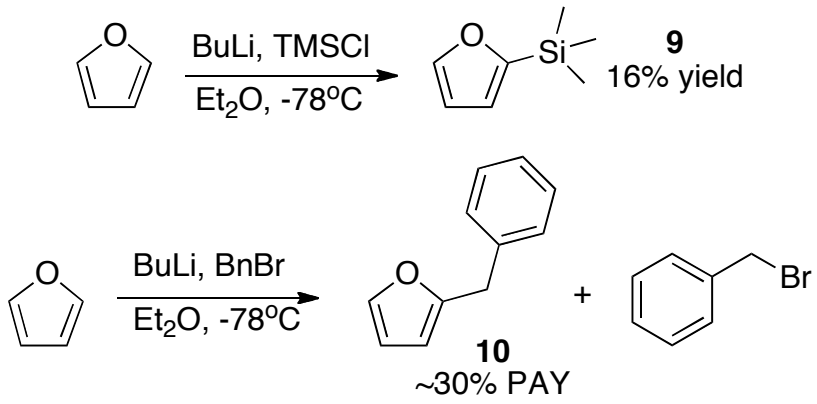


Figure 17: Synthesis of **9** and **10**

2-Furanylmethanol as well as optically pure (*S*)-2-Furanylethanol were protected using TBSCl in DMF solvent with 2 equivalents of imidazole. After stirring for approximately 1 hour at room temperature, products were extracted into ether and chromatographed to afford products **11** and **12** in high yields.

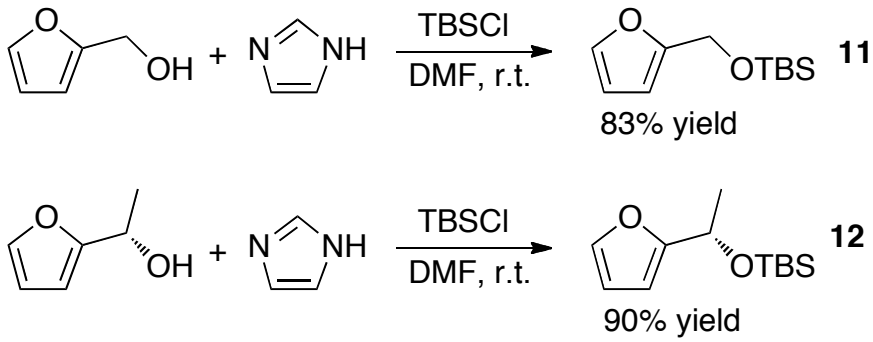
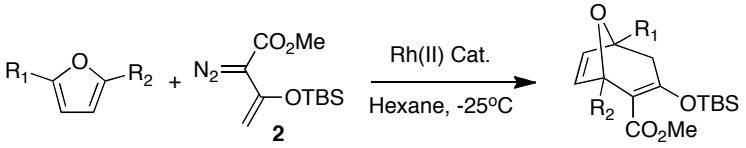


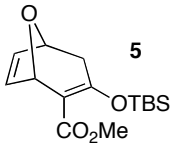
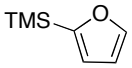
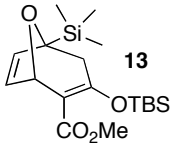
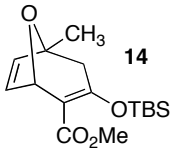
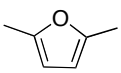
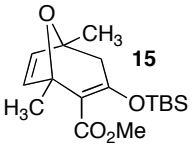
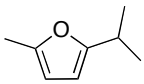
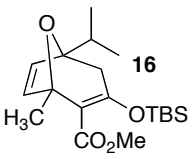
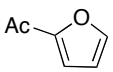
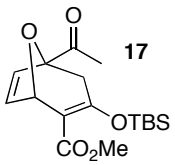
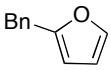
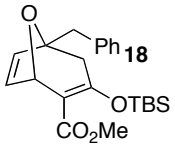
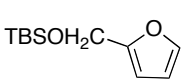
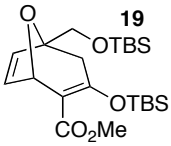
Figure 18: Protection of Furanyl alcohols

Synthesis of 8-oxabicyclo[3.2.1]octane Derivatives:

Upon the synthesis of furan substrates and optimization of the [4+3] cycloaddition reaction protocol using furan, several substrates were subsequently screened for their yields and enantioselectivities in forming 8-oxabicyclo[3.2.1]octane derivatives using Rh_2(*S*-PTAD)$_4$ as well as Rh_2(*R*-DOSP)$_4$. As shown in **Table 7**, the reactions between various furans and diazoacetate **2** afforded the bicyclic products in good yields (58-96%) with moderate to good asymmetric induction (56-86%). Interestingly, the reactions of 2,5-disubstituted furans as well as sterically bulky 2-trimethylsilylfuran using Rh_2(*S*-PTAD)$_4$ gave the same sense of enantioinduction as Rh_2(*R*-DOSP)$_4$, a somewhat unexpected result (Products **13, 15, 16**).

Table 7: Substrate Screening Table



Substrate	Product	Catalyst	Yield	%ee
	 **5**	S-PTAD	98%	77%
	 **13**	S-PTAD *R*-DOSP[1]	96% 46%	63% (+)27%
	 **14**	S-PTAD *R*-DOSP[1]	83% 73%	86% (-)31%
	 **15**	S-PTAD *R*-DOSP[1]	76% 25%	58% (+)36%
	 **16**	S-PTAD *R*-DOSP[1]	40% 51%	46%[2] (+)40%
	 **17**	S-PTAD *R*-DOSP[1]	58% 72%	56% (-)13%
	 **18**	S-PTAD *R*-DOSP[1]	72% 87%	75% (-)8%
	 **19**	S-PTAD *R*-DOSP[1]	82% 75%	76% (-)28%

1. Reaction ran at ambient temperature.
2. Reaction warmed from -25°C-r.t. after 12 hrs of stirring.

In order to prove the stereochemistry of these bicyclic derivatives, compounds **5** and **16** were converted to known compounds from literature[16,18], and their optical rotations were compared.

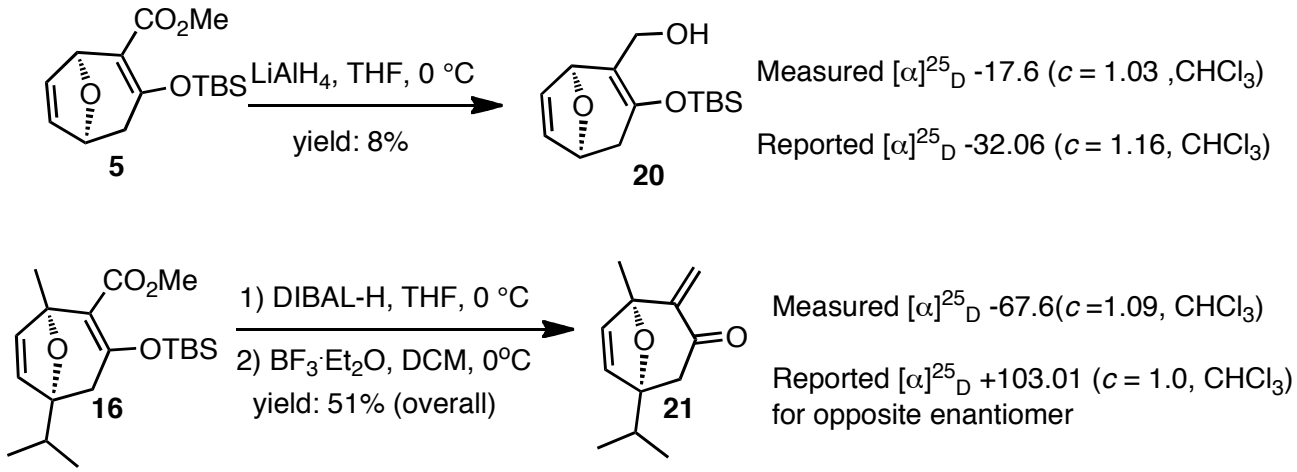


Figure 19: Absolute Stereochemical Determination of 8-oxabicyclo[3.2.1] Derivatives

Based on the optical rotation of **20**, the stereochemistry of monosubstituted furans (**13-14**, **17-19**) were tentatively assigned as the same assuming a similar transition state in the cyclopropanation step. Likewise, based on the optical rotation of **21**, the stereochemistry of compound **15** was tentatively assigned as the same.

A high level of enantiomeric differentiation for the formal [4 + 3] cycloaddition between vinyldiazoacetate **2** and acyclic dienes, as well as in the cyclopropanation of alkenes has been previously reported[7,24,25]. Consequently, it was explored if enantiomeric differentiation would be feasible in this reaction. Reactions with optically-pure furan, **12**, were screened with a variety of Rh(II) catalysts and results were summarized in **Table 8**. The reaction catalyzed by Rh_2(*R*-PTAD)$_4$ successfully provided product **23** as a single diastereomer, while the reaction with Rh_2(*S*-PTAD)$_4$ generated two diastereomers as an

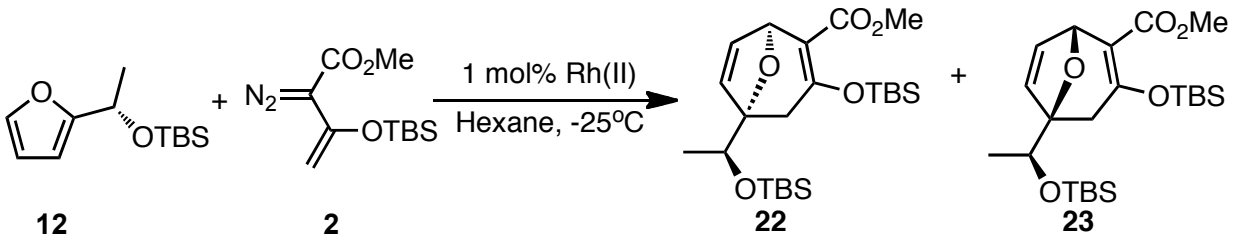
---

[24] Deng, L.; Giessert, A.; Gerlitz, O.; Dai, X.; Diver, S.; Davies, H.M.L. *J. Am. Chem. Soc.* **2005**, *127*, 1342-1343

[25] Nadeau, E.; Ventura, D.; Brekan, J.; Davies, H.M.L. *J. Org. Chem.,* **2010**, *75*, 1927-1939.

inseparable 1:1 mixture. The absolute stereochemical configuration has been tentatively assigned based on the stereochemical preference of Rh_2(*S*-PTAD)$_4$ and Rh_2(*R*-PTAD)$_4$ with monosubstituted furans. This reaction in the presence of achiral catalysts (**Figure 20**) was also interesting. The reaction with $Rh_2(esp)_2$ slightly favored the formation of **22** over **23** in a 3.3:1 ratio, while the chiral center had no effect on the selectivity when the reaction was catalyzed by $Rh_2(Oct)_4$. Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-DOSP)$_4$ both gave the same diastereoselectivity, which was equivalent to that of $Rh_2(esp)_2$, suggesting that these catalysts also had little or no influence on the selectivity of this reaction.

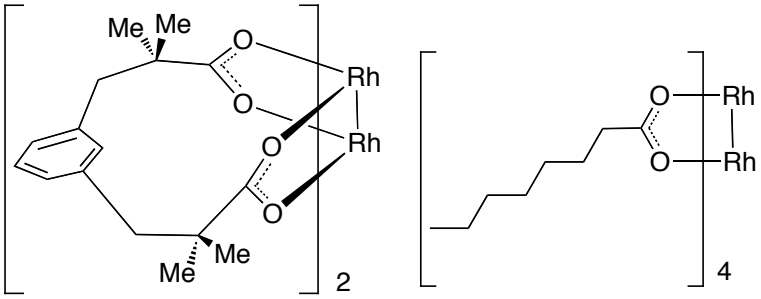
Table 8: Enantiodifferentiation observed with furan **12**



12 **2** **22** **23**

Entry	Catalyst	Combined Yield (%)	dr[1,2] (22:23)
1	Rh_2(*S*-PTAD)$_4$	45%	1:1
2	Rh_2(*R*-PTAD)$_4$	78%	>1:19
3	$Rh_2(esp)_2$	69%	3.3:1
4	$Rh_2(Oct)_4$	66%	1:1
5	Rh_2(*S*-DOSP)$_4$	72%	4:1
6	Rh_2(*R*-DOSP)$_4$	69%	3:1

1. Determined by crude ^{1}H NMR
2. Absolute stereochemistry tentatively assigned.



$Rh_2(esp)_2$ $Rh_2(Ooct)_4$

Figure 20: Structures of $Rh_2(esp)_2$ and $Rh_2(Ooct)_4$

Discussion:

The stereoselectivity of this formal [4+3] cycloaddition is controlled in the initial cyclopropanation step. Several studies have shown that Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-DOSP)$_4$ lead to the same asymmetric induction in the formal [4 + 3] cycloaddition[6,22]. However, the stereochemical outcome of reactions between diazoacetate **2** and furans turned out to be very complicated in this study. The enantioinduction for the cyclopropanation of 2,5-disubstituted furans has generally been known to be *opposite* that of monosubstituted furans when the D_2 symmetric Rh_2(*S*-DOSP)$_4$ catalyst is used[20,26]. Using this model, reactions run with Rh_2(*R*-DOSP)$_4$ successfully yielded products with the predicted stereochemistry. However, reactions with 2,5-disubstituted furan substrates yielded products with the *same* enantioinduction as monosubstituted furans when the Rh_2(*S*-PTAD)$_4$ catalyst was used.

It has been proposed that two possible approach vectors may be involved in the reactions between vinylcarbenoids and furans (**Figure 21**). Depending on its inherent functionalities, furan can either proceed through the cyclopropanation step with initial bond formation at the 2-position (**A**) or 3-position (**B**). Both of these approaches lead to the same compound, but different enantiomers. The reaction with monosubstituted furans (R_1 = H) favors the transition state A, which follows the expected regiochemistry for aromatic electrophilic substitution of furans. Conversely, the reaction with 2,5-disubstituted furans prefers the transition state B, because the R_1 group can sterically interrupt with rhodium "wall" in the transition state A.

---

[26] Hedley, S.J.; Ventura, D.L. Dominiak, P.M.; Nygren, C.L.; Davies, H.M.L. *J. Org. Chem.* **2006**, *71,* 5349.

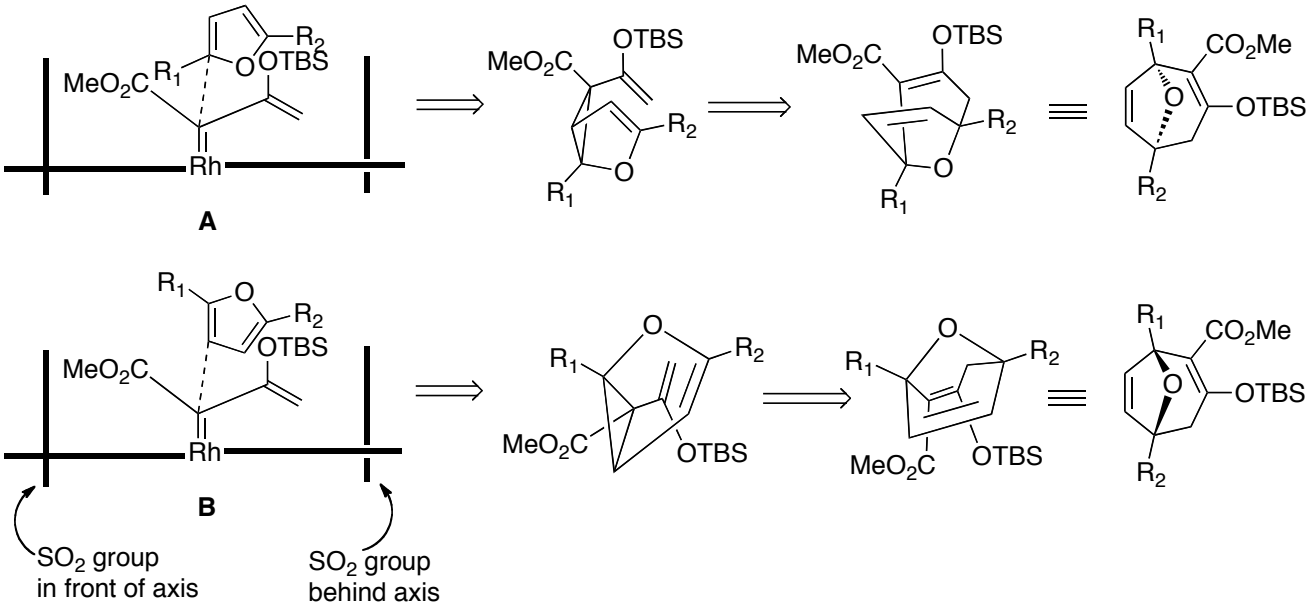


Figure 21 Dual approach vectors towards the side-view of Rh_2(*S*-DOSP)$_4$

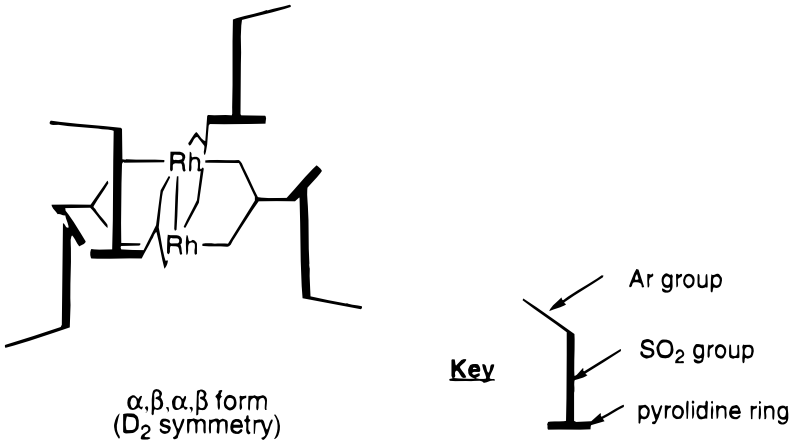


Figure 22 Full view of the Rh_2(*S*-DOSP)$_4$ model[27]

During this study, the product outcome with Rh_2(*R*-DOSP)$_4$ was successfully predicted based on the D_2 symmetric model. Several models have been proposed to account for the asymmetric induction with Rh_2(*S*-PTAD)$_4$, and the actual model is still under debate. The detailed mechanism for the reaction between Rh_2(*S*-PTAD)$_4$-catalyzed vinylcarbenoids and furans is still uncertain. Presumably, the reason that Rh_2(*S*-PTAD)$_4$

[27] Davies, H.M.L., Bruzinsky, P.R.; Lake, D.H.; Kong, N.; Fall, M.J. *J. Am. Chem. Soc.*, **1996**, *118*(29) 6897-6907

may have given the opposite enantioinduction from that predicted for these substrates is likely due to a difference in the catalyst structure bonding with the vinylcarbenoid. It is possible that 2,5-disubstituted furans and 2-trimethylsilylfuran may approach to the catalyst through transition state B, but from the opposite face of the catalyst, which would yield opposite enantioinduction from predicted based on D_2 symmetric model of Rh_2(*S*-DOSP)$_4$. Understanding the detailed transition state and improving the enantioselectivity are currently under investigation.

Another interesting phenomenon noted in this study is the kinetic resolution achieved in the reaction between chiral furan **12** and diazo compound **2**. Excellent diastereoselectivity was achieved in this model reaction when Rh_2(*R*-PTAD)$_4$ was employed (>19:1 dr). Interestingly, the natural diastereoselectivity observed in this reaction preferred the opposite diastereomer when the achiral catalyst $Rh_2(esp)_2$ was used. Reactions run with Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-DOSP)$_4$ yielded similar results as observed with $Rh_2(esp)_2$, suggesting that they exert little to no influence on the diastereoselectivity of this reaction.

Conclusion:

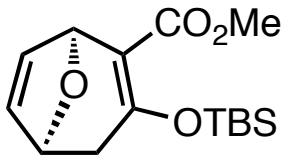
In conclusion to this study, Rh_2(*S*-PTAD)$_4$ has been shown to be an effective catalyst for the synthesis of 8-oxabicyclo[3.2.1]octane derivatives in good yield (58-96% yield). Although Rh_2(*S*-PTAD)$_4$ has been able to achieve excellent enantioselectivity with reactions between vinyldiazoacetate **2** and pyrroles as well as acyclic dienes, the enantioselectivity observed with furans is only moderate to good (56-86% ee).

This study has also shown that the enantioinduction observed with Rh_2(*S*-PTAD)$_4$ is the same as Rh_2(*S*-DOSP)$_4$ for the tandem cyclopropanation/Cope-rearrangement of furan and monosubstituted furan substrates. However, the stereochemical outcome of products synthesized from 2,5-disubstituted furans and highly bulky monosubstituted furans using Rh_2(*S*-PTAD)$_4$ cannot be predicted based solely on the Rh_2(*S*-DOSP)$_4$ model. A better understanding of the transition state of this reaction using Rh_2(*S*-PTAD)$_4$ is currently under investigation, and is necessary for a full explanation of the reactivity displayed in this study.

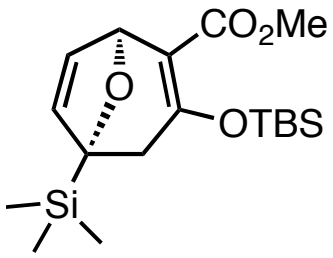
General Methods: All experiments were performed under anhydrous conditions in an atmosphere of argon except where stated, using flame-dried glassware. Toluene and hexane were dried by a solvent purification system (passed through activated alumina columns). Unless otherwise noted, all other reagents were obtained from commercial sources and used as received. ^{1}H Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 or 600 MHz. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δH 7.26 for the residual protons in CDCl3), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 100 or 150 MHz, and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δC 77.23 for CDCl3. Mass spectral determinations were carried out by using APCI as ionization source. Infrared spectral data is reported in units of cm^{-1}. Analytical TLC was performed on silica gel plates using UV light or potassium permanganate stain if stated. Flash column chromatography was performed on silica gel 60A (230-400 mesh). Optical rotations were measured on Jasco polarimeters. Analytical enantioselective chromatographies were measured on Varian Prostar instrument and used isopropanol/hexane as gradient.

General Procedure for the Synthesis of 8-oxabicyclo[3.2.1]octane compounds:

To a 50ml round bottom flask was charged 1mol% Rh_2(*S*-PTAD)$_4$, which was dissolved in a few drops of trifluorotoluene. Then, 6mL of anhydrous hexanes followed by furan (2.5mmol, 5.0 equiv) were charged to reaction vessel, and mixture stirred at -25^{o}C. Diazo compound (0.5mmol, 1.0 equiv.) was dissolved in 6mL hexanes and charged to reaction mixture via syringe pump over about 2hrs. Reaction stirred at -25^{o}C for 18 hrs. and was concentrated to afford crude product. Product was purified by flash chromatography on silica gel (9:1 Hexane/EtOAc).

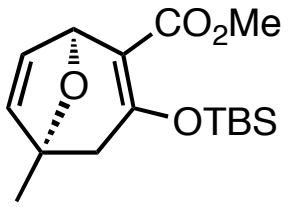


(1*S*,5*S*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (5): Derived from furan (170 mg, 2.5 mmol, 5.0 equiv) and purified by flash chromatography (85/15 pentane/Et_2O, R_f: 0.28) in silica gel to provide **5** as a colorless oil (145.2 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) d 6.56 (d, *J* = 6.5 Hz, 1H), 5.95 (d, *J* = 6.5 Hz, 1H), 5.34 (s, 1H), 4.93 (d, *J* = 6.5 Hz, 1H), 3.71 (s, 3H), 2.71 (dd, *J* = 17.5, 6.0 Hz, 1H), 1.79 (d, *J* = 17.5 Hz, 1H), 0.94 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H). The ^{1}H NMR data were consistent with published data.



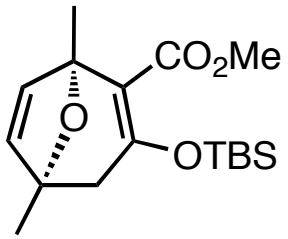
(1S,5R)-methyl 3-((tert-butyldimethylsilyl)oxy)-5-(trimethylsilyl)-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (13)

Derived from 2-trimethylsilyl furan (351 mg, 2.5 mmol, 5.0 equiv) and purified by flash chromatography (5/1 hexane/EtOAc, R_f: 0.50) on silica gel to provide **13** as a colorless oil (177 mg, 96% yield). ^{1}H NMR (400MHz, $CDCl_3$): 6.48 (d, 1H, *J*=6.0), 5.81 (d, 1H, *J*=6.0) 5.31 (s, 3H), 2.55 (d, 1H, *J*=17.6), 1.70 (d, 1H, *J*=18), 0.93 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.5, 157.3, 137.0, 128.9, 114.9, 78.9, 77.0, 51.0, 34.4, 25.8, 18.5, -3.4, -4.6. IR (neat): 2953.1, 1719.5, 1686.5, 1614.7, 1436.7, 1365.5 cm^{-1}; HRMS (EI) calc for $C_{18}H_{33}O_4Si$ $(M+H)^+$ 369.19080 found 369.19119. HPLC: (SS Whelk, 0.0 % isopropanol in hexane, 0.5 mL/min) retention times of 10.56 (minor) and 11.2 (major), 63 % ee. $[\alpha]^{25}_D$ = -27.15 (*c* = 1.08, $CHCl_3$).



(1*S*,5*S*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (14):

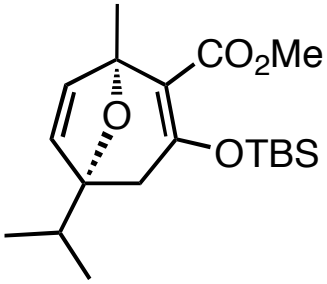
Derived from 2-methylfuran (205 mg, 2.5 mmol, 5.0 equiv) and purified by flash chromatography (9/1 hexane/EtOAc, R_f: 0.44) on silica gel to provide **14** as a colorless oil (129 mg, 83% yield). ^{1}H NMR (500MHz, $CDCl_3$): 6.46 (dd, J = 1.5, 5.5 Hz, 1H), 5.72 (d, J = 5.5 Hz, 1H), 5.34 (d, J = 0.9 Hz, 1H), 3.70 (s, 3H), 2.39 (d, J = 17.7 Hz, 1H), 1.90 (d, J = 17.7 Hz, 1H), 1.46 (s, 3H), 0.93 (s, 9H), 0.18 (d, J = 9.5 Hz, 6H); ^{13}C NMR (75MHz, $CDCl_3$): 165.3, 158.8, 137.7, 130.8, 113.6, 82.5, 50.8, 40.4, 25.6, 23.7, 18.3, -3.6, -3.7; IR (neat): 2952, 2931, 2859, 1720, 1688, 1616, 1375, 1256, 1206, 1052, 882, 785cm^{-1}; HRMS (EI) calc for $C_{15}H_{23}O_4Si$ $(M\text{-}CH3)^+$ 295.1360 found 295.1366; HPLC: (OD-H, 0.7 % isopropanol in hexane, 0.8 mL/min) retention times of 9.1 (major) and 10.5 (minor), 86 % ee; $[\alpha]^{25}_D$ = -29.8 (c = 1.11, $CHCl_3$).



(1*S*,5*S*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (15)

Derived from 2,5-dimethyl furan (240 mg, 2.5 mmol, 5.0 equiv) and purified by flash chromatography (5/1 hexane/EtOAc, R_f: 0.30) on silica gel to provide **15** as a colorless oil (113 mg, 70% yield).

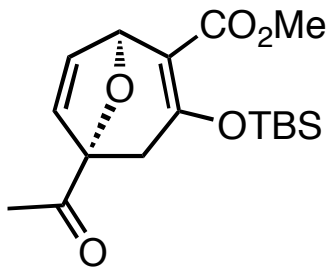
^{1}H NMR (400MHz, $CDCl_3$): 6.42 (d, 1H, *J*=5.2), 5.65 (d, 1H, *J*=5.6), 3.7 (s, 3H), 2.43 (d, 1H, *J*=17.6), 1.87 (d, 1H, *J*=17.2), 1.55 (s, 3H), 1.45 (s, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):167.2, 153.6, 141.9, 130.4, 119.6, 83.5, 82.5, 51.2, 39.9, 25.7, 24.5, 20.5, 19.2, -3.4, -3.5. IR (neat): 2951, 2930, 2894, 2858, 1723, 1966, 1614, 1434. HRMS (EI) calc for $C_{17}H_{29}O_4Si$ $(M+H)^+$ 325.18285 found 325.18296. HPLC: (ADH, 1.0 % isopropanol in hexane, 0.7 mL/min) retention times of 7.7 (minor) and 8.75 (major), 58 % ee, $[\alpha]^{25}_D$ = +9.29 (*c* = 1.10, $CHCl_3$).



(1S,5R)-methyl 3-((tert-butyldimethylsilyl)oxy)-5-isopropyl-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (16)

5-methyl-2-isopropyl furan was synthesized according to literature[21].

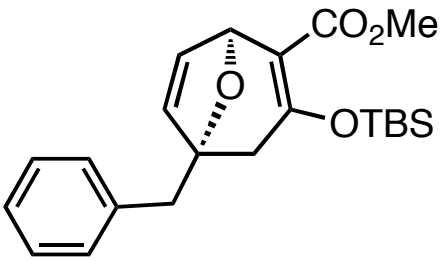
Derived from 5-methyl-2-isopropyl furan (310 mg, 2.5 mmol, 5.0 equiv) and purified by flash chromatography (9/1 hexane/EtOAc, R_f: 0.35) on silica gel to provide **16** as a colorless oil (72 mg, 40% yield). ^{1}H NMR (400MHz, $CDCl_3$): 6.41 (d, 1H, *J*=5.6), 5.70 (d, 1H, *J*=5.6), 3.69 (s, 3H), 2.41 (d, 1H, *J*=17.2), 1.88 (m, 1H), 1.85 (d, 1H, *J*=17.2), 1.53 (s, 3H), 0.99 (d, 3H, *J*=7.2), 0.95 (d, 3H, *J*=6.8), 0.90 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.1, 154.1, 141.8, 126.6, 119.5, 88.5, 83.0, 51.1, 36.6, 34.3, 25.5, 20.3, 18.2, 17.2, 17.1, -3.2, -3.3. IR (neat): 2956, 2931, 2858, 1722, 1698, 1619, 1471 cm^{-1}; HRMS (EI) calc for $C_{19}H_{33}O_4Si$ $(M)^+$ 353.21420 found 353.21426. HPLC: (AD-H, 1.0 % isopropanol in hexane, 1 mL/min) retention times of 13.39 (minor) and 16.8 (major), 46 % ee; $[\alpha]^{25}_D$ = -0.72 (*c* = 1.12, $CHCl_3$).



(1*S*,5*S*)-methyl 5-acetyl-3-((*tert*-butyldimethylsilyl)oxy)-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (17)

Derived from 2-acetyl furan (X mg, 2.5 mmol, 5.0 equiv) and purified by flash chromatography (4/1 hexane/EtOAc, R_f: 0.5) on silica gel to provide **17** as a colorless oil (98 mg, 58% yield).

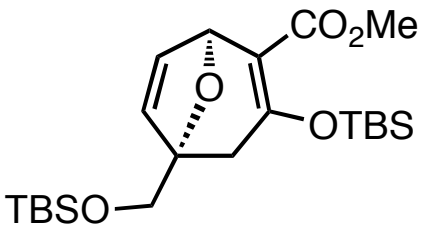
^{1}H NMR ($CDCl_3$, 400MHz): 6.64 (d, 1H, *J*=1.6, 5.2), 5.81 (d, 1H, *J*=5.6), 5.50 (m, 1H), 3.71 (s, 3H), 2.55 (d, 1H, *J*=18), 2.26 (s, 3H), 2.14 (d, 1H, *J*=18), 0.93 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 208.3, 165.3, 158.4, 140.0, 127.3, 113.1, 89.9, 78.1, 77.9, 51.3, 34.9, 25.7, 16.5, -3.4, -3.5.; IR (neat): 2930.8, 2858.5, 1719.4, 1686.6, 1612.2, 1472.6, 1437.3.; HRMS (EI) calc for $C_{17}H_{27}O_5Si$ $(M+H)^+$ 339.16205 found 339.16223. HPLC: (SS whelk, 0.0 % isopropanol in hexane, 0.5 mL/min) retention times of 23.3 (major) and 25.7 (minor), 56 % ee. $[\alpha]^{25}_D$ = +31.00 (*c* = 0.900, $CHCl_3$).



(1*S*,5*S*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)-5-phenethyl-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (18)

Derived from 2-benzyl furan (940 mg (42wt%), 2.5 mmol, 5.0 equiv) and purified by flash chromatography (9/1 hexane/EtOAc, R_f: 0.20) on silica gel to provide **18** as a colorless oil (140 mg, 72% yield).

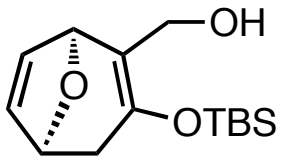
^{1}H NMR (400MHz, $CDCl_3$): 7.25 (m, 5H), 6.44 (dd, 1H, *J*=6, 2), 5.78 (d, 1H, *J*=5.6), 5.39 (br. s., 1H), 3.69 (s, 3H), 3.06 (s, 1H), 3.06 (s, 1H), 2.50 (d, 1H, *J*=17.6), 1.80 (d, 1H, *J*=17.6), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.4, 159.2, 137.9, 137.2, 130.4, 129.7, 128.4, 126.9, 113.7, 85.5, 51.0, 43.7, 38.5, 25.7, 18.5, -3.5, -3.6. IR (neat): 2929.5, 2857.6, 1718.2, 1683.7, 1614.0, 1496.4.; HRMS (EI) calc for $C_{22}H_{31}O_4Si$ $(M+H)^+$ 387.19827 found 387.19861. HPLC: (ADH, 1.0 % isopropanol in hexane, 1.0 mL/min) retention times of 16.2 (minor) and 20.6 (major), 75 % ee. $[\alpha]^{25}_D$ = -36.96 (*c* = 1.14, $CHCl_3$).



methyl 3-((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (19)

Derived from *tert*-butyl(furan-2-ylmethoxy)dimethylsilane (424 mg, 2.5 mmol, 5.0 equiv) and purified by flash chromatography (9/1 hexane/EtOAc, R_f: 0.33) on silica gel to provide **19** as a colorless oil (180 mg, 82% yield).

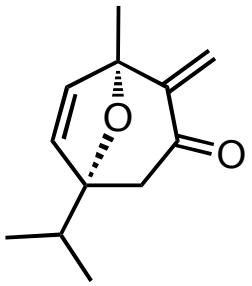
^{1}H NMR (400MHz, $CDCl_3$): 6.51 (dd, 1H, *J*=1.6, 5.2), 5.82 (d, 1H, *J*=5.2), 5.37 (d, 1H, *J*=1.6), 3.78 (s, 2H) 3.69 (s, 3H), 2.67 (d, 1H, *J*=17.2), 1.88 (d, 1H, *J*=17.6), 0.94 (s, 9H), 0.90 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$):165.5, 159.4, 138.5, 128.5, 113.7, 86.2, 77.6, 66.6, 51.1, 35.7, 26.1, 25.8, 18.5, -3.4, -3.5, -5.2. IR (neat):2951.7, 2929.3, 2896.8, 2857.6, 1720.8, 1686.7, 1614.5, 1472.2, 1463.3 1370.8. HRMS (EI) calc for $C_{22}H_{41}O_5Si_2$ $(M+H)^+$ 441.24839 found 441.24871. HPLC: (ODH, 0.7 % isopropanol in hexane, 1.0 mL/min) retention times of 3.6 (major) and 4.1 (minor), 76 % ee. $[\alpha]^{25}_D$ = -34.43 (*c* = 1.12, $CHCl_3$).



((1S,5S)-3-((tert-butyldimethylsilyl)oxy)-8-oxabicyclo[3.2.1]octa-2,6-dien-2-yl)methanol (20)

To a solution of $LiAlH_4$ (266mg, 7mmol, 4 equiv.) in 30mL THF at 0^oC was added (1*S*,5*S*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (515 mg, 1.73mmol, 1 equiv.). Reaction warmed to room temp, and stirred for 2 hrs. Worked up reaction with 1N NaOH, and filtered through celite. Extracted into ether (3x50mL), dried over $MgSO_4$, and concd. to afford crude product. The product was purified by silica gel chromatography in a 1:1 hexane:Et_2O eluent system with 0.5% triethylamine (R_f=0.70 in plain Et_2O), then a second column was run in plain DCM to afford pure **20** (42mg, 8% yield).

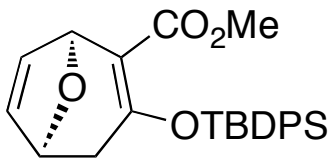
^{1}H NMR (400MHz, $CDCl_3$): 6.56 (dd, 1H, *J*=5.6,1.6), 5.95 (1H, *J*=6, 1.6), 4.94 (dd, 1H, *J*=4.8, 1.2), 4.90 (s, 1H), 4.29 (dd, 1H, *J*=12.0, 3.2), 4.17 (dd, 1H, *J*=12.0, 4.8), 2.65 (dd, 1H, *J*=16.4, 6), 1.70 (d, 1H, *J*=17.2), 1.37 (br. s, 1H), 0.90 (s, 9H), 0.12 (s, 6H). ^{1}H NMR closely matched literature values. $[\alpha]^{25}_D$ =-17.6 (*c*=1.03, $CHCl_3$). Reported [a]=-32.06 (*c*=1.16, $CHCl_3$).



5-isopropyl-1-methyl-2-methylene-8-oxabicyclo[3.2.1]oct-6-en-3-one (21)

Synthesized from **16** according to literature[21] (51% yield).

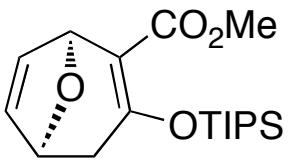
^{1}H NMR (400MHz, $CDCl_3$): 6.05 (d, 1H, *J*=5.2), 5.94 (s, 1H), 5.91 (d, 1H, *J*=5.6), 5.23 (s, 3H), 2.57 (d, 1H, *J*=17.6), 2.46 (d, 1H, *J*=17.6), 1.98-1.88 (m, 1H), 1.60 (s, 3H), 0.98 (d, 1H, *J*=4.0), 0.96 (s, 1H, *J*=3.8). ^{1}H NMR closely matched literature values. $[\alpha]^{25}_D$ =-67.5 (*c*=1.09, $CHCl_3$). Reported $[\alpha]^{25}_D$ =+103.01 (*c*=1.0, $CHCl_3$) for opposite enantiomer.



methyl 3-((*tert*-butyldiphenylsilyl)oxy)-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate

To a 50ml round bottom flask was charged 1mol% Rh_2(*S*-PTAD)$_4$, 6ml anhydrous hexanes and furan (85mg, 1.25mmol, 5equiv.). Reaction stirred at -25^{o}C, and methyl 3-((*tert*-butyldiphenylsilyl)oxy)-2-diazobut-3-enoate (95mg, 0.25mmol, 1 equiv.) dissolved in 6mL hexanes was charged to reaction mixture via syringe pump over about 1.5hrs. Then mixture stirred overnight at -25^{o}C, and was concentrated to afford crude product. Purified by flash chromatography (5/1 hexane/EtOAc, R_f: 0.20) on silica gel to provide a colorless oil (83 mg, 79% yield).

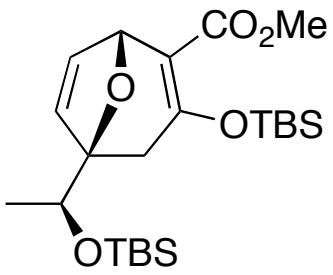
^{1}H NMR (400MHz, $CDCl_3$): 7.75 (dd, 2H, *J*=7.6, 1.6), 7.67 (dd, 2H, *J*=6.8, 1.2). 7.46 (m, 6H), 6.56 (dd, 1H, *J*=5.2, 1.6), 5.75 (dd, 1H, *J*=6.0, 1.6), 3.34 (d, 1H, *J*=1.6), 4.65 (dd, 1H, *J*=6.0, 1.2), 3.70 (s, 3H), 2.39 (dd, 1H, *J*=17.6, 6.0), 1.48 (d, 1H, *J*=18.0), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 157.5, 138.4, 135.4, 133.1, 133.0, 130.4, 128.2, 128.1, 127.0, 113.3, 76.3, 76.1, 51.2, 33.7, 26.4, 19.6. IR (neat):2948, 2858, 1717, 1682, 1610, 1374. HRMS (EI) calc for $C_{25}H_{29}O_4Si_1$ $(M+H)^+$ 421.18296 found 421.18374. HPLC: (ODH, 0.7 % isopropanol in hexane, 1.0 mL/min) retention times of 6.8 (minor) and 7.7 (major), 48% ee. $[\alpha]^{25}_D$ = +1.73 (*c* = 1.19, $CHCl_3$).



methyl 3-((triisopropylsilyl)oxy)-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate

To a 50ml round bottom flask was charged 1mol% Rh_2(*S*-PTAD)$_4$, 6ml anhydrous hexanes and furan (170mg, 2.5mmol, 5equiv.). Reaction stirred at -25^{o}C, and methyl 2-diazo-3-((triisopropylsilyl)oxy)but-3-enoate(95mg, 0.25mmol, 1 equiv.) dissolved in 6mL hexanes was charged to reaction mixture via syringe pump over about 1.5hrs. Then mixture stirred overnight at -25^{o}C, and was concentrated to afford crude product. Purified by flash chromatography (4/1 hexane/EtOAc, R_f: 0.25) on silica gel to provide a colorless oil (163 mg, 96% yield).

^{1}H NMR (400MHz, $CDCl_3$): 6.55 (dd, 1H, *J*=5.6, 2.0), 5.95 (dd, 1H, *J*=6.0, 2.0), 5.34 (br.s, 1H), 4.92 (dd, 1H, *J*=6.4, 1.6), 3.69 (s, 3H), 2.76 (dd, 1H, *J*=17.6, 6.0), 1.83 (d, 1H, *J*=17.6), 1.19 (m, 3H), 1.08 (d, 18H, *J*=4.0). ^{13}C NMR (100 MHz, $CDCl_3$): 165.6, 157.5, 138.3, 127.0, 75.2, 76.0, 51.0, 33.7, 18.0, 13.5. IR (neat): 2945.7, 2866.9, 1719.7, 1682.3, 1610.0, 1463.8, 1436.3, 1375.9, 1200.8. HRMS (EI) calc for $C_{18}H_{31}O_4Si_1$ $(M+H)^+$ 339.19851 found 339.19861. HPLC: (ODH, 0.7 % isopropanol in hexane, 1.0 mL/min) retention times of 5.1 (major) and 6.1 (minor), 83% ee. $[\alpha]^{25}_D$ = -15.88 (*c* = 1.17, $CHCl_3$).



(1*R*,5*R*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)-5-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-8-oxabicyclo[3.2.1]octa-2,6-diene-2-carboxylate (23)

To a 50ml round bottom flask was charged 1mol% Rh_2(*R*-PTAD)$_4$, 6ml anhydrous hexanes and (*S*)-2furanylethanol (68mg, 0.3 mmol, 1equiv.). Reaction stirred at -25^{o}C, and **2** (204 mg, 0.8mmol, 2.6 equiv.) dissolved in 6mL hexanes was charged to reaction mixture via syringe pump over about 1.5hrs. Then mixture stirred overnight at -25^{o}C, and was concentrated to afford crude product. Purified by flash chromatography (9/1 hexane/EtOAc, R_f: 0.25) on silica gel to provide **23** as a colorless oil (107 mg, 78% yield).

^{1}H NMR (400MHz, $CDCl_3$): 6.47 (dd, 1H, *J*=5.6, 1.6), 5.85 (d, 1H, *J*=6), 5.36 (d, 1H, *J*=1.2), 3.98 (q, 1H, *J*=6.4), 3.69 (s, 3H), 2.67 (d, 1H, *J*=17.6), 1.78 (d, 1H, *J*=17.6), 1.20 (d, 3H, *J*=6.0), 0.94 (s, 9H), 0.89 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.5, 159.7, 137.7, 129.1, 113.7, 88.2, 70.47, 51.0, 33.6, 26.0, 25.8, 18.5, 18.2, 17.9, -3.4, -3.5, -3.0, -4.6. IR (neat): 2952, 2930, 2886, 2857, 1721, 1687, 1615, 1472. HRMS (EI) calc for $C_{13}H_{43}O_3Si_2$ $(M+H)^+$ 455.26436, found 455.26420. $[\alpha]^{25}_D$ = +30.69 (*c* = 1.18, $CHCl_3$).