

REACCIÓN DE DIELS-ALDER





Otto Paul Hermann Diels
Tutor de Kurt Alder

1876-1954

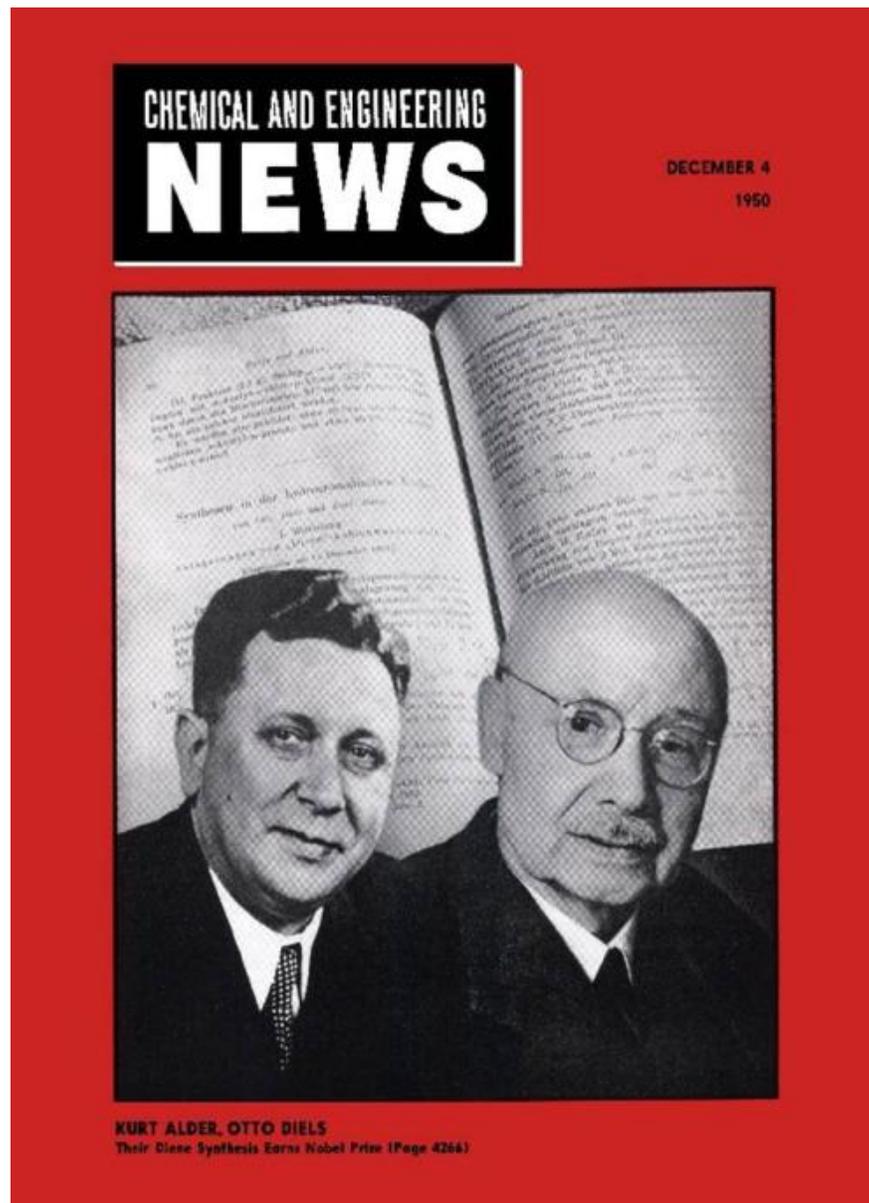


Kurt Alder
Estudiante de doctorado

1902-1958

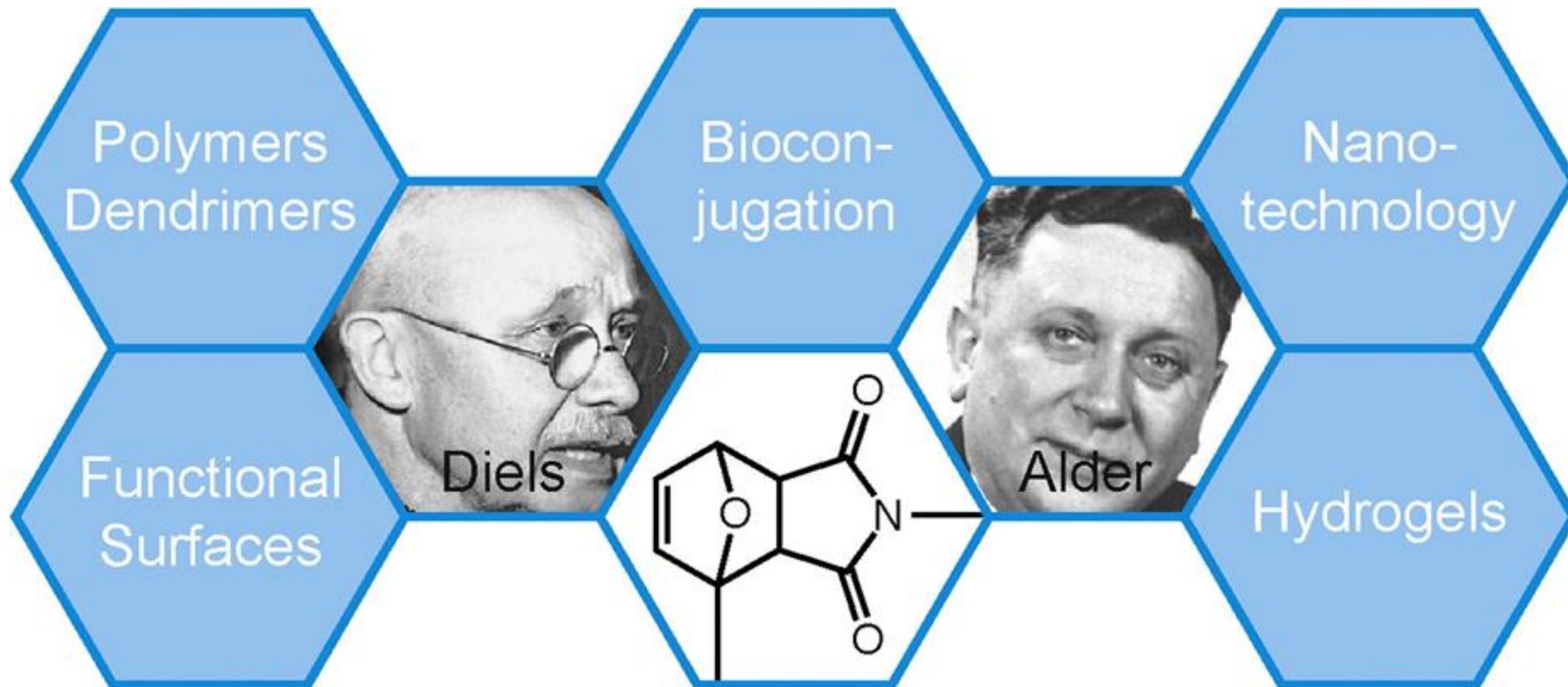


Chemical & Engineering News, December 4, 1950



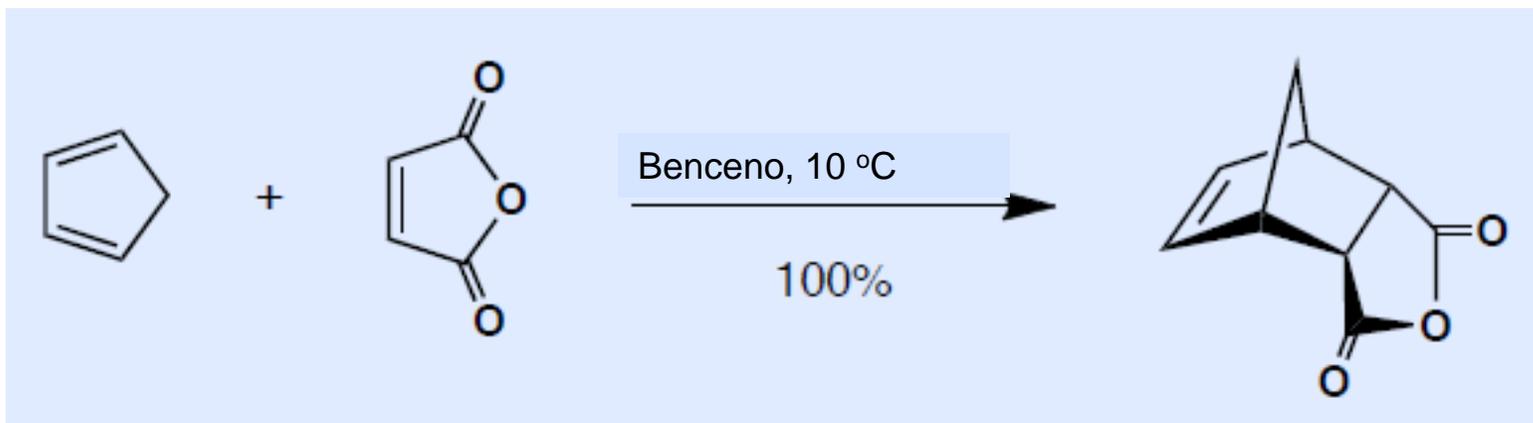
Universidad Nacional Autónoma de México
Facultad de Química
Dr. Fernando León Cedeño





EL DESCUBRIMIENTO DE LA REACCIÓN DE DIELS-ALDER

El trabajo de Diels y Alder se describe en una serie de 28 artículos publicados en *Justus Liebigs Annalen der Chemie* y *Berichte der deutschen chemischen Gesellschaft* de 1928 a 1937. Los primeros 19 artículos fueron escritos por Diels y Alder, mientras que los artículos posteriores fueron escritos por Diels y varios colaboradores



Diels, O.; Alder, K. "Synthesen in der hydroaromatischen Reihe, I". Justus Liebigs Annalen der Chemie. 1928, 460: 98–122.



III. Fraktion (2,2 g), Siedep.₁₃ = 160°. Erstarrt beim Impfen mit o-Acetyl-o-chlor-p-kresol (XXIV, S. 76) und kann durch den Mischschmelzp. 91° mit dem reinen Produkt (S. 84) als solches identifiziert werden.

Es wurden also gebildet: etwa 40 Proc. des theoretisch möglichen o-Acetyl-m-kresols und etwa 60 Proc. o-Acetyl-o-chlor-p-kresol.

Synthesen in der hydroaromatischen Reihe;

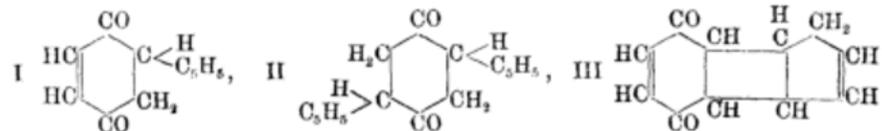
von Otto Diels und Kurt Alder.

I. Mitteilung:

Anlagerungen von „Di-en“-kohlenwasserstoffen.

(Eingelaufen am 13. Dezember 1927.)

In einer Untersuchung über Cyclopentadienchinon berichtet W. Albrecht¹⁾ über die Anlagerung von Cyclopentadien an p-Chinon. Den dabei entstehenden, von ihm als „Cyclopentadienchinon“ und „Di-cyclopentadienchinon“ bezeichneten Verbindungen legt er die Formeln I und II bei:



Er nimmt also an, daß sich Cyclopentadien mit der *Methylengruppe* an die Doppelbindungen des Chinons anlagert und daß die Reaktionsprodukte *noch beide Doppelbindungen des Cyclopentadiens* enthalten.

H. Staudinger²⁾ neigt dagegen der Ansicht zu, daß sich Chinon und Cyclopentadien zu einem *Cyclo-butan-deri-*

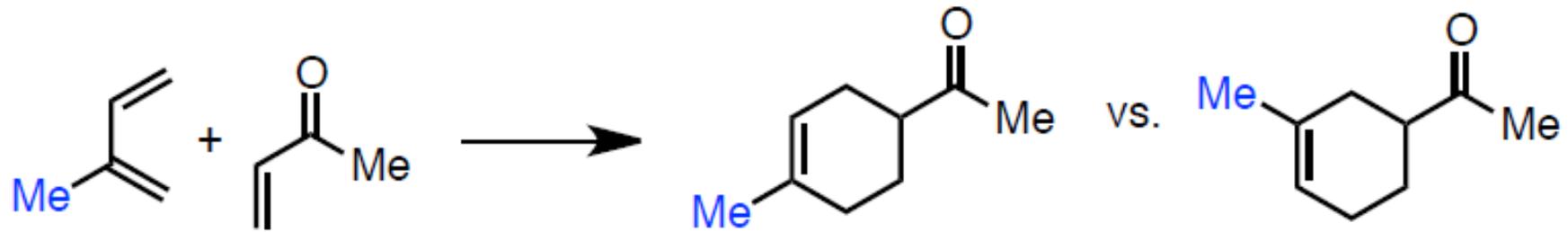
¹⁾ A. 348, 31 (1906). — Walter Albrecht, Über Cyclopentadienchinone. Inauguraldissertation, München 1902.

²⁾ Die Ketene. Stuttgart 1912, S. 59, Anm. 2.



SELECTIVIDAD

Regioselectividad (en cual sitio de la molécula)



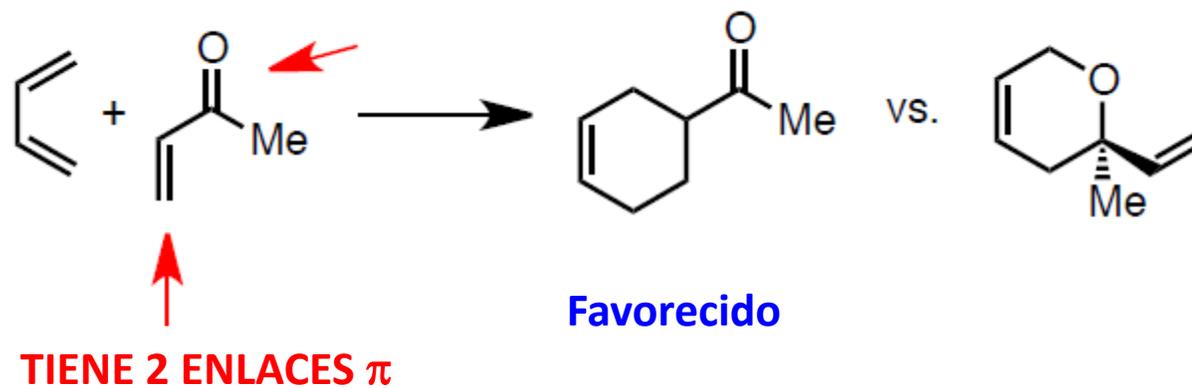
Favorecido

Regioisómeros



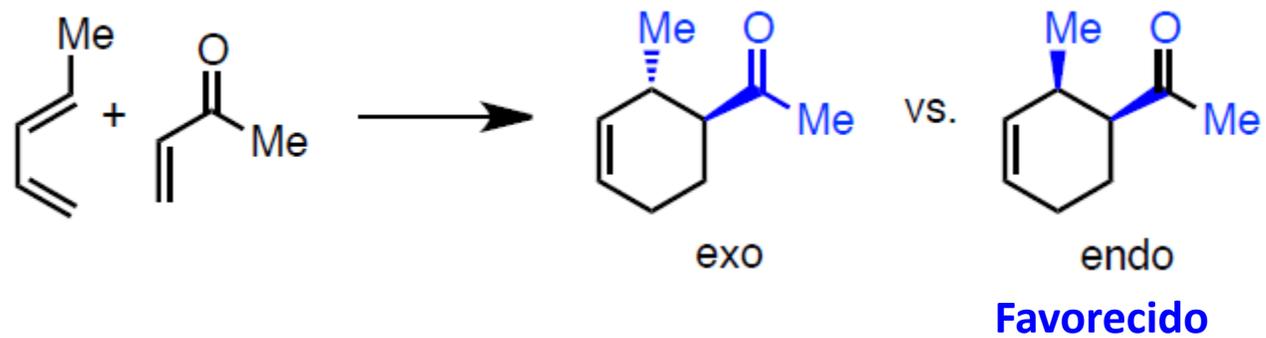
SELECTIVIDAD

Quimioselectividad (en cual grupo de la molécula)



SELECTIVIDAD

Diastereoselectividad (cual diastereoisómero)

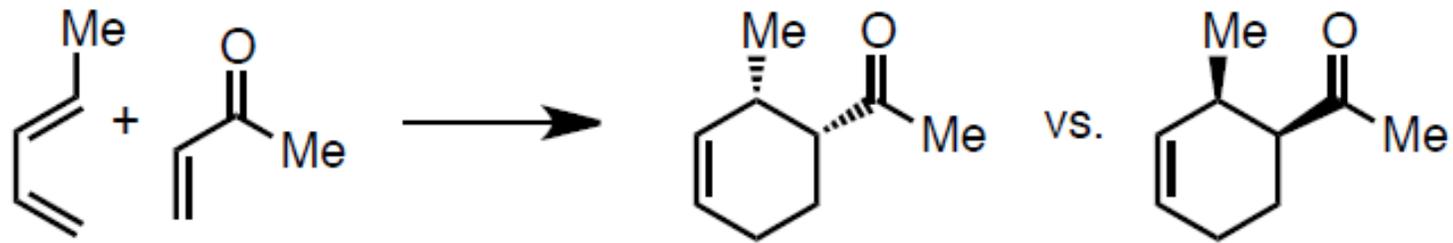


Diastereómeros



SELECTIVIDAD

Enantioselectividad (cual enantiómero)



Enantiómeros



¿Qué está descrito en la literatura?
¿Qué tan cercana es la analogía a la reacción que se quiere hacer?

1 hora en la biblioteca = 1 mes en el laboratorio

Exacto vs. Cercano

Si se acerca, considere:

- FG
- tamaño del anillo
- Sustituyentes
- estereoquímica

Todo puede afectar el resultado

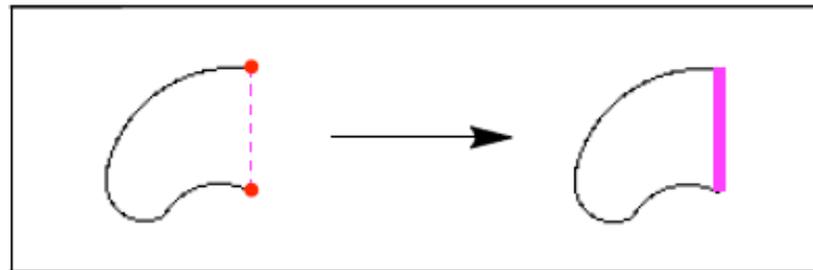


- Residuo generados
- Costo
- Toxicidad
- Contaminantes
- Seguridad
- Escala
- Materiales de partida disponibles
- Cuestiones de propiedad intelectual

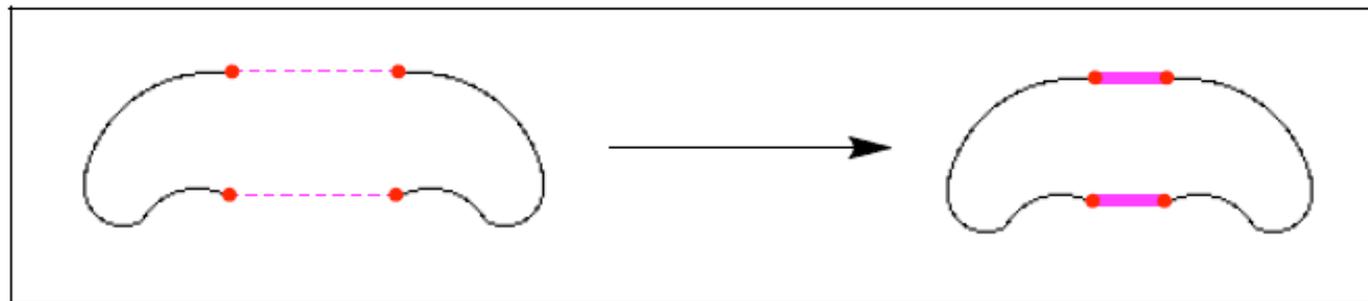


Estrategia para el ensamblaje de compuestos cíclicos

Ciclización



Anillación



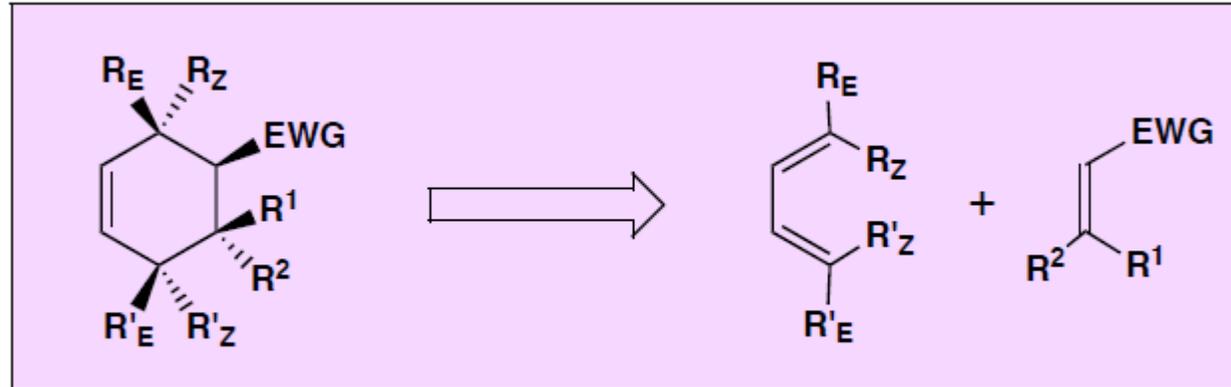
Cicloadiciones concertadas

Anillación no concertada «un sola operación»

Estrategias de anillación en varios pasos



LA REACCIÓN DE DIELS-ALDER



Otto Diels



Kurt Alder



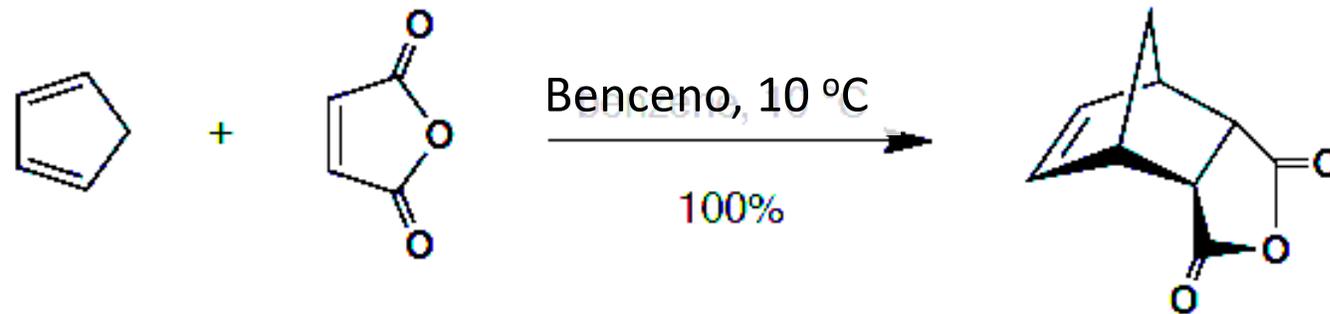
Our results will play a role not only in the discussion of theoretically interesting questions but probably also will yield greater significance in a practical sense. Thus it appears to us that the possibility of synthesis of complex compounds related to or identical with natural products such as terpenes, sesquiterpenes, perhaps also alkaloids, has been moved to the near prospect. We explicitly reserve for ourselves the application of the reaction discovered by us to the solution of such problems.

Otto Diels and Kurt Alder *Justus Liebigs Annalen der Chemie*, **1928**, 460, 98

Nuestros resultados tendrán un papel no sólo en la discusión de cuestiones teóricamente interesantes, pero probablemente también tendrá una mayor importancia en el sentido práctico. Así nos parece que la posibilidad de una síntesis de compuestos complejos relacionados con o bien idénticos a productos naturales tales como terpenos, sesquiterpenos, quizás también alcaloides , se ha movido hacia esta perspectiva. Nos reservamos explícitamente la aplicación de la reacción descubierta por nosotros para la solución de tales problemas .

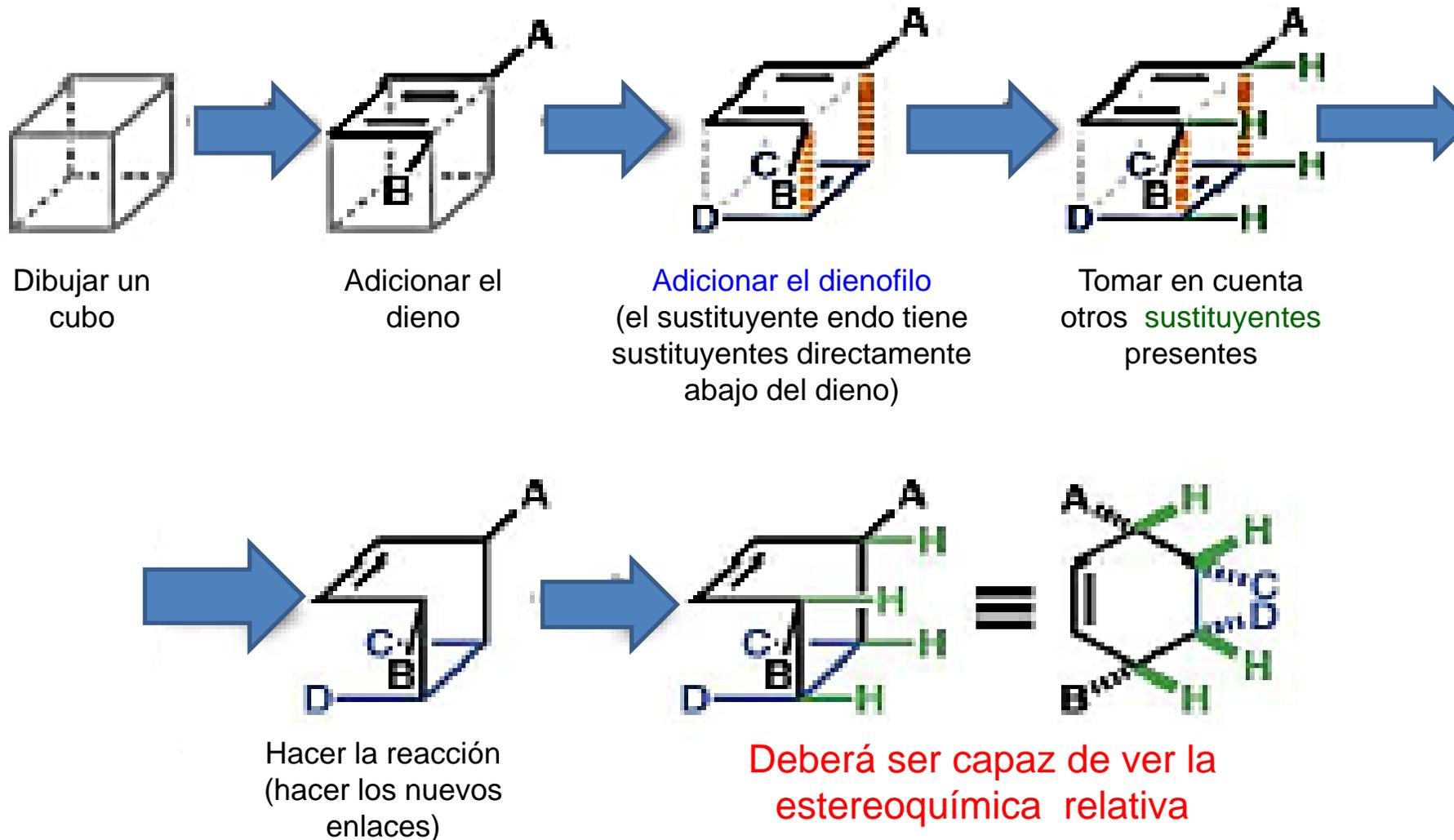


EL DESCUBRIMIENTO DE LA REACCIÓN DE DIELS-ALDER

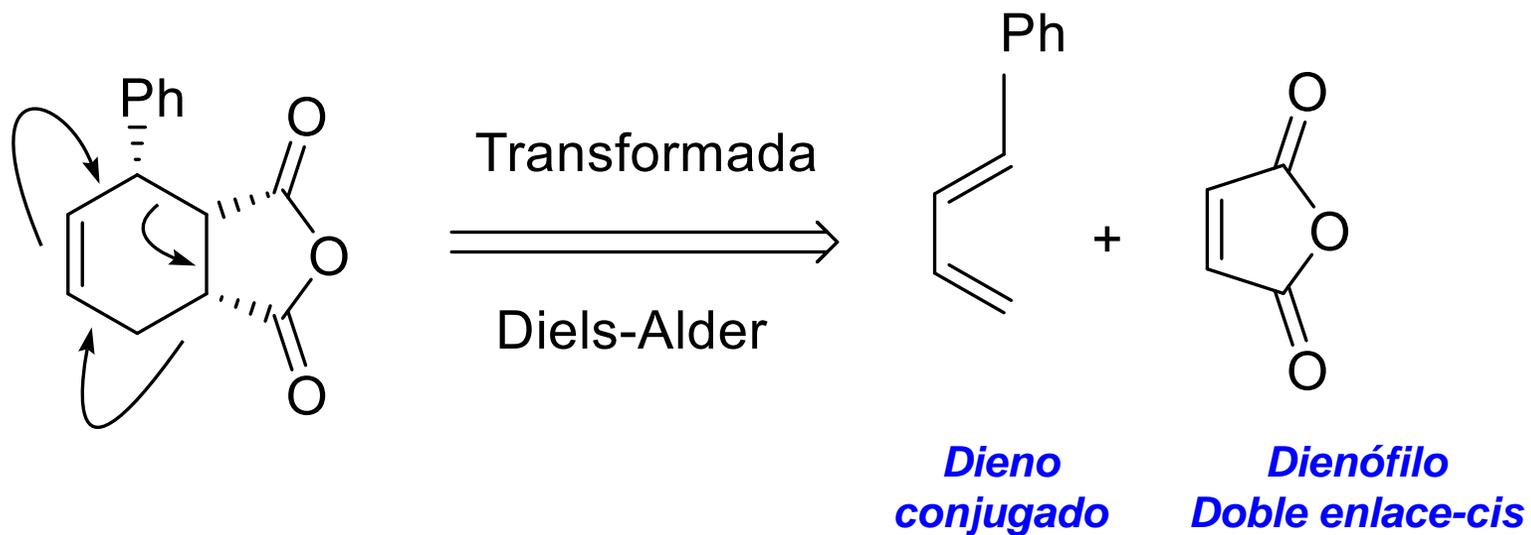


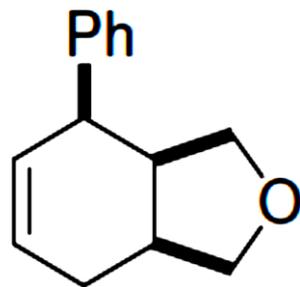
MÉTODO CUBO

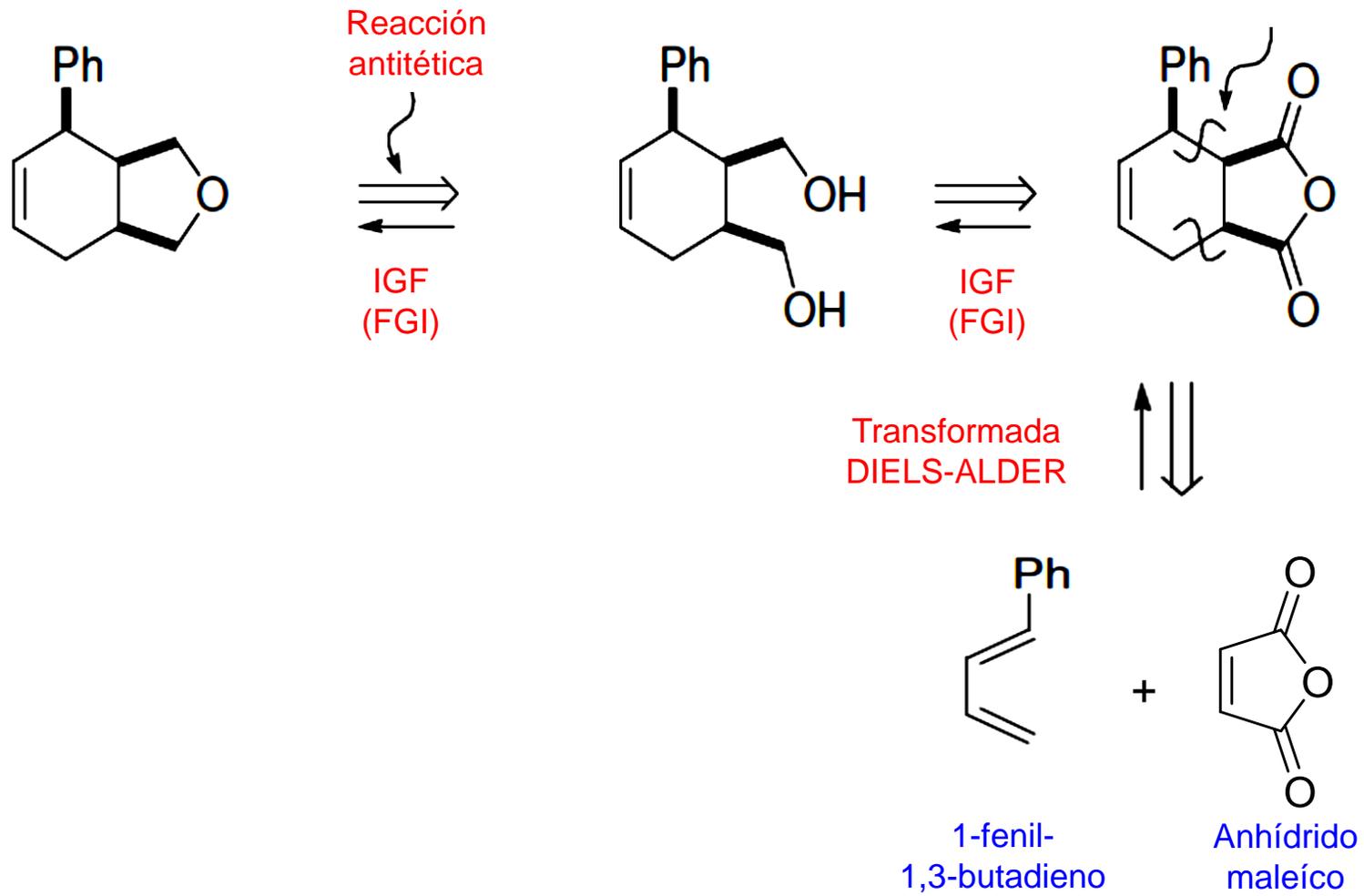
Es una buena manera de visualizar la estereoquímica relativa

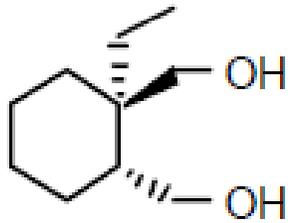


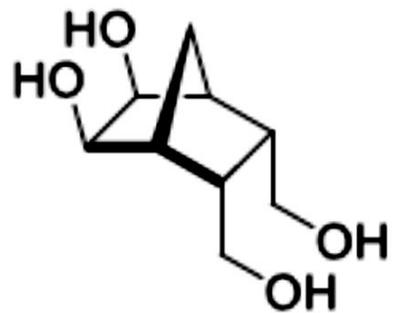
Aquí la reacción de Diels-Alder es apropiada debido a que es una reacción estereoespecífica





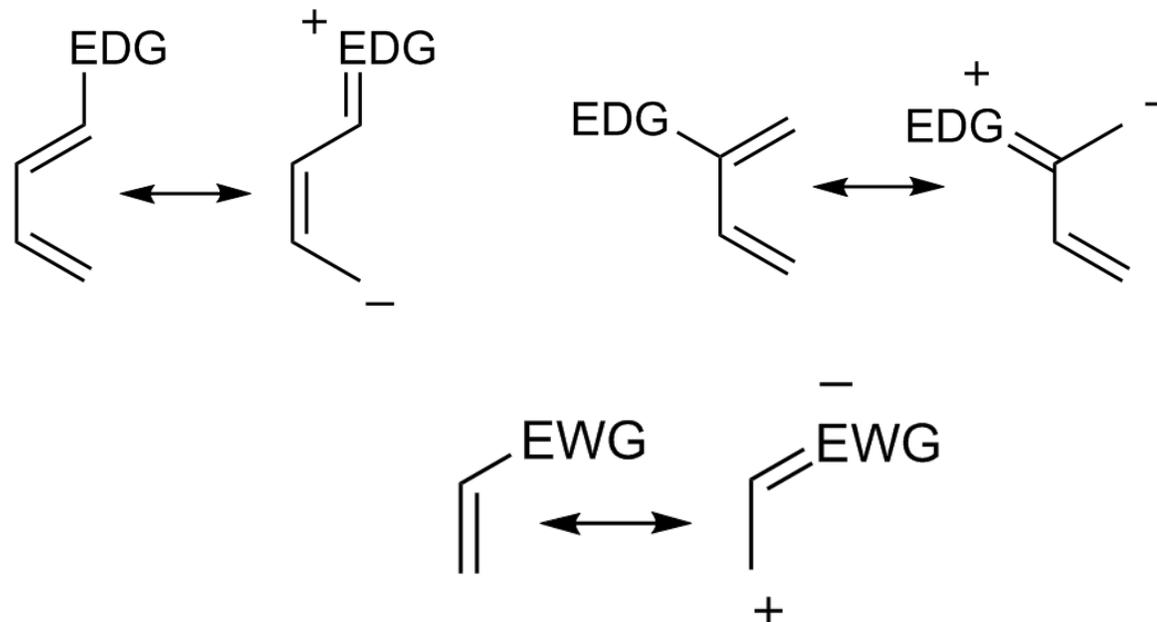






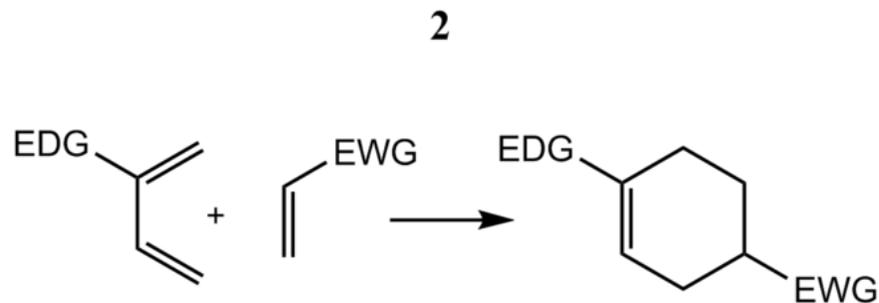
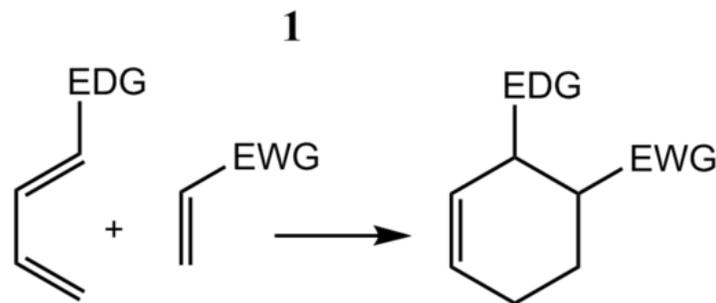
Regioselectividad

La teoría orbital molecular de frontera también se ha utilizado para explicar los patrones de regioselectividad observados en las reacciones de Diels-Alder de sistemas sustituidos. El cálculo de la energía y los coeficientes orbitales de los orbitales frontera de los componentes proporciona una imagen que está de acuerdo con el análisis más directo de los efectos de resonancia de los sustituyentes, como se ilustra a continuación.



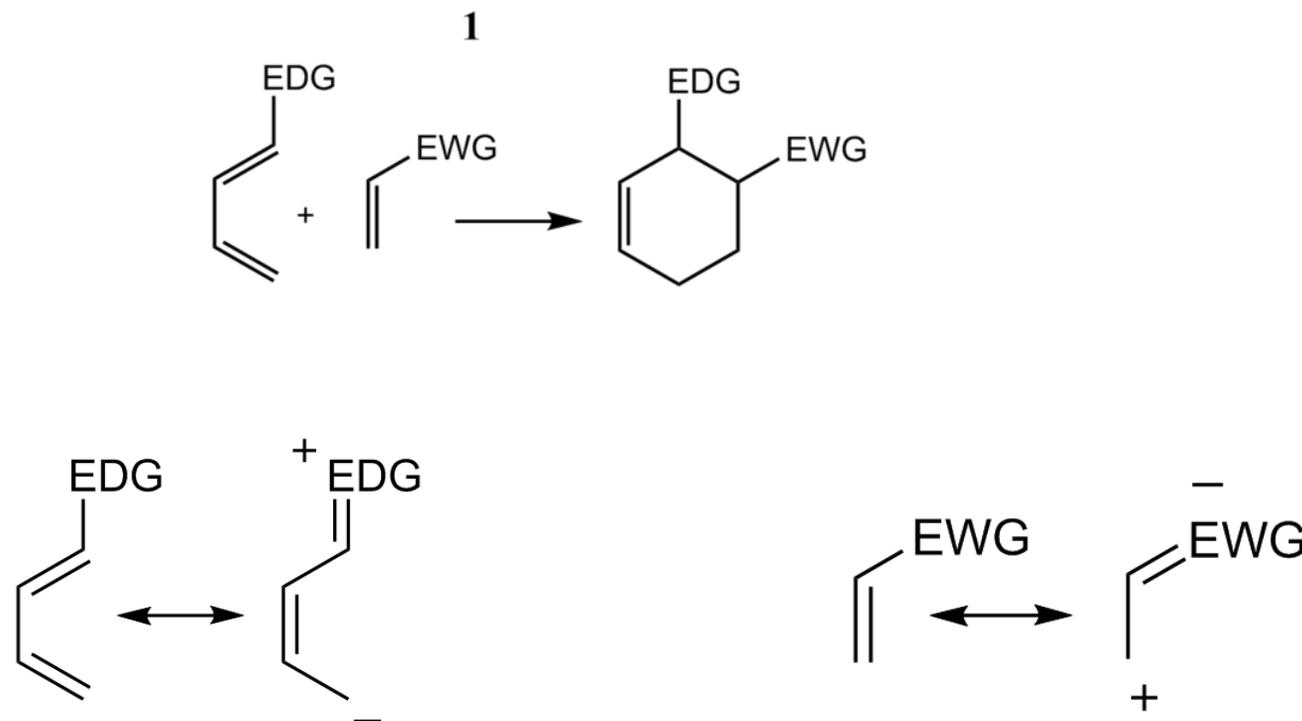
Regioselectividad

En general, la regioselectividad encontrada tanto para la reacción de Diels-Alder normal como para la **demanda inversa** de electrones sigue la regla **orto-para**, llamada así, porque el producto ciclohexeno tiene sustituyentes en posiciones análogas a las posiciones **orto** y **para** de arenos disustituídos.



Regioselectividad

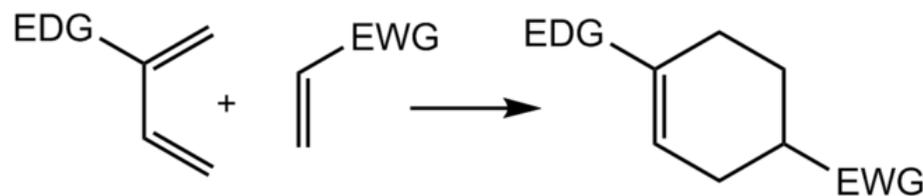
Por ejemplo, en el caso de una demanda normal, un dieno con un grupo donador de electrones (EDG) en C1 tiene su mayor coeficiente HOMO en C4, mientras que el dienófilo con un grupo de extracción de electrones (EWG) en C1 tiene el mayor coeficiente LUMO en C2. El emparejamiento de estos dos coeficientes da el producto "**orto**" como se ve en el caso 1 en la figura siguiente. y polarización.



Regioselectividad

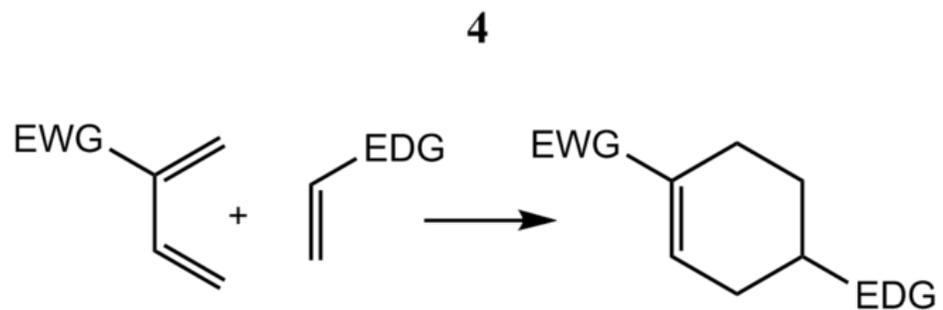
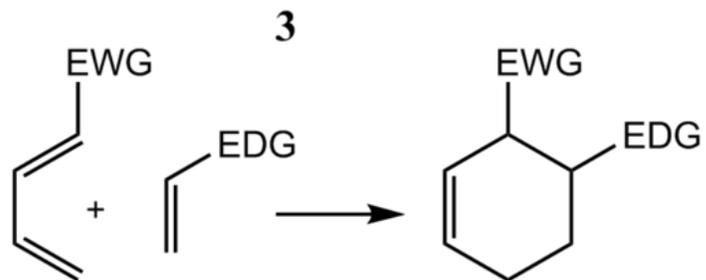
Un dieno sustituido en C2 como en el caso 2 a continuación tiene el mayor coeficiente HOMO en C1, dando lugar al producto "*para*".

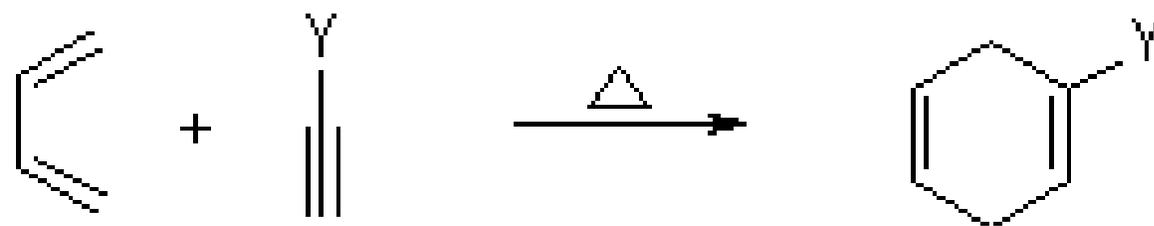
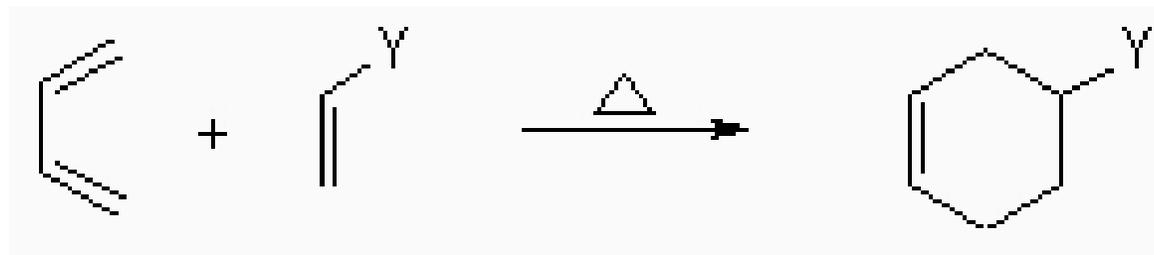
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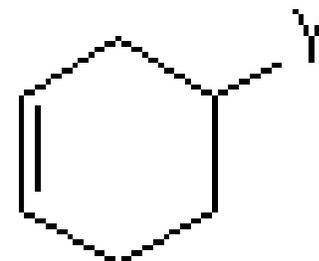
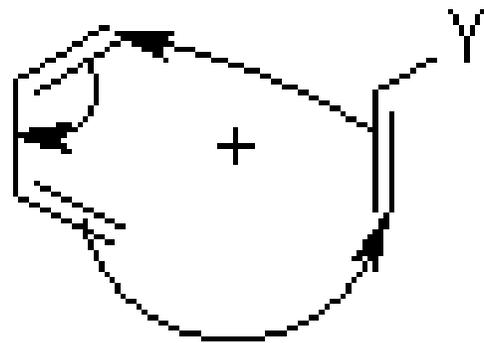


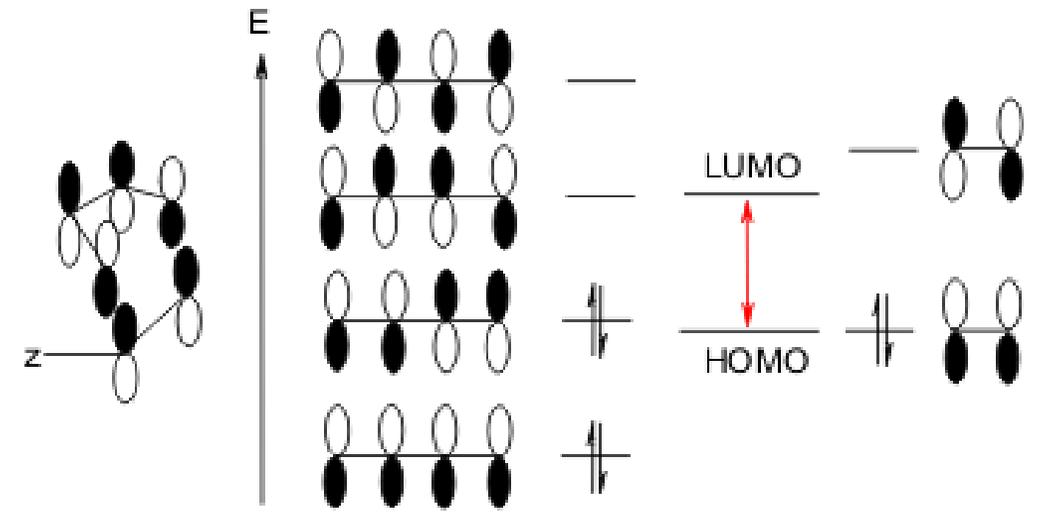
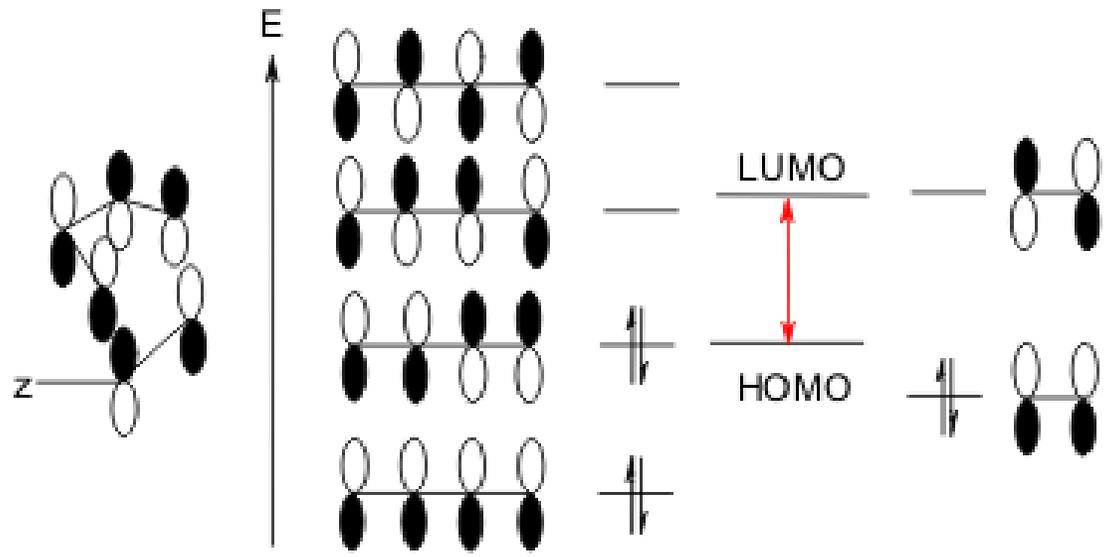
Regioselectividad

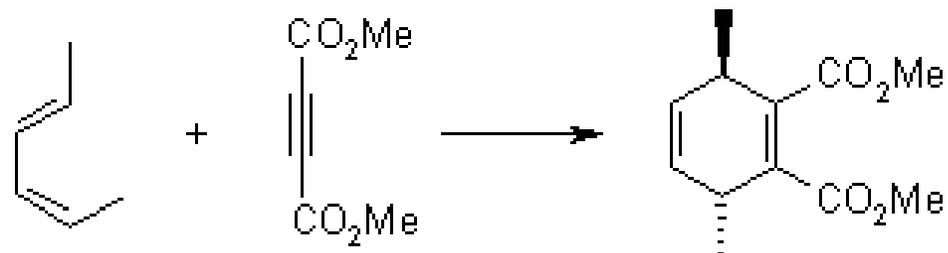
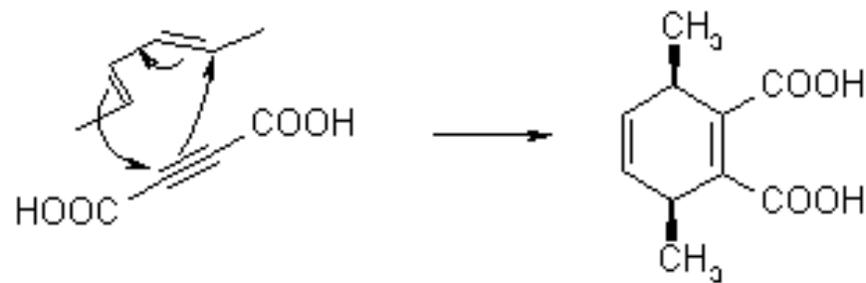
Análisis similares para los escenarios de demanda inversa correspondientes dan lugar a productos análogos, como se ve en los casos 3 y 4. Examinando las formas mesoméricas canónicas anteriores, es fácil verificar que estos resultados están de acuerdo con las expectativas basadas en la consideración de la densidad electrónica y polarización.

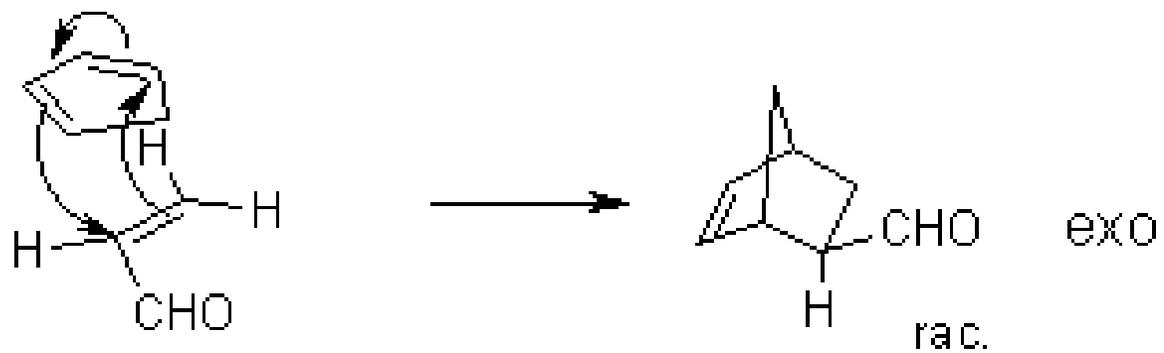
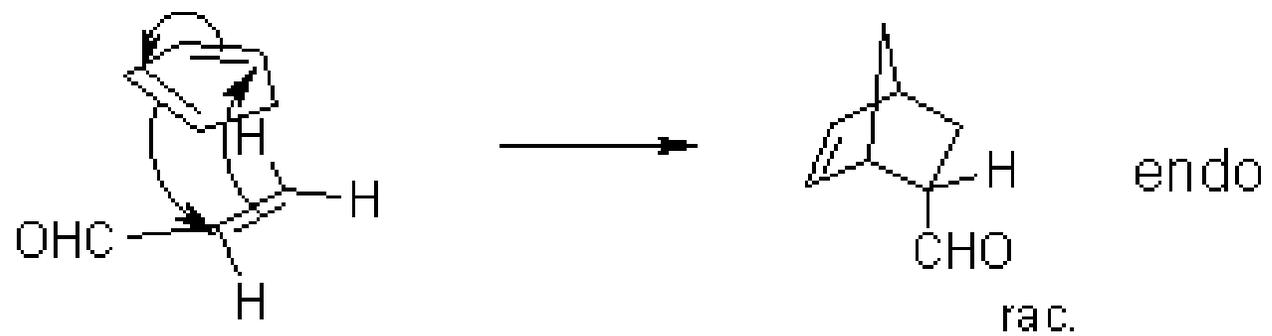


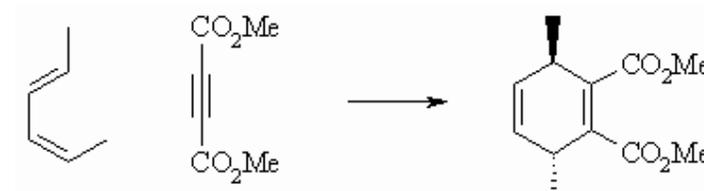
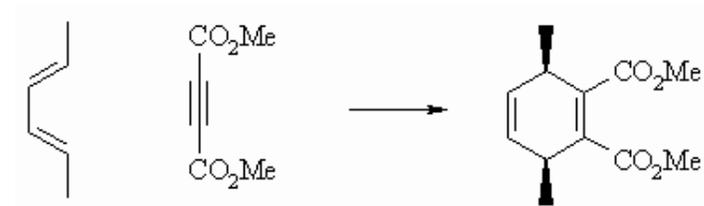
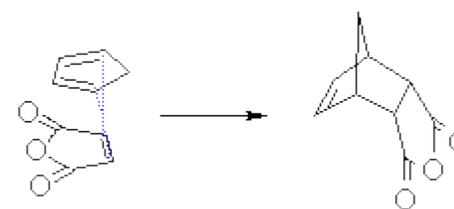
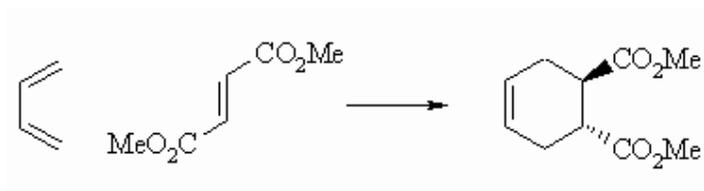
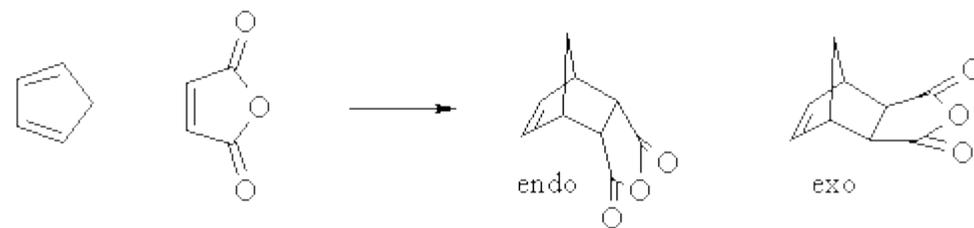
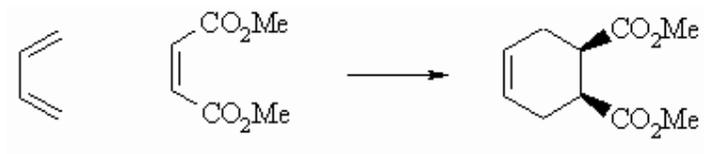


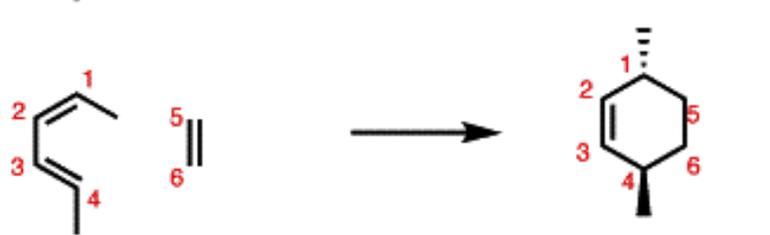
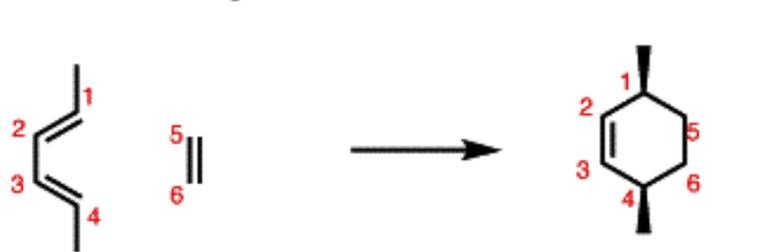
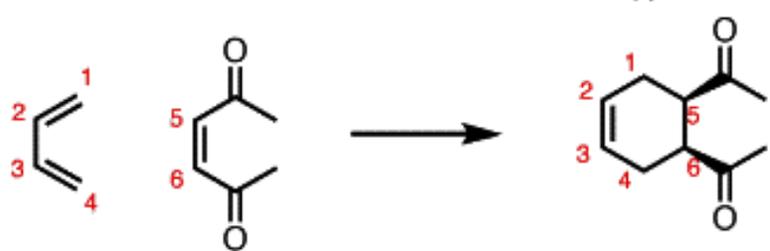
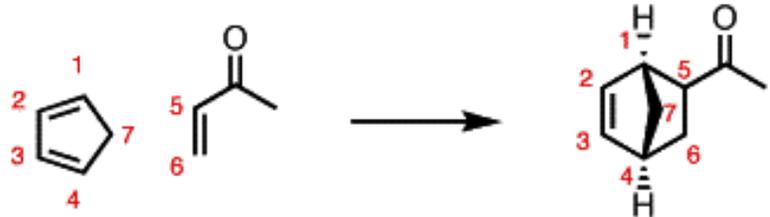
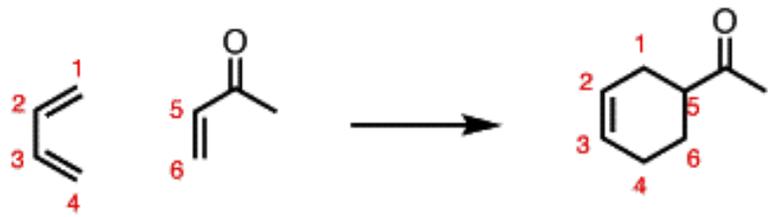






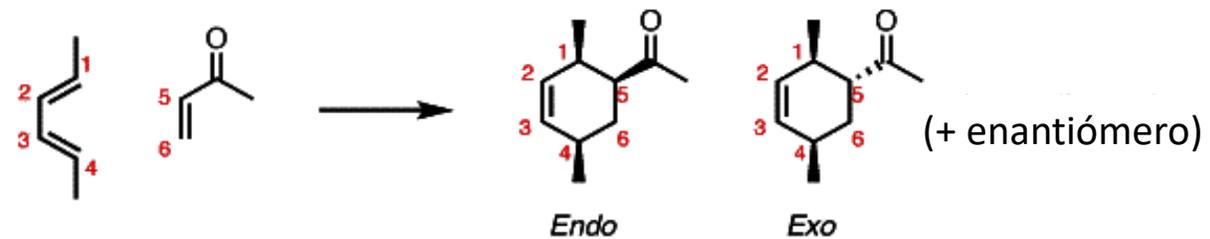






(+ enantiómero)

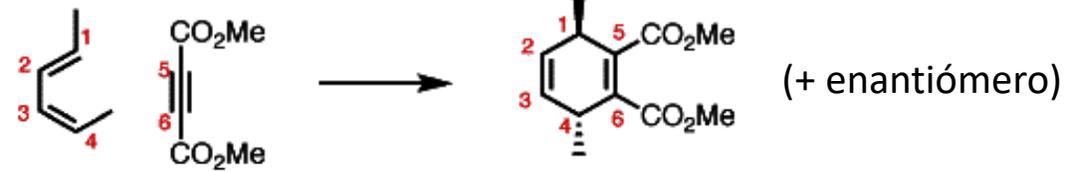
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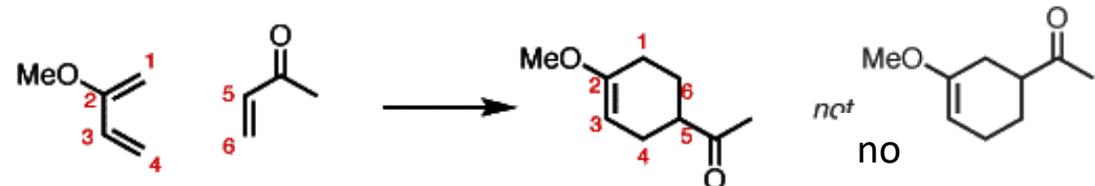
Endo

Exo

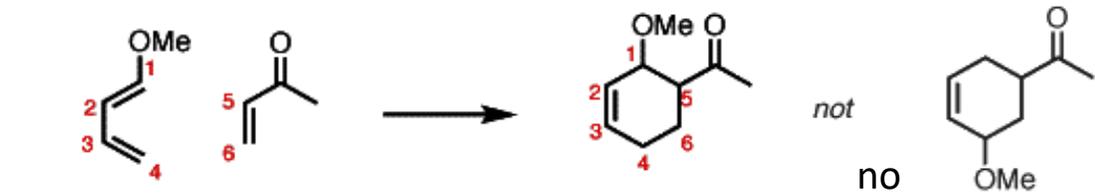
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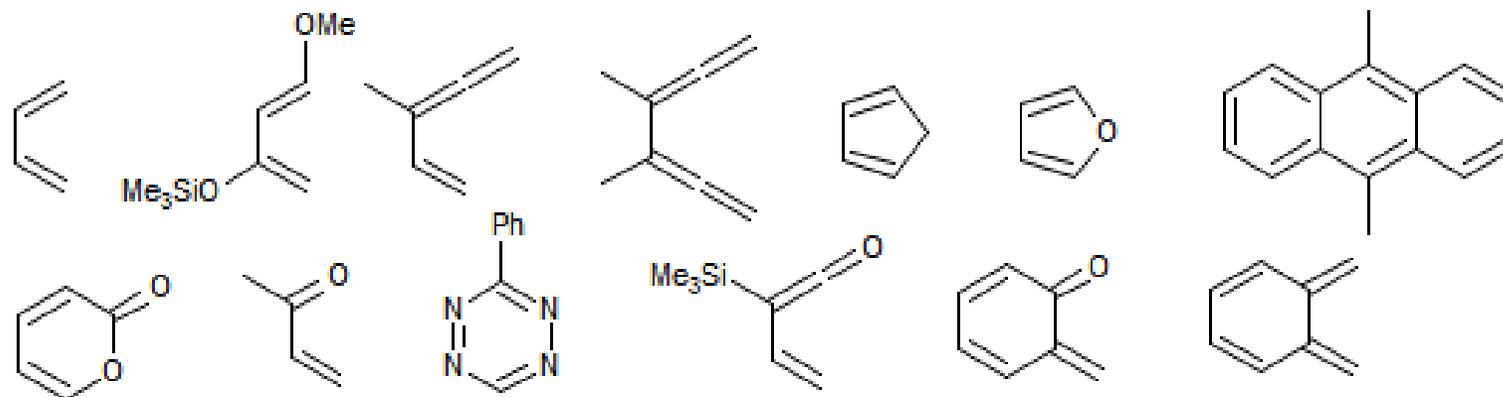
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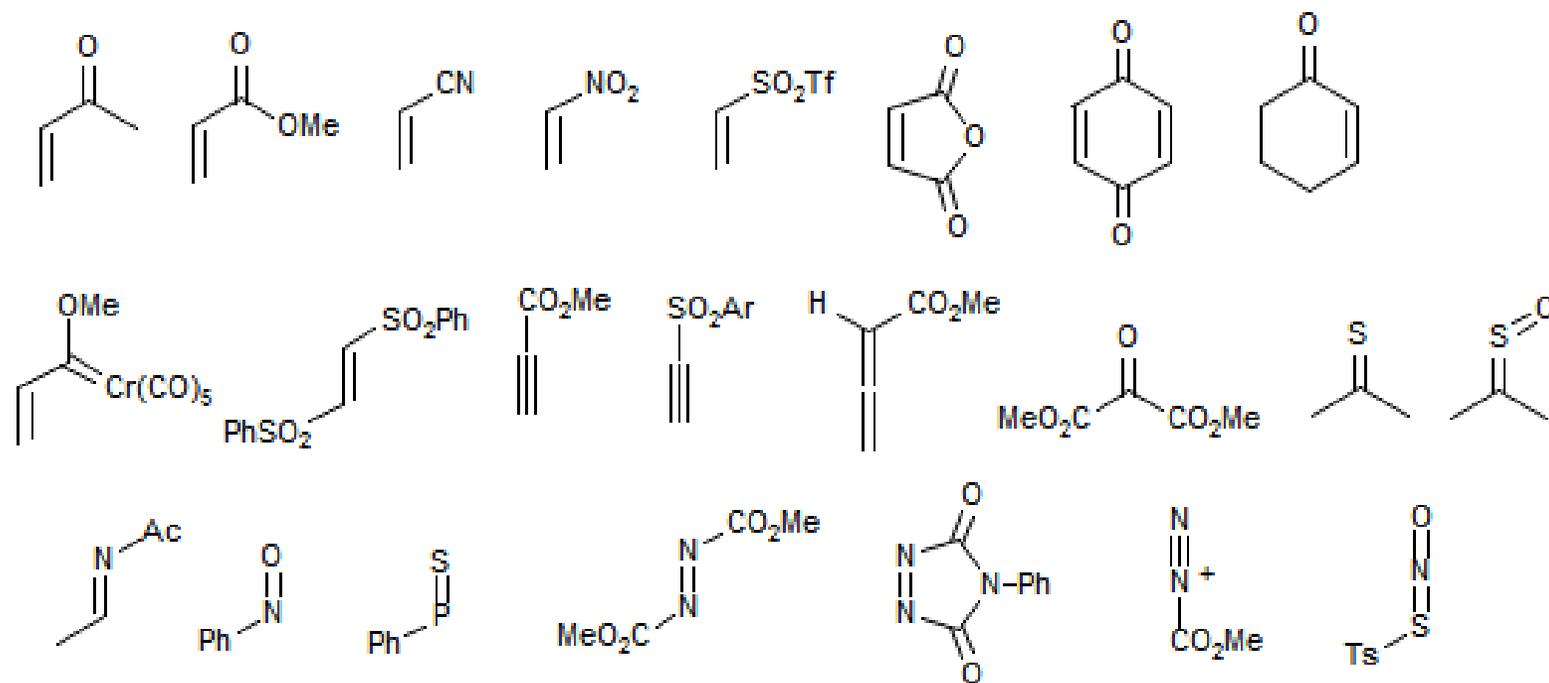
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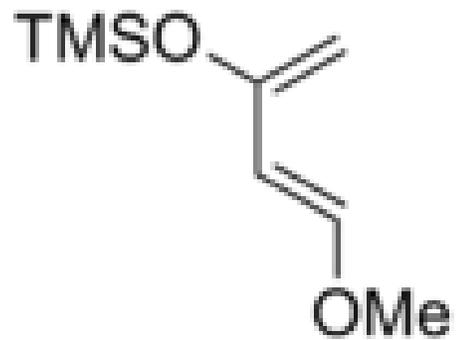


Algunos tipos de dienos que presentan la reacción de Diel-Alder

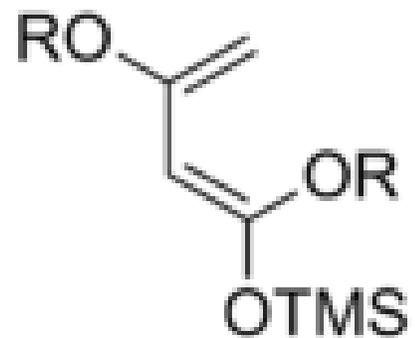


Algunos tipos de dienofilos que presentan la reacción de Diel-Alder

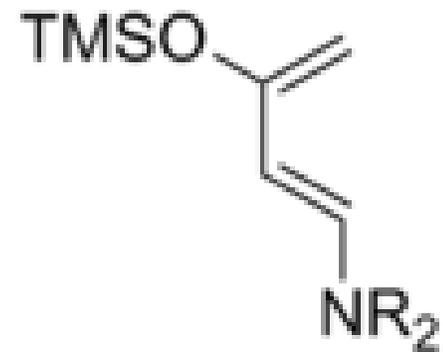




Dieno de Danishefsky

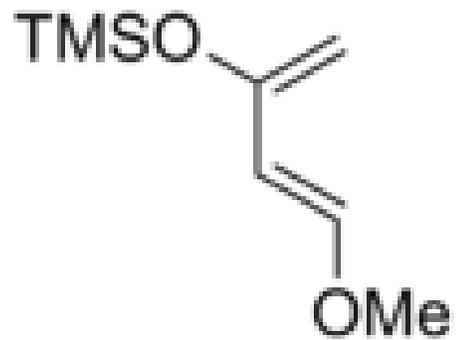


Dieno de Brassard

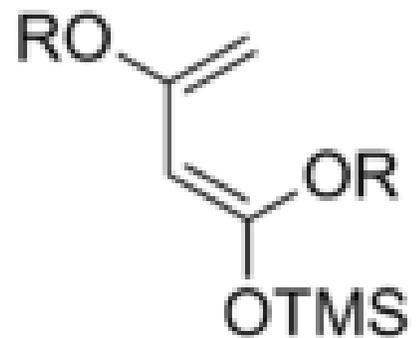


Dieno de Rawal

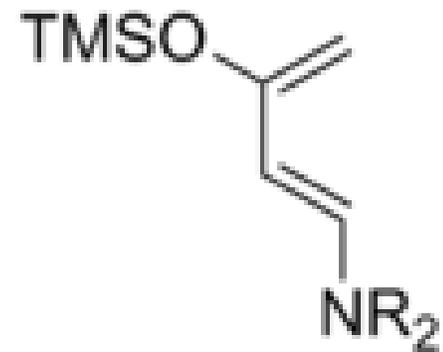




Dieno de Danishefsky



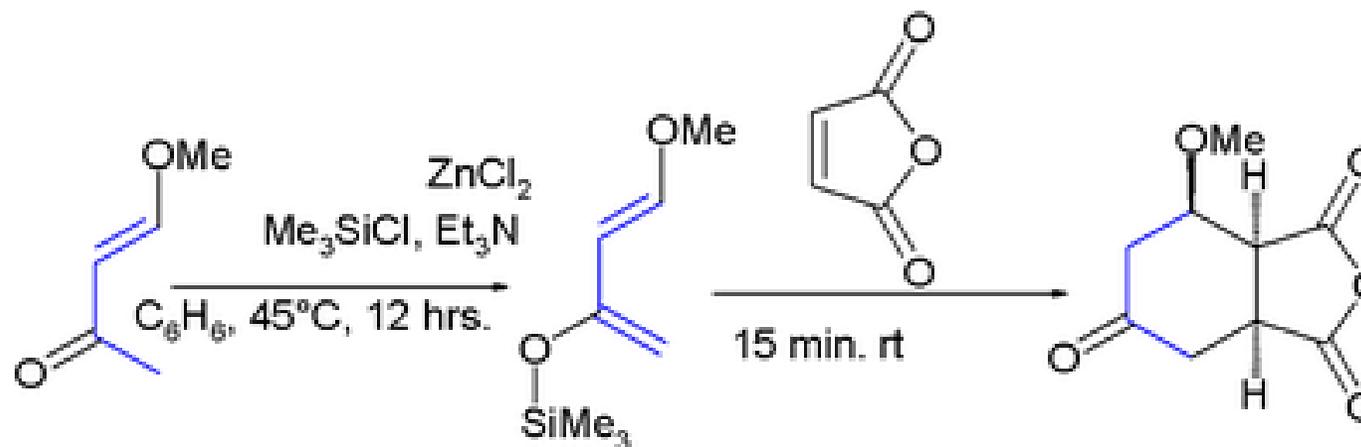
Dieno de Brassard



Dieno de Rawal

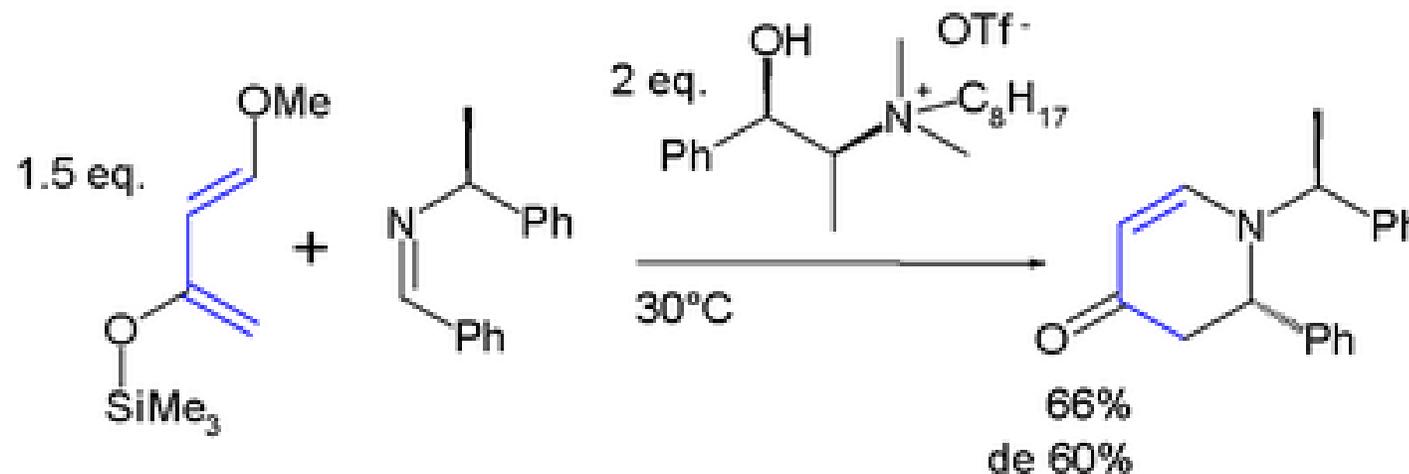


Dieno de Danishefsky



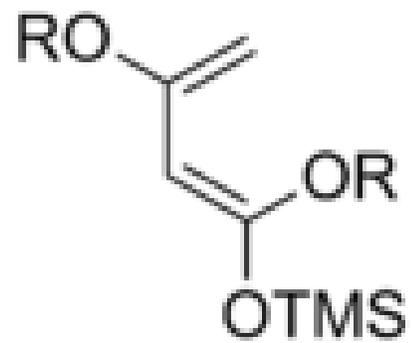
Preparation and Diels-Alder Reaction of a Highly Nucleophilic Diene. *Org. Synth., Coll. Vol. 7*, p.312 (1990); *Vol. 61*, p.147 (1983)

Esta es una reacción asimétrica con un líquido iónico quiral como disolvente quiral. El rendimiento químico informado es del 66% con un exceso de diastereoisómero del 60%.



*Asymmetric aza-Diels-Alder reaction of Danishefsky's diene with imines in a chiral reaction medium Pegot B, Nguyen Van Buu O, Gori D, Vo-Thanh G *Beilstein Journal of Organic Chemistry*, 2006-10-11 at the [Wayback Machine](#)*





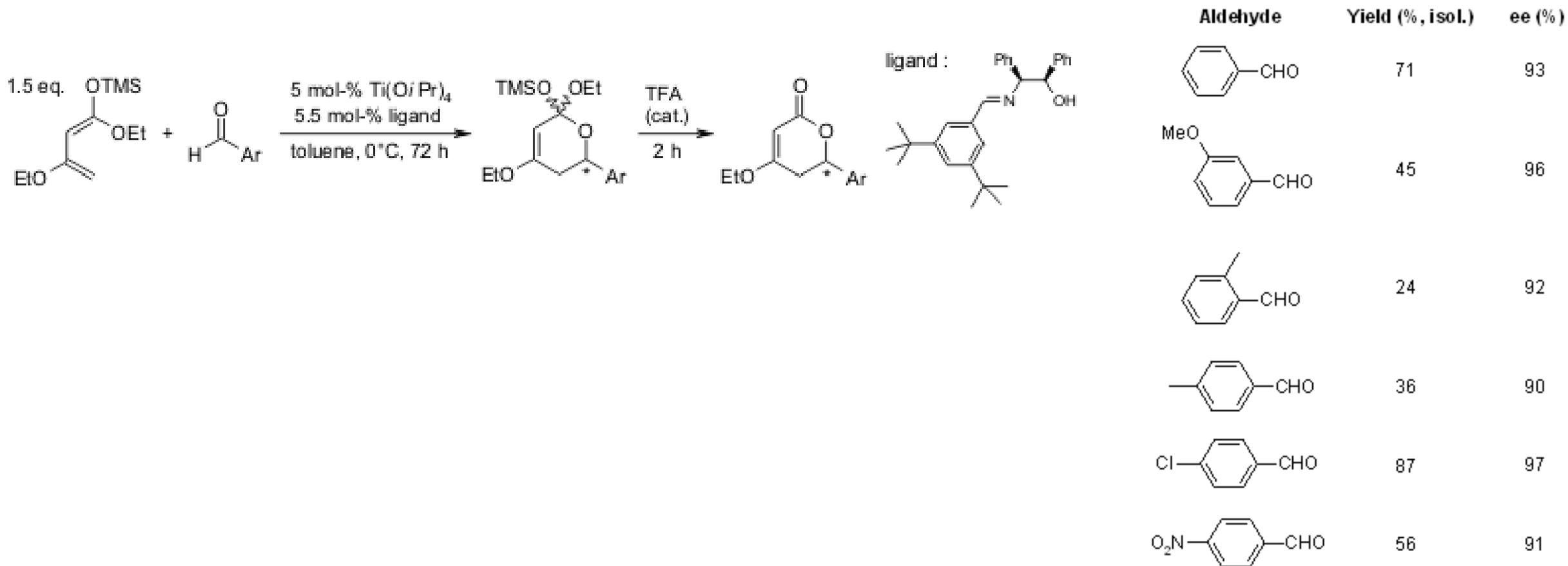
Dieno de Brassard

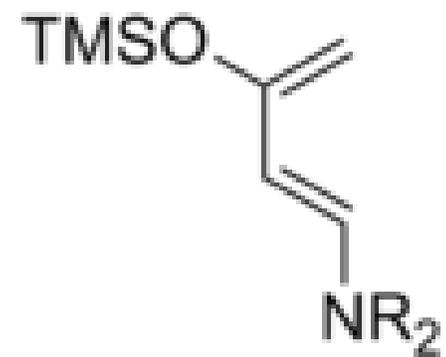


DIENO DE BASSARD

A Mild and Efficient Asymmetric Hetero-Diels-Alder Reaction of the Brassard Diene with Aldehydes

Q. Fan, L. Lin, J. Liu, Y. Huang, X. Feng, *Eur. J. Org. Chem.*, **2005**, 3542-3552.



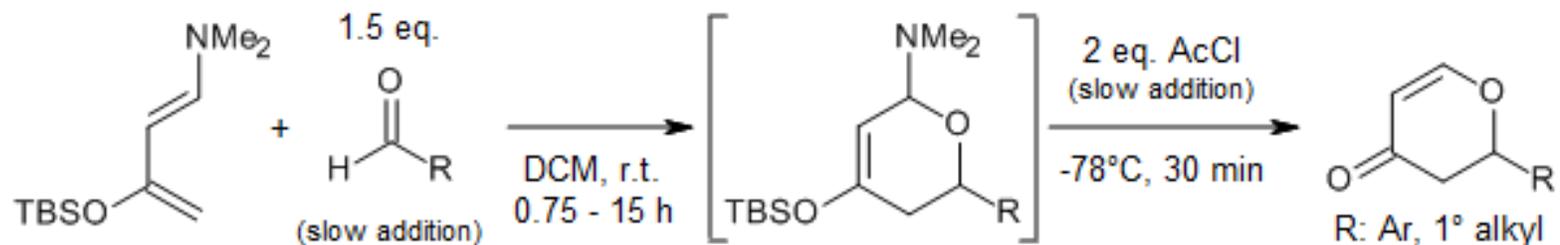


Dieno de Rawal



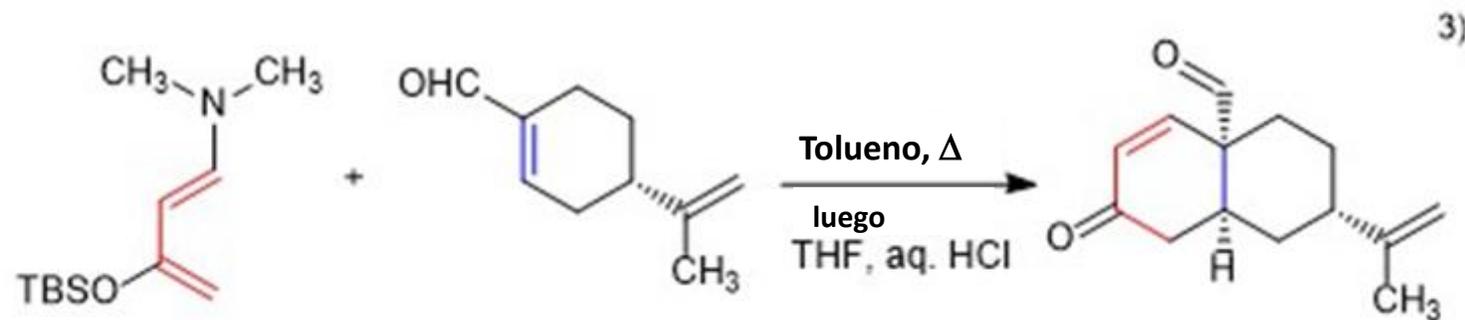
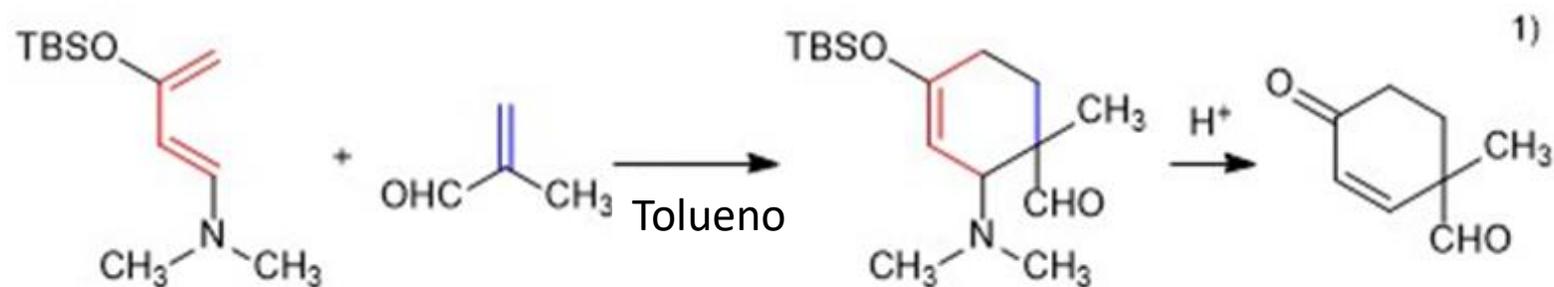
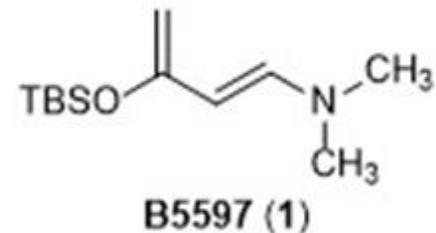
Hetero Diels-Alder Reactions of 1-Amino-3-siloxy-1,3-butadienes under Strictly Thermal Conditions

Y. Huang, V. H. Rawal, *Org. Lett.*, **2000**, 2, 3321-3323.



aldehyde	t (h)	yield (% _o , isol.)
	0.75	81
	15	71
	2	73
	2.5	82





- 1) Preparation and Diels-Alder Reactivity of 1-Amino-3-siloxy-1,3-butadienes
S. A. Kozmin, V. H. Rawal, *J. Org. Chem.* **1997**, *62*, 5252.
- 2) On the Reactivity of 1-Amino-3-siloxy-1,3-dienes: Kinetics Investigation and Theoretical Interpretation
S. A. Kozmin, M. T. Green, V. H. Rawal, *J. Org. Chem.* **1999**, *64*, 8045.
- 3) A Nine-Step Total Synthesis of (-)-Platencin
K. Tiefenbacher, J. Mulzer, *J. Org. Chem.* **2009**, *74*, 2937





Dieno de Danishefsky

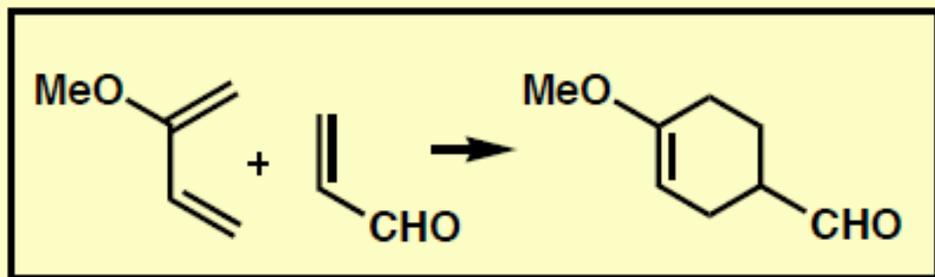
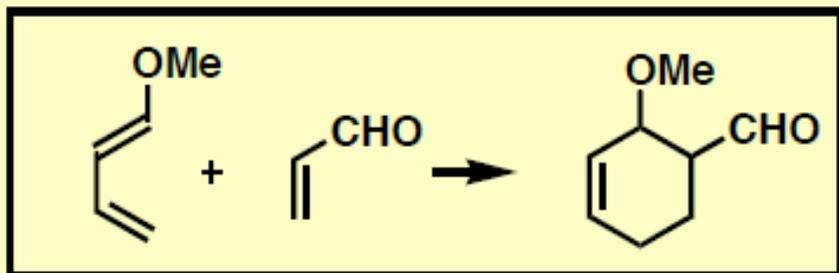
Dieno de Rawal

Ventajas del grupo amino

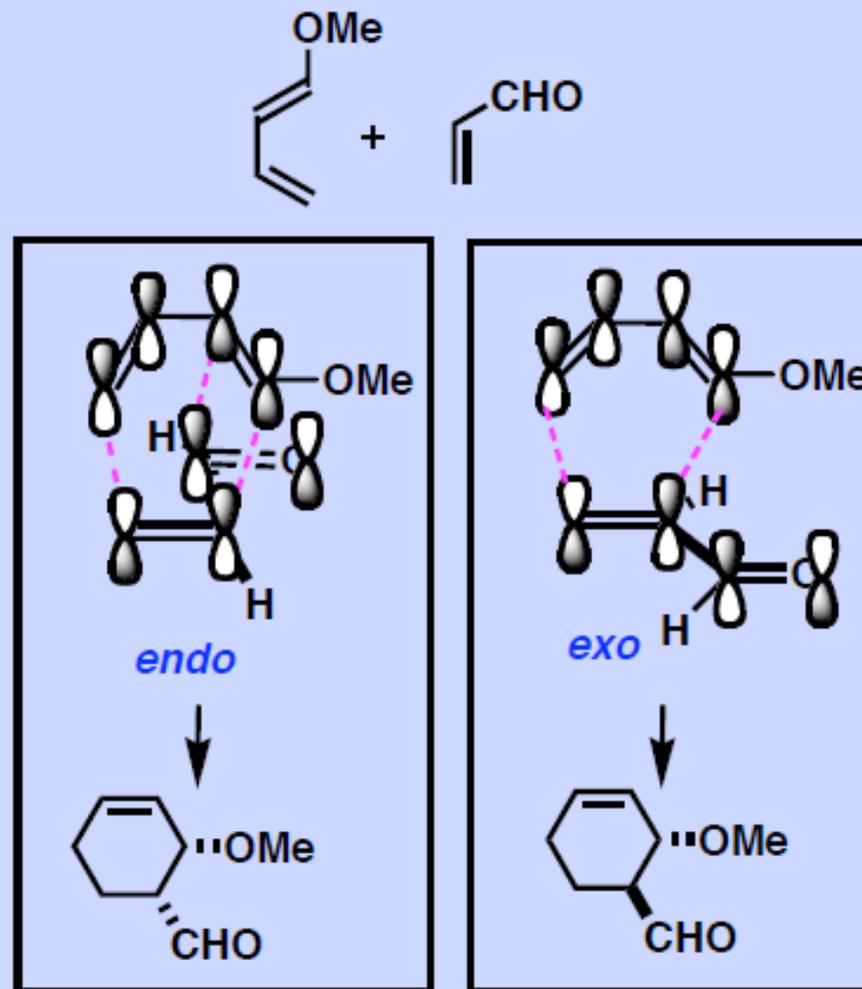
1. La cicloadición proporcionará acceso a la síntesis de alcaloides que contienen N
2. Mayor nucleofilia = mayor reactividad que el dieno Danishefsky
3. Brinda la oportunidad para la introducción de quiralidad



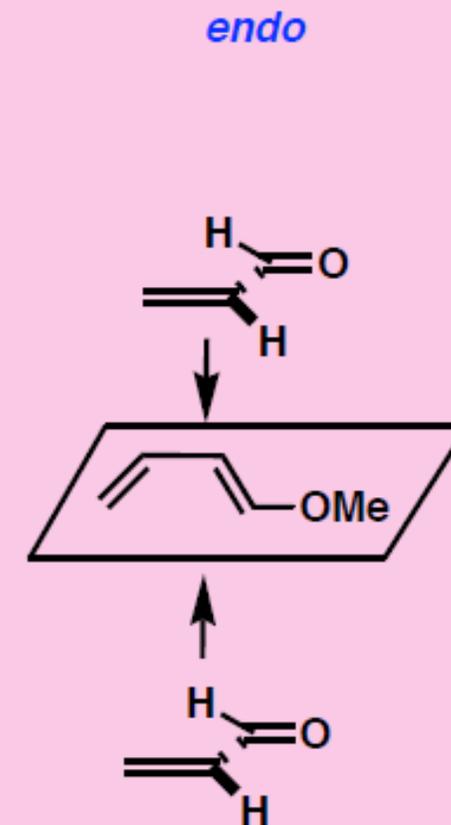
a) Regioquímica

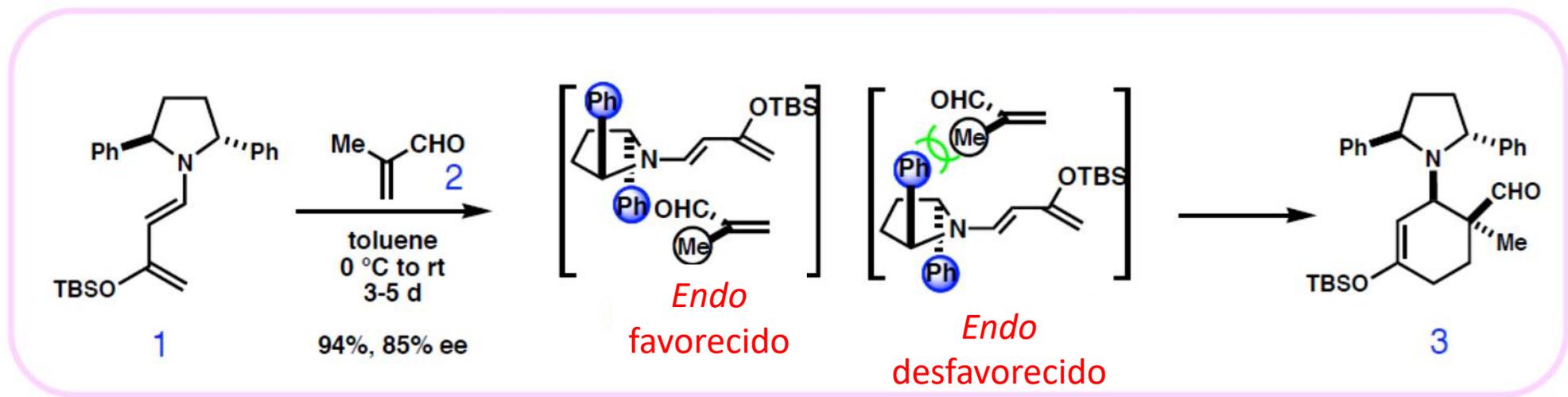


b) Regia *Endo*



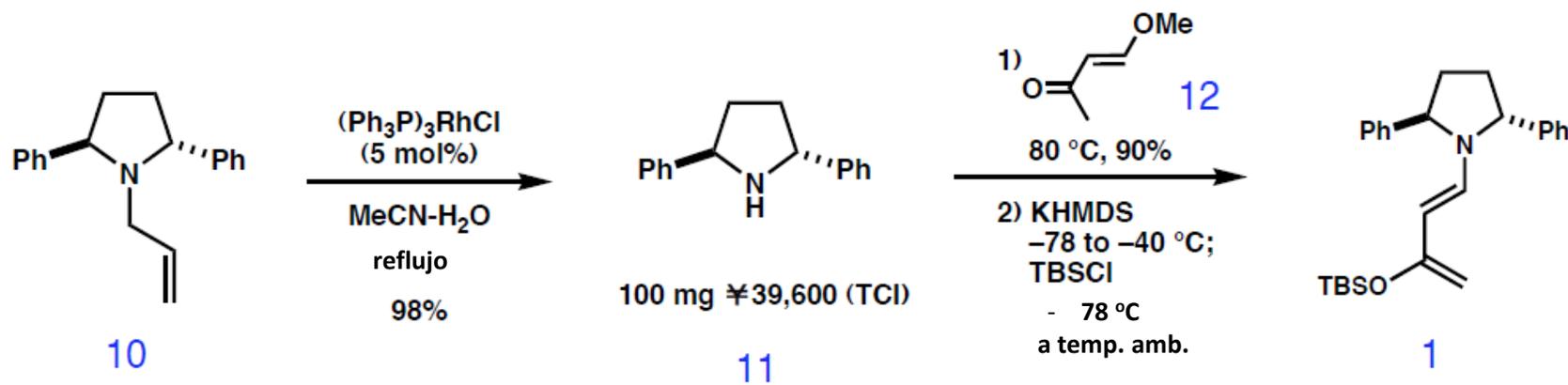
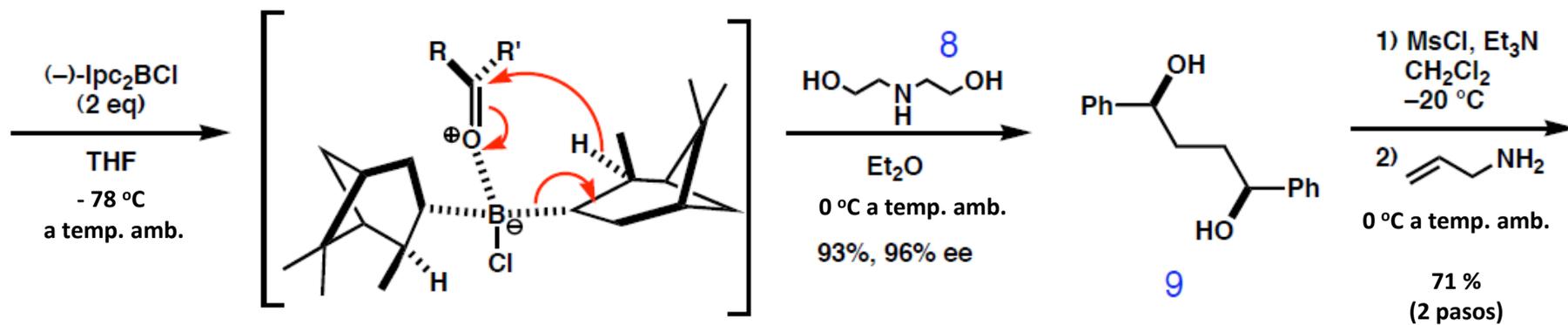
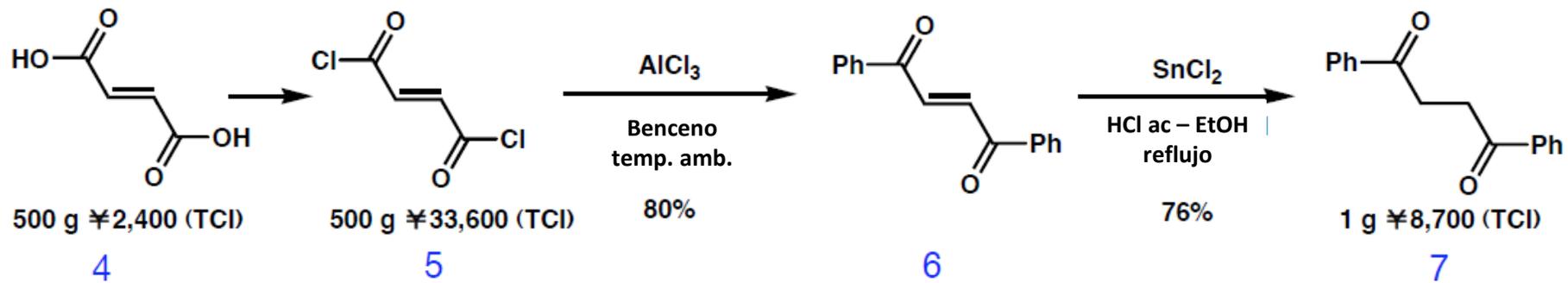
c) Selectividad facial





V. H. Rawal *et al.*, *J. Am. Chem. Soc.*, **119**, 7165 (1997)

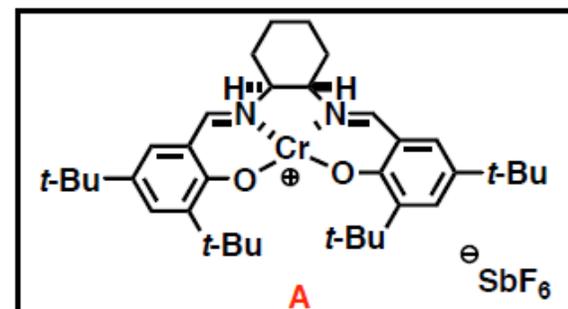
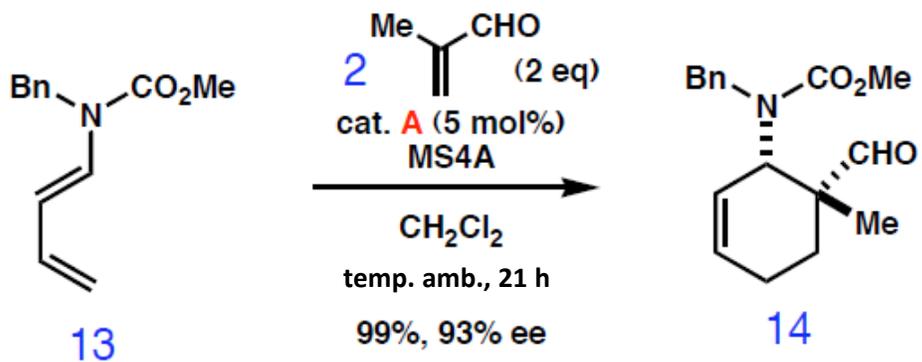




Quantitativo



REACCIÓN DE DIELS-ALDER, CATALÍTICA ASIMÉTRICA
REACCIÓN DE DA CATALIZADA CON ÁCIDO DE LEWIS QUIRAL

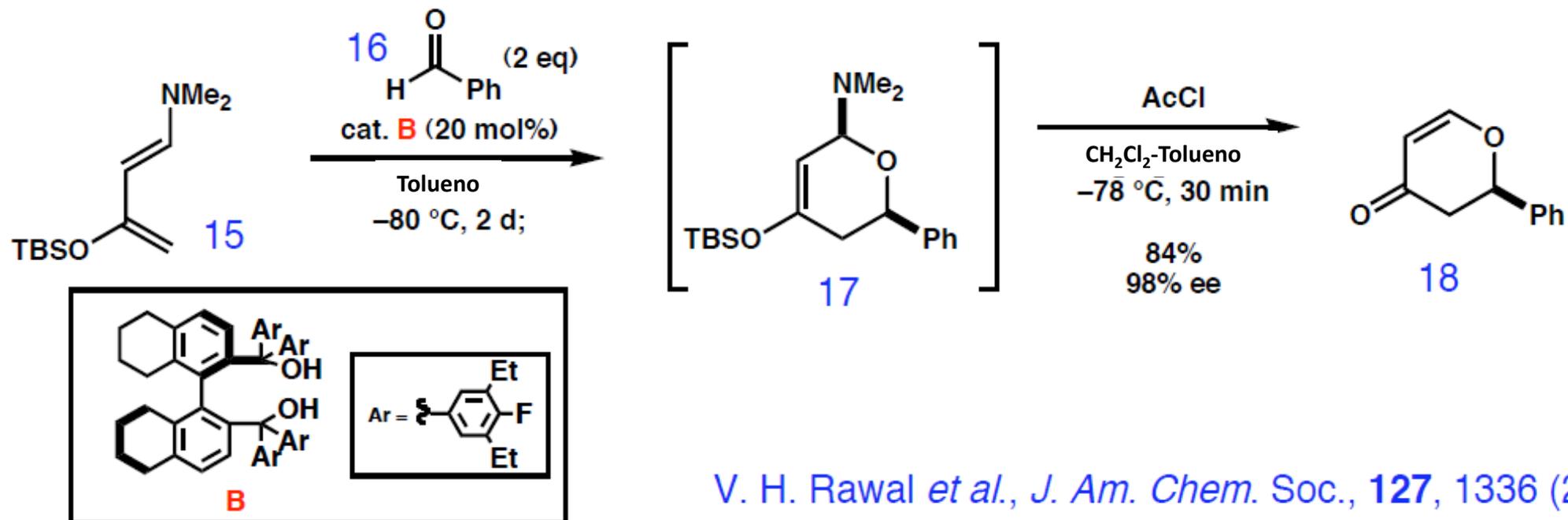


Catalizador de Jacobsen
Salen-Cr (III)

V. H. Rawal *et al.*, *J. Am. Chem. Soc.*, **124**, 5950 (2002)



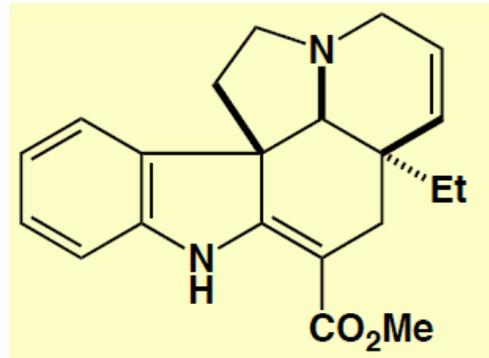
REACCIÓN HETERO DIELS-ALDER A TRAVÉS DE PUENTES DE HIDRÓGENO CATALIZADA CON BIARILDIOLES QUIRALES



V. H. Rawal *et al.*, *J. Am. Chem. Soc.*, **127**, 1336 (2005)



SÍNTESIS TOTAL DE LA (±)-TABERSONINA

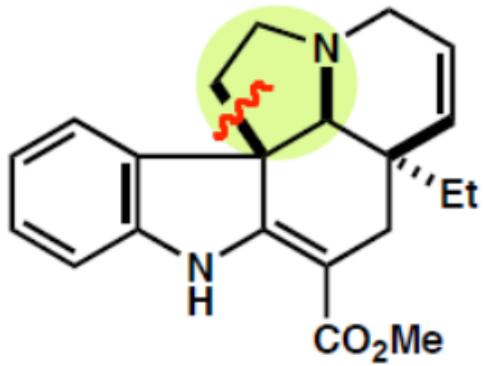


(±)-TABERSONINA

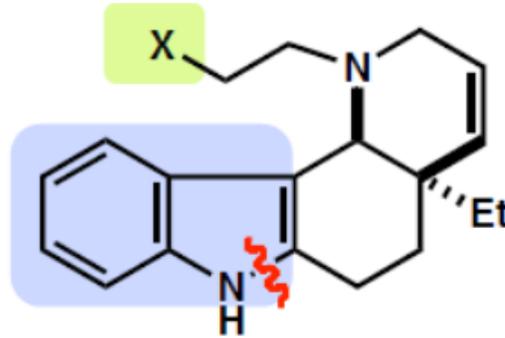
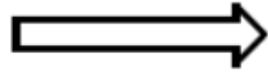
V. H. Rawal *et al.*, *J. Am. Chem. Soc.*, **124**, 4628 (2002)



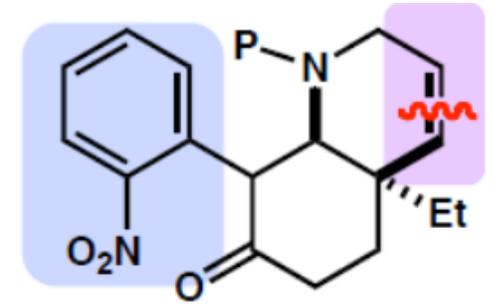
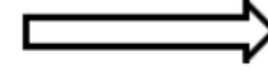
ANÁLISIS RETROSINTÉTICO



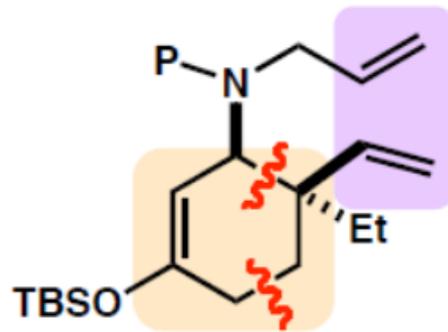
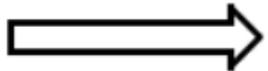
Alquilación intramolecular



Indolización

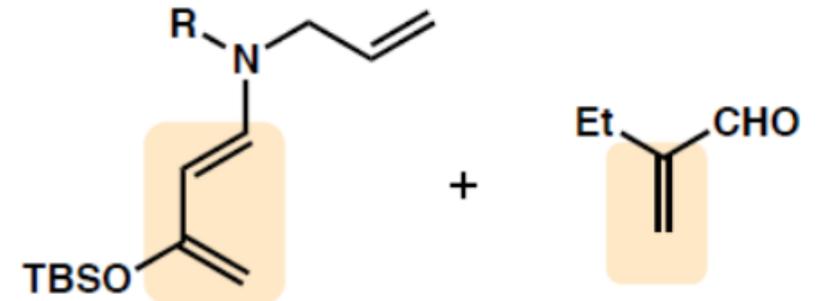
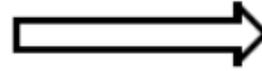


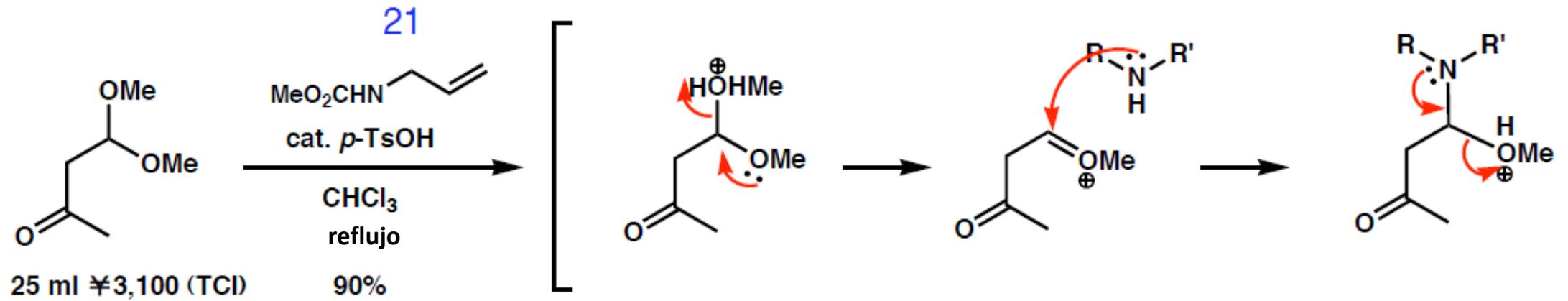
Metátesis olefina



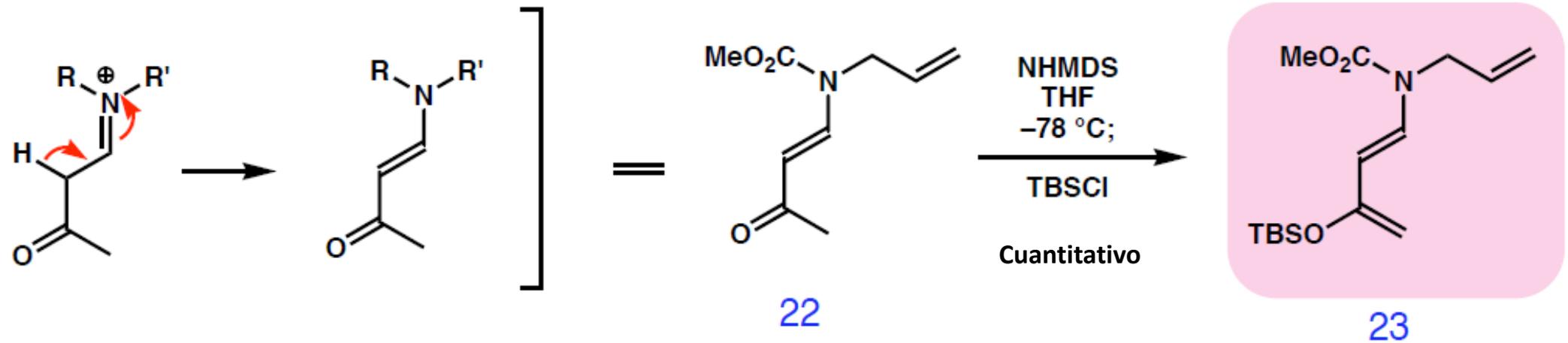
Reacción de Diels-Alder

Endo-selectiva





20

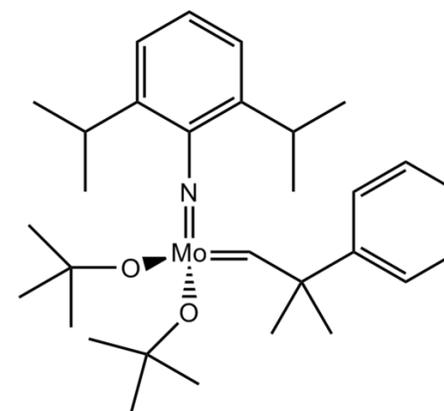
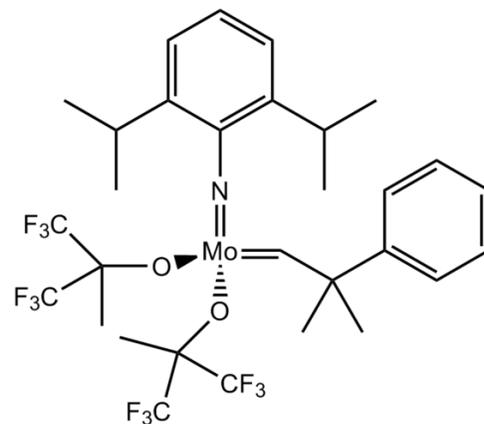
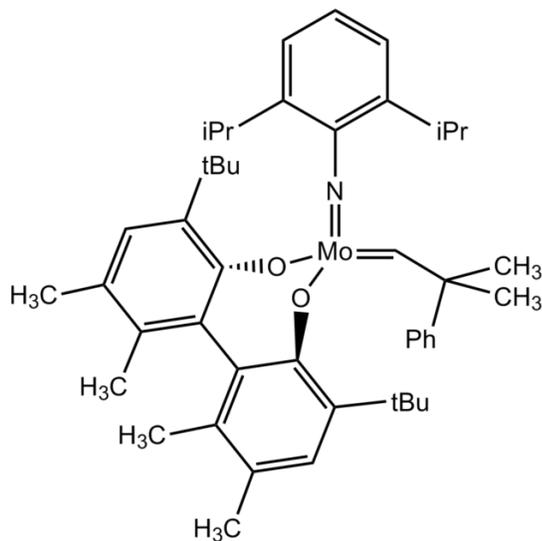


METATESIS

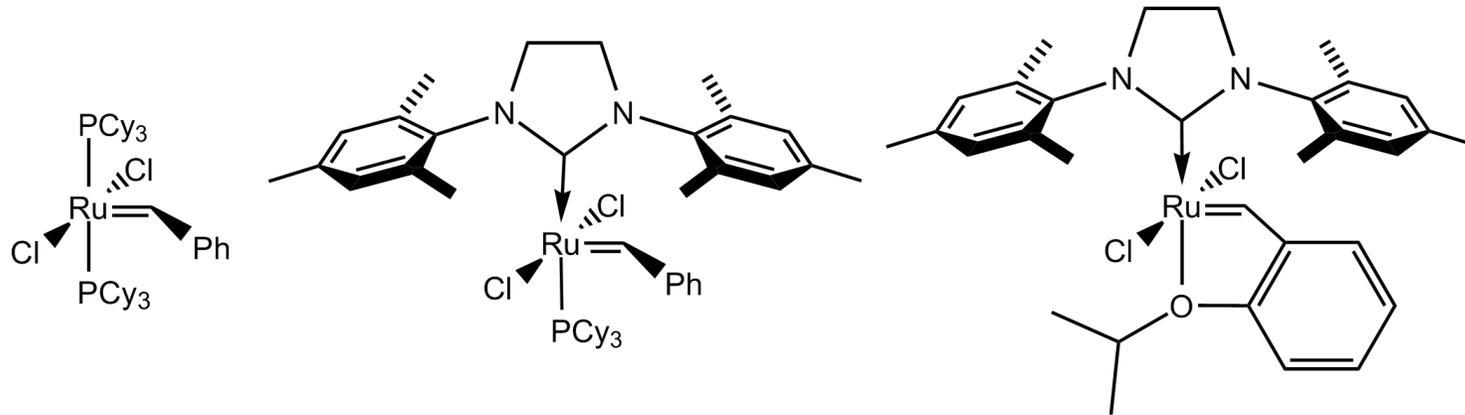
La reacción requiere catalizadores metálicos. La mayoría de los procesos comercialmente importantes emplean catalizadores heterogéneos. Los catalizadores heterogéneos se preparan a menudo mediante activación *in situ* de un haluro metálico (MCl_x) utilizando compuestos de organoaluminio u organoestaño, por ejemplo combinando MCl_x – EtAlCl₂. Un soporte de catalizador típico es la alúmina. Los catalizadores comerciales suelen estar basados en **molibdeno** y **rutenio**.

Los catalizadores homogéneos a menudo se clasifican como catalizadores de **Schrock** y catalizadores de **Grubbs**

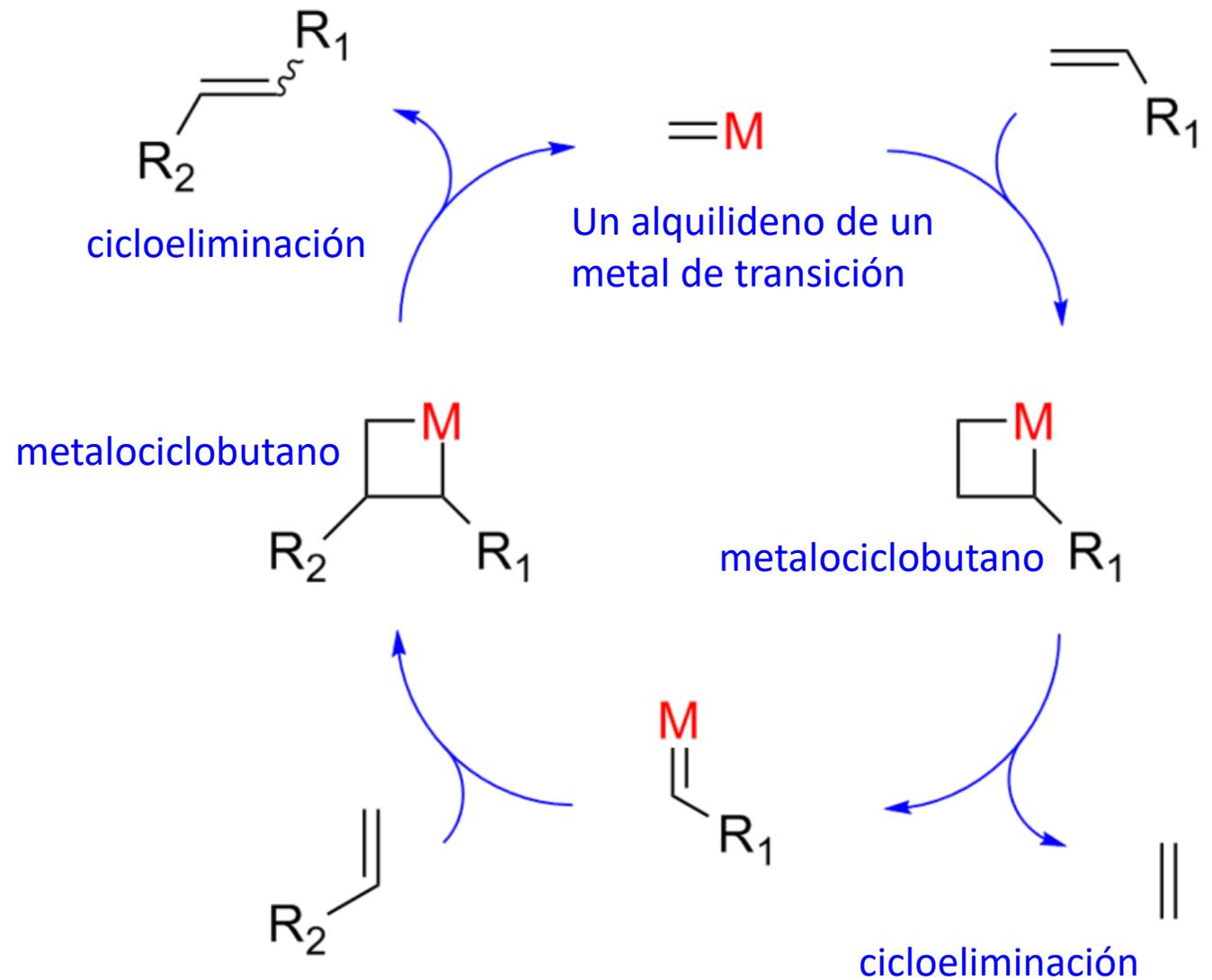
Los catalizadores Schrock cuentan con centros basados en molibdeno (VI) y tungsteno (VI) soportados por ligandos alcóxido e imido.



Los catalizadores de **Grubbs**, por otro lado, son complejos carbenoides de rutenio(II). Se conocen muchas variaciones de los catalizadores de Grubbs. Algunos han sido modificados con un ligando quelante de isopropoxibencilideno para formar el catalizador Hoveyda-Grubbs relacionado.



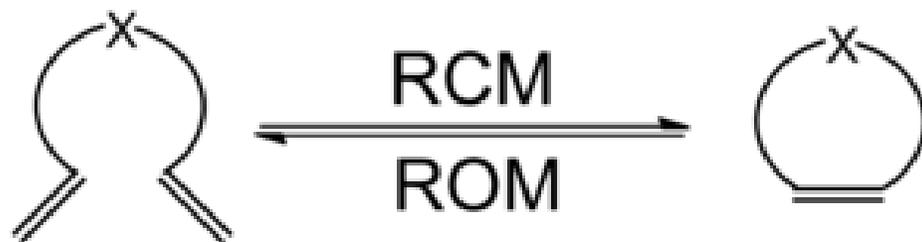
Hérisson y Chauvin propusieron por primera vez el mecanismo ampliamente aceptado de metátesis de alquenos de metales de transición. La **cicloaddición directa [2+2]** de dos alquenos está formalmente **prohibida** por simetría y, por lo tanto, tiene una alta energía de activación. El mecanismo de Chauvin implica la **cicloaddición [2+2]** de un doble enlace **alqueno a un alquilideno de un metal de transición** para formar un intermediario metalociclobutano. El metalociclobutano producido puede luego cicloeliminarse para dar la especie original o un nuevo alqueno y alquilideno. La interacción con los orbitales d del catalizador metálico reduce la energía de activación lo suficiente como para que la reacción pueda desarrollarse rápidamente a temperaturas moderadas.



La metátesis de olefinas implica pocos cambios en la entalpía de los alquenos no tensos. En cambio, las distribuciones de productos están determinadas por el principio de Le Chatelier, es decir, la entropía.

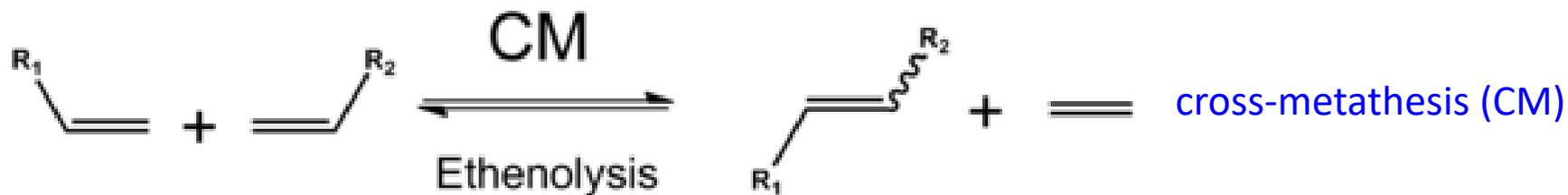


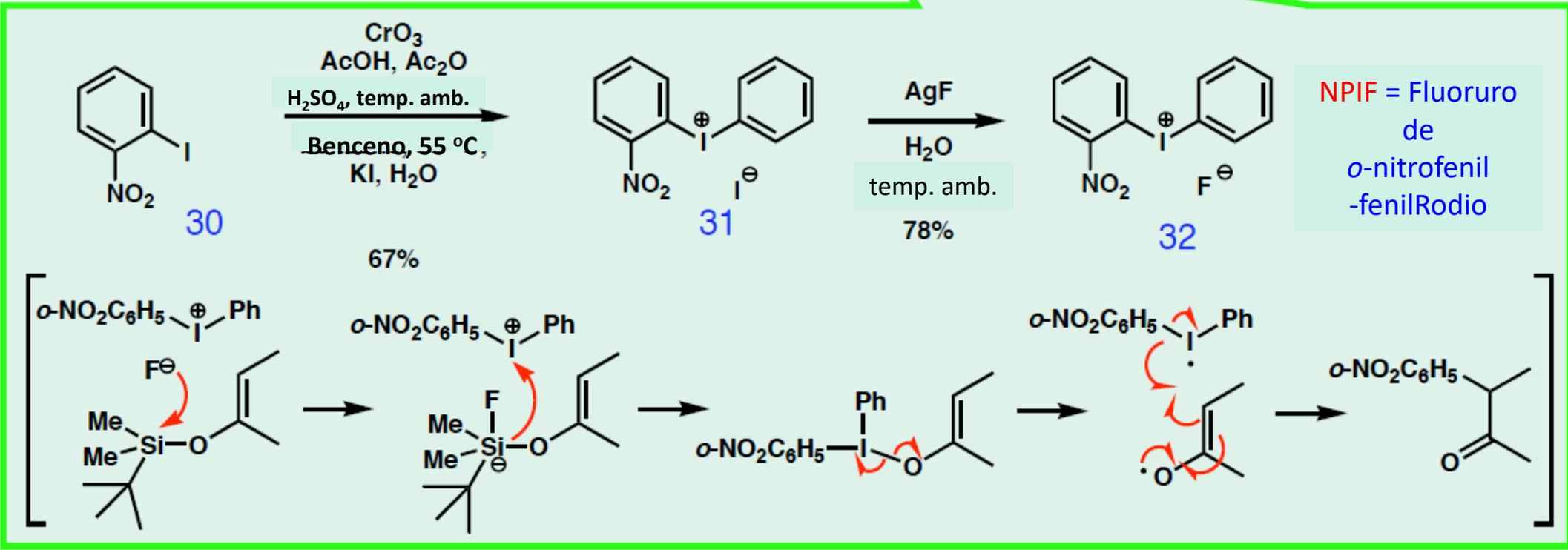
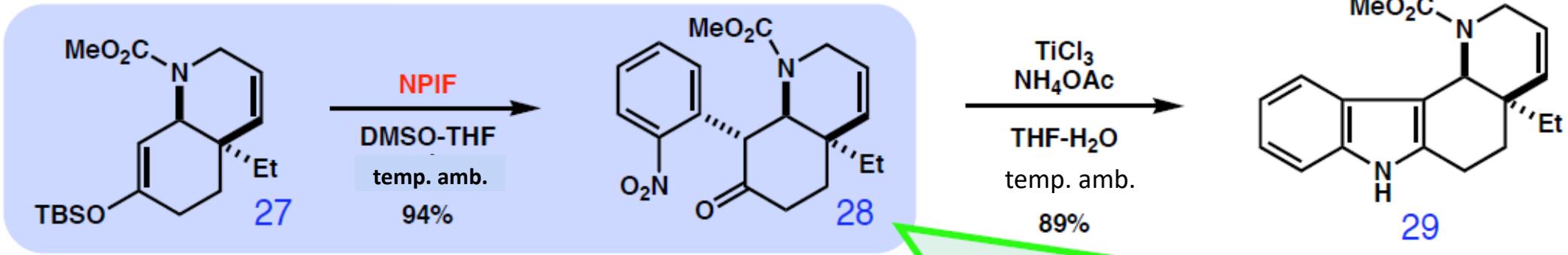
Ring-opening metathesis
polymerisation

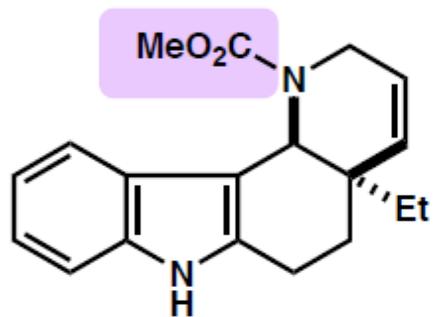


Ring-closing metathesis

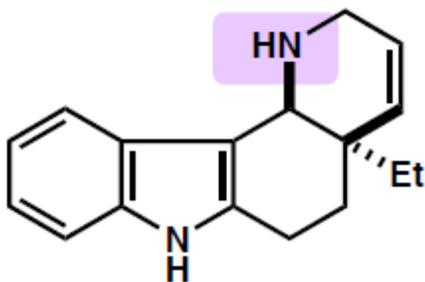
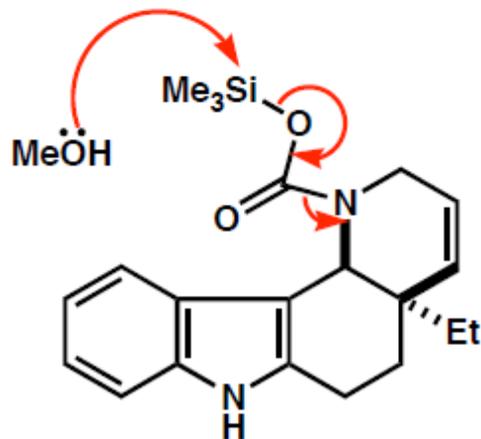
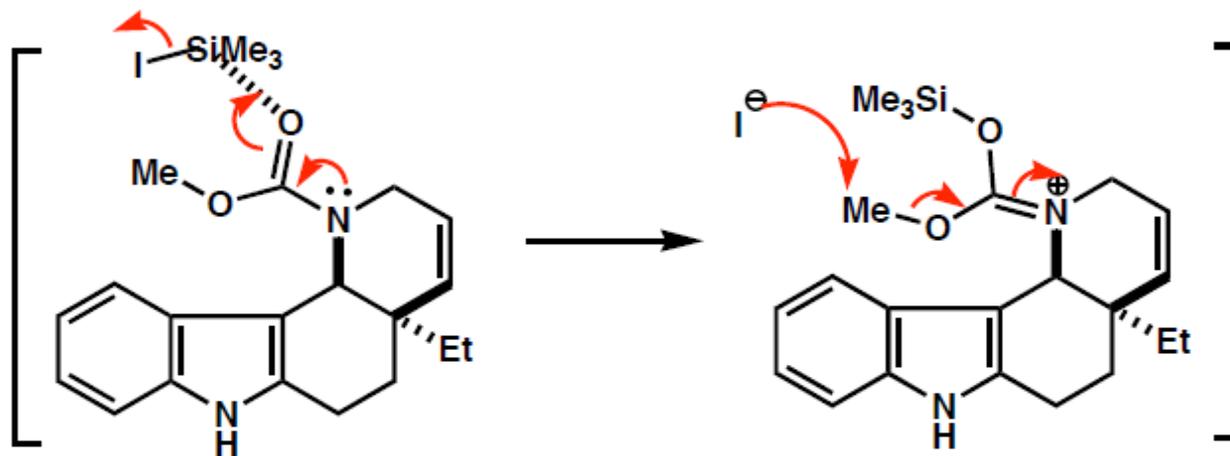
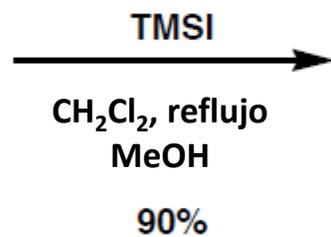
Ring-Opening
Olefin Metathesis



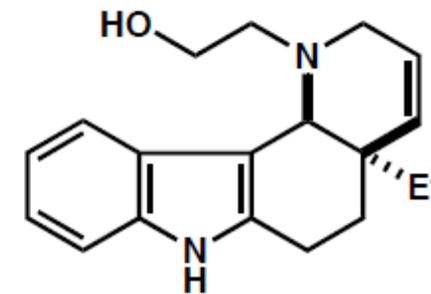
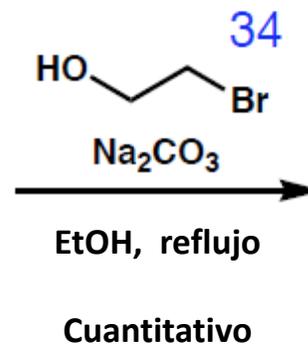




29

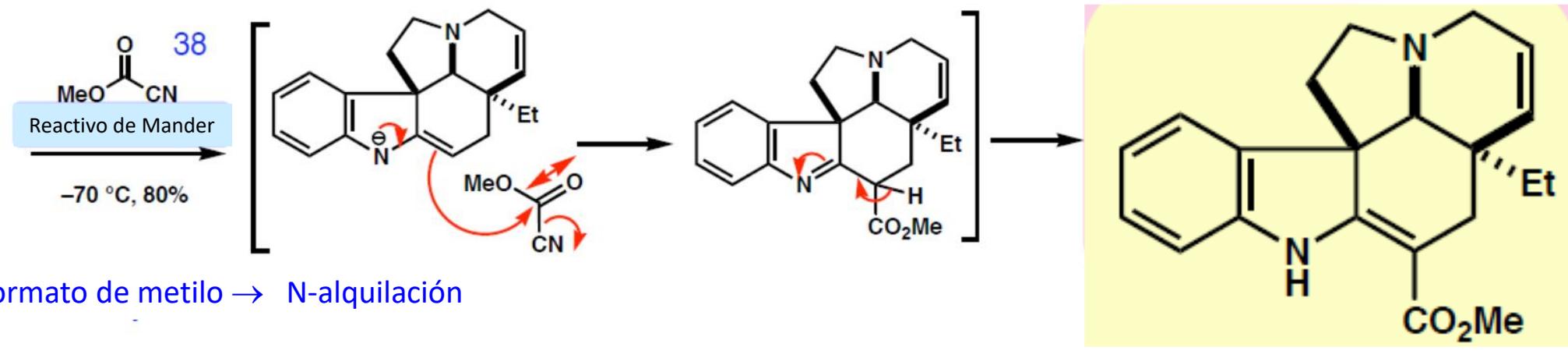
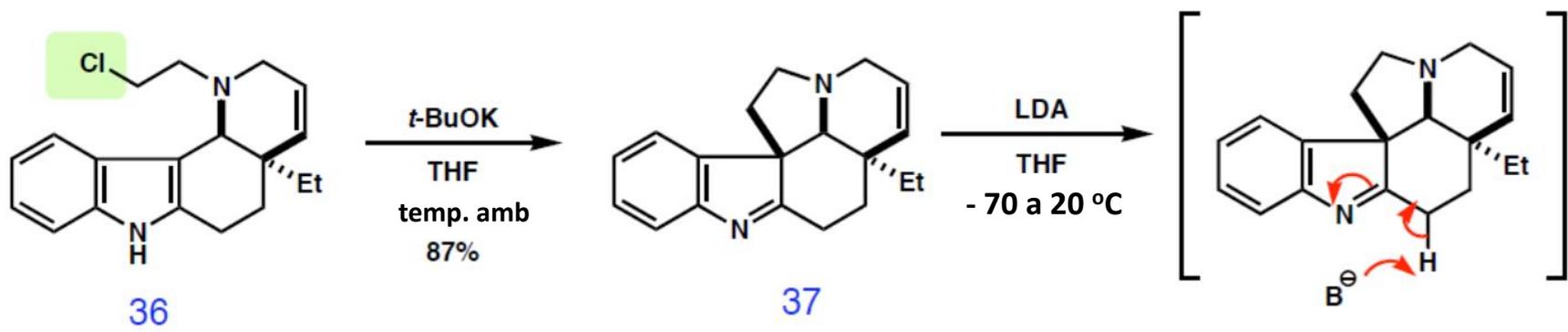
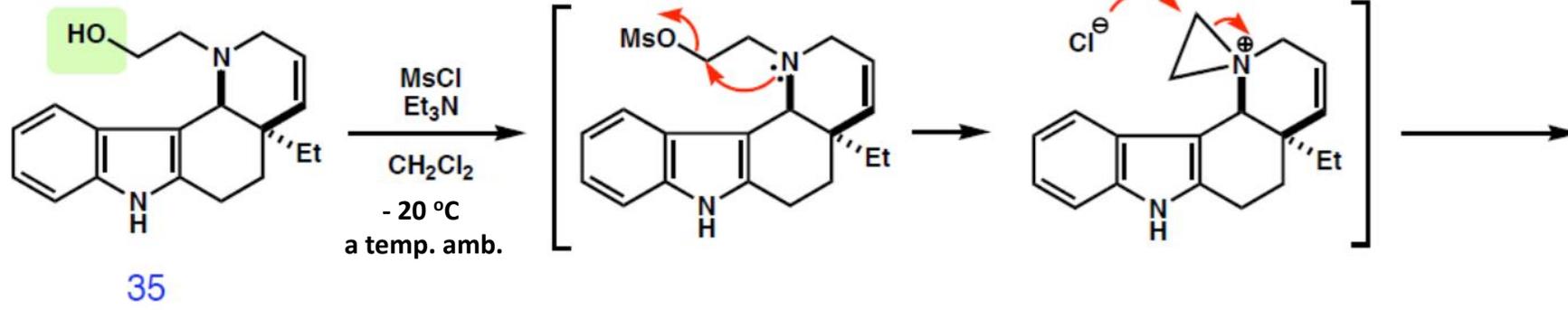


33



35





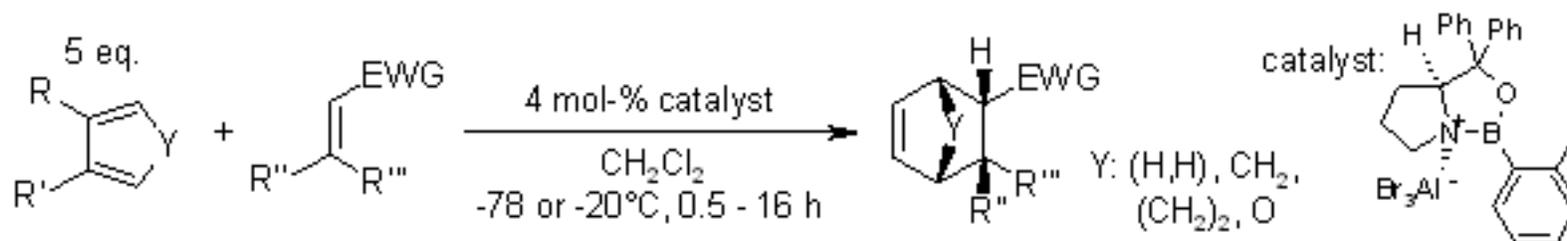
Cloroformato de metilo → N-alkilación

12 pasos
Rendimiento global 30.5 %



Chiral Oxazaborolidine-Aluminum Bromide Complexes Are Unusually Powerful and Effective Catalysts for Enantioselective Diels-Alder Reactions

D. Liu, E. Canales, E. J. Corey, *J. Am. Chem. Soc.*, **2007**, *129*, 1498-1499.

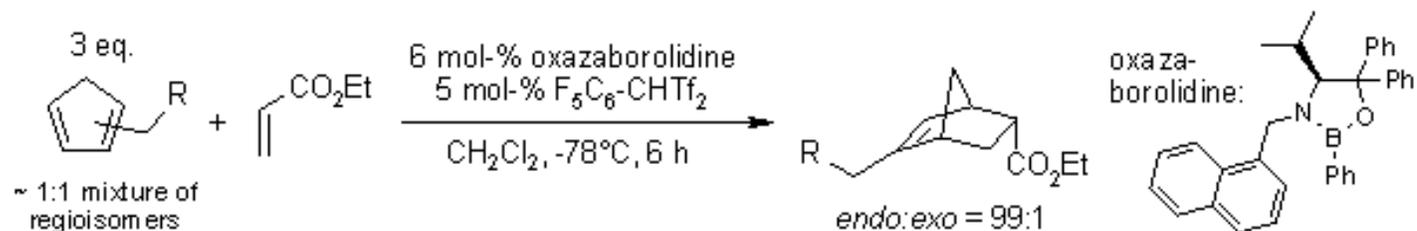


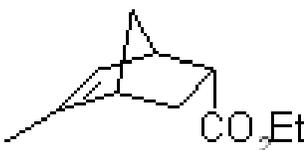
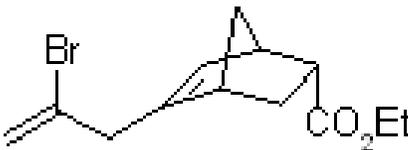
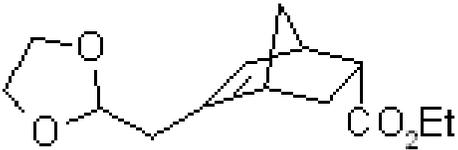
product	T (°C)	t (h)	yield (% , isol.)	ee (%)	product	T (°C)	t (h)	yield (% , isol.)	ee (%)
	-78	8	98	99		-78	16	97	96
	-40	1	95	92		-20	16	96	91
	-78	0.5	99	99		-78	16	99	84
	-78	12	99	88		-78	8	99	99



Regioselective and Asymmetric Diels-Alder Reaction of 1- and 2-Substituted Cyclopentadienes Catalyzed by a Brønsted Acid Activated Chiral Oxazaborolidine

J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc.*, **2007**, *129*, 9536-9537.

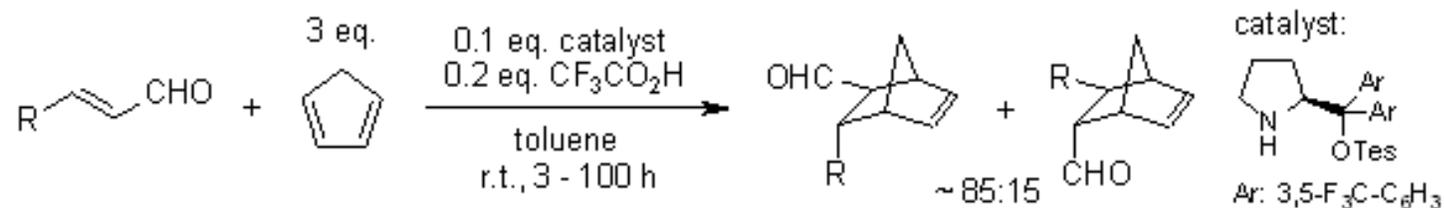


product	yield (% , isol.)	ee (%)	product	yield (% , isol.)	ee (%)
	96	99		81	99
	85	96		98	98



Diarylprolinol Silyl Ether as Catalyst of an *exo*-Selective, Enantioselective Diels-Alder Reaction

H. Gotoh, Y. Hayashi, *Org. Lett.*, **2007**, *9*, 2859-2862.

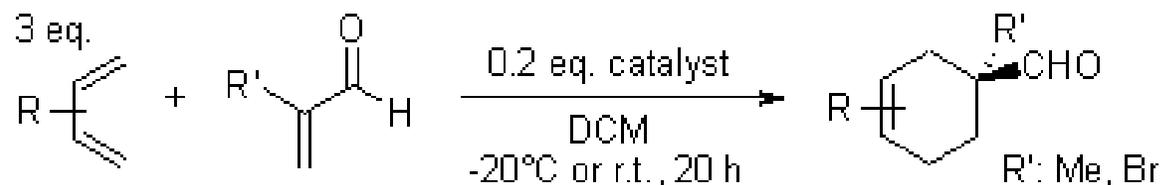


unsaturated aldehyde	t (h)	<i>exo</i> : <i>endo</i>	yield (% , isol.) (mixture)	ee (%) <i>exo</i>	ee (%) <i>endo</i>
	78	78:22	71	96	96
	6	87:13	93	96	82
	17	85:15	78	97	93
	3	78:22	65	94	91



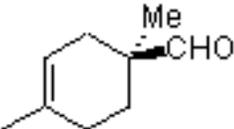
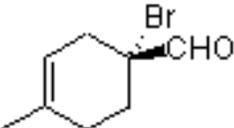
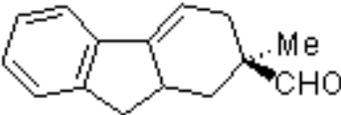
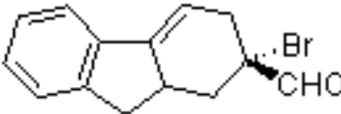
Catalytic Enantioselective Diels-Alder Reaction via a Chiral Indium(III) Complex

Y.-Chua Teo, T.-P. Loh, *Org. Lett.*, **2005**, 7, 2539-2541.



In situ preparation of catalyst:

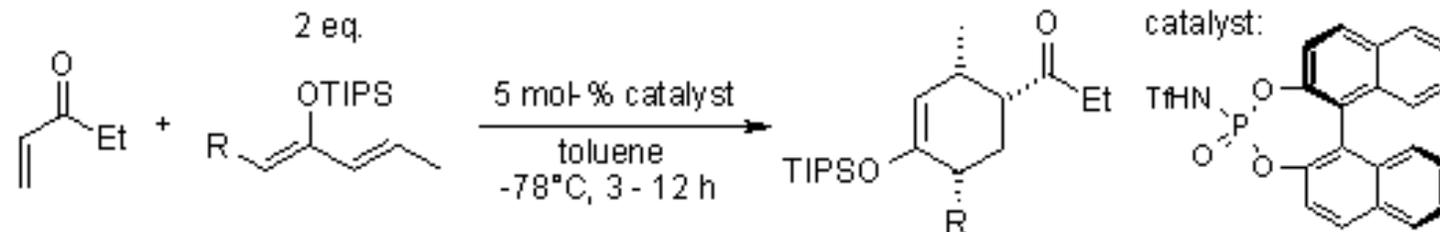
- 0.22 eq. (S)-BINOL, 0.2 eq. InCl₃
MS 4 Å, DCM, r.t., 2h
- 0.6 eq. Bu₃SnAllyl, 10 min

product	T (°C)	yield (% , isol.)	ee (%)
	r.t.	35	90
	-20	70	96
	-20	71	98
	-20	72	98



Design of Chiral *N*-Triflyl Phosphoramidate as a Strong Chiral Brønsted Acid and Its Application to Asymmetric Diels-Alder Reaction

D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.*, 2006, 128, 9626-9627.

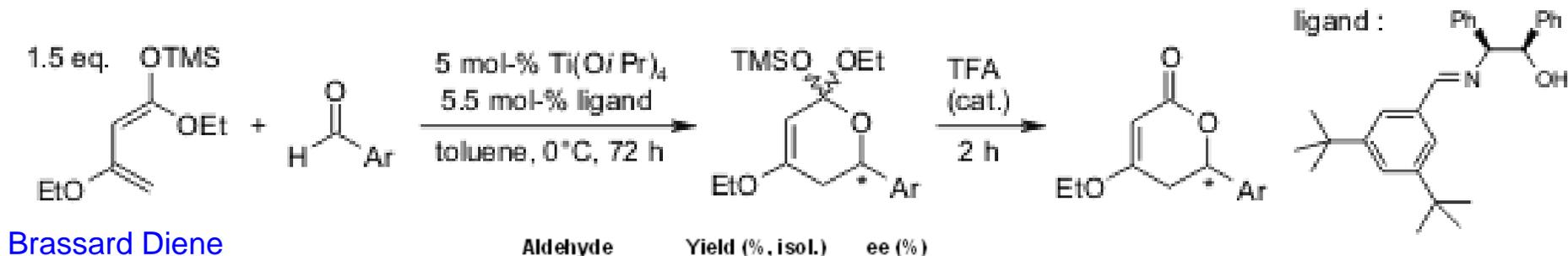


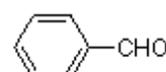
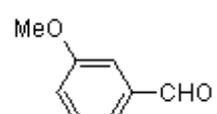
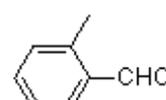
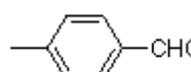
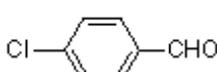
product	t (h)	yield (% , isol.)	ee (%)	product	t (h)	yield (% , isol.)	ee (%)
	3	95	92		12	99	87
	12	99	85		12	99	91



A Mild and Efficient Asymmetric Hetero-Diels-Alder Reaction of the Brassard Diene with Aldehydes

Q. Fan, L. Lin, J. Liu, Y. Huang, X. Feng, *Eur. J. Org. Chem.*, **2005**, 3542-3552.

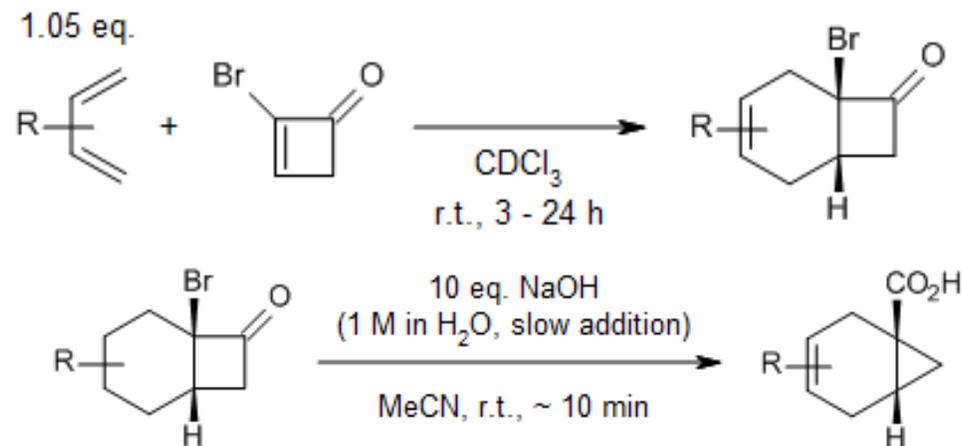


Aldehyde	Yield (% , isol.)	ee (%)
	71	93
	45	96
	24	92
	36	90
	87	97
	56	91



Halocycloalkenones as Diels-Alder Dienophiles. Applications to Generating Useful Structural Patterns

A. G. Ross, S. D. Townsend, S. J. Danishefsky, *J. Org. Chem.*, **2013**, *78*, 204-210.

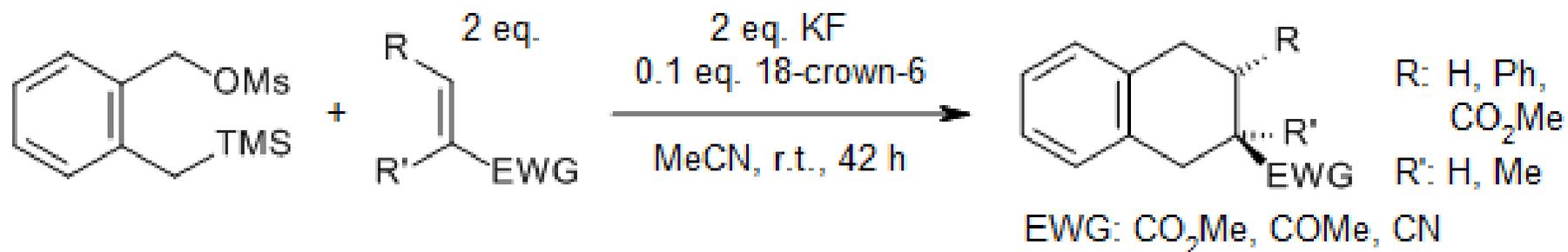


product	t (h)	yield (% , isol.)	product	yield (% , isol.)
	6	88		72
	18	92		56
	18	97		



2-[(Trimethylsilyl)methyl]benzyl Methanesulfonates: Useful Precursors for the Generation of *o*-Quinodimethanes

H. Shirakawa, H. Sano, *Synthesis*, 2014, 46, 1788-1792.

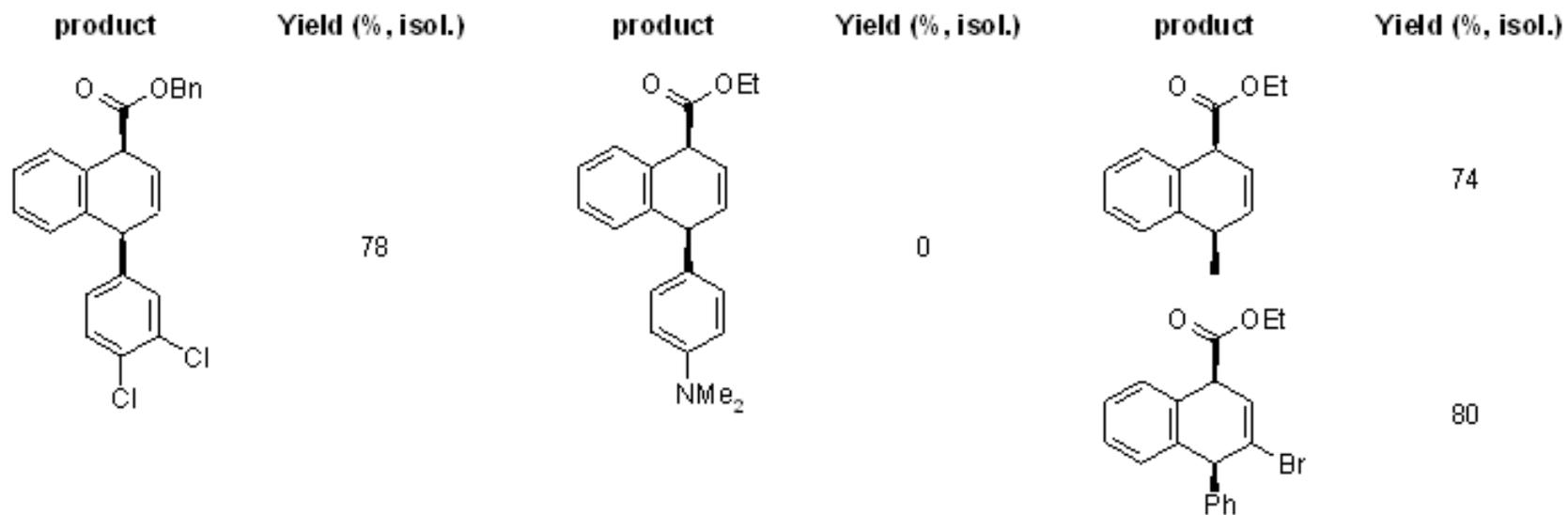
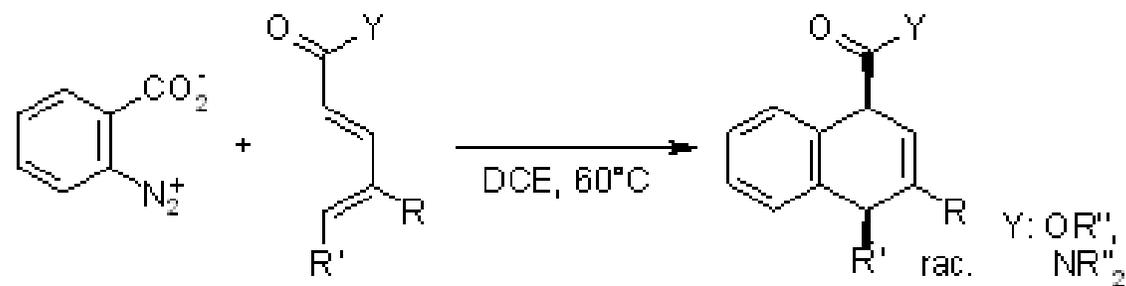


product	yield (% isol.)	product	yield (% isol.)
	81		86
	74		66



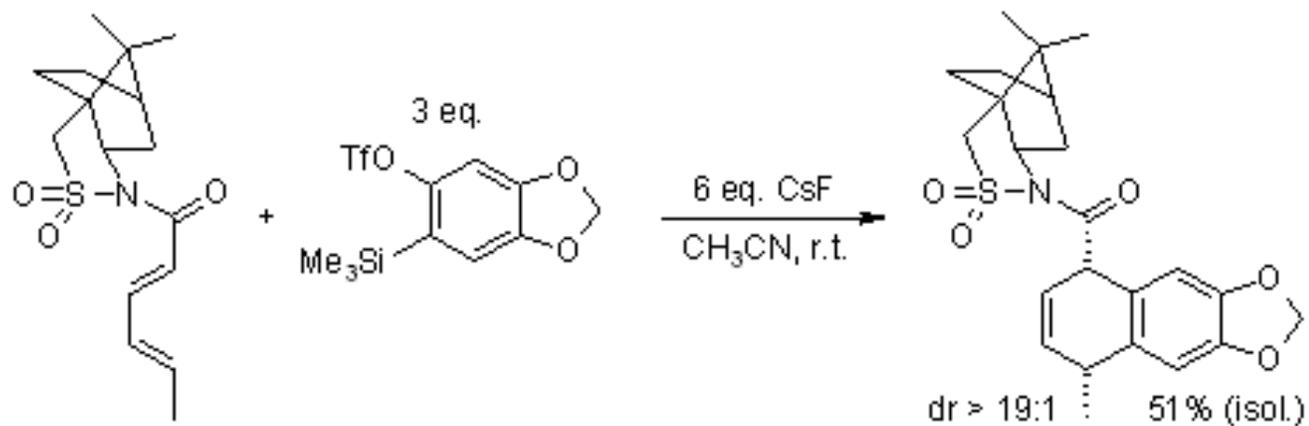
Synthesis of Dihydronaphthalenes via Aryne Diels-Alder Reactions: Scope and Diastereoselectivity

C. Dockendorff, S. Sahli, M. Olsen, L. Milhau, M. Lautens, *J. Am. Chem. Soc.*, **2005**, *127*, 15028-15029.



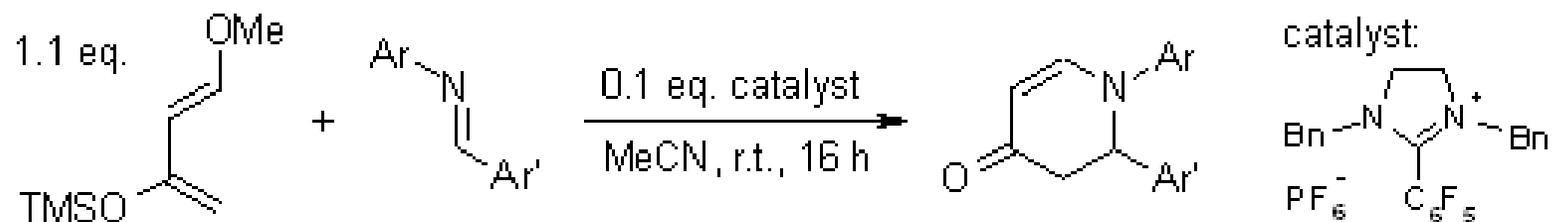
Synthesis of Dihydronaphthalenes via Aryne Diels-Alder Reactions: Scope and Diastereoselectivity

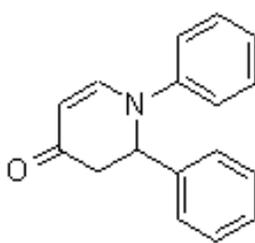
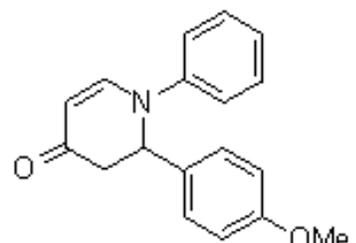
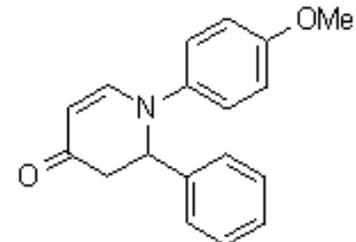
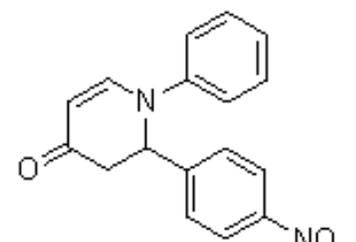
C. Dockendorff, S. Sahli, M. Olsen, L. Milhau, M. Lautens, *J. Am. Chem. Soc.*, **2005**, *127*, 15028-15029.



Imidazolinium salts as catalysts for the aza-Diels-Alder reaction

V. Jurcik, R. Wilhelm, *Org. Biomol. Chem.*, **2005**, 3, 239-244.

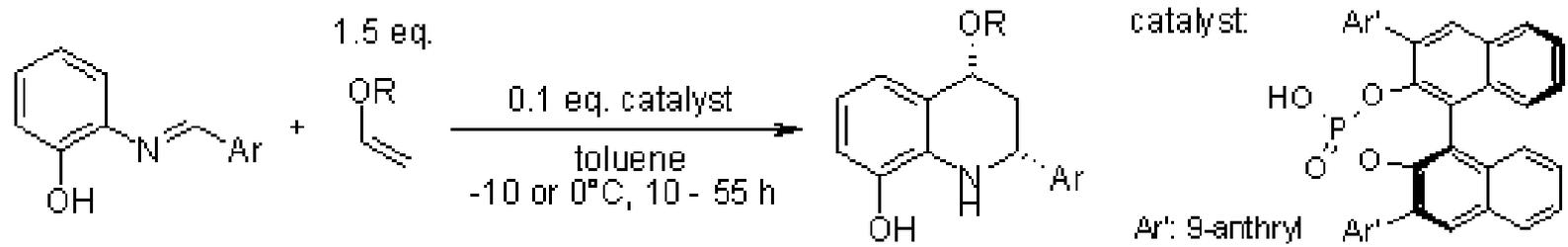


Product	Yield (% , isol.)	Product	Yield (% , isol.)
	95		45
	92		50



Chiral Brønsted Acid-Catalyzed Inverse Electron-Demand Aza Diels-Alder Reaction

T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.*, **2006**, *128*, 13070-13071.

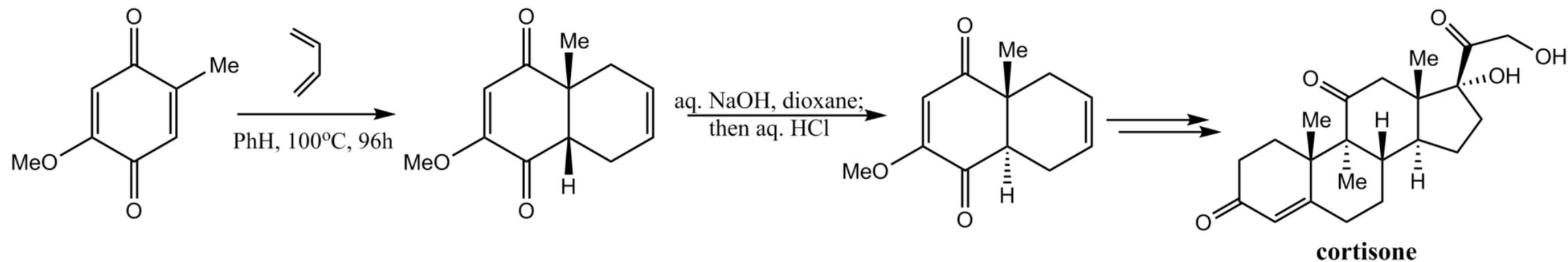


product	T (°C)	yield (% , isol.)	cis/trans	ee (%)	product	T (°C)	yield (% , isol.)	cis/trans	ee (%)
	-10	89	99:1	94		-10	86	99:1	89
	0	76	99:1	91		0	72	96:4	87



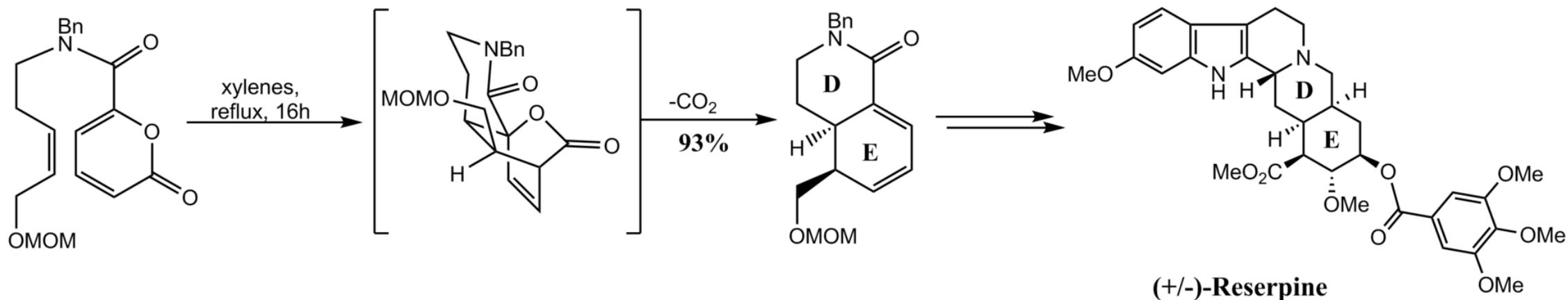
The Total Synthesis of Steroids

Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *Journal of the American Chemical Society*, **1952**, 74(17): 4223–4251. doi:10.1021/ja01137a001.



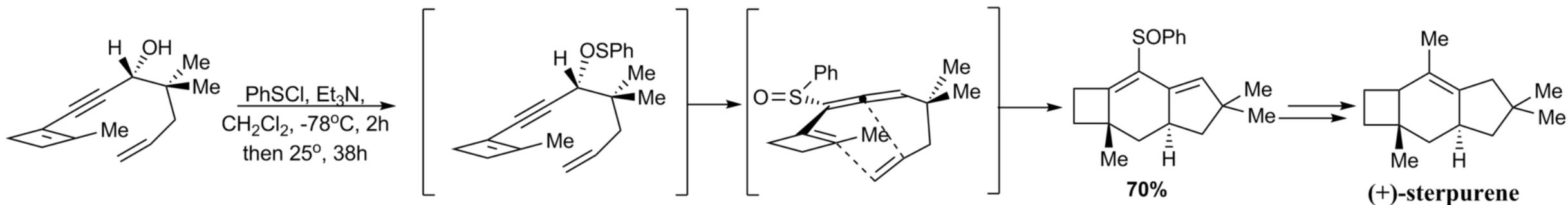
General methodology for cis-hydroisoquinoline synthesis: Synthesis of reserpine

Wender, P. A.; Schaus, J. M.; White, A. W. (). *Journal of the American Chemical Society* **1980**, *102* (19): 6157–6159. doi:10.1021/ja00539a038



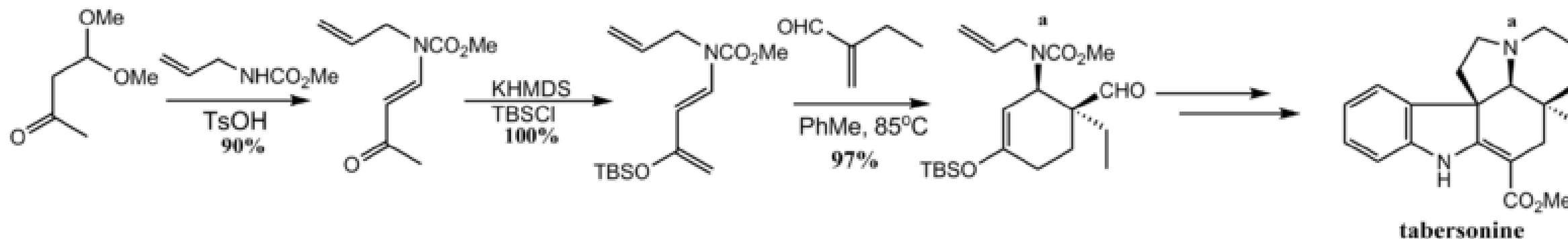
A short enantioselective synthesis of (+)-sterpurene: Complete intramolecular transfer of central to axial to central chiral elements

Gibbs, R. A.; Okamura, W. H. (). . *Journal of the American Chemical Society* **1988**, *110* (12): 4062–4063. doi:10.1021/ja00220a069



A General Strategy to Aspidosperma Alkaloids: Efficient, Stereocontrolled Synthesis of Tabersonine

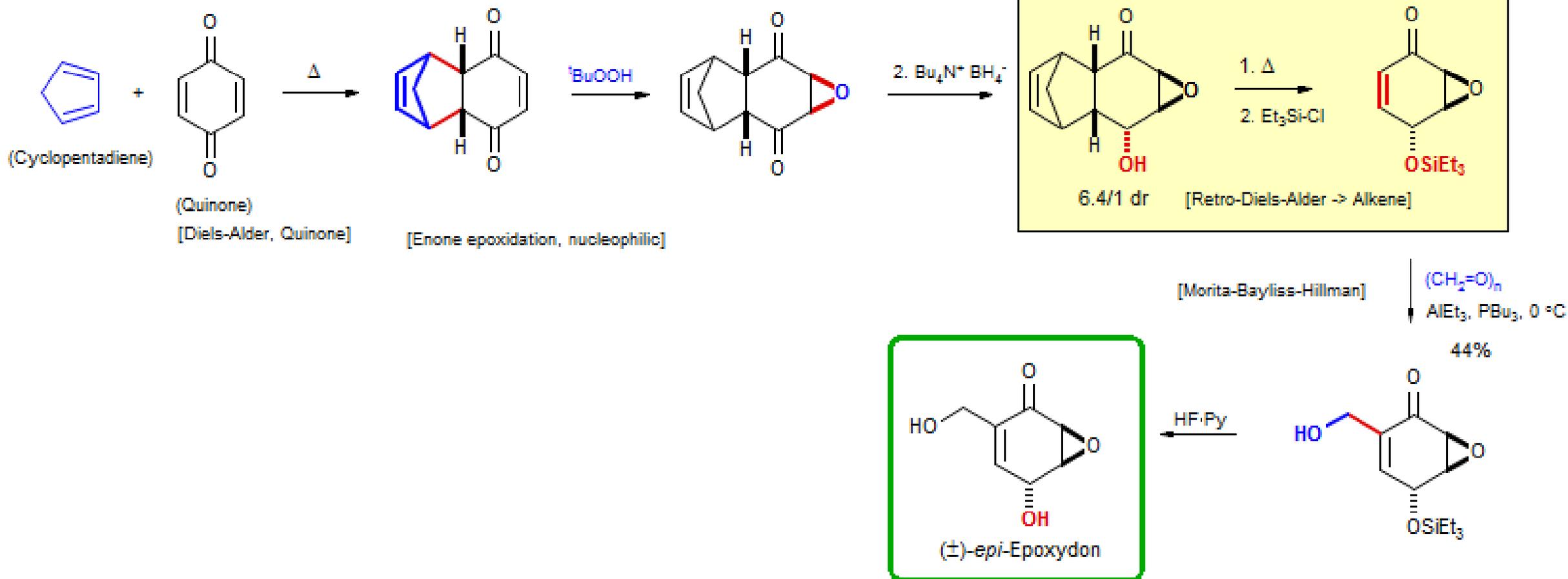
Kozmin, S. A.; Rawal, V. H. *Journal of the American Chemical Society* **1998**, *120*(51): 13523–13524. doi:10.1021/ja983198k.



Epoxydon, Epi-

02-18

Genski, T.; Taylor, R. J. K. *Tetrahedron Lett.* 2002, 43, 3573.

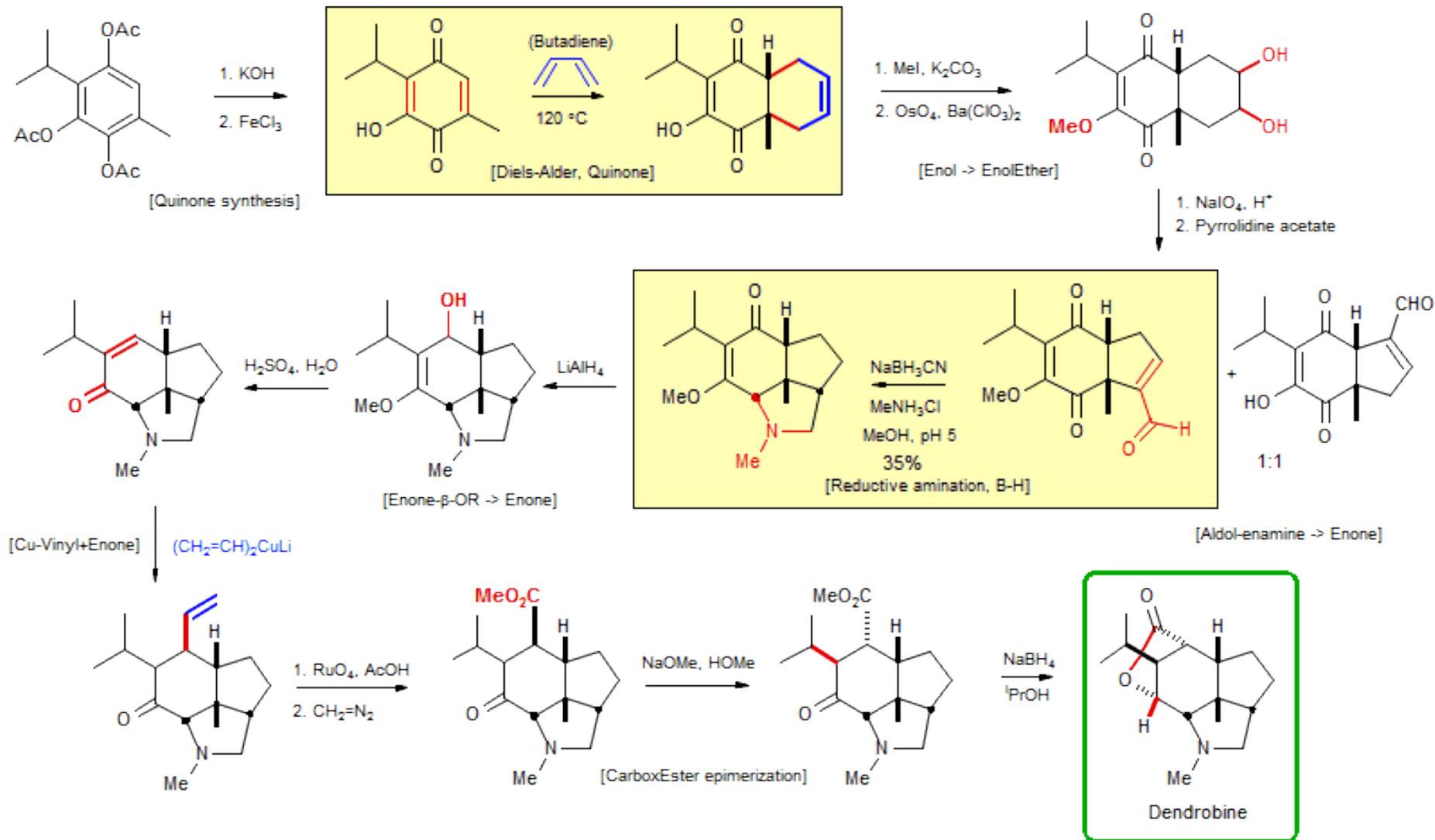


Dendrobine

Kende, A. S.; Bentley, T. J.; Mader, R. A.; Ridge, D. J. *Am. Chem. Soc.* **1974**, *96*, 4332-4334.

74-07

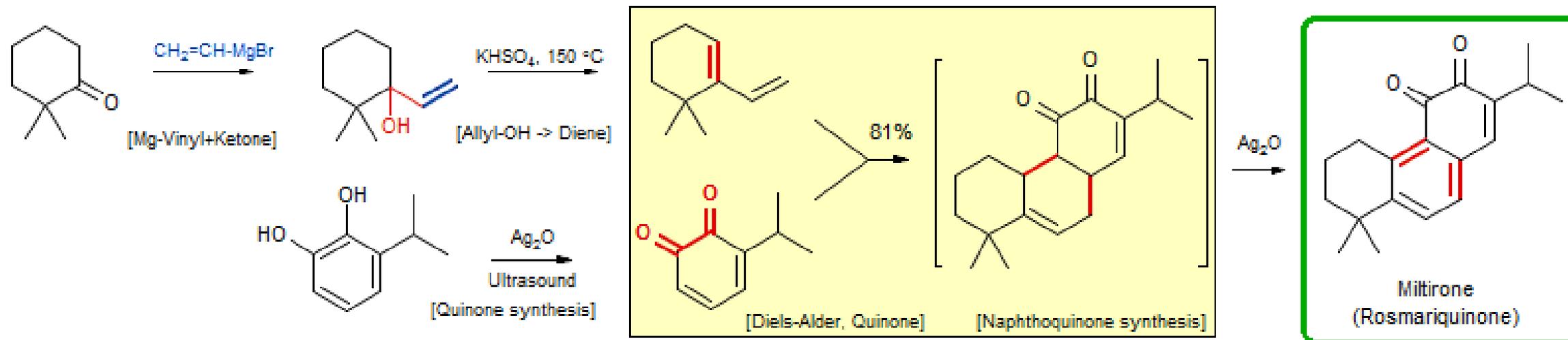
COMM



Miltirone

90-07

Lee, J.; Mei, H. S.; Snyder, J. K *J. Org. Chem.* **1990**, *55*, 5013 (see also *J. Org. Chem.* **1985**, *50*, 4996).



Intramolecular Diels-Alder Reactions

The Intramolecular Diels-Alder Reaction,

E. Ciganek, *Org. React.* **1984**, 32.

Stereochemical Aspects of the Intramolecular Diels-Alder Reactions,

Craig, D. *Chem. Soc. Rev.* **1987**, 16, 187.

Cytochalasan Synthesis: Macrocyclic Formation via Intramolecular Diels-Alder Reactions,

Thomas, E. J. *Acc. Chem. Res.* **1991**, 24, 229.

Pericyclization of Vinylallenes in Organic Synthesis: On the Intramolecular Diels-Alder Reaction,

Okamura, W. H.; Curtin, M. L. *Synlett* **1990**, 1, 1.

Transannular Diels-Alder Reaction on Macrocycles. A General Strategy for the Synthesis of Polycyclic Compounds,

Deslongchamps, P. *Pure Appl. Chem.* **1992**, 64, 1831-47.

Second Generation of Steroid Synthesis via o-Quinodimethane,

Nemoto, H.; Fukumoto, K. *Tetrahedron* **1998**, 54, 5425-64.

Harvesting Diels and Alder's Garden: Synthetic Investigations of Intramolecular [4 + 2] Cycloadditions,

Fallis, A. G. *Acc. Chem. Res.* **1999**, 32, 464-74.

The Type 2 Intramolecular Diels-Alder Reaction: Synthesis and Chemistry of Bridgehead Alkenes,

Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 820-49.

The Transannular Diels-Alder Strategy: Applications to Total Synthesis,

Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, 57, 4243-60.

On the Origins of Diastereofacial Selectivity of [4+2] Cycloadditions in Cage-Annulated and Polycarbocyclic Diene/Dienophile Systems,

Marchand, A. P.; Coxon, J. M. *Acc. Chem. Res.* **2002**, 35, 271-7.

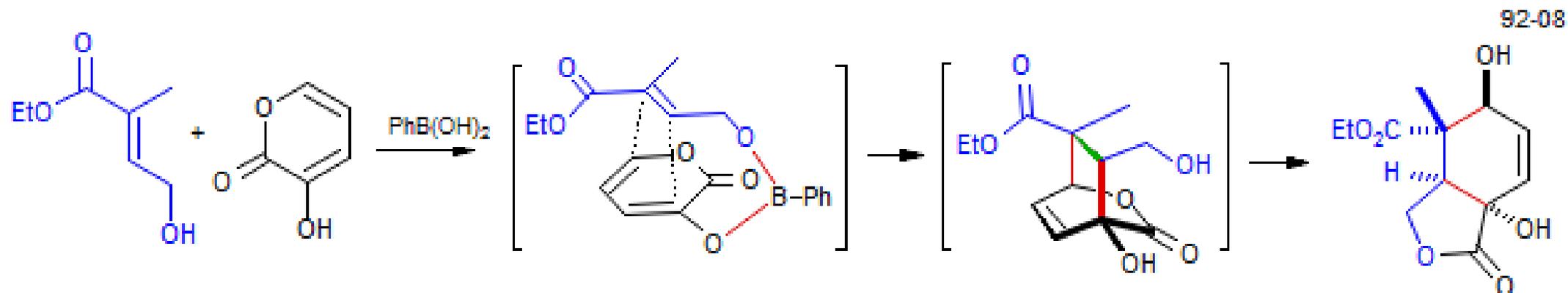


Intramolecular Diels-Alder Reactions

Temporary linkage between diene and dienophile for regiocontrol

Taxol Ring D

Nicolaou, K. C.; Liu, J. J.; Hwang, C.-K.; Pai, W. M.; Guy, R. K. *Chem. Commun.* **1992**, 1118

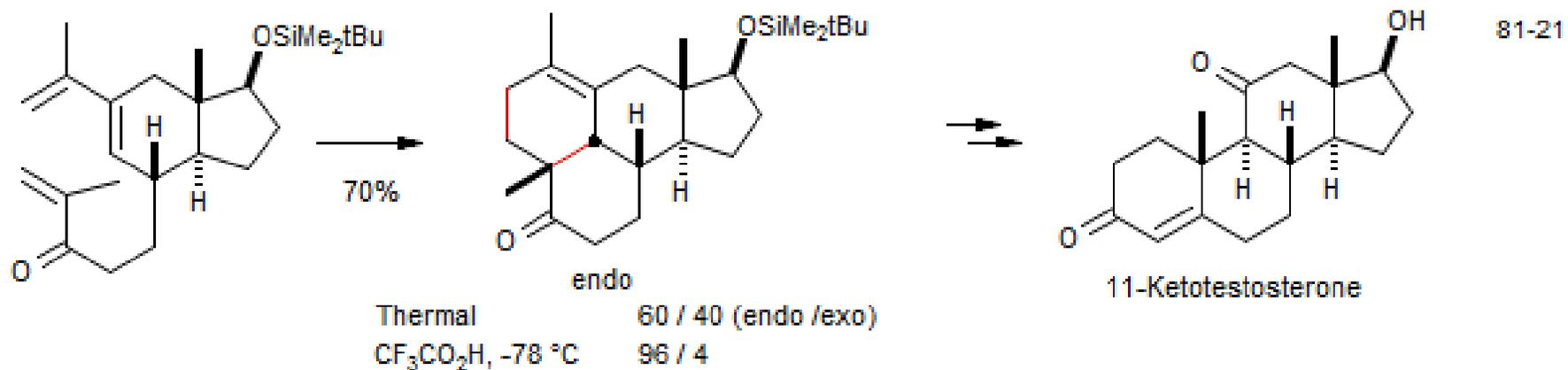


Intramolecular Diels-Alder Reactions

Increased *endo* preference with acid catalysis.

Testosterone, 11-keto

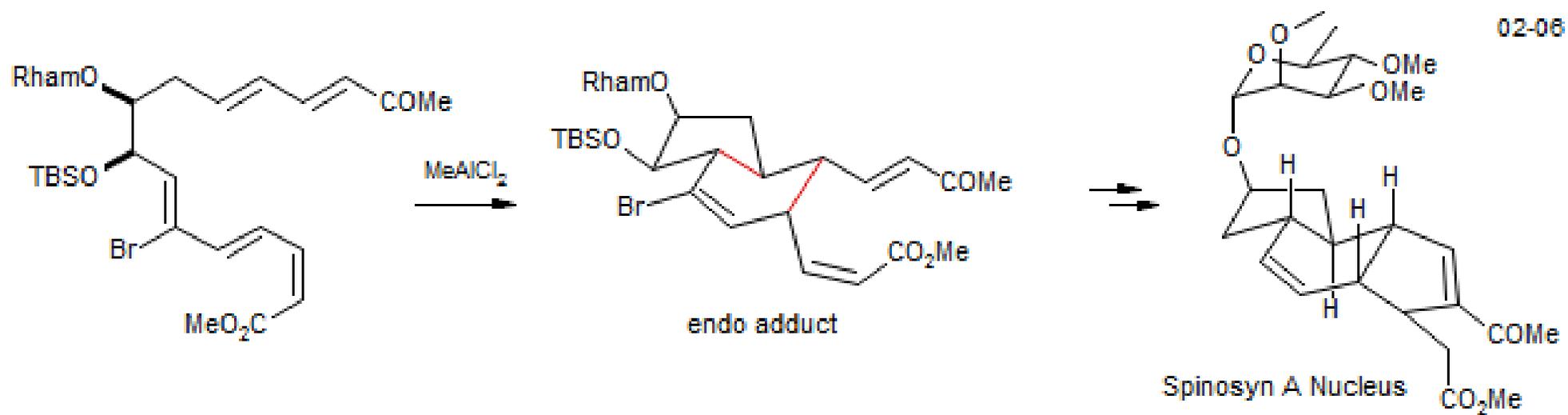
Stork, G.; Clark, G.; Shiner, C. S. *J. Am. Chem. Soc.* **1981**, *103*, 4948.



Intramolecular Diels-Alder Reactions

Spinosyn A Nucleus:

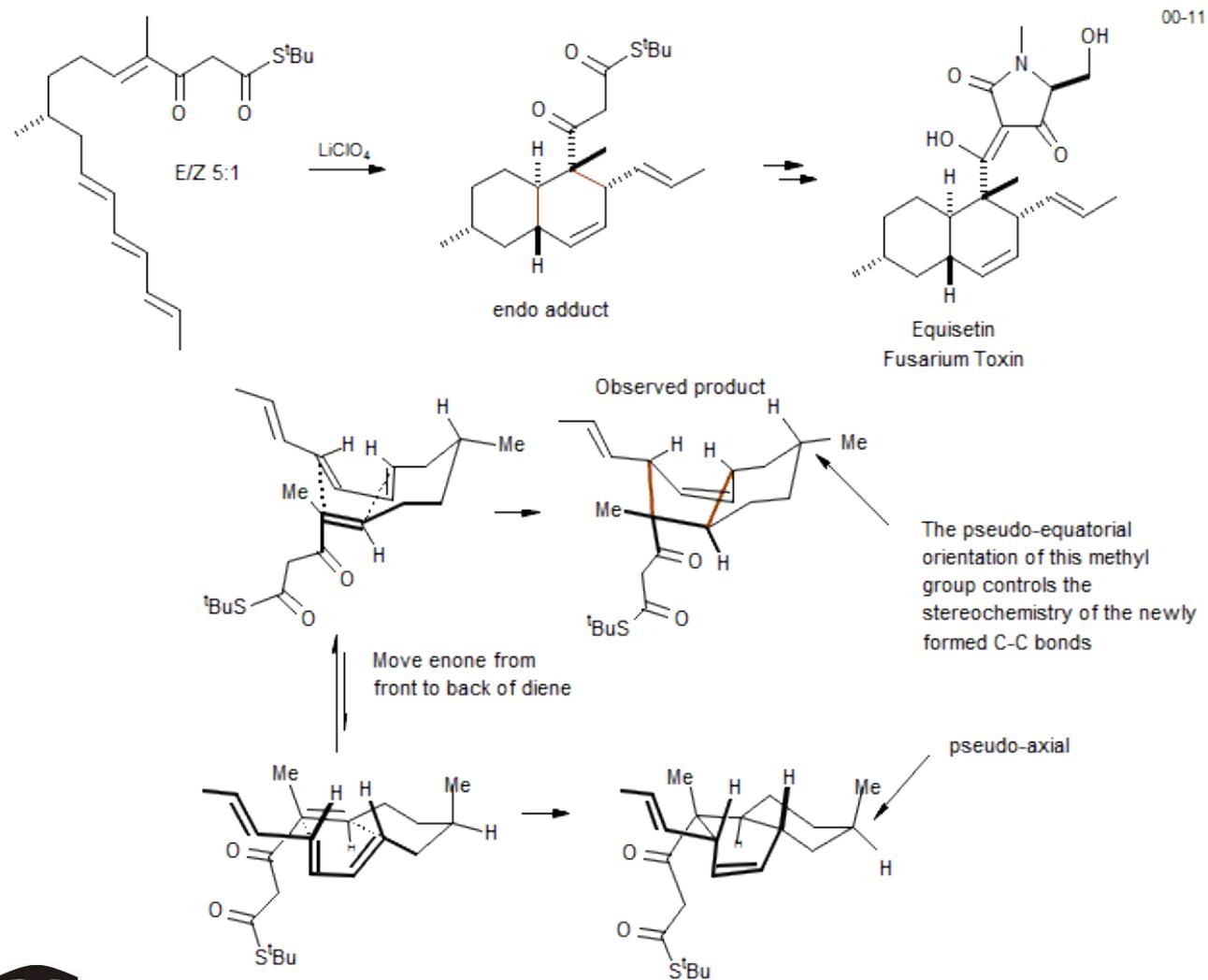
Mergott, D. J.; Frank, S. A.; Rousch, W. R. *Org. Lett.* **2002**, *4*, 3157



Intramolecular Diels-Alder Reactions

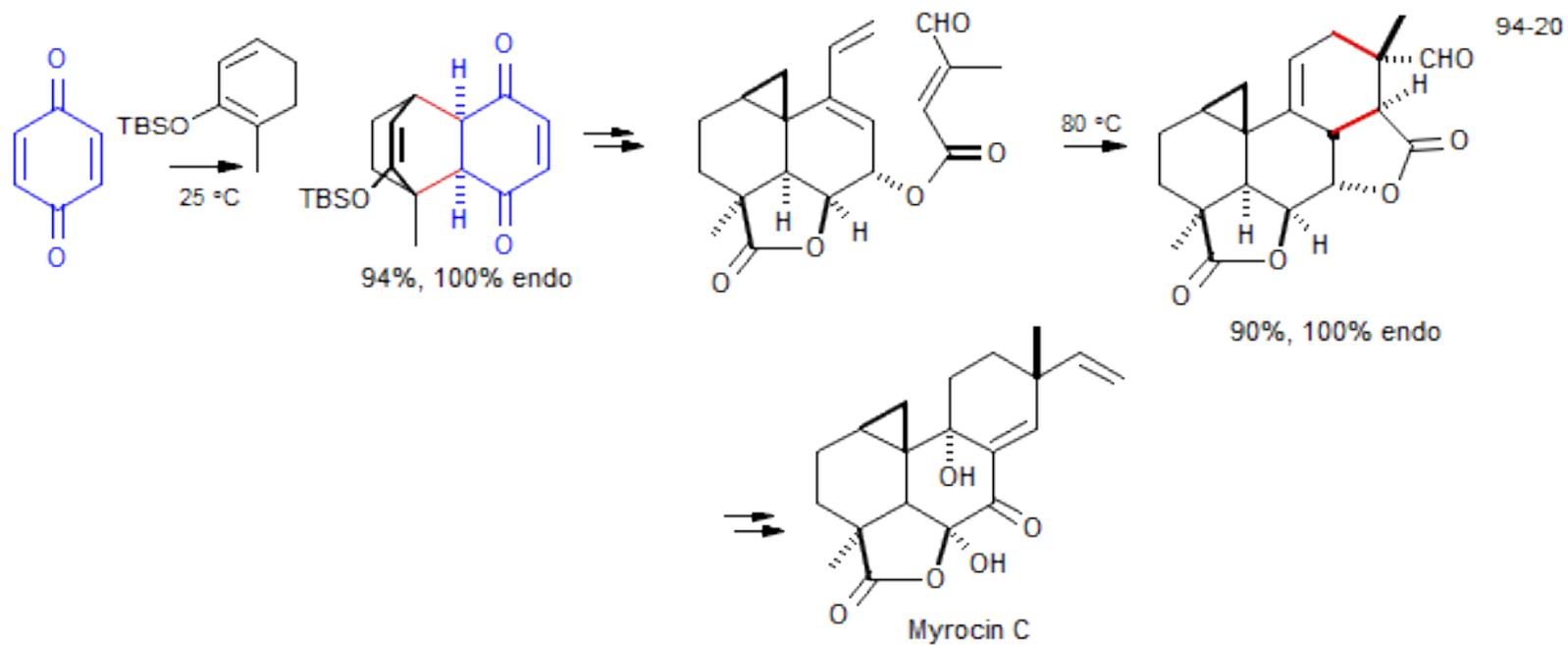
Equisetin

Burke, L T; Dixon, D J.; Ley, S. V.; Rodrigues, F. *Org. Lett.* **2000**, 2, 3611



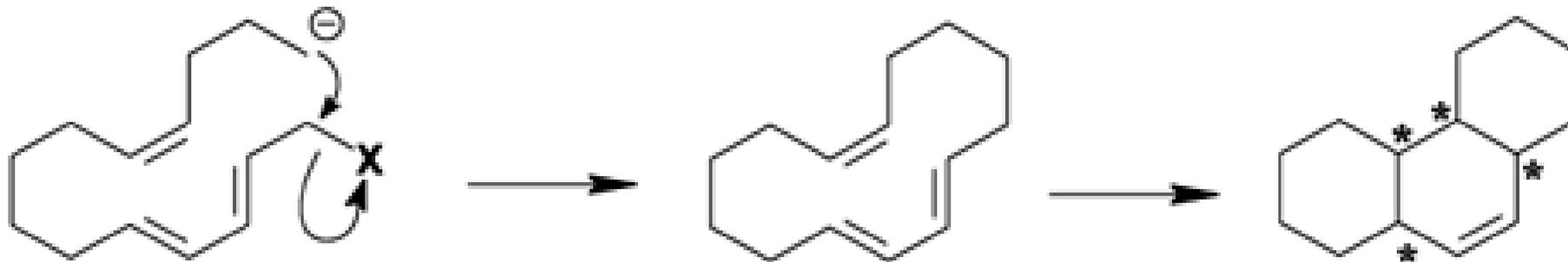
Myrocin C

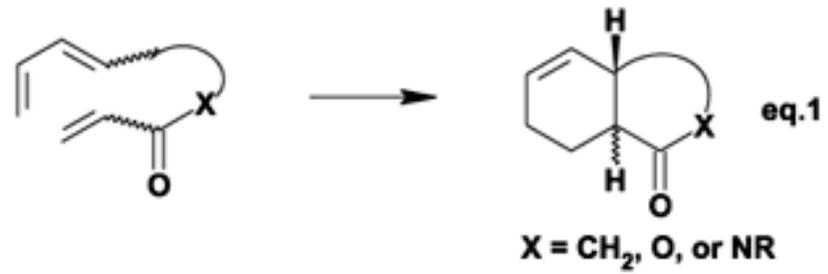
Chu-Moyer, Danishefsky, Schulte *J. Am. Chem. Soc.* **1994**, *116*, 11213



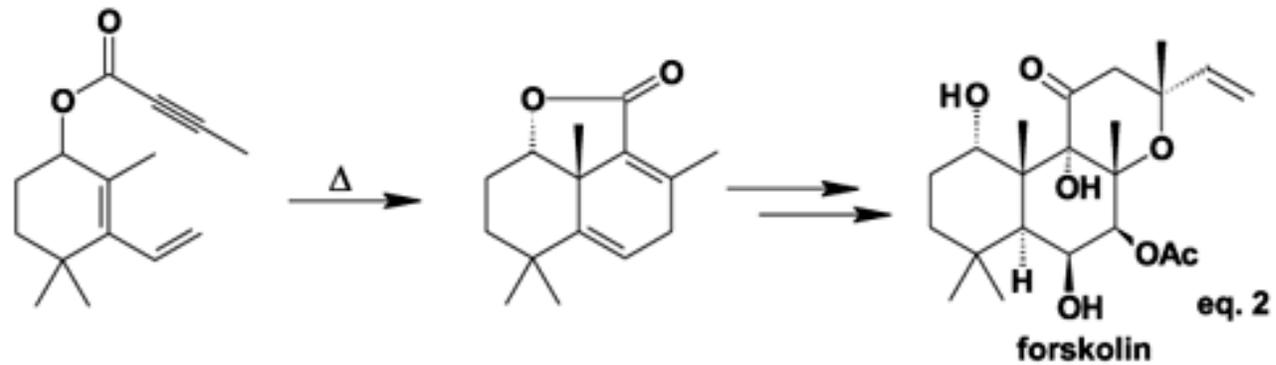
TRANSANNULAR DIELS-ALDER (TADA) REACTION

Deslongchamps, P. *Aldrichimica Acta* **1991**, *24*, 43-56.
Deslongchamps, P. *Pure & Appl. Chem.* **1992**, *64*, 1831-1847.



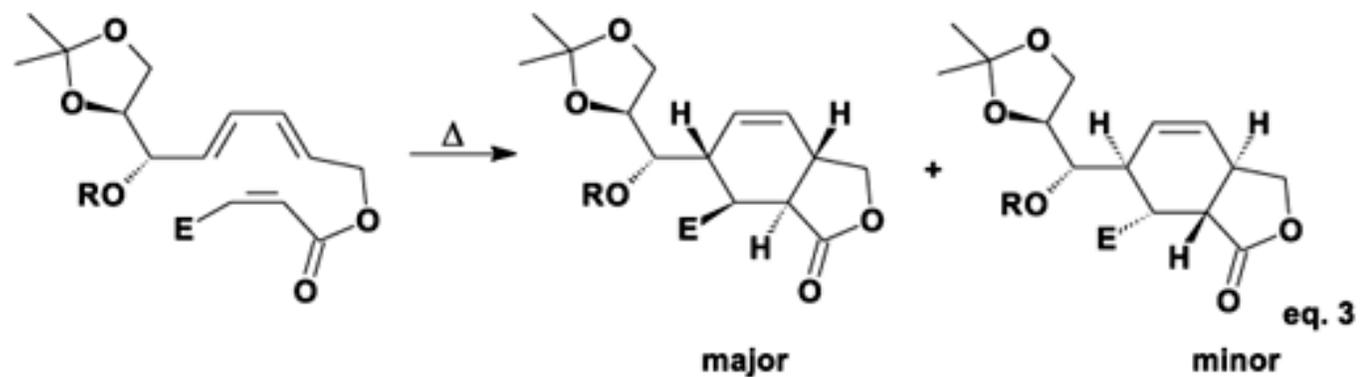


Delpech, B.; Calvo, D.; Lett, R. *Tetrahedron Lett.* **1996**, 37, 1015-1018.

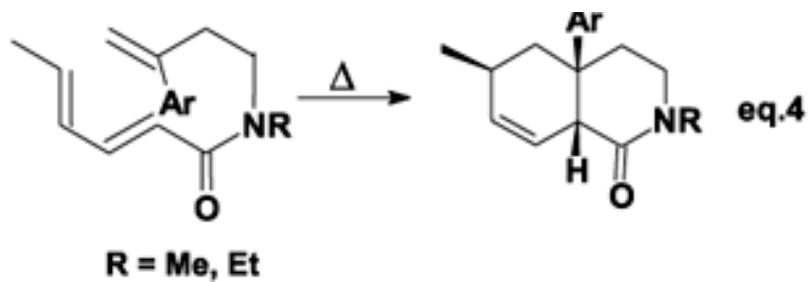


Lilly, M. J.; Sherburn, M. S. *Chem. Commun.* **1997**, 967-968.



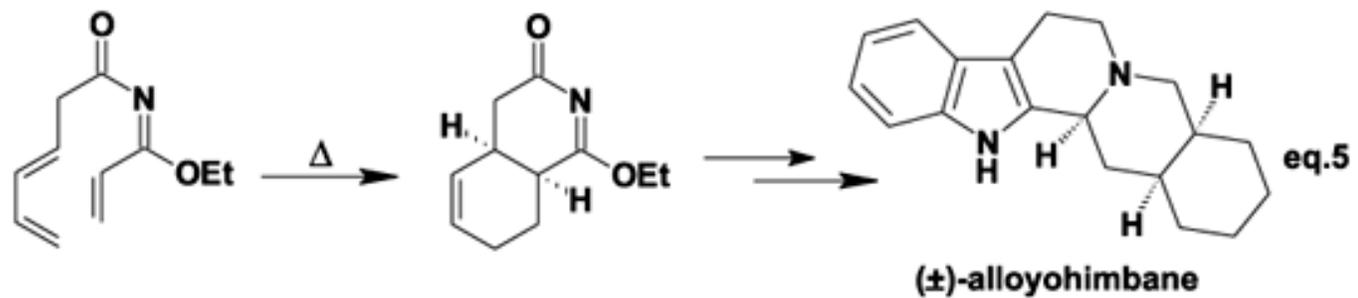


Lilly, M. J.; Sherburn, M. S. *Chem. Commun.* **1997**, 967-968.

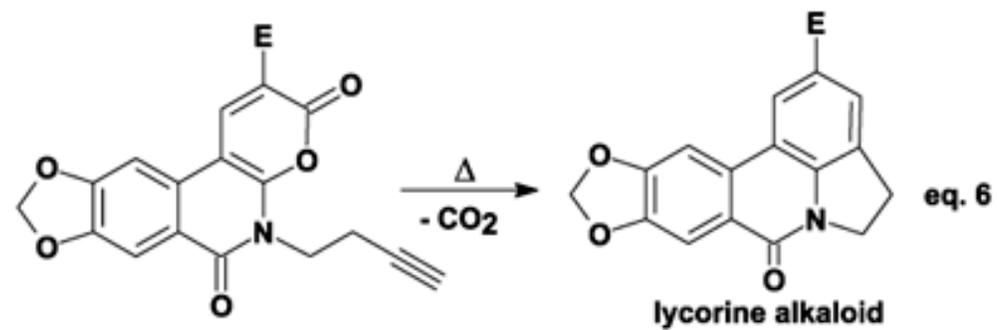


Handa, S.; Jones, K.; Newton, C. G. *J. Chem. Soc., Perkin Trans 1* **1995**, 1623-1633.



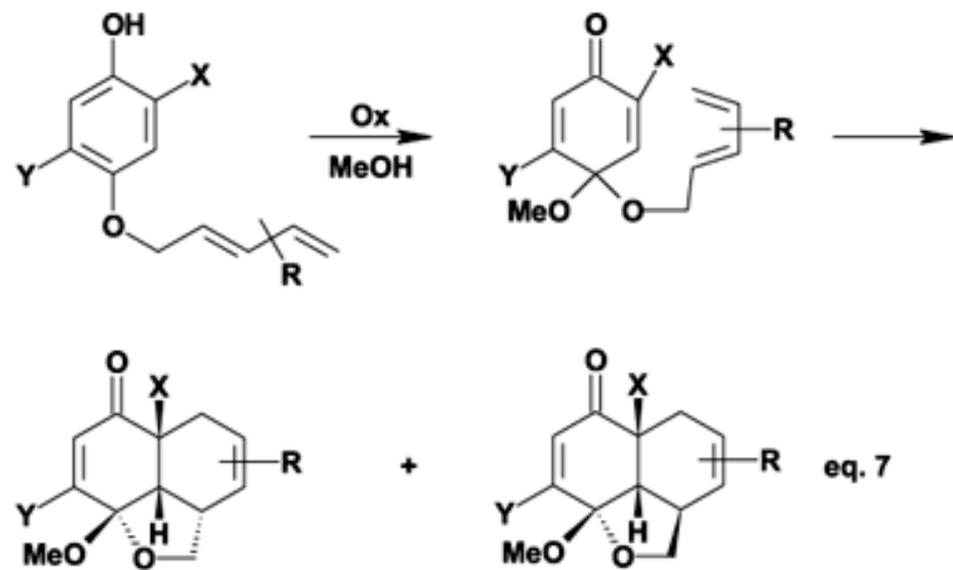


Sparks, S. M.; Shea, K. J. *Tetrahedron Lett.* **2000**, *41*, 6721-6724.



Pérez, D.; Burés, G.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1996**, *61*, 1650-1654.

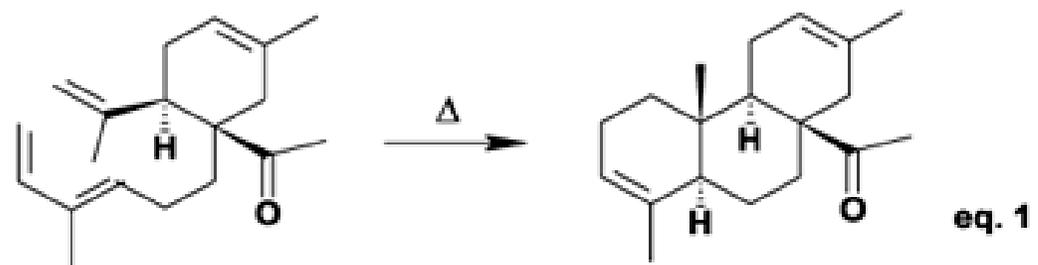




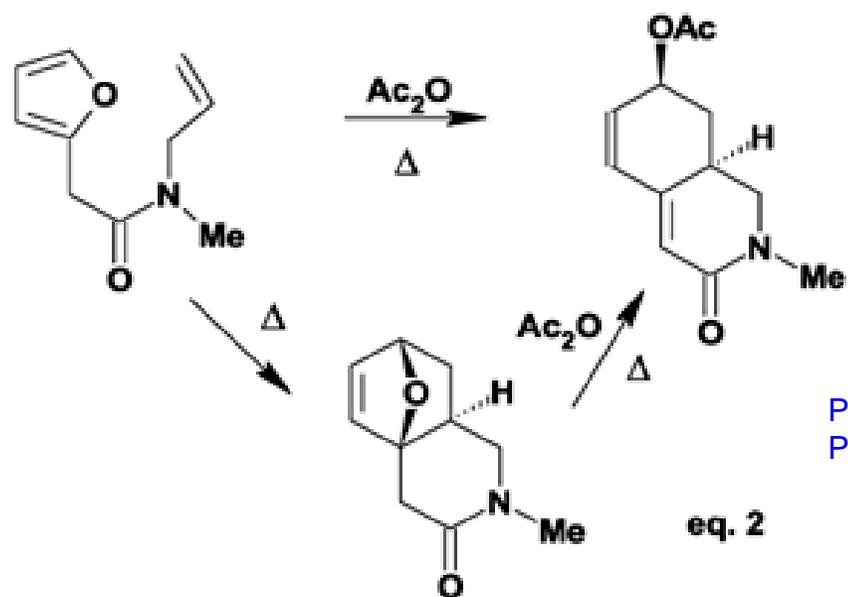
Tsai, Y-F.; Peddinti, R. K.; Liao, C-C. *Chem. Commun.* **2000**, 475-476;

Carlini, R.; Higgs, K.; Older, C.; Randhawa, S.; Rodrigo, R. *J. Org. Chem.* **1997**, 62, 2330-2331.





Abad, A.; Agulló, C.; Cuñat, A. C.; Navarro, I.; de Arellano, M. C. R. *Synlett* **2001**, 349-352.



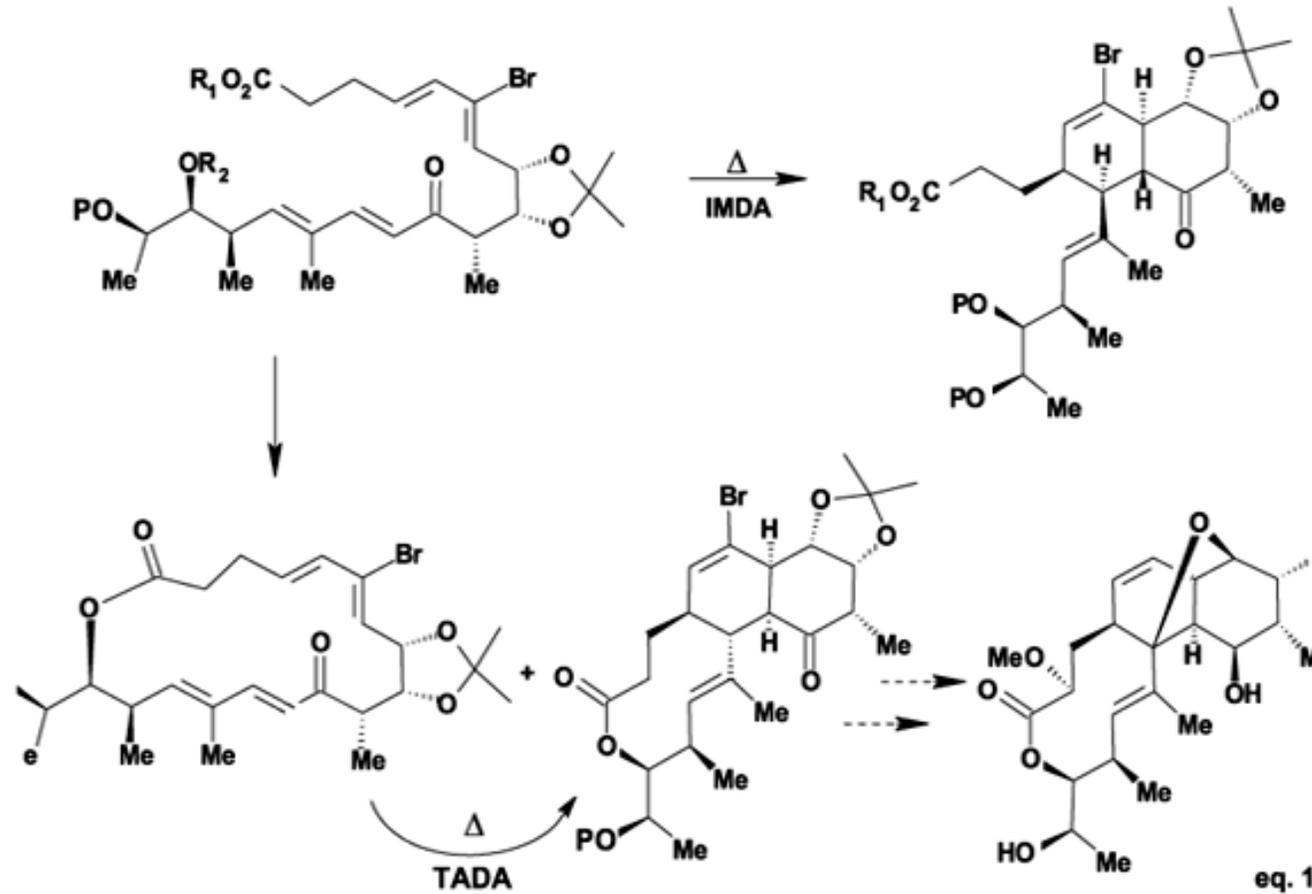
Padwa, A.; Reger, T. S. *Can. J. Chem.* **2000**, *78*, 749-756;
 Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, *66*, 3119-3128.

Scheme 4.



Síntesis de Nodusmicina

H. A. Whaley, C. G. Chidester, S. A. Mizsak, R. J. Wnuk, *Tetrahedron Lett.* **1980**, 21, 3659-3662.

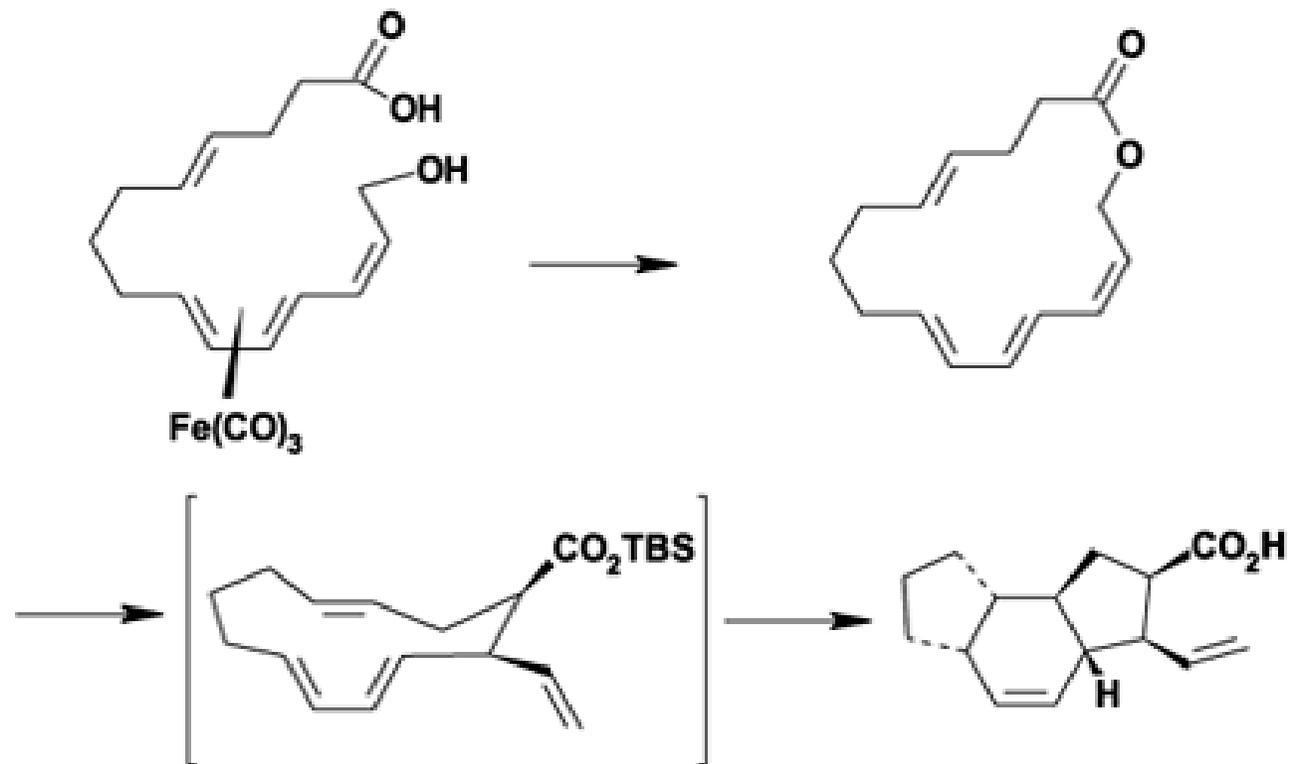


Nodusmicina



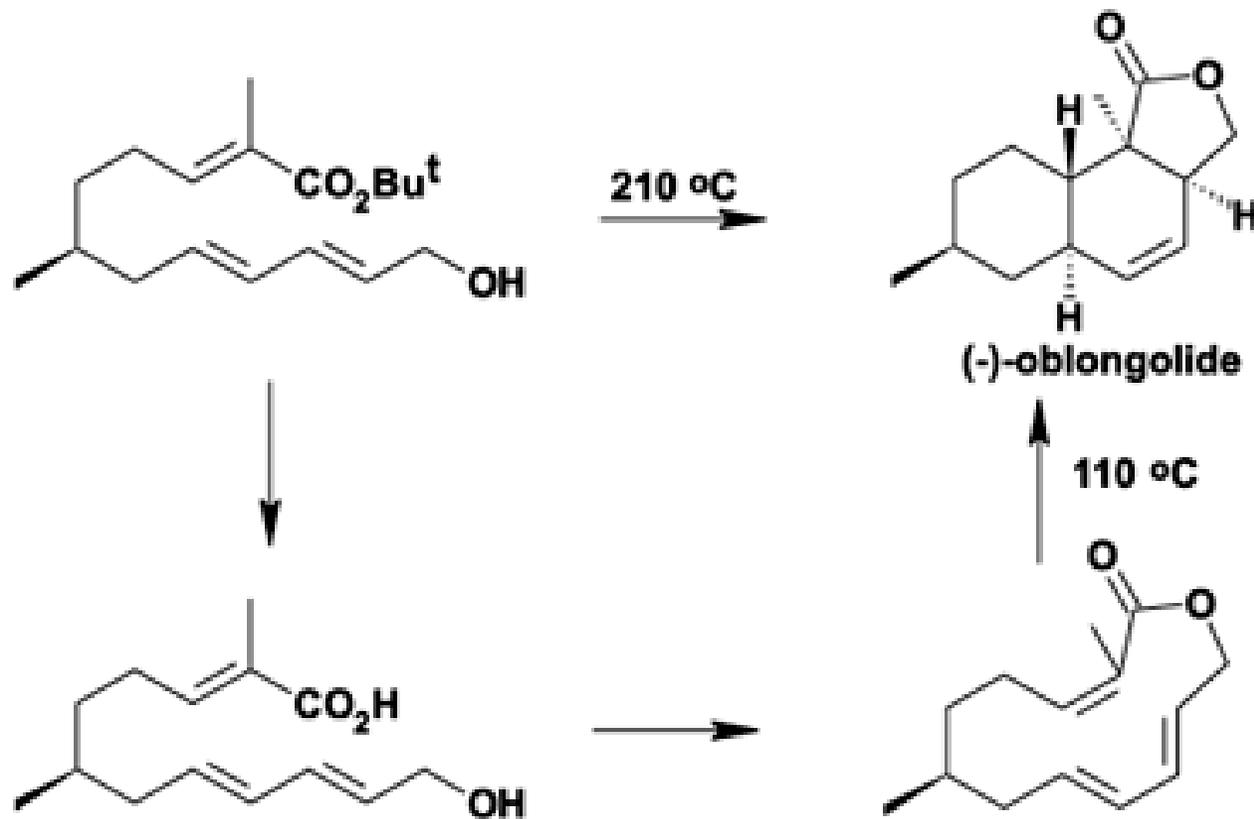
Transposición de Ireland-Claisen y contracción anular para formar un macrociclo ideal de 12 miembros a través de una reacción Diels-Alder transanular llevada a cabo *in situ*

Frank, S. A.; Works, A. B.; Roush, W. R. *Can J. Chem.* **2000**, *78*, 757-771.



Shing and Yang efectuaron la síntesis de (-)-oblongolido tanto por reacciones IMDA como por TADA

Shing, T. K. M.; Yang, J. J. *Org. Chem.* **1995**, *60*, 5785-5789.

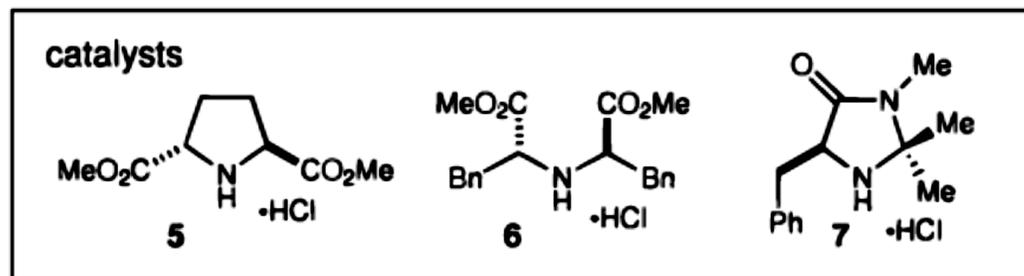
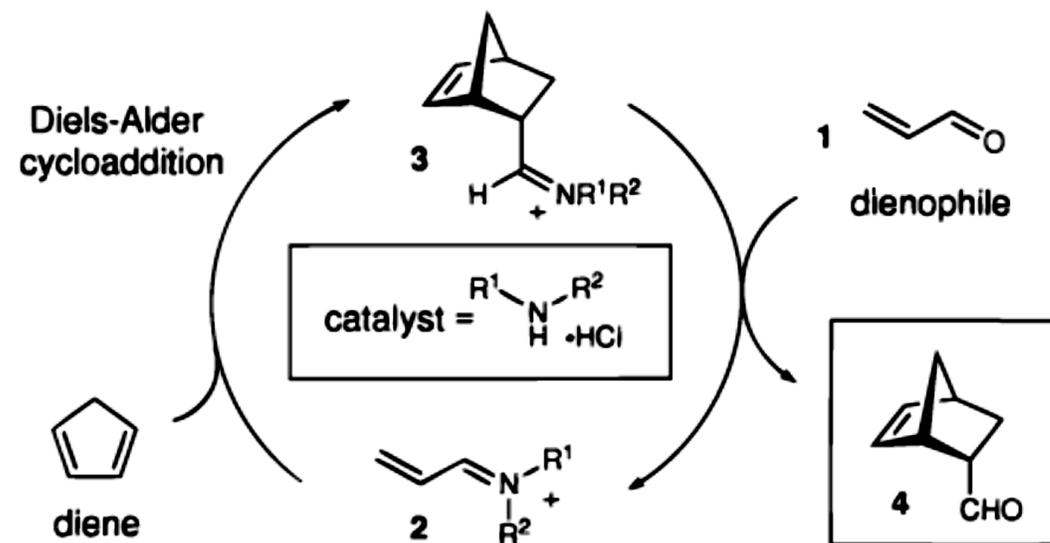
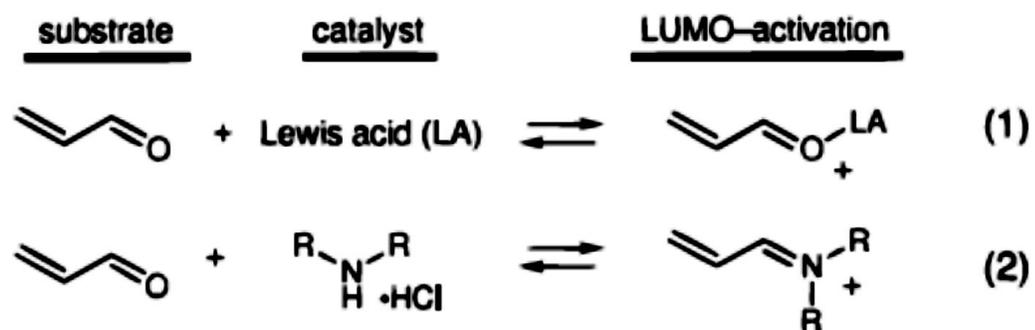


New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels–Alder Reaction

Kateri A. Ahrendt , Christopher J. Borths , and David W. C. MacMillan *

J. Am. Chem. Soc., 2000, 122 (17), pp 4243–4244

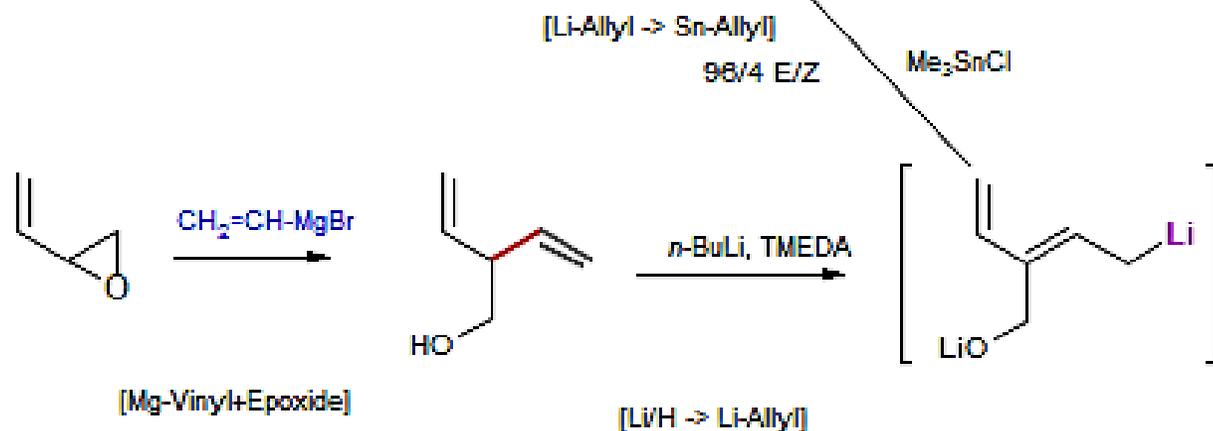
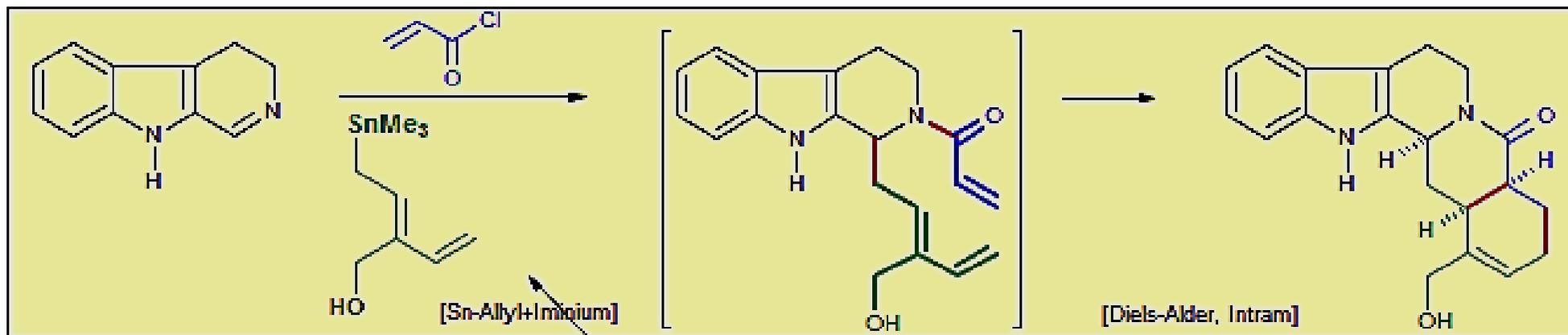
DOI: 10.1021/ja000092s



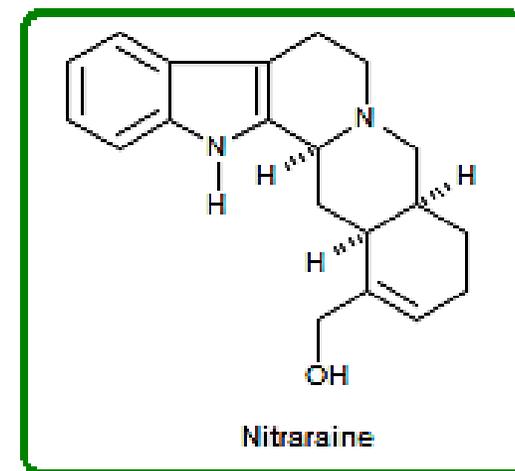
Nitrazine

93-18

Yamaguchi, R.; Hamasaki, T.; Sasaki, T.; Ohta, T. Utimoto, K.; Kozima, S.; Takaya, S. *J. Org. Chem.* 1993, 58, 1138.



1. Me_2BuSiCl
2. LiAlH_4 [CarboxAmide -> Amine]
3. $\text{Bu}_4\text{N}^+ \text{F}^-$



The Asymmetric Diels-Alder Reaction

Asymmetric Diels-Alder and Ene Reactions in Organic Synthesis,

Oppolzer, W. *Angew. Chem. Int. Ed.* **1984**, 23, 876.

Catalytic Asymmetric Diels-Alder Reactions,

Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, 92, 1007.

Reagent-Controlled Asymmetric Diels-Alder Reactions,

Oh, T.; Reilly, M. *Org. Prep. Proc. Int.* **1994**, 26, 129.

Diastereofacial Selectivity in the Diels-Alder Reaction,

Coxon, J. A.; McDonald D. Q.; Steel, P. J.

Advances in Detailed Reaction Mechanisms,

Vol. 3. James M. Coxon, Ed., Jai Press: Greenwich, CT 1994.

Chiral Heterosubstituted 1,3-Butadienes: Synthesis and [4 + 2] Cycloaddition Reactions,

Barluenga, J.; Su'arez-Sobrinio, A.; L'opez, L. A. *Aldrichimica Acta* **1999**, 32, 4-15.

Stereoelectronic Control in Diels-Alder Reaction of Dissymmetric 1,3-Dienes,

Mehta, G.; Uma, R. **2000**, 33, 278-86.

The Sulfinyl Group as a Chiral Inductor in Asymmetric Diels-Alder Reactions,

Ruano, J.L.G.; Carretero, J.C.; Carreno, M.C.; Cabrejas, L.M.M.; Urgano, A. *Pure Appl. Chem.* **1996**, 68, 925-30.

Chiral Sulfinylethenes as Efficient Dienophiles for Asymmetric Diels-Alder Reactions,

Arai, Y.; Koizumi, T. *Sulfur Reports*, **1993**, 15, 41-65.

Asymmetric [4+2] Cycloadditions Mediated by Sulfoxides,

Ruano, J. L. G.; De la Plata, B. C. *Top. Curr. Chem.* **1999**, 204, 1-126.

Catalytic Enantioselective Diels ± Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications

Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, 41, 1650-1667.

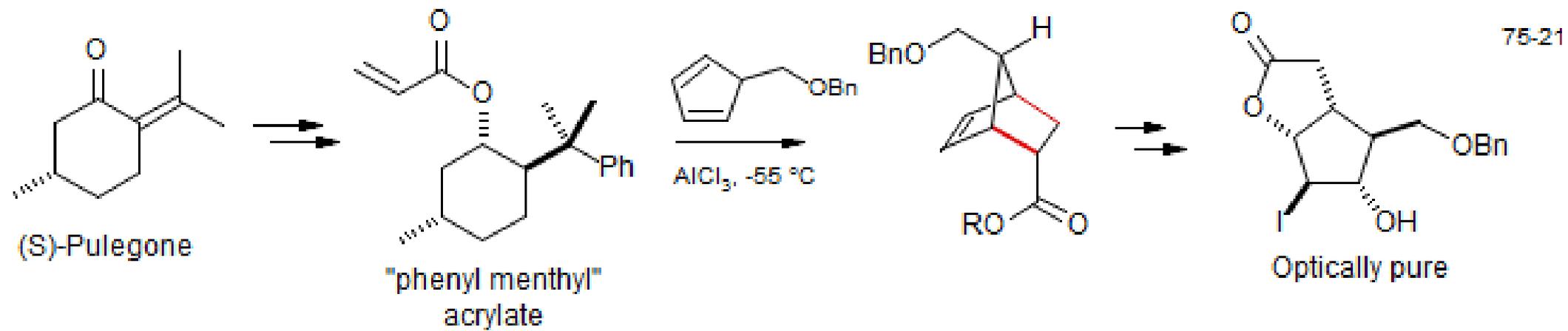
Chiral Auxiliaries in Cycloadditions,

Rück-Braun, K.; Kunz, H. Wiley: New York, 1999



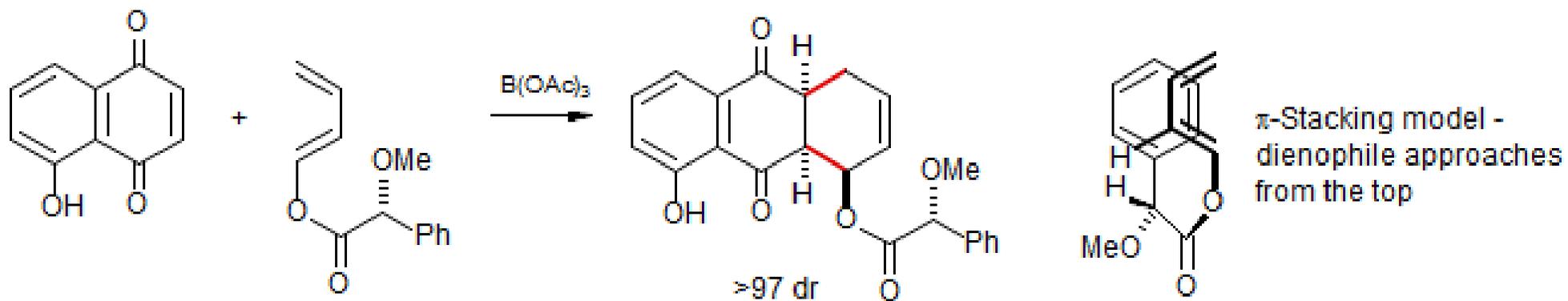
Diels-Alder Chiral Auxiliaries

Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.



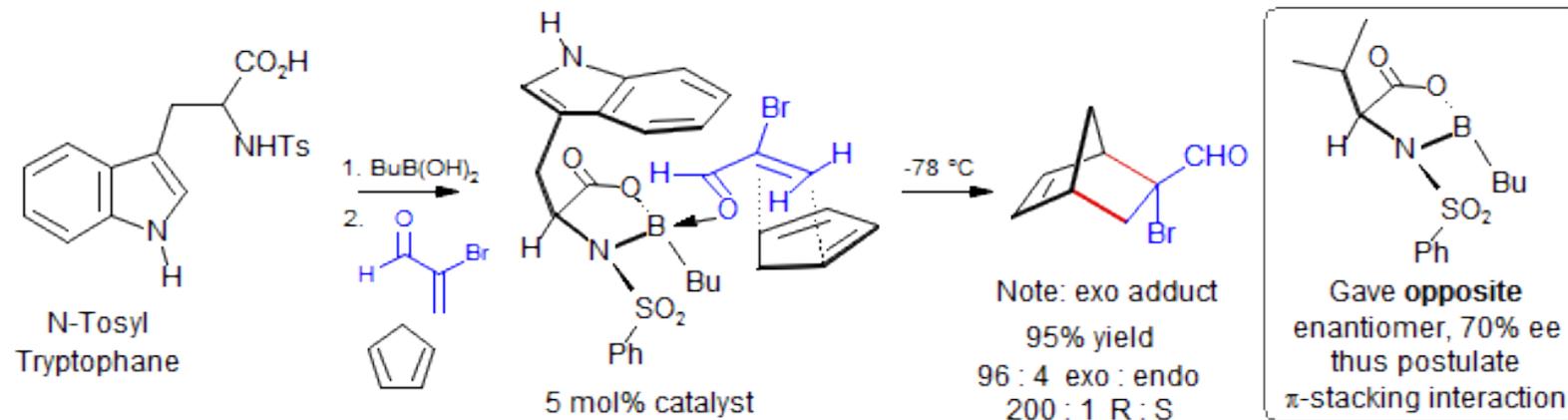
Diels-Alder Chiral Auxiliaries

Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.

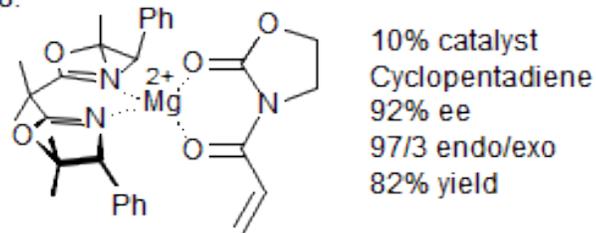


Asymmetric Catalysis in Diels Alder Reactions

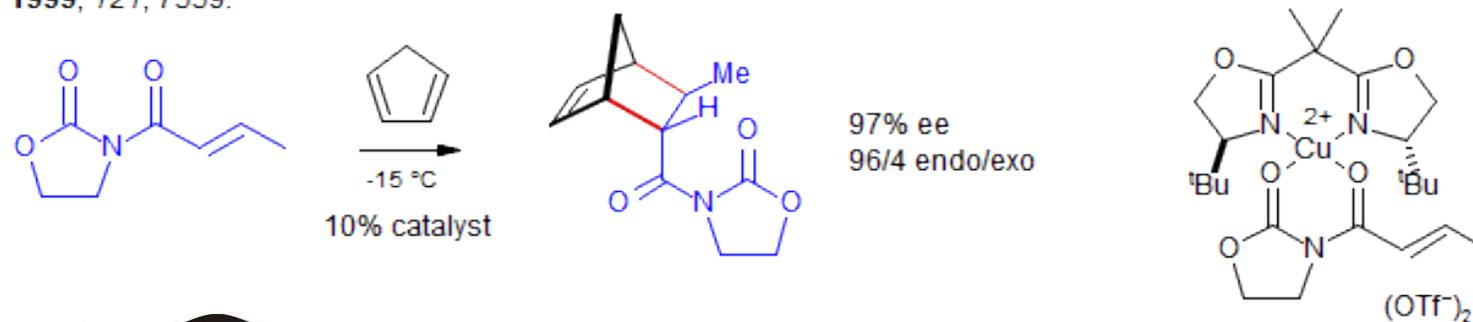
Corey, E. J.; Lo, T.-P. *J. Am. Chem. Soc.*, **1991**, *113*, 8966.



Magnesium complex: Corey, E. J.; Ishihara, K. *Tet. Lett.*, **1992**, *33*, 6807. Similar Fe complex: Corey, *JACS*, **1991**, *113*, 728.

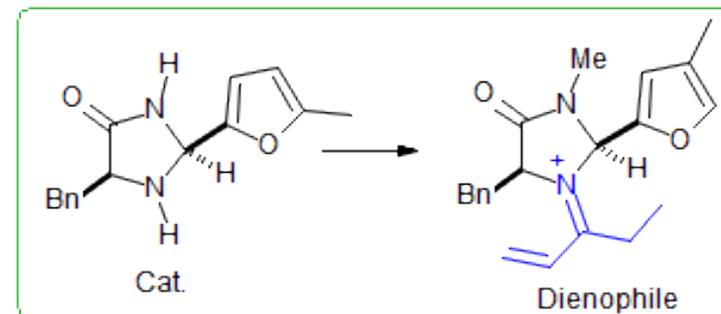
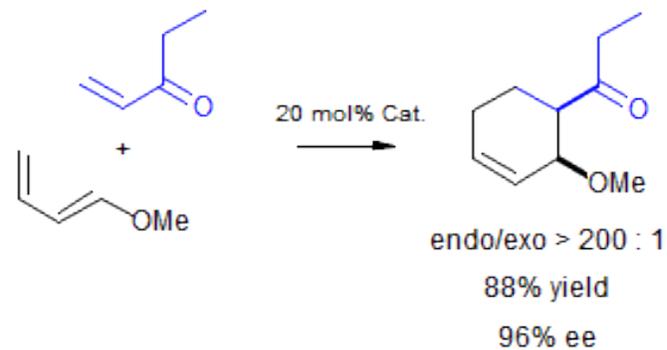


The cupric salts are square planar, and give the opposite enantiomer: Evans, Miller, Lectka, von Matt *J. Am. Chem. Soc.* **1999**, *121*, 7559.



Chiral Organocatalysis of Diels-Alder Reactions

Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.



- Methyl and isopropyl ketones as well as cyclopentenone and cyclohexenone worked poorly
- Variety of dienes worked well
- Reactions can be run in aqueous or ethanolic media

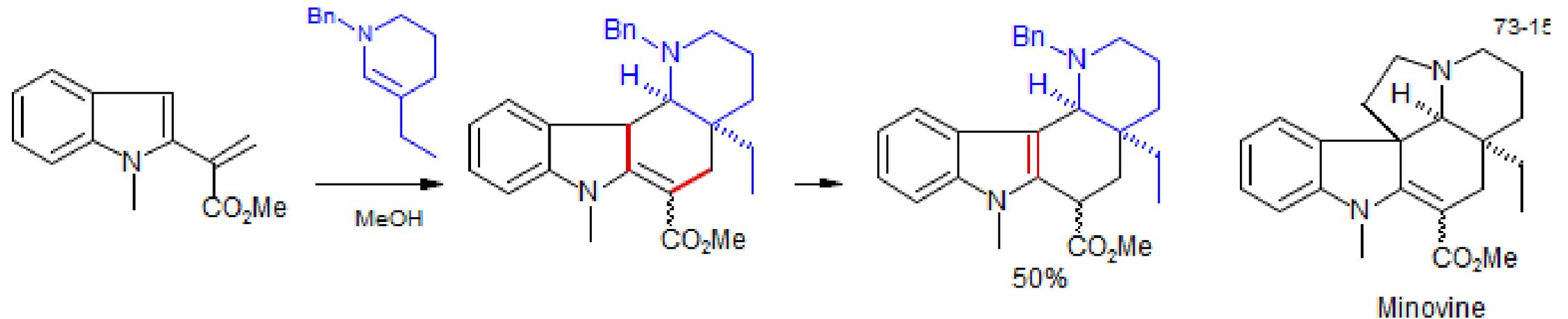


Inverse Electron Demand Diels-Alder Reactions

Recent Applications of the Inverse Electron Demand Diels-Alder Reaction,

D.L. Boger, M. Patel, "Progress in Heterocyclic Chem" Vol. 1, H. Suschitzky, Ed. Pergamon Press (1989).

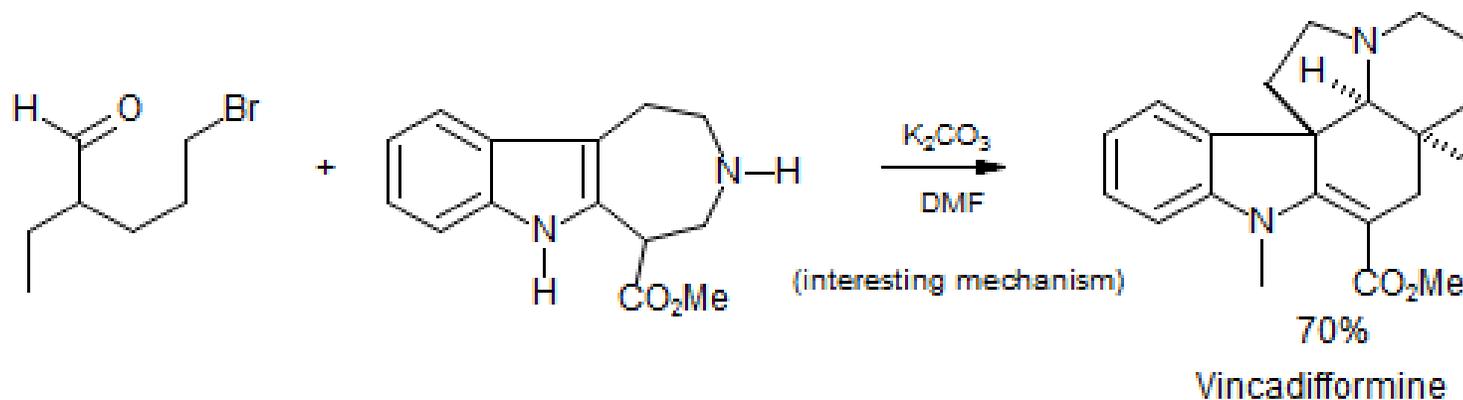
Minovine: Ziegler, F. E.; Spitzner, E. B.. *J. Am. Chem. Soc.* **1973**, *95*, 7146



Inverse Electron Demand Diels-Alder Reactions

Vincadiformine

Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705



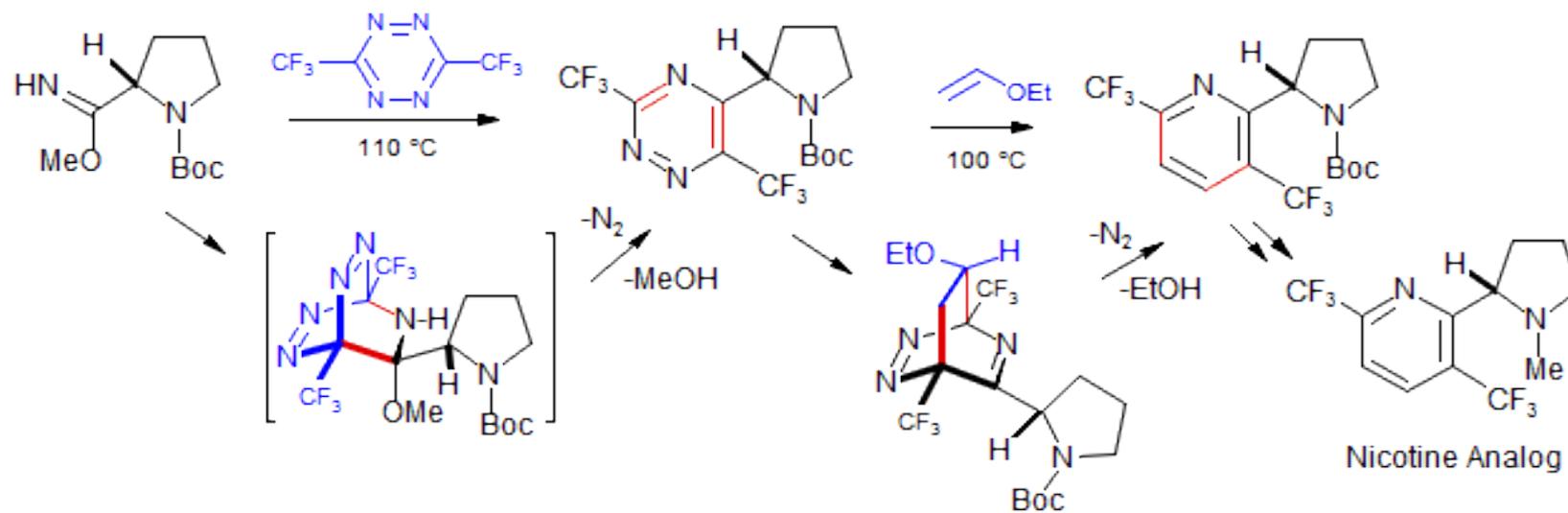
78-41



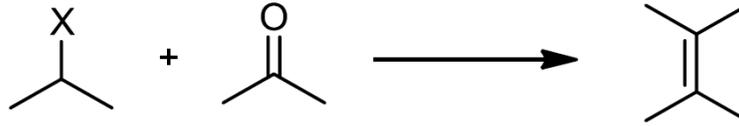
Inverse Electron Demand Diels-Alder Reactions

Synthesis of a nicotine analog

Che, Siegl, Seitz *Tetrahedron Assym.* **1999**, 573.



REACCIONES DE OLEFINACIÓN



- Reacción de Wittig (**Iluros de fósforo**)
- Reacción de Horner-Wadsworth-Emmons (**Fosfonatos**)
- Olefinación de Peterson (**Silanos**)
- Olefinación Julia-Lythgoe (**Sulfonas**)
- Acoplamiento de McMurry (**Complejos de titanio**)
- Olefinación de Takai (**Complejos de cromo**)
- Olefinación de Petasis-Tebbe (**Complejos de carbeno**)



Georg Wittig

(1897 – 1987)

Químico alemán

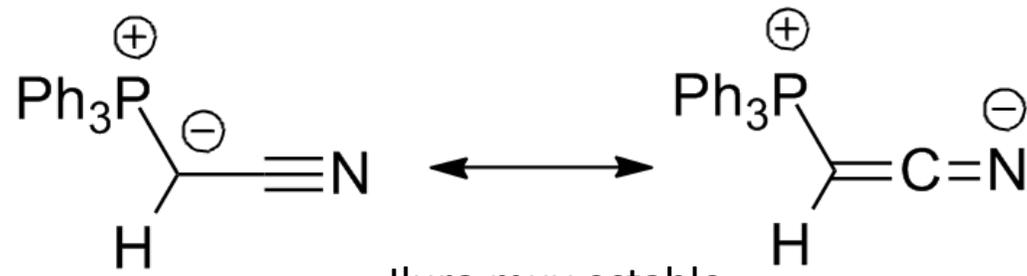
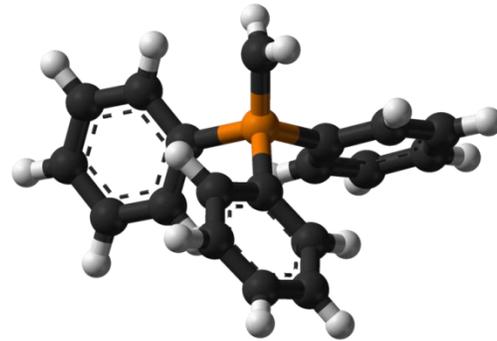
Reacción de Wittig





Fosforano (ilido)

iluro

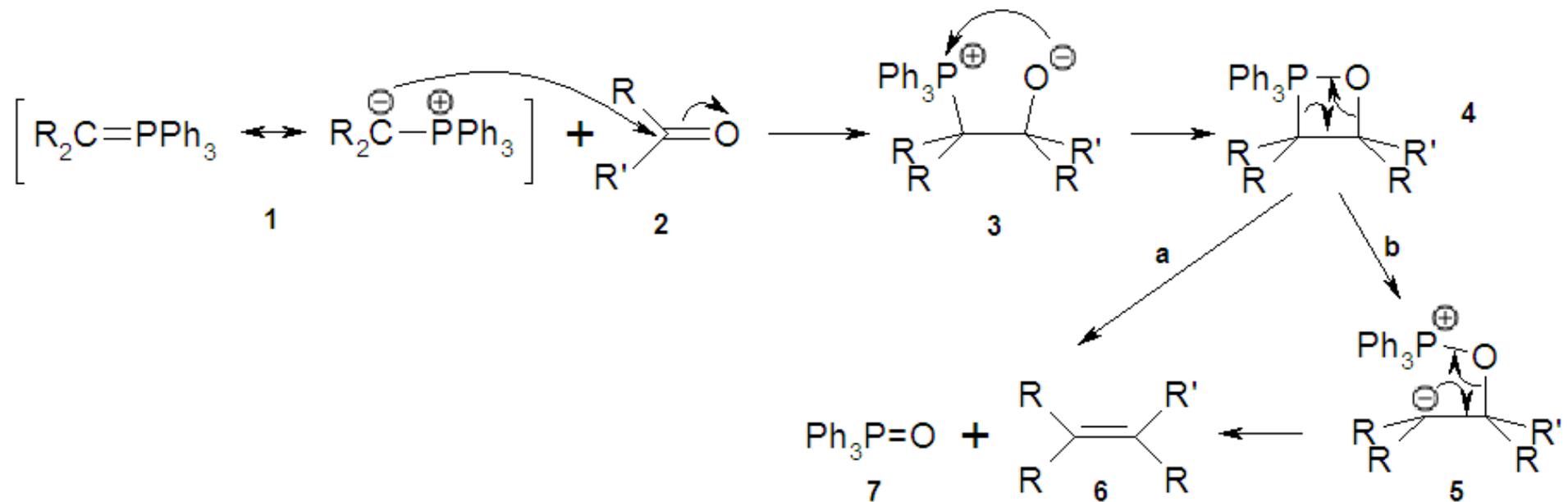


Iluro muy estable

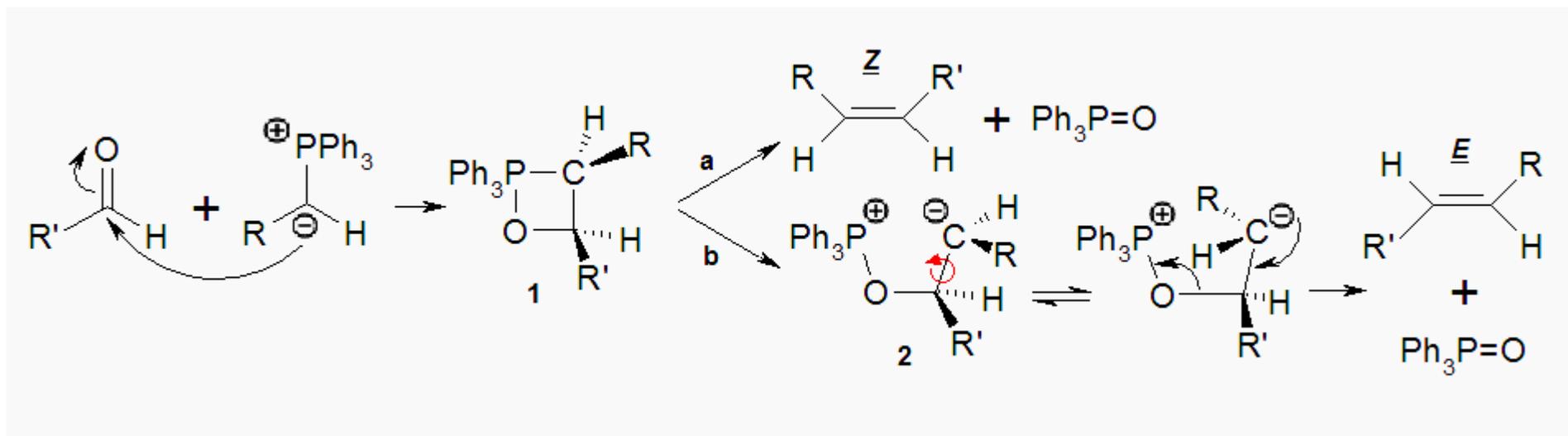
Iluro estabilizado \Rightarrow Alqueno *trans* o *E*

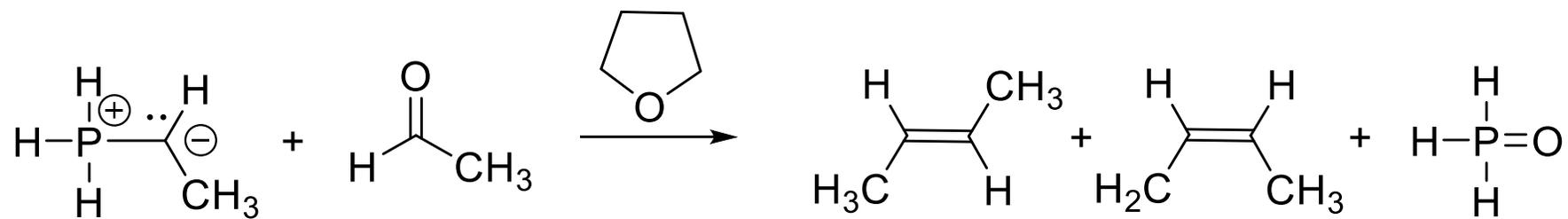
Iluro no estabilizado \Rightarrow Alqueno *cis* o *Z*

Mecanismo



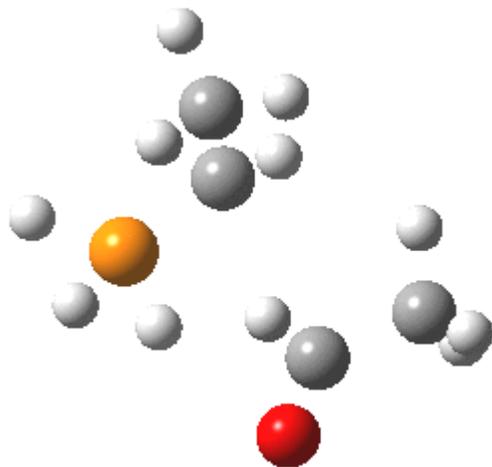
Explicación de la estereoselectividad



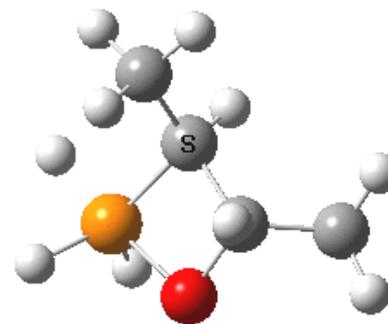


ALQUENO Z

TS1 = 0.0 Kcal/mol

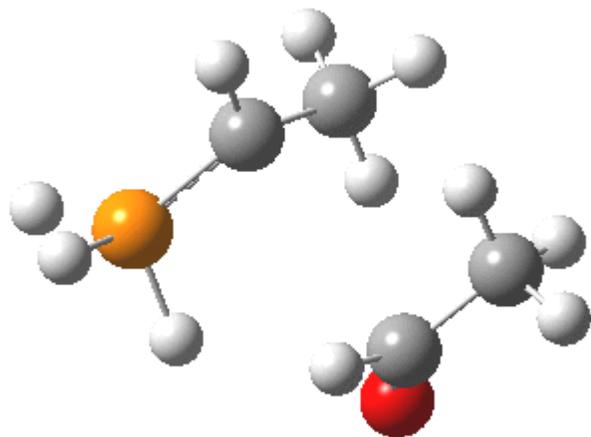


TS2 = -3.9 Kcal/mol

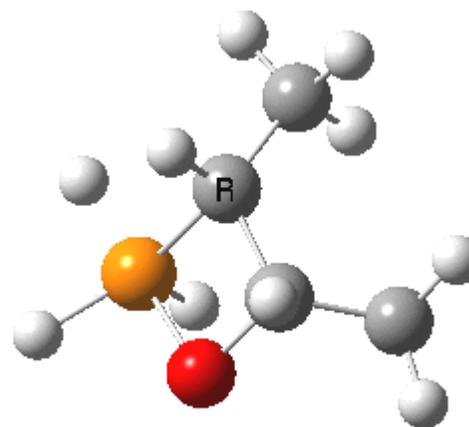


ALQUENO E

TS1 = 0.0 Kcal/mol

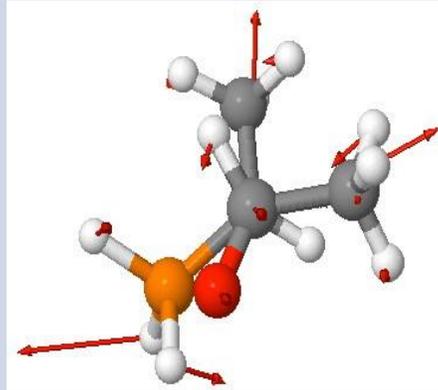


TS2 = -2.6 Kcal/mol



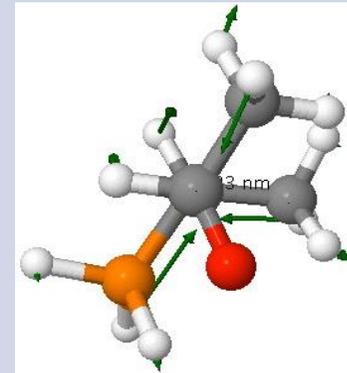
TS1 es mayor en los dos casos y es el paso determinante de la rapidez

Formación del alqueno-*E*



Formación del alqueno-*Z*

Enlaces antiperiplanar

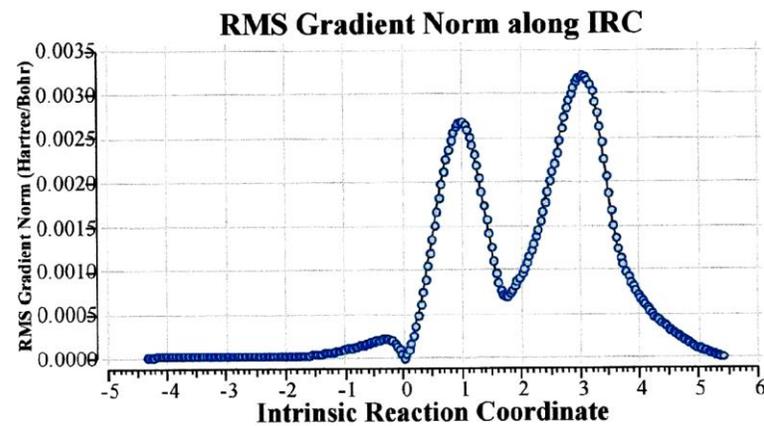


El incremento en la tensión estérica viene después del estado de transición, debido a los metilos del isómero-*Z*

Formación alqueno-*E*

17/4/2015

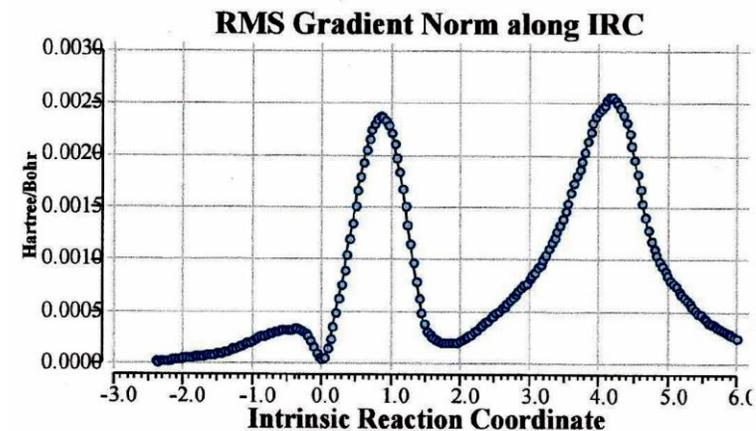
www.ch.imperial.ac.uk/rzepa/blog/wp-content/uploads/2012/08/Wittig-TS1-artig.svg



Formación alqueno-*Z*

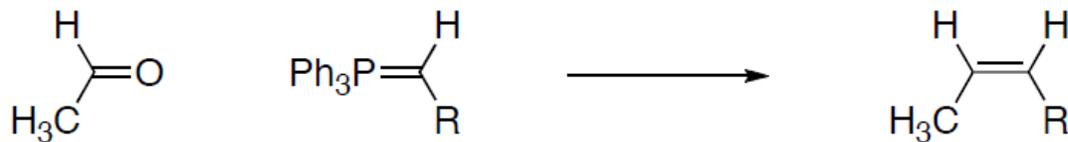
17/4/2015

www.ch.imperial.ac.uk/rzepa/blog/wp-content/uploads/2012/08/Wittig-TS1-syng.svg



Coordenada de reacción intrínseca (IRC)

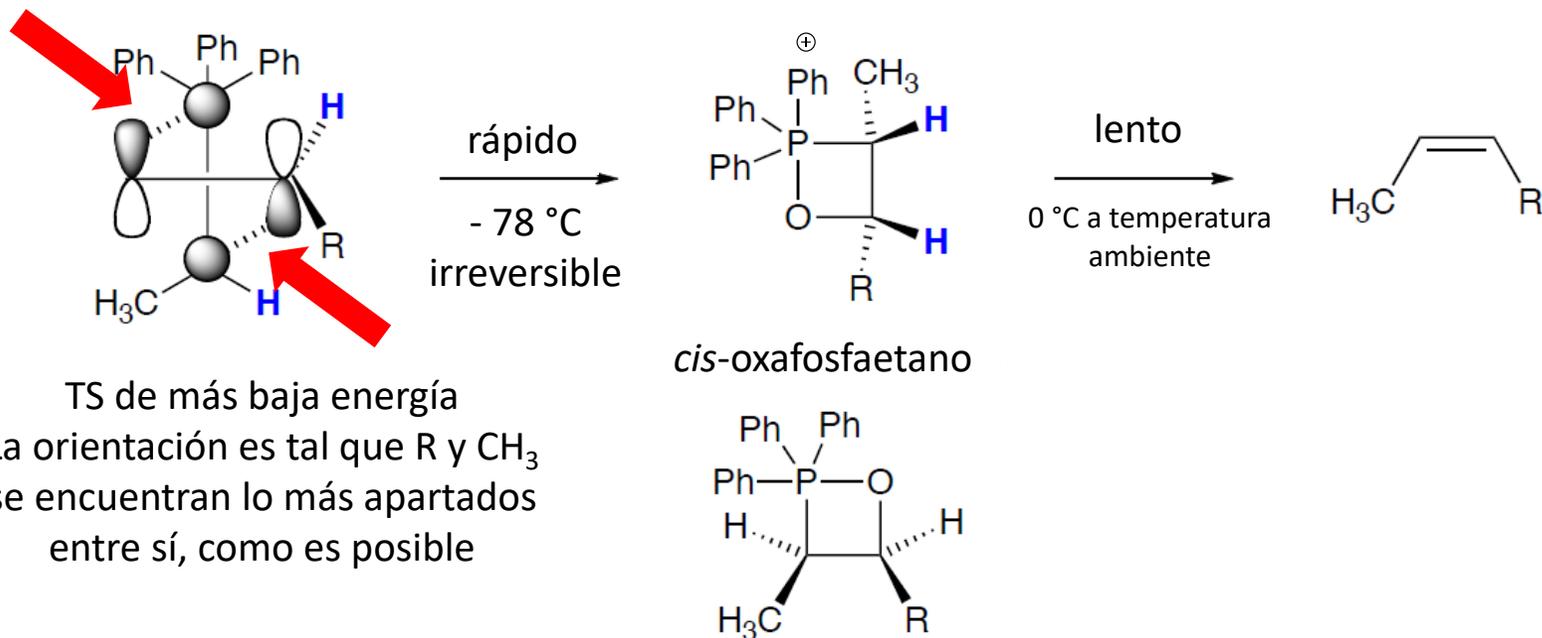
Los gradientes del perfil de IRC para este paso de la reacción de Wittig revelan que gran parte de la acción se produce después de que se pasa el estado de transición TS1, en el IRC = 3 para el alqueno-*E* y IRC = 4 para el alqueno-*Z*, esto comprende la rotación alrededor del enlace C-C para formar el enlace P-O. Aquí es donde el choque estérico de los metilos para el isómero *Z* realmente entra en acción, pero no tiene ningún impacto sobre la energía del estado de transición, ya que demasiado tarde



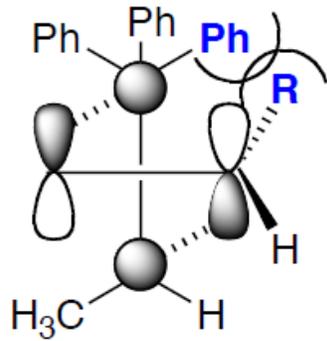
- Reacción de metátesis
- Predominan los productos cis (>90%)
- Conforme R sea más grande se incrementa el producto cis

Mecanismo aceptado:
Cicloadición
 $\pi^2a + \pi^2s$
Antarafacial Suprafacial

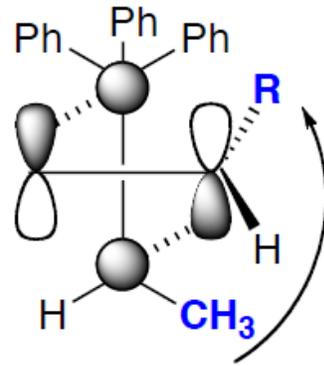
J. Am. Chem. Soc. **1973**, *95*, 5778.



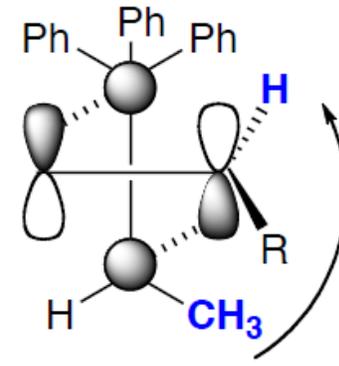
Hay otros estados de transición [2 +2] alternativos



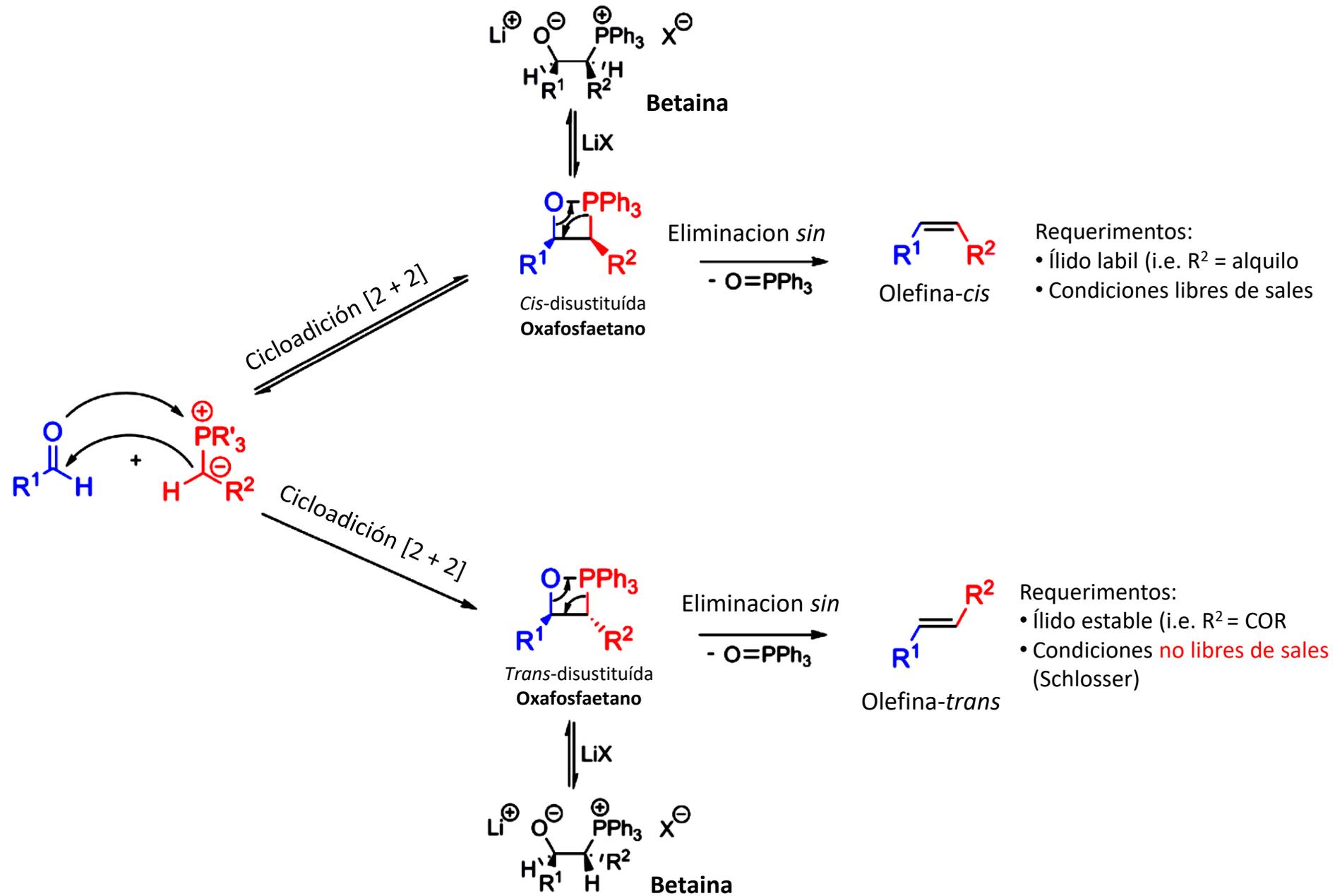
Interacción estérica entre
R y Ph



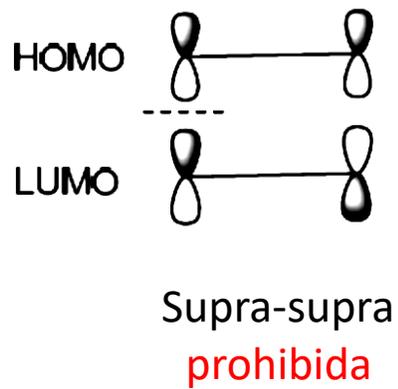
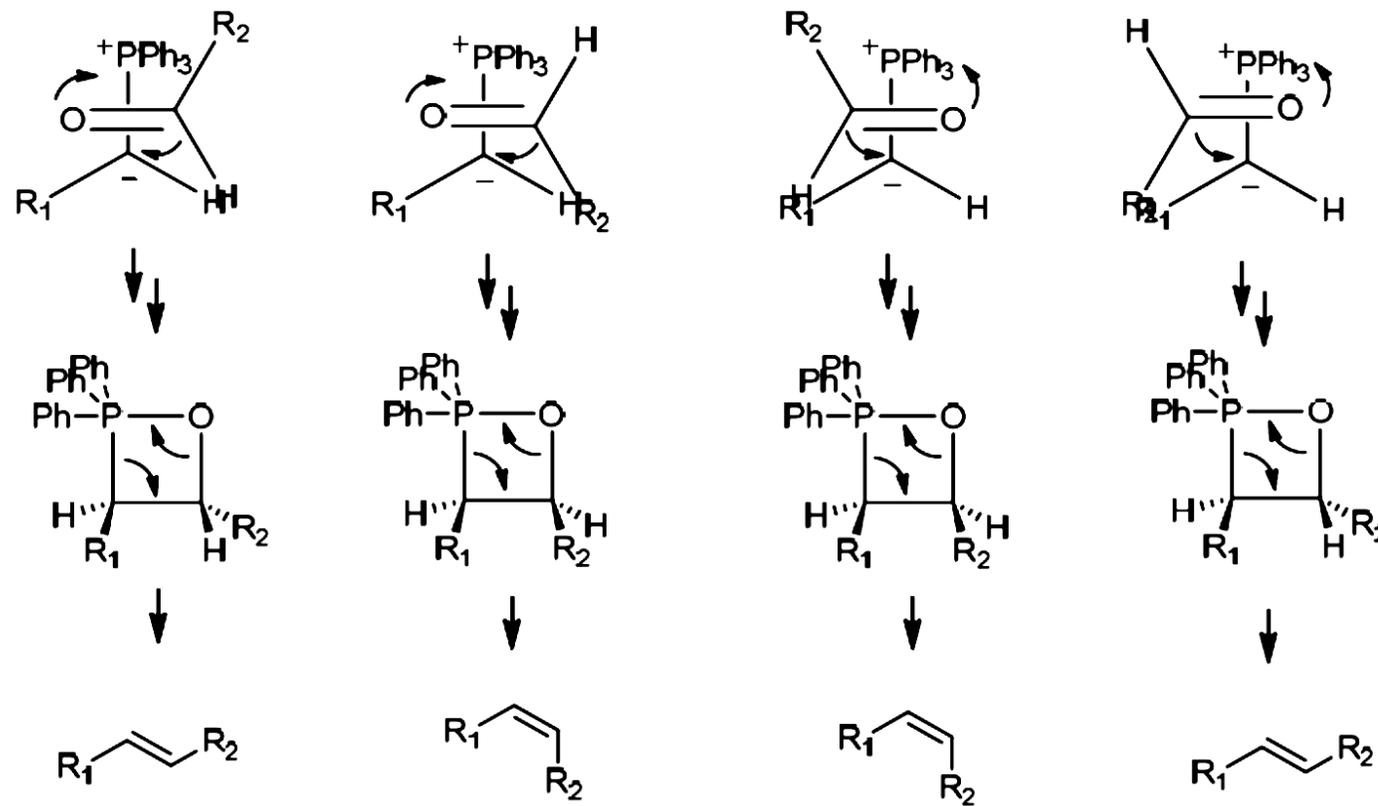
No hay interacción
estérica entre R y CH₃

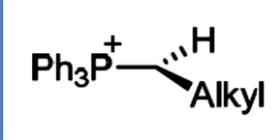
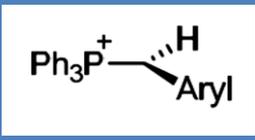
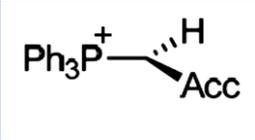


Interacción estérica entre
H y CH₃
Puede dar lugar a
producto *trans*

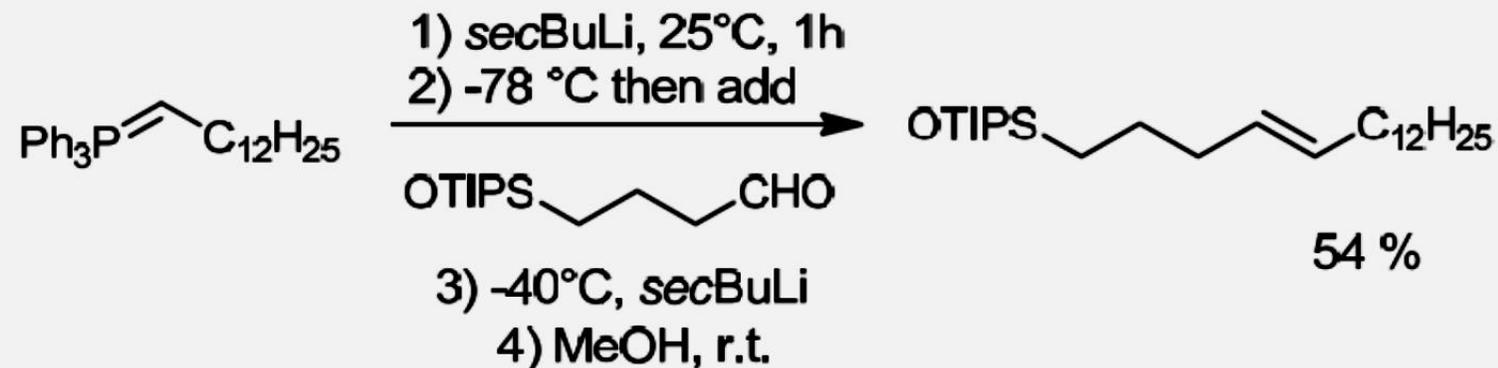
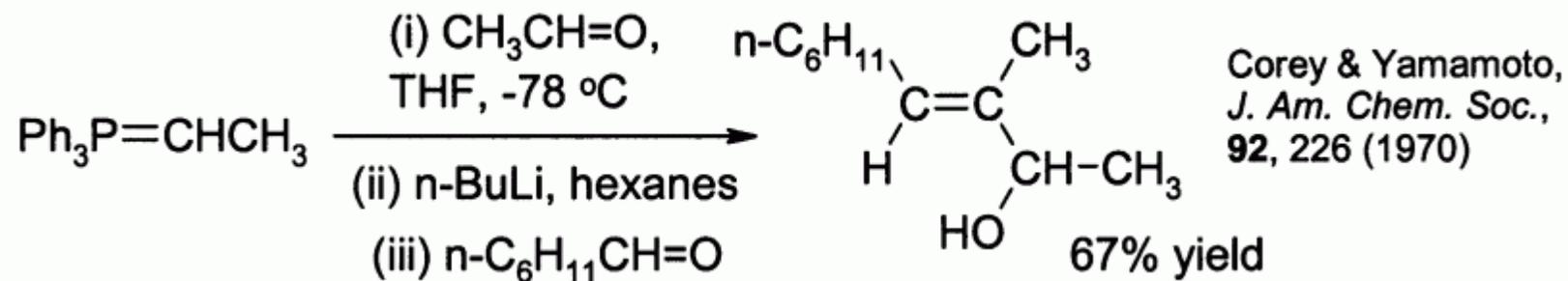


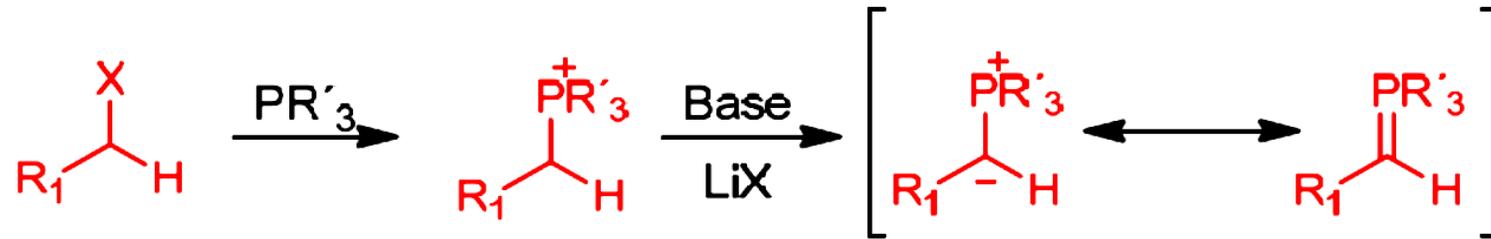
ESTEREOQUÍMICA



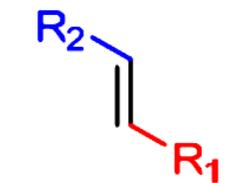
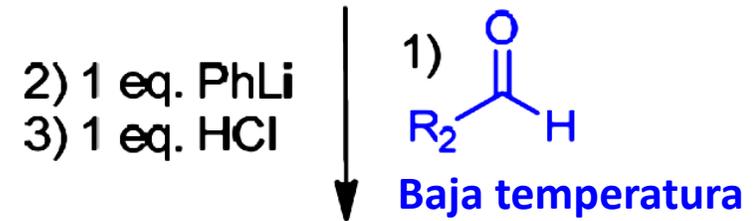
				
Estereoquímica:		Iluro lábil	Iluro semiestable	Iluro estable
1. El producto cis es el favorecido debido al impedimento estérico durante el ataque del iluro al carbonilo	Preparación	<i>in situ</i>	<i>in situ</i>	Se aísla
2. Los disolventes no polares y las condiciones libres de sales induce la formación de la olefina-Z debido a la desestabilización de las betaínas	Base empleada	<i>n</i> -BuLi NaNH ₂ <i>t</i> -BuOK	EtONa NaOH _(acuoso)	NaOH
3. Al incrementar la estabilidad del iluro, la proporción de la olefina- <i>E</i> se incrementa	Selectividad	<i>Cis</i> (≥ 90%)	<i>Trans</i> (≥ 90%)	<i>Trans</i> (≥ 90%)

MODIFICACIÓN DE SCHLOSSER

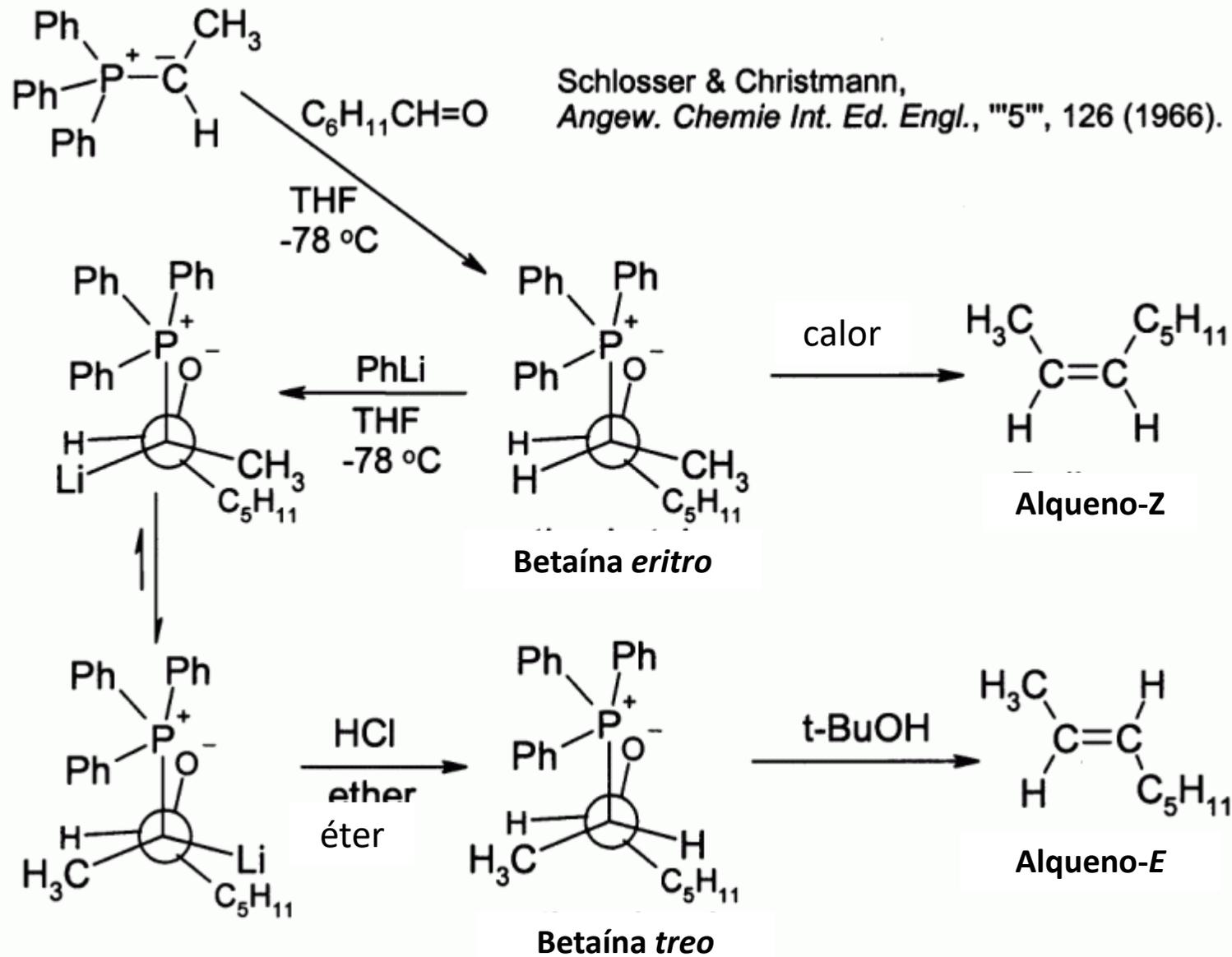




X: Cl, Br, I, OTs

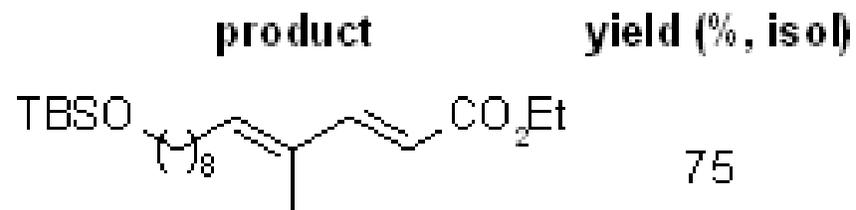
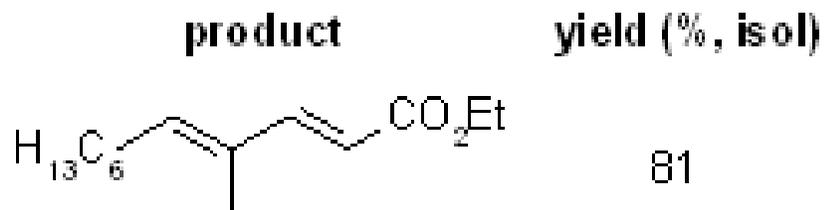
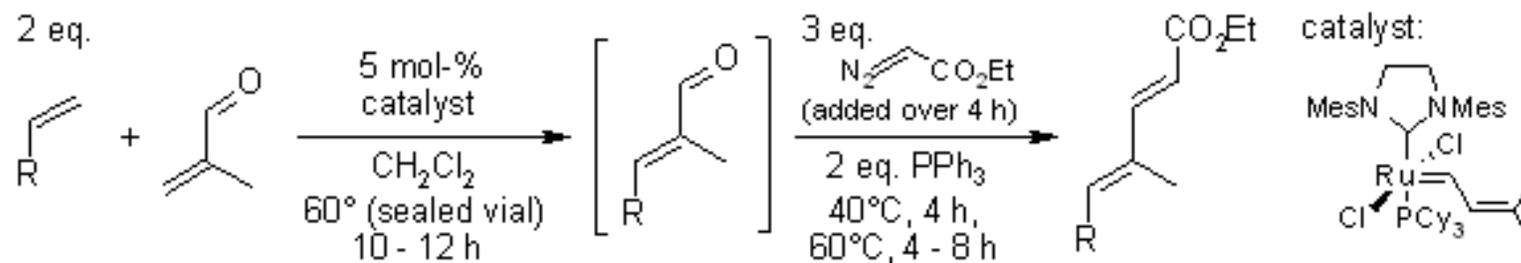


Producto E



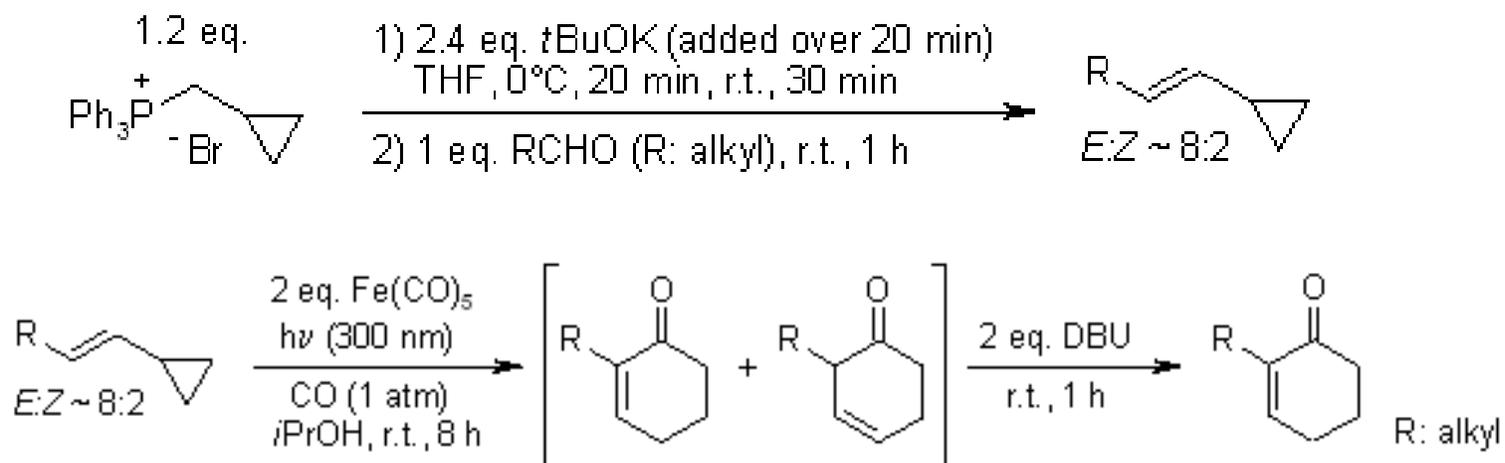
Ruthenium-Catalyzed Tandem Cross-Metathesis/Wittig Olefination: Generation of Conjugated Dienoic Esters from Terminal Olefins

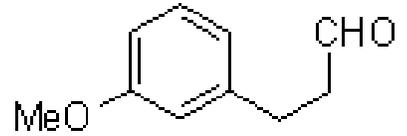
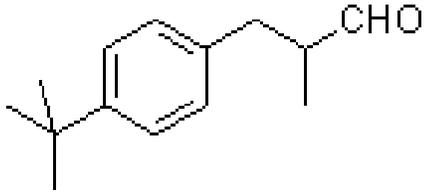
R. P. Murelli, M. L. Snapper, *Org. Lett.*, **2007**, *9*, 1749-1752.



A THREE-STEP ROUTE TO A TRICYCLIC STEROID PRECURSOR

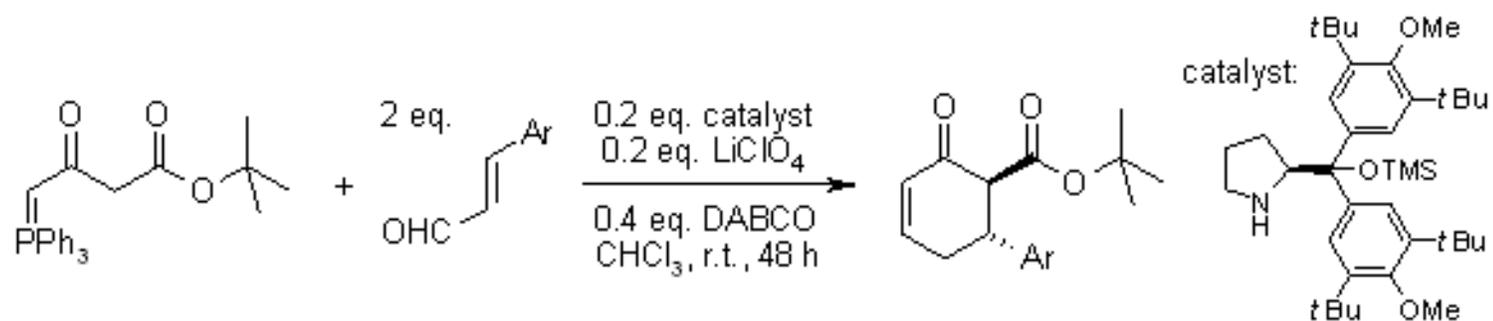
D. F. Taber, R. B. Sheth, *J. Org. Chem.*, **2008**, *73*, 8030-8032



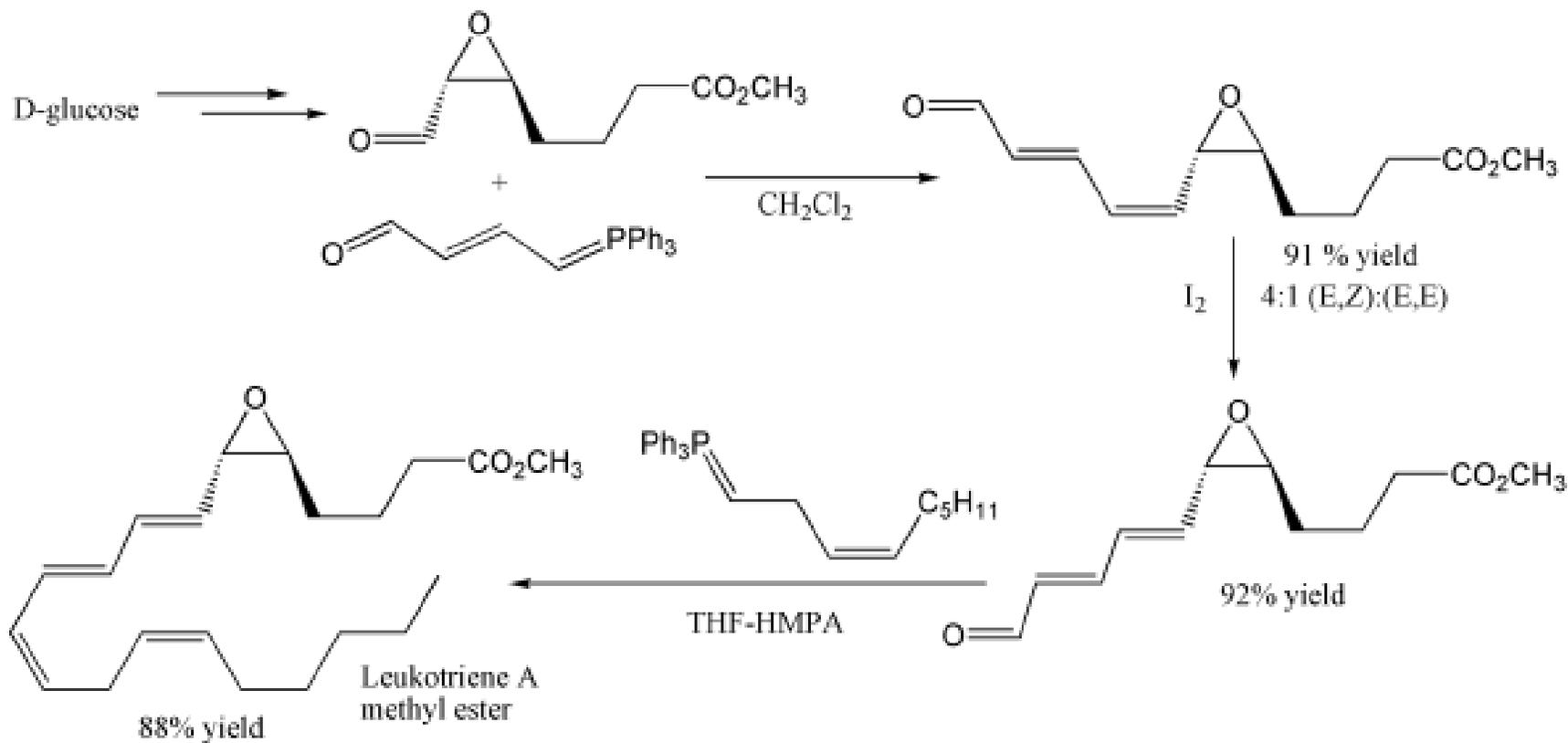
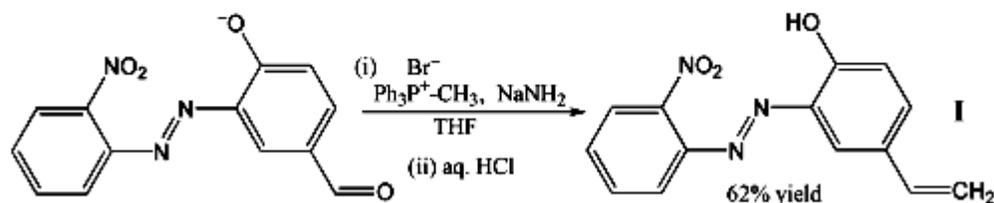
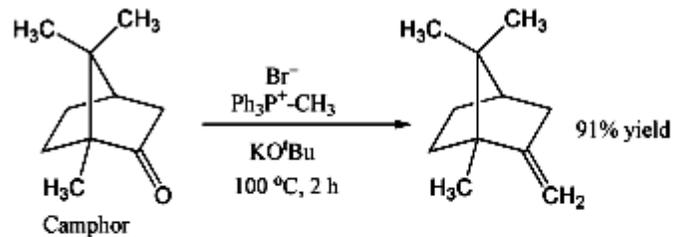
RCHO	Wittig yield (% , isol.)	E:Z	cyclohexenone yield (% , isol.)
	93	77:23	89
	78	85:15	86
	89	77:23	86

Asymmetric Tandem Michael Addition-Wittig Reaction to Cyclohexenone Annulation

Y.-k. Liu, C. Ma, K. Jian, T.-Y. Liu, Y.-C. Chen, *Org. Lett.*, **2009**, *11*, 2848-2851.



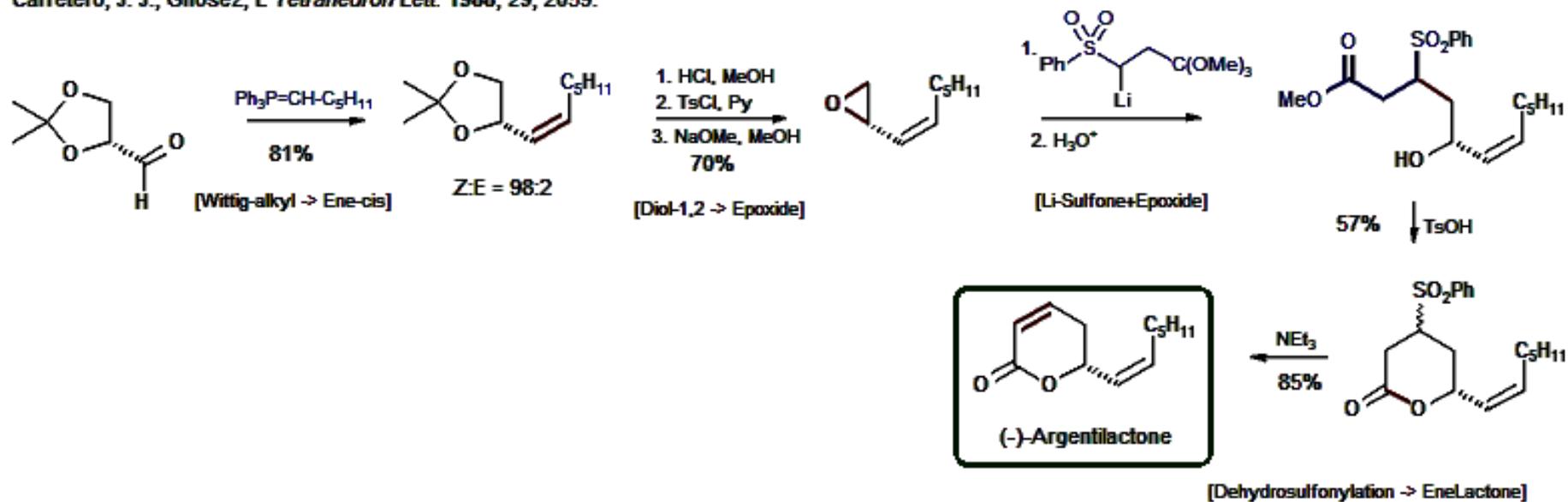
product	yield (% isol.)	dr	ee (%)	product	yield (% isol.)	dr	ee (%)
	67	17:1	99		82	50:1	98
	74	50:1	99		76	50:1	98
	81	50:1	98		80	3:1	96



Argentilactone, (-)

88-14

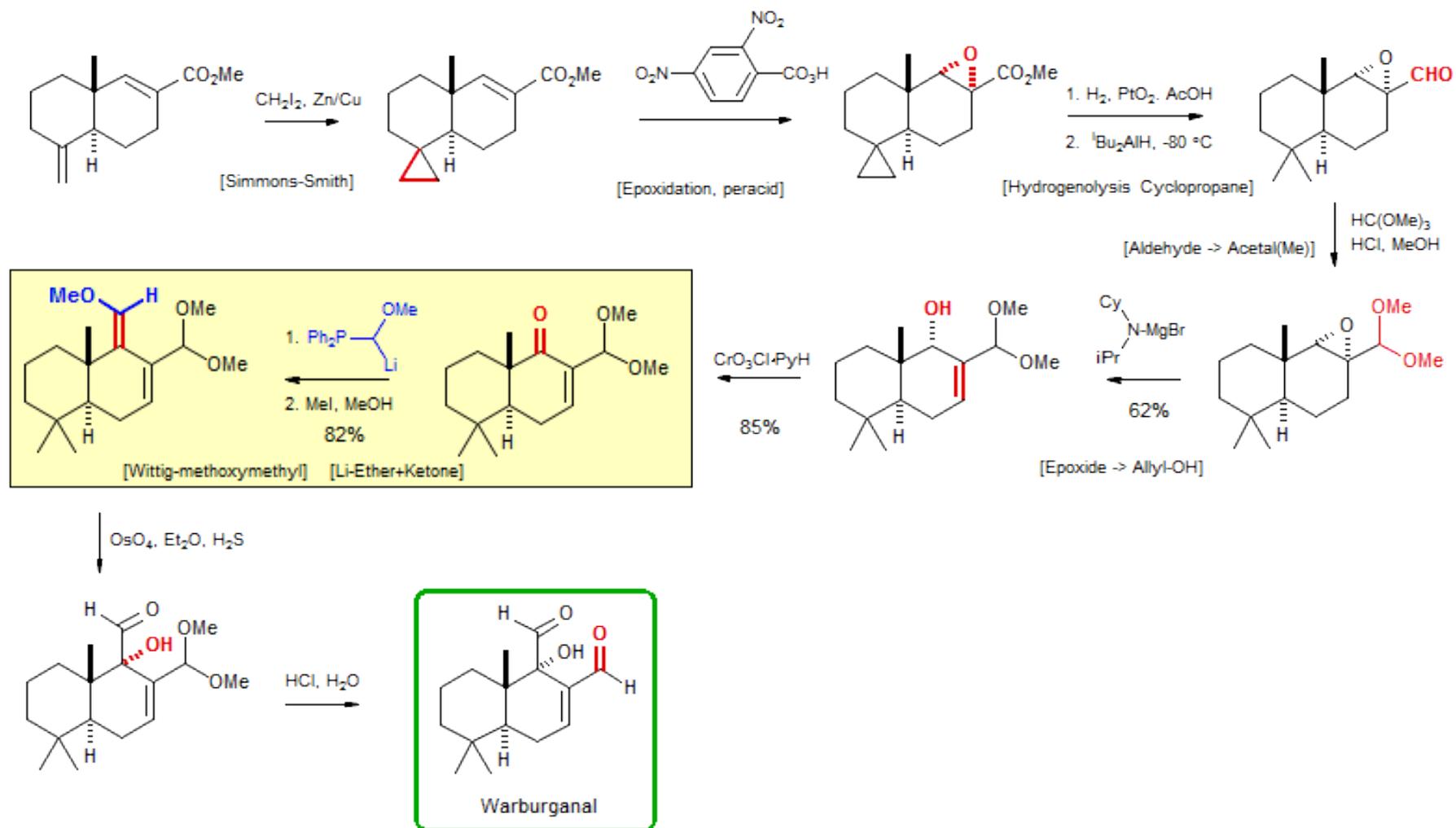
Carretero, J. J.; Ghosez, L. *Tetrahedron Lett.* 1988, 29, 2059.



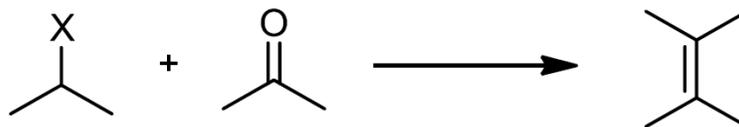
Warburganal

82-05

Wender, P. A.; Eck, S. L. *Tetrahedron Lett.* **1982**, 23, 1871.

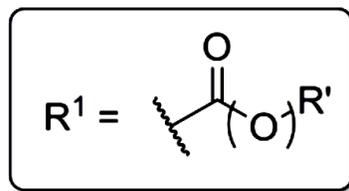
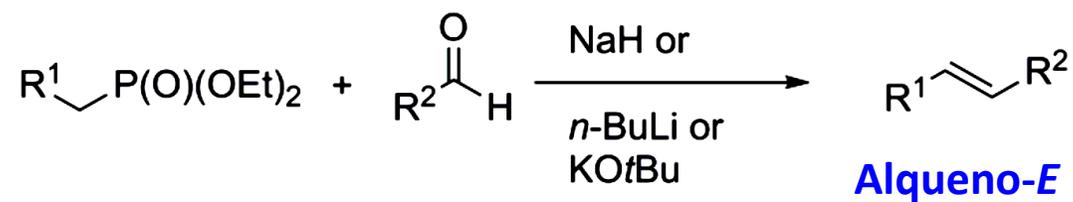
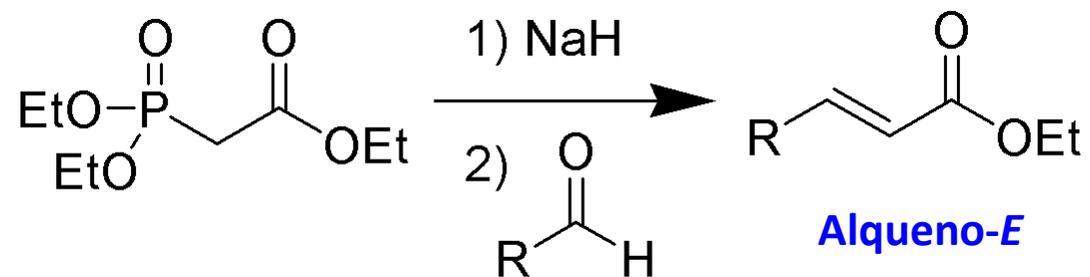


REACCIONES DE OLEFINACIÓN

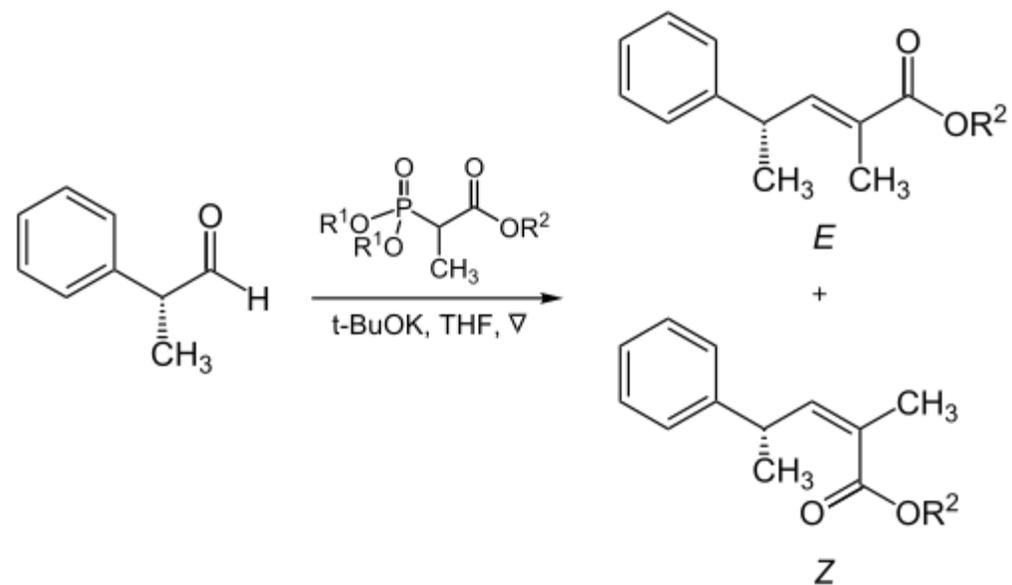


- 
- Reacción de Wittig (**Iluros de fósforo**)
 - Reacción de Horner-Wadsworth-Emmons (**Fosfonatos**)
 - Olefinación de Peterson (**Silanos**)
 - Olefinación Julia-Lythgoe (**Sulfonas**)
 - Acoplamiento de McMurry (**Complejos de titanio**)
 - Olefinación de Takai (**Complejos de cromo**)
 - Olefinación de Petasis-Tebbe (**Complejos de carbeno**)

Reacción Horner–Wadsworth–Emmons



Fosfonatos ramificados



R^1	R^2	Proporción de alquenos (E : Z)
Metilo	Metilo	5 : 95
Metilo	Etilo	10 : 90
Etilo	Etilo	40 : 60
<i>iso</i> -propilo	Etilo	90 : 10
<i>iso</i> -propilo	<i>iso</i> -propilo	95 : 5

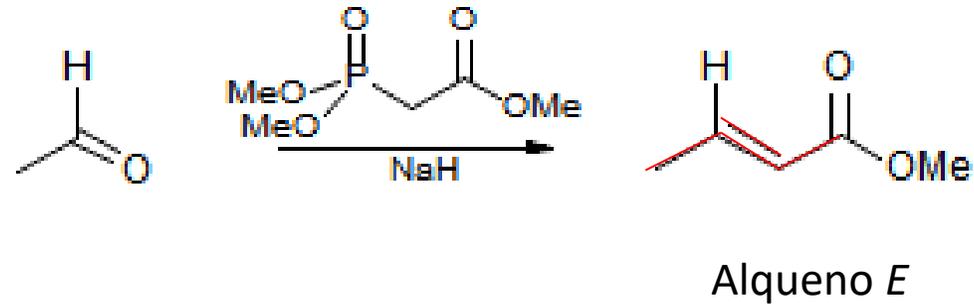
Reacción HWE

Leopold Horner (1911 – 2005). Químico alemán

William S. Wadsworth

William D. Emmons (1924 - 2001). Químico estadounidense

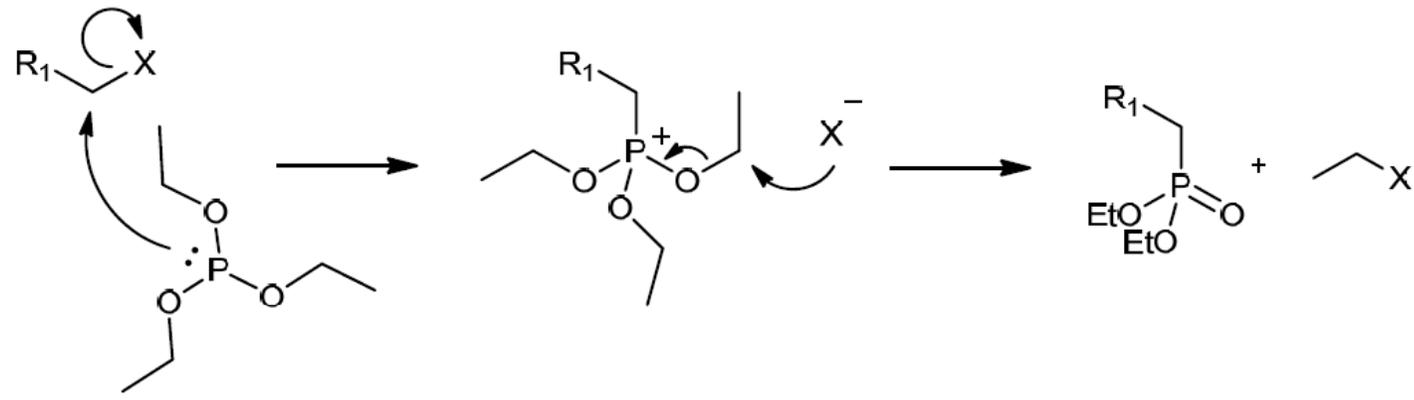
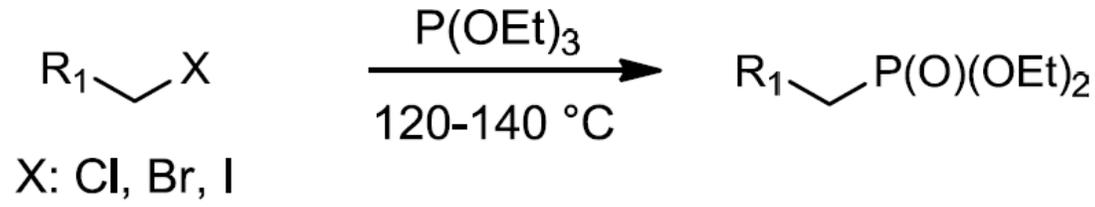
1. "Olefin Synthesis with Organic Phosphonate Carbanions," J. Boutagy and R. Thomas, *Chem. Rev.* **1974**, 74, 87.
2. "Synthetic Applications of Phosphoryl Stabilized Anions," W. S. Wadsworth, Jr. *Org. React.* **1977**, 25, 73.
3. "Wadsworth-Emmons Reaction Revisited," W. J. Stec, *Acc. Chem. Res.* **1983**, 16, 411.
4. "Vinylphosphonates in Organic Synthesis," Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.
5. Minami, T.; Okauchi, T.; Kouno, R. α -Phosphonovinyl Carbanions in Organic Synthesis. *Synthesis* **2001**, 349-57.
6. "Stereocontrol in Organic Synthesis Using the Diphenylphosphoryl Group," Clayden, J.; Warren, S. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 241-70.

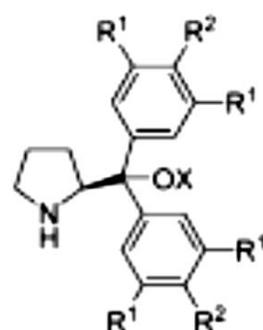
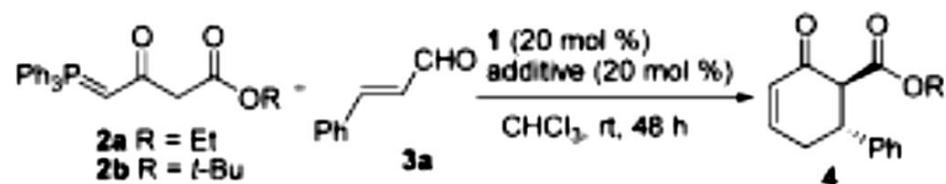


Al igual que en la reacción de Wittig, se obtiene el alqueno-*E*:

- 1) Si en el fosfonato están presentes grupos electroattractores fuertes, que estabilizan al anión (CO_2Me , COMe , COH , CN , SO_2R , SOR , vinilo, fenilo).
- 2) Se obtienen olefinas *trans* si los sustituyentes en el fósforo son grupos alcoxi simples y si se usan contraiones litio o sodio

REACCIÓN DE ARBUZOV

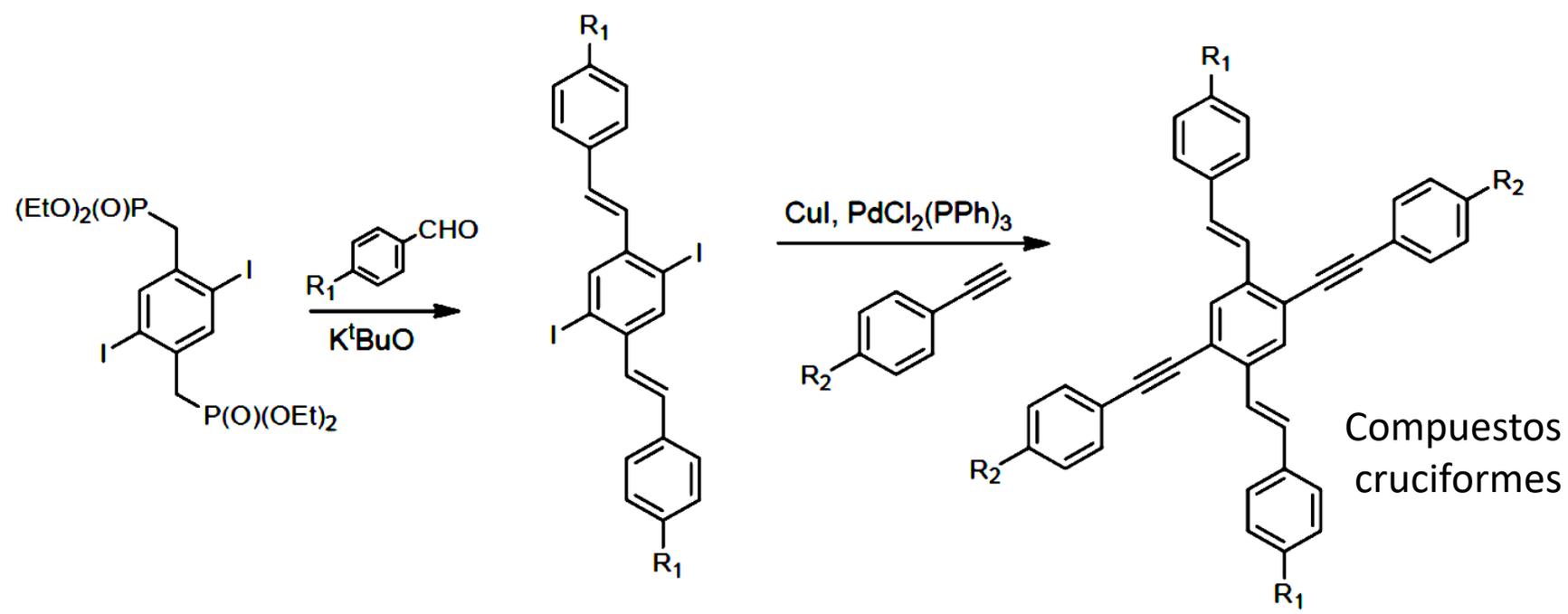
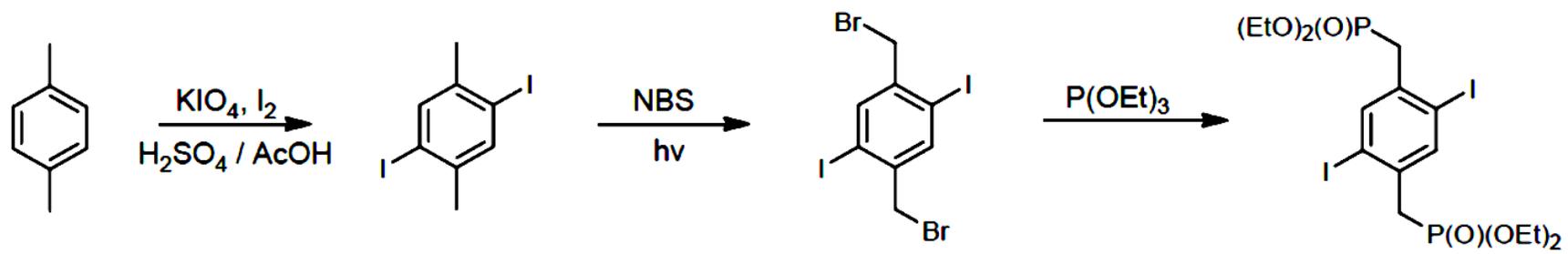




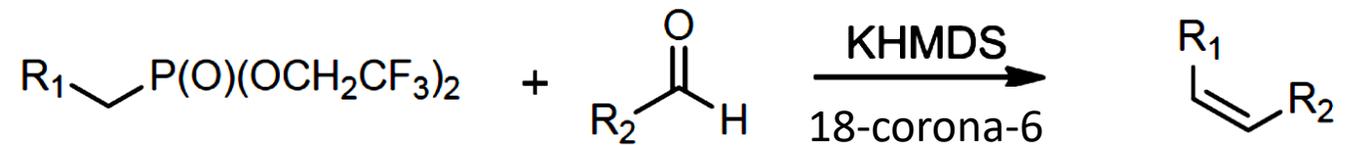
- 1a** X = TMS, R¹ = R² = H
1b X = TES, R¹ = R² = H
1c X = R¹ = R² = H
1d X = TMS, R¹ = CF₃, R² = H
1e X = TMS, R¹ = Me, R² = H
1f X = TMS, R¹ = Me, R² = OMe
1g X = TMS, R¹ = t-Bu, R² = OMe

entry	1	additive	2	yield ^b (%)	dr ^c	ee ^d (%)
1 ^e	1a	BzOH	2a	-	-	-
2 ^e	1a	NaOAc	2a	4a , <10	-	-
3 ^e	1a	DBACO	2a	4a , 21	6:1	65
4 ^e	1a	DABCO + LiClO ₄	2a	4a , 53	9:1	75
5	1a	DABCO + LiClO ₄	2a	4a , 62	7:1	74
6 ^f	1a	DABCO + LiClO ₄	2a	4a , 71	6:1	72
7 ^f	1b	DABCO + LiClO ₄	2a	4a , 46	7:1	80
8 ^f	1c	DABCO + LiClO ₄	2a	-	-	-
9 ^f	1d	DABCO + LiClO ₄	2a	-	-	-
10 ^f	1e	DABCO + LiClO ₄	2a	4a , 75	8:1	80
11 ^f	1f	DABCO + LiClO ₄	2a	4a , 79	8:1	79
12 ^f	1g	DABCO + LiClO ₄	2a	4a , 82	8:1	97
13 ^f	1g	DABCO + LiClO ₄	2d	4b , 85	41:1	98

^a Unless noted otherwise, reactions were performed with ylide **2** (0.1 mmol), cinnamaldehyde **3a** (0.2 mmol), 20 mol % of **1**, and 20 mol % of additive in CHCl₃ (0.8 mL) for 48 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d Determined by chiral HPLC analysis. ^e For 24 h. ^f With 40 mol % of DABCO.

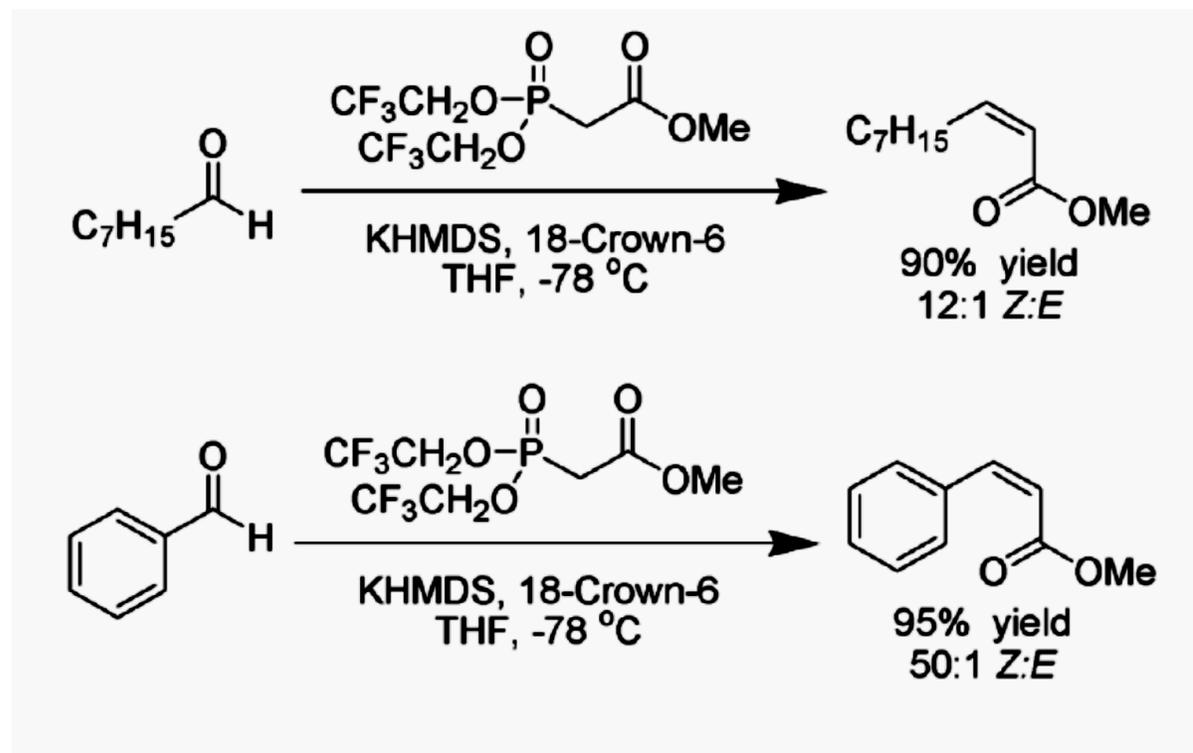
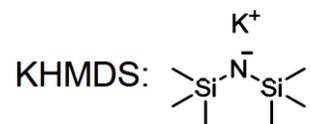


Modificación de Still-Gennari a HWE (Horner-Wadsworth-Emmons)



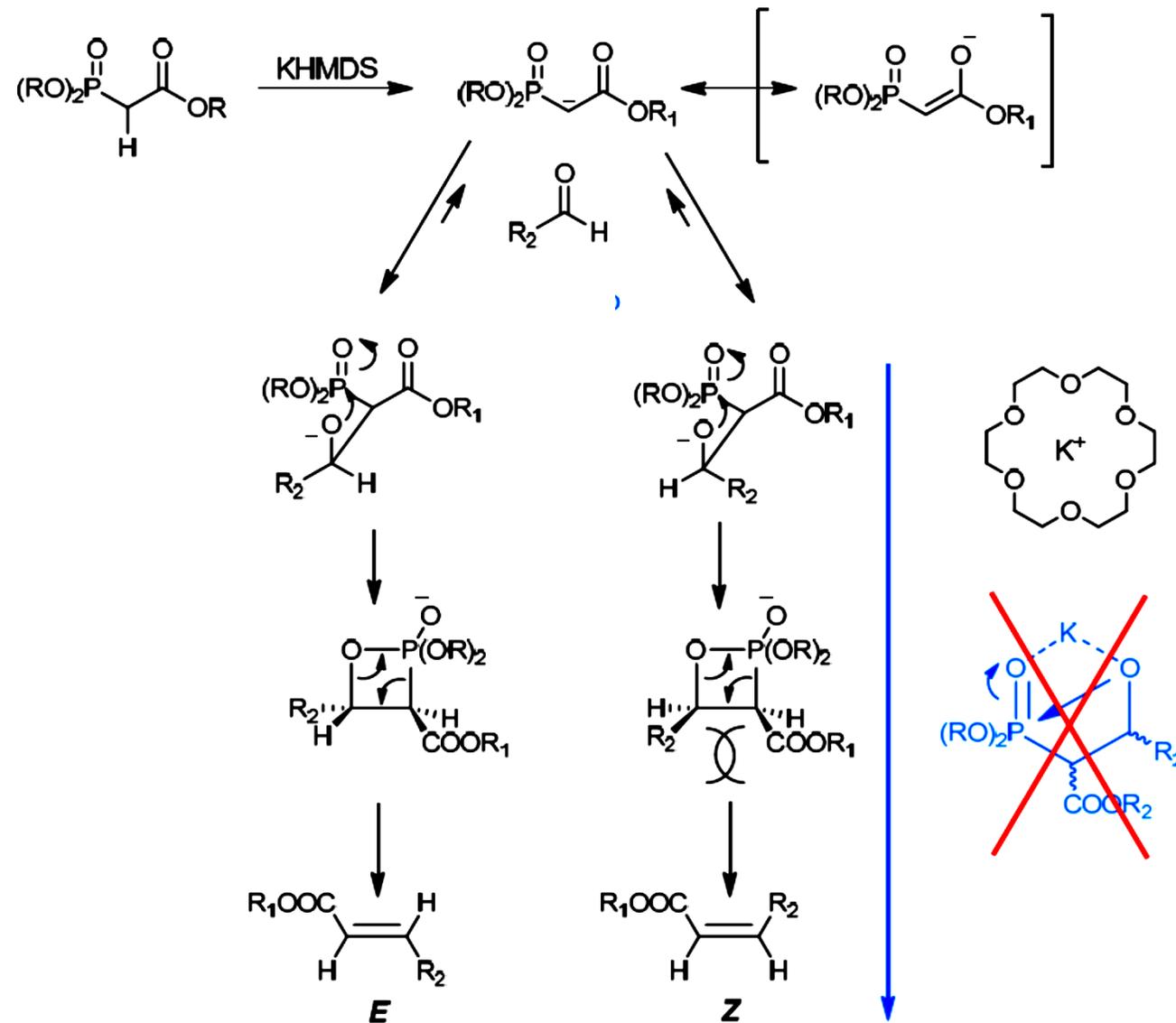
Medio con una alta disociación

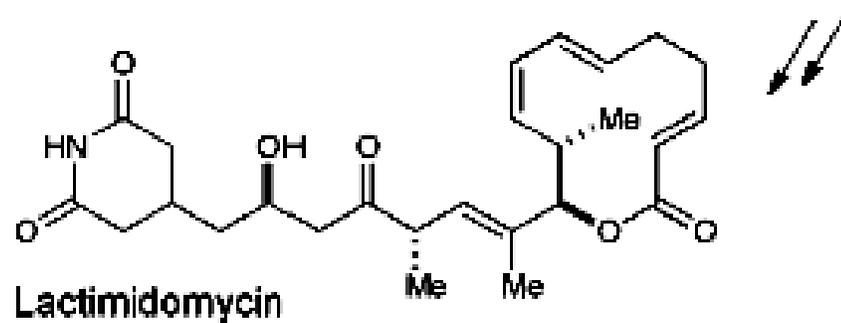
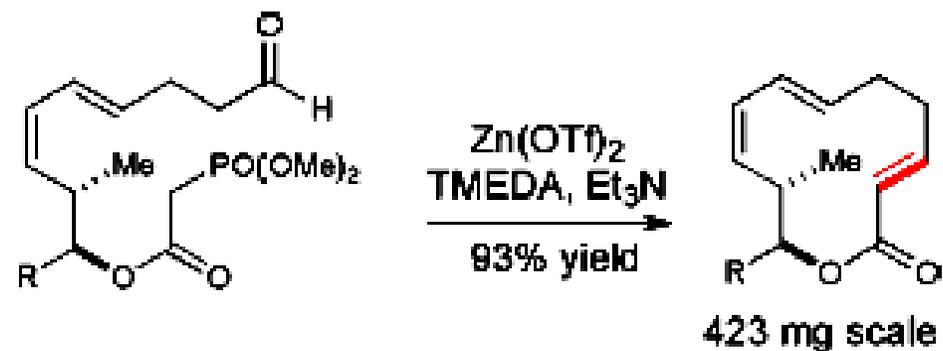
Producto Z



Modificación de Still-Gennari

Mecanismo





Posible actividad anticancerígena

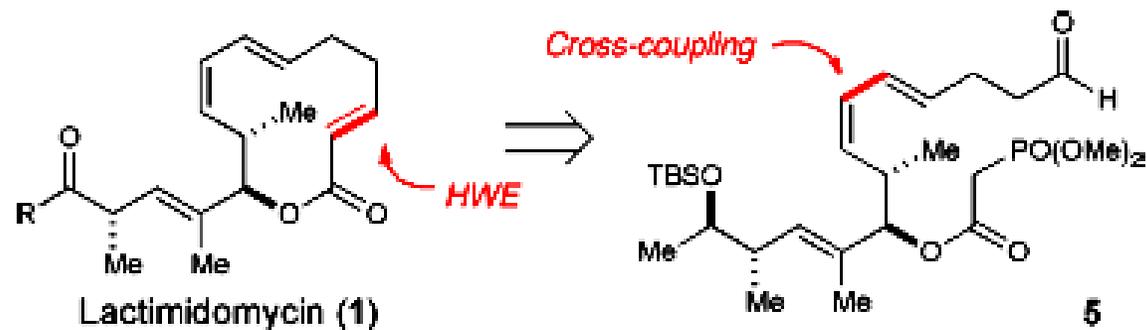
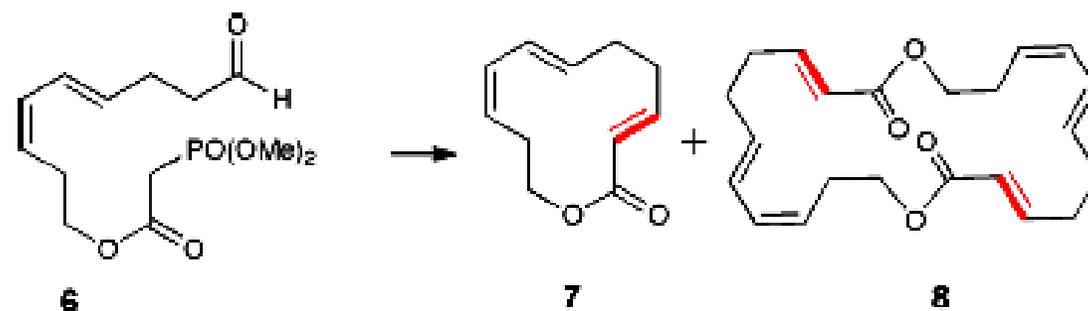


Table 1. Macrocyclization Optimization Studies



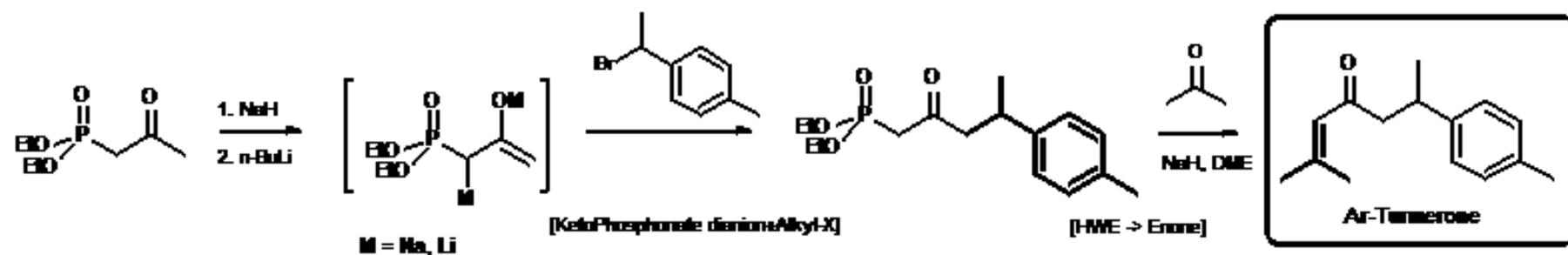
entry	conditions	7 (yield, %) ^a	8 (yield, %) ^a
1	K ₂ CO ₃ , 18-C-6, 1.3 mM in toluene	0	65
2	LiHMDS, 1.3 mM in THF	0	36
3	LiCl, DBU, 1.3 mM in THF	13	60
4	Zn(OTf) ₂ , TMEDA Et ₃ N, 1.7 mM in THF	78	9

^aYields are measured over two steps (oxidation of an alcohol precursor to 6 followed by the HWE cyclization to 7 and 8); 18-C-6 = 18-crown-6; LiHMDS = lithium hexamethyldisilazide; TMEDA = tetramethylethylenediamine.

Tumerone, Ar-

Griceo, P. A.; Finkbeiner, R. S. *J. Org. Chem.* 1973, 38, 2909.

73-11
EXP



50%

2007-10-10