Recent Developments in Asymmetric Gold Catalysis

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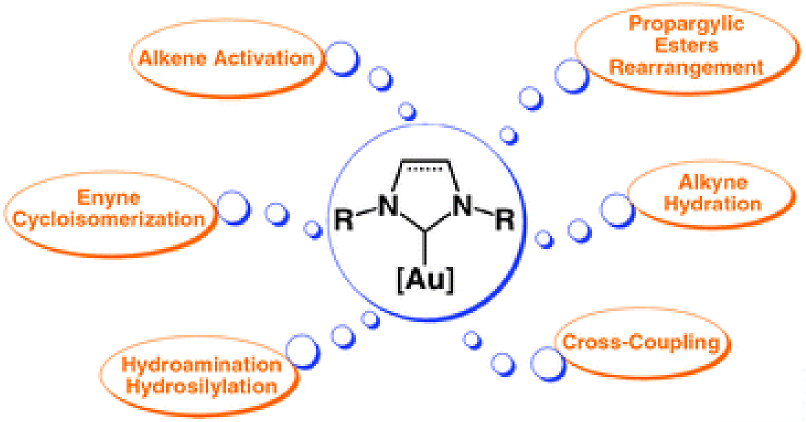
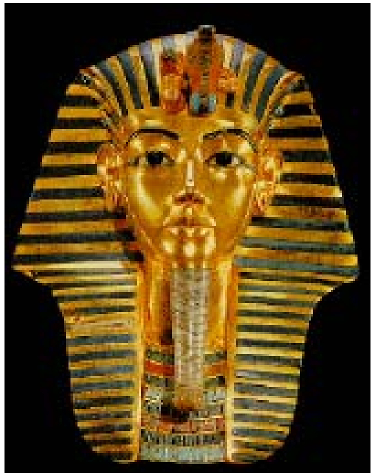
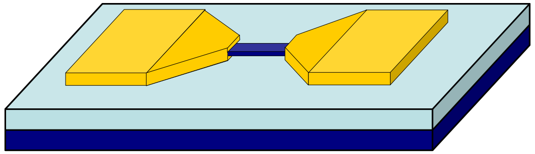
stéRéO

17-03-2011

Introduction







Used in Chemistry, jewelry, electronics, coins, ….

What makes gold so attractive in chemistry

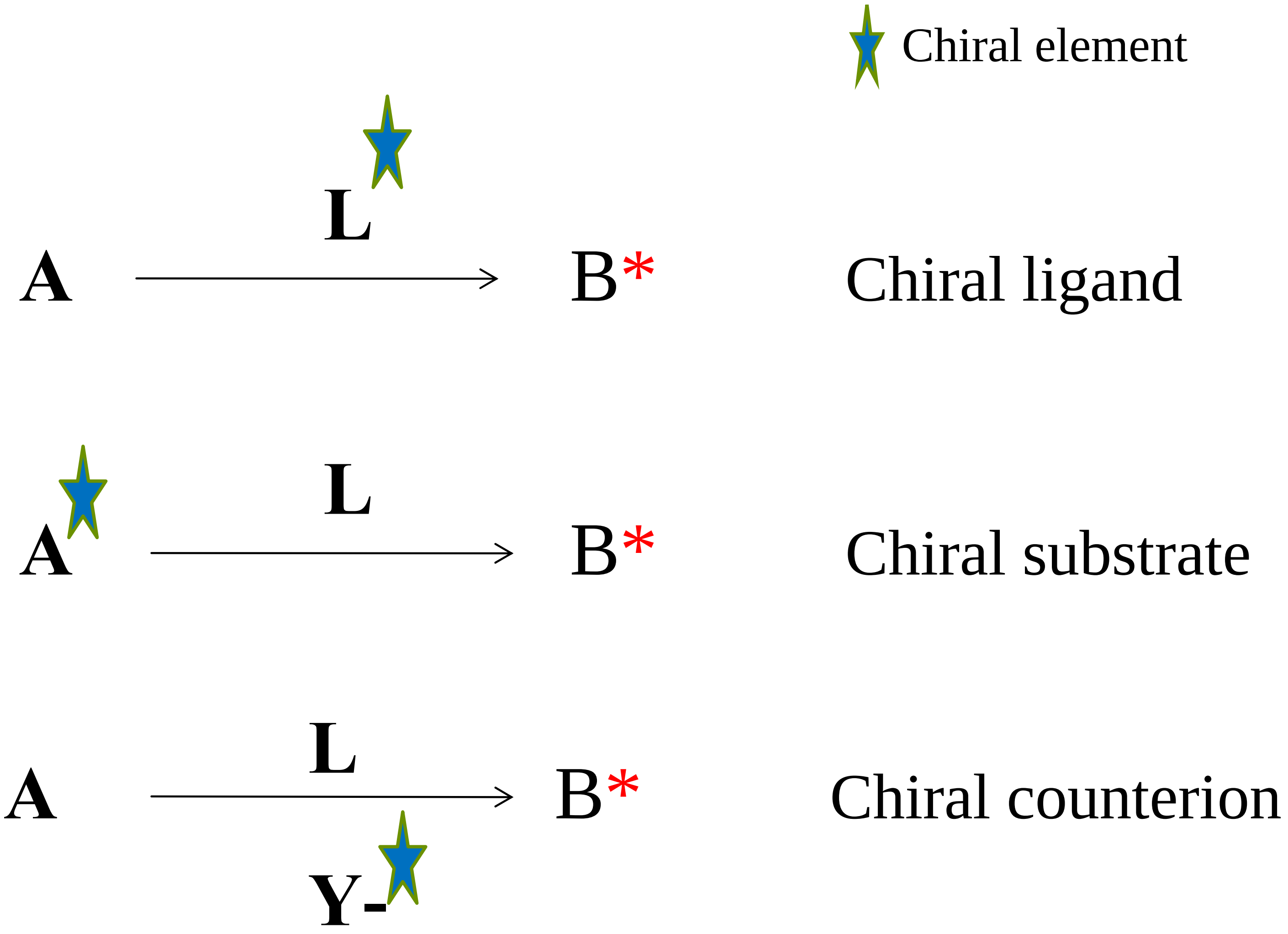
Au^{III}	**Au^{I}**
Four coordination sites	Two binding sites
Square planar complexes	Linear geometry

- **Gold complexes are moisture and air stable**
- **Ability to activate various π-systems**
- **Gold price** (USD/ gram)

Silver (Ag)	Palladium (Pd)	Gold (Au)	Platinum (Pt)	Rhodium (Rh)
1.3	28.6	50.5	64.9	83.9

http://www.kitco.com/

Asymmetric Gold Catalysis Concept



★ Chiral element

$A \xrightarrow{L^{\bigstar}} B^{*}$ Chiral ligand

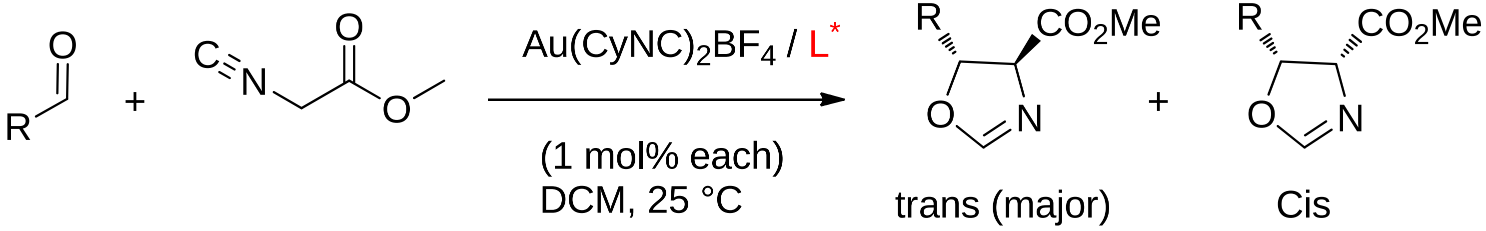
$A^{\bigstar} \xrightarrow{L} B^{*}$ Chiral substrate

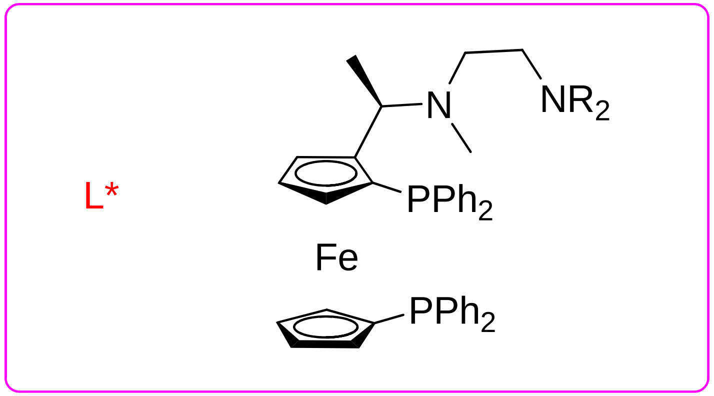
$A \xrightarrow[Y^{-\bigstar}]{L} B^{*}$ Chiral counterion

PLAN

1. **Asymmetric Aldol Addition**
2. **Asymmetric Activation of Allenes**
3. **Asymmetric Alkene Activation**
4. **Cyclopropanation of Vinyl Arene**
5. **Enantioselective 1,3-dipolar Cycloaddition**

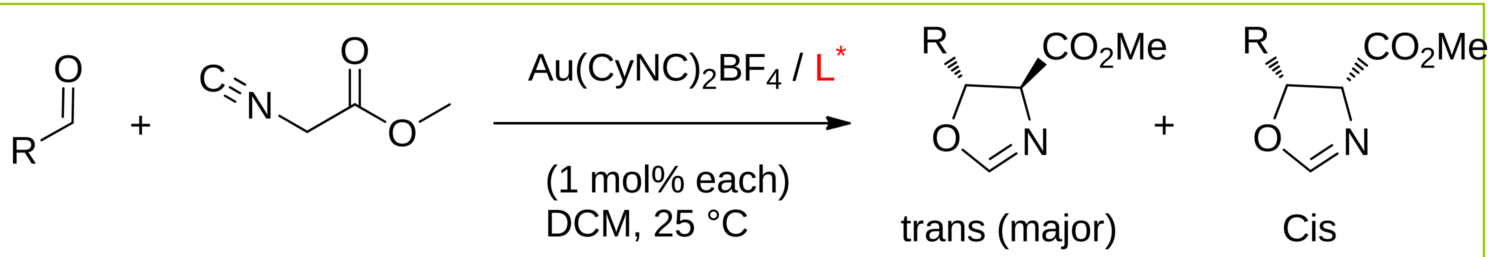
Asymmetric Aldol Addition

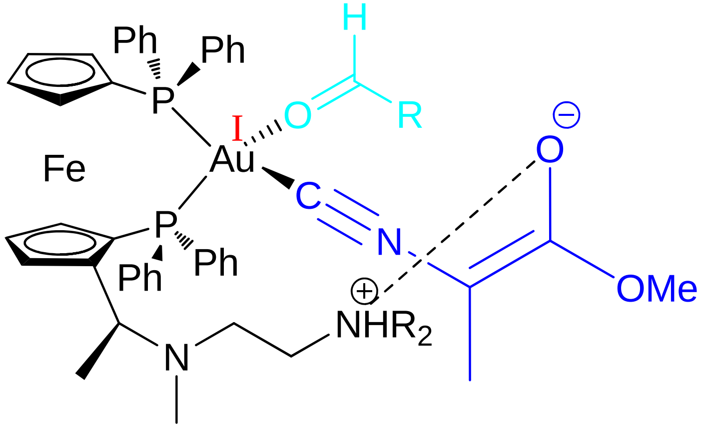




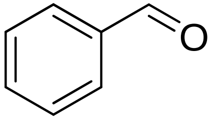
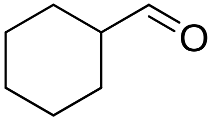
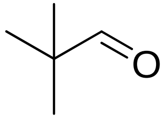
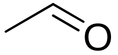
Y. Ito; M. Sawamura; T. Hayashi, *J. Am. Chem. Soc.***1986, 108, 6405.**

Scope of the Reaction



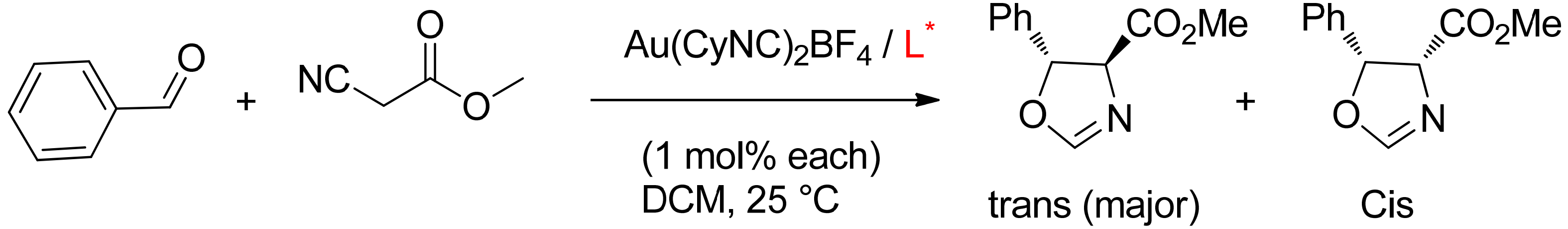


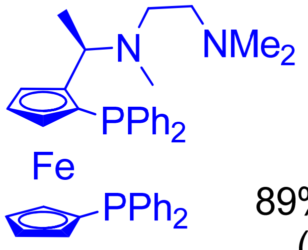
R= Et

 98% yield	89 (96% ee)	11
 95% yield	97 (90% ee)	3
 100% yield	100 (97% ee)	0
 100% yield	84 (72% ee)	16

Y. Ito; M. Sawamura; T. Hayashi, *J. Am. Chem. Soc.* **1986, 108, 6405.**

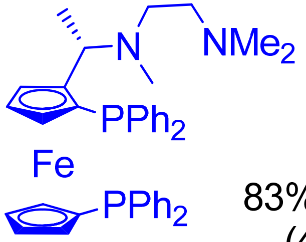
Ligand Screening





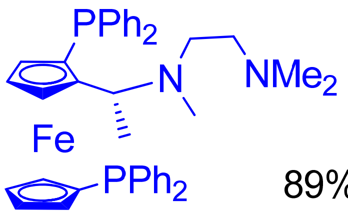
(R)-(S)-L

trans
89%, 91% ee
(4S, 5R)



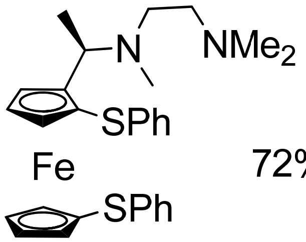
(S)-(S)-L

trans
83%, 41% ee
(4R, 5S)



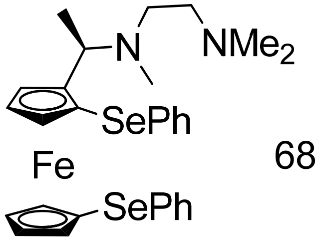
(S)-(R)-L

trans
89%, 90% ee
(4R, 5S)



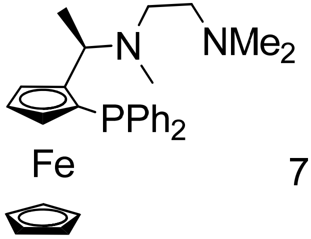
(R)-(S)-L

trans
72%, 0% ee



(R)-(S)-L

trans
68%, 0% ee



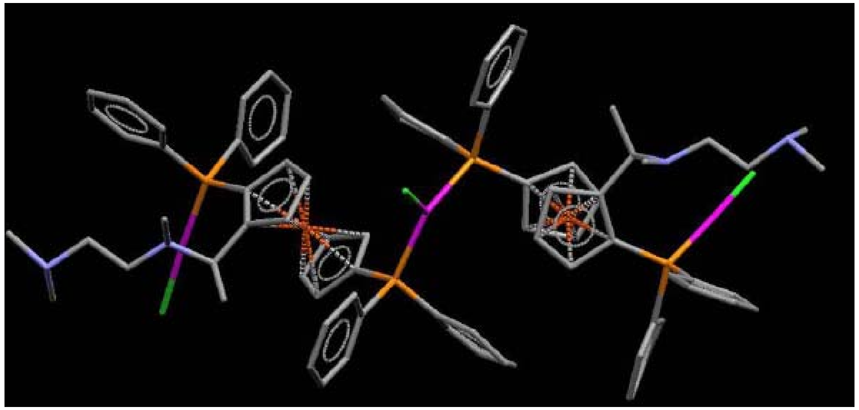
(R)-(S)-L

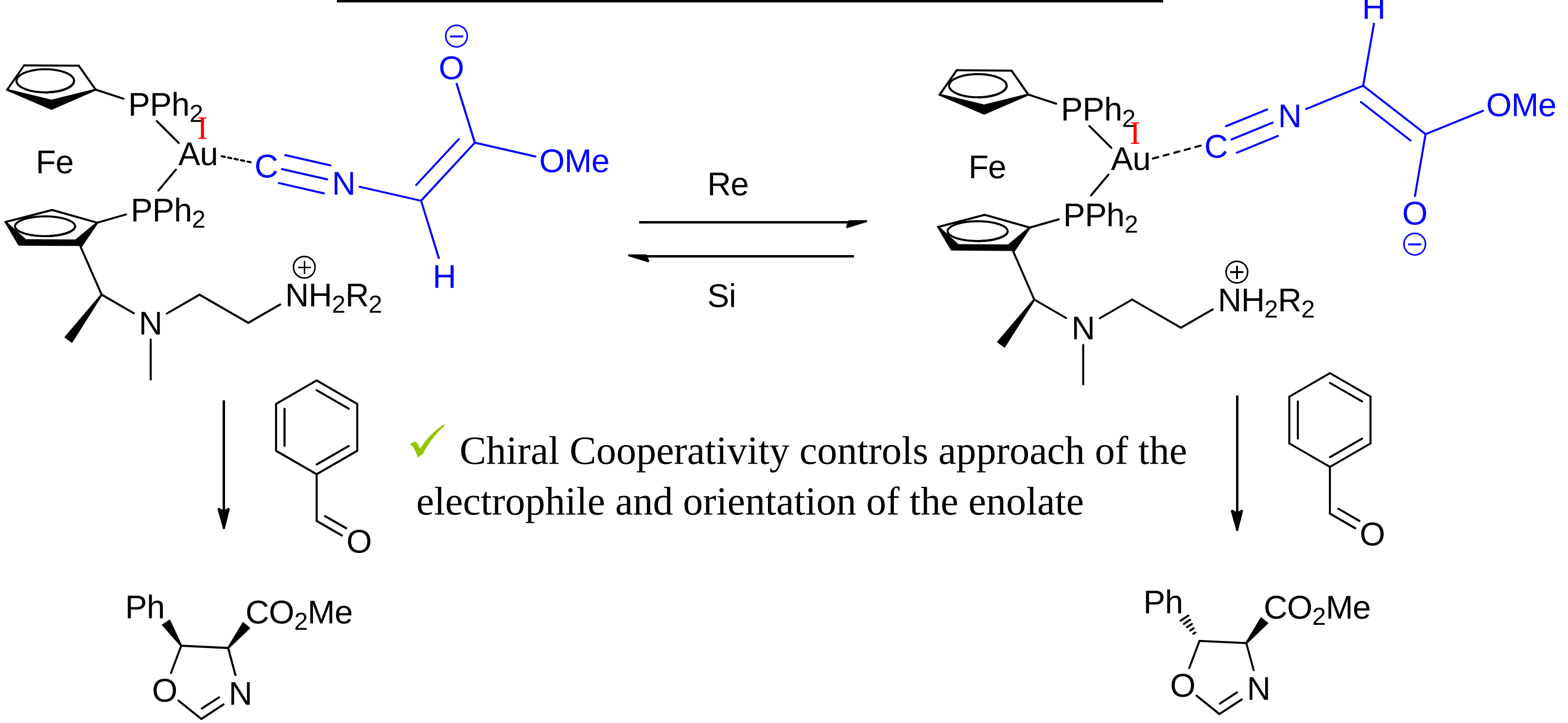
trans
77%, 16% ee

S. D. Pastor; A. Togni, *J. Am. Chem. Soc.***1989, 111, 2333.**

A. Togni; S. D. Pastor, *J. Org. Chem.***1990, 55, 1649.**

Refined Transition-State Model

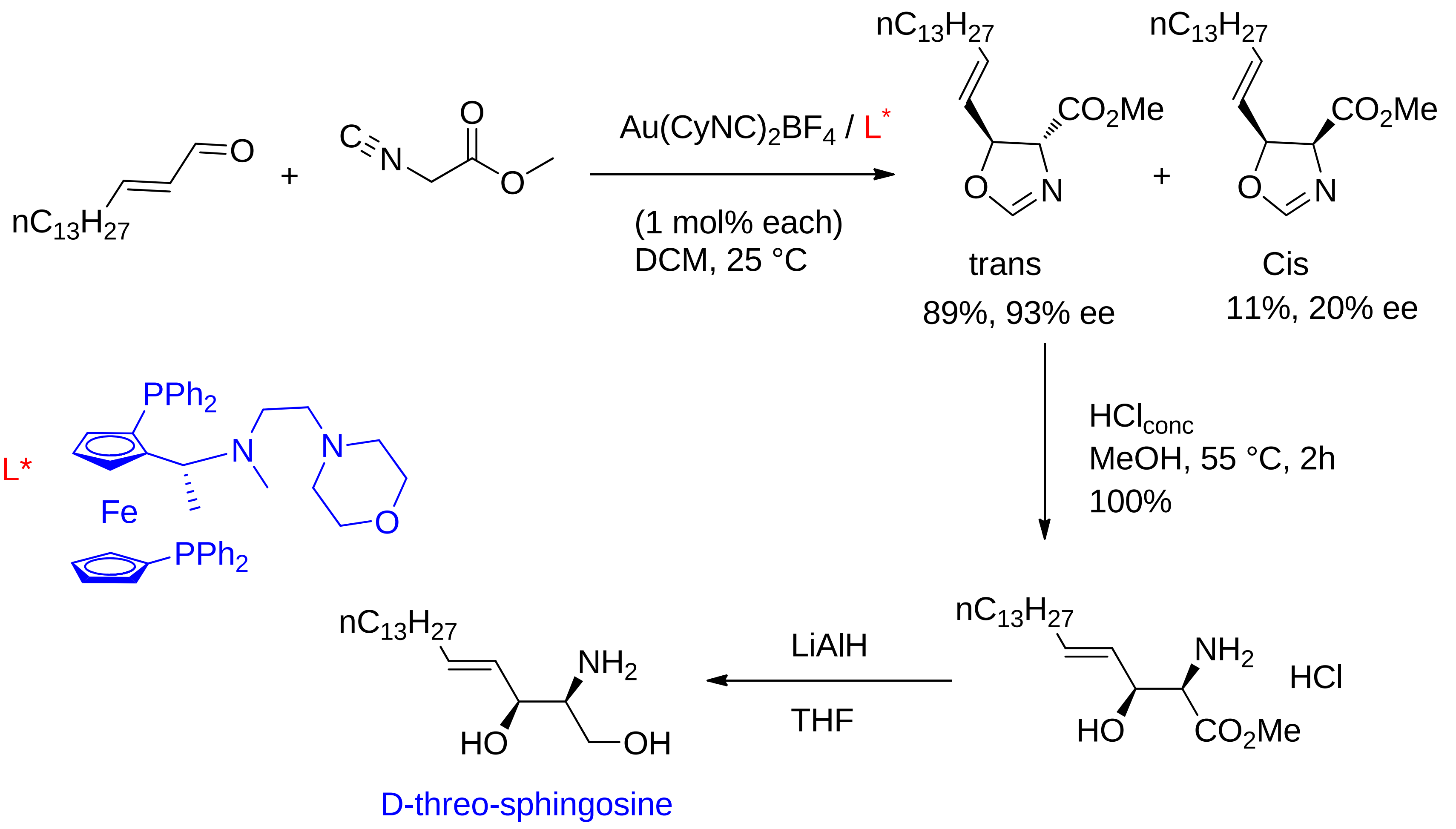




- ✓ Chiral Cooperativity controls approach of the electrophile and orientation of the enolate

A. Togni; S. D. Pastor, *J. Org. Chem.* ***1990, 55, 1649.***

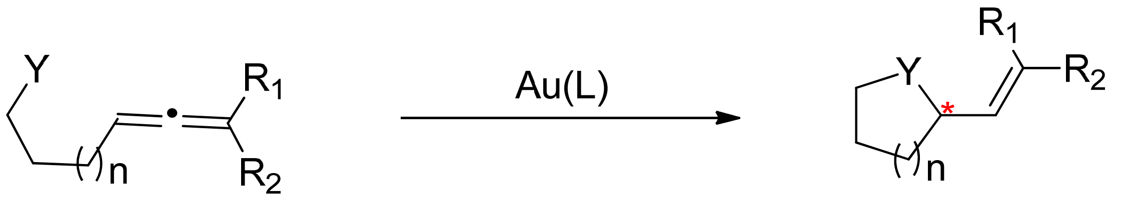
Application to the Asymmetric synthesis of D-threo-Sphingosines



D-threo-sphingosine

Y. Ito; M. Sayamura; T. Hayashi, *Tetrahedron. Lett.* ***1988, 29, 239.***

Asymmetric Activation of Allenes

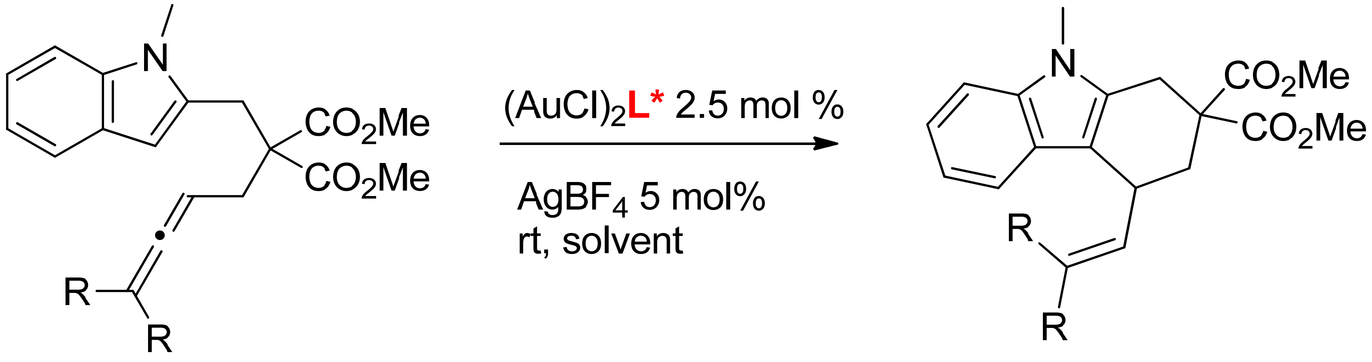


Chiral or achiral

n= 0, 1, or 2

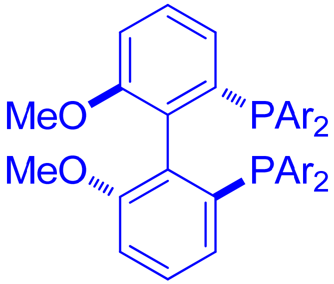
Y= OH, COOH, NHR, CH
L= chiral or achiral

Addition of Carbon Nucleophiles to Allenes



R= H	88% yield, 92% ee
R= Me	82% yield, 91% ee

L*

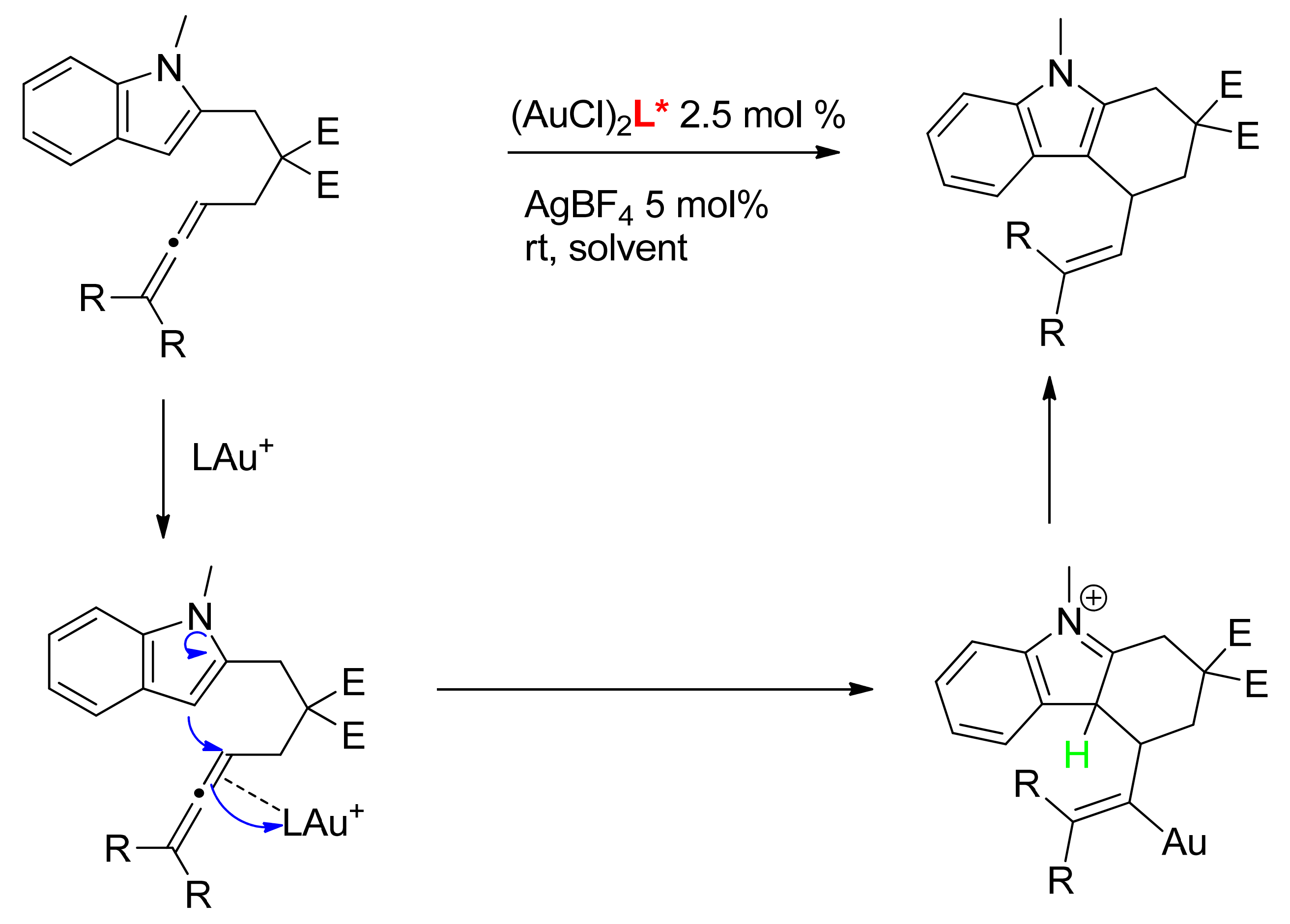


Ar= 3,5-tBu-4-MeO-C6H2

Chiral ligand strategy

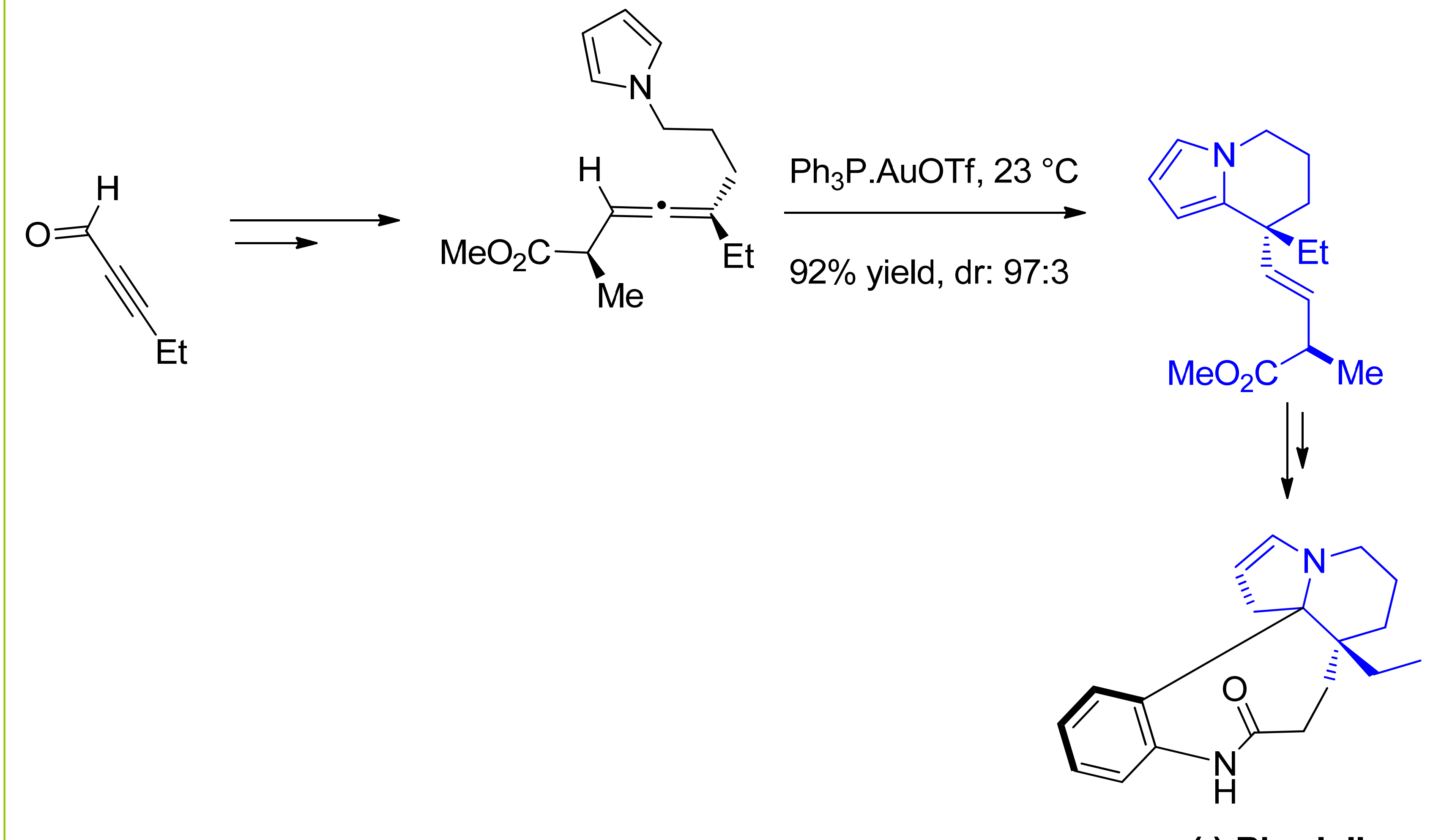
C. Liu, R. A. Widenhoefer, *Org. Lett*. **2007, 9, 1930**.

Proposed Mecanism



C. Liu, R. A. Widenhoefer, *Org. Lett*. **2007, 9, 1930**.

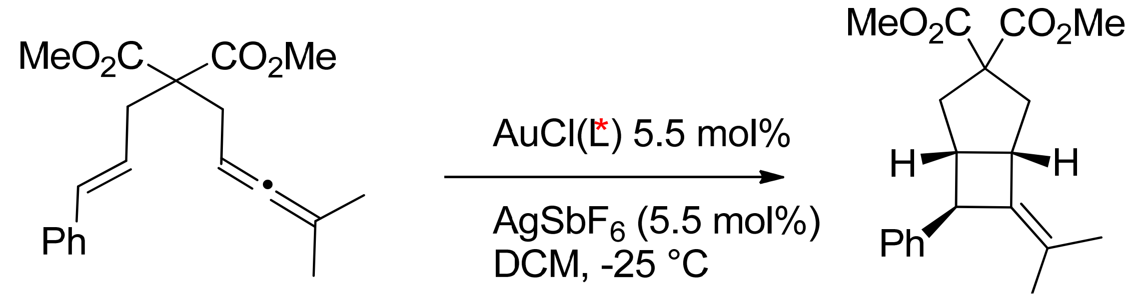
Application to the Total synthesis of (-)-Rhazinilam

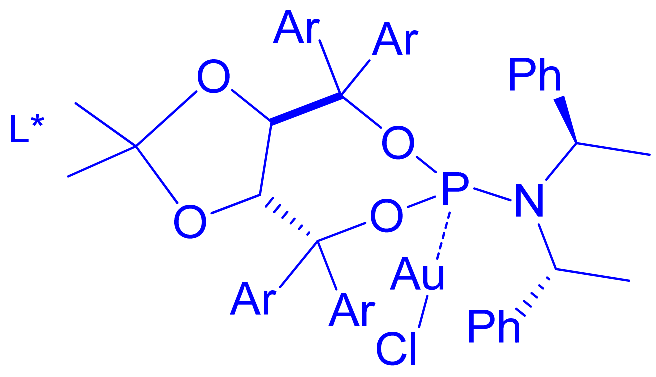


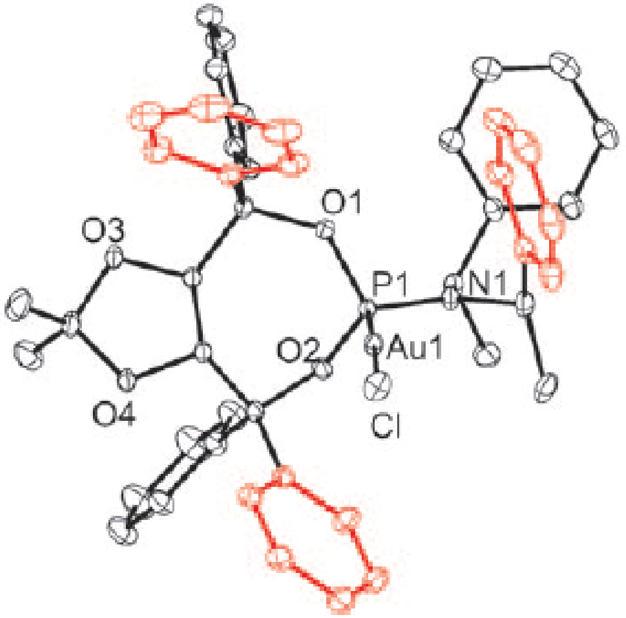
(-)-Rhazinilam

Z. Liu; A. S. Wasmuth; S. G. Nelson, *J. Am. Chem. Soc*, **2006, 128, 10352**.

Addition of Carbon Nucleophiles to Allenes



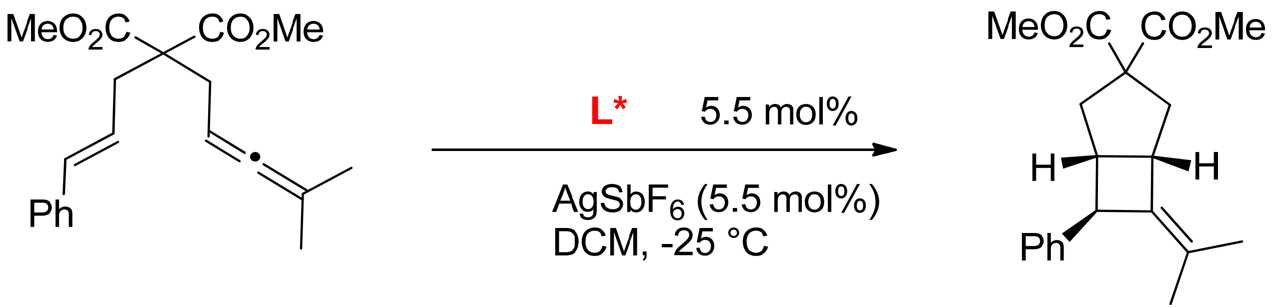


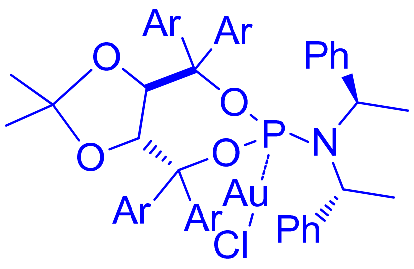


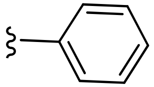
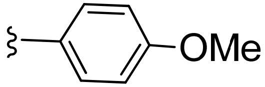
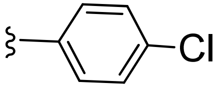
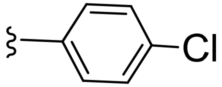
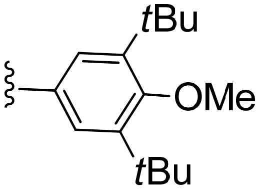
Chiral ligand strategy

H. Teller; S. Flugge; R. Goddard; A. Furstner, *Angew. Chem. Int. Ed.* **2010, 49, 1949.**

Addition of Carbon Nucleophiles to Allenes

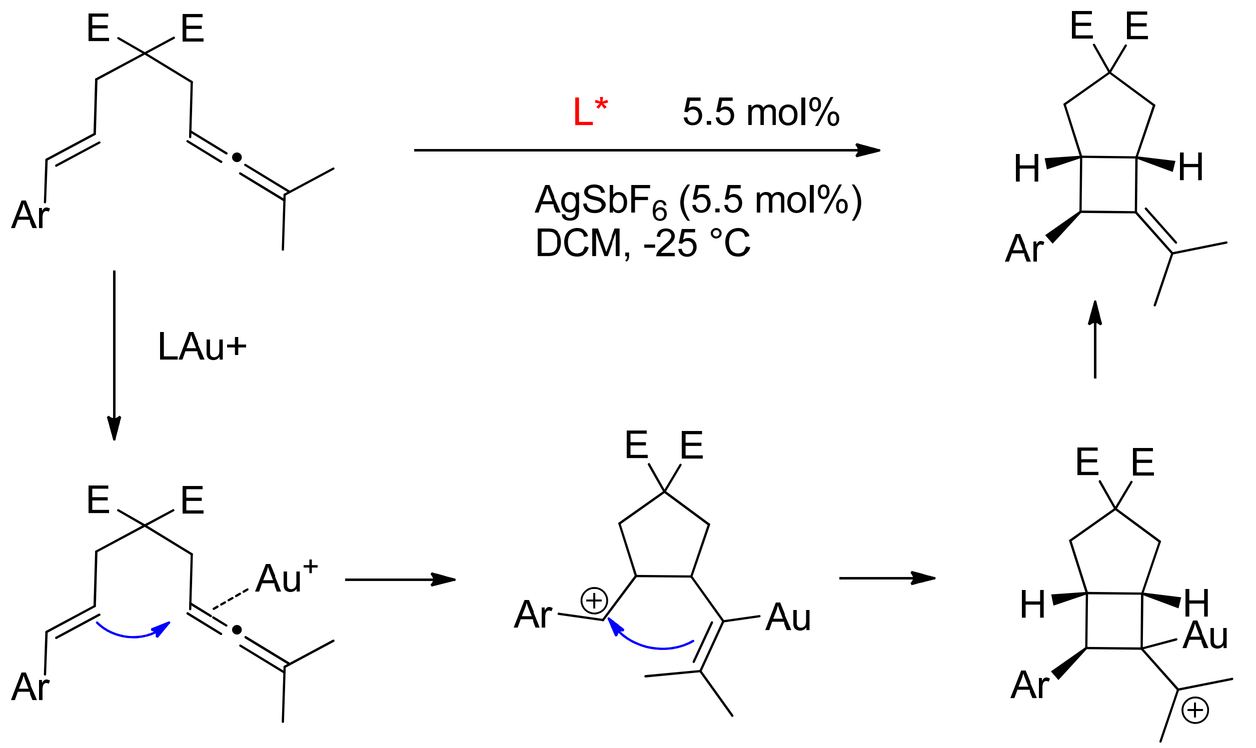




Entry	Ar	t (h)	yield (%)	ee (%)
1		2	93	84
2		16	90	86
3		1	95	75
4		1	84	39
5		> 16	71	63

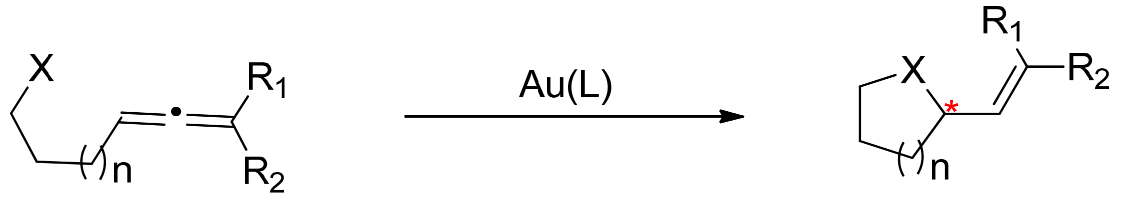
H. Teller; S. Flugge; R. Goddard; A. Furstner, *Angew. Chem. Int. Ed.* **2010, 49, 1949.**

Proposed Mecanism



H. Teller; S. Flugge; R. Goddard; A. Furstner, *Angew. Chem. Int. Ed.* **2010, 49, 1949.**

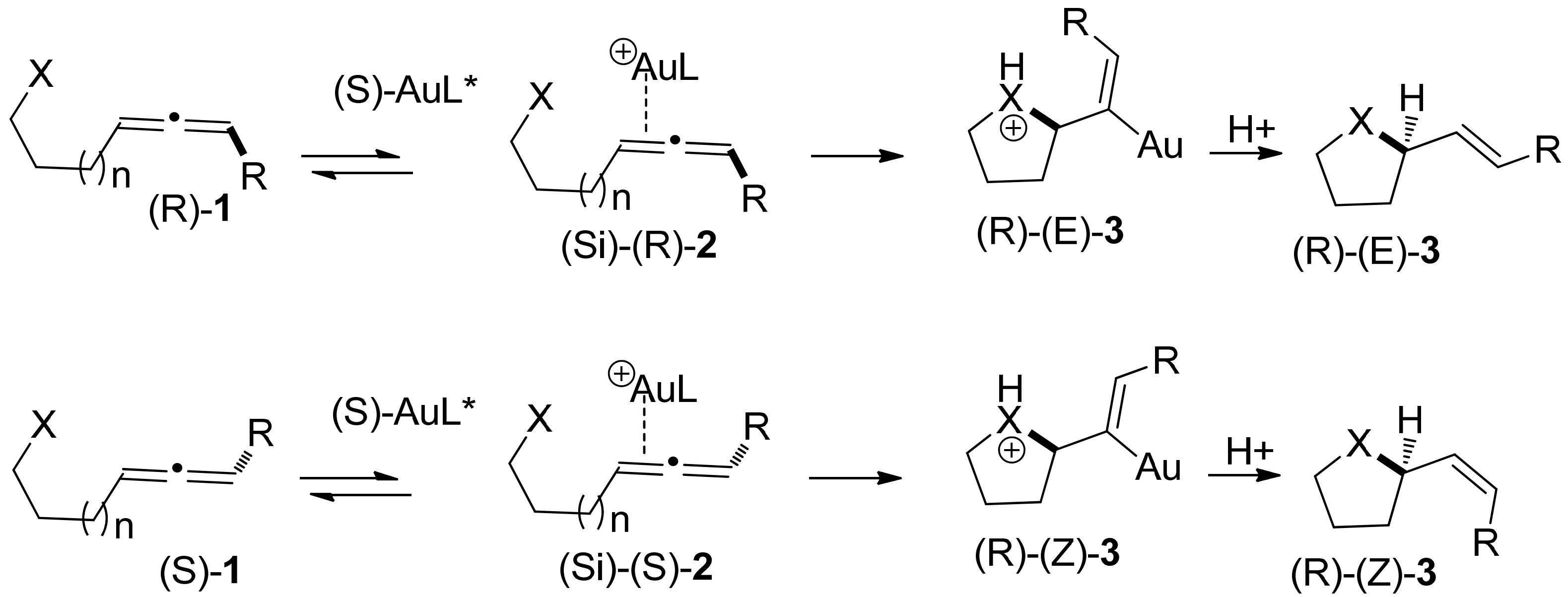
Carbone-Heteroatom Bond Formation



Chiral or achiral

X= OH, COOH, NHR, SH,...
L= chiral or achiral

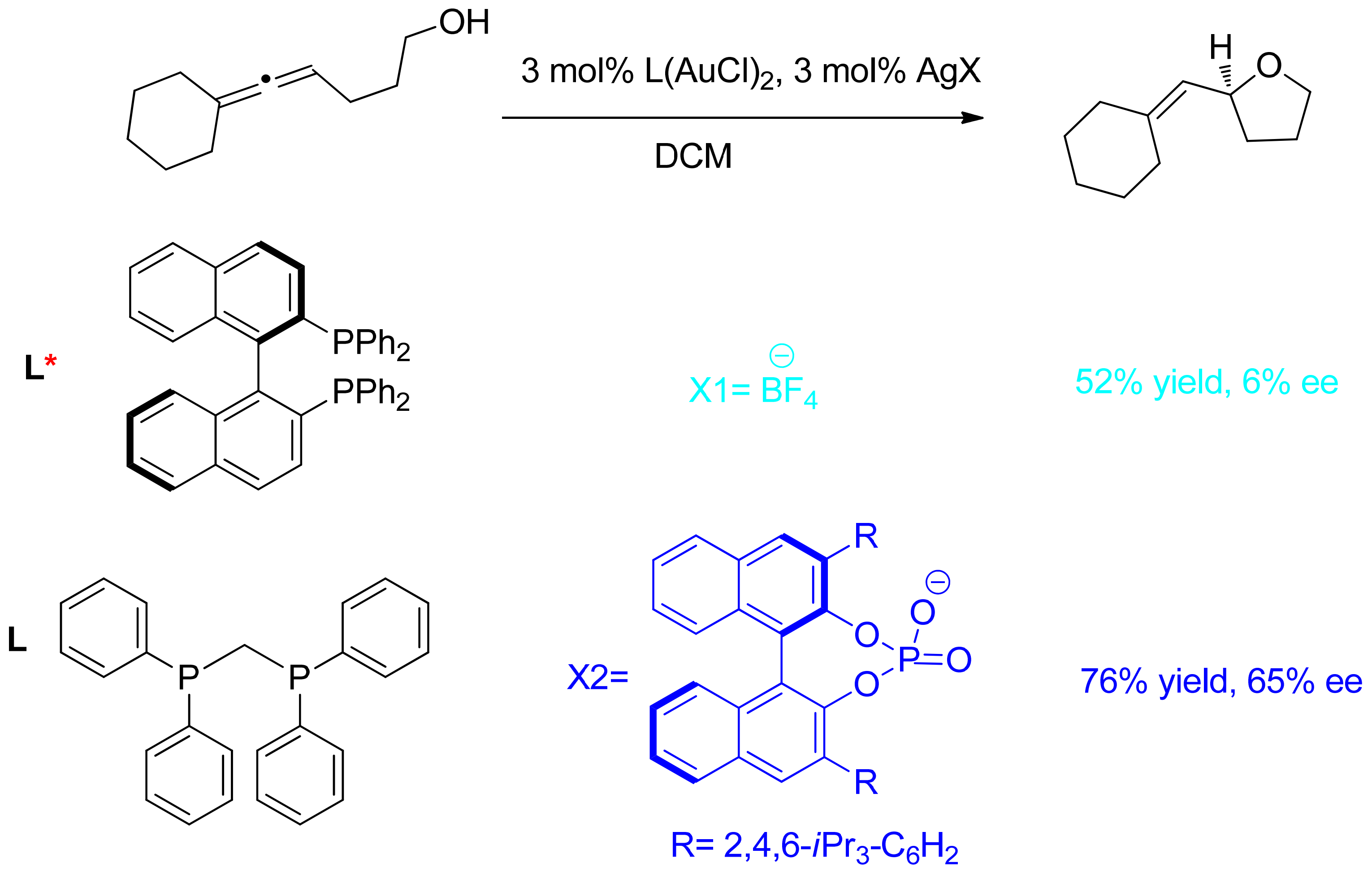
n= 0, 1, or 2



(R)-**1** (Si)-(R)-**2** (R)-(E)-**3** (R)-(E)-**3**

(S)-**1** (Si)-(S)-**2** (R)-(Z)-**3** (R)-(Z)-**3**

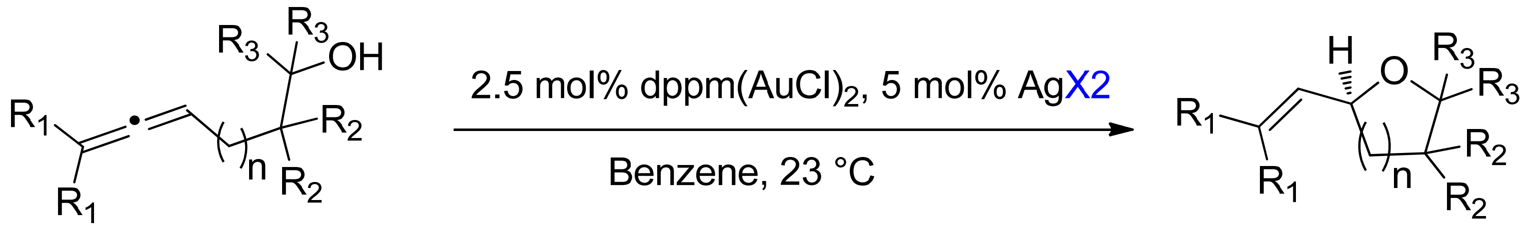
Carbone-Heteroatom Bond Formation



Chiral counterion strategy

G. L. Hamilton; E. J. Kang; M. Mba; F. D. Toste; *Science*, **2007, 317, 496**

Carbone-Heteroatom Bond Formation

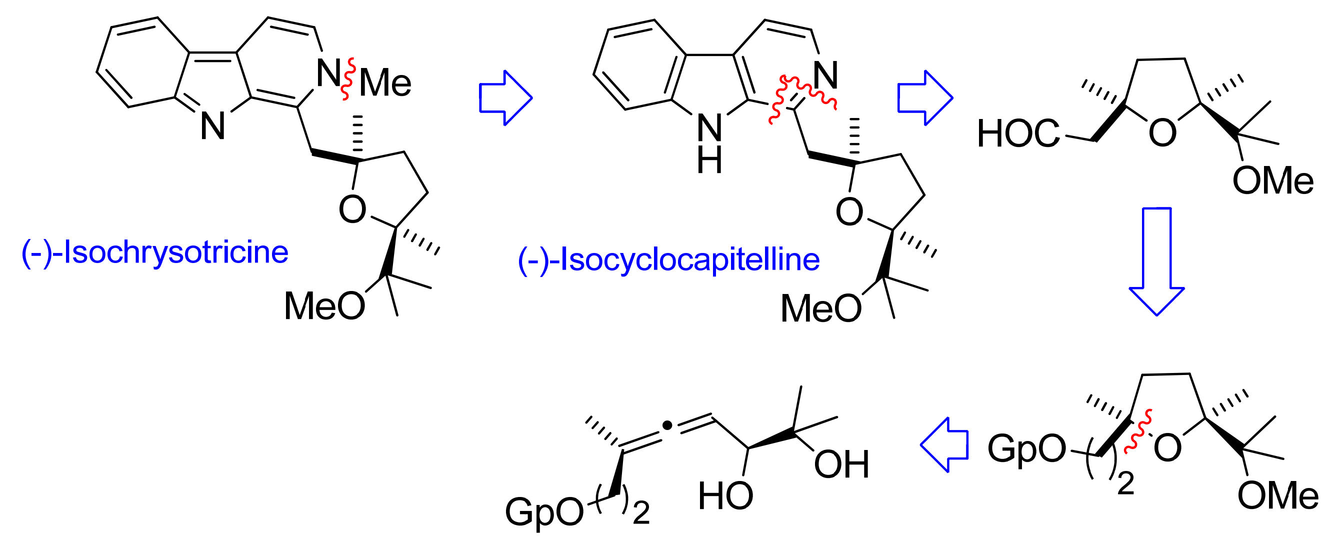


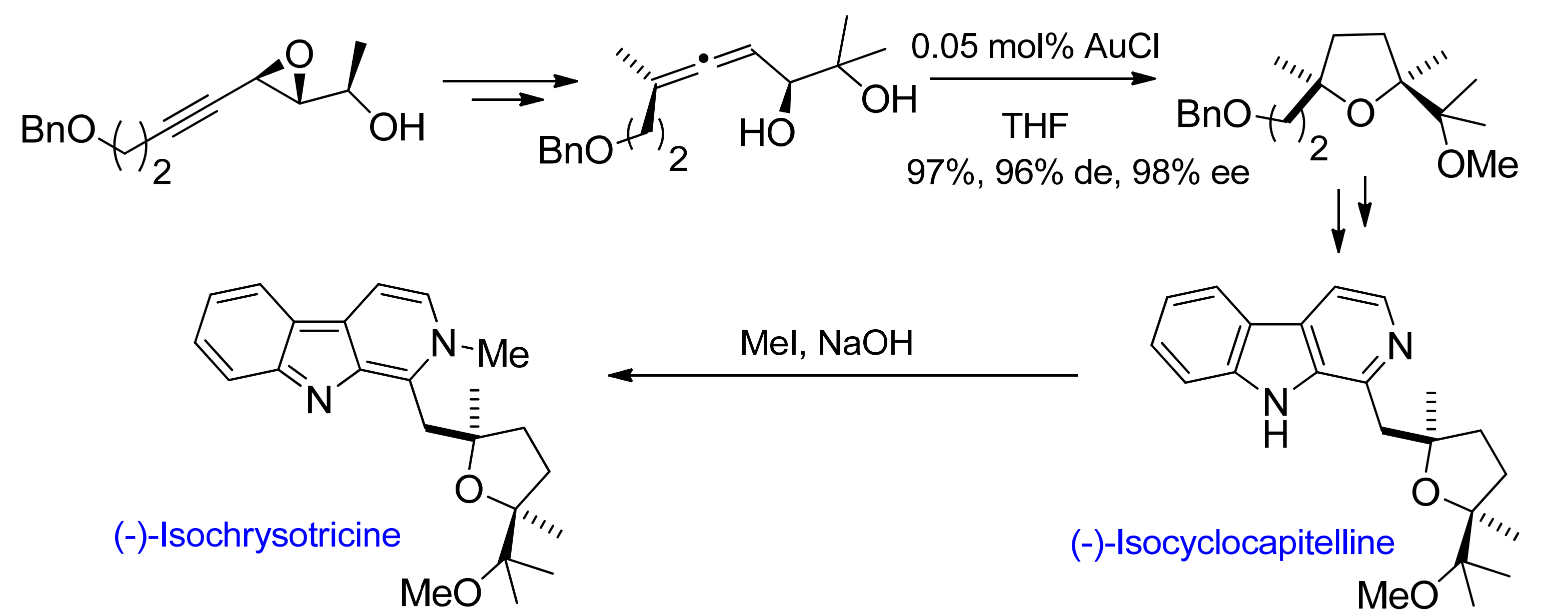
Entry	Substrate	n	R^1	R^2	R^3	Time (h)	Product	% Yield	% ee
1	**1**	1	$-(CH_2)_4-$	H	H	1	**2**	90	97
2	**8**	1	CH_3	H	H	1	**15**	91	95
3	**9**	1	CH_2CH_3	H	H	5	**16**	89	96
4	**10**	1	$-(CH_2)_4-$	H	CH_3	2	**17**	79	99
5	**11**	1	$-(CH_2)_4-$	H	Ph	30	**18**	86	92
6	**12**	1	$-(CH_2)_4-$	CH_3	H	13	**19**	90	90
7	**13**	2	CH_3	H	H	15	**20**	81	90

Chiral counterion strategy

G. L. Hamilton; E. J. Kang; M. Mba; F. D. Toste; *Science*, **2007, 317, 496**

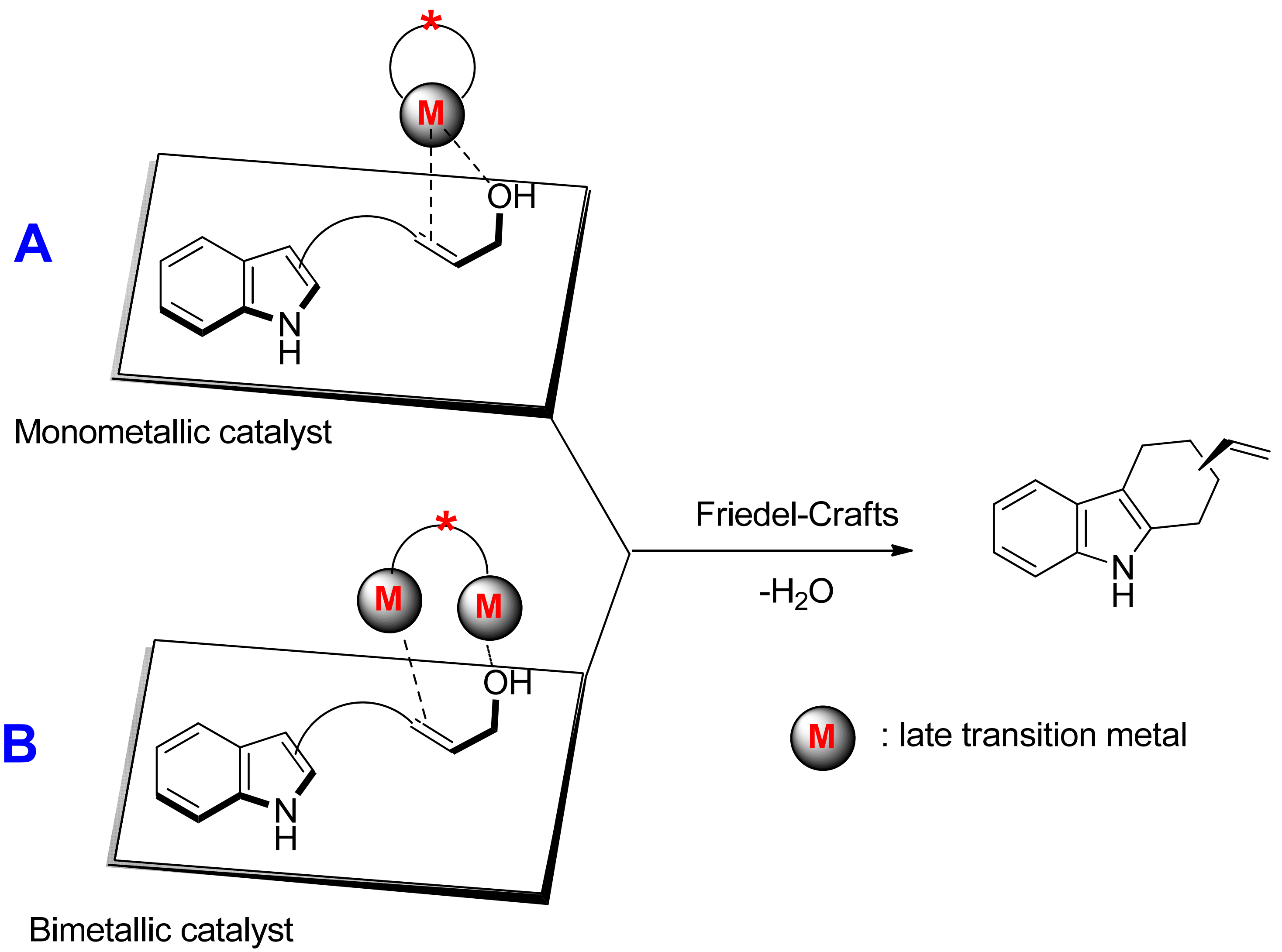
Application to the Total Synthesis of (-)-isochrysotricine





F. Volz; N. Krause, *Org. Biomol. Chem*, **2007, 5, 1519**

Asymmetric Alkene Activation



A

Monometallic catalyst

B

Bimetallic catalyst

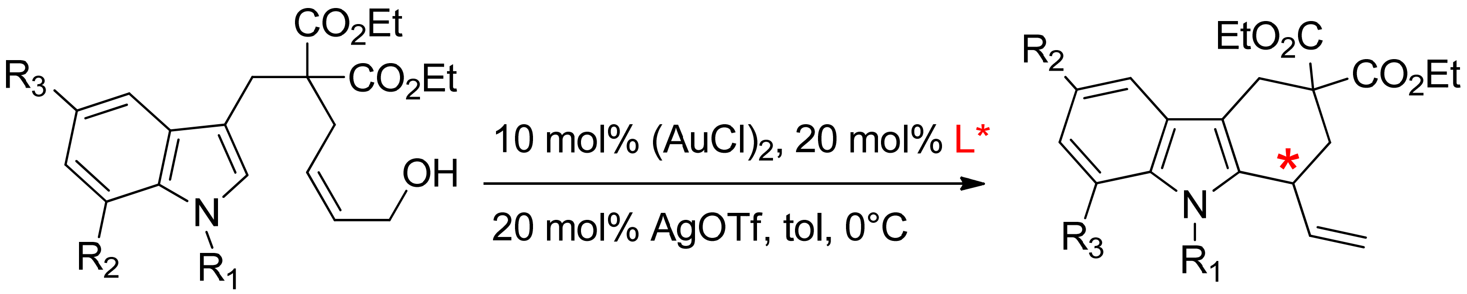
Friedel-Crafts

$-H_2O$

M : late transition metal

M. Bandini; A. Eichholzer, *Angew. Chem. Int. Ed.* **2009, 48, 9533**

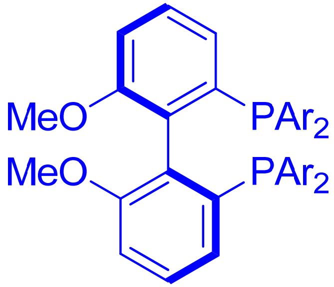
Asymmetric Alkene Activation



10 mol% $(AuCl)_2$, 20 mol% L*

20 mol% AgOTf, tol, 0°C

L*

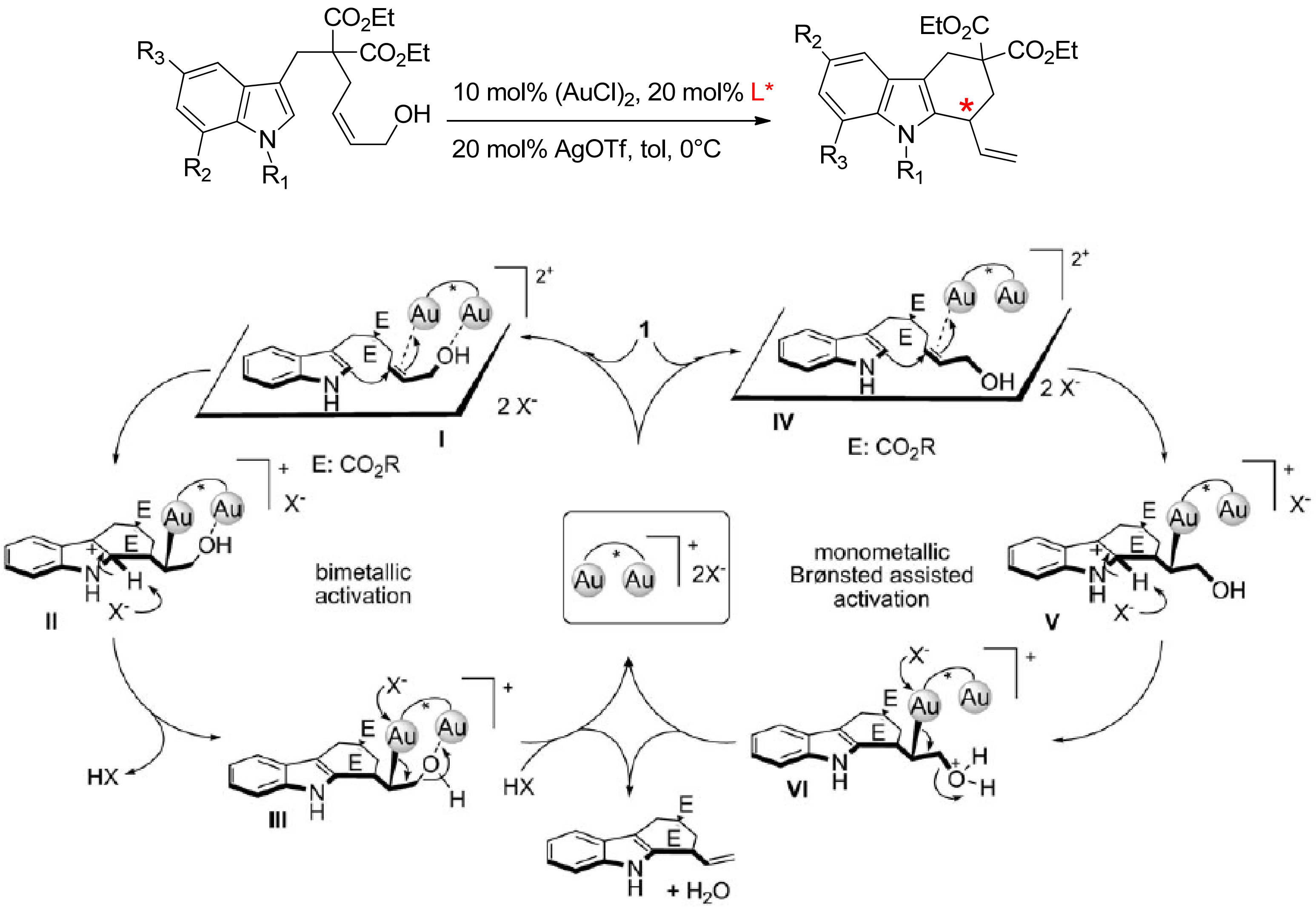


Ar= 3,5-tBu-4-MeO-C6H2

Entry	Alcohol	R/R^1/R^2/R^3	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	1b	Et/H/H/Br	48	60	86
2	1c	Et/H/H/Me	24	68	92
3[d]	1d	Et/H/H/OMe	24	79	84
4	1d	Et/H/H/OMe	48	55	96
5	1e	Et/H/Me/H	48	91	83
6[d]	1f	Et/H/H/Cl	48	52	85
7	1g	Et/Me/H/H	48	–	–[e]
8	1h	Me/H/H/H	24	74	85
9	1i	*t*Bu/H/H/H	48	53	92
10[d]	1j	Et/H/H/OBn	24	78	80
11	1j	Et/H/H/OBn	48	69	82

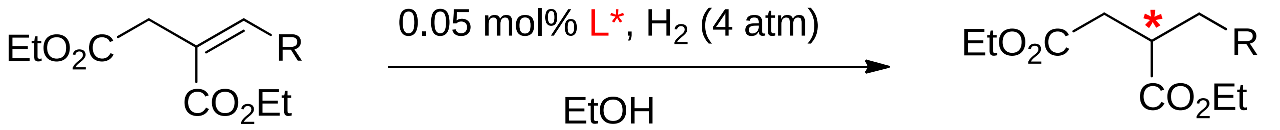
M. Bandini; A. Eichholzer, *Angew. Chem. Int. Ed.* **2009, 48, 9533**

Asymmetric Alkene Activation



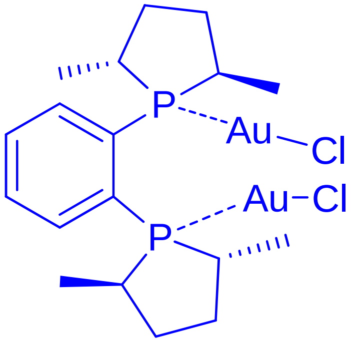
M. Bandini; A. Eichholzer, *Angew. Chem. Int. Ed.* **2009, 48, 9533**

Enantioselective Hydrogenation of Alkenes



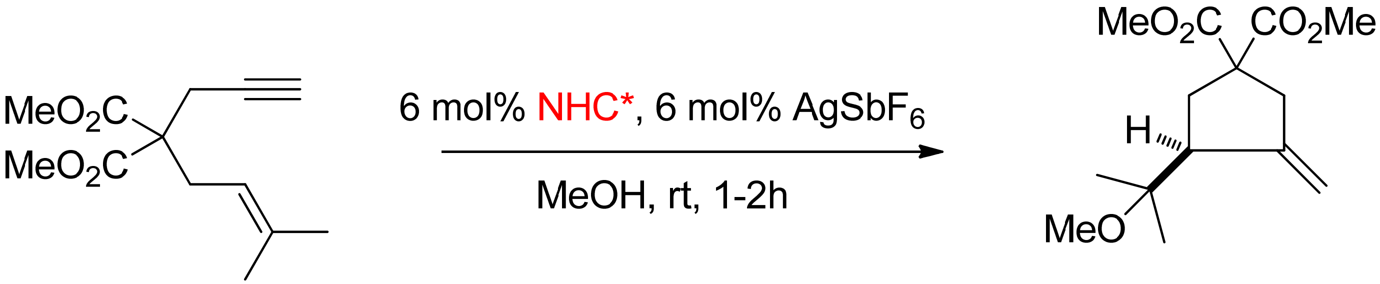
R = H	10 min, 25 °C	100% convn, 20% ee
R= phenyl	150 min, 25 °C	100% convn, 80% ee
R= 2-naphtyl	24 h, 45 °C	75% convn, 95% ee

L*

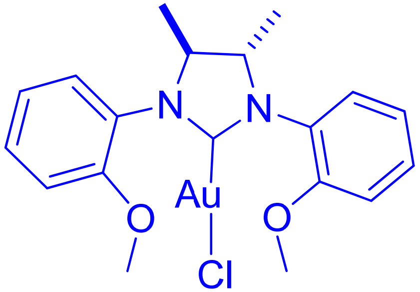


C. Gonzalez-Arellano; A. Corma; M. Iglesias; F. Sanchez, *Chem. Commun*, **2005, 3451**

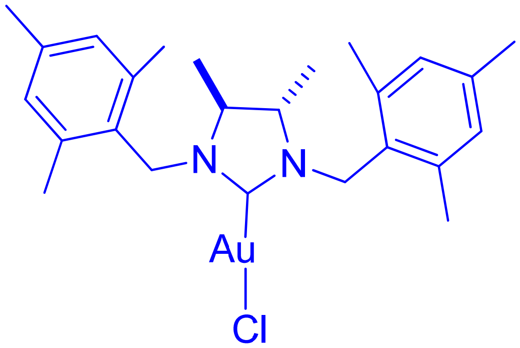
Asymmetric Cyclization of 1,3-enynes



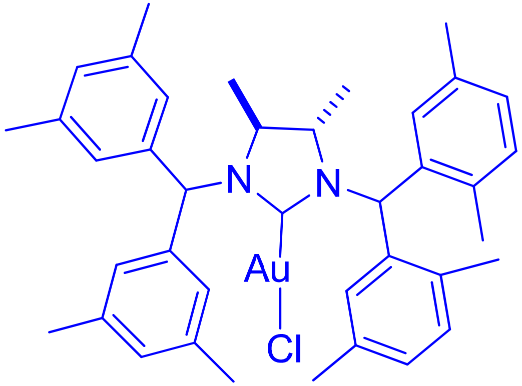
NHC*



94% yield, 5% ee



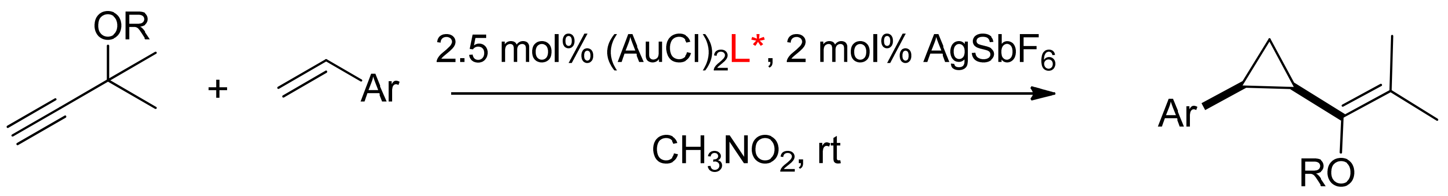
93% yield, 4% ee



95% yield, up to 59% ee

Y. Matsumoto ; K. B. Selim; H. Nakanishi; K. I. Yamada; Y. Yamamoto; K. Tomioka, *Tetrahedron Letters,* **2010, 51, 404**

Cyclopropanation of Vinyl Arene

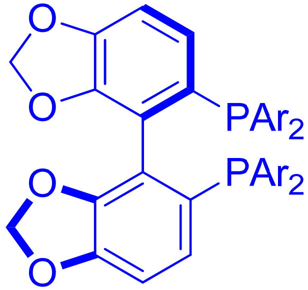


2.5 mol% $(AuCl)_2L^*$, 2 mol% $AgSbF_6$

CH_3NO_2, rt

R = Ac	Ar= ph	70% yield, 81% ee
R= Ac	Ar= 4-FC_6H_4	85% yield, 82% ee
R= Piv	Ar= 2,6-Me-4-*t*BuC_6H_2	71% yield, 94% ee

L*

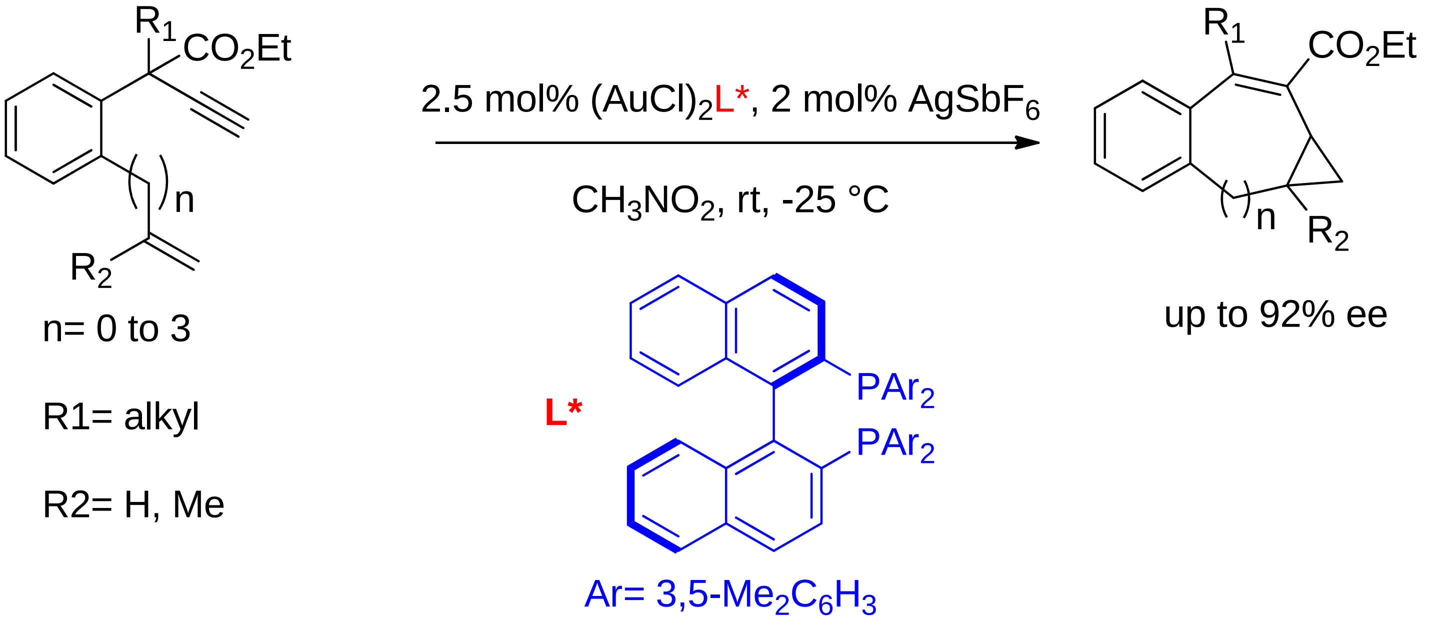


Ar= 3,5-tBu-4-MeO-C6H2

"We can make cyclopropanes without the need for explosive diazo compounds," Toste said

M. J. Johansson; D. J. Gorin; S. T. Staben; F. D. Toste, *J. Am. Chem. Soc*, **2005, 127, 18002**

Cyclopropanation of Vinyl Arene



n= 0 to 3

R1= alkyl

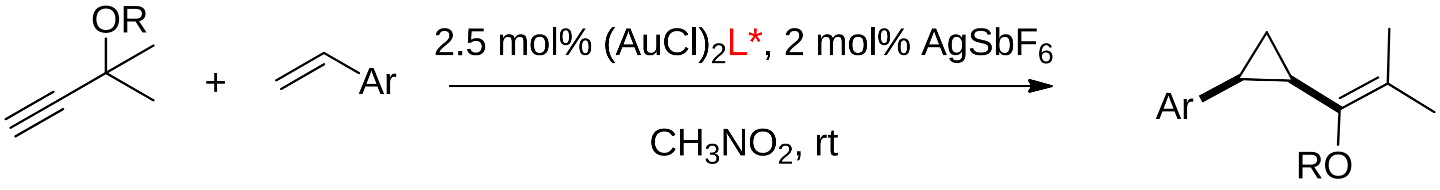
R2= H, Me

Ar= 3,5-$Me_2C_6H_3$

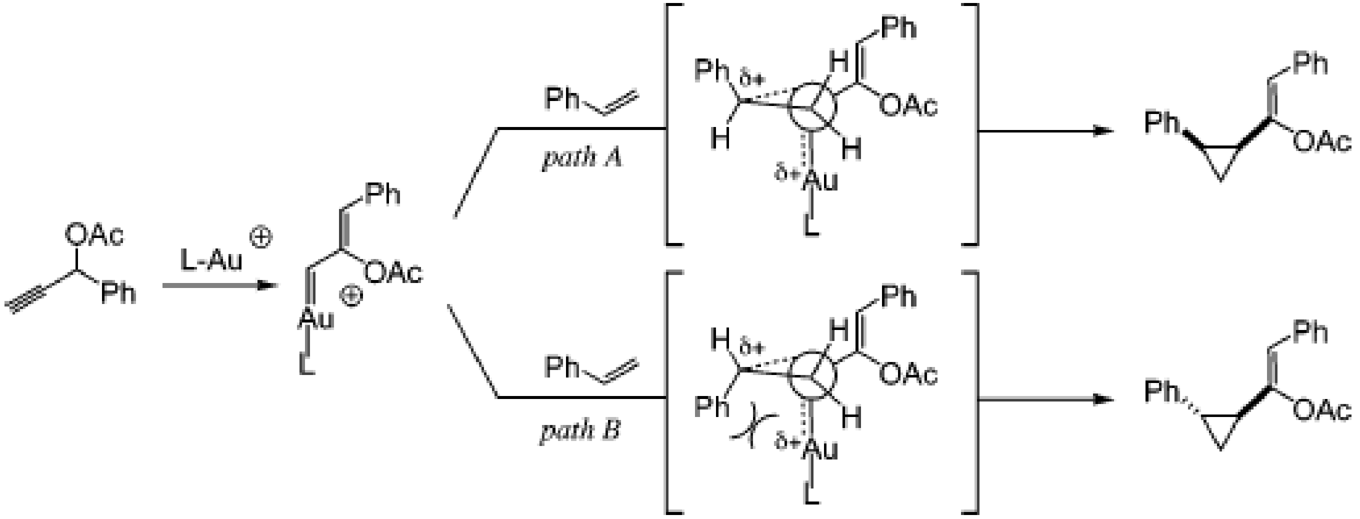
up to 92% ee

L. D. G. Watson; D. J. Gorin; S. Ritter; F. D. Toste, *J. Am. Chem. Soc*, **2009, 113, 2056**

Proposed Mecanism

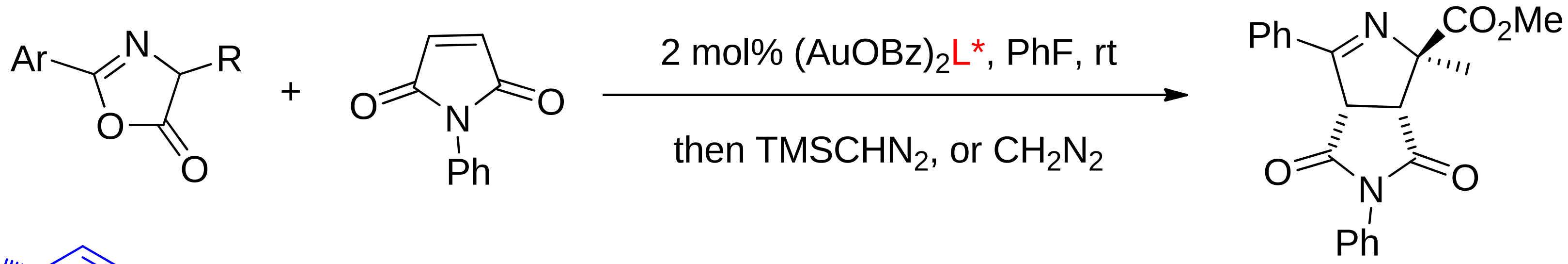


Scheme 1. Mechanistic Hypothesis



M. J. Johansson; D. J. Gorin; S. T. Staben; F. D. Toste, *J. Am. Chem. Soc*, **2005, 127, 18002**

Enantioselective 1,3-Dipolar Cycloaddition



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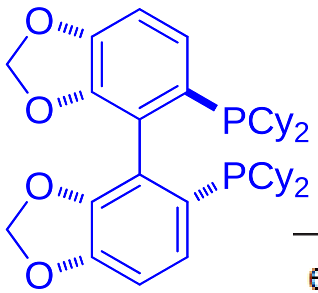
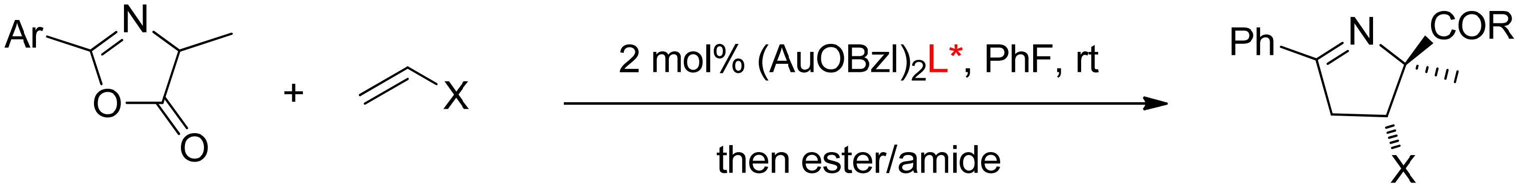


Azlactones and electronic deficient alkenes

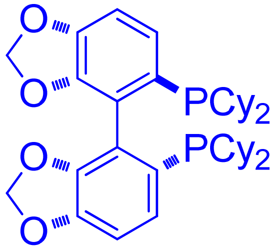
entry		product	time (h)	yield (%)[b]	ee (%)
1	b, R = Me	Ar = *p*-MeO−C_6H_4−	18	77	95
2	c, R = Me	Ar = *p*-Br−C_6H_4−	15	75	93
3	d, R = Me	Ar = *p*-Cl−C_6H_4−	15	72	92
4	e, R = Me	Ar = *p*-$NO_2C_6H_4$−	1.5	98	91
5	f, R = Me	Ar = *o*-Me−C_6H_4−	4	73	86[c]
6	g, R = H	Ar = Ph	24	84	−98[d]
7	h, R = allyl	Ar = Ph	8	86	87[c]
8	i, R = Ph	Ar = Ph	1.5	35	78[e]
9	j, R = Bn	Ar = Ph	36	71	68[c]

A. D. Melhado; M. Luparia; F. D. Toste, *J. Am. Chem. Soc*, **2007, 129, 12638**

Enantioselective 1,3-Dipolar Cycloaddition

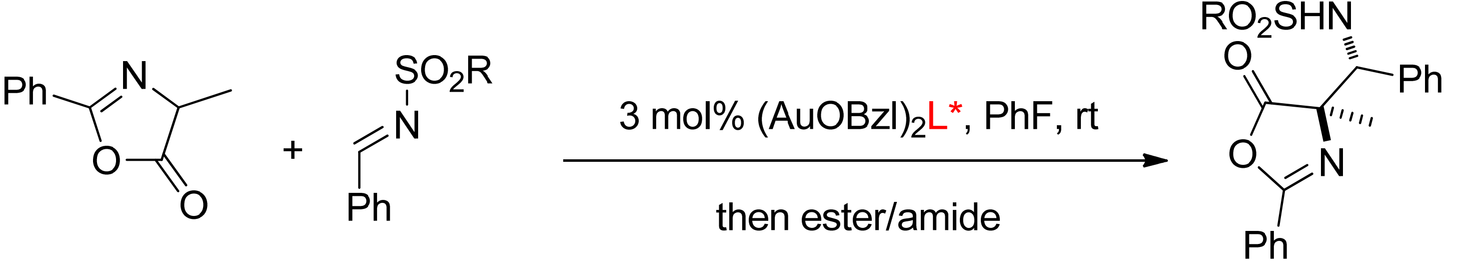


L*



entry	product		time (h)	yield (%)[b]	ee (%)
1	8a, X = $CO_2{}^tBu$	R = OMe	24	56	99[c]
2	8b, X = $CO_2{}^tBu$	R = $NHCH_2Ph$	14	74	95
3	8c, X = CO_2Et	R = OMe	14	66	90
4	8d, X = CO_2Me	R = OMe	14	89[d]	93
5	8e, X = CN	R = $NHCH_2Ph$	14	68	76

- Enatioselective Manich Reaction

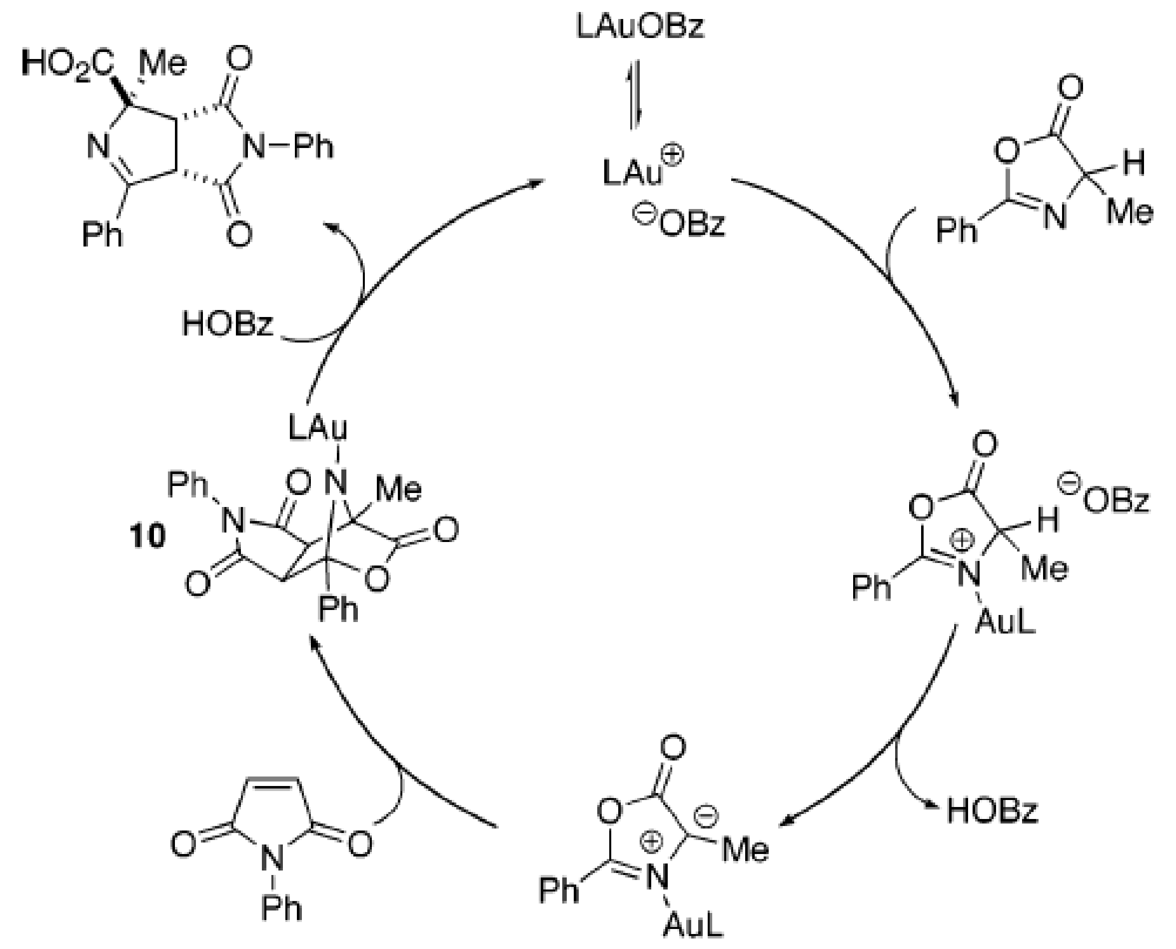


up to 76% yield, 94% ee

A. D. Melhado; M. Luparia; F. D. Toste, *J. Am. Chem. Soc*, **2007, 129, 12638**

A. D. Melhado; G. W. Amarante; Z. J. Wang; M. Luparia; F. D. Toste, *J. Am. Chem. Soc*, **2011, 133, 3517**

Proposed Mecanism



A. D. Melhado; M. Luparia; F. D. Toste, *J. Am. Chem. Soc*, **2007, 129, 12638**

Conclusion

"The future of gold catalysis still involves a lot of theoretical work, and we need to understand more about how it works," Toste said. "But already, some of these reactions are being used by medicinal chemists, and it's a really exciting field.“

Source: University of California - Berkeley

For Review see:
S. Sengupta, X. Shi, *ChemCatChem*. **2010, 2, 609**
R. A. Widenhoefer, *Chem. Eur. J*. **2008, 14, 5382**