28 58.69

Ni

Nickel

Nickel-Catalyzed Multicomponent Coupling of Alkynes

-Recent development in methodologies and applications

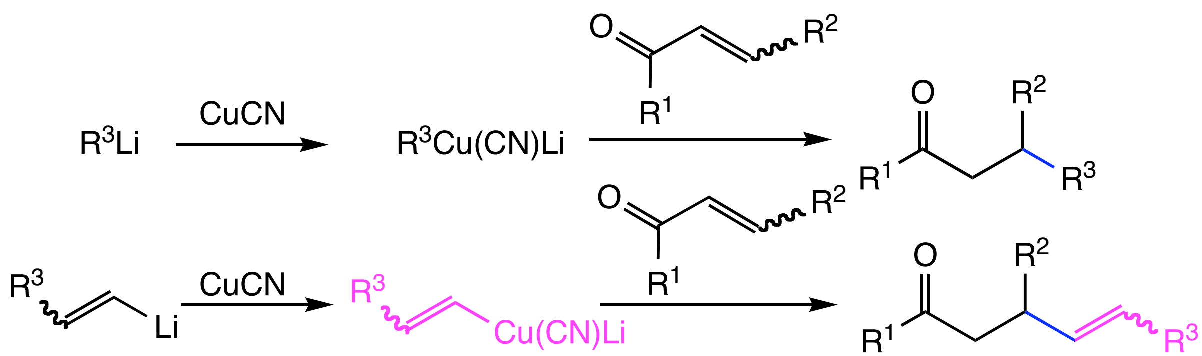
Zhenjie Lu

Department of Chemistry, MSU

January 28, 2004

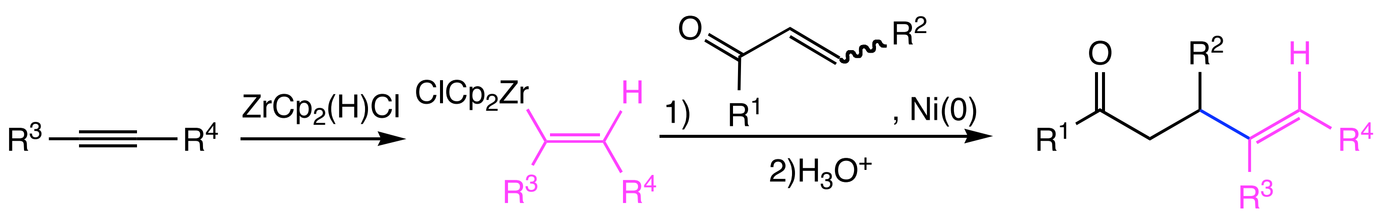
Background Introduction

➢ Conjugate addition using cuprates - well established reactions



- Stoichiometric copper complex must be used.
- Alkenylcuprate are thermally unstable.
- The loss of double bond stereochemistry may occur.

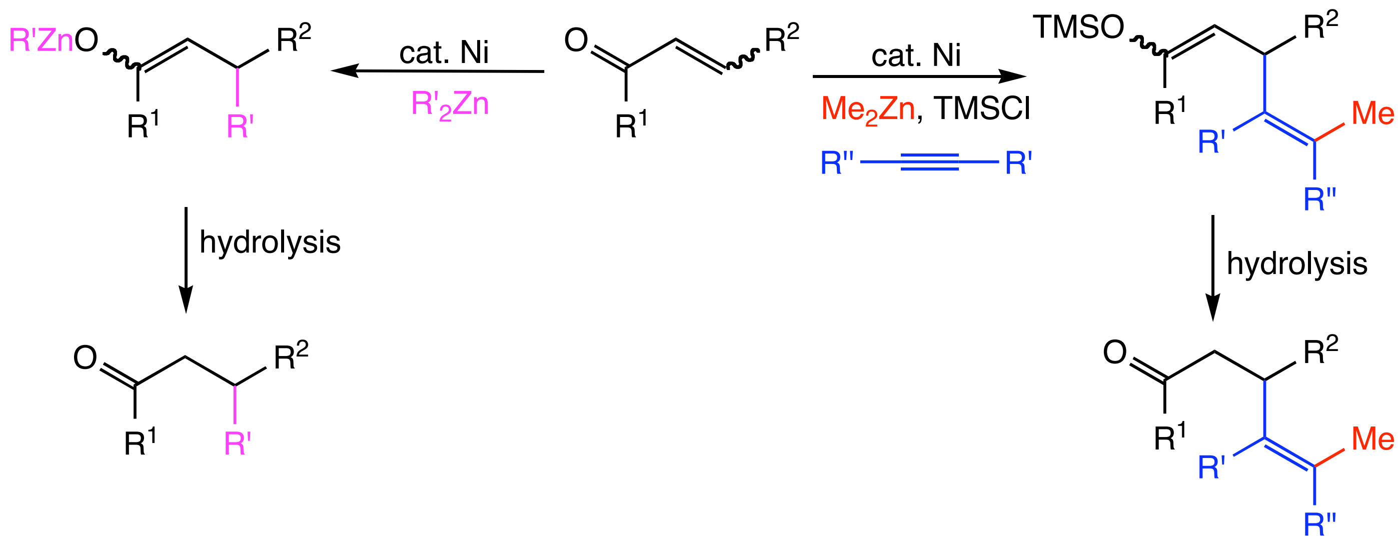
➢ Conjugate addition using nickel-catalyzed transmetallation process



up to 84% yield

1. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*. *Part B*, 2001, 477.
2. Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc*. **1980**, *102*, 1333.

Discovery of Nickel-catalyzed Coupling Reaction with Alkynes

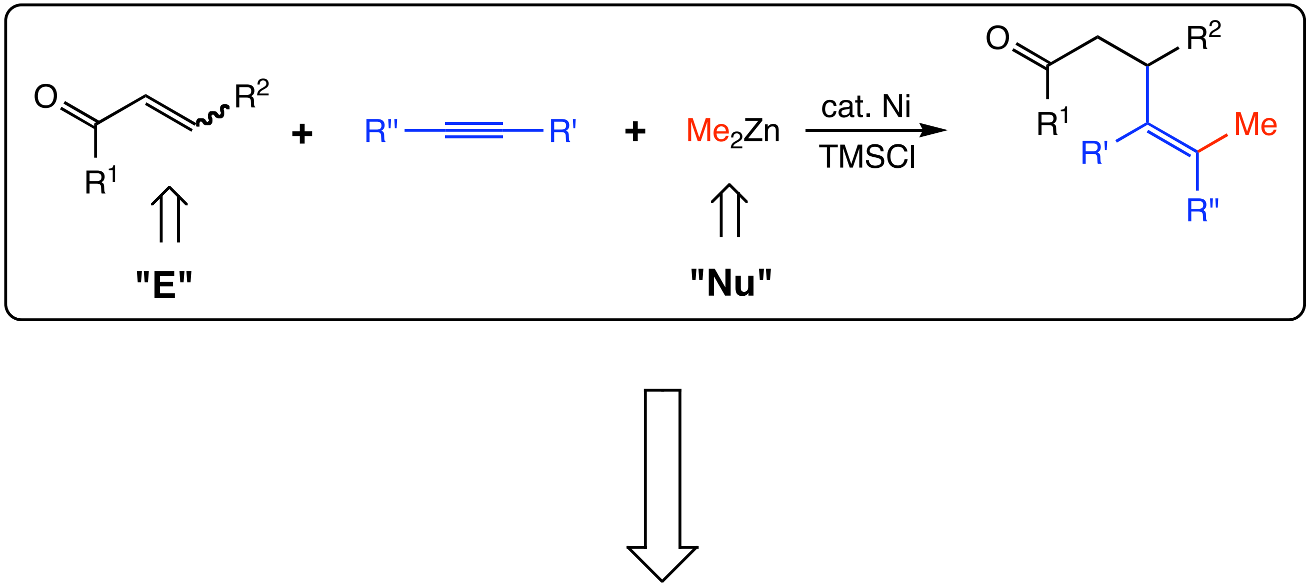


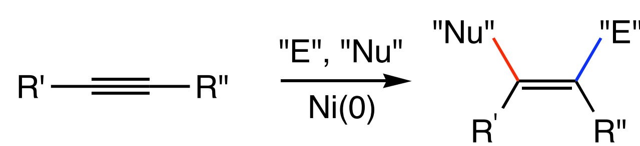
Conjugate addition

Tandem coupling

1. Ikeda, S.; Sato, Y. *J. Am. Chem. Soc*. **1994**, *116*, 5975.
2. Ikeda, S.; Yamamoto, H.; Kondo, K; Sato, Y. *Organometallics*. **1995**, *14*, 5015.

Nickel Catalyzed Multi-Component Coupling of Alkynes - A General Scheme





"E" = enone, enal, aldehyde, imine, CO_2, epoxide

"Nu" = R(M)

1. Ikeda, S.; Sato, Y. *J. Am. Chem. Soc*. **1994**, *116*, 5975.
2. Ikeda, S.; Yamamoto, H.; Kondo, K; Sato, Y. *Organometallics*. **1995**, *14*, 5015.

Major Contributors in the Field

28 58.69
Ni
Nickel

Professor John Montgomery
Wayne State University

- Intramolecular coupling of enones or enals with alkynes

Professor Timothy F. Jamison
Massachusetts Institute of Technology

- Asymmetric coupling of aldehydes, imines and epoxides with alkynes

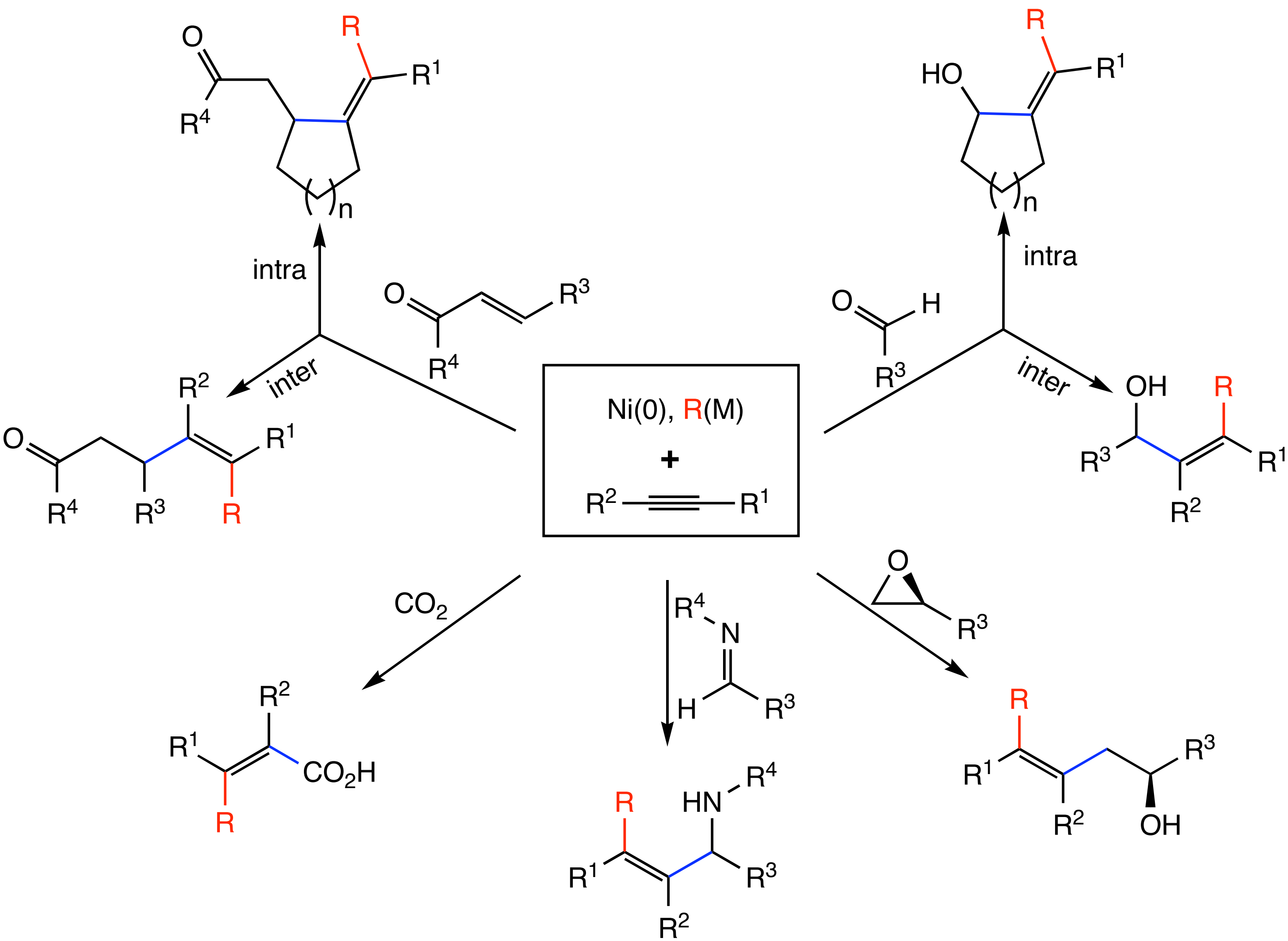
Professor Shin-ichi Ikeda
Nagoya City University

- Intermolecular coupling of enones or enals with alkynes

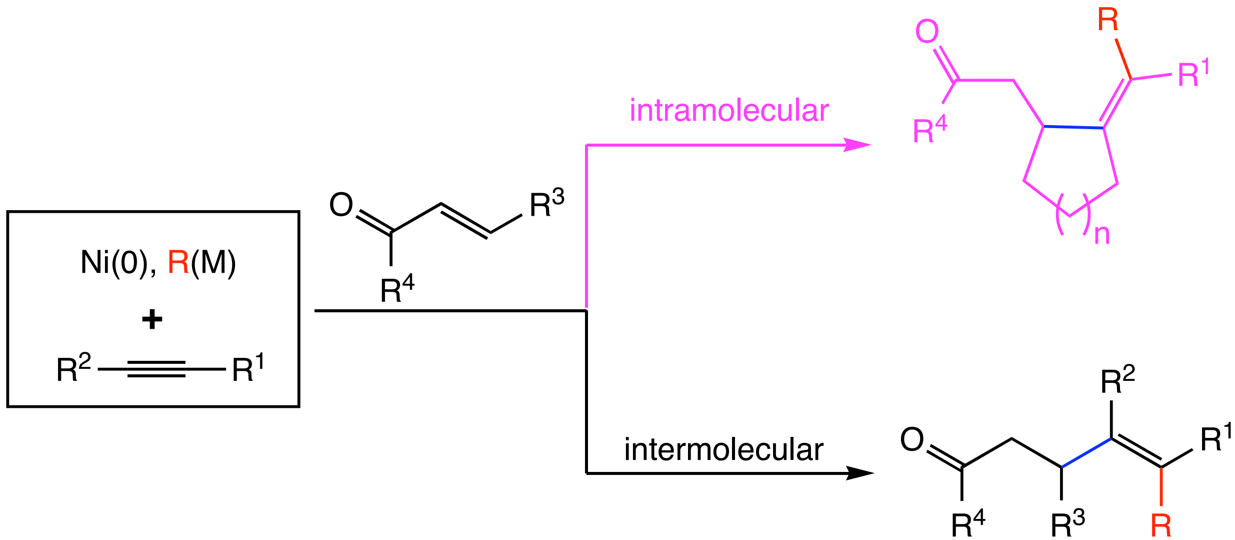
Professor Miwako Mori
Hokkaido University

- Coupling of CO_2 with alkynes, and aldehydes with dienes

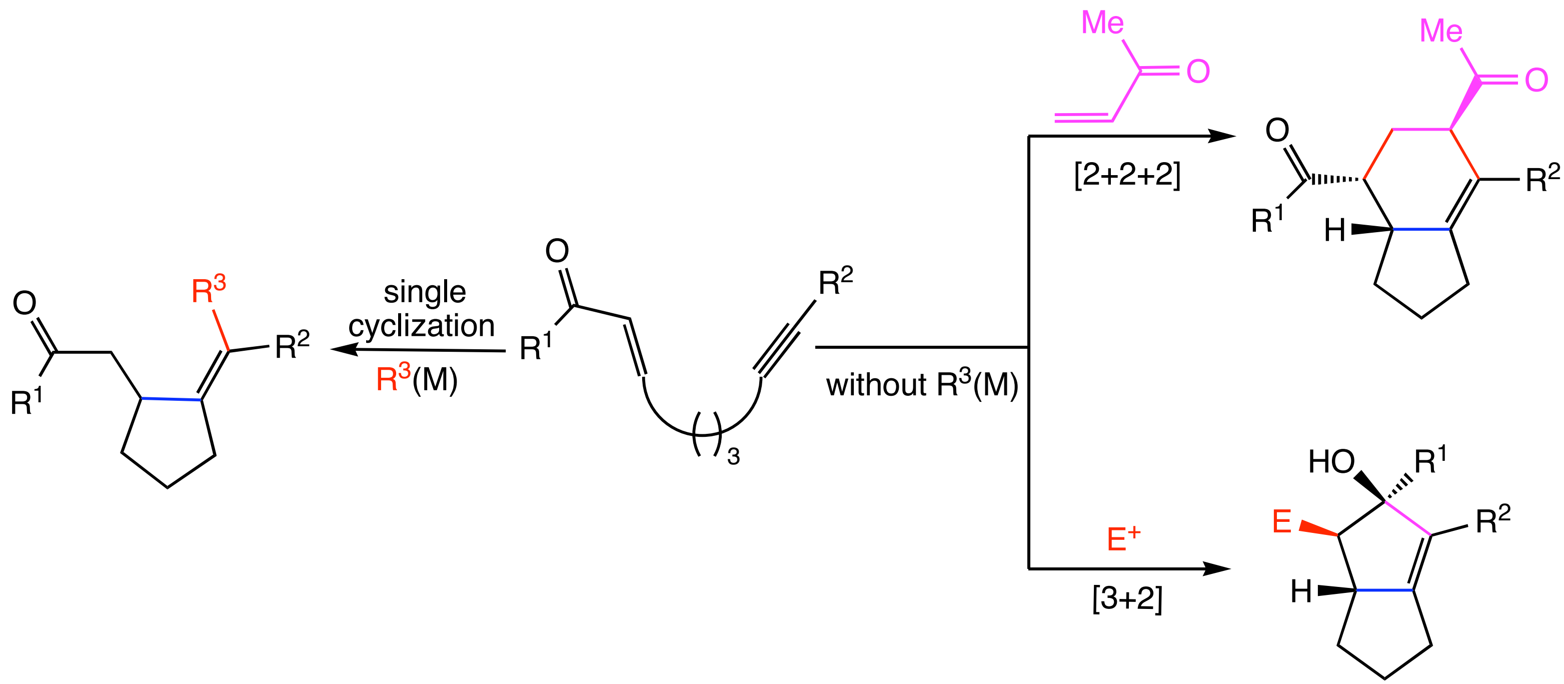
Outline



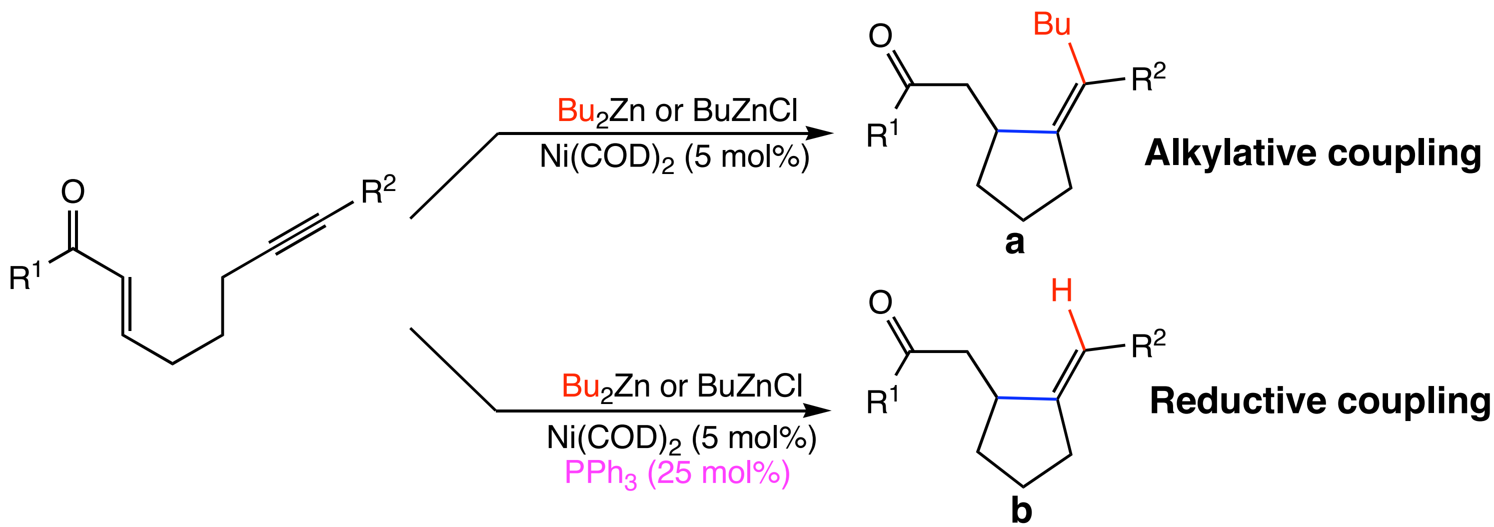
Intramolecular Coupling of Alkynes and Enones



Intramolecular Cyclization of Enones with Alkynes



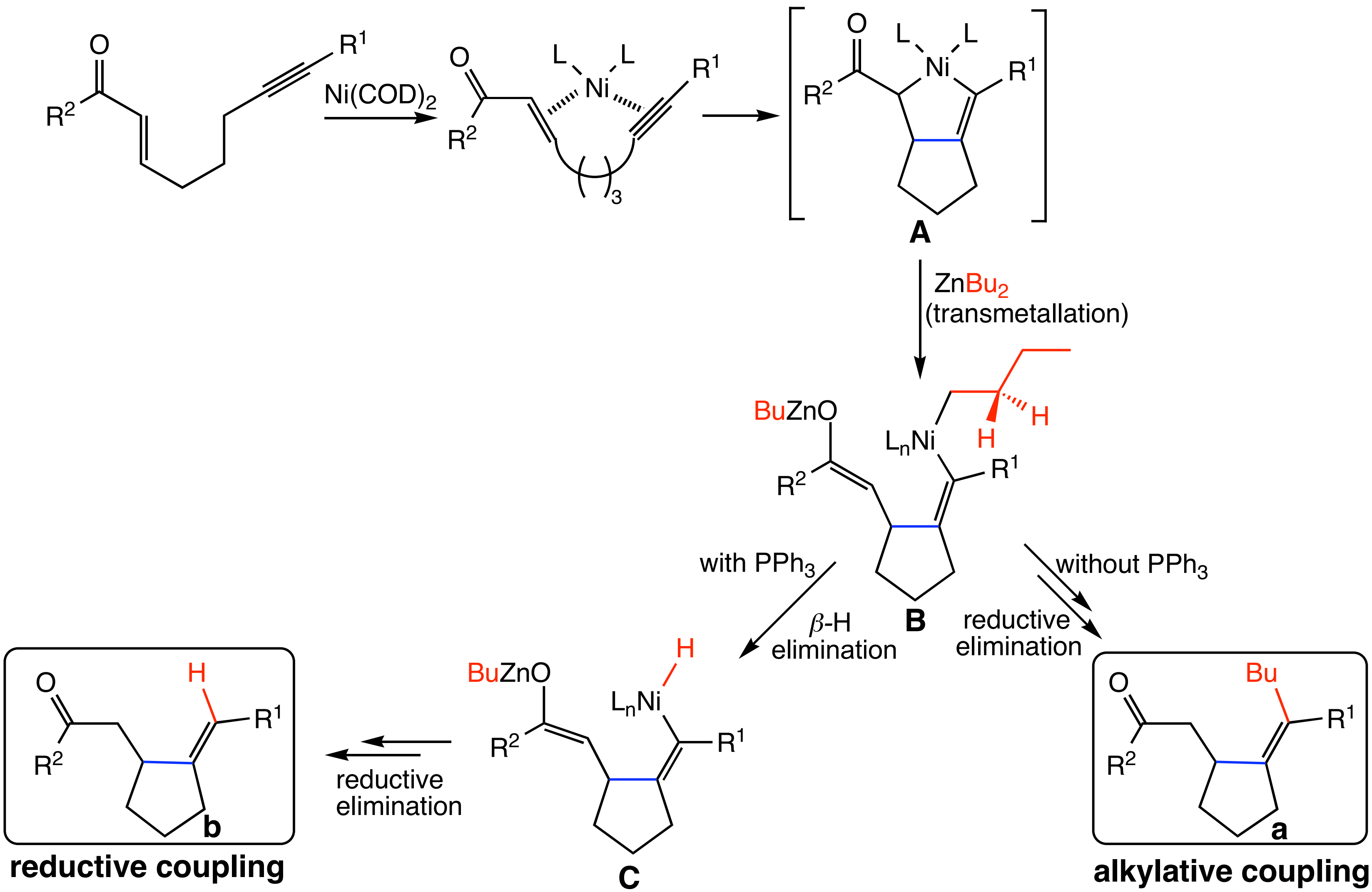
Single Cyclization of Enone and Alkyne



entry	ligand	R^1	R^2	**a** yield, %	**b** yield, %
1	-	H	Me	82	0
2	-	H	Bu	51	11
3	PPh_3	H	Bu	0	92
4	-	Ph	Bu	68	8
5	PPh_3	Ph	Bu	19	47

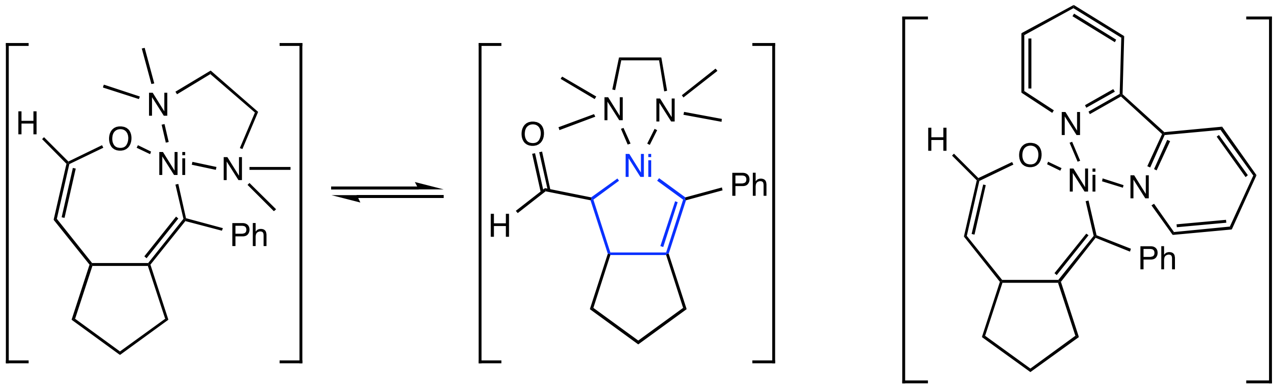
Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099.

Proposed Mechanism



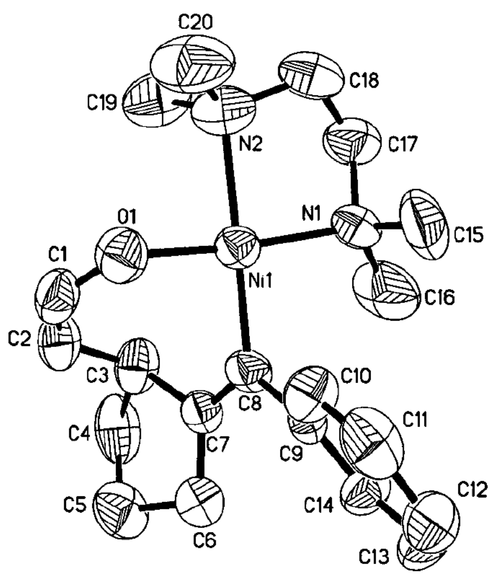
1. Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099.
2. Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911.
3. Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467.

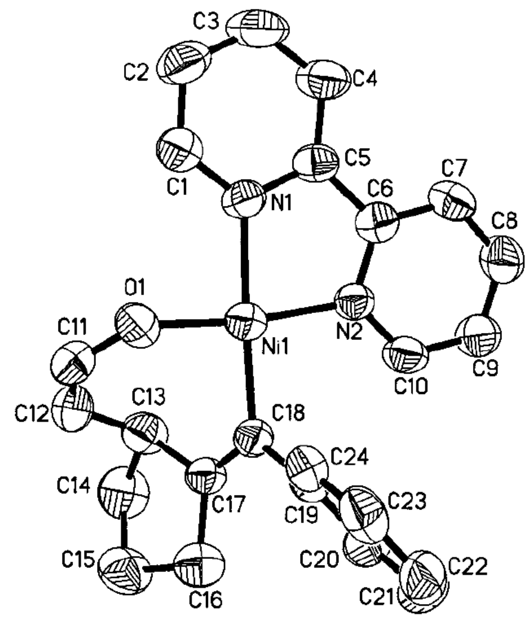
X-ray Structures of Nickel-metallocycles



A

B

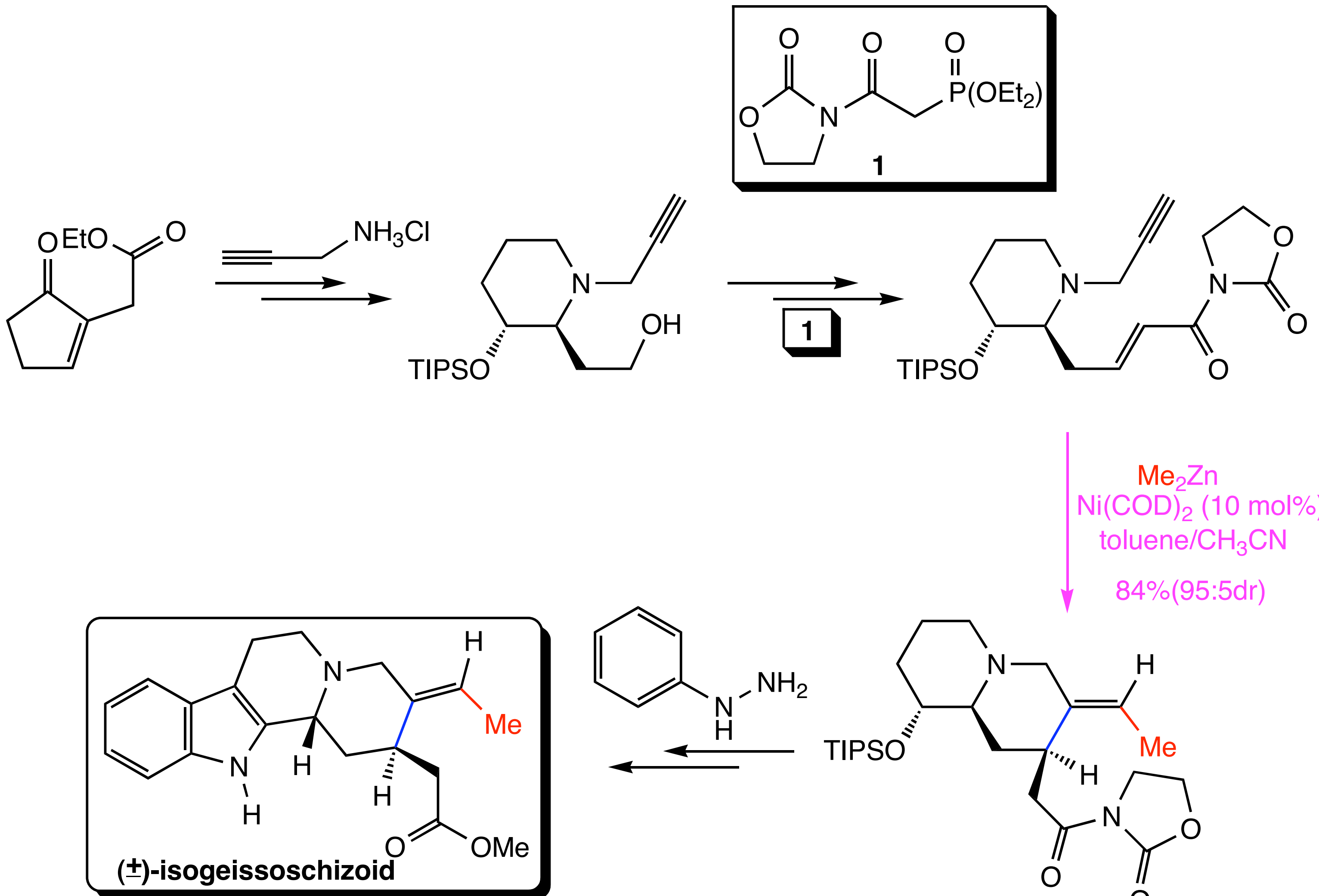




☆ X-ray structures of the nickel-metallocycles supported the proposed mechanism.

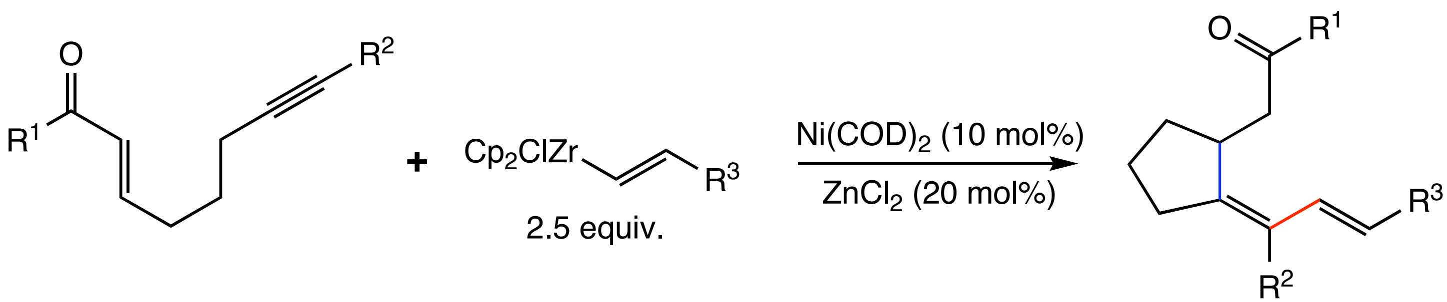
Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics*. **2001**, *20*, 370.

Total Synthesis of Isogeissoschizoid Skeleton



Fornicola, R. S.; Subburaj, K.; Montgomery, J. *Org. Lett*. **2002**, *4*, 615.

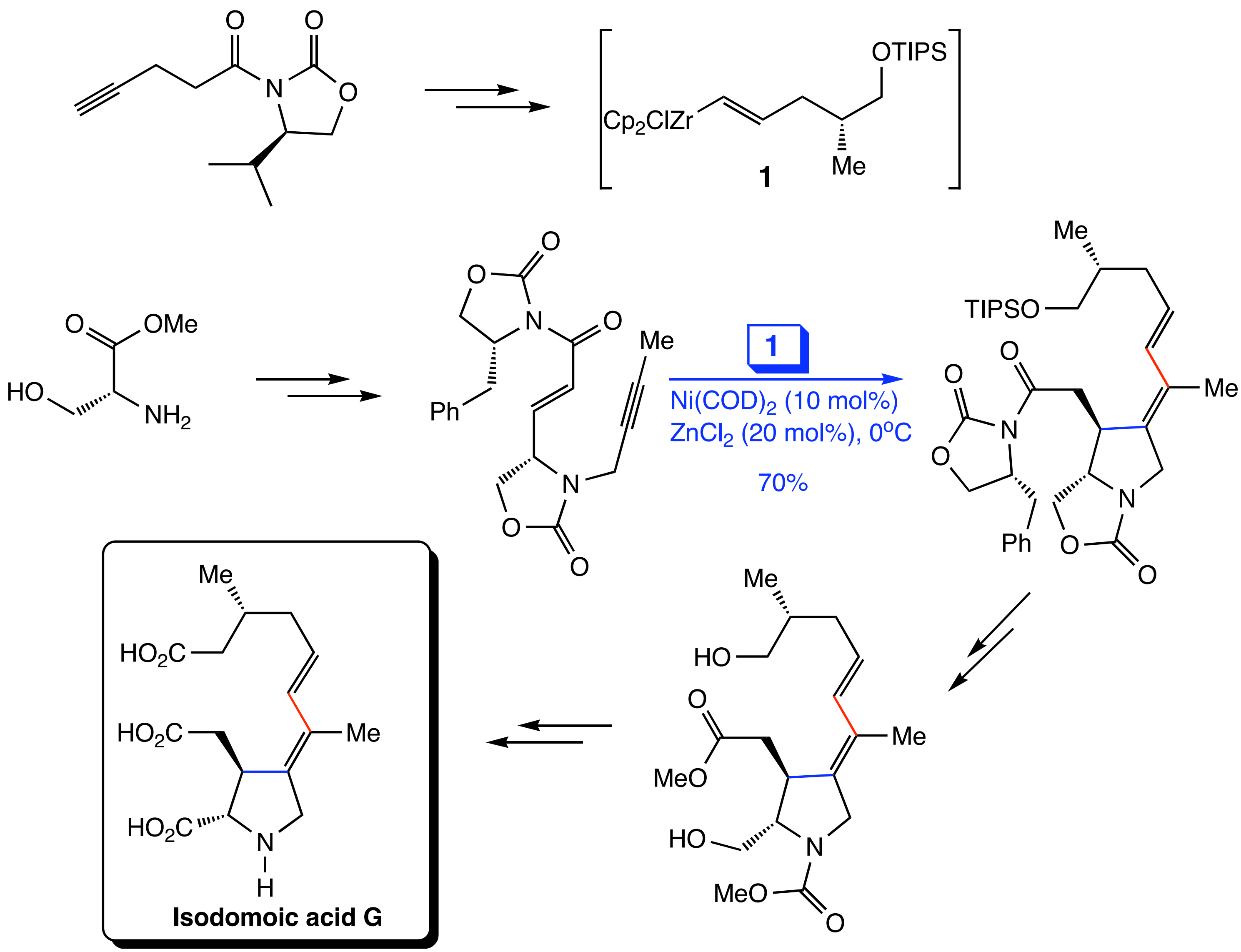
Alkylative Coupling - Vinyl Zr as Coupling Partner



entry	R^1	R^2	R^3	yield, %
1	Me	Ph	C_6H_{13}	74
2	Ph	H	C_6H_{13}	80
3	Ph	Me	$(CH_2)_4$OTBS	75
4	H	Ph	C_6H_{13}	68
5	H	Me	Ph	66

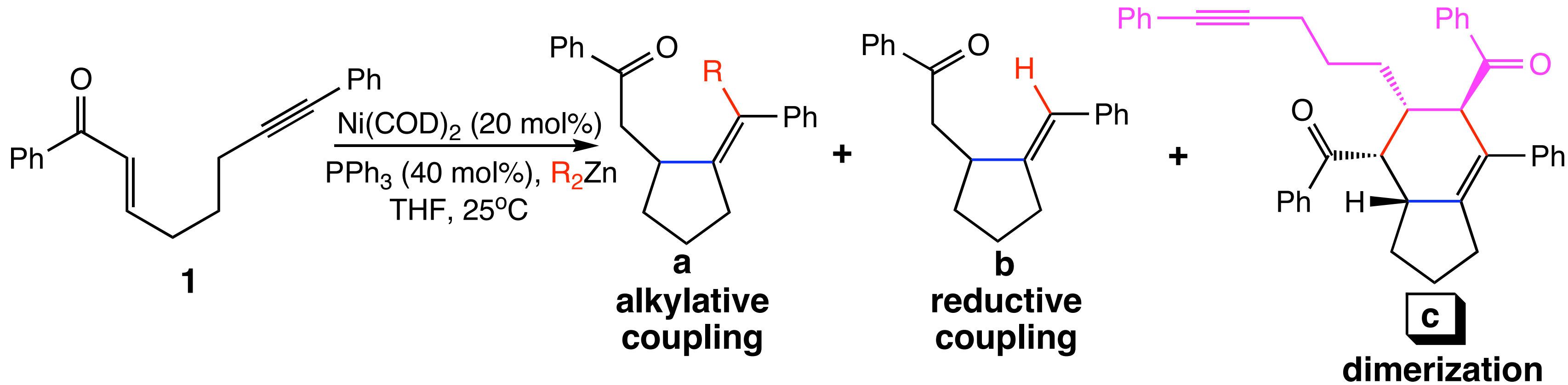
Ni, Y.; Amarasighe, K. K. D.; Montgomery, J. *Org. Lett.* **2002**, *4*, 1743.

Total Synthesis of Isodomoic Acid G



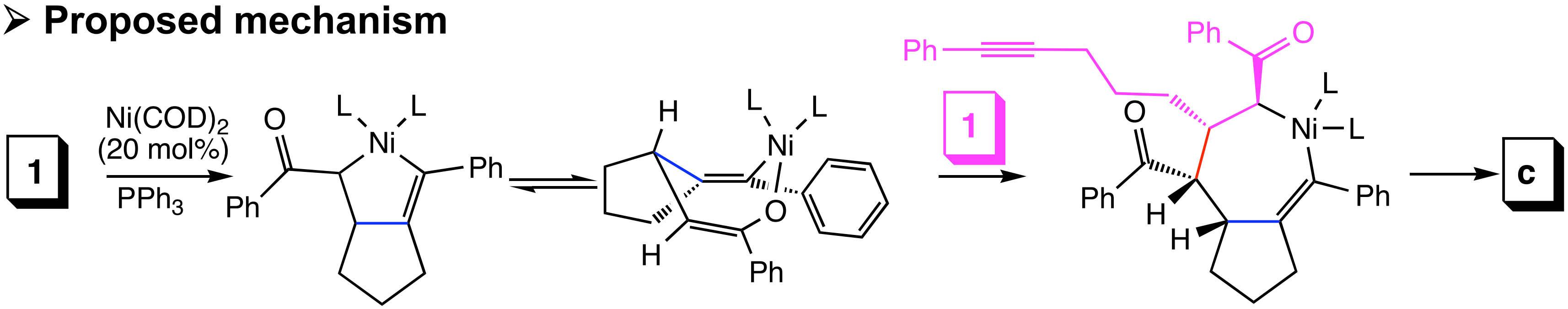
Ni, Y.; Amarasinghe, K. K. D.; Ksebati, B.; Montgomery, J. *Org. Lett.* **2003**, *5*, 3771.

Discovery of [2+2+2] Cyclization



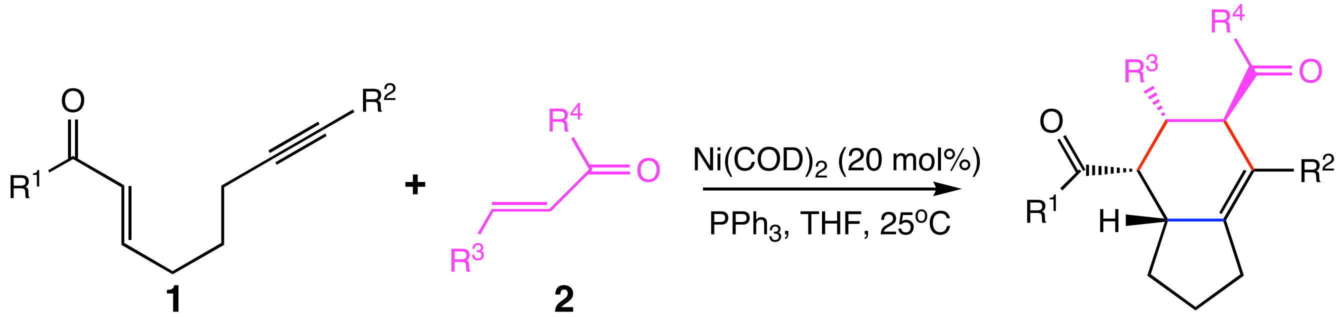
R_2Zn	yield of **a**	yield of **b**	yield of **c**
$(n\text{-Bu})_2Zn$	19	47	trace
$(t\text{-Bu})_2Zn$	0	10	71
none	0	0	99

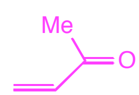
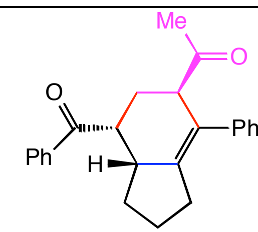
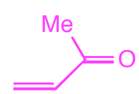
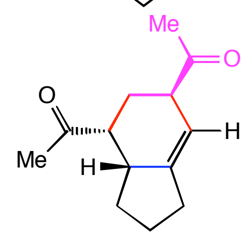
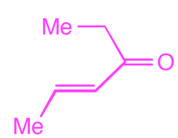
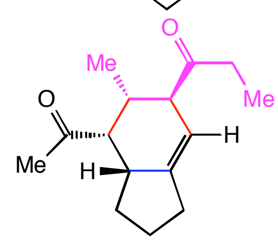
➢ **Proposed mechanism**



Seo, J.; Chui, H. M. P.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 476.

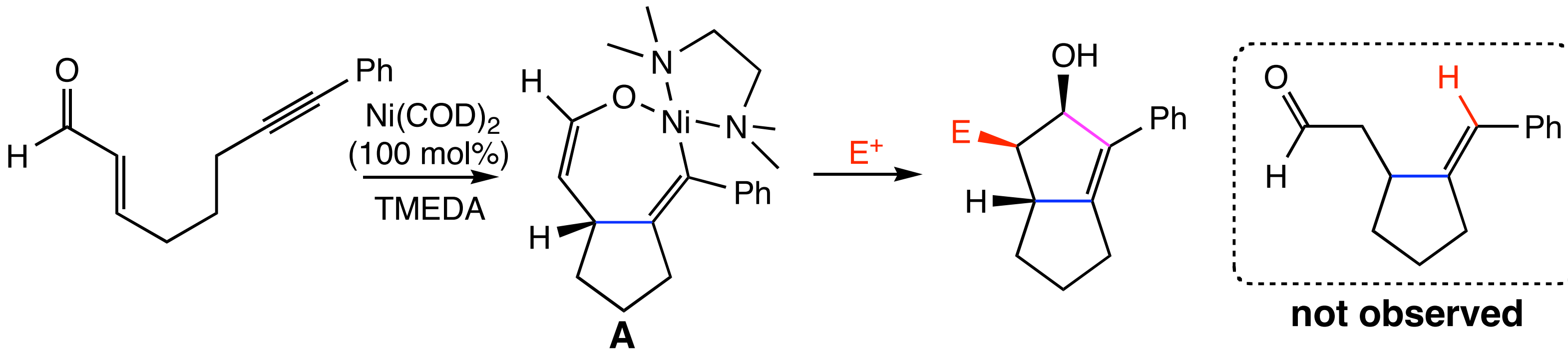
[2+2+2] Cyclization

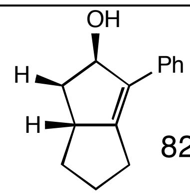
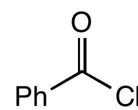
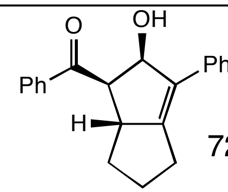
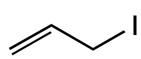
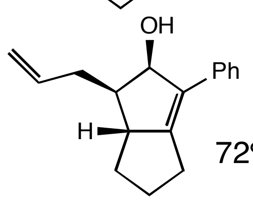
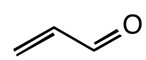
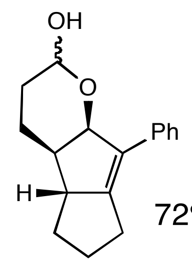
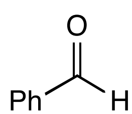
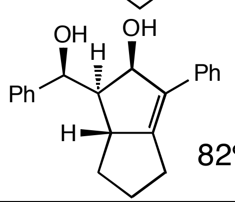


entry	R^1	R^2	**2**	product	Yield (%)
1	Ph	Ph			75
2	Me	H			68, 4:1dr
3	Me	H			36

Seo, J.; Chui, H. M. P.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 476.

[3+2] Cyclization

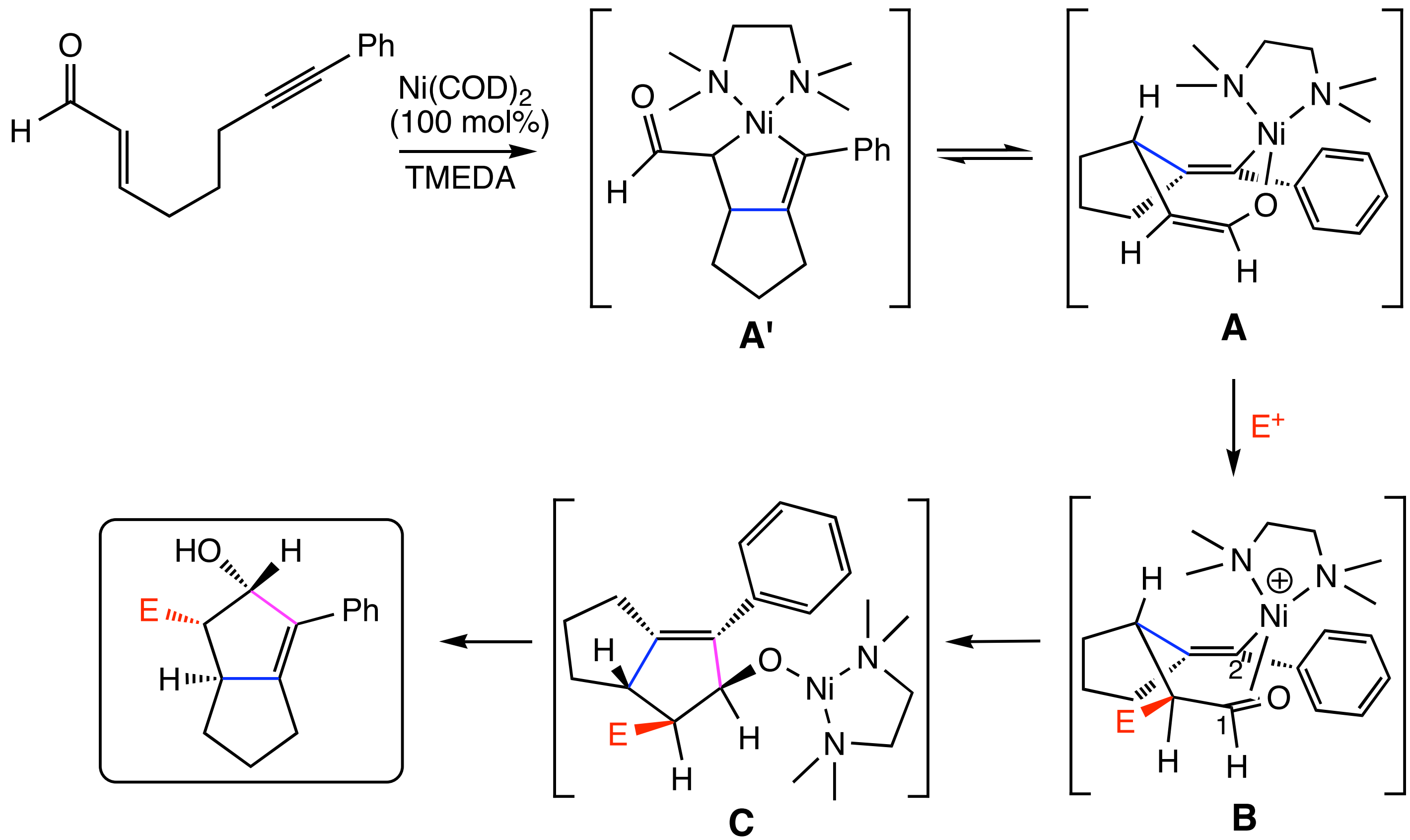


entry	electrophile	product (yield,%)	entry	electrophile	product (yield,%)
1	H_3O^+	 82%	4		 72%
2		 72%	5		 72%
3		 82%			

- Single diastereomer obtained in entry 1~4.

1. Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6775.
2. Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J; Montgomery, J. *J. Am. Chem. Soc*. **2003**, *125*, 13481.

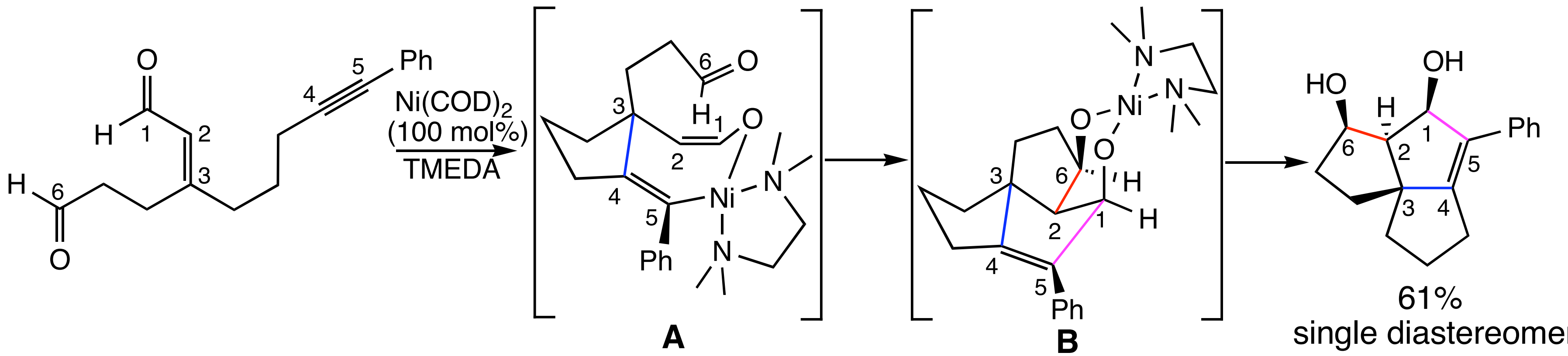
Proposed Mechanism of [3+2] Cyclization



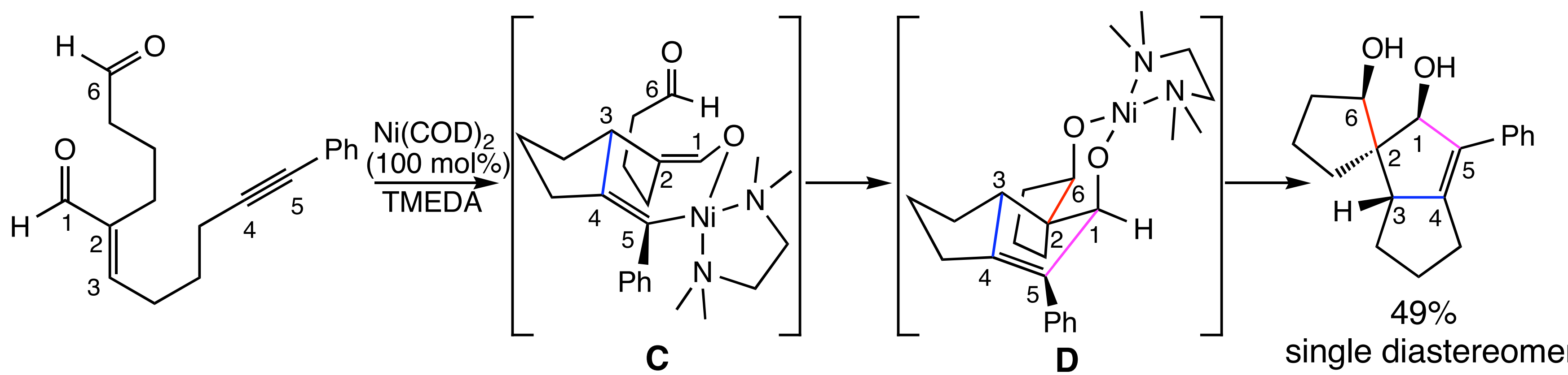
Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J; Montgomery, J. *J. Am. Chem. Soc*. **2003**, *125*, 13481.

Cascade Cyclization

➢ Cyclization of β- substituted enal

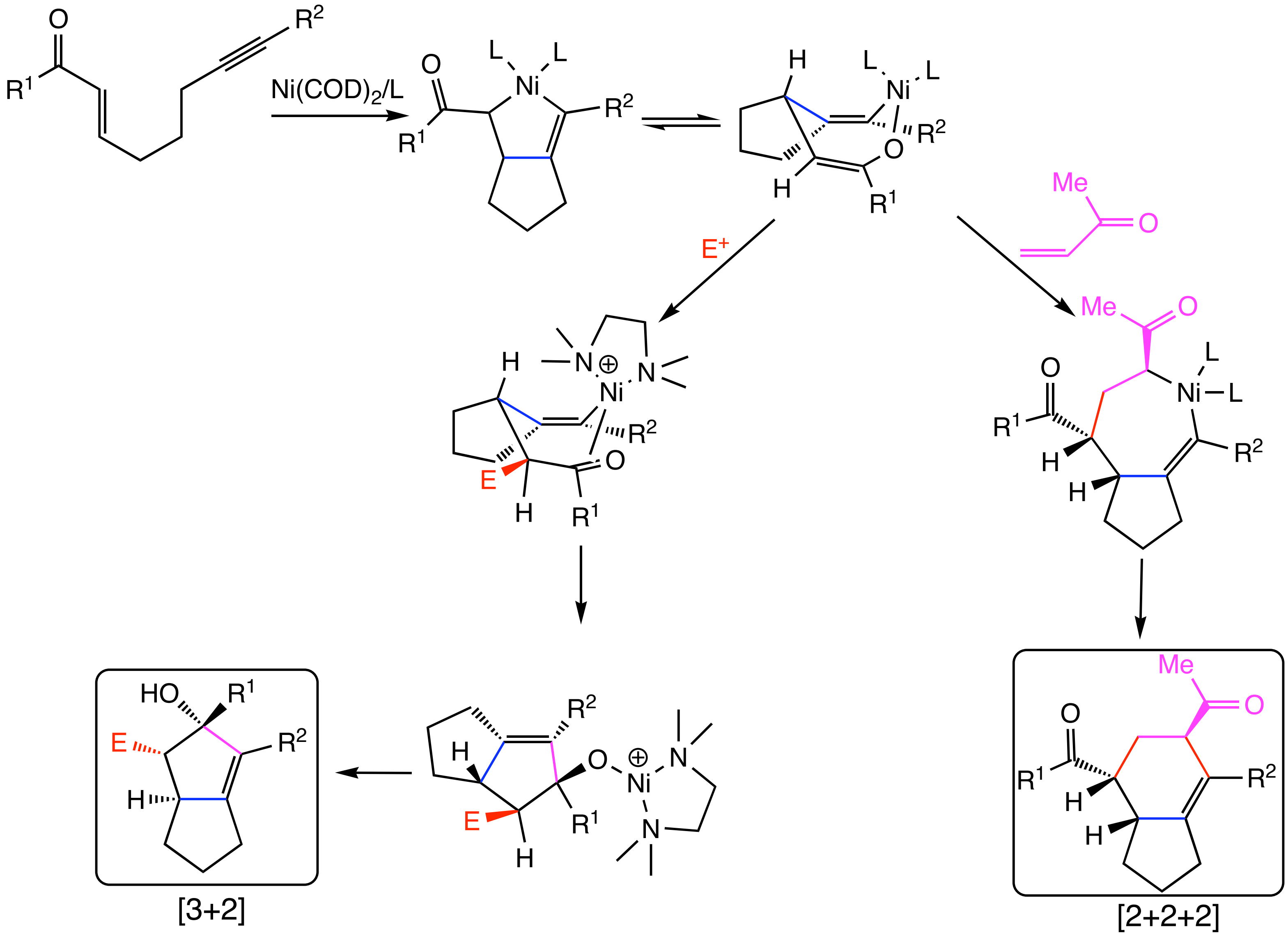


➢ Cyclization of α- substituted enal



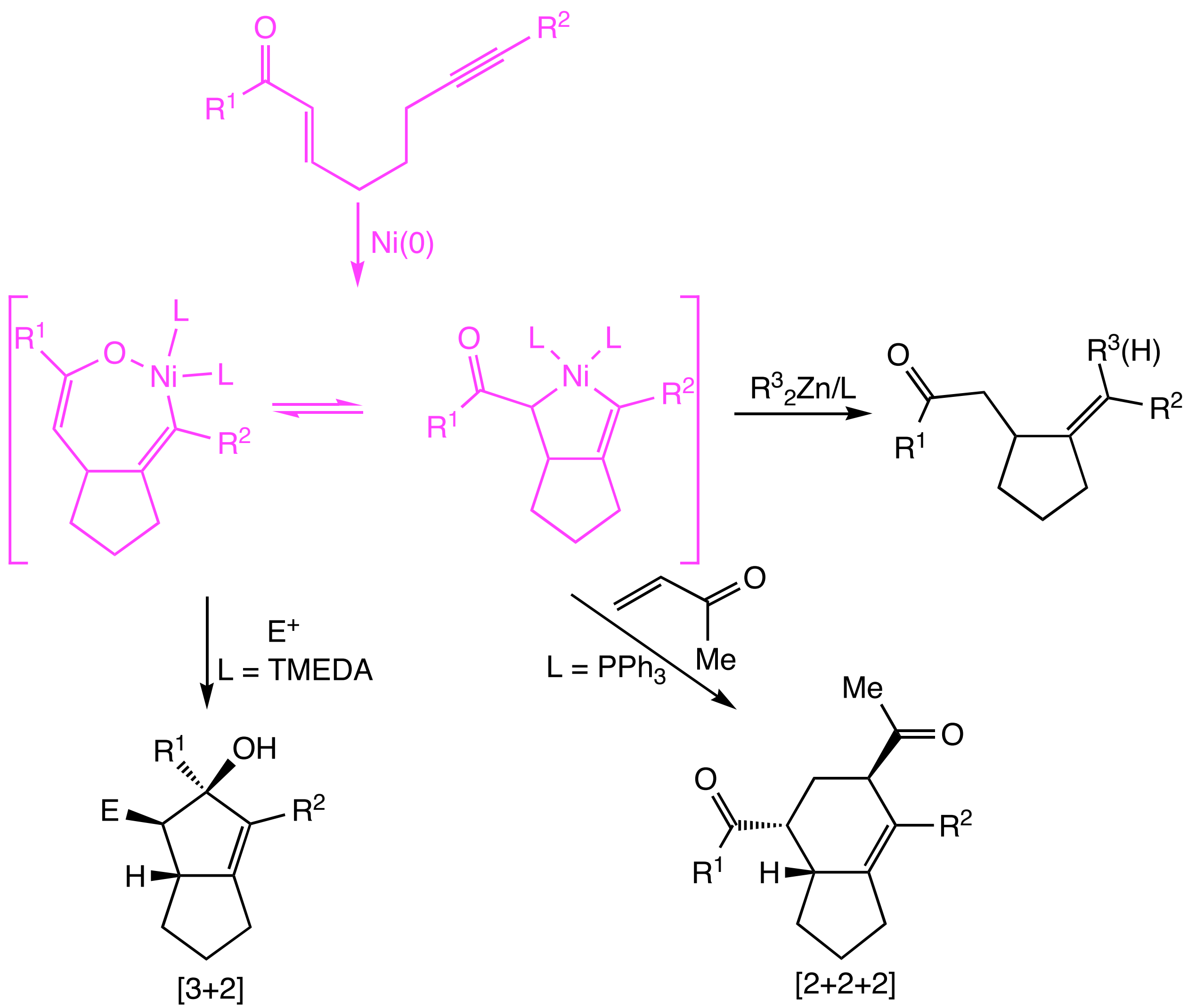
Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 13481.

Proposed Mechanism of Two Cyclizations

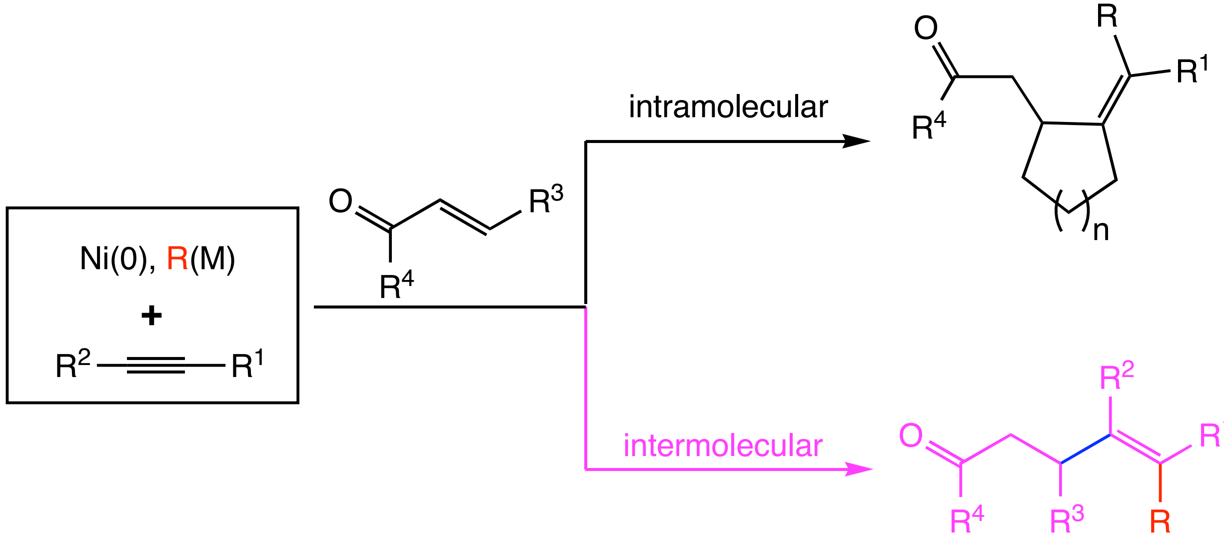


1. Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6775.
2. Montgomery, J.; Amarasinghe, K. K. D.; Chowdhury, S. K.; Oblinger, E.; Seo, J.; Savchenko, A. V. *Pure. Appl. Chem.* **2002**, *74*, 129.

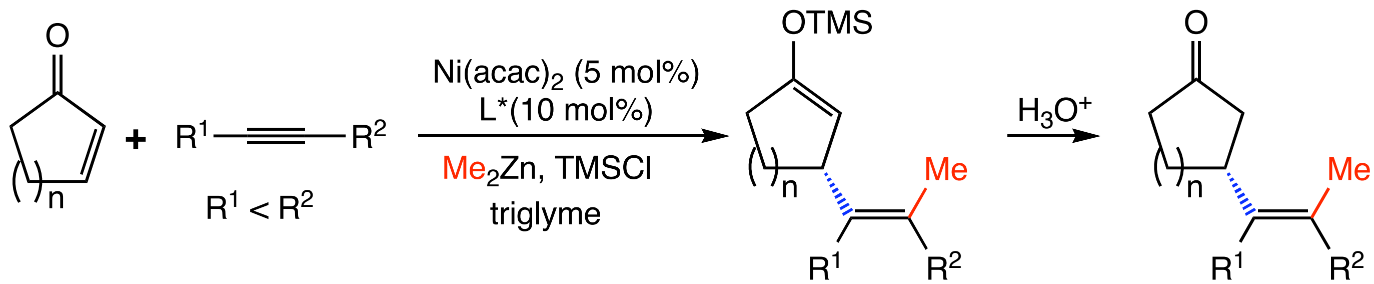
Summary of Intramolecular Coupling

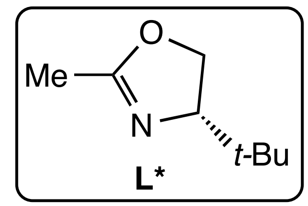


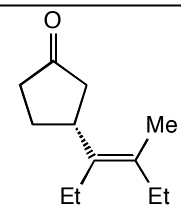
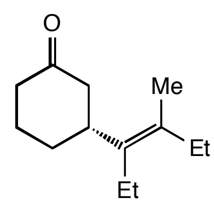
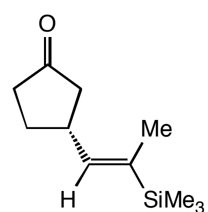
Intermolecular Coupling of Enones and Alkynes



Catalytic Enantiomeric Intermolecular Coupling

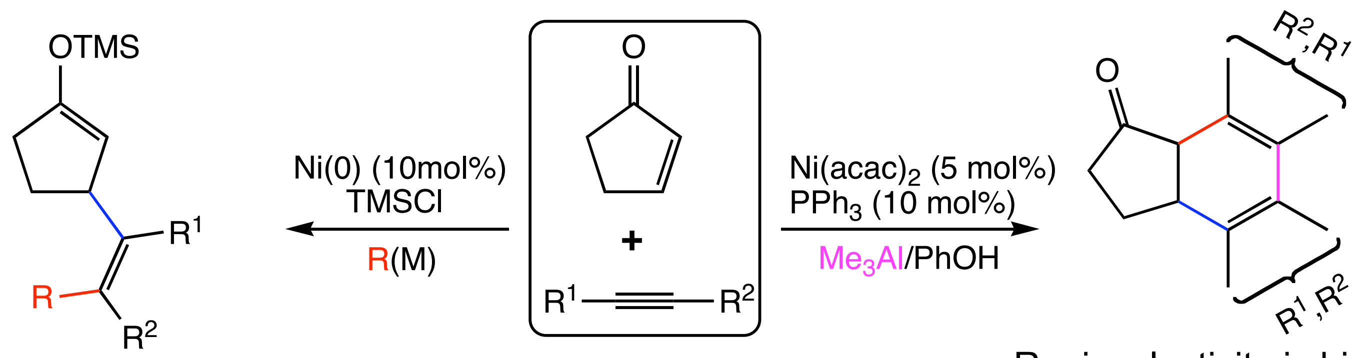




entry	n	alkyne	product	yield, %	ee, %
1	1	Et—≡—Et		61	76
2	2	Et—≡—Et		39	38
3	1	H—≡—$SiMe_3$		60 (100%regio-selectivity)	63

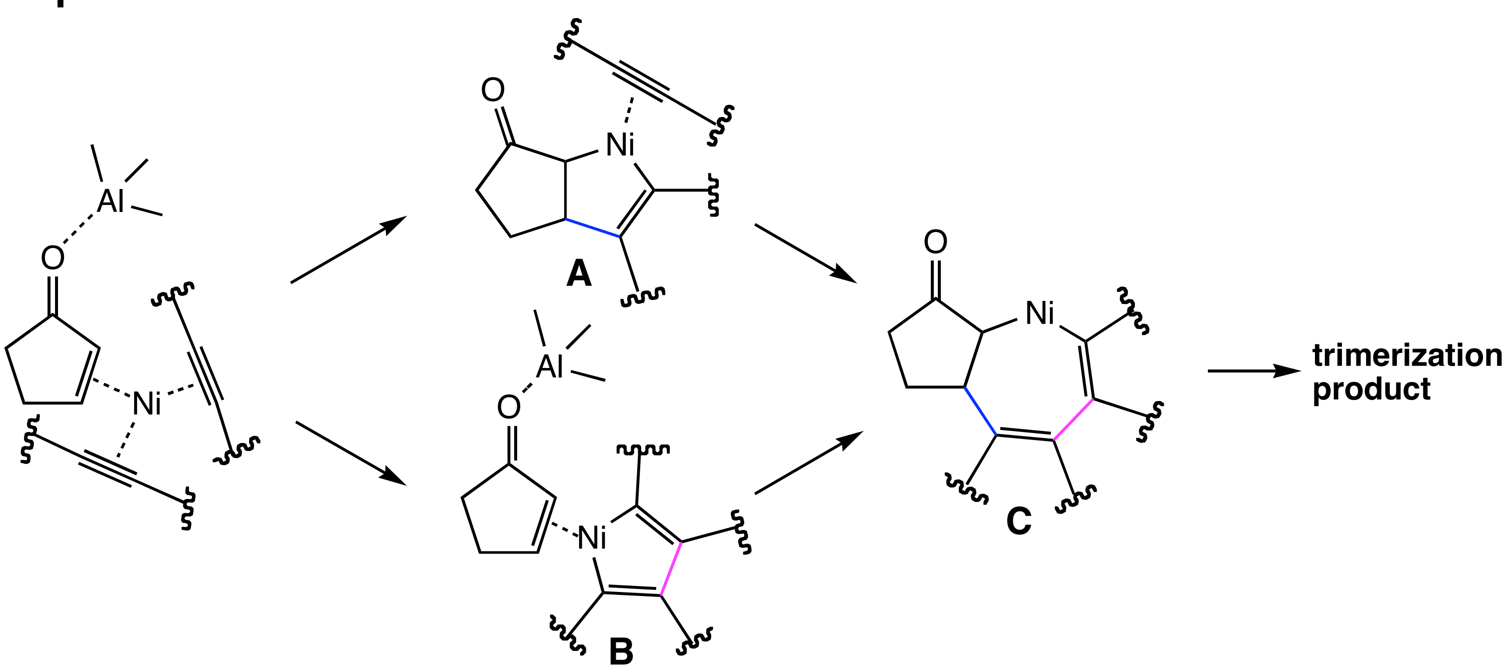
Ikeda, S. I.; Cui, D. M.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4712.

Cyclic Cotrimerization



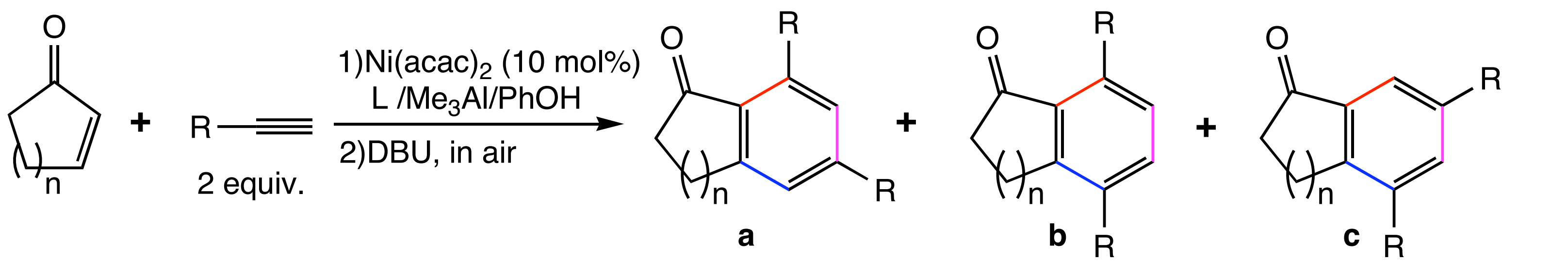
• Regioselectivity is highly substrate dependent.

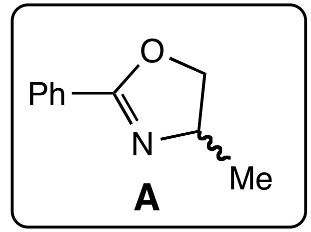
➢ Proposed mechanism



1. Ikeda, S. I.; Mori, N.; Sato, Y. *J. Am. Chem. Soc*. **1997**, *119*, 4779.
2. Ikeda, S. I. *Acc. Chem. Res*. **2000**, *33*, 511.

Control of Regioselectivity in Trimerization with the Same Alkyne

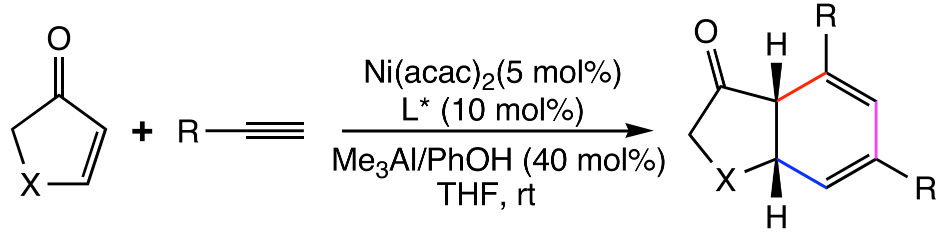


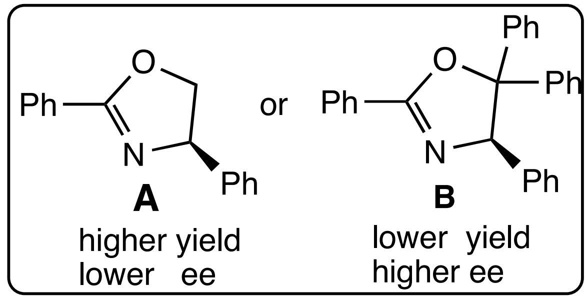


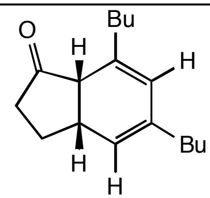
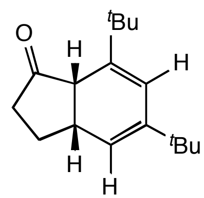
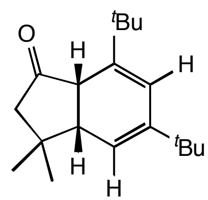
entry	ligand	n	R	yield, % (**a** + **b**)	ratio (**a** : **b**)
1	PPh_3	2	Bu	83	92:8
2	**A**	2	Bu	81	100:0
3	PPh_3	1	TMS	33	0:100
4	**A**	1	TMS	69	96:4
5	PPh_3	1	*t*-Bu	45	11:89
6	**A**	1	*t*-Bu	67	100:0

1. Mori, N.; Ikeda, S. I.; Sato, Y. *J. Am. Chem. Soc*. **1999**, *121*, 2722.
2. Ikeda, S. I.; Kondo, H.; Mori, N. *Chem. Commun*. **2000**, 815.

Control of Enantioselectivity in Trimerization with the Same Alkyne



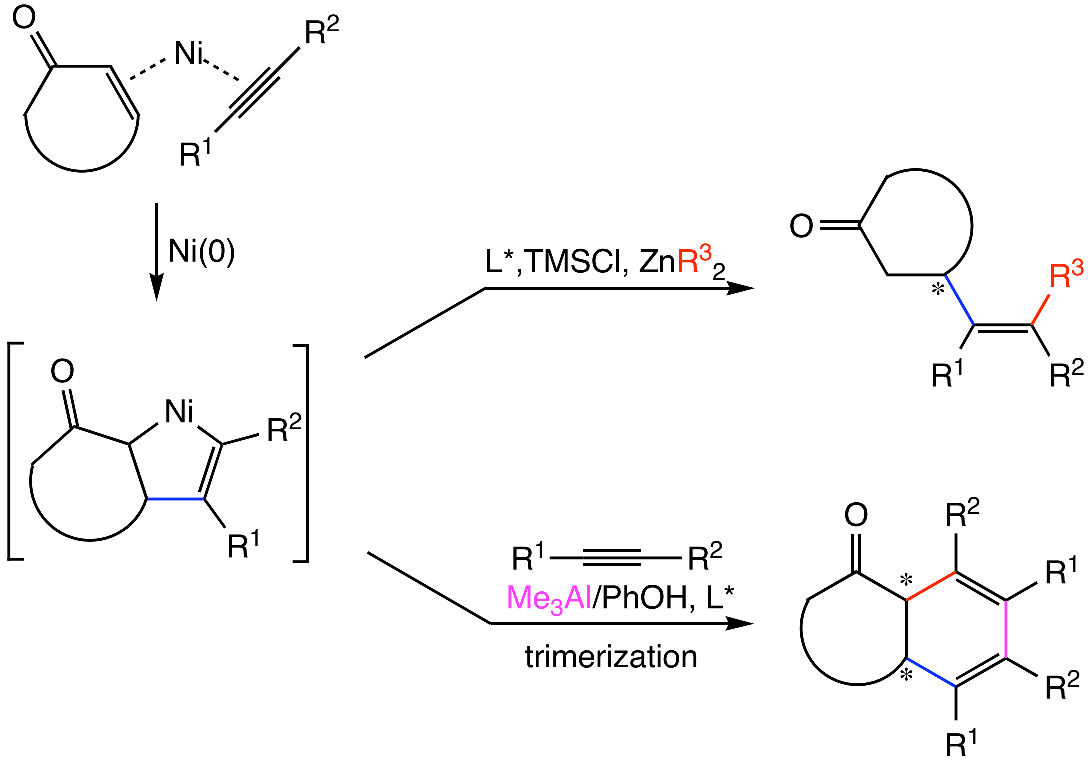


entry	X	R	ligand	product	yield, %	ee, %
1	CH_2	*n*-Bu	**A**		93	25
2			**B**		66	48
3	CH_2	*t*-Bu	**A**		93	22
4			**B**		72	58
5	CMe_2	*t*-Bu	**A**		95	10
6			**B**		25	40

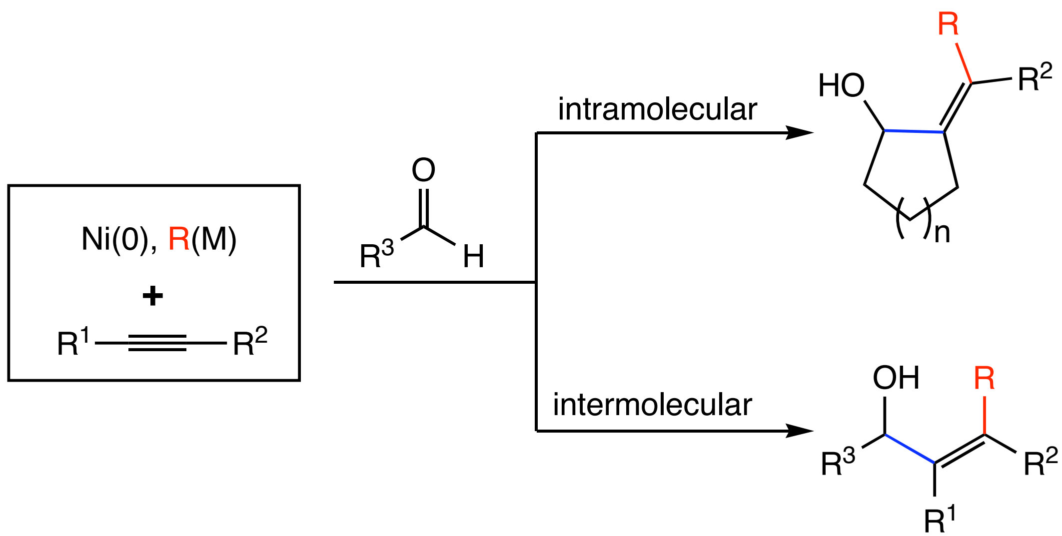
• Regioselectivity > 95:5 in every example.

Ikeda, S. I.; Kondo, H.; Arii, T.; Odashima, K. *Chem. Commun*. **2002**, 2422.

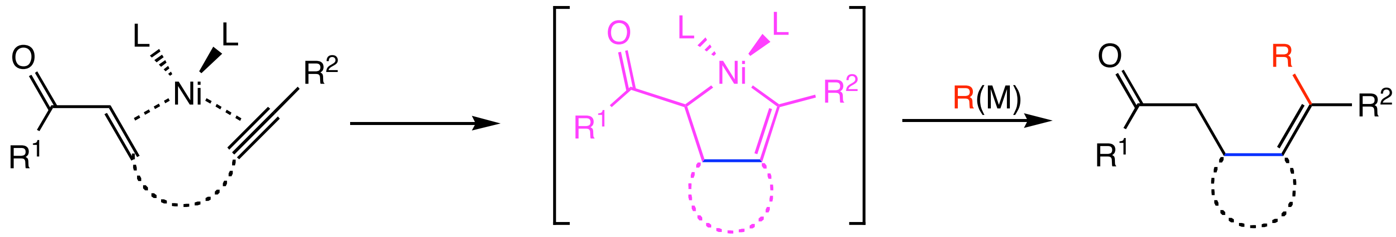
Summary of Intermolecular Coupling



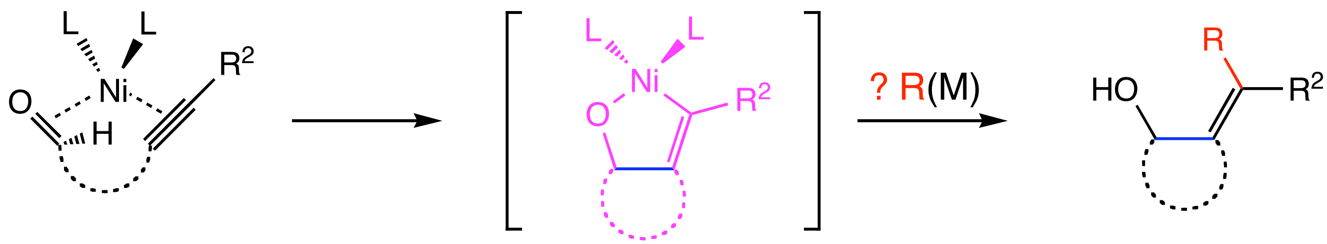
Coupling of Aldehydes and Alkynes



Introduction to The Coupling of Aldehydes and Alkynes



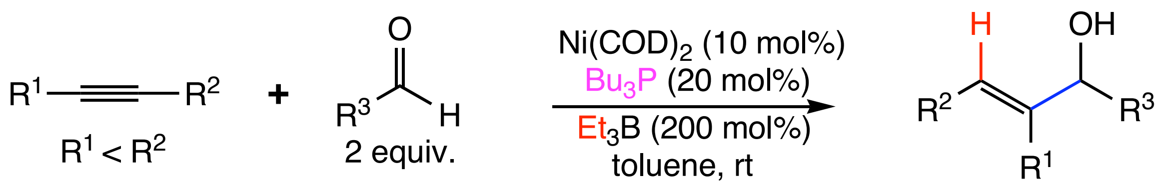
A

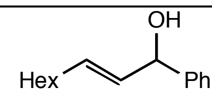
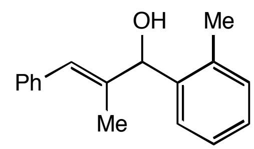
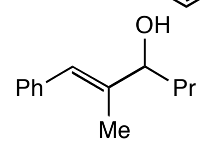
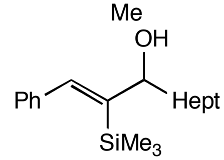


B

Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem*. **1990**, *35*, 2554.

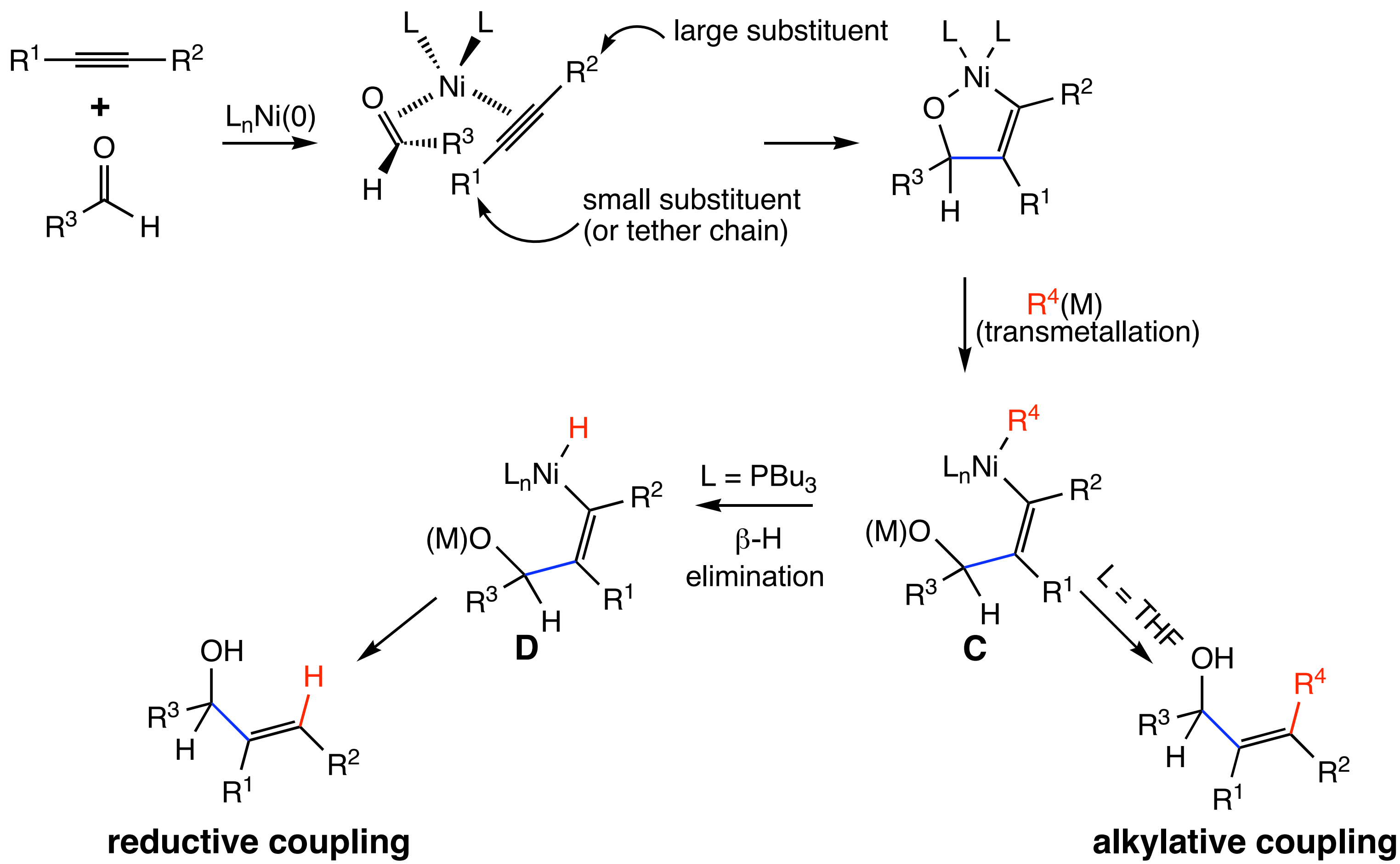
Catalytic Reductive Coupling of Aldehydes



entry	R^3	R^1	R^2	product	yield, %(regioselectivity)
1	Ph	H	*n*-Hex		76% (96:4)
2	*o*-tolyl	Me	Ph		83% (93:7)
3	*n*-Pr	Me	Ph		85% (92:8)
4	*n*-Hept	$SiMe_3$	Ph		89% (>98:2)

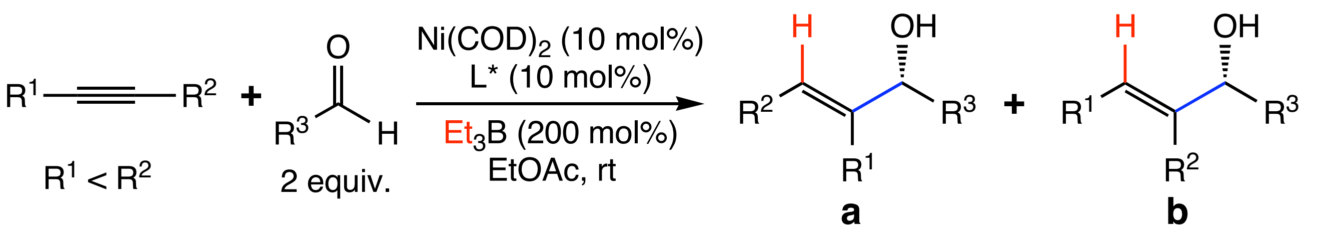
Huang, W. S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221.

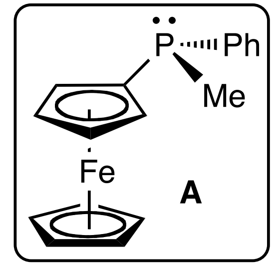
Proposed Mechanism

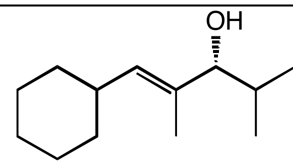
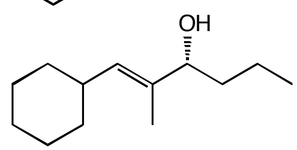
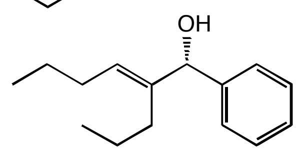


Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.

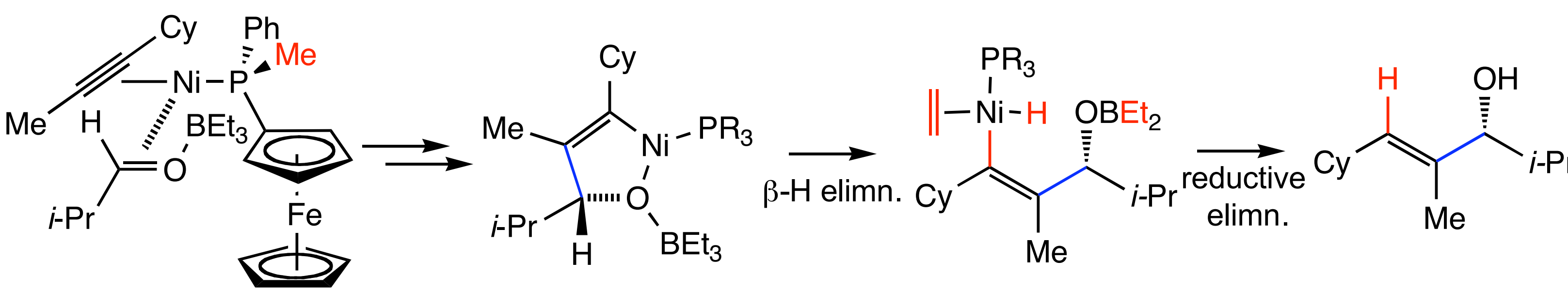
Catalytic Asymmetric Coupling of Aliphatic Alkynes





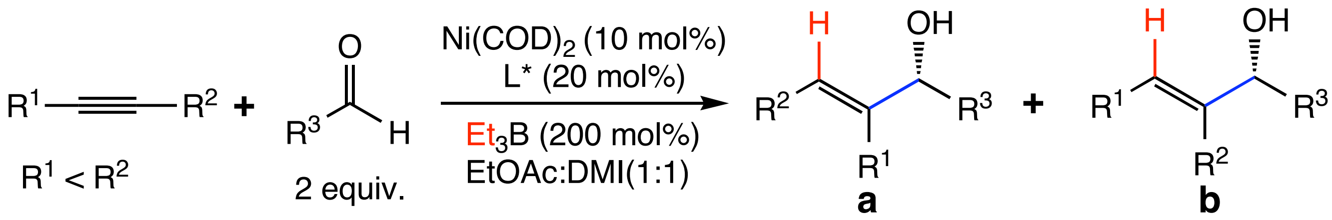
entry	ligand	R3	R1	R2	product	yield,% (a : b)	ee, a (%)	ee, b (%)
1	**A**	*i*-Pr	Me	Cy		65 (2.2:1)	46	45
2	**A**	*n*-Pr	Me	Cy		30 (2.2:1)	67	68
3	**A**	Ph	*n*-Pr	*n*-Pr		85	49	N/A

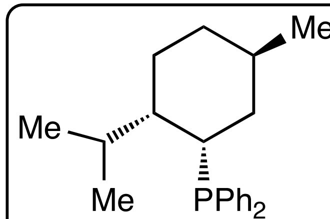
➢ Proposed mechanism



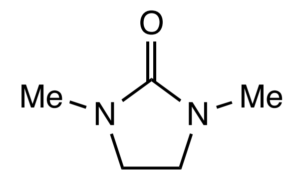
Colby, E. A.; Jamison, T. F. *J. Org. Chem*. **2003**, *68*, 156.

Catalytic Asymmetric Coupling of Aromatic Alkynes

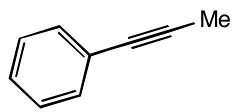
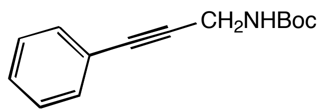
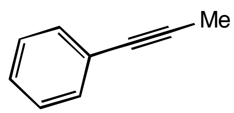
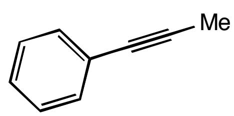




(+)-NMDPP



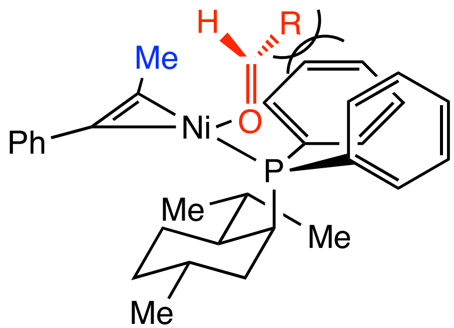
DMI

entry	R^3	alkyne	yield,%(**a** : **b**)	ee of **a** (%)
1	*i*-Pr		95 (>95:5)	90
2	*i*-Pr		60 (>95:5)	96
3	*n*-Pr		82 (>95:5)	65
4	Ph		79 (91:9)	73
5	*i*-Pr		35	42

Miller, K. M.; Huang, W. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442.

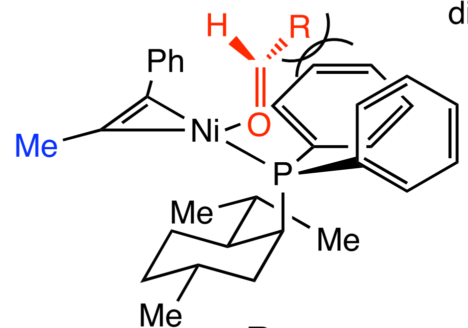
Proposed Model for Enantio- and Regioselectivity

sterically disfavored,
electronically favored



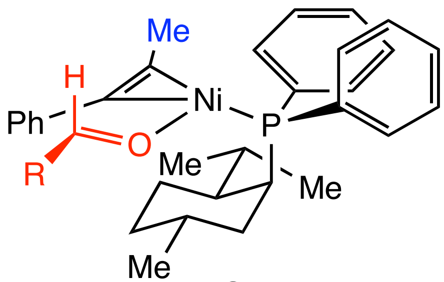
A

sterically and
electronically
disfavored



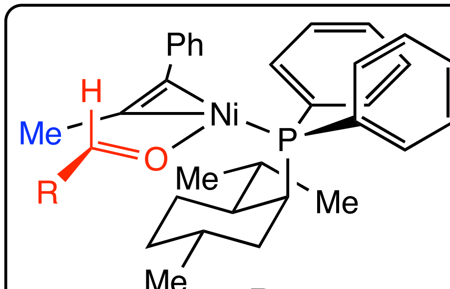
B

sterically favored
electronically disfavored

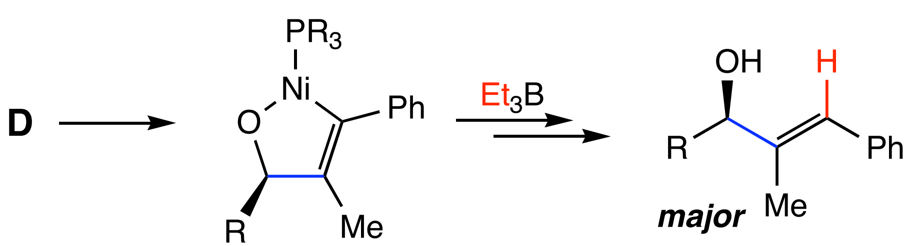


C

sterically and
electronically
favored

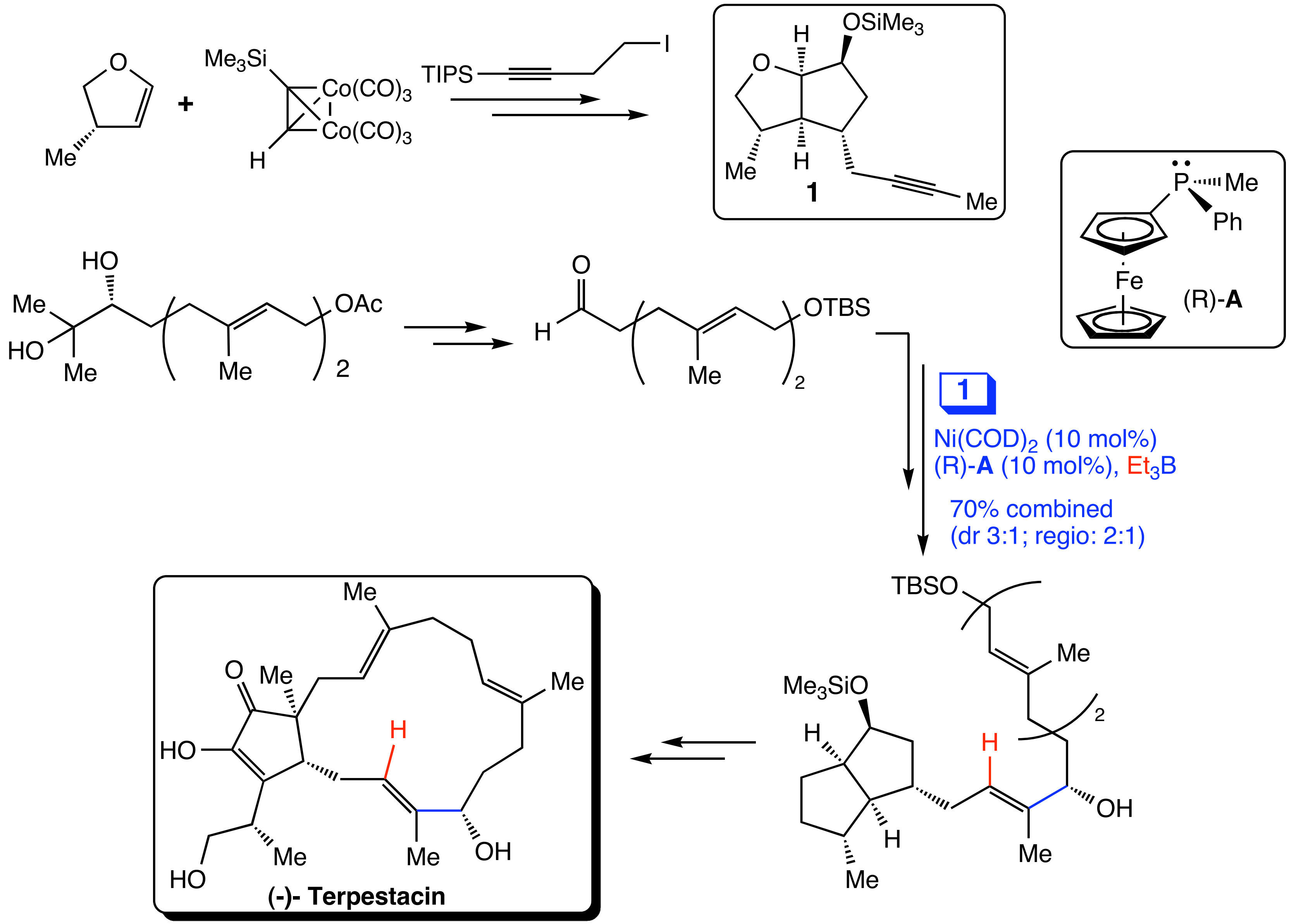


D



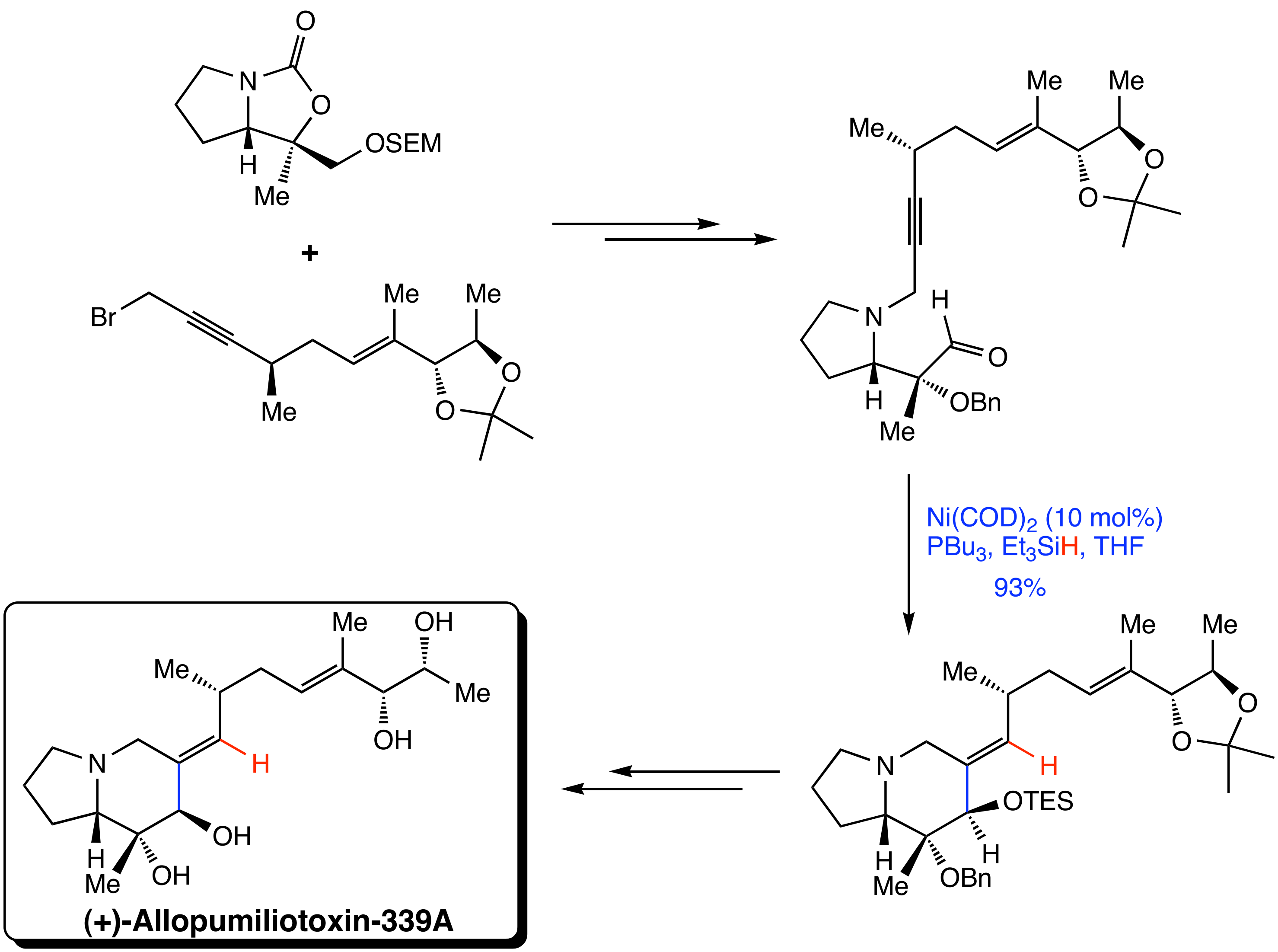
1. Miller, K. M.; Huang, W. S.; Jamison, T. F. *J. Am. Chem. Soc*. **2003**, *125*, 3442.
2. Whittall, I. R.; Humphrey, M. G.; Samoc, M.; Luther-Davies, B.; Hockless, D. C. R. *J. Organomet. Chem*. **1997**, *544*, 189.

Total Synthesis of (-)-Terpestacin



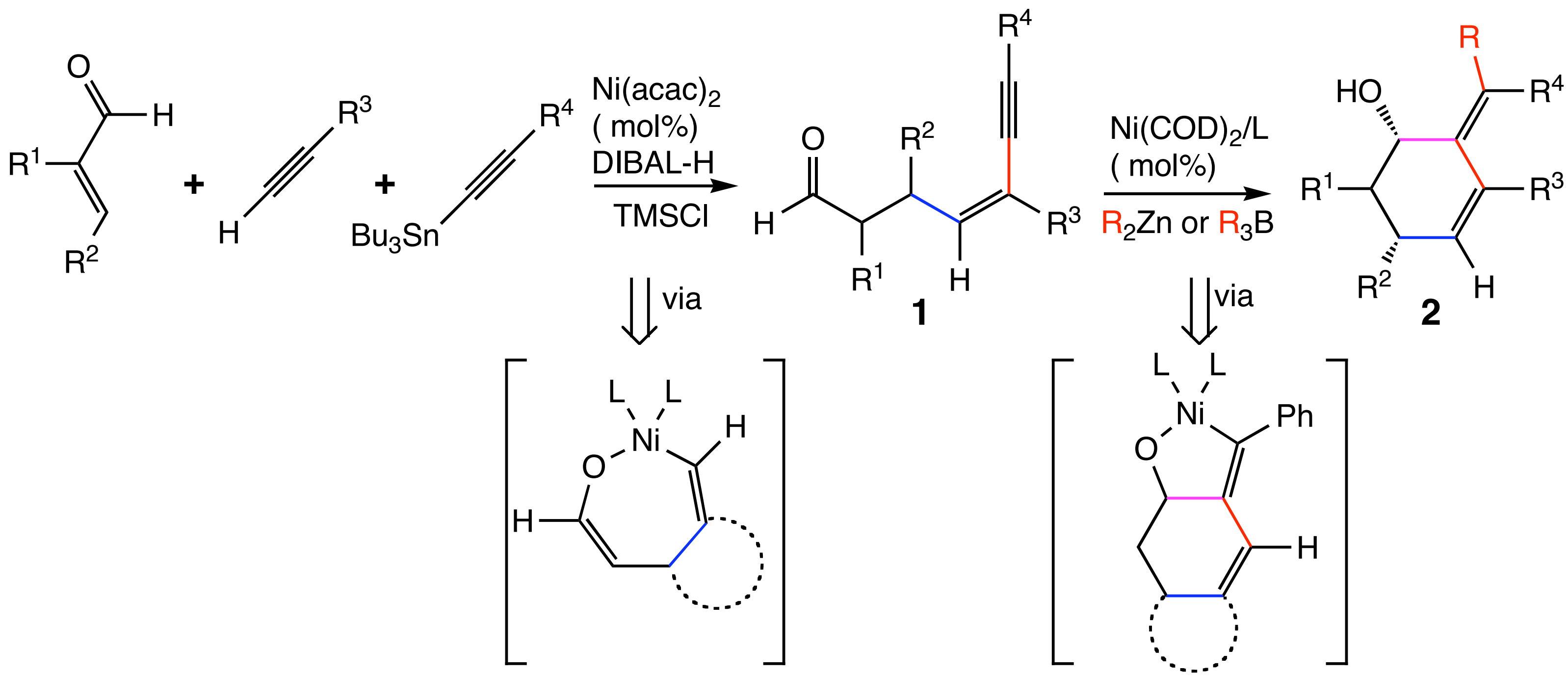
Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 11514.

Total Synthesis of (+)-Allopumiliotoxin 339A



Tang, X.Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950.

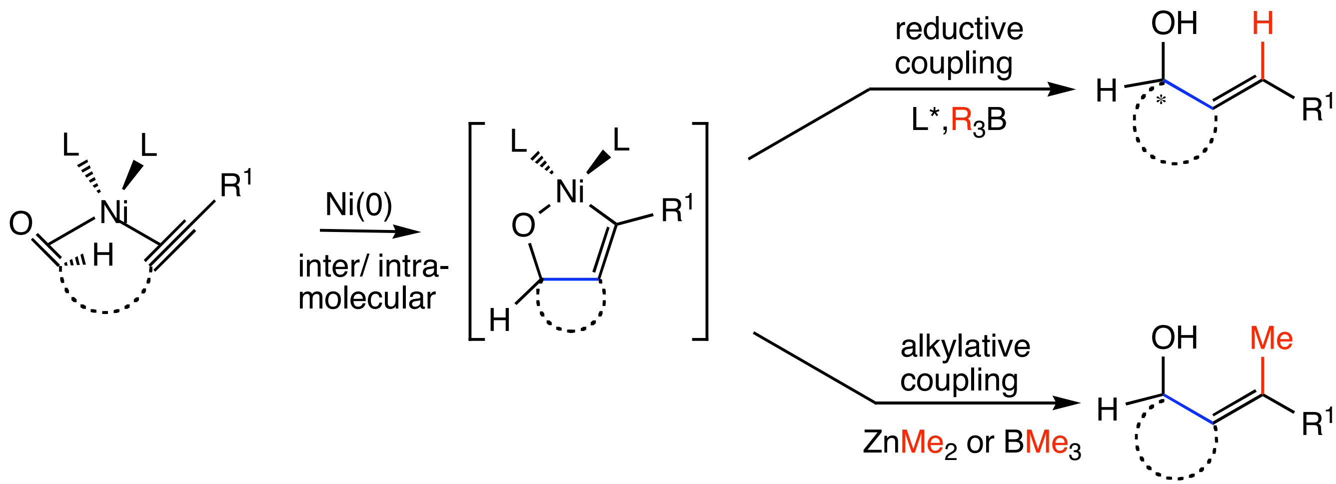
Two-Step Four-Component Coupling



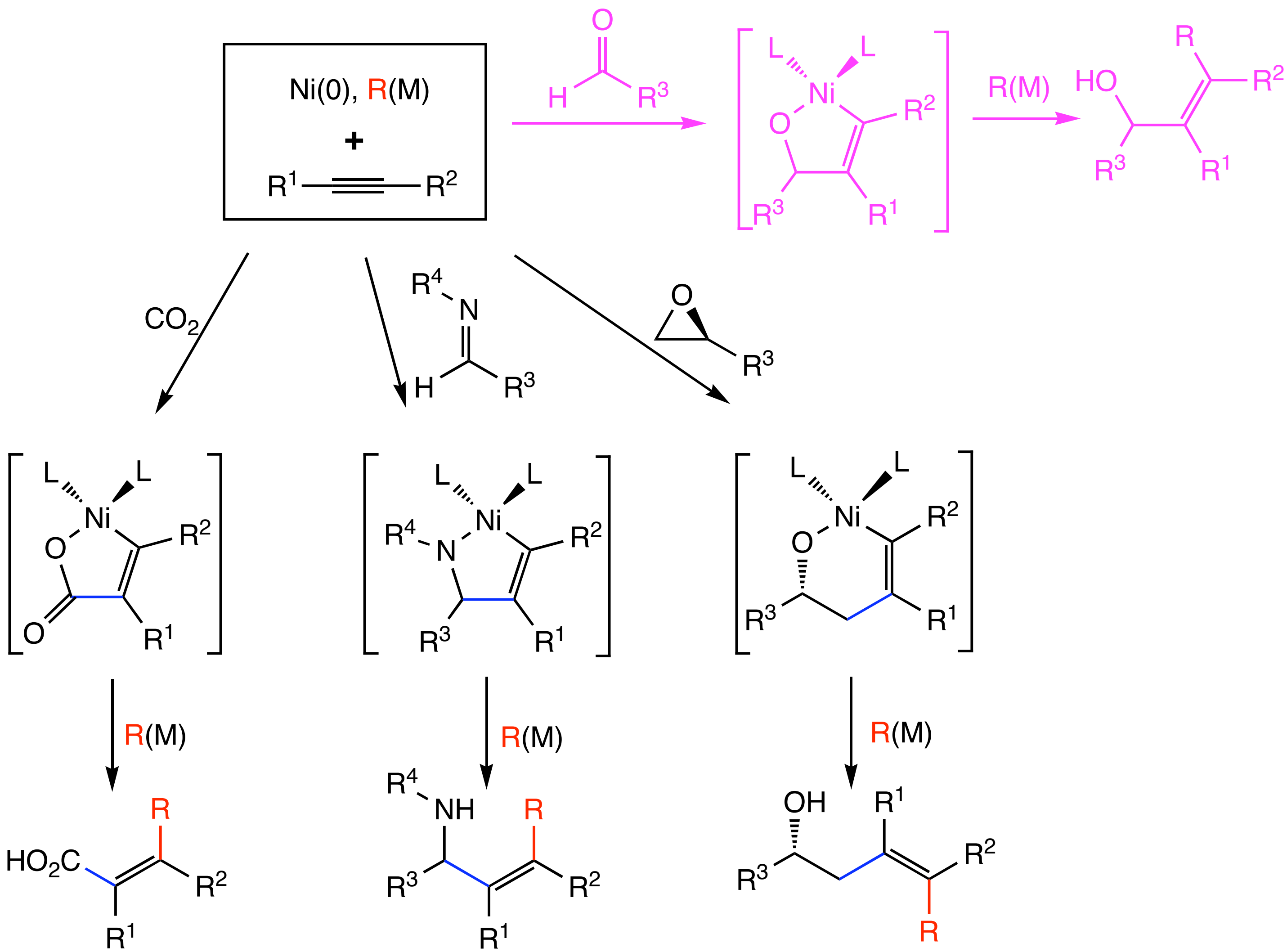
entry	R^1	R^2	R^3	R	L	% yield of **1**	% yield of **2** (dr)
1	H	H	*n*-hexyl	H(Et_3B)	PBu_3	69	85
2	Me	H	H	Me(Me_2Zn)	none	63	74(2.7:1)
3	H	Me	H	Me(Me_2Zn)	none	67	80(5.3:1)

Lozanov, M.; Montgomery, J. *J. Am. Chem. Soc.* **2002**, *124*, 2106.

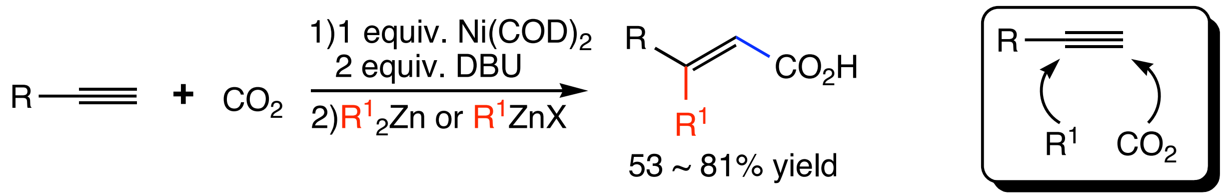
Summary of Coupling Reaction Between Aldehydes and Alkynes



Other Electrophile Equivalents

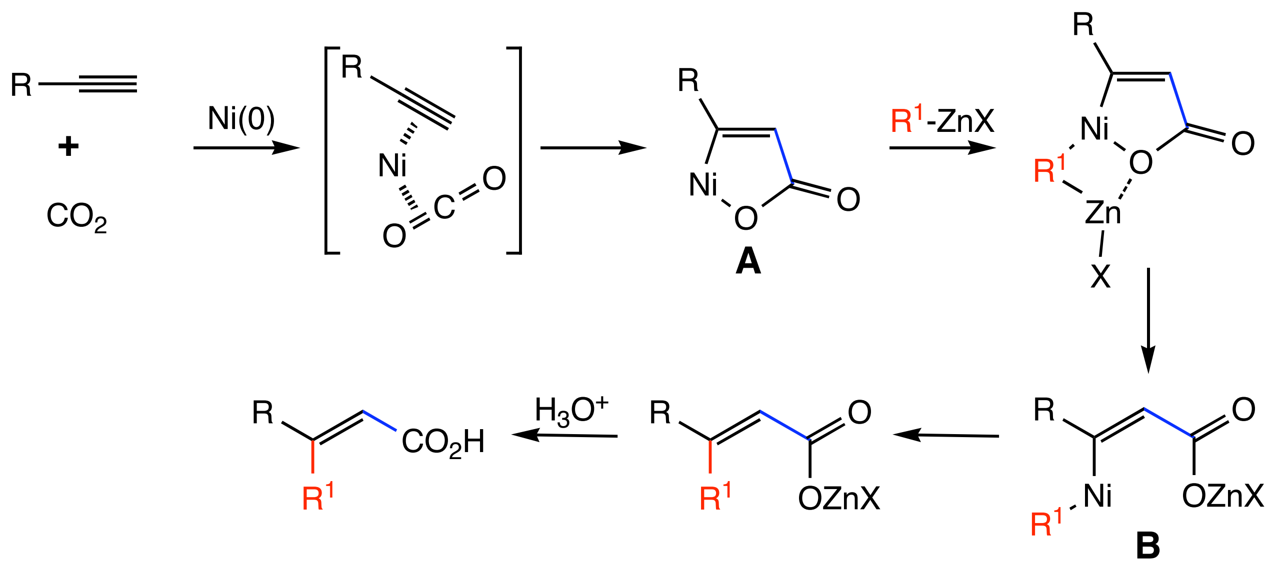


Coupling of Alkynes and CO_2



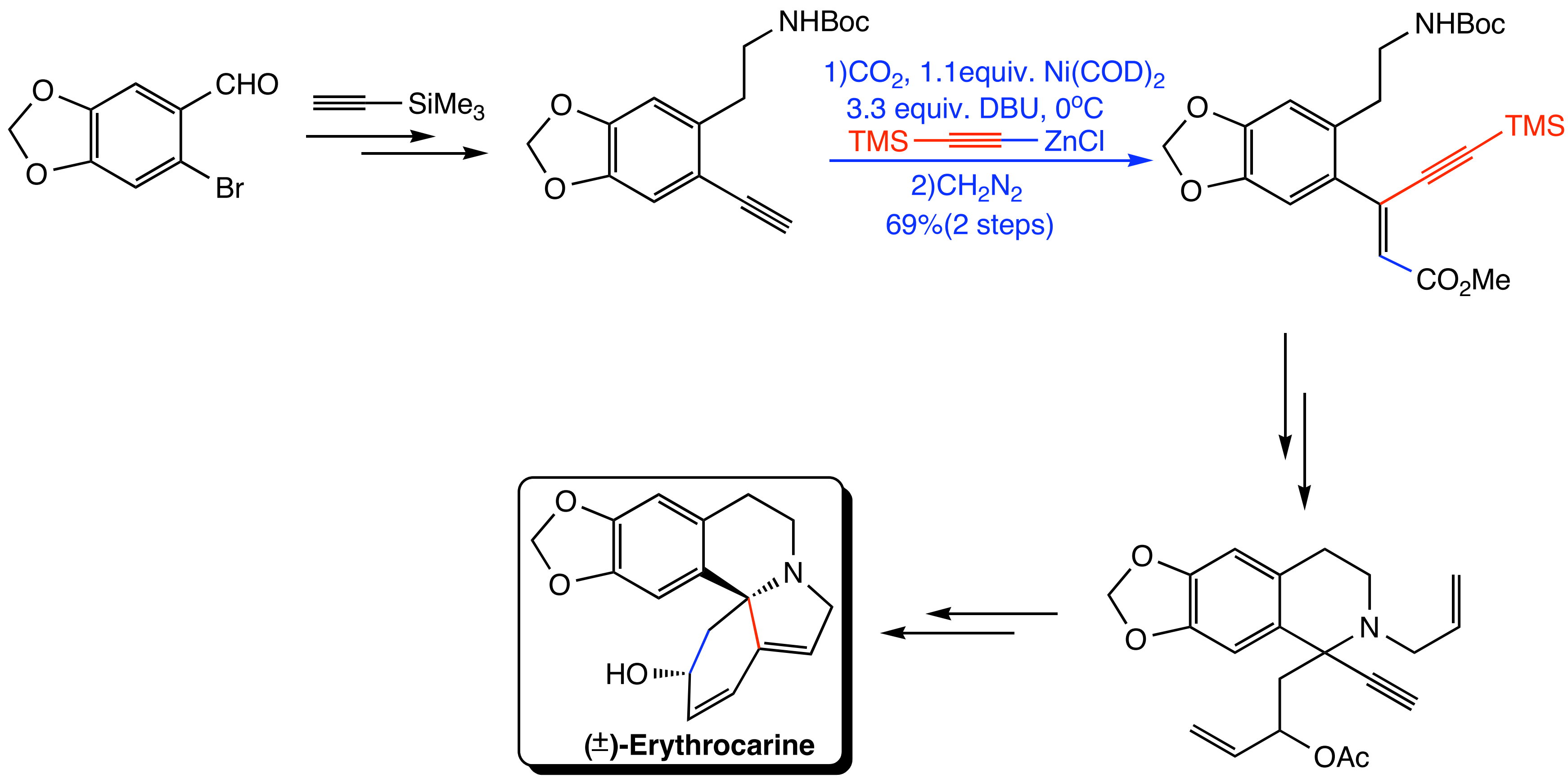
- R^1 = Ph, Bz, Bu, Me, alkylative product; R^1 = Et, major product is reductive coupling product.
- An efficient way to prepare β,β'-disubstituted α,β-unsaturated acid under mild conditions.

➢ Proposed mechanism



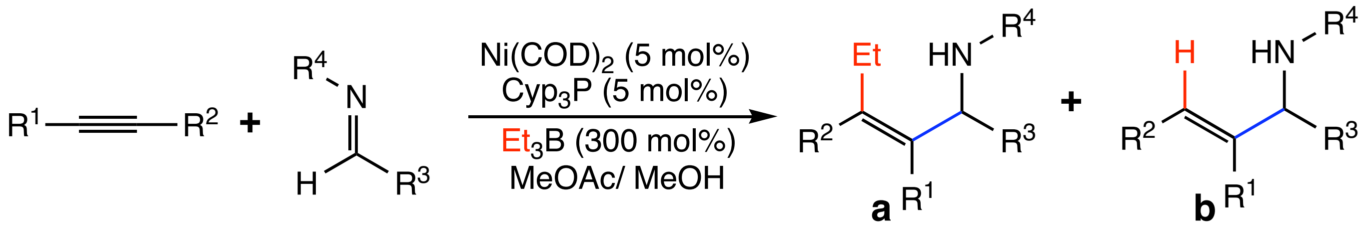
Takimoto, M.; Shimizu, K.; Mori, M. *Org. Lett.* **2001**, *3*, 3345.

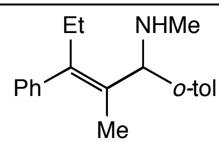
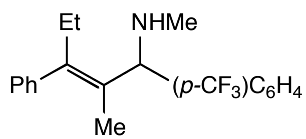
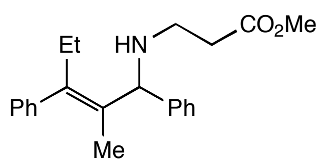
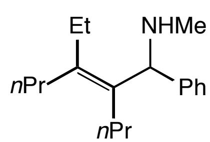
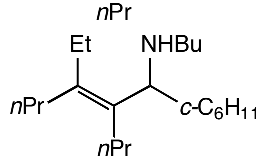
Total Synthesis of Erythrocarine



Shimizu, K.; Takimoto, M. Mori, M. *Org. Lett*. **2003**, *5*, 2323.

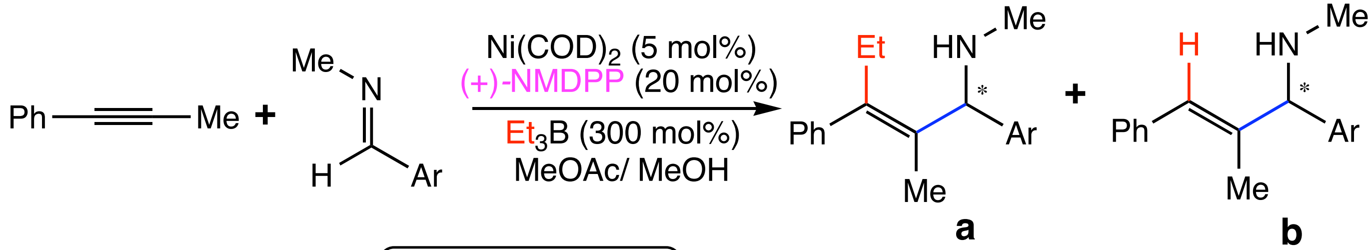
Imine as Electrophile Equivalent

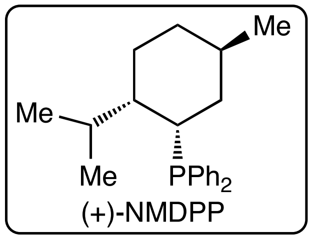


entry	product	yield (%)	**a** : **b**	regioselectivity
1		85	94:6	90:10
2		98	96:4	89:11
3		75	94:6	91:9
4		91	94:6	-
5		52	>96:4	-

1. Patel, S. J.; Jamison, T. F. *Angew.Chem. Int. Ed.* **2003**, *42*, 1364.
2. Miller, K. M.; Molinaro, C.; Jamison, T. F. *Tetrahedron: Asymm.* **2003**, *14*, 3619.

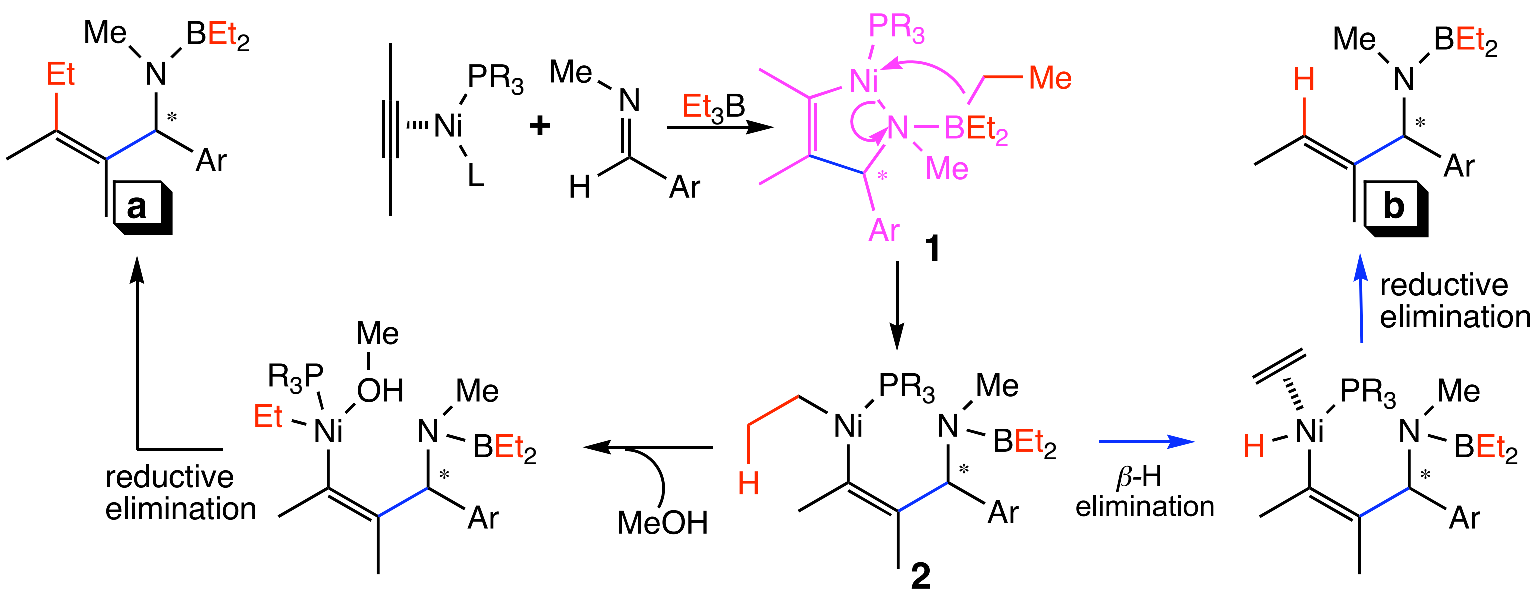
Imine as Electrophile Equivalent





Ar	ee of **a**	ee of **b**
Ph	41	42
p-ClC$_6$H$_4$	33	33
P-CF$_3$C$_6$H$_4$	40	39

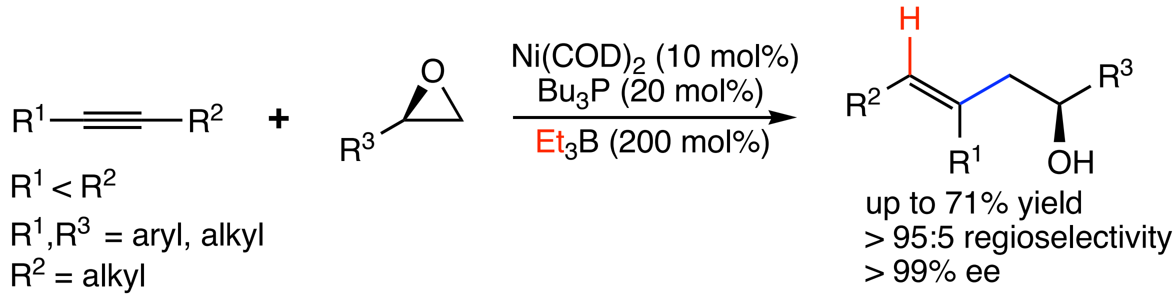
➢ Proposed mechanism



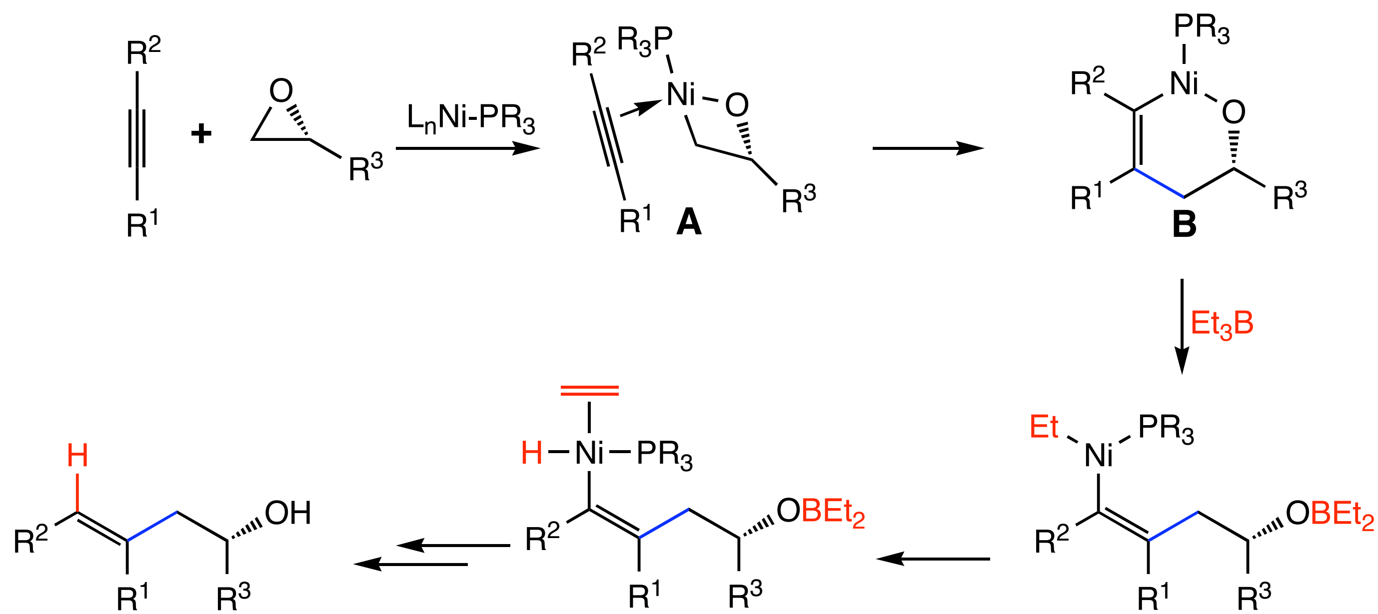
• **a** and **b** were isolated in identical ee.

1. Patel, S. J.; Jamison, T. F. *Angew.Chem. Int. Ed*. **2003**, *42*, 1364.
2. Miller, K. M.; Molinaro, C.; Jamison, T. F. *Tetrahedron: Asymm*. **2003**, *14*, 3619.

Epoxide as Electrophile Equivalent

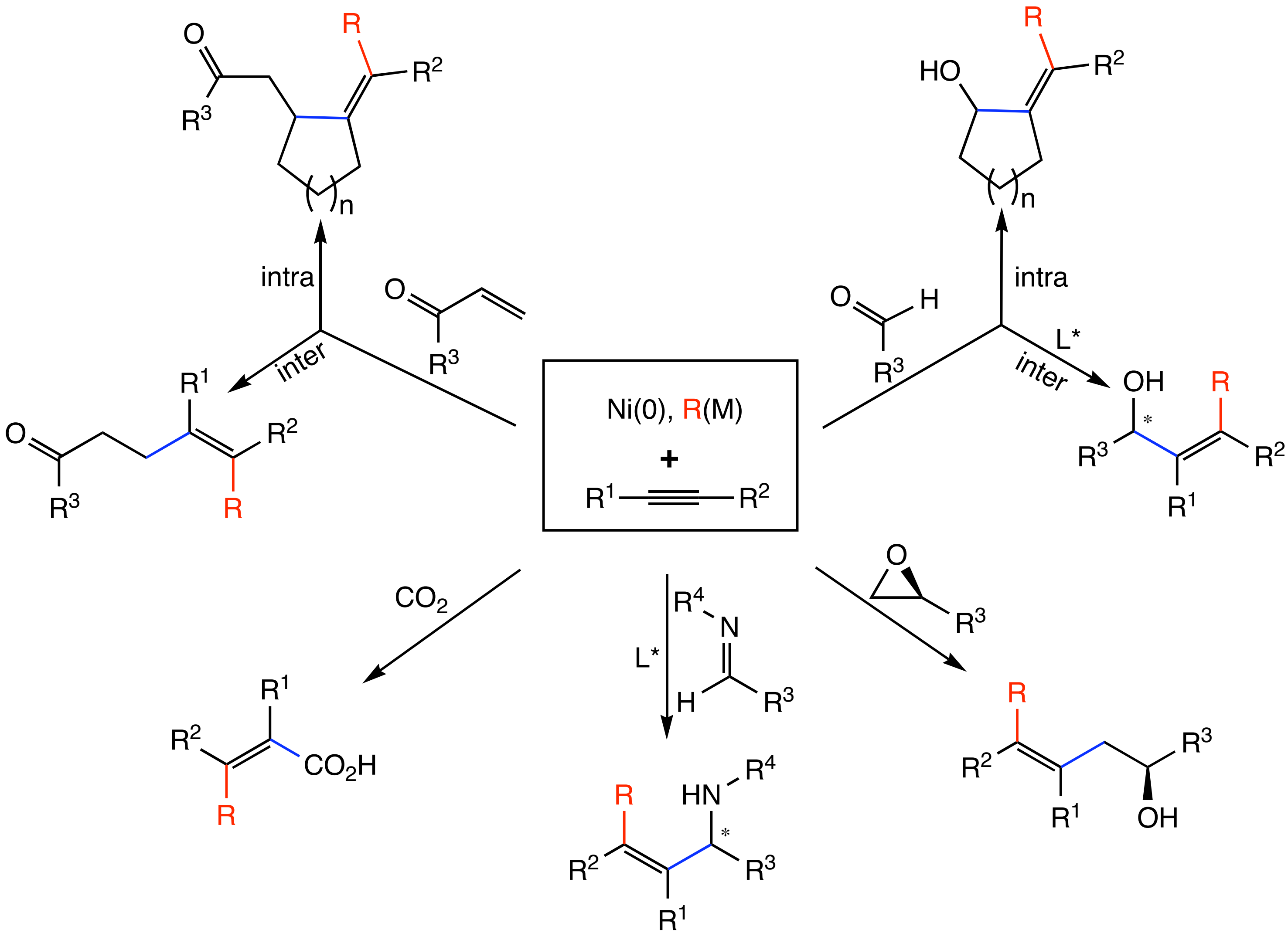


- Proposed mechanism

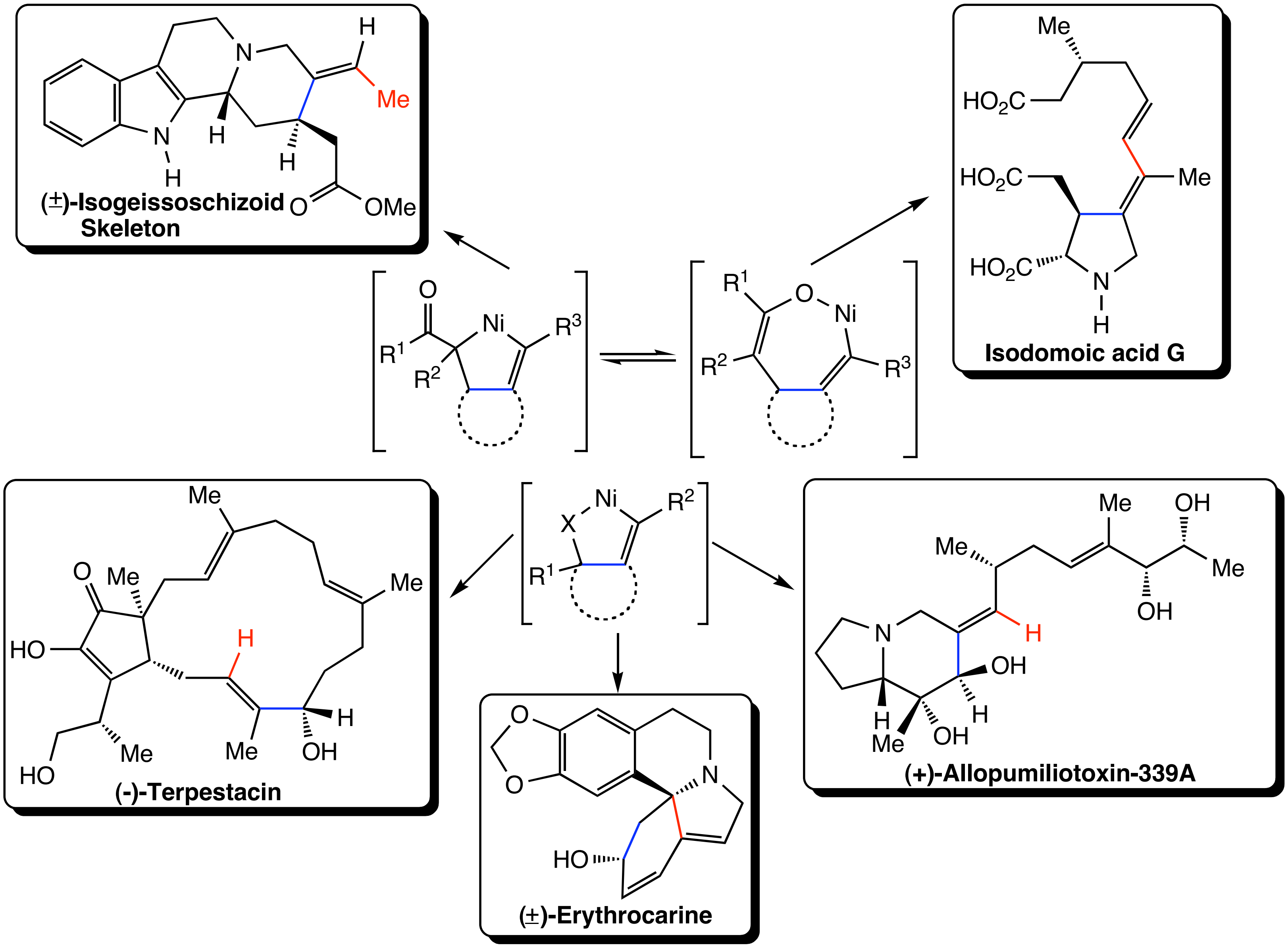


Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc*. **2003**, *125*, 8076.

Summary

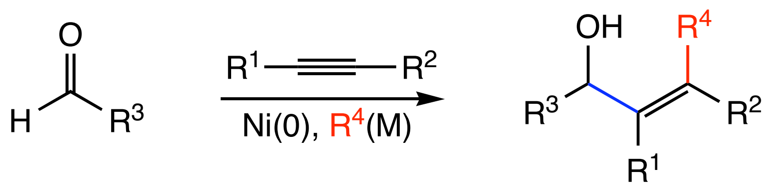

Ni(0), R(M)
+
R1 R2
intra
inter
intra
inter
L*
CO2
L*
OH
HO
O
H
R
R1
R2
R3
R4
HN
N
CO2H
OH
n

Recent Applications in Total Synthesis



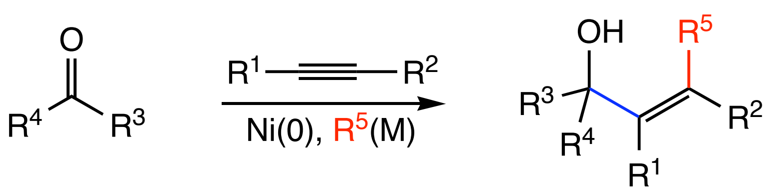
Future Development

➢ Alkylative coupling of aldehyde



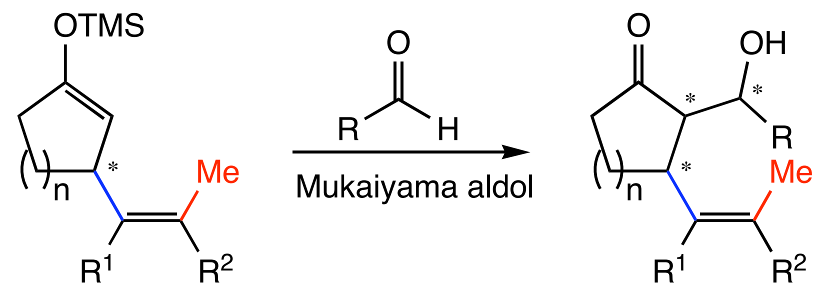
(More complicated R^4)

➢ Coupling of ketone for the generation of tetra-substituted alkene & tertiary allylic alcohol

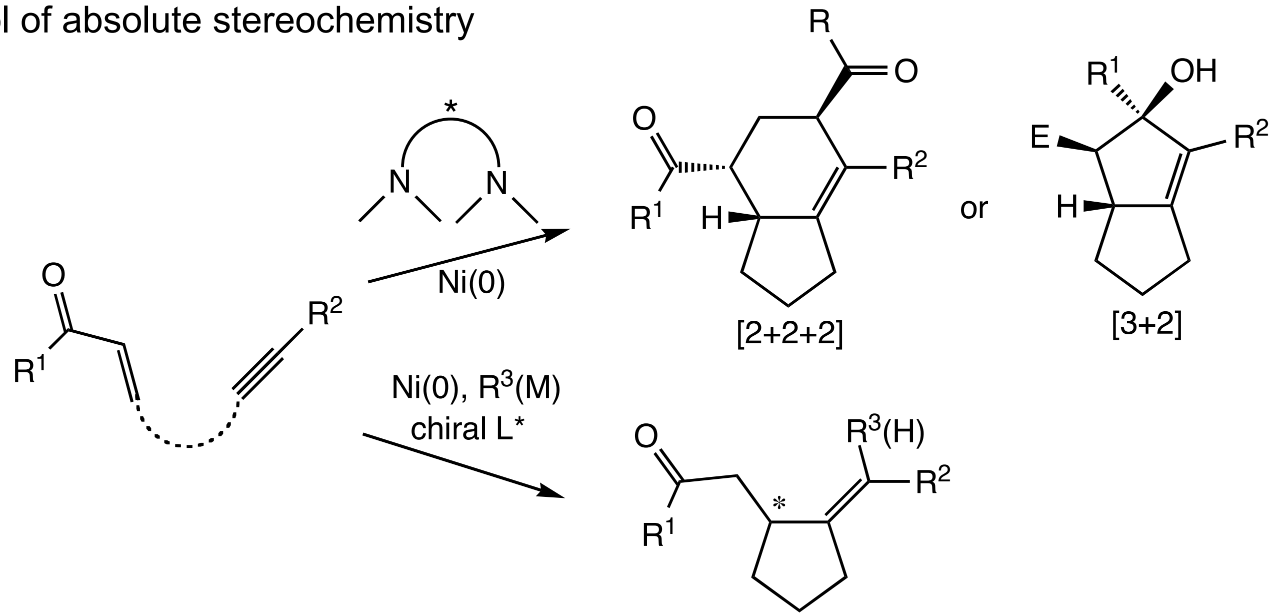


Future Development

- Tandem coupling-aldol condensation



- Control of absolute stereochemistry



Acknowledgement

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Wulff Group Members:

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Kostas
Yu
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Vijay
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Reddy
Alex

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Tao
Chang
Lingling
Xiaoyu
Lei
Jason