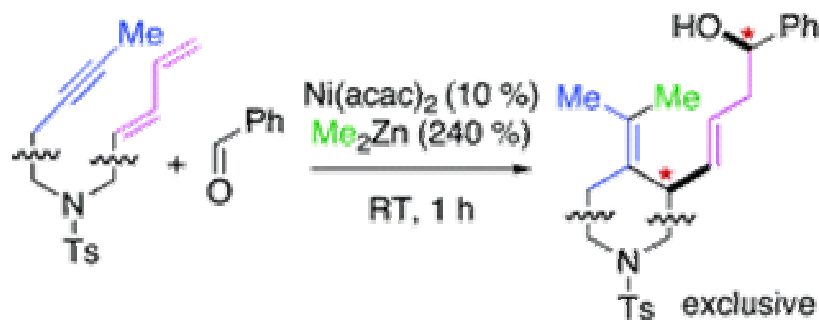


Nickel-Catalyzed Addition of Dimethylzinc to Aldehydes across Alkynes and 1,3-Butadiene: An Efficient Four-Component Connection Reaction

Masanari Kimura, Akihiro Ezoe, Masahiko Mori, and Yoshinao Tamaru

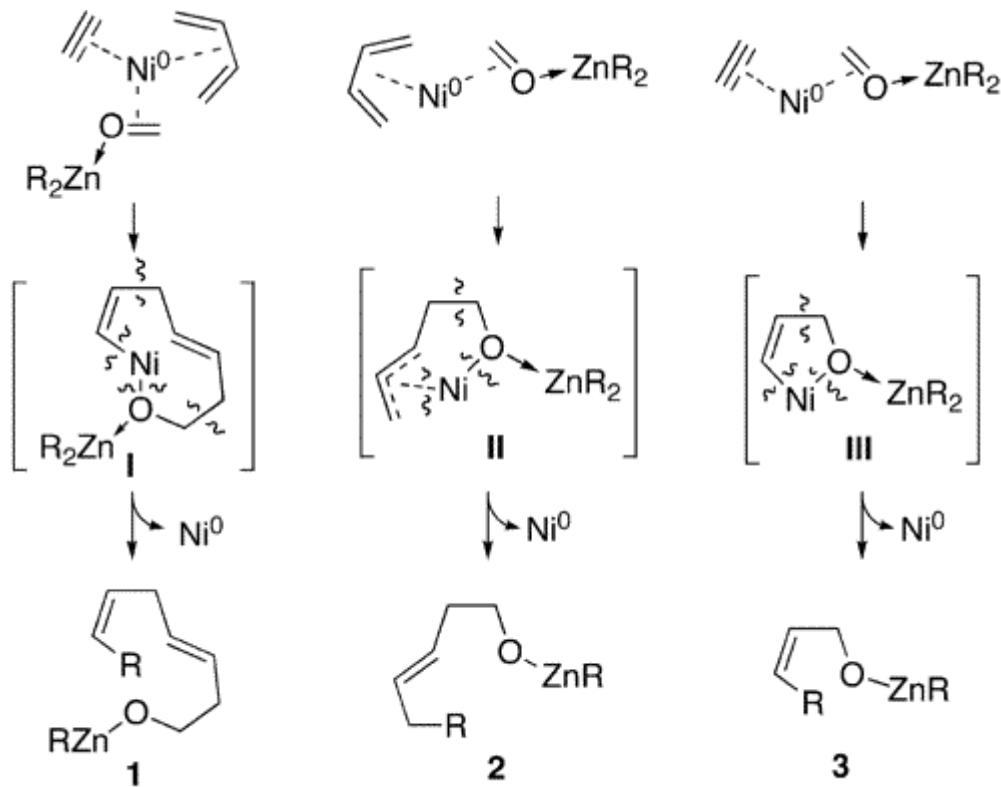
Contribution from the Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo, Nagasaki 852-8521, Japan



- 1 Background
2. Ni^0 -Catalyzed Intermolecular Four-Component Connection Reaction (4-CCR) of Me_2Zn , Alkynes, 1,3-Butadiene, and Carbonyl Compounds.
3. Ni^0 -Catalyzed Intramolecular 4-CCR of Me_2Zn , 1, ω -Dienynes 5, and Carbonyl Compounds.
4. Mechanism

Ni-Catalyzed Multicomponent Connection Reactions

* Many precedents for Ni-Catalyzed linear & cyclic oligomerization, few involving Nu⁻ or reductive attack addition of alkynes and dienes toward RC=O compounds



(a) Present Work

(b) Our previous work

(c) Montgomery's work

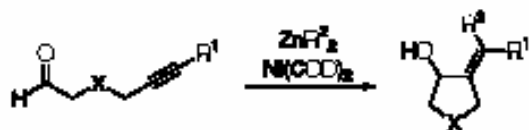
(c) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.

(b) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386.

1. Background

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

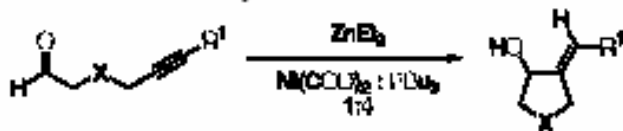
Table 1. Ynal Alkylative Cyclizations



entry	X	R ¹	R ²	yield (%) ^a
1	CH ₂	H	CH ₃	77 ^b
2	CH ₂	H	Ph	72
3	CH ₂	H	n-Bu	62
4	CH ₂	CH ₃	Ph	64
5	CH ₂	CH ₃	n-Bu	70
6	CH ₂	Ph	CH ₃	79
7	CH ₂	Ph	Et	57
8	NOOPh	H	CH ₃	72

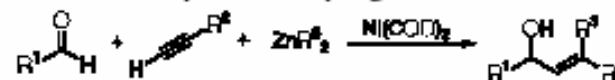
^a Products were obtained as single stereoisomers by 500 MHz ¹H NMR analysis. ^b Isolated as the benzoate ester (two-step yield is reported).

Table 2. Ynal Reductive Cyclizations



entry	X	R ¹	yield (%) ^a
1	CH ₂	H	70 ^b
2	CH ₂	CH ₃	57 ^b
3	CH ₂	Ph	62
4	NOOPh	H	70 ^b

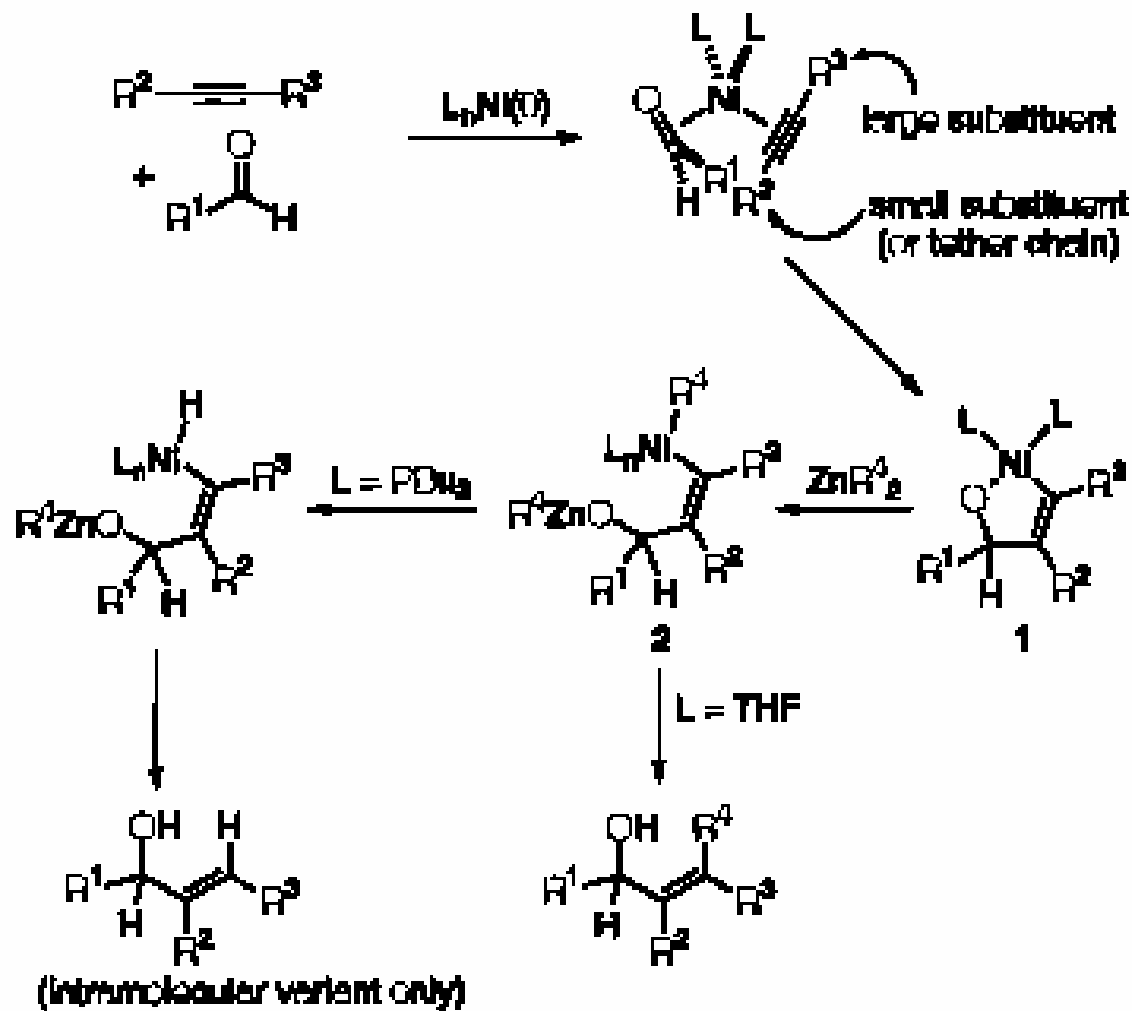
Table 3. Three-Component Couplings



entry	R ¹	R ²	R ³	yield (%) ^a
1	Ph	Ph	Me	60
2	Ph	C ₆ H ₁₃	Me	74
3	Ph	C ₆ H ₁₃	n-Bu	71
4	Apr	Ph	Me	21 ^b
6	Ph	Ph	O(CH ₂) ₂ CH ₃	0 ^c

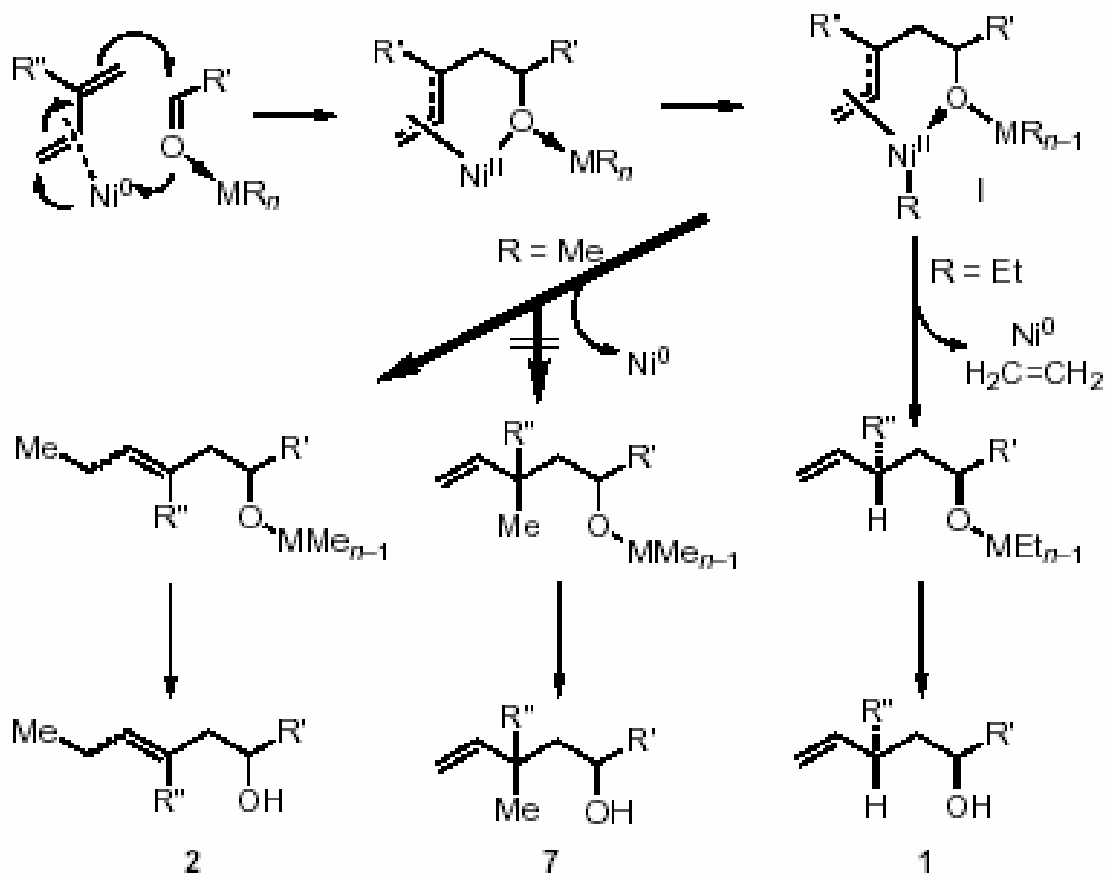
Highly chemo-, regio- and stereoselective addition toward RC=O, affording allylic alcohols.

The Zn substituent is introduced *cis* to the alcohol



Scheme 1. Proposed Mechanism for Ynal Cyclizations and Three-Component Couplings

ii. Ni-Catalyzed 3-CCR with Me_2Zn , 1,3-diene and $\text{RC}=\text{O}$

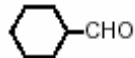

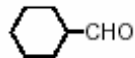



Scheme 1. Nickel-catalyzed coupling of 1,3-dienes with alkylmetal reagents and carbonyl compounds.

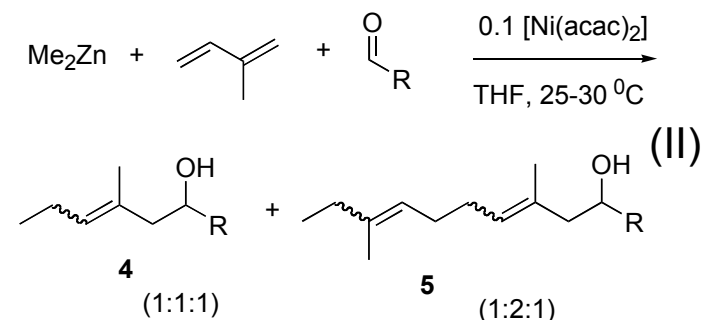
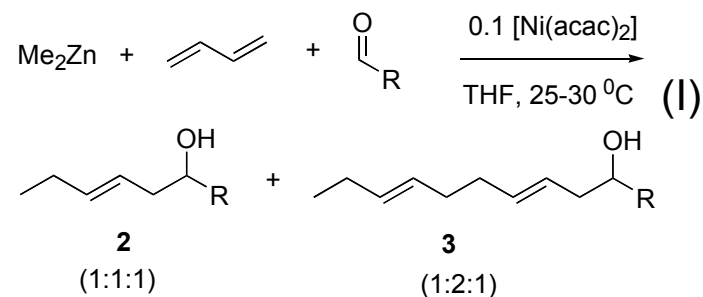
Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386.

Diene as a unsaturated hydrocarbon component

Table 1. Nickel(0)-catalyzed coupling reaction of dimethylzinc, 1,3-dienes, and carbonyl compounds.^[a]

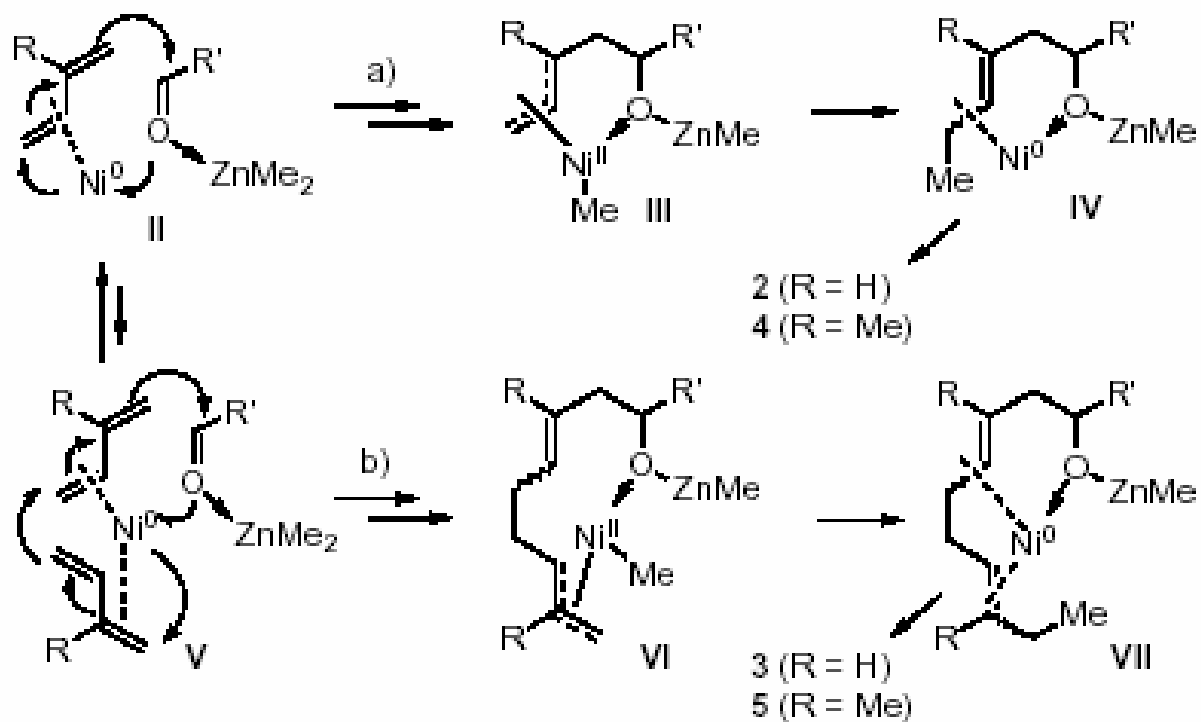
Entry	Carbonyl compound	1,3-Diene	T [°C]/t [h]	Yield [%] ^[b, c]	
				1:1:1 product ^[d]	1:2:1 product ^[e]
1	PhCHO	butadiene	25 (2)	2a : 99	3a : 0
2	Ph-CH ₂ -CH ₂ -CHO	butadiene	25 (1)	2b : 83	3b : 3
3		butadiene	25 (1)	2c : 73	3c : 17
4	<i>t</i> BuCHO	butadiene	25 (3)	2d : 75	3d : 20
5		butadiene	30 (3)	2e : 0	3e : 89
6	PhCHO	isoprene	25 (5)	4a : 92 (<i>E</i> : <i>Z</i> = 2.2:1)	5a : 0
7	Ph-CH ₂ -CH ₂ -CHO	isoprene	30 (1)	4b : 40 (<i>E</i> : <i>Z</i> = 3.8:1)	5b : 10
8		isoprene	30 (1)	4c : 62 (<i>E</i> : <i>Z</i> = 4.0:1)	5c : 11
9	<i>t</i> BuCHO	isoprene	25 (3)	4d : 57 (<i>E</i> : <i>Z</i> = 2.4:1)	5d : 8
10		isoprene	30 (3)	4e : 69 (<i>E</i> : <i>Z</i> = 2.5:1)	5e : 10

[a] A mixture of [Ni(acac)₂](0.2 mmol), 1,3-butadiene or isoprene (8.0 mmol), an aldehyde or a ketone (2.0 mmol), and Me₂Zn (4.8 mmol, 1M in hexane) in dry THF (5 ml) was stirred at the indicated temperature under N₂ [Eqs. (a), (b)]. [b] Yields refer to the isolated materials. All products were characterized by ¹H NMR (400 MHz), ¹³C NMR (100 MHz), and IR spectroscopy, high-resolution mass spectrometry, and/or elemental analysis. [c] In addition to **2**–**5**, 1-methyl-3-phenylpropan-1-ol (15 %, entry 2), 1-cyclohexylethan-1-ol (10 %, entry 3), 1-methyl-3-phenylpropan-1-ol (48 %, entry 7), or 1-cyclohexylethan-1-ol (20 %, entry 8) was obtained. [d] The *E*:*Z* ratios are determined on the basis of ¹H and ¹³C NMR spectroscopy. [e] Compound **3** contains a small amount of an isomer (<10%),



Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386.

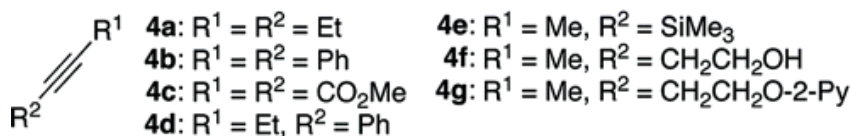
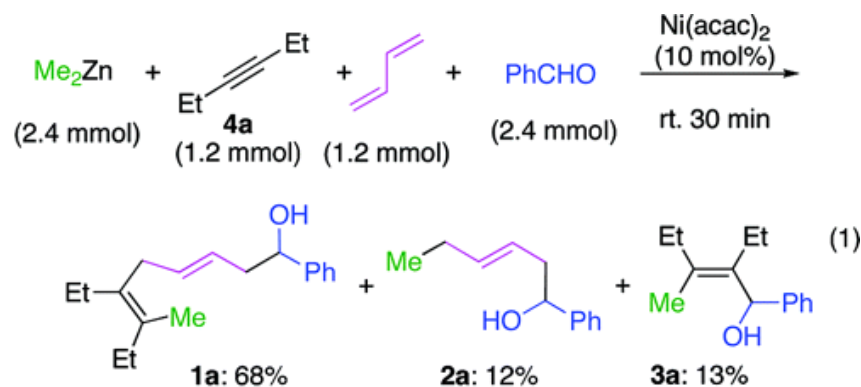
Possible mechanism for the formation of 2/3 and 3/4



Scheme 2. Possible mechanism for the formation of 2/3 and 4/5.

Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386.

Ni⁰-Catalyzed Intermolecular 4-CCR of Me₂Zn, Alkynes, 1,3-Butadiene, and R-C=O .



conditions a:

alkyne (1.2 mmol),
 1,3-butadiene (1.2 mmol),
 aldehyde (1 mmol),
 Me₂Zn (2.4 mmol),
 Ni(acac) (10 mol %)

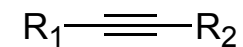
conditions b:

alkyne (4.0 mmol)
 1,3-butadiene (4.0 mmol),
 aldehyde (1 mmol),
 Me₂Zn (2.4 mmol),
 Ni(acac)₂ (10 mol %)

run	alkyne	carbonyl	% isolated yield	
1 ^a	4a	PhCHO	1a : 68	2a : 12 ^d
2 ^b	4a	PhCHO	1a : 73	2a : 1 ^d
3 ^a	4b	PhCHO	1b : 58	2a : 5
4 ^b	4b	PhCHO	1b : 84	2a : 16
5 ^{c,h}	4c	PhCHO	1c : 55	2a : 5
6 ^{b,h}	4c	PhCHO	1c : 43	2a : 0 ^e
7 ^a	4a		1d : 76	2b : 15
8 ^b			1d : 83	2b : 10
9 ^a	4a	Ph-CH ₂ -CHO	1e : 57	2c : 6
10 ^b			1e : 76	2c : 1
11 ^a	4a		1f : 64	2d : 12
12 ^b			1f : 82	2d : 9
13 ^a	4a		1g : 58	2e : 20
14 ^b			1g : 67	2e : 8
15 ^{a,i}	4a		1h : 20	2f : 72
16 ^{b,i}			1h : 51	2f : 20

4-CCR, ^w/unsymmetrical alkynes

run	alkyne	% isolated yield ^e	
1 ^a	4d	1i: 67 (1.3:1) 1i: 82 (1.5:1)	2a: 8 2a: 10
2 ^b			
3 ^a	4e	1j: 64 (1.5:1) 1j: 77 (1.5:1)	2a: 12 2a: 13
4 ^b			3b: 6 3b: 7
5 ^c	4f	1k: 61 (1:1) 1k: 70 (1:1)	2a: 13 2a: 0
6 ^d			3c: 0 3c: 4
7 ^a	4g	1l: 91 (1.4:1) 1l: 94 (1.4:1)	2a: 8 2a: 0
8 ^b			



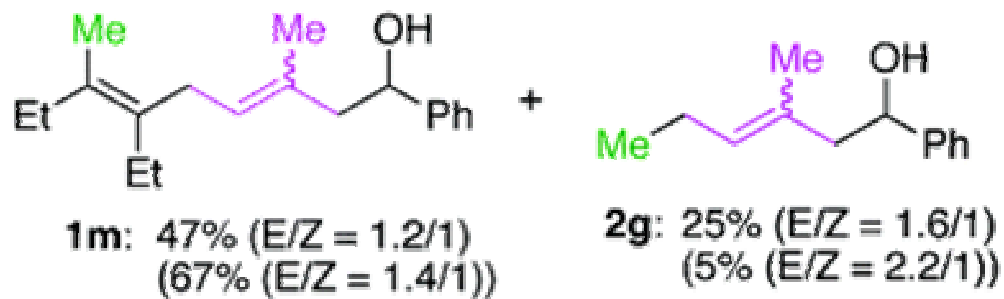
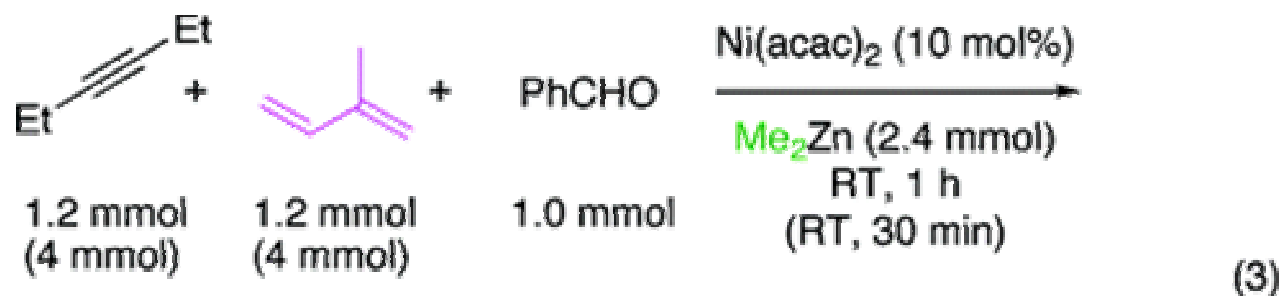
4d: R¹ = Et, R² = Ph

4e: R¹ = Me, R² = SiMe₃

4f: R¹ = Me, R² = CH₂CH₂OH

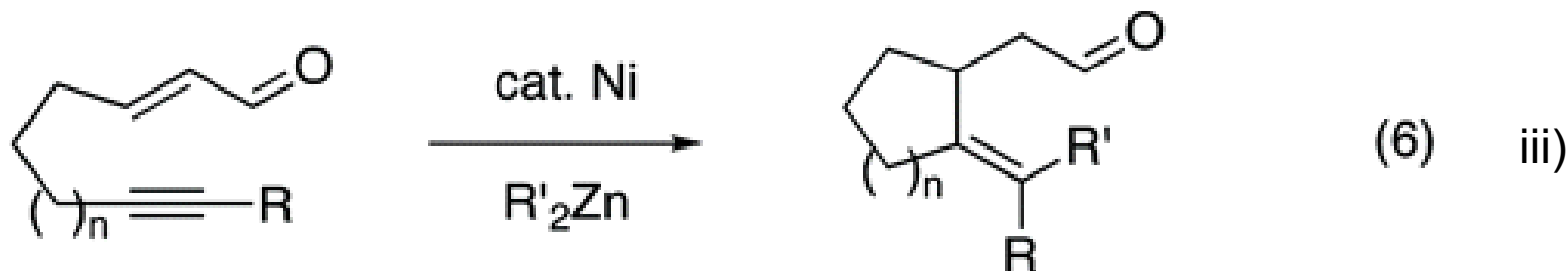
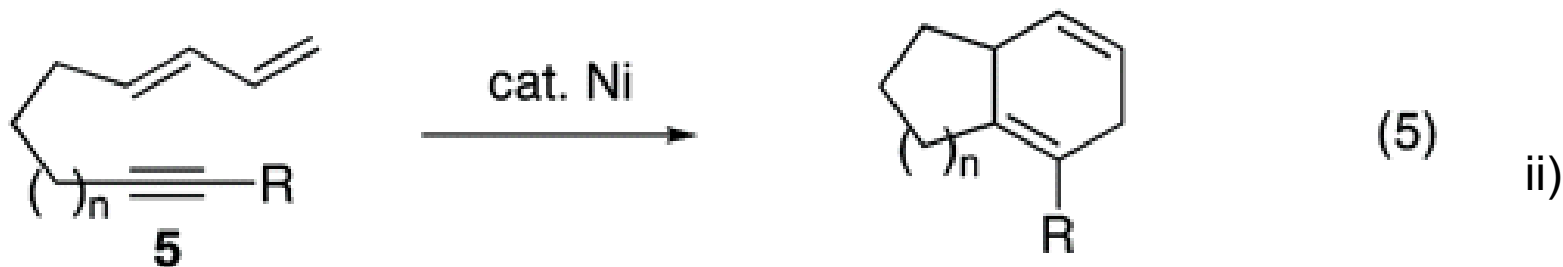
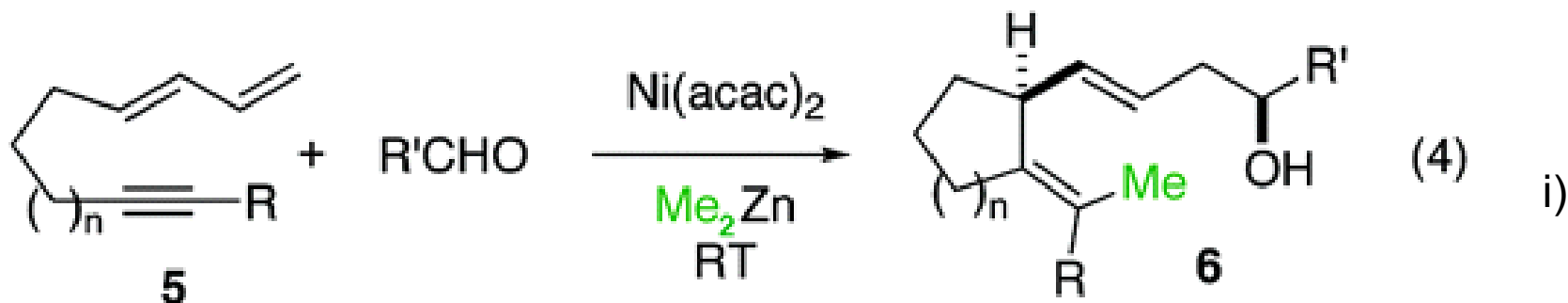
4g: R¹ = Me, R² = CH₂CH₂O-2-Py

Reaction with isoprene



Conditions a
 Conditions b

Ni₀-Catalyzed Intramolecular 4-CCR of Me₂Zn, 1,ω-Dienynes **5**, and Carbonyl Compounds.

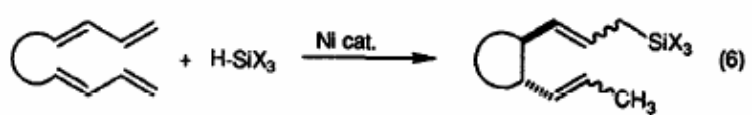
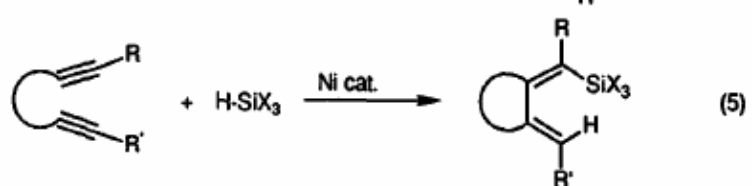
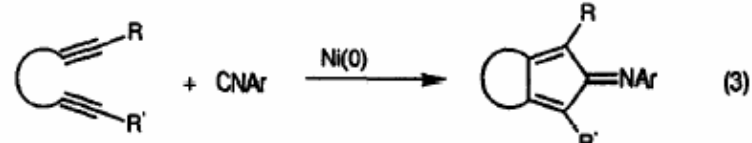
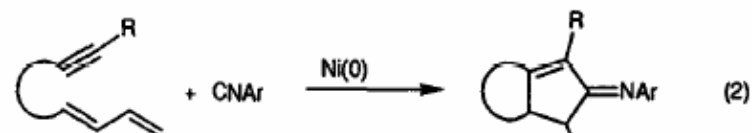
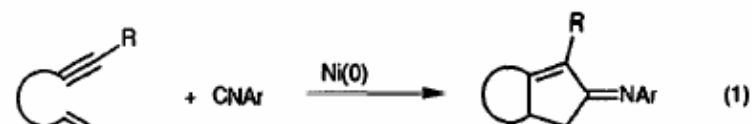


i) Present work

ii) (a) Aubert, C et all. *Chem. Rev.* **2002**, 102, 813. (b) Ito, Y. et all. *Synlett*, **1992**, 539.

iii) (a) Montgomery et all *JACS*, **2004**, 126, 3698. (b) Montgomery et all *Org. Lett.* **2003**, 125, 13481.

Nickel(0)-Mediated Intramolecular Cyclizations of Enynes, Dienynes, Bis-Dienes, and Diynes



4.1.2. Vinylmetal Pathway/Hydrometalation: Nickel-Chromium Catalysts

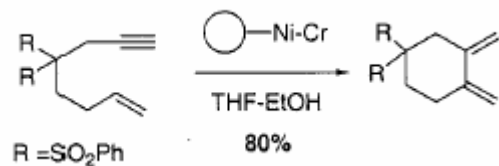
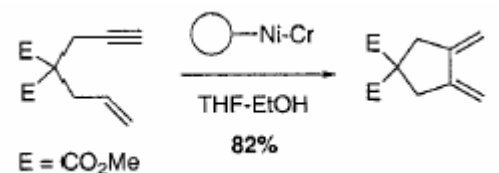
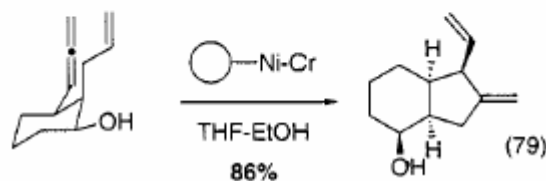
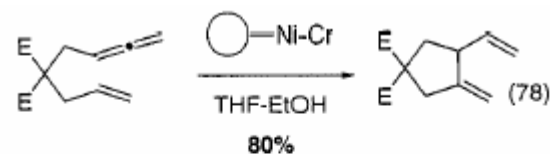


Table 3: Ni-Catalyzed Conjugative addition of Me_2Zn toward PhCHO across 1, ω -dienynes: Formation of 5-membered ring

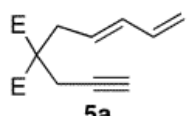
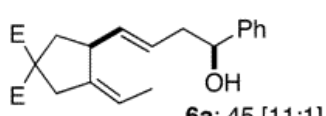
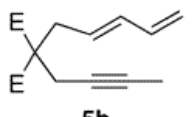
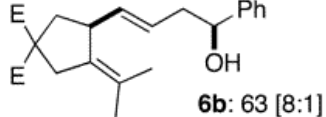
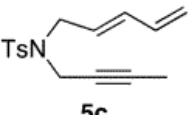
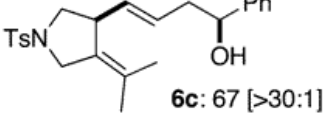
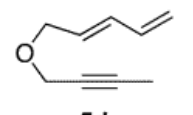
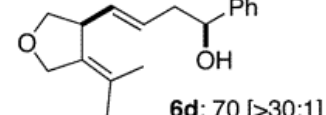
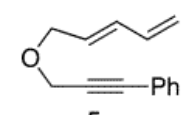
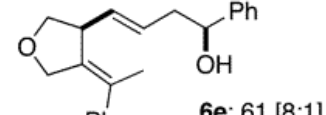
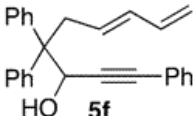
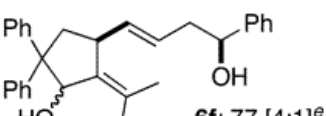
Run	1, ω -Diene 5	Time (h)	Product 6^b (% Isolated) [ratio] ^c
1		1	 6a : 45 [11:1]
2		1	 6b : 63 [8:1]
3		1	 6c : 67 [>30:1]
4		0.5	 6d : 70 [>30:1]
5		1	 6e : 61 [8:1]
6		3.5 ^d	 6f : 77 [4:1] ^e

Table 4. Ni-Catalyzed Conjugative Addition of Me_2Zn toward PhCHO across 1, ω -Dienynes **5**: Formation of 6-Membered Ring

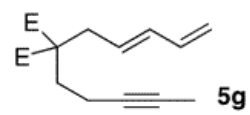
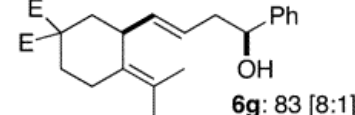
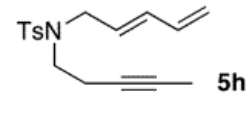
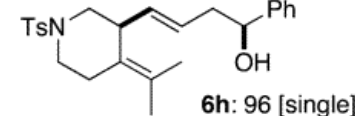
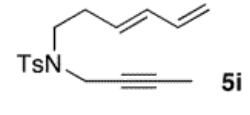
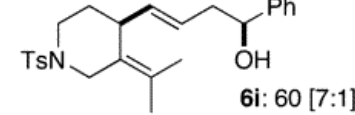
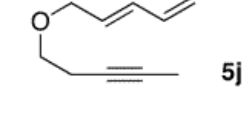
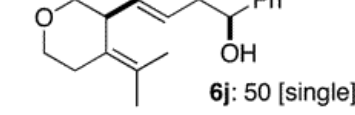
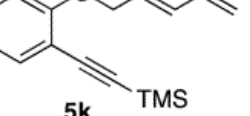
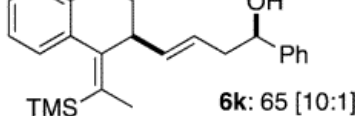
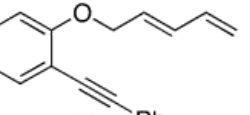
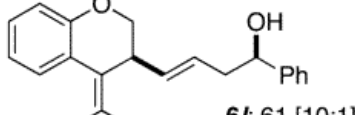

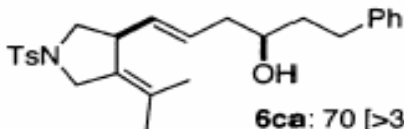

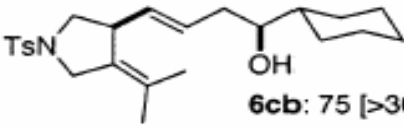
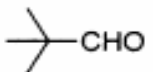
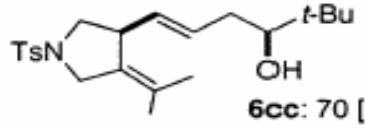

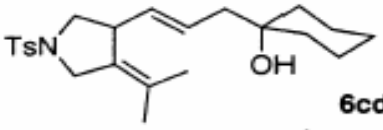

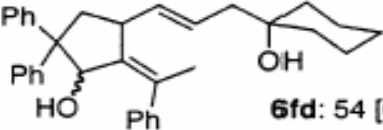

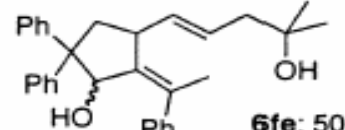
Run	1, ω -Diene 5	Time (h)	Product 6^b (% Isolated) [ratio] ^c
1		1	 6g : 83 [8:1]
2		1	 6h : 96 [single]
3		1	 6i : 60 [7:1]
4		1	 6j : 50 [single]
5		19	 6k : 65 [10:1]
6		2	 6l : 61 [10:1]

Table 5. Ni-Catalyzed Conjugative Addition of Me₂Zn toward Aliphatic Aldehydes and Ketones across **5c** and **5f** Forming 5-Membered Ring Compounds

Run	Carbonyl	Time (h)	Product 6^b (% Isolated) [ratio] ^c
1		1	 6ca : 70 [$>30:1$]
2		1	 6cb : 75 [$>30:1$]
3		2	 6cc : 70 [12:1]
4		1	 6cd : 40
5		22	 6fd : 54 [6:1] ^d
6		22	 6fe : 50 [3:1] ^d

^a Reaction conditions: **5c** or **5f** (1 mmol), an aliphatic aldehyde or an aliphatic ketone (2 mmol), Ni(acac)₂ (10 mol %), Me₂Zn (2.4 mmol for **5c** and 3.6 mmol for **5f**, 1 M hexane) in THF (5 mL) at room temperature under N₂. ^b Yield refers to the isolated, spectroscopically homogeneous material. ^c Diastereomeric ratio determined by ¹H NMR (400 MHz). Only the major isomers are shown. ^d Diastereomer due to OH stereochemistry.

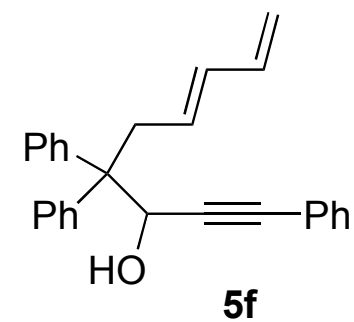
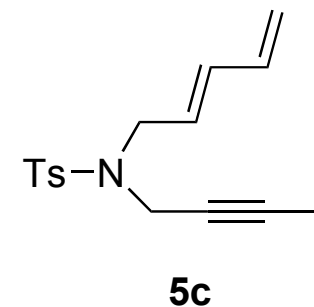

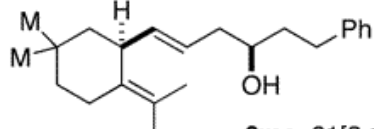

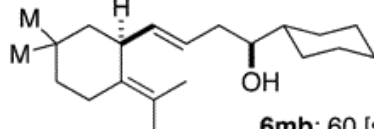
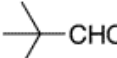
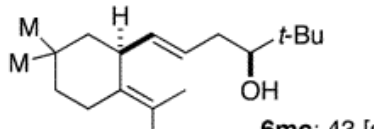

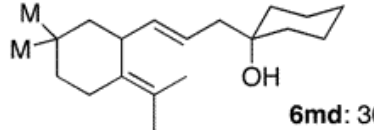
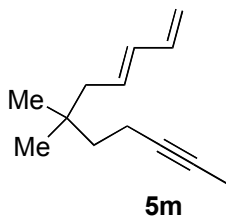
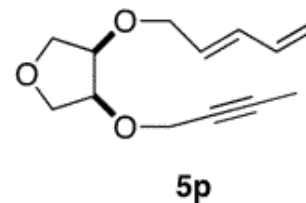
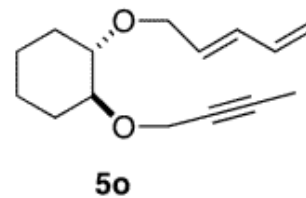
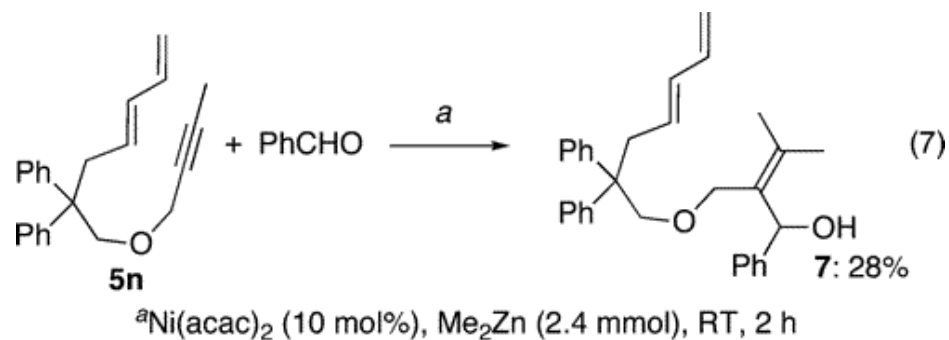


Table 6. Ni-Catalyzed Conjugative Addition of Me₂Zn toward Aliphatic Aldehydes and Ketones across 2-[(2*E*,4)-Pentadienyl]-2-(3-pentynyl)Malonic Acid Dimethyl Ester (**5m**) Forming 6-Membered Ring Compounds

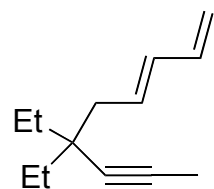
Run	Carbonyl	Time (h)	Product 6 ^b (% Isolated) [ratio] ^c
1		1	 6ma : 61 [8:1] ^d
2		1	 6mb : 60 [single]
3		4	 6mc : 43 [single]
4		5	 6md : 30



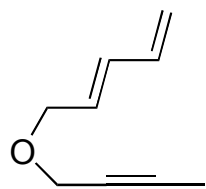
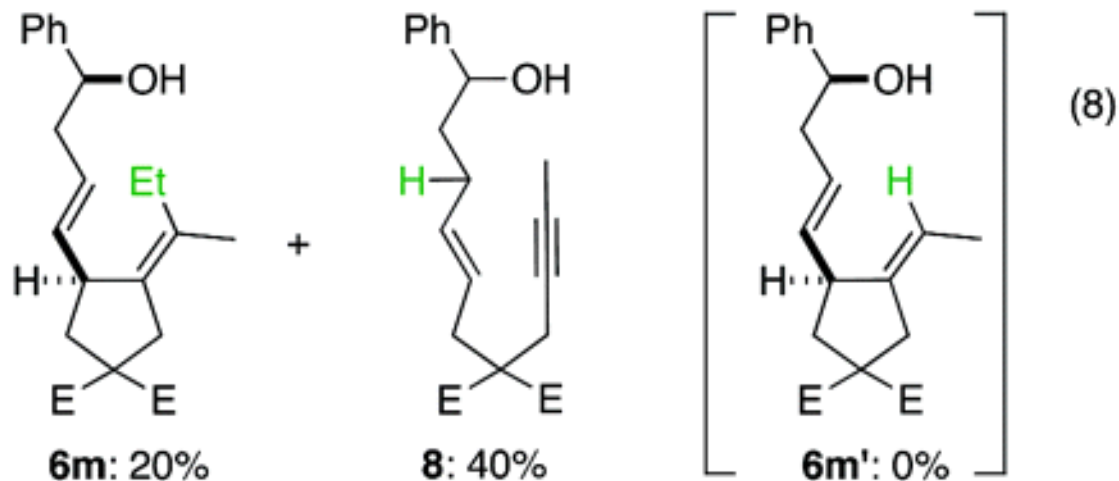
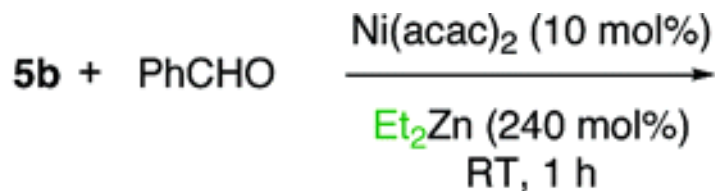
Attempts for 7- and 8-Membered Ring Formation



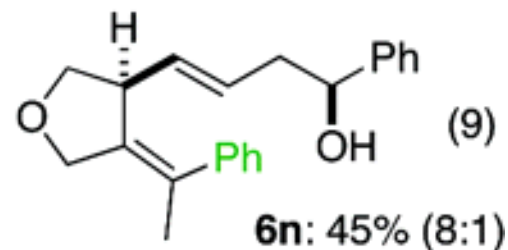
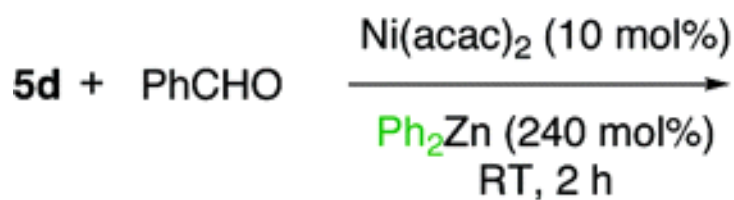
Results with Et₂Zn and Ph₂Zn in place of Me₂Zn



5b

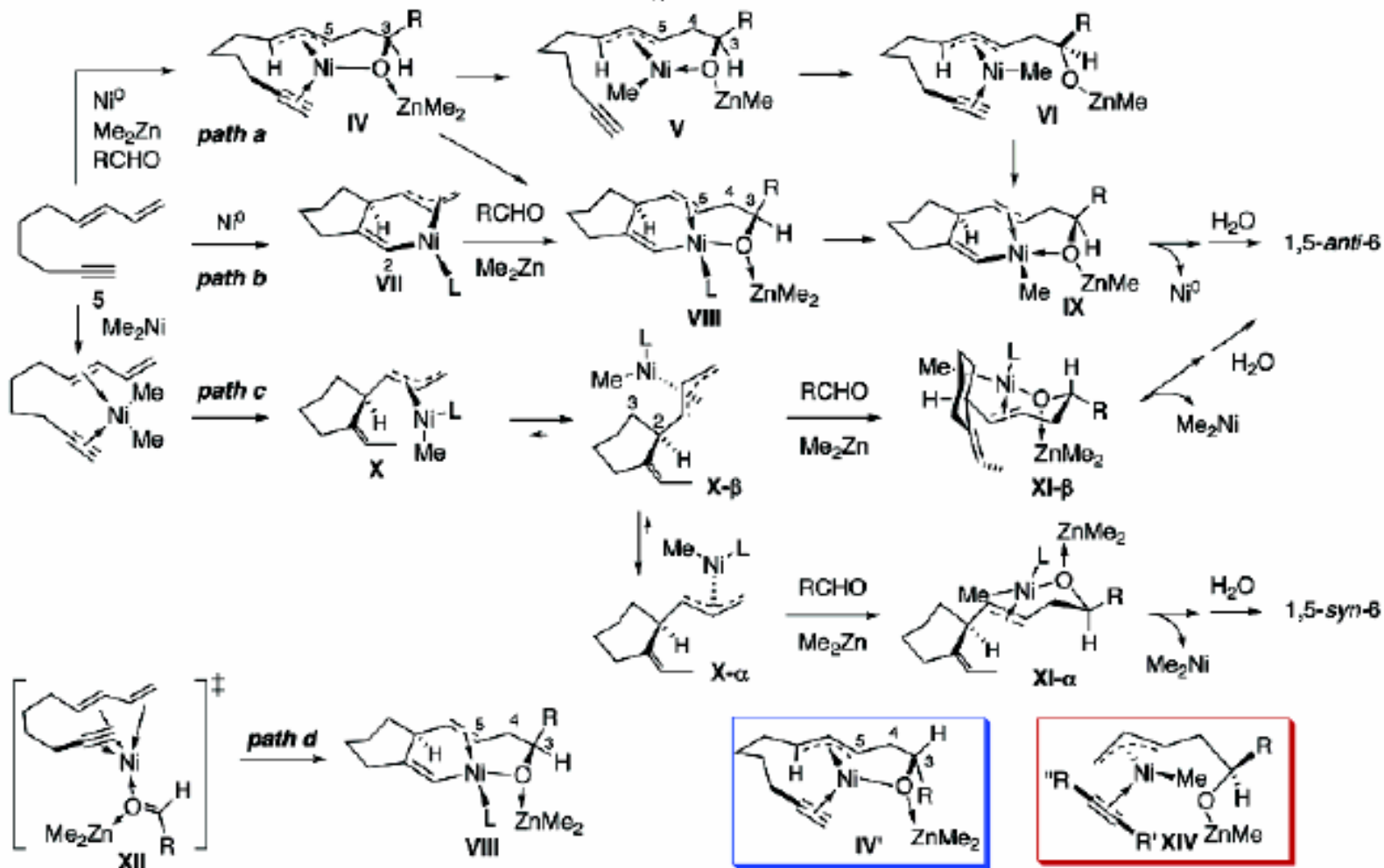
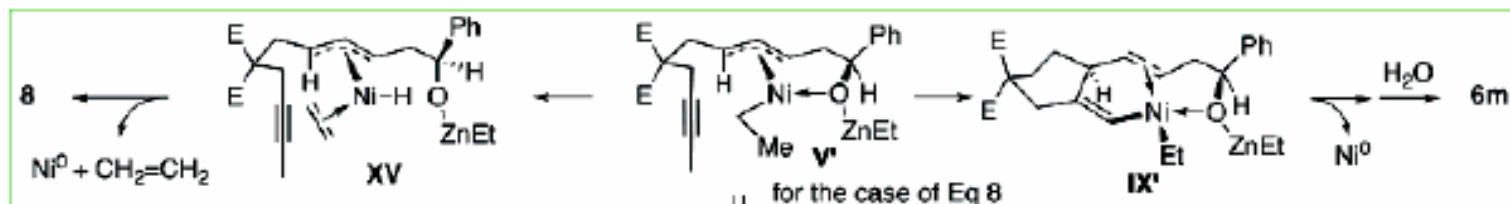


5d



* R₃B works similarly but the yields are lower than dialkylzinc

Mechanistic Consideration



Conclusions

- Ni(acac)₂ catalyst is useful for Intermolecular 4-CCR in 1:1:1 ratio to lead 3*E*, 6*Z*-octadienols-1ols with high stereoselectivity and good yields but only to symmetric alkynes.
- The same conditions are applicable to Intramolecular 4-CCR afforded 1,5-diastereoselectivity and allow to construct 5 and 6 membered Ring with C, O, N, but are not applicable to larger ring sizes.