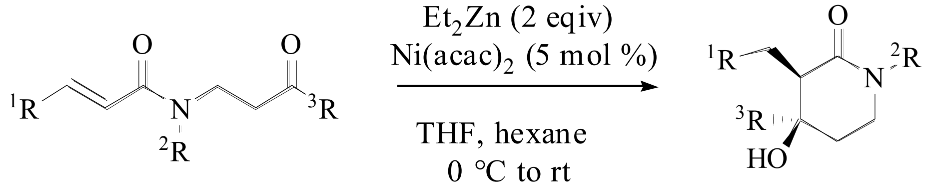
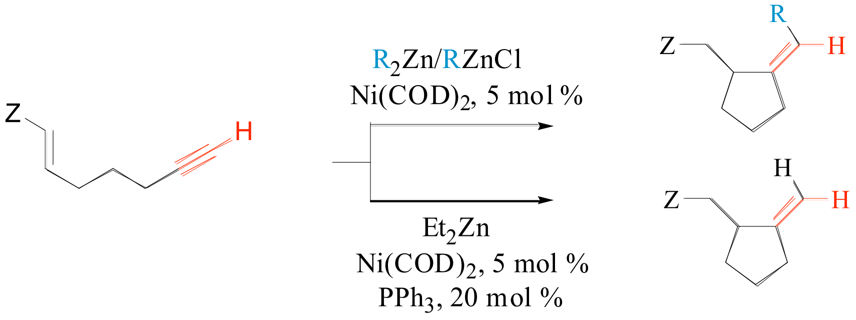
Diastereoselective Nickel-Catalyzed Reductive Aldol Cyclizations Using Diethylzinc as the Stoichiometric Reductant: Scope and Mechanistic Insight

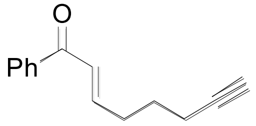
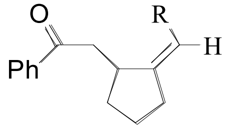
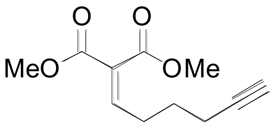
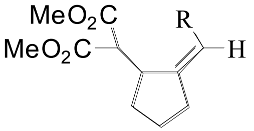
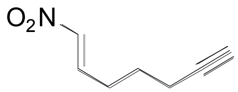
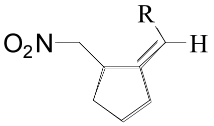
Pekka M. Joensuu, Gordon J. Murray, Euan A. F. Fordyce, Thomas Luebbers
and Hon Wai Lam



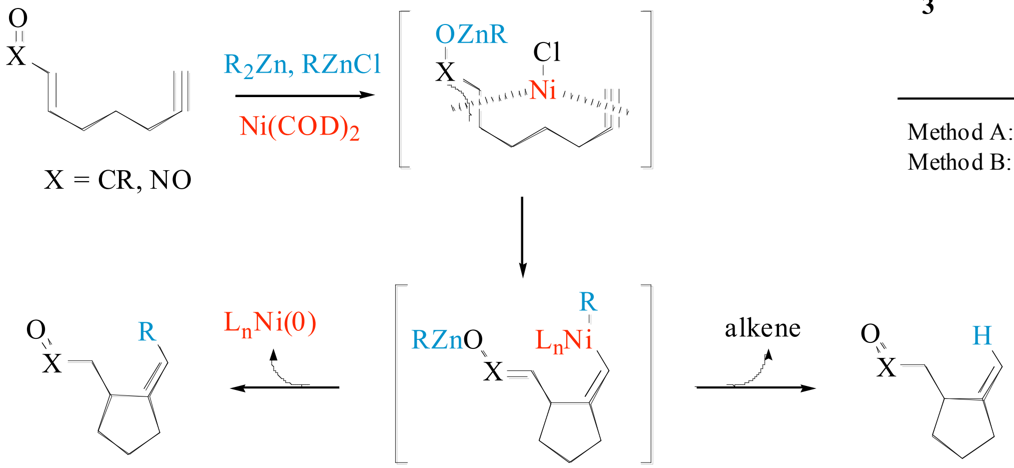
J. Am. Chem. Soc. ASAP

Couplings of Alkenes with Alkynes



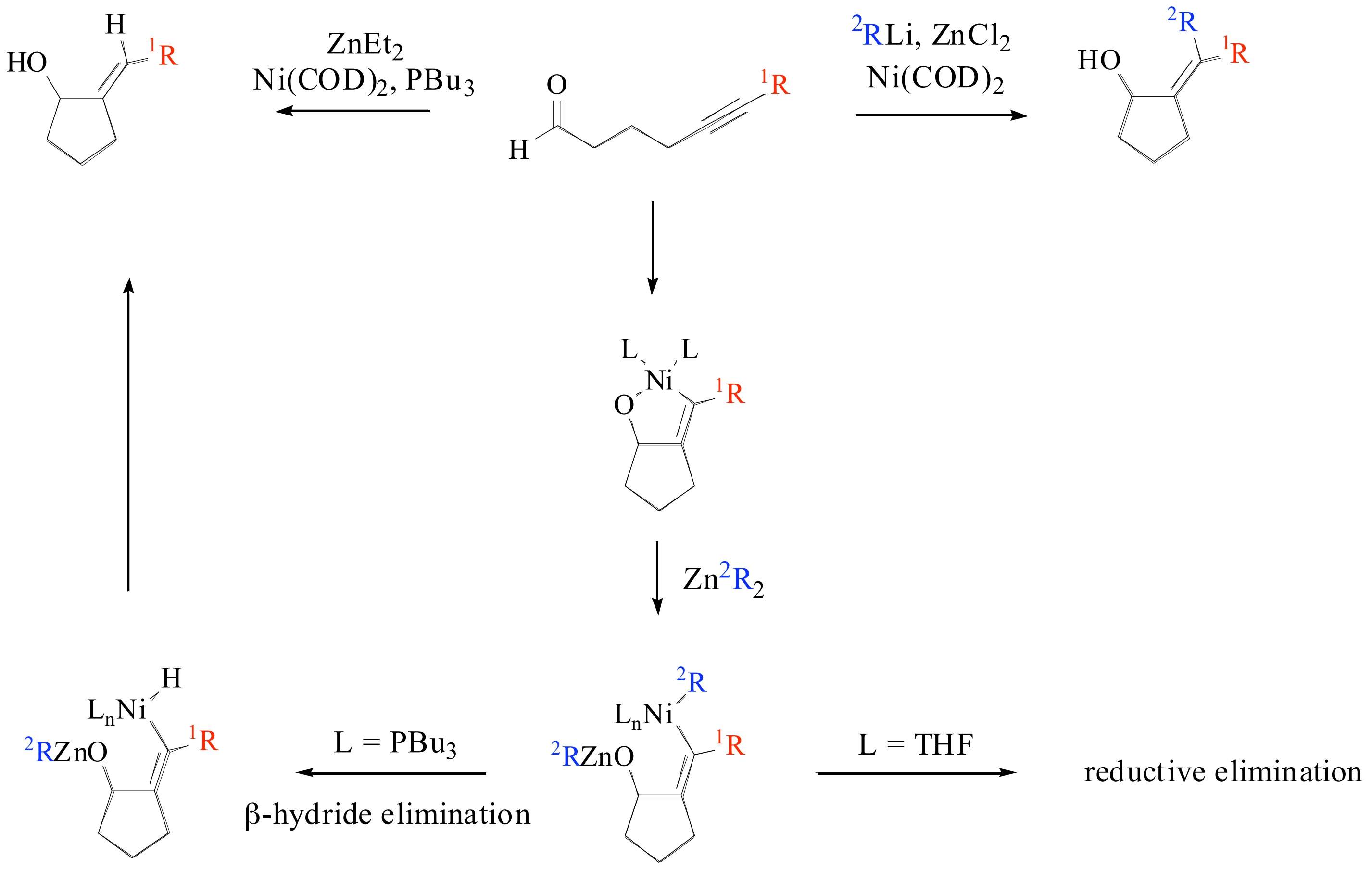
entry	substrate	product	method (yield)
1			**A** (R = Me, 82 %) **B** (R = H, 92 %)
2			**A** (R = Me, 74 %) **B** (R = H, 83 %)
3			**A** (R = Me, 39 %) **B** (R = Et, 47 %; R = H, 13%)

Method A: [MeLi + $ZnCl_2$], 5 mol % $Ni(COD)_2$, THF, 0 °C
Method B: Et_2Zn, 5 mol % $Ni(COD)_2$, 20 mol % PPh_3, THF, 25 °C



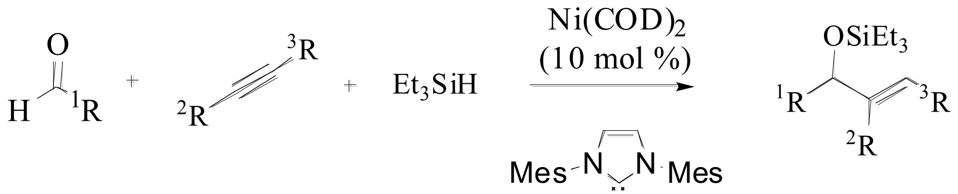
J.Am.Chem.Soc. **1997**, *119(21)*, 4911.

Nickel-Catalyzed Coupling Reactions of Carbonyl Compounds with Alkynes

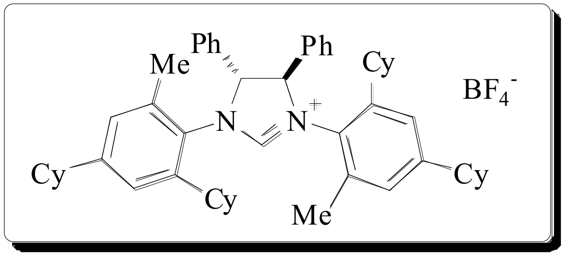


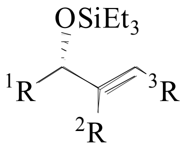
J. Am. Chem. Soc. **1997**, *119*, 9065.

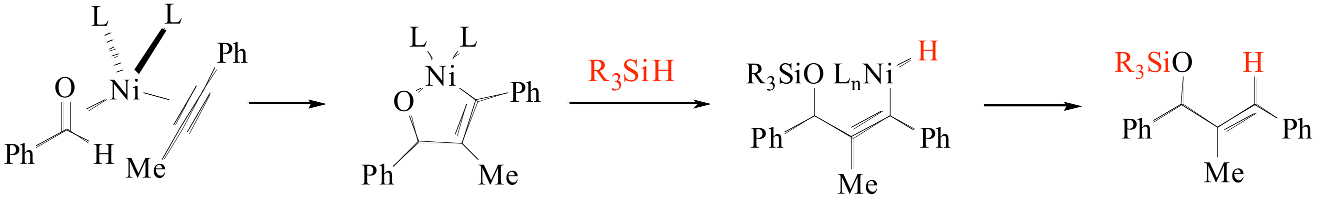
Nickel-Catalyzed Reductive Coupling of Aldehydes and Alkynes (Et_3SiH as a Reductant)



entry	^{1}R	^{2}R	^{3}R	yield
1	Ph	Me	Ph	84%
2	*n*-Hex	Me	Ph	82%
3	Ph	H	*n*-Hex	71%
4	Ph	H	Ph	72%
5	*s*-Bu	Me	Ph	81%

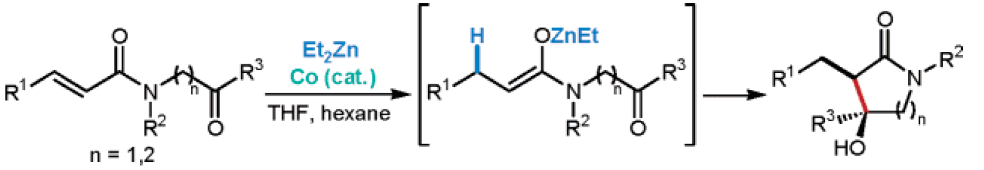




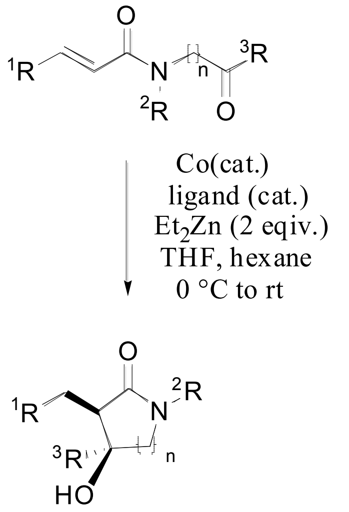


J. Am. Chem. Soc. **2004**, *126*, 3698.
J. Am. Chem. Soc. **2007**, *129*, 9568.

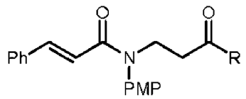
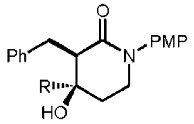
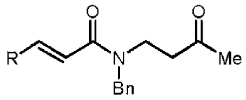
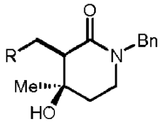
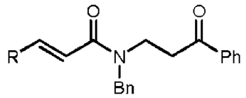
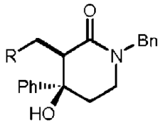
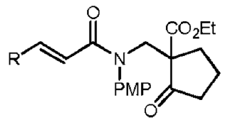
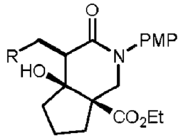
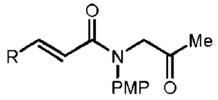
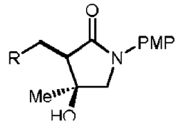
ABSTRACT



Cobalt catalysis enables a new method for the generation of zinc enolates using diethylzinc to reduce α,β-unsaturated amides. This method has been applied to a high-yielding diastereoselective reductive aldol cyclization.

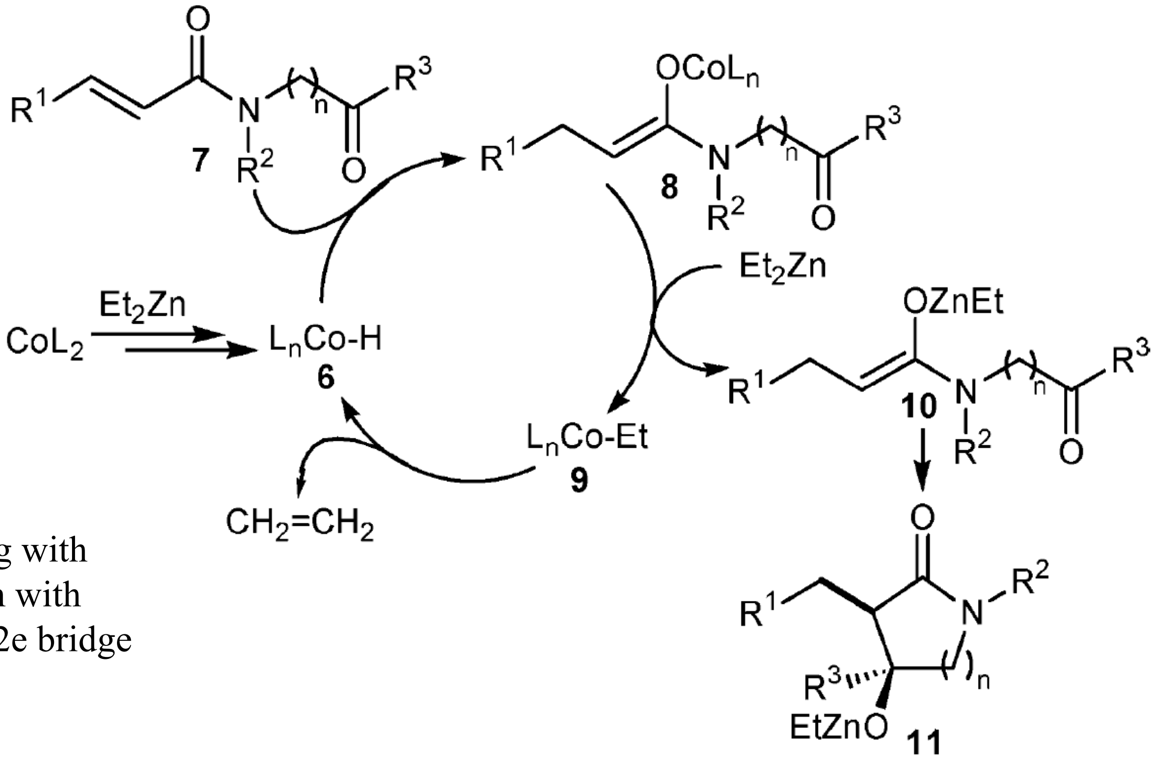


Method A: Co(acac)$_2$ · 2H$_2$O (5 mol %)
Method B: CoCl$_2$ (5 mol %), Cy$_2$PPh (5.5 mol %)

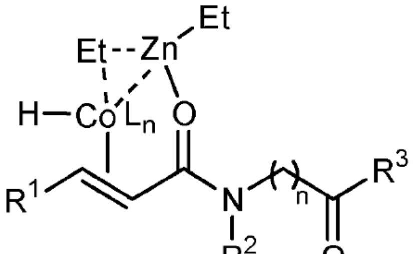
entry	substrate		method	product		dr[b]	yield (%)[c]
1		R = Me **1a**	A		**2a**	12:1	89
2		R = Me **1a**	–[d]		**2a**	12:1	79
3		R = Et **1b**	A		**2b**	9:1	88
4		R = H **1c**	A		**2c**	9:1	88
5		R = *i*-Pr **1d**	A		**2d**	>19:1	>99
6		R = Ph **1e**	A		**2e**	>19:1	97
7		R = 2-furyl **1f**	A		**2f**	>19:1	>99
8		R = Me **1g**	A		**2g**	>19:1	94
9		R = *i*-Bu **1h**	A		**2h**	>19:1	94
10		R = H **1i**	B		**2i**	9:1[e]	56
11		R = Me **1j**	B		**2j**	>19:1[e]	80
12		R = Ph **1k**	B		**2k**	>19:1[e]	88
13		R = H **1l**	A		**2l**	9:1	47
14		R = Ph **1m**	A		**2m**	8:1	56
15		R = OMP **1n**	B		**2n**	14:1	74

Org. Lett. **2006**, *8(17)*, 3729.

Plausible Mechanism



Or binding Et_2Zn along with
Lewis basic interaction with
cobalt hydride via 3c, 2e bridge



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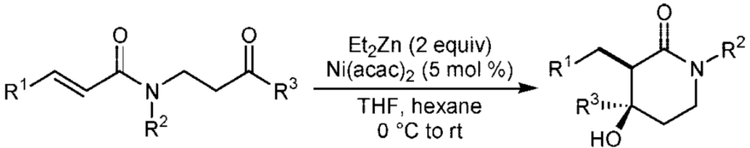
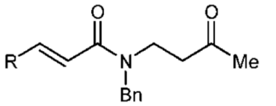
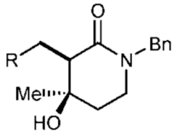
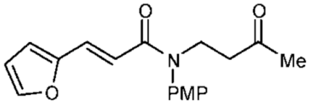
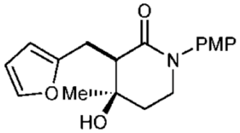
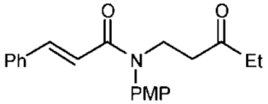
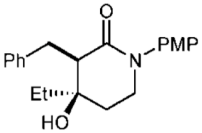
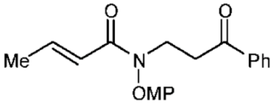
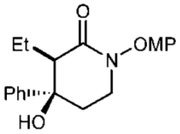
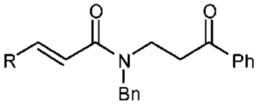
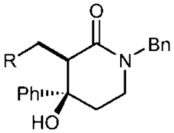
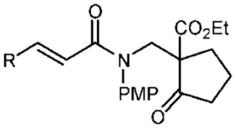
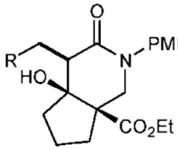
Org. Lett. **2006**, *8(17)*, 3729.

Title Paper: Nickel–Catalyzed Reductive Aldol Cyclization

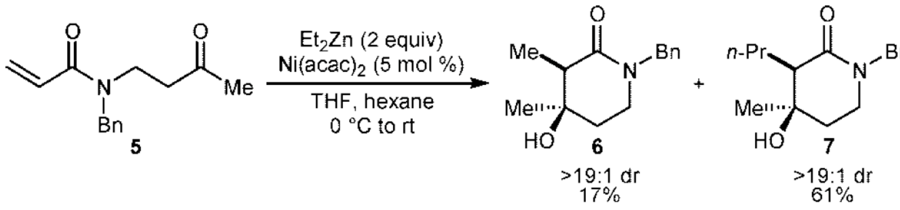


3a-3m → **4a-4m**

entry	substrate		product		dr[b]	yield (%)[c]
1		R = Me **3a**		**4a**	>19:1	97
2		R = *i*-Pr **3b**		**4b**	>19:1	98
3		R = CH_2CH_2Ph **3c**		**4c**	>19:1	95
4		R = Ph **3d**		**4d**	>19:1	97
5		R = 2-furyl **3e**		**4e**	>19:1	>99
6		**3f**		**4f**	>19:1	75
7		**3g**		**4g**	9:1	82
8		**3h**		**4h**	>19:1	62
9		R = Me **3i**		**4i**	9:1	84
10		R = *i*-Bu **3j**		**4j**	12:1	84
11		R = 2-furyl **3k**		**4k**	>19:1	79
12		R = Me **3l**		**4l**	>19:1[d]	62
13		R = Ph **3m**		**4m**	>19:1[d]	50

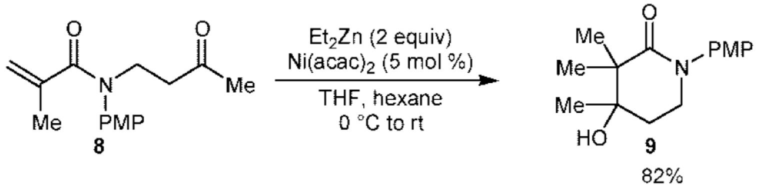
J. Am. Chem. Soc. **2008**, *ASAP*.

Title Paper: Scope of the Reaction



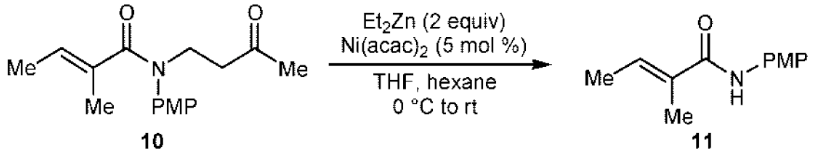
(2)

- simple acrylamides are less competent substrates but using $Co(acac)_2$ x $2H_2O$ gives **6** in 88% yield



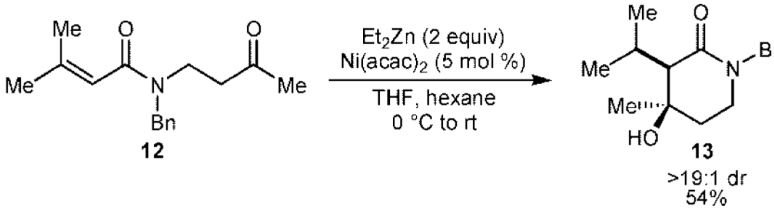
(3)

- substitution at the α-position enforces reductive cyclization *vs.* alkylaive aldol cyclization



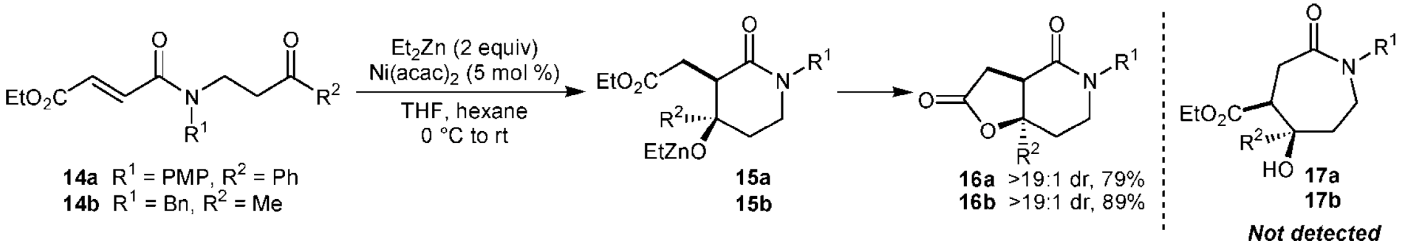
(4)

- the cyclizations of **8**, **10** and **12** using $Co(acac)_2$ were completely unsuccessful



(5)

- tertiary zinc alkoxides produced in reductive cyclization undergo lactonization with the adjacent ester (unsuccessful with Co-catalyst)



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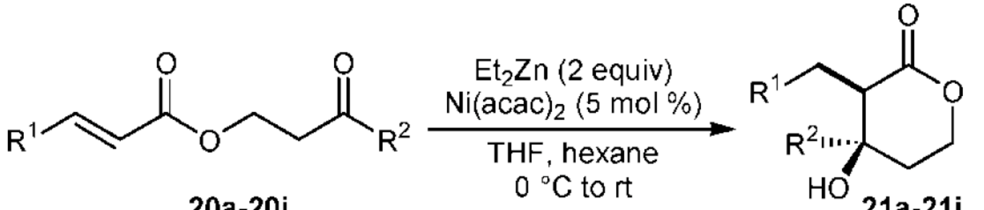
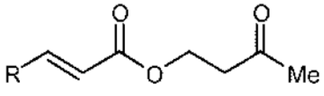
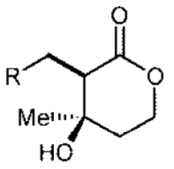
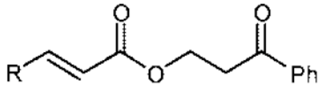
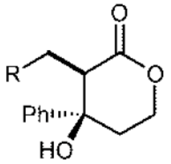
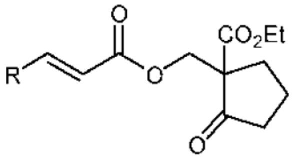
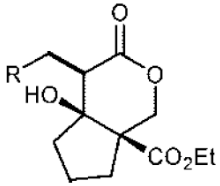
Title Paper: Nickel-Catalyzed Reductive Aldol Cyclization Furnishing β-Hydroxylactones



20a-20j **21a-21j**

entry	substrate		product		dr[b]	yield (%)[c]
1		R = *i*-Bu **20a**		**21a**	>19:1	77
2		R = CH_2CH_2Ph **20b**		**21b**	>19:1	85
3		R = 4-MeOPh **20c**		**21c**	>19:1	76
4		R = 2-furyl **20d**		**21d**	>19:1	81
5		R = *i*-Bu **20e**		**21e**	5.5:1	84[d]
6		R = CH_2CH_2Ph **20f**		**21f**	≥10:1	76[e]
7		R = 2-furyl **20g**		**21g**	n.d[f]	75[f]
8		R = Me **20h**		**21h**	>19:1[g]	88
9		R = *i*-Pr **20i**		**21i**	>19:1[g]	74
10		R = Ph **20j**		**21j**	>19:1[g]	73

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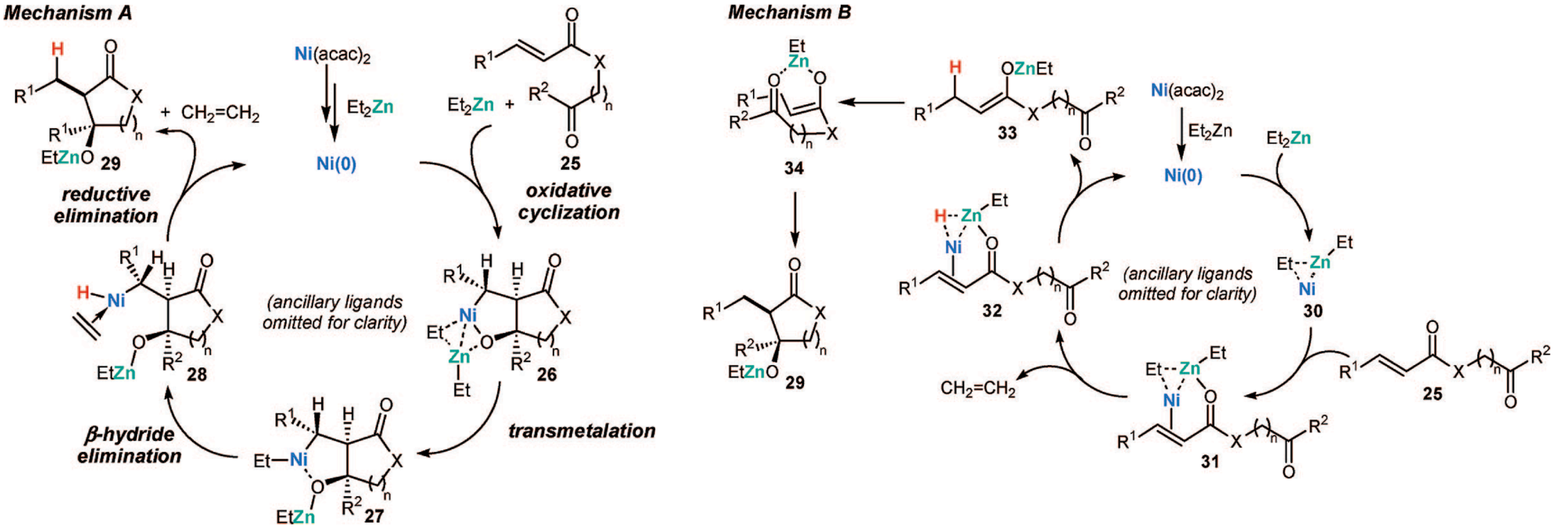
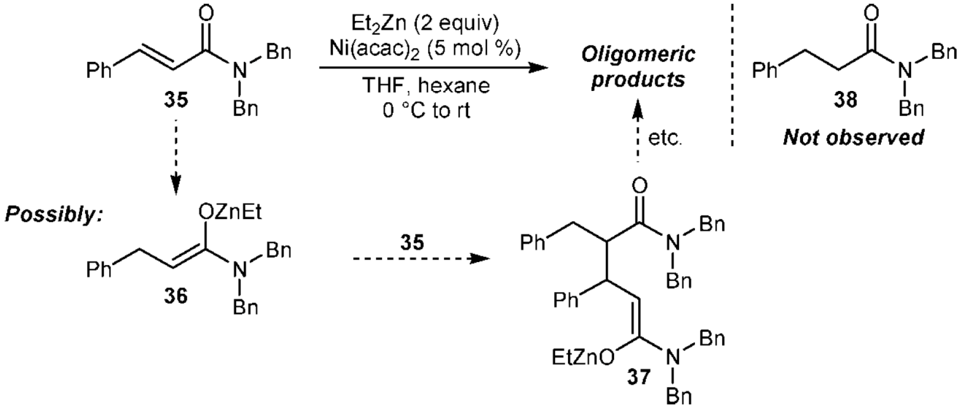
Title Paper: Mechanistic Considerations





- mechanism **B** does not require the partitipation of the ketone until the zinc enolate is formed
- the ketone is an essential component in mechanism **A**
- both mechanisms can be relevant

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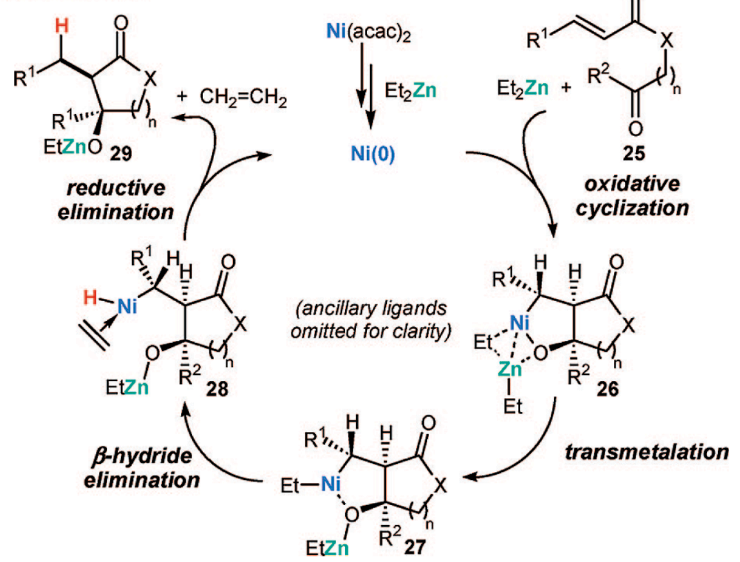
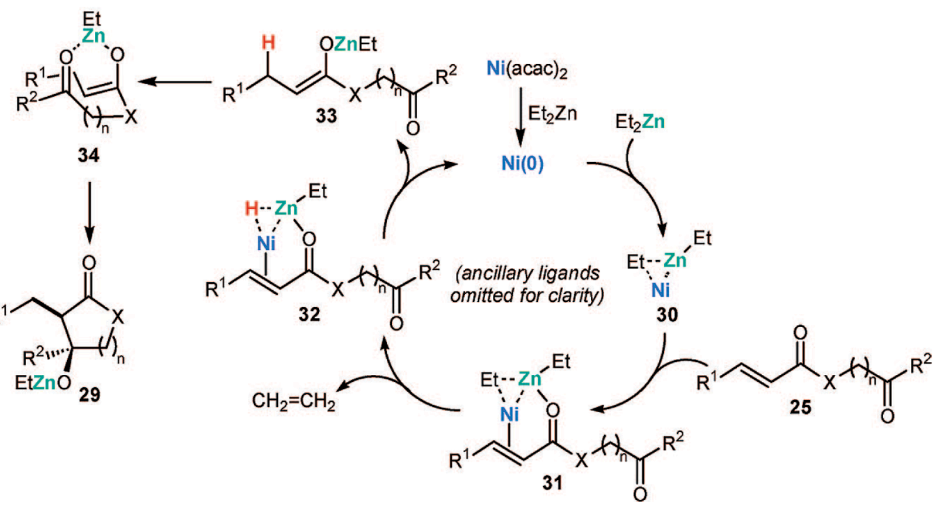
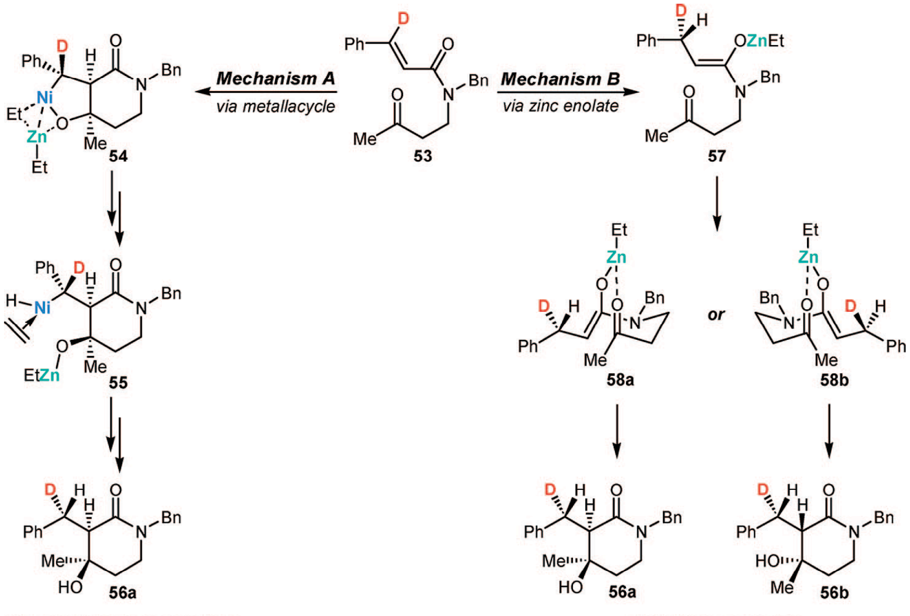
Mechanism A



Mechanism B





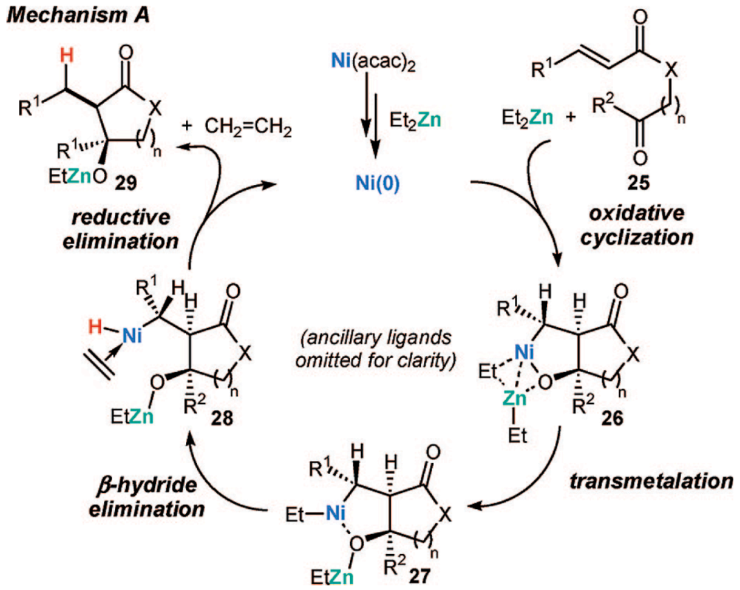
One diastereomer expected

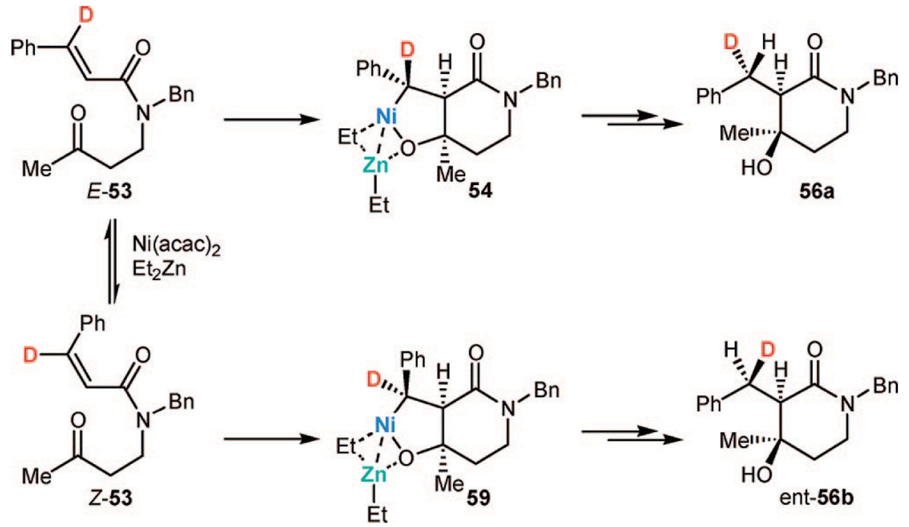
1:1 Mixture expected

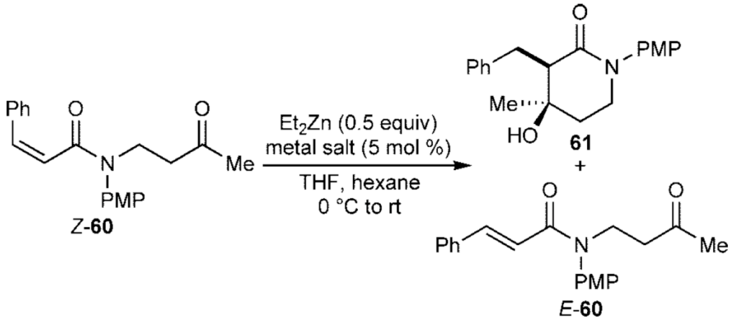
- The nickel-catalyzed reductive cyclization of **53** gave a 1:1.3 inseparable mixtures of **56a** and **56b** (diastereomeric products)
- Mecanisms **A** and **B** are appreciably more complex
- The alkene of the α,β-unsaturated carbonyl can undergo *E*/*Z* equilibration and the diastereoselectivity could result from mechanism **A**

J. Am. Chem. Soc. **2008**, *ASAP*.

Title Paper: Stereochemical Outcome







Relative ratios

	Z-60	61	E-60	
Using Ni(acac)$_2$	trace	1	1.6	(21)
Using Co(acac)$_2$·2H$_2$O	6.9	1	1.4	(22)

- Subjecting the *Z*-**60** to the standard reaction conditions (with 0.5 equiv of Et$_2$Zn) gives the lactam **61** along with the uncycled material (*which had undergone complete E/Z isomerisation)*
- Mechanism **A** cannot be excluded

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Conclusions

- $Ni(acac)_2$ in the presence of diethylzinc is a highly effective catalyst for the reductive aldol cyclization of substrates containing α,β-unsaturated carbonyl functions thetered to the ketone

- Tether can be either an amide or an ester (opposite to $Co(acac)_2$ which is not efficient with esters)

- The role of diethylzinc is to deliver a hydride to the β-position of the cyclization precursor

- The reaction is tolerant to substituents at the β-position of the α,β-unsaturated carbonyl component as well as to different nitrogen protected groups

- Two possible mechanisms were suggested and several mechanistic probes revealed the complex nature of these reactions