June 4, 2012
Seiko KITAHARA (M1)

Nickel(0)-Catalyzed Alkene-Aldehyde Non-Reductive Couping Reaction

-Byproduct-Free Processes-

Contents

0. Introduction

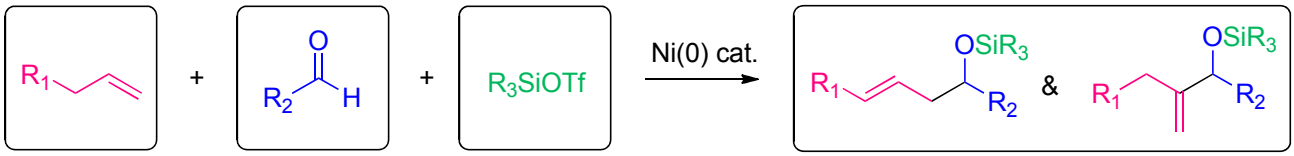
reactions picked out for today

ref) my lit. seminar (B4)

Byproduct-free = ideally atom economy

A + B + C ⟶ product

Alkene-Aldehyde Non-Reductive Coupling

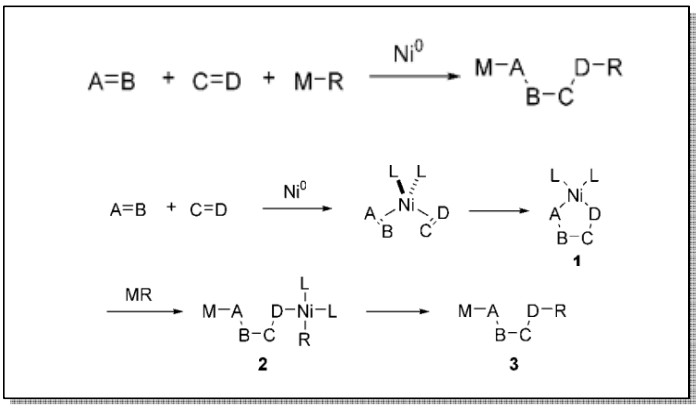


1. Alkene-Aldehyde Reductive Coupling Reaction

two pioneers in this area

John Montgomery

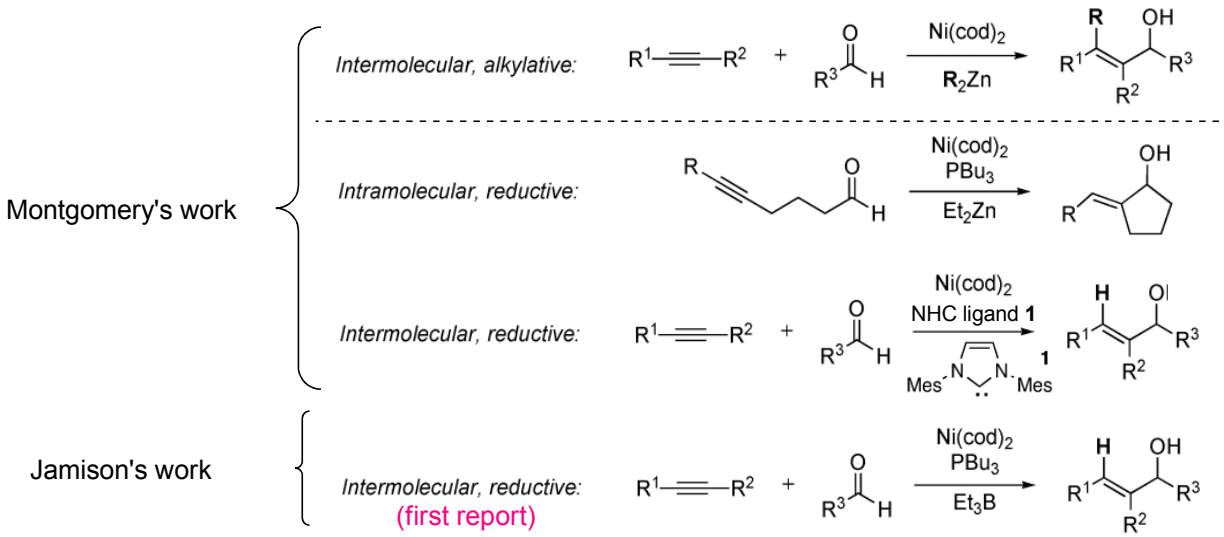
Timothy F. Jamison



- Late-transition metal catalysis has potentical advantages:
  (1)simpler preparation and handling of the catalysts
  (2)better combatibility with Lewis basic functionality
  (3)weaker M-O bond (⇒ more efficient catalytic turnovers of R-O-M intermediates)
  (4)access to reductive elimination chemistry

- Nickel has additinonal properties:
  -chaep
  -air-stable (unless powdered Ni(0))
  -stable in the presence of hard organometallics

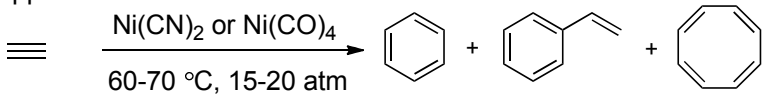
Ni(0)-catalyzed alkyne-aldehyde reductive coupling to form allylic alcohols



background & challenges

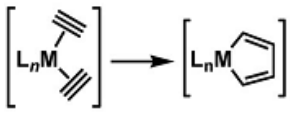
first reports of Ni(0)-catalyzed multi-π-component coupling reactions

Reppe: 1948

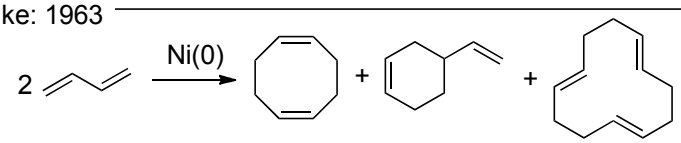


W. Reppe *et al. Justus Liebigs Ann. Chem.*, **1948**, *560*, 104.

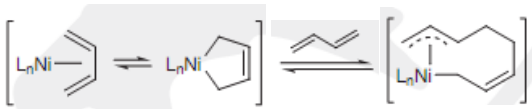
via nickelacycle



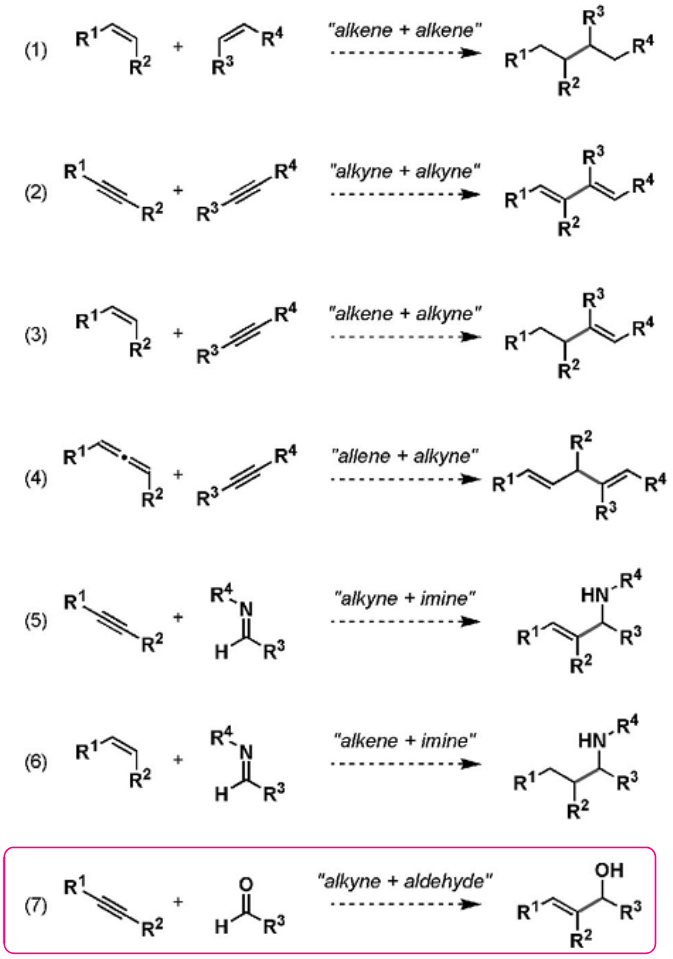
Wilke: 1963



G. Wilke *et al. ACIE*, **1963**, *2*, 105.

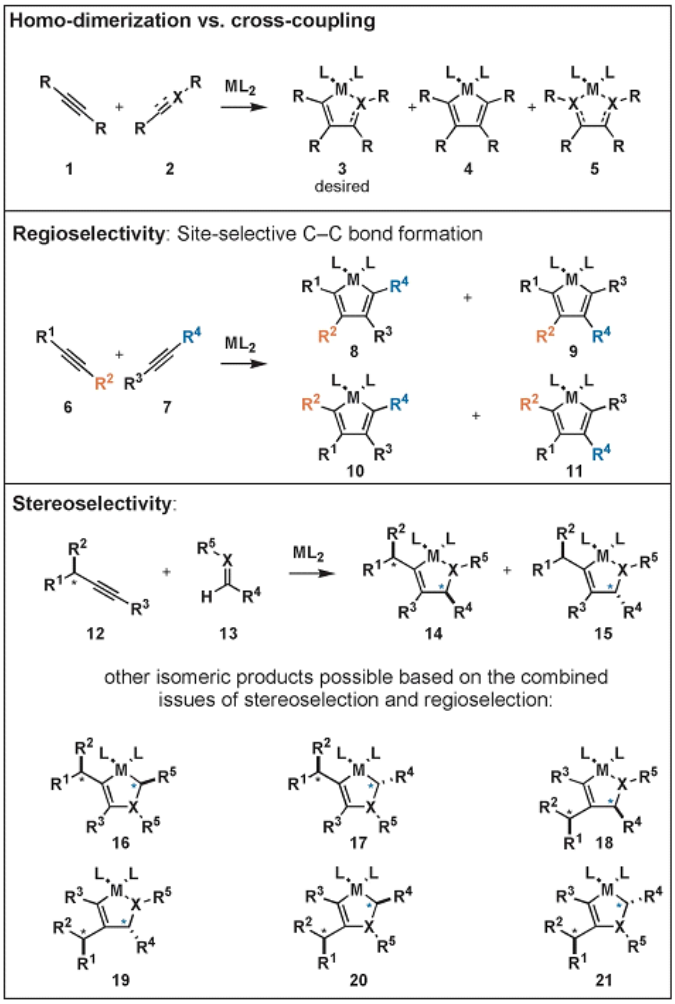


"modern" biomolecular C-C bond formation

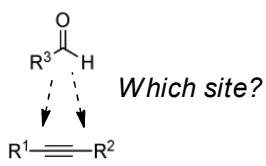


Micalizio, G. C. *et al. EJOC,* **2010**, 391.

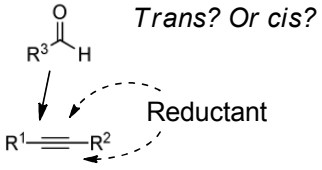
basic challenges



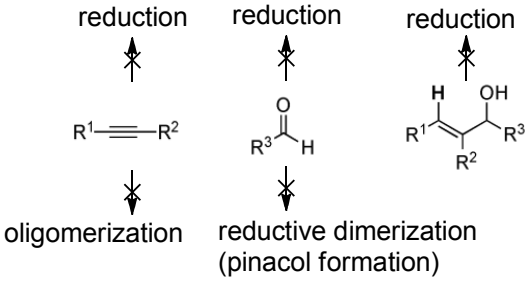
Regioselectivity



Stereoselectivity



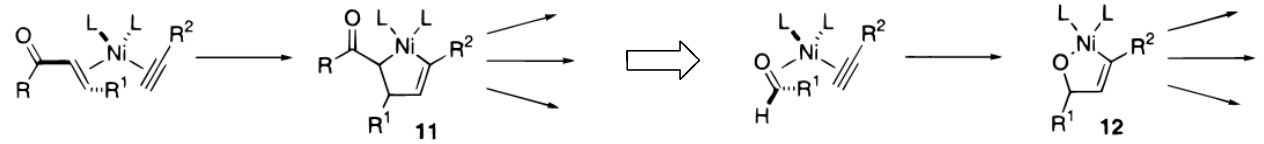
Chemoselectivity



1-1. Some System for Alkyne-Aldehyde Coupling Reactions

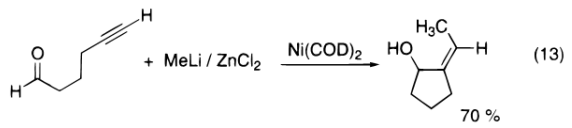
Montgomery's first system: $Ni(COD)_2/PBu_3$ system

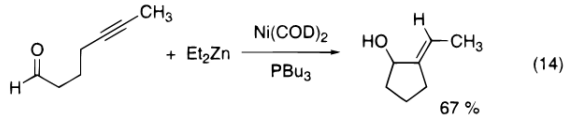
a conceptual framework

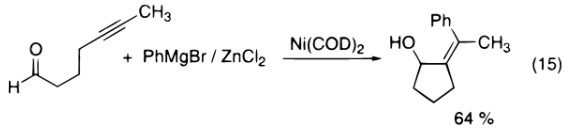


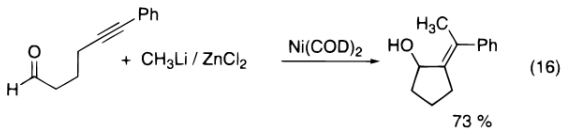
Is it possible to develop a new catalytic processes via analogous oxametallacycles ??

a discovery leading to develop alkyne-aldehyde reductive coupling



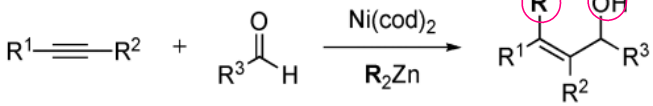




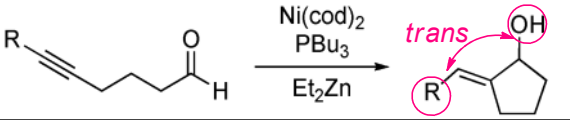


in the absence of phosphine ligands → alkylative
in the presence of phosphine ligands → reductive

• alkylative cyclization

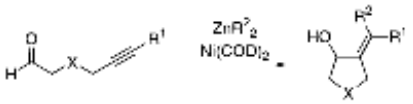


• ynal reductive cyclization (the first report)



substrate scope

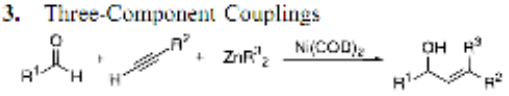
Table 1. Ynal Alkylative Cyclizations



entry	X	R^1	R^2	yield (%)[a]
1	CH_2	H	CH_3	70[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	76
6	CH_2	Ph	CH_3	73
7	CH_2	Ph	Et	67
8	NCOPh	H	CH_3	72

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

Table 3. Three-Component Couplings

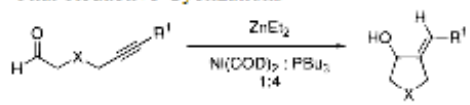


entry	R^1	R^2	R^3	yield (%)[a]
1	Ph	Ph	Me	60
2	Ph	C_6H_{13}	Me	74
3	Ph	C_6H_{13}	*n*-Bu	71
4	*i*-Pr	Ph	Me	21[b]
5	Ph	Ph	$C(CH_3)=CH_2$	0[c]

[a] Products were obtained as single regio- and stereoisomers by 500 MHz ^{1}H NMR analysis. [b] Isolated as the acetate ester (two-step yield is reported). [c] The alcohol derived from isopropenyl addition to benzaldehyde was isolated in 90% yield.

substrate scope

Table 2. Ynal Reductive Cyclizations



entry	X	R^1	yield (%)[a]
1	CH_2	H	74[b]
2	CH_2	CH_3	67[b]
3	CH_2	Ph	62
4	NCOPh	H	70[c]

[a] Products were obtained as single stereoisomers by 500 MHz ^{1}H NMR analysis. [b] Isolated as the benzoate ester (two-step yield is reported). [c] Isolated as a mixture with 9% of the ethyl-substituted alkylative cyclization product.

Montgomery, J. *et al. JACS,* **1997**, *119*, 9065.

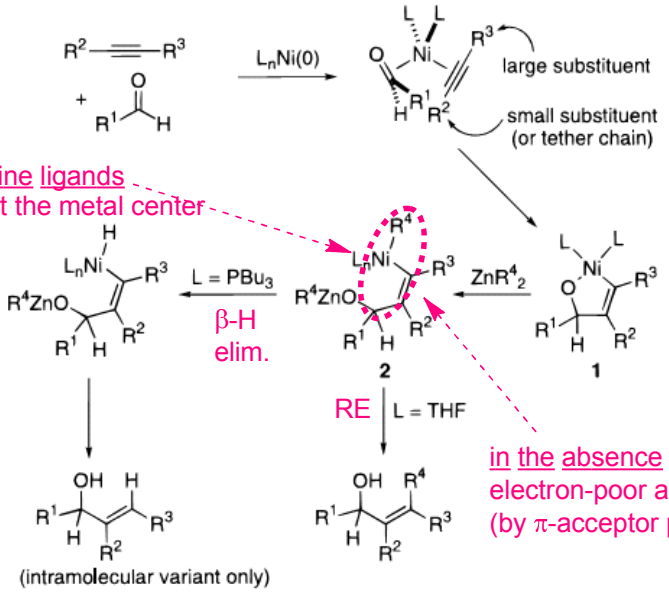
alkylative coupling
☺high chemo-, regio-, stereoselectivity (only *E* isomers)
☺no direct addition (intramolecular)
☺no competitive β-H eliminnation (intramolecular)
☺broad scope of organozincs (intramolecular)
☹direct addition (intermolecular)
☹cometitive β-H elimination (intermolecular)
☹limited scope of organozincs (intermolecular, only sp^3-hybridized)

reductive coupling
☺high stereoselectivity (only *Z* isomers)
☹limited to intramolecular

What is the role of a phosphine ligand in promoting reduction instead of alkylation?
(Why pretreatment of $Ni(COD)_2$ with a basic phosphine resulted in reduction?)

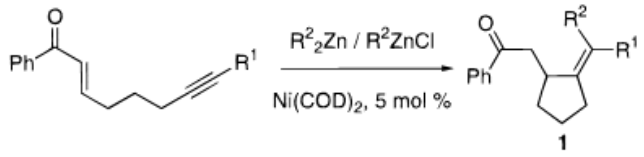
proposed mechanism for reductive/alkylative couplings

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

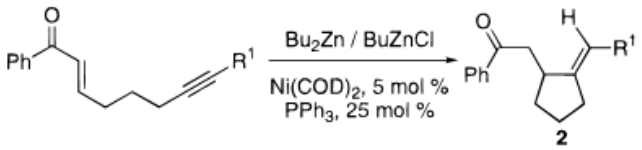


in light of the previous Montgomery's work (Ni(0)-catalyzed cyclizations of alkynyl enones)

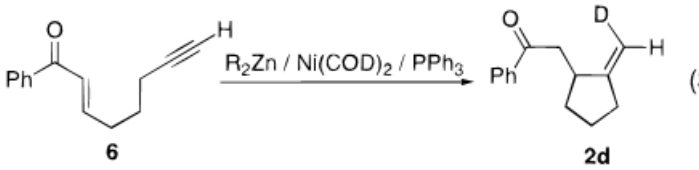
Cyclization with Alkylation[a]



Reductive Cyclizations[a]

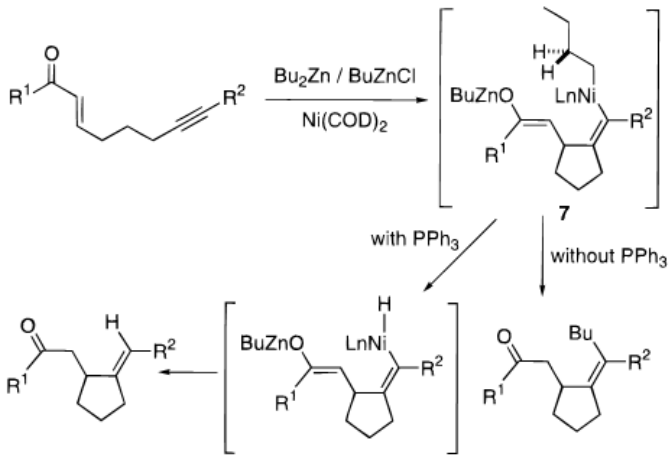


deuterium labeling studies



with Et_2Zn-d_{10} in THF, then H_2O quench: 68 % D incorporation
with Bu_2Zn in THF, then AcOD quench: 12 % D incorporation
with Et_2Zn in THF-d_8, then H_2O quench: 0 % D incorporation

conclusion (mechanism)

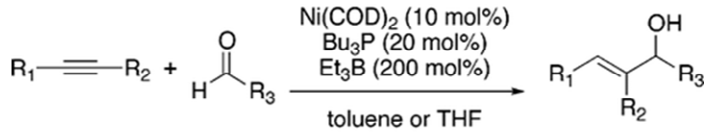


- From these results, at least two pathways are operative:
  1. β-H elimination (major)
  2. protonation on workup,
     most likely of an alkenylzinc spicies (minor)

Montgomery, J. *et al*. *JACS*, **1996**, *118*, 1996.

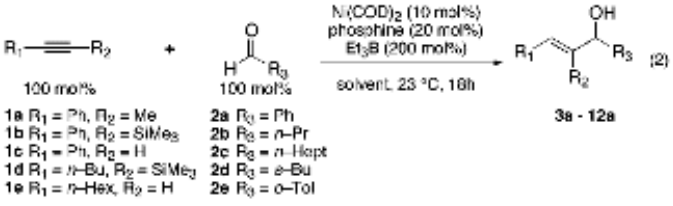
Jamison's system

- the first report of catalytic intermolecular reductive coupling



optimization of reaction conditions

Table 1. Effects of Phosphine, Solvent, and Temperature on Intermolecular Reductive Coupling of 1-Phenylpropyne and Aldehydes[a]



entry	aldehyde	phosphine	product	yield[b]	regioselectivity[c]
1	**2a**	Cy_3P	**3a**	76%	77:23
2		Et_3P	**3a**	46%	91:9
3		$(n\text{-Bu})_3P$	**3a**	77%	92:8
4	**2b**	$(n\text{-Bu})_3P$	**4a**	49%	95:5
5[d]		$(n\text{-Bu})_3P$	**4a**	86%	90:10
6[e]		$(n\text{-Bu})_3P$	**4a**	85%	92:8
7[d,e]		$(n\text{-Bu})_3P$	**4a**	88%	92:8

[a] Except where noted, all reactions were conducted using the conditions indicated in eq 2 (initial concentration of alkyne and aldehyde = 0.16 M, Ar atmosphere, THF). [b] Combined isolated yield of regioisomers. [c] Minor regioisomers (**3b**, **4b**) not shown. Regioselectivity was determined either by separation of regioisomers (silica gel chromatography) or with a ^{1}H NMR spectrum of the product mixture. [d] Reaction conducted at 40 °C. [e] Reaction conducted in toluene.

- trialkylphosphines's effect
  - smaller: yield↓ regioselectivity↑
  - larger: yield↑ regioselectivity↓

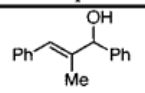
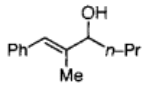
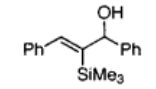
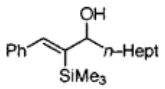
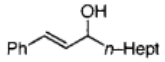
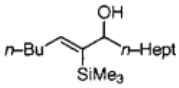
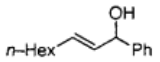
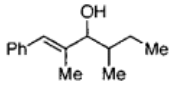
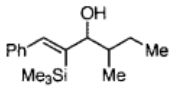
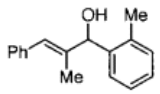
  ⇒Bu_3P gave the best combination

☺high regioselectivity (except internal aliphatic alkynes)
☺compelete stereoselectivity (exclusive *cis*-addition)
☺broad substrate scope (both intra- and inter-molecular)
☺commercially available catalyst and reagents
☺a 1:1 ratio of alkyne to aldehyde
☺no reductive coupling of ketones (e.g. acetophenone)
☹competitive [2+2+2] cyclization of alkynes

applicapable to site-selective fragment coupling reactions at rate stage in complex molecule snthesis ??

substrate scope

Table 2. Intermolecular Catalytic Reductive Couplings of Internal and Terminal Alkynes with Aromatic and Aliphatic Aldehydes[a]

entry	alkyne	aldehyde	major product		yield,[b] regioselectivity[c]
1[d]	**1a**	**2a**		**3a**	77% (92:8)
2	**1a**	**2b**[e]		**4a**	85% (92:8)
3[d,f]	**1b**[e]	**2a**		**5a**	49% (>98:2)
4	**1b**	**2c**		**6a**	89% (>98:2)
5[g]	**1c**[e]	**2c**		**7a**	45% (>98:2)
6	**1d**	**2c**		**8a**	58% (>98:2)
7[d]	**1e**[e]	**2a**		**9a**	76% (96:4)
8[f]	**1a**	**2d**		**10a**	41% (94:6) (66:34 dr)
9[f]	**1b**	**2d**		**11a**	31% (>98:2) (58:42 dr)
10	**1a**	**2e**		**12a**	83% (93:7)

[a] Except where noted, all reactions were conducted using the conditions indicated in eq 2 (1 mmol of alkyne, 1 mmol of aldehyde, toluene, Ar atmosphere). [b] Combined isolated yield of regioisomers. [c] Minor regioisomers (**3b**−**12b**) not shown. Regioselectivity (**a**:**b**) was determined either by separation of regioisomers (silica gel chromatography) or with a ^{1}H NMR spectrum of the product mixture. [d] THF used as solvent. [e] 200 mol % used. [f] Reaction conducted under reflux. [g] Reaction conducted at 0 °C.

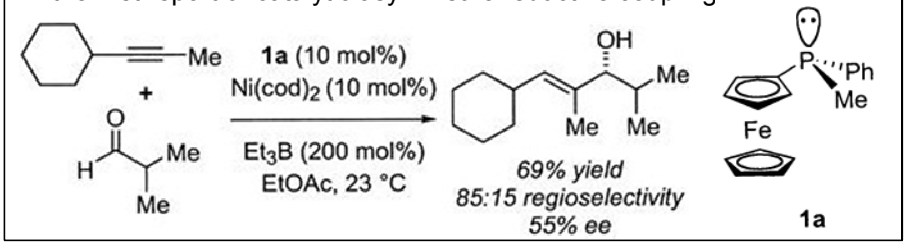
Hypothesis

High regioselectivity observed with aryl-substitued alkynes is likely due to an electronic differentiation between alkyl- and aryl- substituents.
(This is found not to be compelely correct later.)

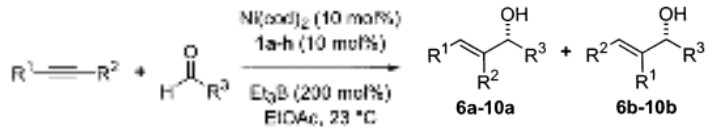
Jamison, T. F. *et al. OL,* **2000**, *2*, 4221.

Jamison's system -Asymmetric induction-

- the first report of catalytic asymmetric reductive coupling



Substrate Scope



6a,b: R^1 = *c*–C_6H_{11}, R^2 = Me, R^3 = *i*–Pr
7: $R^1 = R^2$ = *n*–Pr, R^3 = Ph
8: $R^1 = R^2 = R^3$ = *n*–Pr
9: $R^1 = R^2$ = *n*–Pr, R^3 = *i*–Pr
10a,b: R^1 = *c*–C_6H_{11}, R^2 = Me, R^3 = *n*–Pr

TABLE 2[a]

entry	ligand	product[b]	R^1	R^2	R^3	yield (%)[c]	a:b[d]	ee a (%)[e]	ee b (%)[f]
1	Bu_3P	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	55	2.0:1	na	na
2	$Ph_2P(n\text{-}Bu)$	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	56	1.9:1	na	na
3	$Ph_2P(Cy)$	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	62	2.0:1	na	na
4	$FcPPh_2$	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	60	3.0:1	na	na
5	**1a**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	65	2.2:1	46	45
6	**1b**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	27	1.8:1	8	12
7	**1c**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	53	1.6:1	−34	−28
8	**1d**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	33	1:1	−44	−10
9	**1e**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	60	2.4:1	2	4
10	**1f**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	60	3.8:1	−28	−17
11	**1g**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	46	5.7:1	−55	−19
12	**1h**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	33	1:1	−52	−37
13	**11**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	50	2.0:1	−35	−38
14	**12**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	40	1:1	−20	−17
15	**13**	**6a, 6b**	*c*-C_6H_{11}	Me	*i*-Pr	22	1.2:1	−35	−39
16	**1a**	**7**	*n*-Pr	*n*-Pr	Ph	85	na	49	na
17	**1c**	**7**	*n*-Pr	*n*-Pr	Ph	80	na	−4	na
18	**1f**	**7**	*n*-Pr	*n*-Pr	Ph	81	na	12	na
19	**1g**	**7**	*n*-Pr	*n*-Pr	Ph	79	na	−28	na
20	**1h**	**7**	*n*-Pr	*n*-Pr	Ph	87	na	−36	na
21	**1a**	**8**	*n*-Pr	*n*-Pr	*n*-Pr	80	na	55	na
22	**1a**	**9**	*n*-Pr	*n*-Pr	i-Pr	80	na	55	na
23	**1a**	**10a, 10b**	*c*-C_6H_{11}	Me	*n*-Pr	30	2.2:1	67	68

[a] All reactions were conducted using 10 mol % $Ni(cod)_2$, 10 mol % ligand, and 200 mol % Et_3B. See Scheme 3 and Experimental Section for details. Regioselectivities and enantioselectivities were determined for unpurified product mixtures. [b] Major and minor regioisomers. See Scheme 3. [c] Combined yield of all allylic alcohol products. [d] Regioselectivity (**a**:**b**) determined by ^1H NMR. [e] Enantiomeric excess of regioisomer **a**. Absolute configuration of **6a** assigned by Mosher ester analysis. Absolute configuration of **6b**, **7**–**9**, and **10a**–**b** assigned by analogy. Negative signs indicate opposite sense of induction. [f] Enantiomeric excess of regioisomer **b**.

the higest up to that point of this particular reaction

- in all cases exclusive *cis*-addition (>98:2)

Jamison, T. F. *et al. JOC,* **2003**, *68*, 156.

CHART 1

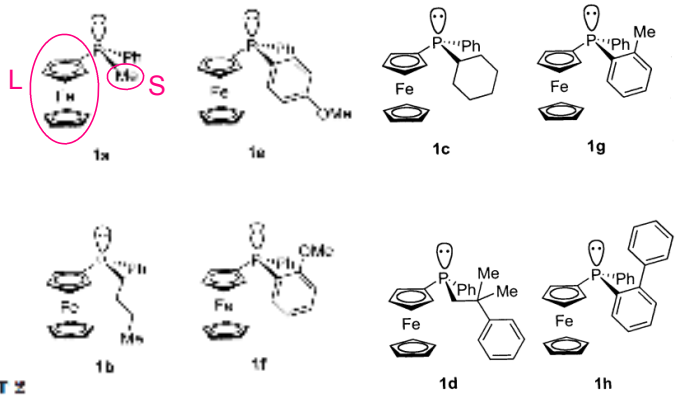
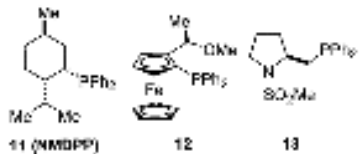


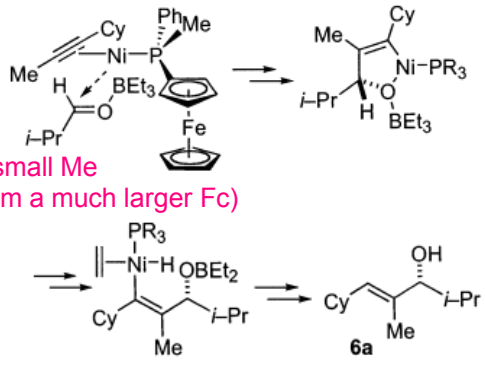
CHART 2



- **1a** has the greatest difference in steric demand between Fc vs. R(Me)

the model for these results

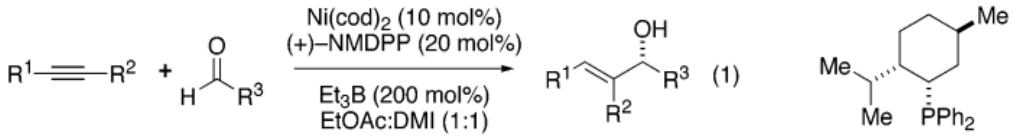
SCHEME 4



syn to a small Me
(away from a much larger Fc)

☹low to moderate regio- and enantioselectivity
☹limited to only a few cases
(alkyl-C≡C-alkyl)

•the complementary system



(+)–NMDPP

R^1 = Ar R^2 = Alkyl, CH_2OTBS, CH_2NHBoc, $SiMe_3$ R^3 = Ar, Alkyl

- ***100%* cis** *addition*
- *90:10 to >95:5 regioselectivity*
- *up to* ***96% ee***

sustrate scope

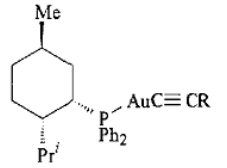
Table 1. Catalytic Asymmetric Reductive Alkyne/Aldehyde Couplings[a]

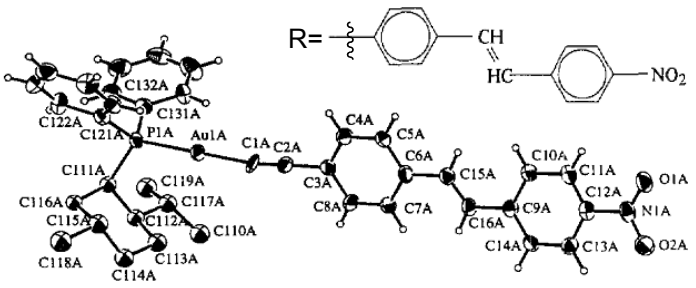
entry/ product	R^1	R^2	R^3	yield (%), regioselectivity	ee (%)
1	Ph	Me	*i*-Pr	95 (>95:5)	90
2	Ph	Me	*c*-C_5H_{11}	97 (>95:5)	90
3	Ph	Me	Ph	79 (91:9)	73
4	Ph	Me	*n*-Pr	82 (>95:5)	65
5	(*p*-MeO)Ph	Me	*i*-Pr	80 (>95:5)	88
6	(*p*-Cl)Ph	Me	*i*-Pr	75 (>95:5)	83
7	1-naphthyl	Me	*i*-Pr	93 (>95:5)	90
8	Ph	Et	*i*-Pr	81 (>95:5)	93
9[b]	Ph	Et	*c*-C_5H_{11}	78 (>95:5)	89
10	Ph	*n*-Pr	*i*-Pr	74 (>95:5)	92
11	Ph	*i*-Pr	*i*-Pr	58[c] (>95:5)	92
12	Ph	CH_2OTBS	*i*-Pr	59 (>95:5)	85
13	Ph	CH_2NHBoc	*i*-Pr	60 (>95:5)	96
14	Ph	$SiMe_3$	*n*-Pr	43[c] (>95:5)	92
15	*n*-Pr	*n*-Pr	*i*-Pr	35[c] (–)	42

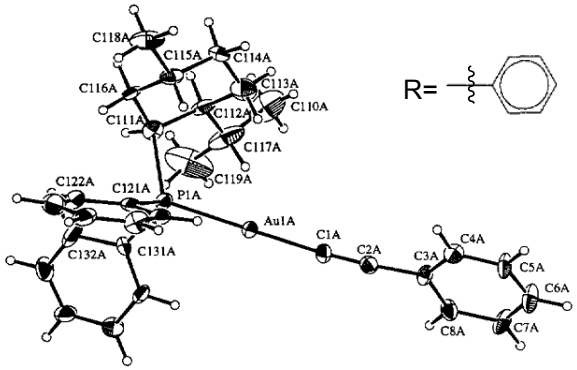
[a] See eq 1. Experimental procedure (see Supporting Information): A solution of Ni(cod)$_2$ (0.05 mmol), (+)-NMDPP (0.10 mmol), and Et$_3$B (1.0 mmol) in EtOAc/DMI (1:1, total volume 0.50 mL) was cooled to −25 °C. An alkyne (0.50 mmol) was added via syringe, and then an aldehyde (1.0 mmol) was added via syringe over 8 h. The solution was allowed to stir 36 h, and silica gel chromatography afforded allylic alcohols **1**−**15**. Regioselectivity was determined by ^{1}H NMR; enantioselectivity was determined by chiral GC or HPLC analysis. [b] Performed on 5.0 mmol scale. [c] Some alkylative coupling was observed (transfer of Et group (instead of H) from Et$_3$B).

Jamison, T. F. *et al. JACS,* **2003**, *125*, 3442.

X-ray diffraction study of NMDPP



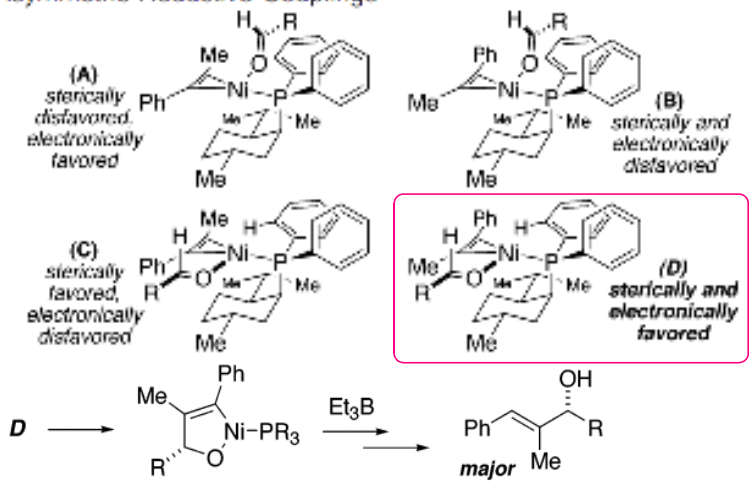




Hackless, D. C. R. *et al. J.Organomet. Chem.,* **1997**, *544*, 189.

the model for these results

Scheme 1. Proposed Steric and Electronic Control in Catalytic Asymmetric Reductive Couplings

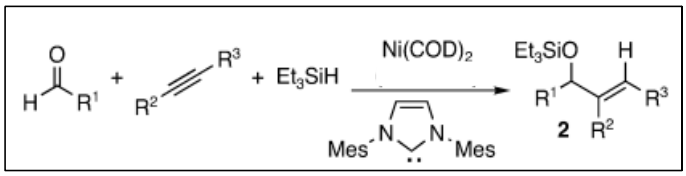


Both the ax placement and the orientation of a M-PPh_2 group over the Cy ring of NMDPP have been observed in the solid state. (See above)

•a cooperative effect
-steric properties of the ligand
-electronic differences of the alkyne substituents

From this framework...
Can more steric differentiation of the two aldehyde coordination sites enhance enantioselectivity ??

Montgomery's second sytem: $Ni(COD)_2$/NHC system



entry	R^1	R^2	R^3	yield (regioselectivity)
1	Ph	CH_3	Ph	84% (>98:2)
2	C_5H_{11}	CH_3	Ph	82% (>98:2)
3	Ph	H	C_6H_{13}	71% (>98:2)
4	Ph	H	Ph	72% (>98:2)
5	Ph	CH_3	C_2H_5	84% (1.3:1)
6	*s*-Bu	CH_3	Ph	81% (>98:2)[e]
7	$C_6H_4OCH_3$	CH_3	Ph	66% (>98:2)
8	Ph	Ph	$C(CH_3)=CH_2$	84% (>98:2)
9	Ph	H	$CH=CHC_6H_{13}$	56% (>98:2)
10	Ph	H	$(CH_2)_4OH$	72% (>98:2)[d]

[a] Reactions were carried out in THF at 25–45 °C.[b] [b] Use of triethylborane or diethylzinc as a reducing agent or $NiCl_2$ as a precatalyst led to lower yields. [c] A 1.5:1 ratio of diastereomers was obtained. [d] Performed with 1.5 equiv of the alkyne.

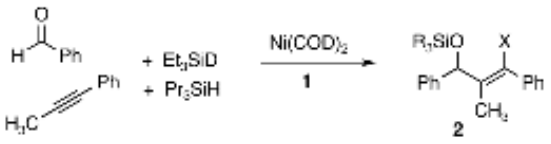
☺high regioselectivity (except internal aliphatic alkynes)
☺compelete stereoselectivity (exclusive *cis*-addition)
☺broad substrate scope
☺stable & easilyhandled reducing agent
☺unprotected alcohol tolerance →entry 10

Montgomery, J. *et al*. *JACS,* **2004**, *126*, 3698.

➤Why is there a significant difference of substrate scopes between two systems ??

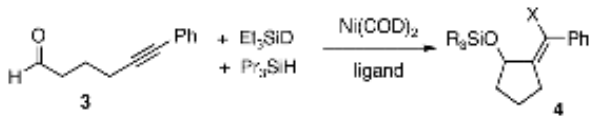
crossover deutrium-labeling experiments

Table 2. Intermolecular Crossover Experiment



R	X	product	relative %
Et	H	**2a**	<1
Et	D	**2b**	48
Pr	H	**2c**	50
Pr	D	**2d**	<1

Table 3. Intramolecular Crossover Experiments

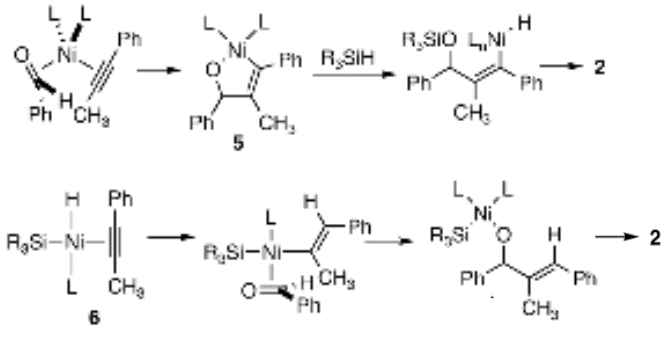


			relative %	
R	X	product	from 1	from PBu_3
Et	H	**4a**	<2	25
Et	D	**4b**	55	34
Pr	H	**4c**	41	23
Pr	D	**4d**	<2	18

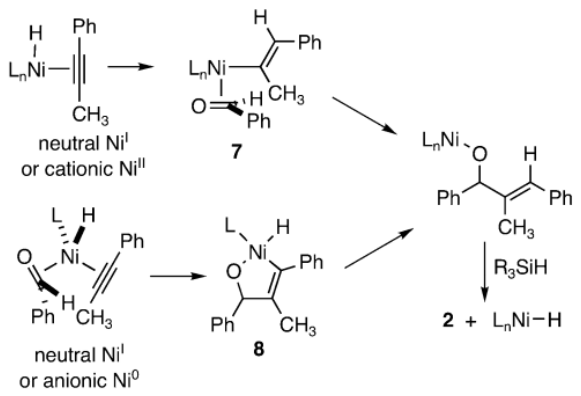
plausible mechanisms from crosspver experiments

Scheme 1. Possible Mechanisms

Mechanisms Consistent with No Crossover



Mechanisms Consistent with Crossover

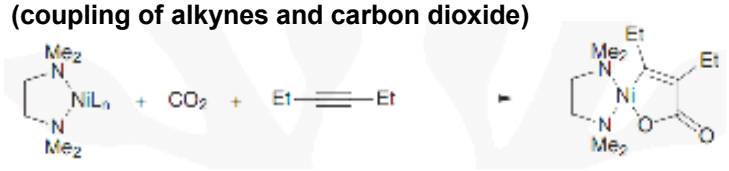


1-2. Mechanistic Analyses

assumption 1: formation of oxanickelacycle

➤Although no metallacycles derived from OA of one alkyne and one adehyde have been isolated, ...

confirmed oxonickelacycle fomation by X-ray anaysis (coupling of alkynes and carbon dioxide)



Tsay, Y.-C. *et al. J. Organomet. Chem.* **1984**, *266*, 203.

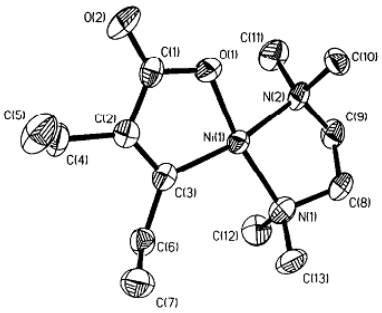


Fig. 3. Molekülstruktur des Metallcyclus A.

assumption 2: β-hydride elimination vs. reductive elimination

➤Some phosphine ligands prompt β-hydride elimination.

the first example of the transition metal complex-catalyzed alkyl group isomerization

$$i\text{-}C_3H_7MgCl + PhCl \xrightarrow{\text{catalyst}} i\text{-}C_3H_7Ph + n\text{-}C_3H_7Ph + HPh$$ (The product is in general a mixture.)

products using various phosphines

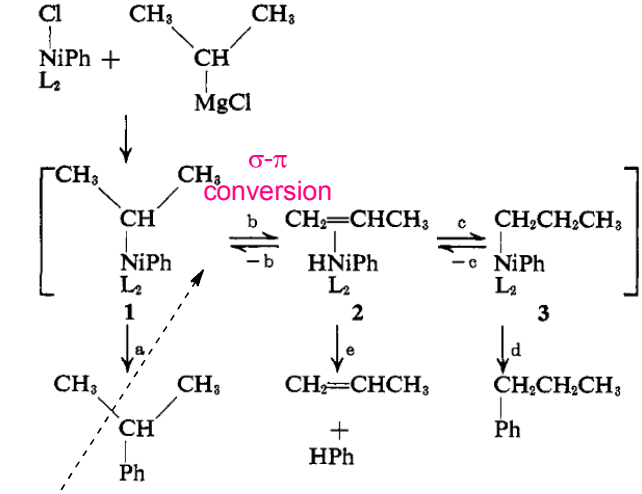
Table I. Products from the Reaction of i-C_3H_7MgCl with PhCl in the Presence of NiL_2Cl_2[a]

L_2 in catalyst	Total yield,[b] %	Products distribution,[b] %		
$Ph_2PCH_2CH_2PPh_2$	74	96	4	0
$Me_2PCH_2CH_2PMe_2$	84	9	84	7
$Ph_2PCH_2CH_2CH_2PPh_2$	89	96	4	0
dmpf[c]	48	8	74	18
dmpc[d]	7	12	88	0
dppc[e]	18	78	1	21
$Ph_2PCH{=}CHPPh_2$	8	92	8	0
$2PEt_3$	9	1	11	88
$2PBu_3$	8	2	16	82
$2PPh_3$	44	16	30	54

[a] To a mixture of chlorobenzene (5 mmol) and a nickel complex (0.05 mmol) in 5 ml of ether was added an isopropyl Grignard solution (6.9 mmol) at 0°. The mixture was refluxed for 20 hr, hydrolyzed, and then analyzed by glpc. [b] Determined by glpc using an internal standard. [c] 1,1′-Bis(dimethylphosphino)ferrocene. [d] Bis(dimethylphosphino)-*o*-carborane. [e] Bis(diphenylphosphino)-*o*-carborane.

plausible mechanism

Scheme I



Kumada, M. *et al. JACS,* **1972**, *94*, 9628.

- The extent is dependent strongly upon electronic nature of the phosphine ligand.
  - -electron donating → *n*-propylbenzene
  - -electron accepting → isopropylbenzene
- Benzene is formed only in the cases where *n*-propylproduct is formed pregerentially. (with a few exception)

"β-effect"
Electron-donating ligands
increase electron density on the metal center
⇒lower the activation energy for the σ-π conversion
⇒facilitate the β-hydride elimination

information which serves as evidence for scheme 1

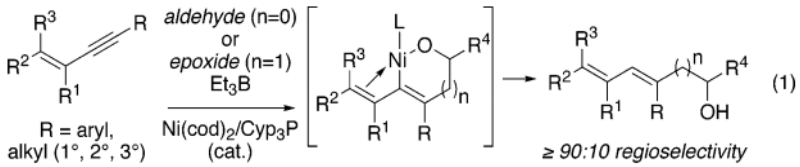
(+)-(*S*)-2-methylbutyl chloride
$[\alpha]^{18}D$ +1.68° (neat)
98% optical purity

Ni(dpp)Cl_2 → (+)-(S)-2-methylbutylbenzene
$[\alpha]^{25}D$ +10.54° (neat)
$n^{25}D$ 1.4869 (lit. $n^{25}D$ 1.4862)
with a little loss of optical purity

Ni(dmpe)Cl_2 → (+)-(S)-2-methylbutylbenzene
$[\alpha]^{25}D$ +9.56° (neat)
relatively low optical purity

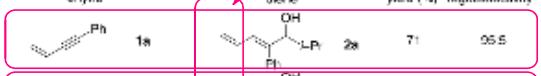
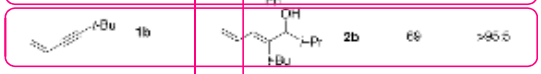
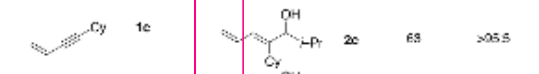
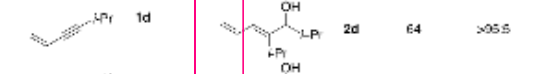
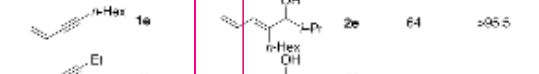
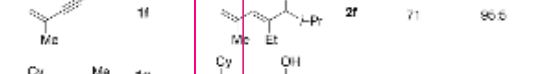
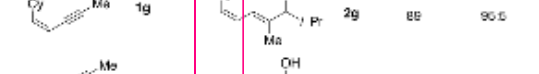
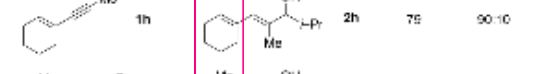
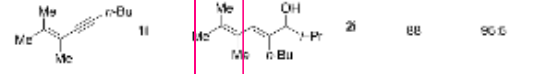
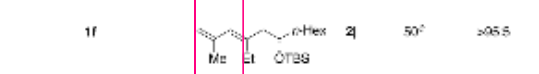
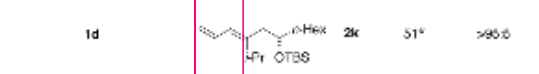
mechanistic study 1: producted-oriented mechanistic analyses

<1,3-enynes (Jamison's system)>



High regioselectivity is just due to an electronic distinction between two alkyne substituents, or... ??

Table 1. Alkene-Directed, Nickel-Catalyzed Coupling Reactions of Alkynes with Aldehydes and Epoxides[a]

entry	enyne		diene		yield (%)	regioselectivity[b]
1		1a		2a	71	95:5
2[c]		1b		2b	69	>95:5
3[c]		1c		2c	68	>95:5
4		1d		2d	64	>95:5
5		1e		2e	64	>95:5
6		1f		2f	71	95:5
7		1g		2g	88	95:5
8		1h		2h	75	90:10
9[c]		1i		2i	88	95:5
10[d]		1f		2j	50[e]	>95:5
11[d]		1d		2k	51[e]	>95:5

[a] See eq 1. Standard procedure (see Supporting Information): To a solution of $Ni(cod)_2$ (0.05 mmol), tricyclopentylphosphine (Cyp_3P) (0.10 mmol), and Et_3B (1.0 mmol) in EtOAc (0.5 mL) at 0 °C were added *i*-PrCHO (1.0 mmol) and the enyne (0.5 mmol). Upon consumption of the enyne, purification by chromatography provided dienes **2a**−**2k**. [b] Regioselectivity determined by ^1H NMR. [c] (+)-Neomenthyldiphenylphosphine used as ligand. [d] Bu_3P and (+)-octene oxide (>99% ee) used in place of Cyp_3P and *i*-PrCHO. EtOAc omitted. [e] Yield over two steps.

Jamison, T. F. *et al. JACS,* **2004**, *126*, 4130.

- due to neither the nature or size of the other alkyne substituent nor the dgree of alkene substitution

Some unique effects

(1)*compelete reversal* regioselectivity

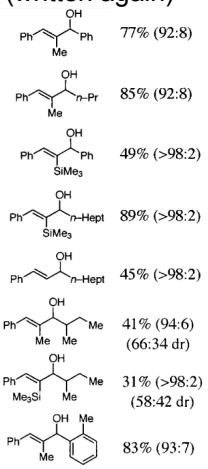
- In the previous result, C-C bond formation favored *distal* to the allyl substituent.

↕

- In the previous result, C-C bond formation favored *proximal* to the allyl substituent. (See entry 1)

A vinyl group is a significantly more potent DG than a phenyl ring ??

substrate scope (written again)

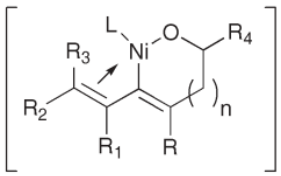


(2)a remarkable increase in reactivity

- *t*-BuC≡C-C-alkyl and *t*-BuC≡C-C-aryl don't react.

↕

- *t*-BuC≡C-CH=CH_2 underwent reaction, and with excellent regioselectivity to favor C-C bond formation at the more hindered alkyne carbon! (See entry 2)



1

Olefins have the ability to form a favorable bonding interaction with Ni in a high-energy intermediate **1** serving to lower the TS energy

conclusion

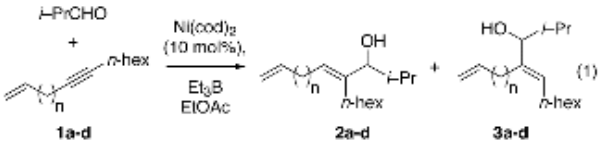
The alkene substituents appears to strongly direct regioselectivity and also significantly increase reactivity.
⇒complexation of the alkene to the metal center during the regioselectivity-determining step?

How about a remote alkene ??

<1,6-enynes (Jamison's system)>

➤A remote, *unconjugated* alkene dictates regioselectivity??

Table 1. Directing Effects of Tethered Alkenes[a]



1a-d 2a-d 3a-d

entry	alkyne	n	yield (%)	regioselectivity (2/3)[b]
1	**1a**	1	<5	nd
2	**1b**	2	<5	nd
3	**1c**	3	53[c]	>95:5
4	**1d**	4	<5	nd
5	*n*-pentyl—C≡C—*n*-hexyl	n.a.	28[c]	50:50

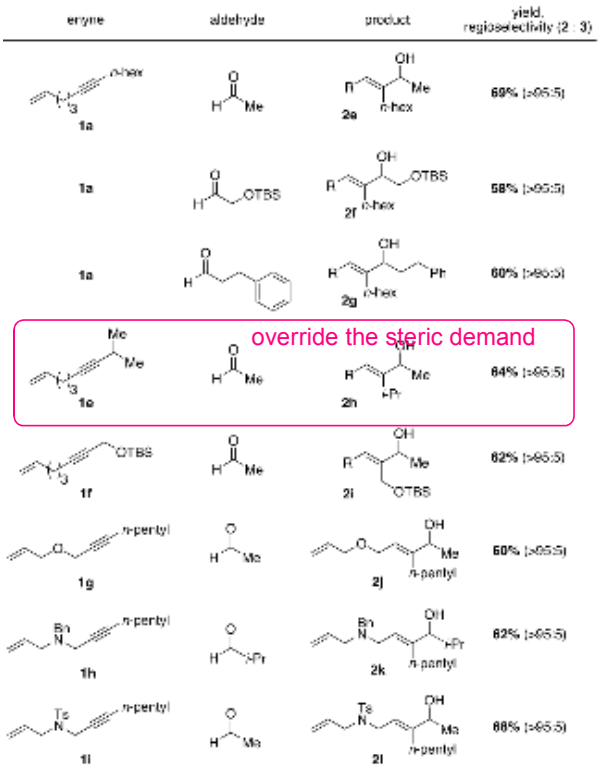
[a] Standard procedure: The alkyne (0.50 mmol) was added to a 0 °C solution of $Ni(cod)_2$ (0.05 mmol), *i*-PrCHO (1.00 mmol), and Et_3B (1.00 mmol) in EtOAc (0.5 mL), and the solution was allowed to stir 15 h at room temperature. See Supporting Information for details. [b] Determined by ^1H NMR and/or GC. [c] Some alkylative coupling (transfer of Et from Et_3B) also observed.

- Only one tether length provided the marked difference in reactivity and selectivity.

with little difference in the steric and electronic properties of the alkyne substituents

A tethered alkene is sufficient to reinforce "inherent" regioselectivities.

Table 2. Highly Regioselective, Catalytic Reductive Coupling Reactions Directed by a Remote Alkene[a]

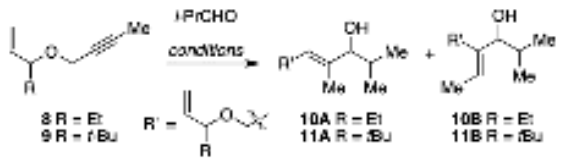


[a] See eq 1, Table 1, and Supporting Information. R = $(CH_2)_3CH{=}CH_2$. Regioselectivity determined by ^1H NMR and/or GC.

Jamison, T. F. *et al. JACS,* **2004**, *126*, 15342.

➤Tethered alkenes is affected by ligand-switchable directing effect.

Table 1. Coupling Reactions of Chiral 1,6-Enynes



entry	enyne[a]	reaction conditions[b]	products	A/B[c]	dr A[c]	dr B[c]
1	8	I	10A, B	>95:5	95:5	
2	(R = Et)	II		<5:95		45:55
3		III		55:45	50:50	45:55
4	9	I	11A, B	>95:5	>95:5	
5	(R = *t*-Bu)	II		<5:95		42:58
6		III		61:48	45:55	42:58

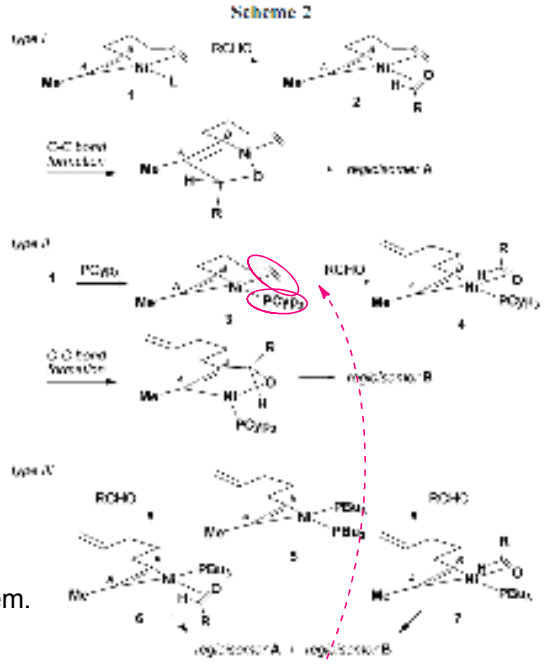
[a] Racemic 8 and 9 were employed in this series of reactions. [b] I: $Ni(cod)_2$ (10 mol %), Et_3B (200 mol %); II: reaction conditions I + $PCyp_3$ (20 mol %); III: reaction conditions I + PBu_3 (20 mol %). [c] Based on isolated yields. [d] Determined by ^1H NMR.

Jamison, T. F. *et al. OL,* **2006**, *8*, 7598.

Don't atom at propargyl position play a key role in the mode of diastereoinduction??

plausible mechanism

Scheme 2



type I
Aldehyde displaces L, *cis* to C(*A*) and the bound olefin.

type II
Aldehyde displaces olefin stereospecifically.

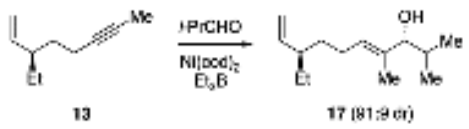
typeIII
2 eq. of phosphines are bound to Ni, and aldehyde displaces one of them.

olefin
=the most weak bound ligand

PCy_3
=more strong bound ligand

➤O and C at propargyl position have similar effect.

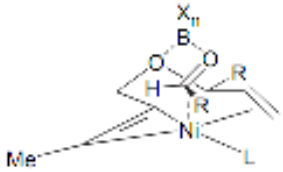
Scheme 5



13 17 (81:9 dr)

... But the effect is measurable different.

One possible explanation



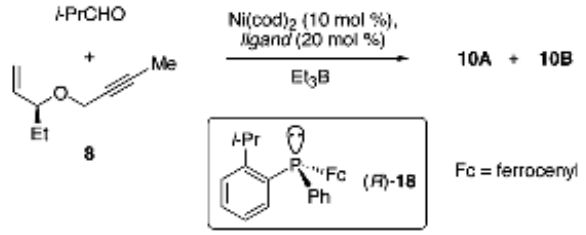
Oxygen in the etheral tether was binding to the aldehyde via the boron??

directing the aldehyde to the top face due to the conformation of the ring chelate

Jamison, T. F. *et al*. *tetrahedron,* **2006**, *62*, 7598.

➤The influence of the chiral center in the tether is minimal.

Table 2. Coupling Reactions of Chiral, Enantiomerically Enriched 1,6-Enynes with Ferrocenyl-Containing Phosphines



ligand	A/B[a]	dr 10A (*R*/*S*)[b]	dr 10B[b,c]
(*R*)-**18**	48:52	30:70	28:72
(*S*)-**18**	55:45	66:34	68:32
$FcPPh_2$	54:46	56:44	48:52

[a] Based on isolated yields. [b] Configuration of allylic alcohol stereogenic center. [c] Relative stereochemistry not determined.

•nearly equimolar amounts of regioisomers
⇒via a type III mechanistic pathway

•modest diastereoinduction
in both the *R* and *S* phosphine ligands cases
⇒no influence of the enyne stereocenters on the diastereoselectivity

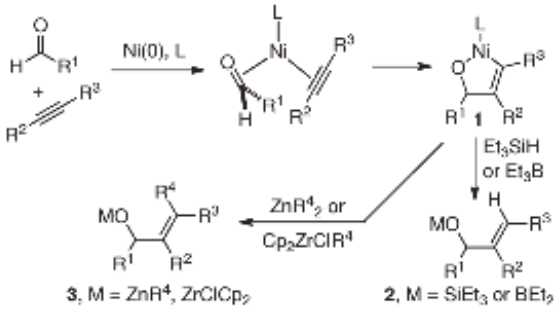
conclusion

Phosphine is bound to Ni during the C-C bond-forming step

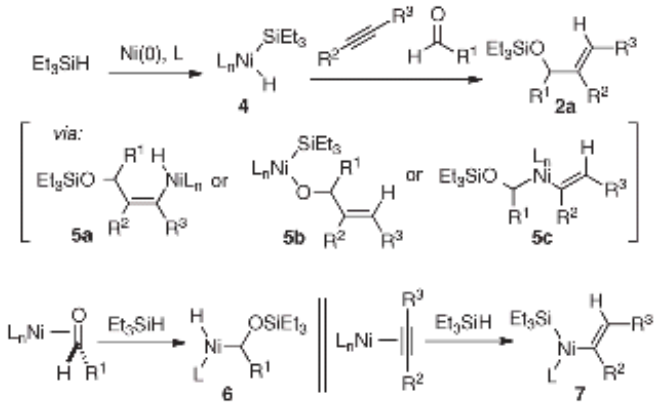
mechanistic study 2: kinetic analysis

Via which pathway the reductive coupling proceed ??

Scheme 1. Nickel-Catalyzed Aldehyde–Alkyne Couplings

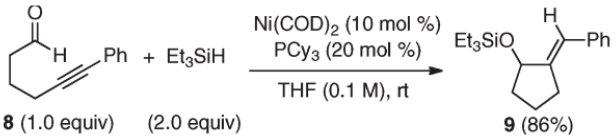


Scheme 2. Mechanisms Initiated by Oxidative Addition to Et_3SiH



Montgomery, J. *et al*. *JACS*, **2011**, *133*, 5728.

a rate study of the cyclization of a ynal by *in situ* IR monitoring



ynal: first-order dependence
$Ni(COD)_2$: first-order dependence
Et_3SiH: zeroth-order dependence

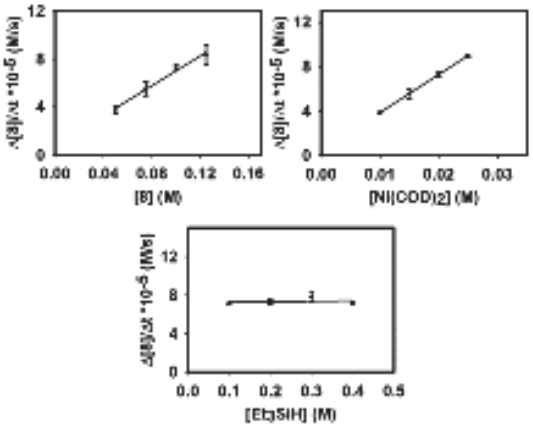
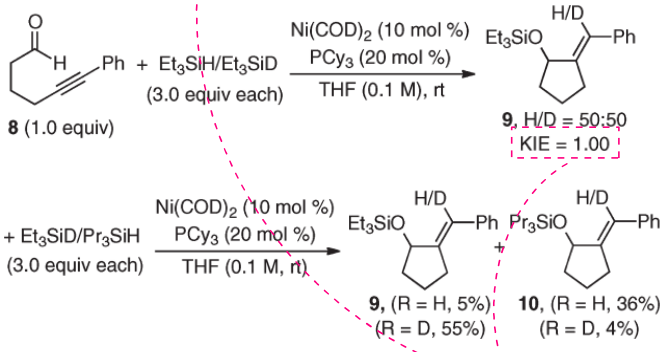


Figure 1. Determination of kinetic order of reaction components. (Top left) Linear dependence of initial reaction rate on [8]. (Top right) Linear dependence of initial reaction rate on $[Ni(COD)_2]$. (Bottom) Zeroth-order dependence of initial reaction rate on $[Et_3SiH]$. Reported values are given as the average of three or more experiments, with error bars representing the standard deviation between individual runs.

a kinetic isotope effect study & a crossover-labeling study



c.f. PBu_3-promoted process originally reporeted
→See Montgomery's second system

- These seem to be inconsistent with rate-determining oxidative addition of Ni(0) to the Si-H bond (Scheme 2).

⇓

- For a mechanism involving the production of nickel hydride **4** to be consistent with the kinetic order studies...
  - a fast reaction between a PCy_3 adduct of $Ni(COD)_2$ with Et_3SiH
  - a slow subsequent insertion step

Is it possible??

***in situ* IR monitoring**

a solution of Et_3SiH ← $Ni(COD)_2/PCy_3$

no consumption or change of the Si-H stretch

- This is inconsistent with formation of **4**(Scheme 2), but consitent with formation of **5** or **6** (Scheme 2).

⇓

a solution of Et_3SiH+aldehyde ← $Ni(COD)_2/PCy_3$

a solution of Et_3SiH+alkyne ← $Ni(COD)_2/PCy_3$

no consumption or change of the Si-H stretch

- These are inconsistent with formation of **5** or **6** (Scheme 2).

Scheme 2 is ruled out! How about Scheme 1?

***in situ* IR monitoring**

a solution of Et_3SiH+enal ← $Ni(COD)_2/PCy_3$

steady depletion of Si

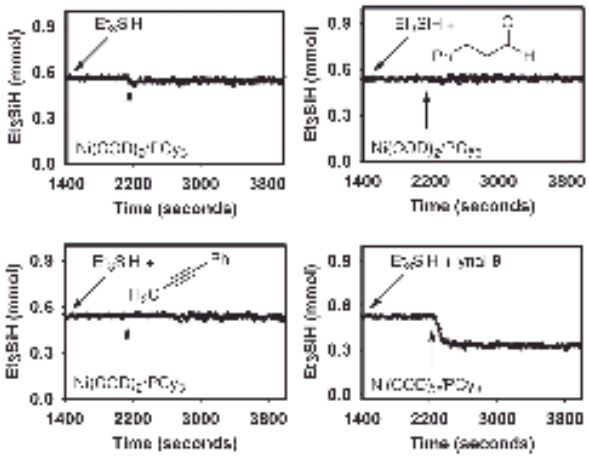


Figure 2. Experiments tracking silane depletion, with monitoring of silane IR stretch at 2100 cm^{-1}. (a, top left) Et_2SiH_2 (1.0 equiv) at −25 °C, then a mixture of $Ni(COD)_2$ (1.0 equiv) and PCy_3 (2.0 equiv). (b, top right) Et_2SiH_2 (1.0 equiv) and hydrocinnamaldehyde (1.0 equiv) at −25 °C, then a mixture of $Ni(COD)_2$ (1.0 equiv) and PCy_3 (2.0 equiv). (c, bottom left) Et_3SiH (1.0 equiv) and phenyl propyne (1.0 equiv) at −35 °C, then a mixture of $Ni(COD)_2$ (1.0 equiv) and PCy_3 (2.0 equiv). (d, bottom right) Et_3SiH (1.0 equiv) and ynal 8 (1.0 equiv) at −35 °C, then a mixture of $Ni(COD)_2$ (1.0 equiv) and PCy_3 (2.0 equiv).

Conclusion

All experiments support the nickelacycle mechanism (Scheme1).

mechanistic study 3: a detailed computational study

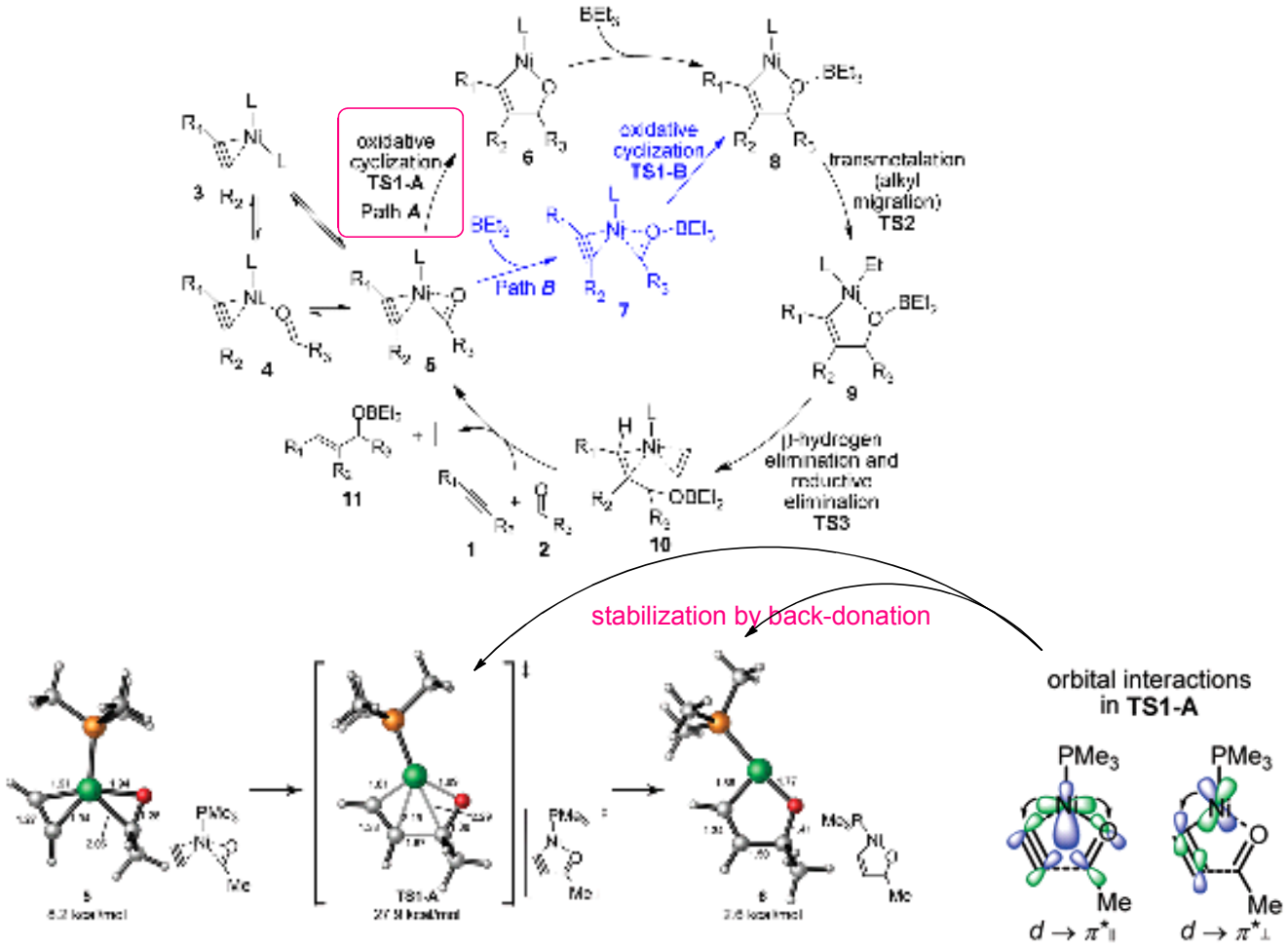


Figure 1. Oxidative cyclization of acetylene and acetaldehyde. Bond lengths in Å. Energies relative to 3.

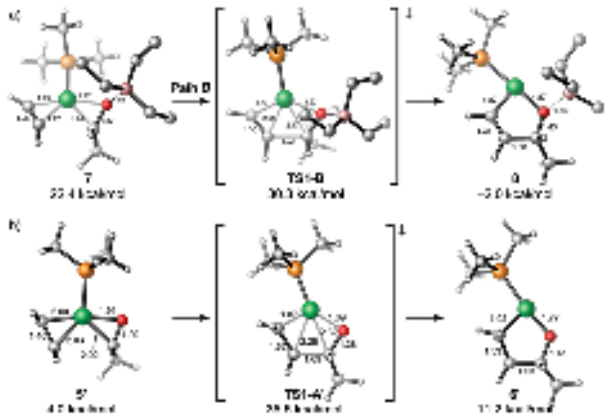


Figure 2. (a) Alternative pathway of alkyne–aldehyde oxidative cyclization: borane coordination to the aldehyde oxygen. Bond lengths in Å. Energies relative to 3. Hydrogens in BEt_3 have been omitted. (b) Oxidative cyclization of ethylene and acetaldehyde. Bond lengths in Å. Energies relative to the catalyst resting state, alkene(bisphosphine)nickel(0) complex 3'.

T.F.Jamison *et al. JACS,* **2009**, *131*, 6654.

appendix: free-energy for the full catalytic cycle

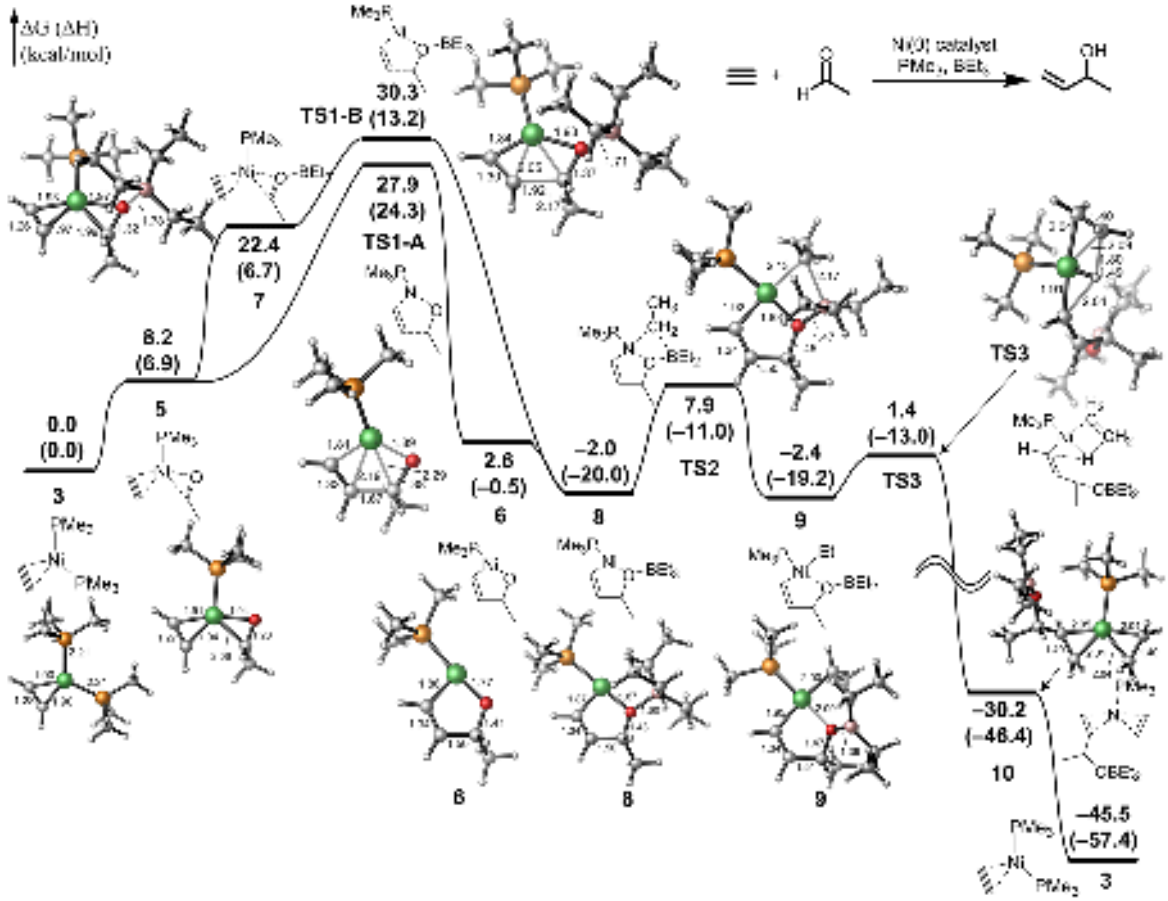


Figure S1. Free energy surface of the Ni(0)-catalyzed reductive coupling of acetylene and acetaldehyde.

2. Akene-Aldehyde Non-Reductive Coupling Reaction

from alkyne to alkene

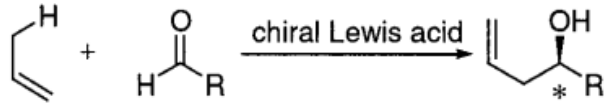
reductive alkyne → (more easily prepared; numoreous olefins commerically avilable & abound synthetic methods for them) → non-reductive alkene

with reducing agents → (have potential to eliminate compatibility issues) → without reducing agents

Non-reductive have some merits, but both aldehydes and alkenes are intrinsically unreactive toward each other.

How can these components are activated? →See reductive coupling of 1,3- and 1,6-enynes

carbonyl-ene reactions catalyzed by transition-metal complexes as Lewis acids

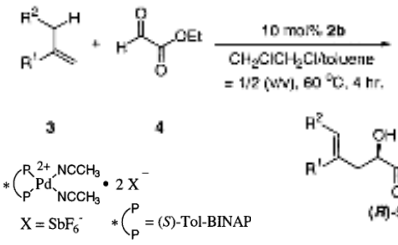


➤Transition-metal-catalyzed intermolecular coupling reactions of alkenes remained elusive.

➤Historically, the most direct method for intermolecular couplings of una*ctivated al*kenes and aldehydes is carbonyl-ene reaction, and late transition-metal complexes (cationic Lewis acid complexes) catalyze it.

a pioneer woek (chiral Pd(II)complexes)

Table 3. Enantioselective Glyoxylate-Ene Reactions with 1,1-Disubstituted and Trisubstituted Olefins

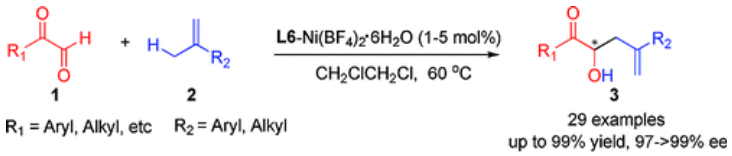


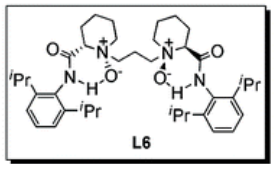
entry	3	5 yield (%)[a]	5 ee (%)[b]	diastereomer ratio
1		97	88	
2		93	74	
3		92	73 (major)	5.6/1
4		94	81 (major)	2.2/1
5[c]		83	75 (major)	5.6/1

[a] Isolated yield. [b] Determined by chiral GC using CP-Cyclodextrin-B-2,3,6-M-19 column. [c] At room temperature.

Mikami, K. *et al. OL,* **2000**, *2*, 34059.

a Ni(II) catalyst system showing excellent ee





Feng, X. M. *et al. JACS,* **2008**, *130*, 15770.

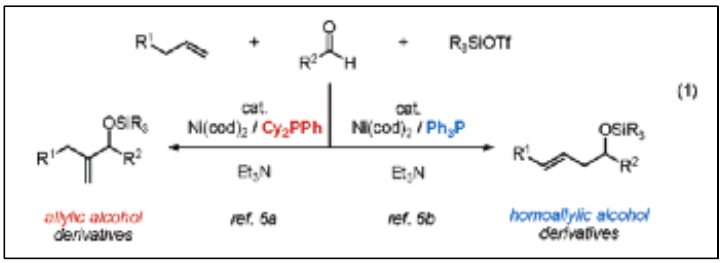
☺excellent enantioselectivity
☺a wide range of "simple" alkenes
(1,1-disubstituted and trisubstituted olefins)
☹limited scope of electrophile
(few aromatic or sterically demanding aldehyde)

⇩

Develop a reaction with features not amenable to exisiting carbonyl-ene methodorog!

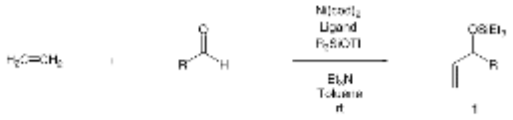
-the ability to transform less activated alkenes
-enhanced and complementary electrophile scope
-the option to produce allylic alcohol in addition to homollylic product

Jamison's unique system



Jamison, T. F. *et al*. *JACS*, **2006**, *128*, 11513.

Table 1. Nickel-Catalyzed Coupling of Ethylene, Aldehydes, and Silyl Triflates[a]



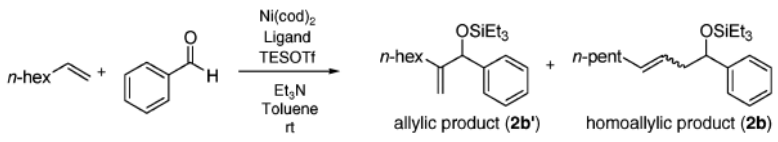
entry	R (aldehyde)	R_3SiOTf	product	isolated yield (%)	entry	R (aldehyde)	R_3SiOTf	product	isolated yield (%)
1	Ph	Et_3SiOTf	1a	82 (82)[b]	8		Et_3SiOTf	1h	89
2	*p*-tolyl	Et_3SiOTf	1b	88 (82)[b]	9	2-furyl	Et_3SiOTf	1i	88
3	*o*-tolyl	Et_3SiOTf	1c	93 (84)[b]	10[c]		Et_3SiOTf	1j	75
4	*p*-anisyl	Et_3SiOTf	1d	96 (86)[c]	11[c]		Et_3SiOTf	1k	94
5	2-naphthyl	Et_3SiOTf	1e	95 (88)[b]	12		Et_3SiOTf	1l	70
6	2-naphthyl	Me_2SiOTf	1f	69	13		Et_3SiOTf	1m	81 (40)[c,d]
7	2-naphthyl	t-BuMe$_2$SiOTf	1g	67	14	cyclohexyl	Et_3SiOTf	1n	95[e] (94)[b,e]

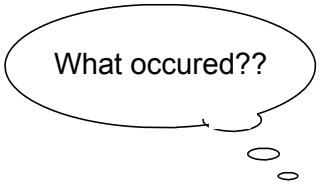
[a] Standard procedure: Ni(cod)$_2$ (20 mol %) and (*o*-anisyl)$_3$P (40 mol %) were dissolved in 2.5 mL of toluene under argon. Ethylene (balloon, 1 atm) was substituted for argon. Triethylamine (600 mol %), the aldehyde (100 mol %, 0.5 mmol), and Et_3SiOTf (175 mol %) were added. The reaction mixture was stirred for 6–18 h at 23 °C. [b] (*o*-anisyl)$_3$P was replaced by Cy_2PPh. [c] (*o*-anisyl)$_3$P was replaced by Ph_3P. [d] Yields determined by ^{1}H NMR using DMF as a standard. [e] Conducted under 2 atm of ethylene. [f] Stirred at room temperature for 30 h.

- Simple aromatic aldehydes react efficiently.
- *o*-Substitution don't deter the reaction.
- Enolizable aldehydes generally are not appropriate (but some are tolerated as in entry 14).
- Heteroaromatic aldehyde are tolerated!
- E-rich aromatic aldehydes are more efficient substrates than e-poor ones.
- Some common silyl triflates can be used.

Byproducts(resulting from a pinacol coupling) are observed only in these enetries.

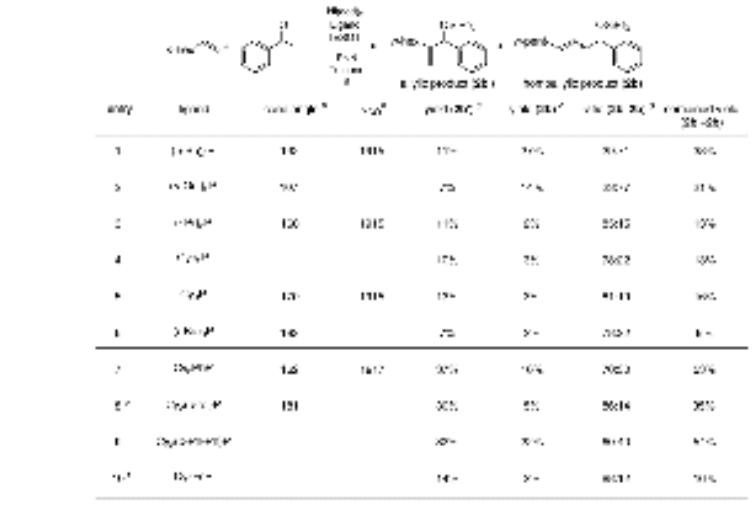
How about regioselectivity, if substituted olefins are used??



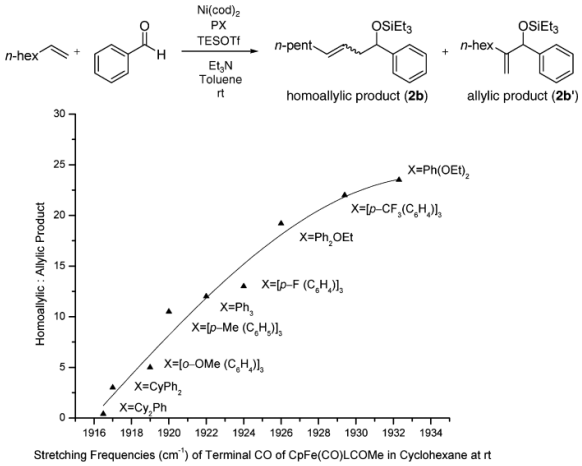


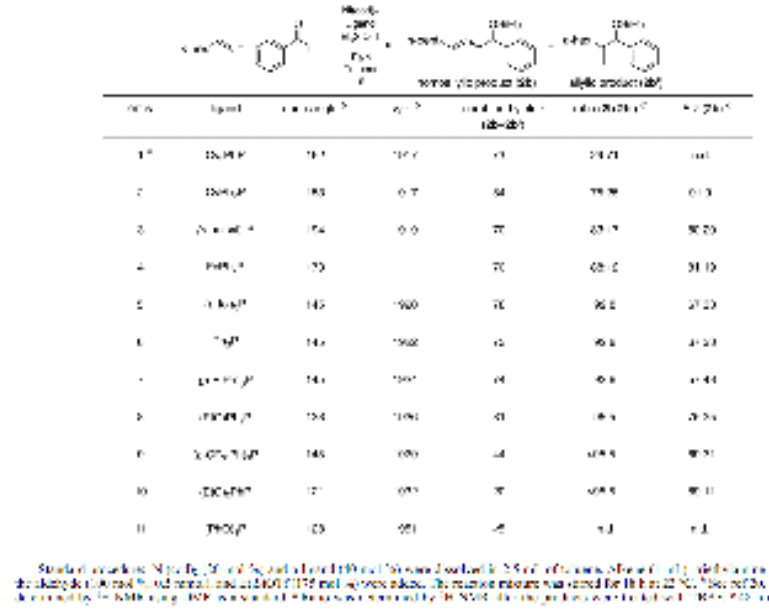
Two distinct types of coupling products are typically observed.
How can the ration of them be controlled?

ligand effect



- A higher H:A ratio can be achieved by decreasing electron-donating ability of the phosphine ligand.



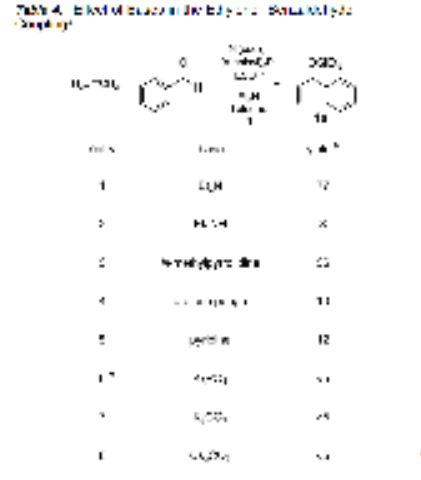


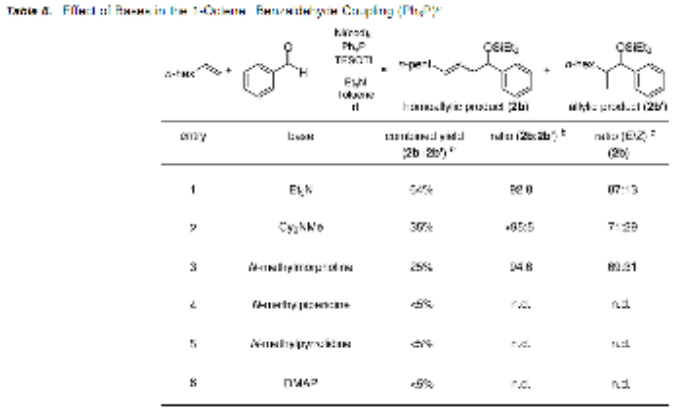
- However, some very electron-deficient phosphines are not effective
  →due to the larger cone angle??

- On the other hand, high A:H ratio can be obtained by using electron-rich phosphines with a large cone angle.

two combined effects:
- -electron-donating ability
- -the cone angle of the phosphine ligands

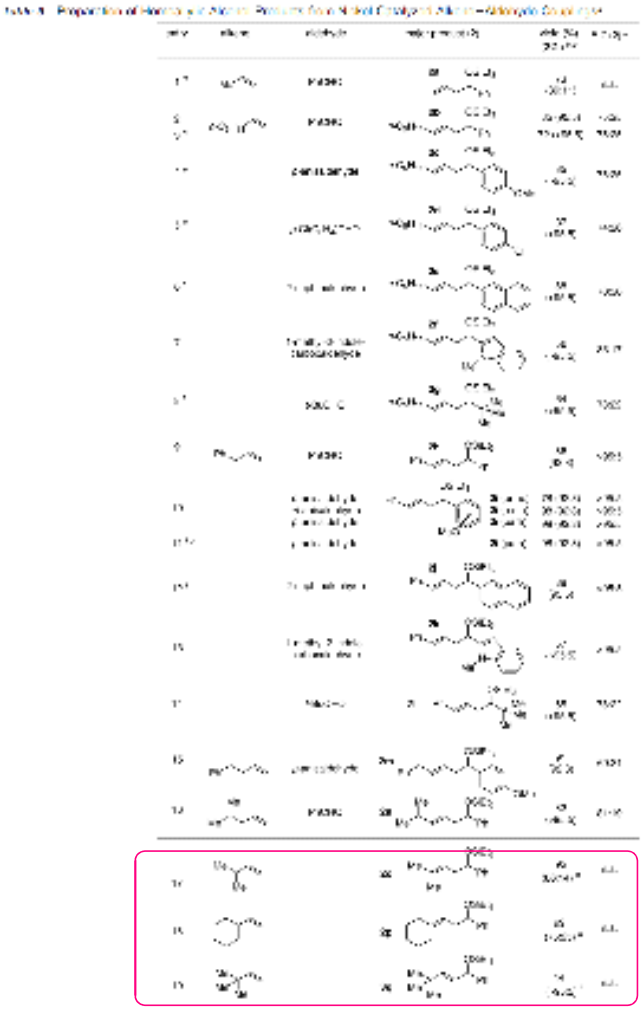
base effect



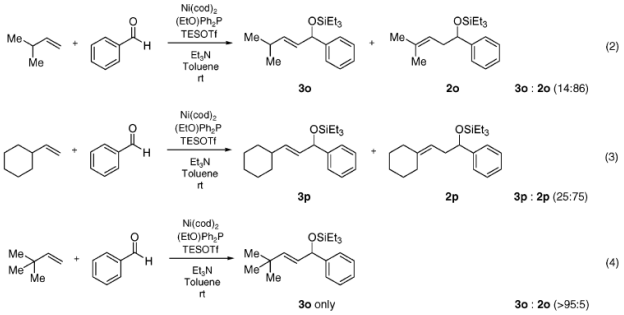


- Et_3N is the bese probable because of a combination of low coordination ability and appropriate basicity

substrate scope (H)



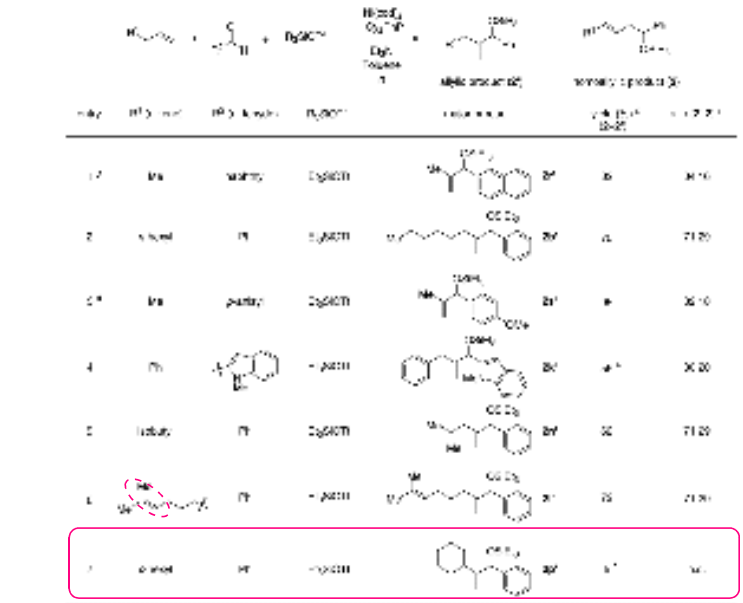
- Highly regioselective & *E*/*Z* serective (favoring *E*)
- Aromatic aldehydes, heteroaromatic aldehydes, and strically demanding aldehydes can be used.
- As the case of ethylene, e-rich aldehydes are more efficiency.
- Substitution at the homoallylic position (of alkenes) don't affect, but at the alylic position different ones.



unusual *E*-1,3-disubstituted allylic alcohol product

an important observation
in understanding the mechanism

substrate scope (A)



- Aromatic aldehydes and heteroaromatic aldehydes can be used.
- As cases above, e-rich aldehydes are more efficiency.
- Substitution at the homoallylic position (of alkenes) don't affect, but at the alylic position different ones.

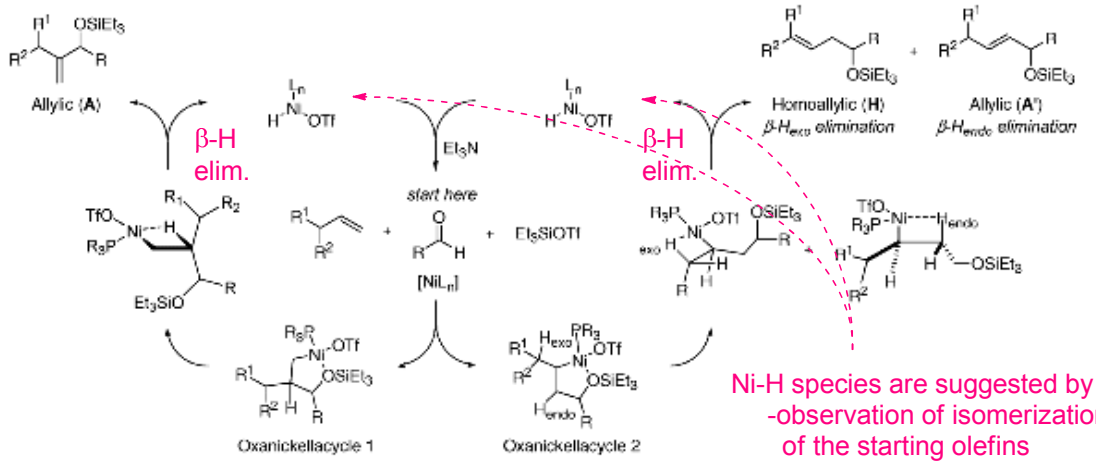
competition study

Trisubstituted alkenes are stable.
→See entry **6**

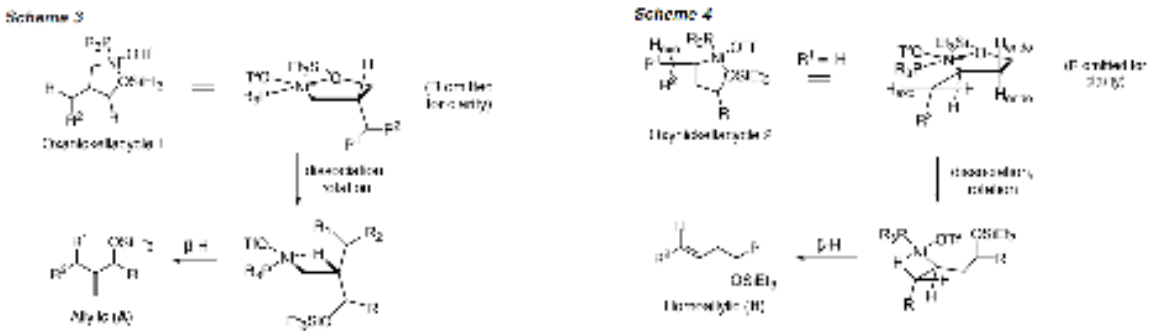
In general, 1,1- and acyclic 1,2-disubstituted alkenes are significantly less reactive, and trisubstituted alkenes don't react under the standard reaction conditions.

poposed reaction mechanism based on some observations and in analogy to the Heck reaction

Scheme 1 nickel-hydride pathway



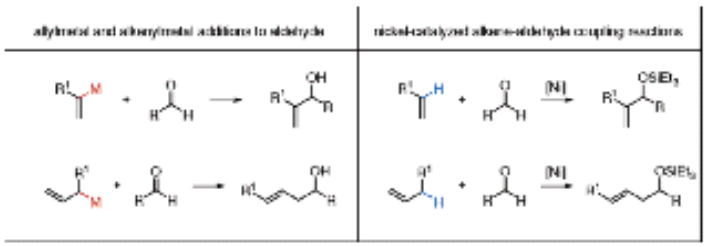
oxanickelacycle model (in more detail)

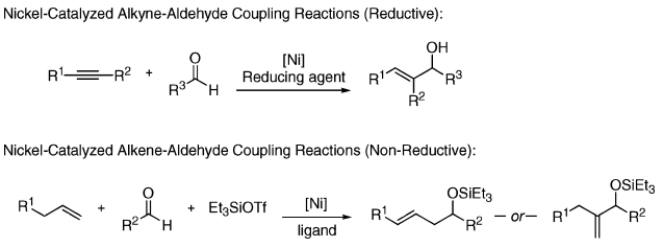


From the entirely difference of both substrate scopes of alkenes and aldehydes,
the direct precursor to the oxanickelacycle is a Ni(0) species, not a cationic Ni(II) Lewis acid species.

3. Summary

Jmaison's non-reductive pocess, different from carbonyl-ene reactions of reductive processes,
conceptually serve alkenes as substituteds for both allylmetal and alkenylmetal reagents.
This system affords two type products with high selcetivity in either direction





1997	2000	2004	2006
Montgomery intramolecular reductive	**Jamison** intermolecular reductive	**Montgomery** intermolecular reductive	**Jamison** intermolecular *non-reductive*