Searching reductive coupling on SciFinder will lead to two major classes of reactions:

1) Coupling of two carbonyl-type species to form pinacol type products
   Example: McMurry coupling in Nicolau's synthesis of taxol

\[
\text{O} \quad \text{TiCl}_3 \quad \text{DME} \quad \text{Zn-Cu, DME} \quad 70\, ^\circ C, 23\%
\]

Nicolau, Nature 1994, 367, 630

Other C=\(X\) (\(X\) = heteroatom, ex. nitrones, oximes) etc can be used. Sml\(_2\) is frequently employed in the literature to induce this transformation

2) Transition metal catalyzed C-C bond forming event where a hydrogen (reductive coupling) is transferred instead of an alkyl group (alkylative coupling) in the reductive elimination step

- Many factors influence the pathway taken such as; ligand, reductant, solvent

\[
\begin{align*}
\text{hydrogen introduction} & \quad \text{on metal either from} \\
\beta\text{-hydride elimination from} & \quad \text{ligand/reducing agent or} \\
\text{introduced} \quad \text{H}_2 & \quad \text{gas}
\end{align*}
\]

Direct reductive elimination

Alkylative coupling product

Reductive elimination product

<table>
<thead>
<tr>
<th>Classes of Reductive Coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Alkyne to carbonyl compounds (aldehydes, imines and ketones): carbonyls lead to allylic alcohols.</td>
</tr>
<tr>
<td>- why is this good? no need for multistep functionalization to form an organometallic species, also more amenable to asymmetric transformations.</td>
</tr>
</tbody>
</table>

\[
\text{R}^1 & \quad \text{Tl(O-i-Pr)}_4 & \quad \text{i-PrMgCl} \\
\text{then} & \quad \text{R}^1 & \quad \text{R}^2 \\
\text{quench with} & \quad \text{R}^3 & \quad \text{R}^4 \\
\text{electrophile} & \quad \text{use H}_2\text{O} & \quad \text{for reductive}
\]

TMS
\[
\text{alkyne used in many cases}
\]

- addition of two molecules of aldehyde to titanocyclopropane not observed


1) Ti(O-i-Pr)\(_4\) / i-PrMgCl

2) \quad \text{then H}_2\text{O}

\[
\text{R}^1 & \quad \text{R}^2 & \quad \text{R}^3 & \quad \text{R}^4 \\
\text{yields 48-94%} & \quad \text{rr} & \quad \text{>20:1 in most cases}
\]


Use of Ni to induce RC. ZnEt\(_2\) is the reducing agent so run risk of alkylative coupling (Et transfer)

\[
\begin{align*}
\text{H} & \quad \text{X} & \quad \text{Et} \\
\text{Ni(COD)}_2 & \quad \text{PBU}_3 & \quad \text{1:4} \\
\text{ZnEt}_2 & \quad \text{Et} \\
\text{yields 62-74%}
\end{align*}
\]

Reductive Coupling

Mechanism

\[ R^2 \equiv R^3 \xrightarrow{L_1 \text{Ni}(0)} \text{large substituent} \]

\[ R^1 \xrightarrow{L = \text{PBU}_3} \text{small substituent or tether chain} \]

\[ R^4 \xrightarrow{L = \text{THF}} \]

\[ R^1 \xrightarrow{\text{ZnR}^2} \]

\[ R^1 \text{OH} \]

\[ R^2 \text{OH} \]

Reductive coupling would only occur on intramolecular substrates with phosphine ligands - inter always led to alkylative with these conditions

(intramolecular variant only)

Applications to Natural Product Synthesis

- diethyl zinc adds to carbonyls in complex substrates

- cyclization step assembles six-membered ring, controls the relative stereochemistry adjacent to a quaternary center and assembles the alkylidene unit (each event occurring in a highly selective manner)

Montgomery J. Am. Chem. Soc. 1999, 121, 6098

First Catalytic in Nickel, also first intermolecular example using Ni

Montgomery Org. Lett. 2008, 10, 811

Jamison Org. Lett. 2000, 2, 4221

Asymmetric Variants By Jamison

- up to 67% ee
  J. Org. Chem. 2003, 68, 156

- (+)-NMDPP, up to 96% ee
  J. Am. Chem. Soc. 2003, 125, 3442
Reductive Coupling

Applications to natural product synthesis

[Diagram showing chemical structures and reactions]

J. Am. Chem. Soc. 2003, 125, 11514

These rhodium procedures require the alkyne to be conjugated for increased reactivity
(Krische Work, uses hydrogen as the reductant)

1,3-dienes and glyoxals: J. Am. Chem. Soc. 2003, 125, 11488
1,3-enedyes and glyoxals: J. Am. Chem. Soc. 2004, 126, 4664
conjugated alkynes and α-ketoesters: J. Am. Chem. Soc. 2006, 128, 7118
silyl substituted diynes to control regioselectivity: Org. Lett. 2006, 8, 3873
intramolecular acetylenic aldehyde cyclizations: J. Am. Chem. Soc. 2006, 128, 10674
heteroaldheydes and chiral Bronsted acid additives: J. Am. Chem. Soc. 2006, 128, 16448
in situ generation of enynes and coupling to carbonyls: J. Am. Chem. Soc. 2006, 128, 16061
in situ generation of enynes and coupling to imines: J. Am. Chem. Soc. 2007, 129, 7242
conjugated alkynes and α-ketoesters: Org. Lett. 2007, 9, 3745
application to the synthesis of hexoses: Org. Lett. 2008, 10, 4133
Reductive Coupling

Reaction of alkynes with epoxides - first example of coupling to sp³ center
(yields homoallylic alcohols)

\[
\begin{align*}
R^1 &= R^2 + \text{cat. Ni(cod)\(_2\)} & \text{yield up to 85\%} \\
& \xrightarrow{\text{Bu\(_3\)P, Et\(_3\)B}} & >99\% \text{ ee} \\
\text{Ph} & \quad \text{enantiomerically} \\
\text{X} & \quad \text{yield up to 88\%} \\
\text{OH} & \quad >20:1 \text{ endo closure}
\end{align*}
\]

Jamison J. Am. Chem. Soc. 2003, 125, 8076

Mechanism - endo opening suggests a different reaction mechanism than alkyne/aldehyde

Applications to Natural Product Synthesis

Jamison J. Org. Chem. 2007, 72, 7451

Jamison J. Am. Chem. Soc. 2004, 126, 998
**Example to Show Fine Balance Between Alkylative and Reductive Coupling**

- desired reaction is three-component alkylative coupling (RC was a competing problem)
- imines less electrophilic - need hydroxyc acid solvent and organoboron reagent
- methanol occupies coordination site, hindering β-hydride elimination

\[
\begin{align*}
R_1 & \quad R_2 \\
R_3 & \quad R_4 \\
N & \quad \text{Me} \\
H & \quad \text{Me}
\end{align*}
\]

\[\text{Ni(COD)}_2 \ (10 \text{ mol\%}) \quad \text{C}_5 \text{H}_{5}\text{P} \ (20 \text{ mol\%}) \quad \text{MeOAc/MeOH} \quad 0 \ ^\circ \text{C}, 20 \text{ h}\]

reductive coupling (major product with MeOH)
yields 30-98%
\[rr = \geq 10:1\]
alk:red = \geq 10:1

*Jamison Angew. Chem. Int. Ed. 2003, 42, 1364*

**Development of NHC Ligands** (allow for efficient intermolecular RC with triethylsilanes)

\[
\begin{align*}
\text{Et}_3\text{SiH} + \text{Ni(COD)}_2 \ (10 \text{ mol\%}) & \quad \rightarrow \quad \text{Et}_3\text{SiO} \\
\text{Et}_3\text{SiD} + \text{Pr}_3\text{SiH} & \quad \rightarrow \quad \text{Et}_3\text{SiO} \\
\end{align*}
\]

yield = 56-84%
\[rr = \geq 98.2\]

Cross Over Experiment to Show that Ligand Identity Affects Mechanism

\[
\begin{align*}
\text{R} & \quad \text{X} & \text{From NHC} & \text{From PBu}_3 \\
\text{Et} & \quad \text{H} & <2 & 25 \\
\text{Et} & \quad \text{D} & 55 & 34 \\
\text{Pr} & \quad \text{H} & 41 & 23 \\
\text{Pr} & \quad \text{D} & <2 & 18 \\
\end{align*}
\]

*Montgomery J. Am. Chem. Soc. 2004, 126, 3698*

**Mechanism demonstrating competing pathways**

- alkylative coupling
- reductive coupling
- reductive elimination
- β-H elimination

*Jamison J. Am. Chem. Soc. 2004, 126, 4130*
Reductive Coupling

Directing effect of remote alkene and impact of phosphine
reaction doesn’t work with 1,2,4 carbon spacer

\[
\text{Et}_2\text{BO} \rightarrow \text{Et}_2\text{B}
\]

**Application of synthetic approach:**

\[
\text{R}^1\text{O} \rightarrow \text{R}^1\text{O}
\]

- Two steps
- Two C-C bonds formed
- Three new stereocenters (•)
- Stereoredefined trisubstituted double bond (•)
- No protecting group manipulations

**Applications to total synthesis**

- Ene-1,5-diol
- Very valuable substrate for polyols (hydration/dihydroxylation), epoxides (olefin epoxidation and 1,5-diols (hydrogenation)

**References**

Irridium Chemistry - non-conjugated alkenes can now be coupled

\[
\begin{align*}
R_1 &= \text{R}_2 \\
R_3 &= \text{O} \\
\text{Ph}_3\text{CCO}_2\text{H} (2 \text{ mol}\%)
\end{align*}
\]

\[
\begin{align*}
\text{Ph}_3\text{CCO}_2\text{H} (2 \text{ mol}\%) \\
\text{H}_2 (1 \text{ atm})
\end{align*}
\]

\[
\begin{align*}
\text{PhCH}_3, 60 \degree\text{C}
\end{align*}
\]


Mechnism

\[
\begin{align*}
\text{Et} \\n\text{LnIr}^{\text{II}} \\n\text{Et} \\n\text{LnIr}^{\text{III}} \\n\text{Et}
\end{align*}
\]

Catalytic Version Mechanism

\[
\begin{align*}
\text{Et}_3\text{Si} - \text{Ni} - \text{H} \\
\text{Ni}(0)
\end{align*}
\]

Applications to total synthesis

Coupling of Other π-Components to Carbonyls

100 mol% Ni(acac)$_2$
200 mol% PPh$_3$

DIBAL-H (2 eq to Ni)

yield 52-86%

Mori Tet. Lett. 1997, 38, 3931

Mitsunobu Reaction

81% (4 steps)
**Reductive Coupling**

1,3-CHD is important to obtain double bond in the desired position. If it is not included it migrates one position closer to the newly formed C-C bond.

Total Synthesis by Mori, *Synlett* 1997, 734

**ketones and alkenes** - stated as the first catalytic for alkene/alkyne with heteroatom containing DB. Mori did it with dienes and aldehydes in 1994...?

**Buchwald J. Am. Chem. Soc. 1995, 117, 6785**

**Crowe J. Am. Chem. Soc. 1995, 117, 6787**

**silylethylene-titanium alkoxide complex** - reagent originally developed by Kulinkovich. Addition to an ester makes cyclopropanols. Utility expanded by Sato.

**Sato J. Org. Chem. 2000, 65, 6217**

**coupling of allenes / alkynes with chiral imines**
- reverse order, Ti reagent is complexed to imine instead of alkyne/allene

**Sato Org. Lett. 2003, 5, 2145**

- chiral group can be removed to produce chiral primary amines

**yields = 45-74%**
**d.r. >98:2**
Reductive Coupling

homo-allylic alcohols and imines
- more complex RC as you generate two new stereocenters.

\[
\text{ROH} + \text{R}^1 \stackrel{\text{C} \text{C}_3 \text{H}_5 \text{MgCl}}{\text{Ti(O-i-Pr)}_4} \rightarrow \text{OH} + \text{R}^1 \text{R}^2 \text{N} \text{R}^3 \text{PPh}_3 / \text{CCl}_4 \text{r.f.} \geq 20:1 \text{d.r.} = 4:1 \text{to} \geq 20:1 \text{cycliclization 76-85%}
\]

Micalizio J. Am. Chem. Soc. 2007, 129, 7514

- reverse prenylation with allenyl metal reagents

\[
\text{C} = \text{C} \stackrel{\text{[Ir(BIPHEP)cod]BARF (5 mol%)}}{\text{O}} \text{Me} \rightarrow \text{OH} \text{Me}
\]

aryl or activate alkyl aldehyde


Mechanism - prenyl group is necessary to prevent over reduction of double bond

Allenes and Transfer hydrogeneration:

\[
\text{C} = \text{C} \stackrel{\text{[Ir(BIPHEP)cod]BARF (5-7.5 mol%)}}{\text{O}} \text{Me} \rightarrow \text{OH} \text{Me}
\]

\[
\text{C} = \text{C} \stackrel{\text{[Ir(BIPHEP)cod]BARF (5-7.5 mol%)}}{\text{H}_2} \text{Me}
\]

- transfer hydrogenation must be used since H\(_2\) over reduces all products besides reverse prenyl
- basic additive Cs\(_2\)CO\(_3\) also helps to inhibit over-reduction
- no stoichiometric by products produced
- in many cases 4 to 8 equivalents of allyl source is required (no mention of this!)


- can also use rhodium based catalysts [RuHCl(CO)(PPh\(_3\))] to affect similar transformations but an acid cocatalyst (m-NO\(_2\)BzOH or CF\(_3\)COH) is required when the alcohol is used as the substrate.

Other sources of allyl derivative metal reagents for transfer hydrogeneration

1,3-cyclohexadiene Org. Lett. 2008, 10, 1033

allyl acetate JACS 2008, 130, 6340

acyclic dienes JACS 2008, 130, 14891

asymmetric crotylation JACS 2009, 131, 2415
**Reducing Coupling**

**Vinyl pyridines and imines**

![Chemical structure](image)

- need substitution at 6-position of pyridine, otherwise catalyst binds to nitrogen and no reaction

**π-π couplings where the π-bonds are all carbon**

Paper was about alkylative cyclization but they found that use of phosphine led to RC **alkylative vs reductive cyclization**

**Effect of alkoxide on stereochemistry**

![Chemical structure](image)

result explained by the fact that the alkoxide is better at locking the transition state in a chair than the -OTBS even though it is "smaller"

**Allenyl-alkyne coupling to prepare 1,3-dienes**

![Chemical structure](image)

yields 47-93% 
**rr = 60:40 to >20:1**

Sato J. Am. Chem. Soc. 1999, 121, 7342
Reductive Coupling

Cobalt Becomes Involved - alkyne / activated alkene coupling

\[
R^1=\mathrm{R}^2 + \mathrm{R}^3 \rightarrow [\text{Co}_2(\text{PPh}_3)_2, \text{PPh}_3, \text{Zn}] \rightarrow \text{R}^1=\text{R}^2 + \text{R}^3
\]

\[
\text{CH}_2\text{CN}, \text{H}_2\text{O}, 80^\circ \text{C}
\]

mechanism

\[
\text{Co}^{\text{II}} + \text{Zn} \rightarrow \text{Co}^{\text{I}} \rightarrow \text{Zn} \rightarrow \text{H}_2\text{O} \rightarrow \text{Co}^{\text{III}} \rightarrow \text{CO}_2\text{-nBu} \rightarrow \text{Me} \rightarrow \text{Me}
\]


previous Krische examples showed metal adding across C-O \( \pi \) bond, why not C-C \( \pi \) bond?

Proposed mechanism shown for diyne:

\[
\text{MeO}_2\text{C} \rightarrow \text{MeO}_2\text{C} \rightarrow \text{Rh}^{\text{III}}\text{LnD}
\]

Alkyne-Alkyne Coupling by Micalizio (Similar to Sato)

- Micalizio different for two reasons: functionalization of the internal alkyne component has only been achieved with TMS-substituted alkyne and conjugated 2-alkynoates (this introduces limits for polyketide synthesis)
- coupling can lead to four possible regioisomers

\[
\text{Rh}(\text{COD})_2\text{OTf} (3 \text{ mol\%}) \rightarrow \text{rac-BINAP or BIPHEP (3 mol\%)} \rightarrow \text{DCE (0.1 M), 25 \degree \text{C}} \rightarrow \text{H}_2 (1 \text{ atm}) \rightarrow \text{yields 51-90\%}
\]

\[
\text{Rh}(\text{COD})_2\text{OTf} (3 \text{ mol\%}) \rightarrow \text{rac-BINAP or BIPHEP (3 mol\%)} \rightarrow \text{DCE (0.1 M), 25 \degree \text{C}} \rightarrow \text{H}_2 (1 \text{ atm}) \rightarrow \text{yields 65-91\%}
\]

diyne and enyne cyclizations: Krische J. Am. Chem. Soc. 2004, 126, 7875

**Reductive Coupling**

Alkoxide directed (intramolecular) coupling of alkynes

\[
\begin{align*}
\text{O}^+ & \text{Li}^+ \quad \text{R}^1 + \quad \text{i-PrO}^+ ~ \text{O}^\text{i-Pr} \\
\text{Ti} & \text{cat.} \quad \text{then} \quad \text{then} \\
\text{nh} \quad \text{Me} & \text{Me} \\
\end{align*}
\]

- Intramolecular carbometalation
- Yields 51-58%

Also works with allenenes to make skipped 1,4-dienes

\[
\begin{align*}
\text{OH} & \text{C} = \text{C} \quad \text{R}^3 \\
\text{R}^1 & \text{C} = \text{C} \quad \text{R}^4 \\
\end{align*}
\]

- Single regioisomer formed in most cases

Application to total synthesis

**Micalizio Angew. Chem. Int. Ed. 2008, 47, 7837.**
**Reductive Coupling**

**Enones and alkynes (enals cyclize)**

\[
\begin{align*}
\text{O} & \quad \text{R}^1 \quad \text{R}^4 \\
\text{O} & \quad \text{R}^2 \quad \text{R}^3 \\
\text{Ni(COD)}_2 & (10 \text{ mol%)} \\
\text{PdCl}_2 & (20 \text{ mol%)} \\
\text{Et}_3\text{B} & (3.0 \text{ equiv}) \\
\text{MeOH, THF (8:1)} \\
\end{align*}
\]

yield = 50-90% rr usually >20:1

- can couple enoates with ynoates without any homocoupling, which is surprising

**Mechanism**

**use remote alkoxide to direct regioselectivity**

- without alkoxide there was no reaction
- only works with allylic and homo allylic alcohols

**Montgomery J. Am. Chem. Soc. 2007, 129, 8712**
Reductive Coupling

Cobalt mediated alkyne-alkene

\[
\text{[Col}_2\text{(dppe)], ZnI}_2, \text{Zn} \rightarrow \begin{array}{c}
\text{CH}_3\text{CN, H}_2\text{O, 80 °C}
\end{array}
\]

\[
\begin{array}{c}
\text{alkyne/allylic alcohol}
\end{array}
\]

application to total synthesis

key step in total synthesis

alkynes and allyl alcohols with transfer of oxygen to catalyst (net allyl transposition)

intermediate

Complimentary Claisen-based methods: a stereodivergent product is produced

This work:

similar results reported by Cha J. Am. Chem. Soc. 2008, 130, 15997

Cha (J. Am. Chem. Soc. 2008, 130, 15997) reported this result first, but allylic alcohols were limited to cyclohexyl derived, except for one case
**Reductive Aldols - no prefunctionalization with stoichiometric reagents**

\[
\text{R}_1^2 \text{R}_3^2 + \text{R}_4^4 \xrightarrow{\text{Me}_3\text{SiH}, \text{RhCl}_3 3\text{H}_2\text{O}} \text{R}_1^2 \text{R}_3^2 \text{R}_4^4 \text{R}_5^5 \text{SiMe}_3 \\
\text{If } \text{R}_1^2 = \text{OMe}, \text{no evidence of silyl ketene formation and then aldol}
\]

Revis *Tetrahedron Lett.* 1987, 28, 4809

**Hydrogen as the reductant - All work by Krische**

\[
\text{Rh(COD)$_2$OTf (10 mol%) (p-CF$_3$Ph)$_2$P (24 mol%)} \\
\text{H}_2 (1 \text{ atm}), \text{KOAc (30 mol%) DCE, 25 }^\circ\text{C}
\]

yield 64-90% syn:anti 5 to 20:1

For For Ketone Additions to Ketone Acceptors: *Org. Lett.* 2003, 5, 1143
For Aldehyde Addition to Glyoxals Acceptors: *J. Org. Chem.* 2004, 69, 1380
For Aldehyde Additions to Ketones Acceptors: *Org. Lett.* 2004, 6, 691
Increase in syn selectivity using tri-2-furylephosphine: *Org. Lett.* 2006, 8, 519
Unsymmetrical divinyl ketone addition to aldehydes: *Org. Lett.* 2006, 8, 5657

**Mechanism**

- The KOAc helps prevent conjugate reduction by deprotonating complex A or B
- treatment of substrate with only phosphine does not lead to Baylis-Hillman

**Enantioselective Variants**

\[
\text{R}_1^2 \text{R}_3^2 + \text{R}_4^4 \xrightarrow{\text{1) 2.5 mol% [(COD)RhCl]}_2 6.5 mol% R-BINAP \text{Et}_2\text{MeSiH}} \xrightarrow{\text{2) H}_2\text{O}^+} \text{R}_1^2 \text{R}_3^2 \text{R}_4^4 \text{Me} \\
\text{yields 48-72% syn:anti 1.8:1 to 5.1:1 ee (syn) = 45-68%}
\]


\[
\text{R}_1^2 \text{R}_3^2 + \text{R}_4^4 \xrightarrow{\text{1) 2.5 mol% [(COD)IrCl]}_2 7.5 mol% ligand \text{Et}_2\text{MeSiH}} \xrightarrow{\text{2) H}_2\text{O}^+} \text{R}_1^2 \text{R}_3^2 \text{R}_4^4 \text{Me} \\
\text{yields 47-68% syn:anti 1.7:1 to 9.1:1 ee (syn) = 82-96%}
\]

Morken *Org. Lett.* 2001, 3, 1829
Reductive Coupling

Role of aryl halides in Ni-Catalyzed Reductive Aldols

\[
\text{Ni(COD)}_2_{\text{Ph}} + \text{Et}_2\text{B} \rightarrow \text{Ni(COD)}_2_{\text{Ph}} \rightarrow \text{Ph} + \text{Et}_2\text{B}
\]

- Phl isn’t just serving as a mechanism to generate Ni(II) from Ni(COD)₂
- proposed to form a boron enolate which then reacts with aldehyde (metal no longer complexed for this step).

Montgomery Org. Lett. 2007, 9, 537

Random Reactions

Intermolecular Enal-Alkyne [3+2] Reductive Cycloadditions
(first example of catalytic and intermolecular)

- synthesis of carbocyclic 5-membered rings via cycloadditions difficult (traditional 3+2’s need a heteroatom in dipole)
- formal solutions is to use strained rings precursors, vinyl carbenoids or dianion equivalents
- the assembly of an odd-membered ring from two even numbered pi systems would require a net two electron oxidation or reduction or a hydride shift
- early stoichiometric work in the field by Sato J. Am. Chem. Soc. 1996, 118, 8729 and

\[
\begin{align*}
\text{Ni(COD)}_2_{(10 \text{ mol} \%) + \text{Et}_2\text{B (4.0 equiv)}} + \text{R}^1\text{R}^2\text{R}^3\text{R}^4 \rightarrow \text{yield 58-85% good dr}
\end{align*}
\]

Montgomery J. Am. Chem. Soc. 2006, 128, 14030

Original Stoichiometric Protocol (only worked for intramolecular)

\[
\begin{align*}
\text{Ni(COD)}_2_{(1 \text{ equiv)}} + \text{L} = \text{Me}_2\text{N} + \text{NMMe}_2_{(1 \text{ equiv)}} \rightarrow \text{OH} + \text{Ph}
\end{align*}
\]

need to add co-reductant

\[
\begin{align*}
\text{LNi(OHMe)}_2_{(doesn’t \ re-enter \ cycle)} \rightarrow \text{H} + \text{Ph} \rightarrow \text{NiL} + \text{NiPh}
\end{align*}
\]

Three-Component Coupling via Internal Redox (leads to esters and malonates!)

Three-Component enal, alkyne, alcohol additions (no reducing agent is necessary, it forces reaction to the cycloaddition pathway).

Mechanism

Montgomery J. Am. Chem. Soc. 2008, 130, 469

Three-Component Enone, Alkyne, Aldehyde Additions

Montgomery J. Am. Chem. Soc. 2008, 130, 469

Baran Group Meeting
3/11/2009
Reductive Coupling

Mechanism

Reviews on Reductive Coupling


