Nickel Catalyzed sp$^3$-sp$^3$ Couplings

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Difficulties in sp$^3$-sp$^3$ Cross Coupling

- Difficult oxidative addition
  - Sterics - three substituents prevent access to the C-X bond
  - Electronics - electrons are more equally shared in an sp$^3$ C-halide bond than in sp$^2$ C-halide bond.

- Slow reductive eliminations
  - Increases reaction time
  - Increases amount of β-Hydride elimination
  - Increases amount of reduction of alkylhalide
Outline

Part I: Knochel
   Development of alkylzinc reagents for coupling

Part II: Fu
   Elaboration of nickel catalyzed alkylzinc couplings

Part III: Vicic
   Mechanistic studies of alkyl zinc couplings

Part IV: Kumada
   Alkyl grignards as the organometallic donor
First Example

Initial substrate scope:
Homoallylic and bishomoallylic primary iodides
Alkene or $\alpha,\beta$-unsaturated ester.

Organozinc
Symmetrical
$1^0$ and $2^0$ Alkyl
TMS protected vinyl alcohols
Esters are tolerated

Knochel Mechanistic Proposal

R=\textsuperscript{n}Bu or Ph
X= Br or I

Higher temperatures promotes dissociation
\textsuperscript{n}Pentyl\textsubscript{2}Zn gives more halide-zinc exchange than Et\textsubscript{2}Zn

Expanding the Scope

\[ \text{[Ni(acac)2] (10mol\%)} \quad n\text{-Pent-Zn} \quad \text{THF/NMP} \quad -35^\circ\text{C}, 4h \]

\[ \text{PhCOMe (0eq)} \quad 20\% \quad \text{PhCOMe (1eq)} \quad 71\% \]

\[ n=2, 65\% \text{ yield} \quad n=3, 71\% \text{ yield} \]

Conclusion: Stronger $\pi$-acids promote coupling

Catalyst Development

Can an external olefin be added as a co-catalyst to facilitate coupling?

All gave similar conversion times and a moderate amount of zinc-bromide exchange.

Completely inhibits the coupling.

Gives fast conversion as well as suppresses formation of zinc halogen exchange.

Broad functional group tolerance
Notable exceptions: alcohols and amines

Reducing Waste: AlkylZnX Reagents

2eq of Dialkylzinc reagents are typically used

\[
\begin{align*}
\text{O} & \quad \text{I} \\
\text{Ph} & \quad \text{(CH}_2\text{)}_3
\end{align*}
\]

Ni(acac)_2 (10mol\%)  
F- \quad \text{20mol\%} 
\begin{align*}
\text{O} & \quad \text{R} \\
\text{Ph} & \quad \text{(CH}_2\text{)}_3
\end{align*}

RZnBr (3eq)  
n-Bu_4NI (3eq)  
THF/NMP  
-35°C, 16h

Allows for more easily prepared RZnI reagents to be used.

RZnI reacts with TMSCH_2Li to give RZnCH_2TMS

\[
\begin{align*}
\text{O} & \quad \text{I} \\
\text{Ph} & \quad \text{(CH}_2\text{)}_3
\end{align*}
\]

Ni(acac)_2 (10mol\%)  
F- \quad \text{20mol\%} 
\begin{align*}
\text{O} & \quad \text{R} \\
\text{Ph} & \quad \text{(CH}_2\text{)}_3
\end{align*}

RZnCH_2TMS (3eq)  
THF/NMP  
-35°C, 6h

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Initial Ligand Development

\[ \text{Br} + \text{BrZn-n-nonyl} \xrightarrow{\text{Ni(cod)\textsubscript{2} (4mol%)}} \text{n-nonyl} \]

\[ \text{R-Pybox} \quad \text{R = t-Bu, i-Pr, Ph, s-Bu} \]

\[ \text{Indanyl-Pybox} \]

1\textsuperscript{0} or 2\textsuperscript{0} alkyl bromides or iodides
Highly functional group tolerant
62-78\% yield

Asymmetric Catalysis

\[
\text{NiCl}_2\text{•glyme (10mol\%) } \\
\text{(R)-i-Pr-Pybox (13mol\%) } \\
\text{R}^1\text{ZnX } \\
\text{DMI/THF, 0°C}
\]

51-90% yield
77-96%ee

\[
\text{NiBr}_2\text{•diglyme (10mol\%) } \\
\text{(S)-i-Pr-Pybox (13mol\%) } \\
\text{R}^1\text{ZnX (1.3eq) } \\
\text{DMI/THF, 0°C}
\]

39-89% yield
91-98%ee

1 example of a benzylic non-indane bromide:
63%, 75%ee

Asymmetric Catalysis (Part II)

When $R^1 \neq R^3$: If $R1$ is smaller, the constitutional isomer is formed.

If $R^1$ is $\text{e}^-$ withdrawing, substitution is always at the $\gamma$ position.

Substrate scope is excellent: esters, amides, silyl ethers, acetals, alkenes, phosphonate ester, and Weinreb amide.

Formal Total Synthesis of Fluvirucinine $A_1$

From all the synthesis is of Fluvirucinine $A_1$

Boranes as the Organometallic Source

Tolerant of protected alcohols (TBS) and amines (Cbz)
Rate: $X = I > Br >> Cl$
  $2^o > 1^o >> 3^o$ (very low yielding)

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Some Mechanistic Insights

Both species shown above are catalytically active. Propose a mechanism for the coupling reaction.
Proposed Mechanism

The Ni(I) alkyl complex was independently synthesized and also shows catalytic competence.

Agrees with Knochel’s observation that 1,4-dinitrobenzene inhibited the reaction.

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Grignards as the Organometallic Source

\[ R-X + R'-\text{MgX} \xrightarrow{\text{NiCl}_2} R-R' + \text{MgX}_2 \]

1 eq RX
R = alkyl
X = F, Cl, Br, OTs

1.3 eq R'\text{MgX}
R' = aryl or alkyl
X' = Cl or Br

Substrate scope is diminished, tolerant of alkenes and arylbromides.

Capable of coupling with alkyl fluorides.

Kambe et. al. JACS. 2002, 124, 4222-4223
Mechanism

\[
\begin{align*}
\text{NiBr}_2 + 2\text{eq } n-C_8H_{17}\text{MgCl} + \text{isoprene} & \xrightarrow{\text{THF}} n-C_8H_{18} + 1\text{-octene} \\
43\% & \quad 45\%
\end{align*}
\]

\[
\begin{align*}
\text{Ni(COD)} + 1\text{eq } n-C_{10}H_{21}\text{Br} + \text{1,3-butadiene} & \xrightarrow{\text{THF}} \text{No Reaction}
\end{align*}
\]

To rule out a radical mechanism:

According to Kambe:
“This result would rule out a radical mechanism.”

Kambe, N.; et. al. JACS. **2002**, *124*, 4222-4223.
Conclusions

- Ni catalyst systems are robust and efficient
- Cross coupling of sp$^3$-sp$^3$ centers can be used in total synthesis
- Cross coupling can be used to set 2$^o$ stereo-centers
For Reviews of Alkyl-Alkyl Couplings

