Metallacycle-Mediated Annulation for the Synthesis of Hydroindanes

**Significance:** Cheng and Micalizio report a stereoselective annulation reaction to afford cross-conjugated triene-containing hydroindanes that are subsequently trapped by a dienophile in a [4+2]-cycloaddition reaction to obtain highly functionalized carbo- and heterocyclic systems.

**Comment:** The tendency of products of type A to undergo Diels–Alder-based dimerization upon standing was harnessed to accomplish this reaction cascade of annulation and intermolecular cycloaddition.
Cyclization of 1-(Trifluoromethyl)-4-alkyn-1-ones with Arylboronic Acids

Significance: Lautens and co-workers report a rhodium-catalyzed cyclization of 1-(trifluoromethyl)-4-alkyn-1-ones with variously substituted arylboronic acids to obtain (trifluoromethyl)cyclobutanol bearing an exocyclic double bond.

Comment: The reactivity of the newly formed exocyclic double bond was explored by subjecting a (trifluoromethyl)cyclobutanol to an epoxidation reaction using MCPBA and an ozonolysis.
An Efficient, Practical, and Selective Multicomponent Copper-Catalyzed Process

Significance: The authors demonstrate the generation of multifunctional alkenylboron fragments starting from two simple unsaturated organic molecules and a commercially available diboron reagent. These fragments were shown to carry several advantageous properties. The catalyst used is generated in situ by the reaction of inexpensive CuCl with a chiral ligand which was prepared on multigram scale in good yield.

Comment: The practical protocol can be performed on large scale and makes gram quantities of a variety of complex organic molecules easily available. The products, which contain a stereogenic carbon center, a monosubstituted alkene, and an easily functionalizable Z-trisubstituted alkenylboron group, are obtained in good yields and excellent selectivities.

Selected examples:

- TBSO Ph\(\text{OPO(OEt)}_2\) + CuCl (5 mol%) ligand (5 mol%) \(\text{t-BuOK} \) (1.5 equiv) B\(_2\)(pin)\(_2\) (1.2 equiv) THF, 4 °C, 24 h

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>Branching</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBSO Ph(\text{OPO(OEt)}_2)</td>
<td>72</td>
<td>&gt;98%</td>
<td>&gt;98% Z, er &gt; 99:1</td>
</tr>
<tr>
<td>TBSO Ph(\text{OPO(OEt)}_2)</td>
<td>68</td>
<td>&gt;98%</td>
<td>&gt;98% Z, er = 94:6</td>
</tr>
<tr>
<td>TBSO Ph(\text{OPO(OEt)}_2)</td>
<td>75</td>
<td>&gt;98%</td>
<td>&gt;98% Z, er = 92:8</td>
</tr>
<tr>
<td>TBSO Ph(\text{OPO(OEt)}_2)</td>
<td>84</td>
<td>&gt;98%</td>
<td>&gt;98% Z, er = 94:6</td>
</tr>
</tbody>
</table>

Application to the total synthesis of rottnestol:

67% overall yield

SYNFACTS Contributors: Paul Knochel, Thomas Klatt

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Accessing 2-(Hetero)arylmethyl-, -allyl-, and -propargyl-2,1-borazaronaphthalenes: Palladium-Catalyzed Cross-Couplings of 2-(Chloromethyl)-2,1-borazaronaphthalenes


Significance: The authors expanded the electrophilic nature of 2-(chloromethyl)-2,1-borazaronaphthalene. In addition to substitution reactions, now also several metal-catalyzed reactions were performed. Potassium (hetero)aryl and alkenyl trifluoroborates as well as terminal alkynes were successfully used as nucleophiles.

Comment: Impressively, a wide variety of substituted azaborines were prepared starting from one common azaborinyl building block. This new methodology gives access to a whole library of pseudobenzylic-substituted azaborines.

Selected examples:

- **80% yield**
- **58% yield**
- **67% yield**
- **70% yield**
- **90% yield**
- **80% yield**
- **83% yield**
- **79% yield**
Palladium-Catalyzed Cross-Coupling of Triorganoindium Reagents

**Significance:** The authors demonstrate that triorganoindium reagents react selectively with N-benzyl-2,4,5-triiodoimidazole under palladium catalysis to give the corresponding C-2-arylated coupling products in good yields. These products can further be used in a subsequent double cross-coupling to afford trisubstituted imidazoles in good yields.

**Comment:** This methodology was further applied to the synthesis of neurodazine, a biologically active compound which is able to specifically induce neurogenesis of non-pluripotent myoblasts and the cells derived from mature human skeletal muscle.

**Selected examples:**

- 

- 

83% yield

- 

78% yield

- 

83% yield

98% yield

90% yield
Nickel-Catalyzed Intramolecular Cyclization of Dihaloalkanes

**Significance:** The authors have developed an intramolecular cyclization of nitrogen- and carbon-tethered dihaloalkanes. The protocol is especially effective for five-membered rings and only moderately for six-membered rings. The reactions were performed under mild reactions conditions.

**Comment:** The coupling involving secondary alkyl halides appears to be more efficient than the cyclization of primary/primary alkyl dihalides. Interestingly, the construction of a seven-membered ring is less efficient. Side-reactions are intermolecular oligomerization and hydrodehalogenation of the substrate.

Palladium-Catalyzed Cross-Coupling of 1,1-Diboronates

Significance: The authors demonstrate a palladium(0)-catalyzed reaction of 1,1-diboronates with substituted vinyl bromides or dibromoalkenes to give 1,4-dienes or allenes in good yields while showing good functional group tolerance.

Comment: When using 1,1-dibromoalkenes bearing a terminal alkynyl group as the substrate, the palladium(0)-catalyzed coupling described above can be followed by a CuI-catalyzed allenation with N-tosylhydrazones to give unsymmetrical diallenes.

\[
\text{R}_1^1 \text{Br} + \text{Bpin} \underset{(0.75 \text{ equiv})}{\text{Bpin}} \text{R}_2^2 \quad \text{[Pd(P-t-Bu$_3$)$_2$]} (5 \text{ mol\%}) \quad \text{LiOH} (5.0 \text{ equiv}) \\
\text{1,4-dioxane-H}_2\text{O} \quad 25^\circ\text{C}, 1-12 \text{ h} \\
\text{R}_1^1 \text{R}_2^2 \quad \text{up to 94\% yield} \\
\]

Selected examples:

- 45\% yield, E/Z > 20:1
- 57\% yield, E/Z > 20:1
- 80\% yield, E/Z = 11:1

\[
\text{R}_1^1 \text{Br} + \text{Bpin} \underset{(1.5 \text{ equiv})}{\text{Bpin}} \text{R}_2^2 \quad \text{[Pd(PPh$_3$)$_4$]} (5 \text{ mol\%}) \quad \text{CsOH} (5.0 \text{ equiv}) \\
\text{1,4-dioxane-H}_2\text{O} \quad 25^\circ\text{C}, 12-24 \text{ h} \quad \text{up to 79\% yield} \\
\]

Selected examples:

- 74\% yield
- 79\% yield
- 76\% yield
Zirconium-Mediated Synthesis of Pyrroles

S. YU, M. XIONG, X. XIE, Y. LIU* (SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA)
Insertion of Nitriles into Zirconocene 1-aza-1,3-diene Complexes: Chemoselective Synthesis of N–H and N-Substituted Pyrroles

Significance: Liu and co-workers report the direct insertion of nitriles into zirconocene 1-aza-1,3-diene complexes for the synthesis of variously substituted N–H and N-substituted pyrroles in high yields.

Comment: The outcome of the reaction is determined by different cyclization patterns that depend on the relative stability and reactivity of the enamine–imine tautomers that are formed upon hydrolysis of the diazazirconacycles.

Zirconium-Mediated Synthesis of Pyrroles

1. R5CN (3 equiv) r.t., 1 h
2. HCl

products A
27–86% yield
products B
61–87% yield

R1 = Ph, Bn, 4-ClC6H4, 4-MeOC6H4
R2 = H, Me
R3 = H, Me, Hex, Ph
R4 = Ph, 4-BrC6H4, 4-FC6H4, 4-MeC6H4
R5 = Ph, Bn, variously substituted Ar, HetAr

Selected examples:
products A:

- 78% yield
- 86% yield
- 27% yield
- 46% yield
- 80% yield
- 61% yield
- 87% yield

products B:

- 87% yield
- 74% yield

Proposed mechanism:

Selected examples:

- R1 = Ph, Bn, 4-ClC6H4, 4-MeOC6H4
- R2 = H, Me
- R3 = H, Me, Hex, Ph
- R4 = Ph, 4-BrC6H4, 4-FC6H4, 4-MeC6H4
- R5 = Ph, Bn, variously substituted Ar, HetAr

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Trans-Selective Radical Silylzincation of Terminal Ynamides

Significance: The authors report a regio- and stereoselective silylzincation reaction of terminal ynamides using \((\text{Me}_3\text{Si})_3\text{SiH}\) and diethyl zinc. The resulting vinylzinc intermediates are trapped by a copper(I)-mediated substitution reaction to obtain Z-β-silylenamides in high yields.

Comment: The radical-chain process involves an addition of the \((\text{Me}_3\text{Si})_3\text{Si}\) radical to the ynamide to provide a Z-configured α-amino vinylic radical which reacts with the dialkylzinc reagent by homolytic substitution to afford a α-zincated β-silylenamide.

Selected examples:

- \((\text{Me}_3\text{Si})_3\text{Si}\) \(\rightarrow\) Et2Zn (3.0 equiv) \((\text{Me}_3\text{Si})_3\text{SiH}\) (1.3 equiv) then CuCN·2LiCl (3.0 equiv) \(R^3X\) (7.0 equiv) \(n\)-hexane, 0 °C then r.t.

41–88% yield

\(R^1, R^2 = \text{H, Me, } \text{i-Pr}\)
\(R^3 = \text{vinyl}\)
\(X = \text{Cl, Br, I}\)

Proposed mechanism:

\[\text{Et}_2\text{Zn} \rightarrow \text{Et}^- \rightarrow \text{Et}H \rightarrow \text{Zn}\]
Titanium-Mediated Cycloaddition

Significance: The authors describe a mild and efficient [3+2] cycloaddition of 2-(trifluoromethyl)-N-tosylaziridine to various nitriles using TiF₄ as a Lewis acid, to give the corresponding 4-(trifluoromethyl)-1,3-imidazolines in good yields and excellent regioselectivity.

Comment: From a mechanistic point of view, the authors assume that the aziridine is activated by TiF₄, which is then attacked by the nitrile to afford the betaine intermediate, which collapses to form the 1,3-imidazole.

Selected examples:

- R = Alk, Bn, Ar, HetAr
- one regiosomer up to 93% yield

80% yield
85% yield
93% yield
81% yield
91% yield
69% yield
Aryl Sulfamate and Tosylate Cross-Coupling with Aryl Grignard Reagents

**Significance:** The authors report the first iron-catalyzed direct coupling of aryl sulfamates and tosylates with aryl Grignard reagents. Interestingly, fluoride counterions were found to increase the yields of the desired products. FeF₃ does not need to be reduced before the reaction, and in fact, reactions performed without the pre-reduction proceed better in almost all cases.

**Comment:** The reaction was shown to tolerate a number of iron pre-catalysts with no significant homocoupling of the aryl Grignard. Studies to understand the reaction mechanism better are underway.

Selected examples:

- MeO 72% yield
- 90% yield
- 80% yield
- 46% yield
- 70% yield
- 87% yield
Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling

**Significance:** The authors developed a novel nickel-based catalyst for the cross-coupling of aryl and benzyl methyl ethers with organoboron reagents. The use of Ni(cod)$_2$ and 1,3-dicyclohexylimidazol-2-ylidene (A) gave the expected products in good yields while showing good functional group tolerance.

**Comment:** Notably, when using A instead of Cy$_3$P, heteroaryl ethers were coupled in good yields (up to 96%), while the same reaction with Cy$_3$P led to no product.

**Selected examples:**

- 76% yield
- 81% yield
- 76% yield
- 65% yield
- 80% yield
- 74% yield
Oxidative Amination of the Zinc Bromide Complex of β-Enamino Esters

**Significance:** Lee and co-workers report a tandem palladium-catalyzed intramolecular oxidative olefin amination of the zinc bromide complex of α-vinylated β-amino esters to afford various 2,3,4-trisubstituted pyrroles in good yields.

**Comment:** The synthetic utility of this efficient and atom-economical procedure is shown by the synthesis of pyrrolophenanthrenes and pyranopyrroloones through selective palladium- and copper-catalyzed C–C and C–O bond-forming reactions.

**Selected examples:**

- \( \text{R}_1\text{CN} \) in THF, reflux, 1 h
  - 1. Zn (2.0 equiv)
    - BrCH\(_2\)CO\(_2\)Et (1.5 equiv)
  - 2. \( \text{R}_2\text{CN} \) (1.1 equiv)
    - THF, 60 °C, 1–1.5 h

\[ \begin{array}{c}
\text{R}_1\text{CN} \\
\text{BrCH}_2\text{CO}_2\text{Et} \end{array} \]

\[ \begin{array}{c}
Pd(OAc)_2 (10 \text{ mol\%}) \\
\text{Cu(OAc)}_2 (2.2 \text{ equiv}) \\
\text{air, AcOH} (2.0 \text{ equiv}) \\
\text{DMF, 90 °C, 1–5 h} \end{array} \]

\[ \text{61–88% yield} \]

**R**\(_1\) = Alk, Ar, HetAr, Bn
**R**\(_2\) = Alk, Ar, CH\(_2\)CH\(_2\)Ph
Copper-Catalyzed Coupling of Indium Reagents

**Significance:** Giri and co-workers describe a copper(I)-catalyzed coupling of triorganoindium reagents with aryl iodides and bromides. This reaction shows high functional group tolerance, while being compatible with sterically hindered substrates, leading to the expected products in good yield.

**Comment:** The reaction can be performed with low catalyst loadings (2 mol%) and only requires 0.33 equivalents of the triorganoindium reagent with respect to the aryl halide.

**Selected examples:**

- **First example:**
  - Reaction conditions:
    - **Cul (2.5 mol%)**
    - **A or no ligand (2.5 mol%)**
    - **NaOMe or no base (1.0 equiv)**
    - DMF, 100 °C, 24 h
  - Result: up to 92% yield
  - **R** = Ar, Alk
  - **X** = Br, I

- **Second example:**
  - **80% yield**
  - **85% yield**
  - **74% yield**

- **Third example:**
  - **81% yield**
  - **87% yield**
  - **54% yield**

**SYNFACTS Contributors:** Paul Knochel, Jeffrey M. Hammann

**SYNFACTS** Contributors: Paul Knochel, Jeffrey M. Hammann

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Construction of a Tetrafluoroethylene-Bridging Structure via Carbocupration

**Significance:** The authors report the synthesis, characterization, and synthetic application of 2-aryl-1,1,2,2-tetrafluoroethane complexes. Starting with a carbocupration of tetrafluoroethylene (TFE), a variety of 1,2-difunctionalized 1,1,2,2-tetrafluoroethanes were prepared in high yields.

**Comment:** The molecular structure of the aryl–TFE–copper species was determined by X-ray crystallography and NMR analysis. Furthermore, the synthetic utility for liquid-crystalline compounds bearing a tetrafluoroethylene-bridging structure was demonstrated.