Deaminative Functionalization of Primary Alkyl Amines by a Radical Mechanism

Group Literature Meeting
Kate Berger
April 2, 2020
Alkyl Radical Functionalization

Conversion to alkanes by use of a hydrogen atom transfer reagent (HAT)
- C-C bond formation by numerous methods including
Giese type coupling with olefins,
Minisci type coupling with aromatics and Ni catalyzed transformations


Demand for Deaminative Functionalization

“As an example of their prevalence, a search of Pfizer’s internal chemical store revealed over 47,000 alkyl primary amines vs about 28,000 primary and secondary alkyl halides.”

Diazotization: R is arene only, harsh conditions, explosion risk

X: halide, alcohol, nitrile

Deaminative Radical Functionalization

- Deamination to produce alkyl radical species has the potential to convert primary amines to a wide range of functional groups.
- Recent advances in radical deaminative functionalization have resulted in new methods for C-C, C-B, and C-S bond formation.
- Organized broadly by method: Ni catalyzed cross coupling and photoredox.

For two recent reviews see:
Pang, Y.; Moser, D.; Cornella, J., Pyrylium Salts: Selective Reagents for the Activation of Primary Amino Groups in Organic Synthesis. Synthesis 2020, 52 (04), 489-503
Early Attempts at Radical Deamination

**Barton-McCombie Deoxygenation**

\[ \text{OH} \rightarrow \text{O} \rightarrow \text{AIBN} \rightarrow \text{H} \]

**Barton-Saegusa Deamination**

Later expanded to other radical reagents including hypophosphorus acid

Reductive Amination with Katritzky Salts

![Chemical Structure]

Thermolysis and pyrolysis of 1,4-dihydropyridines
(22a, c, d, f—j)

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Product a</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(22a) n-C₈H₁₃</td>
<td>180</td>
<td>4</td>
<td>n-Hexane</td>
<td>58</td>
</tr>
<tr>
<td>(22c) n-C₈H₁₇</td>
<td>180</td>
<td>4</td>
<td>n-Octane</td>
<td>88</td>
</tr>
<tr>
<td>(22d) PhCH₂</td>
<td>200</td>
<td>5</td>
<td>Toluene</td>
<td>44</td>
</tr>
<tr>
<td>(22f) ClC₆H₄CH₃(ρ)</td>
<td>220</td>
<td>2</td>
<td>4-Chlorotoluene</td>
<td>62</td>
</tr>
<tr>
<td>(22g) PhCH₂CH₂</td>
<td>180</td>
<td>2</td>
<td>Ethylbenzene</td>
<td>64</td>
</tr>
<tr>
<td>(22h) Ph</td>
<td>230</td>
<td>2</td>
<td></td>
<td>b</td>
</tr>
<tr>
<td>(22i) 2-Pyridyl</td>
<td>&gt;300</td>
<td>0.5</td>
<td>Benzene</td>
<td>54</td>
</tr>
<tr>
<td>(22j) Pyrimidin-2-yl</td>
<td>&gt;300</td>
<td>0.5</td>
<td>Pyridine</td>
<td>c</td>
</tr>
</tbody>
</table>


Katritzky Salts: Evidence for a Radical Mechanism

Modern Applications of Katritzky Salts: Ni Cross Coupling

Functional Group Tolerance: esters, amides, nitriles

Modern Applications of Katritzky Salts: Ni Cross Coupling
Additional Cross Coupling Examples


Deaminative Cross Coupling via Hydroboration

Reductive Cross Couplings of Halides


Functional group tolerance: ketones, nitriles, ethers, thiophene, pyridine, alcohol,

intermediate. In support of the oxidative addition of the aryl bromide, 24% yield of product 4 is observed when tetrakis-(dimethylamino)ethylene (TDAE) is used in place of Mn⁰, suggesting an arylmanganese intermediate is not required (Scheme 5B). The intermediacy of alkyl radical 28 is consistent with the observed opening of cyclopropylmethylpyridinium 3s and the formation of TEMPO-trapped adduct 32.
Reductive Cross Couplings of Halides: DFT Mechanism

Scheme 3  DFT-Computed energy profile for the nickel-catalyzed reductive cross-coupling reaction of aryl halides and pyridinium salts. Free energies in solution (in kcal mol$^{-1}$) at the SMD(DMA)-M06/Def2-QZVPP//ωB97x-D/Def2-TZVP(Ni,Mn)/Def2-SVP (non-metal) level are displayed.

Cis-Hydroalkylation of Alkynes

Functional group tolerance: amides, esters, sulfides, alcohol

Scheme 3  Further investigation on regioselectivity.
Negishi Alkyl-Alkyl Cross Coupling

Reaction Scope:
- primary and secondary alkyl pyridinium salts
- tolerance for benzodioxole, thiophene, pyridine, pyrimidine, azetidine rings
- acetal, ester, nitrile, oxetane
- methylzinc iodide can also be coupled resulting in NH$_2$ being replaced by CH$_3$ isostere
- borylation by methylpinacolboronatezinc bromide

Scheme 4. One-Pot Activation and Cross-Coupling

Deaminative Alkoxy carbonylation

Functional group tolerance:
- indole substituted primary alkyl amine
- ether, bromide, chloride
- cannot have EWG such as nitro

Modern Applications of Katritzky Salts: Photoredox

Photoredox Alkynylation

Functional group tolerance:
- alcohol, bromide, chloride, thiophene

Scheme 3. Scope of Deaminative Alkenylation

Photoredox Deaminative Carbonylative Alkyl-Heck

Functional group tolerance:
- nitriles, esters
Mostly use symmetrical alkenes

Scheme 2. Proposed mechanism.

Three Component Dicarbofunctionalization

Scheme 4. Proposed Mechanism of the Deaminative Dicarbofunctionalization Using Katritzky Salts as Radical Precursors

Deaminative Borylation via an EDA Complex


quantum yield of 7
Deaminative Borylation via an EDA Complex

![Chemical structures and reaction scheme](image)

**Functional Group Tolerance:**
ester, nitrile, sulfonamide, alcohols

---

**Table 2. Substrate Scope**

<table>
<thead>
<tr>
<th>Secondary alkyl:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structures" /></td>
<td></td>
</tr>
<tr>
<td>7: 81% (82%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8: 72%</td>
</tr>
<tr>
<td>9: 76%</td>
<td>10: 84%</td>
</tr>
<tr>
<td>11: 71%</td>
<td>12: 63%</td>
</tr>
<tr>
<td>13: 59%, 80:20 d.r.</td>
<td>14: 70%, 56:44 d.r.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary alkyl:&lt;sup&gt;b&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structures" /></td>
<td></td>
</tr>
<tr>
<td>15: 74%</td>
<td>16: 51%</td>
</tr>
<tr>
<td>17: 73%</td>
<td>18: 67%</td>
</tr>
<tr>
<td>19: 54%</td>
<td>20: 55%</td>
</tr>
<tr>
<td>21: 68%</td>
<td>22: 52%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TBSO&lt;sub&gt;a&lt;/sub&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structures" /></td>
<td></td>
</tr>
<tr>
<td>23: 51%</td>
<td>24: 24% (61%)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>25: 62%</td>
<td>26: 62%</td>
</tr>
<tr>
<td>27: 63%</td>
<td>28: 66%</td>
</tr>
<tr>
<td>29: 31%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Natural products:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Chemical structures" /></td>
<td></td>
</tr>
<tr>
<td>33: 67%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(from ornithine)</td>
</tr>
<tr>
<td>34: 58%, 96% &lt;sup&gt;ee&lt;/sup&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(from lysine)</td>
</tr>
<tr>
<td>35: 68%, &gt;95.5 d.r.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(from pinanamine)</td>
</tr>
<tr>
<td>36: 55%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(from leelamine)</td>
</tr>
<tr>
<td>37: 76%, 95.5 d.r.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(from hecogenin)</td>
</tr>
<tr>
<td>38: 80%, 92.8 d.r.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(from figogenin)</td>
</tr>
</tbody>
</table>

Deaminative Borylation via an EDA Complex

Other Deaminative Functionalizations via an EDA Complex

Functional group tolerance: esters, silyl, boryl, alcohol

Other Deaminative Functionalizations via an EDA Complex

Figure 4. Proposed mechanism for the photoinduced thioesterification.

Used a variety of amino acid derivates with carboxylic acid protected

Deaminative Borylation by a Lewis Base

Figure 2. Gibbs free energy profile for the dtpby induced cleavage of the B–B bond of B$_2$cat$_2$ (all energies are given in kcal mol$^{-1}$).

You Guessed It: Dual Photoredox Ni Cross Coupling

\[ \text{NC} \quad \text{Br} \quad + \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{BF}_4^- \quad \text{Ph} \quad \text{CN} \]

5 mol\% NiBr$_2$(dtbbpy)  
3 mol\% 4CzIPN  
3 NEt$_3$  
THF  
bleuclight, 24 h

Scheme 5. Reductive Nickel/Photoredox Dual Catalysis: Mechanistic Rationale
There is clearly a high demand for new radical deaminative strategies because when one new strategy was reported it led to an explosion of new research.