Practical and economic lithiations of functionalized arenes and heteroarenes using Cy2NLi in the presence of Mg, Zn or La halides in a continuous flow†‡

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The economic amide base lithium dicyclohexylamide (Cy2NLi) allows fast and convenient (40 s, 0 °C) in situ trapping flow metatlations of a broad range of functionalized arenes, heteroarenes and acrylate derivatives in the presence of various metal salts (ZnCl2, 2LiCl, MgCl2, LaCl3, 2LiCl). The resulting Zn-, Mg- or La-organometallic intermediates are trapped with various electrophiles in high yields. These flow metatlations are easily scaled-up without further optimization.

Introduction

The lithiation of arenes and heteroarenes is a common method for the functionalization of unsaturated molecules.1 Pioneering work of Snieckus2 and others3 have demonstrated the utility of aromatic lithiations for the preparation of pharmaceutical and agrochemical targets. Nevertheless, the use of powerful lithium bases has some drawbacks such as low metatlation temperatures and a moderate functional group tolerance. Also, it requires a careful choice of the lithium base used for the metatlation step.

Recently, we have shown that an in situ trapping metatlation sequence using TMPli (TMP = 2,2,6,6-tetramethylpiperidyl) allows the performance of selective lithiations of various arenes and heteroarenes at 0 °C within 40 s if conducted in a continuous flow system (Scheme 1).4,5 Under conventional batch conditions, these in situ trapping metatlations require cryogenic temperatures (−78 °C) in order to avoid unwanted side reactions or decomposition of the organometallic intermediate. Furthermore, the scale-up of these batch metatlations proved to be difficult, requiring much optimization. Despite the convenient reaction conditions in flow mode, the use of stoichiometric amounts of TMPli makes this lithiation still expensive (TMPH = ca. 630 $ mol⁻¹).6 The steric hindrance of the TMP-moiety was required in order to avoid side-reactions. Due to the fast mixing of the reaction components and the prevention of hot spot formation,7 such highly sterically hindered bases may no longer be mandatory when using the flow methodology.8 Preliminary experiments attempting to perform metatlations of various aromatics using cheaper readily available lithium or other metallic amides R₂NMet (R = iPr (isopropyl), Cy (cyclohexyl), TMS (trimethylsilyl); Met = Li, MgHal, ZnHal) were disappointing either due to insufficient reactivity or unwanted side-reactions. The in situ trapping methodology developed in our laboratory, in which we mix the aromatic substrate with a metallic salt and add TMPli proves to be compatible with the replacement of TMPli with much cheaper bases, since this Barbier-type lithiation minimizes the contact time of the lithium base with the aromatic substrate. The replacement of TMPli by Cy2NLi is of special importance since the price of the corresponding amine Cy2NH (ca. 6.40 $ mol⁻¹) is only ca. 1% of TMPH.9,10

Herein we wish to report the use of the economic amide base lithium dicyclohexylamide (Cy2NLi) instead of TMPli for in situ trapping metatlations under continuous flow conditions. Cy2NLi has – to the best of our knowledge – not yet been used for extensive lithiations of functionalized arenes and heteroarenes.10

Scheme 1. Continuous flow set-up for in situ trapping metatlations using TMPli in the presence of metal salts (Met-X = ZnCl2, 2LiCl, MgCl2, CuCN, 2LiCl, LaCl3, 2LiCl) and subsequent batch quenching with electrophiles (E*).
Results and discussion

In a first experiment, we have metalated 1-bromo-4-fluorobenzene (1a) under flow conditions (Scheme 2). Thus, 1a (1.0 equiv.) was mixed with ZnCl₂·2LiCl (0.5 equiv.) and submitted to flow metatation at 0 °C (40 s) using respectively TMPLi and Cy₂NLi. The corresponding arylzinc intermediate (2) was quenched via a Pd-catalyzed Negishi cross-coupling in a batch reactor containing ethyl 4-iodobenzoate (0.8 equiv.) and a standard Pd-catalytic system (2 mol% Pd(dba)₂; dba = dibenzylideneacetone and 4 mol% P(2-furyl)₃) providing the expected biphenyl (3a) in 93% (using TMPLi) and 97% (using Cy₂NLi) yield. Like for reactions with TMPLi, in situ trapping metatalations with Cy₂NLi can be simply scaled up without further optimization just by running the reaction for a longer time. Therefore, the reaction of 2 with 3-iodoanisole (0.8 equiv.) affords after a Negishi cross-coupling the expected product 3b in 97% yield on a 1.7 mmol scale and in 95% yield on a 11 mmol scale (Table 1, entry 1).

Using Cy₂NLi for the ortho-lithiation of 1,3-dihaloarenes (1b, c) abstracts under our standard reaction conditions (0 °C, 40 s) the most acidic hydrogen at position 2. In situ transmetalations with ZnCl₂·2LiCl or MgCl₂ (0.5 equiv., respectively) generate the corresponding aryl-zinc and -magnesium species, which are quenched in subsequent batch reactions with aryl iodides (0.8 equiv.), S-phenyl benzenethiosulfonate (0.8 equiv.) and ethyl cyanoformate (0.8 equiv.) leading to the trisubstituted arenes (3c-f) in 67–98% yield (entries 2–5). The in situ metalations with Cy₂NLi are not limited to haloarenes, and sensitive functionalities such as esters and nitriles are tolerated as well. Thus, diethyl 4-bromoisophthalate (1d) is smoothly flow-zincated in position 6 and a Negishi cross-coupling with ethyl 4-iodobenzoate (0.8 equiv.) produces the expected triester (3g) in 72% yield (entry 6). Similarly, substituted nitriles such as 1e and 1f are in situ metalated in the presence of ZnCl₂·2LiCl (0.5 equiv.) within 40 s at 0 °C, and subsequent quenching reactions with aryl iodides (0.8 equiv.) having either electron-donating or electron-withdrawing substituents lead to the cyano-substituted biphenyls (3h-j) in 70–97% yield (entries 7–9).

Table 1  Continuous flow trapping metatalation of arenes 1 followed by reaction with electrophiles leading to products of type 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Electrophile</th>
<th>Product*</th>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>3b: 97%</td>
<td>(95%)*</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>3c: 98%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>3d: 75%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>3e: 94%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>3f: 67%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>3g: 72%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1e</td>
<td>3h: 70%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1f</td>
<td>3i: 97%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1f</td>
<td>3j: 73%</td>
<td></td>
</tr>
</tbody>
</table>

*a Yield of isolated product. † ZnCl₂·2LiCl (0.5 equiv.) was used. ‡ MgCl₂ (0.5 equiv.) was used. § Obtained using 2% [Pd(dba)₂] and 4% P(2-furyl). ¶ Yield obtained on a 11 mmol scale.

Scheme 2  Continuous flow in situ trapping zincation of 1-bromo-4-fluorobenzene (1a) using TMPLi and Cy₂NLi and subsequent Pd-catalyzed Negishi cross-coupling with ethyl 4-iodobenzoate in a batch reactor.
This in situ trapping methodology with Cy₂NLi in a flow reactor is not limited to functionalized arenes. In fact, it can be readily extended to a broad range of sensitive, electron-deficient heteroarenes (Table 2). Thus, 2-fluoropyridine (4a), which is notoriously difficult to metalate, undergoes a smooth zincation or magnesiation in position 3 in the presence of ZnCl₂·2LiCl or MgCl₂ and quenching with ethyl 4-iodobenzoate (0.8 equiv.) or S-methyl methanethiosulfonate (0.8 equiv.) produces the disubstituted pyridines (5a, 5b) in 75–94% yield (entries 1 and 2). However, using our standard conditions, 2,6-dibromopyridine (4b) is in situ metalated in position 4 and a subsequent Negishi cross-coupling with ethyl 4-iodobenzoate affords the desired pyridine (5c) in 67% yield (entry 3). Similarly, ethyl 2-chloronicotinate (4c) is flow-zincated within 40 s at 0 °C in position 4 affording the trisubstituted pyridine (5d) in 88% yield after a Cu-mediated allylation with 3-bromocyclohexene (0.8 equiv.; entry 4). The sensitive 2,3-dichloropyrazine (4d) is in situ metalated in position 3 and a subsequent Negishi cross-coupling with ethyl 4-iodobenzoate (0.8 equiv.) affords the desired pyrazine (5e) in 67% yield (entry 5). The in situ trapping metalations with Cy₂NLi can also be used for the functionalization of a broad range of substituted 5-membered ring heterocycles. Thus, the lanthanation of 1-methylpyrazole (4e) in the presence of LaCl₃·2LiCl (0.5 equiv.) under standard conditions (0 °C, 40 s) produces the desired alcohol (5f) in 62% yield after addition to p-chlorobenzaldehyde (0.8 equiv.; entry 6).

Ethyl 5-bromo-2-furoate (4f) is regioselectively flow metalated in position 3.
position 3 and a subsequent Cu-catalyzed reaction with 3-bromocyclohexene (0.8 equiv.) leads to the trisubstituted furan (5g) in 76% yield (entry 7). The in situ trapping zirconation of 2-bromothiophene (4g) within 40 s at 0 °C abstracts the most acidic hydrogen at position 5 affording the 2,5-disubstituted thiophenes (5h, i) in 89–91% yield after Negishi cross-couplings with 4-iodobenzotrifluoride (0.8 equiv.) and 1-iodo-3-nitrobenzene (0.8 equiv.; entries 8 and 9).

To demonstrate the broad practicability of the in situ trapping metallocations with Cy2NLi, we investigated the functionalization of acyclic acrylate derivatives, which are prone to polymerize. However, submitting a mixture of (E)-methyl 3-methoxyacrylate (6) with MgCl2 (0.5 equiv.) to the flow metallocation with Cy2NLi (1.5 equiv.) for 40 s at 0 °C leads to the formation of the magnesium intermediate 7 in high conversion (Scheme 3). Subsequent reaction of 7 with 2,6-dichlorobenzaldehyde (0.8 equiv.) produces the lactone 8 in 65% yield. Similarly, (E)-ethyl 3-(dimethylamino)acrylate (9) is in situ metallated at 0 °C, 40 s in the presence of MgCl2 or ZnCl2·2LiCl (Scheme 4). The corresponding magnesium (10) and zinc (12) organometallic intermediates undergo various quenching reactions, such as an addition to 4-(trifluoromethyl)benzaldehyde (0.8 equiv.) and a Negishi cross-coupling with 4-iodobenzotrifluoride (0.8 equiv.), providing the corresponding lactone (11) and the ester 13 in 62–70% yield.

Conclusions

In summary, the economic amidic base lithium dicyclohexyl- amide (Cy2NLi) undergoes fast and convenient (40 s, 0 °C) in situ trapping flow metallocations of a broad range of functionalized arenes, heteroarenes and acrylate derivatives in the presence of various metal salts (ZnCl2·2LiCl, MgCl2, LaCl3·2LiCl). The resulting Zn-, Mg- or La-organometallic intermediates are trapped with numerous electrophiles in high yields. These flow-metallocations are easily scaled-up without further optimization simply by running the reaction for a longer time. Further applications and extensions of this method are currently underway.

Notes and references


6 The price of the corresponding amine TMPH from Sigma-Aldrich is ca. 630 S mol⁻¹ for the largest package.


The price of the corresponding amine Cy2NH from Sigma-Aldrich is ca. 6.40 $ mol\(^{-1}\) for the largest package.


Flow reactions were performed with commercially available equipment from Uniqsis Ltd (FlowSyn; http://www.uniqsis.com).

