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Chiral Diarylmethanes via Copper-Catalyzed Asymmetric Allylic Arylation with Organolithium Compounds

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Supporting Information

ABSTRACT: A highly enantioselective copper/N-heterocyclic carbene catalyzed allylic arylation with organolithium compounds is presented. The use of commercial or readily prepared aryllithium reagents in the reaction with allyl halides affords a variety of chiral diarylmethines, comprising a privileged structural motif in pharmaceuticals, in high yields with good to excellent regio- and enantioselectivities. The versatility of this new transformation is illustrated in the formal synthesis of the marketed drug tolterodine (Detrol).

The enantioselective synthesis of diarylmethane tertiary stereogenic centers, a structural motif that is present in many natural products and pharmaceuticals, has attracted considerable attention in recent years. Examples of compounds bearing this subunit include podoflox (Condylox), nomifensine, CDP-840, (+)-sertraline (Zoloft), and (R)-tolterodine, the latter being a drug with blockbuster status. Catalytic asymmetric synthesis methods to access these compounds comprise both stereospecific and enantioselective transformations. The first approaches, based on chiral starting materials, include a nickel-catalyzed cross-coupling of 1,1-diaryl ethers described by the group of Jarvo and a stereoregulative rhodium-catalyzed decarbonylation of enantioenriched β,β-diarylpropionaldehydes reported by the group of Carreira. Catalytic enantioselective strategies include Friedel–Crafts reactions, iridium-catalyzed asymmetric hydrogenation of 1,1-diarylalkenes, a cooperative rhodium/phosphoric acid-catalyzed asymmetric arylation of α-aryl-α-diazo compounds with aniline derivatives, and a copper-catalyzed enantioselective electrophilic arylation of allylic amides with diarylalkonium salts. Another attractive approach has been reported by Fu and co-workers, where racemic benzylic alcohols were converted into 1,1-diarylalkenes using an enantioselective nickel-catalyzed cross-coupling protocol.

Transition-metal-catalyzed 1,4-addition of organoboron compounds to substituted electron-deficient styrenes has also been shown to be effective in accessing this structural motif, in particular using a rhodium-based catalyst. Additionally, the catalytic enantiotopic group selective cross-coupling of achiral geminal bis(pinacolboronates) and the recently developed additions of malonates or boron reagents to quinone methides provide useful chiral gem-diarylmethines and boronic esters derivatives.

Diarylmethane stereogenic centers can also be accessed via metal-catalyzed arylation of aryl-substituted allyl electrophiles using organometallic reagents. We envisioned that an asymmetric allylic arylation (AAAr) with highly reactive aryllithium reagents, as presented here, would provide a viable and attractive alternative to access these chiral structures. In the case of copper, the use of the corresponding alkyl nucleophiles has been well established, and AAA reactions of a wide range of alkyl metal reagents and allylic systems have been reported. In contrast, the introduction of less reactive aryl groups continues to provide major challenges, and several groups embarked on the development of a general and efficient catalytic system for the formation of chiral diarylmethanes based on this transformation. High regio- and enantioselectivity was demonstrated by Hoveyda and co-workers using chiral bidentate N-heterocyclic carbenes (NHC) for the AAAr with aryl dialkylaluminum reagents derived from the corresponding organolithium compounds. Bidentate NHC have also been employed by the group of Hayashi in the allylic substitution with less reactive aryllithium reagents. Additionally, aryl Grignard reagents have been employed by Tomioka and co-workers using chiral monodentate N-heterocyclic carbenes.

Recently, we reported that organolithium compounds, among the most widely used reagents in organic synthesis, can be directly used as nucleophiles in copper-catalyzed AAA with a variety of allyl systems. The use of Taniaphos or monodentate NHC for the AAAr with aryldialkylaluminum reagents, derived from the corresponding organolithium compounds. Bidentate NHC have also been employed by the group of Hayashi in the allylic substitution with less reactive aryllithium reagents. Additionally, aryl Grignard reagents have been employed by Tomioka and co-workers using chiral monodentate N-heterocyclic carbenes.

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for other organometallic compounds (Al, B, Zn), the development of a general AAAr method using these reagents is highly desirable.

Herein, we report the first regio- and enantioselective method for the copper-catalyzed AAAr with aryllithium compounds to afford optically active diarylvinylmethanes with excellent regio- and enantioselectivities (S<sub>2</sub>:S<sub>2</sub>' up to 98:2, er up to 97:3).

The reaction between allyl bromide 1a and commercially available PhLi, in the presence of catalytic amounts of CuBr-SMe<sub>2</sub> and chiral ligands, was used for the initial optimization (Table 1).<sup>11a</sup> PhLi was diluted with hexane and added over 2 h to a solution of allyl bromide in CH<sub>2</sub>Cl<sub>2</sub>. The presence of chloro or bromo substituents at the aromatic ring of the substrate were well tolerated, affording the corresponding diarylvinylmethanes in high yields and selectivities and providing synthetically useful functionalities for further transformations (2a−d). Importantly, no evidence of lithium−halogen exchange was observed, highlighting the high chemoselectivity of the reaction. Trifluoromethylated and fluorinated compounds, which are very important in the agrochemical and pharmaceutical industries,<sup>15</sup> also were suitable substrates furnishing the corresponding gem-biaryl products with excellent selectivities (2e−g). High selectivities were also obtained when electron-donating substituents (1h, 1i, and 1k) or sterically demanding substrates such as 1-naphthyl-substituted allyl bromide (1i) or compounds 1j and 1k were used with this Cu−NHC-based catalyst system. Aarylation of compound 1l was accomplished with good regio- and enantioselectivity, providing 2l, which is an advanced intermediate in the synthesis of complex derived from L6 gave the same result, avoiding the use of NaOtfBu and simplifying the procedure (entry 7).

Having established optimal conditions, we next investigated the substrate scope and generality of this arylation reaction by using PhLi; the results are summarized in Scheme 1.

**Scheme 1. Substrate Scope for the Cu-Catalyzed Enantioselective Allylic Arylation**

Table 1. Screening of Different Ligands<sup>11a</sup>

<table>
<thead>
<tr>
<th>entry</th>
<th>L</th>
<th>[Cu]</th>
<th>2a:3a&lt;sup&gt;fi&lt;/sup&gt;</th>
<th>2a, er&lt;sup&gt;er&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>CuBr-SMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>10:90</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>CuBr-SMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>70:30</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>CuBr-SMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>47:53</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>CuBr-SMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>37:63</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>CuBr-SMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>63:37</td>
<td>94:6</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>CuBr-SMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>97:3</td>
<td>97:3</td>
</tr>
<tr>
<td>7</td>
<td>CuCl&lt;sub&gt;2&lt;/sub&gt;L6</td>
<td>CuBr-SMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>97:3</td>
<td>97:3</td>
</tr>
</tbody>
</table>

<sup>11a</sup>Conditions: allyl bromide (0.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). PhLi (0.3 mmol, 1.8 M solution in dibutyl ether diluted with hexane to a final concentration of 0.4 M) added over 2 h. All reactions gave full conversion. 2a:3a ratios and conversions determined by GC−MS and 1H NMR spectroscopy. Determined by chiral HPLC after conversion to the corresponding primary alcohol using a hydroboration−oxidation procedure (see the SI).

The presence of chloro or bromo substituents at the aromatic ring of the substrate were well tolerated, affording the corresponding diarylvinylmethanes in high yields and selectivities and providing synthetically useful functionalities for further transformations (2a−d). Importantly, no evidence of lithium−halogen exchange was observed, highlighting the high chemoselectivity of the reaction. Trifluoromethylated and fluorinated compounds, which are very important in the agrochemical and pharmaceutical industries,<sup>15</sup> also were suitable substrates furnishing the corresponding gem-biaryl products with excellent selectivities (2e−g). High selectivities were also obtained when electron-donating substituents (1h, 1i, and 1k) or sterically demanding substrates such as 1-naphthyl-substituted allyl bromide (1i) or compounds 1j and 1k were used with this Cu−NHC-based catalyst system. Aarylation of compound 1l was accomplished with good regio- and enantioselectivity, providing 2l, which is an advanced intermediate in the synthesis of complex derived from L6 gave the same result, avoiding the use of NaOtfBu and simplifying the procedure (entry 7).

Having established optimal conditions, we next investigated the substrate scope and generality of this arylation reaction by using PhLi; the results are summarized in Scheme 1.
sertraline, a major pharmaceutical for the treatment of depression. Compound 2k bearing m-methyl and o-methoxy substituents at the aryl ring was also prepared with excellent regio- (97:3) and enantioselectivity (96:4) serving as precursor for the synthesis of (R)-tolterodine (see below). Importantly, when this reaction was performed on a larger scale (5 mmol, 1.2 g), using a lower catalyst loading (3 mol %), product 2k was still obtained with the same selectivities without erosion of yield. Allylic bromides bearing a phenol ether or protected amine provided highly functionalized chiral building blocks 2m and 2n, with excellent yields and regioselectivity although the enantioselectivity decreased slightly. The use of a dioxolane-containing allylic bromide 1o led to the diastereoselective formation of valuable 1,2-hydroxyallyl moiety 2o with excellent stereocontrol for the anti-isomer.

We next explored the scope of the reaction with respect to the aryllithium component using 1a as the electrophilic counterpart. However, to our surprise, no conversion was observed when p-tolylthioliium or (p-methoxyphenyl)lithium solutions, prepared in THF via bromide—lithium exchange using t-BuLi, were employed in the reaction under previously optimized conditions (entries 1 and 2, Table 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>Lithiation cond (final conc, M)</th>
<th>Conv (%)</th>
<th>2a/2a ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>t-BuLi, −30 °C to rt, 1 h 1:2 THF/pentane (0.57)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>t-BuLi, −30 °C to rt, 1 h 1:2 THF/pentane (0.57)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>t-BuLi, −30 °C to rt, 1 h 1:2 Et3O/pentane (0.57)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Li</td>
<td>Et3O, rt, 2 h (1.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Li, Et3O, rt, 2 h (1.5)</td>
<td>47/95:5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi, −30 °C to rt, 1 h 4:3 Et3O/hexane (0.69)</td>
<td>&gt;99/85:15, 2a 97:3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. Screening of Different Conditions for the Preparation of Reactive Homemade Aryllithium Compounds

Changing THF to less coordinating Et3O as solvent led to the same result (entry 3, Table 2). As the use of t-BuLi to effect lithium—halogen exchange generates 1 equiv of 2-methylpropane, which may coordinatively interfere with the Cu catalyst, we decided to use a different method for the lithiation. Lithium metal in combination with p-bromotoluene was still unsatisfactory, although the use of p-chlorotoluene allowed us to reach 47% conversion in the corresponding AAR reaction (entry 5). Finally, we found that the use of n-BuLi and Et3O as solvent, which avoids SN2 reaction of the resulting ArLi and n-BuBr, allowed us to obtain the desired product with full conversion and high regio- and enantioselectivity (entry 6, Table 2, and 2p, Scheme 2). Under these conditions, aryllithiums bearing electron-donating methoxy- and alkyl groups as well as electron-withdrawing −CF3 substituents participate in the reactions with allyl bromides 1a−f in good to excellent yields and regio- and enantioselectivities (Scheme 2). A limitation found for this Cu−NHC-based catalytic system is that the use of o-methoxy-substituted phenyllithium suffered from diminished enantioselectivity as seen for compound 2v.

In summary, the highly enantioselective Cu-catalyzed direct allylic arylation using organolithium compounds has been described. The use of readily available aryllithium reagents in combination with allyl bromides and use of a copper−NHC catalyst are key factors for the success of this reaction. The only stoichiometric waste produced in this novel transformation is LiBr. The use of n-BuLi was found to be essential for the

Scheme 2. Scope of Aryllithium Compounds

Scheme 3. Conversion of (R)-2k into (R)-4k, a Synthetic Intermediate of Tolterodine

In summary, the highly enantioselective Cu-catalyzed direct allylic arylation using organolithium compounds has been described. The use of readily available aryllithium reagents in combination with allyl bromides and use of a copper−NHC catalyst are key factors for the success of this reaction. The only stoichiometric waste produced in this novel transformation is LiBr. The use of n-BuLi was found to be essential for the
preparation of aryllithium compounds. The broad substrate and reagent scope and the application of the new method in the formal catalytic enantioselective synthesis of (R)-tolterodine illustrates the potential of this allylic arylation for the synthesis of important chiral diarylmethane structures.

**ASSOCIATED CONTENT**

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03396.

Experimental procedures and characterization data (PDF)

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Notes
The authors declare no competing financial interest.

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