Asymmetric Allylic Alkylation of Acyclic Allylic Ethers with Organolithium Reagents
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Asymmetric allylic substitution is one of the most powerful synthetic transformations with numerous applications in the total synthesis of biologically active compounds and natural products.[1] The use of metal complexes such as Pd,[2] Mo,[3] or Ir,[4] in combination with mainly allylic carbonates or acetates represents an excellent methodology for the use of stabilized nucleophiles in this transformation. On the other hand, Cu-catalyzed asymmetric allylic alkylation (AAA)[5–7] is characterized by the formation of C–C bonds with organometallic reagents. Allylic substrates with good leaving groups, such as allylic halides[6] and allylic phosphates,[7] are typically used in these transformations. A major challenge is to accomplish similar catalytic AAA by using allylic substrates with robust protecting groups. In synthesis it might also offer new opportunities if otherwise inert stable protecting groups can be used as leaving groups in later stages of synthetic schemes to perform enantioselective C–C bond formation through asymmetric allylic substitution. A possible strategy will be to apply asymmetric allylic alkylation of quite stable alkyl/aryl protected allylic ethers. Nevertheless their low reactivity is a major limitation to further synthetic schemes to perform enantioselective AAA by using allylic substrates with robust protecting groups. In synthesis it might also offer new opportunities if otherwise inert stable protecting groups can be used as leaving groups in later stages of synthetic schemes to perform enantioselective C–C bond formation through asymmetric allylic substitution. A possible strategy will be to apply asymmetric allylic alkylation of quite stable alkyl/aryl protected allylic ethers. Nevertheless their low reactivity is a major limitation towards their use in allylic alkylation.[8–11] A few non-enantioselective examples of allylic alkylation were described by using allylic ethers including -OMe,[9] -OPh,[9] -OPy in combination with metals such as Cu,[9] Ni,[9] Zr,[9] Co[11] and Rh.[11] As far as we know, the only examples of AAA of allylic ethers were reported by Okamoto et al.[16] using pyridylethers (Cu), and Consiglio et al.[19] with phenyl-ethers (Ni), both in combination with Grignard reagents and with moderate enantiomeric ratios (e.r.). Oxabicyclic alkenes, studied by Lautens[12–c] and others,[12–d] containing a strained bridgehead ether linkage, represent a special case and their particular structural properties were found to be the driving force for their unusual reactivity. Despite the excellent results achieved, their application seems limited to specific cyclic substrates.[12] Therefore, it remains to be established if the satisfactory implementation of asymmetric catalysis to simple acyclic allylic ethers, in which the stable protecting groups is transformed into a leaving group and a stereogenic center is generated, can be accomplished.

Recently, we reported the first example on the application of organolithium reagents in a highly enantioselective catalytic asymmetric allylic alkylation of allylic halides.[13] We have anticipated that the use of organolithium reagents in combination with Lewis acids will be the key to address very low reactivity of acyclic allylic ethers in asymmetric allylic alkylation.[8a,12d]

Herein, we report for the first time that organolithium reagents in combination with a Lewis acid and copper/phosphoramidite catalysis allow to use stable allylic ethers (-OMe, -OBn) in asymmetric allylic alkylation and affords S,S,S products with excellent regio- and enantioselectivity (Scheme 1).

![Scheme 1. Asymmetric allylic alkylation of acyclic allylic ethers.](image-url)

We started our investigation by testing various allylic groups (-OR) in combination with a Lewis acid under the conditions of the copper-catalyzed allylic alkylation (in this case using CuBr2·SMO2 in combination with phosphoramidite L1[14]) and n-butyllithium as the Lewis acid because it is compatible with organolithium and organocopper reagents.[8a,12d]

Allylic esters (-OBz and -OAc) led to low conversions, and a mixture of the ester and corresponding allyl alcohol was recovered from the reaction. The use of allylic ethers, such as -OPh, -OTHP, -OMOM, -OiPr, or -OTBS gave poor results, both in terms of reactivity and regioselectivity (see the Supporting Information, Table S1). However, promising results were observed when -OMe (1a) and -OBn (2a) ethers were used. In these cases complete conversion, regioselectivities around 50%, and encouraging enantiomeric ratios (84:16 and 91:9) were obtained (Table 1, entries 1 and 2).

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increased, excellent regio- and enantioselectivities were obtained; this outcome is comparable to our recent results with allylic halides (Table 1, entry 7).[13] Remarkably, applying these optimized conditions to the allylic benzyl ether 2a afforded a significant increase in regioselectivity (95:5) and a near perfect enantiomeric ratio (99:1 e.r.) (Table 1, entry 8).

With these optimized conditions, we studied the scope of the reaction and for this purpose a number of -OMe (1) and -OBN (2) allylic ethers were tested with various organolithium reagents (Table 2).[17]

Allylic ethers 1a and 2a underwent a facile reaction with nBuLi and nHexLi displaying excellent regio- (S/N2 up to 96:4) and enantioselectivity (up to 99:1), (Table 2, entries 1–4). The more sterically hindered 1-naphthyl-substituted substrates gave different results for both ethers, with exceptional regioselectivity for substrate 2b (>98:2) and a slight decrease for substrate 1b; a similar trend was observed for the e.r. values (Table 2, entries 5–8). The transformation is also compatible with aromatic chlorides (Table 2, entries 9–12). Linear aliphatic substrates can also be used, but in this case the methyl ethers 1d and 1e are less suitable due to problems arising from their volatility and lower reactivity.

Table 1. Screening of reaction conditions and Lewis acids.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>OR</th>
<th>Cu/L[b]</th>
<th>Lewis acid [equiv][c]</th>
<th>Conc. [%][d]</th>
<th>3a/[4a][e]</th>
<th>e.r. 3a [f]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe</td>
<td>C1 (1:1)</td>
<td>A (1.5)</td>
<td>100</td>
<td>55</td>
<td>84:16</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>C1 (1:1)</td>
<td>A (1.5)</td>
<td>100</td>
<td>37:63</td>
<td>91:9</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>C1 (1:1)</td>
<td>A (1.5)</td>
<td>100</td>
<td>63:37</td>
<td>90:10</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>C1 (1:1)</td>
<td>A (1.5)</td>
<td>100</td>
<td>75:25</td>
<td>93:7</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>C1 (1:1)</td>
<td>B (3.0)</td>
<td>100</td>
<td>80:20</td>
<td>99:1</td>
</tr>
<tr>
<td>6</td>
<td>OMe</td>
<td>C2 (1:2)</td>
<td>A (1.5)</td>
<td>100</td>
<td>80:20</td>
<td>99:1</td>
</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>C2 (1:2)</td>
<td>B (4.0)</td>
<td>100</td>
<td>80:20</td>
<td>99:1</td>
</tr>
<tr>
<td>8</td>
<td>OMe</td>
<td>C2 (1:2)</td>
<td>B (6.0)</td>
<td>100</td>
<td>80:20</td>
<td>99:1</td>
</tr>
</tbody>
</table>

[a] Conditions: 0.2 mmol of allylic ether (0.1 m in CH2Cl2), nBuLi (1.5 equiv) diluted in hexane, 2 h addition time. [b] C1 = CuBr2SmE2; C2 = CuTC. [c] A = BF2OEt2; B = TMSOTf. The mixtures of Lewis acids were prepared in CH2Cl2 (0.5 mL) at ~80°C. [d] Isolated product yield. [e] S/N2 ratios were determined by GC analysis. [f] Determined by chiral GC analysis.

Notably, use of a Lewis acid in combination with a copper catalyst was essential for the successful execution of this C−C bond formation. The reaction does not proceed in the absence of either the copper catalyst or the Lewis acid, leading to a complete recovery of the starting material (see the Supporting Information, Table S2). These results show that the addition of a Lewis acid has a dramatic effect on the reactivity of the allylic ether. In particular, the absence of a Lewis acid in this system allows the allylic ether to act as a robust protecting group, if desired.

We next investigated the effect of different conditions, ligands and Lewis acids by using methyl ether 1a (Table 1, entries 3–7). By increasing the copper/ligand ratio from 1:1 to 1:2 the regioselectivity significantly improved (Table 1, entry 3). Different boron-based Lewis acids were tested, but the desired product was not obtained in those cases.[15] We next tested the synergistic effect of combining BF2OEt2 and TMSOTf, as reported by Aggarwal et al.,[16] forming the new Lewis acid “BF2OTf” in situ. TMSOTf was completely inert in our system, however, when used in combination with BF2OEt2 (2:1 ratio), the regio- and enantioselectivity increased again significantly (Table 1, entry 4). Further ligand screening (see the Supporting Information, Table S3) revealed that L2[17] is the preferred ligand in this asymmetric transformation. The use of this ligand in combination with a 2:1 mixture of TMSOTf and BF2OEt2 gave an improved regioselectivity of 87:13 (3a:4a), and an e.r. of 97:3 (Table 1, entry 5). By using CuTC as Cu salt instead of CuBr2SmE2 (see the Supporting Information, Table S4), both regio- and enantioselectivity were further enhanced (Table 1, entry 6). In addition, when the TMSOTf/BF2OEt2 ratio was in...
the same molecule was demonstrated by the use of allyl sub-
strate. The compatibility of two ether moieties in the same molecule was demonstrated by the use of allyl sub-
strate 1g, which bears both an allylic-Om and -OBn ether, and 2g, which contains two allylic -OBn moieties (Table 2, entries 17 and 18). Although the conversion was lower in both cases in comparison with the previous results, the S2′ selectivity observed was complete, with excellent enantio-
metric ratios. Surprisingly, in the case of 1g, with internal competition between -OMe and -OBn moieties as leaving group, we observed that substitution occurred towards the -OMe group instead of the -OBn group (Scheme 2). Despite

The fact that allylic -OBn ethers proved to be more reactive substrates in previous cases (see for example, Table 2, en-
tries 13–16), we envision that a possible interaction between the aromatic ring of the benzyl group and the copper com-
plex could control the regioselectivity of the reaction.[19]

The application of this new concept is illustrated by the shortest enantioselective synthesis of (5)-Arundic acid 7,[20]

Arundic acid 7 is a small but important molecule with out-
standing pharmacological properties that is currently undergo-
ing phase II trials for the treatment of acute ischemic stroke as well as clinical development for Alzheimer’s and Parkinson’s disease.[21]

The synthesis starts with the treatment of commercially available alcohol 5 with BnBr and NaH in THF. Alcohol 6 was obtained by asymmetric allylic alkylation of 2d followed by direct reductive ozonolysis of the alkene 3g in MeOH/

CH2Cl2. The resulting alcohol 6 was oxidized to afford Arundic acid 7 in three steps from alcohol 5 with >99:1 e.r. and in 61 % overall yield (Scheme 3).

In summary, the first example of the highly enantioselective asymmetric allylic alkylation of inert allylic ethers with organolithium reagents is presented. The Lewis acid compat-
ibility with organolithium reagents, under copper/phos-
phoramidite-catalyzed conditions, is essential to allow this novel highly enantioselective transformation to occur. Ex-
cellent results reported for allylic methyl ethers (-OMe), with similar selectivities as those recently reported for al-
lylic halides, were even improved for allylic benzyl ethers

(-OBn). The potential for application in organic synthesis is demonstrated by a three-step synthesis of pharmaceutically important (5)-Arundic acid. Mechanistic studies on the exact nature of this highly selective transformation based on the combination of Lewis acids and organolithium reagents are ongoing.

Experimental Section

Typical procedure: A Schlenk tube equipped with septum and stirring bar was charged with CuTC (0.01 mmol, 1.90 mg, 5 mol%) and the ligand L2 (0.022 mmol, 11 mol%). Dry dichloromethane (0.5 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. In another Schlenk tube BF3·OEt2 (0.4 mmol, 50 µL, 2.0 equiv) was added to a solution of TMSOTf (1.2 mmol, 215 µL, 60 equiv) in dichloromethane (0.5 mL) at −80°C, and the resulting “BF3·OTf” solu-
tion was stirred for 15 min. Then, the corresponding allyl ether 1–2 (0.2 mmol) in CH2Cl2 (1 mL) was added at −80°C to the copper(ligand solution prepared earlier and subsequently a solution of “BF3·OTf” in di-
chloromethane (0.4 mmol, 600 µL, 2.0 equiv) was added. In a separate Schlenk tube, the corresponding organolithium reagent (0.30 mmol, 1.5 equiv) was diluted with hexane (combined volume of 1 mL) under ni-
trogen and added dropwise to the reaction mixture over 2 h using a sy-
ringe pump. The reaction was quenched with a saturated aqueous NH4Cl solution (2 mL) and the mixture was warmed up to room temperature, diluted with dichloromethane and the layers were separated. The aque-
ous layer was extracted with dichloromethane (3 × 5 mL) and the com-
bined organic layers were dried with anhydrous Na2SO4, filtered and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel using different mixtures of n-pentane/Et2O as the eluent.

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Keywords: allylic alkylation · allylic ethers · copper · Lewis acids · organolithium reagents

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**Communication**

