A novel catalytic asymmetric route towards skipped dienes with a methyl-substituted central stereogenic carbon†

Yange Huang, Martín Fañanás-Mastral, Adriaan J. Minnaard and Ben L. Feringa*

A highly efficient method for the enantioselective synthesis of 1,4-dienes (skipped dienes) with a methyl-substituted central stereogenic carbon using copper-catalysed asymmetric allylic alkylation of diene bromides was developed. Excellent regio- and enantioselectivity (up to 97 : 3 SN2/SN2 ratio and 99% ee) were achieved with broad substrate scope.

Natural products containing 1,4-dienes (skipped dienes) such as polyunsaturated fatty acids have important biological functions.1 Particularly interesting molecules with a 1,4-diene bearing a methyl-substituted central stereogenic carbon include hennoxazole A,2 ansalactam A,3 ambruticin S,4 iejimalide5 and phorbasins,6 shown in Scheme 1, which are potent antibiotic, antifungal and cytotoxic agents. These ubiquitous molecules share this common structural motif which imparts unique properties to them.

The efficient preparation of these structural motifs remains a major challenge in organic chemistry, although multi-step synthesis methods7 have been reported. An elegant synthesis of the above motif was reported by the group of Micalizio8 using titanium-promoted reductive cross-coupling reaction between vinylcyclopropanes and alkynes (or vinylsilanes). To the best of our knowledge, the only catalytic asymmetric synthesis of the 3-methyl substituted 1,4-diene unit with broad substrate scope was reported by the group of RajanBabu achieved by hydrovinylation of 1,3-dienes with excellent regio- and enantioselectivity.9 Some examples have been reported in the literature for the synthesis of related structures using copper-catalysed asymmetric allylic alkylation (AAA)10 mainly with longer alkyl chains at the central position. The group of Hoveyda described copper-catalysed AAA of allylic phosphates with a diethylzinc reagent including one example of a skipped diene.11 Li and Alexakis reported an asymmetric allylic substitution of enyne chlorides with Grignard reagents which was also extended to two diene chlorides for the synthesis of 3-ethyl and 3-phenethyl substituted skipped dienes.12 Since the introduction of a methyl branch remains a highly desired goal in view of its importance in natural product synthesis,13 we report here a highly efficient catalytic methodology to prepare this structural motif with broad substrate scope and excellent enantioselectivity using copper-catalysed AAA of diene bromides with methylmagnesium bromide.

Our investigation started with the asymmetric allylic alkylation of [(1E,3E)-5-bromopenta-1,3-diyl]benzene 1a14 with MeMgBr in dichloromethane at −80 °C employing a copper bromide dimethylsulfide complex (CuBr·SMe2) and L1 as ligand (Table 1, entry 1). Product 2a was isolated in 65% yield with 85% ee and the ratio of 2a : 3a (SN2/SN2) was 79 : 21. To increase both the regio- and enantioselectivity of the reaction, a series of catalysts based on the chiral ligands depicted in Table 1 were tested. Both Tol-BINAP (L2) and JosiPhos type...
Table 1  Optimization of the copper-catalysed AAA of 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield [%]</th>
<th>$S_2/Z_2/S_0$ [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>DCM</td>
<td>65</td>
<td>79 : 21</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>DCM</td>
<td>68</td>
<td>36 : 64</td>
<td>-50</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>DCM</td>
<td>66</td>
<td>95 : 5</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>DCM</td>
<td>75</td>
<td>50 : 50</td>
<td>-62</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>DCM</td>
<td>51</td>
<td>23 : 77</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>L3</td>
<td>Toluene</td>
<td>25</td>
<td>80 : 20</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>L3</td>
<td>THF</td>
<td>34</td>
<td>91 : 9</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>L3</td>
<td>Et2O</td>
<td>46</td>
<td>8 : 92</td>
<td>71</td>
</tr>
</tbody>
</table>

* Reaction conditions: MeMgBr (0.3 mmol) was added to a stirred solution of CuBr2-SMe2 and a ligand in dry solvent at -80 °C; 1a (0.25 mmol) in 1 mL of dry solvent was added dropwise over 1 h. Yield represents combined isolated yield. Regioselectivity was determined by $^1$H NMR or GC analysis.

With this highly selective catalyst in hand, we studied the solvent effects on the reaction. We found that dichloromethane was still the most effective solvent. When we used toluene, product 2a was obtained with 95% ee but with lower regioselectivity (Table 1, entry 6). The use of THF gave comparable regioselectivity as DCM but the ee decreased to 87% (entry 7). The situation in diethyl ether was even worse; the enantioselectivity decreased and the regioselectivity was totally switched, with the linear product 3a being the main product of the reaction (entry 8).

To study the scope of this new enantioselective transformation, a series of substrates were tested under the optimized conditions (Table 1, entry 3). Excellent regio- and enantioselectivity were obtained in all cases (Scheme 2).

This new methodology proved to be also very efficient for an alkyl substituted substrate such as 1b ($R^1$ = iso-Bu) which afforded 1,4-diene 2b with excellent selectivity. It should be noted that product 2b represents the side chain of phorbasins (Scheme 1). Notably, both the regio- and enantioselectivity of the reaction dropped considerably when we used a (2E,4E)/ (2Z,4E) isomeric mixture of substrate 1b. The E-geometry of the double bond next to the bromide seems crucial for achieving high ee and regioselectivity (Scheme 3). A remarkable result was obtained with ester-substituted diene bromide 1c which led exclusively to product 2c, without any traces of the 1,2-, 1,4- or 1,6-addition to the carbonyl moiety or of the 1,5-substitution product. Moreover, product 2c is a core unit of ijemalides (Scheme 1). The versatile substituent TBSOCH2, as present in diene 1d, had no influence on the enantioselectivity and diene 2d could be obtained with 99% ee although a slightly lower regioselectivity was observed. The more substituted substrates 1e and 1f, with methyl groups at $R^2$ or $R^3$, could also be used in this transformation. Again, 2e and 2f were obtained exclusively with excellent selectivity. We also tested the effect of the remote double bond geometry as the presence of a Z-double bond is common in some natural products like hennoxazole A. We were
plesed to find that the reaction also proceeded successfully with \( [Z,E]-1g \) affording similar regio- and enantioselectivity to that with \( [E,E]-1f \), while no double bond isomerization was detected in \( 2g \). These remarkable results show that the geometry of the double bond remote from the bromide seems to have no effect on both the regio- and enantioselectivity (Scheme 3). An important feature is the scalability of this reaction. Synthesis of \( 2a \) was executed on a larger scale (1 gram) using only 1 mol% of catalyst and still excellent ee and regioselectivity were obtained, with a similar yield.

Finally we tried further functionalization of the 1,4-diene \( 2d \) vià cross metathesis \( ^{16} \) (Scheme 4) for future synthetic applications. The initially attempted cross metathesis with ethyl acrylate \( 4 \) using Grubbs’ first and second-generation catalysts and Hoveyda–Grubbs first-generation catalyst under different conditions led to complicated products. However, the Hoveyda–Grubbs second-generation catalyst significantly improved the outcome and afforded the product \( 5 \) as a single \( E,E \)-isomer. The presence of a protected alcohol and ester group facilitates the use of optically active \( 5 \) as a versatile multifunctional building block in natural product synthesis allowing for chain elongation at each end of the molecule.

In summary, a copper-catalysed asymmetric allylic alkylation with methylmagnesium bromide as a nucleophile employing prochiral diene bromides as substrates was developed. The reaction leads to important chiral 1,4-diene building blocks with excellent regio- and enantioselectivity (ee values up to 99%; \( S_{R}/S_{S} \) ratio up to 97:3) in nearly all cases. Application of this methodology to the total synthesis of phorbasins is ongoing.

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Notes and references

13. During the preparation of this manuscript Mauduit et al. reported a single example of a 3-methyl substituted skipped diene using copper-catalyzed AAA with dimethylzine. M. Magrez, Y. L. Guen, O. Baslé, C. Crévy and M. Mauduit, J. Org. Chem., 2010, 75, 1199–1203.