Asymmetric Catalysis

Catalytic Regio- and Enantioselective Alkylation of Conjugated Dienyl Amides

Yafei Guo, Johanan Kootstra, and Syuzanna R. Harutyunyan*

Dedicated to Professor Yuri N. Belokon on the occasion of his 80th birthday

Abstract: A method for catalytic asymmetric alkylation of conjugated dienyl amides has been developed and it allows efficient and high-yielding transformations of a wide range of polyconjugated amides into the corresponding chiral products. Smooth addition of organomagnesium reagents to relatively unreactive dienyl amides with excellent 1,6- and 1,4-selectivities, as well as enantioselectivities above 90%, is achieved owing to the complementary action of the Lewis acid and a chiral copper-based catalyst.

Simultaneous catalytic control of regio- and enantioselectivities in reactions that involve molecules featuring several reactive sites remains a major challenge in chemical synthesis. Catalytic asymmetric addition of organometallics to dienyl acceptors is an important example of this challenge. Complete regiocontrol towards either 1,2-, 1,4-, or 1,6-additions, combined with high stereocontrol over the addition process is hard to attain in these systems because of the presence of a supplementary double bond (Scheme 1).

Following impressive advances in catalytic asymmetric conjugate additions (1,4-additions) of organometallics to Michael acceptors, several chiral transition-metal catalysts have been shown to be effective for overcoming these regio- and stereoselectivity issues when using Michael acceptors with extended conjugated double bonds. Although this approach has enabled the selective introduction of carbocyclic nucleophiles, these reactions are confined to reactive polyconjugated Michael acceptors, such as dienes, dienones, and nitrodienes. Catalytic asymmetric additions of organometallics to less reactive polyconjugated systems, for example N,N-dialkyl dienyl carboxamides or dienyl heteroarenes, are unknown. Furthermore, to overcome the poor electrophilicity of adjacent dienyl moieties the reactions need to be carried out at relatively high temperatures, resulting in poor stereocontrol and reduced yields under catalytic conditions, and consequently limiting developments in this area.

Lewis acid (LA) activation of molecules towards nucleophilic addition is a powerful tool that has been used for many decades and has become common practice in organic synthesis. In our previous research we found that a strong LA can be used in combination with organomagnesium reagents. The role of LA in these reports was twofold: prevention of side reactions by effectively acting as an in situ protecting group, and activation of unreactive substrates towards nucleophilic attack.

Herein we show that the synergistic action of a boron-based LA and a readily accessible chiral copper-based catalyst addresses the reactivity and selectivity issues associated with dienyl amides. This finding led us to develop a highly regio- and enantioselective protocol for 1,6- and 1,4-additions of organomagnesium reagents with considerable scope and good yields.

We first examined the addition of ethylmagnesium bromide to α,β,γ,δ-unsaturated N,N-dimethyl amide (1a; Table 1). To evaluate the reactivity of the amide towards nucleophilic addition, we carried out the initial reaction in the absence of a catalyst at 0°C and at cryogenic temperatures (entries 1 and 2). At 0°C the 1,4-addition product was obtained with only 38% yield, similar to the result obtained by Miginiac et al., whereas at −78°C no substrate conversion was observed. Copper-based catalysts are known to promote the addition of various organometallics, including organomagnesium reagents, to extended conjugated enones and enoates with very good selectivities. Adding various copper-based catalysts to the above-mentioned reactions afforded results similar to those obtained in their absence (entries 3 and 4). Suspecting the poor reactivity of the substrate to be the main cause of the inability of the catalyst to promote the reaction, we also carried out the noncatalytic reaction in the presence of 2 equivalents of BF₂Et₂O under cryogenic conditions (entry 5). However, also in this case 1a was not converted, thus highlighting the low reactivity issue associated with amides. Gratifyingly, combining BF₂Et₂O with the chiral copper catalyst Cu/L1 led to an immense acceleration of the addition rate (entry 6). The reaction was completed in a few hours and the 1H NMR analysis of the...
Table 1: Optimization of the enantioselective 1,6-addition of EtMgBr to the substrate 1a.\[a]\n
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Cu/L</th>
<th>LA</th>
<th>2a/3 ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)Cl(_2)</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>2.98 (38)</td>
</tr>
<tr>
<td>2</td>
<td>CH(_2)Cl(_2)</td>
<td>–78</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>CH(_2)Cl(_2)</td>
<td>0</td>
<td>L1</td>
<td>–</td>
<td>9.91 (nd)</td>
</tr>
<tr>
<td>4</td>
<td>CH(_2)Cl(_2)</td>
<td>–78</td>
<td>L1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)Cl(_2)</td>
<td>–78</td>
<td>–</td>
<td>BF(_2) Et(_2)O</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>CH(_2)Cl(_2)</td>
<td>–78</td>
<td>L1</td>
<td>BF(_2) Et(_2)O</td>
<td>94.6 (92)</td>
</tr>
<tr>
<td>7</td>
<td>CH(_2)Cl(_2)</td>
<td>–78</td>
<td>L1</td>
<td>TMSOTf</td>
<td>33.67 (58)</td>
</tr>
<tr>
<td>8</td>
<td>CH(_2)Cl(_2)</td>
<td>–78</td>
<td>L1</td>
<td>TMSBr</td>
<td>41.59 (nd)</td>
</tr>
<tr>
<td>9</td>
<td>CH(_2)Cl(_2)</td>
<td>–78</td>
<td>L1</td>
<td>TBSOTf</td>
<td>68.32 (nd)</td>
</tr>
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<td>10</td>
<td>CH(_2)Cl(_2)</td>
<td>–78</td>
<td>L2</td>
<td>BF(_2) Et(_2)O</td>
<td>99.1 (93)</td>
</tr>
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<td>11</td>
<td>CH(_2)Cl(_2)</td>
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<td>L3</td>
<td>BF(_2) Et(_2)O</td>
<td>95.5 (90)</td>
</tr>
<tr>
<td>12</td>
<td>MTBE</td>
<td>–78</td>
<td>L1</td>
<td>BF(_2) Et(_2)O</td>
<td>90.10 (60)</td>
</tr>
<tr>
<td>13</td>
<td>Et(_2)O</td>
<td>–78</td>
<td>L3</td>
<td>BF(_2) Et(_2)O</td>
<td>87.13 (51)</td>
</tr>
<tr>
<td>14</td>
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<td>–78</td>
<td>L1</td>
<td>BF(_2) Et(_2)O</td>
<td>93.7 (66)</td>
</tr>
<tr>
<td>15[f]</td>
<td>Et(_2)O</td>
<td>–78</td>
<td>L1</td>
<td>BF(_2) Et(_2)O</td>
<td>96.4 (81)</td>
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</table>

\[a\] Reaction conditions: the LA (2 equiv.), EtMgBr (2 equiv.), ligand L (6 mol %), CuBr/SmMe\(_5\) (5 mol %), and 1a (0.2 mmol) in 2 mL of solvent. \[b\] 1,6/1,4 ratio was determined by \(^1\)H NMR spectroscopy. \[c\] The values in brackets are yields for the isolated products. \[d\] The ee values were determined by HPLC using a chiral stationary phase. \[e\] The absolute configuration was determined by conversion of 2a into a known compound (see the Supporting Information). \[f\] 3 equiv of BF\(_2\) Et\(_2\)O was used in this case. MTBE = methyl tert-butyl ether, TBS = tert-butyldimethyl silyl, TF = trifluoromethanesulfonyl, TMS = trimethylsilyl.

crude reaction mixture revealed predominant formation of the 1,6-addition product 2a. Furthermore, 2a was obtained with a promising enantioselectivity of 85%. Encouraged by these results we investigated the effect of the type of L, the catalyst structure, and the nature of the solvent on the stereochemical outcome, and on the overall reactivity of the catalytic system. The silicon-based L led to worse reaction outcomes with decreased regioselectivity, as well as reduced enantioselectivity (entries 7–9). A screening of chiral ligands for the copper catalyst (only selected examples are shown) revealed the ferrocenyl-based ligand L1 to be the best choice in terms of enantioselectivity, while similarly high levels of regioselectivities were obtained for most other chiral ligands (entries 6, 10, and 11). Importantly, switching from dichloromethane to ethereal solvents was detrimental for the reactivity, leading to lower substrate conversion, but it was beneficial for the stereochemical outcome of the reaction when using ligand L1 (entries 12–14). In particular, when the reaction was carried out in diethyl ether the regioselectivity of the addition reaction remained practically the same but the enantioselectivity increased to 93% (entry 14). Finally, increasing the LA amount to 3 equivalents led to higher reaction rates and higher selectivities, namely a regioselectivity of 1,6/1,4 = 96:4, 81% yield upon isolation, and an excellent enantioselectivity of 95% for 2a (entry 15).

With the optimized set of reaction conditions in hand, we investigated the generality of this methodology and the results of this scope study are shown in Schemes 2 and 3. Generally speaking, this catalytic and highly regio- and enantioselective reaction reaches nearly full conversion in 10–16 hours when using 5 mol % of Cu/L1, with regioselectivities above 90%, and in some cases even reaching 100%. A broad substrate and organomagnesium reagent scope is tolerated, and we observed an interesting correlation between substrate substituents and regioselectivity as detailed below.

Evaluation of the addition reaction using EtMgBr and various dienyl amides, differing by the substituent at the δ-position, revealed a strong influence of the substitution pattern on the regioselectivity (Scheme 2). Addition reactions with amide substrates featuring linear, as well as functionalized aliphatic substituents, at the δ-position led predominantly to (more than 90%) 1,6-adducts (2a–e) with high yields and enantioselectivities (80–99%). In contrast, highly regioselective 1,4-addition (more than 92%) was observed with amide substrates featuring electron-rich and electron-poor aromatics, heteroaromatics, and branched aliphatic substituents at the δ-position. The corresponding 1,4-adducts 3k–3p were obtained with high yields and excellent 94 to 99% enantioselectivities.

Next, we studied substrates with various substituents on N, using dienyl amides with a linear aliphatic substituent at the δ-position (Scheme 2). We found that incorporation of various substituents at N is well tolerated and excellent selectivities and yields were obtained for N-dialkyl-, N-phenyl-N-methyl-, N-dialkyl-substituted compounds (2a, 2j, 2g, and 2h). Importantly, the addition to morpholine-substituted enamide leads to the 1,6-addition product 2f with a 78% yield upon isolation and 91% ee, and it is amenable to further synthetic transformations. Remarkably, even the addition of EtMgBr to a secondary amide bearing an acidic proton was possible. Also in this case the corresponding 1,6-addition product 2i was obtained with high regio- and enantioselectivity.

Having established the substrate scope, we moved to assess the scope with respect to the organomagnesium reagents. For this purpose we selected two substrates, the aliphatic dienyl amide 1a and aromatic dienyl amide 1k, as substrates to study both 1,6- and 1,4-additions, respectively (Scheme 3). Our catalytic system enables the introduction of organomagnesium reagents of various chain lengths, for example, Et, nBu, nHex, and iPent, affording the corresponding products 4a–6a with high regio- and enantioselectivities as well as yields. When using β-branched organomagnesium reagent, the increase in steric hindrance caused by the branching led to diminished enantioselectivity (76%) for the product 7a. No reaction was observed with PhMgBr under various reaction conditions.

Methylation has always been challenging because of the diminished reactivity of the corresponding organomagmetals compared to those with a higher number of carbon atoms.\[10\]

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We were pleased to observe smooth addition of MeMgBr to the natural product piperine, providing the addition product 4p with excellent 1,4-regioselectivity and an enantioselectivity of more than 99% (Scheme 3).

Next we extended our methodology to nucleophilic additions to dicarboxylic acid derivatives, namely to the carboxamide derivative of muconic acid 1q (Scheme 4a). This substrate represents some challenges with respect to the control of both reactivity and selectivity. Therefore we were pleased to find that by using our catalytic system, addition of various organomagnesium reagents to this demanding substrate affords predominantly the 1,6-addition products 2q–4q (more than 95%) with enantioselectivities above 95% and high yields.

Finally, we applied our methodology to the synthesis of an important precursor (8) for the synthesis of the natural product Penicillenol A (Scheme 4b).[11] The compound 8 was obtained in two steps, namely catalytic asymmetric 1,6-addition to 1a, followed by the oxidation of the double-bond product 5a.[12]

In summary, we developed the first catalytic asymmetric addition of organometallics to various dienyl carboxamides.

Scheme 2. Scope of the reaction with respect to dienyl amides. Reaction conditions: BF$_3$·Et$_2$O (3 equiv) and EtMgBr (2 equiv), L$_1$ (6 mol%), CuBr·SMe$_2$ (5 mol%), and dienyl amide (0.2 mmol) in diethyl ether at −78 °C overnight. Yields are those for the isolated products. The ee values were determined using chiral-phase HPLC. The 1,4/1,6 ratios were determined by $^1$HNMR spectroscopy. [a] The absolute configuration was determined by conversion into a known compound (see the Supporting Information). [b] CH$_2$Cl$_2$ (2 mL) and TMSOTf (2 equiv) were employed instead of Et$_2$O and BF$_3$·Et$_2$O, respectively, to enhance the substrate conversion.

Scheme 3. Scope of the reaction with respect to organomagnesium reagents. Reaction conditions: BF$_3$·Et$_2$O (3 equiv), EtMgBr (2 equiv), L$_1$ (6 mol%), CuBr·SMe$_2$ (5 mol%), and dienyl amide 1 (0.2 mmol) in 2 mL diethyl ether at −78 °C overnight. Yields are those for the isolated products. The ee values were determined using chiral-phase HPLC. The 1,4/1,6 ratios were determined by H NMR spectroscopy. [a] CH$_2$Cl$_2$ (2 mL) and TMSOTf (2 equiv) were employed instead of Et$_2$O and BF$_3$·Et$_2$O, respectively, to enhance the substrate conversion.

Scheme 4. Application of the methodology: a) to conjugate addition of organomagnesium reagents to carboxamide derivative of (2E,4E)-muconic acid 1q and b) towards the synthesis of the natural product penicillenol A.
leading to α-, β-, or δ-substituted chiral functionalized amides with excellent 1,6- or 1,4-regioselectivities. The combination of Lewis acid activation and the high reactivity of reagents lies at the basis of this feat, as it overcomes the low reactivity of the amide substrates. Although the substrate structure can strongly affect the regioselectivity outcome we have shown that under our catalytic conditions almost exclusively one regioisomer is formed with excellent enantioselectivity.

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Conflict of interest

The authors declare no conflict of interest.

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