Copper-Catalyzed Addition of Grignard Reagents to in situ Generated Indole-Derived Vinylogous Imines

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Abstract: Chiral indole derivatives are ubiquitous motifs in pharmaceuticals and alkaloids. Herein, the first protocol for catalytic asymmetric conjugate addition of Grignard reagents to various sulfonil indoles, offering a straightforward approach for the synthesis of chiral 3-sec-alkyl-substituted indoles in high yields and enantiomeric ratios is presented. This methodology makes use of a chiral catalyst based on copper phosphoramidite complexes and in situ formation of vinylogous imine intermediates.

The chiral 3-sec-alkyl-substituted indole motif is ubiquitous in pharmaceuticals, natural alkaloids, and agrochemicals (Scheme 1 a),[1] making optically active derivatives important building blocks in both natural product synthesis and drug discovery.

Various methods for the production of 3-sec-alkyl-substituted indoles have emerged in recent years with Friedel–Crafts reactions most commonly used (Scheme 1 b).[2] In 2006, a novel methodology was reported by Petroni and co-workers that makes use of 3-(1-arylsulfonylalkyl)indoles as electrophilic precursors.[3] The sulfonyl moiety acts as a good leaving group, allowing the reaction with a base to generate vinylogous imine intermediates in situ, which subsequently are used as Michael acceptors for the addition of nucleophiles. Using this strategy various nucleophiles have been added to sulfonyl indoles,[4] including several examples of enantioselective nucleophilic additions.

All enantioselective methods make use of soft nucleophiles and the addition of an exogenous base to generate the electrophilic species (vinylogous imines) (Scheme 1 c).[5] Even though catalytic enantioselective additions of organometallics to conventional carbonyl based Michael acceptors,[6] mostly copper catalyzed, have been well developed, no examples of enantioselective additions of organometallics to indole derived Michael acceptors have been reported to date. This approach would, however, enable access to structurally new chiral indoles, with the added advantage that no additional base is needed since an organometallic can serve both as a base to form the vinylogous imine intermediate and also as nucleophile. However, although the copper catalyzed enantioselective conjugate addition of organometallics to indole-derived Michael acceptors could be comparable to additions to α,β-unsaturated imines, the examples reported in the literature using of the latter are rare and limited to organozinc reagents.[7]

On the other hand, over the past few years, our research group has developed the synthesis of optically active molecules using a methodology based on copper catalyzed asymmetric addition of Grignard reagents to various Michael acceptors.[8] Building on this experience we pursue in this work the development of a novel catalytic methodology to obtain enantioenriched 3-sec-alkyl-substituted indole derivatives, based on the conjugate addition of alkyl Grignard reagents to vinylogous imines generated in situ from sulfonyl indoles (Scheme 1 d).

At the outset of this work, sulfonylindole 1a was chosen as model substrate and EtMgBr as nucleophile (Table 1). We immediately noticed that in the absence of any catalyst the reaction proceeds with complete conversion to the racemic desired product in CHCl₃ at -78 °C, signifying it might be hard to find a catalyst that can outcompete the background reaction (Table 1, entry 1).

Since chiral copper(I) complexes are the most obvious candidates to serve as catalysts in this chemistry, we started the screening of different classes of chiral ligands L₁ – L₆ (6 mol %) in combination with 5 mol % of Cu I salts (Table 1, entries 2–7, selected examples). While in the presence of copper complex with chiral diphosphine ligands L₁ and L₂ full conversion to nearly racemic product was observed (Table 1, entries 2 and 3), the use of phosphoramidite ligands L₃ – L₅ (Table 1, entries 4–6) led to significant enantioselectivity. The best result in terms of enantiomeric ratio (93.5:6.5), however, was obtained with biaryl based phosphoramidite ligand L₆ (Table 1, entry 7). This enantioselectivity could be further improved to 95:5 by slow addition of EtMgBr within 1 h (Table 1, entry 8). As expected, increasing the reaction temperature to -50 °C had a negative effect, causing the enantiomeric ratio to drop to 91:9 (Table 1, entry 9).

Setting for L₆ as the ligand of choice, we studied the effect of the solvent, only to find all other tested solvents, including tBuOMe, toluene and 2-methyltetrahydrofuran (2-Me-THF), to
afford product 2a with moderate to good conversion but poor enantiomeric ratio. Based on these data the following optimized reaction conditions were selected for the substrate and Grignard reagent scope investigations: 5 mol% of CuBr·SMe₂, 6 mol% L6, 3.0 equiv Grignard reagent in CH₂Cl₂ at 78°C for 16 h.

To kick off our study of the substrate scope we explored different functionalized sulfonylindoles 1 in the addition with EtMgBr (Scheme 2). Firstly, we evaluated the effect of the R₁-substituent on the reaction outcome. Different substitutions with alkyl or phenyl groups led to excellent results in most of the cases. Substituting the propyl group in 1a with a methyl group (1b) afforded the addition product 2b with slightly decreased yield and enantiomeric ratio, while α-branched, β-branched and cyclic substituted sulfonylindoles 1c–1f unexpectedly showed very similar results to 1a, which bears a linear alkyl substituent. Benzyl substituted sulfonyl indole 1g and sulfonyl indole 1h containing a terminal double bond afforded the corresponding products with equally excellent e.r. and only slightly lower yields. On the other hand, sulfonylindole 1i bearing a phenyl group led to decreased enantioselectivity (85.5:14.5 e.r.), but an excellent yield.

Next, we explored different substitution patterns of the aromatic ring (R₂) of the sulfonylindoles. Substrates with either an electron-donating group (methoxy-substituent, 1j) or an electron-withdrawing group (fluoro-substituent, 1k) at the sterically demanding 4-position of the indole ring furnished the corresponding products (2j and 2k) in high yields (≥ 75%) and excellent enantiomeric ratios (97:3 e.r.).

Sulfonylindoles 1l and 1m, bearing a weakly electron-donating (methyl) group and an electron-withdrawing group at the 5-position of the indole ring, provided addition products 2l and 2m with very good yields and very high enantiomeric ratios (95:5 e.r. and 97:2.5 e.r.). Varying the electronic properties of the indole moiety had little effect: similar results were obtained for substrate with either chloro- (1n), bromo- (1o) or methoxy- (1p) substituents at the C6-position of the indole ring. Finally, an electron-withdrawing substituent at the C7-position led to the indole product 2q with in excellent yield (96%) and enantiomeric ratio (97:2.5 e.r.) where the electron-rich MeO-substituent at the same position provided product 2r.
with significantly decreased enantiomeric ratio (88.5:11.5 e.r.). The latter might be attributed not only to the electronic properties but also to increased sterics at the C7-position.

After exploring the substrate scope we investigated the Grignard scope (Scheme 3), which determines the variety of chiral indole derivatives that the catalytic transformation allows to synthesize. We were delighted to observe that our methodology is not only valid for the addition of EtMgBr, but that longer alkyl and branched Grignard reagents can be employed, obtaining excellent enantioselectivities. Using pentyl and butyl magnesium bromide as nucleophiles, the corresponding indole derivatives (4a and 4b, respectively) were obtained with high yields and enantiomeric ratios. Gratifyingly methylmagnesium bromide and cyclopentylmagnesium bromide also can be added to indole derivatives leading to the corresponding products (4c and 4d, respectively). Furthermore, γ-branched Grignard reagents were well tolerated for this reaction as well, affording the corresponding products (4e and 4f) with high yields and enantiomeric ratios. On the other hand racemic product was obtained with PhMgBr. Importantly, Grignard reagents containing a terminal double bond or a chloro substituent, which are interesting derivatives for potential further transformations, provided the corresponding addition products (4g, 4h and 4i, respectively) in good yields and enantiomeric ratios.

To demonstrate the practicality of our catalytic system several additional experiments were conducted (Scheme 4). The reaction with sulfonylindole 1a and EtMgBr was carried out in 1.3 g scale using only 1 mol % of chiral catalyst L6-CuI, leading to the addition product 2c without deterioration of the yield (89 % yield) or the enantiomeric ratio (95.5:4.5 e.r.). Furthermore, product 2c was subjected to subsequent transformations, namely reduction with Et3SiH to get product 2ca, and the oxidation of the indole derivative using DMSO and concentrated HCl obtaining the amide product 2cb.

In conclusion, we have developed the first protocol for catalytic asymmetric conjugate addition of Grignard reagents to various vinylogous imines, generated in situ from sulfonyl indoles. The importance of this work is reflected by the number of biologically active products and natural products, which possess a chiral indole scaffold. This methodology offers a simple and straightforward approach for the synthesis of chiral 3-sec-alkyl-substituted indoles in high yields and enantiomeric ratios. Furthermore, it is possible to scale up the reaction using

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**Table 1. Optimization of the reaction conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Conversion [%][b]</th>
<th>e.r. (2a)[c]</th>
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<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>CH2Cl2</td>
<td>&gt; 99</td>
<td>–</td>
</tr>
<tr>
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<td>L1</td>
<td>CH2Cl2</td>
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<td>47:53</td>
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<td>L3</td>
<td>CH2Cl2</td>
<td>&gt; 99</td>
<td>71:29</td>
</tr>
<tr>
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<td>L4</td>
<td>CH2Cl2</td>
<td>&gt; 99</td>
<td>84:16</td>
</tr>
<tr>
<td>6</td>
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<td>L6</td>
<td>CH2Cl2</td>
<td>&gt; 99</td>
<td>93.5:6.5</td>
</tr>
<tr>
<td>8#</td>
<td>L6</td>
<td>CH2Cl2</td>
<td>&gt; 99</td>
<td>95:5</td>
</tr>
<tr>
<td>9#</td>
<td>L6</td>
<td>tBuOMe</td>
<td>97</td>
<td>89:11</td>
</tr>
<tr>
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<td>L6</td>
<td>toluene</td>
<td>98</td>
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<tr>
<td>11</td>
<td>L6</td>
<td>2-Me-THF</td>
<td>81</td>
<td>52.5:47.5</td>
</tr>
</tbody>
</table>

[a] General conditions: 1a (0.1 mol), CuBr·SMe₂ (5 mol %), Ligand (6 mol %), EtMgBr (3 equiv) in CH2Cl2 (1.0 mL) for 16 h. [b] The ratio was determined by 1H NMR of reaction crude. [c] Enantiomeric ratio (e.r.) was determined by HPLC on a chiral stationary phase. [d] EtMgBr (was diluted in 1.0 mL CH2Cl2) was added over 1 h. [e] In this case the reaction was performed at –50°C.
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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation · asymmetric addition · copper catalysis · Grignard reagents · indoles


[9] a) Deposition Number 2019971 (2e) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.