Synthetic Methods

# 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 sulfonyl 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 Petrini and co-workers that makes use of 3-(1-arylsulfonylalkyl)indoles as electrophilic precursor.[3] The sulfonyl moiety acts as a good leaving group, allowing the reaction with a base to generate vinylogous $\alpha,\beta$-unsaturated 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 $\alpha,\beta$-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 **1 a** 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 $CH_2Cl_2$ at $-78\,^{\circ}C$, 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 $-50\,^{\circ}C$ had a negative effect, causing the enantiomeric ratio to drop to 91:9 (Table 1, entry 9).

Settling for **L6** as the ligand of choice, we studied the effect of the solvent, only to find all other tested solvents, including *t*BuOMe, toluene and 2-methyltetrahydrofuran (2-Me-THF), to

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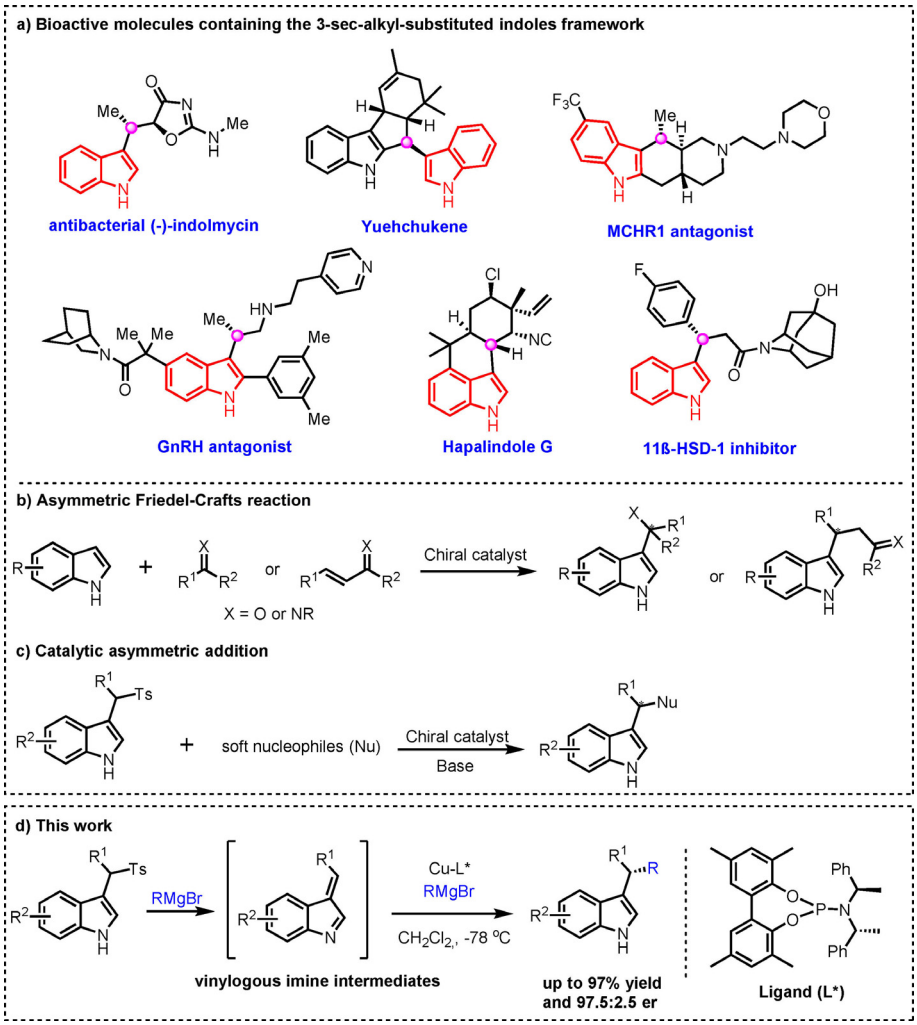


**Scheme 1.** a) Selected examples of natural products and bioactive molecules containing the 3-*sec*-alkyl-substituted indoles framework. b) Catalytic asymmetric Friedel–Crafts reaction with indoles. c) Catalytic asymmetric addition of soft nucleophiles to arylsulfonylalkylindoles. d) This work.

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·$SMe_2$, 6 mol% **L6**, 3.0 equiv Grignard reagent in $CH_2Cl_2$ 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 $R^1$-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 ($R^2$) 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 97.5:2.5 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 (97.5:2.5 e.r.) where the electron-rich MeO-substituent at the same position provided product **2r**


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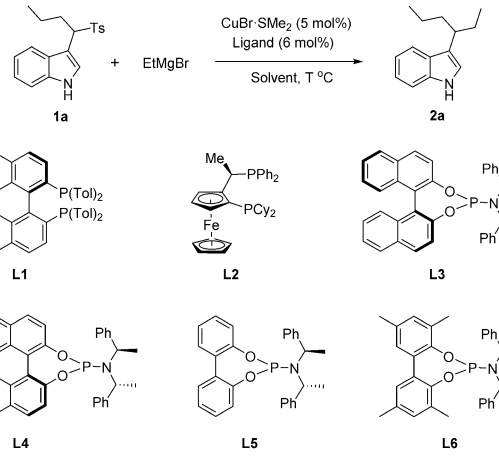
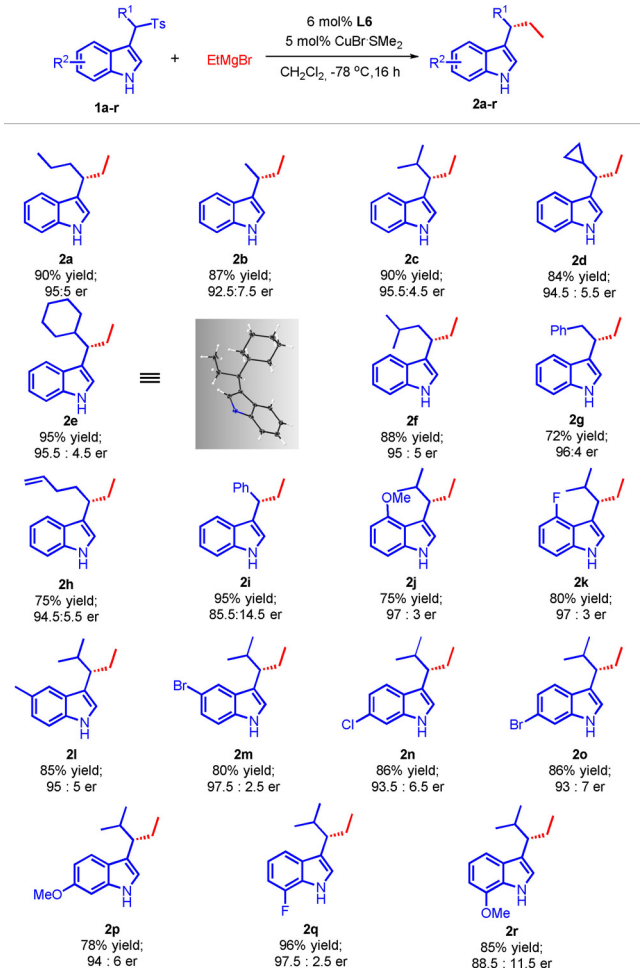
**Table 1.** Optimization of the reaction conditions.[a]




| Entry | Ligand | Solvent | Conversion [%][b] | e.r. (**2a**)[c] |
|---|---|---|---|---|
| 1 | – | $CH_2Cl_2$ | >99 | – |
| 2 | **L1** | $CH_2Cl_2$ | >99 | 48:52 |
| 3 | **L2** | $CH_2Cl_2$ | >99 | 47:53 |
| 4 | **L3** | $CH_2Cl_2$ | >99 | 71:29 |
| 5 | **L4** | $CH_2Cl_2$ | >99 | 84:16 |
| 6 | **L5** | $CH_2Cl_2$ | >99 | 85:15 |
| 7 | **L6** | $CH_2Cl_2$ | >99 | 93.5:6.5 |
| 8[d] | **L6** | $CH_2Cl_2$ | >99 | 95:5 |
| 9[e] | **L6** | $CH_2Cl_2$ | >99 | 91:9 |
| 10 | **L6** | *t*BuOMe | 97 | 89:11 |
| 11 | **L6** | toluene | 98 | 84:16 |
| 12 | **L6** | 2-Me-THF | 81 | 52.5:47.5 |

[a] General conditions: **1a** (0.1 mol), $CuBr{\cdot}SMe_2$ (5 mol%), Ligand (6 mol%), EtMgBr (3 equiv) in $CH_2Cl_2$ (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 $CH_2Cl_2$) was added over 1 h. [e] In this case the reaction was performed at −50 °C.




**Scheme 2.** Scope of the reaction for sulfonylindoles **1** and EtMgBr. Reaction conditions: Sulfonylindoles **1** (0.1 mol), $CuBr{\cdot}SMe_2$ (5 mol%), **L6** (6 mol%), EtMgBr (3.0 equiv, 0.13 M in $CH_2Cl_2$) in 1.0 mL $CH_2Cl_2$ at −78 °C for 16 h. Absolute configuration of **2e** was established by X-ray crystallography.[9]

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 in excellent yields albeit with a slightly decreased enantioselectivity (**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**-$Cu^I$, 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 $Et_3SiH$ 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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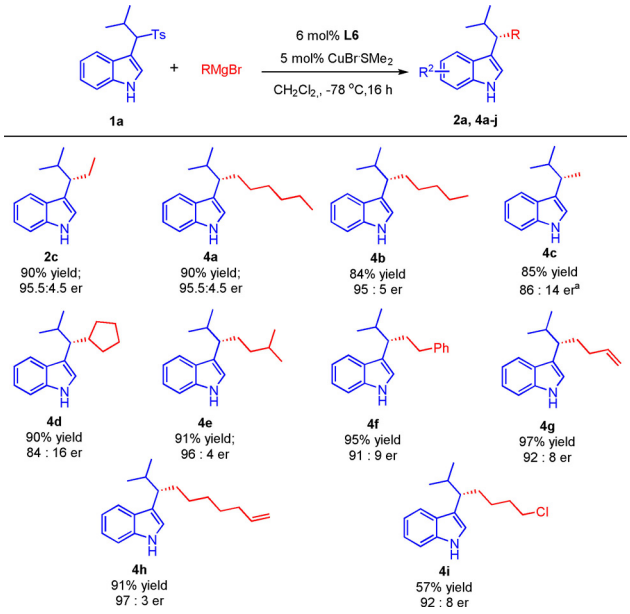
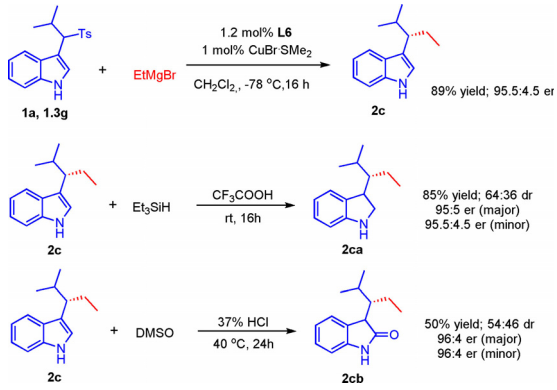



**Scheme 3.** Scope of the reaction for sulfonylindole **1a** with Grignard reagents. Reaction conditions: Sulfonylindole **1a** (0.1 mol), $CuBr{\cdot}SMe_2$ (5 mol%), **L6** (6 mol%), Grignard reagents (3.0 equiv, 0.1M-0.13 M in $CH_2Cl_2$) in 1.0 mL $CH_2Cl_2$ at −78 °C for 16 h. [a] $CuBr{\cdot}SMe_2$ (10 mol%) and **L6** (12 mol%) were used in this case.




**Scheme 4.** Gram-scale reaction and transformations of **2c**.

a minimum amount of catalyst (1 mol%) without any loss of yield or enantiomeric ratio. Further work is currently underway to unravel the mechanism of this transformation.

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## Conflict of interest

The authors declare no conflict of interest.

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

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