Catalytic asymmetric conjugate addition of Grignard reagents to chromones†

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A highly regio- and enantioselective copper catalysed direct conjugate addition of Grignard reagents to chromones has been developed taking advantage of the reduced reactivity of the resulting magnesium enolates. This methodology tolerates a broad scope of alkyl Grignard reagents including secondary alkyl magnesium reagents as well as functionalised chromones.

The chromanone skeleton is present in a large number of natural products, which show a wide range of biological activities including anticancer, antitumor, antibacterial, antioxidant or antimicrobial properties.1 The enantioselective synthesis of chiral 2-aryl substituted chromanones is well described in the literature and several examples have been published.2 However, the synthesis of chiral chromanones bearing an aliphatic substituent at C-2 has been reported in a limited number of studies. Two general strategies for the catalytic synthesis of chiral 2-alkylchromanones3 have been reported: an intramolecular oxa-Michael4,5 reaction and an intermolecular conjugate addition of organometallic reagents (Scheme 1).6,7 Examples of the first methodology are the synthesis of (R)-2-(cyclohexyl)chroman-4-one and (S)-flindersiachromanone by the group of Scheidt using cinchona alkaloids (Scheme 1a).4 Similarily, Feng and coworkers5 reported the synthesis of (S)-2-ethylchromanone (85% ee) using a chiral N,N,N0-dioxide nickel(II) complex. Finally, Wallace et al. described the synthesis of enantio-enriched 2-methylchroman-4-one derivatives by a diastereoselective intermolecular addition to chiral 3-sulfinylchromones.8 As far as we know the only example of catalytic enantioselective conjugate addition to prepare optically active 2-alkylchromanones was described by Hoveyda and co-workers in 2005.7 They reported an enantioselective copper-catalysed conjugate addition of dialkylzinc reagents to chromones (Scheme 1b), providing good yields when the reaction was performed in the presence of benzaldehyde to trap the zinc enolate and avoid undesired reactions. The corresponding 2-alkyl chromanones can subsequently be obtained with excellent ee’s by a retroaldol reaction. However, a direct enantioselective synthesis via catalytic conjugate addition to chromones remains a significant challenge in the preparation of valuable 2-alkylchromanones.

Copper catalysed asymmetric conjugate addition (ACA) represents an important and versatile methodology for the enantioselective formation of C-C bonds.8 Based on our previous reported methodology, we envisioned the possibility of using alkyl Grignard reagents for the synthesis of chiral 2-alkylchromanones through a direct asymmetric conjugate addition. Taking advantage of the lower reactivity of magnesium enolates, we envisioned that one could avoid enolate condensation and other side reactions, thus eliminating the need of benzaldehyde as an enolate trapping reagent. The addition of Grignard reagents catalysed by copper has been successfully applied to acyclic9 and cyclic enones.10 Recently, our group reported the Cu-catalysed 1,4-addition of Grignard reagents to unsaturated heterocycles such as coumarins11 and 2H-pyran-2-ones.12 We envisioned that this approach might...
provide a direct, efficient and versatile method for the synthesis of 2-alkylchromanones in an enantioselective way. Herein, we present the copper catalysed asymmetric conjugate addition of Grignard reagents to chromones using ferrocenyl-based bisphosphine ligands. The corresponding 2-alkylchromanones are obtained in high yields and with excellent regio- and enantioselectivities.

The reaction between 4H-chromen-4-one (1a) and ethylmagnesium bromide was chosen as a model reaction for the optimisation of this conjugate addition (Table 1). First we tested different chiral diphosphine ligands using MTBE as a solvent at −80 °C. With (R)-BINAP (L1), the corresponding 2-ethylchroman-4-one 2a was isolated in 49% yield (60% conversion) as a racemic mixture. Interestingly, when (R,S)-Josiphos (L2) was used as a ligand (Table 1, entry 2) the conversion was much higher, providing the product 2a in 83% yield and high enantioselectivity (86% ee). The regioselectivity of the reaction was excellent, and only the formation of the 1,4-addition product was observed. Ligand L3, (R,S)-Rev-Josiphos, used previously in the successful asymmetric conjugate addition to other unsaturated heterocycles,⁵,¹² proved to be the best ligand in terms of both reactivity and enantioselectivity. Thus, the use of L3 afforded 2a in 93% yield and with 91% ee (entry 3). However, when L4 (R,R)-Taniaphos,⁹ which has been applied in the conjugate addition to cyclic enones, was used product 2a was obtained in low yield and as a nearly racemic mixture (entry 4). Next, we turned our attention to the effect of the solvent on the enantioselectivity of the reaction. 2-Ethylchroman-4-one was obtained as a racemic compound when THF was used as a solvent (entry 5), probably, due to the coordinating nature of THF. When diethyl ether or toluene were used as a solvent (entries 6 and 7) a decrease in the enantioselectivity was observed.

Finally, the best solvent turned out to be dichloromethane affording product 2a in 90% yield with an excellent enantioselectivity of 94% (entry 8). Furthermore, the catalyst loading could be lowered to 2.5 mol% without compromising the yield (98%) or the enantiomeric excess (95%) (entry 9).

We next examined a broad range of alkyl Grignard reagents and different substituted chromones to demonstrate the potential of this new transformation (Scheme 2). The use of linear alkyl reagents such as pentyl, hexyl or dodecylmagnesium bromide afforded the corresponding chromones 2b–d with good yields and high enantioselectivities, although with a longer linear alkyl chain (R = dodecyl) a lower conversion was observed. The addition of a branched Grignard reagent (R² = t-Bu) provided the alkylated chromanone 2e with an excellent enantioselectivity of 98%. A functionalized Grignard reagent bearing an alkene moiety also worked well and the corresponding product 2f was obtained with good yield and enantiomeric excess (79% and 85%, respectively). The use of 2-phenethylmagnesium bromide afforded the

### Table 1 Optimisation of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>MTBE</td>
<td>60 (49)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>MTBE</td>
<td>87 (83)</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>MTBE</td>
<td>Full (93)</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>MTBE</td>
<td>35 (34)</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>THF</td>
<td>Full (95)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>L5</td>
<td>Toluene</td>
<td>Full (76)</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>L5</td>
<td>Ether</td>
<td>96 (84)</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>L3</td>
<td>DCM</td>
<td>Full (90)</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>L3</td>
<td>DCM</td>
<td>Full (98)</td>
<td>95</td>
</tr>
</tbody>
</table>

*Reaction conditions: CuBr·SMe₂ (0.01 mmol, 5 mol%, 2.02 mg) and 6 mol% (0.012 mmol) of ligand, 1.25 eq. of EtMgBr and 0.2 mmol of 1a in 2 mL of solvent at −80 °C. Conversions were determined by GC. *Isolated yields obtained after column chromatography. *Determined by chiral HPLC analysis. (R) configuration assigned by comparison of the optical rotation with literature data (ref. 5). *2.5 mol% of CuBr·SMe₂ and 3 mol% of L3 were used at 0.4 mmol scale.

### Scheme 2 Substrate scope for the enantioselective addition of Grignard reagents to chromones.

- **2a**: 95% ee, 81% yield, 94% ee
- **2b**: 80% yield, 96% ee
- **2c**: 87% yield, 96% ee
- **2d**: 53% yield, 86% ee
- **2e**: 82% yield, 98% ee
- **2f**: 79% yield, 85% ee
- **2g**: 77% yield, 75% ee
- **2h**: 70% yield, 94% ee
- **2i**: 79% yield, 97% ee
- **2j**: 93% yield, 92% ee
- **2k**: 75% yield, 92% ee
- **2l**: 85% yield, 90% ee
- **2m**: 81% yield, 89% ee
- **2n**: 81% yield, 92% ee
corresponding natural product ent-flindersiachromone\(^\text{14}\) (2g) in 77% yield and 75% ee. Remarkably, the catalytic system tolerates the use of more challenging secondary alkyl Grignard reagents affording the corresponding products 2h, i with good yields and enantioselectivities.

Different substituted chromones bearing electron-donating and electron-withdrawing groups at the 6 or 7 position were also studied. Under the optimised reaction conditions, good yields and high enantiomeric excesses were obtained independently of the electronic character of the substituent in the aromatic ring of the chromone. In addition, the reaction could be carried out on a 2.0 mmol scale with 1 mol% of the catalyst (Scheme 3) to give the corresponding \((R)\)-2-ethylchroman-4-one 2a in 81% yield and 94% ee.

Once we examined the scope of this asymmetric conjugate addition, we turned our attention to the study of the reactivity of the corresponding chiral magnesium enolate 8.\(^\text{15}\) After the addition of ethylmagnesium bromide, enolate 8 was subsequently trapped with benzaldehyde (Scheme 3) to provide the corresponding aldol product in excellent yield. The trans-substituted\(^\text{7}\) product 9 was exclusively obtained in 90% yield, as a mixture of only 2 diastereomers as determined by \(^1\)H NMR analysis.

The chiral 2-ethylchromanone 2a (Scheme 4) can also be easily transformed into versatile building blocks such as benzodioxepinones. \((R)\)-2-ethylchroman-4-one 2a was oxidised to the corresponding \((R)\)-4-ethyl-3,4-dihydro-2H-benzo[b][1,4]dioxepin-2-one (10) in the presence of meta-chloroperoxybenzoic acid in good yield without erosion of the enantiomeric excess.

In summary, we have developed a highly regio- and enantioselective copper catalysed conjugate addition of Grignard reagents to chromones. The corresponding chiral 2-alkylchromanones are obtained in good yields (up to 98%) and with high enantioselectivities (75–98% ee). These compounds are valuable intermediates for the synthesis of versatile optically active building blocks.

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**Notes and references**


14. When MeMgBr was used a low yield and low enantiomeric excess were obtained.
