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Copper-Catalyzed Asymmetric 1,2-Addition of Grignard Reagents to 3-Acyl 2H-chromenes

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Abstract Enones in which the carbon–carbon double bond is part of the pharmacologically important 2H-chromene (2H-1-benzopyran) nucleus undergo asymmetric copper-catalyzed 1,2-addition of Grignard reagents. High yields and enantiomeric excesses up to 84% are obtained and access to these novel enantio-enriched tertiary alcohols is provided.

Key words asymmetric catalysis, Grignard reagents, copper catalysis, 1,2-addition, 2H-chromenes

Complementary to the well-known asymmetric copper-catalyzed conjugate addition (1,4-addition) of Grignard reagents¹ we reported in 2011 on a copper-diphosphine catalyst that performs enantioselective 1,2-addition reactions of Grignard reagents to enones.^{2–4} The alkylcopper species apparently outcompetes the Grignard reagent in the addition to the carbonyl group, and for several types of enones the yields and ee obtained are very high.⁵ Until then, just a few examples of enantioselective 1,2-addition reactions employing Grignard reagents had been described. Seebach reported on the use of stoichiometric TADDOL ligand combined with alkyl Grignard reagents and organolithium reagents for the enantioselective 1,2-addition to ketones.⁶ A catalytic enantioselective 1,2-addition of Grignard reagents to ketones had been reported in 2006 by Hatano et al.⁷ In this system, the addition of catalytic ZnCl₂ to the alkyl Grignard reagents is required. More recent examples, also using aryl Grignard reagents, were reported by the groups of Yus⁸ and Gilheany.⁹

It turned out that the substrate scope of the alkyl Grignard reagent/copper-diphosphine catalyst system could be considerably expanded with arylalkyl ketones,¹⁰ aryl heteroaryl ketones,¹¹ acylsilanes,¹² silyl ketimines,¹³ alkenyl-substituted aromatic N-heterocycles,¹⁴ and ketimines.¹⁵ In

addition, the method was applied in natural product synthesis.¹⁶ The originally used enone substrates, however, had a rather fixed substitution pattern with a methyl, phenyl, or bromide substituent at the α -position of the double bond (Scheme 1). In order to get more insight into the substrate

requirements for this reaction, and to expand the substrate scope, we desired to vary the substituent at the α -position and study the effect on the selectivity and the enantioselectivity of the copper-catalyzed Grignard addition reaction.

A hydroxy-methylene unit at the α -position, as in **1** (Figure 1), was chosen as a suitable expansion of the substrate scope.

Figure 1 Target substrate for the 1,2-addition reaction

The synthesis of **1** proceeded according to literature (Scheme 2).¹⁷ Baylis–Hillman reaction of benzaldehyde and methyl vinyl ketone afforded **2**, although due to concomitant polymerization of the methyl vinyl ketone the yield was with 50% just moderate. As the starting materials are low cost, this was compensated for by performing the reaction at a large scale. Subsequent acetylation, rearrangement, and acetate hydrolysis,¹⁸ gave **1** in 50% yield over two steps.

Scheme 2 Synthesis of enone **1**

With **1** in hands, the 1,2-addition reaction was studied at low temperature employing isobutylmagnesium bromide, one of the Grignard reagents that gave the highest *ee* in this reaction with the previous substrates employed. Tertiary alcohol **7** was obtained in a very low yield, however, and turned out to be racemic (Scheme 3). Mainly unreacted starting material was observed, even with an excess of Grignard reagent.

From previous studies we know that enolization of the substrate takes over if the addition reaction is slow. We speculate that the lack of reactivity is due to coordination of the magnesium alkoxide, formed upon deprotonation by the Grignard reagent, to the ketone. This coordination results in a change of conformation of the enone from the

(preferred) *s-cis* conformation to the *s-trans* conformation (Scheme 4), the last one being apparently ineffective in the reaction. Alternatively, the copper catalyst is inhibited by bidentate coordination to this alkoxy ketone. As depicted in Scheme 4, the reaction mechanism for the 1,2- and 1,4-addition reactions probably both run via copper–Grignard complex **I**. It forms a π -complex with the double bond of the *s-cis* enone and, upon alkyl transfer, the 1,2-addition product is formed.

The reaction was subsequently studied using the TBDMS-protected derivative of **1**, but the result was the same; a low yield and absence of enantioselectivity. We assume that as long as the oxygen can participate in bidentate coordination of either the magnesium or the copper, this will prohibit (enantioselective) addition.

To challenge this hypothesis, it was decided to 'lock' the oxygen in a cyclic ether, so that the *s-trans* conformation could no longer be stabilized by coordination of the alkoxy group and the ketone to the copper/magnesium. The 3-acyl-substituted 2*H*-chromenes **8–13** were synthesized by reacting a series of substituted salicyl aldehydes with methyl vinyl ketone under basic conditions (Scheme 5).¹⁹ The deprotonated hydroxyl group of the salicyl aldehyde adds in a Michael-type addition reaction to the enone. Subsequent aldol condensation gives the corresponding 2*H*-chromenes.

These substrates are interesting as the 2*H*-chromene core is pharmacologically important and is found in natural products.^{20–22} Nevertheless, except for **9**, the synthesis of which gave in our hands a somewhat lower yield than reported, the other compounds had not been described before. 3-Acyl-substituted 2*H*-chromenes have not been used in 1,4- or 1,2-addition reactions.

The copper-catalyzed asymmetric 1,2-addition to **9** was carried out employing isobutylmagnesium bromide. Product **14** was obtained in good yield and a high *ee* of 80% (Table 1, entry 1). This result supports our hypothesis that preventing the alkoxide or ether from coordinating to the catalyst or magnesium leads to (a larger amount of) the *cis* enone and in turn to an enantioselective addition reaction. The yields and the enantioselectivities are slightly lower compared to the previous studied substrates, the α -bromo- and α -methyl-substituted enones. With the same substrate we performed the reaction with the linear Grignard reagent

Proposed mechanism for the 1,4- and 1,2-addition reactions

Proposed ineffective *s-trans* enone conformations:

Scheme 4 The proposed mechanism for the 1,2- and 1,4-addition reaction

ethylmagnesium bromide, and product **15** was obtained in a lower yield and a considerably lower *ee*, in line with our previous reports.⁴

Subsequently, we decided to study the effect of substituents on the aromatic ring of the substrate on the yield and

enantioselectivity of the addition reaction. Substrates **10**, **11**, and **12** were reacted with isobutylmagnesium bromide, and in all cases the products were obtained in good yields and high *ee*. Varying the substituent on the ring apparently does not have a large influence on the *ee*, a similar trend as

Table 1 Copper-Catalyzed 1,2-Addition of Grignard Reagents to 3-Acyl 2H-chromenes²³

Entry	Starting material	R ¹	R ²	R ³	R ⁴	Product	Yield (%) ^a	<i>ee</i> (%) ^b
1	9	H	H	Me	<i>i</i> -Bu	14	70	80
2	9	H	H	Me	Et	15	50	40
3	11	Cl	H	Me	<i>i</i> -Bu	16	91	80
4	12	F	H	Me	<i>i</i> -Bu	17	97	84
5	10	Me	H	Me	<i>i</i> -Bu	18	80	80
6	9	H	H	Me	CH ₂ Cy	19	78	58
7	9	H	H	Me	<i>i</i> -Pr	20	70	18
8	8	H	H	Et	<i>i</i> -Bu	21	70	80
9	13^c	H	Me	Me	<i>i</i> -Bu	22	62	70

^a Isolated yield.

^b Enantiomeric excess determined by chiral HPLC.

^c de = 68%.

Scheme 5 Synthesis of the desired substrates for the asymmetric 1,2-addition reaction

observed for asymmetric 1,2-addition reactions to methyl arylketones.¹⁰

Subsequently, we used different branched Grignard reagents in combination with **9**. Cyclohexylmagnesium bromide was employed, giving the expected product with a lower *ee* compared to isobutylmagnesium bromide. When isopropylmagnesium bromide was used, the product was obtained with very low *ee* (Table 1, entry 7). Isopropylmagnesium bromide is an α -branched Grignard reagent, that consistently gives low enantioselectivities in asymmetric 1,2-addition reactions.⁵ Apparently the highest *ee* are obtained with β -branched Grignard reagents.

Next, the steric effect of a larger substituent on the carbonyl function was studied. The combination of **8**, in which the 2*H*-chromene has a propionyl instead of an acyl substituent, with isobutylmagnesium bromide afforded the product with the same yield and *ee* as for **9**. Increasing the sterics at that position apparently does not affect the *ee*. Finally, steric effects at the 2-position were studied. When the reaction was performed with *rac*-**13**, the product was obtained with a *de* of 68% and an *ee* of 70%. Apparently, a substituent at the 3-position does have an effect on the asymmetric 1,2-addition and leads to some extent to a kinetic resolution.

Unfortunately, the absolute configuration of the products could not be determined despite attempts to obtain crystals suitable for X-ray diffraction or chemical correlation to a compound of known configuration. The absolute configuration is therefore conferred from that of the substrates studied previously (Scheme 1).

In this study, the substrate scope of the enantioselective copper/diphosphine-catalyzed 1,2-addition of Grignard reagents has been enlarged. Employing substrates with a CH₂OH or CH₂OTBDMS group at the α -position of the double bond led to very poor conversions and no enantioselectivity. We hypothesize that this is due to coordination of this oxygen to copper or magnesium, leading to a substrate conformation that is not suitable for asymmetric 1,2-addi-

tion. Upon locking the oxygen substituent in a 2*H*-chromene core, thereby preventing chelation, high *ee* and good yields are obtained. The regioselectivity for the reaction was remarkable; no conjugate addition product was observed. The observation that the 2*H*-chromene core can be equipped with an enantio-enriched tertiary hydroxyl group might be interesting for medicinal chemistry applications, all the more so because methods to prepare enantio-enriched tertiary alcohols are still scarce.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1588532>.

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(23) **General Procedure for the Enantioselective 1,2-Addition 1-[2-(2*H*-Chromen-3-yl)]-4-methylpentan-2-ol (**14**)**

To a flame-dried Schlenk tube containing a magnetic stirring bar, CuBr-SMe₂ (15 μmol, 3.1 mg), **L1** (18 μmol, 10.7 mg), and 3 mL of dry *t*-BuOMe were added. The mixture was left to stir for 10 min. Subsequently, **9** (0.3 mmol, 52 mg) was added to the solution. The mixture was left to stir for 30 min at -78 °C. Isobutylmagnesium bromide (2 M in Et₂O, 1.7 equiv, 0.25 mL) was then added dropwise over 15 min, and the reaction was left to stir for 2 h at -78 °C. The reaction was quenched with H₂O (2 mL), allowed to warm up to r.t., and diluted with Et₂O. NH₄Cl_{aq} was added, and the layers were separated. The aqueous layer was extracted with Et₂O, and the combined organic layers were dried over MgSO₄, filtered, and concentrated at reduced pressure to

afford **14** in 70% yield as a yellowish oil after flash chromatography (SiO₂, *n*-pentane/Et₂O (90:10)); 80% *ee*. Retention times on chiral HPLC: *t*_R = 28.2 min and 31.8 min. ¹H NMR (400 MHz, CDCl₃): δ = 7.11 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.03 (dd, *J* = 7.4, 1.5 Hz, 1 H), 6.92–6.86 (m, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.46 (s, 1 H), 4.73 (d, *J* = 0.7 Hz, 2 H), 1.75 (m, 1 H), 1.57 (dd, *J* = 5.9, 2.2 Hz, 3 H), 1.40 (s, 3 H), 0.96 (t, *J* = 7.0 Hz, 6 H). ¹³C NMR (101 MHz, CDCl₃): δ = 153.2, 134.0, 128.7, 126.8, 123.0, 121.5, 117.7, 115.4, 74.3, 65.6, 48.8, 28.0, 24.5, 24.5, 24.4. [α]_D²⁰ -7.8 (c 1.0, CHCl₃). HRMS (ESI⁻): *m/z* calcd for [C₁₅H₂₀O₂ - H]⁻: 231.139; found: 231.138.

Analytical Data for Compound 21

80% *ee*. Retention times on chiral HPLC: *t*_R = 13.2 min and 14.4 min.

¹H NMR (400 MHz, CDCl₃): δ = 7.11 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.04 (dd, *J* = 7.5, 1.6 Hz, 1 H), 6.90 (td, *J* = 7.4, 1.1 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.48 (s, 1 H), 4.63 (s, 2 H), 1.86–1.74 (m, 1 H), 1.64–1.46 (m, 5 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H), 0.87 (t, *J* = 7.4 Hz, 3 H). ¹³C NMR (101 MHz, CDCl₃): δ = 153.1, 138.1, 128.6, 126.7, 123.0, 121.5, 119.0, 115.4, 65.8, 47.9, 32.9, 24.6, 24.4, 24.2, 7.5. [α]_D²⁰ +11.0 (c 1.0, CHCl₃). HRMS (ESI⁺): *m/z* calcd for [C₁₆H₂₂O₂ + H]⁺: 247.169; found: 247.169.