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Catalytic asymmetric conjugate addition of Grignard reagents to coumarins—synthesis of versatile chiral building blocks†

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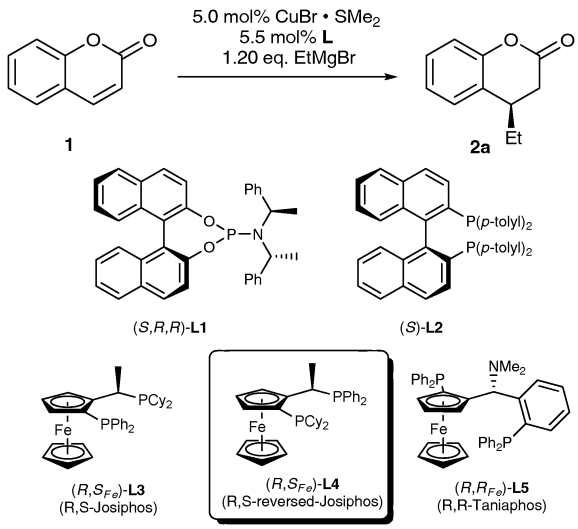
A new protocol for the Cu-catalysed asymmetric conjugate addition of Grignard reagents to coumarins has been developed. The corresponding products are formed in high yields and enantioselectivities. Through a sequential protocol involving conjugate addition followed by nucleophilic ring opening of the chiral enolate, chiral esters and amides are readily accessible.

The Cu-catalysed asymmetric conjugate addition reaction with organometallic reagents represents important methodology for the construction of stereogenic centers and has found widespread application in synthesis.[1–6] We were interested in the expansion of this transformation for the construction of chiral heterocycles, in particular coumarin derivatives. Coumarins are important synthetic intermediates, as the resulting chiral lactones serve as starting points for a variety of further transformations.

The enantioselective conjugate addition to coumarins with arylboronic acids employing chiral Rh-complexes has been reported,[7,8] as well as the asymmetric conjugate reduction[9] with Cu–H complexes.[10,11] The possibility to introduce alkyl groups at the newly formed stereogenic center, however, has been investigated only with the related activated nitro- and 3-acyl coumarin derivatives.[12,13] We report herein the development of the Cu-catalysed asymmetric conjugate addition of Grignard reagents to unactivated coumarins using ferrocenyl-based bisphosphine ligands.

The low reactivity of coumarin (**1**) made it necessary to develop a new catalyst system. Our investigation started with the Cu-catalysed conjugate addition of dialkylzinc reagents to **1** employing phosphoramidite ligands.[14,15] This catalytic system did not prove to be reactive enough and did not result in any turnover (Table 1, entry 1). When we turned our attention to the conjugate addition reaction with the more reactive Grignard reagents[1,2] employing Josiphos ligand **L3**, full conversion to the desired 1,4-adduct **2a** with 82% ee was observed,[16] when **1** was reacted with ethylmagnesium bromide (Table 1, entry 3). Ligand **L4**, which had been successfully employed in the related 1,6-conjugate addition previously,[17] proved to be the ligand of choice to reach high levels of enantiocontrol. At −78 °C, the conjugate addition product **2a** was formed with 96% ee, albeit in low yield (Table 1, entry 4). Neither the Taniaphos ligand **L5** nor the Cu-tolBINAP

Table 1 Ligand screening/optimisation[a]



Entry	Ligand	Solvent	Temperature/°C	Conversion (yield)[b]	ee[c]
1[d]	**L1**	Toluene	−40	—	—
2[e]	**L2**	MTBE	−40	Full (55%)	21% (*R*)
3	**L3**	MTBE	−78	Full (57%)	82% (*R*)
4	**L4**	MTBE	−78	50% (26%)	96% (*R*)
5	**L4**	CH_2Cl_2	−78	40% (25%)	81% (*R*)
6[f]	**L4**	MTBE	−78	80% (62%)	95% (*R*)
7	**L4**	**MTBE**	**−72**	**Full (92%)**	**95% (*R*)**
8	**L5**	MTBE	−78	Traces (−)	—

[a] Reaction conditions: $CuBr{\cdot}SMe_2$ (0.01 mmol, 5.0 mol%, 2.1 mg) and 5.5 mol% (0.0105 mmol) of the appropriate ligand were dissolved in 5 mL solvent and stirred at RT for 15 min. After cooling to the appropriate temperature, 1.20 eq. of EtMgBr solution (c = 3.0 in Et_2O, 0.24 mmol, 0.08 mL) were added dropwise over a period of 10 min. Then, 1.00 eq. of a coumarin solution (0.20 mmol, 0.029 g) in 2.5 mL solvent was added dropwise over a period of 1 h. Quenching with 2.0 mL of HCl in Et_2O (2 M). [b] Isolated yield. [c] Determined by chiral HPLC. [d] 11.0 mol% of ligand, and 5.0 mol% of $Cu(OTf)_2$ and 2.0 eq. $ZnEt_2$ were used. [e] 5.0 mol% of CuI was used. [f] 2.5 eq. of EtMgBr were used.

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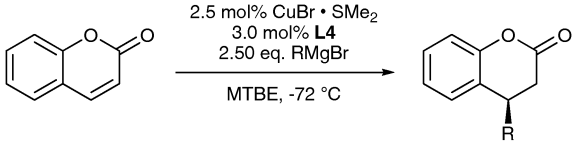
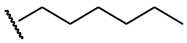
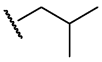
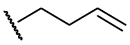
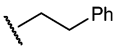
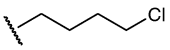
† Electronic supplementary information (ESI) available: Full experimental details and characterization of all compounds. See DOI: 10.1039/c0cc05160h

Table 2 Scope of Grignard reagents[a]

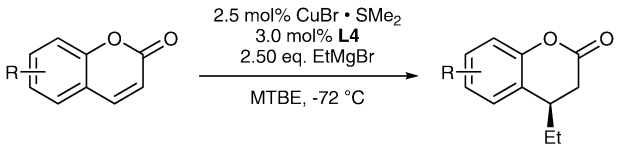


1 **2a-i**

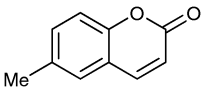
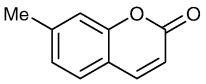
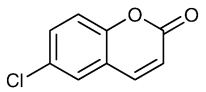
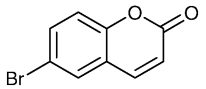
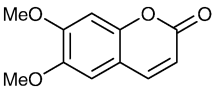
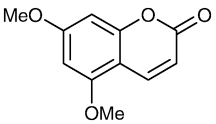
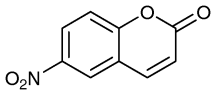
Entry	R		Yield[b]	ee[c]
1		**2a**	96%	95%
2		**2b**	—	—
3		**2c**	95%	99%
4		**2d**	95%	63%
5		**2e**	72%	93%
6[d]		**2f**	66%	93%
7[d]		**2g**	73%	94%
8[d,e]		**2h**	46%	98%
9		**2i**	Traces	—

[a] For reaction conditions, see ESI.† [b] Isolated yields. [c] Determined by chiral HPLC. [d] 5.0 mol% $CuBr{\cdot}SMe_2$ and 5.5 mol% **L4** were used. [e] The product was isolated as a 1 : 1 mixture with the dehalogenated product, the yield indicated corresponds to pure **2h**.

Table 3 Scope of coumarins[a]



3a-h **4a-h**

Entry	Coumarin **3**	Product	Yield[b]	ee[c]
1		**4a**	92%	94%
2		**4b**	93%	97%
3		**4c**	80%	95%
4		**4d**	86%	96%
5[d]		**4e**	55%	64%
6[d]		**4f**	66%	48%
7[d]		**4g**	Traces	—

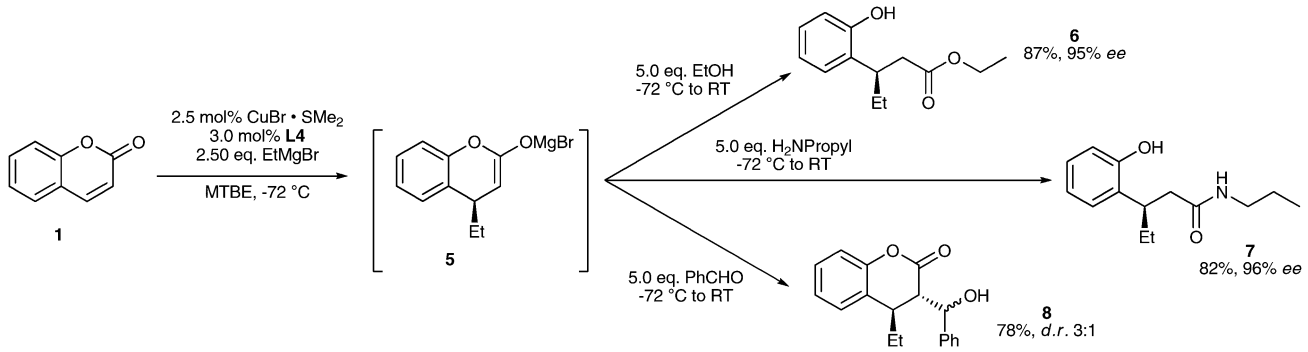
[a] For reaction conditions, see ESI.† [b] Isolated yields. [c] Determined by chiral HPLC. [d] 5.0 mol% $CuBr{\cdot}SMe_2$ and 5.5 mol% **L4** were used.

catalyst[18] (**L2**) could compete with these findings in terms of conversion or enantioselectivity (Table 1, entries 2 and 8). It appeared that fine-tuning of the electronic properties of the ligand was essential to obtain the conjugate addition product with high enantioselectivity. To achieve full conversion with **L4**, higher amounts of Grignard reagent (2.50 eq.) were necessary along with a slightly higher reaction temperature of −72 °C (Table 1, entry 7).[19] Furthermore, the catalyst loading could be lowered to 2.5 mol% of Cu without compromising the yield or the enantioselectivity.

With the optimised conditions in hand, we set off to investigate the scope of the reaction. A variety of alkyl Grignard reagents are compatible with this transformation (Table 2).

Compared to our previously reported conditions with ferrocenyl-based ligands,[4–6] similar trends in reactivity were observed, which typically implies high catalyst control of this asymmetric transformation. There is a preference for linear unfunctionalised alkyl Grignard reagents, which can be employed to produce chiral lactones **2** in high yields and excellent enantioselectivites ranging from 93% to 99% ee (Table 2, entries 1, 3, and 5–8). Use of the relatively unreactive methylmagnesium bromide gave no conjugate addition product. As previously observed for enones,[6] α-branched reagents such as isopropylmagnesium bromide gave lower enantioselectivity for **2d**, whereas the β-branched reagent was smoothly transformed into the desired chiral products **2e** with high ee (Table 2, entries 4 and 5). One key feature of the catalyst is the fact that it tolerates functionalised Grignard reagents; an important advantage with foresight to possible synthetic applications of this method. However, slightly higher catalyst loadings (5.0 mol%) were necessary to achieve acceptable results in terms of yields. Butenyl-substituted (**2f**) as well as halogenated products (**2h**) are accessible with excellent enantioselectivities when a higher catalyst loading was employed (Table 2, entries 6 and 8). Attempts to use aryl Grignard reagents such as phenylmagnesium bromide resulted only in trace amounts of the desired product (Table 2, entry 9).

Subsequently, the scope of our new catalytic transformation with regard to substituted coumarins **3** was investigated (Table 3). Methyl substituents in positions 6 and 7 were readily tolerated as the desired conjugate addition products could be isolated with very good yields and enantioselectivities (Table 3, entries 1 and 2). Furthermore, halogen substituents



Scheme 1 Trapping/ring opening reactions of enolate **5**.

are tolerated and addition products **4c** and **4d** are formed with similarly good results (Table 3, entries 3 and 4). Dimethoxy-coumarins **3e** and **3f** could also be converted to the corresponding conjugate addition products, albeit with lower yield and enantioselectivity (Table 3, entries 5 and 6). This marks a limitation of this transformation. Two electron-donating groups on the aromatic ring result in a lower reactivity to conjugate addition reactions compared to coumarin itself. The lower enantioselectivity of **4f** compared to **4e** could be explained by the fact that the methoxy-substituent in the 5-position of **3f** interferes with the Cu-catalyst. The strongly electron-withdrawing nitro-group (Table 3, entry 7) is not tolerated due to fast decomposition of the starting material under the reaction conditions.

One of the major advantages of the conjugate addition to coumarins was discovered during the course of this study: the intermediate chiral magnesium enolate **5** is a highly versatile chiral intermediate and can be converted *in situ* to a variety of important chiral products (Scheme 1).

The high reactivity of intermediate **5** can be exploited in subsequent transformations with both nucleophiles to invoke a ring-opening as well as electrophiles to trap the enolate. When enolate **5** was quenched with ethanol at −72 °C and the solution allowed to warm to room temperature, the resulting chiral ester **6** was isolated in a very good yield and 95% ee. It is important to note that *o*-phenol esters were so far not accessible *via* the known conjugate addition methodology.[1–6] In a similar fashion, amide **7** could be obtained with a good yield. This result marks the first formal catalytic asymmetric conjugate addition to amides, a reaction pathway that was previously elusive. It should be emphasised that catalytic asymmetric conjugate addition to α,β-unsaturated amides is not achieved due to the poor electron-withdrawing ability of the amide group.[2]

It is known in the literature that the enolates of conjugate addition reactions can be trapped with a variety of electrophiles.[14,20–22] Accordingly, enolate **5** could be reacted with electrophiles such as benzaldehyde to give the corresponding aldol product with three contiguous stereocenters in good yields. As expected, the *trans*-disubstituted product is exclusively formed, as only two diastereomers could be detected on the basis of ^{1}H NMR experiments, which we attribute to incomplete stereocontrol at the exocyclic stereocenter.

To conclude, we have developed a new, highly selective Cu-catalysed conjugate addition of Grignard reagents to coumarins. The corresponding chiral products are available with excellent enantioselectivities. Furthermore, we have demonstrated that the corresponding enolate is a highly versatile starting point for the synthesis of a variety of chiral products such as esters and amides which were previously unavailable *via* direct conjugate addition to protocols. The final example marks the first formal conjugate addition to amides. The investigation of the scope of this interesting transformation is currently underway.

Notes and references

1 T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2009, **38**, 1039–1075.
2 S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824–2852.
3 A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies and M. Diéguez, *Chem. Rev.*, 2008, **108**, 2796–2823.
4 F. López, S. R. Harutyunyan, A. Meetsma, A. J. Minnaard and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2005, **44**, 2752–2756.
5 R. D. Mazery, M. Pullez, F. López, S. R. Harutyunyan, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2005, **127**, 9966–9967.
6 F. López, S. R. Harutyunyan, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2004, **126**, 12784–12785.
7 G. Chen, N. Tokunaga and T. Hayashi, *Org. Lett.*, 2005, **7**, 2285–2288.
8 C. Defieber, J. F. Paquin, S. Serna and E. M. Carreira, *Org. Lett.*, 2004, **6**, 3873–3876.
9 C. Deutsch, N. Krause and B. H. Lipshutz, *Chem. Rev.*, 2008, **108**, 2916–2927.
10 B. D. Gallagher, B. R. Taft and B. H. Lipshutz, *Org. Lett.*, 2009, **11**, 5374–5377.
11 H. Kim and J. Yun, *Adv. Synth. Catal.*, 2010, **352**, 1881–1885.
12 J. P. G. Versleijen, A. M. van Leusen and B. L. Feringa, *Tetrahedron Lett.*, 1999, **40**, 5803–5806.
13 X. P. Tang, A. J. Blake, W. Lewis and S. Woodward, *Tetrahedron: Asymmetry*, 2009, **20**, 1881–1891.
14 J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486–2528.
15 B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos and A. H. M. de Vries, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2620–2623.
16 Trace amounts of 1,2-addition products were observed.
17 T. den Hartog, S. R. Harutyunyan, D. Font, A. J. Minnaard and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2008, **47**, 398–401.
18 S. Y. Wang, S. J. Ji and T. P. Loh, *J. Am. Chem. Soc.*, 2007, **129**, 276–277.
19 The enantioselectivity was unaffected up to a temperature of −65 °C.
20 L. A. Arnold, R. Naasz, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2001, **123**, 5841–5842.
21 G. P. Howell, S. P. Fletcher, K. Geurts, B. ter Horst and B. L. Feringa, *J. Am. Chem. Soc.*, 2006, **128**, 14977–14985.
22 X. Rathgeb, S. March and A. Alexakis, *J. Org. Chem.*, 2006, **71**, 5737–5742.