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Catalytic asymmetric conjugate addition of Grignard reagents to chromones†

Cite this: *Chem. Commun.*, 2013, **49**, 5933

Received 26th April 2013,
Accepted 16th May 2013

DOI: 10.1039/c3cc43105c

www.rsc.org/chemcomm

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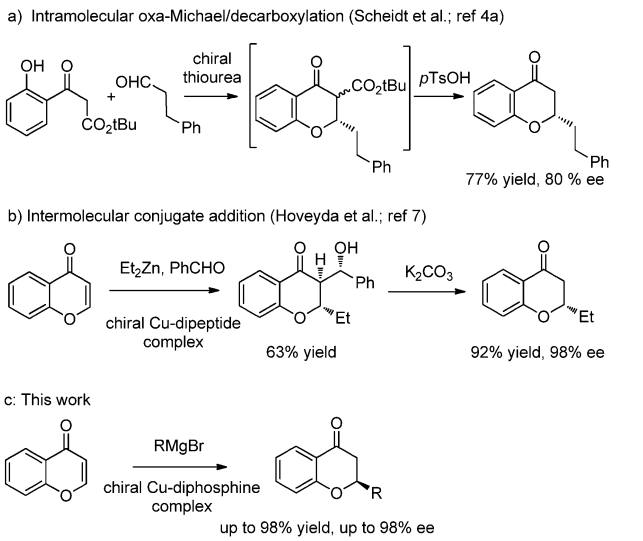
A highly regio- and enantioselective copper catalysed direct conjugate addition of Grignard reagents to chromones has been developed taking advantage of the reduced reactivity of the resulting magnesium enolates. This methodology tolerates a broad scope of alkyl Grignards including secondary alkyl magnesium 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-alkylchromanones[3] have been reported: an intramolecular oxa-Michael[4,5] 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).[4a] Similarly, Feng and coworkers[5] reported the synthesis of (*S*)-2-ethylchromanone (85% ee) using a chiral *N*,*N*′-dioxide nickel(II) complex. Finally, Wallace *et al*. described the synthesis of enantioenriched 2-methylchroman-4-one derivatives by a diastereoselective intermolecular addition to chiral 3-sulfinylchromones.[6] 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



Scheme 1 General catalytic methods for the synthesis of chiral 2-alkylchromanones.

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 acyclic[9] and cyclic enones.[10] Recently, our group reported the Cu-catalysed 1,4-addition of Grignard reagents to unsaturated heterocycles such as coumarins[11] and 2*H*-pyran-2-ones.[12] We envisioned that this approach might

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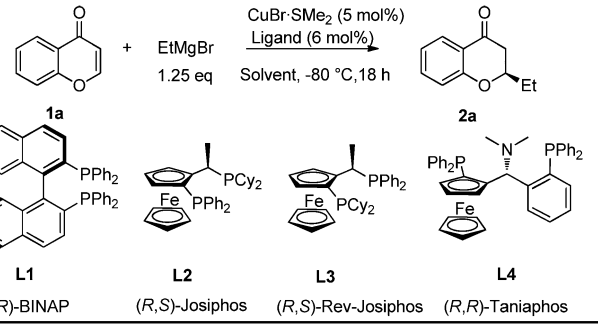
† Electronic supplementary information (ESI) available: General procedures, characterization data, ^{1}H and ^{13}C NMR spectra, and chiral analysis of all the products. See DOI: 10.1039/c3cc43105c

Table 1 Optimisation of the reaction conditions[a]

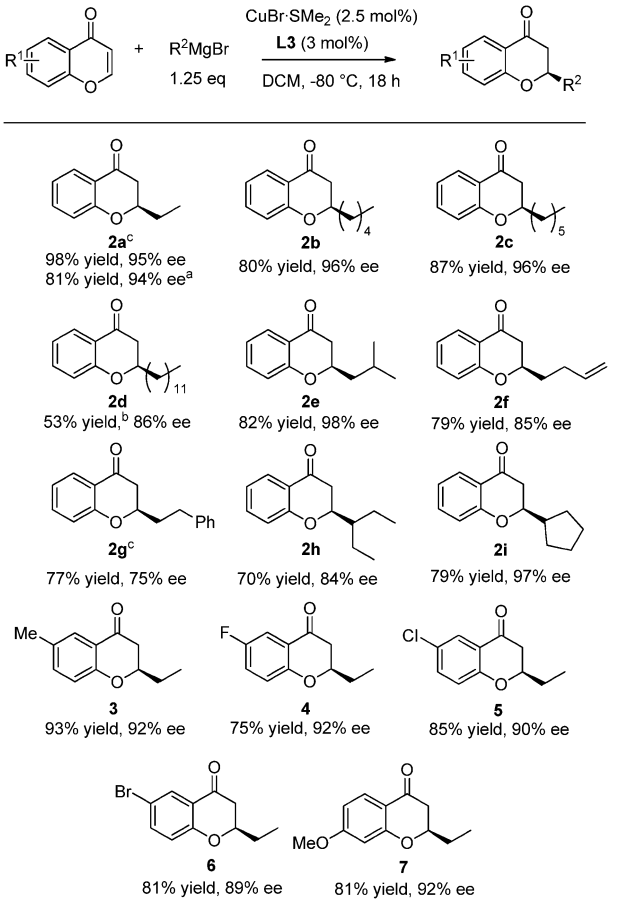


Entry	Ligand	Solvent	Conversion[b] (yield)[c]	ee[d]
1	**L1**	MTBE	60% (49%)	0
2	**L2**	MTBE	87% (83%)	86
3	**L3**	MTBE	Full (93%)	91
4	**L4**	MTBE	35% (34%)	4
5	**L3**	THF	Full (95%)	0
6	**L3**	Toluene	Full (76%)	75
7	**L3**	Ether	96% (84%)	73
8	**L3**	DCM	Full (90%)	94
9[e]	**L3**	DCM	Full (98%)	95

[a] Reaction conditions: $CuBr{\cdot}SMe_2$ (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. [b] Conversions were determined by GC. [c] Isolated yields obtained after column chromatography. [d] Determined by chiral HPLC analysis. (*R*) configuration assigned by comparison of the optical rotation with literature data (ref. 5). [e] 2.5 mol% of $CuBr{\cdot}SMe_2$ and 3 mol% of **L3** were used at 0.4 mmol scale.

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.

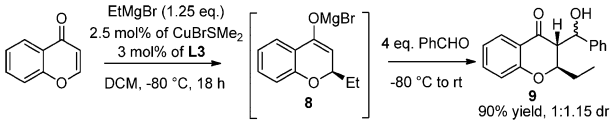
The reaction between 4*H*-chromen-4-one (**1a**) and ethylmagnesium bromide was chosen as a model reaction for the optimisation of this conjugate addition (Table 1). First we tested different chiral diphosphine ligands using MTBE as a solvent at −80 °C. With (*R*)-BINAP (**L1**), the corresponding 2-ethylchroman-4-one **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,[11,12] 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,[9b] 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.



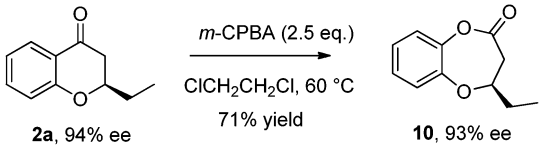
Scheme 2 Substrate scope for the enantioselective addition of Grignard reagents to chromones. Reaction conditions: R^2MgBr (0.5 mmol, 1.25 eq.) was added to a stirred solution of $CuBr{\cdot}SMe_2$ (0.01 mmol) and **L3** (0.012 mmol) in 2 mL of dry DCM at −80 °C; chromone (0.4 mmol) in 1 mL of DCM was added dropwise over 1 h. Isolated yields obtained after column chromatography. Enantiomeric excess was determined by chiral HPLC. [a]2 mmol scale, 1 mol% of $CuBr{\cdot}SMe_2$ and 1.5 mol% of **L3**. [b]Full conversion was not achieved. [c](*R*) configuration assigned by comparison of the optical rotation with literature data of compounds **2a** (ref. 5) and **2g** (ref. 4*a*), and on the assumption of a uniform mechanistic pathway for the rest of the compounds.

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[13] 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 (R^2 = ^{i}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



Scheme 3 Trapping of enolate **8** with benzaldehyde.



Scheme 4 Baeyer–Villiger oxidation of compound **2a**.

corresponding natural product *ent*-flindersiachromanone[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 to afford 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**.[15] After the addition of ethylmagnesium bromide, enolate **8** was subsequently trapped with benzaldehyde (Scheme 3) to give the corresponding aldol product in excellent yield. The *trans*-substituted[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-2*H*-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.

Financial support from The Netherlands Organization for Scientific Research (NWO-CW) and Dutch National Research School Combination Catalysis Controlled by Chemical Design (NRSC-Catalysis) is gratefully acknowledged. C.V. was supported by Intra-European Marie Curie fellowship (FP7-PEOPLE-2011-IEF) (Contract number: 300826). We thank T. D. Tiemersma-Wegman (HRMS) and M. Smith (GC and HPLC) for technical assistance.

Notes and references

1 (*a*) B. A. Bohm and J. B. Harbone, *The Flavonoids. Advances in Research Since 1980*, ed. B. A. Bohm and J. B. Harbone, Chapman and Hall, New York, 1988; (*b*) Ø. M. Andersen and K. R. Markham, *Flavonoids: Chemistry, Biochemistry and Applications*, CRC, Taylor & Francis, Boca Raton, FL, 2006; (*c*) B. A. Bohm, *Introduction to Flavonoids*, Harwood Academic Publishers, Amsterdam, 1998; (*d*) G. P. Ellis, *Chromenes, Chromanones and Chromones*, John Wiley & Sons, New York, 1977.
2 A. E. Nibbs and K. A. Scheidt, *Eur. J. Org. Chem.*, 2012, 449–462.
3 For synthesis of chiral 2-alkylchromanones *via* enzymatic resolution see: (*a*) M. Kawasaki, H. Kakuda, M. Goto, S. Kawabata and T. Kometani, *Tetrahedron: Asymmetry*, 2003, **14**, 1529–1534; (*b*) M. Kawasaki, H. Yoshikai, H. Kakuda, N. Toyooka, M. Goto, S. Kawabata and T. Kometani, *Heterocycles*, 2006, **68**, 483–493; (*c*) M. Kawasaki, Y. Asano, K. Katayama, A. Inoue, C. Hiraoka, H. Kakuda, A. Tanaka, M. Goto, N. S. Toyooka and T. Kometani, *J. Mol. Catal. B: Enzym.*, 2008, **54**, 93–102.
4 (*a*) M. M. Biddle, M. Lin and K. A. Scheidt, *J. Am. Chem. Soc.*, 2007, **129**, 3830–3831; (*b*) For other synthesis of chiral 2-alkylchromones using cinchona alkaloids see: T. Ishikawa, Y. Oku, T. Tanaka and T. Kumamoto, *Tetrahedron Lett.*, 1999, **40**, 3777–3780; (*c*) H.-F. Wang, H.-F. Cui, Z. Chai, P. Li, C.-W. Zheng, Y.-Q. Yang and G. Zhao, *Chem.–Eur. J.*, 2009, **15**, 13299–13303.
5 L. Wang, X. Liu, Z. Dong, X. Fu and X. Feng, *Angew. Chem., Int. Ed.*, 2008, **47**, 8670–8673.
6 (*a*) S. T. Saengchantara and T. W. Wallace, *Tetrahedron*, 1990, **46**, 6553–6564; (*b*) K. J. Hodgetts, K. I. Maragkou, T. W. Wallace and R. C. R. Wotton, *Tetrahedron*, 2001, **57**, 6793–6804; (*c*) For other synthesis of chiral 2-methylchromones see: A. V. Ramao Rao, A. S. Gaitonde, K. R. C. Prakash and S. Prahlada Rao, *Tetrahedron Lett.*, 1994, **35**, 6347–6350; (*d*) Y. Noda and M. Watanabe, *Helv. Chim. Acta*, 2002, **85**, 3473–3477; (*e*) Z. Zhang, C. Pana and Z. Wang, *Chem. Commun.*, 2007, 4686–4688.
7 M. K. Brown, S. J. Degrado and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2005, **44**, 5306–5310.
8 For reviews see: (*a*) F. López, A. J. Minnaard and B. L. Feringa, *Acc. Chem. Res.*, 2007, **40**, 179–188; (*b*) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies and M. Diéguez, *Chem. Rev.*, 2008, **108**, 2796–2823; (*c*) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824–2852; (*d*) T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2009, **38**, 1039–1075; (*e*) S. Y. Wang and T. P. Loh, *Chem. Commun.*, 2010, **46**, 8694–8703.
9 (*a*) M. van Klaveren, F. Lambert, D. J. F. M. Eijkelamp, D. M. Grove and G. van Koten, *Tetrahedron Lett.*, 1994, **35**, 6135–6138; (*b*) F. López, S. R. Harutyunyan, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2004, **126**, 12784–12785.
10 (*a*) B. L. Feringa, R. Badorrey, D. Peña, S. R. Harutyunyan and A. J. Minnaard, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5834–5838; (*b*) D. Martin, S. Kehrli, M. d'Augustin, H. Clavier, M. Mauduit and A. Alexakis, *J. Am. Chem. Soc.*, 2006, **128**, 8416–8417; (*c*) Y. Matsumoto, K.-I. Yamada and K. Tomioka, *J. Org. Chem.*, 2008, **73**, 4578–4581; (*d*) T. Robert, J. Velder and H.-G. Schmalz, *Angew. Chem., Int. Ed.*, 2008, **47**, 7718–7721; (*e*) Q. Naeemi, T. Robert, D. P. Kranz, J. Velder and H.-G. Schmalz, *Tetrahedron: Asymmetry*, 2011, **22**, 887–892; (*f*) G. M. Villacorta, C. Pulla Rao and J. S. Lippard, *J. Am. Chem. Soc.*, 1988, **110**, 3175–3182.
11 J. F. Teichert and B. L. Feringa, *Chem. Commun.*, 2011, **47**, 2679–2681.
12 B. Mao, M. Fañanás-Mastral and B. L. Feringa, *Org. Lett.*, 2013, **15**, 286–289.
13 When MeMgBr was used a low yield and low enantiomeric excess were obtained.
14 K. Picker, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, 1976, **29**, 2023–2036.
15 Z. Galeštoková and R. Šebesta, *Eur. J. Org. Chem.*, 2012, 6688–6695.