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COMMUNICATION

A Highly Enantioselective Access to Chiral Chromanones and Thiochromanones by Copper-Catalyzed Asymmetric Conjugated Reduction of Chromones and Thiochromones

Received 00th January 20xx,
Accepted 00th January 20xx

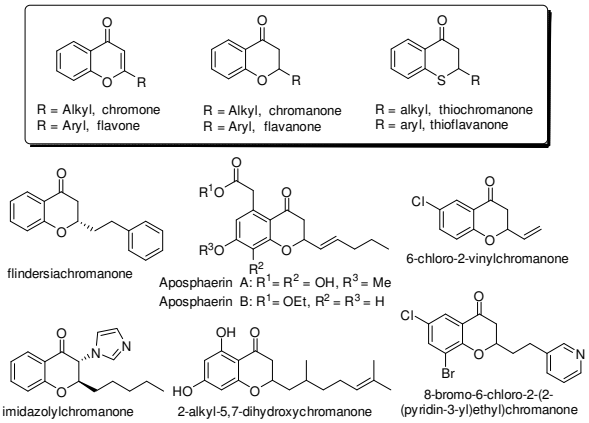
DOI: 10.1039/x0xx00000x

www.rsc.org/

Donglu Xiong, [a] Wenxi Zhou, [a] Zhiwu Lu, [a] Suping Zeng [a] and Jun (Joelle) Wang [a,*]

Chromanone scaffold is a privileged structure in heterocyclic chemistry and drug discovery. A highly efficient copper-catalyzed asymmetric conjugated reduction of chromones is developed to give chiral chromanones with good yields (80-99%) and excellent ees (94->99% *ee*). Particularly noteworthy is that chiral thiochromanones are also constructed by this method in 74-87% yields with 96-97% *ee*. The established asymmetric synthesis paves the way for their further pharmaceutical studies.

Flavonoids are privileged structural motifs in numerous natural products and pharmaceutical molecules, which show many biological activities such as antitumor, antioxidant, antibacterial and anti-inflammatory properties.[1] Chromanone and flavanone which feature a chiral center are subgroups of flavonoid. The structure of chromanone is distinct from chromone by reduction of C_2-C_3 double bond (Scheme 1). This small difference between chromanones and chromones resulted in diverse differences in their bioactivity. Besides naturally occurring chromanone, the synthetic chromanones are important intermediates and interesting building blocks in organic synthesis and design of new lead compounds in drug discovery. Several representative biologically active chromanones are shown in Scheme 1. The natural product flindersiachromanone was isolated from the extracts of the bark of Flindersia laevicarpa.[2] 2-Vinylchromanones, synthetic antibacterial agents, were developed from the natural fungal metabolite Aposphaerin A and B.[3] Imidazolylchromanone showed high potent activity against yeasts comparable to fluconazole.[4] Inspired by the natural products abyssinone II and olympicin A, 2-alkyl-5,7-dihydroxychromanone was designed and synthesized against a broad set of bacterial pathogens.[5] 8-Bromo-6-chloro-2-(2-(pyridin-3-yl)ethyl) chromanone was a synthetic Sirtuin 2 inhibitor, and also showed high antiproliferative activity in breast cancer and lung carcinoma cell lines.[6] Given the high usefulness of this skeleton, the investigation towards facile access of chromanone unites has gained increasing attention.



Scheme 1 Representative structures of biologically active chromanones.

Although the synthesis of chromanones has been reported more intensely in recent years,[7] facile accessing to optically active chromanones remains limited. Besides asymmetric intermolecular conjugate addition to 4-chromanones[8] and intramolecular oxa-Michael addition[9], asymmetric reduction of C_2-substituted chromones is one of the most straightforward ways to synthesize chromanones and their derivatives. Nevertheless, this strategy has not been explored extensively, perhaps due to the tendencies towards overreduction to chromanol or chromane skeletons.[10] In 2013, Glorius report the first asymmetric hydrogenation of chromone and flavone using a chiral Ru–NHC (NHC =*N*-heterocyclic carbene) complex (Scheme 2, Method a).[11] The hydrogenation is not stepwise, and afforded chromanols and flavanols directly. Chiral chromanones and flavanones could be obtained in excellent yields and up to 97% ee after further oxidation with pyridindium chlorochromate (PCC). In the same year, Metz reported a kinetic resolution of racemic flavanones with Rh (III) complex in a mixture of formic acid and triethylamine,

[a] *Department of Chemistry, South University of Science and Technology of China, Shenzhen, Guangdong, 518055, China. Fax: (+86) 755-88018304; E-mail: wang.j@sustc.edu.cn*

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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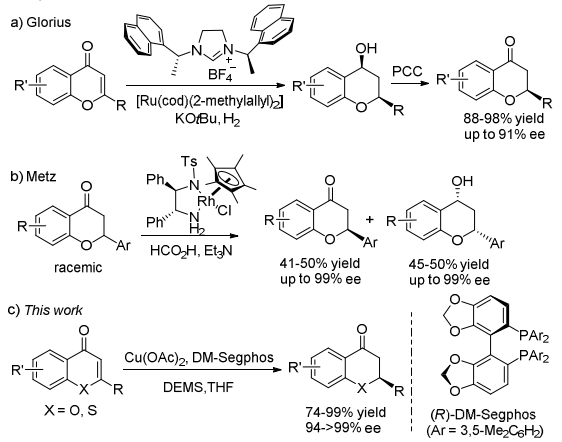
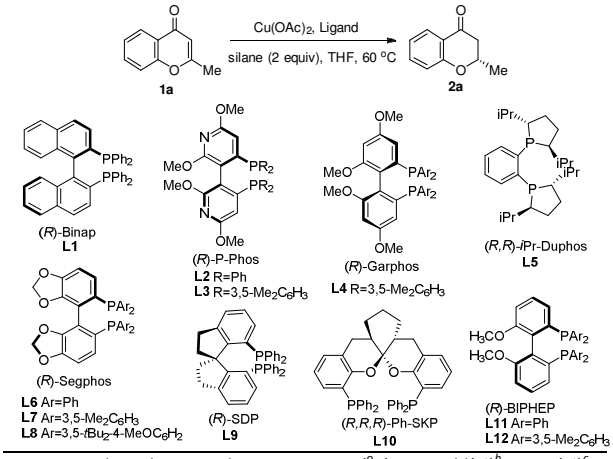
producing chiral flavanones and flavanol in high yields with excellent enantioselectivities (Scheme 2, Method b).[12] These two examples about enantioselective synthesis of flavanones have been successful, but additional studies, which provide practical and direct access to chiral chromanones, are still very desirable. Copper, an abundant base metal, is much cheaper than rhodium and ruthenium. Inspired by the work of Lipshutz and Buchwald in the field of Cu-catalyzed asymmetric conjugate hydrosilylation of α, β-unsaturated carbonyl compounds,[13,14] we develop a Cu-catalyzed asymmetric reduction of chromones, which gives a direct and general access to chiral chromanones with good yields and excellent ees. Particularly noteworthy is that this method could also be applied to thiochromones which were considered as sensitive substrates in transition metal-catalyzed reactions. Furthermore, this method could also give C3-substituted chromanones by trapping the intermediate silyl enol with electrophiles.



Scheme 2 Synthetic strategies for chiral chromanones by asymmetric reduction.

We embarked on this investigation using 2-methyl-chromone **1a** as benchmarked substrate and DEMS (diethoxymethylsilane) as stoichiometric reductant. Initial screening of copper precursors revealed that $Cu(OAc)_2$ and CuOAc were superior to other commonly used CuCl, $CuCl_2$. Further optimizations using 2.5 mol % $Cu(OAc)_2$ in combination with a series of chiral bisphosphine ligands were carried out (Table 1, entries 1-12). Gratifyingly, the two bulky Segphos ligands **L7** and **L8** both showed high activity and high chiral induction in this transformation (Table 1, entries 7-8). Other common silanes, such as PMHS, Ph_2SiH_2, EtO_3SiH and Et_3SiH, were also investigated (Table 1, entries 13-16). Some of them also gave good yields and *ee* values, but the best product yield and enantioselectivity was still obtained by employing DEMS as source of hydride, and 2 equivalent DEMS was desired to give high yield (Table 1, entry 7 *vs* 17). Comparable yield and *ee* was obtained when the reaction was catalyzed by CuOAc instead of $Cu(OAc)_2$ (Table 1, entry 7 *vs* 18). To this substrate **1a**, the higher temperature did not show obvious influence on the product yield and enantioselectivities (Table 1, entry 7, 19 vs 20). Thus, the optimal reaction conditions were obtained when 2.5 mol % $Cu(OAc)_2$ was used in combination with 2.75 mol % (*R*)-DM-Segphos **L7** in THF at room temperature, using 2 equivalent DEMS as the hydride source (Table 1, entry 20).

Table 1 Optimization of Cu-catalyzed asymmetric conjugate reduction of chromones.[a]



entry	ligand	silane	temp (°C)	yield(%)[b]	ee(%)[c]
1	**L1**	DEMS	60	18	87
2	**L2**	DEMS	60	71	92
3	**L3**	DEMS	60	78	90
4	**L4**	DEMS	60	75	75
5	**L5**	DEMS	60	78	7
6	**L6**	DEMS	60	trace	-
7	**L7**	DEMS	60	94	94
8	**L8**	DEMS	60	90	94
9	**L9**	DEMS	60	trace	-
10	**L10**	DEMS	60	trace	-
11	**L11**	DEMS	60	trace	-
12	**L12**	DEMS	60	75	90
13	**L7**	PMHS	60	71	90
14	**L7**	Ph_2SiH_2	60	82	74
15	**L7**	$(EtO)_3SiH$	60	85	92
16	**L7**	Et_3SiH	60	trace	-
17[d]	**L7**	DEMS	60	73	91
18[e]	**L7**	DEMS	60	95	92
19	**L7**	DEMS	40	94	96
20	**L7**	DEMS	rt	95	96

[a]Reaction conditions: 2.5 mol % $Cu(OAc)_2$ and 2.75 mol % (*R*)-DM-Segphos was mixed in THF (1.0 mL) and stirred at room temperature for 30 min under Ar. Silane (2 equiv.) was added and stirred for another 60 min. **1a** (0.2 mmol) was added and stirred at 60 °C for 16 h unless otherwise noted. [b]Isolated yields. [c]Determined by HPLC analysis. [d]Performed with DEMS (1.2equiv.). [e]Performed with CuOAc instead of $Cu(OAc)_2$. DEMS = diethoxymethylsilane, PMHS = polymethylhydrosiloxane.

With the optimal reaction conditions in hand, we next examined the scope of substrates (Table 2). No significant electronic effects were observed as most of the chromanones **2a**-**2r** were obtained in good yields (80-99%) and very high enantioselectivities (94->99% *ee*). The natural product flindersiachromanone **2i** could be obtained in 97% yield with 98% ee in this efficient transformation. 6-Fluoro-chromanone-2-carboxylate **2r** is the key intermediate in the synthesis of Fidarestat,[15] which is an aldose reductase inhibitor, shows promise in the treatment of complications associated with diabetes. In the previous report, chiral **2i** was always synthesized by chemical resolution or from D-mannitol by multi-steps synthesis.[16] Here, conjugated reduction of 6-

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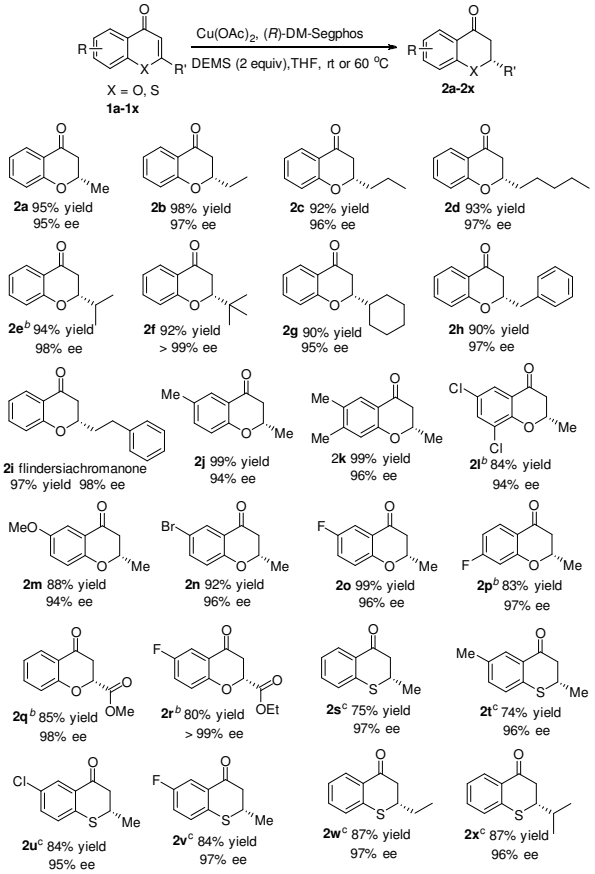
fluoro-chromone-2-carboxylate resulted in the key intermediate **2r** in 80% yield with 98% ee. Particularly noteworthy is this method could also be applied to thiochromones where the affinity of sulfur to transition metals always makes the catalyst inefficient and reaction complicated.[17] Thiochromanones **2r**-**2w** were obtained in moderate-to-good yields (74-87%) with excellent enantioselectivities (96-97% *ee*) when the reactions were performed with 10 mol % $Cu(OAc)_2$ and 11 mol% (*R*)-DM-Segphos at 60 °C. To evaluate the efficacy of this reduction in gram scale, the reaction was performed with 1.23g (6.5 mmol) of chromone **1c** with lower catalyst loading (0.8 mol % Cu). Product **2c** was isolated in excellent yield (1.24g, 99%) without compromising the enantioselectivity (96% ee).

Table 2 Cu-catalyzed asymmetric conjugate reduction of chromones and thiochromones.[a]



[a]Reaction conditions: 2.5 mol % $Cu(OAc)_2$ and 2.75 mol % (*R*)-DM-Segphos was mixed in THF (1.0 mL) and stirred at room temperature for 30 min,and then DEMS (2 equiv) was added and stirred for another 60 min. **1a-x** (0.2 mmol) was added and the resulting mixture was stirred at room temperature until the reaction completed (3-16 h). All were isolated yield. [b]Performed with 10 mol % $Cu(OAc)_2$ and 11 mol % (*R*)-DM-Segphos. [C]Performed with 10 mol % $Cu(OAc)_2$ and 11 mol % (*R*)-DM-Segphos at 60 °C.

The relative configuration of chromanones were assigned as *S* configuration by comparison with literature data for the known compound (*R*)-**2b**,[8m] and this absolute configuration was further corroborated by X-ray crystal structure analysis (**2t**, Figure 1).[18]

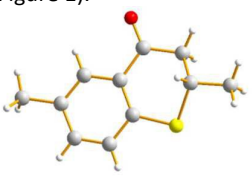
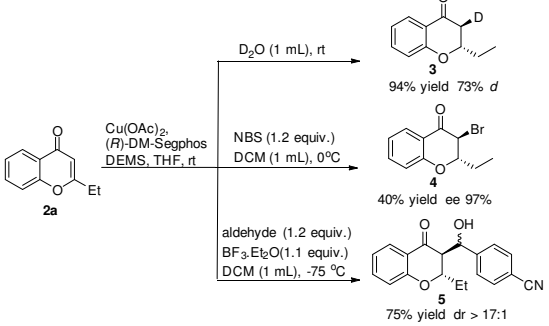


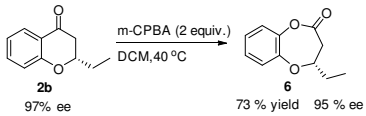
Figure 1 ORTEP drawing of **2t**.

Another advantage of this method is to construct C3-substituted chromanones. The intermediate silyl enol ethers generated can be utilized in tandem reactions in a one-pot process. Trapping reaction by the addition of D_2O or NBS is shown in Scheme 3 to give the corresponding deuterated product **3** (94% yield, 73% *d*) and brominated product **4** (40% yield, 97% ee). The Br group of product **4** allows further potential functionalization to assemble carbon skeleton. It is also known the in situ-derived silyl enol ether can also be trapped with benzaldehyde to give the corresponding trans aldol product.[8k,8m] The product **5** was obtained in 75% yield with 17:1 dr determined by 1H NMR analysis.



Scheme 3 One-pot tandem reactions.

The chiral 2-ethylchromanone **2b** can be easily oxidized to benzodioxepinone **6** in the presence of meta-chloroperoxybenzoic acid in 73% yield without erosion the enantiomeric excess (Scheme 4).



Scheme 4 Baeyer-Villiger oxidation of compound **2b**.

In conclusion, we have successfully developed an efficient copper-catalyzed asymmetric conjugated reduction of chromones, which gave a direct and general access to chiral chromanones with high yields (80-99%) and excellent ees (94->99% *ee*). Notably, thiochromanones were also obtained in moderate to good yields (74-87%) with remarkably high enantioselectivities (96-97% *ee*). The method also allows the introduction of substituents at C3-position of chromanone by tandem reactions which unlock the opportunities of chromanone scaffold with structural diversity in drug design and discovery.

Acknowledgements

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DOI: 10.1039/C7CC03939E

We gratefully thank Shenzhen Basic Research Program (JCYJ20150630145302229) for financial support.

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18 CCDC 1546860 [for **2t**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.