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Cu-Catalyzed Conjugate Addition of Grignard Reagents to Thiochromones: An Enantioselective Pathway for Accessing 2-Alkylthiochromanones

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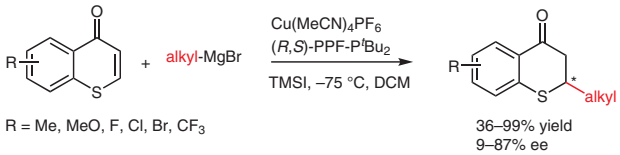

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Abstract The enantioselective incorporation of alkyl groups in thiochromones was realized for the first time by a Cu/(*R*,*S*)-PPF-P^{t}Bu$_2$-catalyzed conjugate addition of Grignard reagents to thiochromones. With this method, a series of 2-methylthiochromanones were obtained in good yields (up to 96% yield) with moderate-to-good ee values (up to 87% ee). The established method expedites the synthesis of a large library of chiral thiochromanones for further synthetic applications and biological studies.

Key words asymmetric synthesis, Grignard reagents, conjugate addition, thiochromanones, flavonoids

Flavonoids are privileged structural motifs in many natural products and pharmaceutical molecules, which show many biological activities such as antitumor, antioxidant, antibacterial, and anti-inflammatory properties.[1] Chromanones, belonging to the subgroup of flavonoids, are important intermediates and interesting building blocks in organic synthesis and the design of new lead compounds in drug discovery.[2] Thiochromanones, the sulfur analogues of chromanones, are as important as these heterocycles and exhibit plentiful bioactivities, such as antimicrobial, antioxidant, inhibition of nitric oxide production, and antifungal.[3] 2-Methyl thiochromanones, such as 7-methoxy-2-methyl thiochromanone and 3-[(dimethylamino)methyl]-6-fluoro-2-methyl thiochromanone, have shown strong antifungal ability (Figure 1).[4] A number of 2-alkenylthiochromanones exhibit a considerable antimicrobial activity.[5] Thiochromanones have also been reported to significantly inhibit cellular proliferation with weak cytotoxicity and induce apoptosis in human breast cancer cells.[6] However, thiochromanones, rarely found in nature, have not been studied as thoroughly as chromanones, which are widely present in many plants. Thus, the development of efficient synthetic routes to access structurally diverse thiochromanones is requisite for their further biological studies.

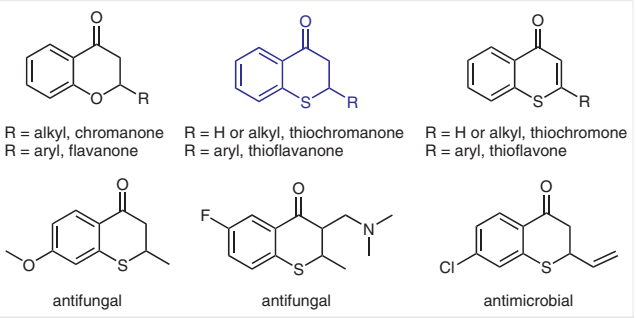
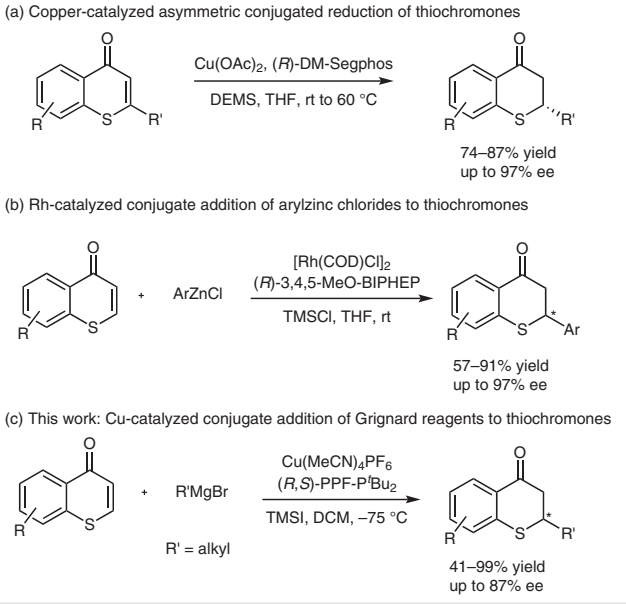


Figure 1 Representative structures of biologically active thiochromanones

In recent years, there have been reported several efficient routes to construct thiochromanones. Among them, the intramolecular thio-Michael addition and related cascade reactions are the most common methods to give thiochromanones.[7] The reaction of chiral (*Z*)-5-ylidene-1,3-dioxan-4-one and 2-bromothiophenol, followed by bromo–lithium exchange, provided optically active thiochromanones.[7e] Intramolecular Friedel–Crafts acylation of thiopropanoic acid[8] and hydrogenation of thiochromones[9] also can afford thiochromanones. In 2017, our group succeeded in developing a copper-catalyzed asymmetric conjugated reduction of thiochromones to afford chiral thiochromanones

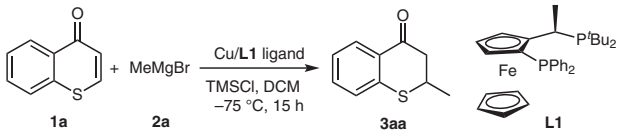
in good yields and excellent ee values (Scheme 1, method a) .[9c] Actually, the transition-metal-catalyzed asymmetric 1,4-addition of organometallic reagents to thiochromone is one of the most convenient and efficient methods to obtain the thiochromanone and thioflavanone compounds.[10] Recently, a conjugate addition of diarylcuprates to thiochromones was reported to give thioflavanones in good yields.[10a] The asymmetric conjugate addition to thiochromones was realized by our group through rhodium-catalyzed addition of arylzinc chlorides to thiochromones, which gave a direct and general access to chiral thioflavanones in good yields and excellent ee values (Scheme 1, method b).[10b] However, only arylzinc reagents can be directly employed in this transformation. Thus, the development of asymmetric conjugate addition of alkylmetal species to thiochromones, which targets enantioenriched thiochrmanones, is still highly needed. In 2005, Hoveyda reported a copper–peptide complex for the catalytic enantioselective addition of dialkylzincs to chromone.[11] More recently, Feringa found that Grignard reagents undergo enantioselective additions to chromone in the presence of a copper catalyst and Josiphos-based ligands.[12] Both of these strategies enable the addition of aliphatic groups to chromones with good yields and high stereoselectivities. Inspired by their work, we studied the conjugate addition of methyl Grignard reagent to thiochromones, which is noted as a more challenging substrate in metal-catalyzed transformations as the affinity of sulfur with transition metals invariably makes the catalytic reaction complicated.



Scheme 1 Asymmetric synthesis of thioflavanones and thiochromanones

On the basis of our previous experience, chiral bisphosphine ligands always have a better coordination with the metal to overcome catalyst poisoning.[9c,10b] Trimethylsilyl chloride (TMSCl) has been reported to activate the substrate toward 1,4-addition (as a Lewis acid) and stabilize the product (by forming a silyl enol ether).[13] We embarked on this investigation using thiochromone **1a** and methyl Grignard reagent **2a** as model substrates. Firstly, we screened different copper salts with ferrocene-based chiral ligand (*R*,*S*)-PPF-P^{t}Bu$_2$ (Table 1). In general, most Cu(I) and Cu(II) salts gave the expected 2-methylthiochromanones in moderate to good yields and ee values. Among them, Cu(MeCN)$_4$PF$_6$ was superior to others both regarding the product yield and enantioselectivity (Table 1, entry 7). Further optimizations using Cu(MeCN)$_4$PF$_6$ in combination with a series of chiral bisphosphine ligands were carried out, and the results are presented in Scheme 2. The best product enantioselectivity was still obtained by employing (*R*,*S*)-PPF-P^{t}Bu$_2$ as a chiral ligand.

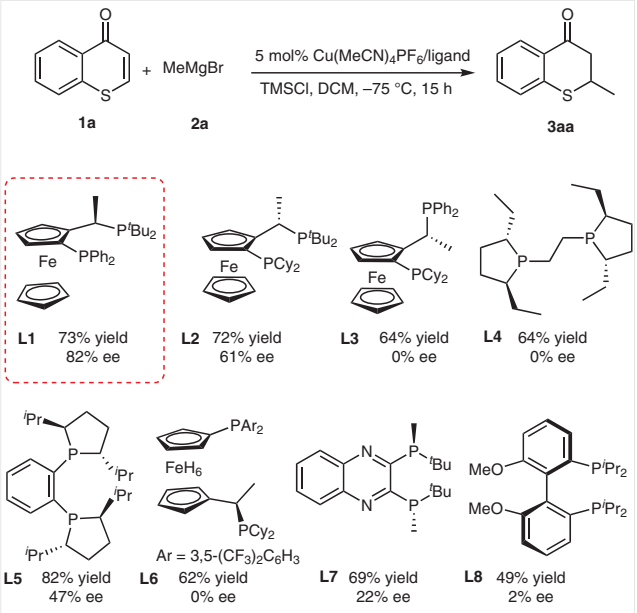
Table 1 Effects of Copper Salts[a]



1a 2a 3aa L1

Entry	Copper salt	Yield (%)[b]	ee (%)[c]
1	CuCl	64	82
2	CuBr	64	79
3	CuI	68	79
4	CuOAc	31	72
5	CuCN	52	69
6	Cu(MeCN)$_4$BF$_4$	49	72
7	Cu(MeCN)$_4$PF$_6$	73	82
8	CuTc	57	83
9	CuOTf	60	82
10	CuBr·SMe$_2$	62	75
11	CuBr$_2$	48	58
12	Cu(OTf)$_2$	48	63
13	(CF$_3$CO$_2$)$_2$Cu	42	78
14	Cu(acac)$_2$	49	80
15	Cu(ClO$_4$)$_2$	64	82

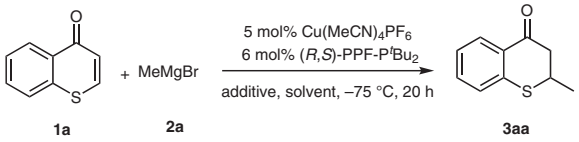
[a] *Reaction conditions:* Unless indicated otherwise, Cu (5 mol%) and **L1** ligand (6 mol%) in DCM (1.0 mL) were stirred at rt for 30 min under Ar. Then, the reaction was cooled down to –75 °C, and **1a** (0.1 mmol), **2a** (0.125 mmol), and TMSCl (0.03 mmol) were added, and the mixture was stirred at –75 °C for 24 h. CuTc = copper(I)-thiophene-2-carboxylate.
[b] Isolated yields.
[c] Determined by HPLC analysis.



Scheme 2 Ligand screening. *Reaction conditions*: Unless indicated otherwise, $Cu(MeCN)_4PF_6$ (5 mol %) and ligand (6 mol%) in DCM (1.0 mL) were stirred at rt for 30 min under Ar. Then, the reaction was cooled down to –75 °C. Compound **1a** (0.1 mmol), **2a** (0.125 mmol), and TMSCl (0.03 mmol) were added, and the mixture was stirred at –75 °C for 24 h. Isolated yields are given. Enantiomeric excess determined by HPLC analysis

Apart from screening of the catalyst complex, some other factors that may affect the reactivity and selectivity of the reaction were investigated as well (Table 2). Firstly, we tested the catalyst loading by halving or doubling the standard catalyst loading. When 2.5 mol% of catalyst was used, the enantioselectivity decreased dramatically from 82 to 25% (Table 2, entry 2). The ee value was maintained by using 10 mol% catalyst. However, the yield was reduced from 73 to 42%, which resulted from the increasing amount of by-product (Table 2, entry 3). Next, the solvents of the reaction were screened. When $CHCl_3$ was used as a solvent, the enantiomeric excess was slightly improved but the yield was decreased to 38% (Table 2, entry 4). Other solvents, such as DCE, C_6H_5Cl, and MeO^{t}Bu did not offer any enhancement of reactivity and stereoselectivity in this transformation (Table 2, entries 5–7). Then, we tried to slow down the reactivity to increase the enantioselectivity by diluting the system. An increased dilution with 4 mL of CH_2Cl_2 provided product **3aa** in higher yield and higher ee (Table 2, entry 8 versus 1). Finally, the additives were investigated. The anion of the silane played an important role regarding the reaction reactivity. The yield dropped to 11% when TMSCN was used (Table 2, entry 9), while TMSOTf offered 82% yield with a slightly higher enantioselectivity (Table 2, entry 10). The best additive was TMSI, which provided the corresponding product in 93% yield with 87% ee (Table 2, entry 11). Therefore, the optimal reaction conditions were determined as follows: 5 mol% $Cu(MeCN)_4PF_6$ in combination with 6 mol% (*R*,*S*)-PPF-P^{t}Bu$_2$ in 4 mL CH_2Cl_2 at –75 °C, using TMSI as an additive.

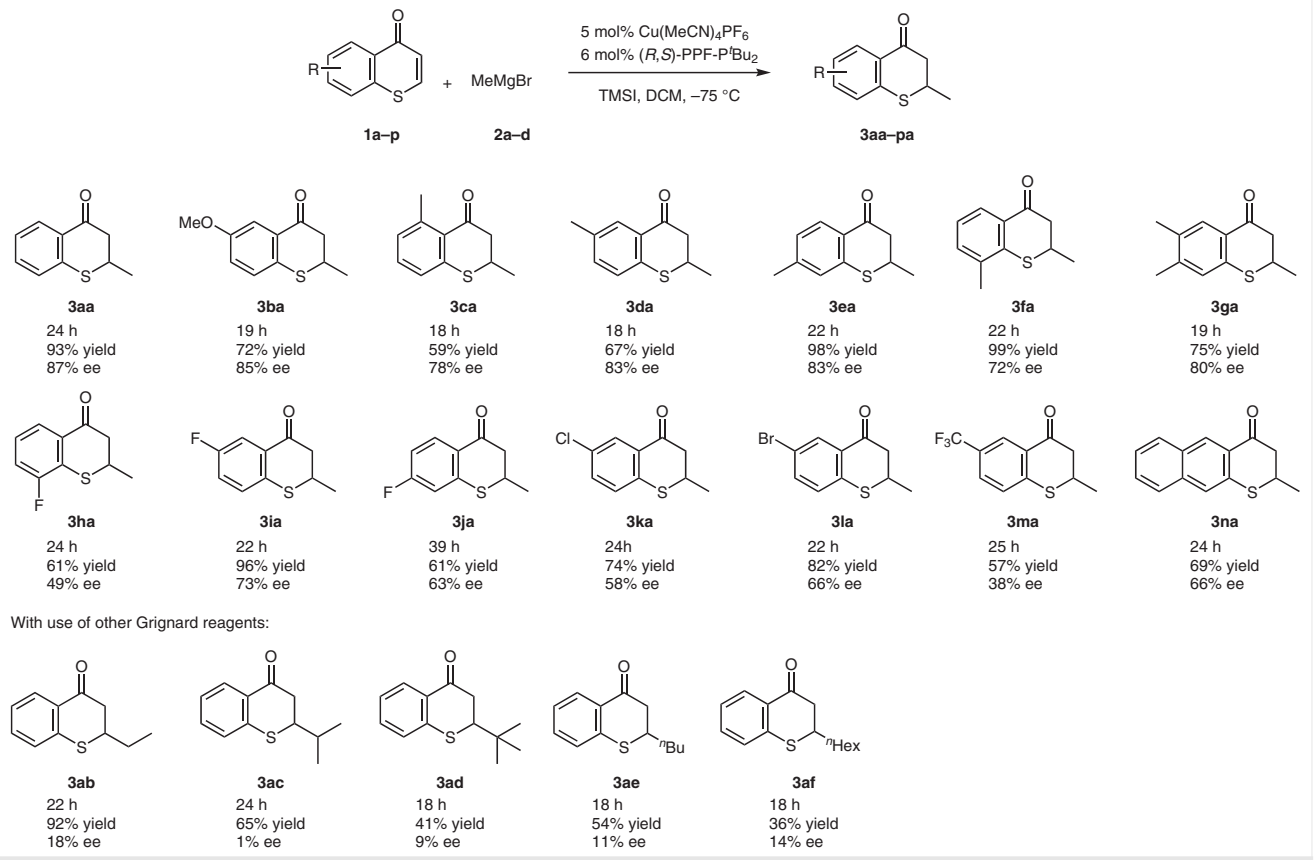
Table 2 Optimization of Reaction Conditions[a]



Entry	Catalyst loading (mol% Cu)	Solvent	Additive	Yield (%)[b]	ee (%)[c]
1	5	DCM	TMSCl	73	82
2	2.5	DCM	TMSCl	73	25
3	10	DCM	TMSCl	42	85
4	5	$CHCl_3$	TMSCl	38	85
5	5	DCE	TMSCl	23	30
6	5	C_6H_5Cl	TMSCl	18	8
7	5	MeO^{t}Bu	TMSCl	17	3
8[d]	5	DCM	TMSCl	81	85
9[d]	5	DCM	TMSCN	11	87
10[d]	5	DCM	TMSOTf	82	87
11[d]	5	DCM	TMSI	93	87

[a] *Reaction conditions*: Unless indicated otherwise, $Cu(MeCN)_4PF_6$ (5 mol%) and **L1** ligand (6 mol%) in solvent (1.0 mL) was stirred at rt for 30 min under Ar. Then, the reaction was cooled down to –75 °C, and **1a** (0.1 mmol), **2a** (0.125 mmol), and additive (0.03 mmol) were added at –75 °C, and the mixture was stirred at –75 °C for 24 h.
[b] Isolated yields.
[c] Determined by HPLC analysis (OJ-3, hexane/2-propanol = 99.5:0.5, 1.0 mL/min).
[d] DCM (4.0 mL) was used instead.

With the optimized reaction conditions in hand, we further examined the scope of substituted thiochromones (Scheme 3). Most of the substrates with Me or MeO groups reacted with methyl magnesium bromide smoothly and afforded the expected thiochromanones **3aa–ga** in good to moderate yields (59–99%) and enantioselectivities (72–87%). The enantioselectivity was a bit decreased in reactions with substrates containing F, Cl, or Br groups (**3ha–la**). When substrate **1m** bearing a strong electron-withdrawing group (CF_3) was used under these conditions, only 38% ee was obtained (**3ma**). Substrate **1n** with extended aromatic structure gave 69% yield and 66% ee (**3na**). Both the reactivity and enantioselectivity were significantly influenced by the steric properties of the nucleophile. Unexpectedly, ethyl magnesium bromide, which was assumed to be a better alkyl nucleophile in the asymmetric conjugate addition, gave 92% yield but only with 18% ee (**3ab**). Other much bulkier groups gave worse ee values in this transformation. Actually, methyl organometallic nucleophiles have always been problematic in asymmetric conjugate additions of organometallic nucleophiles to electron-deficient α,β-unsatu-



Scheme 3 Scope of thiochromones and Grignard reagents. *Reaction conditions*: Unless indicated otherwise, $Cu(MeCN)_4PF_6$ (5 mol%) and **L1** ligand (6 mol%) in DCM (4.0 mL) were stirred at rt for 30 min under Ar. Then, the mixture was cooled down to –75 °C, and **1a–p** (0.2 mmol), **2a–d** (0.3 mmol), and TMSI (0.06 mmol) were added. Isolated yields are given. Enantiomeric excess determined by HPLC analysis. See ref. 15

rated systems.[14] Herein, we provide an alternative and efficient method for the enantioselective incorporation of methyl groups into thiochromones.

In conclusion, we have successfully developed the $Cu(MeCN)_4PF_6$/(*R*,*S*)-PPF-P^{t}Bu$_2$-catalyzed conjugate addition of alkyl Grignard reagents to thiochromones, providing an efficient access to a series of chiral 2-methylthiochromanones in good yield (up to 96% yield) and relatively high enantioselectivity (up to 87% ee). Although there are some limitations in this transformation, the method allows the introduction of methyl groups to thiochromanones in an asymmetric version which will unlock the opportunities of the thiochromanone scaffold leading to more structural diversity in drug design and discovery.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610225.

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(15) **General Procedure for the Addition of Methylmagnesium Bromide to Thiochromones**

An oven-dried vial fitted with a stirring bar was charged with $[Cu(MeCN)_4]PF_6$ (3.73 mg, 5 mol%) and (*R*,*S*)-PPF-P^{t}Bu$_2$ (6.51 mg, 6 mol%) in DCM (4.0 mL) and the mixture was stirred at rt for 30 min. Then, thiochromone **1a** (0.20 mmol) was added and the mixture was then stirred at –75 °C for another 10 min. MeMgBr (0.30 mL, 0.30 mmol, 1.5 equiv; 1 M solution in THF) and iodotrimethylsilane (85 µL, 0.6 mmol, 3.0 equiv) were simultaneously added dropwise to the vial and the resulting mixture was stirred at –75 °C until the reaction was completed. The reaction was quenched with HCl aq (10%) and the mixture was stirred for 30 min at rt. Then, it was extracted with EtOAc and the organic layer was collected and concentrated under vacuum. The residue was purified by chromatography on silica gel (EtOAc/*n*-pentane 1:80) to obtain the desired products.

6-Methoxy-2-methylthiochroman-4-one (3ba)

Yellow liquid (29.8 mg, 72% yield). $[\alpha]_D^{25}$ = –59.320 (*c* 1.00, CH_2Cl_2). ee was determined to be 85% by HPLC analysis with a Chiralcel OJ-3 column (hexane/2-propanol 99.5:0.5, 1.0 mL/min, 254 nm); t_r (minor) = 36.8 min, t_r (major) = 44.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 2.9 Hz, 1 H), 7.18 (d, *J* = 8.7 Hz, 1 H), 7.03 (dd, *J* = 8.7, 2.9 Hz, 1 H), 3.84 (s, 3 H), 3.62 (dqd, *J* = 13.7, 6.8, 3.1 Hz, 1 H), 3.02 (dd, *J* = 16.6, 3.0 Hz, 1 H), 2.76 (dd, *J* = 16.5, 11.6 Hz, 1 H), 1.44 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.69, 157.40, 133.23, 131.16, 128.79, 122.50, 111.15, 55.57, 48.00, 36.68, 20.37 ppm. HRMS (ESI-ion trap): *m/z*: [M + H]$^+$ calcd for $C_{11}H_{13}O_2S$: 209.0631; found: 209.0627.

6-fluoro-2-methylthiochroman-4-one (3ia)

Yellow liquid (38 mg, 96% yield). $[\alpha]_D^{25}$ = –85.050 (*c* 1.00, CH_2Cl_2). ee was determined to be 73% by HPLC analysis with a Chiralcel OJ-3 column (hexane/2-propanol 97:3, 1.0 mL/min, 254 nm); t_r (minor) = 9.0 min, t_r (major) = 9.8 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 9.3, 2.9 Hz, 1 H), 7.24 (dd, *J* = 8.7, 5.0 Hz, 1 H), 7.14 (ddd, *J* = 8.7, 7.8, 2.9 Hz, 1 H), 3.72–3.56 (m, 1 H), 3.02 (dd, *J* = 16.6, 3.0 Hz, 1 H), 2.75 (dd, *J* = 16.6, 11.6 Hz, 1 H), 1.44 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.82, 160.62 (d, *J* = 244 Hz), 137.10 (d, *J* = 3.0 Hz), 131.90 (d, *J* = 5.8 Hz), 129.39 (d, *J* = 6.9 Hz), 121.52 (d, *J* = 23 Hz), 115.13 (d, *J* = 22 Hz), 47.68, 36.76 20.44 ppm. HRMS (ESI-ion trap): *m/z*: [M + H]$^+$ calcd for $C_{10}H_{10}OFS$: 197.0431; found: 197.0424.