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# Rh-Catalyzed Conjugate Addition of Arylzinc Chlorides to Thiochromones: A Highly Enantioselective Pathway for Accessing Chiral Thioflavanones

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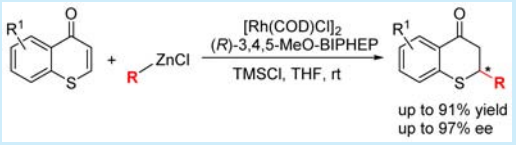
Supporting Information

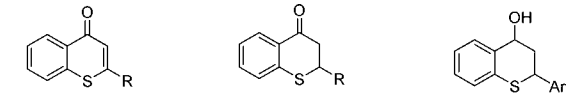
**ABSTRACT:** A highly efficient asymmetric synthesis of chiral thioflavanones is developed via conjugate addition of arylzinc reagents to thiochromones using $Rh(COD)Cl_2$/(*R*)-3,4,5-MeO-MeOBIPHEP catalyst. This method overcomes catalyst poisoning and substrate inertness and affords a series of chiral thioflavanones (2-arylthiochroman-4-ones) in good yields (up to 91% yield) with excellent ee values (up to 97% ee). The established asymmetric synthesis paves the way for further pharmaceutical studies.




Flavonoids are privileged structural motifs in numerous natural products and pharmaceutical molecules that show many biological activities such as antitumor, antioxidant, and anti-inflammatory properties.[1] The isosteric replacement of an oxygen atom by a sulfur atom is very useful and common for the design and synthesis of analogues, which are expected to improved bioavailability and bioactivity.[2] Thioflavonoids, the sulfur analogues of naturally existing flavonoids, are responsible for continuing the importance of these heterocycles and exhibit numerous bioactivities, including antifungal, antimicrobial, antioxidant, and inhibitory activity of nitric oxide production (Scheme 1).[3] As a crucial catalogue of thioflavonoids, thioflavanones (2-arylthiochroman-4-ones) have been reported to significantly inhibit cellular proliferation with a weak cytotoxicity and serve as potential treatments for breast cancer.[4] Furthermore, thioflavanones could be valuable precursors for many pharmaceuticals, such as 1,5-benzothiazepine, a versatile pharmacophore in the field of drug research.[5] Therefore, investigation of the properties, synthetic methods, and applications of thioflavanones is increasingly gaining much attention.

To date, many approaches of synthesis of 2-substituted thiochomanones (Scheme 2) have been described.[6] Several efficient preparations for thiochromone and thioflavone have also been reported in recent years.[7] However, the efficient synthesis methods for construction of thioflavanones is very limited. The intramolecular thio-Michael addition and related cascade reactions are the most common methods to give thioflavanones (Scheme 2, method A).[8] Recently, a copper-catalyzed cascade reaction of 2′-iodochalcones or 2′-bromochalcones with xanthate was reported by Sekar to construct thioflavanone very efficiently.[8f] Wang developed organocatalyzed enantioselective thio-Michael−aldol reactions to give thioflavanol in high ee and dr.[8g] Intramolecular Friedel−Crafts acylation of thiopropanoic acid[9] (Scheme 2, method B) and hydrogenation of thiochromones[10] (Scheme 2, method C) also can afford thiochromanones. However, these two methods are not always suitable for the synthesis of thioflavanones with 2-substituted phenyl groups. To the best of our knowledge, an asymmetric, catalyzed synthetic route for thioflavanones has not been reported yet. Our group has a long-term interest in exploring the enantioselective synthesis of flavonoids.[11] Recently, we disclosed a Rh/chiral diene-catalyzed asymmetric

**Scheme 1. Structures of Thiochromone, Thiochromanone, Thioflavone, Thioflavanone, and Thioflavanol**




**Scheme 2. Typical Synthesis Methods for Thioflavanone**

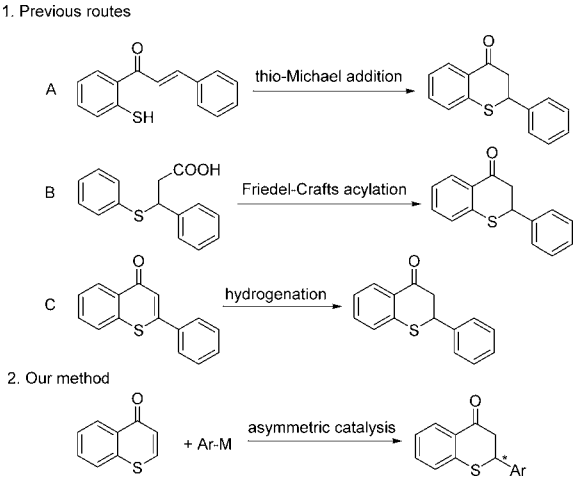



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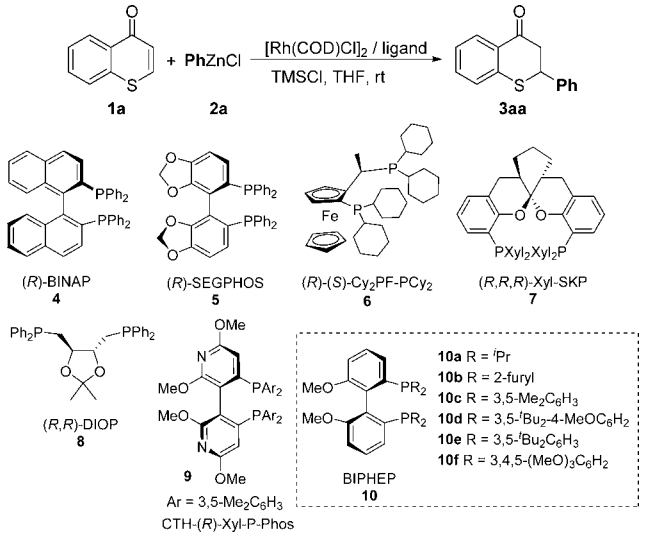
**Table 1. Optimization of Conjugate Addition of Arylzinc Reagent to Thiochromone**



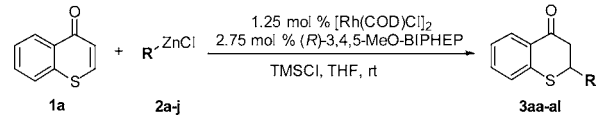

| entry | ligand | temp (°C) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1[d] | | 25 | trace | ND |
| 2 | | 25 | 27 | ND |
| 3 | **4** | 25 | 59 | 65 |
| 4 | **5** | 25 | 46 | 62 |
| 5 | **6** | 25 | 22 | 27 |
| 6 | **7** | 25 | 21 | 5 |
| 7 | **8** | 25 | 21 | 0 |
| 8 | **9** | 25 | 54 | 71 |
| 9 | **10a** | 25 | 16 | 10 |
| 10 | **10b** | 25 | 27 | 52 |
| 11 | **10c** | 25 | 68 | 83 |
| 12 | **10d** | 25 | 25 | 62 |
| 13 | **10e** | 25 | 50 | 96 |
| 14 | **10f** | 25 | 63 | 95 |
| 15[e] | **10f** | 25 | 79 | 95 |
| **16**[f] | **10f** | **25** | **91** | **97** |
| 17[g] | **10f** | 25 | 60 | 84 |
| 18 | **10f** | 0 | 85 | 97 |
| 19 | **10f** | −20 | 60 | 98 |

[a]$[Rh(COD)Cl]_2$ (10 mol % Rh) and 11 mol % of ligand in THF (1.0 mL) was stirred at 25 °C for 30 min under Ar. Then 0.1 mmol of **1a**, 0.2 mmol of **2a**, and 0.3 mmolof TMSCl were added, and the mixture was stirred for 12 h. [b]Isolated yields. [c]Determined by HPLC analyses. [d]Without addition of TMSCl. [e]5 mol % of Rh was used and the mixture stirred for 2 h. [f]2.5 mol % of Rh was used and the mixture stirred for 2 h. [g]1 mol % of Rh were used and the mixture stirred for 72 h.

1,4-addition of arylboronic acids to chromones in good yields with remarkably high enantioselectivities.[11a] As part of our continuing studies of flavonoids, we attempted to extend these studies to thiochromones. It is known that chromone and 4-quinolone have been shown to be some of the most challenging substrates in asymmetric conjugate addition to $\alpha,\beta$-unsaturated carbonyl compounds for their aromatic properties.[12,13] Herein, we meet this challenge of developing a highly enatioselective synthesis of thioflavanones via conjugate addition of arylmetal species to thiochromones.

Based on our previous research, we initially attempted a $[Rh(C_2H_4)_2Cl]_2$/(*R*,*R*)-Ph-bod*-catalyzed asymmetric 1,4-addition of phenylboronic acid to thiochromone **1a** at 90 °C (see the Supporting Information). Under this condition, only a small amount of 1,4-adduct **3aa** was obtained (8% yield, 23% ee) with recovery of unreacted **1a** (75%). In an attempt to improve

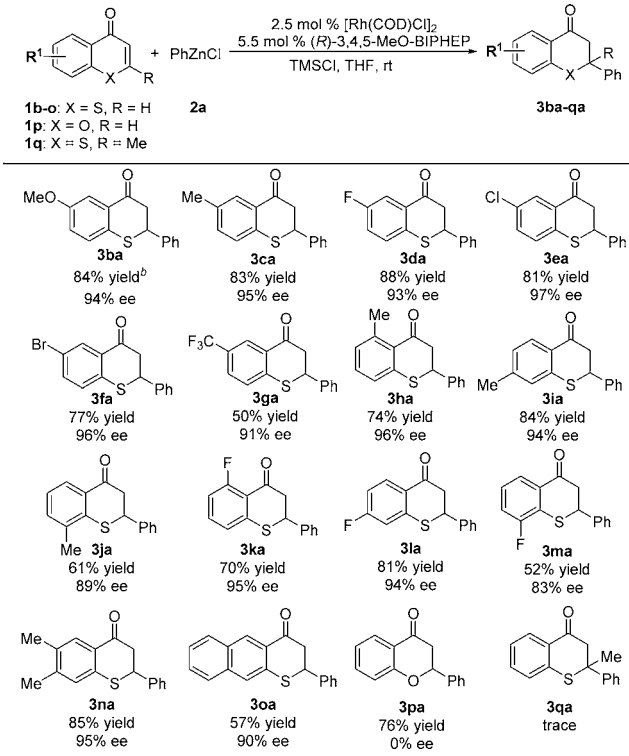
**Table 2. Scope of Arylzinc Reagents**




| entry | R | product | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | **3aa** | 2 | 91 | 97 |
| 2[d] | 4-$MeOC_6H_4$ | **3ab** | 2 | 84 | 85 |
| 3 | 4-$MeC_6H_4$ | **3ac** | 3 | 87 | 94 |
| 4 | 3-$MeC_6H_4$ | **3ad** | 3 | 74 | 95 |
| 5 | 2-$MeC_6H_4$ | **3ae** | 24 | 60 | 7 |
| 6 | 4-$FC_6H_4$ | **3af** | 48 | 47 | 91 |
| 7 | 4-$BrC_6H_4$ | **3ag** | 72 | 52 | 95 |
| 8 | 4-$CF_3C_6H_4$ | **3ah** | 72 | 20 | 10 |
| 9 | 3,5-$Me_2C_6H_3$ | **3ai** | 3 | 90 | 95 |
| 10[e] | 2-Nap | **3aj** | 48 | 85 | 95 |
| 11 | 2-furyl | **3ak** | 72 | 64 | 4 |
| 12 | 2-thienyl | **3al** | 72 | 49 | 2 |

[a]Unless otherwise specified, the reactions were carried out with 1.25 mol % of $[Rh(COD)Cl]_2$, 2.75 mol % of (*R*)-3,4,5-MeO-BIPHEP, 0.15 mmol of **1a**, 0.3 mmol of **2**, and 0.45 mmol of TMSCl in 1.0 mL of THF, at rt. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]$T$ = 0 °C. [e]$[Rh(COD)Cl]_2$ (2.5 mol %)/(*R*)-3,4,5-MeO-BIPHEP (5.5 mol %) was used.

**Scheme 3. Scope of Thiochromones**




[a]The reactions were performed using $[Rh(COD)Cl]_2$ (2.5 mol %), (*R*)-3,4,5-MeO-BIPHEP (5.5 mol %), **1** (0.15 mmol, 1.0 equiv), **2a** (0.3 mmol, 2.0 equiv), THF (1.0 mL), and TMSCl (0.45 mmol, 3.0 equiv) at room temperature for 24 h. For all reactions, yields are of the isolated products and the ee values were determined by HPLC analysis (Chiralcel OJ-3). [b]Reaction time: 72 h.



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the reactivity, we then explored the possibility of phenylzinc chloride with the same catalyst at room temperature; a 5% yield and 80% ee was obtained. The affinity of sulfur with transition metals invariably makes the catalytic reaction complicated.[14] We then turned our interests to chiral phosphine ligands, which have better coordination with metal to overcome catalyst poisoning (Table 1). It was reported that the addition of chlorotrimethylsilane might facilitate the activation of substrate toward 1,4-addition (as a Lewis acid) and the stabilization of the product (by forming a silyl enol ether),[15] and we then conducted a reaction in the presence of chlorotrimethylsilane. The product yield was improved from trace to 27% (Table 1, entries 1 and 2). Various chiral biphosphine ligands with different backbones utilizing $[Rh(COD)Cl]_2$ as the catalyst precursor were investigated (Table 1, entries 3−14). Among them, BIPHEP-type ligands always gave better yields and enantioselectivities (Table 1, entries 9−14). In general, the aryl-substituted BIPHEP ligands always promote this reaction better than other BIPHEP ligand having alkyl or heteroaromatic substitution on the phosphorus donor (entries 11−14 vs 9, 10). When ligand **10c** (R = 3,5-$Me_2C_6H_3$) was compared with **10e** (R = 3,5-$^tBu_2C_6H_3$), the more sterically hindered phosphine group in the ligands was observed to have a more effective stereocommunication to the substrate. Subtle differences of substituents on the phosphorus donor in BIPHEP ligands often significantly affect both the catalytic activity and enantioselectivity.[16] As clearly observed in the BIPHEP series, (*R*)-3,4,5-MeO-BIPHEP was identified as the best ligand, which gave the product **3a** with 63% yield in 95% ee (Table 1, entry 14). We further explored the effect of catalyst loading on the reaction. The ee values were maintained at excellent levels with the yield increasing from 63% to 91%, while the rhodium catalyst loading deceased from 10 to 2.5 mol % (Table 1, entries 14−16). When the catalyst loading was furthre decreased to 1 mol %, both yield and ee decreased (Table 1, entry 17). Experiments showed that enantioselectivity was improved slightly and reactivity was slowed when the reaction temperature was decreased (Table 1, entries 18 and 19). Thus, optimal reaction conditions were obtained when 1.25 mol % of $[Rh(COD)Cl]_2$ was used in combination with 2.75 mol % of (*R*)-3,4,5-MeO-BIPHEP in THF at room temperature using TMSCl as additive (Table 1, entry 16).

With the optimized reaction conditions in hand, we next examined the scope of organozinc reagents for the 1,4-addition (Table 2). Both the reactivity and enantioselectivity were influenced by the steric and electronic properties of the organozinc reagents. Compared to *para*- and *meta*-substituted arylzinc reagents, sterically hindered *o*-tolylzinc chloride **2e** gave lower yields and dramatically decreased the ee (only 7%) (Table 2, entries 3−5). The organozinc reagents with electron-donating groups always showed higher reactivities than those with electron-withdrawing groups (Table 2, entries 2−5 vs entries 6−8). The arylzinc reagent with a strong electron-withdrawing group (4-$CF_3$) was very sluggish under these conditions, and the expected product **3ah** was only obtained in 20% yield with 10% ee (Table 2, entry 8). Both disubstituted phenylzinc reagent and naphthylzinc chloride gave the products with high yields and high ee (Table 2, entries 9 and 10). Apart from arylzinc reagents, heterocyclic zinc chlorides were also investigated. Products **3ak** and **3al** were obtained in moderate yields, yet almost in racemic forms (entries 11 and 12).

To investigate the substrate scope further, a series of substituted thiochromones **1b−q** were examined (Scheme 3). No significant steric effects were observed, as most of the desired adducts were obtained in good to moderate yields (50−85%) and high enantioselectivities (83−97% ee). Substrate **2g** with a strong electron-withdrawing group ($CF_3$) reacted with the phenylzinc chloride smoothly, affording the desired thioflavanones **3ga** in 50% yields with 91% ee. When the reaction conditions were applied to chromone as well, unfortunately, racemic product **3pa** was obtained in good (76%) yield. Attempted investigation of this catalyst system to 2-methyl thiochromones **1q** to construct quaternary carbon resulted in trace product **3qa**.

In summary, we have successfully developed the $[Rh(COD)Cl]_2$/(*R*)-3,4,5-MeO-BIPHEP-catalyzed conjugate addition of organozinc reagents to thiochomonones, realizing a facial approach to synthesize a series of optically active thioflavanones in good yield (up to 91%) and high enatioselectivity (up to 97%). Further studies with regard to both expansion of the substrate scope and application of this method to the pharmaceutical synthesis are currently ongoing in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02453.

Experimental procedures and characterization/HPLC data of products (PDF)

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### Notes

The authors declare no competing financial interest.

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