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Copper Bis(oxazoline)-Catalyzed Enantioselective Alkynylation of Benzopyrylium Ions

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Abstract

The stereocontrolled construction of biologically relevant chromanones and tetrahydroxanthones has been achieved through the addition of alkynes to benzopyrylium triflates under the influence of copper bis(oxazoline) catalysis. Excellent levels of enantiocontrol (63–98% *ee*) are achieved in the addition of a variety of alkynes to an array of chromenones with a hydrogen in the 2-position. Promising levels of enantiocontrol (54–67% *ee*) are achieved in the alkynylation of chromenones with esters in the 2-position, generating tertiary ether stereocenters resembling those frequently found in naturally occurring metabolites.

Keywords

asymmetric catalysis; heterocycles; natural products; synthetic design; synthetic methods

Naturally occurring chromanones and tetrahydroxanthones frequently possess attractive biological properties, including anticancer, antibacterial, and antifungal activity (Figure 1).^[1] These molecules, existing in both monomeric and dimeric forms, often present significant synthetic challenges. One aspect contributing to their difficult synthesis is the 2-stereocenter (for the purposes of this manuscript, a chromanone numbering scheme has been adopted, Figure 1). Given the frequency with which the 2-stereocenter emerges in several families of bioactive chromenones and tetrahydroxanthones, there has been significant interest in learning how to create this bond with high levels of enantiocontrol.^[2]

In the context of natural product synthesis, there are only a limited number of strategies with demonstrated success. Porco has shown a racemic siloxyfuran addition to benzopyrylium triflates followed by a sequence that includes a Birman resolution can be a productive approach to synthesizing tetrahydroxanthones with excellent levels of enantiomeric excess (Scheme 1A).^[3] Tietze uses an intramolecular Wacker reaction to control the formation of the 2-stereocenter and several steps are required to convert the alkene to the desired chromanone natural product (Scheme 1B).^[4] Despite the success of these tactics, a direct

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Conflict of interest

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and general method for the installation of the 2-stereocenter remains a lucrative pursuit. Our group has been interested in learning how to synthesize the 2-stereocenter of chromenones with enantiocontrol. Our efforts initially focused on the addition of silyl ketene acetals to benzopyrylium triflates, reactive species generated in situ from chromenones and silyl triflates.^[5] Initially inspired by Porco's success, we took advantage of silanediol anion-binding catalysis to control, for the first time, addition reactions of silyl ketene acetals to benzopyrylium triflates affording 2-alkyl chromanones in up to 57% enantiomeric excess (Scheme 1D).^[6] We were delighted to see Mancheño and co-workers further improved upon these findings, obtaining greater than 90% enantiomeric excess under the influence of her triazolium catalysts with select substrates.^[7] Despite the promise of anion-binding catalysis, the synthesis of tertiary ether 2-chromanones in high enantiomeric excess directly from chromone precursors remains a topic of great interest.

Considering the limitations of anion-binding catalysis (Table 1), we expanded our investigations to other catalytic platforms for controlling addition reactions to chromone, such as alkynylation.^[8] We hypothesized that copper bis(oxazoline)^[9] complexes would influence the enantioselective addition of terminal acetylides onto benzopyrylium triflates (Scheme 1E). This reasoning was inspired by Watson's work demonstrating that copper acetylides undergo addition to in situ-generated oxocarbenium ions with high levels of enantiomeric excess when a bis(oxazoline) ligand was present.^[10] While this manuscript was under preparation, Aponick and co-workers recently reported enantioselective alkynylation of chromones with their StackPhos ligands (Scheme 1C).^[11] Herein, we describe our findings of copper bis(oxazoline) catalysis as an excellent platform for the reaction of terminal alkynes and unhindered benzopyrylium triflates (R=H) to generate desirable products with excellent levels of enantiocontrol. This method represents a more practical approach because it requires readily accessible bis(oxazoline) ligands. Furthermore, we have found that copper bis(oxazoline) catalysis provides promising levels of enantiocontrol in the addition of terminal acetylides to substituted benzopyrylium triflates (R=esters) to create chromanones with highly substituted 2-stereocenters.

Our investigations were initiated with the addition of phenyl acetylene to benzopyrylium triflate **2**, generated in situ from **1**, in the presence of a suitable copper source and ligand (Table 1). During a systematic investigation of the reaction parameters it was found that the nature of the copper source, bis(oxazoline) ligand, and silyl triflate significantly affected the outcome of the reaction with respect to both yield and enantioselectivity. Cu(OTf)₂, CuOTf, and CuBr gave rise to **4** with yields between 40–44% and low enantiomeric excess (Table 1, entries 1–3). CuI was identified as the best reagent for this process, producing **4a** with 69% yield and 95% enantiomeric excess (entry 4). The screening of several bis(oxazoline) ligands demonstrated the enantiomeric excess and yield were readily influenced by the structure of the ligand. The highest enantiomeric excess was realized with ligand **5a** (R'=Bn, 95% ee, entry 4). Lower enantiomeric excesses were observed with ligands **5b**, **5c**, and **5d** (R' = Ph, *i*Pr, *t*Bu, respectively) but the yields were higher in some cases (entries 4–7). Finally, the silyl triflate employed in the reaction had a small influence on the yield and stereocontrol. Specifically, *tert*-butyldimethylsilyl triflate (TBSOTf) gave rise to the best enantiomeric

excess when compared to trimethylsilyl triflate (TMSOTf) and triisopropylsilyl triflate (TIPSOTf) (entries 4, 8–9).

The yield of the reaction was improved from 69 to 72% by conducting the reaction in a single flask, the enantiomeric excess remained excellent at 97% (Table 1, entry 10). The reduction of the catalyst loading from 10 to 5 mol% and 1 mol% resulted in small losses in enantiomeric excess (entries 11–12).

After having identified a promising set of reaction conditions for the enantioselective alkynylation of chromenone **1**, the scope of the reaction with respect to chromenone and alkyne was tested. First, the substituents on the alkyne were probed (Table 2). A variety of aryl acetylides were found to operate well in the reaction regardless of their substitution pattern. For instance, nearly identical enantiomeric excesses were observed for phenyl acetylene, *p*-methoxy phenyl acetylene, *p*-trifluoromethyl phenyl acetylene, *p*-methyl phenyl acetylene, *p*-chloro phenyl acetylene, and *m*-methyl phenyl acetylene (Table 2, entries 1–6). The sterically encumbered *o*-methyl phenyl acetylene gave rise to product **4g** in 67% yield and 82% enantiomeric excess (entry 7). Alkynes containing non-aryl substituents (R=TMS, alkyl, vinyl) were also accommodated in the reaction (entries 8–12), although optimal yields and stereocontrol was achieved with different bis(oxazoline) ligands (entries 8–10). For example, trimethylsilyl acetylene, a reaction partner of interest in the context of tetrahydroxanthone synthesis, afforded product **4h** in 86% yield and 95% enantiomeric excess under the influence of bis(oxazoline) **5d** (entry 8). Synthetically relevant chromanone products **4i** and **4j** were also produced in high yield and high enantiomeric excess in the presence of ligands **5e** and **5f**, respectively (entries 9 and 10).

Chromones with substituents on the 5-, 6-, 7-, and 8-positions were generally well tolerated, yielding corresponding 2-(phenylethynyl)chromanones in high enantiomeric excess. (Scheme 2). Chromenones with a variety of substituents in the 6-position (e.g., R=CF₃, CH₃, F, Cl, Br) performed well in the reaction giving rise to products **4m–q** in excellent yield and enantiomeric excess. Donating substituents in the 7-position enabled formation of the desired products **4r–s** with excellent enantiomeric excess but with reduced yield. 8-Phenyl chromenone (**1t**), was also a competent reaction partner affording **4t** with 93% yield and 84% enantiomeric excess. The naturally-inspired substitution pattern on chromenone **1u** was also easily incorporated into the reaction platform generating product **4u** in 75% yield and with 93% *ee*. Moderate enantiomeric excess was obtained in the case of 3-(*p*-tolyl) chromone **1v**, which yielded **4v** as a 2:1 mixture of diastereomers in 63% *ee*.

The relevance of the methodology to natural product construction was tested in the synthesis of chromanones **6–7** and tetrahydroxanthone **9** (Scheme 3). The partial hydrogenation of the alkyne in chromanone **4a** was easily achieved with a Pd/CaCO₃, Pb catalyst system, 3,6-dithia-1,8-octanediol, and H₂ to afford chromanone **6** in excellent yield with no loss in enantiomeric excess (Scheme 3A). Under the influence of Pd/CaCO₃, Pb, and H₂, the synthesis of **7** was affected in 84% yield with no loss in enantiomeric excess. The application of the methodology to the synthesis of tetrahydroxanthones is depicted in Scheme 3B. Chromanone **4w** is prepared in 77% yield and excellent enantiomeric excess (92% *ee*) under the influence of CuI and ligand **5d**. Silyl group deprotection in the presence

of cesium fluoride (CsF), insertion of ethyldiazoacetate into the terminal alkyne C—H bond, [12] and hydrogenation of the intermediate allene gives rise to **8** in 40% yield and 90% *ee* over three steps. Tetrahydroxanthone formation is achieved by a Lewis acid promoted intramolecular Dieckmann cyclization to yield **9**.^[4b] The final cyclization step does erode the enantiomeric excess slightly and investigations are ongoing to overcome this issue.

The high levels of enantiocontrol and extensive substrate scope observed in the synthesis of 2-*H* chromanones **4a–w** inspired us to stress the limits of the reaction system in the synthesis of more highly substituted stereogenic centers. Specifically, it was envisioned that chromenones containing esters in the 2-position would render the methodology even more valuable in the context of naturally occurring tetrahydroxanthone synthesis by enabling the enantioselective construction of tertiary ether stereocenters. The reaction was put to the test with the addition of phenyl acetylene to chromone-2-carboxylate esters (Table 3). We were delighted to find an initial enantiomeric excess of 34% with the bis(oxazoline) ligand **5a** containing a benzyl group (R=Bn, Table 3, entry 1). A quick screen of other readily available bis(oxazoline) ligands resulted in the identification of *t*Bu as the best substituent identified to date with respect to both the yield and enantiomeric excess (entry 3). Upon cooling the reaction from 0 to –28 °C a very encouraging 67% enantiomeric excess was observed (entry 4). Ethyl, *iso*-propyl, and *tert*-butyl chromone-2-carboxylate esters were also tolerated but with reduced enantiomeric excess (entries 5–7).

In conclusion, copper bis(oxazoline) complexes have proven to be easy to use, general catalyst systems for the synthesis of 2-stereogenic centers found in biologically relevant chromanones. Excellent levels of enantiocontrol can be achieved in the reaction of a diverse array of chromenone and alkyne reaction partners, generating desirable 2-ethynyl chromanone products in high yield. The reaction system can also be extended to the synthesis of more highly substituted 2-stereogenic centers that may have direct applications in naturally occurring bioactive chromanone and tetrahydroxanthone synthesis. Our current efforts, directed toward the continued exploration of these reactions in the synthesis of naturally occurring dimeric tetrahydroxanthones, will be reported as soon as possible.

Experimental Section

General method

To an 8 mL screw-top vial was added chromone (29.2 mg, 0.2 mmol, 1.0 equiv), CuI (3.8 mg, 0.02 mmol, 10 mol%), (S)-Bn-BOX (8.8 mg, 0.024 mmol, 12 mol%), *o*-xylene (2 mL), *i*Pr₂NEt (52.3 mL, 0.3 mmol, 1.5 equiv), and phenyl acetylene (28.6 mL, 0.26 mmol, 1.3 equiv) in that order at room temperature. This mixture was then allowed to stir for 30 min. The vial was purged with dry N₂ and then cooled to –78 °C. TBSOTf (60 mL, 0.26 mmol, 1.3 equiv) was added at –78 °C, and then the reaction was transferred to the lab freezer at –28 °C and allowed to react for 48 h. The reaction was quenched by the addition of 6*N* HCl (2 mL) and stirred for 2 h. The reaction mixture was extracted with EtOAc (3×2 mL), washed with saturated NaHCO₃ solution, dried over anhydrous NaSO₄, and the solvent removed under vacuum to obtain the crude product. The crude product was purified by column chromatography on silica gel with hexane:EtOAc (9:1) to afford an off-white solid (48.8 mg, 98% yield, 97% *ee*).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Select bioactive chromanones and tetrahydroxanthones.

A. Porco Approach **B. Tietze Approach** **C. Aponick Approach** **Our Approach:** **Scheme 1.**

Methods for synthesis of chromanones with a chiral tertiary ether stereocenter.

4m: 90% yield
95% ee

4n: 90% yield
97% ee

X=F, **4o:** 96% yield, 97% ee
 X=Cl, **4p:** 69% yield, 94% ee
 X=Br, **4q:** 71% yield, 96% ee

4r: 68% yield
98% ee

4s: 23% yield
97% ee

4t: 93% yield
84% ee

4u: 75% yield
93% ee

4v: 54% yield
d.r. 2:1, 63% ee

Scheme 2.

Chromenone substrate scope. See the Supporting Information for detailed procedures.

Scheme 3.

Demonstration of methodology in chromanone and tetrahydroxanthone synthesis. See the Supporting Information for detailed procedures.

Table 1.

Optimization.

Entry ^[a]	Copper source	Ligand R'', R'	Silyl triflate	Yield [%] ^[b]	ee [%]
1	Cu(OTf) ₂	Me, Bn (5a)	TBSOTf	44	14
2	CuOTf	Me, Bn (5a)	TBSOTf	40	16
3	CuBr	Me, Bn (5 a)	TBSOTf	41	14
4	CuI	Me, Bn (5a)	TBSOTf	69	95
5	CuI	Me, Ph (5 b)	TBSOTf	85	86
6	CuI	Me, <i>i</i> Pr (5 c)	TBSOTf	64	93
7	CuI	Me, <i>t</i> Bu (5d)	TBSOTf	92	70
8	CuI	Me, Bn (5 a)	TMSOTf	68	94
9	CuI	Me, Bn (5 a)	TIPSOTf	87	91
10	CuI ^[c]	Me, Bn (5 a)	TBSOTf	72	97
11	CuI ^[d]	Me, Bn (5 a)	TBSOTf	73	94
12	CuI ^[e]	Me, Bn (5 a)	TBSOTf	76	84

^[a] See the Supporting Information for detailed procedures.^[b] NMR yields.^[c] Reaction conducted in a single flask with *o*-xylenes.^[d] 5 mol% catalyst loading, *o*-xylenes as the solvent.^[e] 1 mol% catalyst loading, *o*-xylenes as the solvent.

Table 2.

Alkyne substrate scope.

Entry ^[a]	Alkyne R=	4	Yield [%] ^[b]	ee [%]
1	Ph	4 a	98	97
2	<i>p</i> -MeOPh	4 b	63	96
3	<i>p</i> -CF ₃ Ph	4 c	85	97
4	<i>p</i> -tolyl	4 d	83	96
5	<i>p</i> -ClPh	4 e	86	97
6	<i>m</i> -tolyl	4 f	82	97
7	<i>o</i> -tolyl	4 g	67	82
8 ^[c]	TMS	4 h	86	95
9 ^[d]	CH ₂ OBn	4 i	85	85
10 ^[e]	CH ₂ CH ₂ OBn	4 j	96	85
11	cyclopropyl	4 k	45	82
12	1-cyclohexenyl	4 l	50	71

^[a] See the Supporting Information for detailed procedures.^[b] Isolated yields.^[c] Ligand **5d** was used.^[d] Ligand **5e** (R'=Ph, R''=Bn) was used.^[e] Ligand **5f** (R'=2-naphthyl, R''=Bn) was used. (*S*)-Enantiomer was obtained.

Table 3.

Tertiary ether stereocenter formation.

Entry ^[a]	Ligand R' =	R =	T [°C]	Yield [%]	ee [%]
1 ^[b]	Bn (5 a)	Me	0	29	34
2 ^[b]	Ph (5 b)	Me	0	86	15
3 ^[b]	<i>t</i> Bu (5d)	Me	0	87	-38
4	<i>t</i> Bu (5d)	Me	-78 to -28	87	-67
5	<i>t</i> Bu (5d)	Et	-78 to -28	91	-65
5	<i>t</i> Bu (5d)	<i>i</i> Pr	-78 to -28	88	-54
7	<i>t</i> Bu (5d)	<i>t</i> Bu	-78 to -28	15	-60

^[a] See the Supporting Information for detailed procedures.^[b] Conducted in a two-step process in toluene, see procedure 1 in the Supporting Information for details.