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Catalytic Enantioselective Synthesis of Flavanones and Chromanones

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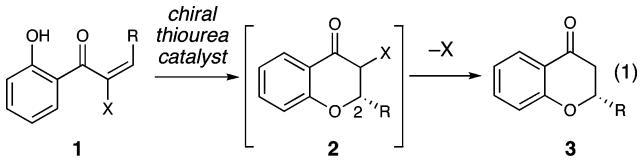
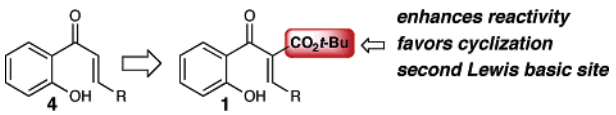
The flavanone structure is abundant in natural products that possess a broad array of biological activity.[1] Due to their favorable anti-tumor and anti-inflammatory properties, flavanones have been investigated as selective estrogen receptor modulators[2] and TNF-α inhibitors. A limited number of strategies have been developed for the asymmetric synthesis of flavanones, such as resolution of the related alcohols[3] or substitution reactions.[4] Recently, Hoveyda has reported asymmetric copper(I)-catalyzed diethylzinc addition to 2-chromene with high enantioselectivity.[5] In this approach, the addition of benzaldehyde is required to trap the resulting zinc enolate. Ideally, asymmetric catalysis could provide a direct route to natural and synthetic flavanones that are currently difficult to access in optically active form. An enantioselective synthesis of flavanones that controls the C2 stereocenter remains a significant challenge due to the potential for reversible phenoxide elimination to form the achiral 2′-hydroxy chalcones.[6] In this Communication, we report the asymmetric synthesis of flavanones (**3**, R = aryl) and chromanones (**3**, R = alkyl) from α-substituted chalcones (**1**) by an intramolecular conjugate addition catalyzed by chiral thioureas (eq 1).

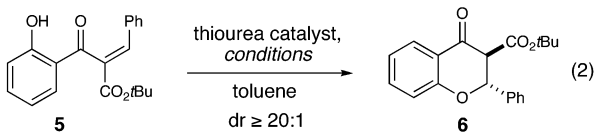


We envisioned the intramolecular conjugate addition of a phenol to an activated unsaturated ketone as a way to access this oxygen heterocycle under mild conditions that would minimize elimination to the undesired chalcones. Our strategy was to incorporate a functional group on the potential substrate that would (a) enhance the reactivity of the conjugate acceptor, (b) favor the flavanone products over the acyclic chalcones, and (c) provide a second Lewis basic site for potential interaction with a catalyst. The *tert*-butyl ester group addresses these criteria, and importantly, it is removable under mild conditions with minimal impact on the C2 stereochemistry.

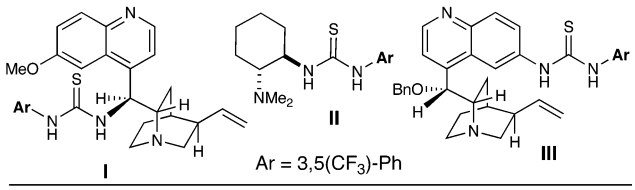


To test our hypothesis, the starting alkylidene β-ketoesters **1** were accessed via Knoevenagel condensation. The *E*-alkene is isolated by crystallization in >95:5 *E*:*Z* for the aldehydes employed.[7] We envisaged that a bifunctional catalyst that would activate the 1,3-dicarbonyl moiety of **1** and deprotonate the phenol would lead to the desired asymmetric conjugate addition. Accordingly, we surveyed chiral thioureas containing a tertiary amine as catalysts for the intramolecular conjugate addition (Table 1, eq 2).[8] Thiourea catalysts **I**,[9] **II**,[10] and **III**[11b] (at 20 mol % in toluene) provided good

Table 1. Optimization of Enantioselective Conjugate Addition[a]



entry	catalyst	mol%	temp (° C)	ee (%)[b]	yield (%)[c]
1	**I**	20	22	–80	97
2	**II**	20	22	80	82
3	**III**	20	22	71	88
4	**I**	20	–25	–80	78
5	**II**	20	–25	80	nd[d]
6	**III**	20	–25	88	nd[d]
7	**III**	10	–25	92	85



[a] Reaction conditions: 0.1 M **5**. [b] Determined by HPLC analysis (Chiralcel OD−H). [c] Yield after chromatography. [d] Not determined.

yields and encouraging selectivities for the 3-carboxy flavanone product **6** as the *trans*-2,3-diastereomer (entries 1−3). Surprisingly, lower reaction temperatures do not improve the level of enantioselectivity observed for catalysts **I** or **II** (Table 1, entries 4 and 5). Catalyst **III**, originally disclosed by Hiemstra,[11b] is highly enantioselective (>90% ee) at lower temperatures and lower catalyst loadings (entry 6 vs 7). Lowering the temperature beyond −25 °C does not improve selectivity, and the unusual dependence of ee on loading has been observed in other thiourea-catalyzed reactions.[11] Importantly, the parent 2′OH chalcone (**4**) does not undergo cyclization with **I**, **II**, or **III**, thus underscoring the importance of the carboxy group.

A key aspect of the process is that after cyclization, the 3-carboxy group can be removed by treatment with acid in toluene without compromising the integrity of the newly formed stereocenter at C2. For example, the exposure of **6** (89% ee) to *p*-TsOH in toluene at 70 °C affords the corresponding decarboxylated flavanone **7** in 88% ee.[12]

Since the thiourea-catalyzed conjugate addition and decarboxylation are performed in toluene, we can combine these reactions into a single-flask synthesis of a variety of flavanones (Table 2). A variety of aryl groups can be accommodated on the starting alkenes, and these compounds undergo cyclization with excellent enantioselectivity and good yields in the presence of 10 mol % of **III** (entries 1−6). Many of the 3-carboxy flavanone products are formed as mixtures of *cis* and *trans* diastereomers, but the in situ decarboxylation delivers highly enantioenriched flavanones in

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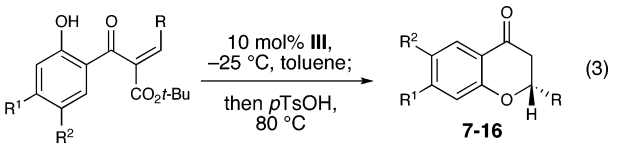
Table 2. Scope of Cyclization/Decarboxylation[a]



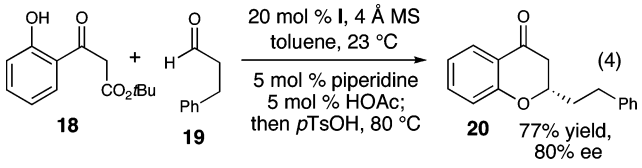
(3)

entry	R	R^1	R^2	product	ee (%)[b,c]	yield (%)[d]
1	Ph	H	H	**7**	94	92
2	4-BrPh	H	H	**8**	92	65
3	2-naphthyl	H	H	**9**	91	89
4	4-CH_3-Ph	H	H	**10**	90	83
5	2-Cl-Ph	H	H	**11**	88	67
6	4-OMe-Ph	H	H	**12**	91[e]	94
7	Ph	OMe	H	**13**	89	71
8	Ph	Me	H	**14**	90	97
9	Ph	$-(CH)_4-$		**15**	89	78
10	cyclohexyl	H	H	**16**	80	65

[a] Reaction conditions: 0.1 M of ester. [b] Determined by HPLC analysis (Chiralcel OD−H). [c] Absolute configuration determined by comparison of optical rotation to literature values.[7] [d] Yield after chromatography. [e] Determined prior to decarboxylation; see ref 12.

excellent yield. Different phenol moieties can also be accommodated in the reaction, including electron-rich (entry 7) and extended aromatic substrates (entry 9). The cyclohexyl-substituted alkylidene also undergoes cyclization to afford chromanone **16** in good enantioselectivity (80% ee, entry 10).[13]

Alkyl-substituted alkenes (R = alkyl) are challenging to purify due to minor amounts of nonselective cyclization. Since the Knoevenagel and conjugate addition reactions are both performed in toluene, these reactions can be merged in a tandem procedure (eq 4). The combination of **18**, hydrocinnamaldehyde (**19**), acetic acid, piperidine, and **I**[14] in the presence of molecular sieves in toluene at room temperature affords the natural product flindersiachromanone[15] (**20**) in 80% ee and 77% overall yield after decarboxylation with *p*-TsOH.



(4)

Our preliminary understanding of this reaction invokes hydrogen bonding between the β-ketoester substrate and chiral thiourea. The interaction between the quinuclidine nitrogen and phenol then promotes the selective intramolecular conjugate addition. Importantly, tertiary amine and thiourea functional groups together in a single catalyst deliver high selectivity. For example, quinine as a catalyst for the reaction (20 mol %) results in low enantioselectivity (17% ee), and the bis(3,5-CF_3phenyl)thiourea alone does *not* promote cyclization when combined with **5** in toluene. Additionally, the combination of 20 mol % each of quinine and bis(3,5-CF_3-phenyl)thiourea affords only 23% ee of **6**.

In summary, we have developed an enantioselective method for the synthesis of flavanones and chromanones. This is a novel example of a bifunctional quinine-derived thiourea catalyst activating a β-ketoester alkylidene substrate and promoting a conjugate addition of a phenol to deliver enantioenriched flavanones and chromanones. Mechanistic investigations of the reaction and its application toward biologically active molecules are currently in progress.

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Supporting Information Available: Complete ref 2b, experimental procedures, and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The 4′-methoxyphenyl substrate (**12**, R = 4-OMe-Ph) affords racemic product under *p*-TsOH conditions. The decarboxylation using $MgBr_2 \cdot OEt_2$ affords the 4′methoxy flavanone in 78% ee.

(13) The *Z*-isomer alkylidenes have not been synthesized yet. However, no equilibration of the *E*-isomers has been observed under the reaction conditions (^{1}H NMR spectroscopy).

(14) The use of catalyst **III** instead of **I** affords lower enantioselectivity at 23 °C, the temperature required for the Knoevenagel reaction.

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