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Stereodivergent Synthesis of Chromanones and Flavanones via Intramolecular Benzoin Reaction

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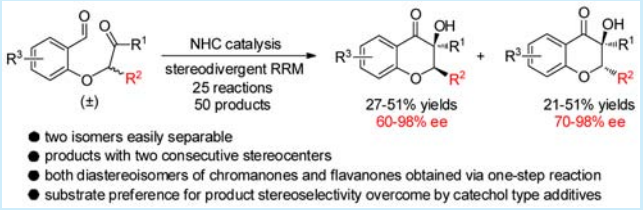
Supporting Information

ABSTRACT: The strategy of stereodivergent reactions on racemic mixtures (stereodivergent RRM) was employed for the first time in intramolecular benzoin reactions and led to the rapid access of chromanones/flavanones with two consecutive stereocenters. The easily separable stereoisomers of the products were obtained with moderate to excellent enantioselectivities in a single step. Catechol type additives proved crucial in achieving the desired diastereo- and enantioselectivities.



Chromanones and flavanones are a class of compounds containing the core structure of dihydrobenzopyranone. These molecules have drawn long-term research focus in both chemical and medicinal communities owing to their ubiquitous pharmacological properties such as anticancer, anti-HIV, antibacteria, antiparasitic, etc.[1] Besides the chromanones/flavanones with only one stereocenter, there remains a large amount of these compounds bearing two stereogenic centers. In many cases, both enantiomers and/or diastereoisomers show bioactivities, and sometimes, they even display different ones (Figure 1).[1]

Therefore, addressing the issue of producing both isomers of these substances in a concise and efficient approach is extraordinarily significant and urgent. However, a comprehensive literature survey reveals markedly limited approaches that can directly build enantioenriched chromanones/flavanones bearing two consecutive stereocenters. In most cases several steps have to be applied.[2] Recently, an elegant chiral thiourea catalyzed intramolecular conjugate addition approach for the synthesis of chromanone related products was developed by Scheidt and coworkers.[3] However, methods that are able to assemble both diastereoisomers (*cis*- and *trans*-) of this class of compounds remain extremely scarce. In recent years, the strategy of divergent reactions on racemic mixtures (divergent RRM) has drawn increasing research interest owing to its capability of readily assembling molecules with structural diversity.[4] We envisioned that the merger of N-heterocyclic carbene (NHC) catalyzed benzoin reactions[5] and the strategy of stereodivergent RRM would accomplish the mission of furnishing stereodiversified chromanone related compounds in an efficient and atom-economic fashion (Scheme 1).

However, a concomitant challenge in the study of stereodivergent RRM is that the inherent substrate preference for the product stereoselectivity must be overcome.[4f] As illustrated in Scheme 2, in a matched case, both the substrate preference and

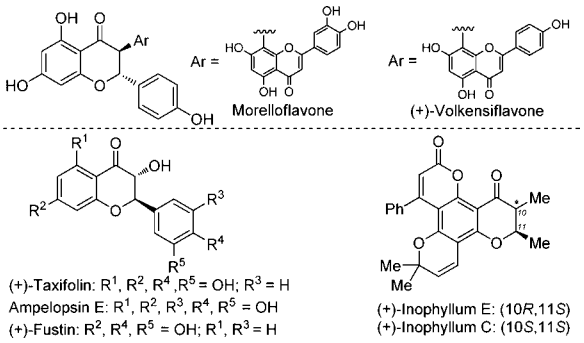
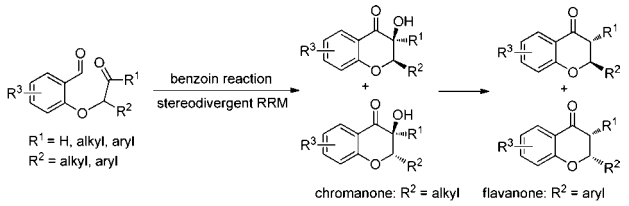


Figure 1. Selected examples of chromanones/flavanones.

Scheme 1. Stereodivergent Benzoin Reaction for the Synthesis of Chromanones/Flavanones



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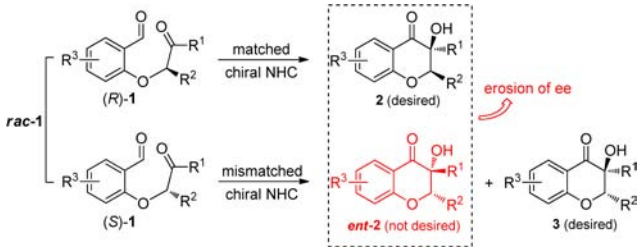
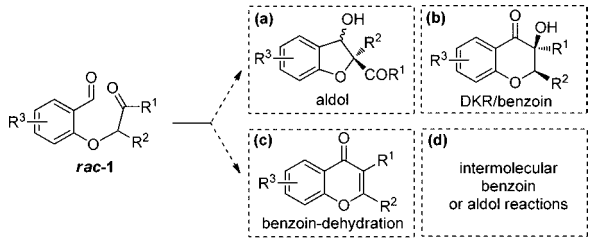
Scheme 2. Challenge of Overcoming Substrate Preference



the catalyst preference favor the formation of chiral product **2**; however, a mismatched pair shows diminished selectivity and produces not only the catalyst controlled product **3** but also minor product ***ent*-2** due to the inherent substrate preference, thereby resulting in the enantioselectivity erosion of product **2**. In the worst case, both enantiomers of the substrate would not match the chiral catalyst and provide both products with low ee values.[4a] This point is also in sharp contrast to conventional benzoin reactions that lead to products with only one stereocenter.[6]

Furthermore, to achieve a successful stereodivergent reaction in this study, several side reactions such as an intramolecular aldol reaction (Scheme 3a), a possible dynamic kinetic resolution

Scheme 3. Challenge of Suppressing Side Reactions

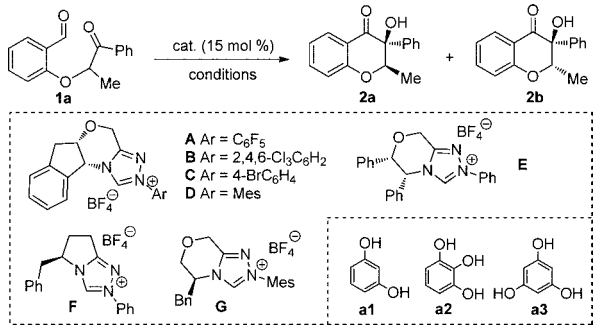


(DKR) process (Scheme 3b), a dehydration reaction that forms 4*H*-chromen-4-one (Scheme 3c), and intermolecular benzoin or aldol reactions (Scheme 3d) must be suppressed. It is also noteworthy that the two diastereoisomers obtained in this work need to be easily separable from each other via flash chromatography; otherwise, the practicality of this method will be significantly discounted.[4e]

With the goal of addressing all the above challenges and developing a general approach for the synthesis of multiply substituted chromanones and flavanones in a concise, efficient, and highly enantioselective manner, we recently conducted the NHC-catalyzed stereodivergent reaction on racemic aldehyde-ketones to furnish the title compounds. Herein we report the results.

Easily available substrate **1a** and triazoliums **A**–**D** (used initially by Rovis and Bode groups),[7] which have proven extremely successful in a large range of NHC-catalyzed reactions including intramolecular benzoin processes,[6d,e] were selected for conditions optimization. Not unexpectedly, the initial evaluation of several triazoliums with different *N*-aryl substituents induced very low levels of enantioselectivity, probably because of the inability to overcome the substrate preference for the product stereoselectivity (Table 1, entries 1–4). For instance, C_6F_5-substituted catalyst **A** afforded products **2a** and **3a** with a ratio of 5:1 and low enantioselectivities (10% and 56% ee, respectively, Table 1, entry 1). Similar results were observed when catalysts **B**, **C**, and **D** were utilized (Table 1, entries 2–4), with **B** giving a

Table 1. Reaction Conditions Optimization[a]



entry	cat.	base (equiv), addi. (equiv), temp	yield (%)[b]	ee (%)[c]
			2a/3a	**2a/3a**
1	**A**	DBU (0.2), 23 °C	72/14	10/56
2	**B**	DBU (0.2), 23 °C	74/25	14/66
3	**C**	DBU (0.2), 23 °C	66/33	22/56
4	**D**	DBU (0.2), 23 °C	58/41	2/58
5	**B**	Et_3N (0.2), 23 °C	75/19	16/67
6	**B**	K_2CO_3 (0.2), 23 °C	66/33	0/62
7	**B**	KOH (0.2), 23 °C	75/24	18/62
8	**B**	KOH (1.0), 23 °C	74/25	16/54
9	**B**	KOH (1.0), −20 °C	50/42	62/90
10	**B**	KOH (1.2), **a1** (1.0), −20 °C	30/21	83/96
11	**B**	KOH (1.2), **a2** (1.0), −20 °C	45/45	80/98
12	**B**	KOH (1.2), **a3** (1.0), −20 °C	66/33	40/94
13	**B**	KOH (0.8), **a1** (0.25), **a2** (0.75), −20 °C	51/46	82/98
14	**B**	KOH (0.8), **a1** (0.5), **a2** (0.5), −20 °C	**49/45**	**86/98**
15	**E**	KOH (0.8), **a1** (0.5), **a2** (0.5), −20 °C	19/14	54/56
16	**F**	KOH (0.8), **a1** (0.5), **a2** (0.5), −20 °C	77/22	34/68
17	**G**	KOH (0.8), **a1** (0.5), **a2** (0.5), −20 °C	60/17	38/84

[a]Reaction conditions: **1a** (0.2 mmol), NHC (0.03 mmol), THF (2 mL), argon protection. [b]Isolated yields based on **1a**. [c]Determined via HPLC analysis on a chiral stationary phase. The absolute configuration was determined via the single-crystal X-ray structure analysis of **3h** (Scheme 4). cat. = catalyst, addi. = additive, temp = temperature.

slightly better result considering the ee of **3a**. We then screened several bases using **B** as the catalyst but did not observe the promotion of ee values (Table 1, entries 5–8). Further screening of the reaction parameters indicated that decreasing the temperature to −20 °C can lead to an apparent enhancement of ee's (62% and 90% for **2a** and **3a**, respectively), and a ratio of 1.2:1 (**2a** versus **3a**) was observed (Table 1, entry 9). We then sought aid from adding additives such as **a1**–**a3**, an approach that has been used by Rovis, Chi, and other groups and proven useful in improving the yields and ee's of the products.[8] To our delight, a remarkable enhancement of ee values of both **2a** (83% ee) and

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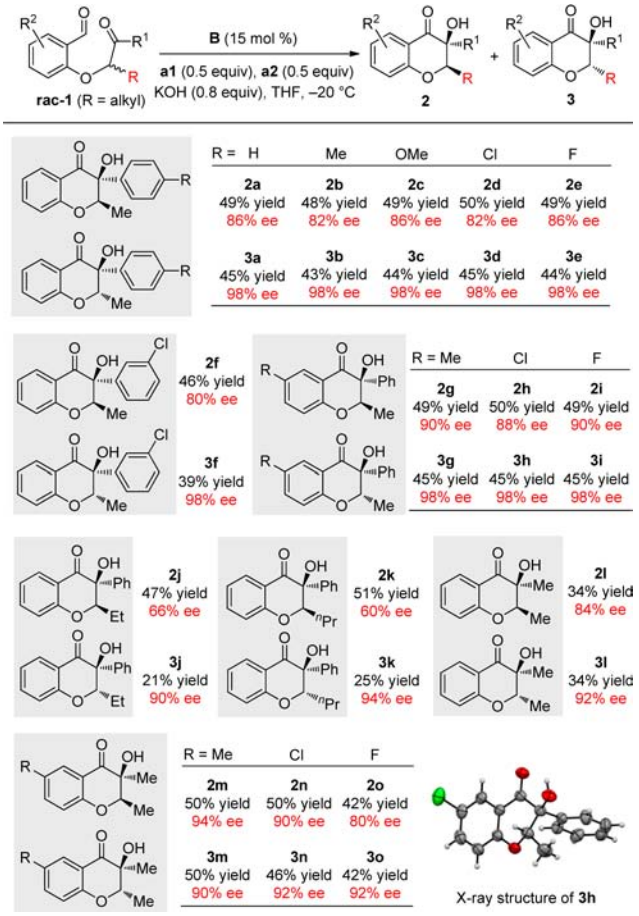
3a (96% ee) was furnished when a1 was added, albeit with moderate conversion (Table 1, entry 10). Various results were perceived with different additives (Table 1, entries 11 and 12). Cheerfully, the combination of additives a1 and a2 can increase the ee values to 82% (2a) and 98% (3a), adjust their ratio to 1.1:1, and maintain almost quantitative conversion (Table 1, entry 13). Finally a slight change in the ratio of a1 versus a2 resulted in the optimal results (Table 1, entry 14). Although the exact model of function is not well established to date, we believe that the catechol-type additives work through H-bonding that combines both the Breslow intermediate and the carbonyl group of the ketone moiety.[8d] Several widely used triazoliums with different chiral skeletons were also tested but did not deliver better results (Table 1, entries 15−17).

With the optimal conditions established, we first examined a variety of substrates with different substituents to evaluate the synthetic potential of accessing chromanones. As shown in Scheme 4, variations on the substitution pattern of the aromatic ketone moiety were possible. For example, substrates with additional electron-donating Me or OMe groups at the *para*-position were tolerated well, providing the corresponding diastereoisomers in excellent yields and with good to excellent enantioselectivities (Scheme 4, 2b/3b and 2c/3c). Similarly, electron-withdrawing groups such as F or Cl groups had little effect on the yields and ee values (Scheme 4, 2d/3d, 2e/3e, and 2f/3f). Substrates with different substituents on the formyl phenyl ring were also surveyed and proved amenable under the standard conditions, delivering the chromanones in an almost 1:1 ratio and without any erosion of the enantioselectivities (Scheme 4, 2g/3g, 2h/3h[9], and 2i/3i). Ketones with α-ethyl or propyl groups were also evaluated, and the corresponding 3j and 3k can be delivered with excellent enantioselectivities; however, moderate ee values were detected for 2j and 2k and the ratios of 2j/3j and 2k/3k changed to about 2:1 in both cases, indicating an increased substrate preference when sterically more bulky substituents were introduced. Replacement of the aromatic substituents with an aliphatic methyl group at the ketone moiety had no significant influence on the outcomes, with the enantioselectivities retained, albeit with a moderate total yield (Scheme 4, 2l/3l). Moreover, the methodology proved compatible with substituents of Me, Cl, or F at the formyl units, releasing both isomers with excellent enantioselectivities (Scheme 4, 2m/3m, 2n/3n, and 2o/3o).

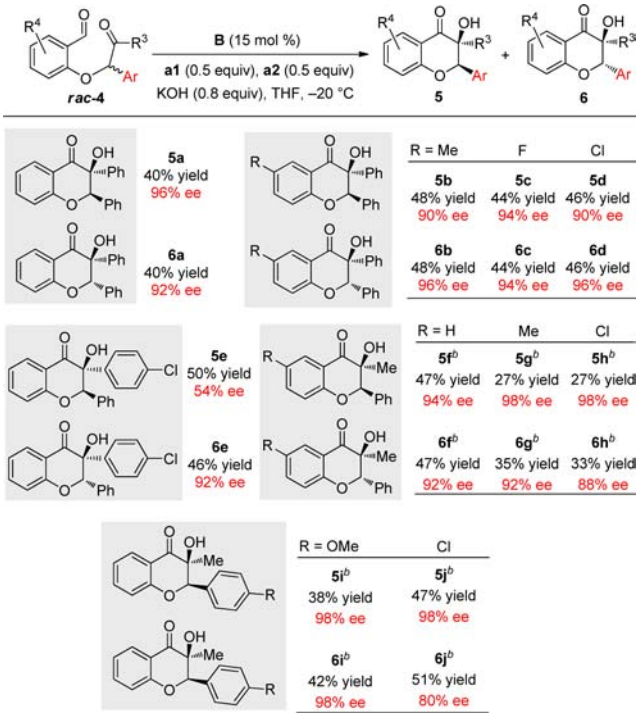
Having been successful in the stereodivergent synthesis of chromanones, we then transferred our focus to flavanones. As displayed in Scheme 5, although the introduction of an aryl group into substrates such as 4 will increase the enolizability of the ketone moiety, thereby facilitating an intramolecular aldol reaction and a dynamic kinetic resolution process, we found that the optimal conditions used in Scheme 4 worked well in this range of substrates. For instance, diastereoisomers 5a and 6a were both isolated with excellent ee values (96% and 92%, respectively), and substrates equipped with electron-donating and -withdrawing groups at the formyl units were also

Scheme 4. Stereodivergent Synthesis of Chromanones[a]



[a]All reactions were run on a 0.2 mmol scale; all yields were of isolated products; ee values were determined via HPLC analysis on a chiral stationary phase; in most cases, the dr values are close to the ratio of 2/3.

Scheme 5. Stereodivergent Synthesis of Flavanones[a]



[a]All reactions were run on a 0.2 mmol scale; all yields were of isolated products; ee values were determined via HPLC analysis on a chiral stationary phase; in most cases, the dr values are close to the ratio of 5/6. [b]Catalyst C (15 mol %), NaOH (1.2 equiv), a1 (0.75 equiv), and a2 (0.25 equiv) were used for the synthesis of 5f−j and 6f−j.

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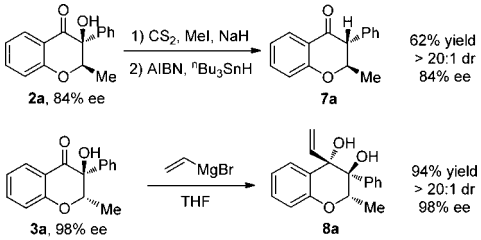
compatible under the standard conditions (Scheme 5, **5b**/**6b**, **5c**/**6c**, **5d**/**6d**, and **5e**/**6e**). Slightly modified conditions were used for aliphatic ketone substrates to guarantee high enantioselectivities (Scheme 5, **5f**/**6f**), and the introduction of substitution groups on both the formyl aryl rings and the phenyl groups at the α-position of ketones was also possible (Scheme 5, **5g**/**6g**, **5h**/**6h**, **5i**/**6i**, and **5j**/**6j**). The relatively lower total yields of **5g**/**6g** and **5h**/**6h** were mainly due to the formation of some side products.

Further transformations based on the products can be realized through the nucleophilic attack of **2a** by a vinyl Grignard reagent and the two-step dehydroxylation of **3a**, releasing corresponding chromanone **7a**[10] and 1,2-diol **8a**[11] without any erosion in ee values (Scheme 6).

Scheme 6. Products Derivatizations



In summary, the first stereodivergent intramolecular benzoin reaction on racemic aldehyde-ketone substrates was developed and applied in the synthesis of chromanones/flavanones bearing two consecutive stereocenters. Chromatographically separable stereoisomers of this series of compounds were obtained with moderate to excellent enantioselectivities in a concise approach. The protocol also highlights the use of catechol type additives in overcoming the substrate preference and eventually assisting the diastereo- and enantioselective control of both isomers. Further study on the access of useful synthons and natural products through the combination of stereodivergent RRM with benzoin reactions is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01767.

Experimental procedures, optimization details, data for all new compounds, NMR and HPLC spectra (PDF)
X-ray structure of **3h** (CIF)

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Notes

The authors declare no competing financial interest.

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