

Modular Design of Chiral Conjugate-Base-Stabilized Carboxylic Acids: Catalytic Enantioselective [4+2] Cycloadditions of Acetals.

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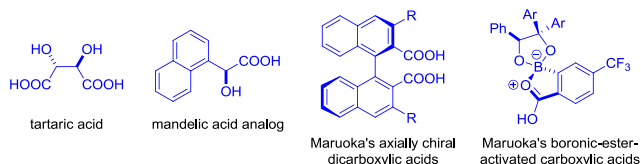
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Supporting Information Placeholder

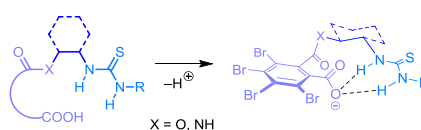
ABSTRACT: Readily available 1,2-amino alcohols provide the framework for a new generation of chiral carboxylic acid catalysts that rival the acidity of the widely used chiral phosphoric acid catalyst (*S*)-TRIP. Covalently linked thiourea sites stabilize the carboxylate conjugate bases of these catalysts via anion-binding, an interaction that is largely responsible for the low pK_a values. The utility of the new catalysts is illustrated in the context of challenging [4+2] cycloadditions of salicylaldehyde-derived acetals with homoallylic and bishomoallylic alcohols, providing polycyclic chromanes in highly enantioselective fashion.

The burgeoning field of asymmetric Brønsted acid catalysis continues to be driven largely by chiral phosphoric acids, first introduced by Akiyama and Terada in 2004.^{1,2} Although chiral carboxylic acids such as tartaric acid and mandelic acid are abundant in nature, they have only occasionally been used in asymmetric Brønsted acid catalysis.³ This is likely due to the rather weak acidity of simple carboxylic acids, significantly limiting the types of substrates that can be activated.^{2g} Indeed, the most successful chiral carboxylic acids developed thus far contain elements that further acidify the catalyst, as exemplified by the elegant contributions of the Maruoka group (Figure 1).⁴ In this context, we recently reported a new class of easily prepared chiral carboxylic acid catalysts that derive their high acidity from conjugate-base-stabilization through anion-binding, facilitating a number of asymmetric transformations (Figure 1).^{5,6} Computational studies suggest that the catalyst anions can adopt a bowl-shaped structure, enabling the formation of well-defined ion pairs with cationic substrate intermediates.^{5e,7} Our original design of these catalysts was based on chiral 1,2-diamine backbones, limiting the structural variety of catalysts that are easily accessible. We now report second-generation catalysts that are based on chiral 1,2-amino alcohols. Not only are these backbones more readily available and offer a range of other advantages, the resulting catalysts show dramatically enhanced reactivity and selectivity profiles as illustrated in the catalytic enantioselective synthesis of polycyclic oxygenated chromanes.

Examples of carboxylic acids previously employed in asymmetric catalysis:



Design of highly acidic carboxylic acids:



- Chiral backbone
- Anion receptor installed by addition to isothiocyanate
- COOH installed via anhydride opening

- Stabilization of conjugate base via anion-binding
- Rigid bowl-shaped anion with multiple sites for interaction with cationic intermediates

Comparison of backbones:

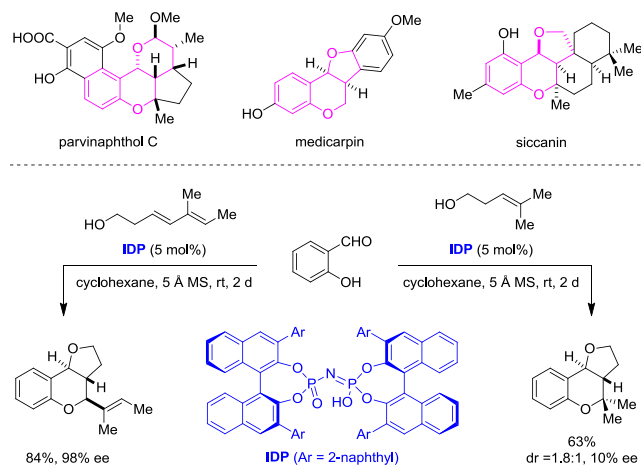
- 1,2-diamines (X = NH₂)
- Limited availability
 - Prolonged catalyst synthesis if R ≠ R'
 - Meso-isomers require desymmetrization
- 1,2-amino alcohols (X = OH)
- Widely available enantiopure
 - No issues of regioselectivity
 - No meso-isomers
 - Form more active catalysts

Figure 1. Catalyst Design.

Furanochromanes and pyranochromanes are common substructures of natural products such as parvinaphthol C, medicarpin, and siccanin (Scheme 1).⁸ While there are various examples of catalytic enantioselective cycloadditions of *o*-quinone methide intermediates that provide access to simple chromane frameworks lacking oxygenation in the 4-position,^{9,10} direct catalytic enantioselective approaches to 4-oxygenated chromanes remain extremely rare.¹¹ As the latter cycloadditions require the intermediacy of oxocarbenium ions or protonated *o*-quinone methides, they present a significant challenge to asymmetric catalysis.^{12,13} Although a number of Brønsted and Lewis acids have been shown to facilitate condensations/cycloadditions of salicylaldehyde derivatives with homoallylic and bishomoallylic alcohols to provide furanochromanes and pyranochromanes in high yields and diastereoselectivities,¹⁴ the only catalytic enantioselective variant of such a reaction was recently published by the List group (Scheme 1).^{11a} Specifically, these researchers accomplished highly enantioselective [4+2] cycloadditions of salicylaldehydes with dienyl homoallylic alcohols, utilizing an imidodiphosphoric

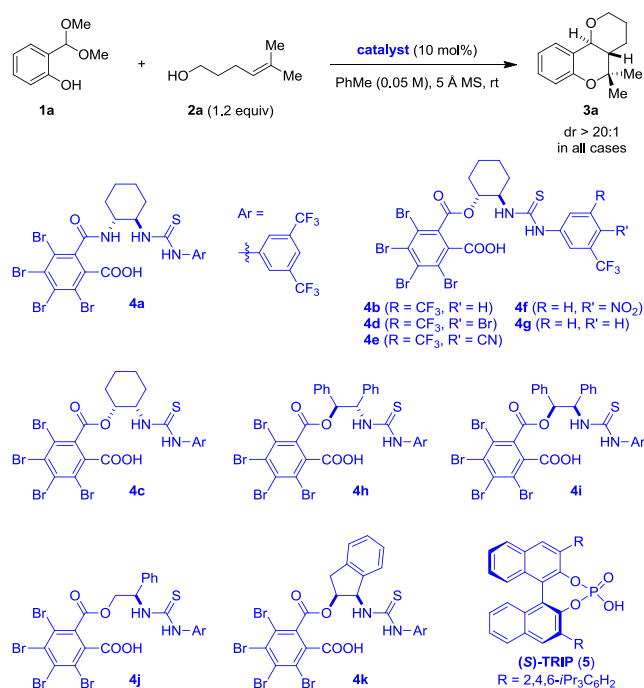
acid catalyst (IDP). However, under identical conditions, a simple homoallylic alcohol provided the desired product with poor levels of stereocontrol, illustrating the need for a conjugated alkene in this particular approach.

Scheme 1. Natural products containing 4-oxochromanes and previous catalytic enantioselective approach to furanochromanes.



With the goal of developing an intramolecular [4+2] cycloaddition with simple alkene substrates, we initiated our investigations with salicylaldehyde dimethyl acetal **1a** and bishomoallylic alcohol **2a** (Table 1). The previously reported thiourea-carboxylic acid **4a** was found to be a highly active catalyst, furnishing the desired product **3a** in good yield albeit low ee (entry 1). Remarkably, the new 1,2-amino alcohol-based catalyst **4b**, differing from **4a** only in the type of linker connecting the thiourea and carboxylic acid functionalities (ester-linkage vs. amide-linkage), was not only markedly more active, but also provided a dramatic boost in enantioselectivity (entry 2). The corresponding *cis*-isomeric catalyst **4c** exhibited similarly high activity but furnished the opposite enantiomer of **3a** in low ee (entry 3). Notably, no product was obtained with either of the catalysts when **1a** was replaced with salicylaldehyde (not shown). Increasing the electron-withdrawing character of the thiourea aryl group resulted in the even more active and selective catalysts **4d** and **4e** (entries 4 and 5). In contrast, catalysts **4f** and **4g** provided slightly less favorable results (entries 6 and 7). Thiourea-carboxylic acids **4h–4k** were also prepared from a range of other chiral 1,2-amino alcohols. Although their evaluation did not result in further improvements (entries 8–11), these catalysts appear to hold significant potential for the future use in other reactions. Finally, a modest reduction in reaction temperature to 0 °C further enhanced the performance of catalyst **4e**, providing product **3a** in 89% yield and 99% ee after a reaction time of just 30 min (entry 12). For comparison purposes, the reaction was conducted with the chiral phosphoric acid catalyst (*S*)-TRIP (**5**)¹⁵ which was found to be relatively inactive. While low substrate conversion was observed after 15 h, **3a** was obtained in nearly racemic form (entry 13). No improvement in selectivity was achieved with IDP, although this catalyst proved to be significantly more active than (*S*)-TRIP (**5**) (entry 14). It should be noted that all ester-linked thiourea-carboxylic acids prepared in the course of this study are stable and easily available in two steps from their corresponding 1,2-amino alcohols, isothiocyanates, and cheap tetrabromophthalic anhydride.

Table 1. Reaction development.^a

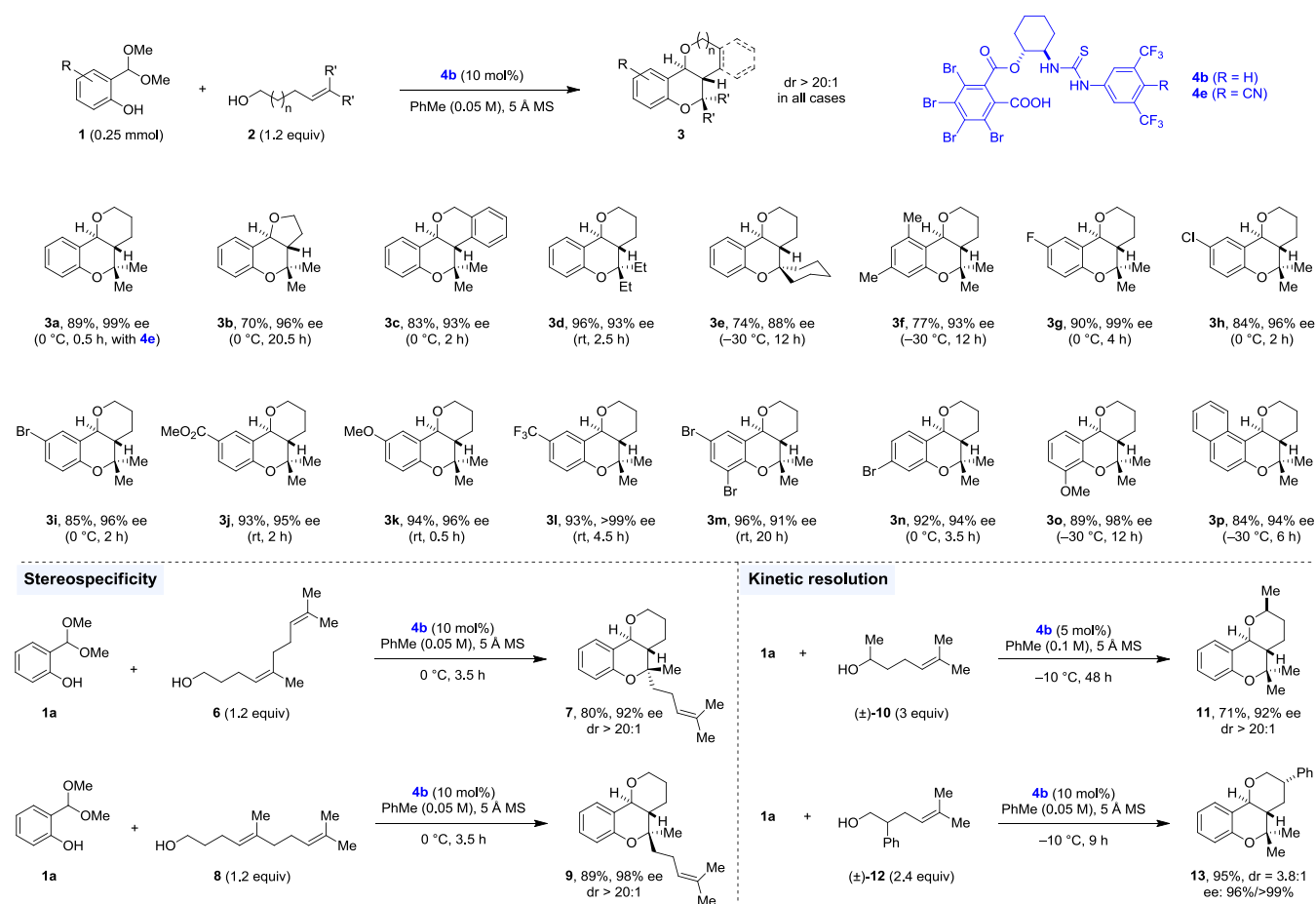


entry	catalyst	time	yield (%)	ee (%)
1	4a	30 min	86	25
2	4b	15 min	89	94
3	4c	15 min	80	–30
4	4d	10 min	97	95
5	4e	5 min	96	96
6	4f	5 min	95	90
7	4g	30 min	96	92
8	4h	30 min	92	–69
9	4i	50 min	75	19
10	4j	50 min	83	71
11	4k	30 min	88	55
12 ^b	4e	30 min	89	99
13	S-TRIP (5)	15 h	19	6
14	IDP	4 h	89	2

^a Reactions were performed with 0.1 mmol of **1a** and 1.2 equiv of **2a**. All yields correspond to yields of isolated product. The ee values were determined by SFC analysis. ^b Reaction was performed at 0 °C.

The scope of the catalytic enantioselective [4+2] cycloaddition reaction is summarized in Scheme 2. While the use of catalyst **4e** was optimal for the synthesis of product **3a** from bishomoallylic alcohol **2a** (Table 1), catalyst **4b** (readily prepared on scale in just two steps from commercial materials) was found to be more general and was therefore used for all other substrates. The corresponding homoallylic alcohol also participated in this transformation, providing furanochromane **3b** in high ee. A benzylic alcohol was also efficiently converted into the corresponding product **3c**. Different substituents on the alkene moiety were well tolerated. Salicylaldehyde acetals containing electronically diverse substituents in the 3-, 4-, 5-, and 6-positions were readily accommodated. Excellent enantioselectivities and good yields were generally achieved. In all cases, only the *trans*-fused diastereomers of products **3** were observed.¹⁶

Scheme 2. Reaction scope.



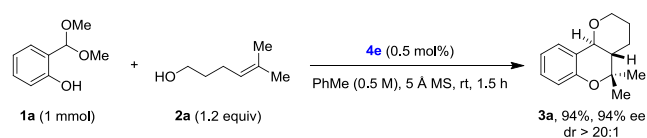
To gain insights into the stereospecificity of the [4+2] cycloaddition and possibly its nature (concerted vs. stepwise), reactions of **1a** were conducted with the two *E/Z*-isomeric bishomoallylic alcohols **6** and **8**. Diastereomeric products **7** and **9** were formed as the only observable isomers in high albeit nonidentical levels of enantioselectivity (Scheme 2). As pointed out recently by Spivey and coworkers in an elegant mechanistic/computational paper involving closely related substrates,^{14g} this does not necessarily imply a concerted cycloaddition pathway. Therefore, a Prins-like process with a tertiary carbocation intermediate cannot be ruled out at present and may in fact be more likely.

The possibility of achieving kinetic resolution or diastereodivergent reactions was explored with representative, racemic bishomoallylic alcohols **10** and **12** (Scheme 2).¹⁷ Interestingly, while the α-stereogenic center in substrate **10** dictates the diastereoselectivity of the reaction, consistent with what has been observed in the corresponding non-asymmetric reaction,^{14a,e} one enantiomer of **10** reacts significantly faster, leading to an efficient kinetic resolution process and the formation of product **11** as a single observable diastereomer in 71% yield and 92% ee. In contrast, the β-stereogenic center in substrate **12** seems to not greatly bias the innate diastereoselectivity of the reaction. Here a diastereodivergent process was observed with each enantiomer of **12** providing a different product diastereomer, both of which were obtained in excellent enantioselectivity.¹⁸ Judging from the fact that the product dr is 3.8:1 (rather than 1:1), a kinetic resolution process also took place simultaneously. These transformations illustrate the ability to install additional

stereogenic centers by utilizing readily available racemic starting materials.¹⁷

To further improve the overall efficiency of the [4+2] cycloaddition, we evaluated the synthesis of pyranochromane **3a** at different substrate concentrations and catalyst loadings. Gratifyingly, using only 0.5 mol% of catalyst **4e** at a tenfold increased substrate concentration in toluene solution allowed for the preparation of product **3a** in excellent yield and ee (Scheme 3). Even at this low catalyst loading, the reaction went to completion within 1.5 hours at room temperature. Thus, the amount of solvent needed for conducting the reaction on a 0.1 mmol scale is the same as for a 1 mmol scale.

Scheme 3. Reaction at low catalyst loading



Detailed acidity measurements in acetonitrile were conducted for several thiourea-carboxylic acid catalysts and control compounds (Figure 2).¹⁹ As reported previously, the amide-linked catalyst **4a** has a pK_a value of 12.4.^{5f} Comparison of this value to the pK_a values of truncated versions of the catalyst, namely thiourea **14** and carboxylic acid **15**, suggests that conjugate-base-stabilization is responsible for an increase in acidity of nearly seven orders of magnitude. To gauge the potential role of the amide NH in stabilizing or destabilizing the conjugate base of the catalyst, we subsequently prepared ester **16**. Interestingly, **16** was found to be two orders of magnitude more acidic than amide **15**, suggesting

that stabilization of the carboxylate anion via hydrogen bonding to the amide NH is unlikely to play a significant role. Rather, the increase in acidity when replacing the amide substituent with an ester group can be attributed to inductive effects. It was in fact this observation that provided some of the motivation for pursuing 1,2-amino alcohol based catalysts as a potential avenue to more acidic catalysts. However, the expected acidity trend does not hold. The pK_a value of **4b** was determined to be 13.6. Clearly, the model compounds do not fully capture all aspects that are responsible for the overall pK_a values of the actual catalysts. Coincidentally, the acidities of **4b** and (*S*)-TRIP (**5**) are identical.²⁰ Their vastly different performances in the [4+2] cycloaddition nicely illustrate that the acidity of a Brønsted acid catalyst is not necessarily correlated with its activity in a given transformation. Comparing once again catalysts **4a** and **4b**, it is clear that this consideration also applies to catalysts that are structurally closely related. Finally, the *cis*-configured catalyst **4c** was found to be the most acidic catalyst in the series with a pK_a value of 11.8, close to the pK_a values of typical imidodiphosphoric acids (pK_a values ~ 11.5)²¹ and significantly more acidic than trifluoroacetic acid.²¹ Presumably, the relative spatial arrangement of the carboxylic acid and thiourea moieties enables a more efficient stabilization of the conjugate base in the *cis*-isomer **4c** than is possible in the *trans*-isomer **4b**.

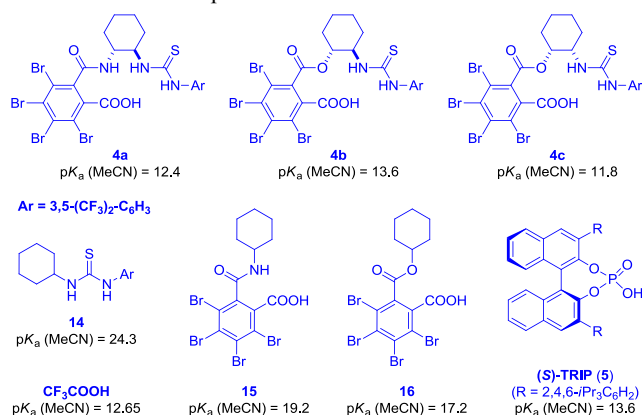


Figure 2. pK_a values of thiourea-carboxylic acid catalysts and comparison to other acids.

In conclusion, we have achieved highly efficient [4+2] cycloadditions of salicylaldehyde-derived acetals with homoallylic and bishomoallylic alcohols to provide polycyclic furanochromanes and pyranochromanes in good to excellent yields and enantioselectivities. This advance was enabled through the development of a new generation of conjugate-base-stabilized carboxylic acid catalysts. The observation that Brønsted acids with identical pK_a values can exhibit vastly different catalytic activities makes a compelling case for the continued exploration of more structurally diverse catalysts.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data, including X-ray crystal structure of product **3n**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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