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Enantioselective Multicomponent Condensation Reactions of Phenols, Aldehydes, and Boronates Catalyzed by Chiral Biphenols

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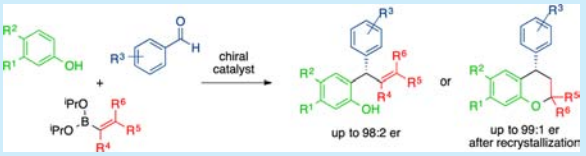
Supporting Information

ABSTRACT: Chiral diols and biphenols catalyze the multicomponent condensation reaction of phenols, aldehydes, and alkenyl or aryl boronates. The condensation products are formed in good yields and enantioselectivities. The reaction proceeds via an initial Friedel–Crafts alkylation of the aldehyde and phenol to yield an *ortho*-quinone methide that undergoes an enantioselective boronate addition. A cyclization pathway was discovered while exploring the scope of the reaction that provides access to chiral 2,4-diaryl chroman products, the core of which is a structural motif found in natural products.



ortho-Quinone methides (*o*QMs) are reactive intermediates with wide-ranging applications in organic synthesis.[1] As transient species, they have been exploited in biomimetic syntheses as heterodiene partners in Diels–Alder reactions.[2] The propensity to rearomatize prompts nucleophilic additions at the methide carbon, which has frequently been exploited asymmetrically within the past decade.[3] The formation of metal-coordinated *o*QM complexes and bench stable conjugated *o*QMs have enabled their use in synthesis.[4,5] More typically, however, *o*QMs are short-lived species, making their detection and utility in synthesis challenging.[6] Therefore, *in situ* synthesis of the *o*QM would be an attractive approach to alleviate any issues involved in constructing a reactive intermediate.

Herein, we report a multicomponent condensation reaction to form *o*QMs through a bimolecular process involving a phenol and an aldehyde mediated by boronates and catalyzed by chiral phenols resulting in an enantioselective nucleophilic addition to the methide carbon. Enantioselective additions of boronates to *o*QMs catalyzed by chiral biphenols provide access to chiral motifs that appear in natural products and drugs.[7] For instance, myristinin A is a potent inhibitor of DNA polymerase β and contains a chiral diaryl methane within its chroman core.[8] Other notable examples include myristicyclin A, dracoflavans C and D, and cochinchinenins B and C.[9−11] Methods to form *o*QMs typically require oxidation, acid/base chemistry, photolysis, or thermolysis.[12] Asymmetric, multicomponent reactions (MCR) provide access to structural complexity within a single transformation.[13] A convergent approach in constructing this moiety leads to higher process efficiency.[14] Despite these potential benefits, there are currently no examples of an asymmetric multicomponent reaction utilizing *o*QM chemistry.[15] The efficiency of a possible MCR led us to investigate using boronates to mediate *o*QM formation.[16] Our investigations to develop a multicomponent strategy began with an electron-rich phenol, an aldehyde, and a styrenyl boronate. Mediated by the boronate, a Friedel–Crafts hydroxyalkylation reaction occurs to yield a dioxaborin intermediate.[17] Nucleophilic attack by an activated and chiral boron ate complex forms the product in a stereoselective fashion.

Experiments were designed to evaluate chiral diol catalysts in the reaction (Table 1, entries 1−3). 1,1′-Bi-2-naphthol (BINOL) derived catalysts containing substituents at the 3,3′ positions led to higher enantioselectivities (Table 1, entries 4−6). In agreement with our previous studies, (*R*)-3,3′-Br_2-BINOL was identified as the catalyst for further evaluation giving the best combination of yield and enantioselectivity.[7] Higher concentrations improved the yield but resulted in lower enantioselectivity (Table 1, entries 7−9). A temperature of 80 °C was found to be ideal for promoting the condensation while maintaining enantioselectivity. As such, other high boiling solvents were examined, but did not yield product (Table 1, entries 10 and 11). Use of trifluorotoluene resulted in a higher yield, but the enantioselectivity was lower; likely due to an increase in a competing uncatalyzed background reaction rate (Table 1, entry 12). We rationalized that the boronate ester group would have an important influence on the selectivity of the reaction.[18] It was found that changing the ethyl group to an isopropyl group led to a higher enantiomeric ratio (Table 1, entry 13). By adjusting the concentration and catalyst loading, we identified conditions resulting in a 70% yield and a 95:5 enantiomeric ratio (Table 1, entry 14). These reaction conditions proved optimal to explore the scope of the reaction (Figure 1).

A wide range of aldehydes and boronates could be used in the reaction, but the phenol needed to be electron-rich in order to promote the Friedel–Crafts alkylation reaction. Halogen substitution at the 4-position of the aldehyde was well tolerated, providing high enantioselectivity (**4b**, **4c**). Electron-rich aldehydes maintained selectivity, however, in lower yield (**4d**). Conversely, electron-deficient substitution resulted in lower enantioselectivity, but higher yield (**4e**) supporting the

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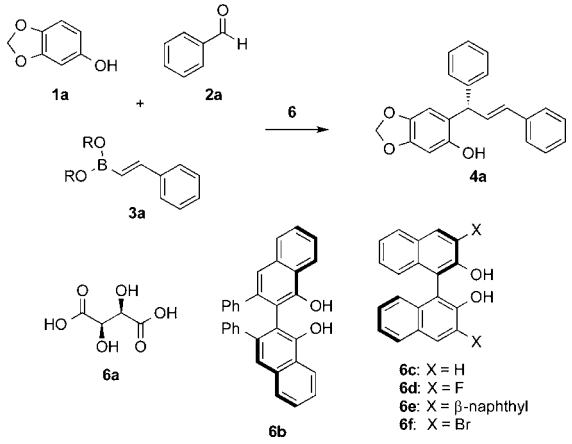
Table 1. Chiral Diols in the Multicomponent Boronate Condensation Reaction[a]



entry	catalyst	6 (mol %)	concn [M]	R	yield [%][b]	er[c]
1	**6a**	15	0.3	Et	77	50:50
2	**6b**	15	0.3	Et	51	85:15
3[d]	**6c**	15	0.3	Et	96	57:43
4	**6d**	15	0.3	Et	100	80:20
5	**6e**	15	0.3	Et	77	91:9
6	**6f**	20	0.2	Et	55	94:6
7	**6f**	20	0.4	Et	78	92:8
8	**6f**	20	0.8	Et	94	88:12
9[e]	**6f**	20	0.8	Et	50	86:14
10[f]	**6f**	20	0.2	Et	–	–
11[g]	**6f**	20	0.2	Et	–	–
12[h]	**6f**	20	0.2	Et	75	92:8
13	**6f**	10	0.2	*i*-Pr	51	95:5
14	**6f**	15	0.3	*i*-Pr	70	95:5

[a]Reactions were run at 80 °C with 0.4 mmol of phenol, 0.8 mmol of aldehyde, and 0.8 mmol of boronate for 24 h in toluene unless otherwise indicated. [b]Yield of isolated product. [c]Enantiomeric ratios (er) determined by HPLC analysis using a chiral stationary phase. [d]Reaction was run for 48 h. [e]Reaction was run at 60 °C for 24 h. [f]Ethanol used as solvent. [g]1,4-Dioxane used as solvent. [h]Tri-fluorotoluene used as solvent.

hypothesis of a rate-determining Friedel–Crafts alkylation. Heterocyclic aldehydes could be used in the reaction; 2-thenaldehyde gave a quantitative yield (**4f**). Comparison of **4f** to the previously reported compound confirmed the absolute stereochemistry of the product and is consistent with the reported *o*QM mechanistic model of enantioselectivity.[7] 2-Naphthaldehyde was tolerated in the reaction; however, sterics limited the reactivity of 1-naphthaldehyde (**4g**, **4h**). Notably, *ortho*-substitution improved the selectivity in the case of 2-bromobenzaldehyde (**4i**).

A similar observation was made with 2-methylbenzaldehyde, suggesting a steric interaction during the enantio-determining event (**4j**). The boronate constituents were evaluated in the reaction, and each were prepared from the boronic acid precursor.[19] Both styrenyl and aryl boronates performed well in the reaction (**4k**, **4l**, **4m**). Despite being less nucleophilic, electron-deficient boronate also afforded the product with good results (**4n**). The furanyl boronate was evaluated in the reaction proving to be highly reactive; it resulted in quantitative yield with low selectivity due to a competitive uncatalyzed background reaction (**4o**). Finally, the use of aliphatic hexenyl boronate resulted in excellent yield and enantioselectivity (**4p**). Phenol

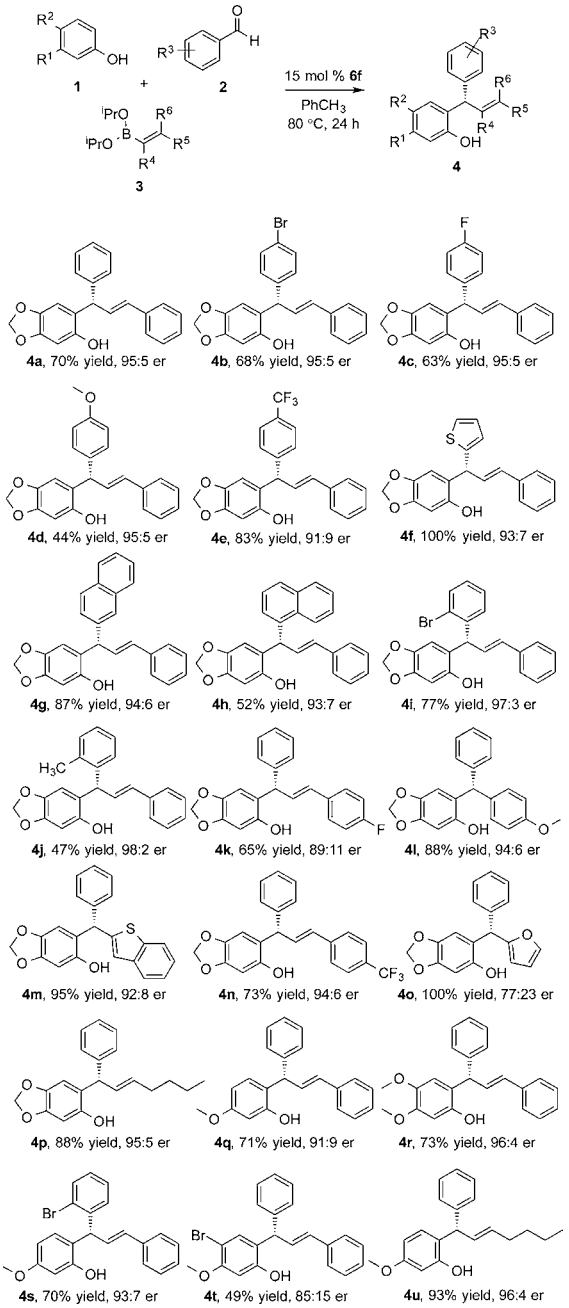


Figure 1. Multicomponent boronate condensation reactions.

substitution was investigated; 3-methoxyphenol and 3,4-dimethoxyphenol both gave high yields and enantioselectivity (**4q**, **4r**). Substrate combinations were tested and indicate this would likely work well for others (**4s**–**4u**). In the course of evaluating reaction components in the MCR, an unanticipated reaction pathway was identified. Using 4-methoxystyrenyl boronate afforded the 2,4-diarylchroman structure as the major product (**5a**). Identification of the chroman encouraged us to explore preferential chemoselectivity for the cyclization pathway. We initiated studies to evaluate catalysts that would promote chemo-, enantio-, and diastereoselective formation of the chroman (Table 2).

Of the chiral diol catalysts assessed, (*R*)-3,3′-I_2BINOL (**6g**) was found to give the best combination of yield and enantioselectivity (Table 2, entry 4). Next, we turned our attention to the reaction conditions. We hypothesized that the

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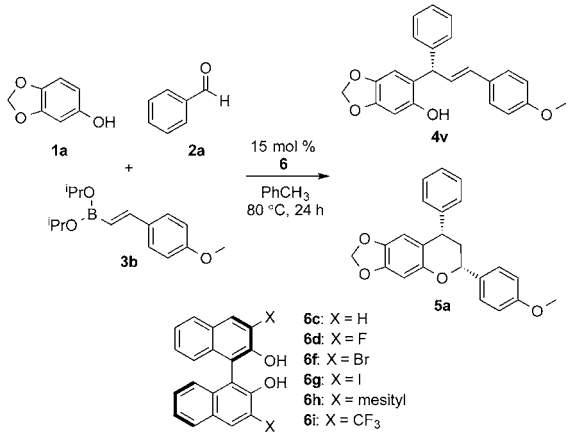
Table 2. Chroman Formation[a]



entry	catalyst 6	product 4v yield [%]	product 4v er	product 5a yield [%]	product 5a er
1	6c	22	70:30	28	60:40
2	6d	46	66:33	33	60:40
3	6f	22	80:20	55	79:21
4	6g	31	82:18	59	87:13
5[b]	6h	37	21:79	16	49:51
6	6i	39	89:11	50	81:19
7[c]	6g	5	–	69	84:16
8[d]	6g	–	–	72	85:15
9[d,e]	6g	–	–	40	99:1

[a]Reactions were run at 80 °C with 0.4 mmol of phenol, 0.8 mmol of aldehyde, and 0.8 mmol of boronate for 24 h in toluene (0.3 M) unless otherwise indicated. Diastereomeric ratios were 2:1 as determined by ^{1}H NMR unless otherwise indicated. Enantiomeric ratios are reported for the major diastereomer. [b](*S*)-Enantiomer of catalyst used. Mesityl = 2,4,6-trimethyl ofbenzene. [c]Reaction was run in sealed tube at 120 °C for 24 h. [d]Reaction was run in a sealed tube at 80 °C for 24 h and then 150 °C for 1 h. [e]Product was recrystallized from hot hexanes. The diastereomeric ratio was >20:1 as determined by ^{1}H NMR.

electron-rich nature of the styrene component under acidic conditions at higher temperatures facilitated the cyclization process. To test this hypothesis, the reaction was run in a sealed tube at 120 °C. A significant shift in chemoselectivity was observed, yielding the chroman product in 69% yield (Table 2, entry 7). We found that an increase in temperature for a brief time following the standard reaction conditions afforded the chroman product and maintained modest levels of selectivity (Table 2, entry 8). It was later determined that recrystallization from hot hexanes afforded the product with enhanced diastereo- and enantioselectivity (Table 2, entry 9). A few substrates are illustrated to show the potential of this reaction type (Figure 2).

As postulated, electron-rich π-conjugation displayed a propensity to cyclize (**5a**–**5e**), while electron-neutral styrene remained slow with regard to chroman formation, even at higher temperatures (**5f**). This observation led us to believe that the cyclization proceeds through protonation of the electron-rich olefin with subsequent nucleophilic attack of the phenol oxygen. Experiments were designed to further investigate the nature of the cyclization. Enantioenriched addition product (*S*)-**4v** (81:19 er) was isolated and subjected to reaction conditions used to afford the chroman product: 15 mol % (*R*)-3,3′-I_2-BINOL, benzaldehyde, and boronate **3b**, omitting phenol **1a**, at 150 °C for 24 h. Chroman (*S*,*S*)-**5a** was isolated in a 90:10 enantiomeric ratio. The result demonstrates a stepwise pathway leading to the formation of the chromans and enhanced selectivity in the

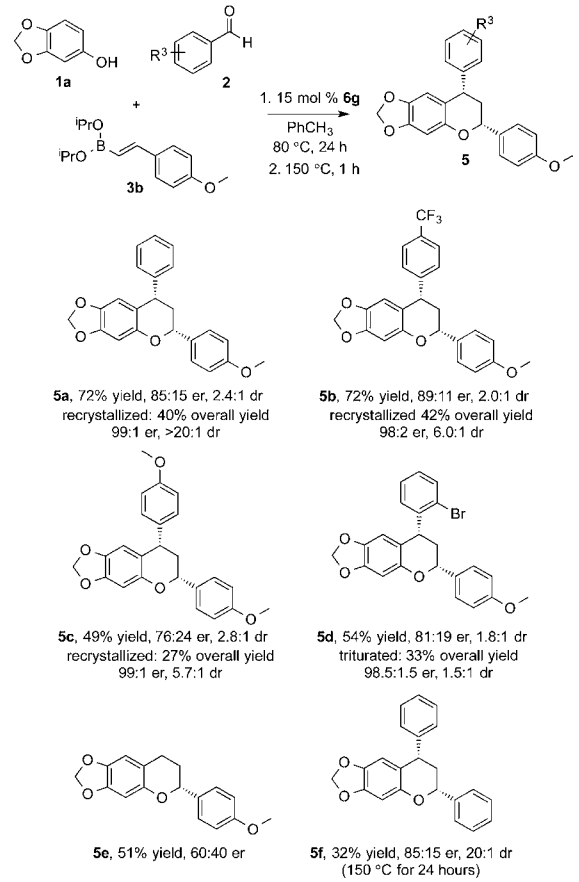
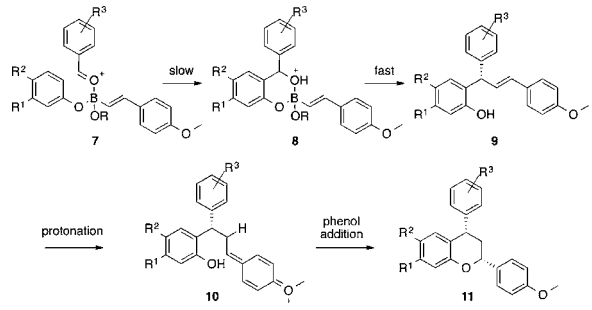


Figure 2. MCR chroman synthesis.

cyclization step facilitated by the catalyst; a matched cyclization to afford the *syn* product was confirmed by 1D NOE. We have developed a mechanistic model consistent with our observations (Scheme 1). Boron-mediated Friedel–Crafts hydroxyalkylation

Scheme 1. Proposed Mechanism for the Asymmetric Boronate MCR



condensation of the phenol and aldehyde in complex **7** is most likely rate limiting. There is no product formation at lower temperatures, also consistent with observations made in the literature.[17] Next, boronate complex **8** dissociates and ligand transfer occurs rapidly forming product **9**, the enantiodetermining event. This is consistent with our earlier studies in which enantioselective additions of boronates to *o*QMs occur at low temperatures.[7] The facile nature of this dissociation–ligand transfer also explains why there is no observation of a dioxaborin intermediate during the reaction.[20] The cyclization is initiated by protonation of the electron-rich olefin. A resonance-stabilized

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intermediate **10** is produced and quickly trapped by subsequent attack of the phenol oxygen to provide **11**.

In summary, an enantioselective multicomponent reaction was developed that provides access to chiral di- and triaryl methane products with high levels of yield and selectivity. We observed an unanticipated cyclization pathway, which yielded chiral 2,4-diaryl chromans. Further studies of this reaction are underway and involve optimizing the stereocontrol of the cyclization process as well as exploring its utility in natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02954.

Synthetic procedures, chiral HPLC analysis, characterization and spectral data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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