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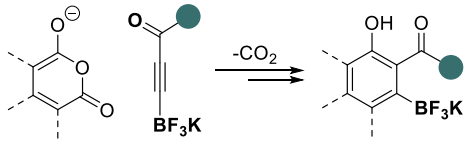
Base-Mediated Annulation Strategy to Naphthol Boronic Ester Derivatives

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Supporting Information Placeholder



ABSTRACT: The base promoted annulation reaction of homophthalic anhydrides with potassium ynone trifluoroborate salts offers a convenient method to access a range of *ortho*-acylphenol derivatives with complete regiocontrol. The products can be further functionalized chemoselectively by cross-coupling, *O*-alkylation and oxidative coupling processes.

INTRODUCTION

Cycloaddition strategies have emerged as an effective means for the synthesis of aromatic and heterocyclic boronic acid derivatives, allowing the assembly of complex and functionalized analogs to be undertaken directly from simple starting materials.[1] In this context, we have introduced ynone trifluoroborate salts which have proven to be a versatile vehicle for the synthesis of heteroaromatic boronates based on pyrazoles,[2] thiophenes,[3] pyrimidines[4] and oxaboracycles[5] (Figure 1). In an effort to access benzenoid derivatives, we speculated that the ynone salts could participate in the Hauser-Kraus annulation reaction[6,7] to generate the corresponding naphthol boronates. This approach could offer significant advantages over existing methods to this important class of compounds[8] by avoiding the need for stoichiometric chromium[9] or high loadings of air sensitive $Ni(COD)_2$.[10]

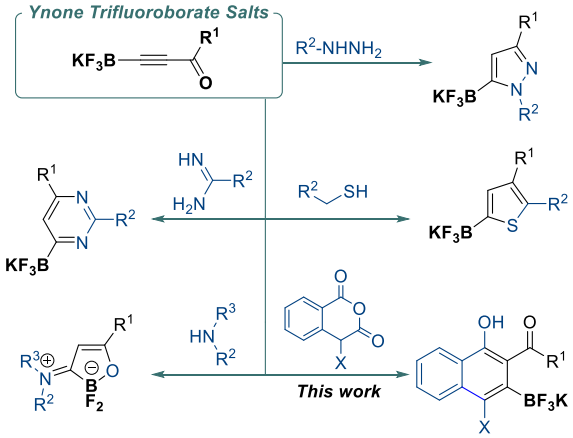
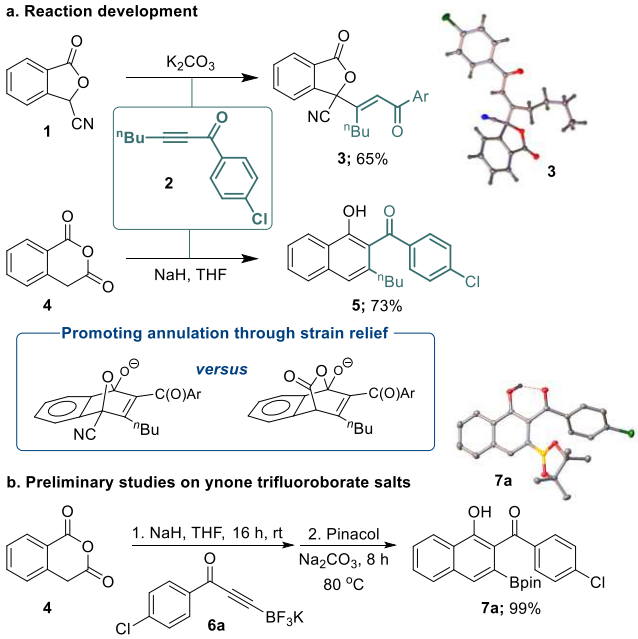


Figure 1. Use of ynone trifluoroborate salts in annulation reactions.

Scheme 1. Reaction development

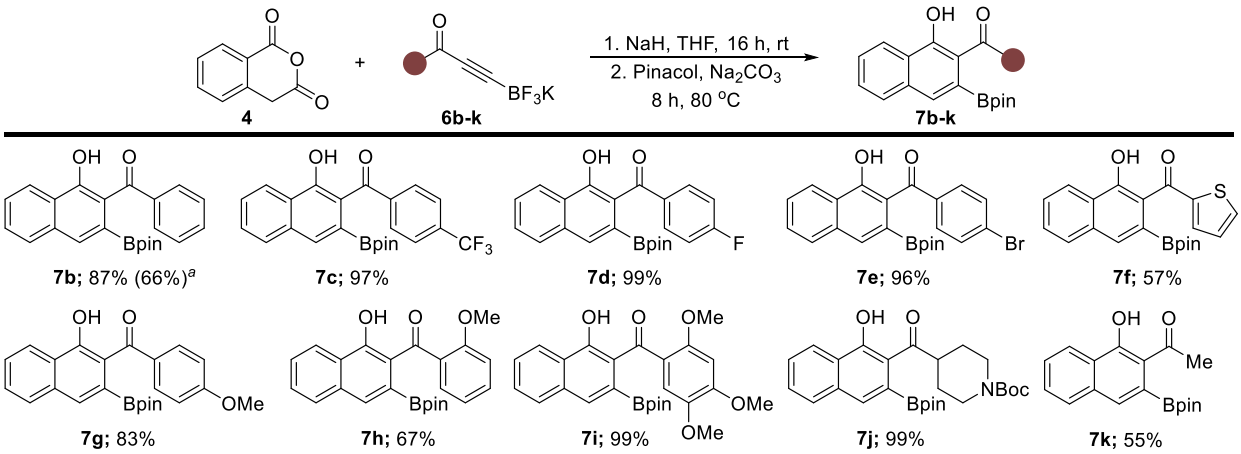


RESULTS AND DISCUSSION

A search of the literature uncovered only a single report of the Hauser-Kraus annulation of an ynone.[11,12] This method employed 3-cyanophthalide **1** and generated the corresponding annulated product in low yield. Indeed, our preliminary efforts to undertake the annulation of **1** with model ynone **2** resulted in the isolation of the lactone **3**. Evidently, in this case the conjugate addition step is

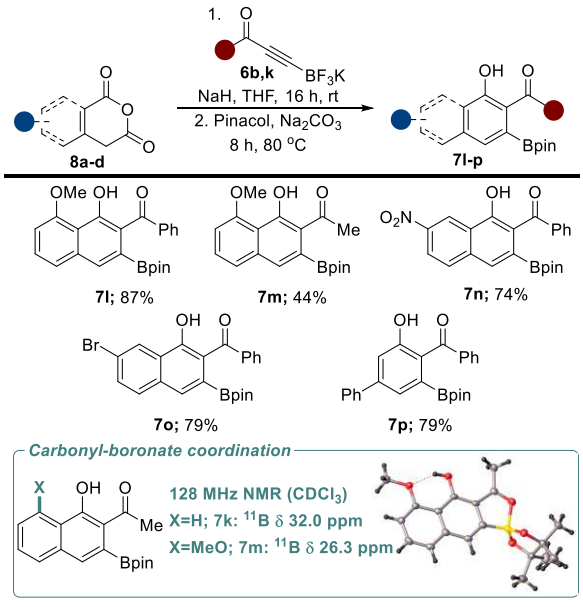
successful but the intermediate fails to cyclize. In contrast, the use of homophthalic anhydride **4** instead of **1** was found to undergo efficient cyclization.[13] We attribute this stark difference in reactivity to reduced strain in the generation of the bicyclic intermediate in the latter case (Scheme 1a). Having established efficient conditions for ynone annulation, we set out to generate the corresponding naphthol boronates. Pleasingly, the reaction of **4** and **6a** proceeded smoothly and the annulation product could be conveniently isolated as the pinacol boronic ester **7a** in excellent yield (Scheme 1b). We next explored the scope of the benzannulation reaction with respect to the ynone substrate. As shown in Table 1, the reaction was tolerant of a range of aromatic ketones, including electron rich and deficient benzene moieties. In addition, products bearing heteroaromatic and heterocyclic groups (**7f** and **7j**, respectively) could be generated in good to excellent yield. Finally, methyl-ketone **7k** was also accessible, albeit in a more modest yield. This latter observation may arise due to the known propensity for aliphatic ynones to undergo base catalyzed dimerization reactions.[14]

Table 1. Ynone trifluoroborate scope



Homophthalic anhydride **4** (4.0 equiv), NaH (4.0 equiv) and ynone (1.0 equiv) in THF (0.02 M) stirred at rt overnight, followed by addition of pinacol (5.0 equiv) and Na_2CO_3 (2.0 equiv), and the mixture heated at 80 °C for 8 h. [a]Gram scale reaction.

Table 2. Phthalic anhydride scope

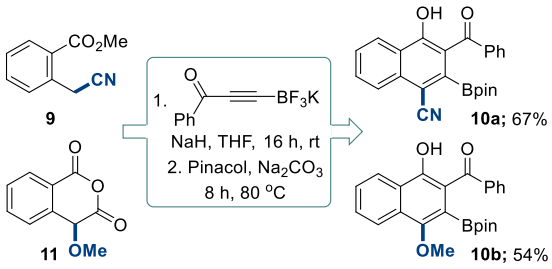


Homophthalic anhydride **8a-d** (4.0 equiv), NaH (4.0 equiv) and ynone (1.0 equiv) in THF (0.02 M) stirred at rt overnight, followed by addition of pinacol (5.0 equiv) and Na_2CO_3 (2.0 equiv), and the mixture heated at 80 °C for 8 h.

We next explored a series of anhydrides as shown in Table 2. Homophthalic anhydrides bearing electron donating and withdrawing groups, as well as halides, were well tolerated. Once again, the use of a methyl ketone substituted ynone led to lower yields (in the synthesis of **7m**) whereas the corresponding phenyl ketone performed more efficiently. In the case of **7m** we were surprised to note that the ^{11}B NMR spectrum showed a significant upfield shift of ~5 ppm. The X-ray crystal structure of **7m** suggests that this is due to a switch in H-bonding of the phenolic OH to the methoxy (instead of the ketone, see **7a** Scheme 1a) which then allows the carbonyl to undertake a Lewis acid-base interaction with the adjacent boronate.

We also took the opportunity to generate more heavily substituted products by employing functionalized enolate partners (Scheme 2). In this regard, the use of Wang's 2-(cyanomethyl)benzoates **9** successfully generated the corresponding naphthol **10a** in high yield. In addition, we were particularly interested in exploring the potential of 4-methoxyhomophthalic anhydride **11** in the annulation process as this would deliver directly comparable boronate esters to those generated using the existing Cr- and Ni-mediated methods discussed in the introduction.[9,10] We devised a modified and scalable approach to **11**[15] and were delighted to find that this delivered the corresponding hydroquinone **10b** in good overall yield.

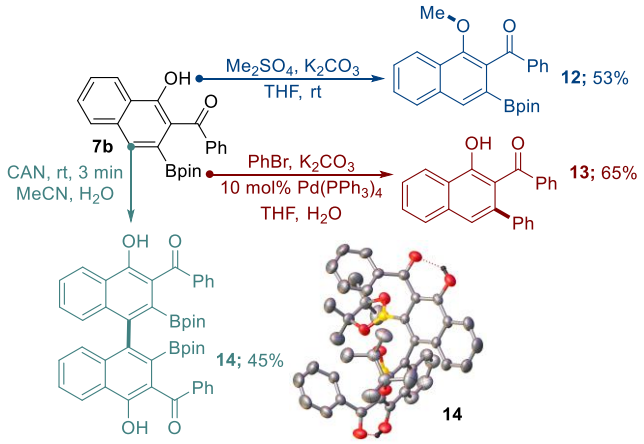
Scheme 2. Synthesis of densely substituted naphthols



Finally, we explored the potential of these compounds to undergo chemoselective functionalization reactions. Pleasingly, as shown in Scheme 3, alkylation of the phenolic hydroxyl group as well as cross-coupling at the boronate ester all proceeded with acceptable

yield. Interestingly, while we expected that **7b** would be transformed into the corresponding napthoquinone by CAN oxidation, we instead observed almost instantaneous oxidative dimerization to provide **14**.

Scheme 3. Chemoselective functionalization reactions



In conclusion we report a simple and convenient method for the synthesis of a range of aromatic boronic esters via a base mediated annulation of ynone trifluoroborate salts. This method allows access to *ortho*-acylphenol derivatives with excellent levels of regiocontrol, and rivals previously established metal mediated approaches.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information..

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization of the compounds obtained (PDF).

Accession Codes

CCDC 2472924 (**3**), 2472922 (**7a**), 2472923 (**7m**) and 2472925 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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