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Dual Catalysis Using Boronic Acid and Chiral Amine: Acyclic Quaternary Carbons via Enantioselective Alkylation of Branched Aldehydes with Allylic Alcohols

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Supporting Information

ABSTRACT: A ferrocenium boronic acid salt activates allylic alcohols to generate transient carbocations that react with in situ-generated chiral enamines from branched aldehydes. The optimized conditions afford the desired acyclic products embedding a methyl-aryl quaternary carbon center with up to 90% yield and 97:3 enantiomeric ratio, with only water as the byproduct. This noble-metal-free method complements alternative methods that are incompatible with carbon−halogen bonds and other sensitive functional groups.

The advent of new strategies for the catalytic activation of organic molecules creates new opportunities to design unconventional bond forming processes. In dual catalysis, two mutually compatible catalysts are combined to independently activate two different substrates and expand the scope of reactions with substrates that are unreactive under standard conditions.[1] From this perspective, the concept of boronic acid catalysis (BAC), which exploits the ability of boronic acids to form reversible covalent bonds with hydroxyl functionalities, was examined by our group and others in the catalytic direct activation of carboxylic acids and alcohols.[2] For instance, we recently reported direct boronic acid-catalyzed Friedel−Crafts alkylations of neutral arenes with readily available allylic and benzylic alcohols as a way to circumvent the use of toxic organohalide electrophiles.[3] With a view to extend this strategy toward other classes of nucleophiles such as carbonyl enolates, we envisaged the possibility of merging BAC with chiral amine catalysis to achieve alkylation of enamines with carbocations via dual activation of aldehydes and alcohols, respectively.[4,5] A priori, the combined use of Lewis acidic and Brønsted basic catalysts poses challenging issues of chemoselectivity, including the threat of catalysts' inter-annihilation. Moreover, the use of alcohols as precursors of reactive carbocations can lead to side reactions like homoetherification or alkylation of the amine catalyst. Cozzi and co-workers overcame these challenges by employing $InBr_3$ and imidazolidinone catalysts to alkylate linear aldehydes with secondary allylic alcohols in high enantioselectivities.[4b] Similar approaches to asymmetric allylation of branched aldehydes with allylic alcohols engaging transition metals[6] as co-catalysts were reported. In 2011, List and co-workers prepared acyclic quaternary carbon centers with a clever combination of palladium, Brønsted acid, and amine catalysis (Figure 1a).[6b] Similarly, Carreira and co-workers

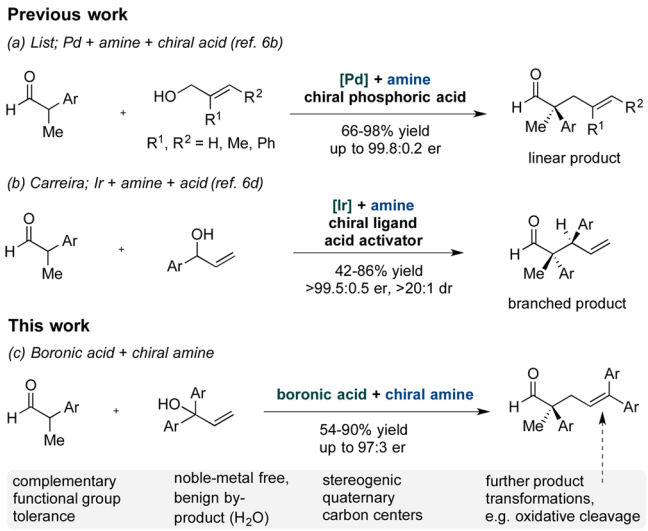

Figure 1. Methods for dual catalytic asymmetric allylation of branched aldehydes with allylic alcohols.

employed dual iridium and amine catalysis as a complementary strategy to obtain the branched products of allylic alkylation in high enantio- and diastereoselectivity (Figure 1b).[6d]

As highlighted through these key contributions, the preparation of acyclic quaternary all-carbon centers remains an important objective in organic synthesis.[7] For instance, methyl-aryl quaternary carbons are present in a number of bioactive natural products and drug candidates (Figure 2).[8] Although several methods exist based on the use of chiral auxiliaries,[9] there are relatively few strategies available through asymmetric catalysis. Furthermore, preparative methods based on palladium catalysis are not orthogonal with functionalities like aryl halides and are often incompatible with nitro or other basic functional groups. Herein, we describe a conceptually novel, noble-metal-free methodology based on dual BAC and amine catalysis that is compatible with these functional groups and provides methylated quaternary carbon centers in high enantioselectivity (Figure 1c).

The initial optimization was performed on the racemic reaction and focused on selecting the best boronic acid co-catalyst and allylic alcohol partner with aldehyde **1a** and

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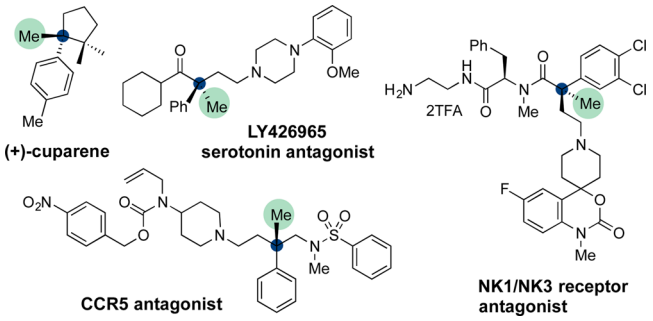
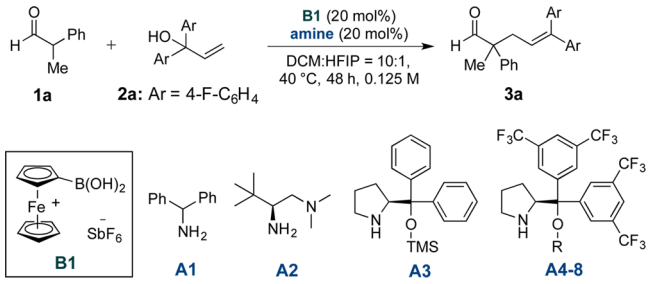


Figure 2. Examples of biologically active compounds containing stereogenic methylated quaternary carbon centers.

benzhydrylamine **A1**[6d] (see Supporting Information (SI)). This effort identified the most promising conditions with ferrocenium boronic acid **B1** and alcohol **2a** in a dichloromethane/hexafluoroisopropanol mixture (v:v = 10:1) at 40 °C for 48 h, affording product **3a** in 88% yield (Table 1, entry 1). The use of

Table 1. Chiral Amine Optimization in the Dual Catalytic Asymmetric Allylation[a]



entry	amine	R	yield (%)[b]	er[c]
1	**A1**	-	88	50:50
2	**A2**	-	86	76.5:23.5
3	**A3**	-	n.r.	n.d.
4	**A4**	-$SiMe_3$	20	87.5:12.5
5	**A5**	-$SiEt_3$	34	83.5:16.5
6	**A6**	-$Si(i\text{-}Pr)_3$	51	85.5:14.5
7	**A7**	-$SiPh_3$	31	85.5:14.5
8	**A8**	-$Si(t\text{-}Bu)Me_2$	47	90:10

[a]Reactions conditions: 0.25 mmol of aldehyde and 0.50 mmol of alcohol in a solvent mixture of dichloromethane (2.0 mL) and hexafluoroisopropanol (0.2 mL) under nitrogen at 40 °C for 48 h. [b]Yields were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as internal standard. [c]Determined by chiral HPLC analysis of the corresponding alcohol product of aldehyde reduction (see SI).

HFIP was critical to increase the solubility of ferrocenium boronic acid **B1** as well as stabilizing the putative carbocation intermediate.[10] Allylic alcohol **2a** with para fluoride substituents, was employed to best suppress the boronic acid-catalyzed 1,3-rearrangement of allylic alcohols, a process competing with the desired allylation.[11] Even though a limited number of allylic alcohols were suitable (see SI), it is often inconsequential because one of the most compelling synthetic transformation of the diaryl alkene moiety of products like **3a** is its oxidative cleavage.

The enantioselectivity of the allylation was examined by screening over 30 different chiral amines, based on conditions of the optimized racemic reaction (see SI). Chiral primary amines were investigated first because they are less sterically hindered for branched aldehydes.[12] Unfortunately, these amines generally provided poor performance, as exemplified with **A2**[13] affording an enantiomeric ratio (er) of 76.5:23.5 (Table 1, entry 2). The more common chiral secondary amines were evaluated even though α-functionalization of branched aldehydes catalyzed by secondary amines is generally more challenging and less successful.[14] When diphenylprolinol trimethylsilyl ether **A3**[15] was employed, the reaction provided no product (Table 1, entry 3). We hypothesized that this failure may be due to the nucleophilic secondary amine center, which could deactivate the ferrocenium boronic acid **B1**. To our satisfaction, upon using the less nucleophilic diarylprolinol silyl ether **A4**, the desired product was observed in high enantioselectivity (87.5:12.5 er) albeit with low yield (20%). Encouraged by this result, we eventually identified **A8** as the best amine catalyst providing 47% yield and 90:10 er (Table 1, entry 8). With this optimal chiral amine in hand, we turned our attention to the optimization of other reaction parameters. A brief solvent screening identified toluene/HFIP (v:v = 10:1), at a concentration of 0.25 M, as the solvent system providing the highest enantioselectivity, albeit in 32% yield (see SI). Additives (water, acetic acid[16]) provided no improvement. According to Bräse and co-workers, the use of microwave irradiation can accelerate enamine formation for branched aldehydes.[17] By applying the same strategy with a catalyst loading of 30 mol%, the yield of **3a** nearly doubled. Catalyst ratios other than 1:1 **B1**:**A8** led to no improvement (see SI). At this stage, a re-optimization of the allylic alcohol showed that **2b** can serve as a cheaper and more effective allylation agent providing a higher yield of 60% while maintaining the enantioselectivity. The remainder of the mass balance consists mostly of unreacted aldehyde and transposed alcohol.

The scope of aldehyde substrate was assessed under the optimal conditions (Scheme 1). Branched aldehydes with an aryl group bearing electron-donating substituents (-OMe, -Me) provided products **4b** and **4c** in slightly lower yield and enantioselectivity compared to **4a**. While existing methods[6b] also reported high yield and high enantioselectivity for select aldehydes containing simple aryl substituents (-OMe, -Me, -F), we were delighted to observe a wider functional group tolerance with our reaction system, especially for electron-withdrawing aryl substituents. Branched aldehydes with bromo/chloro aryl substituents, which are particularly useful for further derivatization by cross-coupling chemistry, were well tolerated and gave high yield and high enantioselectivity in the preparation of products **4d**–**f**.[18] Highly enantioselective catalytic α-functionalization of aldehydes **1g**–**j** has been shown to be challenging with other methods.[6f,14d,19] In contrast, with our system, polar basic functional groups such as -CO_2Me, -NO_2, and -CF_3 fared well, affording products **4g**–**j**.[20] An aldehyde with a naphthyl group afforded product **4k** in good yield and enantioselectivity. The auspicious applicability of this method toward heterocyclic substrates is highlighted with indolyl product **4l**, which despite a lower yield, was obtained in high er. Unfortunately, the α-ethyl aldehyde **1m** was not readily applicable. The absolute configuration of the allylation products **4a**–**m** was assigned as (*S*) based on the derivatization of **4a** into a known compound (see SI).[21]

To demonstrate the practicality of this method, a gram-scale reaction with aldehyde **1f** was performed (Scheme 2). Even though a lower yield was observed compared to the exploratory

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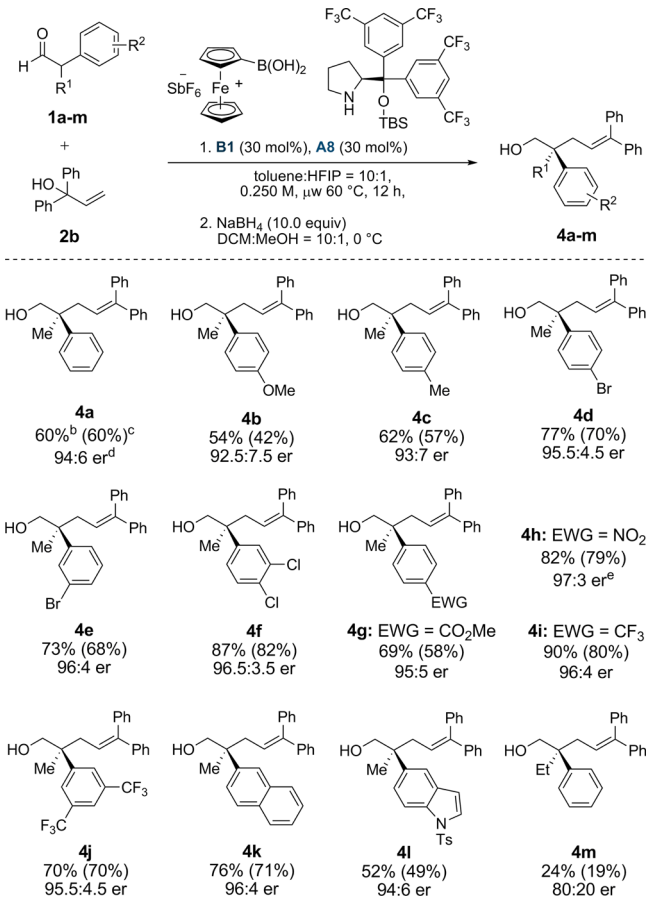
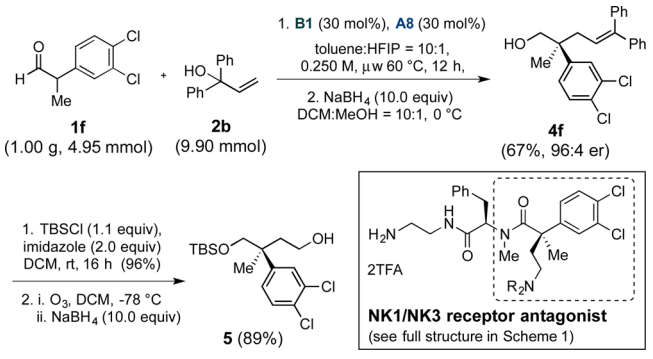
Scheme 1. Substrate Scope of Dual Catalytic Asymmetric Allylation[a]



[a]Reactions conditions: 0.25 mmol of aldehyde and 0.50 mmol of alcohol in 1.1 mL of solvent in a microwave reactor under nitrogen at 60 °C for 12 h. [b]Yield of first step were determined by ^{1}H NMR analysis of the reaction mixture with 1,4-dinitrobenzene as internal standard. [c]Isolated yield of the alcohol product of aldehyde reduction over two steps. [d]Determined by chiral HPLC analysis of the alcohol products **4** (see SI). [e]Enantiomeric ratio of **4h** was obtained by Mosher's acid analysis of the reduced alcohol product.

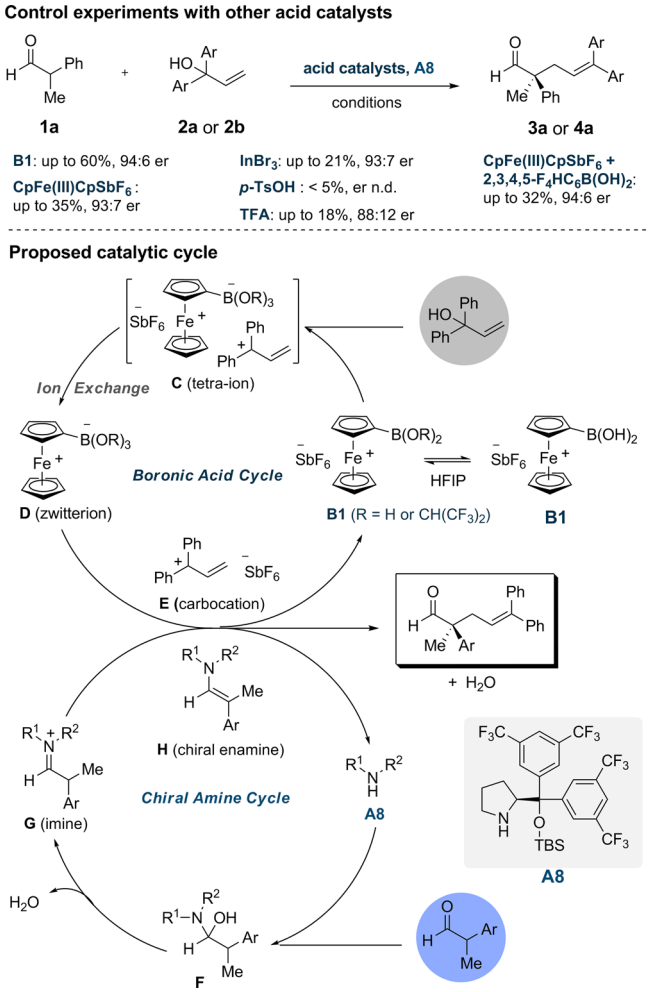
Scheme 2. Application of Dual Catalytic Allylation



scale of Scheme 1, the enantioselectivity was maintained. Oxidative cleavage of the double bond of product **4f** afforded compound **5** as a key building block, possessing correctly differentiated side chains for the quaternary carbon fragment of Servier's NK1/NK3 receptor antagonist,[8d] which could not be prepared previously in catalytic asymmetric fashion.

Mechanistic control experiments were conducted. Ferrocenium boronic acid **B1** was shown to be a superior acid catalyst compared to TFA,[4a] $InBr_3$,[4b] and *p*-TsOH[5b] for the asymmetric allylation (Scheme 3, top). Though it provides a significantly

Scheme 3. Mechanistic Controls and Proposed Catalytic Cycle of Dual Catalytic Asymmetric Allylation



lower yield, the ferrocenium catalyst devoid of a boronyl group, $CpFe(III)CpSbF_6$, is also active (Scheme 3, top). This result indicates that cooperative activation involving both Lewis acidic sites of **B1** cannot be ruled out. In the presence of HFIP, with none or trace water, a complex dynamic equilibrium is likely to establish consisting of the free boronic acid, the bis-(hexafluoroisopropoxide), the hydroxy (hexafluoroisopropoxide) hemiester, and the corresponding anionic species (Scheme 3). Formation of boronic anhydrides was not detected by mass spectrometry. The possible existence of inter-catalyst interactions was examined by NMR spectroscopy in the reaction solvent (10:1 d_8-toluene/HFIP). In the presence of the amine catalyst, a new ^{11}B NMR resonance appears at ~5 ppm, possibly indicative of reversible catalyst interactions in the form of tetrahedral amine-borate, or, more likely a base-promoted formation of the tri(hexafluoroisopropoxy)borate complex observed by MS (see SI). According to ^{11}B NMR analysis, catalyst **B1** appears largely transformed at the end of the reaction. Although a slow destructive interaction between the Fe(III) ion and nucleophilic reagents cannot be ruled out,[22]

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reversible interaction of the catalyst with the water byproduct or unreacted substrates is also possible and would require further studies. Altogether, based on these preliminary experiments and previous work[3b] with catalyst **B1**, an S_N1 mechanism is proposed with the dual-catalyzed cycles depicted in Scheme 3. Face-selective attack of the in situ-formed chiral enamine (**H**) to the reactive carbocation (**E**) results in the allylation product. Substitution of boronic acid **B1** for a mixture of 2,3,4,5-$F_4HC_6B(OH)_2$ and $Cp_2Fe(III)SbF_6$ provided a lower yield (32%), which lends further support to an ion redistribution mechanism that is possible only with ionic boronic acid **B1**.[3b]

In summary, we have disclosed the first application of BAC in asymmetric dual catalysis. This noble-metal-free method for allylation of branched aldehydes provides moderate to high yields with high enantioselectivity, and it displays broad functional group tolerance. The reliability of this asymmetric allylation was demonstrated on a gram scale for the preparation of a quaternary carbon fragment of Servier's NK1/NK3 receptor antagonist. A dual catalyzed S_N1 mechanism was proposed. We envision that more dual catalyzed transformations of synthetic interest can be developed based on the BAC concept.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06101.

Experimental details; analytical and spectral reproductions for the prepared compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(19) For a comparison of substrate **1h** under Pd/amine/chiral phosphoric acid catalysis similar to ref 6b, a lower enantioselectivity 67% ee was observed; see ref 6f.

(20) The racemic background enol allylation did not undermine the enantioselectivity as proposed by Bräse and co-workers.[17]

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