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Enantioselective α-Alkenylation of Aldehydes with Boronic Acids via the Synergistic Combination of Copper(II) and Amine Catalysis

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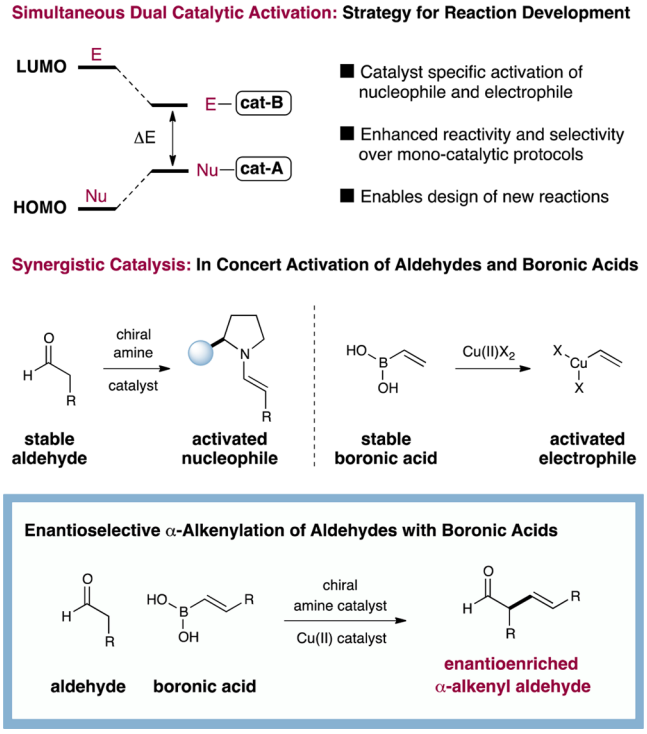
Supporting Information

ABSTRACT: The enantioselective α-alkenylation of aldehydes has been accomplished using boronic acids via the synergistic combination of copper and chiral amine catalysis. The merger of two highly utilized and robust catalytic systems has allowed for the development of a mild and operationally trivial protocol for the direct formation of α-formyl olefins employing common building blocks for organic synthesis.

Synergistic catalysis has emerged in recent years as a powerful concept for the design of new chemical reactions in organic chemistry.[1] The use of two discrete catalysts that simultaneously activate orthogonal reaction partners (e.g., electrophile and nucleophile) enables a significant opportunity to dramatically lower the HOMO−LUMO gap for any desired bimolecular transformation. Indeed, the resulting levels of rate accelerations and mechanistic discrimination allow for the discovery of new chemical reactions between otherwise benign substrates. Our lab has recently applied the synergistic catalysis paradigm to the development of several new asymmetric bond formations that were previously elusive, namely, the enantioselective α-trifluoromethylation,[2] α-arylation,[3] α-alkenylation,[4] and α-oxidation[5] of aldehydes. As part of these ongoing efforts in dual catalysis, we recently sought to merge the broad utility of chiral enamine catalysis with the capacity of transition metals, specifically Cu^{II}, to undergo transmetalation with vinyl boronic acids to form highly electrophilic Cu^{III}−olefin intermediates (after a subsequent oxidation step). By targeting the merger of catalytic systems that presently enjoy widespread use, yet employ practical and economical substrates and catalysts, we presumed that these technologies would allow new operationally convenient bond-forming processes to be developed that could not be accessed using monocatalysis mechanisms. Specifically, the enantioselective α-alkenylation of carbonyls has been a long-standing problem in chemical synthesis that has only recently begun to come to fruition.[6−8] Herein, we describe a mild, room temperature protocol for the enantioselective α-alkenylation of aldehydes with boronic acids[9] using readily available, bench-stable catalysts and reagents through the successful application of synergistic copper(II)-organocatalysis.

DESIGN PLAN

From the outset, we questioned whether a transient and highly electrophilic d^8-organocopper(III) species, which have shown a remarkable propensity for reactions with π-nucleophiles,[3,4,10] could undergo productive and enantioselective coupling with nucleophilic enamines generated through chiral amine catalysis. As outlined in Scheme 1, we proposed that an oxidase-style mechanism (as first delineated by Stahl[11] for the Chan−Evans−Lam reaction)[12] could be employed to generate a transient electrophilic organocopper(III) species **4** from a simple boronic acid substrate. More precisely, the transmetalation of copper(II) catalyst **1** with a boronic acid would furnish organocopper(II) **3**, which after oxidation by copper(II) would deliver the desired alkenylcopper(III) **4**. Thereafter, the HOMO-activated enamine **6**, generated through a concomitant organocatalytic cycle, would intercept organocopper(III) **4** to access the critical dual catalysis intermediate (enamine−organocopper(III) complex **7**),[13] which after reductive elimination would furnish α-alkenyl iminium **8** and the corresponding copper(I) salt **9**. Regeneration of each catalyst would be accomplished through hydrolysis of iminium **8** and single-electron oxidation of the copper(I) salt **9** under an oxygen atmosphere, while delivering the enantioenriched α-alkenyl aldehyde product. With respect to enantiocontrol, computational studies predict that the *Si*-face of this enamine



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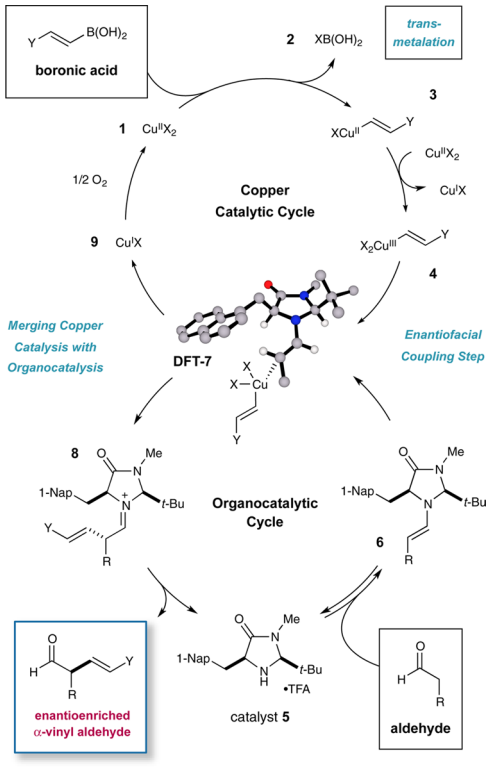
Scheme 1. Proposed Mechanism for Aldehyde α-Alkenylation



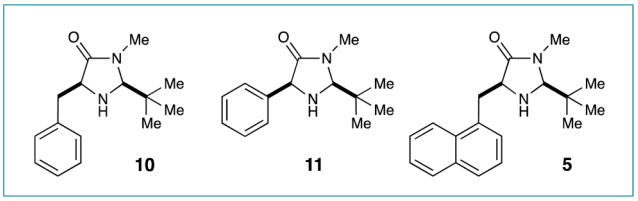
will be shielded by the naphthyl ring of the imidazolidinone framework, leaving the *Re*-face accessible to electrophilic attack (see DFT-7). Importantly, we recognized that if such a synergistic mechanism could be realized, then boronic acids, one of the most prevalent building blocks in organic chemistry, would become a viable and practical substrate for the enantioselective α-functionalization of simple aldehydes.

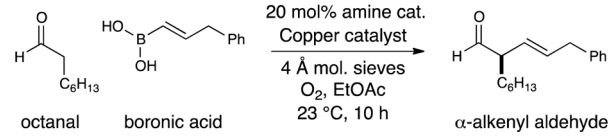
RESULTS

As shown in Table 1, we were delighted to find that the proposed coupling of aldehydes and boronic acids under the simultaneous action of copper and aminocatalysis is indeed feasible. Furthermore, a survey of copper salts (entries 3−8) revealed that copper(II) acetate was the optimal metal catalyst in terms of reactivity and enantioselection when employed in concert with commercially available amine catalyst **10** (entry 8, 58% yield, 86% ee). Further improvements in reaction efficiency were realized via the use of higher copper loadings (30 mol %) in combination with the addition of methylboronic acid as a reaction supplement to deliver the desired α-vinyl adduct in 73% yield (entry 10, 86% ee). The success of methylboronic acid as a suitable additive for this protocol presumably arises from the *in situ* formation of mixed boronic anhydrides,[14−18] a species from which boron to copper transmetalation is accelerated.[18] Finally, an evaluation of **5**·TFA, **10**·TFA, and **11**·TFA (entries 10−12) revealed that organocatalysts **5**·TFA and **11**·TFA provide superior levels of enantiocontrol (entries 11 and 12, 93% ee); however, the superior efficiencies demonstrated by amine **5**·TFA in combination with $Cu(OAc)_2$ defined this system as the optimal synergistic protocol for aldehyde vinylation.

As outlined in Table 2, we have found that a broad range of formyl components are suitable for this enantioselective coupling with boronic acids. Of particular importance is the facility with which propionaldehyde can be employed (entry 1, 72% yield,

Table 1. Evaluation of Dual Copper and Amine Catalysts





octanal boronic acid α-alkenyl aldehyde

entry	amine cat.	Copper catalyst (mol%)	yield (%)[a]	ee (%)[b]
1	none	$Cu(OAc)_2$ (20 mol%)	0	--
2	**10** · TFA	none	0	--
3	**10** · TFA	$Cu(OTf)_2$ (20 mol%)	26	84
4	**10** · TFA	$Cu(OMe)_2$ (20 mol%)	45	82
5	**10** · TFA	$Cu(OTFA)_2$ (20 mol%)	47	78
6	**10** · TFA	$Cu(Oi\text{-}Bu)_2$ (20 mol%)	50	82
7	**10** · TFA	CuOAc (20 mol%)	42	84
8	**10** · TFA	$Cu(OAc)_2$ (20 mol%)	58	86
9[c]	**10** · TFA	$Cu(OAc)_2$ (20 mol%)	69	86
10[c]	**10** · TFA	$Cu(OAc)_2$ (30 mol%)	73	86
11[c]	**11** · TFA	$Cu(OAc)_2$ (30 mol%)	69	93
12[c]	**5** · TFA	$Cu(OAc)_2$ (30 mol%)	77	93

[a]Yields determined via ^{1}H NMR analysis vs Bn_2O standard. [b]Determined by chiral HPLC analysis of the corresponding alcohol. [c]Performed with 2.0 equiv $MeB(OH)_2$.

93% ee), a substrate which enables modular access to diverse propionate motifs of utility in macrolide total syntheses. Additionally, arene functionality on the aldehydic component is well tolerated (entry 2, 74% yield, 90% ee). Sterically demanding β-branched products were also generated in high yield and excellent enantioselection (entries 3 and 4, 67−73% yield, 85−90% ee).[19] Remarkably, given the context of a multicatalytic system, diverse heteroatom-containing functionalities, including protected amines, alcohols, and esters, do not interfere with the reactivity of either the metal or organocatalyst (entries 4−7, 67−76% yield, 85−94% ee). Moreover, a variety of aldehydes containing pendent alkyne and alkene functional handles are excellent substrates for this coupling protocol (entries 8−10, 72−84% yield, 91−94% ee).

As shown in Table 3, a broad spectrum of alkenylboronic acids can be successfully employed as substrates in this enantioselective aldehyde α-alkenylation transformation. For example, alkyl substituted alkenylboronic acids were found to be excellent substrates (entries 1−4, 76−80% yield, 93−96% ee), tolerating 1°, 2°, and 3° substitution at the allylic position of the alkenylboronic acid. Notably, the 3-phenylpropenylboronic acid adduct (entry 4) did not undergo olefin isomerization to the corresponding enal or styrene regioisomers in the presence of the copper transition-metal catalyst. The boronic acid component can also tolerate halide and heteroatom functionalities (entries 5 and 6), a chemoselectivity feature that will be important in the use of these synthons in complex molecule construction. Moreover, a wide range of electronically diverse styrenylboronic acids was found to be compatible with these

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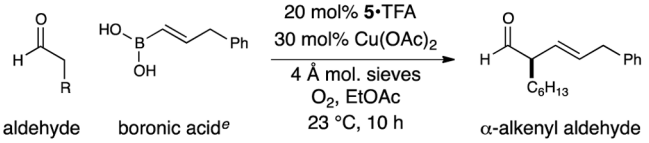
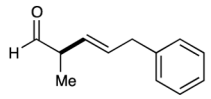
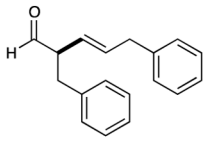
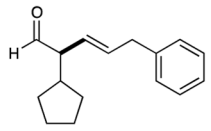
Table 2. Scope of Enantioselective α-Alkenylation of Aldehydes[a,b,c]

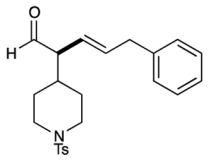


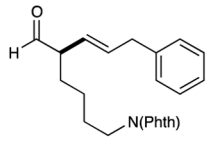
aldehyde | boronic acid[e] | α-alkenyl aldehyde

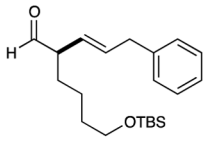
1  72% yield, 93% ee

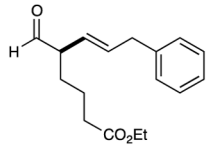
2  74% yield, 90% ee

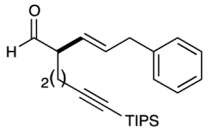
3[d]  73% yield, 90% ee

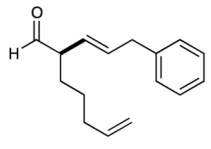
4[d]  67% yield, 85% ee

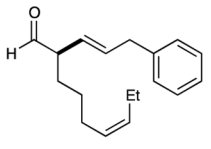
5  69% yield, 94% ee

6  75% yield, 93% ee

7  76% yield, 94% ee

8[d]  72% yield, 94% ee

9  84% yield, 92% ee

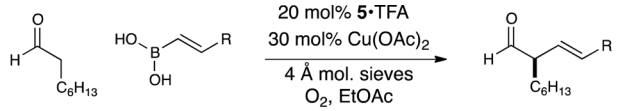
10  82% yield, 91% ee

[a]Absolute configuration assigned by chemical correlation or analogy. [b]Isolated yield of the corresponding alcohol. [c]Enantiomeric excess determined by chiral HPLC analysis of the corresponding alcohol. [d]25 mol % 5·TFA. [e]Performed with 2.0 equiv $MeB(OH)_2$.

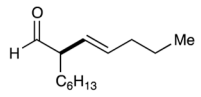
synergistic catalysis conditions. For example, electron-poor styrene substrates proved to be excellent coupling partners, achieving and maintaining high levels of enantiopurity, despite the increased potential for these adducts to undergo *in situ* racemization (entries 7–9, 67–77% yield, 91–93% ee). Furthermore, electron-neutral and -rich styrenes[20] were also found to furnish the α-vinyl formyl adducts with excellent levels of efficiency and enantiocontrol (entries 10–12, 70–73% yield, 92–94% ee). To demonstrate operational utility, we have executed our α-alkenylation reaction on a 10 mmol scale to prepare 1.7 g of (*E*)-2*R*-(2-phenyleth-1-en-1-yl)octan-1-ol in 72% yield and in 92% ee (cf. Table 3, entry 10, 73% yield, 93% ee).

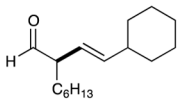
To highlight the value of this new enantioselective vinylation reaction, we have demonstrated that this protocol can be used to accelerate the production of a diverse series of enantioenriched iodolactones,[21] potentially valuable intermediates en route to

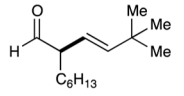
Table 3. Scope of the Alkenyl Boronic Acid Component[a,b,c]

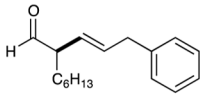


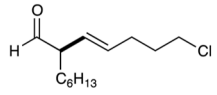
octanal | boronic acid[f] | α-alkenyl aldehyde

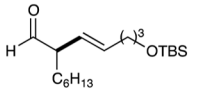
1  76% yield, 96% ee

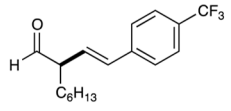
2  76% yield, 95% ee

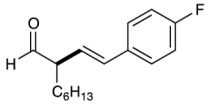
3  80% yield, 95% ee

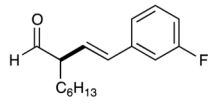
4  77% yield, 93% ee

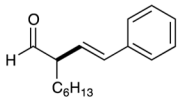
5  76% yield, 96% ee

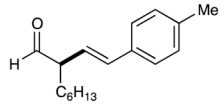
6  81% yield, 96% ee

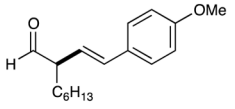
7[d]  67% yield, 91% ee

8[e]  77% yield, 93% ee

9[e]  71% yield, 91% ee

10[e]  73% yield, 93% ee

11[e]  71% yield, 94% ee

12[e]  70% yield, 92% ee

[a]Absolute configuration assigned by chemical correlation or analogy. [b]Isolated yield of the corresponding alcohol. [c]Enantiomeric excess determined by chiral HPLC analysis of the corresponding alcohol. [d]30 mol % 5·TFA. [e]25 mol % 5·TFA. [f]Performed with 2.0 equiv $MeB(OH)_2$.

natural products containing γ-butyrolactone motifs (Scheme 2).[21,22] These stereochemically rich heterocycles were prepared from their corresponding α-alkenyl aldehydes via a short two-step sequence involving aldehyde oxidation followed by iodolactonization[23] without loss in enantiopurity. The rapid development of molecular complexity obtained via this straightforward procedure is further underscored by the value and convenience of employing bench-stable and readily available catalysts and starting materials. An epoxy-lactonization variant of the sequence is currently being employed for the total synthesis of blastmycinone.

In conclusion, we have demonstrated the capacity of amine and copper catalysis to be combined in a synergistic fashion to allow the enantioselective construction of α-vinyl aldehydes. The scope of this new dual catalysis transformation has been found to be extensive in both the aldehyde and vinyl boronic acid coupling partners. We previously described asymmetric, organocatalytic α-alkenylation protocols that employ either vinyl potassium trifluoroborate salts[6a] or vinyl iodonium salts[4] as coupling partners. Importantly, the dual catalysis strategy described herein

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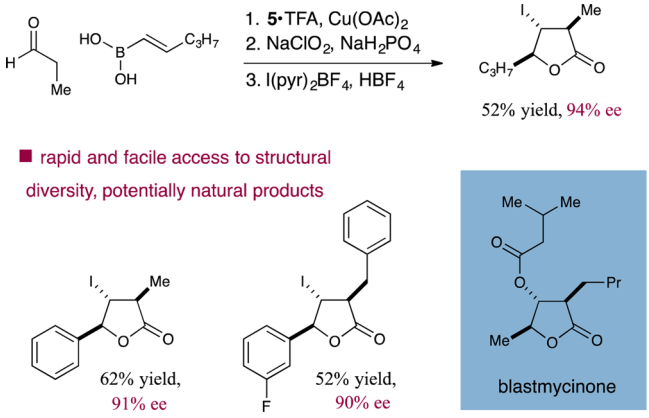
Scheme 2. Synergistic Catalysis Enabled Synthesis of Complex Structures from Commercially Available Building Blocks



offers a major practical advantage over existing methods, as it has enabled boronic acids, one of the most pervasive building blocks in organic chemistry, to become a viable and practical substrate for electrophilic additions in the context of enamine catalysis. Application of this new methodology to the synthesis of stereochemically complex β-iodo-γ-butyrolactones has been accomplished in a concise three-step sequence.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data.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 interest.

■ ACKNOWLEDGMENTS

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