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Homogeneous Catalysis

Copper(I)-Catalyzed Asymmetric Conjugate 1,6-, 1,8-, and 1,10-Borylation

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Dedicated to the 100th Anniversary of Chemistry at Nankai University

Abstract: *Catalytic asymmetric remote conjugate borylation is challenging as the control of regioselectivity is not trivial, the electrophilicity of remote sites is extenuated, and the remote asymmetric induction away from the carbonyl group is difficult. Herein, catalytic asymmetric conjugate 1,6-, 1,8- and 1,10-borylation was developed with excellent regioselectivity, which delivered α-chiral boronates in moderate to high yields with high enantioselectivity. The produced chiral boronate smoothly underwent oxidation, cross-coupling, and one-carbon homologation to give synthetically versatile chiral compounds in moderate yields with excellent stereoretention. Furthermore, a stereomechanistic analysis was conducted using DFT calculations, which provides insights into the origins of the regioselectivity. Finally, the present 1,6-borylation was successfully applied in an efficient one-pot asymmetric synthesis of (−)-7,8-dihydrokavain.*

Introduction

Organoboron compounds are versatile synthetic intermediates, which can undergo a variety of transformations to construct C–C, C–O and C–N bonds.[1] Among them, α-chiral boronates are employed in various stereospecific reactions to rapidly assemble chiral molecules.[2] Therefore, there is an increasing need for the easy and reliable methods to prepare such organoboron compounds. One of the most common and intensively investigated methods is the catalytic asymmetric conjugate 1,4-borylation, which leads to the generation of α-chiral boronates in high yields together with high enantioselectivity.[3–6] Chiral catalysts based on transition metals, especially on copper,[3,4] have significantly contributed to the fast development in this fascinating field.

However, compared to catalytic asymmetric 1,4-borylation, 1,6-borylation was much less studied largely due to the issue of regioselectivity.[7] In 2013, the Kobayashi group disclosed the first example of catalytic asymmetric 1,6-borylation, in which the complex of $Cu(OH)_2$ and a chiral bipyridine ligand was employed as the catalyst in water (Scheme 1 a).[8a,b] Later, the Lam group discovered a powerful copper(I)-catalyzed high regio- and enantioselective 1,6-addition of $B_2(Pin)_2$ to α,β,γ,δ-unsaturated esters and ketones with alkyl substituents at δ-positions (Scheme 1 b).[9a] However, a substrate bearing a phenyl group at the δ-position generated a complex mixture of unidentified products, which led to an imperfect substrate scope. The similar reaction tendency was also observed in the copper(I)-catalyzed enantioselective 1,6-borylation of α,β,γ,δ-unsaturated phosphonates.[9b] In 2018, the Lam group found that both *Z*-allylic and *E*-allylic boronates can be obtained as the major product with high enantioselectivity, simply by tuning the reaction solvent and the concentration in the copper(I)-catalyzed 1,6-borylation of α,β,γ,δ-unsaturated ketones.[9c]

In 2015, Liao and co-workers reported a copper-catalyzed enantioselective 1,6-conjugate borylation of *para*-quinone with a sulfoxide-phosphine ligand (Scheme 1 c), which provided an attractive method for the construction of chiral *gem*-diarylmethine boronates.[10a] Almost at the same time, the Tortosa group also realized a copper-catalyzed 1,6-conjugate borylation of *para*-quinone with DM-SEGPHOS (Scheme 1 c).[10b] In both cases, the produced chiral *gem*-diarylmethine boronates were successfully employed either in Suzuki–Miyaura coupling or in the coupling with furans to furnish chiral triarylmethanes with excellent stereoretention.

1,8-Borylation has been rarely accomplished and 1,8-borylated product was only found as a side product with low enantioselectivity in Kobayashi's pioneering 1,6-borylation (Scheme 1 a).[8b] In fact, as far as 1,8-conjugate addition is concerned, only several examples of non-enantioselective metal-catalyzed reaction have been reported.[11] In 2012, Ooi and co-workers uncovered a highly regio-, diastereo- and enantioselective 1,8-addition of azalactones to trienyl *N*-acylpyrroles.[12] In 2014, Minnaard and Feringa reported two enantioselective examples of conjugate 1,8-addition with a copper catalyst and Grignard reagents.[13] However, low to moderate regio- and enantioselectivities were observed. To the best of our knowledge, these were the only two reports of catalytic asymmetric 1,8-conjugate addition. Moreover, there is no report of 1,10-borylation in literature. Only sporadic non-enantioselective metal-catalyzed 1,10-conjugate addition[14] and one catalytic asymmetric version have been described.[13] Minnaard and Feringa disclosed two examples of copper-catalyzed enantioselective conjugate 1,10-addition

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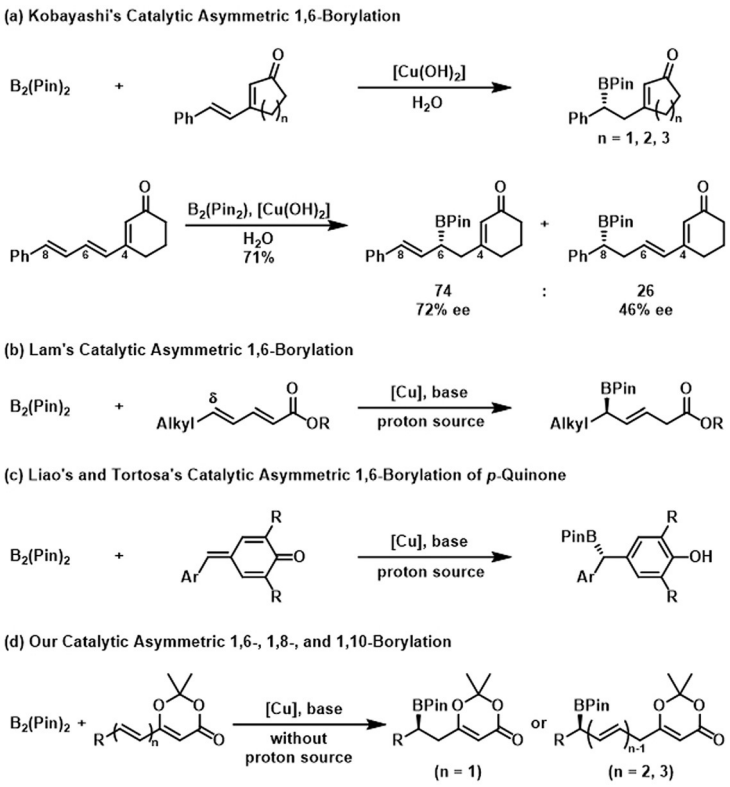


Scheme 1. Prior arts in catalytic asymmetric 1,6-borylation and our catalytic asymmetric 1,6-, 1,8-, and 1,10-borylation.

with Grignard reagents.[13] Unfortunately, very low regio- and enantioselectivity were obtained.

It is evident that considerable difficulties exist in the remote asymmetric conjugate borylation. First, the regioselectivity is inevitably a troublesome issue. 1,4-Addition, 1,6-addition, 1,8-addition and 1,10-addition would compete with one another, which could lead to a complex reaction mixture. Second, the electrophilicity of remote sites gradually decreases as those sites are more distal to the carbonyl group ($C_4 > C_6 > C_8 > C_{10}$). Third, the remote asymmetric addition is remarkably challenging as the reactive sites are far away from the coordinating carbonyl group. Therefore, catalytic asymmetric conjugate 1,8- and 1,10-borylation has been rarely achieved. Here, by using a powerful copper(I)-JOSIPHOS catalyst, we develop asymmetric 1,6-, 1,8-, and 1,10-borylation of unsaturated dioxinones with excellent regio- and high enantioselectivities. Previously, we disclosed a copper(I)-NHC complex-catalyzed asymmetric 1,6-allylation of 2,2-dimethyl-6-alkenyl-4*H*-1,3-dioxin-4-ones.[15] The 2,2-dimethyl-4*H*-1,3-dioxin-4-one group was easily transformed to β-keto-ester, α,β-unsaturated ester, and pyrazole in moderate yields, which demonstrated its synthetical versatility.

Results and Discussion

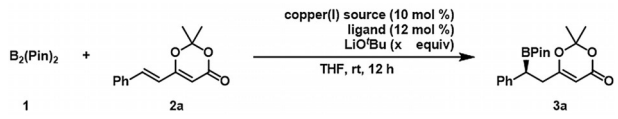
At the outset, the reaction of **1** and (*E*)-2,2-dimethyl-6-styryl-4*H*-1,3-dioxin-4-one (**2a**) was studied for the optimization of reaction conditions (Table 1). In the presence of 10 mol% $CuPF_6(CH_3CN)_4$, 12 mol% (*R*)-TOL-BINAP and 10 mol% LiO^{t}Bu, conjugate 1,6-borylation afforded product **3a** in 58% yield with 28% *ee* (entry 1). Switching the ligand to (*R*)-DIFLUORPHOS increased both the yield and the enantioselectivity (entry 2). Unfortunately, other bisphosphine ligands, such as (*R*)-DTBM-SEGPHOS, (*R*,*R*)-QUINOXP* and (*R*,*R*)-Ph-BPE, led to inferior reaction results (entries 3–5). Ferrocene-embedded bisphosphine ligands, (*R*)-(*S*)-JOSIPHOS and (R,R_P)-TANIAPHOS enhanced the enantioselectivity (entries 6,7). Notably, product **3a** was obtained in 78% *ee* in the case of (R,R_P)-TANIAPHOS (entry 6).

By increasing the amount of LiO^{t}Bu to 1 equivalent, the reaction with (R,R_P)-TANIAPHOS had an increased yield but with decreased *ee* while the reaction with (*R*)-(*S*)-JOSIPHOS had a slightly decreased yield but with increased *ee* (entries 8,9). The yield was further enhanced by increasing the amount of $B_2(Pin)_2$ to 3 equivalents (entry 10). Then, a simple screening of five commercially available derivatives of (*R*)-(*S*)-JOSIPHOS (from Strem Chemicals, Inc.) was performed. However, no enhanced enantioselectivity was observed but (*R*)-(*S*)-JOSIPHOS-5 led to the highest yields (entries 11–15). Screening of the copper(I) source identified $CuF(PPh_3)_3{\cdot}2MeOH$ as the best catalyst, as **3a** was obtained in 85% yield with 91% *ee*. A beneficial alcohol effect,[9,10] generally presenting in the copper(I)-catalyzed conjugate 1,4-borylation,[16] was not detected in the present 1,6-borylation (entry 17).

Under the optimized reaction conditions, the scope of aryl and heteroaryl groups in **2** was assessed as depicted in Table 2. Both electron-donating groups (such as methoxyl, methylthio, methyl, and ^{t}butyl) and electron-withdrawing groups (such as fluoro, bromo, and iodo) were acceptable (**3a**–**3k**). The enantioselectivity was not sensitive to the position (*ortho*-, *meta*-, and *para*-) of a substituent on the phenyl ring. Intriguingly, labile *para*-iodo-phenyl group was not touched by the highly nucleophilic Cu–BPin species (**3f**). Moreover, several heteroaryls (including 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, and benzo[*b*]thiophen-2-yl) were well tolerated (**3l**–**3p**). Generally, 1,6-borylated products were obtained in moderate to high yields with high enantioselectivity (ca. 90% *ee*). It should be noted that in Lam's catalytic asymmetric 1,6-conjugate borylation,[9a] aryls were not tolerated and only alkyls without significant steric hindrance were well accepted. Therefore, the present methodology serves as a nice complement to Lam's report.

The scope of alkyl groups was evaluated. Substrates with linear alkyls (such as ethyl, ^{n}propyl, ^{n}pentyl, and ^{n}heptyl) led to the boronates in good to high yields with high enantioselectivity (**3q**–**3t**). α-Branched alkyls (such as ^{i}propyl, ^{c}propyl, ^{c}pentyl, and ^{c}hexyl), β-branched alkyl (^{i}butyl), and γ-branched alkyl (2-phenyl-ethyl) did not disturb the enantioselectivity (**3u**–**3z**). Moreover, functionalized alkyls (containing benzoxyl, tosylate, alkyl chloride, and phthalimide) were nicely tolerated (**3aa**–**3ad**), which allow further structure elaboration. Substrate **2ae** derived from (+)-citronellal underwent

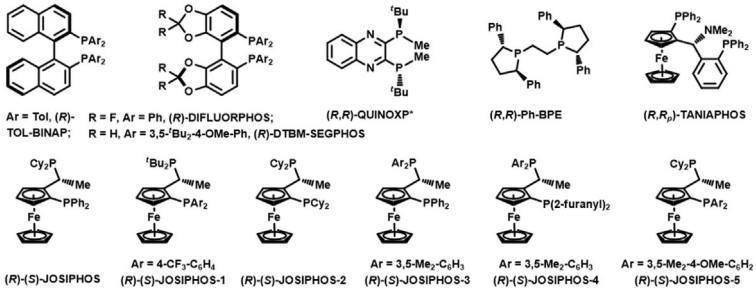
Table 1: Optimization of the reaction conditions with **2a**.[a]



1 2a 3a

Entry	Copper(I) source	Ligand	*x*	Yield [%][b]	*ee* [%][c]
1	$CuPF_6(CH_3CN)_4$	(*R*)-TOL-BINAP	0.1	58	28
2	$CuPF_6(CH_3CN)_4$	(*R*)-DIFLUORPHOS	0.1	64	47
3	$CuPF_6(CH_3CN)_4$	(*R*)-DTBM-SEGPHOS	0.1	43	−21
4	$CuPF_6(CH_3CN)_4$	(*R*,*R*)-QUINOXP*	0.1	trace	–
5	$CuPF_6(CH_3CN)_4$	(*R*,*R*)-Ph-BPE	0.1	78	−23
6	$CuPF_6(CH_3CN)_4$	(*R*,R_p)-TANIAPHOS	0.1	50	78
7	$CuPF_6(CH_3CN)_4$	(*R*)-(*S*)-JOSIPHOS	0.1	67	66
8	$CuPF_6(CH_3CN)_4$	(*R*,R_p)-TANIAPHOS	1.0	71	67
9	$CuPF_6(CH_3CN)_4$	(*R*)-(*S*)-JOSIPHOS	1.0	61	89
10[d]	$CuPF_6(CH_3CN)_4$	(*R*)-(*S*)-JOSIPHOS	1.0	80	89
11[d]	$CuPF_6(CH_3CN)_4$	(*R*)-(*S*)-JOSIPHOS-1	1.0	88	77
12[d]	$CuPF_6(CH_3CN)_4$	(*R*)-(*S*)-JOSIPHOS-2	1.0	84	10
13[d]	$CuPF_6(CH_3CN)_4$	(*R*)-(*S*)-JOSIPHOS-3	1.0	83	19
14[d]	$CuPF_6(CH_3CN)_4$	(*R*)-(*S*)-JOSIPHOS-4	1.0	89	−4
15[d]	$CuPF_6(CH_3CN)_4$	(*R*)-(*S*)-JOSIPHOS-5	1.0	84	89
16[d]	$CuF(PPh_3)_3{\cdot}2MeOH$	(*R*)-(*S*)-JOSIPHOS-5	–	85	91
17[d,e]	$CuF(PPh_3)_3{\cdot}2MeOH$	(*R*)-(*S*)-JOSIPHOS-5	–	67	89

[a] **1a**, 0.10 mmol; **2**, 0.15 mmol. [b] Determined by ^{1}H NMR analysis of reaction crude mixture using mesitylene as an internal standard. [c] Determined by chiral-stationary-phase HPLC analysis. [d] 3 equiv $B_2(Pin)_2$ used. 2 h. [e] 2 equiv ^{i}PrOH added.



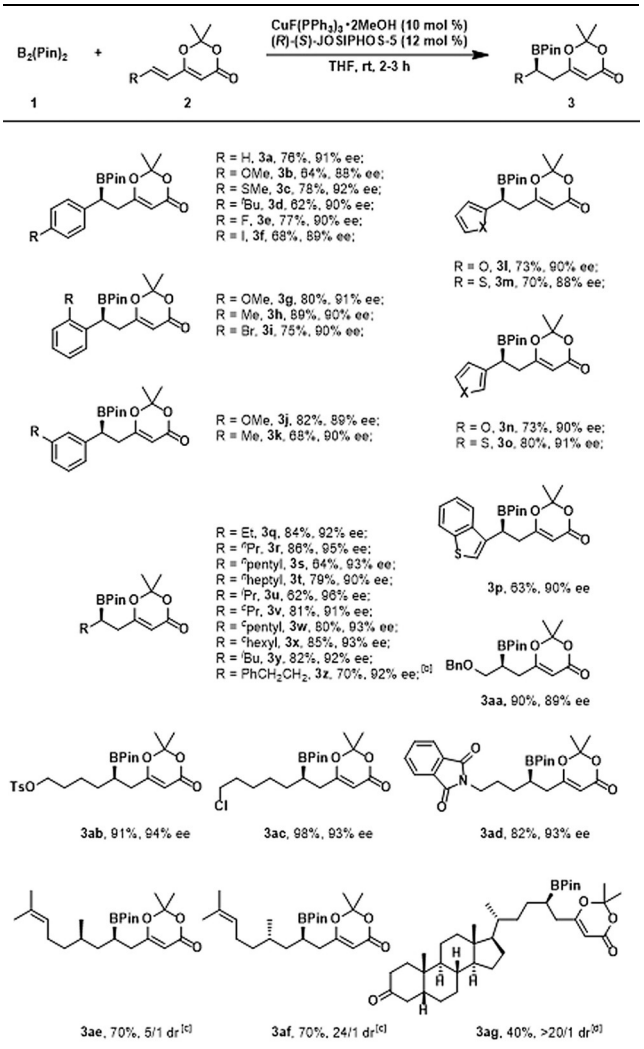
1,6-borylation in 70% yield with 5/1 dr, whereas substrate **2af** derived from (−)-citronellal led to 1,6-borylated product **3af** in 70% yield with 24/1 dr, which clearly demonstrated a "match and mismatch" phenomenon in asymmetric induction. Furthermore, substrate **2ag** prepared from lithocholic acid delivered product **3ag** in moderate yield with excellent diastereoselectivity.

Conjugate 1,8-borylation is historically challenging, presumably owing to the extenuated electrophilicity at the remote 8-position and competing 1,4- and 1,6-borylation, which is reflected by the shortage of examples in literature. When substrate **4a** was submitted to the present reaction conditions, unusual 1,8-borylation instead of 1,6-borylation was observed with excellent regioselectivity. Then, a preliminary substrate scope of catalytic asymmetric 1,8-borylation was described in Table 3. In substrate **4**, linear alkyls (**5a** and **5b**), α-branched alkyl (**5c**), and functionalized alkyls (**5d**, **5e**, and **5f**) were well accepted. Six chiral allylic boronates were isolated in moderate yields with good enantioselectivity and good to excellent *E*/*Z* ratio. Encouragingly, the present reaction protocol was further extended to very challenging and unprecedented catalytic asymmetric 1,10-borylation. Although the *E*,*E*/*others* ratio was moderate in some cases, the targeted boronates were generated in moderate yields with good enantioselectivity. Particularly noteworthy were **7g** and **7h** as the olefin group and alkyl chloride group paved the way for further structure modification. For 1,8- and 1,10-borylation, when R = Ph, complicated reaction mixtures were obtained, which were indicated by both messy TLC and messy crude ^{1}H NMR spectra. Evidently, the control of the regioselectivity failed in these two cases.

Transformations of product **3a** toward construction of C–O bonds and C–C bonds were carried out (Scheme 2). The oxidation of C–BPin was easily accomplished to afford chiral alcohol **8** in excellent yield with a slight erosion of *ee*. By comparing the optical rotation of **8** with reported data,[17] the absolute configuration of **3a** was determined to be *S*. Moreover, the absolute configurations of **5a** and **7a** were determined to be *R* by their transformations (for the details, see the Supporting Information). Analogously, the absolute configurations of **3**, **5**, and **7** were deduced as shown in Tables 1–3. By following Aggarwal's powerful enantiospecific sp^3–sp^2 coupling of secondary boronic ester with electron-rich heteroarenes,[18] 2-furanyl was successfully introduced to give **9** in 64% yield with enantioselectivity maintained. Meanwhile, the coupling of chiral boronic ester **3a** and thiophene smoothly occurred to generate **10** in 70% yield with enantioselectivity retained. Moreover, a reported procedure[19] was employed to enable the one-carbon homologation of **3a**, which furnished chiral alcohol **11** in 60% yield with slightly decreased enantioselectivity after oxidation. It should be note that absolute configurations of the products (**8**–**11**) were retained.

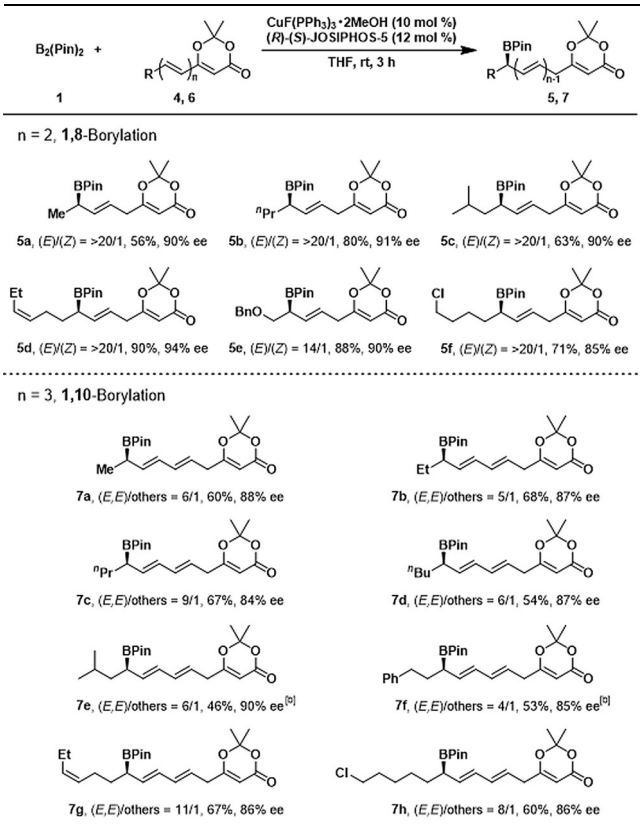
To understand the interesting regio- and enantioselectivity observed in this study, DFT calculations were performed for the reactions of **5a** and **7a** (Figure 1 and Figure 2) at the B3LYP-D3/LANL2DZ(Cu,Fe)/6-31G(d) level of theory with the SMD continuum solvation model for THF.[20–22] The calculated $\Delta\Delta G^{\ddagger}$ values were found to favor the formation of the experimentally observed products via $INT2_{1,8}$ and $INT2_{1,10}$ (for **5a** and **7a**, respectively). These terminal addition products were the most kinetically and thermodynamically favored products. However, one surprising finding to note is that calculations suggested high regioselectivity even though the 1,8-borylation reaction of **7a** involved the formation of a more stable coordinated intermediate $INT1_{1,8}$ (Figure 2).

Table 2: Substrate scope of catalytic asymmetric 1,6-borylation.[a]

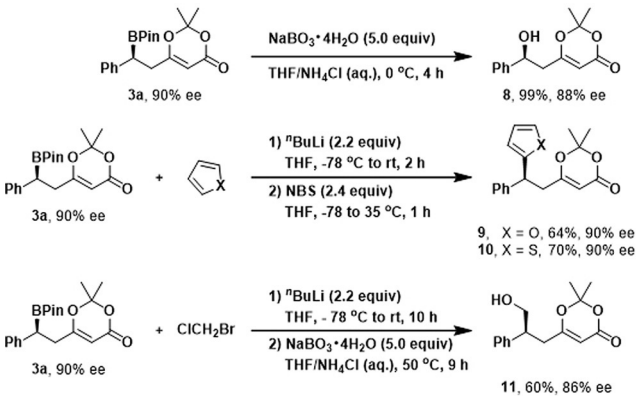


[a] **1**, 0.6 mmol; **2**, 0.2 mmol. Isolated yield was reported. The *ee* was determined by chiral-stationary-phase HPLC analysis. [b] Reaction performed on a 1-mmol scale (**2**). [c] Diastereoselectivity was determined by chiral-stationary-phase HPLC analysis. [d] Diastereoselectivity was determined by ^{1}H NMR analysis.

Table 3: Substrate scope of catalytic asymmetric 1,8- and 1,10-borylation.[a]



[a] **1**, 0.6 mmol; **4** or **6**, 0.2 mmol. Isolated yield was reported. (*E*)/(*Z*) ratio or (*E*,*E*)/others ratio was determined by the ^{1}H NMR analysis of crude reaction mixture. Ee was determined by chiral-stationary-phase HPLC analysis. [b] Conditions in entry 7 in Table 1 were employed. 2 equiv $B_2(Pin)_2$ was employed.



Scheme 2. Transformations of product **3a**.

Of particular utility is the structural information provided through the transition state calculations, which provides insight into the specific interactions that drive the regio- and enantioselectivity. It is evident that proximal additions would suffer steric interaction between the dioxinone and the metal substituents.[21c,23] Additionally, our stereomechanistic analysis highlighted by the insert in Figure 2 shows one important feature dictating the facial selectivity. For the major enantiomer, a less severe steric interaction is observed between the substrate's alkenyl C–H and the phosphine ligand, rather than the substrate's terminal substituent (here, methyl). This analysis provides visual insight into the observed outcome while also suggesting future ligand modifications.

Finally, the present methodology was applied in the catalytic asymmetric synthesis of (−)-7,8-dihydrokavain (Scheme 3), the enantiomer of natural (+)-7,8-dihydrokavain, which was isolated from Kava plant (*Piper methysticum*). Kavalactones are thought to be the main active components responsible for the medication for a range of conditions including anxiety, stress, and insomnia.[24] The one-pot synthesis started from the copper(I)-catalyzed asymmetric 1,6-borylation of **2z**, which afforded the chiral alcohol after oxidation. The subsequent deprotection and etherifica-

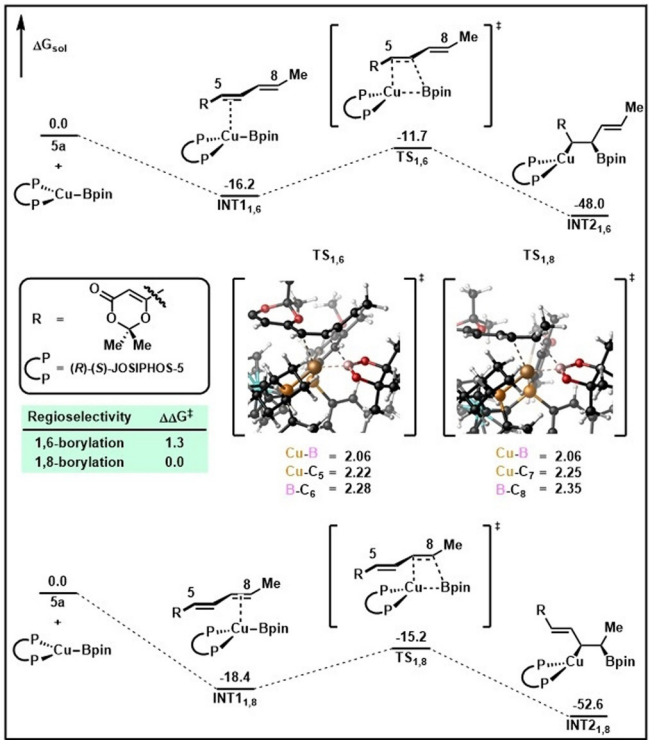


Figure 1. Calculated energy profile of 1,6- (top) and 1,8-addition (bottom) of **5a**. Bond lengths are in angstroms and energies in kcal mol^{-1} at the B3LYP-D3/LANL2DZ(Cu,Fe)/6-31G(d) level of theory.

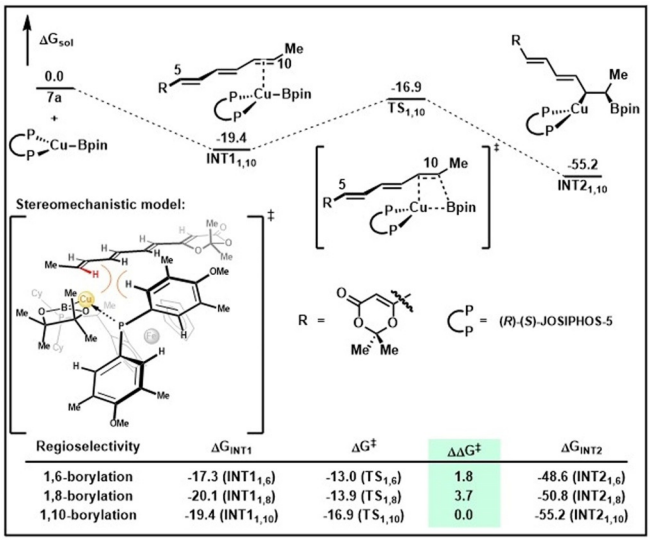
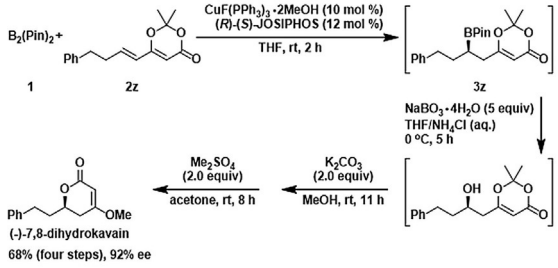


Figure 2. Calculated energy profile of 1,6-, 1,8-, and 1,10-addition of **7a**. Bond lengths are in angstroms and energies in kcal mol^{-1} at the B3LYP-D3/LANL2DZ(Cu,Fe)/6-31G(d) level of theory.

tion furnished (−)-7,8-dihydrokavain in 68% total yield with 92% *ee* for four steps. It was noteworthy that most reported synthetic approaches gave less than 32% overall yield in more than five steps.[25]



Scheme 3. One-pot asymmetric synthesis of (−)-7,8-dihydrokavain.

Conclusion

Copper(I)-catalyzed asymmetric conjugate 1,6-borylation was achieved in moderate to high yields with high regio- and enantioselectivity. A series of α-chiral boronates was prepared with a broad substrate scope including aryls, heteroaryls, simple alkyls, and functionalized alkyls. It was particularly outstanding that the present reaction protocol was successfully applied to the challenging and unprecedented catalytic asymmetric 1,8- and 1,10-borylation in moderate yields with high enantioselectivity. Moreover, the generated α-chiral boronate was successfully transformed to synthetically useful compounds through C−O bond and C−C bond formations. Importantly, a stereomechanistic analysis clarifies the non-covalent interactions that dictate the regioselectivity and enantioselectvity. Finally, the methodology found application in the efficient one-pot asymmetric synthesis of (−)-7,8-dihydrokavain. Expansion of the present reaction protocol to other processes is currently underway in our laboratories.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,6-addition · 1,8-addition · 1,10-addition · borylation · copper catalysts

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