RESEARCH ARTICLE

Copper-Catalyzed Regio- and Diastereoselective Borylacylation of α,β-Unsaturated Esters

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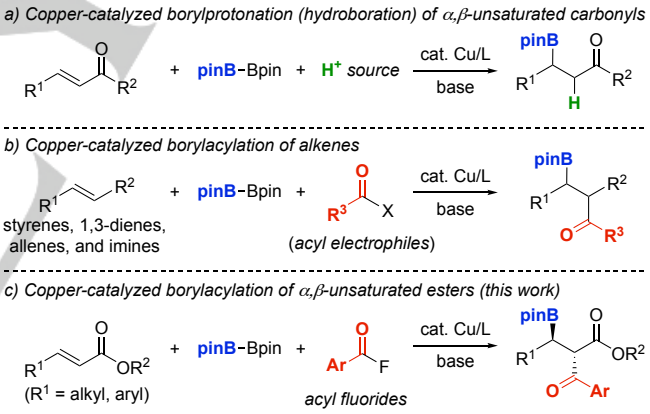
Abstract: A copper-catalyzed regio- and diastereoselective borylacylation of *α,β*-unsaturated esters with B_2pin_2 and acyl fluorides has been developed to afford the *β'*-boryl-*β*-ketoesters with high *anti*-diastereoselectivity (up to >99:1). Additionally, the borylcarbamoylation is possible by using isocyanates as electrophiles instead of acyl fluorides. Moreover, the enantioselective borylacylation and borylcarbamoylation are also achieved by judicious choice of a chiral phosphoramidite-ligated copper complex.

Introduction

Boron-containing organic molecules are ubiquitous in functional materials and biologically active compounds.[1] Additionally, they are versatile and important synthetic intermediates in modern organic synthesis because the C–B bond can be converted into C–C and C–heteroatom bonds with high efficiency and stereospecificity.[2] Thus, the preparation of densely functionalized organoboron compounds has attracted significant attention. In this context, transition-metal-catalyzed addition reactions of boryl groups to alkenes have emerged as useful strategies for synthesis of alkyl borons.[3] In particular, copper-catalyzed boryl-conjugate additions to α,*β*-unsaturated carbonyl compounds with B_2pin_2 have been intensely investigated to provide a straightforward approach to *β*-borylated carbonyl compounds (Scheme 1a).[4] On the other hand, the copper-catalyzed borylative difunctionalization of alkenes is more attractive from the synthetic point of view because it enables the simultaneous introduction of both boron moieties and other functional groups to organic molecules and gives highly functionalized alkyl boronates from relatively simple starting materials.[5] Among them, the borylacylation reaction is an efficient method for the rapid construction of borylated carbonyl compounds. In 2017, Brown reported pioneering work on the copper-catalyzed borylacylation of styrenes, 1,3-dienes, and strained alkenes with B_2pin_2 and acyl chlorides.[6a] Since then, the borylacylation of versatile π-systems such as allenes, imines, and enynes has been developed by many research groups.[6b-i] Despite the aforementioned certain progress, there is no successful report on borylacylation of α,*β*-unsaturated carbonyl compounds.[7] Recently, our group developed a copper-catalyzed borylamination of *α,β*-unsaturated esters with B_2pin_2 and hydroxylamines to deliver the *β*-boryl-*α*-amino acid derivatives.[8] Because of our continuing interest in this chemistry, we envisioned that the borylacylation of acrylates could proceed by the replacement of hydroxylamines with acyl electrophiles.

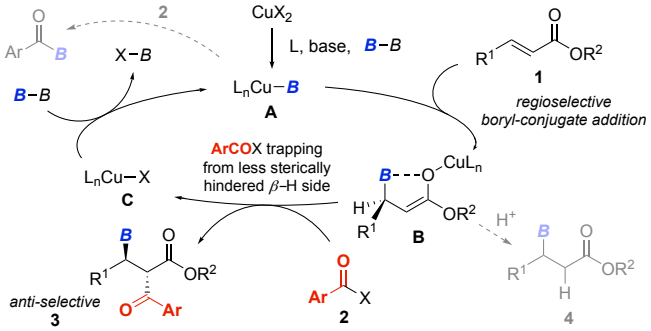
Herein, we report a copper-catalyzed regio- and diastereoselective borylacylation of *α,β*-unsaturated carboxylic acid derivatives with B_2pin_2 and acyl fluorides, giving the *β'*-boryl-*β*-ketoesters with high *anti*-diastereoselectivity (up to >99:1; Scheme 1c). Additionally, the borylcarbamoylation is also possible by using isocyanates as electrophiles. Moreover, an appropriate chiral phosphoramidite ligand successfully induces the enantioselectivity to afford optically active *β*-borylated 1,3-dicarbonyl compounds.



Scheme 1. Copper-catalyzed borylprotonation and borylacylation of alkenes.

Results and Discussion

Our working scenario for the borylacylation of the *α,β*-unsaturated ester is shown in Scheme 2. A catalytically active borylcopper species **A** is initially formed from a starting copper salt, ligand, and diboron *B–B*. Subsequent 1,4-addition of L_nCu-*B* **A** to the *α,β*-unsaturated ester **1** furnishes the *β*-borylated *O*-bound copper enolate **B**. The complex **B** then reacts with the acyl electrophile **2** to give the desired *β'*-boryl-*β*-ketoesters **3** with generation of the L_nCu-X **C**. In this step, the diastereoselectivity can be controlled; the intramolecular interaction between the boron and oxygen in the intermediate **B** regulates the molecular conformation.[9] Accordingly, the face-selective C-C bond formation with the acyl electrophile proceeds on the more sterically accessible β-H side, giving the *anti*-product selectively. Finally, the L_nCu-X **C** is conve-



Scheme 2. Working hypothesis. L = ligand, X = leaving group.

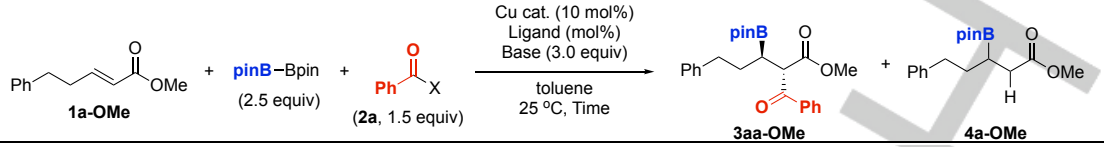
ted back to the borylcopper species **A** by the base-assisted ligand exchange with the diboron to complete the catalytic cycle. However, there are several challenges associated with the reaction design: 1) the competitive protonation of the copper enolate **B** over the desired acylation with **2**; 2) the direct borylation of the acyl electrophile **2** with the borylcopper **A**.[10] Therefore, suitable choice of a base, catalyst, and leaving group of the acyl electrophile is critical for the development of borylacylation of *α*,*β*-unsaturated esters.

Our optimization studies commenced with the *α*,*β*-unsaturated methyl ester **1a-OMe**, B_2pin_2 (2.5 equiv), and benzoyl fluoride (**2a**; 1.5 equiv) as model substrates (Table 1). The first trial using $Cu(OAc)_2$/PPh_3 catalyst and CsOPiv base in toluene at 25 ˚C afforded the desired *β'*-boryl-*β*-ketoester **3aa-OMe** in 33% ^{1}H NMR yield along with 24% of the hydroborylated product **4a-OMe** (entry 1). Inconsistent with the hypothesis in Scheme 2, the diastereoselectivity was low (*anti*/*syn* = 36:64).[11] We then tested several monodentate (entries 2 and 3) and bidentate (entries 4 and 5) phosphine ligands, but the satisfactory yield was not obtained. Thus, we investigated modified PPh_3 ligands. While the introduction of electron-donating group resulted in a lower yield (entry 6), the electron-withdrawing F or CF_3 group generally improved the ratio of **3aa**/**4a** (entries 7–9). In particular, P(3,5-$(CF_3)_2C_6H_3)_3$ was proved to be optimal in term of the yield (entry 8). The 1,4-addition proceeded even in the absence of a ligand, but **4a-OMe** was dominantly formed (entry 10), thus suggesting the indispensable role of phosphine ligand in the acylation step. We next examined several copper catalyst precursors: other copper salts such as $Cu(OTf)_2$, $Cu(CH_3CN)_4OTf$, and CuCl showed lower performance (entries 11–13). The acrylate **1a** was almost recovered without any copper catalysts (entry 14). The choice of base was crucial for the successful *α*-acylation: several other acetate-type bases also furnished **3aa-OMe** albeit in moderate yields (entry 15 and 16). On the other hand, Cs_2CO_3, CsF, Li*O*t*B*u, and 4-picoline afforded the hydroborylated **4a-OMe** as the major product (entries 17-20). The absence of base resulted in no product formation, and only the undesired **4a-OMe** was formed in 60% yield (entry 21). The reaction also proceeded with benzoyl chloride or benzoic anhydride, but the yield of **3aa-OMe** largely dropped (entries 22 and 23). Although additional screening of solvent, concentration, and temperature was performed, no improvement of the yield and diastereoselectivity was observed (see the Supporting Information for more detailed optimization studies). We thus monitored the reaction mixture of **1a-OMe**, B_2pin_2, and **2a** in toluene-d_8 by using ^{1}H NMR to check the reaction progress in detail (entry 24 and Figure 1, left). Surprisingly, the reaction was quite rapid; even after 45 min, the starting material **1a** was completely consumed, and **3aa-OMe** was generated in 70% ^{1}H NMR yield along with 20% of **4a-OMe**. However, the yield of **3aa-OMe** decreased down to 62% yield in 120 min. The result suggests that the product **3aa-OMe** gradually decomposed in the reaction mixture. Moreover, it is noteworthy that the high diastereomeric ratio (>99:1 *anti*/*syn*) was observed at 30 min but in 120 min dropped to 76:24 *anti*/*syn*, thus indicating the epimerization of **3aa-OMe** probably caused by the deprotonation of active methine proton. Actually, the isolated, stereochemically pure *anti*- and *syn*-**3aa-OMe** underwent the rapid epimerization under the standard conditions (see the Supporting Information for details). Subsequently, we also monitored the reaction mixture of the *tert*-butyl ester **1a-O*t*Bu**, B_2pin_2, and **2a** (entry 25 and Figure 1, right). While a similar reaction efficiency was observed, the rate of epimerization of **3aa-O*t*Bu** was considerably lower than that of **3aa-OMe** (97:3 *anti*/*syn* in 120 min) probably because of steric factors. Furthermore, the investigation of reaction stoichiometry revealed that the use of **2a** as the limiting agent was better, and the target **3aa-O*t*Bu** was formed in 90% ^{1}H yield with >99:1 *anti*/*syn* ratio and finally isolated in 87% yield with 93:7 *anti*/*syn* ratio (Table 1, entry 26).[12]

With conditions of entry 26 in Table 1, we examined the scope of the acyl fluorides **2** with **1a-O*t*Bu** (Scheme 3). In general, the reduced byproducts **4a-OR** was formed but able to be separated by chromatographic purification. Both the electron-donating methoxy and electron-withdrawing chloro groups were tolerated to afford the corresponding *β'*-boryl-*β*-ketoesters **3ab-O*t*Bu** and **3ac-O*t*Bu** in good yields. The ortho-substitution was not detrimental to the reaction (**3ad-O*t*Bu**). The substrates that bear higher fused naphthalene and heteroaromatic benzofuran also worked well to deliver the targeted products **3ae-O*t*Bu** and **3af-O*t*Bu** in 81 and 95% yields, respectively, with high diastereomeric ratios (97:3–98:2 *anti*/*syn*). We next investigated the scope of the *α*,*β*-unsaturated esters **1**. The crotonate and *γ*-branched acrylates underwent the reaction smoothly to deliver the desired products **3be-de-O*t*Bu** in 76-95% yields with good to excellent *anti*-diastereoselectivity. The copper catalysis accommodated versatile functional groups including alkyl chloride, bromide, silyl ether, pivaloyl ester, acetal, and nitrile moieties to give the corresponding *β'*-boryl-*β*-ketoesters **3ee-je-O*t*Bu**. Additionally, several cinnamates could also be coupled with **2a**; whereas the reaction with *tert*-butyl cinnamate **1k-O*t*Bu** showed lower efficiency, the methyl cinnamate **1k-OMe** was converted to the target **3ke-OMe** in a better yield, and both diastereomers could be separated to each other by chromatographic purification. The reaction was compatible with the methoxy and fluoro groups at the *para* position of the phenyl ring in **1k-OMe** to form the *β'*-boryl-*β*-ketoesters **3le-OMe** and **3me-OMe** in synthetically acceptable yields. Additionally, the heteroaromatic thiophene was also tolerated (**3ne-OMe**). The reaction could also be performed on a 1.0 mmol scale with comparable efficiency and stereoselectivity (**3ae-O^{t}Bu**), thus indicating good reproducibility and reliability. On the other hand, *α*,*β*-unsaturated ketones, amides, and lactones gave the targeted product in much lower yields or only the corresponding reduced byproducts corresponding to **4** (see the Supporting Information for details).

The success of borylacylation of acylates prompted us to explore

Table 1. Optimization studies for copper-catalyzed borylacylation of *α,β*-unsaturated ester **1a** with B_2pin_2 and acyl electrophile **2a**.[a]



Entry	X	Cu cat.	Ligand (mol%)	Base	Time	Yield of **3aa** [%], d.r.[b]	Yield of **4a** [%][b]
1	F	$Cu(OAc)_2$	PPh_3 (20)	CsOPiv	18 h	33, 36:64	24
2	F	$Cu(OAc)_2$	$PCyPh_2$ (20)	CsOPiv	18 h	26, 38:62	28
3	F	$Cu(OAc)_2$	$P(OEt)_3$ (20)	CsOPiv	18 h	21, 38:62	37
4	F	$Cu(OAc)_2$	dppbz (10)	CsOPiv	18 h	29, 41:59	57
5	F	$Cu(OAc)_2$	dppe (10)	CsOPiv	18 h	21, 38:62	45
6	F	$Cu(OAc)_2$	$P(4\text{-}MeOC_6H_4)_3$ (20)	CsOPiv	18 h	26, 42:58	30
7	F	$Cu(OAc)_2$	$P(3,5\text{-}F_2C_6H_3)_3$ (20)	CsOPiv	18 h	41, 40:60	9
8	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	18 h	56, 37:63	13
9	F	$Cu(OAc)_2$	$P(4\text{-}CF_3C_6H_4)_3$ (20)	CsOPiv	18 h	53, 40:60	17
10	F	$Cu(OAc)_2$	none	CsOPiv	18 h	2, -	73
11	F	$Cu(OTf)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	18 h	21, 37:63	18
12	F	$Cu(CH_3CN)_4OTf$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	18 h	24, 38:62	16
13	F	CuCl	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	18 h	34, 38:62	23
14	F	none	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	18 h	0, -	0
15	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	KOPiv	18 h	35, 37:63	10
16	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOAc	18 h	29, 41:59	24
17	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	Cs_2CO_3	18 h	12, 42:58	33
18	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsF	18 h	< 5, -	53
19	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	LiO*t*Bu	18 h	0, -	37
20	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	4-picoline	18 h	23, 39:61	51
21	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	none	18 h	0, -	60
22	Cl	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	18 h	5, 38:62	30
23	OBz	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	18 h	30, 37:63	24
24[c]	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	45 min	70, 93:7	22
25[c, d]	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	45 min	66, >99:1	25
26[e]	F	$Cu(OAc)_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	CsOPiv	30 min	90, >99:1 (87, 93:7)	49

[a] Conditions: **1a-OMe** (0.25 mmol), B_2pin_2 (0.63 mmol), **2a** (0.38 mmol), Cu cat. (0.025 mmol), Ligand, Base (0.75 mmol), toluene (1.0 mL), 25 ˚C, N_2. [b] Estimated by ^1H NMR based on 0.25 mmol with 1-methylnaphthalene as the internal standard. The diastereomeric ratio (d.r., *anti*/*syn*) is determined in the crude mixture. Isolated yield is in parentheses. [c] The results of monitoring study with toluene-d_8 (Figure 1). [d] **1a-O*t*Bu** (0.25 mmol) was used. [e] **1a-O*t*Bu** (0.50 mmol), **2a** (0.25 mmol).

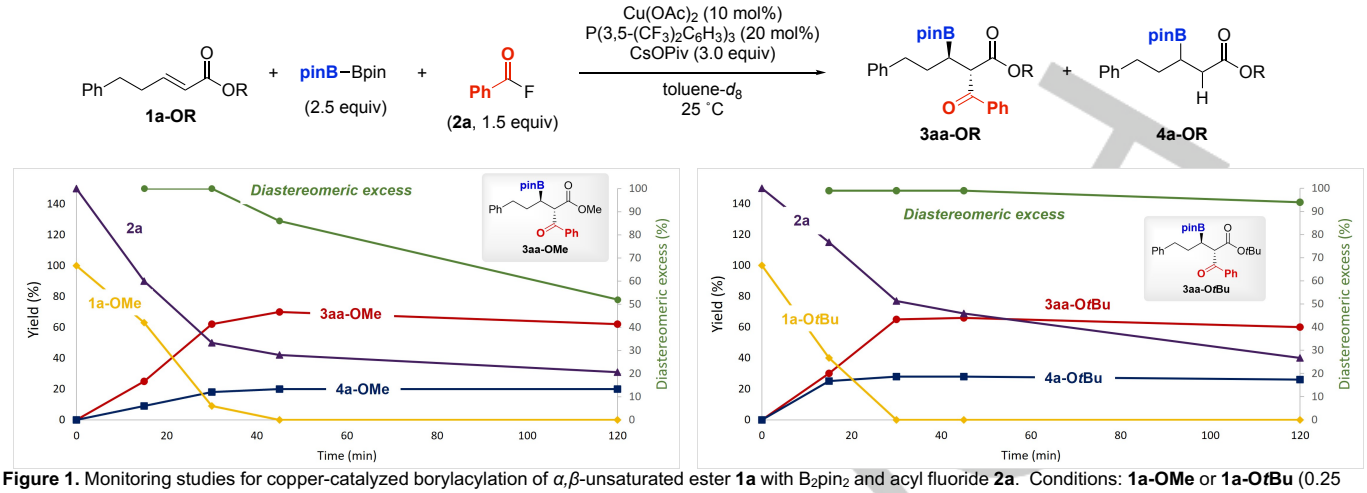
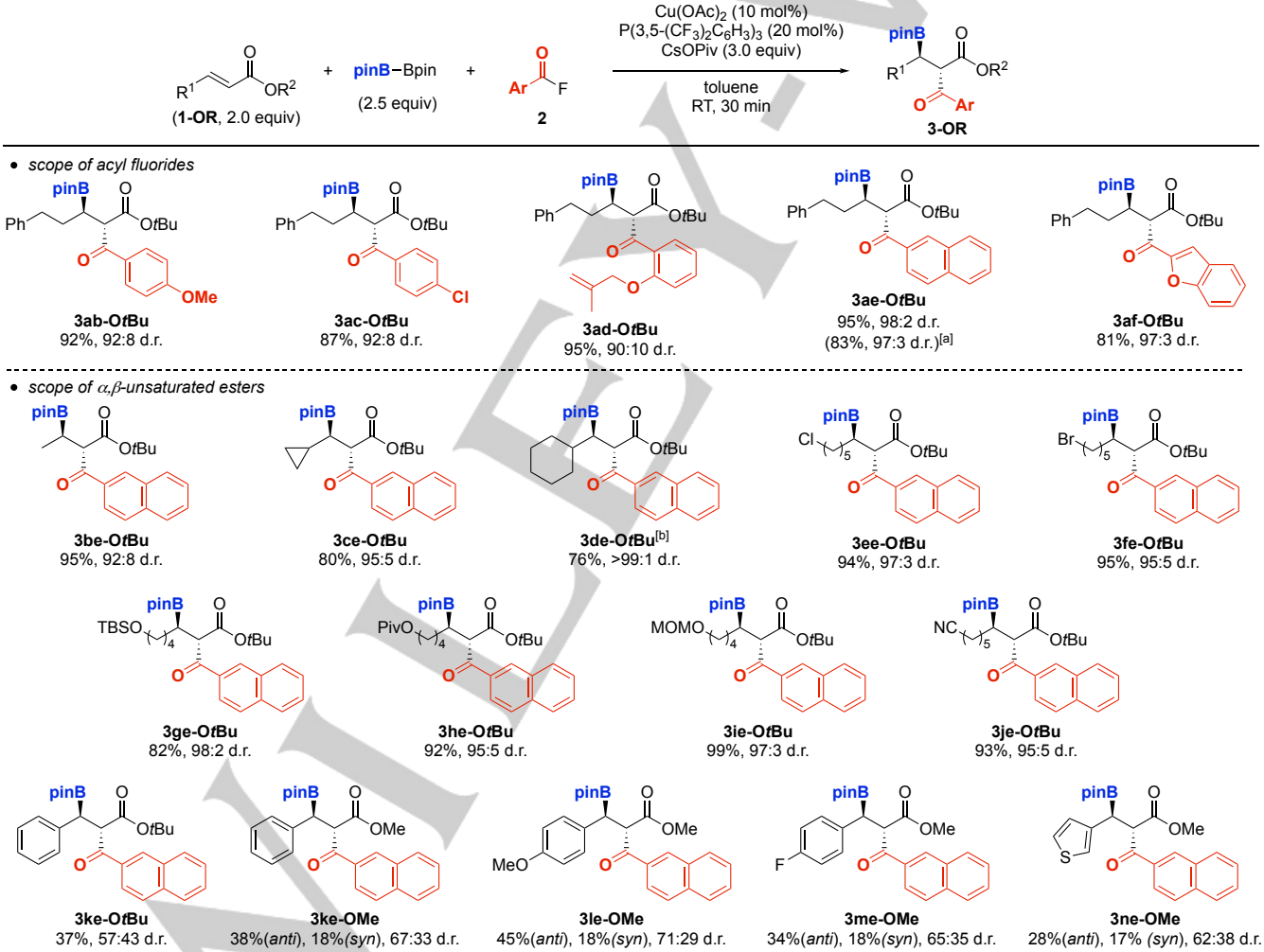
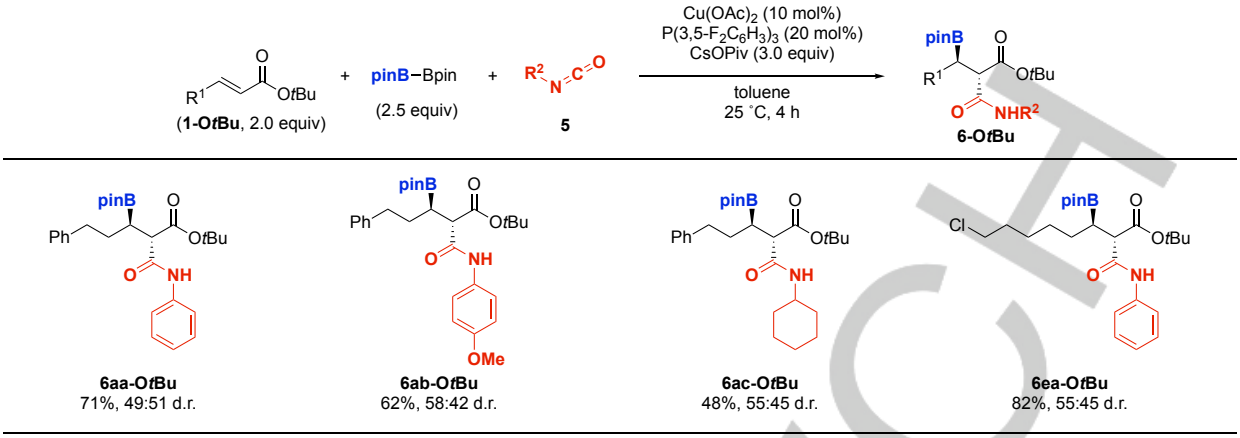


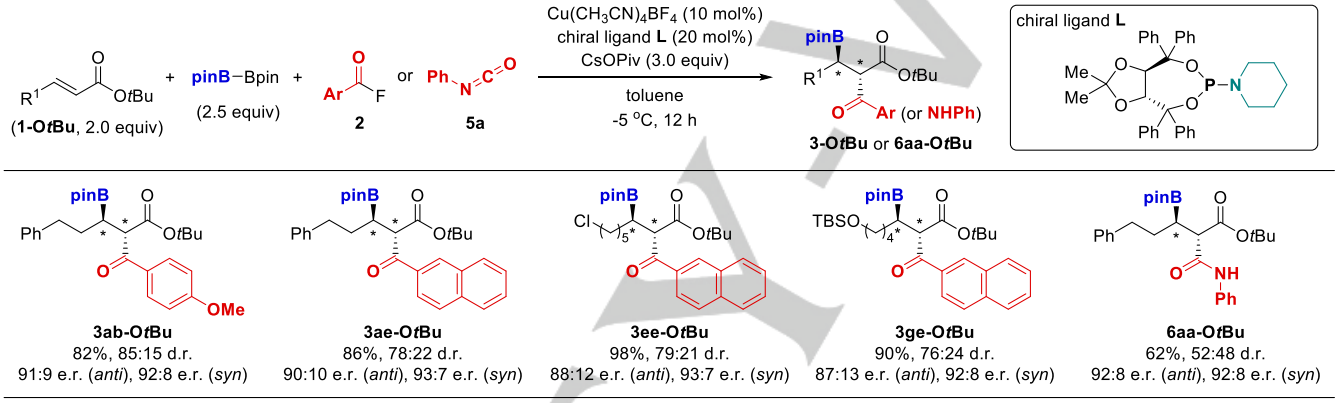
Figure 1. Monitoring studies for copper-catalyzed borylacylation of *α,β*-unsaturated ester **1a** with B_2pin_2 and acyl fluoride **2a**. Conditions: **1a-OMe** or **1a-O*t*Bu** (0.25 mmol), B_2pin_2 (0.63 mmol), **2a** (0.38 mmol), $Cu(OAc)_2$ (0.025 mmol), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (0.050 mmol), CsOPiv (0.75 mmol), toluene-d_8 (1.0 mL), 25 °C, N_2. Estimated by ^1H NMR based on 0.25 mmol with 1-methylnaphthalene as the internal standard.



Scheme 3. Scope of copper-catalyzed borylacylation of *α,β*-unsaturated ester **1** with B_2pin_2 and acyl fluoride **2**. Conditions: **1** (0.50 mmol), B_2pin_2 (0.63 mmol), **2** (0.25 mmol), $Cu(OAc)_2$ (0.025 mmol), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (0.050 mmol), CsOPiv (0.75 mmol), toluene (1.0 mL), 25 °C, N_2. Isolated yields are given. [a] On a 1.0 mmol scale. [b] 2 h.



Scheme 4. Copper-catalyzed borylcarbamoylation of *α,β*-unsaturated ester **1-O*t*Bu** with B_2pin_2 and isocyanates **5**. Conditions: **1-O*t*Bu** (0.50 mmol), B_2pin_2 (0.63 mmol), **5** (0.25 mmol), $Cu(OAc)_2$ (0.025 mmol), $P(3,5\text{-}F_2C_6H_3)_3$ (0.050 mmol), CsOPiv (0.75 mmol), toluene (1.0 mL), 25 °C, N_2. Isolated yields are given.



Scheme 5. Copper-catalyzed enantioselective borylacylation or borylcarbamoylation of *α,β*-unsaturated ester **1-O*t*Bu** with B_2pin_2 and acyl fluoride **2** or phenyl isocyanate **5a**. Conditions: **1-O*t*Bu** (0.50 mmol), B_2pin_2 (0.63 mmol), **2** or **5a** (0.25 mmol), $Cu(CH_3CN)_4BF_4$ (0.025 mmol), **L** (0.050 mmol), CsOPiv (0.75 mmol), toluene (1.0 mL), -5 °C, 12 h, N_2. Isolated yields are given.

other borylcarbonylation reactions. Consequently, the borylcarbamoylation with isocyanates[13] was found to proceed to give the *β*-borylamide derivatives (Scheme 4). Screening of several triarylphosphine ligands identified $P(3,5\text{-}F_2C_6H_3)_3$ to be slightly better than $P(3,5\text{-}(CF_3)_2C_6H_3)_3$, and the target product **6aa-O*t*Bu** was isolated in 71% yield from **1a-O*t*Bu** and phenyl isocyanate **5a** albeit with poor diastereoselectivity.[14] 4-Methoxyphenyl isocyanate and cyclohexyl isocyanate also underwent the reaction to form the corresponding *β*-borylamide derivatives **6ab-O*t*Bu** and **6ac-O*t*Bu** in moderate to good yields. The chloro-substituted unsaturated ester **1e-O*t*Bu** was also a viable substrate.

Finally, we applied this borylcarbonylation protocol to the catalytic asymmetric variant. After the evaluation of copper catalyst precursors, chiral monodentate ligands, and various reaction parameters, we were pleased to find that the optically active **3ab-O*t*Bu** was formed in 82% isolated yield with high enantioselectivity (91:9 e.r. (*anti*), 92:8 e.r. (*syn*))[15] in the presence of a $Cu(CH_3CN)_4BF_4$/TADDOL-based piperidine phosphoramidite **L**[16] catalyst at -5 °C (Scheme 5). The asymmetric catalysis was compatible with naphthoyl fluoride (**3ae-O*t*Bu**) and some functional groups (**3ee-O*t*Bu** and **3ge-O*t*Bu**) to deliver the enantioenriched *β'*-boryl-*β*-ketoesters with good enantiomeric ratios (87:13 to 93:7 e.r.). Moreover, the enantioselective borylcarbamoylation could also be operated, and chiral *β*-borylamide derivatives **6aa-O*t*Bu** was obtained with 92:8 e.r.

Conclusion

We have developed an *anti*-selective copper-catalyzed borylacylation of *α,β*-unsaturated esters with B_2pin_2 and acyl fluorides as boron nucleophile and acyl electrophiles, respectively. The copper catalysis is the first successful example of borylacylation reaction of acrylates to the best of our knowledge. Furthermore, the replacement of acyl fluoride with the isocyanate allows the borylcarbamoylation. While still preliminary, the asymmetric synthesis of *β*-borylated 1,3-dicarbonyl compounds is also possible by using a chiral phosphoramidite ligand. More detailed mechanistic studies and manipulations of the borylcarbonylated products are ongoing in our laboratory.

Experimental Section

Experimental Procedure for Copper-Catalyzed Borylacylation of *α,β*-Unsaturated Esters with Diboron and Acyl Fluorides: Synthesis of **3ab-O*t*Bu** (Scheme 3) is representative. $Cu(OAc)_2$ (4.5 mg, 0.025 mmol), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (33.5 mg, 0.050 mmol), and CsOPiv (175.5 mg, 0.75 mmol) were placed in a 20 mL Schlenk tube, which was filled with nitrogen by using the Schlenk technique. Toluene (1.0 mL) was then added to the tube, and the suspension was stirred for 15 min at 25 ˚C (a heat block). Bis(pinacolato)diboron (158.7 mg, 0.63 mmol) was then added in one portion, and the resulting solution was stirred at the same temperature. After 5 min, 4-methoxybenzoyl fluoride (**2b**, 38.5 mg, 0.25 mmol) was then added in one portion, and *tert*-butyl (*E*)-5-phenylpent-2-enoate (**1a-O*t*Bu**, 116.2 mg, 0.50 mmol) was finally added dropwise. The reaction solution was stirred at 25 ˚C for additional 30 min. The resulting mixture was directly loaded on neutral silica gel and purified by column chromatography with hexane/ethyl acetate (10/1 → 5/1, v/v) and GPC ($CHCl_3$) to give *tert*-butyl 2-(4-methoxybenzoyl)-5-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (**3ab-O*t*Bu**, 113.7 mg, 0.23 mmol) in 92% yield with 92:8 *anti*/*syn* ratio.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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[11] The relative stereochemistry was assigned by the comparison of coupling constants and dihedral angles of calculated optimal structures of *anti*- and *syn*-diastereomers. See the Supporting Information for more details.

[12] Unfortunately, the minor epimerization (>99:1 to 93:7 *anti*/*syn*) was inevitable during the chromatographic purification. In addition, we confirmed no formation of **3aa-O^{t}Bu** from the reduced byproduct **4a-O^{t}Bu**. See the Supporting Information for details.

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[14] We also monitored the reaction mixture of **1a-O*t*Bu**, B_2pin_2, and **5a**; the diastereomeric ratio of **6aa-O*t*Bu** was low (*anti*/*syn* = 71:29) even in 30 min, and no change of diastereomeric ratio was observed during the course of reaction (see the Supporting Information for details). This result suggests the stereoselectivity in the carbamoylation step with the isocyanate is kinetically less controlled, compared to the reaction with the acyl fluoride. Upon workup, the diastereomeric ratio dropped to the finally observed 49:51.

[15] The (2*R*,3*R*) absolute configuration was assigned by comparison of specific rotation of hydroborylated byproduct **4a-O*t*Bu** with the reported value after the oxidative derivatization (see the Supporting Information for details).

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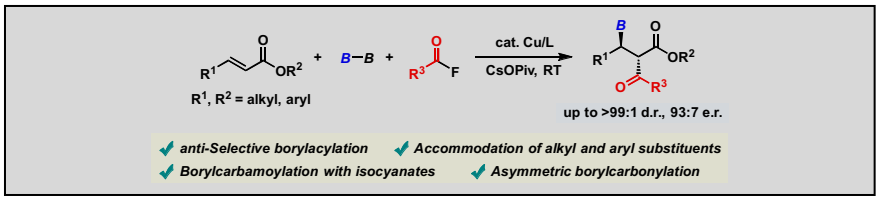
Entry for the Table of Contents



A copper-catalyzed borylacylation of *α,β*-unsaturated esters with B_2pin_2 and acyl fluorides has been developed to afford the *β'*-boryl-*β*-ketoesters with high *anti*-diastereoselectivity (up to >99:1). Additionally, the borylcarbamoylation can also be operated by using isocyanates as electrophiles to give the *β*-borylamide derivatives. Furthermore, an appropriate chiral phosphoramidite ligand makes the reaction enantioselective, delivering optically active *β*-borylated 1,3-dicarbonyl compounds.