Cu-Catalyzed Asymmetric Acylboration of 1,3-Butadienylboronate with Acyl Fluorides

Shang Gao[+], Jiaming Liu[+], Diego Troya, and Ming Chen*

In memory of Professor David A. Evans

Abstract: We report herein a Cu-catalyzed regio-, diastereo- and enantioselective acylboration of 1,3-butadienylboronate with acyl fluorides. Under the developed conditions, the reactions provide (*Z*)-β,γ-unsaturated ketones bearing an α-tertiary stereocenter with high *Z*-selectivity and excellent enantioselectivities. While direct access to highly enantioenriched *E*-isomers was not successful, we showed that such molecules can be synthesized with excellent *E*-selectivity and optical purities via Pd-catalyzed alkene isomerization from the corresponding *Z*-isomers. The orthogonal chemical reactivities of the functional groups embedded in the ketone products allow for diverse chemoselective transformations, which provides a valuable platform for further derivatization.

Introduction

Transition-metal-catalyzed asymmetric functionalization of carbon-carbon multiple bonds represents a valuable approach to generate molecular complexity from structurally simple π-bonds.[1] In this regard, enantioselective functionalization of conjugated dienes is particularly attractive, as these processes could form several chemical bonds with defined stereochemistry, and produce synthetically useful chiral, nonracemic molecules.[2] In the past a few decades, functionalization of feedstock chemicals such as 1,3-butadiene and isoprene has been the major focus of the chemical industries and chemistry communities.[3,4] More recently, significant efforts have been devoted to asymmetric functionalization of structurally more diverse 1,3-dienes.[2,5]

Transition metal complexes derived from precious metals, such as Ru, Rh, Pd, Ir and Pt, have been successfully utilized for asymmetric diene functionalizations.[5] Recent studies in this research area, however, have placed much more emphases on developing catalytic systems that are derived from earth-abundant metals.[6] Toward this end, Cu-catalyzed asymmetric functionalization of 1,3-dienes [7] is appealing because these catalysts are inexpensive and generally considered less toxic.[7a]

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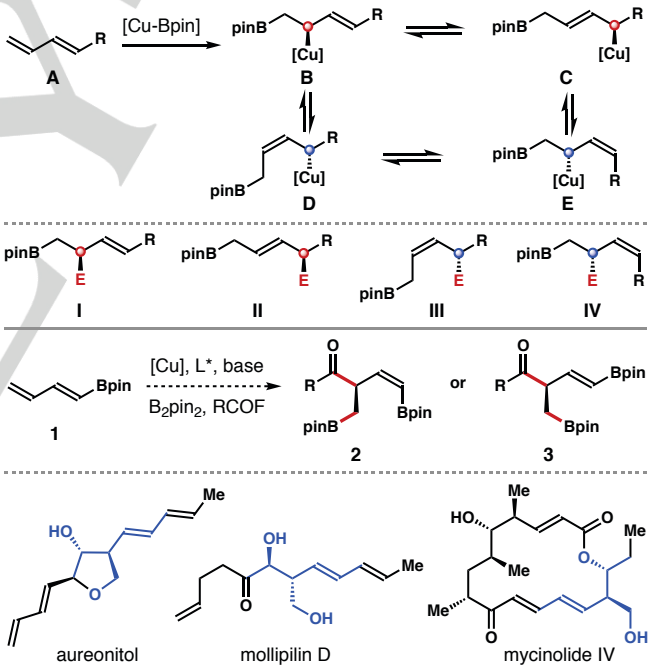
In particular, Cu-catalyzed borylative functionalization of 1,3-dienes has attracted significant attention.[8] A general scheme of such reactions is shown in Scheme 1. Starting from diene **A**, addition of [Cu-Bpin] complex to **A** forms allylic copper species **B**-**E**, which can be converted into each other through facile and reversible 1,3-metallo shifts. Allylic copper species **B**-**E** are nucleophilic, and can react with a variety of electrophiles to give products **I**-**IV**.[9] The boryl and alkene groups in the products can be utilized as handles for further manipulations. Moreover, these processes can be rendered in an enantioselective manner by employing an appropriate chiral nonracemic ligand on the copper precatalyst.[8] The resulting enantioenriched products **I**-**IV** are highly useful intermediates for chemical synthesis.



Scheme 1. Proposed asymmetric acylboration of dienylboronate **1**

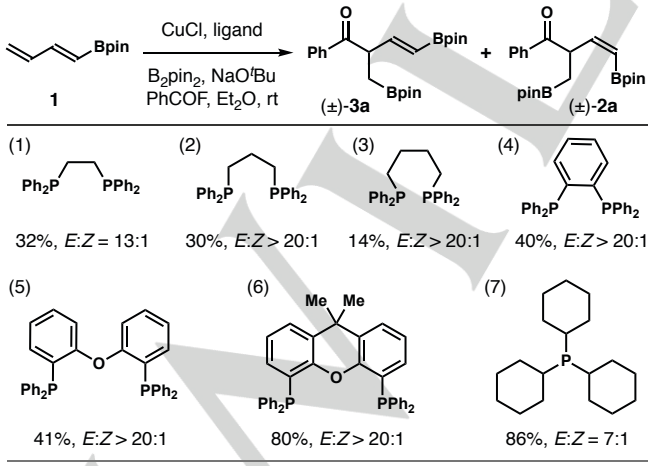
With our continuing interest in asymmetric synthesis with organoboron compounds,[10] we were keen to develop a regio-, diastereo- and enantioselective acylboration of 1,3-butadienyl boronate **1** with acyl fluorides as the electrophile.[11] Successful implementation of such a process would allow for the access to enantioenriched ketones **2** or **3** with defined alkene geometry. Ketones **2** or **3** are valuable as they can be further converted into important structural motifs in many biologically active natural products (via a carbonyl reduction and Bpin oxidation reaction sequence), such as aureonitol, mollipilin D and mycinolide IV (highlighted in blue in Scheme 1).[12] However, there are several

inherent challenges associated with this proposal, owing to the complexities of potential reaction pathways. First, allylic copper intermediates **B**-**E** are chiral nonracemic; their enantiopurities will dictate the optical purities of ketones **2** or **3**. Identifying a catalytic system (i.e., a chiral ligand on Cu) that permits highly enantioselective addition of [Cu-Bpin] to dienylboronate **1** is critically important, as this is the enantio-determining step. Second, all nucleophilic allylcopper species **B**-**E** can react with an electrophile (e.g., acyl fluorides). It is not apparent whether or not such an acylboration of diene **1** will be regioselective. Third, ketones **2** or **3** contain an alkenyl boronate unit. To be more synthetically useful, proper control of the alkene geometry in **2** or **3** is crucial. Lastly, there is an epimerizable tertiary stereogenic center at the α-position of the carbonyl group in ketones **2** or **3**. The typical basic conditions required for generating reactive [Cu-Bpin] species could erode the optical purities of products **2** or **3**. In addition, the basic reaction conditions could also promote the isomerization of β,γ-unsaturated ketones **2** or **3** to α,β-unsaturated ketones that are thermodynamically more stable. Despite these challenges, we developed suitable conditions and report herein the successful implementation of asymmetric acylboration of dienylboronate **1**. By using a proper catalyst-ligand combination, this process allows for the generation of enantioenriched ketones **2** with high *Z*-selectivities. Additionally, *E*-isomers **3** can also be obtained from ketones **2** with excellent enantioselectivities and *E*-selectivities. The orthogonal chemical reactivities of the functional groups embedded in products **2** and **3** allow for diverse chemoselective transformations, thereby providing a valuable platform for further derivatization.

Results and Discussion

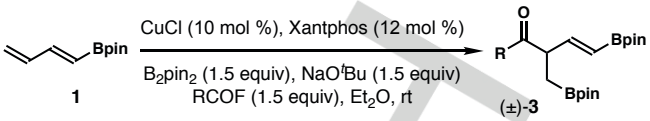
Reaction Development: We began our studies by identifying a proper catalytic system to couple diene **1** with acyl fluorides. As shown in Table 1, initial experiments were conducted with CuCl

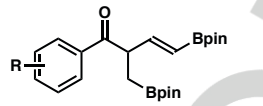
Table 1. Reaction conditions for racemic acylboration of diene **1** [a-c]



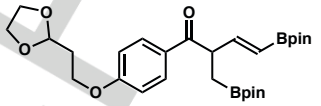
(a) Reaction conditions: dienylboronate **1** (0.1 mmol, 1.0 equiv), CuCl (10 mol %), ligand (12 mol %), B_2pin_2 (1.5 equiv), NaO^{t}Bu (1.5 equiv), PhCOF (1.5 equiv), Et_2O (1.5 mL), rt. (b) The *E*/*Z*-selectivities were determined by ^{1}H NMR analyses of the crude reaction mixture. (c) Yields of isolated product are listed.

Table 2. Scope of racemic acylboration of diene **1** [a-c]

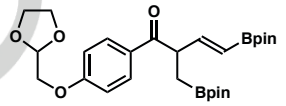




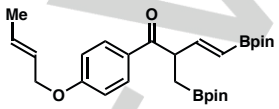
3a, 80%, *E*:*Z* > 20:1, R = H
3b, 82%, *E*:*Z* > 20:1, R = 4-Me
3c, 88%, *E*:*Z* > 20:1, R = 4-OEt
3d, 73%, *E*:*Z* > 20:1, R = 4-Br
3e, 67%, *E*:*Z* > 20:1, R = 4-CF_3
3f, 87%, *E*:*Z* > 20:1, R = 3-Cl
3g, 89%, *E*:*Z* > 20:1, R = 3-Me
3h, 65%, *E*:*Z* > 20:1, R = 2-Cl
3i, 73%, *E*:*Z* > 20:1, R = 2-Br
3j, 90%, *E*:*Z* > 20:1, R = 2-OEt



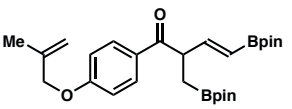
3k, 62%, *E*:*Z* > 20:1



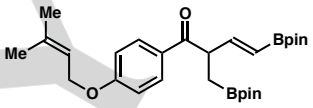
3l, 68%, *E*:*Z* > 20:1



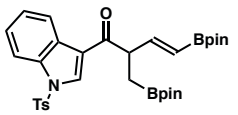
3m, 89%, *E*:*Z* > 20:1



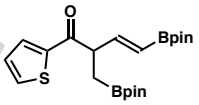
3n, 87%, *E*:*Z* > 20:1



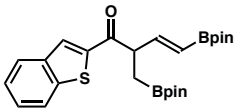
3o, 83%, *E*:*Z* > 20:1



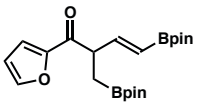
3p, 61%, *E*:*Z* > 20:1



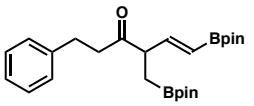
3q, 62%, *E*:*Z* > 20:1



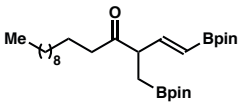
3r, 68%, *E*:*Z* > 20:1



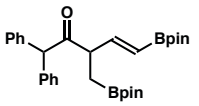
3s, 57%, *E*:*Z* > 20:1



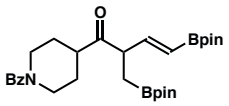
3t, 75%, *E*:*Z* > 20:1



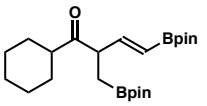
3u, 78%, *E*:*Z* > 20:1



3v, 56%, *E*:*Z* > 20:1



3w, 54%, *E*:*Z* > 20:1



3x, 74%, *E*:*Z* > 20:1

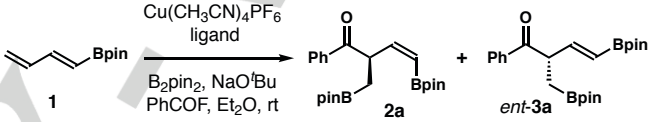
(a) Reaction conditions: diene **1** (0.1 mmol, 1.0 equiv), CuCl (10 mol %), Xantphos (12 mol %), B_2pin_2 (1.5 equiv), NaO^{t}Bu (1.5 equiv), RCOF (1.5 equiv), Et_2O (1.5 mL), rt. (b) The *E*/*Z*-selectivities were determined by ^{1}H NMR analyses of crude reaction products. (c) Yields of isolated products are listed.

as the catalyst and NaO^{t}Bu as the base. In the presence of 10 mol % of CuCl, 12 mol % of DPPE, 1.5 equiv of B_2pin_2, and 1.5 equiv of NaO^{t}Bu, the reaction of diene **1** with PhCOF occurred at ambient temperature in Et_2O to give a 13:1 mixture of racemic *E*-adduct **3a** and *Z*-adduct **2a** in a combined 32% yield (entry 1). The reaction with DPPP as the ligand under otherwise identical conditions gave product **3a** in 30% yield with >20:1 *E*-selectivity (entry 2). A similar *E*-selectivity was observed in the reaction with DPPB as the ligand, albeit in a low yield (14%, entry 3). The reaction with either DPPBZ or DPEPhos as the ligand gave *E*-isomer **3a** in a similar yield with excellent *E*-selectivity (~40%, >20:1, entries 4 and 5). The yield of **3a** was significant improved with Xantphos as the ligand, and **3a** was isolated in 80% yield with >20:1 *E*-selectivity (entry 6). High yield was observed in the reaction with Cy_3P as the ligand, although with a diminished 7:1 *E*-selectivity (entry 7). Other copper precatalysts, such as CuOAc, and $Cu(CH_3CN)_4PF_6$, also worked well to give ketone **3a** in comparable yields and *E*-selectivities with Xantphos as the ligand. The reactions in other ethereal solvents such as THF or dioxane gave product **3a** in much lower yields.

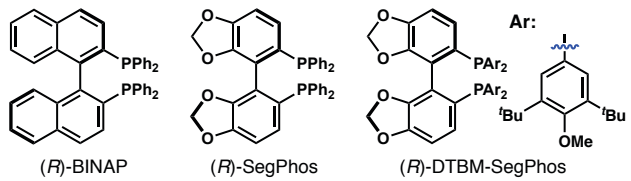
Substrate Scope: Table 2 summarizes the scope of acyl fluorides that participated in the racemic acylboration of diene **1** under the developed conditions. In general, the reaction worked well with a broad range of acyl fluorides, including aromatic, heteroaromatic, and aliphatic acyl fluorides. For instance, reactions of aromatic acyl fluorides with a substituent at the *para*-position gave ketones **3b**–**e** in 67–88% yields and excellent *E*-selectivities (>20:1). Reactions of aromatic acyl fluorides with a substituent at either the *meta*- or *ortho*-position proceeded smoothly to furnish products **3f**–**j** in 65–90% yields with >20:1 *E*-selectivities. Acyl fluorides containing a cyclic acetal group are suitable substrates for the reaction, and products **3k**–**l** were obtained in 62–68% yields with excellent *E*-selectivities. The reaction tolerates alkenes with different substitution patterns, affording ketones **3m**–**o** in 83–89% yields with >20:1 *E*-selectivities. Acyl fluorides containing a heterocycle such as indole, thiophene, benzothiophene, or furan reacted under the standard conditions to generate products **3p**–**s** in 57–68% yields with >20:1 *E*-selectivities. A variety of aliphatic acyl fluorides also participated in the reactions to deliver ketones **3t**–**x** in 54–78% yields with excellent *E*-selectivities.

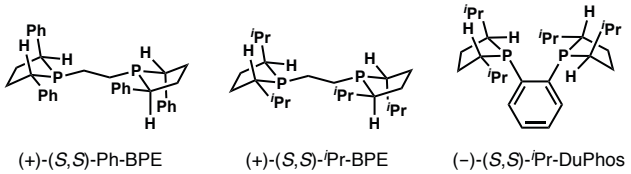
Development of Asymmetric Acylboration of 1,3-Diene 1: In order to obtain enantioenriched ketones **3**, we conducted the reaction of diene **1** in the presence of a chiral nonracemic ligand. As shown in Table 3, the reaction with $Cu(CH_3CN)_4PF_6$ (10 mol %) as the catalyst and (*R*)-BINAP (12 mol %) as the ligand formed a 1:3 mixture of ketones **2a** and *ent*-**3a** in a combined 32% yield, with *ent*-**3a** as the major product (entry 1). While the ee of *ent*-**3a** is moderate (55% ee), excellent optical purity of *Z*-isomer **2a** was observed (97% ee). Intriguingly, the formation of thermodynamically more stable α,β-unsaturated ketones was not detected. Similar results were obtained with (*R*)-SegPhos as the ligand (entry 2), affording a 1:4 mixture of **2a** (99% ee) and *ent*-**3a** (52% ee) in 68% yield. The reaction with (*R*)-DTBM-SegPhos as the ligand produced a 6:1 mixture of ketones **2a** and *ent*-**3a**, unexpectedly, with *Z*-isomer **2a** as the major product in 98% ee (entry 3). It is remarkable that the *E*/*Z*-selectivity was reversed even though both (*R*)-SegPhos and (*R*)-DTBM-SegPhos bear the same chiral backbone. The *Z*-selectivity was significantly upgraded when ligand (*S*,*S*)-Ph-BPE was employed, furnishing **2a** in 68% yield with >20:1 *Z*-selectivity and 96% ee (entry 4). The reaction with a structurally analogous ligand, (*S*,*S*)-^{i}Pr-BPE, gave a 1:3 mixture of **2a** and *ent*-**3a** in a combined 66% yield, with *Z*-isomer **2a** (77% ee) as the minor component of the mixture (entry 5). Further improvement was achieved when the reaction was conducted with (*S*,*S*)-^{i}Pr-DuPhos as the ligand, and *Z*-isomer **2a** was isolated in 70% yield with >99% ee (entry 6). The reaction with $Cu(OMe)_2$/(*S*,*S*)-^{i}Pr-DuPhos as the catalytic system formed **2a** in 85% yield with >99% ee (entry 7).

Table 3. Reaction optimizations for asymmetric acylboration of diene **1** [a]



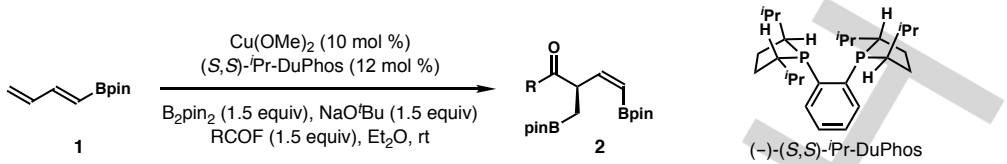
Entry	Ligand	**2a**:*ent*-**3a** [b]	yield (%) [c]	**2a** (% ee) [d]
1	(*R*)-BINAP	1:3	32	97
2	(*R*)-SegPhos	1:4	68	99
3	(*R*)-DTBM-SegPhos	6:1	46	98
4	(*S*,*S*)-Ph-BPE	>20:1	68	96
5	(*S*,*S*)-^{i}Pr-BPE	1:3	66	77
6	(*S*,*S*)-^{i}Pr-DuPhos	>20:1	70	>99
7 [e]	(*S*,*S*)-^{i}Pr-DuPhos	>20:1	85	>99
8 [f]	(*S*,*S*)-^{i}Pr-DuPhos	>20:1	82	>99

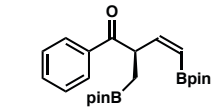




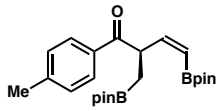
(a) Reaction conditions: diene **1** (0.1 mmol, 1.0 equiv), $Cu(CH_3CN)_4PF_6$ (10 mol %), ligand (12 mol %), B_2pin_2 (1.5 equiv), NaO^{t}Bu (1.5 equiv), PhCOF (1.5 equiv), Et_2O (1.5 mL), rt. (b) The *Z*/*E*-selectivities were determined by ^{1}H NMR analyses of crude reaction products. (c) Yields of isolated products are listed. (d) Enantiopurities of **2a** and *ent*-**3a** were determined by HPLC analysis. (e) 10 mol % of $Cu(OMe)_2$ was used. (f) The reaction was conducted with 5 mol % of $Cu(OMe)_2$ and 6 mol % of (*S*,*S*)-^{i}Pr-DuPhos.

Table 4. Scope of acyl fluorides for asymmetric acylboration of dienylboronate **1**[a-d]

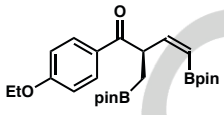




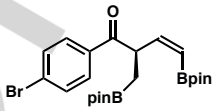
2a, 85%, *Z*:*E* > 20:1, >99% ee



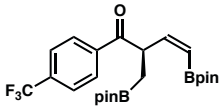
2b, 84%, *Z*:*E* > 20:1, >99% ee



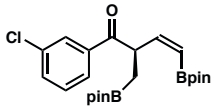
2c, 92%, *Z*:*E* > 20:1, >99% ee



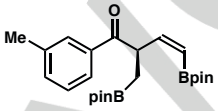
2d, 69%, *Z*:*E* = 8:1, 98% ee



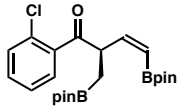
2e, 67%, *Z*:*E* = 6:1, 96% ee



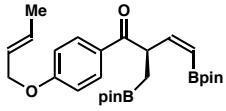
2f, 74%, *Z*:*E* = 7:1, 96% ee



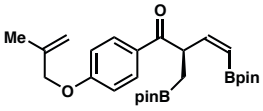
2g, 75%, *Z*:*E* = 18:1, >99% ee



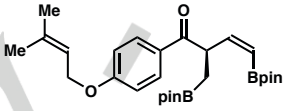
2h, 81%, *Z*:*E* > 20:1, >99% ee[e]



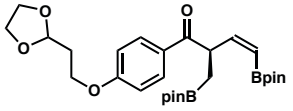
2i, 85%, *Z*:*E* > 20:1, >99% ee



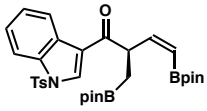
2j, 73%, *Z*:*E* > 20:1, >99% ee



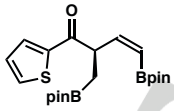
2k, 73%, *Z*:*E* > 20:1, >99% ee



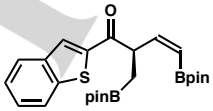
2l, 70%, *Z*:*E* > 20:1, >99% ee



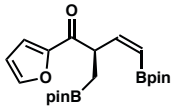
2m, 66%, *Z*:*E* > 20:1, >99% ee



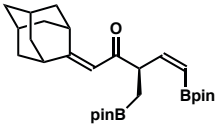
2n, 62%, *Z*:*E* = 14:1, >99% ee



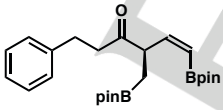
2o, 64%, *Z*:*E* = 6:1, 98% ee



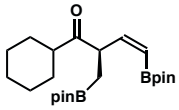
2p, 72%, *Z*:*E* = 6:1, >99% ee[e]



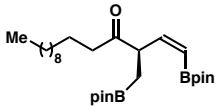
2q, 46%, *Z*:*E* > 20:1, 98% ee[e]



2r, 61%, *Z*:*E* > 20:1, >99% ee[e]



2s, 72%, *Z*:*E* > 20:1, >99% ee[e]



2t, 61%, *Z*:*E* > 20:1, >99% ee

(a) Reaction conditions: dienylboronate **1** (0.1 mmol, 1.0 equiv), $Cu(OMe)_2$ (10 mol %), (−)-(*S*,*S*)-^{i}Pr-DuPhos (12 mol %), B_2pin_2 (1.5 equiv), NaO^{t}Bu (1.5 equiv), RCOF (1.5 equiv), Et_2O (1.5 mL), rt. Reactions of several substrates with 5 mol % catalyst and 6 mol % ligand gave products **2** with similar levels of yields, *Z*-selectivities and enantioselectivities. (b) *Z*/*E*-selectivities were determined by ^{1}H NMR analyses of the crude reaction mixtures. (c) Yields of isolated *Z*-products are listed. (d) Enantiomeric excesses of **2** were determined by HPLC analysis using a chiral stationary phase. (e) CuOAc (10 mol %) was used as the catalyst.

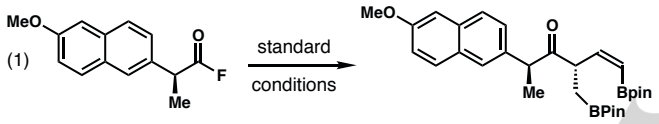
The loadings of $Cu(OMe)_2$ and (*S*,*S*)-^{i}Pr-DuPhos can be reduced to 5 mol % and 6 mol %, respectively, without compromising the yield, *E*/*Z*-selectivity, and enantioselectivity of **2a** (entry 8).

Scope of the *Z*-Selective Asymmetric Diene Acylboration: The scope of acyl fluorides that could undergo enantioselective acylboration of diene **1** was explored. As summarized in Table 4, in the presence of 10 mol % of $Cu(OMe)_2$, 12 mol % of (*S*,*S*)-^{i}Pr-DuPhos, 1.5 equiv of B_2pin_2, and 1.5 equiv of NaO^{t}Bu, the reaction worked well with a wide variety of acyl fluorides to give ketones **2** with excellent enantioselectivities and good to excellent *Z*-selectivity. For example, reactions with aromatic acyl fluorides bearing an electron-donating substituent at the *para*-position of the arene provided ketones **2b**–**c** in 84–92% yields with >20:1 *Z*-selectivity and >99% ee. Diminished *Z*-selectivity (6–8:1) was observed in reactions with aromatic acyl fluorides bearing an electron-withdrawing substituent at the *para*-position, such as Br or a CF_3 group. In these cases, ketones **2d**–**e** were isolated in 67–69% yields with 96–98% ee. The reaction of *meta*-chloro-benzoyl fluoride gave product **2f** in 74% yield with 7:1 *Z*-selectivity and 96% ee. The reaction of *meta*-methyl-benzoyl fluoride gave ketone **2g** in 75% yield and >99% ee, by contrast, with a much higher *Z*-selectivity (18:1). Substitution at the *ortho*-position of aromatic acyl fluoride did not seem to have any impact on the reaction, as ketone **2h** was obtained in 81% yields with >20:1 *Z*-selectivity and >99% ee. The reaction is compatible with alkenes with different substitution patterns, affording ketones **2i**–**k** in 73-85% yields with >99% ee and >20:1 *Z*-selectivity. An acyl fluoride appended with a cyclic acetal

reacted under the developed conditions to give ketone **2l** in 70% yield with excellent *Z*-selectivity and enantioselectivity. Acyl fluorides containing a heterocycle such as indole, thiophene, benzothiophene or furan are also suitable substrates for the reactions, and ketones **2m**–**p** were isolated in 62–72% yields. Although the *Z*-selectivity for ketones **2o** and **2p** is moderate compared to that of **2m** and **2n**, the optical purities of these four compounds are excellent (98-99% ee). The reaction with an α,β-unsaturated acyl fluoride afforded ketone **2q** in 46% yield with >20:1 *Z*-selectivity and 98% ee. Finally, the reactions occurred with several aliphatic acyl fluorides to deliver ketone products **2r**–**t** in 61–72% yields with >20:1 *Z*-selectivity and >99% ee. In addition, reactions of several substrates with 5 mol % catalyst and 6 mol % ligand gave products **2** with similar levels of yields, *Z*-selectivity and enantioselectivities.

The reaction can also be applied to enantioenriched acyl fluoride **4** derived from (*S*)-naproxen (eq. 1). Although **4** has an epimerizable α-stereocenter, the reaction with ligand (*R*,*R*)-^{i}Pr-DuPhos proceeded without any issue, affording ketone **5** in 75% yield with >20:1 *Z*-selectivity and diastereoselectivity.

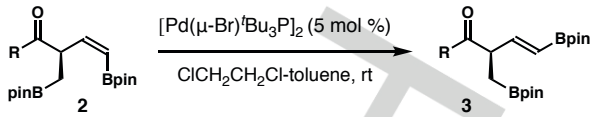
(1)

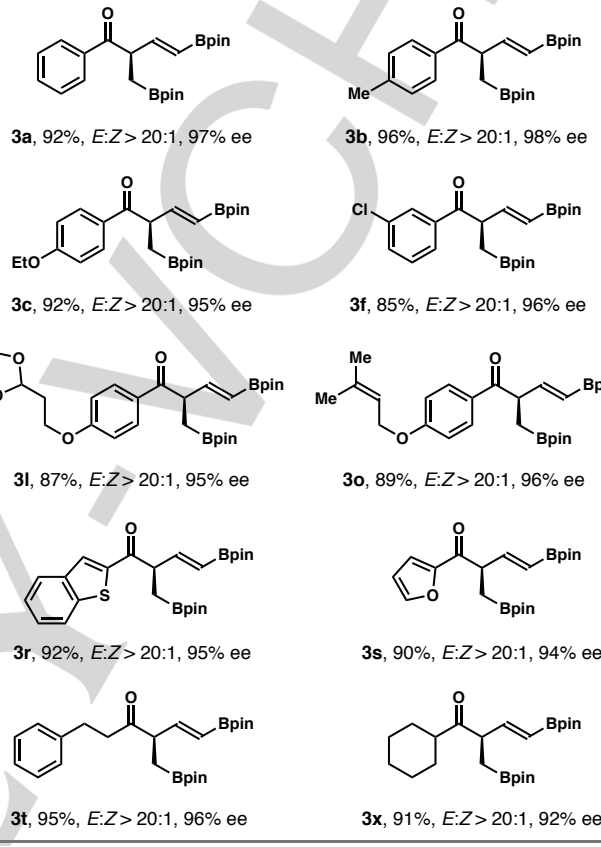


4 (98% ee) **5**, 75% yield, *Z*:*E* > 20:1, dr > 20:1

We attempted to synthesize enantioenriched ketones **3** (or *ent*-**3**) through further investigations of the reaction conditions. While we were able to achieve excellent *E*-selectivities (>20:1) through ligand modification, the enantioselectivities were not satisfactory (<60% ee, please see the SI for more details). On the other hand, ketones **2** we synthesized are uniformly highly enantioenriched. If the *Z*-alkene unit of **2** could be isomerized to the corresponding *E*-alkene by a transition metal complex, it would be a valuable approach to form highly enantioenriched ketones **3**. However, the success of this strategy hinges on: (1) the isomerization event will not epimerize the stereogenic center α to the carbonyl group of ketones **2**; (2) isomerization to α,β–unsaturated ketones cannot occur, as it will abolish the α-stereogenic center. After some investigations, Pd-complex, [Pd(*μ*-Br)^{t}Bu$_3$P]$_2$, [13] was identified as the optimal catalyst for the isomerization. In the event, ketone **2a** (99% ee) was treated with [Pd(*μ*-Br)^{t}Bu$_3$P]$_2$ in a mixed solvent system (DCE-toluene, v:v = 2:1) for 1 h at ambient temperature. Ketone **3a** was isolated in 92% yield and >20:1 *E*-selectivity, and remarkably, with 97% ee (Table 5). This protocol was then adopted for the isomerization of a variety of β,γ-unsaturated ketones **2**. As illustrated in Table 5, the reaction conditions are compatible with aryl chloride, cyclic acetal, alkene and heterocycles. And ketones **3** were obtained in 85–96% yields and >20:1 *E*-selectivities in all cases with minimum loss of enantiomeric purities (92–98% ee).

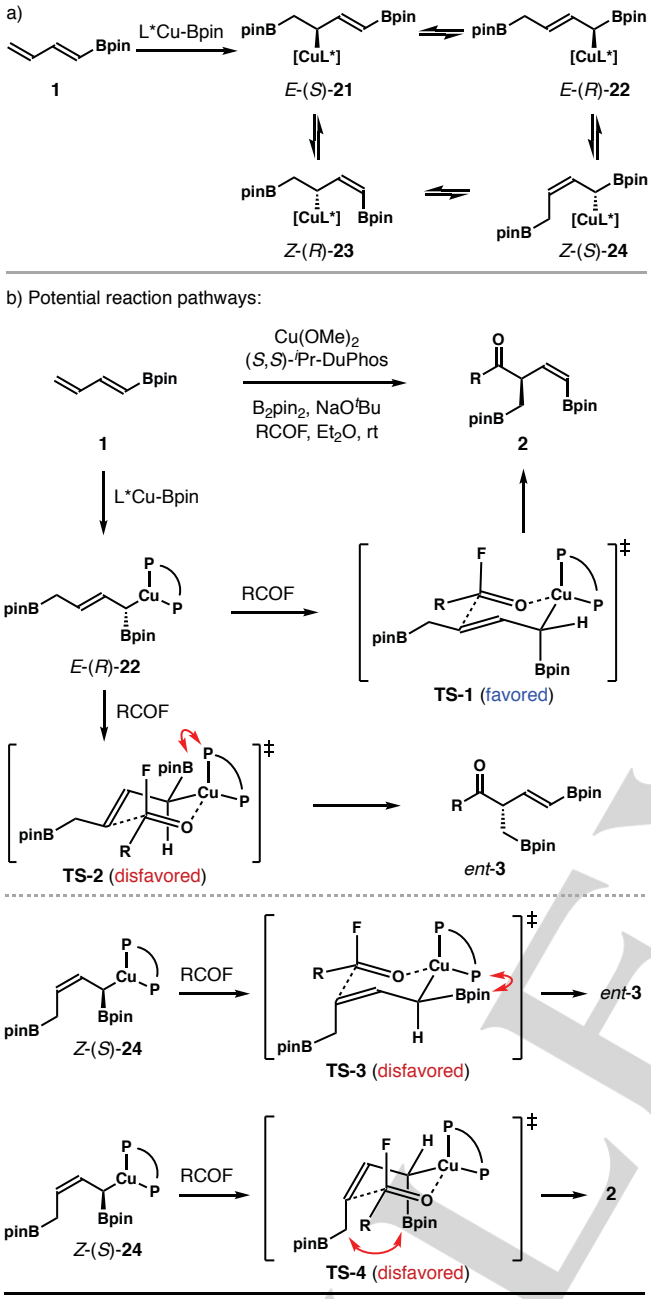
Table 5. Scope of alkene isomerization to *E*-isomers **3** [a-d]





(a) Reaction conditions: **2** (0.1 mmol, 1.0 equiv), [Pd] (5 mol %), $ClCH_2CH_2Cl$-toluene (1.5 mL, v:v = 2:1), rt. (b) The *E*/*Z*-selectivities were determined by ^{1}H NMR analyses of the crude reaction products. (c) Yields of isolated products are listed. (d) Ees of **3** were determined by HPLC analysis.

Mechanistic Analyses: It has been shown that the addition of a bidentate phosphine ligand-ligated Cu-Bpin complex, L*Cu-Bpin, to 1,3-dienes occurs in 1,2-addition manner.[7,8] Therefore, it was envisaged that the analogous reaction with 1,3-dienylboronate **1** should form initial adduct *E*-(*S*)-**21**, which then equilibrates with α-boryl allylcopper species *E*-(*R*)-**22** and the *Z*-isomers [*Z*-(*R*)-**23** and *Z*-(*S*)-**24**] through facile and reversible 1,3-metallo shifts as shown in Scheme 2a. (*E*)-γ-Borylmethyl allylboronate **25**, obtained from the protoboration of **1**, further corroborates the 1,2-addition pathway (Scheme 2c). [14] Reactions of allylcopper species with carbonyl compounds are known to proceed by way of a chair-like, Zimmerman-Traxler transition state. [9,15] The structural features of product **2** (bearing a vinyl boronate unit) indicate that the allylation event of acyl fluorides should occur with α-boryl allylcopper species *E*-(*R*)-**22** and/or *Z*-(*S*)-**24** as the reactive intermediate(s). The acyl fluoride addition with allylic copper intermediate *E*-(*S*)-**21** or *Z*-(*R*)-**23** did not occur. Such reactivity discrepancy is presumably due to the steric

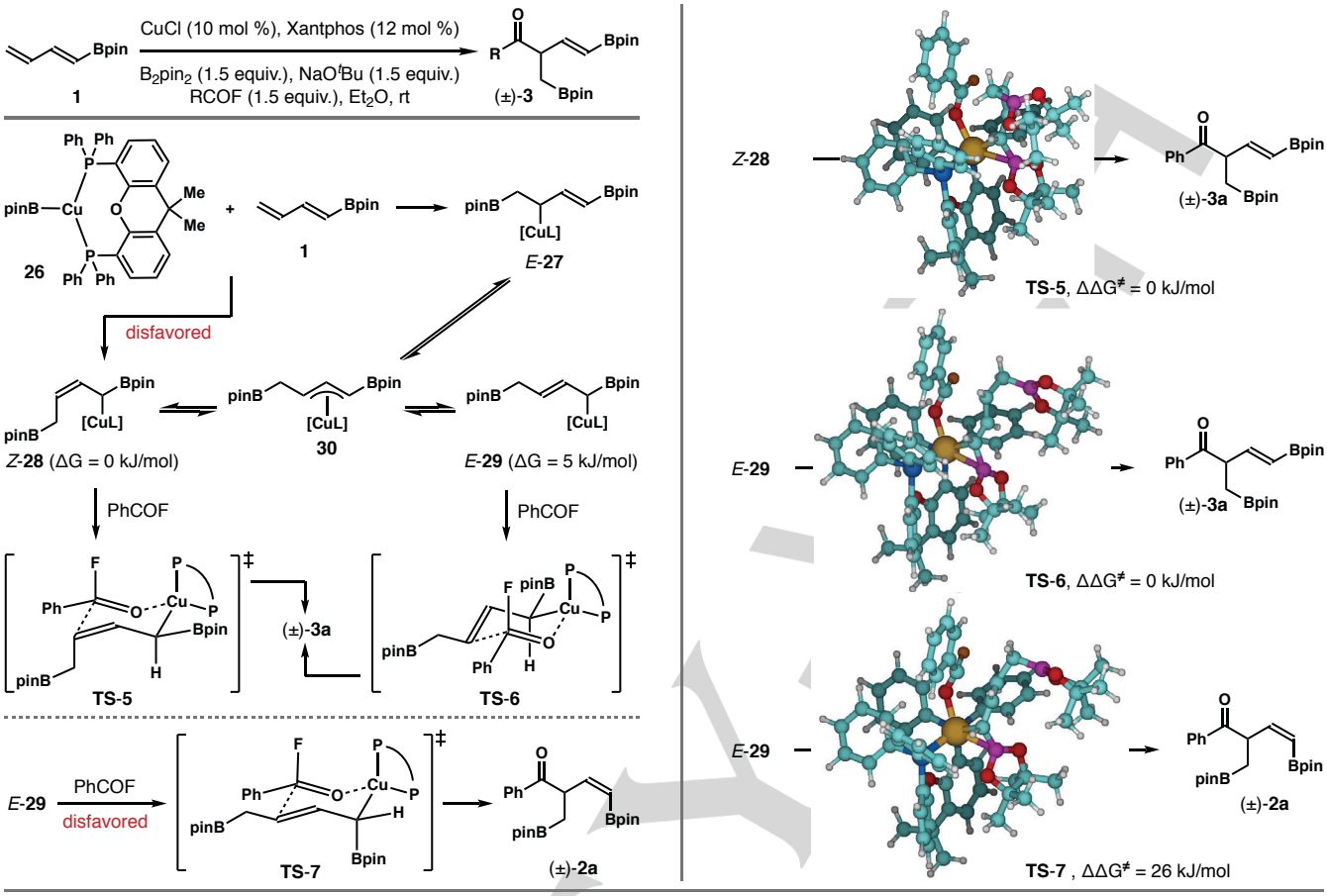


Scheme 2. Mechanistic analyses of the *Z*-selective reaction pathways

environment at the reactive site: a sterically more hindered Bpin group at the γ-positions of *E*-(*S*)-**21** and *Z*-(*R*)-**23** *vs*. a less bulky CH_2Bpin group at the γ-positions of *E*-(*R*)-**22** and *Z*-(*S*)-**24**. Moreover, the electronic stabilization [16] of the α-Bpin group in *E*-(*R*)-**22** and *Z*-(*S*)-**24** could also help to lower the energies of reaction transition states. This energetic benefit is absent in the transition state with allyl copper species *E*-(*S*)-**21** or *Z*-(*R*)-**23**.

As shown in Scheme 2b, the reaction of *E*-(*R*)-**22** with acyl fluorides via transition state **TS-1** generates product **2** bearing a *Z*-alkenyl boronate unit. In this transition state, the α-Bpin group of *E*-(*R*)-**22** occupies a pseudo axial orientation to minimize the steric repulsion with the (*S*,*S*)-^{i}Pr-DuPhos ligand on copper. By contrast, the reaction of *E*-(*R*)-**22** through competing transition state **TS-2** should form *E*-isomer *ent*-**3**. However, this transition state suffers from the non-bonding steric interactions between the pseudoequatorially positioned Bpin group and the phosphine ligand on Cu (shown with a red arrow in **TS-2**), and therefore it is disfavored. On the other hand, the addition of copper intermediate *Z*-(*S*)-**24** to acyl fluorides also forms *E*-product *ent*-**3**. The reaction occurs at the *re* face of acyl fluorides via transition state **TS-3** with the α-Bpin group oriented in a pseudoequatorial position. The *si* face addition with *Z*-(*S*)-**24** is highly disfavored owing to the $A^{1,3}$ allylic strains developed between the Bpin and CH_2Bpin groups, [17] as these two groups adopt the pseudo axial positions (**TS-4**). In comparison to **TS-1**, the *re* face addition with *Z*-(*S*)-**24** via **TS-3** is also disfavored due to the steric repulsion between the α-Bpin group and the ligand on Cu (shown with a red arrow in **TS-3**). Because the reactions of acyl fluorides with *in situ* generated allylcopper intermediate *E*-(*R*)-**22** proceed via chirality transfer, the 1,2-addition of L*Cu-Bpin to diene **1** is therefore the enantiodetermining step. The (*S*,*S*)-^{i}Pr-DuPhos ligand on copper allows for highly face selective 1,2-addition of L*Cu-Bpin to diene **1**. The initial adduct, *E*-(*S*)-**21**, is funneled to the more reactive α-boryl allylcopper intermediate, *E*-(*R*)-**22**, via reversible 1,3-metallo shifts. The acyl fluoride addition step operates under the Curtin-Hammett principle via the favored transition state **TS-1** to form β,γ-unsaturated ketones **2**.[18] The interactions between the phosphine ligand on copper and the α-Bpin group of *E*-(*R*)-**22** in the reaction transition states ultimately dictate the *Z*-alkene geometry of ketones **2**.

While the reaction with (*S*,*S*)-^{i}Pr-DuPhos as the ligand formed *Z*-isomers **2** as the products, it is quite intriguing that the same reaction gave *E*-isomers **3** when Xantphos was employed (Table 2). To gain insights into the origin of the *E*-selectivity, DFT calculations on the reaction process were conducted (B3LYP functional with the 6-31G* basis set). As shown in Scheme 3, the reaction of Xantphos-ligated copper complex **26** with diene **1** should occur in a 1,2-addition fashion to give racemic copper species *E*-**27**. The rate of competing 1,4-addition pathway that leads to *Z*-isomer *Z*-**28** is much lower, and it is disfavored. Meanwhile, Cu-complex *E*-**27** can equilibrate with $^3\eta$-allylcopper species **30**, which can further isomerize to



Scheme 3. Mechanistic analyses of the *E*-selective reaction pathways. Atom Color Code: Gold: Cu; Cyan: C; Red: O; Gray: H, Blue: P, Brown: F, Fuchsia: B.

copper complexes *Z*-**28** and/or *E*-**29** via reversible 1,3-metallo shifts. The DFT calculations indicate that copper species *Z*-**28** is about 5 kJ/mol thermodynamically more stable than *E*-**29**. The addition of *Z*-**28** to benzoyl fluoride proceeds through transition state **TS-5** to generate ketone (±)-**3a** with an *E*-alkene unit. Benzoyl fluoride addition with *E*-**29** occurs via transition state **TS-6** to form the same ketone product **3a**. Both transition states, **TS-5** and **TS-6**, place the α-Bpin group in a pseudoequatorial position, and have comparable activation energy. On the other hand, the reaction of *E*-**29** with benzoyl fluoride could occur via transition state **TS-7** that places the α-Bpin group of *E*-**29** in a pseudoaxial orientation. This pathway will form racemic ketone (±)-**2a** with a *Z*-alkene unit. However, transition state **TS-7** is about 26 kJ/mol higher in energy when compared to **TS-5** and **TS-6**. As a result, the formation of ketone (±)-**2a** is disfavored, and the data is fully consistent with experimental results (*E*:*Z* > 20:1). Computational studies also suggest that both *Z*-**28** and *E*-**29** are involved in the formation of *E*-product (±)-**3a**. Because Cu-complex *E*-**29** is about 5 kJ/mol higher in energy than *Z*-**28**, it is anticipated that, under thermodynamic equilibration conditions, the population of *Z*-**28** is about six times greater than *E*-**29** at 298 K. The DFT calculations showed that the energy barriers for the reactions of *Z*-**28** and *E*-**29** with PhCOF are similar to each other. Therefore, *Z*-**28** might contribute slightly more to ketone product (±)-**3a** than *E*-**29**.

Conclusion

In summary, we developed a Cu-catalyzed asymmetric acylboration of 1,3-butadienylboronate with acyl fluorides. Under the developed conditions, (*Z*)-β,γ-unsaturated ketones bearing an α-tertiary stereocenter were obtained with excellent optical purities and high *Z*-selectivities. Enantioenriched *E*-isomers can be prepared from the (*Z*)-β,γ-unsaturated ketones with excellent *E*-selectivities via Pd-catalyzed alkene isomerization. Therefore, both *Z*- and *E*-isomers can be obtained from dienylboronate **1**. The orthogonal reactivities of the functional groups embedded in the products allow for diverse chemoselective transformations, thereby providing a valuable platform for further derivatization.[19] Synthetic applications of this method are currently ongoing.

Acknowledgements

Financial supports provided by Auburn University, the National Institutes of Health (R35 GM147523-01), the National Science

Foundation (CAREER Award CHE-2042353) are acknowledged. Virginia Tech Advanced Research Computing is acknowledged for the computational resources used in this work.

Keywords: Unsaturated Ketones • Dienes • Acylboration • Acyl Fluorides • Asymmetric Catalysis

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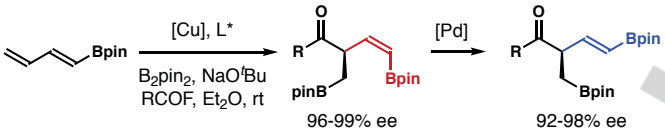
[19] Please see the Supporting Information for details.

RESEARCH ARTICLE

A Cu-catalyzed regio-, diastereo- and enantioselective acylboration of 1,3-butadienylboronate with acyl fluorides is reported. The reaction provided (*Z*)-β,γ-unsaturated ketones bearing an α-tertiary stereocenter with high *Z*-selectivity and excellent enantioselectivities. Highly enantioenriched (*E*)-β,γ-unsaturated ketones can also be synthesized with excellent *E*-selectivity via Pd-catalyzed alkene isomerization from the corresponding *Z*-isomers.



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Cu-Catalyzed Asymmetric Acylboration of 1,3-Butadienylboronate with Acyl Fluorides