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Stereoconvergent Synthesis of Chiral Allylboronates from an *E*/*Z* Mixture of Allylic Aryl Ethers Using a 6-NHC−Cu(I) Catalyst

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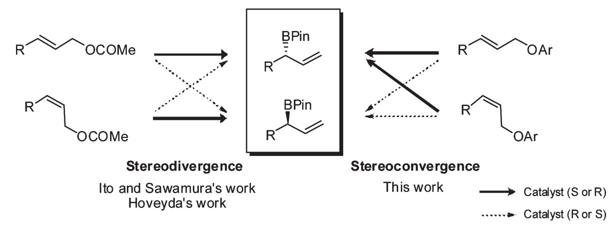
S *Supporting Information*

ABSTRACT: We present a 6-NHC−Cu(I) complex that provides α-substituted allylboronates using allylic aryl ether substrates. The method was discovered by comparison of the chemoselectivities exhibited by complexes **1a**, **1b**, **2**, and **3**. We observed that **1a** preferentially reacts with electron-rich alkenes over electron-deficient alkenes. Development of an asymmetric method revealed that **1b** reacts with both the *E* and *Z* isomers to provide the same absolute configuration without showing *E*−*Z* isomerization. This stereoconvergent reaction occurs with high yields (av 86%), high S_N2' selectivity (>99:1), and high ee (av 94%) and exhibits wide functional-group tolerance using pure *E* or *Z* isomer or *E*/*Z* alkene mixtures. The stereoconvergent feature enables the use of many different olefination strategies for substrate production, including cross-metathesis. Chiral allylboronates could be purified by silica gel chromatography and stored in the freezer without decomposition.

Synthetic methods that convert racemic starting materials into single enantiomers are valuable tools. These stereoconvergent methods can be achieved through a number of mechanisms, including dynamic kinetic resolution, dynamic kinetic transformation,[1] or direct enantioconvergent transformation.[2] Despite recent interest in stereoconvergent reactions, there are only a few methods that transform both *E* and *Z* alkenes into a single enantiomer.[3] Among these, we found only one example involving direct enantioconvergence, and it exhibits low enantioselectivity.[3a] In most asymmetric reactions involving alkenes, *E* and *Z* alkenes provide stereodivergent products, that is, products with different absolute configurations.[4,5]

Chiral allylboronates are very versatile reagents that can provide allylic alcohols, amines, or C−C bonds via direct reaction of the C−B bond or homoallylic alcohols or amines through addition to carbonyls (e.g., Brown or Roush allylation).[6] Approaches to the synthesis of chiral allylboronates include (1) stoichiometric reactions using chiral auxiliaries,[7] (2) asymmetric catalysis such as [4 + 2] reactions,[8a] (3) 1,4-silaboration,[8b] (4) diboration,[8c] and (5) alkylation.[8d,8e] Recently, chiral allylboronates have been synthesized using a Cu(I)-catalyzed asymmetric allylic substitution reaction.[2a,5b,5c] In a series of reports, the Ito and Sawamura group demonstrated first a nonasymmetric version of this reaction[5a] and then an asymmetric version using a chiral diphosphine ligand (QuinoxP).[5b] While excellent enantioselectivity was observed using pure cis substrates, the trans substrates showed poor enantioselectivity. More recently, the Ito and Sawamura group reported enantioconvergent allylic substitutions using racemic *cyclic* allylic alkyl ethers with excellent selectivity.[2a] The Hoveyda group has expanded the substrate scope of these allylic substitutions from disubstituted to trisubstituted alkenes using chiral five-membered N-heterocyclic carbene (5-NHC)−Cu(I) complexes with excellent enantioselectivity. For disubstituted substrates, they have shown that both (*E*)- and (*Z*)-alkenes afford high enantioselectivity.[5c] Both Ito/Sawamura's and Hoveyda's reactions exhibit stereodivergence with respect to *acyclic E* and *Z* substrates.[5b,5c]



Herein we present a stereoconvergent asymmetric synthesis of chiral allylboronates. The transformation proceeds using bis(pinacolato)diboron (B_2Pin_2) and allylic aryl ethers and is catalyzed by six-membered N-heterocyclic carbene (6-NHC)−Cu(I) complexes **1a** and **1b** (see Table 3 for the structure of **1b**). Aryl ether substrates provide higher reaction rates and offer another variable for maximizing the enantioselectivity, namely, changing of substituents on the phenyl ring, in comparison with allylic carbonates. The use of allylic aryl ethers in substitution reactions is uncommon.[9] The method requires a low loading of B_2Pin_2 (1.1 equiv) and catalyst (1 mol %) and provides high yields using benchtop techniques.

We recently reported an efficient asymmetric *β*-borylation reaction using chiral 6-NHC−Cu(I) complex **1a**.[10] While establishing that **1a** catalyzes *β*-borylations with high selectivity and excellent activity, we also found that **1a** provides unique chemoselectivity relative to catalysts **2** and **3**, which are known to perform *β*-borylations[4g,11] or allylic substitution reactions.[5] As shown in Table 1, we observed that **4** was converted into **5a** by **1a**, in contrast to the results using **2** (which yields **5b** exclusively) and **3**−Cu(I) (which yields both products in low yield).[12]

Intrigued by the chemoselectivity preference of **1a**, we compared allylic substitution on a simpler disubstituted alkene using catalysts **1a**, **2**, and **3** (Table 2). Only catalyst **1a** provided the branched allylic substitutions in high yield. Catalyst **2** gave a low yield of only the branched product (entry 2), and **3** gave a low yield with a detectable amount of linear product. Excited by the observed reactivity

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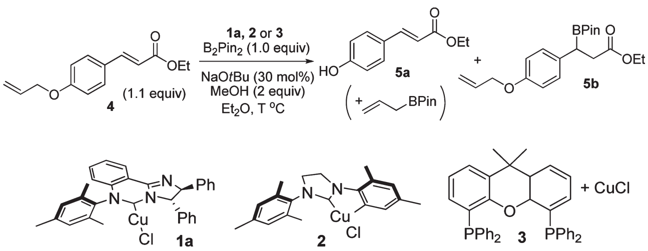
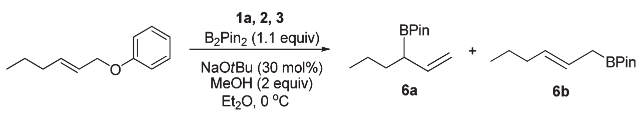
Table 1. Chemoselectivity Comparison Results



entry	catalyst	temp	time	5a/5b ratio[a]	yield (%)[b]
1	**1a**	−20 °C	10 min	25/1	88 (**5a**) (70)
2	**2**	−20 °C	20 min	1/24	88 (**5b**) (71)
3[c]	**3**	rt	6 h	1/1.5	65 (**5a** + **5b**) (16[d])

[a] Ratios were determined by ^{1}H NMR spectroscopy. [b] Yields were determined by ^{1}H NMR spectroscopy; isolated yields are shown in parentheses. [c] The reaction was run in THF (see the Supporting Information). [d] Isolated yield of **5a**.

Table 2. Catalyst Comparison for Allylic Substitution Reactions



entry	catalyst (mol %)	time	6a/6b[a]	yield (%)[b]
1	**1a** (1)	20 min	>99/1	91 (47[c])
2	**2** (1)	3 h	>99/1	17
3[d]	**3** (3)	22 h	14/1	11

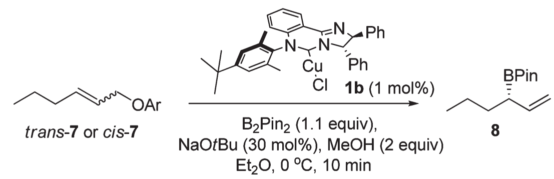
[a] Ratios were determined by GC analysis (see the Supporting Information for more details). [b] Yields were determined by GC using an internal standard. [c] Product ee. [d] The reaction was carried out in THF at rt.

differences, we compared aryl ethers to carbonates using **1a** and found that allyl carbonates required much longer reaction times under the same conditions (3 h vs 20 min).

While the 6-NHC−Cu(I) complex **1a** appeared to be optimal for the formation of the branched product, its enantioselectivity was modest (47% ee; Table 2, entry 1). On the basis of molecular models, we hypothesized that installation of a bulky substituent (*tert*-butyl) at the para position of the *N*-aryl group would enhance the energy difference between the favored and unfavored transition states (see eq 2 below). We were gratified to discover that **1b** provided much higher enantioselectivity (84% ee; Table 3, entry 1).

We then screened aryl leaving groups by changing the steric and electronic properties with the goal of optimizing the enantioselectivity. We found that *m*-dimethyl (entry 3) and *m*- or *p*-nitro groups (entries 5 and 7) on the aryl leaving group are optimal. In the course of this optimization study, we were surprised to observe entries 5 and 6. We had expected to find that cis and trans substrates would yield products with opposite configurations but instead observed that the (*Z*)-allylic substrate provided the same configuration as the

Table 3. Optimization of the Leaving Group for Allylic Substitutions



entry	substrate (Ar)	yield (%)[a]	ee (%)[b]
1	*trans*-**7a** (phenyl)	91	84 (*S*)
2	*trans*-**7b** (2-methylphenyl)	91	80 (*S*)
3	*trans*-**7c** (3,5-dimethyphenyl)	86	88 (*S*)
4	*trans*-**7d** (3,5-bis(trifluoromethyl)phenyl)	95	65 (*S*)
5	***trans*-7e (3-nitrophenyl)**	**79**	**89 (*S*)**
6	***cis*-7e (3-nitrophenyl)**	**47**	**91 (*S*)**
7	*trans*-**7f** (4-nitrophenyl)	94	87 (*S*)
8	*trans*-**7g** (3-methyl-4-nitrophenyl)	74	84 (*S*)
9	*trans*-**7h** (4-methoxyphenyl)	92	62 (*S*)

[a] Determined by GC using an internal standard. [b] Determined by GC analysis after oxidation and acetylation.

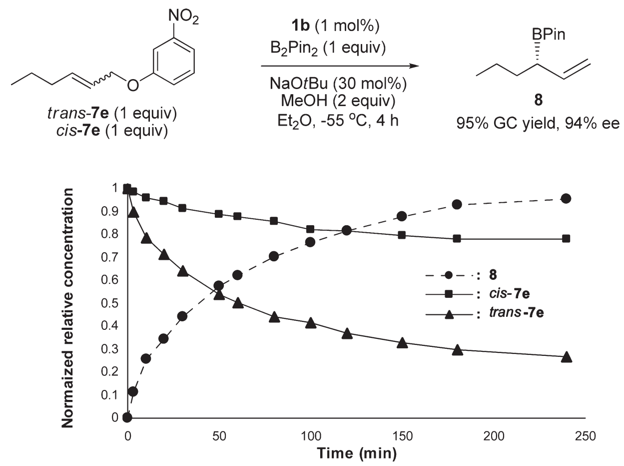
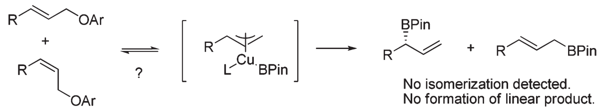


Figure 1. Reaction profiles for the trans and cis substrates.

(*E*)-allylic substrate with 91% ee (entry 6); this was our first evidence of stereoconvergence. This finding is in contrast to the Ito/Sawamura and Hoveyda allylic substitution methods, which provide stereo*divergent* outcomes.[5,13]

We suspected this result might arise from *E*−*Z* isomerization[14] through a π-allyl−copper complex (eq 1):



(1)

However, no isomerization was detected by ^{1}H NMR analysis during the course of the reaction using the pure cis isomer as the substrate. In addition, though the π-allyl−copper complex should provide some linear product, none was observed by NMR or GC analysis. However, we also recognized that this observation cannot

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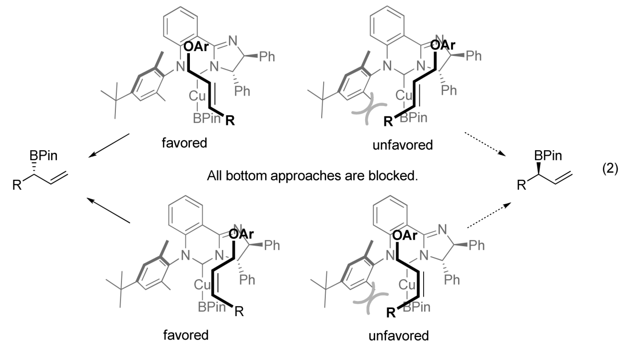
rule out the hypothesis of irreversible formation of a π-allyl−copper complex.

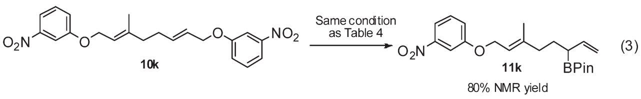
After monitoring the reaction by GC and ^{1}H NMR spectroscopy using a 1:1 E/Z mixture of alkenes, we observed that the reaction of the trans isomer is faster than that of the cis isomer [the mixture provides a 94% ee outcome, which is between 93 and 96% (Figure 1; also see Table 4, entry 1)]. On the basis of this result, we speculate that the (E)-alkene has a lower-barrier transition state than the (Z)-alkene and that the catalyst reacts with the same face of the (E)- and (Z)-alkenes as shown in eq 2.



There are many olefination methods for the synthesis of disubstituted alkenes that provide excellent E/Z selectivity.[15] However, access to allylic substrates (i.e., allylic ethers and allylic carbonates) using these methods often requires multiple steps. On the other hand, methods providing direct access, such as cross-metathesis, suffer from poor E/Z selectivity and require difficult separations.[16] The stereoconvergent nature of the reactivity of complex **1b** enables the formation of allylic substrates from many entry points, including cross-metathesis (Scheme 1).

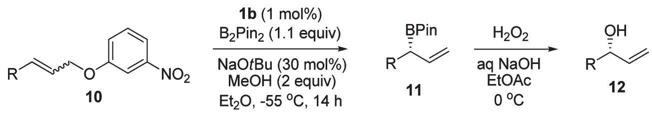
The data in Table 4 underscore the flexibility of our method, as we used E/Z mixtures for many of the entries. The synthesis of the substrates for entries 3−9 was accomplished via cross-metathesis. Pure *trans*- and *cis*-3-nitrophenyl ether starting materials (entries 1 and 2) were prepared using nucleophilic aromatic substitutions,[17] and the substrate for entry 9 was prepared using CuI and phenanthroline.[18] The Williamson ether synthesis was used for entry 10.

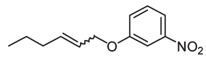
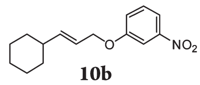
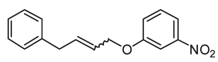
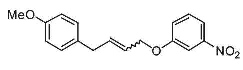
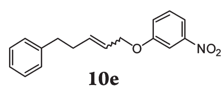
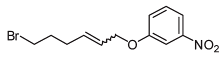
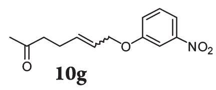
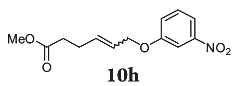
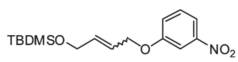
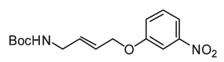
As shown in Table 4, E/Z mixtures of various allylic aryl ethers were successfully reacted with 1 mol % **1b** to give products in high ee and yield. Pure *cis*-**10a** gave a higher ee than the trans isomer (entry 1). A pure trans substrate with a bulky group in the α-position gave >99% ee (entry 2). E/Z mixtures of substrates featuring aryl, bromide, ketone and ester substituents were well-tolerated (entries 3−8). TBDMS-protected alcohols and Boc-protected amines were also excellent substrates, providing highly functionalized chiral allylboronates (entries 9 and 10). As a comparison of steric accessibility, **10k** was tested, and only the disubstituted alkene reacted (eq 3).



In summary, both complexes **1a** and **1b** exhibit unique chemoselectivity relative to the 5-NHC−Cu(I) complex **2** and the complex of diphosphine **3** with Cu(I). Complex **1b** catalyzes allylic substitutions with diboron using aryl ether substrates and shows high ee and yield. This catalyst also exhibits a preference for the same face of both (E)- and (Z)-alkenes, providing stereoconvergent outcomes. Studies to better understand the

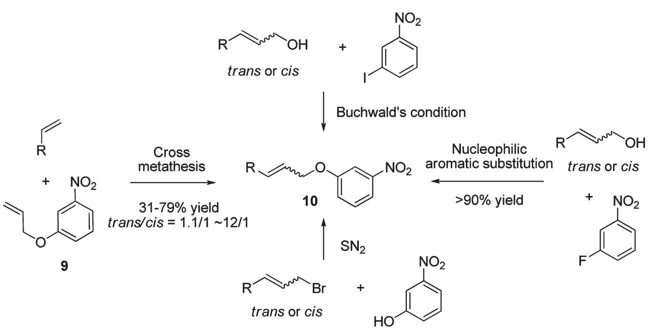
Table 4. Substrate Scope for Allylic Substitutions



Entry	Substrate	**10** (*trans*/*cis*)	Yield of **11** (%)[a]	Ee (%)[b]
1	 **10a**	>30/1	90	93 (S)
		<1/30	80	96 (S)
2	 **10b**	26/1	84[d]	>99 (R)
3	 **10c**	4.7/1[c]	95	93 (S)
4	 **10d**	5.5/1[c]	87	92
5	 **10e**	6.6/1[c]	95	93 (S)
6	 **10f**	3.3/1[c]	92	93
7	 **10g**	3.2/1[c]	50	94
8	 **10h**	1.1/1[c]	>95	94
9	 **10i**	12/1[c]	83	93 (S)
		<1/30	91	93 (S)
10	 **10j**	>30/1	92[d]	90

[a] Isolated yields. [b] Determined by GC analysis after transformation to an alcohol or acetate. [c] Synthesized by cross-metathesis. [d] Isolated yield of **12**.

Scheme 1. Substrate Synthesis



stereoconvergence and exploit its unique properties and reaction mechanism are currently in progress.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental procedures and spectroscopic data for the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Phenol seems to decompose the active catalyst. More information is shown in the Supporting Information.

(13) We observed stereoconvergence using allylic carbonate substrates with modest ee. For the reaction profile, see the Supporting Information.

(14) For examples of *E*−*Z* isomerization in stereoconvergent reactions, see ref 3b−3d.

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