Note

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Chiral Bicyclic NHC/Cu Complexes for Catalytic Asymmetric Borylation of α,β-Unsaturated Esters

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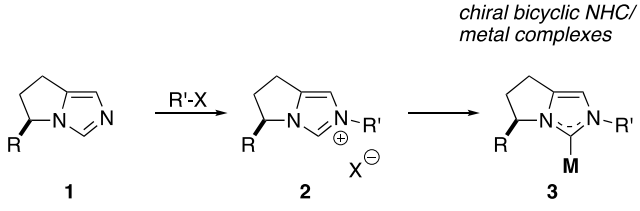
ABSTRACT: The potential of using chiral bicyclic NHC ligands that exhibit modularity was investigated in the Cu-catalyzed asymmetric borylation reaction of α,β-unsaturated esters. After screening for ligands and optimization of the reaction conditions, the corresponding products were afforded with good enantioselectivities (up to 85% ee).

A quarter of a century has passed since immense attention has been devoted to N-heterocyclic carbenes (NHCs) as strong σ-donor ligands for transition metal catalysis.[1] NHC ligands have often been compared with phosphine ligands, and catalytic reactions in which the former show better performance than the latter have become commonplace. However, when the range of ligands is narrowed to asymmetric ones,[2] there are no chiral NHCs that show superior performance comparable to privileged phosphine ligands,[3] such as BINAP and Josiphos. Therefore, efforts to develop chiral NHC ligands from various perspectives are still required in this field.

In recent years, our group has conducted research and development of optically active bicyclic NHC ligands that have a rigid and effective chiral environment (Scheme 1).[4] An important feature of our previous study is the modularity of the ligand, which is realized by combining various chiral imidazoles **1** and electrophiles (R'–X). By utilizing this feature effectively, we developed an excellent catalyst precursor for the Ir-catalyzed asymmetric transfer hydrogenation of ketones (ee values of up to 98% and turnover numbers of up to 4,500).[4b] Currently known as the catalyst precursor containing a monodentate chiral NHC ligand, it shows the highest performance for this transformation.[5]

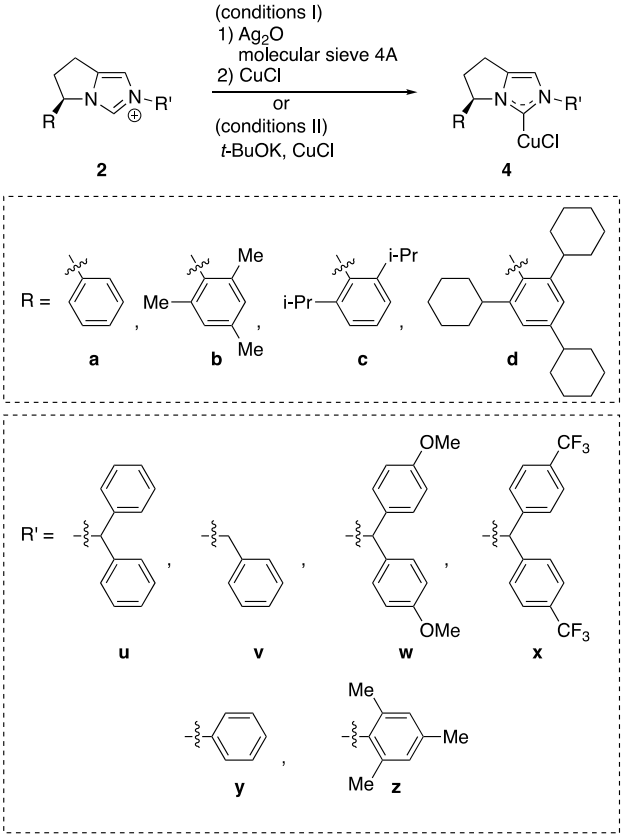
Scheme 1. Conversion of Chiral Bicyclic Imidazoles **1** into Chiral Bicyclic NHC/Metal Complexes **3**.



In this study, we applied the same system using our ligands to the Cu-catalyzed asymmetric borylation reaction of α,β-unsaturated esters, in which NHCs are known to act as monodentate chiral ligands effectively.[6,7] Herein we describe the details of the results.

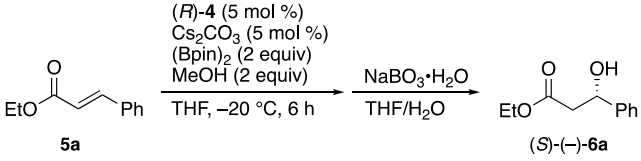
Two synthetic procedures were employed for the preparation of desired NHC/Cu complexes **4** (Scheme 2). One is the carbene transfer approach from NHC/Ag complexes that are generated by the *in situ* deprotonation of imidazolium salts **2** using Ag_2O (conditions I),[8,9] and the other is a more straightforward approach in which imidazolium salts **2** are mixed with CuCl and *t*-BuOK in THF (conditions II).[10] Although our ligands are characterized by having variations at substituents R (at the chiral center) and R' (on the nitrogen atom), the preparation of **4** with a diarylmethyl or benzyl group (**u–x**) as the R' substituent must be performed under conditions I. On the other hand, because the preparation of **4** with an aryl group (**y** and **z**) as the R' substituent is acceptable under either conditions, we preferentially employed the simpler conditions II.

Scheme 2. Synthesis and Structures of Chiral Bicyclic NHC/Cu Complexes **4**.



With Cu complexes **4** in hand, catalyst screening for the asymmetric borylation reaction of α,β-unsaturated esters was performed (Table 1), where ethyl cinnamate (**5a**) as the model substrate was reacted with $(Bpin)_2$ (2 equiv) in the presence of Cu catalyst (5 mol %), Cs_2CO_3 (5 mol %), and methanol (2 equiv) in THF at –20 °C for 6 h.[11] Unexpectedly, under those conditions, the desired transformation proceeded with even NHC-free CuCl as the catalyst to give racemic alcohol **6a** after routine oxidative workup with $NaBO_3 \cdot 4H_2O$ (entry 1). In regard to NHC/Cu complexes **4**, first, by fixing a diphenylmethyl group (**u**) as the R' substituent, the influence of the steric hindrance of the R substituent (**a**–**d**) was examined (entries 2–5). As a result, complexes **4bu** having a mesityl group (**b**) and **4cu** having a 2,6-diisopropylphenyl group (**c**) showed preferable enantioselectivities (entries 3 and 4). Then, we investigated the influence of the R' substituent on the nitrogen atom of NHC, where the R substituent was fixed to the 2,6-diisopropylphenyl group (**c**) (entries 4 and 6–10). The results demonstrated that aryl groups (**y** and **z**) made positive contributions to the enantioselectivity. Complexes **4cy** having a phenyl group (**y**) and **4cz** having a mesityl group (**z**) showed 60% ee or higher selectivity (entries 9 and 10). Finally, we tested combinations of a mesityl group (**b**) as the R substituent and an aryl group (**y** or **z**) as the R' substituent (entries 11 and 12), and found that **4by** was the best catalyst for this screening, giving a product with 69% ee (entry 11).

Table 1. Catalyst Screening for Cu-catalyzed Enantioselective β-Borylation of α,β-Unsaturated Ester.[a]

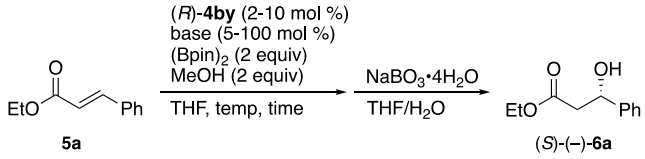


entry	catalyst	yield[b] (%)	ee[c] (%)
1	CuCl	23	-
2	(*R*)-**4au**	47	36
3	(*R*)-**4bu**	72	41
4	(*R*)-**4cu**	67	44
5	(*R*)-**4du**	62	30
6	(*R*)-**4cv**	70	51
7	(*R*)-**4cw**	23	34
8	(*R*)-**4cx**	62	48
9	(*R*)-**4cy**	51	62
10	(*R*)-**4cz**	28	60
11	(*R*)-**4by**	77	69
12	(*R*)-**4bz**	34	47

[a] The reaction was carried out with ethyl cinnamate (**5a**) and $(Bpin)_2$ (2 equiv) in the presence of (*R*)-**4** (5 mol %), Cs_2CO_3 (5 mol %), and methanol (2 equiv) in THF at –20 °C for 6 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H).

Using Cu complex **4by**, optimization of the reaction conditions was carried out (Table 2). In order to facilitate comparison of results, the best conditions in Table 1 (entry 11) are shown again in Table 2 (entry 1). Initial efforts focused on screening of solvents (entries 2-4). However, THF was found to be the best after all in terms of both yield and enantioselectivity (entries 1 vs 2-4). When the temperature was decreased from –20 °C to –40 °C, little improvement of the enantioselectivity was observed (entry 1 vs. 5). When the temperature was decreased further to –80 °C, not only isolated yield but also selectivity deteriorated (entry 6). Then, we fixed the temperature at –40 °C and examined the choice of base (entries 2, 7-10). We found that replacing Cs_2CO_3 with *t*-BuONa or *t*-BuOK improved the enantioselectivity (entries 9 and 10). In regard to the reaction time, prolongation of the time increased the yield slightly but decreased enantioselectivity (entries 10–13). Therefore, considering the balance of yield and selectivity, we chose 3 h as the reaction time. Then, we examined the catalyst loading. Whereas decreasing it from 5 mol % to 2 mol % led to a negative outcome in terms of both yield and enantioselectivity (entry 11 vs. entry 14), the enantioselectivity remained unchanged when the catalyst loading was increased to 10 mol % (entry 11 vs. entry 15). From these results, we decided that 5 mol % is appropriate. Finally, the effect of additive was investigated (entries 16 and 17). As the use of 1 equiv of *t*-BuOK with molecular sieve gave a meaningful outcome in the isolated yield, this was determined as the optimum condition (entry 17).

Table 2. Optimization of Reaction Conditions with (*R*)-**4by**.[a]

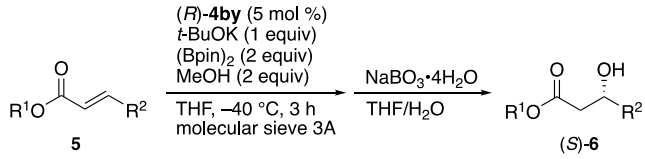


entry	catalyst loading (mol %)	solvent	base (mol %)	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	5	THF	Cs_2CO_3 (5)	–20	6	77	69
2	5	Et_2O	Cs_2CO_3 (5)	–20	6	76	58
3	5	toluene	Cs_2CO_3 (5)	–20	6	65	63
4	5	CH_3CN	Cs_2CO_3 (5)	–20	6	56	43
5	5	THF	Cs_2CO_3 (5)	–40	6	65	71
6	5	THF	Cs_2CO_3 (5)	–80	6	42	66
7	5	THF	K_2CO_3 (5)	–40	6	71	63
8	5	THF	EtONa (5)	–40	6	81	71
9	5	THF	*t*-BuONa (5)	–40	6	54	77
10	5	THF	*t*-BuOK (5)	–40	6	61	77
11	5	THF	*t*-BuOK (5)	–40	3	57	78
12	5	THF	*t*-BuOK (5)	–40	1	48	78
13	5	THF	*t*-BuOK (5)	–40	15	66	73
14	2	THF	*t*-BuOK (5)	–40	3	44	69
15	10	THF	*t*-BuOK (5)	–40	3	68	78
16	5	THF	*t*-BuOK (100)	–40	3	70	78
17[d]	5	THF	*t*-BuOK (100)	–40	3	75	79

[a] The reaction was carried out with ethyl cinnamate (**5a**) and $(Bpin)_2$ (2 equiv) in the presence of (*R*)-**4by** (2–10 mol %), base (5–100 mol %), and methanol (2 equiv) in THF. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H) . [d] Molecular sieve 3A was added.

Then, adopting the above conditions, the Cu-catalyzed asymmetric β-borylation reaction of several α,β-unsaturated esters was accomplished (Table 3). The data in entry 1 are identical to those in entry 17 in Table 2, in which ethyl cinnamate (**5a**) was employed as the substrate. It has become apparent that the size of the ester moiety of the substrate affects the enantioselectivity. When bulkier isopropyl cinnamate **5b** was used, decreased enantioselectivity was observed (entry 2). In contrast, when less bulky methyl cinnamate **5c** was used, a product with increased enantioselectivity was obtained (entry 3). Then, we standardized the ester group to a methyl group and investigated the effect of R^2 group (entries 4–11). When a methyl group was introduced to the aryl group at *para*- or *meta*-position, the results were comparable to that of unsubstituted substrate **5c** (entry 3 vs. entries 4 and 5). However, use of sterically demanding *ortho*-substituted derivative **5f** resulted in decreased enantioselectivity (entry 6). The employment of other substituents and substitution patterns at the *para*- and *meta*-positions of the aryl group did not cause serious problems (entries 7–11). The best enantioselectivity (85% ee) was observed for **5j** and **5k** having a trifluoromethyl group and a chloro group at the *para*-position, respectively (entries 10 and 11). An attempt to expand the substrate scope to *β*-alkyl-substituted unsaturated ester did not succeed. When we conducted the reaction of **5l**, a product with decreased enantioselectivity was obtained (entry 12).

Table 3. Enantioselective β-Borylation of α,β-Unsaturated Ester with (*R*)-**4by**.[a]



entry	R^1	R^2	product	yield[b] (%)	ee[c] (%)
1	Et	Ph	(*S*)-**6a**	75	79
2	i-Pr	Ph	(*S*)-**6b**	83	73
3	Me	Ph	(*S*)-**6c**	69	81
4	Me	4-$CH_3C_6H_4$	(*S*)-**6d**	88	81
5	Me	3-$CH_3C_6H_4$	(–)-**6e**	87	84
6	Me	2-$CH_3C_6H_4$	(–)-**6f**	76	75
7	Me	3-ClC_6H_4	(*S*)-**6g**	89	84
8	Me	3,5-$(CH_3)_2C_6H_3$	(–)-**6h**	89	83
9	Me	2-Naphthyl	(*S*)-**6i**	79	83
10	Me	4-$CF_3C_6H_4$	(*S*)-**6j**	46	85
11	Me	4-ClC_6H_4	(*S*)-**6k**	89	85
12	Me	i-Pr	(*S*)-**6l**	73	68 [d]

[a] The reaction was carried out with α,β-unsaturated ester **5** and $(Bpin)_2$ (2 equiv) in the presence of (*R*)-**4by** (5 mol %), *t*-BuOK (1 equiv), molecular sieve 3A, and methanol (2 equiv) in THF at –40 °C for 3 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, Chiralpak AD-H, or Chiralpak AS-H). [d] Determined by HPLC analysis after conversion into the corresponding benzoate using a chiral stationary phase column (Chiralpak AD-H).

Proposed models rationalizing the enantioselectivities of the asymmetric reaction with (*R*)-**4by** is shown in Figure 1, where disfavored and favored approaches of methyl cinnamate (**5c**) to an NHC/Cu intermediate are shown. To avoid a steric interaction between the phenyl ring on the nitrogen atom of NHC and the carbomethoxy group of **5c**, it is likely that the substrate favorably coordinates to the Cu intermediate with its *Si*-face. There may also be π-π stacking, stabilizing interaction between the phenyl ring on the nitrogen atom of NHC and the phenyl ring of **5c** to contribute the favored approach.

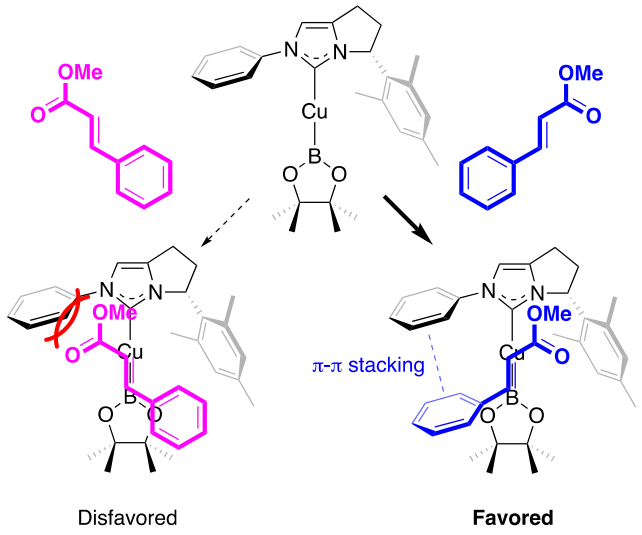


Figure 1. Models Rationalizing the Enantioselectivity of β-Borylation of Methyl Cinnamate (**5c**) with (*R*)-**4by**.

In conclusion, we have applied optically active bicyclic NHC ligands to the Cu-catalyzed asymmetric borylation reaction of α,β-unsaturated esters. After screening for the ligands and optimization of the reaction conditions, corresponding nonracemic compounds were obtained with good enantioselectivity (up to 85% ee). Further modifications of the ligands and studies of their application to other asymmetric reactions are in progress in our laboratory.

EXPERIMENTAL SECTION

General. All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or glove box techniques under prepurified argon. NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for $^{13}C\{^1H\}$. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^1H NMR and chloroform-*d* (δ 77.0) for $^{13}C\{^1H\}$ NMR. High-resolution mass spectra were recorded on Orbitrap mass spectrometers.

Materials. 1,2-Dichloroethane and CH_2Cl_2 were distilled from CaH_2 under nitrogen and stored in a glass flask with a Teflon stopcock under nitrogen. THF was distilled from sodium benzophenone-ketyl under argon prior to use. MeOH was distilled from magnesium under nitrogen and stored in a glass flask with a Teflon stopcock under nitrogen. Imidazoles **1** were prepared according to the reported procedures[4] or by slightly modified proce-

dures (*vide infra*). 1-Mesityl-3-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol,[4b] 2-alkyl-imidazolium salts **2** (**u**-**x**),[4] and alkyl cinnamates **5**[12] were prepared according to the reported procedures. Diaryliodonium tetrafluoroborates were prepared from the corresponding aryl iodides and aryl boronic acids according to the reported procedures.[13] *p*-Toluenesulfonyl chloride, trimethylamine hydrochloride, triethylamine, anhydrous DMF, Ag_2O, $Cu(OAc)_2 \cdot H_2O$, CuCl, Cs_2CO_3, *t*-BuOK, *t*-BuONa, $(Bpin)_2$, and $NaBO_3 \cdot 4H_2O$ were used as received. Molecular sieve 3A and 4A were predried in a microwave oven before use.

*Procedures for the Preparation of (R)-5-Mesityl-6,7-dihydro-5H-pyrrolo[1,2-c] imidazole ((R)-**1b**) (modified procedures).*[4] A mixture of 1-mesityl-3-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (1.58 g, 3.25 mmol), *p*-toluenesulfonyl chloride (926 mg, 4.86 mmol, 1.5 equiv), trimethylamine hydrochloride (30.9 mg, 0.32 mmol), triethylamine (900 μL, 6.49 mmol, 2.0 equiv) in CH_2Cl_2 (32 mL) was stirred at room temperature for 1 h. Then, the mixture was quenched by addition of sat. $NaHCO_3$ aq. The crude product was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Then the crude product was dissolved in 48.6 mL of CH_3CN and stirred at 75 °C in an oil bath. After 20 h, the mixture was cooled to room temperature, added 48.6 mL of MeOH, and stirred at 75 °C for 10 h. After concentration, the residue was partitioned between Et_2O and H_2O. The organic layer was extracted with 1N HCl twice. The combined aqueous extracts were adjusted to pH = 8 by addition of NaOH solution and extracted with CH_2Cl_2 three times. The organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by short silica gel column chromatography (first CH_2Cl_2 only, then MeOH) to give (*rac*)-**1b** (674 mg, 2.98 mmol, 92% yield). The enantiomerically pure (*R*)- and (*S*)-**1b** were obtained by separation using preparative HPLC.[4b]

*Procedures for the Preparation of 2-Aryl-imidazolium Salts **2***

General Procedure A: A mixture of imidazole **1**, diaryliodonium tetrafluoroborate (1.5 equiv), and $Cu(OAc)_2 \cdot H_2O$ (7.25 mol%) in DMF was heated to 100 ºC in an oil bath and stirred for 4 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and purified by silica gel column chromatography to give the desired imidazolium salt **2**.

*(R)-2-Phenyl-5-mesityl-6,7-dihydro-5H-pyrrolo[1,2-c] imidazol-2-ium tetrafluoroborate ((R)-**2by**)*. Following the General Procedure A: (*R*)-**1b** (100.0 mg, 0.442 mmol), diphenyliodonium tetrafluoroborate (243.8 mg, 0.663 mmol), $Cu(OAc)_2 \cdot H_2O$ (6.4 mg, 0.032 mmol), and DMF (4.1 mL) were used; purified by silica gel column chromatography (CH_2Cl_2/hexane/MeOH = 5/5/1) to give the title compound (151.2 mg, 0.387 mmol, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.82 (s, 3H), 2.26 (s, 3H), 2.54 (s, 3H), 2.74 (dq, *J* = 13.6, 9.6 Hz, 1H), 3.10 (dtd, *J* = 14.0, 8.8, 2.8 Hz, 1H), 3.24-3.39 (m, 2H), 6.41 (t, *J* = 9.2 Hz, 1H), 6.82 (s, 1H), 6.95 (s, 1H), 7.33 (d, *J* = 1.2 Hz, 1H), 7.49-7.59 (m, 5H), 8.21 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 19.2, 20.3, 20.7, 22.8, 34.1, 60.5, 114.2, 122.5, 128.2, 129.0, 130.0, 130.1, 130.3, 131.6, 135.1, 135.2, 138.2, 138.9, 140.2. HRMS (ESI) calcd for $C_{21}H_{23}N_2$ (M–BF_4^-) 303.1861, found 303.1857. $[\alpha]^{24.6}_D$ = +84.8 (*c* = 1.00, $CHCl_3$).

*Procedures for the Preparation of NHC/Cu Complexes **4***

General Produce B-1 (conditions I): A mixture of **2**, Ag_2O (2.5 equiv), and molecular sieves 4A in 1,2-dichloroethane was heated to 80 °C in an oil bath and stirred overnight in dark. After cooling to room temperature, the resulting suspension was filtered through Celite to remove insoluble silver salts. Then the filtrate was concentrated under reduced pressure, dissolved in CH_2Cl_2 under nitrogen, and added a solution of CuCl (1.2 equiv) in CH_2Cl_2. The mixture was stirred for 1 h at room temperature, then filtered through Celite, and purified by reprecipitation to give **4**.

General Produce B-2 (conditions II): To a mixture of CuCl (1.0 equiv), *t*-BuOK (1.2 equiv), and molecular sieve 4A in THF was added a solution of **2** in THF. The resulting mixture was stirred for 4 h at room temperature. Then, the mixture was concentrated under reduced pressure and purified by reprecipitation to give **4**.

*((R)-5-Mesityl-2-phenyl-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-2-ylidene) copper chloride ((R)-**4by**)*; Following the General Procedure B-2 (conditions II): (*R*)-**2by** (117.6 mg, 0.301 mmol), CuCl (29.8 mg), *t*-BuOK (40 mg), molecular sieves 4A (90.3 mg), and THF (3 and 9 mL) were used; purified by reprecipitation (CH_2Cl_2/hexane) to give (*R*)-**4by** (71.6 mg, 0.178 mmol, 59% yield) (Although reprecipitation was repeated multiple times, it was difficult to obtain as a completely pure product suitable for elemental analysis.); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.79 (s, 3H), 2.27 (s, 3H), 2.52 (s, 3H), 2.72 (dq, *J* = 13.2, 8.8 Hz, 1H), 3.00 (dtd, *J* = 13.6, 8.8, 2.8 Hz, 1H), 3.05-3.22 (m, 2H), 5.87 (t, *J* = 8.8 Hz, 1H), 6.82 (s, 1H), 6.97 (s, 1H), 7.00 (t, *J* = 0.8 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ = 19.5, 20.8, 21.1, 22.2, 33.5, 58.7, 112.5, 123.2, 128.1, 129.5, 129.8, 131.2, 131.8, 135.6, 137.0, 137.6, 138.3, 140.3, 169.4. HRMS (DART) calcd for $C_{42}H_{44}CuN_4$ (M–Cl^-+**4by**) 667.2857, found 667.2849. Elemental analysis of the impure product indicated that the main complex is probably CuCl((*R*)-**4by**) and not $[Cu((R)\text{-}\mathbf{4by})_2]Cl$. Anal. Calcd for $C_{21}H_{22}ClCuN_2$ (CuCl((*R*)-**4by**)) C, 62.84; H, 5.72; N, 6.98, for $C_{42}H_{44}ClCuN_4$ ($[Cu((R)\text{-}\mathbf{4by})_2]Cl$) C, 71.67; H, 6.30; N, 7.96, found C, 60.43; H, 5.24, N, 6.27. $[\alpha]^{25.4}_D$ = +216.3 (*c* = 0.10, $CHCl_3$).

Procedures for the Asymmetric Borylation of α,β-Unsaturated Esters

General Procedure C: (*R*)-**4by** (5 mol %, 0.017 mmol), $(Bpin)_2$ (2.0 equiv, 0.704 mmol), *t*-BuOK (1.0 equiv, 0.352 mmol), and molecular sieve 3A (300 mg/mmol) were weighed into a flask. To this was added THF (1.76 mL). Then the mixture was stirred at room temperature for 10 min. After cooling to −40 °C, alkyl cinnamate **5** (0.352 mmol) and MeOH (2.0 equiv, 0.704 mmol) were added to the mixture. The resulting mixture was stirred at −40 °C for 3 h and quenched with $NaBO_3 \cdot 4H_2O$ (1.94 mmol) and water (1.76 mL). After stirring for 1.5 h at room temperature, the crude product was extracted with EtOAc, dried over Na_2SO_4, concentrated under reduced pressure, and purified by silica gel column chromatography (EtOAc/hexane = 2/1) to give **6**. The enantiomeric excess of the product was determined by HPLC analysis with chiral stationary phase column (Daicel Chiralcel OD-H, Chiralpak AS-H, or Chiralpak AD-H).

*(S)-Ethyl-3-hydroxy-3-phenylpropanate ((S)-(−)-**6a**)*; Following the General Procedure C; 75% yield (37.8 mg, 0.195 mmol); This product was characterized by comparison of the spectroscopic data with those reported previously;[14a] Daicel Chiralcel OD-H, hexane/i-PrOH = 90/10, flow rate 0.5 mL/min, t_S = 13.5 min (major), t_R = 16.4 min (minor), 79% ee. $[\alpha]^{25.0}_D$ = −39.6 (*c* = 1.00, $CHCl_3$).

*(S)-Isopropyl-3-hydoxy-3-phenylpropanoate ((S)-(−)-**6b**)*; Following the General Procedure C; 83% yield (56.5 mg, 0.271 mmol); This product was characterized by comparison of the spectroscopic data with those reported previously;[14a] Daicel Chiralpak AD-H, hexane/i-PrOH = 98/2, flow rate 0.5 ml/min, t_R = 53.9 min (minor), t_S = 56.9 min (major), 73% ee. $[\alpha]^{25.4}_D$ = −32.1 (*c* = 1.00, $CHCl_3$).

*(S)-Methyl-3-hydroxy-3-phenylpropanoate ((S)-(−)-**6c**)*; Following the General Procedure C; 69% yield (18.4 mg, 0.102 mmol); This product was characterized by comparison of the spectroscopic data with those reported previously[14b]; Daicel Chiralcel OD-H, hexane/i-PrOH = 90/10, flow rate 0.5 mL/min, t_S = 18.3 min (major), t_R = 28.4 min (minor), 81% ee. $[\alpha]^{25.2}_D$ = −32.1 (*c* = 1.00, $CHCl_3$).

*(S)-Methyl 3-hydroxy-3-(p-tolyl)propanoate ((S)-(−)-**6d**)*; Following the General Procedure C; 88% yield (85.1 mg, 0.438 mmol). This product was characterized by comparison of the spectroscopic data with those reported previously[14b]; Daicel Chiralpak AD-H, hexane/i-PrOH = 98/2, flow rate 0.8 mL/min, t_R = 47.0 min (minor), t_S = 48.9 min (major), 81% ee. $[\alpha]^{25.4}_D$ = −31.6 (*c* = 1.00, $CHCl_3$).

*(−)-Methyl 3-hydroxy-3-(m-tolyl)propanoate ((−)-**6e**)*; Following the General Procedure C; 87% yield (58.2 mg, 0.300 mmol). ^{1}H

NMR (400 MHz, $CHCl_3$) δ = 2.35 (s, 3H), 2.17-2.76 (m, 2H), 3.17 (s, 1H), 3.73 (s, 3H), 5.10 (dt, *J*= 9.2, 4.0 Hz, 1H) 7.09-7.26 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 21.4, 43.1, 51.9, 70.3, 122.7, 126.3, 128.4, 128.5, 138.2, 142.4, 172.8. Daicel Chiralcel OD-H, hexane/i-PrOH = 90/10, flow rate 0.5 ml/min, *t* = 15.4 min (major), *t* = 19.6 min (minor), 84% ee. $[\alpha]^{25.7}_D$ = −17.7 (*c* = 1.00, $CHCl_3$). HRMS (ESI) calcd for $C_{11}H_{14}O_3Na$ (M+Na^+) 217.0841, found 217.0831.

*(−)-Methyl 3-hydroxy-3-(o-tolyl)propanoate ((−)-**6f**)*; Following the General Procedure C; 76% yield (52.3 mg, 0.269 mmol).^1H NMR (400 MHz, $CHCl_3$); δ = 2.34 (s, 3H), 2.67-2.70 (m, 2H), 3.12 (s, 1H), 3.74 (s, 3H), 5.35 (dt, *J* = 9.2, 3.2 Hz, 1H), 7.13-7.25 (m, 3H), 7.50 (d, *J* = 7.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 18.9, 41.9, 51.9, 66.9, 125.1, 126.4, 127.6, 130.4, 134.2, 140.4, 172.9. Daicel Chiralcel OD-H, hexane/i-PrOH = 90/10, flow rate 0.5 ml/min, *t* = 17.0 min (major), *t* = 26.3 min (minor), 75% ee. $[\alpha]^{25.6}_D$ = −31.2 (*c* = 1.00, $CHCl_3$). HRMS (ESI) calcd for $C_{11}H_{14}O_3Na$ (M+Na^+) 217.0841, found 217.0831.

*(S)-Methyl 3-(3-chlorophenyl)-3-hydroxypropanoate ((S)-(−)-**6g**)*; Following the General Procedure C; 89% yield (33.9 mg, 0.147 mmol). This product was characterized by comparison of the spectroscopic data with those reported previously[14b]; Daicel Chiralpak AD-H, hexane/i-PrOH = 90/10, flow rate 0.5 mL/min, t_R = 17.6 min (minor), t_S = 19.7 min (major), 84% ee. $[\alpha]^{25.5}_D$ = −19.0 (*c* = 1.00, $CHCl_3$).

*(−)-Methyl 3-(3,5-dimethylphenyl)-3-hydroxypropanoate ((−)-**6h**)*; Following the General Procedure C; 89% yield (30.7 mg, 0.147 mmol). ^1H NMR (400 MHz, $CHCl_3$); δ = 2.31 (s, 6H), 2.70-2.73 (m, 2H), 3.12 (d, *J* = 3.6 Hz, 1H), 3.73 (s, 3H), 5.07 (dt, *J* = 9.6, 3.6 Hz, 1H), 6.92 (s, 1H), 6.98 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ = 21.3, 43.1, 51.8, 70.3, 123.4, 129.4, 138.1, 142.4, 172.9. Daicel Chiralpak AS-H, hexane/i-PrOH = 90/10, flow rate 0.5 mL/min, *t* = 13.8 min (minor), *t* = 15.7 min (major), 83% ee. $[\alpha]^{24.9}_D$ = −42.7 (*c* = 1.00, $CHCl_3$). HRMS (ESI) calcd for $C_{12}H_{16}O_3Na$ (M+Na^+) 231.0997, found 231.0986.

*(S)-Methyl 3-hydroxy-3-(naphthalen-2-yl)propanoate ((S)-(−)-**6i**)*; Following the General Procedure C; 79% yield (41.8 mg, 0.182 mmol). This product was characterized by comparison of the spectroscopic data with those reported previously[14c]; Daicel Chiralpak AD-H, hexane/i-PrOH = 90/10, flow rate 0.5 mL/min, t_R = 34.8 min (minor), t_S = 37.4 min (major), 83% ee. $[\alpha]^{25.6}_D$ = −32.7 (*c* = 1.00, $CHCl_3$).

*(S)-Methyl 3-hydroxy-3-(4-trifluoromethylphenyl)propanoate ((S)-(−)-**6j**)*; Following the General Procedure C; 46% yield (19.6 mg, 0.078 mmol). This product was characterized by comparison of the spectroscopic data with those reported previously[14c]; Daicel Chiralpak AD-H, hexane/i-PrOH = 90/10, flow rate 0.5 ml/min, t_S = 19.7 min (major), t_R = 21.0 min (minor), 85% ee. $[\alpha]^{25.4}_D$ = −6.8 (*c* = 1.00, $CHCl_3$).

*(S)-Methyl 3-(4-chlorophenyl)-3-hydroxypropanoate ((S)-(−)-**6k**)*; Following the General Procedure C; 89% yield (35.1 mg, 0.163 mmol). This product was characterized by comparison of the spectroscopic data with those reported previously[14b]; Daicel Chiralpak AS-H, hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, t_R = 17.9 min (minor), t_S = 19.8 min (major), 85% ee. $[\alpha]^{25.0}_D$ = −18.5 (*c* = 0.40, $CHCl_3$).

*(S)-Methyl 3-hydroxy-4-methylpentanoate ((S)-(−)-**6l**)*; Following the General Procedure C; 73% yield (49.1 mg, 0.335 mmol). This product was characterized by comparison of the spectroscopic data with those reported previously[14b]; Enantiomeric excess was determined by HPLC analysis after conversion into the corresponding benzoate[6i] using a chiral stationary phase column Daicel Chiralpak AD-H, hexane/i-PrOH = 95/5, flow rate 0.8 mL/min, t_R = 8.84 min (minor), t_S = 10.4 min (major), 68% ee. $[\alpha]^{25.7}_D$ = −28.2 (*c* = 1.00, $CHCl_3$).

Lager Scale Procedure for the Asymmetric Borylation of α,β-Unsaturated Esters

*(S)-Ethyl-3-hydroxy-3-phenylpropanate ((S)-(−)-**6a**)*; Following the General Procedure C; 81% yield (304 mg, 1.56 mmol), 76% ee.

(*R*)-**4by** (5 mol %, 39.0 mg, 0.0969 mmol), $(Bpin)_2$ (2.0 equiv, 984 mg, 3.86 mmol), *t*-BuOK (1.0 equiv, 217 mg, 1.93 mmol), molecular sieve 3A (579 mg), THF (9.7 mL), ethyl cinnamate (**5a**) (340 mg, 1.93 mmol), and MeOH (2.0 equiv, 156 μL, 3.86 mmol) were used.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.xxxxxxx.
^1H, $^{13}C\{^1H\}$ NMR spectra of new compounds; ^1H spectra of known compounds; chiral HPLC analysis of compound **6** (PDF).

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Notes

The authors declare no competing financial interest.

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