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Asymmetric Catalytic Hydroboration of Enol Carbamates Enables an Enantioselective Matteson Homologation

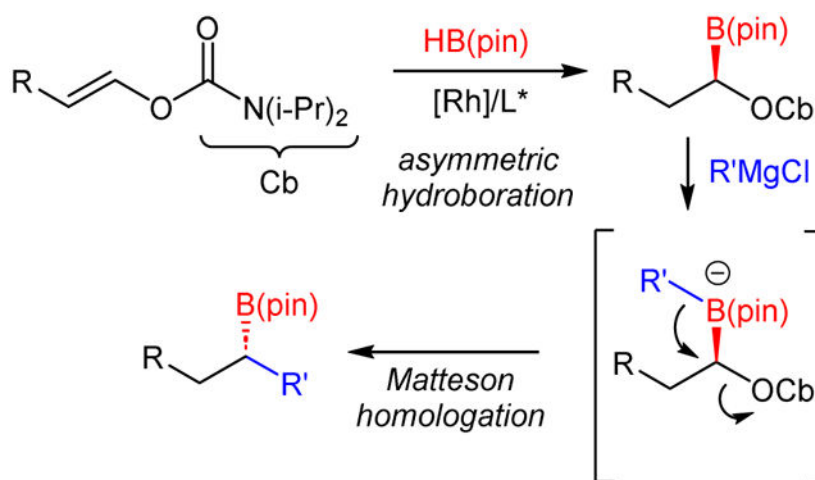
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Abstract

Rh-catalyzed asymmetric hydroboration of enol carbamates yields α -boryl carbamates in good enantioselectivity. The enol carbamate starting materials can be prepared with moderate *Z* selectivity using a modified Julia olefination and used as an *E/Z* mixture, taking advantage of the faster reactivity of the major *Z* isomer in the directed hydroboration. Optically active α -boryl carbamates participate in a Matteson-type homologation with Grignard reagents in which the O-carbamate is substituted with high conservation of optical activity to provide enantioenriched secondary boronic esters.

Graphical Abstract



Keywords

Hydroboration; Matteson homologation; Julia olefination; boronic esters; Rh catalysis

The Matteson homologation remains a valuable synthetic transformation and the subject of continued development 60 years after its initial disclosure.¹ The homologation involves a

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Conflict of Interest

The authors declare no conflict of interest.

1,2-metalate rearrangement of a boronate that features a leaving group alpha to boron (**A**, Scheme 1A). Noteworthy characteristics include 1) the ability to access the key intermediate **A** via addition of an organometallic to an α -functionalized boronic ester or via addition of a carbene equivalent (e.g. LiCH_2Cl) to a boronic ester, 2) the stereospecificity of the reaction, both in terms of the migrating group (retention) and the carbon undergoing substitution (inversion), and 3) the synthetic utility of the resulting boronic ester, which can be converted to a wide range of useful functional groups.^{2,3}

Several strategies have been described to use the Matteson homologation to generate optically active boronic esters. Boronic acids derived from chiral non-racemic diols can lead to α -chloroboronic ester with high diastereoselectivity (Scheme 1B).² These products can participate in a second, stereospecific homologation reaction (not shown). Alternatively, optically active α -sulfinyl benzoates can undergo metalation with retention of stereochemistry and subsequent trapping with boronic esters (Scheme 1C).⁴ Substitution of the benzoate provides enantioenriched boronic esters. Similarly, Hoppe demonstrated that directed, asymmetric lithiation of terminal carbamates provides a route to α -boryl carbamates (**B**), which can participate in Matteson homologation with Grignard reagents (Scheme 1D).⁵ Finally, Lewis acids complexed with chiral non-racemic ligands have been shown to promote the enantioselective Matteson rearrangement with lithium dichloromethane. A Yb(III)(bisoxazoline) complex was shown to work in superstoichiometric quantities,⁶ while an in-situ generated Li salt was found to catalyze a highly enantioselective reaction (Scheme 1E).^{7,8}

The Hoppe asymmetric lithiation/borylation strategy is attractive because it relies on readily available alcohol starting materials and gives rise to a reagent that can be used in asymmetric Matteson homologations.⁵ However, it requires stoichiometric quantities of sparteine, which has become challenging to access as the natural (–)-enantiomer⁹ while the unnatural (+)-enantiomer requires de novo synthesis.¹⁰ We reasoned that asymmetric hydroboration of enol carbamates could produce α -boryl carbamates with equal access to either enantiomer and the requirement for only catalytic quantities of the chiral controller (Scheme 1F). Here we describe the realization of this objective.

Asymmetric hydroboration has emerged as an effective strategy to synthesize optically active boronic esters.¹¹ Directing groups near the olefin can impart high regioselectivity, as shown by Takacs with oximes and phosphonates.¹² Takacs¹³ and Li¹⁴ also demonstrated that amides are also effective directing groups (Scheme 2A), while both Li¹⁵ and Tang¹⁶ have shown that enamides can direct asymmetric hydroboration (Scheme 2B). Since carbamates are effective directing groups for lithiation,¹⁷ we hypothesized that they might direct asymmetric hydroboration as well.^{18, 19}

We started our investigation by examining the hydroboration of enol carbamate **3a**, which was prepared with modest *E/Z* selectivity using a modified Julia-Kocienski olefination (Table 1).^{20, 21} A survey of ligands identified bisphosphines as a promising class to pursue, selected examples of which are shown in Table 1. Additional optimization studies shown in the supporting information. While Duanphos, BPE and Duphos gave poor reactivity and selectivity (Entries 1–3), ferrocene-containing ligands showed encouraging results.

Ferrocene gave modest yield and selectivity (Entry 4) while Josiphos-type ligands showed good reactivity but poor selectivity (Entry 5). JoSPOphos ligand **L6b**, featuring an alkyl phosphine and an aryl secondary phosphine oxide, combined high enantioselectivity with promising reactivity. By contrast, the isomeric ligand **L6a** did not support catalysis (Entries 6, 7). An evaluation of solvents revealed trifluorotoluene as optimal (see supporting information for more details) for reactivity. Whereas reactions in THF consumed only the *Z* isomer, the hydroboration in trifluorotoluene converted both olefin isomers. Since enantioselectivity dropped in this experiment, we speculated that *E* and *Z* olefin isomers could react with different rates and enantioselectivities (Entry 8). A control reaction with a ~1:1 *E/Z* mixture further depressed enantioselectivity and suggested that the *E* isomer might be converted with lower selectivity than the *Z* isomer (Entry 9 and see below). Finally, shorter reaction times or lower reaction temperatures selectively consumed the *Z* isomer and provided the hydroboration product in good yield and excellent enantioselectivity (Entries 10, 11).

Two optimized conditions emerged from these studies. Conditions A were generally best for aryl-substituted olefins (35 °C, 18h, 5 mol% Rh), while Conditions B (rt, 48h, 10 mol% Rh) were usually preferred for alkyl-substituted olefins (Scheme 3).²²

For aryl substituted olefins, the electronic properties of the aryl ring had minimal impact, with strongly electron donating substituents like alkoxy (**4c**, **4g**, **4h**) and amino (**4i**) groups performing similarly as electron withdrawing -CF₃ (**4e**) and esters (**4f**). Substitution was tolerated in the meta and para positions, and an *ortho*-Br (**4l**) potentially gives rise to various ortho substitution patterns. Non-basic heteroaryl rings were accommodated by the reaction, including indole (**4p**, **4w**), phenothiazine (**4q**), benzothiophene (**4r**) and furan (**4s**). Alkyl-substituted enol carbamates also reacted selectively, with both linear (**4t**) and cyclic (**4u**) substrates providing the hydroboration product in high ee. Single crystals derived from thioether **4d** were suitable for X-ray diffraction analysis (CCDC 226136). The crystal structure showed coordination of the carbamate carbonyl to the boron and established the absolute stereochemistry of **4d**. Other products were assigned by analogy.

Collectively, the examples in Scheme 3 demonstrate the functional group compatibility of the reaction. Tolerated groups include esters (**4f**, **4h**, **4x**), silyl ethers (**4g**, **4t**), imides, amides and sulfonamides (**4k**, **4u**, **4w**), and halides (**4e**, **4l**, **4w**). Basic amines and strongly coordinating heterocycles (e.g., pyridines) are not tolerated under the current reaction conditions. With regard to other unsaturated C-C bonds, alkyne **3j**, conjugated diene **3o**, and the trisubstituted olefin derived from citronellal (**3v**) showed group-selective reduction of the enol carbamate. By contrast, a terminal olefin reacted at similar rates as the enol carbamate, giving diborated product **4m** exclusively. Disubstituted olefins appear to react slightly slower than enol carbamates, as **4n** was isolated with the unactivated olefin intact, albeit in reduced yield due to partial double hydroboration. Finally, hydroboration of the enol carbamates derived from citronellal demonstrated a matched/mismatched effect wherein the *S*-methyl isomer was formed with substantially higher ee than the *R*-methyl isomer.

During optimization studies with a 20:80 *E/Z* mixture of **3a**, we noticed that ee was dependent on conversion. In particular, high ee was obtained when only the *Z* isomer was

consumed, but it decreased as the E isomer reacted. Many of the enol carbamates could not be isolated as pure olefin isomers, but ester **3f** could be resolved flash chromatography, allowing us to investigate the issue more carefully (Scheme 4). Purified *E*-**3f** reacted slowly under the reaction conditions, providing <20% of the hydroboration product. The main product in this reaction results from hydrogenation, which proved impossible to separate from the hydroboration product. By contrast, *Z*-**3f** reacted cleanly and provided the hydroboration product in 96% ee. For comparison, a 20:80 *E:Z* mixture generated the **4f** in 88% ee. Estimates based on ee and conversion indicate that the E isomer generates the same major enantiomer, albeit in substantially reduced selectivity and rate. Thus, high ee can generally be obtained by monitoring the reaction for conversion of the *Z* isomer.

Hoppe originally reported that α -boryl carbamates undergo stereospecific substitution with Grignard reagents.⁶ We confirmed this reactivity with products derived from asymmetric hydroboration, but also revealed some limitations (Scheme 5). Boronic ester **4a** underwent substitution with a secondary (**5a**), aryl (**5b**) and alkenyl (**5c**) Grignard reagent in reasonable yields and high conservation of optical purity. However, reactions with linear or methyl Grignards were not successful, and PhLi and MeLi did not provide the desired product. Boronic ester **4c** likewise reacted cleanly with PhMgCl, but alkyl and alkenyl Grignard reagents gave complex reaction mixtures. In general, the reactions were rapid, and performed best when the boronate was formed at $-78\text{ }^{\circ}\text{C}$ and then quickly placed into an ice bath. Prolonged stirring at $-78\text{ }^{\circ}\text{C}$ appeared to lead to racemization whereas starting the reaction at $4\text{ }^{\circ}\text{C}$ resulted in messier reaction mixtures. Freshly prepared Grignard reagents performed most effectively, although the identity of the halogen (RMgBr vs RMgCl) did not appear to have a significant impact. Under the optimal conditions, several different boronate/Grignard combinations proved successful.²³

In summary, Julia olefination of aryl and alkyl aldehydes with carbamate **1** offers a general route to enol carbamates with predominantly *Z* stereochemistry. Asymmetric hydroboration using a Rh(I)(JoSPOphos) complex selectively converted the *Z*-olefin to α -boryl carbamates with high enantioselectivity. Finally, the resulting α -boryl carbamates participate in Matteson-type homologation reactions with high stereospecificity, although opportunities exist to further improve the generality of this transformation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Information

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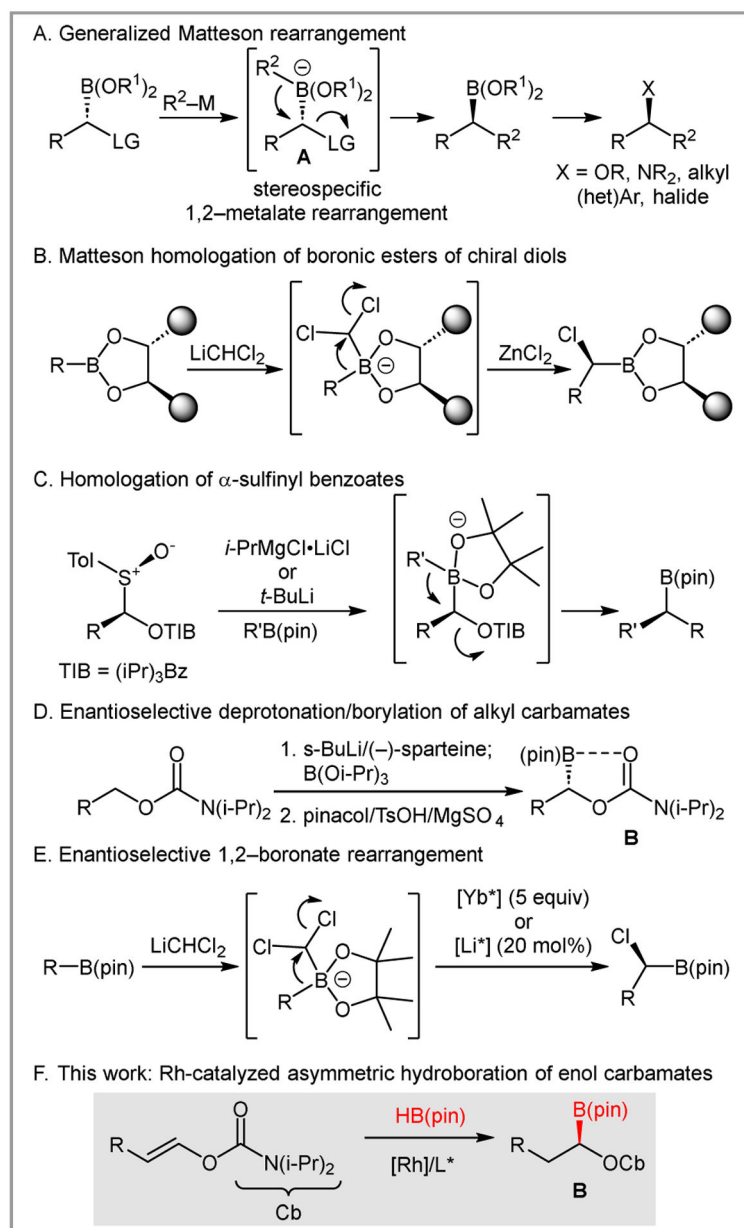
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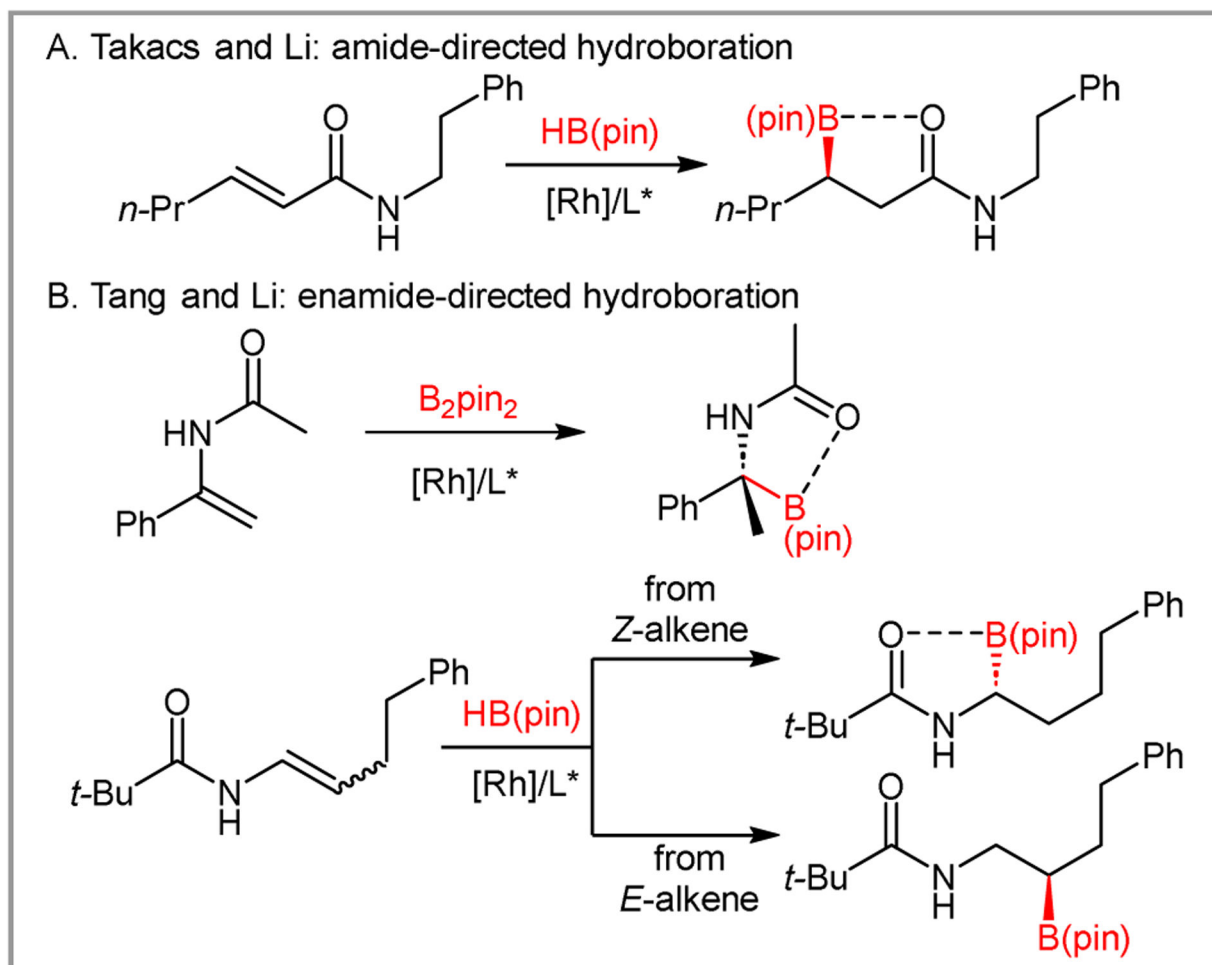
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- (21). Representative procedure: Under an argon atmosphere, a solution of sulfone 1 (2.09 g, 6.0 mmol, 1.50 equiv) in anhydrous THF (40 mL) was cooled to -78°C . LiHMDS (6.8 mL of 1.0 M in THF, 6.8 mmol, 1.7 equiv) was added dropwise, maintaining the temperature below -60°C . The mixture was stirred with dry ice/acetone cooling for 40 min. Then a solution of 2-(4-methoxyphenyl)acetaldehyde 2a (0.60 g, 4.0 mmol, 1.00 equiv) in anhydrous THF (5.3 mL) was added dropwise, maintaining the temperature below -60°C , and the mixture was stirred at ambient temperature overnight. Methanol (3 mL) was added to quench the reaction, and the volatiles were removed under vacuum. Subsequent flash chromatography on silica gel (hexanes/Et₂O = 90:10) afforded 0.714 g (61%) of the product 3a as a yellow oil (Z : E = 80 : 20). ¹H NMR (400 MHz, CDCl₃) δ 7.19 – 7.09 (m, 3H, Z + 3H, E), 6.89 – 6.79 (m, 2H, Z + 2H, E), 5.43 (dt, J = 12.4, 7.5 Hz, 1H, E), 4.91 (td, J = 7.5, 6.4 Hz, 1H, Z), 4.11 (br s, 1H, Z + 1H, E), 3.81 (br s, 1H, Z + 1H, E), 3.79 (s, 3H, Z + 3H, E), 3.46 (dd, J = 7.5, 1.7 Hz, 2H, Z), 3.27 (dd, J = 7.4, 1.7 Hz, 2H, E), 1.30 – 1.19 (br m, 12H, Z + 12H, E). ¹³C NMR (151 MHz, CDCl₃) δ 158.05, 153.05, 137.26, 135.63, 132.65, 132.57, 129.48, 129.31, 113.97, 111.35, 109.82, 55.41, 46.98, 45.82, 33.02, 30.46, 21.70, 20.51. ESI MS calcd for C₁₇H₂₆NO₃⁺ [M+H]⁺ 292.2, found 292.2.17263⁺⁺
- (22). Enol carbamate 3a (102 mg, 0.35 mmol, 1.0 equiv) was weighed in a 2 dram screw-cap vial, which was then transferred into a N₂-filled glove box. Inside a glove box ligand L6b (10 mg, 21 μmol , 6 mol%) was weighed in a 1 dram screw-cap vial. [Rh(cod)₂]OTf (8.5 mg, 17.5 μmol , 5 mol%) was weighed in a separate 20-mL screw-cap vial equipped with a stir bar. Substrate 3a was dissolved in PhCF₃ (2.8.0 mL), and the resulting solution was transferred to the vial with ligand (additional 0.7 mL PhCF₃ was used for rinsing). The solution of substrate 3a and ligand L6b was then transferred to the vial with catalyst. HBpin (0.10 mL, 0.090 g, 0.70 mmol, 2.0 equiv) was then added, and the mixture was briefly stirred. The reaction vial was sealed with Teflon-coated screw cap. The reaction mixture was removed from the glove box and stirred at room temperature for 48 h. The mixture was concentrated, and pinacol was removed by transferring the crude product into a 250 mL round-bottom flask, dissolving in MeOH (2 mL), adding water (0.4–0.8 mL) until the solution became cloudy, and concentrating on a rotary evaporator. After 6–9 azeotropic evaporation cycles pinacol was removed completely. Flash chromatography on silica gel (hexanes/EtOAc = 70:30) afforded 98 mg (67%) of the product 4a

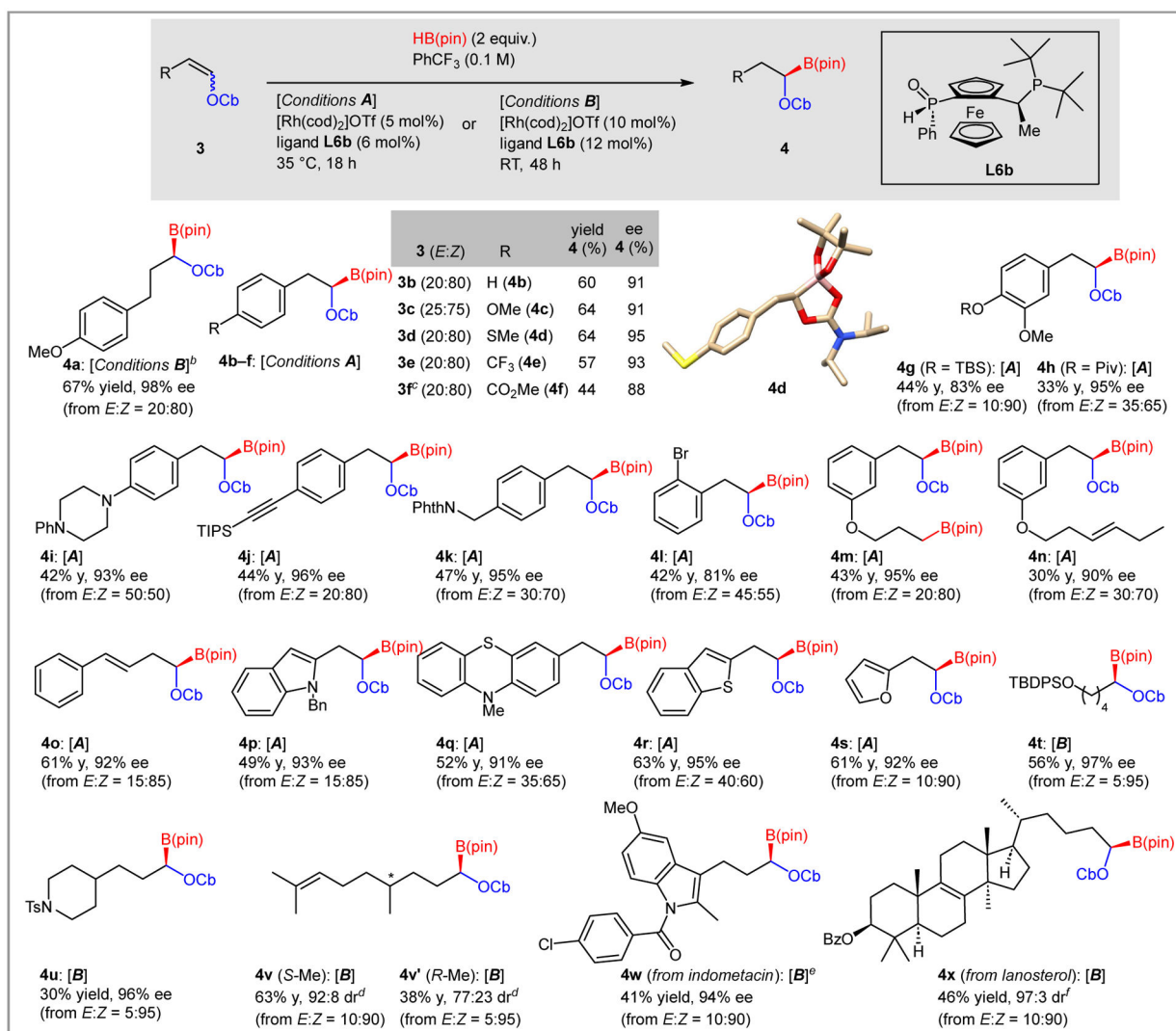
as a pale-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.16 – 7.07 (m, 2H), 6.87 – 6.77 (m, 2H), 4.07 (hept, J = 6.9 Hz, 1H), 3.82 (dd, J = 10.6, 3.9 Hz, 1H), 3.78 (s, 3H), 3.76 (hept, J = 6.9 Hz, 1H), 2.79 (ddd, J = 14.7, 9.9, 5.3 Hz, 1H), 2.65 (ddd, J = 13.8, 9.4, 6.6 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.92 – 1.80 (m, 1H), 1.28 – 1.20 (m, 12H), 1.17 (s, 12H). ¹³C NMR (101 MHz, CDCl₃) δ 162.77, 157.66, 134.60, 129.42, 113.70, 79.74, 55.26, 48.44, 46.61, 33.61, 33.35, 25.30, 24.96, 20.62, 20.61, 20.35, 20.26 (the carbon attached to boron was not observed due to quadrupolar relaxation). ¹¹B NMR (128 MHz, CDCl₃) δ 12.86. ESI MS calcd for C₂₃H₃₉BNO₅⁺ [M+H]⁺ 420.3, found 420.2. Chiral HPLC CHIRALCEL[®] OZ-3, 0.75% IPA in hexane, 1.0 mL/min, 220 nm: 98% ee (7.1 and 11.7 min).[®]

- (23). At –78 °C and under argon, freshly c-HexMgCl (0.12 mmol, 1.4 equiv) was added dropwise (over 2 min) to a solution of 4a (35 mg, 0.083 mmol, 1.0 equiv, 98% ee) in anhydrous Et₂O (1.0 mL). The mixture was stirred under argon in a cold room (4 °C) for 2 h. After that, insoluble solids were removed by filtration through a Pasteur pipette with a silica gel plug (ca. 1 mL of silica gel was used; additional 2-mL portion of Et₂O was used for washing), and the filtrate was concentrated under vacuum. The crude secondary boronate was then redissolved in THF (1.0 mL), and the solution was cooled to 0 °C and treated with 3M NaOH (0.17 mL) and 30% aq. H₂O₂ (0.17 mL). The mixture was stirred at ambient temperature for 2 h. At 0 °C, sat. aq. Na₂S₂O₃ (1 mL) was carefully added to quench the reaction, and the product was extracted with EtOAc (3 × 2 mL). Combined organic layers were dried over Na₂SO₄, filtered and concentrated. Subsequent flash chromatography eluting with hexanes/EtOAc = 85:15 afforded 15 mg (71%) of the 5a as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.18 – 7.08 (m, 2H), 6.88 – 6.79 (m, 2H), 3.79 (s, 3H), 3.38 (ddd, J = 8.9, 5.4, 3.2 Hz, 1H), 2.77 (ddd, J = 13.8, 9.9, 5.4 Hz, 1H), 2.59 (ddd, J = 13.8, 9.7, 6.7 Hz, 1H), 1.88 – 1.58 (m, 6H), 1.42 – 0.91 (m, 7H). ¹³C NMR (151 MHz, CDCl₃) δ 157.83, 134.53, 129.43, 113.92, 75.72, 55.39, 43.90, 36.26, 31.56, 29.30, 27.91, 26.65, 26.46, 26.32. ESI MS calcd for C₁₆H₂₃O⁺ [M–OH]⁺ 231.17, found 231.2. Chiral HPLC CHIRALCEL[®] OD-H, 3.5% IPA in hexane, 1.5 mL/min, 220 nm: 95% ee, 97% es.²²¹⁶²³⁺[®]



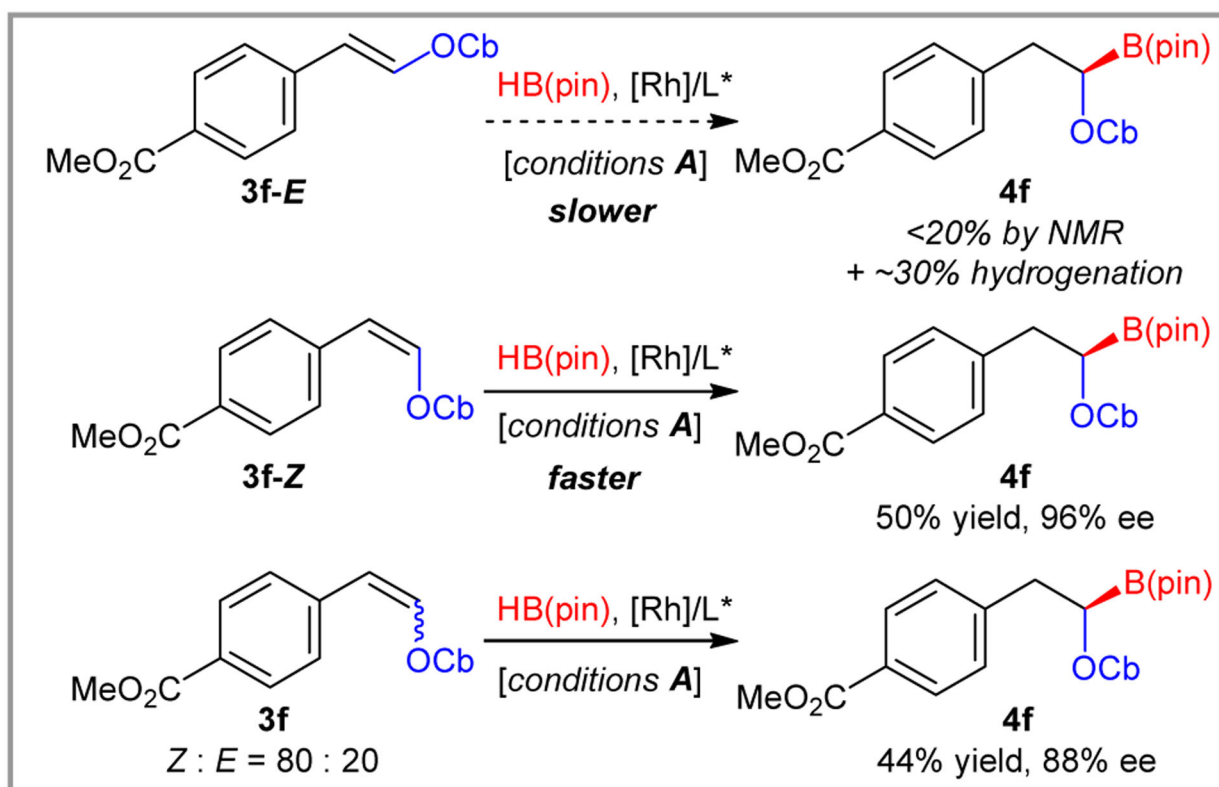
Scheme 1.
Approaches to stereoselective Matteson homologations.



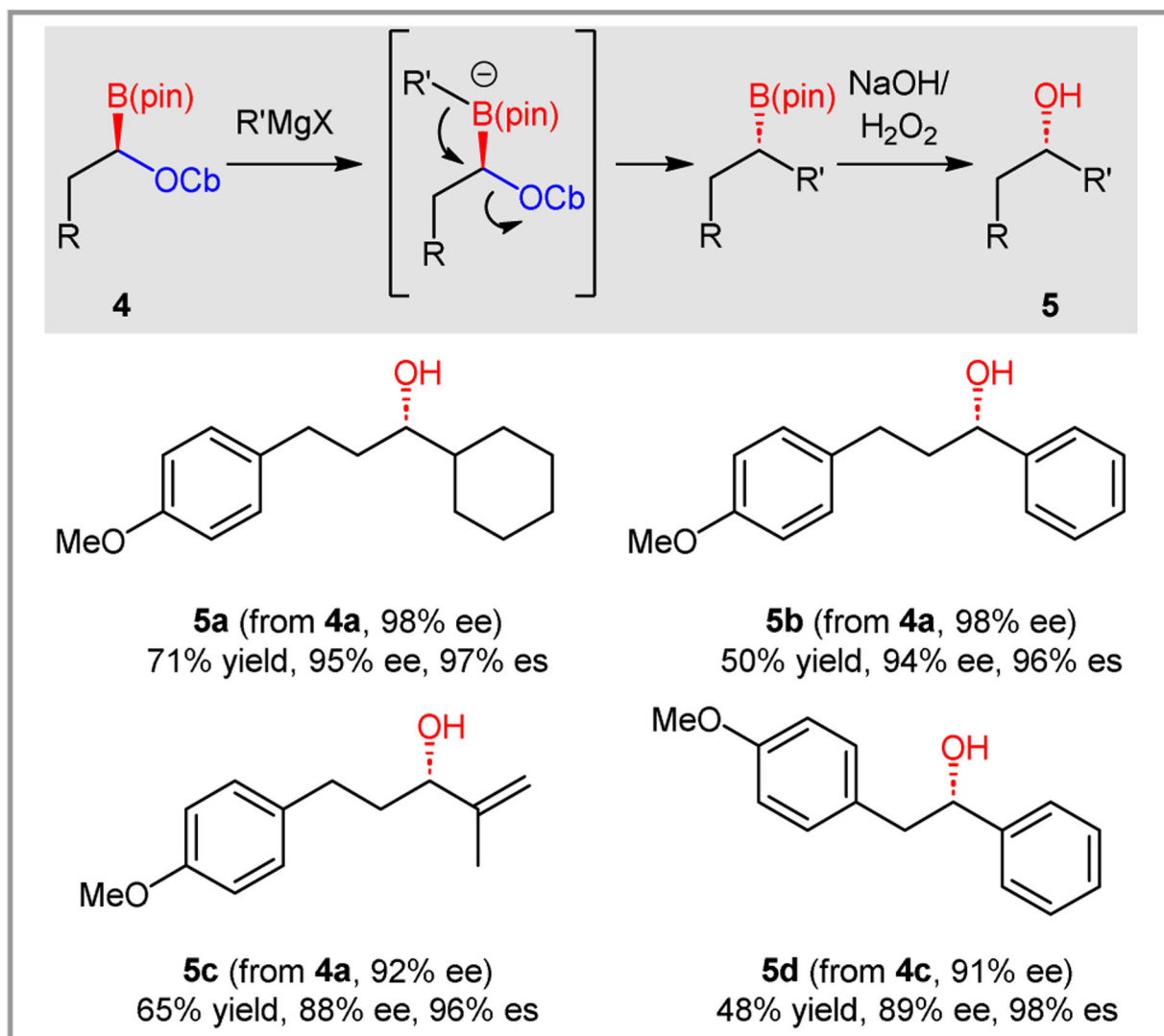


Scheme 3.

Substrate scope for the asymmetric hydroboration. ^aAll reactions were run in PhCF₃ (0.10 M) using enol carbamate 3 (1.0 equiv), [Rh(cod)₂]OTf (5–10 mol%), ligand L6b (6–12 mol%) and HB(pin) (2.0 equiv). Starting material, reagents and solvent were mixed in a N₂-filled glove box. Yields of isolated products. Enantiomeric excess (ee) values were determined by HPLC. ^bWith [Rh(cod)₂]OTf (5 mol%) and ligand L6b (6 mol%). ^cWith [Rh(cod)₂]OTf (10 mol%) and ligand L6b (12 mol%). ^dDiastereomeric ratio (dr) was determined by ¹³C NMR. ^eReaction time = 14 h. ^fDiastereomeric ratio (dr) was determined by HPLC.

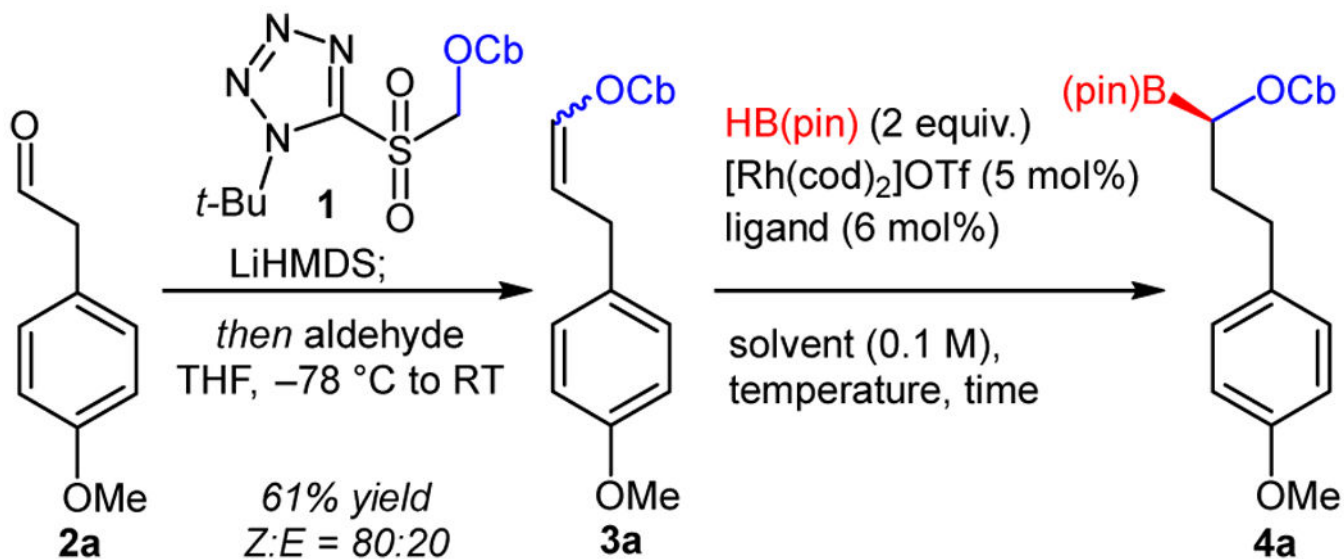
**Scheme 4.**

Impact of olefin stereochemistry on the asymmetric hydroboration. See Scheme 3 for reaction conditions.

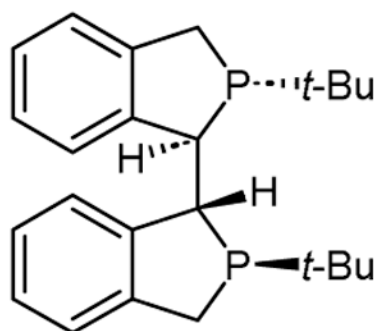
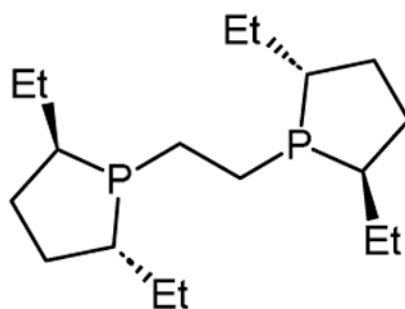
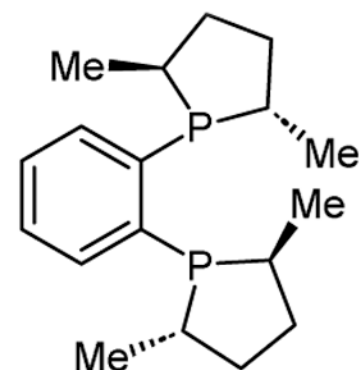
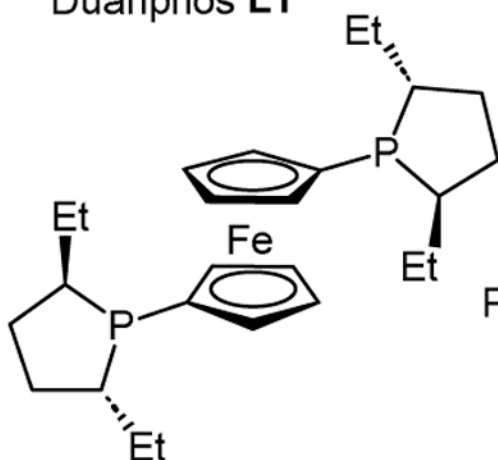
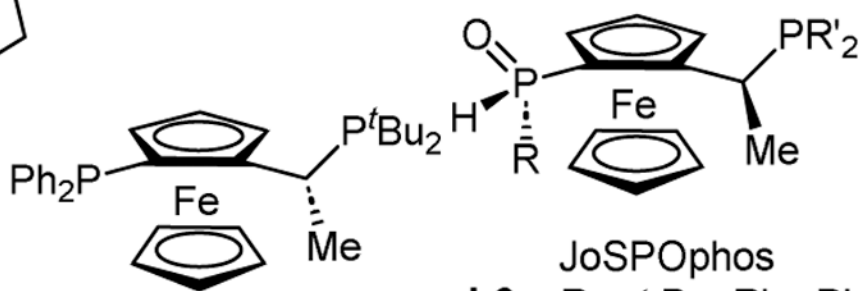
**Scheme 5.**

Reactions of hydroboration products with Grignard reagents. Reaction conditions: Et₂O (0.1 M), Grignard reagent (1.4 equiv.), -78 to 4 °C, 2 h. Yields are given for products isolated after oxidation. Enantiomeric excess (ee) values were determined by HPLC. Enantioselectivity (es) = ee of product / ee of starting material.

Table 1

Synthesis of Z-Enriched Enol Carbamate^a and Optimization of Hydroboration Conditions^b

Entry	L	Solvent	Temp (°C)	Time (h)	Yield (%) ^c	Ee (%) ^d
1	L1	THF	50	12	<5	7
2	L2	THF	50	12	13	34
3	L3	THF	50	12	21	n.d.
4	L4	THF	50	12	52	65
5	L5	THF	50	12	69	10
6	L6a	THF	50	12	0	n.d.
7	L6b	THF	50	12	50	91
8 ^e	L6b	PhCF ₃	50	12	80 ^f	78
9 ^g	L6b	PhCF ₃	50	12	77	70
10 ^e	L6b	PhCF ₃	35	18	65 ^f	97
11 ^e	L6b	PhCF ₃	rt	48	67 ^f	97

Duanphos **L1**BPE **L2**Duphos **L3**Josiphos **L5**

JoSPOphos

L6a: R = *t*-Bu; R' = Ph**L6b:** R = Ph; R' = *t*-Bu

^aReaction carried out on a 4.0 mmol scale in THF (0.1 M) using Julia reagent 1 (1.5 equiv), LiHMDS (1.7 equiv) and aldehyde 2a (1.0 equiv).

^bReactions were run on a 0.05 mmol scale using enol carbamate 3a (1.0 equiv), [Rh(cod)₂]OTf (5 mol%), ligand (6 mol%) and HBpin (2.0 equiv) unless noted otherwise.

^cYields determined by ¹H NMR.

^dEe values determined by HPLC (n.d. = not determined).

^e0.35 mmol scale.

^fIsolated yield.

^g3a with Z : E = 55 : 45 was used.