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Diastereoselective Radical Hydrogen Transfer Reactions using N-Heterocyclic Carbene Boranes

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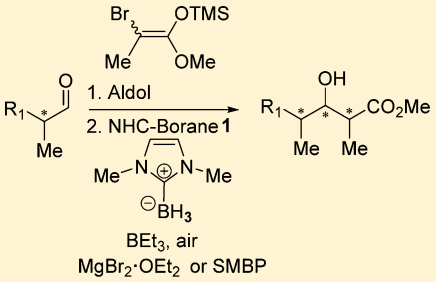
Supporting Information

ABSTRACT: Reported herein are the first diastereoselective and Lewis acid-mediated radical reactions of N-heterocyclic carbene (NHC) boranes. We applied these reactions to the synthesis of four propionate diastereoisomers combining an aldol reaction, followed by a stereoselective radical-based reduction in which the NHC borane serves as the hydrogen donor, thus obviating the use of tin-based reagents. The 2,3-*syn* isomer is obtained by combining an NHC-borane and a Lewis acid ($MgBr_2 \cdot OEt_2$), while using a reverse polarity strategy provides the 2,3-*anti* isomer.



Despite recent advances in diastereoselective and enantioselective free-radical-based processes,[1] their usefulness and practicability continue to be plagued by the necessity of tin reagents, such as Bu_3SnH, to achieve an effective hydrogen transfer. Aside from the biological and environmental toxicities of tin reagents,[2] the removal of residual tin hydrides and corresponding tin halides has proven difficult and time-consuming. Not surprisingly, finding an alternative to tin-based reagents has been the focus of several research groups. Seminal contributions by Curran, Malacria, and colleagues have shown the recent emergence of NHC-boranes as hydrogen transfer agents in free-radical reactions.[3]

NHC-boranes, such as 1,3-dimethylimidazole-3-ylidene borane (**1**), are easy to access,[4] bench stable, and reduce xanthates, bromides, iodides, and ketones through a radical chain reaction.[3a,5] In addition, secondary alkyl halides possessing an adjacent electron-withdrawing group can be efficiently reduced.[6] Due to the lower reactivity of NHC-boranes, as compared to Bu_3SnH, these reactions are typically performed at room temperature or higher,[3d,5a] potentially diminishing the diastereoselective control of reactions occurring under kinetic conditions. No precedent exists for the creation of stereogenic centers using a radical-based approach with NHC-boranes. Due to our interest in the synthesis of polypropionates[7] and the desire to form these motifs in the absence of tin, we investigated if NHC-boranes could be employed as effective hydrogen transfer reagents at low reaction temperatures in the presence of a Lewis acid.

Our group has previously reported a combined aldol and hydrogen transfer reaction using Bu_3SnH to synthesize all possible polypropionate stereopentads starting from a single stereogenic center.[7a,b] As illustrated in Figure 1, precomplexing the β-hydroxy ester with Me_3Al (**TS A**), followed by addition of Et_3B, as the initiator, and tributyltin hydride provides the 2,3-*syn*−3,4-*anti* isomer (**3a**) at −78 °C. The 2,3-*anti*−3,4-*anti* isomer (**3b**) is obtained using dibutylboron triflate to initially form the corresponding C3-borinate (**TS B**). Reduction at −78 °C using tributyltin hydride and Et_3B generates the 2,3-*anti* isomer with high diastereoselectivity (dr >20:1).

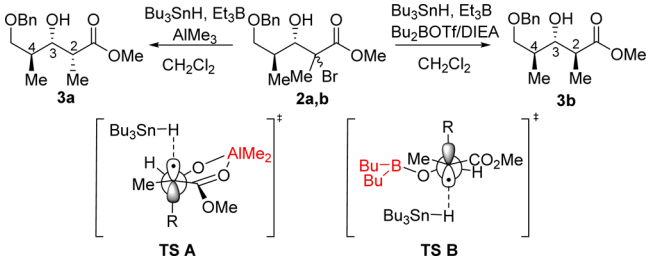


Figure 1. Radical reduction and transition states for the synthesis of 2,3-*syn* and 2,3-*anti* polypropionate motifs.

The selectivity of such hydrogen transfer reactions as well as their mechanisms have been extensively studied both experimentally and theoretically.[7c,8] The presence of Lewis acids, such as Me_3Al, also increases the rate of radical reactivity toward allylation using allyltrimethylsilane or allyltributylstannane.[9] This improved reactivity is attributed to a decrease in the SOMO energy of the radical embedded in the cyclic chelate (ground state **C**, Figure 2). DFT calculations confirmed that the SOMO energy of the chelate radical (ground state **C**) is −239.1 kcal/mol, while the C3 aluminate (ground state **D**) is −146.7 kcal/mol, thereby predicting an enhanced reactivity for the chelated substrate.[8a,10]

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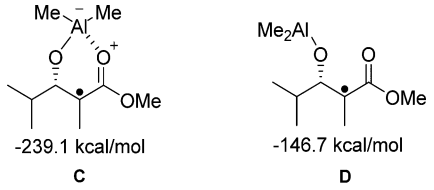
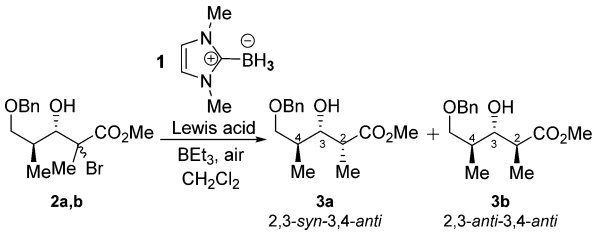


Figure 2. Ground-state SOMO energies of sluminate radical intermediates **C** and **D**.

The radical reduction precursors (**2a,b**) with an α-tertiary bromide were prepared as previously described.[7a] An aldol reaction using $TiCl_4$ or $BF_3{\cdot}OEt_2$ provided the 3,4-*anti* (**2a,b**, Table 1) and 3,4-*syn* isomers (**4a,b**, Table 3), respectively,

Table 1. Diastereoselective Hydrogen Atom Transfer for the Synthesis of the 2,3-*syn*-3,4-*anti* Diastereomer 3a



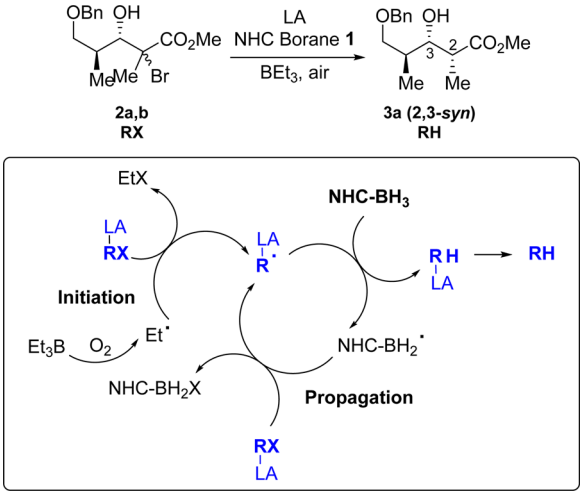
entry	Lewis acid	temp (°C)	time (h)	ratio[a] (**3a**: **3b**)	yield[b] (%)
1	–	−78	24	5:1	30
2	Me_3Al	−78	24	>20:1	40
3	Me_3Al	−40	24	–	traces
4	$MgBr_2{\cdot}OEt_2$	−78	3	>20:1	81
5	$MgBr_2{\cdot}OEt_2$	−10	2	>20:1	85

[a]Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. [b]Isolated yields. Equivalents of reagents used can be found in the Experimental Section.

which were used to investigate the hydrogen transfer reaction with NHC-boranes.[11] The 3,4-*anti* substrate (**2a,b**) was reacted with NHC-borane **1** and Et_3B in CH_2Cl_2 at −78 °C in the absence of a Lewis acid (Table 1, entry 1). Preferential formation of the desired 2,3-*syn* isomer **3a** (dr 5:1) was observed, however, only in a modest 30% yield. The low diastereselectivity could be attributed to a competition between **TS A** and **TS B** (Figure 1). Hydrogen bonding between the free hydroxyl group at C3 and the ester would allow the endocyclic pathway (**TS A**) to be competitive with the acyclic pathway (**TS B**). Upon addition of Me_3Al (entry 2), the 2,3-*syn* isomer was formed with a > 20:1 diastereoselectivity, albeit still in low yield (40%). Upon increasing the reaction temperature to −40 °C, only a trace amount of product was observed, suggesting that the Me_3Al reacts with the NHC-borane (a mild Lewis base).[12] The complete decomposition of **1** by Me_3Al was in fact observed by ^{1}H NMR in 10 min in the presence of the Lewis acid at room temperature in deuterated dichloromethane. A milder Lewis acid, $MgBr_2{\cdot}OEt_2$, was next considered. At −78 °C, an excellent ratio (>20:1) and yield (81%) were obtained for the formation of the 2,3-*syn* diastereomer **3a** (entry 4). This high diastereoselectivity and yield were maintained when the reaction was done at −10 °C (entry 5).[13]

The possible reaction pathway for the synthesis of the 2,3-*syn* isomer **3a** is illustated in Scheme 1. Initiation involves reaction of dioxygen with Et_3B to generate the ethyl radical (Et$^\bullet$).[14] Abstraction of the bromide from the Lewis acid complexed

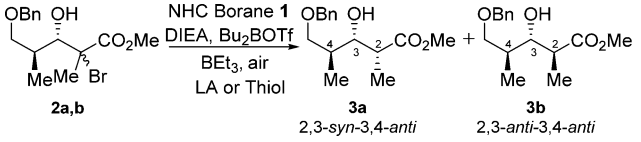
Scheme 1. Possible Reaction Pathway for the Formation of the 2,3-*syn* Diastereomer 3a



radical precursor (RX-LA) furnishes radical LA-R$^\bullet$. This radical reacts with the NHC-borane, resulting in a hydrogen atom transfer to form the 2,3-*syn* product (RH) and NHC-$BH_2^\bullet$. The NHC-$BH_2^\bullet$ species propagates the chain through further reaction with RX-LA. 1,4-Dinitrobenzene is added as the chain terminator prior to reaction workup.

Reduction of tertiary bromide **2a,b** was further investigated to access the 2,3-*anti* isomer **3b**. To generate this *anti* selectivity, the β-hydroxyl group needs to be protected to prevent chelate formation with the ester. As previously demonstrated,[7c,15] this can be achieved by installing a C3-borinate as a temporary protecting group. Addition of NHC-borane **1** to the C3-borinate, prepared in situ from reaction of the β-hydroxy ester with dibutylboron triflate and diisopropylamine, provided an 8:1 mixture in favor of the desired 2,3-*anti* product **3b** at −78 °C (Table 2, entry 1). In an effort to lower the energy of the SOMO and thus enhance reactivity, $MgBr_2{\cdot}OEt_2$ was added (entries 2 and 3). The yields of the reduction were significantly improved, but the diastereoselectivity was

Table 2. Diastereoselective Hydrogen Atom Transfer for the Synthesis of the 2,3-*anti* Diastereomer 3b[a]



entry	Lewis acid or thiol (equiv)	temp (°C)	ratio[b] (**3a**:**3b**)	yield[c] (%)
1	–[d]	−78	1:8	30
2	$MgBr_2{\cdot}OEt_2$	−78	1:1	71
3	$MgBr_2{\cdot}OEt_2$	0	1:2	81
4	$BF_3{\cdot}OEt_2$[d]	−78	–	–
5	MAD	−78	1:8	30
6	SMBP (0.2)	−78	1:12	50
7	SMBP (0.8)	−78	1:>20	75
8	SMBP (0.8)	−10	1:15	91

[a]MAD: methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide); SMBP: methyl-5-*tert*-butylthiophenol. Equivalents of reagents used can be found in the Experimental Section. [b]Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yield. [d]Reaction was stirred for 24 h opposed to 2−3 h.

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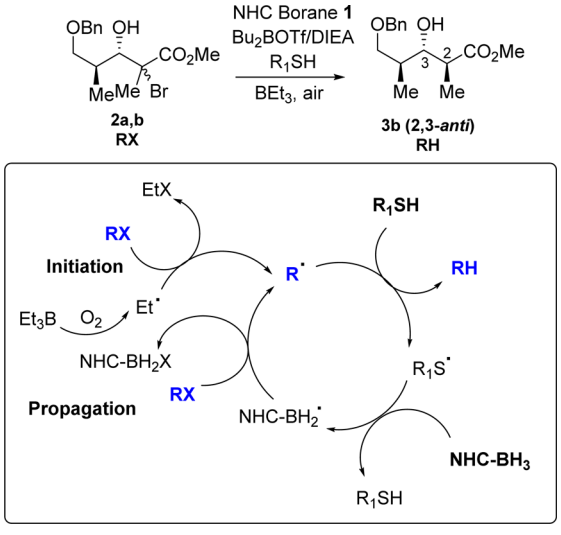
lost. This implied that the two reaction pathways leading to the *syn* and *anti* isomers were activated, indicating that the C3-borinate was partly cleaved under these conditions.

Other Lewis acids were next considered. As seen in Table 2, entry 4, no reactivity was observed with monodentate Lewis acid $BF_3{\cdot}OEt_2$, only starting material **2a,b** was recovered. It is possible that the NHC-borane reacts with $BF_3{\cdot}OEt_2$, providing NHC-BF_3.[16] This may be the reason that the reaction does not work with this Lewis acid. A sterically encumbered Lewis acid, methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD), which has been employed in free-radical reactions,[17] did not improve the yields (entry 5). It is assumed that competitive decomposition of the NHC-borane was again at play. To increase the yields and diastereoselectivity of the halide reduction using NHC-boranes with our borinates, we examined the use of polar reversal catalysis. Curran and colleagues reported that unproductive radical reductions of alkyl and aryl halides with NHC-boranes could be overcome by the addition of a thiol.[5a,18]

The reverse polarity catalysis approach is based on the fact that the NHC-$BH_2^{\bullet}$ radical reacts quickly with the alkyl halide, while NHC-BH_3 is a relatively poor hydrogen donor when the carbon-centered radical is unactivated. Thiyl radicals have been recognized as compatible hydrogen transfer agents and react well with NHC-BH_3 to propagate the radical chain.[18a,19] Methyl-5-*tert*-butylthiophenol (SMBP), a commercially available and odorless thiol, was considered. The borinates were prepared at −40 °C, and upon lowering the reaction temperature to −78 °C, SMBP (0.2 equiv), Et_3B, and NHC-borane **1** were added. As seen in Table 2, entry 6, the increase in yield and ratio was only marginal. However, by increasing the amount of SMBP (0.8 equiv), the yield and ratio were significantly enhanced (entry 7). An excellent yield (91%) and ratio (1:15) were obtained when the reaction was performed at −10 °C. We have thus developed a tin-free protocol to access one of the most challenging 2,3-*anti*−3,4-*anti* propionate motifs.

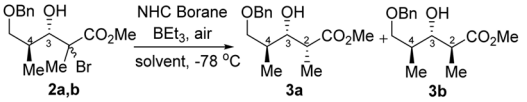
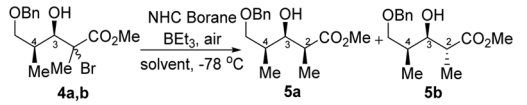
A possible reaction pathway leading to the 2,3-*anti* diastereomer **3b** is illustrated in Scheme 2. The first initiation step involving Et_3B and RX proceeds as described above to generate the radical R$^{\bullet}$. Transfer of a hydrogen atom to R$^{\bullet}$ from R_1SH, which has a higher polarity affinity than NHC-BH_3, results in the formation of the desired product (RH). The generated $R_1S^{\bullet}$ reacts with NHC-BH_3 (nucleophilic) to form R_1SH and also propagates the chain through generation of NHC-$BH_2^{\bullet}$.

Scheme 2. Possible Reaction Pathway for the Formation of the 2,3-*anti* Diastereomer 3b



The optimized conditions for generation of the 2,3-*syn*−3,4-*anti* (**3a**) and 2,3-*anti*−3,4-*anti* (**3b**) scaffolds (Table 3, entries 1 and 2) were tested for the 3,4-*syn* diastereoisomers (entries 3 and 4). The synthesis of 2,3-*syn*−3,4-*syn* (**5a**) (entry 3) and 2,3-*anti*−3,4-*syn* (**5b**) (entry 4) occurred with excellent yields and selectivity.

Table 3. Diastereoselective Hydrogen Transfer Reactions with 3,4-*anti* and 3,4-*syn* α-Bromoesters

entry	additive	solvent	*dr* (**a**:**b**)[a]	Yield[b] (%)
				
1	$MgBr_2{\cdot}OEt_2$	CH_2Cl_2	>20:1	81
2	DIEA/Bu_2BOTf/SMBP	toluene	1:>20	75
				
3	$MgBr_2{\cdot}OEt_2$	CH_2Cl_2	>20:1	75
4	DIEA/Bu_2BOTf/SMBP	toluene	1:>20	81

[a]Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yields. Reactions were performed at −78 °C. Equivalents of reagents used can be found in the Experimental Section.

As summarized in Table 3, this strategy provides access to four different propionate motifs. These reactions also worked well using other thiols, such as *tert*-dodecylmercaptan and different NHC-boranes, such as 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene, attesting to the general nature of our findings.[4]

CONCLUSIONS

We have demonstrated that the use of mild Lewis acids can expand the scope of NHC-boranes in hydrogen transfer radical reductions, providing excellent 2,3-*syn* selectivity. A diastereoselective radical-based reduction, leading to the 2,3-*anti* isomer, can be achieved by combining the efficacy of NHC-boranes as a chain propagator with that of thiol derivatives. This work demonstrates that the four possible propionate derivatives can be synthesized using tin-free-radical-based reactions. A new synthetic method for stereoselective radical reductions without the use of tin hydride has thus been developed.

EXPERIMENTAL SECTION

General Comments. All reactions requiring anhydrous conditions were carried out under an atmosphere of nitrogen or argon in flame-

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dried glassware using standard syringe techniques. Dichloromethane, THF, and toluene were dried with 4 Å molecular sieves prior to use. The 4 Å molecular sieves (1−2 mm beads) were activated by heating at 180 °C for 48 h under a vacuum prior to adding to new bottles of solvent purged with argon. Commercially available reagents were used as received. Flash chromatography was performed on silica gel 60 (0.040−0.063 mm) using forced flow flash chromatography or an automated flash purification system. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) silica gel aluminum plates. Visualization was performed with UV short wavelength and/or revealed with ammonium molybdate or potassium permanganate solutions. ^{1}H NMR spectra were recorded at room temperature on 500 MHz NMR spectrometers. The data are reported as follows: chemical shift in ppm referenced to residual solvent ($CDCl_3$ δ 7.26 ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, m = multiplet, q= quartet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded at room temperature using 125 MHz. The data are reported as follows: chemical shift in ppm referenced to residual solvent ($CDCl_3$ δ 77.16 ppm). Infrared spectra were recorded using a FTIR spectrophotometer on a NaCl support, and signals are reported in cm^{-1}. Mass spectra were recorded through electrospray ionization (ESI) positive ion mode. A Q exactive mass analyzer was used for HRMS measurements. Optical rotations were measured at room temperature from the sodium D line (589 nm) using CH_2Cl_2 as solvent unless otherwise noted and calculated using the formula $\alpha_D = (100)\alpha_{obs}/(l \cdot (c))$, where c = (g of substrate/100 mL of solvent) and l = 1 dm.

Synthesis of NHC-Borane. *1,2-Dimethyl-1,2,4-triazol-3-ylidene borane (1).* Following a modified Curran's protocol,[6a] a solution of 1-methyl-1*H*-imidazole (10 mL, 100 mmol) and iodomethane (2 equiv, 15 mL) in dry toluene (1.0 M, 100 mL) was stirred at reflux for 16 h. The reaction was cooled to 25 °C with vigorous stirring to break aggregates. After stirring for 1 h at 25 °C, the solid was filtered and washed with toluene (2 × 50 mL). Solid was dried under vacuum for 3 h and was used as a crude for the next step. To a solution of the crude (24 g, 100 mmol) in dry THF (0.5 M, 200 mL) at −78 °C was added NaHMDS (1.2 equiv, 120 mL). The reaction mixture was stirred at −78 °C for 1 h before slow addition of $BH_3{\cdot}NEt_3$ (1.1 equiv, 16.4 mL). The mixture was then warmed to 25 °C and refluxed for 16 h. After evaporation of volatiles *in vacuo*, a saturated solution of NH_4Cl (50 mL) and CH_2Cl_2 (50 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting solid was filtered and washed (3 × 50 mL) with cold hexanes/Et_2O (1:1) and dried under vacuum to afford **1** as a white powder (11 g, quantitative yield). ^{1}H and ^{13}C NMR spectra correspond with those reported.[6a]

1: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.79 (s, 2H), 3.73 (s, 6H), 1.01 (q, J = 86.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 119.9, 35.9.

Synthesis of Tertiary Bromides (2a,b) and (4a,b). Preparation and characterization of **2a,b**[7a] and **4a,b**[7b] have been previously reported by our laboratory. The synthesis was done starting with racemic compounds.

Synthesis of Polypropionate (3a,b and 5a,b). *General Procedure A: Diastereoselective Hydrogen Atom Transfer for the Synthesis of the 2,3-syn Diastereomer (Endocyclic Effect).* To a stirred solution of the appropriate α-bromoesters (1.0 equiv) in dry CH_2Cl_2 (0.1 M) at the corresponding temperature (see Table 1) was added the corresponding Lewis acid (3.5 equiv for Me_3Al and 5 equiv for $MgBr_2{\cdot}OEt_2$). The reaction mixture was stirred for 1 h at the same temperature before adding NHC-borane **1** (1.2 equiv), Et_3B (0.4 equiv of a 1.0 M solution in hexanes), and air (for 100 μL of Et_3B, 1 mL of air was added in the solution via syringe). The resulting suspension was stirred at the corresponding temperature, then 0.2 equiv of Et_3B followed by air was added every 45 min until the reaction was judged complete by TLC (around 2−3 h). 1,4-Dinitrobenzene (0.2 equiv) was then added to the solution, and the mixture was stirred for an additional 15 min. A saturated solution of NH_4Cl was added to the reaction mixture followed by evaporation of CH_2Cl_2 *in vacuo*. The aqueous layer was extracted with Et_2O (3×). The organic layer was successively washed with $NaHCO_3$ sat. solution and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes:Et_2O 70:30) to afford the desired compound.

Note: Radical propagation is more efficient in toluene, but due to the low solubility of $MgBr_2{\cdot}OEt_2$ in toluene at low temperatures, the synthesis of the 2,3-*syn* diastereomers was done in CH_2Cl_2.

(±)Methyl (2R,3S,4S)-5-(Benzyloxy)-3-hydroxy-2,4-dimethylpentanoate (3a). General Procedure A was followed using 1.18 g of **2a,b**. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a >20:1 mixture in favor of **3a** (entry 5, Table 1). Purification by flash chromatography (hexanes:Et_2O 70:30) provided **3a** in 85% yield (700 mg). The ^{1}H and ^{13}C NMR for compound **3a** correspond to those previously reported by our lab.[7a]

3a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 4.53 (s, 2H), 3.95−3.88 (m, 1H), 3.71 (s, 3H), 3.69−3.64 (m, 1H), 3.58−3.54 (m, 2H), 2.66−2.60 (m, 1H), 1.95−1.87 (m, 1H), 1.21 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 137.8, 128.4, 127.74, 127.65, 75.9, 74.7, 73.5, 51.8, 42.5, 35.8, 13.9, 9.8.

(±)Methyl (2S,3S,4S)-5-(benzyloxy)-3-hydroxy-2,4-dimethylpentanoate (5a). General Procedure A was followed using 82 mg of **4a,b**. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a >20:1 mixture in favor of **5a** (entry 3, Table 3). Purification by flash chromatography (hexanes:Et_2O 70:30) provided **5a** in 75% yield (47 mg).

5a: R_f = 0.37 (hexanes:Et_2O, 80:20); Formula $C_{15}H_{22}O_4$; M_W 266.33 g/mol; IR (neat) υ_{max} = 3529, 2950, 1734, 1452, 1262 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.27 (m, 5H), 4.55−4.48 (m, 2H), 3.94 (dd, J = 7.4, 3.9 Hz, 1H), 3.69 (s, 3H), 3.57−3.46 (m, 2H), 2.94 (bs, 1H) 2.68 (m, 1H), 1.90−1.80 (m, 1H), 1.27 (d, J = 6.7 Hz, 3H), 1.04 (d, J = 7.1 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 138.0, 128.4, 127.7, 127.6, 76.8, 74.7, 73.4, 51.7, 43.1, 36.1, 13.3, 11.3; HRMS calcd for $C_{15}H_{23}O_4$ $[M + H]^+$: 267.1591, found: 267.1588 (−1.1 ppm).

General Procedure B: Diastereoselective Hydrogen Atom Transfer for the Synthesis of the 2,3-anti Diastereomer (Acyclic Effect). To a stirred solution of the appropriate α-bromoesters (1.0 equiv) in dry toluene (0.1 M) at −40 °C were added iPr$_2$NEt (1.5 equiv) and Bu_2BOTf (1.3 equiv). The reaction mixture was stirred for 1 h at −40 °C before adjusting to the corresponding temperature (see Table 2). Addition of SMBP (0.8 equiv), NHC borane **1** (1.5 equiv), Et_3B (0.4 equiv of a 1.0 M solution in hexanes), and air (for 100 μL of Et_3B, 1 mL of air was added in the solution via syringe). The resulting suspension was stirred at the corresponding temperature, then 0.2 equiv of Et_3B with air was added every 45 min until the reaction was judged complete by TLC (around 1−3 h). 1,4-Dinitrobenzene (0.2 equiv) was then added to the solution, and the mixture was stirred for an additional 15 min. The reaction mixture was brought to −40 °C, and MeOH (0.1 M) was added slowly keeping the internal temperature below −35 °C. After stirring for 5 min, H_2O_2 (30%, 1.5 mL/mmol of starting material) was added very slowly, again keeping the internal temperature below −35 °C. The solution was stirred at −40 °C for 45 min and then warmed to 0 °C. H_2O was poured into the reaction mixture. The aqueous layer was extracted with Et_2O (3×), and the organic layer was successively washed with $NaHCO_3$ sat. solution and brine. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (hexanes:Et_2O 70:30) to afford the desired compound.

(±)Methyl (2S,3S,4S)-5-(Benzyloxy)-3-hydroxy-2,4-dimethylpentanoate (3b). General Procedure B was followed using 76 mg of **2a,b**. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a >20:1 mixture in favor of **3b** (entry 7, Table 2). Purification by flash chromatography (hexanes:Et_2O 70:30) provided **3b** in 75% yield (43 mg). The ^{1}H and ^{13}C NMR for compound **3b** correspond to those previously reported by our lab.[7a]

3b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23−7.39 (m, 5H), 4.52 (s, 2H), 3.70 (s, 3H), 3.61- 3.68 (m, 2H), 3.52−3.61 (m, 1H), 3.41 (d, J = 7.0 Hz, 1H), 2.70- 2.79 (m, 1H), 1.84−2.00 (m, 1H), 1.22 (d, J = 7.5 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

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176.1, 138.0, 128.5, 128.4, 127.6, 73.6, 73.5, 73.3, 51.7, 43.1, 36.2, 14.9, 14.6.

*(±)Methyl (2R,3R,4S)-5-(Benzyloxy)-3-hydroxy-2,4-dimethylpentanoate (**5b**).* General Procedure B was followed using 195 mg of **4a**,**b**. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a >20:1 mixture in favor of **5b** (entry 4, Table 3). Purification by flash chromatography (hexanes:Et_2O 70:30) provided **5b** in 81% yield (120 mg). The ^{1}H and ^{13}C NMR for compound **5b** correspond to those previously reported by our lab.[7b]

5b: R_f = 0.17 (hexanes:Et_2O, 70:30); Formula $C_{15}H_{22}O_4$; M_W 366.33 g/mol; IR (neat) υ_{max} = 3504, 3063, 2973, 1736, 1456 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 4.51 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 3.93 (dd, J = 2.8, 8.8 Hz, 1H), 3.69 (s, 3H), 3.53 (m, 2H), 3.04 (bs, 1H), 2.62 (qd, J = 8.8, 7.1 Hz, 1H), 1.95−1.87 (m, 1H), 1.12 (d, J = 7.1 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 138.3, 128.6, 127.9, 127.8, 74.9, 74.7, 73.6, 52.0, 43.5, 35.2, 14.4, 10.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02066.

^{1}H NMR and ^{13}C NMR spectra are available for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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