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Asymmetric Conjugate Addition of Chiral Secondary Borylalkyl Copper Species

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Dedication ((optional))

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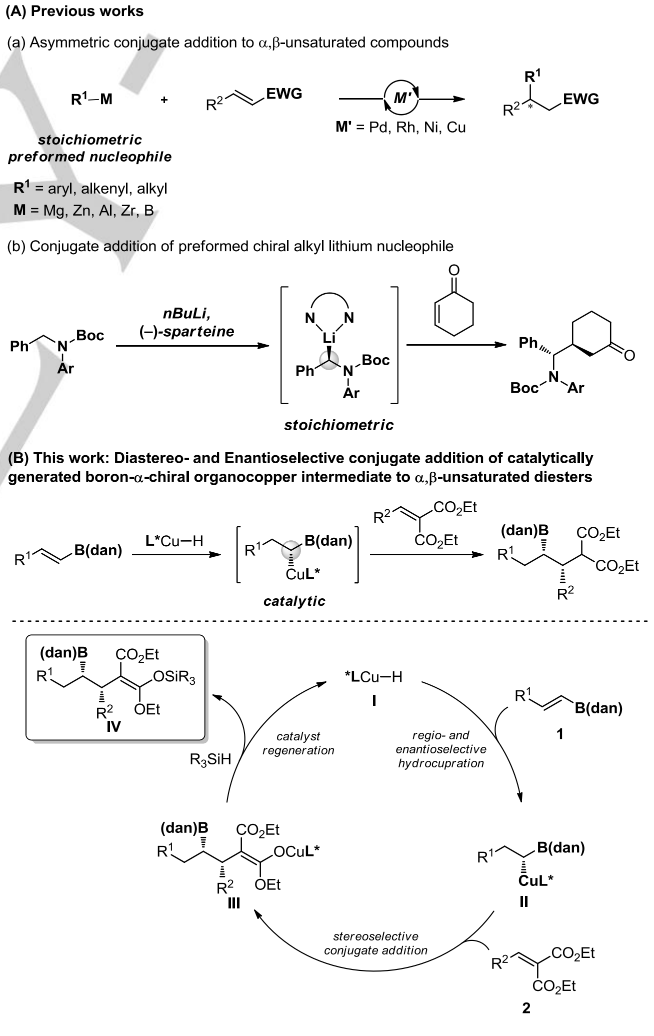
Abstract: We report the diastereo- and enantioselective conjugate addition of chiral secondary borylalkyl copper species derived from borylalkenes in situ to α,β-unsaturated diesters. In the presence of a chiral bisphosphine-ligated CuH catalyst, the conjugate addition provides a direct access to enantioenriched alkylboron compounds containing two contiguous carbon stereogenic centers in good yield with high diastereo- and enantioselectivity (up to >98:2 dr, >99:1 er) by assembling readily available starting alkenyl reagents in a single operation without using preformed organometallic reagents or chiral auxiliaries. The resulting products were used in various organic transformations. The utility of the synthetic approach was highlighted by the synthesis of (–)-phaseolinic acid.

Asymmetric conjugate addition of organometallic reagents to Michael acceptors is an efficient and powerful method for the construction of new carbon stereogenic centers.[1] In general, the conjugate addition reaction has been extensively investigated via a stoichiometric use of preformed organometallic reagents such as Mg,[2] Zn,[3] Al,[4] and Zr,[5] and B-based reagents[6] in the presence of a chiral catalyst (Scheme 1A, a). Despite several important research advances have been made in this research field, the conjugate addition with a chiral secondary alkyl metal nucleophile for the C–C bond formation with two contiguous stereogenic centers has been rarely reported and represents an enormous challenge. Early advances include diastereo- and enantioselective conjugate additions based on the stoichiometric strategy using preformed, configurationally stable chiral organolithium reagents via enantioselective deprotonation of alkyl pronucleophiles (Scheme 1A, b).[7] Other examples were limited to the use of stoichiometric chiral nucleophiles derived from compounds containing chiral auxiliaries.[8]

Catalytic asymmetric tandem reactions convert readily available starting materials to complex chiral building blocks in a single step.[9] A variety of catalytic tandem reactions have been developed in the past in which the precise control of chemoselectivity between the catalyst and competing reagents is essential to ensure the desired reaction pathway. Recently, CuH-catalyzed asymmetric hydrofunctionalization has been used for the synthesis of chiral organic molecules from π-unsaturated pronucleophiles with appropriate electrophiles.[10]

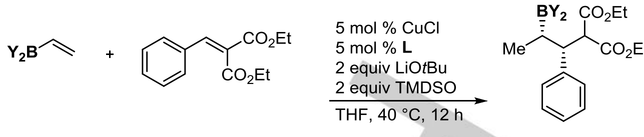


Scheme 1. Overview of asymmetric conjugate addition.

This strategy accessing a catalytic amount of a chiral alkylcopper from olefin successfully avoids stoichiometric preparation of chiral auxiliary-attached substrates or organometallic reagents.[11] We and others have recently reported several examples of CuH-catalyzed hydrofunctionalization of borylalkenes with various electrophiles, which efficiently yielded valuable chiral organoboron compounds.[12,13] More recently, our group described the enantioselective catalytic conjugate addition of a primary borylalkyl NHC-copper complex generated by transmetalation from 1,1-diborylmethane.[14] While it was the first asymmetric conjugate addition of a catalytically generated borylalkyl copper, the conjugate addition of a branched borylalkyl copper species derived from 1,1-diborylethane was not successful under our previous reaction conditions. Pursuing the diastereo- and enantioselective conjugate addition of chiral secondary borylalkyl copper complexes, we tried to access the chiral borylalkyl copper species via enantioselective hydrocupration of prochiral borylalkenes in the presence of Michael acceptors (Scheme 1B). However, such an asymmetric conjugate addition of catalytically generated chiral nucleophiles has yet to be established. The success of the reaction strategy is determined by two important issues: 1) distinguishing the two alkenes by the CuH catalyst chemoselectively in order to generate the corresponding borylalkyl copper species, and 2) adequate reactivity of a secondary chiral borylalkyl copper complex to facilitate the conjugate addition. It is plausible that the catalytic cycle is composed of enantioselective formation of a borylalkyl copper intermediate (**II**), diastereoselective conjugate addition, and the regeneration of the CuH catalyst with the formation of the silylated alkylboron product **IV**.

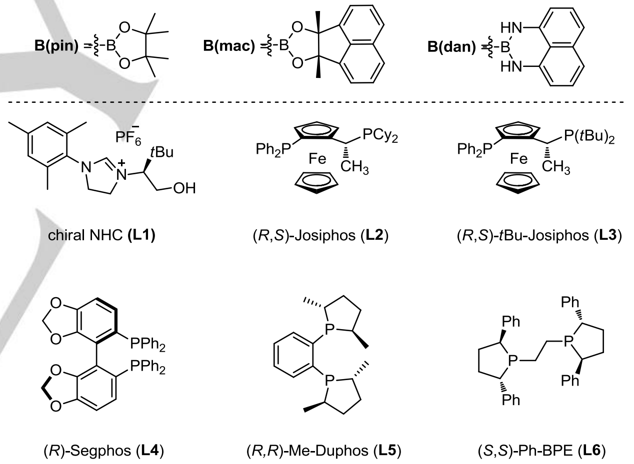
We initiated our study with vinylboronic acid pinacol ester (**1a-Bpin**) and diethyl benzylidenemalonate (**2a**) in the presence of copper chloride with chiral NHC ligand (**L1**), which was the optimal ligand in our previous asymmetric conjugate addition[14] (Table 1, entry 1). Under the reaction conditions, only reduced diethyl benzylmalonate was obtained without the desired product **3a**, which suggests low chemoselectivity of the NHC-Cu catalyst. However, with the chiral bisphosphine ligand (*R*,*S*)-Josiphos (**L2**), surprisingly, the desired product was obtained in 73% yield with high diastereoselectivity, but with low enantiomeric ratio (entry 2). The reaction was then carried out in the absence of a chiral ligand to determine the possible background reaction (entry 3), and no conversion of starting material was observed (entry 3), indicating the importance of ligands in reactivity and enantioselectivity of this transformation. Next, the effect of boryl group (BY$_2$) on the enantio- and diastereoselectivity of this reaction was investigated. The reactions with **1a-Bmac** (mac = methylated acenaphthoquinone)[15] and **1a-Bdan** (dan = 1,8-diaminatonaphthalene)[16] instead of **1a-Bpin** yielded the corresponding addition products with 66:34 er and >98:2 dr (entry 4) and 90:10 er and 88:12 dr (entry 5). With **1a-Bdan** and *t*Bu-Josiphos ligand (**L3**) containing bulkier *t*Bu groups on the phosphine, most promising results were obtained in terms of both enantio- and diastereoselectivity (95:5 er, 94:6 dr) (entry 6).[17] Further evaluation of bisphosphine ligands revealed that the C_2-symmetric ligand (*R*)-Segphos (**L4**), (*R*,*R*)-Me-Duphos (**L5**), and (*S*,*S*)-Ph-BPE (**L6**) containing two phospholane rings were less efficient than **L3** (entry 6–9; 55:45–58:42 er, 48:52–36:64 dr). Finally, the use of Cu(OAc)$_2$ as the copper precursor furnished the desired product with increased yield and thus, it was selected as the optimal precursor for reaction (entry 10).[18]

Table 1. Optimization of reaction conditions.[a]



1a-BY$_2$ **2** **3a-BY$_2$**

Entry	BY$_2$	L	Yield [%][b]	er[c] (major)	dr[d]
1	Bpin	**L1**	0	-	-
2	Bpin	**L2**	73	52:48	95:5
3	Bpin	-	0	-	-
4	Bmac	**L2**	89	66:34	>98:2
5	Bdan	**L2**	76	90:10	88:12
6	Bdan	**L3**	82	95:5	94:6
7	Bdan	**L4**	82	55:45	36:64
8	Bdan	**L5**	74	58:42	35:65
9	Bdan	**L6**	59	55:45	48:52
10[e]	Bdan	**L3**	85	95.5:4.5	95:5



[a] General reaction conditions: **1a-BY$_2$** (0.75 mmol), **2a** (0.5 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), LiO*t*Bu (1 mmol), and TMDSO (1 mmol) in THF (1 mL) at 40 ºC; see the Supporting Information for details. [b] Isolated yield as a mixture of diastereomers. [c] Enantiomeric ratio (er) was determined by chiral HPLC analysis. [d] Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of a crude reaction mixture. [e] Cu(OAc)$_2$ was used instead of CuCl.

We next explored the scope of the asymmetric conjugate addition of various alkenylboron compounds (**1**) with α,β-unsaturated diesters (**2**) under optimized reaction conditions (Table 2). A range of enantioenriched alkylboron products with two adjacent stereogenic centers were efficiently synthesized in high yield and with high levels of enantio- and diastereoselectivity. First, a large scale reaction (2 mmol) of **1a** with a reduced amount of catalyst and ligand (2.5 mol %) was also effective and generated the chiral product **3a** similar to the 0.5 mmol scale reaction. Next, we investigated various α,β-unsaturated diesters (**2**) in the conjugate addition with a terminal vinylboron compound (**1a-Bdan**). A variety of aryl-

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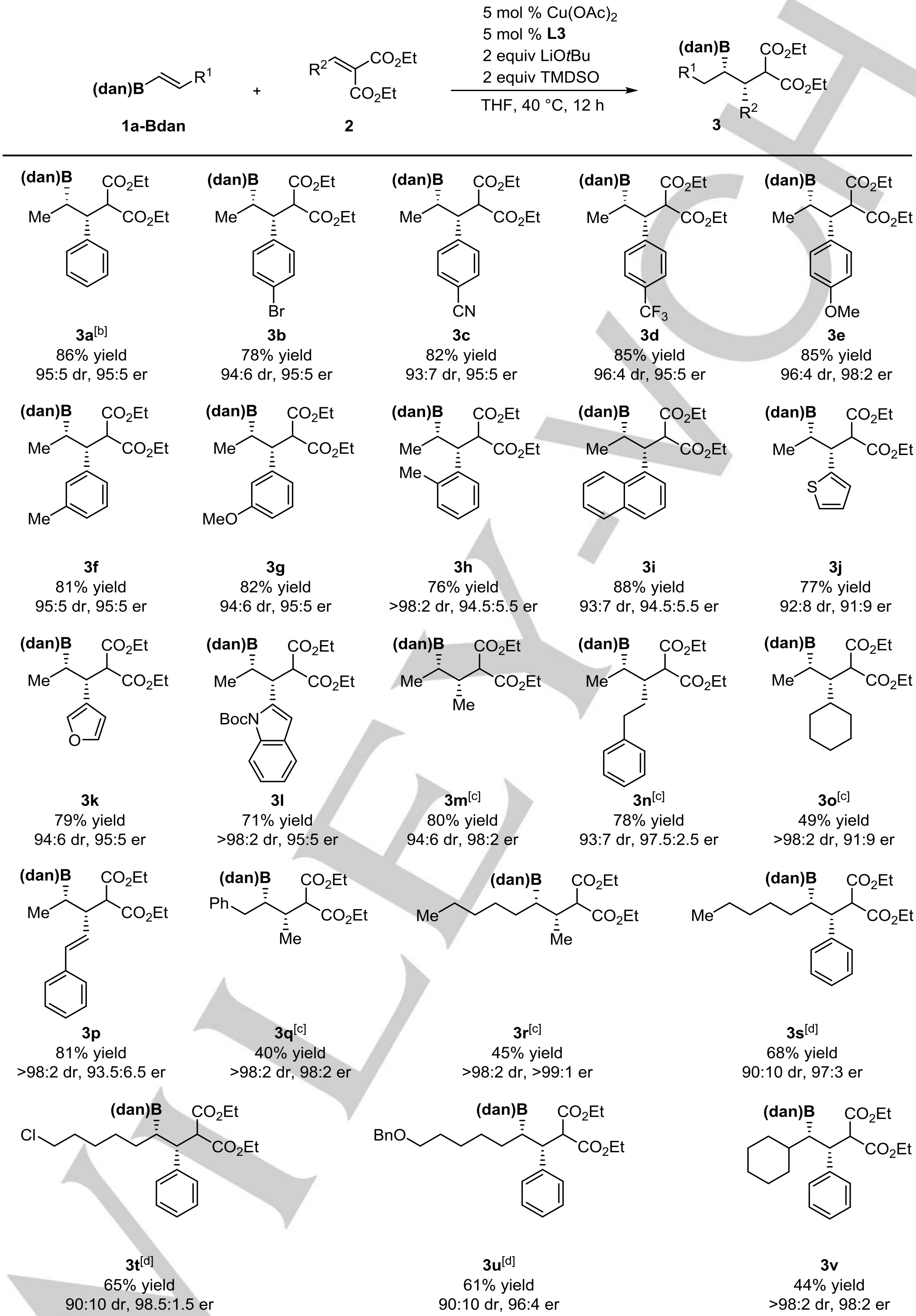
Table 2. CuH-catalyzed asymmetric reductive conjugate addition of borylalkenes to α,β-unsaturated diesters.[a]



3a[b] 86% yield, 95:5 dr, 95:5 er

3b 78% yield, 94:6 dr, 95:5 er

3c 82% yield, 93:7 dr, 95:5 er

3d 85% yield, 96:4 dr, 95:5 er

3e 85% yield, 96:4 dr, 98:2 er

3f 81% yield, 95:5 dr, 95:5 er

3g 82% yield, 94:6 dr, 95:5 er

3h 76% yield, >98:2 dr, 94.5:5.5 er

3i 88% yield, 93:7 dr, 94.5:5.5 er

3j 77% yield, 92:8 dr, 91:9 er

3k 79% yield, 94:6 dr, 95:5 er

3l 71% yield, >98:2 dr, 95:5 er

3m[c] 80% yield, 94:6 dr, 98:2 er

3n[c] 78% yield, 93:7 dr, 97.5:2.5 er

3o[c] 49% yield, >98:2 dr, 91:9 er

3p 81% yield, >98:2 dr, 93.5:6.5 er

3q[c] 40% yield, >98:2 dr, 98:2 er

3r[c] 45% yield, >98:2 dr, >99:1 er

3s[d] 68% yield, 90:10 dr, 97:3 er

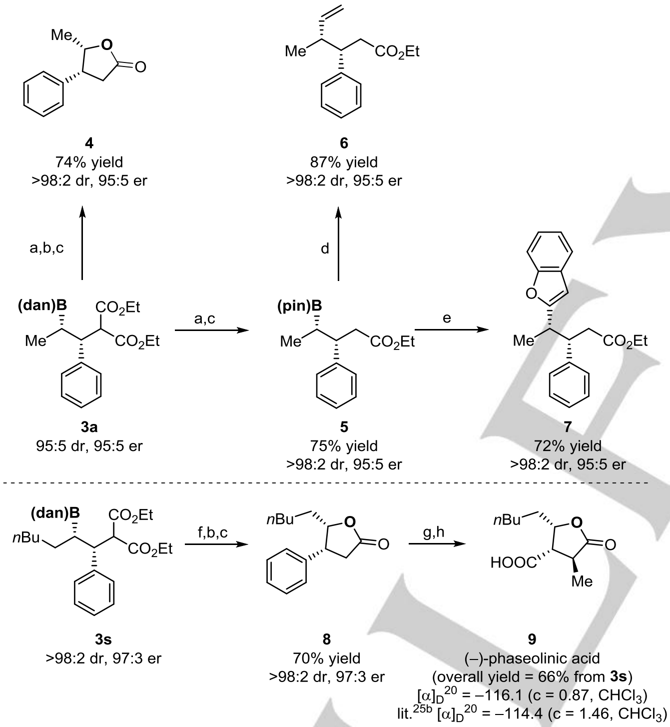
3t[d] 65% yield, 90:10 dr, 98.5:1.5 er

3u[d] 61% yield, 90:10 dr, 96:4 er

3v 44% yield, >98:2 dr, 98:2 er

[a] Isolated yields containing a mixture of two diastereomers. Enantiomeric ratio (er) was determined by chiral HPLC analysis. Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of a crude reaction mixture. 0.5 mmol scale reaction. Isolated yields on a 0.5 mmol scale. The enantiomeric ratio was determined by HPLC analysis. [b] 2.5 mol% of copper/ligand on a 2 mmol scale. [c] The reaction was carried out with 1 equivalent of LiO*t*Bu, 2.5 mol % copper catalyst and 3.75 mol % ligand on a 3 mmol scale. [d] Isolated yield of pure *syn*-diastereomer.

substituted α,β-unsaturated diesters (**2**) with halogen, electron-withdrawing, and electron-donating substituents at *ortho*-, *meta*-, *para*-positions of the aryl group resulted in the desired products with high yield (76–85%), high enantiomeric (94.5:5.5–97:3), and diastereomeric ratios (93:7–98:2) (**3b**–**3h**). Substrates containing a napthyl, and a heteroaryl group such as thiophene, furan, indole were also compatible under the optimal reaction conditions (**3i**–**3l**). Furthermore, primary alkyl substituted diesters afforded the corresponding chiral alkylboron compounds (**3m** and **3n**) without significantly affecting the reactivity and selectivity of the reaction.[19] However, β-cyclohexyl substituted α,β-unsaturated diester yielded the desired product (**3o**) with moderate yield and slightly decreased er value. We also tested the 1,4- vs. 1,6-selectivity of the addition with α,β,γ,δ-unsaturated dienoate **2p**, and exclusively obtained the corresponding 1,4-addition product **3p** in high er and dr.[20] Next, we investigated the addition reaction with internal borylalkenes (**3q**–**3v**). Notably, the challenging internal borylalkenes containing phenyl-, primary-, and secondary alkyl substituents were all efficient, yielding the corresponding chiral products in moderate to good yields with high enantio- and diastereoselectivity. However, other Michael acceptors such as α,β-unsaturated monoester, ketone, diethyl fumarate and dinitrile were not effective for producing desired products under our conditions; a methyl diester substrate yielded the coupled product in 79% yield with slightly decreased dr and er.[21]



Scheme 2. Organic transformation of the conjugate addition products (**3**): Reaction conditions: [a] H_2SO_4, pinacol, THF/H_2O, rt. [b] $NaBO_3$, THF/H_2O, rt. [c] NaCl, DMSO/H_2O, 160 °C. [d] Vinylmagnesium bromide, I_2, THF, -78 °C. [e] Furan, *n*BuLi, NBS, THF, –78 °C. [f] H_2SO_4, THF/H_2O, 50 °C. [g] $RuCl_3$, $NaIO_4$, CCl_4/MeCN/H_2O, rt. [h] NaHMDS, MeI, THF, –78 °C.

To demonstrate the potential synthetic power of the current asymmetric conjugate addition protocols in practical organic synthesis, we performed various organic transformations with the resulting chiral alkylboron products (**3a** and **3s**) (Scheme 2). A chiral γ-lactone (**4**) with two chiral centers was prepared via hydrolysis of the Bdan group of **3a**, intramolecular transesterification, and decarboxylation.[22] β,γ-Chiral alkylboronate ester (**5**) was obtained via conversion of Bdan to Bpin, and decarboxylation. Conversion of the C–B bond of **5** to C–C bonds by vinylation[23] and heteroarylation[24] yielded chiral organic molecules **6** and **7**, respectively. In addition, (–)-phaseolinic acid (**9**), isolated from culture filtrates of fungi such as *Macrophomina phaseolina*, was synthesized from **3s** via the chiral γ-lactone intermediate (**8**).[25]

In summary, we developed a CuH-catalyzed asymmetric reductive conjugate addition of borylalkenes to α,β-unsaturated diesters with high chemo-, diastereo-, and enantioselectivity. This method provides efficient and direct access to enantioenriched alkylboron compounds carrying two contiguous stereogenic centers by assembling readily available starting alkenyl reagents in a single operation without using preformed organometallic reagents or chiral auxiliaries, which greatly expands the scope of asymmetric conjugate addition. Moreover, the utility of the resulting products was demonstrated in the efficient synthesis of (–)-phaseolinic acid and other derivatives. Efforts to expand the use of other chiral alkylcopper species in the asymmetric conjugate addition are currently underway.

Acknowledgements

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Keywords: Asymmetric catalysis • Borylalkene • Conjugate addition • Copper • Enantioselective synthesis

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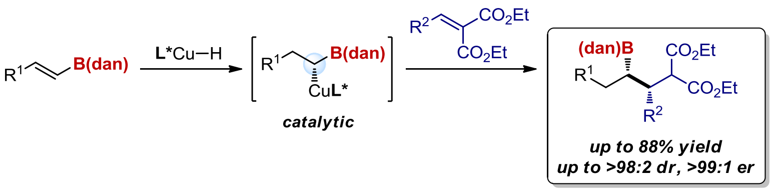

Catalytic diastereo- and enantioselective conjugate addition of chiral secondary borylalkyl copper species derived from borylalkenes in situ to α,β-unsaturated diesters is reported. This method provides enantioenriched alkylboron compounds containing two contiguous carbon stereogenic centers in good yield with high diastereo- and enantioselectivity (up to >98:2 dr, >99:1 er).