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Catalytic 1,3-Difunctionalisation of Organic Backbones through a Highly Stereoselective, One-Pot, Boron Conjugate-Addition/Reduction/Oxidation Process

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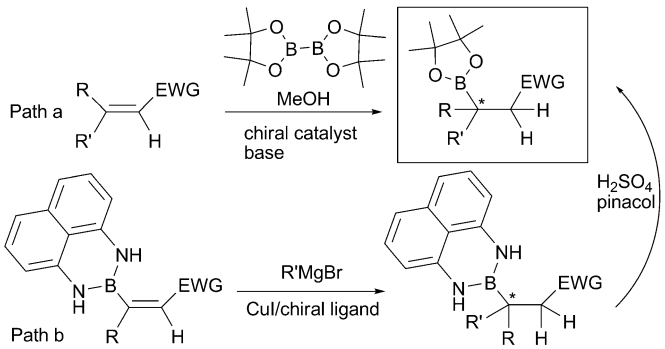
Abstract: A simple one-pot, three-step synthetic route to chiral 1,3-amino alcohols and 1,3-diols has been established. Considering the overall stereocontrol of the synthetic protocol, the first and key step is an enantioselective β-boration of α,β-unsaturated imines and ketones, respectively. The enantioselectivity provided by the Cu^I catalyst modified with Josiphos- and Mandyphos-type ligands has been examined. The oxidative substitution of the boryl unit with a hydroxyl group proceeds with complete retention of configuration at the C_β-atom. In parallel, the stoichiometric reduction of the imino or carbonyl group provides a second stereogenic centre. Depending on the nature of the reducing reagent, exceptionally high diastereoselectivity is achieved, especially for *syn*-1,3-amino alcohols and 1,3-diols.

Keywords: amino alcohols · borates · copper · diastereoselectivity · enantioselectivity

Introduction

Over the course of the last few decades, control of stereochemistry has become very important and, more recently, is a common requirement in organic synthesis. The number of stereoselective reactions is steadily increasing, providing newer and more effective tools to control the formation of new stereogenic elements in organic target molecules. One of the most recently developed and fascinating synthetic tools is the asymmetric boron conjugate addition reaction,[1] which allows the functionalisation of electron-deficient olefins through a Michael type boron addition. In these reactions, the boron nucleophile is generated from common diboron reagents, such as bis(pinacolato)diboron (B_2pin_2, pin = $OC(CH_3)_2C(CH_3)_2O$), whereas the proton electrophile usually derives from an alcohol. In the case of prochiral olefins, enantiocontrol is usually achieved by the use of chiral transition-metal complexes as catalysts,[2] although efficient chiral organocatalytic systems have also been developed.[3a] Of the various chiral catalysts, chiral copper(I)-complexes stand out as the most economical, versatile, active and selective systems for performing the catalytic asymmetric β-boration of activated olefins at room temperature (Scheme 1, Path a).



Scheme 1. Straightforward routes to α-chiral β-functionalised organoboranes.

Alternatively, Hall and co-workers[3b] have developed an interesting asymmetric route to α-chiral boranes by a copper-mediated enantioselective 1,4-addition of Grignard reagents to β-boron-substituted α,β-unsaturated esters and thioesters, with high yields and enantioselectivities up to 98% (Scheme 1, Path b).

Importantly, taking into account the well-established methods for converting C–B bond into C–C, C–O, C–N

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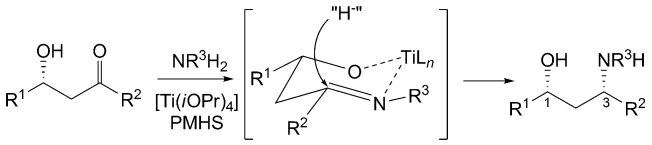
and C–F bonds with complete retention of configuration,[4] the products of the asymmetric boron conjugate addition seem to be highly versatile intermediates, from which densely functionalised organic molecules can be obtained. For instance, Yun and co-workers were able to apply β-boration to cinnamic acid *N*-methylamide in 99% *ee* with a Cu^{I}–Josiphos complex.[2e] Oxidation of the C–B carbon atom to C–O, with complete retention of configuration, afforded a suitable intermediate for the synthesis of (*S*)-fluoxetine.[5] As another example of practical applications of the enantioselective conjugate boron additions, we have recently shown that these reactions can also be used in the synthesis of enantioenriched γ-amino alcohols.[6] To demonstrate this synthetic method, we have optimised the copper-catalysed asymmetric β-boration of three imine derivatives of benzylideneacetone, screening a relatively small, yet diverse library of chiral phosphorus ligands. The chiral copper(I)-complexes provided the β-boryl imines in up to 99% *ee*. A highly diastereoselective, stoichiometric reduction of the C=N bond, followed by oxidative substitution of the boryl functionality with OH, provided the corresponding enantioenriched *syn*- and *anti*-γ-amino alcohols in good to excellent isolated yields (Scheme 2).

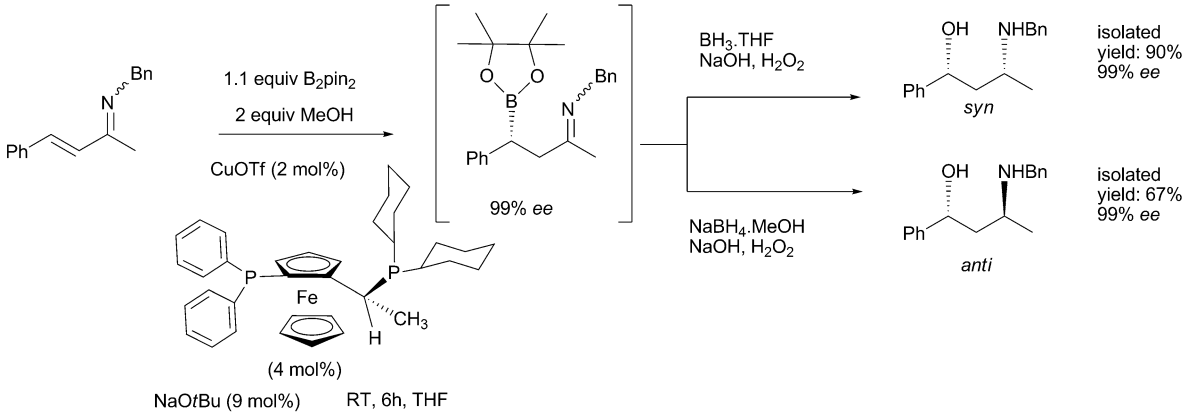
Our described methodology can be considered to be an efficient alternative to currently reported methods. For example, Zhang and co-workers[7] found that rhodium complexes could efficiently be used to perform the enantioselective reduction of β-secondary amino ketones, and Troung and co-workers[8] also described the directed reduction of β-amino ketones to *syn*- or *anti*-1,3-amino alcohols in the presence of Sm complexes. Both methodologies were based on the use of β-secondary amino-ketones as substrates. Alternatively, Rudolph and co-workers[9] reported a directed reductive amination of β-hydroxy-ketones as a convergent assembly towards *syn*-1,3-amino alcohols. In this work, the imino functionality is formed "in situ" in the presence of a primary amine and the intermediate imino alcohol was proposed to strongly coordinate to $[Ti(OiPr)_4]$, and, therefore, the reduction could proceed through a Zimmerman–Traxler type transition state, leading to the desired 1,3-*syn* product (Scheme 3). However, probably all these types of strategies involving β-amino ketones were eclipsed by an efficient, two-step procedure combining organo-, organometallic and



Scheme 3. Directed reductive amination of β-hydroxy-ketones postulated by Rudolph and co-workers.

enzymatic catalysis described by Bäckvall and co-workers.[10] By using this methodology, an elegant enantioselective synthesis of *syn*- and *anti*-1,3-amino alcohols followed by a subsequent reduction/dynamic kinetic asymmetric transformation was achieved. Alternatively, Palmieri and co-workers[11] also described an interesting stereoselective synthesis of enantiopure γ-amino alcohols by reduction of chiral β-enamino ketones. Although the substrate was already chiral, the authors described important mechanistic aspects to justify the preference for formation of the *syn*- or the *anti*-diastereomer, in the presence of AcOH.[12]

In a different context, White and co-workers[13] reported an elegant palladium-mediated allylic C–H amination procedure to synthesise exclusively *syn*-1,3-amino alcohols. Most recently, Ellman and co-workers[14] used a chiral auxiliary substituted on the imino group to control the asymmetric addition of a nucleophile to *N*-sulfinyl imines through a metalloenamine. Reduction of the resulting α-hydroxysulfinyl imines with catecholborane and $LiBHEt_3$ provided *syn*- and *anti*-1,3-amino alcohols, respectively, with very high diastereoisomeric ratios. It is also noteworthy that the *syn*-diastereoisomer was suggested to be formed due to a B–N interaction between the substrate and catecholborane (Scheme 4), as we have suggested in the present work (see below).



Scheme 2. Synthesis of enantioenriched *syn*- and *anti*-γ-amino alcohols from 1-phenyl-*N*-(4-phenylbut-3-en-2-ylidene)methanamine through a one-pot β-boration/reduction/oxidation process.

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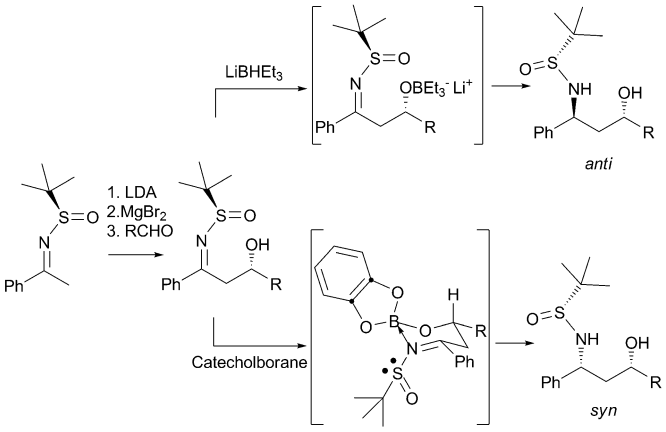


Scheme 4. Asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols from chiral *N*-sulfinyl imines.

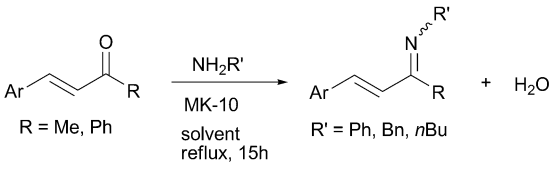
Considering the importance in pharmaceutical applications of chiral γ-amino alcohols (for example, nikkomycin, negamycin, ritonavir and lopinavir)[15] and their notable role as chiral synthons,[16] chiral auxiliaries[17] and chiral ligands in transition-metal catalysis,[18] we decided to survey the possibility of extending the range of α,β-unsaturated imines employed, and compare the results of this study with those obtained from the analogous transformations of the corresponding α,β-unsaturated ketones into chiral 1,3-diols. In this paper we give a full account of this work.

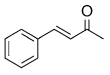
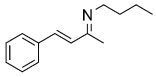
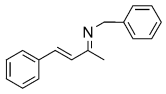
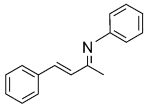
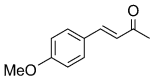
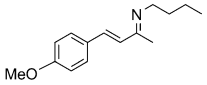
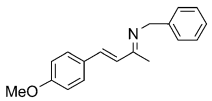
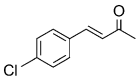
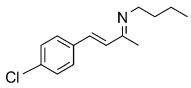
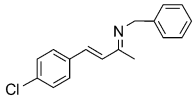
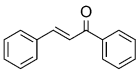
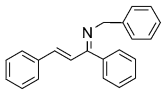
Results and Discussion

Synthesis of α,β-unsaturated imines: Non-functionalised ketones and aldehydes readily react with primary amines to afford the corresponding imines. The equilibrium can be shifted towards imine formation, for example, by using dehydrating agents, or by azeotropic distillation or crystallisation of the imine from the reaction mixture. In early work, we prepared a series of α,β-unsaturated imines and oximes with different electronic and steric properties.[19] The ketones reacted with substituted amines and hydroxylamine in the presence of montmorillonite clay K-10 (MK10), and the rate of condensation of these reactants in the presence of MK10[20] was found to be comparable to the conversion when molecular sieves were used as dehydrating agent.[21] The yields of the isolated α,β-unsaturated imines were high (Table 1, entries 1–3) and comparable to the yields obtained from other synthetic procedures described in the literature.[22,23]

Examining the substrate scope of the present approach involved the synthesis of a series of α,β-unsaturated imines with variations of electronic properties on the structure. The imines *N*-[4-(*p*-methoxyphenyl)but-3-en-2-ylidene]butan-1-amine (**2b**) and 1-phenyl-*N*-[4-(*p*-methoxyphenyl)but-3-en-2-ylidene]methanamine (**2c**) were prepared and isolated in high yields by condensation of the corresponding ketones and amines in the presence of MK-10 (Table 1, entries 4 and 5). Similarly, the imines *N*-[4-(*p*-chlorophenyl)but-3-en-2-ylidene]butan-1-amine (**3b**) and phenyl-*N*-[4-(*p*-chlorophenyl)-but-3-en-2-ylidene]methanamine (**3c**) were synthesised; however, the isolated yields in these cases were only moderate (Table 1, entries 6 and 7). To analyse the influence of bulkier substituents on the imine functionality, the benzylimine **4c** of benzylideneacetophenone was prepared and isolated in 43% yield (Table 1, entry 8). Figure 1 shows the molecular structure of imine **4c** determined by X-ray crystallographic analysis. The C(1)–N(1) distance is 1.285 Å, indicating the double bond character of the imino group. The C(1)–C(2)–C(3)–C(4) dihedral angle of 179.5° confirms the E-geometry around the C=C bond. The co-planarity found for the imine N(1)–C(1) and alkene C(2)–C(3) atoms, and the short distance for a single bond between C(1)–C(2), indicates some degree of conjugation along the N(1)=C(1)–C(2)=C(3) π-electron system. We have found that, to obtain

Table 1. Substrate scope: α,β-unsaturated ketones and the corresponding synthesised α,β-unsaturated imines.[a]



	Ketone		Imine		Isolated yield [%]
1		**1a**		**1b**	73[11]
2		**1a**		**1c**	89[11]
3		**1a**		**1d**	78[11]
4[b]		**2a**		**2b**	95
5[b]		**2a**		**2c**	91
6[b]		**3a**		**3b**	73
7[b]		**3a**		**3c**	73
8[c]		**4a**		**4c**	43

[a] Standard conditions for the imine synthesis: ketone (1 mmol), amine (1.1 mmol), MK-10 (100 mg), CH_3CN (2.5 mL), RT, 15 h. [b] Solvent: MeOH. [c] Solvent: hexane, $T = 70\,°C$.

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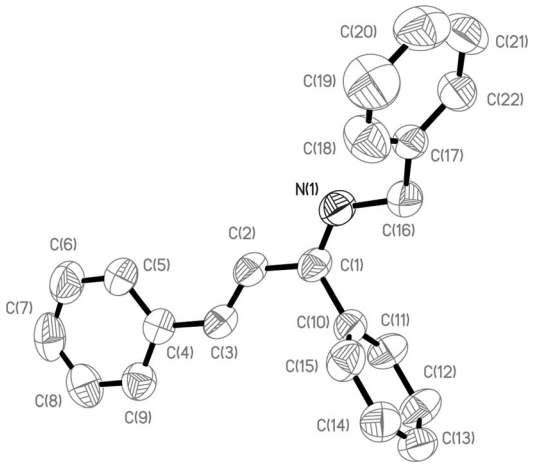
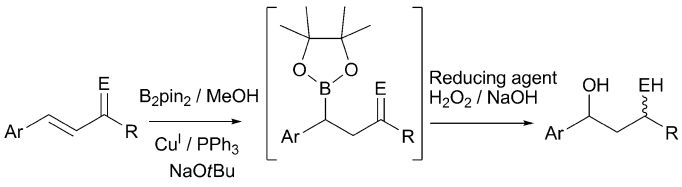


Figure 1. Molecular diagram of benzylimine **4c**. Ellipsoids at 50% probability level. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): C(1)–N(1) 1.285(3), C(1)–C(2) 1.465(3), C(1)–C(10) 1.501(3), N(1)–C(16) 1.462(3), C(2)–C(3) 1.322(3), C(3)–C(4) 1.472(3), N(1)-C(1)-C(2) 117.12(19), N(1)-C(1)-C(10) 124.87(19), C(2)-C(1)-C(10) 118.00(19), C(1)-N(1)-C(16) 119.92(19). C(1)-C(2)-C(3) 125.9(2).



1-6 **7-12** **13-18**

1: Ar= Ph, R= Me, **1a**: E= O, **1b**: E= N(*n*Bu), **1c**: E= N(Bn), **1d**: E= N(Ph)
2: Ar= *p*-MeO-C_6H_4, R= Me, **2a**: E= O, **2b**: E= N(*n*Bu), **2c**: E= N(Bn),
3: Ar= *p*-Cl-C_6H_4, R= Me, **3a**: E= O, **3b**: E= N(*n*Bu), **3c**: E= N(Bn),
4: Ar= Ph, R= Ph, **4a**: E= O, **4c**: E= N(Bn),
5: 2-cyclohexen-1-one
6: *trans*-3-nonen-2-one

Scheme 5. Synthesis of 1,3-diols and 1,3-amino alcohols from α,β-unsaturated ketones and imines through a one-pot catalytic β-boration/reduction/oxidation process.

sufficient chemoselectivity towards imine formation, an aryl substituent on the β-carbon of the ketones is a crucial structural feature. In the case of aliphatic ketones 2-cyclohexen-1-one (**5**) and *trans*-3-nonen-2-one (**6**), the aza-Michael addition dominated, irrespective of the reaction conditions.

Copper/PPh_3-catalysed β-boration of α,β-unsaturated ketones and imines, followed by in situ reduction/oxidation; the origin of the diastereoselectivity: The stereoselectivity of the β-boration/reduction/oxidation process is determined by two independent factors, that is, the enantioselectivity of the boron conjugate addition reaction, and the diastereoselectivity of the stoichiometric reduction of the C=O and C=N double bond. We decided to address the two issues separately. Firstly, we examined the diastereoselectivity of the formation of the 1,3-diols and 1,3-aminoalcohols in a one-pot reaction sequence, whereby the β-boration of substrates **1**–**6** was carried out by using achiral Cu^I catalysts, and the racemic organoboranes were converted in situ into the corresponding products through stoichiometric reduction of the carbon–heteroatom double bond, followed by oxidative substitution of the Bpin moiety, as outlined in Scheme 5.

The catalyst system CuCl/PPh_3 efficiently β-borated the α,β-unsaturated ketones and imines **1**–**6** into the organoboronate intermediates **7**–**12**, in the presence of 1.1 equivalents of bis(pinacolato)diboron (B_2pin_2) at room temperature (Table 2). The addition of base (NaO*t*Bu) was crucial for the quantitative transformation of the substrates into the desired products.[11]

Quantitative conversions were observed for all the substrates (Table 2), except for the β-boration of (*E*)-*N*-(4-phenylbut-3-en-2-ylidene)aniline (**1d**; Table 2, entry 4), which is probably due to the steric hindrance around the imine functionality. We also explored the β-boration of aliphatic ketones 2-cyclohexen-1-one and *trans*-3-nonen-2-one, resulting in complete conversion into the desired organoboranes.

The isolated β-boryl products **7**–**12** have very different boron signals in their $^{11}B\{^1H\}$-NMR spectra, depending on the nature of the C=E functionality (Table 2). Whereas β-boryl ketones show boron signals between $\delta = 33.0$–37.0 ppm (Table 2, entries 1, 5, 8 and 11), the corresponding boron signals for β-boryl imines appear between $\delta = 18.1$–21.7 ppm (Table 2, entries 2–4, 6, 7, 9, 10 and 12). The shift to higher fields of the boron signals in β-boryl imines is diagnostic of the intramolecular interaction between N and B.[24] For the analogous β-boryl ketones, there is no evidence of any intramolecular B–O interaction in solution phase, which is confirmed by solid phase structures of organoboranes **7a** and **10a** (Figures 2 and 3). The B(1)–O(1) distance in compound **7a** is 2.706 Å, which is significantly higher than the sum of the covalent radii of boron and oxygen, indicating negligible interaction between the boron and oxygen centres. The same situation is observed in the case of compound **10a**, however, in this case, the B(1)–O(1) distance is 2.854 Å, which is even higher than in compound **7a**.

From our previous study on the synthesis of enantioenriched γ-amino alcohols,[6] we identified selective reducing agents for the C=N reduction, which, when coupled with the stereospecific oxidation reaction of the B–C bond, provided exclusively the *syn*- or *anti*-γ-amino alcohols. The reducing agents studied were: BH_3·THF, $NaBH_4$·EtOH, $NaBH_4$·MeOH, $NaBH_4$·THF (2% H_2O), DIBAL-H·THF and DIBAL-H/$ZnCl_2$·THF (DIBAL-H = diisobutylaluminium hydride). A pronounced tendency to obtain the *syn*-diastereoisomer was observed in the reduction/oxidation sequence of β-boryl benzylimine **7c** and β-boryl phenylimine **7d** with BH_3·THF. However, selective formation of the *syn*-diastereoisomer of β-boryl butylimine **7b** was only achieved for the reduction/oxidation sequence with DIBAL-H·THF, DIBAL-H/$ZnCl_2$·THF and $NaBH_4$·MeOH.[6] In this work, the reagent BH_3·THF was chosen for the reduction step, whereas the oxidative cleavage of the C–B bond was carried

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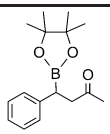
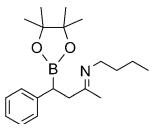
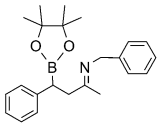
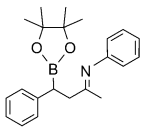
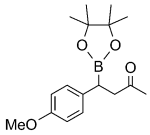
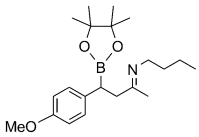
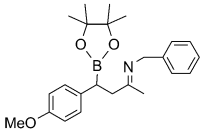
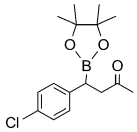
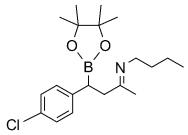
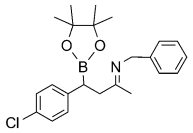
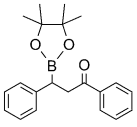
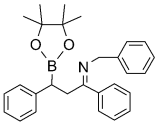
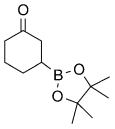
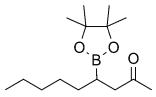
Table 2. $CuCl/PPh_3$ catalysed β-boration of α,β-unsaturated ketones and α,β-unsaturated imines.[a]

	Organoborane		Conv. [%][b]	Isolated yield [%]	$^{11}B\{^1H\}$-NMR δ [ppm]
1		**7a**	99	42	37.0
2		**7b**	99	70	21.7
3		**7c**	99	82	21.1
4		**7d**	40	29	21.4
5		**8a**	90	82	33.6
6		**8b**	99	97	20.2
7		**8c**	99	85	19.2
8		**9a**	98	91	33.1
9		**9b**	99	89	19.0
10		**9c**	99	85	18.9
11		**10a**	99[c]	57	34.1
12		**10c**	99[c]	78	18.1
13		**11a**	100	88	33.4
14		**12a**	100	52	38.1

[a] Standard conditions for the β-boration: substrate (0.25 mmol), CuCl (2 mol%), PPh_3 (4 mol%), B_2pin_2 (1.1 equiv), NaO*t*Bu (3 mol%), MeOH (2 equiv), THF (2.5 mL), RT, 6 h. [b] Conversion calculated on the basis of ^1H NMR spectroscopic analysis. [c] 12 h.

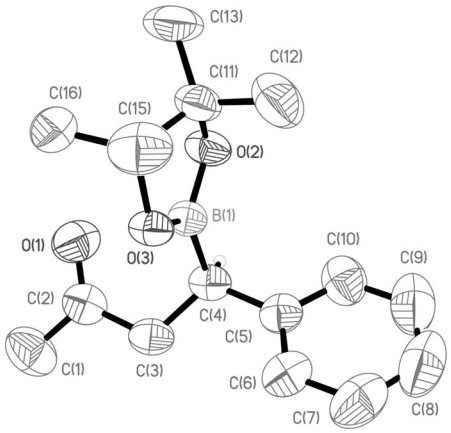


Figure 2. Molecular diagram of β-boryl imine **7a**. Ellipsoids at 50% probability level. Hydrogen atoms have been omitted for clarity except H(4). Selected bond lengths (Å) and angles (°): B(1)–O(1) 2.706, O(1)–C(2) 1.204(2), B(1)–O(3) 1.3580(18), B(1)–O(2) 1.3594(18), B(1)–C(4) 1.567(2), C(1)–C(2) 1.493(3), C(2)–C(3) 1.493(2), C(3)–C(4) 1.517(2), O(3)-B(1)-O(2) 113.37(13), O(2)-B(1)-C(4) 123.21(13), O(1)-C(2)-C(3) 121.31(15).

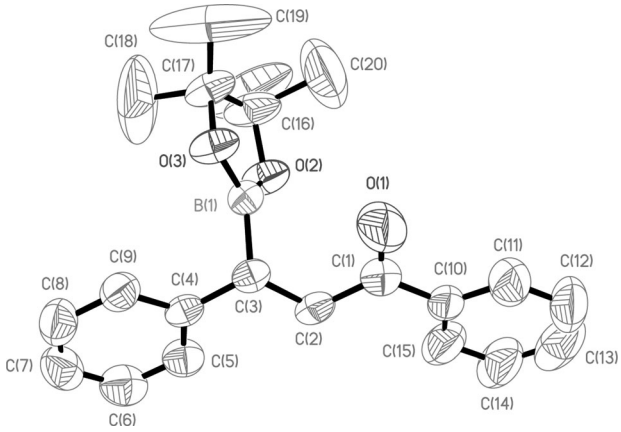


Figure 3. Molecular diagram of β-boryl imine **10a**. Ellipsoids at 50% probability level. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): B(1)–O(1) 2.854, O(1)–C(2) 1.206(6), B(1)–O(3) 1.354(5), B(1)–O(2) 1.357(5), B(1)–C(3) 1.565(6), C(1)–C(2) 1.491(7), C(2)–C(3) 1.518(6), C(3)–C(4) 1.521(6), O(3)-B(1)-O(2) 112.8(3), O(1)-C(1)-C(10) 120.3(5), O(2)-B(1)-C(3) 122.3(4), C(1)-C(2)-C(3) 112.9(4), C(4)-C(5)-C(6) 120.6(5).

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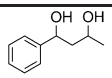
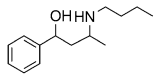
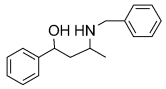
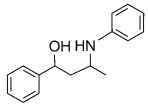
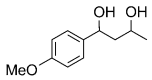
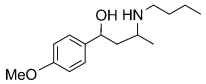
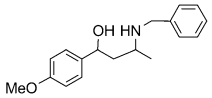
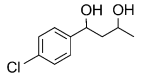
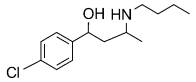
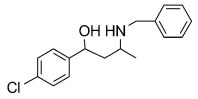
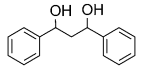
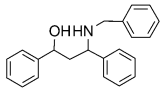
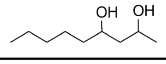
out in the presence of alkaline hydrogen peroxide. With these model reagents for reduction/oxidation, we intended to identify those structural features of the substrates that influence the diastereoselectivity of the reduction/oxidation of organoboranes **7**–**12** (Table 3) to the greatest extent. The diastereoselectivity of the reactions was determined by ^{1}H NMR spectroscopic analysis of the crude and isolated 1,3-diols and 1,3-amino alcohols **13**–**18**. We found that, in most cases, the stoichiometric reduction/oxidation of organoborane intermediates indeed takes place with good to excellent *syn*-selectivity (Table 3, entries 1, 3, 4, 7, 11 and 12). It is worth mentioning that, in addition to ^{1}H NMR spectroscopic evidence, the formation of the *syn*-products was also confirmed by X-ray studies on **16a** (Figure 4). Notable exceptions are the reduction/oxidation of β-boryl *n*-butylimines, which afforded 1,3-amino alcohols with comparable amounts of both the *syn*- and *anti*-diastereoisomers (Table 3, entries 2, 6 and 9). To improve the diastereoselectivity of the *syn*-1,3-amino alcohol, we turned our attention to the alternative reducing reagent, DIBAL-H·THF, which provided high *syn*-diastereoselection on the β-boryl *n*-butylimine (Table 4, entry 1).[6] When β-boryl-*n*-butylimines **8b** and **9b** were reduced and oxidised with DIBAL-H·THF and H_2O_2/NaOH, respectively, the formation of the *syn*- versus the *anti*-diastereoisomer increased, although no exclusive formation of either *syn*-**14b** or *syn*-**15b** products could be achieved. In contrast to the case of acyclic substrates, the reduction/oxidation of 3-boryl-cyclohexen-1-one (**11a**) with BH_3·THF and H_2O_2/NaOH, gave the *anti*-diastereoisomer as the major product (Table 3, entry 13).

Table 3. Diastereoselective reduction/oxidation of β-boryl ketones and β-boryl imines with BH_3·THF and H_2O_2/NaOH.[a]

	Difunctionalised product[b]		*syn*/*anti* ratio	Isolated yield [%]	*syn*/*anti* product
1[6]		**13a**	95:5	85	99:1
2[6]		**13b**	53:47	–	–
3[6]		**13c**	95:5	82	99:1
4		**13d**	99:1	95	99:1
5		**14a**	83:17	71	99:1
6		**14b**	54:46	–	–
7		**14c**	77:23	80	98:2
8		**15a**	86:14	82	99:1
9		**15b**	60:40	–	–
10		**15c**	87:13	73	98:2
11		**16a**	99:1	95	99:1
12		**16c**	99:1	90	99:1
13		**17a**	30:70	60	1:99
14		**18a**	80:20	63	99:1

[a] Standard conditions for the reduction: β-boryl ketone or imine (0.5 mmol), BH_3·THF (1 M, 1.5 mL, 1.5 mmol), THF (2 mL), 0 °C to 25 °C, 15 h. Standard conditions for the oxidation: NaOH (aq.) (1.0 M, 10 mL, 10 mmol), H_2O_2 (aq.) (30 % v/v, 750 mL, 7.6 mmol), RT, 3 h. [b] Conversion calculated on the basis of ^{1}H NMR spectroscopic analysis were more than 99 % in all the examples, in at least two reproducible reactions.

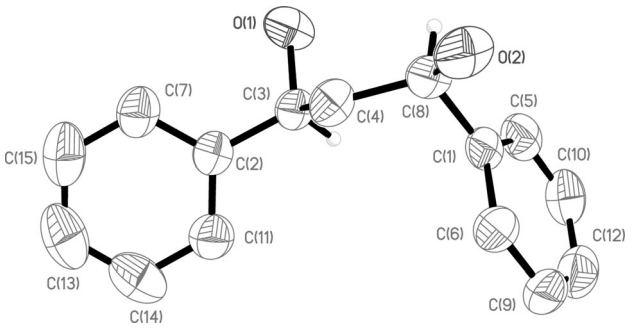


Figure 4. Molecular diagram of 1,3-diol **16a**. Ellipsoids at 50 % probability level. Hydrogen atoms have been omitted for clarity except H(3) and H(8). Selected bond lengths (Å) and angles (°): O(1)–C(3) 1.432(3), C(1)–C(8) 1.516(3), O(2)–C(8) 1.434(3), C(2)–C(3) 1.512(3), C(3)–C(4) 1.522(4), C(4)–C(8) 1.524(3), O(1)–C(3) 1.432(3), O(1)-C(3)-C(2) 111.66(19), C(2)-C(3)-C(4) 113.14(19), C(2)-C(3)-C(4) 113.14(19).

Table 4. Diastereoselective reduction/oxidation of β-boryl *n*-butylimines with DIBAL-H·THF and H_2O_2/NaOH.[a]

	Difunctionalised product	Conv. [%][b]	*syn*/*anti*	Isolated yield [%]	*syn*/*anti* ratio of pure product
1	**13b**	90	99:1	84	99:1
2	**14b**	99	77:23	47	99:1
3	**15b**	99	82:18	52	99:1

[a] Standard conditions for the reduction: β-boryl *n*-butylimines (0.5 mmol), DIBAL-H·THF (3 eq), THF (2 mL), −78 °C to 25 °C, 15 h. Standard conditions for the oxidation: NaOH (aq.) (1.0 M, 10 mL, 10 mmol), H_2O_2 (aq.) (30 % v/v, 750 mL, 7.6 mmol), RT, 3 h. [b] Conversion calculated on the basis of ^{1}H NMR spectroscopic analysis.

To explain the pronounced *syn*-selectivity of the reaction sequence (Scheme 5), we suggest a model based on the

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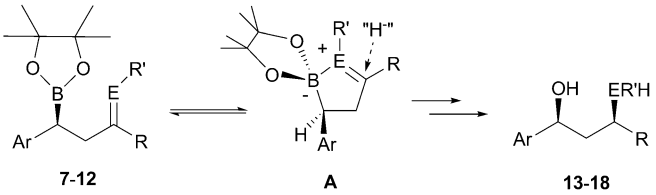
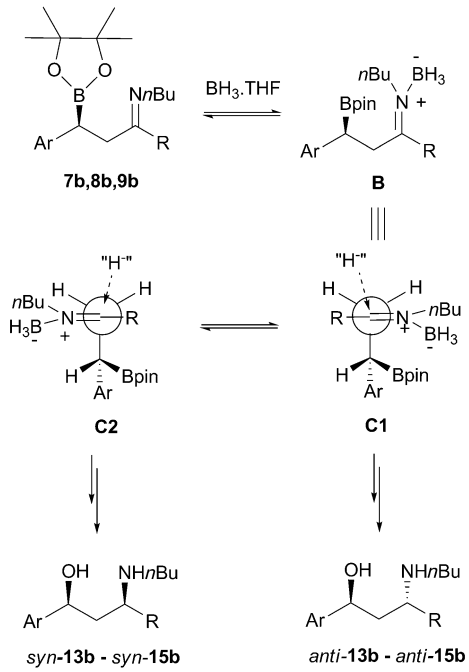
close proximity of the Lewis acidic boryl group and the Lewis basic ketone/imine functionalities in the organoborane intermediates **7–12**. If we consider an intramolecular Lewis acid/Lewis base interaction between the two functional groups (i.e., **A**; Scheme 6), the cyclic B–N chelate structures formed upon such an interaction have two sterically different diastereotopic faces. The primary factor that creates the facial differentiation is the substituent on the β-carbon, as shown in Scheme 6. Other steric features of the molecules (such as the large boronate ester group) are expected to exert a similar steric influence on both sides of the C=E functionality, however, they could contribute by amplifying or reducing the effect of the β-substituent. It is important to note that the existence of such interactions are widely accepted in the literature,[25] even on ketone and aldehyde systems;[26] however, to the best of our knowledge, direct proof has never been presented.



Scheme 6. Predicted intramolecular Lewis acid complex involved in organoboronates **7–12** resulting in the formation of the *syn*-diastereoisomers **13–18**.

For the reasons outlined above, we have made a considerable effort to find structural and spectroscopic evidence for the internal Lewis acid–Lewis base interaction shown schematically in Scheme 6 by structure **A**. Despite the lack of solid-state structural evidence, there is a clear spectroscopic indication of intramolecular B–N interaction as shown in Table 2. The observed $\Delta\delta$ between the $^{11}B\{^{1}H\}$-NMR chemical shifts of the β-boryl ketones and the corresponding β-boryl imines are consistent with partial rehybridisation of the boron atom from pure sp^2 towards sp^3 in the case of the β-boryl imines upon the formation of the intramolecular Lewis adducts. We can presume, therefore, that the controlling element in the formal hydride addition that results in high *syn*-diastereocontrol is indeed a complex of type **A** (Scheme 6). In cases where E is NR′, the evidence for the chelates is strong (especially from ^{11}B NMR spectroscopic analysis). In the case of ketones, the explanation forwarded by previous workers in this area,[24] that a transient activated intramolecular complex is likely to be involved, seems to be a sound hypothesis because such complexes can effect remote asymmetric induction processes.[24,25]

In contrast to the highly *syn*-diastereocontrolled reduction reaction, the origin of the dominant *anti*-selectivity in the reduction/oxidation of 3-boryl-cyclohexen-1-one (**11a**) can be explained by the lack of intramolecular Lewis acid–Lewis base interactions between the B and O centres, due to the cyclic conformational restrictions of the molecule. As expected with 3-substituted cyclohexanones, hydride reduction occurs to give predominantly 1,3-*anti*-stereocontrol, as explained elsewhere.[27] However, the origin of the reduced *syn*-diastereocontrol upon formation of the *N*-*n*-butyl amino alcohols **13–15b** (see Table 3) is less clear. In these cases, the *syn*-diastereocontrol remains in place to some extent, perhaps by intramolecular B–N complex **7b–9b**, as outlined in Scheme 6. However, a more likely explanation is that in the presence of BH_3·THF, there is the competing effect of intermolecular N–B complexation with the reducing agent BH_3·THF due to the more electron-rich *n*-butyl imine (see Scheme 7). This would have the effect of allowing acylic stereoselection processes to occur, which are likely to be governed by the types of effects used to explain additions to chiral ketone systems.[28] Hence, *n*-butyl-BH_3 activated complexes of type **B** could undergo additions as outlined in Scheme 5 to derive both *syn*- and *anti*-products via reactive conformations **C1** and **C2**. In these types of models, we predict that the Ar group behaves as the larger group, leaving the Bpin moiety to stabilise or destabilise either of the possible reactive conformations. In fact, there may be little to choose between conformations **C1** and **C2**, with the former having possible stereoelectronic repulsion between the electropositive formal imminium ion, and the latter having steric repulsion between the R-group and Bpin. The net result would be approximately equal amounts of both the *syn*- and *anti*-diastereoisomers being formed, as is indeed observed.



Scheme 7. Proposed origin of the competing *anti*-diastereoselection in the BH_3-mediated reduction to derive amino alcohols **13–15b**.

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Copper–chiral-ligand-catalysed β-boration of α,β-unsaturated ketones and imines, followed by in situ reduction/oxidation—the origin of the enantioselectivity: The overall stereoselectivity of the β-boration/reduction/oxidation reaction was next addressed through the enantioselective β-boration of the α,β-unsaturated ketones and imines **1**–**3**, in the presence of copper(I) modified with chiral bidentate ligands, followed by in situ reduction/oxidation with the appropriate reducing reagent (BH_3·THF or DIBAL-H·THF) and H_2O_2/NaOH. The chiral ligands explored were Josiphos diphosphanes **19** and **20** and Mandyphos diphosphanes **21**–**22**.[29] Most of the reactions were complete within 6 h at room temperature (Table 5).

Table 5. Enantio- and diastereo-selective β-boration/reduction/oxidation of α,β-unsaturated imines and ketones with Cu-chiral ligands.[a]

	Product	Chiral ligand	NMR yield [%][b]	*syn*/*anti*	*ee*
1	**13a**	**19**	99	92:8	8
2	**13a**	**20**	99	90:10	66
3	**13a**	**21**	99	95:5	75
4	**13a**	**22**	99	90:10	52
5[c][6]	**13b**	**19**	94	99:1	80
6[6]	**13c**	**19**	99	91:9	99
7[6]	**13d**	**19**	99	99:1	52
8	**14a**	**19**	99	83:17	3
9	**14a**	**20**	99	82:18	65
10	**14a**	**21**	44	83:17	10
11	**14a**	**22**	71	83:17	42
12[c]	**14b**	**19**	99	54:46	79
13	**14c**	**19**	99	71:29	93
14	**15a**	**19**	99	88:12	5
15	**15a**	**20**	99	84:16	42
16	**15a**	**21**	90	86:14	61
17	**15a**	**22**	96	84:16	65
18[c]	**15b**	**19**	99	57:43	56
19	**15c**	**19**	99	82:18	61
21[d]	**16a**	**19**	99	99:1	2
22[d]	**16a**	**20**	99	99:1	42
23[d]	**16a**	**21**	90	99:1	73
24[d]	**16a**	**22**	96	99:1	84
25[d]	**16c**	**19**	99	99:1	65

[a] Standard conditions for the reduction: β-boryl ketone or imine (0.5 mmol), BH_3·THF (1 M, 1.5 mL, 1.5 mmol), THF (2 mL), 0 °C to 25 °C, 15 h. Standard conditions for the oxidation: NaOH (aq.) (1.0 M, 10 mL, 10 mmol), H_2O_2 (aq.) (30 % v/v, 750 mL, 7.6 mmol), RT, 3 h. [b] Calculated on the basis of ^{1}H NMR spectroscopic analysis. [c] Standard conditions for the reduction: β-boryl *n*-butylimines (0.5 mmol), DIBAL-H·THF (3 equiv), THF (2 mL), −78 °C to 25 °C, 15 h. [d] 12 h.

The enantiomeric excess of **1a** was variable, ranging from 8 % with the catalytic system CuCl/ligand **19**, to 75 % with CuCl/ligand **21** (Table 5, entries 1–4). The asymmetric induction observed is in agreement with related reports.[2] Ligand **20** and the two Mandiphos type ligands **21** and **22** had a positive influence on the asymmetric β-boration of the analogous substrates **2a** and **3a**, whereas the chiral ligand **19** was quite inefficient (*ee* < 10 %; Table 5, entries 8–11 and 14–17). Neither electron-donating nor electron-releasing substituents on the phenyl group in the β-position of the substrate had a significant influence on the asymmetric β-boration. However, when the corresponding α,β-unsaturated imines were involved in the asymmetric β-boration, it is worth mentioning that the catalytic system CuCl/ligand **19** provided the best results (Table 5, entries 5–7, 12, 13, 17 and 18). Electron-rich substrates could be transformed into the corresponding γ-amino alcohols with *ee* values of between 93 and 99 % (Table 5, entries 6 and 13). Substituents on the nitrogen atom of the imines had an influence on the enantioselectivity of the β-boration, as shown in Table 5 and Figure 5. The electronic and steric properties of the imino benzyl group also had a beneficial effect on the enantioselectivity of the asymmetric β-boration.

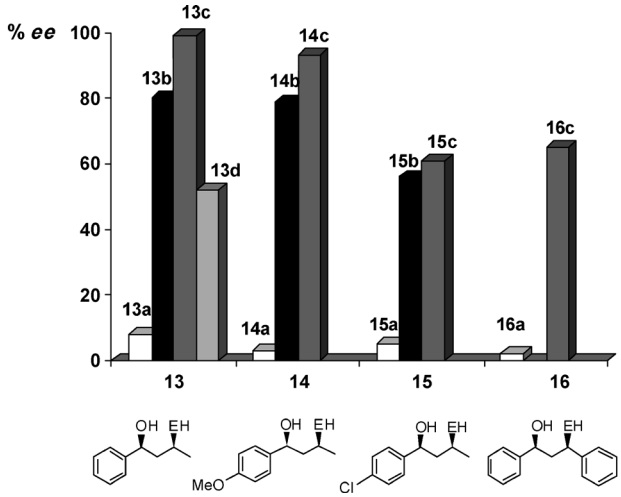

Figure 5. Relative values of enantiomeric excesses on the catalytic β-boration/reduction/oxidation of α,β-unsaturated ketones and imines.

The benefits of our methodology with respect to the reported methodologies is based on the use of simple, achiral, activated ketones or imines and the use of inexpensive copper catalyst for the β-boration. The asymmetric β-boration is achieved by the use of catalytic amounts of chiral diphosphanes, and the reduction/oxidation procedure can be performed with appropriate reducing agents to obtain the *syn*-diastereoisomer with retention of configuration, in a one-pot sequence.

Conclusion

This comparative study on the catalytic β-boration/reduction/oxidation of α,β-unsaturated ketones and imines has highlighted two important features. The asymmetric induction of the β-boration of α,β-unsaturated imines has been performed with more success than in the case of the corresponding α,β-unsaturated ketones, when the catalytic system is CuCl modified with Josiphos type ligand **19**. The imine group itself and the aryl and alkyl substituents on the imino group seem to provide a beneficial effect on the enantioselection of the reaction, and configuration is maintained along the subsequent reduction and oxidation, which allows the reaction to proceed in a one pot system. As far as the

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reduction protocol is concerned, it has also been observed that when BH_3·THF is used as reducing reagent, the *syn*-diastereoisomer is favoured, probably due to an intramolecular B–N interaction. This hypothesis has also been supported by $^{11}B\{^1H\}$-NMR studies that confirm intramolecular B–N chelation. The lack of this intramolecular interaction for the corresponding β-boryl ketones (supported by $^{11}B\{^1H\}$-NMR spectroscopic analysis and by X-ray diffraction studies), could also explain why the diastereoselectivity of the *syn*-isomer is lower. However, when *n*-butyl groups are the substituents of the imino group, the ratio of *syn*- versus *anti*-diastereoisomer decreases to close to 1/1. In this case, a plausible explanation is the presence of competitive inter- and intra-molecular interactions of the imine nitrogen atom with both the BH_3·THF and the Bpin, respectively, which could explain the lack of diastereoselectivity. *n*-Butyl amino alcohols with improved *syn*-diastereomer selectivity can be obtained using DIBAL-H·THF as the reducing reagent. The one-pot reaction sequence β-boration/reduction/oxidation of activated ketones and imines offers a convenient method for the direct synthesis of enantioenriched 1,3-diols and 1,3-amino alcohols. Experimental and theoretical efforts to elucidate the intrinsic mechanism of the asymmetric induction are being developed in our laboratories.

Experimental Section

General method for one-pot copper-catalysed asymmetric β-boration/reduction/oxidation of α,β-unsaturated imines and ketones: CuCl (0.01 mmol), phosphorus bidentate ligand (0.01 mmol) and *t*BuONa (0.045 mmol) were transferred into a Schlenk tube and dissolved in THF (1.5 mL) under nitrogen. The suspension was stirred for 30 min and bis(-pinacolato)diboron (140 mg, 0.55 mmol) was added. The suspension was stirred for 10 min. Afterwards, a solution of the corresponding α,β-unsaturated imine or ketone (0.5 mmol) was added in THF (1 mL). Finally, MeOH (40 μL, 2 equiv) was added, and the mixture was allowed to stir at RT for 6 h. The reaction mixture was cooled to low temperatures (0 °C and −78 °C, and the reducing agent (1.5 mmol) was added "in situ" according to the reduction procedures (see the Supporting Information). The solution was treated with NaOH (aq.) (1.0 M, 5 mL, 5 mmol) and H_2O_2 (aq.) (30 % w/v, 500 μL, ca. 4 mmol) and stirred for 3 h at RT to give a colourless solution, which was partitioned between dichloromethane and saturated NaCl (aq.). The organic phase was dried over $MgSO_4$ and the organic solvents were evaporated to yield the crude products as cloudy oils, which were purified by column chromatography.

CCDC-829890 (**4c**), -829889 (**7a**), -829887 (**10a**) and -829888 (**16a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[29] Ligand **19**: (*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine ethanol adduct; ligand **20**: (*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldi(3,5-xylyl)phosphine; ligand **21**: (α*R*,α*R*)-2,2′-bis(α-N,N-dimethylaminophenylmethyl]-(*S*,*S*)-1,1′-bis(-diphenylphosphino)feroocene; ligand **22**: (α*R*,α*R*)-2,2′-Bis(α-*N*,*N*-(dimethylamino)benzyl)((*S*,*S*)-1,1'-bis[di(3,5-dimethyl-4-methoxy phenyl)phosphino]ferrocene.

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