Full Paper

Applied Organometallic Chemistry

Received: 18 October 2012 Revised: 21 November 2012 Accepted: 2 December 2012 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/aoc.2957

Basic $CuCO_3$/ligand as a new catalyst for 'on water' borylation of Michael acceptors, alkenes and alkynes: application to the efficient asymmetric synthesis of β-alcohol type sitagliptin side chain

Gaj Stavber[a] and Zdenko Časar[a,b,c]*

The efficient 'on water' β-borylation using bis(pinacolato)diboron agent was achieved with a newly developed catalytic system based on basic copper carbonate and various ligands. The catalytic system was used for β-borylation of various Michael acceptors, alkenes and alkynes. The presented methodology was successfully applied to the novel synthesis of β-alcohol type sitagliptin side chain precursor via water-based highly enantioselective β-borylation followed by an oxidation process. Copyright © 2013 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: water; copper catalysis; boron; asymmetric synthesis; drugs

Introduction

Introduction of a boron moiety into organic molecules constitutes a central research interest in the field of modern organoboron chemistry.[1] This is due to the immense synthetic versatility[2] and unique biological activity[3] of organoboron compounds. Besides hydroboration with R'_2BH,[4] diboron reactions[5] based on bis(pinacolato)diboron (B_2pin_2) or bis(catecholato)diboron (B_2cat_2) as boron source gained strong impetus in the last decade as an attractive method for the introduction of boron into organic frameworks via unsaturated precursors (Scheme 1). This is due to the discovery of a catalytic version of the reaction catalyzed by transition metal salts in the presence of additional base additives and ligands, which also enables asymmetric β-borylation.[6] Recent advances in the preparation process of B_2pin_2 rendered this boron precursor easily and effectively accessible, which should further extend its use as a prime borylation reagent.[7]

Therefore, there is a wide interest in further developing B_2pin_2-based β-borylation methodology. Although Michael acceptors have been widely studied as model compounds in catalytic β-borylation reactions[8–10] and very recently the β-borylation of alkynes was achieved,[11] catalytic systems with a broad substrate acceptance are still scarce. Moreover, catalytic β-borylation is still conducted in organic solvents such as CH_2Cl_2, THF and toluene in the presence of a proton donor such as methanol.[12] Furthermore, the copper-catalyzed reactions are very often conducted in the presence of additional base additives such as alkali metal alkoxides (e.g. NaO^tBu). Based on these facts we presumed that existing catalytic systems based on copper species could be simplified and become more economical by removing the alkali metal alkoxide base additives from the catalytic system. For this purpose we envisioned that basic copper carbonate [$Cu_2(OH)_2CO_3$][13] could be used as an appropriate transition metal precursor incorporating metal species as well as basic functionality. Moreover, the recent discovery of some 'on water' accelerated reactions, which can be simply carried out by vigorous stirring of the neat reactants in an aqueous suspension,[14] stimulated us to investigate the proposed catalytic system in pure water† in order to make the overall method more sustainable. It is worth mentioning that in many cases the incompatibility of organic substrates, intermediates and catalysts with water, which is a result of hydrophobic interactions, represents a potential obstacle to efficiently perform organic reactions in aqueous medium.[15] This finally leads us to take up the challenge of discovery and development of the water-compatible catalytic system based on basic copper carbonate/ligand for efficient and (stereo)selective β-borylation of a wide range of organic compounds.[16]

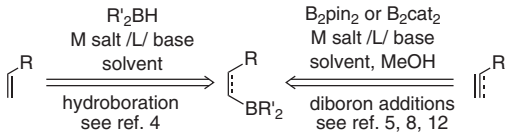
* *Correspondence to: Zdenko Časar, Sandoz GmbH, Global Portfolio Management API, Biochemiestrasse 10, 6250 Kundl, Austria. E-mail: zdenko.casar@sandoz.com*

a *Lek Pharmaceuticals d.d., Sandoz Development Center Slovenia, API Development, Organic Synthesis Department1234 Mengeš, Slovenia*

b *Sandoz GmbH, Global Portfolio Management API, 6250Kundl, Austria*

c *Faculty of Pharmacy, University of Ljubljana, 1000Ljubljana, Slovenia*

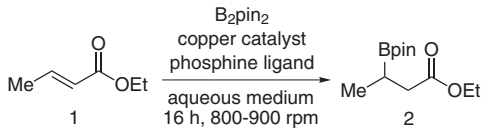
† During the preparation of this manuscript and corresponding patent application (see reference 16) an amine base promoted β-borylation of Michael acceptors in water was reported by Santos *et al.* (see reference 10) For a detailed explanation of conceptual differences between this and Santos's reports see supporting information (S27).



Scheme 1. Main methodologies for introduction of a boron moiety into unsaturated precursors.

Results and Discussion

We started our investigation by screening reaction conditions on (*E*)-ethyl crotonate **1** as a model substrate (Scheme 2 and Table 1). First we tested the compatibility of some newly established catalytic β-borylation methods with water, using an aqueous solution of α-tocopheryl polyethylene glycol succinate (TPGS) amphiphile. The recently described method of Bonet *et al.*[9f] provided a low 12% conversion to **2** (entry 1) also at an elevated temperature of 60 °C. Furthermore, the method of Mun *et al.*[12] resulted in incomplete conversion of **1** to **2** (entry 2). Next, we were eager to perform control experiments using the proposed catalytic system based on basic $CuCO_3$. The important information would



Scheme 2. β-Borylation of (*E*)-ethyl crotonate **1** in aqueous medium.

Table 1. β-Borylation of (*E*)-ethyl crotonate **1** in aqueous medium[a]

Entry	Catalyst (load) (mol%)	Ligand (load) (mol%)	*T* (°C)	Method	Conv. (%)
1[b]	Cs_2CO_3 (15)	Ph_3P(20)	60	A	12
2[c]	CuCl/NaO*t*Bu (15)	Ph_3P(20)	60	A	63
3	Basic $CuCO_3$ (7.5)	—	60	A	30
4	—	Ph_3P(10)	60	A	—[d]
5	Basic $CuCO_3$ (15)	Ph_3P(20)	60	A	100
6	Basic $CuCO_3$ (15)	Ph_3P(20)	25	A	100
7	Basic $CuCO_3$ (7.5)	Ph_3P(10)	25	A	100
8	Basic $CuCO_3$ (4)	Ph_3P(5)	25	A	100
9	Basic $CuCO_3$ (3)	Ph_3P(3.5)	25	B	100
10	Basic $CuCO_3$ (2)	Ph_3P(2.5)	30	B	100[e]

[a]General reaction conditions: **1** (1.00 mmol), B_2pin_2 (1.10 mmol), basic $CuCO_3$ (0.02–0.15 mmol), PPh_3 (0.025–0.2 mmol), H_2O (2.5 ml), 25–60 °C, 16 h, 800–900 rpm. Method A: reaction was performed in 2 wt% aqueous solution of TPGS amphiphile (micelle-based system). Method B: reaction was performed on pure H_2O.
[b]According to method of Bonet *et al.*[9f]
[c]According to method of Mun *et al.*[12]
[d]No reaction.
[e]92% isolated yield after column chromatography (see supporting information for further details and explanation).

be obtained by the reaction outcome in the absence of the ligand. Encouragingly, when only basic $CuCO_3$ was used, 30% conversion to **2** was attained (entry 3). When a transition metal free β-borylation was attempted in aqueous medium by employing only B_2pin_2 and PPh_3, no reaction took place (entry 4). To our delight, combining both the basic $CuCO_3$ and PPh_3 in aqueous solution of amphiphile resulted in a full conversion of **1** to **2** at 60 °C (entry 5). Lowering the temperature to 25 °C at the same catalyst load did not affect the reaction outcome and a complete conversion of **1** to **2** was obtained (entry 6). Lowering the catalyst load still provided a full conversion in a TPGS micelle-based aqueous system (entries 7–8). This stimulated us to test the efficiency and compatibility of the catalytic system also with the pure aqueous medium, in which the problematic hydrophobic character of a substrate and reagent is even more expressed. We were delighted to find that full conversion to **2** using B_2pin_2 (1.1 equiv.) in the presence of basic $CuCO_3$ (3.0 mol%) and PPh_3 (3.5 mol%) was surprisingly established (entry 9). By applying even lower catalyst load, **2** was isolated in 92% yield (entry 10).

By identifying basic $CuCO_3$ in combination with PPh_3 as an efficient catalytic system for 'on water' β-borylation, we continued with exploration of its potential with other ligands (Scheme 2 and Table 2). Interestingly, P^P ligands like DPE-phos, Dppbz, Dtpf and Dppf proved to be compatible with the established method 'on water' and afforded a full conversion of **1** to **2** (entries 2–6) as PPh_3 (entry 1). Of note, Dppbz ligand provided a full conversion to **2** in only 2 mol% load and in significantly shorter time (entry 4). On the other hand, diamino-type ligand tetramethylethylenediamine (TMEDA) performed poorly and provided low 40% conversion to **2** (entry 7). Finally, to emphasize the environmentally friendlier aspect of our water-based methodology, application of naturally occurring sugar type ligands were undertaken (entries 8–9). Interestingly, while D-glucose gave 65% conversion to **2** in 7 h, D-glucosamine ligand afforded a full conversion to **2** after 20 h.

Having outlined the optimal reaction conditions and the optimal ligand profile, we were intrigued to explore whether the applied catalytic system actually reaches its full potential in pure aqueous medium. For this purpose the efficiency of the catalytic system for **1** to **2** was carefully tested in series of other solvents such as acetonitrile, methanol, tetrahydrofuran, aqueous tetrahydrofuran, methyl *tert*-butyl ether, toluene and chloroform. All these solvents performed with significantly lower efficiency compared to the pure aqueous system, demonstrating the uniqueness of the selected catalytic system and the proof of concept for water-accelerated reaction based on basic copper carbonate. Moreover, the 'on water' acceleration effect was demonstrated and proved also with the influence of speed of stirring on the outcome of the reaction.[†] It is well known that a stirring effect plays an important role by 'on water' accelerated reactions.[14c–e,15f]

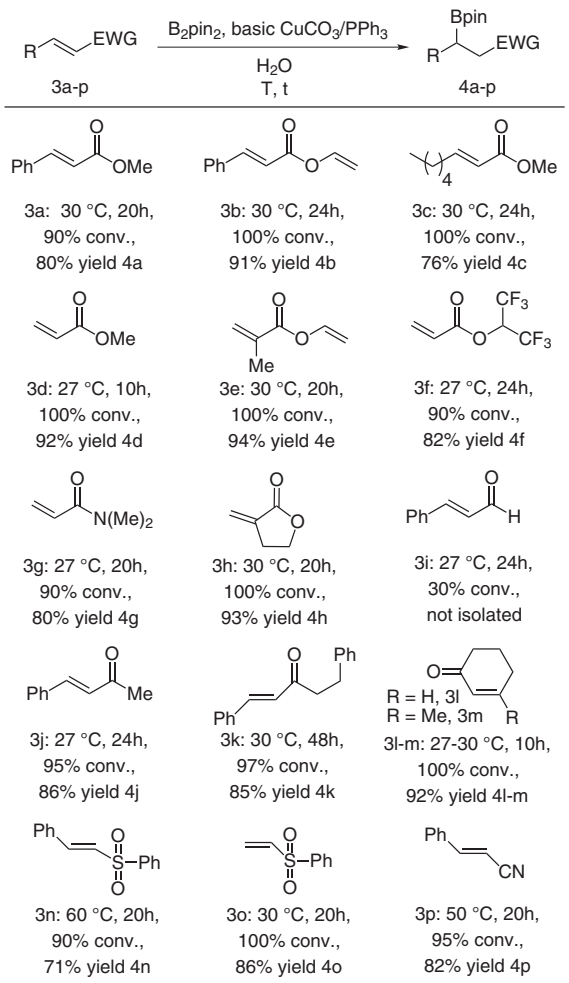
With established efficient reaction conditions for 'on water' β-borylation of the model compound **1** we next investigated the scope of the reaction by its application to a variety of structurally diverse Michael acceptors (Scheme 3). Although several ligands could be applied for this purpose, as demonstrated in

[†]For the effect of stirring speed on the efficiency of the 'on water' accelerated β-borylation see supporting information (S13).

Table 2. Screening of various ligands for β-borylation of **1** to **2**[a]

Entry[a]	Ligand	*t* (h)	Conversion (%)[b]
1	Ph_3P	7	100
2	DPE-phos	7	100
3	Dppbz	7	100
4	Dppbz (2 mol%)	3	100
5	Dtpf	7	100
6	Dppf	7	100
7	TMEDA	7	40
8	D-Glucose	7	65
9	D-Glucosamine	20	100

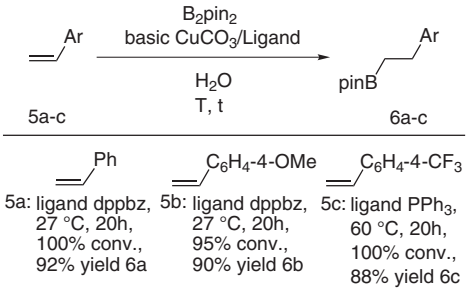
[a]Standard conditions: 1.1 equiv. B_2pin_2, 3 mol% basic $CuCO_3$ and 3.5 mol% ligand unless otherwise stated, pure water (2.5 ml), 27–30 °C, 800–900 rpm.
[b]Conversion was determined from ^{1}H NMR spectra of crude reaction mixture.



Scheme 3. 'On water' β-borylation of Michael acceptors (see supporting information for further details and explanation). General reaction conditions: **3** (1.00 mmol), B_2pin_2 (1.10 mmol), PPh_3 (0.035–0.05 mmol), basic $CuCO_3$ (0.03–0.04 mmol), H_2O (2.5 ml), 27–60 °C, 800–900 rpm. Examples **3a**, **3c–j**, **3 l–m** carried with 3 mol% of basic $CuCO_3$ and 3.5 mol% PPh_3. Example **3n** carried with 3.5 mol% of basic $CuCO_3$ and 4 mol% PPh_3. Examples **3b**, **3 k**, **3o–p** carried with 4 mol% of basic $CuCO_3$ and 5 mol% PPh_3. Isolated yield after column chromatography.

Table 2, we decided to utilize PPh_3 since it represents a cost-beneficial ligand alternative, which plays a significant factor in industrial processes. To our delight the catalytic method proved to be quite general with respect to the variation of structure of R and EWG functionalities, providing good functional group tolerance and a diverse array of products. In most cases conversions of over 90% were achieved under mild conditions: 27–60 °C in 10–24 h. Indeed, cinnamic esters **3a** and **3b** gave 90–100% conversion and 80–91% isolated yield of desired pinacol esters **4a** and **4b**. It is worth mentioning that in the case of **3b** the reaction was fully regioselective, giving rise only to the Michael β-borylated product, while the vinyl alcohol moiety remained unaffected. Similarly, variation of R substituent from aryl to alkyl did not affect the efficacy of the catalyst, and 2-octenoic acid methyl ester **3c** gave 100% conversion and 76% isolated yield of **4c**. Further modification of substrate structure by the change of R to H did not result in aggravation of the reaction outcome. Acrylic acid derivatives **3d–g** gave 90–100% conversions and 80–94% isolated yield of β-borylated products **4d–g**. Interestingly, methacrylic acid vinyl ester **3e** reacted regioselectively, giving only Michael addition product, while vinyl moiety remained fully intact. Furthermore, this set of substrates revealed that the method is not limited to acyclic substrates; moreover cyclic Michael acceptors like 2-methylene-γ-butyrolactone **3 h** were prone to undergo β-borylation and the corresponding pinacol ester **4 h** was isolated in excellent yield. Limitation of the method came to light when formyl group was installed on the EWG position. Disappointingly, when cinnamaldehyde **3i** was reacted under similar reaction conditions to other substrates, 30% conversion was obtained with some impurities present, which did not allow us to isolate a desired pure product. This is in contrast to results obtained with the ester analogues **3a–b**. Further variation of EWG led us to explore the keto derivatives **3j–m**. In sharp contrast to aldehyde **3i**, the keto analogue methyl styryl ketone **3j** enabled 95% conversion and gave 86% isolated yield of **4j**. An amazing result was obtained also with a highly hydrophobic substrate **3 k**. Furthermore, cyclic ketones like 2-cyclohexenone **3 l–m** enabled full conversion and excellent 92% isolated yields. Another interesting modification of Michael substrates includes application of sulfone functionality on the EWG position. Reactions of phenyl styryl sulfone **3n** and phenyl vinyl sulfone **3o** also gave excellent 90–100% conversion and 71–86% isolated yields of products **4n–o**. Finally, reaction with β-phenylacrylonitrile **3p** at 50 °C provided 95% conversion and the desired product **4p** was isolated in 82% yield. A preparative gram-scale model experiment featuring 'green' isolation protocol after completion of the reaction by utilizing only simple phase separation without using any organic solvents provided pure **4p** in 64% isolated yield (see supporting information S16–S17).

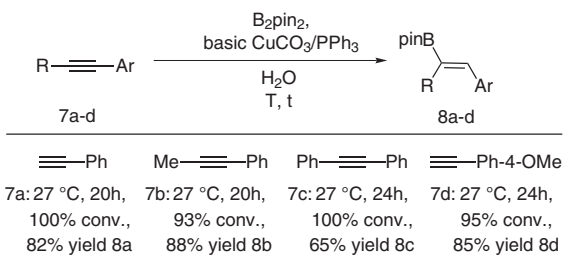
Encouraged by these results we wanted to further establish the utility of the present catalytic system for 'on water' β-borylation and to explore its potential on model styrenes with different electronic properties (Scheme 4). Reaction with styrene **5a** provided full conversion and 92% isolated yield of **6a**. The reaction is marginally affected by the substituents on the aromatic rings. Both electron-donating groups (e.g. 4-methoxystyrene **5b**) and electron-withdrawing groups (e.g. 4-trifluoromethylstyrene **5c**) on the phenyl ring performed well in this reaction, providing 95–100% conversion and 88–90% isolated yield of **6b–c**. When α-methylstyrene and β-methylstyrene were submitted to β-borylation under similar reaction conditions as used in **5a–c**, no reaction took place.



Scheme 4. 'On water' β-borylation of model alkenes (see supporting information for further details and explanation). General reaction conditions: **5** (1.00 mmol), B_2pin_2 (1.10 mmol), basic $CuCO_3$ (0.05 mmol), phosphine (0.035 mmol for dppbz and 0.065 mmol for PPh_3), H_2O (2.5 ml), 800–900 rpm. Isolated yield after column chromatography.

Furthermore, we were interested in testing the ability of the developed catalytic system on model phenyl-substituted alkynes (Scheme 5), which have recently been successfully borylated exclusively in organic solvents using well-known catalytic methodologies.[11] We were pleased to observe that the full conversion of 1-phenylethyne **7a** was obtained 'on water' under mild conditions, which enabled isolation of **8a** in high 92% isolated yield. Changing the R to methyl and phenyl did not affect the reaction significantly and methylphenylethyne **7b** and diphenylethyne **7c** provided 93–100% conversion, giving **8b** in 88% and **8c** in 65% isolated yield respectively. Aromatic ring substitution also a showed marginal difference in reactivity and *p*-methoxyphenylethyne **7d** reached 95% conversion and afforded **8d** in 85% isolated yield. It is worth mentioning that in all studied cases the overall syn addition of (pinacolato)boron moiety and H across the double bond was established and confirmed with NMR NOESY experiments (see supporting information S25–S26).

Finally, we were intrigued to determine if an asymmetric version of 'on water' β-borylation methodology could be developed. It is worth mentioning that asymmetric induction in aqueous medium is problematic due to sensitivity, solubility and incompatibility of chiral metal catalysts and ligands with water.[15f] Nevertheless, we decided to explore the possibility of asymmetric 'on water' β-borylation of olefinic precursor **9**[17] to pinacol ester **10** and its subsequent oxidation to the target alcohol **11**,[18] which is a known key intermediate in the synthesis of the antidiabetic drug sitagliptin.[19] Therefore, basic $CuCO_3$ as catalyst in combination with chiral P^P, N^N and P^N ligands was investigated (Scheme 6, Fig. 1 and Table 3). It was pleasing to find that application of



Scheme 5. 'On water' β-borylation of model alkynes (see supporting information for further details and explanation). General reaction conditions: **7** (1.00 mmol), B_2pin_2 (1.10 mmol), basic $CuCO_3$ (0.05 mmol for **7a–b**,**d** and 0.075 mmol for **7c**), PPh_3 (0.065 mmol for **7a–b**,**d** and 0.01 mmol for **7c**), H_2O (2.5 ml), 800–900 rpm. Isolated yield after column chromatography.

(*R*,*R*)-DIOP ligand **L1** afforded 80% conversion to **10** and promising enantiomeric excess (ee) of 22% (entry 1). Similar performance was observed with (*S*,*S*)-Me-DUPHOS ligand **L2** (entry 2). (*R*)-P-Phos ligand **L3** provided full conversion, while enantioselectivity remained at the modest level of 35% ee (entry 3). DuanPhos ligand **L4** and (*R*,*R*)-Et-Ferrocelane ligand **L5** performed similarly in terms of enantioselectivity (40–41% ee) and provided 75–93% conversion (entries 4–5). N^N type ligand **L6** afforded the first efficient and optimistic result, with a full conversion and good enantioselectivity of 62% ee (entry 6). Comparable performance was also observed with (*R*)-BINAP ligand **L7** and POX ligand **L8** (entries 7–8). High asymmetric induction but not quantitative conversion was obtained with Josiphos type ligand **L9** (entry 9). Finally, we were delighted to find that Walphos type ligand **L10** in combination with basic $CuCO_3$ afforded full conversion and excellent enantioselectivity (95% ee) 'on water' (entry 10). Subsequently, the optically active pinacol ester **10**, which was also isolated without the use of any organic solvents (see supporting information S17-S18), was converted using a newly developed environmentally benign oxidation method based on NaOCl in AcOEt (see supporting information S15–S16) to an β-alcohol type sitagliptin side chain **11**, which can be easily transformed to sitagliptin according to the known literature procedures.[18]

Conclusions

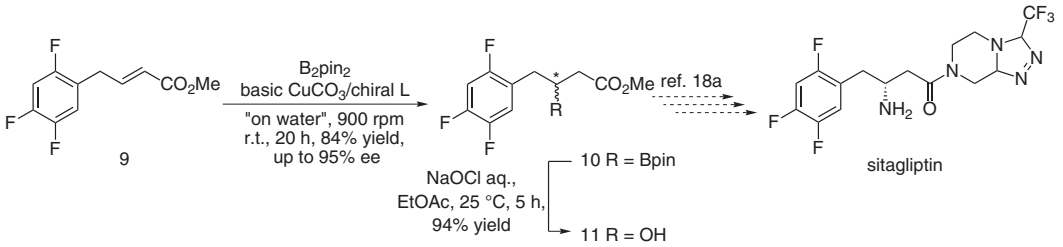
We have demonstrated that basic $CuCO_3$ in combination with appropriate ligands provides a simple and efficient catalytic system for 'on water' β-borylation.[20]‡ We believe that our discovery will open new perspectives towards environmentally friendlier β-borylation methodologies. The discovered catalytic system enables β-borylation of broad range of substrates including Michael acceptors, alkenes and alkynes under mild reaction conditions in high yields. Finally, we also successfully established for the first time that a basic $CuCO_3$/chiral ligand catalytic system can be efficiently applied to asymmetric β-borylation in aqueous medium, which has been demonstrated on a model target system. This opens a very useful industrial synthetic method to optical active precursors for target bioactive agents. Indeed, β-borylation of the important alkene precursor of sitagliptin synthesis gave the corresponding boronic ester and its further oxidative transformation afforded well-known alcohol derivative of sitagliptin side chain in high yields and excellent enantioselectivity.

Experimental

General Remarks

Unless otherwise noted, all reactions were performed in dry, two-necked, round-bottom flasks under a nitrogen atmosphere. Reactions were conducted in deionized water. Starting materials (Michael acceptors, alkenes and alkynes) were commercially available and used as received. Bis(pinacolato)diboron (B_2pin_2) and copper(II) carbonate basic (purity > 95%) were used as purchased. *N*,*O*-containing ligand D-glucosamine hydrochloride

‡For additional information related to the efficiency of $[Cu_2(OH)_2CO_3]$ vs. $Cu(OH)_2$ and other catalytic systems see supporting information (S28).



Scheme 6. Application of asymmetric 'on water' β-borylation of olefin **9** to pinacol ester **10** and its subsequent oxidation to β-alcohol **11** precursor of sitagliptin.

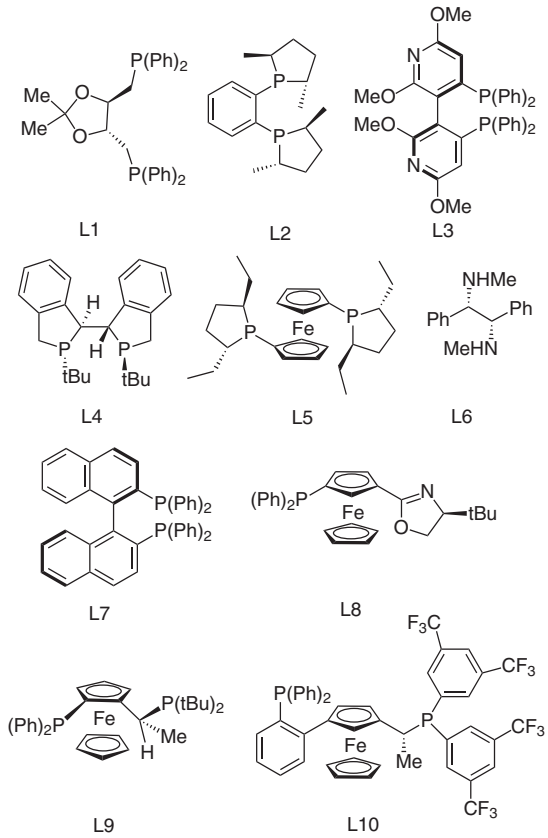


Figure 1. Various chiral ligands screened for asymmetric β-borylation of **9** to **10**.

(98% purity) and other phosphine type ligands including chiral ones were used as purchased. NMR spectra were recorded on a Bruker Avance III spectrometer: 500 MHz for ^{1}H NMR; 160 MHz for ^{11}B NMR; 125 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR. Chemical shifts are reported in δ ppm referenced to tetramethylsilane as an internal standard. High-resolution mass spectra were acquired on an Agilent 6224 accurate mass TOF LC/MS mass spectrometer. IR spectra were recorded on a Nicolet FTIR Nexus spectrometer.

General Experimental Procedure for 'On Water' β-Borylation of Michael Acceptors, Alkenes and Alkynes (see supporting information for further details and explanation)

In a dry, two-necked, round-bottom flask were placed catalyst $CuCO_3$ basic (2–7.5 mol% according to starting material; see Schemes 2–6) and ligand (2.5–10 mol%) under a nitrogen atmosphere. Afterwards, 2.5 ml deionized water was added and the reaction mixture was vigorously (800–900 rpm) stirred at ambient temperature for 15 min. The β-borylating reagent bis(pinacolato)diboron (B_2pin_2; 1.1 equiv. according to starting material) was added in one portion and the reaction mixture was stirred at ambient temperature for another 30 min. Starting material (1.0 mmol) was added to the reaction system and the reaction mixture was intensively stirred at 27–60 °C for 3–48 h (see Schemes 2–6). The reaction mixture was diluted with brine (5 ml) and extracted with EtOAc (2 × 35 ml). Combined organic layers were again washed with brine (30 ml) and dried over Na_2SO_4, and organic solvent was removed under reduced pressure. The crude product was purified by column chromatography using a Biotage SP4 flash purification system (SiO_2; *n*-hexane: EtOAc = 9:1) to obtain pure β-borylated product, which was characterized by ^{1}H, ^{11}B and ^{13}C NMR analysis.

Table 3. Screening of various chiral ligands for borylation of **9** to **10**

Entry[a]	Ligand	Conversion (%)[b]	ee (%)[c]
1	L1	80	22
2	L2	70	25
3	L3	100	35
4	L4	75	40
5	L5	93	41
6	L6	100	62
7	L7	100	70
8	L8	92	77
9	L9	90	86
10	L10	100	95

[a]Standard conditions: 1.1 equiv. B_2pin_2, 4 mol% basic $CuCO_3$ and 5 mol% ligand.
[b]Conversion was determined from ^{1}H NMR spectra of crude reaction mixture.
[c]Enantiomeric excess was measured by chiral HPLC analysis (see supporting information for further details).

Representative Spectral and Analytical Data for some New Borylated Compounds (see supporting information for further details and explanation)

*Vinyl-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (**4e**)*

Liquid; ^{11}B (160 MHz, $CDCl_3$, ppm) δ = 33.3 (br); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.26 (dd, J = 14.0 Hz, J = 6.3 Hz, $1H_c$), 4.85 (dd, J = 14.0 Hz, J = 1.5 Hz, $1H_a$), 4.52 (dd, J = 6.3 Hz, J = 1.5 Hz, $1H_b$), 2.68–2.79 (m, 1H), 1.24 (d, 3H), 1.21 (s, 6H), 1.18 (s, 6H), 1.15 (dd, J = 16.0 Hz, J = 7.4 Hz, 1H), 0.97 (dd, J = 16.0 Hz,

$J = 7.5$ Hz, 1H); ^{13}C (125 MHz, $CDCl_3$, ppm) δ 174.3, 141.5, 97.2, 83.2, 35.14, 24.8, 24.7, 19.0, 15.9 (broad, **C**-B); IR (neat): $\nu = 2979$, 2935, 1753, 1646, 1372, 1322, 1143 cm^{-1}. Anal. Calcd for $C_{12}H_{21}BO_4$: C, 60.03; H, 8.82%. Found: C, 60.25; H, 9.03%.

*4,4,5,5-Tetramethyl-2-(4-trifluoromethyl)phenethyl)-1,3,2-dioxoborolane (**6c**)*

^{11}B (160 MHz, $CDCl_3$, ppm) δ 33.7 (br); ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.66–7.55 (m, 2H), 7.46–7.35 (m, 2H), 2.84 (t, $J = 8.1$ Hz, 2H), 1.26 (s, 12H), 1.16 (t, $J = 8.1$ Hz, 2H); ^{19}F (470 MHz, $CDCl_3$, ppm) δ −63.2; ^{13}C (125 MHz, $CDCl_3$, ppm) δ 148.5, 128.3, 128.2, 125.1, 125.0, 83.2, 29.8, 24.8, 12.5 (broad, **C**-B); IR (neat): $\nu = 2982$, 2938, 1326, 1162, 1143, 1115 cm^{-1}. Anal. Calcd for $C_{15}H_{20}BF_3O_2$: C, 60.03; H 6.72%. Found: C, 59.92; H, 6.62%.

(E)-2-(4-Methoxystryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**8d**)

Liquid; ^{11}B (160 MHz, $CDCl_3$, ppm) δ 30.2 (br); ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.45 (m, 2H), 7.36 (d, $J = 18.4$ Hz, 1H), 6.87 (m, 2H), 6.05 (d, $J = 18.4$ Hz, 1H), 3.82 (s, 3H), 1.30 (s, 12H); ^{13}C (125 MHz, $CDCl_3$, ppm) δ 160.3, 149.0, 130.4, 128.9, 128.4, 113.9, 113.6, 83.1, 55.2, 24.7; IR (neat): $\nu = 2977$, 2934, 1625, 1605, 1511, 1421, 1356, 1143, 1035, 996, 970, 815 cm^{-1}. Anal Calcd for $C_{15}H_{21}BO_3$: C, 69.26; H, 8.14%. Found: C, 69.41; H, 8.02%.

*Protocol for 'On Water' Asymmetric β-Borylation of Sitagliptin Intermediate (**9**) to Corresponding β-Boronic Ester (**10**) (see supporting information for further details and explanation)*

In a dry, two-necked, round-bottom flask were placed catalyst $CuCO_3$ basic (0.02 mmol, 4 mol% according to starting material **9**) and Walphos ligand (0.025 mmol, 5 mol%; see Table 3 and Scheme 6) under a nitrogen atmosphere. Afterwards, 2.5 ml deionized water was added and the reaction mixture was vigorously stirred (900 rpm) at ambient temperature for 20 min. The β-borylating reagent bis(pinacolato)diboron (0.55 mmol, 140 mg, 1.1 equiv.) was then added in one portion to the reaction system and stirred for an hour. Finally, α,β-unsaturated ester (*E*)-methyl-4-(2,4,5-trifluorophenyl)-but-2-enoate (**9**) (0.5 mmol, 115 mg) was added to the reaction system and the reaction mixture was intensively stirred at ambient temperature for 20 h. The reaction mixture was diluted with brine (5 ml) and extracted with EtOAc (2×40 ml). Combined organic layers were again washed with brine (30 ml) and dried over Na_2SO_4, and organic solvent was removed under reduced pressure. The crude product was simply purified by flash chromatography (silica; EtOAc) to obtain the final product (**10**; 150 mg; 84% yield) as determined by ^1H, ^{11}B, ^{13}C NMR and high-resolution mass spectrometry (HRMS) analysis. Enantiomeric purity (95% ee) was determined using high-performance liquid chromatography (HPLC) chiral analysis.

*Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(2,4,5-trifluorophenyl)-butanoate (**10**)*

Yellow liquid; ^{11}B (160 MHz, $CDCl_3$, ppm) δ 33.6 (br); ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 7.01–7.05 (m, 1H), 6.80–6.86 (m, 1H), 3.65 (s, 3H), 2.75 (dd, $J = 15$ Hz, $J = 5.0$ Hz, 1H), 2.61 (dd, $J = 15$ Hz, $J = 5.0$ Hz, 1H), 2.37 (d, $J = 10.1$ Hz, 2H), 1.60 (pentet, 1H), 1.20 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 173.7, 156.0 (dd, $J = 242.5$ Hz, $J = 2.5$ Hz), 149.4 (m), 147.3 (m), 124.5 (m), 118.5 (dd, $J = 20.2$ Hz, $J = 6.3$ Hz), 105.0 (dd, $J = 28.8$ Hz, $J = 21.3$ Hz), 83.5, 51.5, 34.5, 28.5, 24.7, 20.4 (broad **C**–B); ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ −144.7 (m), −138.1 (m), −120.3 (m); IR (neat): $\nu = 2980$, 1737, 1631, 1518, 1381,1329, 1143 cm^{-1}. HRMS (electrospray ionization): calculated mass ion for $C_{17}H_{23}BF_3O_4$ (M + H)+: 358.1672; found: 358.1684.

Supporting information

Supporting information may be found in the online version of this article, including characterization data of known and copies of spectra for all new borylated compounds, specific procedures and experimental protocols for gram-scale experiments emphasizing 'green' isolation procedures. A study for development of a new oxidation method and conceptual experiments showing 'on water' accelerated borylation are also included.

Acknowledgments

We thank A. Vesković for help with experimental work, S. Borišek and Dr M. Črnugelj for NMR spectra, D. Orkič and M. Uštar for GC and HPLC analysis, M. Borišek for IR spectra, Dr S. J. Roseblade (Johnson Matthey) for chiral HPLC method development, Dr D. Urankar and Prof. J. Košmrlj (University of Ljubljana) for HRMS analysis.

References

[1] a) A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, Academic Press, London, **1988**; b) D. S. Matteson, Reactivity and Structure Concept in Organic Synthesis: Stereodirected Synthesis with Organoboranes, *32*, Springer, New York, **1994**; c) D. G. Hall (Ed.), Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine, Wiley-VCH, Weinheim, **2005**; d) G. A. Molander, R. Figueroa, *Aldrichim. Acta* **2005**, *38*, 49; e) E. R. Burkhardt, K. Matos, *Chem. Rev.* **2006**, *106*, 2617; f) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275; g) N. A. Petasis, *Aust. J. Chem.* **2007**, *60*, 795; h) S. Darses, J.-P. Genet, *Chem. Rev.* **2008**, *108*, 288; (i) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890.

[2] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) D. S. Matteson, *Chem. Rev.* **1989**, *89*, 1535; c) D. S. Matteson, *Tetrahedron* **1989**, *45*, 1859; d) D. S. Matteson, *Tetrahedron* **1998**, *54*, 10555; e) G. J. Irvine, M. J. G. Lesley, T. B. Marder, N. C. Norman, C. R. Rice, E. G. Robins, W. R. Roper, G. R. Whittell, L. J. Wright, *Chem. Rev.* **1998**, *98*, 2685; f) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; g) V. M. Dembitsky, H. A. Ali, M. Srebnik, *Appl. Organometal. Chem.* **2003**, *17*, 327; h) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127; i) C. Kleeberg, L. Dang, Z. Lin, T. B. Marder, *Angew. Chem. Int. Ed.* **2009**, *48*, 5350; j) C. T. Yang, Z. Q. Zhang, H. Tajuddin, C. C. Wu, J. Liang, J. H. Liu, Y. Fu, M. Czyzewska, P. G. Steel, T. B. Marder, L. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 528.

[3] a) W. Yang, X. Gao, B. Wang, *Med. Res. Rev.* **2003**, *23*, 346; b) D. S. Matteson, *Med. Res. Rev.* **2008**, *28*, 233; c) S. J. Baker, C. Z. Ding, T. Akama, Y.-K. Zhang, V. Hernandez, Y. Xia, *Future Med. Chem.* **2009**, *1*, 1275; d) V. M. Dembitsky, A. A. Al Quntar, M. Srebnik, *Chem. Rev.* **2011**, *111*, 209; e) R. Smoum, A. Rubinstein, V. M. Dembitsky, M. Srebnik, *Chem. Rev.* **2012**, *112*, 4156.

[4] a) H. C. Brown, B. C. Subba Rao, *J. Am. Chem. Soc.* **1956**, *78*, 5694; b) K. Burgess, M. J. Ohlmeyer, *Chem. Rev.* **1991**, *91*, 1179; c) H. Wadepohl, *Angew. Chem. Int. Ed.* **1997**, *36*, 2441; d) I. Beletskaya, A. Pelter, *Tetrahedron* **1997**, *53*, 4957; e) C. M. Crudden, D. Edwards, *Eur. J. Org. Chem.* **2003**, 4695; f) D. R. Edwards, Y. B. Hleba, C. J. Lata, L. A. Calhoun, C. M. Crudden, *Angew. Chem. Int. Ed.* **2007**, *46*, 7799; g) Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 3160; h) D. Noh, H. Chea, J. Ju, J. Yun, *Angew. Chem. Int. Ed.* **2009**, *48*, 6062.

[5] a) T. Ishiyama, N. Miyaura, *Chem. Rec.* **2004**, *3*, 271; b) T. B. Marder, N. C. Norman, *Top. Catal.* **1998**, *5*, 1–4, 63.

[6] J. A. Schiffner, K. Müther, M. Oestreich, *Angew. Chem. Int. Ed.* **2010**, *49*, 1194.

[7] H. Braunschweig, F. Guethlein, *Angew. Chem. Int. Ed.* **2011**, *50*, 12613.

[8] a) V. Lillo, A. Bonet, E. Fernández, *Dalton Trans.* **2009**, 2899; b) L. Dang, Z. Lin, T. B. Marder, *Chem. Commun.* **2009**, 3987; c) A. Bonet, C. Sole, H. Gulyás, E. Fernández, *Curr. Org. Chem.* **2010**, *14*, 2531; d) A. Bonet, H. Gulyás, E. Fernández, *Curr. Org. Chem.* **2011**, *15*, 3908; e) E. Hartmann, D. J. Vyasab, M. Oestreich, *Chem. Commun.* **2011**, *47*, 7917; f) J. Cid, H. Gulyás, J. J. Carbó, E. Fernández, *Chem. Soc. Rev.* **2012**, *41*, 3558.

[9] a) J.-E. Lee, J. Yun, *Angew. Chem. Int. Ed.* **2008**, *47*, 145; b) H.-S. Sim, X. Feng, J. Yun, *Chem. Eur. J.* **2009**, *15*, 1939; c) K. S. Lee, A. R. Zhugralin, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 7253; d) I.-H. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 11664; e) H. Chea, H.-S. Sim, J. Yun, *Bull. Korean Chem. Soc.* **2010**, *31*, 551; f) A. Bonet, H. Gulyás, E. Fernández, *Angew. Chem. Int. Ed.* **2010**, *49*, 5130; g) J. M. O'Brien, K.-S. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10630; h) J. C. H. Lee, R. McDonald, D. G. Hall, *Nat. Chem.* **2011**, *3*, 894; i) Y. Sasaki, Y. Horita, C. Zhong, M. Sawamura, H. Ito, *Angew. Chem. Int. Ed.* **2011**, *50*, 2778; j) M. Gao, S. B. Thorpe, C. Kleeberg, C. Slebodnick, T. B. Marder, W. L. Santos, *J. Org. Chem.* **2011**, *76*, 3997; k) B. Liu, M. Gao, L. Dang, H. Zhao, T. B. Marder, Z. Lin, *Organometallics* **2012**, *31*, 3410; l) H. Wu, S. Radomkit, J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 8277.

[10] a) S. B. Thorpe, J. A. Calderone, W. L. Santos, *Org. Lett.* **2012**, *14*, 1918; b) J. A. Calderone, W. L. Santos, *Org. Lett.* **2012**, *14*, 2090.

[11] a) L. Dang, H. Zhao, Z. Lin, T. B. Marder, *Organometallics* **2007**, *26*, 2824; b) L. Dang, H. Zhao, Z. Lin, T. B. Marder, *Organometallics* **2008**, *27*, 1178; c) H. R. Kim, J. Yun, *Chem. Commun.* **2011**, *47*, 2943; d) H. Jang, A. R. Zhugralin, Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 7859; e) H. Yoshida, S. Kawashima, Y. Takemoto, K. Okada, J. Ohshita, K. Takaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 235; f) H.-Y. Jung, J. Yun, *Org. Lett.* **2012**, *14*, 2606; g) H.-Y. Jung, X. Feng, H. Kim, J. Yun, *Tetrahedron* **2012**, *68*, 3444; h) K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Chem. Eur. J.* **2012**, *18*, 4179; i) W. Yuan, S. Ma, *Org. Biomol. Chem.* **2012**, *10*, 7266.

[12] S. Mun, J.-E. Lee, J. Yun, *Org. Lett.* **2006**, *8*, 4887.

[13] S. D. Solomon, S. A. Rutkowsky, M. L. Mahon, E. M. Halpern, *J. Chem. Educ.* **2011**, *88*, 1694.

[14] a) D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816; b) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275; c) J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *435*, 746; d) Y. Jung, R. A. Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5492; e) G. Stavber, J. Iskra, M. Zupan, S. Stavber, *Green. Chem.* **2009**, *11*, 1262; f) A. Chanda, V. V. Fokin, *Chem. Rev.* **2009**, *109*, 725; g) S. Mellouli, L. Bousekkine, A. B. Theberge, W. T. S. Huck, *Angew. Chem. Int. Ed.* **2012**, *51*, 7981.

[15] a) P. A. Grieco (Ed.), Organic Synthesis in Water, Blackie Academic and Professional, London, **1998**; b) N. T. Southall, K. A. Dill, A. D. J. Haymet, *J. Phys. Chem. B* **2002**, *106*, 521; c) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751; d) O. Sijbren, J. B. F. N. Engberts, *Org. Biomol. Chem.* **2003**, *1*, 2809; e) D. Chandler, *Nature* **2005**, *437*, 640; f) U. M. Lindström (Ed.), Organic Reactions in Water: Principles, Strategies and Applications, Blackwell, Oxford, **2007**; g) R. N. Butler, A. G. Coyne, *Chem. Rev.* **2010**, *110*, 6302; h) C. Reichardt, T. Welton, in Solvents and Solvent Effects in Organic Chemistry (4th edn), Wiley-VCH, Weinheim, **2011**. (i) M.-O. Simon, C.-J. Li, *Chem. Soc. Rev.* **2012**, *41*, 1415; j) S. Kobayashi (Ed.), Science of Synthesis: Water in Organic Synthesis, Georg Thieme, Stuttgart, **2012**.

[16] G. Stavber, Z. Časar, European patent application EP 12002520.0, submitted 6 April **2012**.

[17] a) F. Liu, W. Yu, W. Ou, X. Wang, L. Ruan, Y. Li, X. Peng, X. Tao, X. Pan, *J. Chem. Res.* **2010**, *34*, 230; b) S. G. Davies, A. M. Fletcher, L. Lv, P. M. Roberts, J. E. Thomson, *Tetrahedron Lett.* **2012**, *53*, 3052.

[18] a) K. B. Hansen, J. Balsells, S. Dreher, Y. Hsiao, M. Kubryk, M. Palucki, N. Rivera, D. Steinhuebel, J. D. Armstrong III, D. Askin, E. J. J. Grabowski, *Org. Process Res. Dev.* **2005**, *9*, 634; b) M. Fistikci, O. Gundogdu, D. Aktas, H. Secen, M. F. Sahin, R. Altundas, Y. Kara, *Tetrahedron* **2012**, *68*, 2607.

[19] A. A. Desai, *Angew. Chem. Int. Ed.* **2011**, *50*, 1974.

[20] J. F. Scaife, *Can. J. Chem.* **1957**, *35*, 1332.

