Homogeneous Catalysis

International Edition: DOI: 10.1002/anie.201507171
German Edition: DOI: 10.1002/ange.201507171

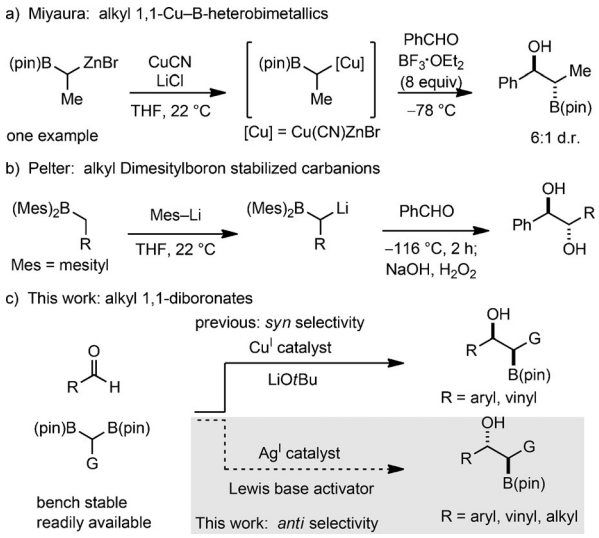
Silver(I)-Catalyzed Diastereoselective Synthesis of *anti*-1,2-Hydroxyboronates

*Matthew V. Joannou, Brandon S. Moyer, Matthew J. Goldfogel, and Simon J. Meek**

Abstract: *A catalytic protocol for the diastereoselective synthesis of anti-1,2-hydroxyboronates is described. The process provides access to secondary alkyl organoborons. The deborylative 1,2-addition reactions of alkyl 1,1-diborons proceed in the presence of a silver(I) salt with either KOtBu or nBuLi as an activator. The catalytic diastereoselective protocol can be extended to aryl, alkenyl, and alkyl aldehydes with up to 99:1 d.r.*

Functionalized secondary alkyl boronate esters are enabling reagents for chemical synthesis, thus catalytic stereoselective methods for their preparation are a compelling objective.[1] Carbon–carbon bond-forming reactions of boron-stabilized alkyl nucleophiles provide direct approaches to functionalized molecules containing C(sp^3)–B bonds. Specifically, alkylation of aldehydes with α-boryl nucleophiles serves to generate secondary alcohols bearing a vicinal alkyl boron unit.[2] Such processes form two contiguous stereogenic centers with a versatile C(sp^3)–B bond.[3,4] Despite progress in this area, several shortcomings preclude their synthetic utility, the most apparent of which are the lack of catalytic processes to afford products in high yield and stereoselectivity. Existing protocols for the stereoselective synthesis of 1,2-hydroxyboronates are achieved through organocuprates and deprotonations of bis(mesityl)-substituted alkyl boranes. Miyaura and co-workers reported one example of the addition of Knochel's α-B(pin) cyanocuprate [B(pin) = (pinacolato)boron] to benzaldehyde to afford a 1,2-hydroxyboronate in 6:1 d.r. (*anti*/*syn*; Scheme 1a).[2b] Pelter et al. reported excellent levels of *anti* selectivity for the addition of dimesityl-boron-stabilized carbanions to aldehydes. However, strong lithium bases and cryogenic conditions (−116 °C) are required for carbanion generation and reaction, thus limiting functional-group compatibility.[2c]

Bench-stable alkyl germinal diborons have emerged as useful difunctional reagents which provide effective methods to access α-boryl anion synthons. In the presence of an alkoxide or hydroxide activator 1,1-diborons participate in alkylation and cross-coupling reactions. Morken and co-workers demonstrated that the corresponding borates decompose to α-boryl-stabilized carbanions, which undergo efficient and diastereoselective alkylation with alkyl halides to generate substituted quaternary carbon atoms.[5] Catalytic reactions developed with difunctional alkyl organoboron reagents have focused on Suzuki cross-couplings.[6] Shibata and co-workers demonstrated that palladium-catalyzed cross-couplings of alkyl 1,1-diborons effectively proceed under ambient conditions to afford secondary alkyl boronates.[6a] More recently, the groups of Morken and Hall independently reported catalytic enantioselective variants for the stereoselective synthesis of secondary benzylic and allylboronates.[7] Advances notwithstanding, catalytic diastereoselective protocols for the addition of 1,1-diborons to carbonyls remain limited. Previously, we reported the enantio- and diastereoselective copper(I)-catalyzed additions of substituted alkyl 1,1-diborons to aldehydes to afford 1,2-hydroxyboronates in high *syn* selectivity (Scheme 1c).[8] The reaction most likely proceeds via a chiral α-boron copper(I)/alkyl intermediate adding to the aldehyde, and simultaneously forming a new C–C bond and two vicinal stereogenic centers, one of which comprises a secondary alkyl boron unit for further synthetic elaboration.



Scheme 1. Addition of α-boryl reagents to aldehydes. Previous work: a) Diastereoselecitve cuprate 1,2-addition. b) Deprotonation/1,2-addition of alkyl borons. c) This work: Catalytic *anti*-selective 1,2-addition of 1,1-diboronates. pin = pinacol, THF = tetrahydrofuran.

Herein, we outline the first catalytic protocol for the diastereoselective synthesis of *anti*-1,2-hydroxyboronates through the silver-catalyzed addition of 1,1-diboronates to aryl and alkyl aldehydes (Scheme 1c). Reactions are promoted by 10 mol% of a readily available silver(I) salt catalyst in conjunction with an alkoxide or alkyl lithium activator. The

[*] M. V. Joannou, B. S. Moyer, M. J. Goldfogel, Prof. S. J. Meek
Department of Chemistry
The University of North Carolina at Chapel Hill
Chapel Hill, NC 27599-3290 (USA)
E-mail: sjmeek@unc.edu

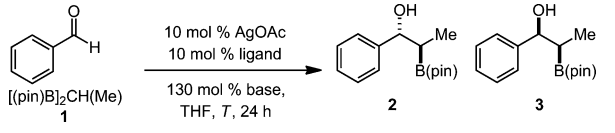
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201507171.

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

products are delivered in up to 77% yield and 99:1 d.r. The reaction is also tolerant of several functional groups, including silyl-ether-protected alcohols, N-Boc-protected nitrogen atoms, esters, and acetal-protected aldehydes.

Initial studies of catalytic reaction conditions identified silver(I) salts as effective promoters for the *anti*-selective addition of 1,1-diboryl reagents to aldehydes. The data illustrated in Table 1 summarize the optimization of the

Table 1: Optimization of reaction conditions for the synthesis of the *anti*-1,2-hydroxyboronate **2**.[a]

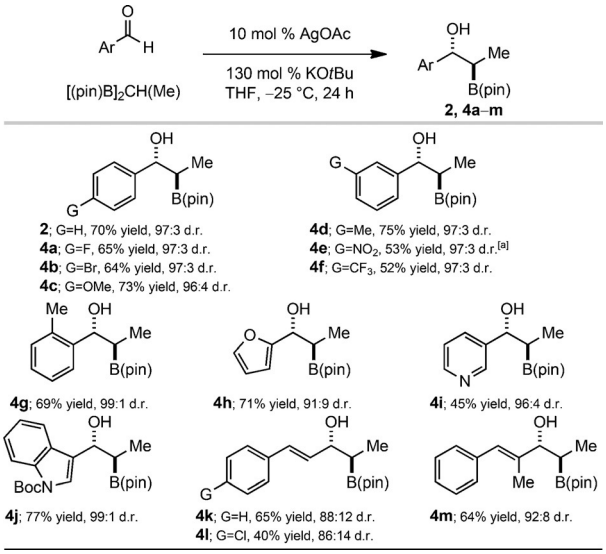


Entry	Silver salt	Ligand	Base	*T* [°C]	Conv. [%][b]	d.r. (**2**/**3**)[b]
1	–	–	NaO*t*Bu	22	63	50:50
2	–	–	NaO*t*Bu	0	<2	–
3	AgOAc	–	NaO*t*Bu	0	18	50:50
4[c]	AgOAc	PPh_3	NaO*t*Bu	0	47	54:46
5	AgOAc	*rac*-binap	NaO*t*Bu	0	42	84:16
6	AgOAc	*rac*-binap	NaO*t*Bu	−25	33	92:8
7[d]	AgOAc	*rac*-binap	KO*t*Bu	−25	50	93:7
8[c]	AgOAc	PPh_3	KO*t*Bu	−25	47	95:5
9	AgOAc	PCy_3	KO*t*Bu	−25	64	93:7
10	***AgOAc***	**–**	***KOtBu***	***−25***	***84***	***97:3***
11	–	–	KO*t*Bu	−25	<2	–

[a] Reactions performed under N_2 atm. [b] Conversion and diastereomeric ratio (d.r.) determined by analysis of either 400 MHz or 600 MHz ^{1}H NMR spectra of unpurified reaction mixtures using an internal standard. [c] 20 mol% PPh_3. [d] Use of (*R*)-binap delivers **2** in 0% *ee*. The reaction conditions of entry 10 represent the optimized reaction conditions. binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

reaction conditions. As entry 1 shows, there is a significant nonselective background reaction with 130 mol% NaO*t*Bu at 22°C and it affords **2** and **3** in (63% conversion) 50:50 d.r., and a less than 2% conversion is observed at 0°C (entry 2).[9] Catalytic AgOAc (10 mol%) was found to promote the addition at 0°C but with no diastereoselectivity (entry 3). Monodentate (PPh_3; entry 4), and bidentate (*rac*-binap; entry 5) phosphines were evaluated for their ability to deliver **2** in high diastereoselectivity and yield, and *rac*-binap affords **2** in 42% conversion and 84:16 d.r. (*anti*/*syn*; entry 5). Decreasing the temperature to −25°C results in lower conversions to **2**, but increases the *anti* selectivity (92:8 d.r.; entry 6). Application of KO*t*Bu in place of NaO*t*Bu leads to an improved yield at −25°C with no significant loss in d.r. value.[10] Monodentate aryl (entry 8) and alkyl (entry 9) phosphines were found to deliver **2** with a conversion and selectivity, in the presence of KO*t*Bu, which are similar to those obtained with *rac*-binap. Optimal reaction conditions for the catalytic diastereoselective addition of **1** to benzaldehyde are those run in the absence of a phosphine ligand. Treatment of benzaldehyde and **1** with 10 mol% AgOAc with KO*t*Bu in THF (−25°C) delivers **2** in 84% yield (NMR analysis) and 97:3 d.r. No reaction is observed in the absence of a silver(I) salt (entry 11).[11] Increasing the catalyst loading or reaction times result in only slight increases (<5%) in yield.[12]

We next evaluated the scope of the silver(I)-catalyzed protocol for the addition of **1** to aryl- and alkenyl-substituted aldehydes (Scheme 2), and several points are noteworthy:

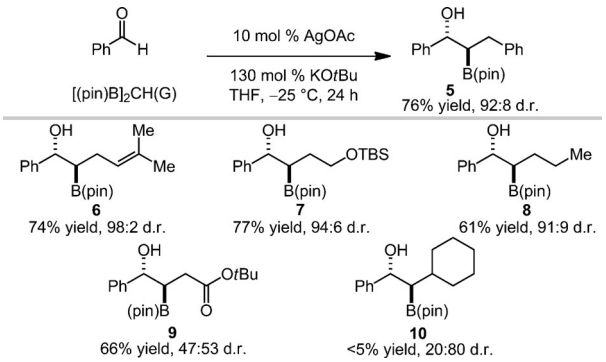


Scheme 2. The *anti*-selective silver(I)-catalyzed 1,2-addition of the 1,1-diboronate **1** to aryl and vinyl aldehydes. Yields of the purified products are an average of two runs. Diastereomeric ratio (d.r.) determined by analysis of either 400 MHz or 600 MHz ^{1}H NMR spectra of the unpurified reaction mixtures using hexamethyldisiloxane as an internal standard. [a] Yield determined by ^{1}H NMR spectroscopy.

1) *para*-substituted aryl aldehydes bearing either halogens (**4a**,**b**) or electron-donating methoxy (**4c**) groups undergo diastereoselective additions to yield hydroxyboronates in good yield (64–73%) and high selectivity (up to 97:3 *anti*/*syn*). 2) Substitution at the *meta* and *ortho* positions of the aryl aldehyde are tolerated, as demonstrated by the formation of **4d–g** in 52–75% yield and 97:3 d.r. (*anti*/*syn*). 3) Synthesis of furyl-, pyridyl-, and Boc-indole-substituted products (**4h–j**) demonstrate that heteroaryl aldehydes are effective substrates with no apparent inhibition. The expected 1,2-hydroxyboronates were isolated in 45–77% yield and 91:9–99:1 d.r.[13] 4) Transformations with sterically unhindered alkenyl aldehydes proceed with diminished selectivity, thus producing the allylic alcohols **4k** and **4l** in 88:12 and 86:14 d.r., respectively. However, α-methylcinnamaldehyde-derived **4m** was obtained in 64% yield and 92:8 d.r. with 10 mol% AgOAc.

Catalytic *anti*-selective 1,2-additions were extended to include substituted alkyl 1,1-diboron compounds (see **5–9**; Scheme 3). The transformations proceed effectively with 10 mol% AgOAc in up to 77% yield at −25°C in 24 hours. The expected 1,2-hydroxyboronates, including those that contain functional groups such as a phenyl ring (**5**), an alkene (**6**), a silyl ether (**7**), or an *n*-alkyl (**8**), or an ester (**9**), were obtained in up to 77% yield and greater than 98:2 d.r. (*anti*/*syn*) selectivity. Only in the case of a *tert*-butyl-ester-

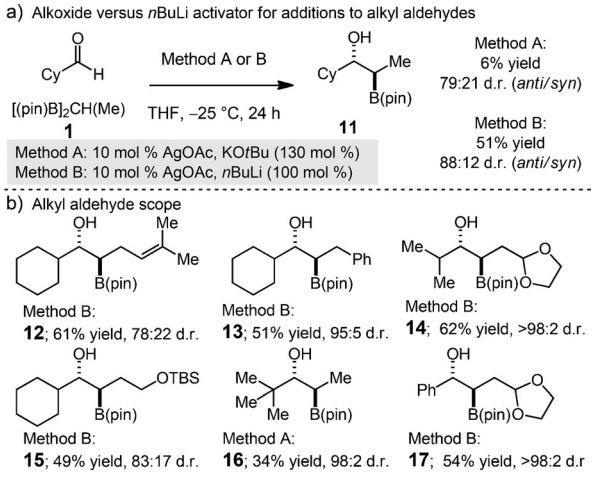
 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 3. Scope with respect to substituted 1,1-diboronates in *anti*-selective 1,2-hydroxy boronate synthesis. Yields of the purified products are an average of two runs. Diastereomeric ratio (d.r.) determined by analysis of either 400 MHz or 600 MHz ^{1}H NMR spectra of the unpurified reaction mixtures using hexamethyldisiloxane as an internal standard. G = attached group.

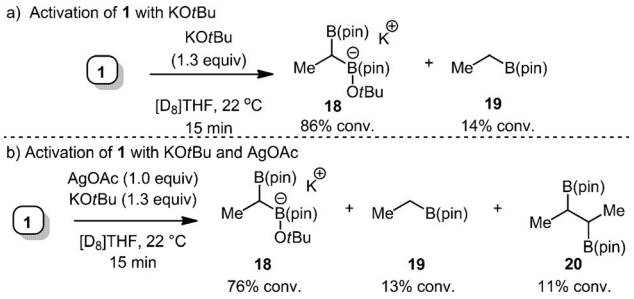
containing reagent was low diastereoselectivity observed. **9** was isolated in 66% yield and 47:53 d.r., (*anti*/*syn*). One shortcoming of the method relates to the use of β-branched 1,1-diboryl alkanes, and as an example, the cyclohexyl **10** is formed in less than 5% yield.

Addition of α-boryl nucleophiles was next extended to alkyl aldehydes (Scheme 4a). With cyclohexane carboxaldehyde, under otherwise identical reaction conditions (see Scheme 2), there was 6% conversion to **11** in 79:21 d.r. (Method A, Scheme 4a). We reasoned that deprotonation of the aldehyde by KO*t*Bu was responsible for low conversion to product.[14] To discourage enolization caused by unreacted alkoxide in solution, we substituted *n*BuLi for KO*t*Bu (Method B, Scheme 4a), as an irreversible activation of the 1,1-diboryl alkane should minimize undesired side reactions. Treatment of **1** with 1 equivalent of *n*BuLi in the presence of AgOAc followed by cyclohexane carboxaldehyde at −25 °C afforded **11** in 51% yield and 88:12 d.r. (*anti*/*syn*). A less than 5% conversion to **11** is observed in the absence of the silver(I) salt. The *n*BuLi protocol proved effective for alkyl and aryl aldehydes in combination with substituted 1,1-diboron reagents which contain an alkene (**12**), phenyl ring (**13**), acetal (**14**), or silyl ether (**15**; Scheme 4b). In general, the yields and *anti*-selectivity of the 1,2-hydroxyboronate products are slightly lower than in the case of aryl aldehydes. Alkyl aldehydes lacking α-protons do not require *n*BuLi as an activator. For example, pivaldehyde undergoes diastereoselective (98:2 d.r., *anti*/*syn*) addition promoted by KO*t*Bu, but **16** is isolated in only 34% yield. The acetal-containing product **17**, while derived from an aryl aldehyde, requires Method B for formation (Method A furnishes the product in < 5% yield).



Scheme 4. Silver(I)-catalyzed additions of 1,1-diboryl alkanes to alkyl aldehydes. Yields of the purified products are an average of two runs. Diastereomeric ratio (d.r.) determined by analysis of either 400 MHz or 600 MHz ^{1}H NMR spectra of unpurified reaction mixtures using hexamethyldisiloxane as an internal standard. TBS = *tert*-butyldimethylsilyl.

To investigate the mechanism of the *anti*-selective 1,2-addition reaction, activation of **1** was monitored by ^{1}H and ^{11}B NMR spectroscopy. Addition of 1.3 equivalents of KO*t*Bu to **1** in [D_8]-THF at 22 °C (Scheme 5a) leads to 86% conversion into the *t*BuO-activated borate species **18**.[15] If left at room temperature, **18** slowly decomposes to **19**, (14% conv. in 15 min, and 75% conv. after 18 h). Morken and coworkers have shown that borates such as **18** will deborylate at room temperature to form α-boryl-stabilized carbanions,[5a] however, we could not confirm the presence of the carbanion in concentrations of greater than 5% conversion by ^{1}H or ^{11}B NMR spectroscopy.



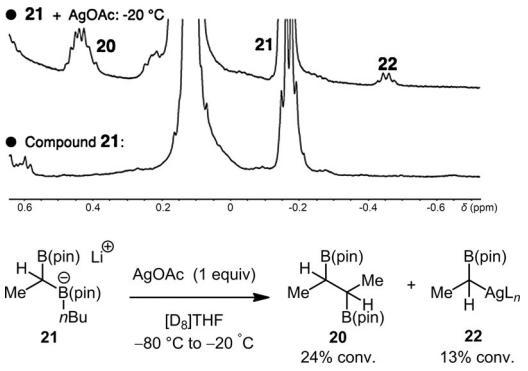
Scheme 5. Investigation into the activation of **1** with KO*t*Bu and the role of AgOAc in the 1,2-addition reaction. In all cases, **1** was completely consumed. ^{11}B NMR spectroscopy for both reactions shows three signals: $\delta = 34.0$, $\delta = 7.8$, and $\delta = 4.9$ ppm. The latter signal corresponds to potassium bis(*tert*-butoxypinacolborate). See the Supporting Information for details.[16]

To determine the role of AgOAc in the reaction, activation of **1** with KO*t*Bu in the presence of 1 equivalent of AgOAc was monitored by ^{1}H and ^{11}B NMR spectroscopy (Scheme 5b). Complete consumption of **1** and borate formation were observed, but the presence of an α-boryl carbanion could not be confirmed (Scheme 5a). Another species forms after 5 minutes at 22 °C, and can be assigned to the homocoupled product **20**. Signals for the diastereotopic protons at the base of the B(pin) groups produce a multiplet at $\delta = 0.45$ ppm. Homocoupling of Grignard and organoboron species can be promoted by stoichiometric and catalytic amounts of various silver(I) salts.[17] Whitesides and

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

co-workers demonstrated that these reactions proceed by reductive dimerization of alkyl silver compounds to form silver metal.[18] Bis(alkyl) boryl compounds are known to cyclize in the presence of KOH/MeOH/$AgNO_3$, thus indicating organoboron compounds can be transmetalated to silver.[19] The presence of **20** suggests that an α-boryl alkyl silver(I) species is forming in the ^{1}H NMR reaction, but homocouples too quickly to be observed at 22 °C.

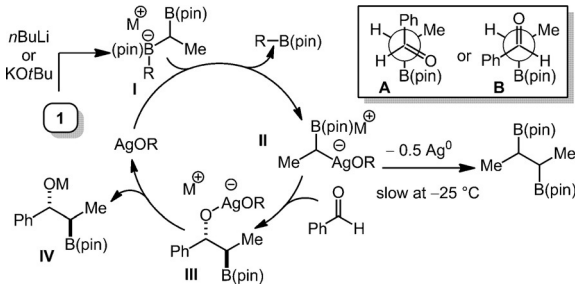
To identify the presence of an alkyl silver intermediate under the reaction conditions, the *n*-butyllithium-activated diboryl ethane **21**[20] was treated with 1 equivalent of AgOAc at −80 °C in [D_8]-THF and monitored by ^{1}H and ^{11}B NMR spectroscopy as it warmed to −20 °C (Scheme 6).[21] A new



Scheme 6. Low-temperature ^{1}H NMR detection (−80 to −20 °C) of a putative α-boryl alkyl silver species.

signal grew in as the reaction warmed ($\delta = -0.46$ ppm, q, $J =$ 8.0 Hz) and is tentatively assigned as the α-boryl alkyl silver(I) species **22** (with a maximum conversion of 13% at −20 °C). The homocoupled product **20** was also detected, thus further supporting the theory that an alkyl silver species is present and slowly undergoing reductive dimerization. It is unlikely that the resonance corresponds to the α-boryl-stabilized carbanion, as Morken and co-workers have shown that this species is only generated after several hours at ambient temperature.[5a,22]

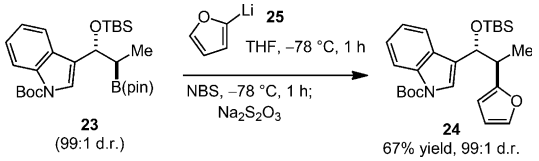
With these data, we propose a mechanism of how the *anti*-selective 1,2-addition reaction proceeds: Interaction of AgOAc with either **18** or **21** produces an α-boryl alkyl silver species. The rate of homocoupling of **22** is likely reduced under the reaction conditions and is slower than the productive carbonyl 1,2-addition as only catalytic AgOAc is used (**22** is only formed in 13% conversion with stoichiometric AgOAc; Scheme 6). Catalytic quantities of an alkyl silver intermediate would react faster with a large excess of aldehyde, rather than dimerizing to form **20**. A catalytic cycle for the diastereoselective reaction is illustrated in Scheme 7. Activation of **1** with KO*t*Bu or *n*BuLi forms a borate (**I**), which interacts with AgOR (OR = OAc, O*t*Bu) to form an α-boryl alkyl silver species (**II**), which then undergoes addition to the aldehyde to form the 1,2-hydroxyboronate **III**. The compound **III** subsequently undergoes a salt metathesis to regenerate the silver(I) salt and release the product. The *anti* selectivity of the silver-catalyzed reaction is the same as



Scheme 7. Proposed mechanism of the silver(I)-catalyzed reaction of 1,1-diborons with carbonyls. OR = OAc or O*t*Bu.

that observed by the groups of Miyaura[2b] and Pelter[2c] in the 1,2-addition reactions of cyanocuprates, and can be rationalized by the anti- or synclinal stereochemical model **A** or **B**, respectively, in Scheme 7. The role of silver(I) as a Lewis acid activator for the aldehyde cannot be completely ruled out.[23]

To showcase the synthetic utility of *anti*-1,2-hydroxyboronates, the TBS-protected hydroxyboronate **23** (isolated in 77% yield from the parent hydroxyboronate) was subjected to stereospecific aryl coupling (Scheme 8). The boronate **23**



Scheme 8. Stereospecific heteroarylation of 1,2-hydroxyboronate products. Boc = *tert*-butoxycarbonyl.

was treated with 1.2 equivalents of the lithiated furan **25** at −78 °C, followed by *N*-bromosuccinimide, and finally a saturated solution of $Na_2S_2O_3$ to furnish 1,2-diarylated product **24** in 67% yield and 99:1 d.r.[24] As we demonstrated previously, these compounds are amenable to oxidation, amination, and carbon homologation.[9]

In summary, we have developed the first catalytic *anti*-selective addition of various 1,1-diboryl alkanes to a range of aryl-, alkenyl-, and alkyl-substituted aldehydes. Through ^{1}H NMR experiments, we have determined that an α-boryl alkyl silver compound is likely the active species in the reaction. Functionalization of the hydroxyboronates is demonstrated by a stereospecific aryl coupling with furan. Investigations regarding scope, enantioselective variants of the current diastereoselective protocol, and applications to stereoselective chemical synthesis are underway.

Acknowledgements

Financial support was provided by the University of North Carolina at Chapel Hill and an Eli Lilly New Faculty award.

Keywords: alcohols · asymmetric catalysis · boron · diastereoselectivity · silver

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 14141 – 14145
Angew. Chem. **2015**, *127*, 14347 – 14351

[1] *Boronic Acids*, (Ed: D. G. Hall), Wiley-VCH, Weinheim, **2000**.
[2] a) P. Knochel, *J. Am. Chem. Soc.* **1990**, *112*, 7431 – 7433; b) M. Sakai, S. Saito, G. Kanai, A. Suzuki, N. Miyaura, *Tetrahedron* **1996**, *52*, 915 – 924; c) A. Pelter, S. Peverall, A. Pitchford, *Tetrahedron* **1996**, *52*, 1085 – 1094.
[3] For examples of 1,2-additions of 1,1-diboron-stabilzed carbanions to aldehydes and ketones followed by elimination, see: a) D. S. Matteson, R. J. Moody, P. K. Jesthi, *J. Am. Chem. Soc.* **1975**, *97*, 5608 – 5609; b) D. S. Matteson, R. J. Moody, *J. Org. Chem.* **1980**, *45*, 1091 – 1095; c) D. S. Matteson, K. H. Arne, *Organometallics* **1982**, *1*, 280 – 288; d) K. Endo, M. Hirokami, T. Shibata, *J. Org. Chem.* **2010**, *75*, 3469 – 3472; e) J. R. Coombs, L. Zhang, J. P. Morken, *Org. Lett.* **2015**, *17*, 1708 – 1711.
[4] For reviews of stereospecific reactions of alkyl boronic esters, see: a) H. C. Brown, B. Singaram, *Pure Appl. Chem.* **1987**, *59*, 879 – 894; b) S. P. Thomas, R. M. French, V. Jheengut, V. K. Aggarwal, *Chem. Rec.* **2009**, *9*, 24 – 39; c) H. K. Scott, V. K. Aggarwal, *Chem. Eur. J.* **2011**, *17*, 13124 – 13132; d) D. Leonori, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2015**, *54*, 1082 – 1096; *Angew. Chem.* **2015**, *127*, 1096 – 1111. For a review on catalytic enantioselective diboration, see: e) H. E. Burks, J. P. Morken, *Chem. Commun.* **2007**, 4717 – 4725; For a recent review on copper-catalyzed boryl addition reactions, see: f) K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Tetrahedron* **2015**, *71*, 2183 – 2197.
[5] a) K. Hong, X. Liu, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 10581 – 10584; b) J. R. Coombs, L. Zhang, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 16140 – 16143.
[6] a) K. Endo, T. Ohkubo, M. Hirokami, T. Shibata, *J. Am. Chem. Soc.* **2010**, *132*, 11033 – 11035; b) K. Endo, T. Ohkubo, T. Shibata, *Org. Lett.* **2011**, *13*, 3368 – 3371; c) K. Endo, T. Ohkubo, T. Ishioka, T. Shibata, *J. Org. Chem.* **2012**, *77*, 4826 – 4831; d) J. C. H. Lee, R. McDonald, D. G. Hall, *Nat. Chem.* **2011**, *3*, 894 – 899.
[7] a) C. Sun, B. Potter, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 6534 – 6537; b) B. Potter, A. A. Szymaniak, E. K. Edelstein, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 17918 – 17921; c) H. Y. Sun, K. Kubota, D. G. Hall, *Chem. Eur. J.* **2015**, *21*, 1 – 10.
[8] M. V. Joannou, B. S. Moyer, S. J. Meek, *J. Am. Chem. Soc.* **2015**, *137*, 6176 – 6179.
[9] Catalytic NaO*t*Bu does not promote the addition of **1** to benzaldehyde.
[10] Preliminary enantioselective results have been obtained with chiral phosphine/Ag^I complexes employing the optimal reaction conditions in Table 1: (a) 10 mol% AgOAc, 10 mol% (*R*)-Monophos, −25 °C; 61% conv., 90:10 d.r., 61:39 e.r; (b) 10 mol% AgOAc, 10 mol% (R)-(+)-1-[(R)-2-(2′-dicyclohexylphosphinophenyl)ferrocenyl]ethyldi(bis-3,5-trifluoromethylphenyl)phosphine, −40 °C; 11% conv., 95:5 d.r., 77.5:22.5 e.r.
[11] Use of silver(I) salts with more dissociating counter ions [e.g., AgOTf, $AgBF_4$, $AgSbF_6$, $AgClO_4$, Ag(TFA)] afford < 10% conversion.
[12] Further optimization demonstrates that increasing the number of equivalents of KO*t*Bu or the boron reagent results in lower conversion and decreased *anti*/*syn* selectivity. For example, 200 mol% KO*t*Bu or 2.0 equivalents **1** affords **2**/**3** in 13% conv. in 86:14 d.r., and 48% conv. in 85:15 d.r., respectively.
[13] The lower yield of the pyridyl alcohol is attributed to slight decomposition during purification.
[14] The presence of significant unreacted aldehyde upon aqueous workup supports this hypothesis.
[15] This reactivity is in sharp contrast to the previously reported activation of **1** by LiO*t*Bu, where only 21% conversion to the borate species is observed.
[16] a) I. P. Query, P. A. Squier, E. M. Larson, N. A. Isley, T. Clark, *J. Org. Chem.* **2011**, *76*, 6452; b) H. C. Brown, J. S. Cha, B. Nazer, *Inorg. Chem.* **1984**, *23*, 2929.
[17] a) G. M. Whitesides, E. J. Panek, E. R. Stedronsky, *J. Am. Chem. Soc.* **1972**, *94*, 232 – 239; b) T. Nagano, T. Hayashi, *Chem. Lett.* **2005**, *34*, 1152 – 1153.
[18] G. M. Whitesides, D. E. Bergbreiter, P. E. Kendall, *J. Am. Chem. Soc.* **1974**, *96*, 2806 – 2813.
[19] a) R. Murphy, R. H. Prager, *Tetrahedron Lett.* **1976**, *17*, 463 – 464; b) H. C. Brown, C. Verbrugge, C. H. Snyder, *J. Am. Chem. Soc.* **1961**, *83*, 1001; c) H. C. Brown, C. H. Snyder, *J. Am. Chem. Soc.* **1961**, *83*, 1002 – 1003; d) H. C. Brown, N. C. Hebert, C. H. Snyder, *J. Am. Chem. Soc.* **1961**, *83*, 1001 – 1002.
[20] See the Supporting Information for the synthesis of **21**.
[21] The boroate **21** was chosen because of its stability and the irreversible activation of boron, which limits side reactions and protodeborylation products.
[22] ^{11}B NMR analysis proved inconclusive as the products were generated in low quantities, and the line broadening of ^{11}B NMR signals is large.
[23] Monitoring a mixture of AgOAc (or the more soluble [(binap)AgOAc]) and benzaldehyde at 22 °C by ^{1}H and ^{13}C NMR spectroscopy shows no change in the chemical shift for the aldehyde signals. This indicates that there is unlikely to be a significant interaction between the silver(I) salt and the aldehyde at −25 °C.
[24] a) A. Bonet, M. Odachowski, D. Leonori, S. Essafi, V. K. Aggarwal, *Nat. Chem.* **2014**, *6*, 584 – 589. For an additional example of diastereoselective cross-couplings of secondary alkyl trifluoroborates, see: b) D. N. Primer, I. Karakaya, J. C. Tellis, G. A. Molander, *J. Am. Chem. Soc.* **2015**, *137*, 2195 – 2198.

Received: August 1, 2015
Published online: September 25, 2015

 © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim