Check for updates

Enantioselective γ-borylation of unsaturated amides and stereoretentive Suzuki–Miyaura cross-coupling†

Gia L. Hoang [ID] and James M. Takacs [ID]*

The rhodium-catalyzed, directed catalytic asymmetric hydroboration of γ,δ-unsaturated amides affords a direct route to chiral acyclic secondary γ-borylated carbonyl derivatives in high enantiomeric purity. In contrast to a similar β-borylated amide derivative, the γ-borylated amide undergoes Suzuki–Miyaura cross-coupling with stereoretention. The utility of the boronic ester products is further illustrated by other stereospecific C–B bond transformations leading to γ-amino acid derivatives, 1,4-amino alcohols, and 5-substituted-γ-lactone and γ-lactam ring systems.

Introduction

Chiral boronic esters are valuable synthetic intermediates for a variety of stereospecific transformations.[1–3] Consequently, an assortment of enantioselective routes for their preparation are under active development.[4–19] We have focused on the rhodium-catalyzed catalytic asymmetric hydroboration (CAHB) of β,γ-unsaturated amides,[20] esters,[20a] and oxime ethers[21] for the preparation of functionalized chiral boronic esters. For example, disubstituted alkenes such as (E)-**1** undergo highly enantioselective β-borylation by pinacolborane (pinBH) when catalyzed by the combination of (R)-**L1** with [Rh(nbd)₂BF₄] (i.e., 2 : 1 **L1** : Rh). CAHB followed by oxidation of the C–B bond affords β-hydroxy amide (S)-**2** in an enantiomeric ratio (er) greater than 99 : 1 (Fig. 1).[20e]

In an effort to expand the scope of CAHB, γ,δ-unsaturated amides such as **3** were explored.[22] Such substrates differ from **1** in a number of important ways including, (i) the alkene is more remote than in the β,γ-unsaturated amides, (ii) substrate **3** contains two distinctly different alkene moieties, although each is ostensibly positioned γ,δ- with respect to the carbonyl directing group, and (iii) enantioselective borylation of the endocyclic alkene requires controlling the stereochemical course by desymmetrization rather than π-facial discrimination, a fundamentally different set of requirements.[23] In the event, substrate **3** undergoes CAHB/oxidation to give the monounsaturated γ-hydroxy amide (1S,3S)-**4** in high yield (80%), regioselectivity (>20 : 1) and enantioselectivity (99 : 1 er). Only the endocyclic double bond in **3** undergoes reaction; the

pendant acyclic alkene is untouched. We now report the efficient, regioselective γ-borylation of a similarly disposed alkene in γ,δ-unsaturated amide **5a** (Fig. 1). CAHB by pinBH (0.5% [Rh(nbd)₂BF₄/2 (R)-**L1**]) followed by oxidation affords chiral γ-hydroxy amide (S)-**7a** in 79% overall yield (97 : 3 er). While conjugate addition[11] and C–H activation[10a] methodologies provide efficient alternatives to CAHB for enantioselective β-borylation of carbonyl compounds, direct γ-borylation is unique to CAHB.
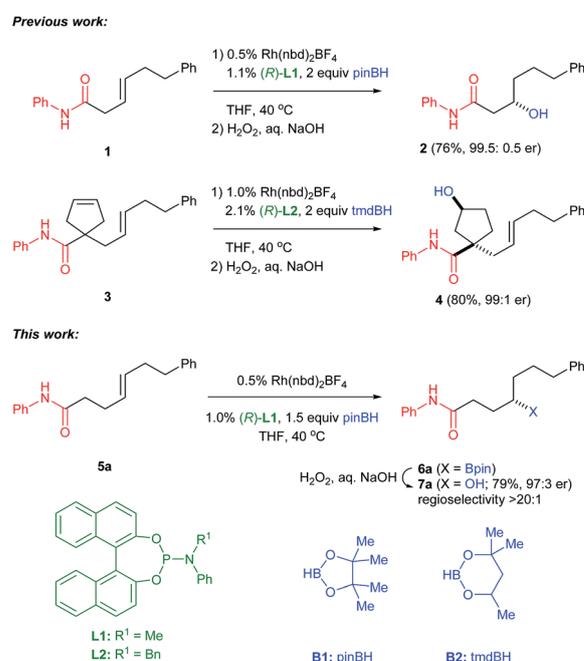

Fig. 1 CAHB/oxidation of β,γ- *versus* γ,δ-unsaturated amides.

Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE 68588-0304, USA. E-mail: jtakacs1@unl.edu

Results and discussion

The γ,δ-unsaturated amides (*E*)-**5b–n** shown in Fig. 2, along with several related structures, were treated with the catalyst system for γ-borylation (*i.e.*, 2 : 1 combinations of **L1** or **L2** with [Rh(nbd)$_2$BF$_4$], 0.5 mol% unless otherwise noted). In addition to phenyl amide **5a** described above, the corresponding Weinreb amide **5b**, the morpholine amide[24] **5c** and benzyl amide **5d** undergo CAHB to afford the intermediate γ-borylated amides **6b–d** with high levels of enantioselectivity. Within this series of amides, the secondary amides (*i.e.*, *N*-phenyl and *N*-benzyl) give the highest γ-selectivity (>20 : 1). Oxidations of **6b–d** afford the corresponding chiral γ-hydroxy amides **7b–d** (≥94 : 6 er). CAHBs of **5c** and **5d** were carried out on gram scale giving chiral boronic esters **6c** (82%, 94.5 : 5.5) and **6d** (81%, 96.5 : 3.5 er) in good yield and without loss of enantioselectivity. CAHB/oxidation of an isomeric (*Z*)-alkene, benzyl amide (*Z*)-**5d**, affords results similar to those obtained with the (*E*)-isomer.

In contrast to amides **5a–d**, the analogous ester **8** is largely recovered unchanged upon attempted CAHB; only trace amounts of borylated products are identified along with some evidence for alkene isomerization. δ,ε-Unsaturated amide **9**, a one-carbon homologue of benzyl amide (*E*)-**5d**, is found to be considerably less reactive and less selective. Complete consumption of starting material requires 2% catalyst loading to afford 56% yield of a mixture of borylated products.[25]

Benzyl amides **5e–g** containing heteroaromatic ring systems are nonetheless good substrates under the standard CAHB/ oxidation conditions yielding **7e–g**, respectively. Certain branched alkyl substituents (*i.e.*, **5h–j**) are also well tolerated. In particular, the chiral substrate (*E*)-**5j** demonstrates that (i) the proximal disubstituted alkene with respect to the amide directing group undergoes CAHB while the more distal trisubstituted alkene is untouched and (ii) the stereochemical course of γ-borylation is efficiently catalyst controlled. CAHB/oxidation with (*R*)-**L2** affords (4*S*,7*S*)-**7j**; (*S*)-**L2** affords (4*R*,7*S*)-**7j**. The silyl ether moiety in **5k** is tolerated and affords **7k** (78%, 97 : 3 er). Chiral acetal **5l** again undergoes catalyst controlled γ-borylation with high diastereoselectivity; (*R*)-**L1** affords (*S*,*S*)-**7l** (72%, 95 : 5 dr); (*S*)-**L1** affords (*R*,*S*)-**7l** in the same yield and diastereomer ratio. However, substrate **5m**, in which the chiral acetal moiety is in closer proximity to the site of hydroboration, shows a strong matched/mismatched effect. While (*R*)-**L1** affords (*R*,*S*)-**7m** (70%, 92 : 8 dr), the catalyst employing (*S*)-**L1** gives rise to a complex mixture of regioisomers **10**. Substrate **5n** (R^1 = Me) also exhibits only modest regioselectivity (3 : 1), perhaps due to
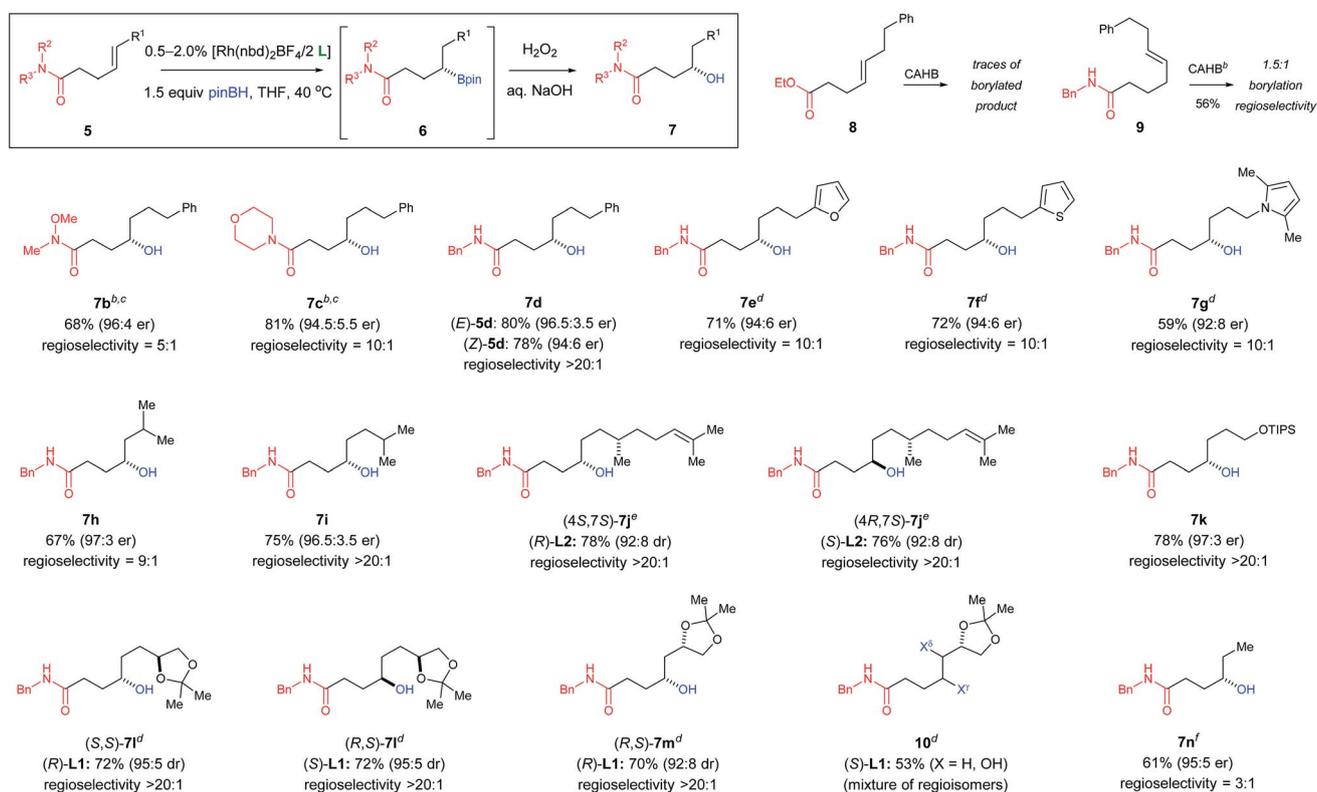

Fig. 2 Substrate scope for CAHB of γ,δ-unsaturated amides. [a]Unless otherwise noted all reaction use 0.5% [Rh(nbd)$_2$BF$_4$/2 (*R*)-**L1**], 1.5 equiv. pinBH, THF, 40 °C (12 h) followed by oxidation using H$_2$O$_2$/aq. NaOH. Unless otherwise noted, the isolated yield is that of the major regioisomer and reflects the average of three experiments generally exhibiting a spread of ±2%; regioselectivity is determined from the crude ^{1}H NMR of **7**. Enantiomer ratios (er) are determined by chiral HPLC analysis; diastereomer ratios (dr) are determined for the purified mixture of diastereomers by integrating major and minor ^{13}C NMR resonances. [b]2.0% [Rh(nbd)$_2$BF$_4$/2 (*R*)-**L1**]. [c]Oxidation conditions: NaBO$_3$/H$_2$O. [d]1.0% [Rh(nbd)$_2$BF$_4$/2 **L1**]; (*R*)-**L1** is used unless noted otherwise in the figure. [e]1.0% [Rh(nbd)$_2$BF$_4$/2 **L2**]. [f]er is determined by ^{19}F NMR of the corresponding Mosher ester (see ESI for details†).

the size of the vinyl substituent compared to other derivatives described above; however, CAHB proceeds in good yield and high enantioselectivity (61%, 95 : 5 er).

Having developed an efficient method for the γ-borylation of γ,δ-unsaturated amides, Suzuki–Miyaura cross-coupling of **11** was examined (Fig. 3). Stereochemical aspects of the palladium-catalyzed cross-coupling of chiral secondary organoboron derivatives have recently attracted a great deal attention. Molander,[26] Suginome,[27] and Hall[28] reported that β-borylated carbonyl derivatives **12–14**, whether as the boronic ester or the trifluoroborate salt, undergo cross-coupling with stereo-inversion. The stereochemical course is rationalized by intra-molecular coordination between the carbonyl oxygen and the boron atom of the boronic ester or the partially hydrolyzed tri-fluoroborate. The intramolecular coordination promotes invertive transmetallation resulting in overall stereoinversion for cross-coupling. Biscoe[19a,29] also found stereoinversion for simple substrates lacking functionality needed for coordination to boron during the course of transmetallation (*e.g.*, **15**). On the other hand, Suginome[30] reported that boracyclic intermediate **16** undergoes cross-coupling with stereoretention. Similarly, Morken[31] reported that **17** undergoes hydroxyl-directed, inner-sphere, retentive transmetallation and overall cross-coupling with stereoretention. However, when the hydroxyl is one-carbon further removed, **18** fails to undergo cross-coupling under the otherwise same conditions. We have previously shown that **19** undergoes cross-coupling with overall stereoretention.[22]

Chiral boronic ester **6c** (*i.e.*, the morpholine amide) was converted to its corresponding trifluoroborate salt **11c**[32] and subjected to palladium-catalyzed cross-coupling using the Buchwald cataCXium® A Pd G3 (**20**) precatalyst.[22,33] Cross-coupling with chlorobenzene yields amide (*S*)-**21c** (63%); 4-chloroanisole yields (*S*)-**22c** (52%). The products are obtained with essentially complete overall stereoretention.[34] We find that
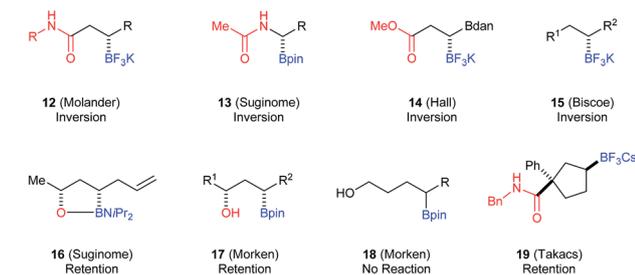

Fig. 3 Stereochemical course of Suzuki–Miyaura cross-coupling with chiral secondary boronic esters or trifluoroborate salts.
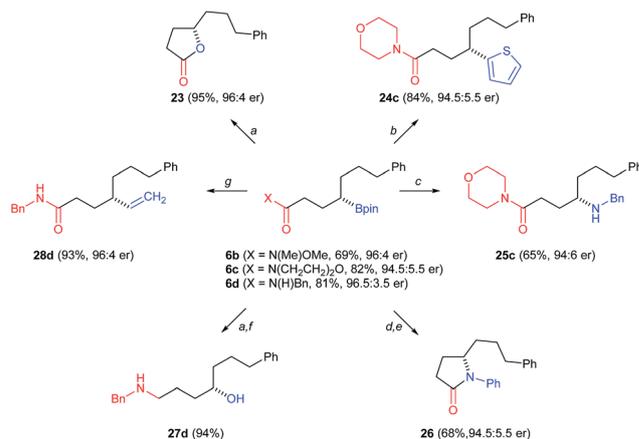

Fig. 4 Stereospecific transformations of organoboranes **6b–d**. Conditions: (a) NaOH/H₂O₂; (b) (i) n-BuLi, thiophene, (ii) NBS; (c) BCl₃, BnN₃; (d) BCl₃, PhN₃; (e) 6 M HCl; (f) LiAlH₄; (g) (i) vinylMgBr, (ii) I₂/NaOMe.

the nature of the amide is important to the success of the cross-coupling. In contrast to the tertiary morpholine amide, the analogous secondary amide **11d** does not undergo cross-coupling under the conditions employed for **11c**. Hall *et al.*[28a] reported that β-boronic esters of secondary amides failed to cross-couple in cases where the corresponding tertiary amide coupled smoothly.

Chiral organoboronates are useful for a variety of other stereospecific transformations. Fig. 4 illustrates several examples starting from chiral boronic esters **6b–d**; the latter are isolated in 69–82% yield from the corresponding alkenes. Treating **6b** with H₂O₂/aq. NaOH affords the known chiral 5-substituted-γ-lactone **23** (95%).[35] As an alternative to palladium-catalyzed cross-coupling, the morpholine amide derivative **6c** undergoes stereoretentive cross-coupling with 2-lithiothiofuran under the conditions developed by Aggarwal[2e] to give **24c** (84%). Compound **6c** also undergoes BCl₃-assisted amination with benzyl azide under the conditions reported by Knochel[36] to form the γ-amino acid derivative **25c** (65%). Phenyl azide also serves as a good nucleophile in such amination reactions, and **6c** is converted to the corresponding N-phenyl γ-amino acid en route to the 5-substituted-γ-lactam **26** (68%) by acid catalyzed cyclization. Benzyl amide derivative **6d** is efficiently converted to 1,4-aminoalcohol **27d** after oxidation of the C–B bond followed by amide reduction with LAH (94%). While the secondary N-benzyl amide **11d** failed in the attempted palladium-catalyzed cross-coupling described above, **6d** undergoes efficient vinylation in a sequence initiated the by treatment with excess vinyl Grignard;[2h] amide **28d** is formed in high yield (93%).

Conclusions

γ,δ-Unsaturated secondary (*i.e.*, N-phenyl and N-benzyl) and tertiary (*i.e.*, Weinreb and morpholine) amides undergo efficient rhodium-catalyzed CAHB to afford γ-borylated derivatives in good yield and with high levels of asymmetric induction; enantioselectivity as high as 97 : 3 er is observed. While two

good alternative methods are available to prepare chiral secondary β-borylated carbonyl compounds, the present method of directed-CAHB provides to our knowledge the first direct route to chiral acyclic secondary γ-borylated carbonyl compounds with high regio- and enantioselectivity.

A previous study found β- and γ-borylation of related substrates differ in the sense of stereoinduction, i.e., π-facial discrimination.[20a] However, it is not the case in the present study; β-borylation of β,γ-unsaturated amide **1** and γ-borylation of the one-carbon homologue γ,δ-unsaturated amide **5** add to the same face of the alkene. In the present study, CAHB of a substrate bearing both di- and trisubstituted alkene moieties (i.e., **5j**) occurs only on the disubstituted double bond proximal to the carbonyl group. Chiral substrates **5j** and **5l** undergo highly diastereoselective CAHB with catalyst control; however, substrate **5m**, in which the resident oxygen-bearing stereocenter resides adjacent to the alkene, exhibits a strong matched and mismatched effect with enantiomeric catalysts.

The γ-borylated products are found to undergo stereo-retentive palladium-catalyzed Suzuki–Miyaura cross-coupling, presumably via amide-directed inner-sphere stereoretentive transmetallation, as well as stereoretentive C–B to C–C trans-formations using main group organometallic reagents (e.g., lithium and magnesium). In addition, a variety of other stereospecific transformations are highlighted by the conversions of chiral, secondary γ-boronic esters **6b–d** to 1,4-amino alcohols, γ-amino acid derivatives, and 5-substituted-γ-lactone and γ-lactam ring systems. Further studies are in progress.

Acknowledgements

Notes and references

1 For selected recent reviews, see: (a) C.-Y. Wang, J. Derosa and M. R. Biscoe, Chem. Sci., 2015, **6**, 5105; (b) L. Xu, S. Zhang and P. Li, Chem. Soc. Rev., 2015, **44**, 8848; (c) A. H. Cherney, N. T. Kadunce and S. E. Reisman, Chem. Rev., 2015, **115**, 9587; (d) D. Leonori and V. K. Aggarwal, Angew. Chem., Int. Ed., 2015, **54**, 1082.

2 (a) Y. Wang, A. Noble, E. L. Myers and V. K. Aggarwal, Angew. Chem., Int. Ed., 2016, **55**, 4270; (b) A. Noble, S. Roesner and V. K. Aggarwal, Angew. Chem., Int. Ed., 2016, **55**, 15920; (c) A. Fawcett, D. Nitsch, M. Ali, J. M. Bateman, E. L. Myers and V. K. Aggarwal, Angew. Chem., Int. Ed., 2016, **55**, 14663; (d) A. Millán, J. R. Smith, J. L.-Y. Chen and V. K. Aggarwal, Angew. Chem., Int. Ed., 2016, **55**, 2498; (e) M. Odachowski, A. Bonet, S. Essafi, P. Conti-Ramsden, J. N. Harvey, D. Leonori and V. K. Aggarwal, J. Am. Chem. Soc., 2016, **138**, 9521; (f) J. Llaveria, D. Leonori and V. K. Aggarwal, J. Am. Chem. Soc., 2015, **137**, 10958; (g) C. Sandford, R. Rasappan and V. K. Aggarwal, J. Am. Chem. Soc., 2015, **137**, 10100; (h) R. P. Sonawane, V. Jheengut, C. Rabalakos,

R. Larouche-Gauthier, H. K. Scott and V. K. Aggarwal, Angew. Chem., Int. Ed., 2011, **50**, 3760.

3 (a) J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk and G. C. Fu, Science, 2016, **354**, 1265; (b) B. Potter, E. K. Edelstein and J. P. Morken, Org. Lett., 2016, **18**, 3286; (c) T. Rybak and D. G. Hall, Org. Lett., 2015, **17**, 4156; (d) S. C. Matthew, B. W. Glasspoole, P. Eisenberger and C. M. Crudden, J. Am. Chem. Soc., 2014, **136**, 5828; (e) A. W. Buesking and J. A. Ellman, Chem. Sci., 2014, **5**, 1983; (f) D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, J. Am. Chem. Soc., 2009, **131**, 5024.

4 Stoichiometric reagents: J. M. Brown and B. N. Nguyen, Stereoselective hydroboration and diboration of carbon–carbon double bonds, Georg Thieme Verlag, 2011, vol. 1, p. 295.

5 For a review on recent advances in the preparation and application of allylboron species, see: C. Diner and K. J. Szabó, J. Am. Chem. Soc., 2017, **139**, 2.

6 Enantioselective allyl- and arylborylation: (a) H. M. Nelson, B. D. Williams, J. Miró and F. D. Toste, J. Am. Chem. Soc., 2015, **137**, 3213; (b) T. Jia, P. Cao, B. Wang, Y. Lou, X. Yin, M. Wang and J. Liao, J. Am. Chem. Soc., 2015, **137**, 13760.

7 Enantioselective allylic substitution with diborylmethane: (a) Y. Shi and A. H. Hoveyda, Angew. Chem., Int. Ed., 2016, **55**, 3455; (b) M. Zhan, R.-Z. Li, Z.-D. Mou, C.-G. Cao, J. Liu, Y.-W. Chen and D. Niu, ACS Catal., 2016, **6**, 3381.

8 Enantioselective aminoborylation: (a) D. Nishikawa, K. Hirano and M. Miura, Org. Lett., 2016, **18**, 4856; (b) N. Matsuda, K. Hirano, T. Satoh and M. Miura, J. Am. Chem. Soc., 2013, **135**, 4934; (c) K. Hong and J. P. Morken, J. Am. Chem. Soc., 2013, **135**, 9252.

9 Enantioselective B–H bond insertion: (a) D. Chen, X. Zhang, W.-Y. Qi, B. Xu and M.-H. Xu, J. Am. Chem. Soc., 2015, **137**, 5268; (b) Q.-Q. Cheng, S.-F. Zhu, Y.-Z. Zhang, X.-L. Xie and Q.-L. Zhou, J. Am. Chem. Soc., 2013, **135**, 14094.

10 Enantioselective C–H borylation: (a) J. He, Q. Shao, Q. Wu and J.-Q. Yu, J. Am. Chem. Soc., 2017, **139**, 3344; (b) L.-L. Li, Z.-L. Tao, Z.-Y. Han and L.-Z. Gong, Org. Lett., 2017, **19**, 102.

11 Enantioselective conjugate borylation: (a) Q. Jiang, T. Guo and Z. Yu, J. Org. Chem., 2017, **82**, 1951; (b) C. Jarava-Barrera, A. Parra, A. López, F. Cruz-Acosta, D. Collado-Sanz, D. J. Cárdenas and M. Tortosa, ACS Catal., 2016, **6**, 442; (c) J.-B. Xie, S. Lin, S. Qiao and G. Li, Org. Lett., 2016, **18**, 3926; (d) Z. Niu, J. Chen, Z. Chen, M. Ma, C. Song and Y. Ma, J. Org. Chem., 2015, **80**, 602; (e) H. Wu, J. M. Garcia, F. Haeffner, S. Radomkit, A. R. Zhugralin and A. H. Hoveyda, J. Am. Chem. Soc., 2015, **137**, 10585; (f) S. Radomkit and A. H. Hoveyda, Angew. Chem., Int. Ed., 2014, **53**, 3387; (g) Y. Luo, I. D. Roy, A. G. E. Madec and H. W. Lam, Angew. Chem., Int. Ed., 2014, **53**, 4186.

12 Enantioselective conjunctive cross-coupling: (a) G. J. Lovinger, M. D. Aparece and J. P. Morken, J. Am. Chem. Soc., 2017, **139**, 3153; (b) L. Zhang, G. J. Lovinger, E. K. Edelstein, A. A. Szymaniak, M. P. Chierchia and J. P. Morken, Science, 2016, **351**, 70.

13 Enantioselective diboration: (a) L. Fang, L. Yan, F. Haeffner and J. P. Morken, J. Am. Chem. Soc., 2016, **138**, 2508; (b) Z. Yu,

R. J. Ely and J. P. Morken, *Angew. Chem., Int. Ed.*, 2014, **53**, 9632; (c) J. R. Coombs, F. Haeffner, L. T. Kliman and J. P. Morken, *J. Am. Chem. Soc.*, 2013, **135**, 11222; (d) G. E. Ferris, K. Hong, I. A. Roundtree and J. P. Morken, *J. Am. Chem. Soc.*, 2013, **135**, 2501.

14 Stereospecific catalytic Miyaura borylation: (a) Q. Zhou, H. D. Srinivas, S. Zhang and M. P. Watson, *J. Am. Chem. Soc.*, 2016, **138**, 11989; (b) C. H. Basch, K. M. Cobb and M. P. Watson, *Org. Lett.*, 2016, **18**, 136.

15 Enantioselective nucleophilic addition to aldehyde: (a) M. V. Joannou, B. S. Moyer and S. J. Meek, *J. Am. Chem. Soc.*, 2015, **137**, 6176; (b) K. Kubota, E. Yamamoto and H. Ito, *J. Am. Chem. Soc.*, 2015, **137**, 420.

16 Group-selective cross-coupling of diboranes: (a) S. N. Mlynarski, C. H. Schuster and J. P. Morken, *Nature*, 2014, **505**, 386; (b) C. Sun, B. Potter and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 6534; (c) R. D. Dewhurst and T. B. Marder, *Nat. Chem.*, 2014, **6**, 279.

17 Enantioselective homologation of organoboron *via* lithiation–borylation: (a) A. Varela, L. K. B. Garve, D. Leonori and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2017, **56**, 2127; (b) D. J. Blair, D. Tanini, J. M. Bateman, H. K. Scott, E. L. Myers and V. K. Aggarwal, *Chem. Sci.*, 2017, **8**, 2898; (c) For a review on lithiation–borylation methodology and its application in synthesis, see: D. Leonori and V. K. Aggarwal, *Acc. Chem. Res.*, 2014, **47**, 3174; (d) For related computational studies, see: S. Essafi, S. Tomasi, V. K. Aggarwal and J. N. Harvey, *J. Org. Chem.*, 2014, **79**, 12148.

18 From vinylboronates: (a) J. T. Han, W. J. Jang, N. Kim and J. Yun, *J. Am. Chem. Soc.*, 2016, **138**, 15146; (b) D. Nishikawa, K. Hirano and M. Miura, *J. Am. Chem. Soc.*, 2015, **137**, 15620; (c) J. J. Verendel, O. Pamies, M. Dieguez and P. G. Andersson, *Chem. Rev.*, 2014, **114**, 2130.

19 Examples of CAHB by copper catalysts (a–j), cobalt catalysts (k–m), iron catalysts (n), iridium catalysts (o–p), and rhodium catalysts (q–r): (a) M. G. Ceinos, A. Parra, V. M. Heras and M. Tortosa, *Angew. Chem., Int. Ed.*, 2016, **55**, 6969; (b) Y. Xi and J. F. Hartwig, *J. Am. Chem. Soc.*, 2016, **138**, 6703; (c) D. Wang, P. Cao, B. Wang, T. Jia, Y. Lou, M. Wang and J. Liao, *Org. Lett.*, 2015, **17**, 2420; (d) A. Parra, L. Amenós, M. Guisán-Ceinos, A. López, J. L. G. Ruano and M. Tortosa, *J. Am. Chem. Soc.*, 2014, **136**, 15833; (e) Z.-T. He, Y.-S. Zhao, P. Tian, C.-C. Wang, H.-Q. Dong and G.-Q. Lin, *Org. Lett.*, 2014, **16**, 1426; (f) X. Feng, H. Jeon and J. Yun, *Angew. Chem., Int. Ed.*, 2013, **52**, 3989; (g) D. Noh, S. K. Yoon, J. Won, J. Y. Lee and J. Yun, *Chem.–Asian J.*, 2011, **6**, 1967; (h) Y. Sasaki, C. Zhong, M. Sawamura and H. Ito, *J. Am. Chem. Soc.*, 2010, **132**, 1226; (i) D. Noh, H. Chea, J. Ju and J. Yun, *Angew. Chem., Int. Ed.*, 2009, **48**, 6062; (j) R. Corberán, N. W. Mszar and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2011, **50**, 7079; (k) H. Zhang and Z. Lu, *ACS Catal.*, 2016, **6**, 6596; (l) L. Zhang, Z. Zuo, X. Wan and Z. Huang, *J. Am. Chem. Soc.*, 2014, **136**, 15501; (m) J. Chen, T. Xi, X. Ren, B. Cheng, J. Guo and Z. Lu, *Org. Chem. Front.*, 2014, **1**, 1306; (n) J. Chen, T. Xi and Z. Lu, *Org. Lett.*, 2014, **16**, 6452; (o) M. Magre, M. Biosca, O. Pàmies and

M. Diéguez, *ChemCatChem*, 2015, **7**, 114; (p) C. Mazet and D. Gérard, *Chem. Commun.*, 2011, **47**, 298; (q) N. Hu, G. Zhao, Y. Zhang, X. Liu, G. Li and W. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 6746; (r) S. A. Moteki, K. Toyama, Z. Liu, J. Ma, A. E. Holmes and J. M. Takacs, *Chem. Commun.*, 2012, **48**, 263.

20 (a) S. M. Smith, G. L. Hoang, R. Pal, M. O. B. Khaled, L. S. W. Pelter, X. C. Zeng and J. M. Takacs, *Chem. Commun.*, 2012, **48**, 12180; (b) S. M. Smith, M. Uteuliyev and J. M. Takacs, *Chem. Commun.*, 2011, **47**, 7812; (c) S. M. Smith and J. M. Takacs, *Org. Lett.*, 2010, **12**, 4612; (d) S. M. Smith and J. M. Takacs, *J. Am. Chem. Soc.*, 2010, **132**, 1740; (e) S. M. Smith, N. C. Thacker and J. M. Takacs, *J. Am. Chem. Soc.*, 2008, **130**, 3734.

21 V. M. Shoba, N. C. Thacker, A. J. Bochat and J. M. Takacs, *Angew. Chem., Int. Ed.*, 2016, **55**, 1465.

22 G. L. Hoang, Z.-D. Yang, S. M. Smith, R. Pal, J. L. Miska, D. E. Pérez, L. S. W. Pelter, X. C. Zeng and J. M. Takacs, *Org. Lett.*, 2015, **17**, 940.

23 The symmetry in substrate **3** was also exploited in a DFT study of potential catalytic cycle for the reaction; see: Z.-D. Yang, R. Pal, G. L. Hoang, X. C. Zeng and J. M. Takacs, *ACS Catal.*, 2014, **4**, 763.

24 R. Peters, P. Waldmeier and A. Joncour, *Org. Process Res. Dev.*, 2005, **9**, 508.

25 When reacted separately substrate **9** requires higher catalyst loading for complete consumption as stated above (*i.e.*, 2.0% Rh for **9** *versus* 0.5% for **5d**). However, the direct competition of **9** and **5d** for limiting pinBH (equivalent amounts of each) affords only a modest excess of recovered **9** (74% recovered) relative to recovered **5d** (61% recovered). The results suggest that **5d** is consumed only slightly faster than **9** by active catalyst. A relatively slow conversion of the rhodium precatalyst to active catalyst by **9** in the absence of **5d** could account of the conflicting observations; see ref. 22 for a similar example.

26 D. L. Sandrock, L. Jean-Gerard, C. Chen, S. D. Dreher and G. A. Molander, *J. Am. Chem. Soc.*, 2010, **132**, 17108.

27 (a) T. Awano, T. Ohmura and M. Suginome, *J. Am. Chem. Soc.*, 2011, **133**, 20738; (b) T. Ohmura, T. Awano and M. Suginome, *J. Am. Chem. Soc.*, 2010, **132**, 13191.

28 (a) J. C. H. Lee, H.-Y. Sun and D. G. Hall, *J. Org. Chem.*, 2015, **80**, 7134; (b) J. C. Lee, R. McDonald and D. G. Hall, *Nat. Chem.*, 2011, **3**, 894.

29 L. Li, S. Zhao, A. Joshi-Pangu, M. Diane and M. R. Biscoe, *J. Am. Chem. Soc.*, 2014, **136**, 14027.

30 M. Daini and M. Suginome, *J. Am. Chem. Soc.*, 2011, **133**, 4758.

31 T. P. Blaisdell and J. P. Morken, *J. Am. Chem. Soc.*, 2015, **137**, 8712.

32 A. J. J. Lennox and G. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2012, **51**, 9385.

33 N. C. Bruno, M. T. Tudge and S. L. Buchwald, *Chem. Sci.*, 2013, **4**, 916.

34 Authentic (R)-**21c** was prepared *via* enolate allylation using the Evans chiral auxiliary: *in situ* half reduction to aldehyde followed by Wadsworth–Horner–Emmons

olefination, Pd/C hydrogenation and transamidation with morpholine is described in the accompanying ESI.†

35 (a) C. H. Larsen, B. H. Ridway, J. T. Shaw, D. M. Smith and K. A. Woerpel, *J. Am. Chem. Soc.*, 2005, **127**, 10879; (b) M. Aquino, S. Cardani, G. Fronza, C. Fuganti, R. P. Fernandez and A. Tagliani, *Tetrahedron*, 1991, **47**, 7887.

36 (a) E. Hupe, I. Marek and P. Knochel, *Org. Lett.*, 2002, **4**, 2681, see also; (b) P. Y. Chavant, F. Lhermitte and M. Vaultier, *Synlett*, 1993, 519; (c) D. S. Matteson and G. Y. Kim, *Org. Lett.*, 2002, **4**, 2153; (d) V. Bagutski, T. G. Elford and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2011, **50**, 1080.