Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7900

www.rsc.org/obc

PAPER

Chemoselective palladium-catalyzed α-allylation of α-boryl aldehydes†

Jeffrey D. St. Denis, Zhi He and Andrei K. Yudin*

Received 19th July 2012, Accepted 2nd August 2012
DOI: 10.1039/c2ob26503f

Herein we report the development of an α-allylation reaction of α-boryl aldehydes that preserves the carbon–boron bond under Pd^0/Pd^{II} catalysis. A variety of α-boryl aldehydes and allylic alcohols participate in this chemoselective transformation. The α-allylated products were obtained as single regioisomers.

The development of chemoselective processes is an active field of modern synthetic organic chemistry.[1] Boronic acids have been instrumental in the area of chemoselective transition metal-catalyzed cross-coupling transformations and recently in the generation of stereodefined substrates through lithium boronate intermediates.[2–4] In addition to our interest in amphoteric aziridine aldehydes, a novel class of bench-stable α-boryl aldehydes, equipped with a MIDA-chelated sp^3-boron centre, were recently developed.[5–7] The MIDA group attenuates the Lewis acidity of the boron centre and is essential for the stabilization of the α-boryl aldehyde.[5,7] Amphoteric α-boryl aldehydes have been utilized in several chemo- and stereoselective bond forming processes,[5–8] including the synthesis of a series of functionalized vinyl boronates and their use in the three component Petasis reaction.[9]

In order to explore the synthetic potential of α-boryl aldehydes, we were determined to selectively activate the pro-nucleophilic α-C–H bond in preference to the C–B bond (Fig. 1a). Our hope was to find mild reaction conditions that would enable functionalization of the sp^3 α-carbon stereocentre while keeping the dense array of reactive functional groups (nucleophilic C–B bond and electrophilic aldehyde group) intact. In doing so, we hoped to develop access to novel *C*,*O*-bis enolate intermediates (Fig. 1b).[10]

Subjecting α-boryl hexanaldehyde to palladium-catalyzed allylation with allyl alcohol resulted in recovery of the starting α-boryl aldehyde (Table 1, entries 1–3).[11] More forcing conditions failed to produce any desired product (Table 1, entry 4).

It was evident that the active Pd^0 catalyst was not being formed under the reaction conditions. Gratifyingly, by changing the palladium source to $Pd(PPh_3)_4$, an efficient α-allylation reaction was found to take place at 5 mol% loading (Table 1, entries 5–7). When we decreased the catalyst loading, the reaction became sluggish and failed to reach completion in an acceptable amount of time. We also observed that the addition of 4 Å molecular sieves was necessary to improve the reaction efficiency by absorbing the water that was formed as a by-product.

With the appropriate reaction conditions for the α-allylation in hand, we investigated the scope of α-MIDA boryl aldehyde reactivity. Due to higher acidity of the benzylic C–H bond, α-aryl derivatives performed better than the corresponding α-alkyl variants under our allylation conditions. α-Boryl cyclohexyl aldehyde did not undergo allylation (Table 2, entry 11). This lack of reactivity can be attributed to the difficulty in forming a quaternary centre adjacent to two β-branched substituents. A similar outcome was recorded in the case of cyclohexene-2-ol (Table 2, entries 4 and 8), which failed to react. Unsymmetrical allyl alcohols were also subjected to allylation. The use of (*E*)-cinnamyl alcohol (Table 3, entry 1) afforded the linear product in 72% yield. Examination of the crude ^1H NMR showed no formation of the branched or (*Z*)-isomer.

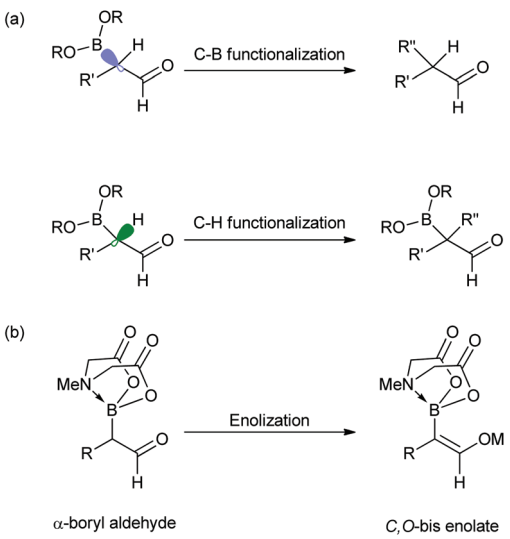
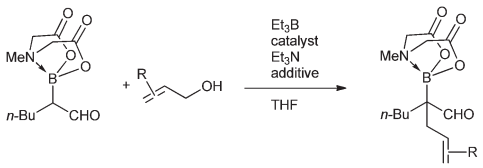


Fig. 1 (a) C–B *versus* C–H functionalization, (b) enolization of α-boryl aldehyde to form a *C*,*O*- bis-enolate.

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5H 3H5, Canada. E-mail: ayudin@chem.utoronto.ca; Fax: (+1)416-946-7676

†Electronic supplementary information (ESI) available: ^1H, ^{13}C, ^{11}B, HRMS. See DOI: 10.1039/c2ob26503f

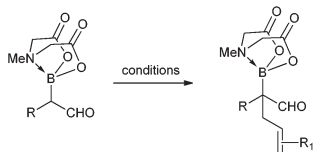
Table 1 Optimization of α-allylation conditions[a]

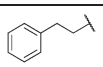
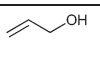
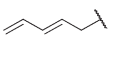
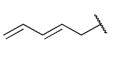


Entry	Catalyst (mol%)	Allyl component (eq)	Additive (eq)	Base (eq)	Temp (°C)	Time (h)	Yield (%)
1	$Pd(OAc)_2$ (10)	Allyl alcohol (1.5)	Et_3B (2.4)/LiCl (1.0)	Et_3N (1.5)	50	24	Trace
2	$Pd(OAc)_2$ (10)	Allyl alcohol (3)	Et_3B (3.0)/LiCl (1.0)	Et_3N (1.5)	50	48	Trace
3	$Pd(OAc)_2$ (10)	Allyl alcohol (5)	Et_3B (2.4)/LiCl (1.0)	Et_3N (1.5)	50	72	Trace
4	$Pd(OAc)_2$ (10)	Allyl alcohol (3)	Et_3B (2.4)/LiCl (1.0)	Et_3N (1.5)	Reflux	72	Trace
5	$Pd(PPh_3)_4$ (10)	Allyl alcohol (2)	Et_3B (3.0)/4 Å MS[b]	Et_3N (1.5)	50	48	57
6	$Pd(PPh_3)_4$ (5)	2-Methyl allyl alcohol (2)	Et_3B (3.0)/4 Å MS[b]	Et_3N (1.5)	50	48	48
7	$Pd(PPh_3)_4$ (5)	1,4-Pentadienol (2)	Et_3B (3.0)/4 Å MS[b]	Et_3N (1.5)	50	48	45

[a] Reaction was performed in a sealed vial under an atmosphere of nitrogen. [b] 2 equiv. of 4 Å MS were used (weight/weight of α-boryl aldehyde).

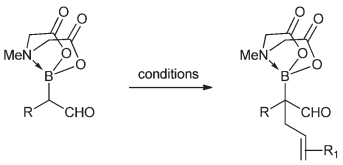
Table 2 Substrate scope of allylation with symmetrical allylic alcohols[a]

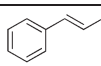
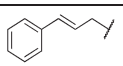
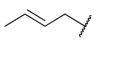


Entry	R	Starting alcohol	R_1 [b]	Yield[c] (%)
1				60
2				65
3				61
4			N/A	NR
5				78
6				70
7				70
8			N/A	NR
9				72
10				86
11			N/A	NR

[a] Reaction conditions: 5 mol% $Pd(PPh_3)_4$, 2 equiv. alcohol, 1.5 equiv. Et_3N, 3 equiv. 1.0 M Et_3B in THF, 2 equiv. 4 Å MS (based on weight), THF, 50 °C 48 h. [b] N/A: not applicable. [c] NR: no reaction.

Table 3 Substrate scope of allylation with unsymmetrical allylic alcohols[a]

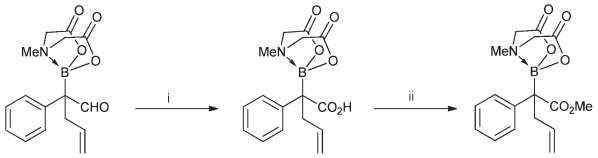


Entry	R	Starting alcohol	R_1	Yield (%)
1				78
2				77
3				79
4				76
5				72

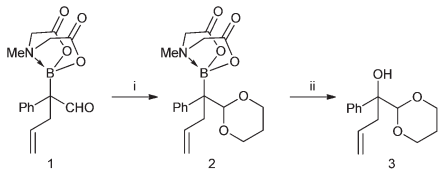
[a] Reaction conditions: 5 mol% $Pd(PPh_3)_4$, 2 equiv. allylic alcohol, 1.5 equiv. Et_3N, 3 equiv. 1.0 M Et_3B in THF, 2 equiv. 4 Å MS, THF, 50 °C, 48 h.

We also evaluated the performance of allylic alcohols containing *cis*-alkenes under our reaction conditions. The crude ^1H NMR of the allylation reaction using (*Z*)-penten-2-ol (Table 3, entry 3) showed exclusive formation of the linear *trans*-product. Presumably, the palladium catalyst coordinates with the *in situ* formed triethylborane-activated allyl alcohol to generate the electrophilic η^3-allyl Pd complex, which isomerizes the alkene through the η^3–η^1–η^3 mechanism to the most stable *trans*-isomer.[12–14] The allyl-Pd species undergoes nucleophilic attack by the boryl enolate at the most sterically accessible carbon atom. This is consistent with most Pd-catalyzed allylation reactions, whereby isomerization of the allylic alcohol to the most thermodynamically stable intermediate occurs.[14]

The newly formed α-allyl α-boryl aldehydes can be used in further transformations. The allylated boryl aldehydes have been oxidized to the corresponding carboxylic acids under Pinnick conditions. The reaction was slower as compared to that of non-



Scheme 1 Pinnick oxidation and methyl ester formation. Reaction conditions: i) $NaClO_2$, $NaHPO_4$, *t*-BuOH, H_2O, 50 °C overnight, ii) $TMSCHN_2$, DCM : MeOH RT 2 h.



Scheme 2 Oxidative elaboration of the C–B bond. Reaction conditions: i) 1,3-propanediol, $MgSO_4$, $TsOH{\cdot}H_2O$, DCM 72 h 76%, ii) 1.0 M NaOH, 30% H_2O_2, THF, 15 h 92%.

allylated α-boryl aldehydes, presumably due to the steric hindrance brought about by the quaternary centre (Scheme 1).[5] When the crude carboxylic acid was treated with $TMSCHN_2$ in a DCM–MeOH solvent mixture, the methyl ester was produced in good yield (Scheme 1). In addition, α-boryl carboxylic acids have been used to synthesize α-boryl ureas, further highlighting the synthetic application of this novel class of compounds.[15]

In an attempt to form unsymmetrically substituted tertiary alcohols, we exposed the phenyl α-boryl aldehyde **1** to standard carbon-boron oxidation conditions (30% H_2O_2, 1.0 M NaOH in THF) and obtained the proto-deborylated product exclusively. In effort to manipulate the aldehyde functionality, we resorted to the protection of aldehyde **1** as the 1,3-propane acetal **2**. This acetal intermediate was easily oxidized using alkaline hydrogen peroxide to the desired benzylic alcohol **3**, which was isolated as a clear oil in 92% yield (Scheme 2).

Conclusions

In summary, the pro-nucleophilic carbon–hydrogen bond can be functionalized in the presence of a nucleophilic carbon–boron bond in α-boryl aldehydes. This has been accomplished through the palladium-catalyzed allylation of α-MIDA boryl aldehydes. Under our conditions, a wide variety of allylic alcohols can be utilized to generate the linear *trans*-alkenyl products (Fig. 1b). Facile access to *C*,*O*-bis enolate intermediates should lead to useful synthetic opportunities.

Acknowledgements

Funding for this work was provided by Natural Science and Engineering Research Council (NSERC). JSD would also like to thank NSERC for PGS-D funding.

Notes and references

1 (*a*) N. A. Afagh and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2010, **49**, 262; (*b*) T. Gaich and P. S. Baran, *J. Org. Chem.*, 2010, **75**, 4657; (*c*) T. Newhouse, P. S. Baran and R. W. Hoffmann, *Chem. Soc. Rev.*, 2009, **38**, 3010; (*d*) R. A. Shenvi, D. P. O'Malley and P. S. Baran, *Acc. Chem. Res.*, 2009, **42**, 530; (*e*) I. S. Young and P. S. Baran, *Nat. Chem.*, 2009, **1**, 193.
2 D. G. Hall, *Boronic Acids*, Wiley-VCH, Weinheim, Germany, 2005.
3 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
4 Lithium boronate organometallics: (*a*) R. Larouche-Gauthier, T. G. Elford and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2011, **133**, 16794; (*b*) R. S. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott and V. K. Aggrawal, *Angew. Chem., Int. Ed.*, 2011, **50**, 3760.
5 Z. He and A. K. Yudin, *J. Am. Chem. Soc.*, 2011, **133**, 13770.
6 For amphoteric aziridine aldehydes developed in our lab: (*a*) R. Hili and A. K. Yudin, *J. Am. Chem. Soc.*, 2009, **131**, 16404; (*b*) L. L. W. Cheung, Z. He, S. Decker and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2011, **50**, 11798; (*c*) R. Hili and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2008, **47**, 4188; (*d*) X. Li and A. K. Yudin, *J. Am. Chem. Soc.*, 2007, **129**, 14152; (*e*) R. Hili and A. K. Yudin, *J. Am. Chem. Soc.*, 2006, **128**, 14772. For amphoteric aziridine ketones: (*f*) L. Yu, A. Kokai and A. K. Yudin, *J. Org. Chem.*, 2007, **72**, 1737.
7 J. Li and M. D. Burke, *J. Am. Chem. Soc.*, 2011, **133**, 13774.
8 For sp^3-B(Pin) coupling, see: (*a*) B. W. Glasspoole, K. Ghozati, J. W. Moir and C. M. Crudden, *Chem. Commun.*, 2012, **48**, 1230; (*b*) B. W. Glasspoole and C. M. Crudden, *Nat. Chem.*, 2011, **3**, 912; (*c*) C. M. Crudden, B. W. Glasspoole and C. J. Lata, *Chem. Commun.*, 2009, **44**, 6704; (*d*) D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, *J. Am. Chem. Soc.*, 2009, **131**, 5024. For RBF_3K coupling reactions see: (*e*) V. Colombel, F. Rombouts, D. Oehlrich and G. A. Molander, *J. Org. Chem.*, 2012, **77**, 2966; (*f*) G. A. Molander and I. Shin, *Org. Lett.*, 2011, **13**, 3956; (*g*) D. L. Sandrock, L. Jean-Gerard, C.-Y. Chen, S. D. Dreher and G. A. Molander, *J. Am. Chem. Soc.*, 2010, **132**, 17108; (*h*) G. A. Molander, O. A. Argintaru, I. Aron and S. D. Dreher, *Org. Lett.*, 2010, **12**, 5783; (*i*) G. A. Molander and D. E. Petrillo, *Org. Lett.*, 2008, **10**, 1795.
9 (*a*) N. A. Petasis and I. Akriopoulou, *Tetrahedron Lett.*, 1993, **34**, 583; (*b*) N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1997, **119**, 445; (*c*) R. A. Batey, D. B. MacKay and V. Santhakumar, *J. Am. Chem. Soc.*, 1999, **121**, 5075.
10 (*a*) A. Abiko, T. Inoue and S. Masamune, *J. Am. Chem. Soc.*, 2002, **124**, 10759; (*b*) C. J. Cowden and I. Paterson, *Org. React.*, 1997, **51**, 1; (*c*) K. M. Cergol and M. J. Coster, *Nat. Protoc.*, 2007, **2**, 2568.
11 M. Kimura, Y. Horino, R. Mukai, S. Tanaka and Y. Tamaru, *J. Am. Chem. Soc.*, 2001, **123**, 10401.
12 Initial attempts to generate optically active material using (*R*,*R*)-DACH Naphthyl TROST ligand gave 64% ee. See ESI† for details.
13 (*a*) B. M. Trost, M. R. Machacek and A. Aponick, *Acc. Chem. Res.*, 2006, **39**, 747; (*b*) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 258.
14 I. Dudovyk, D. Pichugin and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2011, **50**, 5924.
15 Z. He, A. Zajdlik, J. D. St. Denis, N. Assem and A. K. Yudin, *J. Am. Chem. Soc.*, 2012, **134**, 9926.

