

Aldol Reaction

International Edition: DOI: 10.1002/anie.201603270
German Edition: DOI: 10.1002/ange.201603270A *syn*-Selective Aza-Aldol Reaction of Boron Aza-Enolates Generated from *N*-Sulfonyl-1,2,3-Triazoles and 9-BBN-H

Tomoya Miura,* Takayuki Nakamuro, Sho Miyakawa, and Masahiro Murakami*

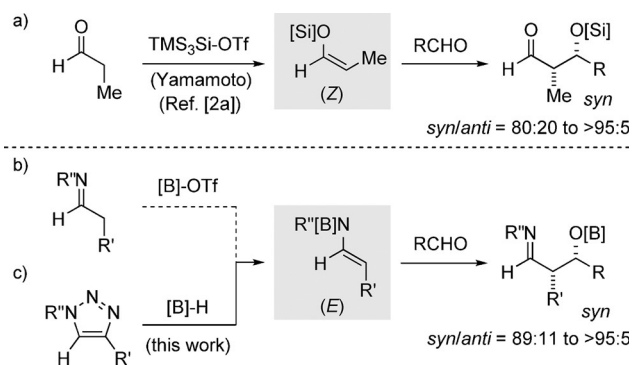
Dedicated to Professor Tien-Yau Luh on the occasion of his 70th birthday

Abstract: A *syn*-selective aza-aldol reaction of boron aza-enolates, generated from *N*-sulfonyl-1,2,3-triazoles and 9-BBN-H, is reported. It provides a sequential one-pot procedure for the stereoselective construction of 1,3-amino alcohols, having contiguous stereocenters, starting from terminal alkynes.

The stereoselective construction of acyclic systems having multiple contiguous stereocenters has been an area of intensive research in organic synthesis. An aldol reaction which employs metal enolates derived from ketones and esters serves as a powerful approach for this purpose.^[1] However, it is rather troublesome to use metal enolates of aldehydes because of competing side-reactions. Recently, tris(trimethylsilyl)silyl enol ethers derived from aldehydes have emerged as useful nucleophiles for the aldol reaction, thus leading to the formation of β -siloxy- α -substituted aldehydes with high diastereoselectivities (Scheme 1a).^[2] In contrast, there is no report about an analogous transformation using metal aza-enolates derived from aldimines, presumably because of the paucity methods for their preparation (Scheme 1b).^[3,4] We now report a new procedure for the

stereoselective synthesis of boron aza-enolates from *N*-sulfonyl-1,2,3-triazoles and 9-borabicyclo[3.3.1]nonane (9-BBN-H; Scheme 1c). Triazoles, which are readily available from terminal alkynes and azides, act as the alternative aza-enolate precursors to aldimines.^[5] The aza-aldol reaction of the resulting boron aza-enolates, followed by DIBALH reduction or Grignard addition reaction, produces 1,3-amino alcohols stereoselectively.

N-Sulfonyl-1,2,3-triazoles have received considerable attention as the precursors of α -imino metal carbene complexes.^[6] The generated carbene complexes possess an electrophilic carbene carbon atom and a nucleophilic imino nitrogen atom in the molecule. This characteristic feature results in an interesting transformation of α -imino metal carbene complexes. Fokin et al. reported a stereoselective arylation of α -imino rhodium carbene complexes with arylboroxines, in which the nucleophilic imino nitrogen atom would assist in the arylation step by coordinating to the vacant orbital on the boron atom.^[7] We envisaged that a reaction with a boron reagent having a B–H bond (R^1R^2B-H) might cause B–H insertion, thus leading to the stereoselective formation of a boron aza-enolate.^[8] Thus, we initially prepared 1-mesyl-4-phenyl-1,2,3-triazole (**1a**) from phenylacetylene and mesyl azide according to a literature procedure using copper(I) thiophen-2-carboxylate (CuTC).^[9] Then, the isolated **1a** (1.0 equiv) was treated with 9-BBN-H dimer (**2**; 1.2 equiv B), $[Rh_2(OPiv)_4]$ (1.0 mol %), and 4 Å molecular sieves (M.S.) in toluene (0.2 M), and the mixture was heated at 40 °C for 6 hours.^[10] The reaction mixture was cooled to room temperature, passed through a short pad of celite, and concentrated under reduced pressure. ¹H NMR analysis of the residue indicated that the boron aza-enolate (*E*)-**3a** was formed in 95% yield with excellent *E* selectivity^[11] (>95:5) [Eq. (1); Ms = methanesulfonyl, Piv = pivaloyl]. The *Z* isomer was not observed within the detection limit of ¹H NMR spectroscopy. The outlined mechanism explains the formation of (*E*)-**3a**. The reaction is initiated by a ring-chain tautomerization of **1a** to generate the α -diazo imine **1a'**, which reacts with a rhodium(II) complex to afford the α -imino rhodium carbene complex **A**. Rotation along the C–C bond axis achieves a conformation in which the Rh=C bond is perpendicular to the plane of the C=N bond. The lone pair electrons of the imino nitrogen atom of **A** coordinate to the vacant orbital of the boron atom of **2**, forming the ate complex **B** in situ. The complexation of the imino nitrogen atom invokes the intramolecular hydride migration from the boron atom to the carbene carbon atom of **B**^[12] to afford the zwitterionic complex **C**. The stereochemistry of (*E*)-**3a** is

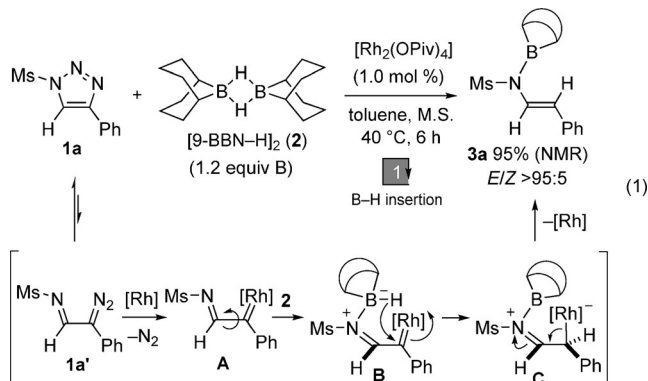


Scheme 1. a) Aldol reaction via silyl enol ethers of aldehydes. b) Aza-aldol reaction via metal aza-enolates of aldimine. c) This work: alternative route to boron aza-enolates and aza-aldol reaction. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

[*] Dr. T. Miura, T. Nakamuro, S. Miyakawa, Prof. Dr. M. Murakami
Department of Synthetic Chemistry and Biological Chemistry
Kyoto University, Katsura, Kyoto 615-8510 (Japan)
E-mail: tmiura@sbchem.kyoto-u.ac.jp
murakami@sbchem.kyoto-u.ac.jp

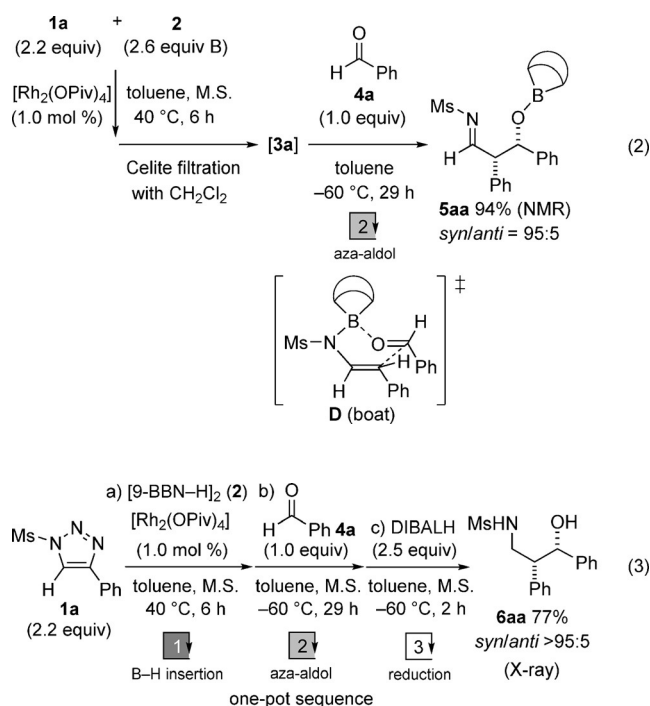
Supporting information for this article can be found under:
<http://dx.doi.org/10.1002/anie.201603270>.

proposed to be dictated by this migration step.^[7] Finally, the rhodium species immediately eliminates from **C** prior to rotation around the C–C bond, thus giving the boron aza-enolate (*E*)-**3a**.



The boron aza-enolate (*E*)-**3a** generated from **1a** and 9-BBN-H was readily hydrolyzed during chromatographic purification to form the NH enamide even in a glovebox. Thus, the crude reaction mixture of (*E*)-**3a** was directly subjected to a subsequent reaction with aldehydes. The unpurified (*E*)-**3a** (ca. 2.0 equiv) obtained by celite filtration was mixed with benzaldehyde (**4a**, 1.0 equiv) at –60 °C in toluene (0.2 M). After 29 hours, the reaction mixture was passed through a short pad of celite and concentrated under reduced pressure. ¹H NMR analysis of the reaction mixture showed that the β-oxygenated imine *syn*-**5aa** was formed in 94% yield with high *syn* selectivity (95:5) [Eq. (2)]. Other identified products, which resulted from dehydration of *syn*-**5aa** and further addition of (*E*)-**3a** to the imine moiety of **5aa**, were not obtained. The isolation of *syn*-**5aa** was also difficult because of its lability. Thus, it is observed that the geometry of the (*E*)-**3a** is transferred to give *syn*-**5aa**. This outcome is in sharp contrast to the reaction of the aldehyde-derived tris(trimethylsilyl)silyl enol ethers mentioned above,^[2a] as they furnish an aldol product containing *syn* stereochemistry from the *Z* geometry of the enolates. The stereochemical outcome of *syn*-**5aa** is reasonably explained by assuming that the aza-aldol reaction proceeds via a six-membered boatlike transition state (**D**), which is proposed by a previous computational study on the aza-aldol reaction with boron aza-enolates of ketimines.^[3b]

The rhodium-catalyzed B–H insertion and aza-aldol reaction were successfully combined in one pot, and the product was isolated in the more stable form through hydride reduction [Eq. (3)].^[13] Thus, diisobutylaluminum hydride (DIBALH) was added to the reaction mixture at –60 °C and the mixture was stirred for 2 hours. After chromatographic purification, the 1,3-amino alcohol **6aa** was obtained in 77% yield upon isolation with a *syn/anti* ratio of greater than 95:5. The structure of **6aa** was determined by single-crystal X-ray analysis, thus confirming the relative stereochemistry as *syn*.^[14] An experiment in a larger scale using 500 mg of **4a** (4.7 mmol) also gave a comparable result (**6aa**, 69% yield, *syn/anti* > 95:5).



With these encouraging results in hand, the scope of aldehydes was examined in the reaction of **1a** (Table 1). An electronically and sterically diverse array of aromatic al-

Table 1: Stereoselective aza-aldol reaction of triazole **1a** with various aldehydes.^[a]

Entry	4	R ²	6	Yield [%] ^[b]	<i>syn/anti</i> ^[c]
1	4b	<i>p</i> -MeC ₆ H ₄	6ab	80 ^[d]	> 95:5
2	4c	<i>p</i> -NO ₂ C ₆ H ₄	6ac	67	94:6
			(X-ray)		
3	4d	<i>p</i> -ClC ₆ H ₄	6ad	76	> 95:5
4	4e	<i>m</i> -MeC ₆ H ₄	6ae	72	> 95:5
5	4f	<i>m</i> -MeOC ₆ H ₄	6af	79 ^[e]	> 95:5
6	4g	<i>o</i> -MeC ₆ H ₄	6ag	80	> 95:5
7	4h	2-furyl	6ah	76 ^[d]	> 95:5
8	4i	1- <i>tert</i> -butoxy-carbonyl-3-indolyl	6ai	49	> 95:5
9	4j	(<i>E</i>)-PhCH=CH	6aj	75 ^[f]	93:7
10	4k	CH ₃ CH ₂	6ak	75	89:11
11	4l	PhCH ₂ CH ₂	6al	70 ^[d]	> 95:5
12	4m	(CH ₃) ₂ CHCH ₂	6am	65	> 95:5
13	4n	<i>t</i> BuMe ₂ SiO(CH ₂) ₃	6an	67	95:5
14	4o	HC≡C(CH ₂) ₄	6ao	50 ^[e]	> 95:5
15	4p	cyclohexyl	6ap	74	> 95:5

[a] Reaction conditions: a) **1a** (0.44 mmol), **2** (0.52 mmol B), [Rh₂(OPiv)₄] (4.4 μmol), toluene (2.2 mL), M.S. (80 mg); b) **4** (0.20 mmol); c) DIBALH (0.50 mmol). [b] Yield of isolated product (average of two runs). [c] The *syn/anti* ratios were determined by ¹H NMR analysis of the crude reaction mixture of the imine intermediates **5**. [d] b) 26 h. [e] b) 31 h. [f] b) 48 h. [g] a) **1a** (0.48 mmol), **2** (0.44 mmol B).

hydes (**4b–g**) gave the corresponding 1,3-amino alcohols **6ab–ag** in yields ranging from 67 to 80 % with high *syn* selectivities of over 94:6 (entries 1–6).^[14] The heteroaromatic aldehydes **4h** and **4i** were also converted into the products **6ah** and **6ai**, respectively (entries 7 and 8). In addition, the α,β -unsaturated aldehyde **4j** was a suitable substrate, thus furnishing the product **6aj** in 75 % with a *syn/anti* ratio of 93:7 (entry 9). In addition to the reactions with aromatic aldehydes, was the successful transformation of the aliphatic counterparts **4k–p**. In these cases except propionaldehyde (**4k**), the reaction exhibited excellent *syn* selectivities over 95:5 (entries 10–15). In contrast, ketones such as acetophenone and 4-phenyl-2-butanone failed to undergo the aza-aldol reaction with **3a**.

Variation of the triazoles was also examined in the aza-aldol addition with *p*-chlorobenzaldehyde (**4d**; Table 2). The triazoles **1b–h**, possessing aryl and heteroaryl groups at the 4-position, reacted well to afford the corresponding 1,3-amino

Table 2: Stereoselective one-pot synthesis of 1,3-amino alcohols from various triazoles and *p*-chlorobenzaldehyde (**4d**, R² = *p*-ClC₆H₄).^[a]

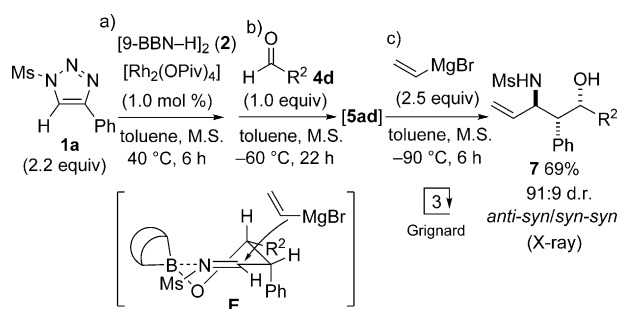
Entry	1	R ¹	6	Yield [%] ^[b]	<i>syn/anti</i> ^[c]
1	1b	<i>p</i> -MeC ₆ H ₄	6bd	60 ^[d]	> 95:5
2	1c	<i>p</i> -CF ₃ C ₆ H ₄	6cd	76 ^[e]	92:8
3	1d	<i>p</i> -MeOC ₆ H ₄	6dd	55	> 95:5
4	1e	<i>p</i> -FC ₆ H ₄	6ed	74 ^[f]	> 95:5
5	1f	<i>p</i> -IC ₆ H ₄	6fd	76	> 95:5
6	1g	<i>m</i> -MeC ₆ H ₄	6gd	70	> 95:5
7	1h	3-thienyl	6hd	69	> 95:5

[a] On a 0.20 mmol scale of **4d**. [b] Yield of isolated product (average of two runs). [c] The *syn/anti* ratios were determined by ¹H NMR analysis of a crude reaction mixture of the imine intermediates **5**. [d] b) 24 h. [e] b) 48 h. [f] c) 14 h.

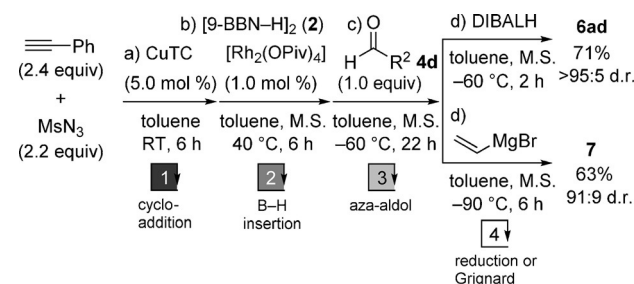
alcohols **6bd–hd** in yields ranging from 55 to 76 %. In most cases, the *syn*-isomers were obtained with excellent stereoselectivities (> 95:5). The alkyl-substituted triazoles failed to undergo the B–H insertion of α -imino rhodium carbene, and so did not give the desired product.

Intrigued by the possibility of preparing three contiguous stereocenters of 1,3-amino alcohols, we used Grignard reagents as carbon nucleophiles to the imine moiety of the aza-aldol product (Scheme 2). When the reaction mixture of **5ad** was reacted with vinylmagnesium bromide at –90 °C for 6 hours, the vinylated product **7** was obtained in 69 % isolated yield with high diastereoselectivity (*anti-syn/syn-syn* = 91:9). The relative configuration of **7** was determined by single-crystal X-ray analysis.^[14] This stereochemical outcome suggests that the chelation model **E** is preferred over the open-chain model (Felkin–Anh model).^[15]

A sequential four-step one-pot reaction starting from terminal alkynes was performed to save time and solvent required for a workup/purification after the triazole synthesis (Scheme 3).^[16] A solution of phenylacetylene, mesyl azide,



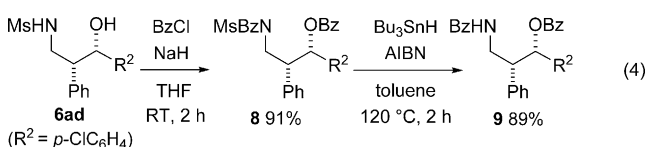
Scheme 2. Sequential aza-aldol/Grignard addition reaction to construct three contiguous stereocenters (**4d**, R² = *p*-ClC₆H₄).



Scheme 3. One-pot reaction starting from terminal alkynes (**4d**, R² = *p*-ClC₆H₄).

and CuTC (5.0 mol %) in toluene was stirred at room temperature for 6 hours, thus producing **1a** quantitatively. Then, the rhodium-catalyzed B–H insertion/aza-aldol reaction followed by reduction and vinylation gave the corresponding products **6ad** and **7** in good yields with high diastereoselectivities. Thus, this procedure enabled us to directly introduce contiguous stereocenters onto terminal alkynes.

The methanesulfonyl group of **6ad** could be replaced with a benzoyl group in a two-step reaction using tributyltin hydride to yield the benzamide **9** with an unchanged *syn/anti* ratio [Eq. (4); Bz = benzoyl].^[17]



In summary, we have disclosed the interesting reactivity of α -imino rhodium carbene with 9-BBN-H, thus providing an efficient method for the stereoselective synthesis of boron aza-enolates starting from noncarbonyl precursors. The resulting boron aza-enolates were successfully applied to *syn*-selective aza-aldol reaction.

Acknowledgments

We thank Dr. Y. Nagata (Kyoto University) for his kind help in an X-ray analysis. This work was supported in part by

Grants-in-Aid for Scientific Research (S) (15H05756) and (C) (16K05694) from MEXT. T. N. acknowledged JSPS fellowship for young scientists.

Keywords: aldol reaction · boron · carbenoids · rhodium · triazoles

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 8732–8735
Angew. Chem. **2016**, *128*, 8874–8877

- [1] For recent reviews related to the aldol reaction using metal enolates, see: a) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086; *Angew. Chem.* **2013**, *125*, 9256; b) S. B. J. Kan, K. K.-H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097; *Angew. Chem.* **2013**, *125*, 9267; c) J. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109; *Angew. Chem.* **2013**, *125*, 9280.
- [2] a) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48; b) J. Saadi, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.* **2011**, *133*, 14248; c) P. B. Brady, S. Oda, H. Yamamoto, *Org. Lett.* **2014**, *16*, 3864. See also, d) S. E. Denmark, T. Bui, *J. Org. Chem.* **2005**, *70*, 10190.
- [3] For the aza-aldol reaction of boron aza-enolates derived from ketimines, see: a) T. Sugawara, T. Toyoda, *Tetrahedron Lett.* **1979**, *20*, 1423; b) A. Bernardi, C. Gennari, J. M. Goodman, V. Leue, I. Paterson, *Tetrahedron* **1995**, *51*, 4853. For the aza-aldol reaction of boron aza-enolates derived from oxazolins, see: c) A. I. Meyers, Y. Yamamoto, *J. Am. Chem. Soc.* **1981**, *103*, 4278; d) S. Florio, V. Capriati, R. Luisi, A. Abbotto, *Tetrahedron Lett.* **1999**, *40*, 7421.
- [4] There are other examples of generation of boron aza-enolates, although they were not applied to an aza-aldol reaction. See: a) M. Ueda, H. Miyabe, T. Kimura, E. Kondoh, T. Naito, O. Miyata, *Org. Lett.* **2009**, *11*, 4632; b) Z. He, A. K. Yudin, *J. Am. Chem. Soc.* **2011**, *133*, 13770.
- [5] For recent selected examples on the in situ generation of metal enolates from non-carbonyl precursors, see: a) C. Körner, P. Starkov, T. D. Sheppard, *J. Am. Chem. Soc.* **2010**, *132*, 5968; b) P. R. Jagtap, L. Ford, E. Deister, R. Pohl, I. Císařová, J. Hodek, J. Weber, R. Mackman, G. Bahador, U. Jahn, *Chem. Eur. J.* **2014**, *20*, 10298; c) R. Guo, K.-N. Li, B. Liu, H.-J. Zhu, Y.-M. Fan, L.-Z. Gong, *Chem. Commun.* **2014**, *50*, 5451; d) T. Miura, T. Nakamuro, K. Hiraga, M. Murakami, *Chem. Commun.* **2014**, *50*, 10474; e) L. Lin, K. Yamamoto, H. Mitsunuma, Y. Kanzaki, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2015**, *137*, 15418. For a review, see: f) T. D. Sheppard, *Synlett* **2011**, 1340.
- [6] For initiative examples on the synthetic transformation of triazoles: [Rh] a) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 14972; [Ni] b) T. Miura, M. Yamauchi, M. Murakami, *Chem. Commun.* **2009**, 1470. For recent selected examples, see: c) Y. Yang, M.-B. Zhou, X.-H. Ouyang, R. Pi, R.-J. Song, J.-H. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 6595; *Angew. Chem.* **2015**, *127*, 6695; d) T. Miura, Y. Fujimoto, Y. Funakoshi, M. Murakami, *Angew. Chem. Int. Ed.* **2015**, *54*, 9967; *Angew. Chem.* **2015**, *127*, 10105; e) J. H. Kim, T. Gensch, D. Zhao, L. Stegemann, C. A. Strassert, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 10975; *Angew. Chem.* **2015**, *127*, 11126; f) D. J. Lee, D. Ko, E. J. Yoo, *Angew. Chem. Int. Ed.* **2015**, *54*, 13715; *Angew. Chem.* **2015**, *127*, 13919; g) V. N. G. Lindsay, H. M.-F. Viart, R. Sarpong, *J. Am. Chem. Soc.* **2015**, *137*, 8368; h) D. Yadagiri, P. Anbarasan, *Chem. Sci.* **2015**, *6*, 5847; i) J. He, Y. Shi, W. Cheng, Z. Man, D. Yang, C.-Y. Li, *Angew. Chem. Int. Ed.* **2016**, *55*, 4557; *Angew. Chem.* **2016**, *128*, 4633; For reviews: j) A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2013**, *52*, 1371; *Angew. Chem.* **2013**, *125*, 1411; k) H. M. L. Davies, J. S. Alford, *Chem. Soc. Rev.* **2014**, *43*, 5151; l) P. Anbarasan, D. Yadagiri, S. Rajasekar, *Synthesis* **2014**, *46*, 3004; m) S. C. Hockey, L. C. Henderson, *Aust. J. Chem.* **2015**, *68*, 1796.
- [7] N. Selander, B. T. Worrell, S. Chuprakov, S. Velaparthi, V. V. Fokin, *J. Am. Chem. Soc.* **2012**, *134*, 14670.
- [8] For the formation of an enolate equivalent using Hooz insertion chemistry, see: a) J. Hooz, S. Linke, *J. Am. Chem. Soc.* **1968**, *90*, 6891; b) D. J. Pasto, P. W. Wojtkowski, *Tetrahedron Lett.* **1970**, *11*, 215; c) Y. Luan, S. E. Schaus, *Org. Lett.* **2011**, *13*, 2510.
- [9] J. Raushel, V. V. Fokin, *Org. Lett.* **2010**, *12*, 4952.
- [10] Other borane reagents such as dicyclohexylborane, dimesitylborane, and pinacolborane gave inferior results. In the absence of rhodium catalyst, the boron aza-enolate (*E*)-**3a** was not formed.
- [11] The configuration of the double bond of (*E*)-**3a** was confirmed as *E* by NOE studies. See the Supporting Information for details.
- [12] The formation of the ate complexes, that is, amine-boranes and phosphine-boranes, would be important for the B–H insertion of metal carbene complexes. See: a) X. Li, D. P. Curran, *J. Am. Chem. Soc.* **2013**, *135*, 12076; b) Q.-Q. Cheng, S.-F. Zhu, Y.-Z. Zhang, X.-L. Xie, Q.-L. Zhou, *J. Am. Chem. Soc.* **2013**, *135*, 14094; c) D. Chen, X. Zhang, W.-Y. Qi, B. Xu, M.-H. Xu, *J. Am. Chem. Soc.* **2015**, *137*, 5268.
- [13] Various attempts to prepare the aldehydes by imine hydrolysis of aza-aldol products were unsuccessful, thus giving a complex mixture of products.
- [14] CCDC 1475057 (**6aa**), 1475058 (**6ac**), and 1475059 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
- [15] D. A. Evans, B. D. Allison, M. G. Yang, *Tetrahedron Lett.* **1999**, *40*, 4457.
- [16] For reviews on sequential multistep catalytic processes, see: a) L. M. Ambrosini, T. H. Lambert, *ChemCatChem* **2010**, *2*, 1373; b) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350; c) J. E. R. Sadig, M. C. Willis, *Synthesis* **2011**, *1*; d) L. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2011**, *50*, 8492; *Angew. Chem.* **2011**, *123*, 8642; e) Y. Hayashi, *Chem. Sci.* **2016**, *7*, 866.
- [17] C. Röben, J. A. Souto, Y. González, A. Lishchynskyi, K. Muñoz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9478; *Angew. Chem.* **2011**, *123*, 9650.

Received: April 4, 2016

Revised: April 25, 2016

Published online: June 3, 2016