JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Ruthenium-Catalyzed (*Z*)-Selective Hydroboration of Terminal Alkynes with Naphthalene-1,8-diaminatoborane

Kensuke Yamamoto, Yusei Mohara, Yuichiro Mutoh, and Shinichi Saito

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b06910 • Publication Date (Web): 14 Sep 2019

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Ruthenium-Catalyzed (*Z*)-Selective Hydroboration of Terminal Alkynes with Naphthalene-1,8-diaminatoborane

Kensuke Yamamoto, Yusei Mohara, Yuichiro Mutoh,* and Shinichi Saito*

Department of Chemistry, Faculty of Science, Tokyo University of Science, 1-3 Kagurazaka, Shinjuku-ku, Tokyo 162-8601.

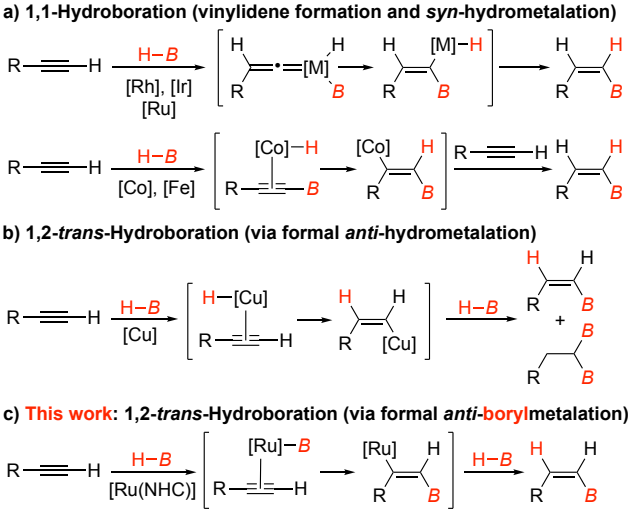
Supporting Information Placeholder

ABSTRACT: The metal-catalyzed (*Z*)-selective hydroboration of terminal alkynes is synthetically challenging due to the usually (*E*)-selective nature of the hydroboration and the formation of the thermodynamically unstable (*Z*)-isomer. Herein, we report that N-heterocyclic-carbene-ligated ruthenium complexes catalyze the (*Z*)-selective hydroboration of terminal alkynes with H–B(dan) (dan = naphthalene-1,8-diaminato), which generates a diverse range of synthetically valuable (*Z*)-alkenylboranes. Mechanistic studies, particularly the isolation of a catalytically relevant borylruthenium complex, revealed a mechanism that involves the insertion of the alkyne into a Ru–B bond, which provides a catalytic cycle that is distinctly different from that of previously reported (*Z*)-selective hydroborations. The direct cross-coupling of the obtained (*Z*)-alkenyl-B(dan) enables the rapid synthesis of biologically active Combretastatin A-4 analogues.

Alkenylboranes are attractive building blocks in organic synthesis due to their low toxicity and broad functional-group compatibility.[1] The hydroboration of alkynes using transition-metal catalysts represents a reliable and straightforward synthetic route to alkenylboranes.[1d,f] Compared to readily available (*E*)-alkenylboranes, which can be obtained from the hydroboration of terminal alkynes, the selective synthesis of (*Z*)-alkenylboranes is challenging due to the *syn*-selective nature of the hydroboration and the thermodynamic instability of the obtained (*Z*)-isomer. It is thus hardly surprising that only few examples of transition-metal-catalyzed (*Z*)-selective hydroborations, e.g., 1,1-[2–5] and formal *trans*-1,2-hydroborations[6] of terminal alkynes, have been reported.[1d,7–9] The 1,1-hydroborations involve the formation of a vinylidene intermediate of rhodium,[2] iridium,[2] or ruthenium,[3] whereas a *syn*-hydrometalation of the in-situ-generated alkynylboranes is involved in the cobalt-[4] or iron-[5] catalyzed reactions (Scheme 1a). The formal 1,2-*trans*-hydroboration has been achieved via a hydrometalation of alkynes using a copper complex, even though the corresponding overreduction products were also formed (Scheme 1b).[6] The development of other 1,2-*trans*-hydroborations is desirable to further the understanding of the metal-catalyzed (*Z*)-selective hydroboration of terminal alkynes, which generates synthetically valuable (*Z*)-alkenylboranes. A palladium-catalyzed (*Z*)-selective hydroboration using 1,3-enynes has also been reported,[7a] and an outer-sphere mechanism was proposed based on a computational study.[7b]

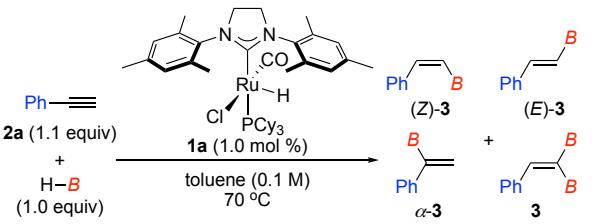
We have recently discovered that the N-heterocyclic-carbene-(NHC)-ligated ruthenium complex [RuHCl(CO)(H$_2$IMes)(PCy$_3$)] (**1a**; H$_2$IMes = 1,3-dimesitylimidazolin-2-ylidene) exhibits high catalytic activity for the (*Z*)-selective hydrosilylation of terminal alkynes with HSiMe(OSiMe$_3$)$_2$.[10] The NHC ligand is essential for increased catalytic activity and high (*Z*)-selectivity. We envisioned that [Ru(NHC)] complexes could also catalyze the (*Z*)-selective 1,2-hydroboration of terminal alkynes. Herein, we report the (*Z*)-selective 1,2-hydroboration of terminal alkynes, which leads to various (*Z*)-alkenylboranes, catalyzed by air-stable [Ru(NHC)] complexes (Scheme 1c). Based on the isolation of a catalytically relevant borylruthenium complex, we propose a mechanism that involves a formal *anti*-borylmetalation of the alkynes, which provides a pathway that is distinctly different from that of the previously reported metal-catalyzed (*Z*)-selective hydroborations of alkynes.[2–8]

Scheme 1. Transition-metal-catalyzed (*Z*)-Selective Hydroborations of Terminal Alkynes



Initially, we screened a suitable borane reagent for the (*Z*)-hydroboration of phenylacetylene (**2a**) in the presence of **1a** (1 mol %) at 70 °C in toluene (Table 1). When H–B(dan) (dan = naphthalene-1,8-diaminato) was used, styrylborane **3a** was obtained in 98% yield (*Z*/*E* = 98:2) together with trace amounts of 1,1-diborylalkene **3′** (entry 1). In contrast, catecholborane and pinacolborane were not suitable reagents for this (*Z*)-selective hydroboration in terms of the yields of the products and the *Z*/*E* ratio (entries 2 and 3).

Table 1. Screening of Borans for the (*Z*)-Selective Hydroboration of 2a[a]

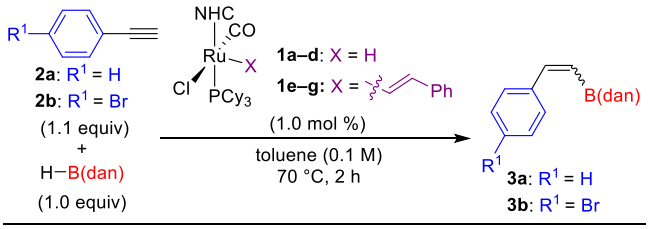


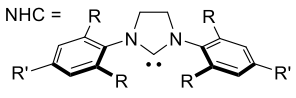
entry	*B*	time (h)	yield (%)[b]	ratio[c]			
				(*Z*)-**3**	(*E*)-**3**	α-**3**	**3′**
1	B(dan)	2	98	98	2	0	<1
2[d]	B(cat)	20	60	75	25	0	0
3	B(pin)	24	34	45	54	3	0

[a]General reaction conditions: **1a** (1.0 mol %), **2a** (1.1 equiv), H–*B* (1.0 equiv), toluene ([**2a**]$_0$ = 0.1 M). [b]Isolated yields relative to the borane. [c]The product ratio was estimated based on the ^{1}H NMR analysis of the unpurified product mixture. [d]The catecholate moiety was replaced by 1,8-diaminatonaphthalene before purification.

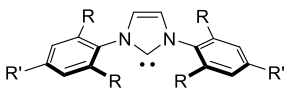
Next, we studied the impact of the structure of the NHC ligand on the (*Z*)-selectivity in the hydroboration of **2a** and 4-bromophenylacetylene (**2b**) with H–B(dan) (Table 2). When other ruthenium complexes with unsaturated and/or bulkier NHC ligands (**1b–d**) were used as the precatalysts, the (*Z*)-selectivity toward **3a** decreased (entries 1–4). In the reaction of **2b**, **1a** was less effective (entry 5). To develop a catalyst with a wider scope in the (*Z*)-selective hydroboration, we examined the reaction of **2b** with several [Ru(NHC)] complexes (**1e–g**; entries 6–8). The catalytic activity of the styryl complex [RuCl(CH=CHPh)(CO)(H_2IMes)(PCy_3)] (**1e**), which we discovered to be air-stable in the solid state and in solution, exhibited comparable activity to that of **1a** (entry 6). When a methoxy group was introduced at the *para*-position of the *N*-aryl moiety in the NHC ligand, the yield and (*Z*)-selectivity toward **3b** increased (entry 7). Assuming that the steric effect of the substituent in the NHC ligand on the reaction would be significant, we tested [RuCl(CH=CHPh)(CO)(H_2IMes$^{t\text{-Bu}}$)(PCy_3)] (**1g**) as a precatalyst. The reaction of **2b** with H–B(dan) furnished **3b** in a 94:6 *Z*/*E* ratio (entry 8).

Table 2. Impact of the Structure of the Ruthenium Complex on the (*Z*)-Selective Hydroboration[a]





	R	R'
H_2IMes	Me	Me
H_2IMes^{OMe}	Me	OMe
H_2IMes$^{t\text{-Bu}}$	Me	*t*-Bu
H_2IPr	*i*-Pr	H



	R	R'
IMes	Me	Me
IPr	*i*-Pr	H

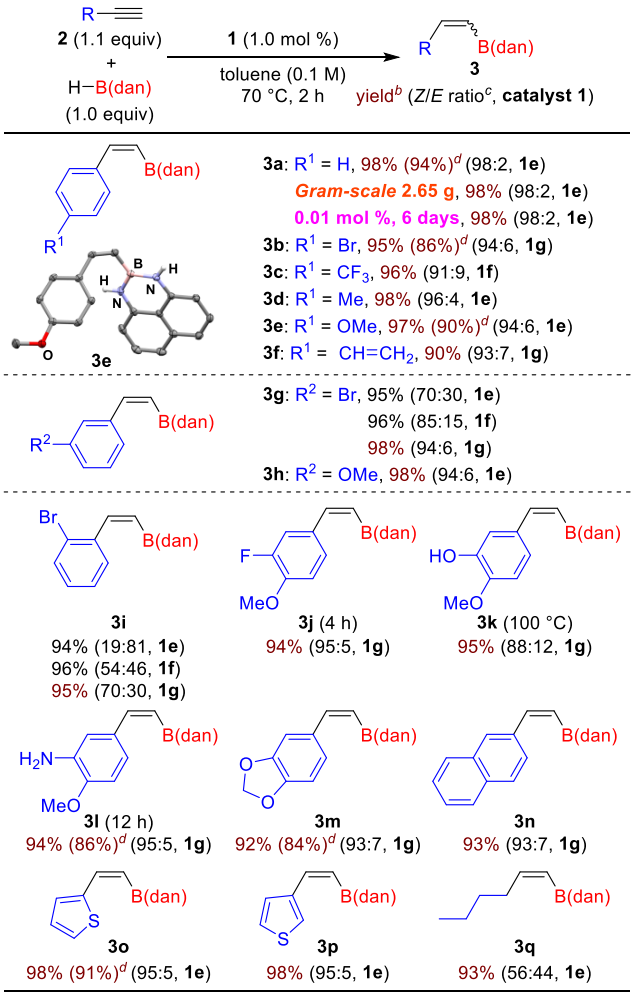
entry	**2**	**1**	NHC	time (h)	**3**, yield (%)[b]	*Z*/*E* ratio[c]
1[d]	**2a**	**1a**	H_2IMes	2	**3a**, 98	98:2
2	**2a**	**1b**	IMes	4	**3a**, 94	88:12
3	**2a**	**1c**	H_2IPr	3	**3a**, 93	83:17
4	**2a**	**1d**	IPr	4	**3a**, 95	78:22
5	**2b**	**1a**	H_2IMes	2	**3b**, 89	76:24
6	**2b**	**1e**	H_2IMes	2	**3b**, 88	76:24
7	**2b**	**1f**	H_2IMes^{OMe}	3	**3b**, 96	89:11
8	**2b**	**1g**	H_2IMes$^{t\text{-Bu}}$	2	**3b**, 95	94:6

[a]General reaction conditions: **1** (1.0 mol %), **2a** (1.1 equiv), H–B(dan) (1.0 equiv), toluene ([**2**]$_0$ = 0.1 M). [b]Isolated yields relative to H–B(dan). [c]The *Z*/*E* ratio was estimated based on the ^{1}H NMR analysis of the unpurified product mixture. [d]Taken from entry 1 in Table 1.

Subsequently, we investigated the scope of this hydroboration with respect to alkyne substrates, testing various aryl, heteroaryl, and aliphatic terminal alkynes **2** (Table 3). Generally, the products (**3**) were isolated in > 90% yields under the established optimal conditions, and the isomers can be separated by column chromatography. 4-Substituted (*Z*)-styrylboranes **3a–f** were obtained with high (*Z*)-selectivity from the corresponding arylacetylenes, regardless of the substituents. The (*Z*)-selectivity of the products should be affected by not only the substrates but also the ruthenium complexes. Moreover, the reaction of **2a** could be carried out i) on the gram-scale and ii) with 0.01 mol % of **1e**, which indicates that the turnover number of the [Ru(NHC)] complex reached *ca.* 9800. The hydroboration of the alkynyl moiety in 4-vinylphenylacetylene (**2f**) proceeded selectively to afford **3f** in a 93:7 *Z*/*E* ratio, and the hydroboration of the vinyl group was not observed. Although the *Z*/*E* ratio of **3g** was low in the reaction of 3-bromophenylacetylene (**2g**) in the presence of **1e**, the ratio increased to 94:6 when **1g** was employed as the precatalyst. In contrast, the (*Z*)-selective hydroboration of 3-methoxyphenylacetylene (**2h**) using **1e** afforded **3h** in a 94:6

Z/E ratio. The *meta*-substituent appears to be the main factor that determines the (Z)-selectivity in these reactions. Although the observed (Z)-selectivity was low for the reaction of 2-bromophenylacetylene (**2i**) in the presence of **1e**, the Z/E ratio of **3i** increased to 70:30 when the bulkier $H_2IMes^{t\text{-}Bu}$-ligated complex **1g** was employed.

Table 3. Scope and Limitations Regarding the Terminal Alkynes [a]

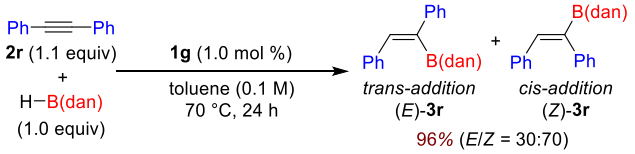


[a]General reaction conditions: **1** (1.0 mol %), **2** (1.1 equiv), H–B(dan) (1.0 equiv), toluene ($[\mathbf{2}]_0$ = 0.1 M). [b]Isolated yields relative to H–B(dan). [c]The Z/E ratio was estimated based on the ^{1}H NMR analysis of the unpurified product mixtures. [d]Isolated yields of the (Z)-isomers after chromatographic separation are shown in parenthesis.

The high functional-group tolerance was demonstrated by employing disubstituted phenylacetylenes **2j**–**m**, 2-ethynylnaphthalene (**2n**), as well as heteroarylalkynes **2o** and **2p** as substrates. The reactions of **2j**–**m** in the presence of **1g** produced **3j**–**m** with high (Z)-selectivity, even when hydroxy and amino groups were introduced at the benzene ring, albeit longer reaction time and/or higher temperature were required for the reactions of **2j**–**k**. The compatibility of the thiophene ring is noteworthy (*cf.* **3o** and **3p**), as it provides two very rare examples of a metal-catalyzed (Z)-selective hydroboration of ethynylthiophenes, particularly when using 2-ethynylthiophene (**2o**). The hydroboration of 1-hexyne (**2q**) afforded **3q** in high yield, albeit that the Z/E ratio was lower compared to other examples.

Moreover, we found that the current catalytic system can be applied to hydroboration of an internal alkyne. Thus, diphenylacetylene (**2r**) was treated with H–B(dan) in the presence of **1g** to furnish 1,2-addition product **3r** in 96% yield (E/Z = 30:70) (Scheme 2). This result reveals promising potential for the development of metal-catalyzed *trans*-hydroborations of diarylalkynes that would complement the existing *trans*-hydroborations of internal alkynes.[7a,11–13]

Scheme 2. Hydroboration of Diphenylacetylene with H–B(dan)[a]

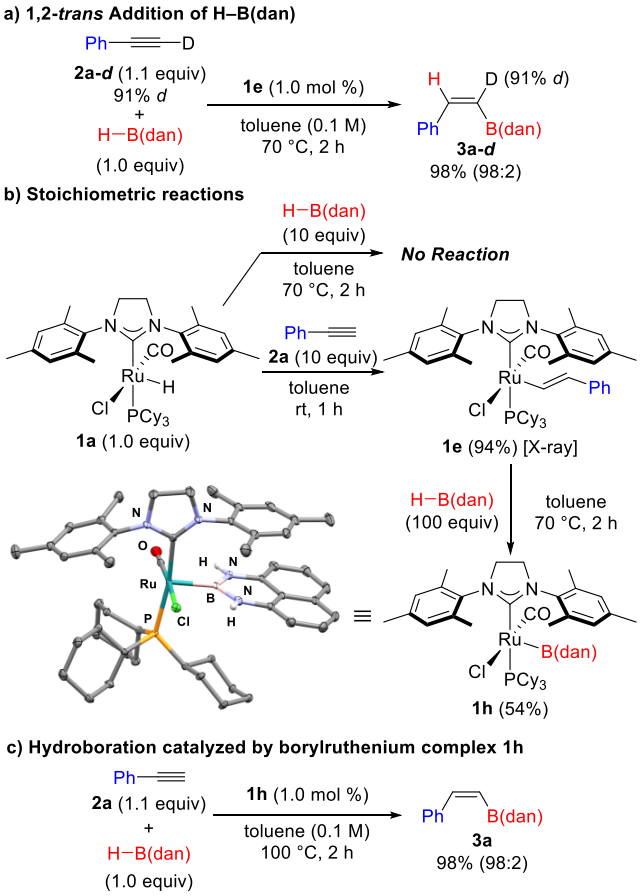


[a]The E/Z ratio was estimated based on the ^{1}H NMR analysis of the unpurified product mixture.

To gain insight into the mechanism underlying this (Z)-selective hydroboration, we carried out a deuterium-labeling experiment and stoichiometric reactions (Scheme 3). The hydroboration of 1-phenylacetylene-2-*d* (**2a-*d***) with H–B(dan) in the presence of **1e** furnished the deuterium-retention product **3a-*d*** (Scheme 3a). This result indicates that the present ruthenium-catalyzed (Z)-selective hydroboration with H–B(dan) involves a formal 1,2-*anti*-addition of H–B(dan) to the terminal alkynes and proceeds via a pathway that is distinctly different from previously reported metal-catalyzed (Z)-selective hydroboration reactions that shown in Scheme 1a.[2–5,7]

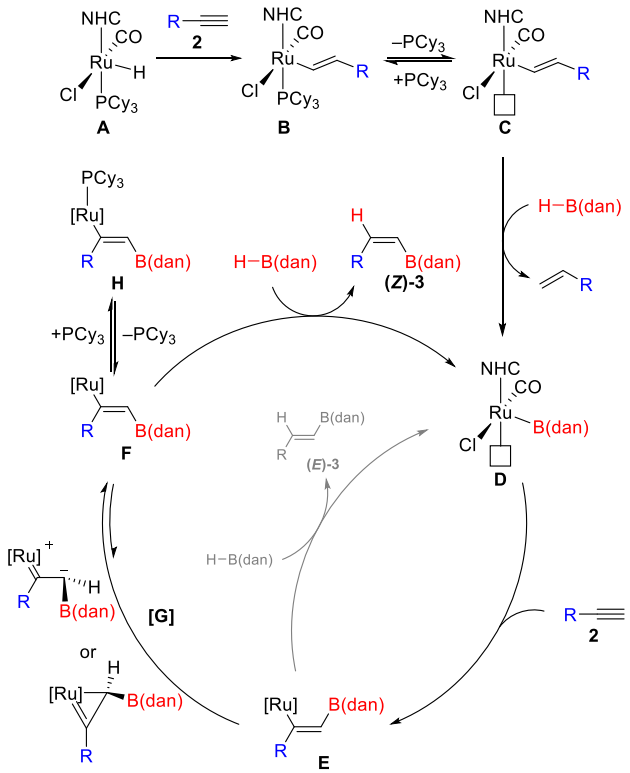
A reaction between hydrido complex **1a** and H–B(dan) was not observed at 70 °C,[14] but the reaction of **1a** and **2a** proceeded at room temperature to afford styryl complex **1e** in 94% yield (Scheme 3b).[15] The treatment of **1e** with H–B(dan) for 2 h at 70 °C resulted in the formation of the boryl complex [RuCl{B(dan)}(CO)(H_2IMes)(PCy_3)] (**1h**) in 54% isolated yield (Scheme 3b).[16] When **1h** was employed as the precatalyst, **3a** was obtained in yield and Z/E ratio comparable to those when using **1a** and **1e**, albeit a higher temperature was required (Scheme 3c).[17]

Scheme 3. Mechanistic Studies



On the basis of the aforementioned experiments, a modified Chalk-Harrod-type mechanism, which has been proposed for transition-metal-catalyzed hydrosilylation reactions of alkynes and alkenes,[18,19] should be operative in the present ruthenium-catalyzed (*Z*)-selective hydroboration of terminal alkynes with H–B(dan) (Scheme 4). A migratory insertion of the terminal alkyne into the Ru–H bond of hydrido complex **A** generates styryl complex **B**,[15] which should undergo σ-bond metathesis with H–B(dan) after liberation of PCy_3 to yield boryl complex **D** and styrene.[16] Subsequently, the migratory insertion of **2** into the Ru–B bond of **D** would afford borylethenyl complex **E**.[20] Due to the steric repulsion between the NHC ligand in the ruthenium complex and the B(dan) group, the rapid isomerization from **E** to **F** should proceed through a zwitterionic species[21] or a metallacyclopropene intermediate (**G**).[22,23] A similar metallacyclopropene intermediate has been proposed in the ruthenium-catalyzed *trans*-hydroboration of internal alkynes,[11b,c] albeit the overall process is significantly different from that shown in Scheme 4. We assume that the **E**-to-**F** isomerization is fast and reversible, and that **F**, which should be in equilibrium between a potential catalytic resting state **H**,[24] is the major isomer in most examples. When the **E**-to-**F** isomerization does not proceed smoothly, or when the **E**/**F** ratio is high, (*E*)-alkenylboranes could be formed via the σ-bond metathesis of **E** with H–B(dan). Finally, **F** could react with H–B(dan) to afford (*Z*)-alkenylboranes **3** under concomitant regeneration of borylruthenium **D**. The **E**-to-**F** isomerization should be the critical step to achieve high (*Z*)-selectivity in this reaction. The presence of a bulky substituent at the *para*-position of the *N*-aryl group bound to the NHC ligand and/or the use of a bulky H–B(dan) would accelerate the isomerization and the (*Z*)-isomer would be generated as the major product.

Scheme 4. Proposed Catalytic Cycle

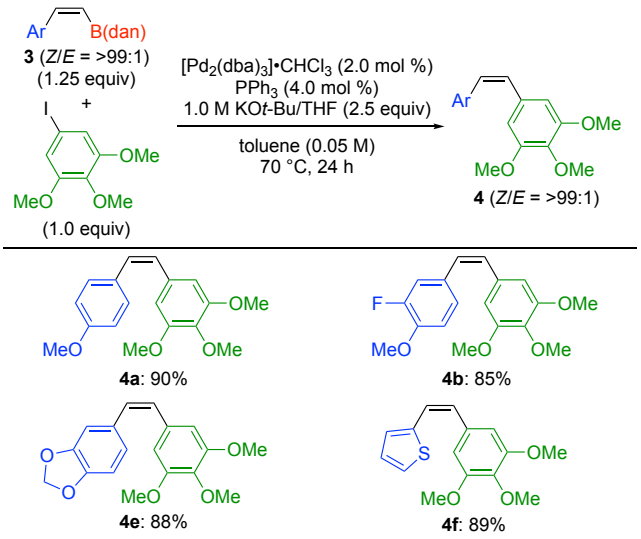


Finally, we demonstrated the synthetic utility of the obtained (*Z*)-alkenyl-B(dan) **3** by synthesizing analogues of Combretastatin A-4.[25] Although Suzuki–Miyaura cross-coupling reactions of alkenyl-B(dan) derivatives usually require the removal of the dan moiety under acidic conditions, which generates the corresponding reactive boronic acids,[26] we accomplished the first Suzuki–Miyaura cross-coupling of **3** without removing the dan group (Table 4).[27] Thus, when (*Z*)-**3**, which was obtained by chromatographic separation, was treated at 70 °C with 3,4,5-trimethoxyiodobenzene in toluene in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$, PPh_3, and KO*t*-Bu, the corresponding (*Z*)-diarylethenes (**4a**–**d**) were obtained in high yields under retention of the stereochemistry. These compounds represent prospective inhibitors of tubulin polymerization and exhibit antifeedant activity.[28–31] This hydroboration–cross-coupling sequence thus enables the rapid synthesis of sterically demanding (*Z*)-diarylethenes.

In conclusion, we have developed a (*Z*)-selective hydroboration of terminal alkynes with H–B(dan) using well-defined [Ru(NHC)] complexes. Mechanistic studies provide a new rationale for the (*Z*)-selective hydroboration of terminal alkynes based on the borylmetalation of the alkynes followed

by the rapid isomerization. The obtained (*Z*)-alkenyl-B(dan) derivatives are useful substrates for Suzuki–Miyaura cross-coupling reactions that afford potentially bioactive (*Z*)-diarylethene substances.

Table 4. Direct Cross-Coupling of (*Z*)-Alkenyl-B(dan) 3[a]



[a]General reaction conditions: **3** (1.25 equiv), 3,4,5-trimethoxyiodobenzene (1.0 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (2.0 mol %), PPh_3 (4.0 mol %), KO*t*-Bu (2.5 equiv), toluene ($[aryliodide]_0$ = 0.05 M). The *Z*/*E* ratio (> 99:1) was estimated based on the ^1H NMR analysis of the unpurified product mixtures. Isolated yields are shown.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF)
X-ray crystallographic data (CIF)

AUTHOR INFORMATION

Corresponding Author

* E-mail: ymutoh@rs.tus.ac.jp (Y.M.).
* E-mail: ssaito@rs.kagu.tus.ac.jp (S.S.).

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This research was supported by the Foundation for Interaction in Science and Technology (FIST), Japan. We would also like to thank Mr. Shotaro Ito, Dr. Takuya Kuwabara, and Prof. Youichi Ishii at Chuo University (Japan) for elemental analysis measurements.

REFERENCES

(1) (a) *Organoboranes for Syntheses*, ACS Symposium Series 783; Ramachandran, P. V.; Brown, H. C., Eds.; American Chemical Society: Washington, DC, **2011**. (b) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, **2011**. (c) Dembitsky, V. M.; Ali, H. A.; Srebnik, M. Contemporary Aspects of Boron: Chemistry and Biological Applications. *Stud. Inorg. Chem.* **2005**, *22*, 551–598. (d) Carreras, J.; Caballero, A.; Pérez, P. J. Alkenyl Boronates: Synthesis and Applications. *Chem. - Asian J.* **2019**, *14*, 329–343. (e) Akgun, B.; Hall, D. G. Boronic Acids as Bioorthogonal Probes for Site-Selective Labeling of Proteins. *Angew. Chem., Int. Ed.* **2018**, *57*, 13028–13044. (f) Yoshida, H. Borylation of Alkynes under Base/Coinage Metal Catalysis: Some Recent Developments. *ACS Catal.* **2016**, *6*, 1799–1811. (g) Lennox, A. J. J.; Lloyd-Jones, G. C. Selection of boron reagents for Suzuki–Miyaura coupling. *Chem. Soc. Rev.* **2014**, *43*, 412–443. (h) Wang, H.; Zeng, Y.-F.; Lv, W.-X.; Tan, D.-H. Synthetic Transformations of Alkenyl MIDA Boronates toward the Efficient Construction of Organoborons. *Synlett* **2018**, *29*, 1415–1420.

(2) (a) Ohmura, T.; Yamamoto, Y.; Miyaura, N. Rhodium- or Iridium-Catalyzed *trans*-Hydroboration of Terminal Alkynes, Giving (*Z*)-1-Alkenylboron Compounds. *J. Am. Chem. Soc.* **2000**, *122*, 4990–4991. (b) Cid, J.; Carbó, J. J.; Fernández, E. Catalytic non-conventional *trans*-hydroboration: A theoretical and experimental perspective. *Chem. - Eur. J.* **2012**, *18*, 1512–1521.

(3) Gunanathan, C.; Hölscher, M.; Pan, F.; Leitner, W. Ruthenium Catalyzed Hydroboration of Terminal Alkynes to *Z*-Vinylboronates. *J. Am. Chem. Soc.* **2012**, *134*, 14349–14352.

(4) Obligacion, J. V.; Neely, J. M.; Yazdani, A. N.; Pappas, I.; Chirik, P. J. Cobalt Catalyzed *Z*-Selective Hydroboration of Terminal Alkynes and Elucidation of the Origin of Selectivity. *J. Am. Chem. Soc.* **2015**, *137*, 5855–5858.

(5) (a) Gorgas, N.; Alves, L. G.; Stöger, B.; Martins, A. M.; Veiros, L. F.; Kirchner, K. Stable, Yet Highly Reactive Nonclassical Iron (II) Polyhydride Pincer Complexes: *Z*-Selective Dimerization and Hydroboration of Terminal Alkynes. *J. Am. Chem. Soc.* **2017**, *139*, 8130–8133. For a mechanistic study, see: (b) Gorgas, N.; Stöger, B.; Veiros, L. F.; Kirchner, K. Iron(II) Bis(acetylide) Complexes as Key Intermediates in the Catalytic Hydrofunctionalization of Terminal Alkynes. *ACS Catal.* **2018**, *8*, 7973–7982.

(6) Jang, W. J.; Lee, W. L.; Moon, J. H.; Lee, J. Y.; Yun, J. Copper-Catalyzed Trans-Hydroboration of Terminal Aryl Alkynes: Stereodivergent Synthesis of Alkenylboron Compounds. *Org. Lett.* **2016**, *18*, 1390–1393.

(7) (a) Xu, S.; Zhang, Y.; Li, B.; Liu, S. Y. Site-Selective and Stereoselective Trans-Hydroboration of 1,3-Enynes Catalyzed by 1,4-Azaborine-Based Phosphine-Pd Complex. *J. Am. Chem. Soc.* **2016**, *138*, 14566–14569. (b) Yang, Y.; Jiang, J.; Yu, H.; Shi, J. Mechanism and Origin of the Stereoselectivity in the Palladium-Catalyzed trans Hydroboration of Internal 1,3-Enynes with an Azaborine-Based Phosphine Ligand. *Chem. - Eur. J.* **2018**, *24*, 178–186.

(8) For the (*Z*)-selective hydroboration of terminal alkynes in the absence of transition-metals, see: (a) McGough, J. S.; Butler, S. M.; Cade, I. A.; Ingleson, M. J. Highly selective catalytic *trans*-hydroboration of alkynes mediated by borenium cations and $B(C_6F_5)_3$. *Chem. Sci.* **2016**, *7*, 3384–3389.

(9) For the cross-metathesis of vinylboranes that leads to (*Z*)-alkenylboronates, see: Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. Synthesis of *Z*-(Pinacolato)Allylboron and *Z*-(Pinacolato)Alkenyl-boron Compounds through Stereoselective Catalytic Cross-Metathesis. *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029.

(10) Mutoh, Y.; Mohara, Y.; Saito, S. (*Z*)-Selective Hydrosilylation of Terminal Alkynes with $HSiMe(OSiMe_3)_2$ Catalyzed by a Ruthenium Complex Containing an N-Heterocyclic Carbene. *Org. Lett.* **2017**, *19*, 5204–5207.

(11) (a) Fürstner, A. *trans*-Hydrogenation, *gem*-Hydrogenation, and *trans*-Hydrometalation of Alkynes: An Interim Report on an Unorthodox Reactivity Paradigm. *J. Am. Chem. Soc.* **2019**, *141*, 11–24. (b) Sundararaju, B.; Fürstner, A. A *trans*-selective hydroboration of internal alkynes. *Angew. Chem., Int. Ed.* **2013**, *52*, 14050–14054. (c) Song, L.-J.; Wang, T.; Zhang, X.; Chung, L. W.; Wu, Y.-D. A Combined DFT/IM-MS Study on the Reaction Mechanism of Cationic Ru(II)-Catalyzed Hydroboration of Alkynes. *ACS*

Catal. **2017**, 7, 1361–1368. (d) Longobardi, L. E. L.; Fürstner, A.; Longobardi, L. E. L. *trans*-Hydroboration of Propargyl Alcohol Derivatives and Related Substrates. *Chem. - Eur. J.* **2019**, *25*, 10063–10068.

(12) For a copper-catalyzed indirect *trans*-hydroboration of internal alkynes, see: Kim, H. R.; Yun, J. Highly regio- and stereoselective synthesis of alkenylboronic esters by copper-catalyzed boron additions to disubstituted alkynes. *Chem. Commun.* **2011**, *47*, 2943–2945.

(13) For the *trans*-hydroboration of internal alkynes in the absence of transition-metals, see: (a) Yuan, K.; Suzuki, N.; Mellerup, S. K.; Wang, X.; Yamaguchi, S.; Wang, S. Pyridyl Directed Catalyst-Free *trans*-Hydroboration of Internal Alkynes. *Org. Lett.* **2016**, *18*, 720–723. (b) Nagao, K.; Yamazaki, A.; Ohmiya, H.; Sawamura, M. Phosphine-Catalyzed *Anti*-Hydroboration of Internal Alkynes. *Org. Lett.* **2018**, *20*, 1861–1865. (c) Fritzemeier, R.; Gates, A.; Guo, X.; Lin, Z.; Santos, W. L. Transition Metal-Free *Trans* Hydroboration of Alkynoic Acid Derivatives: Experimental and Theoretical Studies. *J. Org. Chem.* **2018**, *83*, 10436–10444. (d) Zi, Y.; Schömberg, F.; Seifert, F.; Görls, H.; Vilotijevic, I. *trans*-Hydroboration *vs.* 1,2-reduction: divergent reactivity of ynones and ynoates in Lewis-base-catalyzed reactions with pinacolborane. *Org. Biomol. Chem.* **2018**, *16*, 6341–6349. (e) Shimoi, M.; Watanabe, T.; Maeda, K.; Curran, D. P.; Taniguchi, T. Radical *trans*-Hydroboration of Alkynes with N-Heterocyclic Carbene Boranes. *Angew. Chem., Int. Ed.* **2018**, *57*, 9485–9490. (f) Grams, R. J.; Fritzemeier, R. G.; Slebodnick, C.; Santos, W. L. *trans*-Hydroboration of Propiolamides: Access to Primary and Secondary (*E*)-β-Borylacrylamides. *Org. Lett.* **2019**, *21*, 6795–6799.

(14) For similar reactions of an 18-electron bis(phosphine)rutheniumhydrido and a cationic 14-electron rutheniumhydrido complex with a borane, see: (a) Irvine, G. J.; Roper, W. R.; Wright, L. J. Five-Coordinate Ruthenium(II) and Osmium(II) Boryl Complexes. *Organometallics* **1997**, *16*, 2291–2296. (b) Riddlestone, I. M.; McKay, D.; Gutmann, M. J.; Macgregor, S. A.; Mahon, M. F.; Sparkes, H. A.; Whittlesey, M. K. Isolation of $[Ru(IPr)_2(CO)H]^+$ (IPr = 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene) and Reactivity toward E-H (E = H, B) Bonds. *Organometallics* **2016**, *35*, 1301–1312.

(15) For a similar reaction of a 16-electron bis(phosphine)ruthenium hydrido complexes with terminal alkynes, see: (a) Werner, H.; Esteruelas, M. A.; Otto, H. Insertion reactions of the 16-electron complexes $MHCl(CO)(P\text{-}i\text{-}Pr_3)_2$ (M = Ru, Os) with alkynes. The x-ray crystal structure of $[(E)\text{-}PhCH{=}CHOs(Cl)(CO)(P\text{-}i\text{-}Pr_3)_2]$. *Organometallics* **1986**, *5*, 2295–2299. (b) Jung, S.; Brandt, C. D.; Wolf, J.; Werner, H. Vinyl and Carbene Ruthenium(II) Complexes from Hydridoruthenium(II) Precursors. *Dalton Trans.* **2004**, *0*, 375–383.

(16) A similar reaction of a five-coordinate 16-electron bis(phosphine)osmiumphenyl complex with catecholborane that leads to an osmiumboryl complex has been reported, see: ref. 14a.

(17) We presume that the higher temperature is required to liberate PCy_3 from **1h**, which generates the catalytically active 14-electron ruthenium complex $[RuCl\{B(dan)\}(CO)(H_2IMes)]$. When we carried out phosphine exchange reactions using **1e** or **1h** at 70 °C, **1e** was gradually consumed, whereas the content of **1h** remained unchanged. For details, see the Supporting Information.

(18) For selected reviews, see: (a) Zaranek, M.; Marciniec, B.; Pawluć, P. Ruthenium-catalysed hydrosilylation of carbon-carbon multiple bonds. *Org. Chem. Front.* **2016**, *3*, 1337–1344. (b) Roy, A. K. A Review of Recent Progress in Catalyzed Homogeneous Hydrosilation (Hydrosilylation). *Adv. Organomet. Chem.* **2007**, *55*, 1–59.

(19) For selected examples, see: (a) Esteruelas, M. A.; Herrero, J.; Oro, L. A. Exclusive formation of *cis*-$PhCH{=}CH(SiEt_3)$ by addition of triethylsilane to phenylacetylene catalyzed by ruthenium complex $[(Me_2CH)_3P]_2RuHCl(CO)$. *Organometallics* **1993**, *12*, 2377–2379. (b) Maddock, S. M.; Rickard, C. E. F.; Roper, W. R.; Wright, L. J. Insertion of Ethyne into the Ru–Si Bonds of Coordinatively Unsaturated Ruthenium Silyl Complexes. X-ray Crystal Structures of $Ru(CHCHSiMe_2OEt)Cl(CO)_2(PPh_3)_2$ and $[Ru(CHCHSiMe_2OH)(CN\text{-}p\text{-}tolyl)(CO)(PPh_3)_2]ClO_4$. *Organometallics* **1996**, *15*, 1793–1803. (c) Katayama, H.; Taniguchi, K.; Sagawa, T.; Minami, T.; Ozawa, F. Ruthenium-Catalyzed Hydrosilylation of Terminal Alkynes: Stereodivergent Synthesis of (*E*)- and (*Z*)-Alkenylsilanes. *J. Organomet. Chem.* **2002**, *645*, 192–200. (d) Gao, R.; Pahls, D. R.; Cundari, T. R.; Yi, C. S. Experimental and Computational Studies of the Ruthenium-Catalyzed Hydrosilylation of Alkynes: Mechanistic Insights into the Regio- and Stereoselective Formation of Vinylsilanes *Organometallics* **2014**, *33*, 6937–6944.

(20) For a similar reaction of a five-coordinate 16-electron bis(phosphine)ruthenium boryl complex, see: Clark, G. R.; Irvine, G. J.; Roper, W. R.; Wright, L. J. Insertion of Ethyne into the Ru–B Bond of a Coordinatively Unsaturated Ruthenium Boryl Complex. X-ray Crystal Structure of $Ru(CHCH[BOC_6H_4O])Cl(CO)(PPh_3)_2$. *Organometallics* **1997**, *16*, 5499–5505.

(21) Ojima, I.; Clos, N.; Donovan, R. J.; Ingallina, P. Hydrosilylation of 1-Hexyne Catalyzed by Rhodium and Cobalt–Rhodium Mixed-Metal Complexes. Mechanism of Apparent Trans Addition. *Organometallics* **1990**, *9*, 3127–3133.

(22) (a) Tanke, R. S.; Crabtree, R. H. Unusual Activity and Selectivity in Alkyne Hydrosilylation with an Iridium Catalyst Stabilized by an O-Donor Ligand. *J. Am. Chem. Soc.* **1990**, *112*, 7984–7989. (b) Jun, C. H.; Crabtree, R. H. Dehydrogenative Silation, Isomerization and the Control of Syn- vs. Anti-Addition in the Hydrosilation of Alkynes. *J. Organomet. Chem.* **1993**, *447*, 117–187.

(23) In the mechanistic studies on the pertinent $[RuHCl(CO)(PCy_3)_2]$-catalyzed (*Z*)-selective hydrosilylation of terminal alkynes, the ruthenacyclopropene species could not be located as a local minimum structure. See, ref 19d.

(24) When we monitored the progress of the reaction of **2a** with H–B(dan) in the presence of **1e** as the precatalyst at 70 °C by $^{31}P\{^1H\}$ NMR spectroscopy, we observed a signal that was tentatively assigned to **H** during the catalytic turnover. For details, see the Supporting Information.

(25) For reviews, see: (a) Bukhari, S. N. A.; Kumar, G. B.; Revankar, H. M.; Qin, H. L. Development of combretastatins as potent tubulin polymerization inhibitors. *Bioorg. Chem.* **2017**, *72*, 130–147. (b) Liekens, S.; Bueno, O.; Canela, M.-D.; Priego, E.-M.; Martins, M. S.; Pérez-Pérez, M.-J. Blocking Blood Flow to Solid Tumors by Destabilizing Tubulin: An Approach to Targeting Tumor Growth. *J. Med. Chem.* **2016**, *59*, 8685–8711. (c) Tron, G. C.; Pirali, T.; Sorba, G.; Pagliai, F.; Busacca, S.; Genazzani, A. A. Medicinal chemistry of combretastatin A4: Present and future directions. *J. Med. Chem.* **2006**, *49*, 3033–3044.

(26) (a) Iwadate, N.; Suginome, M. Synthesis of B-Protected β-Styrylboronic Acids via Iridium-Catalyzed Hydroboration of Alkynes with 1,8-Naphthalenediaminatoborane Leading to Iterative Synthesis of Oligo(Phenylenevinylene)s. *Org. Lett.* **2009**, *11*, 1899–1902. (b) Noguchi, H.; Hojo, K.; Suginome, M. Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki-Miyaura Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 758–759.

(27) For the direct use of aryl-B(dan) derivatives, see: (a) Mutoh, Y.; Yamamoto, K.; Saito, S. Suzuki–Miyaura Cross-Coupling of 1,8-Diamononaphthalene (dan)-Protected Arylboronic Acids. Submitted (Manuscript ID: cs-2019-036672). (b) Yamamoto, K.; Mutoh, Y.; Saito, S. Suzuki–Miyaura Cross-Coupling of Aryl-B(dan). 99th Annual Meeting of the Chemical Society of Japan, Kobe, Japan, March 15–19, 2019; Abstract 1 H5-48. (c) Seki, M.; Osaka, I.; Yoshida, H. Suzuki–Miyaura cross-coupling reaction of dan-substituted organoboranes through direct activation of the B(dan) moiety. 99th Annual Meeting of the Chemical Society of Japan, Kobe, Japan, March 15−19, 2019; Abstract 2 H5-03. For the direct use of alkynyl-B(dan) compounds, see: (d) Tsuchimoto, T.; Utsugi, H.; Sugiura, T.; Horio, S. Alkynylboranes: A Practical Approach by Zinc-Catalyzed Dehydrogenative Coupling of Terminal Alkynes with 1,8-Naphthalenediaminatoborane. *Adv. Synth. Catal.* **2015**, *357*, 77–82. (e) Tani, T.; Sawatsugawa, Y.; Sano, Y.; Hirataka, Y.; Takahashi, N.; Hashimoto, S.; Sugiura, T.; Tsuchimoto, T. Alkynyl-B(dan)s in Various Palladium-Catalyzed Carbon-Carbon Bond-Forming Reactions Leading to Internal Alkynes, 1,4-Enynes, Ynones, and Multiply Substituted Alkenes. *Adv. Synth. Catal.* **2019**, *361*, 1815–1834.

(28) (a) Chang, J.-Y.; Yang, M.-F.; Chang, C.-Y.; Chen, C.-M.; Kuo, C.-C.; Liou, J.-P. *J. Med. Chem.* **2006**, *49*, 6412–6415. (b) Cushman, M.; Nagarathnam, D.; Gopal, D.; Chakraborti, A. K.; Lin, C. M.; Hamel, E. Synthesis and evaluation of stilbene and dihydrostilbene derivatives as

potential anticancer agents that inhibit tubulin polymerization. *J. Med. Chem.* **1991**, *34*, 2579–2588.

(29) (a) Conesa-Milián, L.; Falomir, E.; Murga, J.; Carda, M.; Meyen, E.; Liekens, S.; Alberto Marco, J. Synthesis and biological evaluation of carbamates derived from aminocombretastatin A-4 as vascular disrupting agents. *Eur. J. Med. Chem.* **2018**, *147*, 183–193. (b) Pettit, G. R.; Rhodes, M. R.; Herald, D. L.; Hamel, E.; Schmidt, J. M.; Pettit, R. K. Antineoplastic agents. 445. Synthesis and evaluation of structural modifications of (*Z*)- and (*E*)-combretastatin A-4. *J. Med. Chem.* **2005**, *48*, 4087–4099. (c) Ohsumi, K.; Nakagawa, R.; Fukuda, Y.; Hatanaka, T.; Morinaga, Y.; Nihei, Y.; Ohishi, K.; Suga, Y.; Akiyama, Y.; Tsuji, T. Novel Combretastatin Analogues Effective against Murine Solid Tumors: Design and Structure–Activity Relationships. *J. Med. Chem.* **1998**, *41*, 3022–3032.

(30) Liu, Y. Q.; Li, X. J.; Zhao, C. Y.; Lu, Y.; Li, W. Q.; Liu, Z. L.; Feng, G.; Yang, L. Synthesis and insect antifeedant activity of stilbene derivatives against Brontispa longissima Larvae. *Med. Chem. Res.* **2013**, *22*, 2196–2206.

(31) (a) Do, C. V.; Faouzi, A.; Barette, C.; Farce, A.; Fauvarque, M.-O.; Colomb, E.; Catry, L.; Berthier-Vergnes, O.; Haftek, M.; Barret, R.; Lomberget, T. Synthesis and biological evaluation of thiophene and benzo[b]thiophene analogs of combretastatin A-4 and isocombretastatin A-4: A comparison between the linkage positions of the 3,4,5-trimethoxystyrene unit. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 174–180. (b) Nguyen, T. T. B.; Lomberget, T.; Tran, N. C.; Barret, R. Synthesis of (*Z*) isomers of benzoheterocyclic derivatives of combretastatin A-4: a comparative study of several methods. *Tetrahedron* **2013**, *69*, 2336–2347. (c) Bazin, M.-A.; Jouanne, M.; El-Kashef, H.; Rault, S. An Efficient Microwave-Promoted Route to (*Z*)-Stilbenes from trans-Cinnamic Acids: Synthesis of Combretastatin A-4 and Analogues. *Synlett* **2009**, *2009*, 2789–2794.

For Table of Contents Only