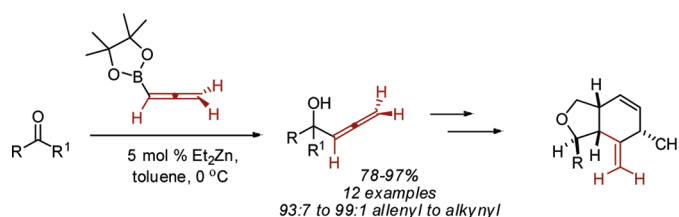# Zinc-Catalyzed Allenylations of Aldehydes and Ketones

Daniel R. Fandrick,* Jaideep Saha, Keith R. Fandrick, Sanjit Sanyal, Junichi Ogikubo, Heewon Lee, Frank Roschangar, Jinhua J. Song, and Chris H. Senanayake

Chemical Development, Boehringer-Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, P.O. BOX 368, Ridgefield, Connecticut 06877-0368, United States

daniel.fandrick@boehringer-ingelheim.com

ABSTRACT

The general zinc-catalyzed allenylation of aldehydes and ketones with an allenyl boronate is presented. Preliminary mechanistic studies support a kinetically controlled process wherein, after a site-selective B/Zn exchange to generate a propargyl zinc intermediate, the addition to the electrophile effectively competes with propargyl-allenyl zinc equilibration. The utility of the methodology was demonstrated by application to a rhodium-catalyzed [4 + 2] cycloaddition.

The importance of the allene functional group relates to its presence in biologically active natural products[1] as well as the broad synthetic versatility as a synthetic handle for derivatization and couplings.[2] The addition of an organometallic reagent to carbonyl and imine species provides a convenient approach to incorporate a functional group into a substrate through the construction of a C–C bond.[2,3] The most common allenylation of an aldehyde involves the direct addition with a propargyl aluminum,[4] borane,[5] or silicon[6] reagent wherein, due to

a Zimmerman–Traxler transition state, the addition proceeds with inversion and high preference for the allene product. To maintain reactivity for the addition, these methodologies require the use of reagents that must be prepared under inert conditions or utilized *in situ* for the reaction. Alternatively, an open transition state has also led to allenylation of aldehydes through a Lewis acid-catalyzed addition with a propargyl stannane or silane.[7] Other transition metal-mediated processes with In,[8] Cr,[9] Ti,[10] and Sn/Rh[11] provide a mixture of allenyl and homo-propargyl products wherein site selectivity is dictated by the substitution on the allene or propargyl moiety of the organometallic intermediate and good selectivity for the allene product has been obtained with some substrates. Accordingly, the selective formation of an allenylic alcohol requires either the site-selective formation of a

(1) For selected examples of syntheses of naturally occurring allenes, see: (a) Hoffmann-Roder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933–2935. (b) Hoffmann-Roder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196–1216. (c) Marshall, J. A.; Mulhearn, J. J. *Org. Lett.* **2005**, *7*, 1593–1596.

(2) *Modern Allene Chemistry*; Krause, N., Hashmi, S. K., Eds.; Whiley-VCH: Weinheim, 2004.

(3) *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Whiley-VCH: Weinheim, 2005.

(4) For selected examples, see: (a) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579–1582. (b) Mesnard, D.; Miginiac, L. *J. Organomet. Chem.* **1990**, *397*, 127–137.

(5) For selected examples, see: (a) Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1985**, *60*, 8130–8131. (b) Corey, E. J.; Yu., C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878–879. (c) Hernandez, E.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 5397–5400.

(6) For selected examples, see: (a) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392–6393. (b) Schneider, U.; Sugiura, M.; Kobayashi, S. *Tetrahedron* **2006**, *62*, 496–502.

(7) (a) Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. *Angew Chem., Int. Ed.* **1998**, *37*, 2392–2395. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodriguez-Acebes, R. *J. Org. Chem.* **2001**, *66*, 5208–5216.

(8) (a) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472–7480. (b) Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042–13043. (c) Alcaide, B.; Almendros, P.; Martinez del Campo, T. *Eur. J. Org. Chem.* **2008**, 2628–2634.

(9) Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252–255.

(10) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207–3210.

(11) Banerjee, M.; Roy, S. *Org. Lett.* **2004**, *6*, 2137–2140.

stoichiometric propargyl intermediate or a specific substitution pattern on the reagent for transition metal-catalyzed processes. Herein, we report an operationally simple and general zinc-catalyzed allenylation of aldehydes and ketones with an allenyl boronate.

Additions to carbonyl species with allenyl zinc reagents is a prominent approach for the preparation of homopropargylic alcohols.[3,12] This site selectivity is generally rationalized by a rapid equilibration between propargyl and allenyl zinc intermediates wherein both the allenyl zinc

Scheme 1. Typical Site Selectivity for the Preference of Propargylation with Propargyl/Allenyl Zinc Reagents
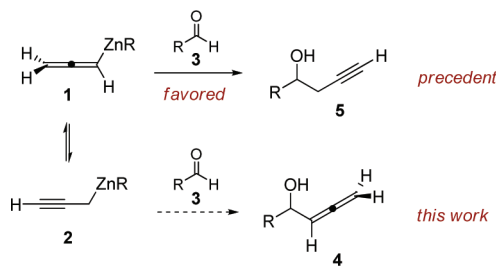
intermediate and propargylation pathway is favored (Scheme 1).[2,13] The few cases wherein a zinc-mediated addition proceeded with selectivity for allenylation are exclusively related to a specific substitution pattern on the allenyl/propargyl zinc moiety that favors allenylations wherein propargylation is favored when an unsubstituted allenyl/propargyl zinc intermediate is utilized.[7b,14] Our zinc-catalyzed propargylation of aldehydes and ketones with both propargyl and allenyl boronates was based on these principles and a facile B/Zn exchange.[15]

When the zinc-catalyzed addition with an allenyl boronate to an aldehyde was examined under different conditions, a mixture of the allenylic and homopropargylic alcohols was observed (Table 1). More importantly, either isomer can be favored based predominately on the solvent and catalyst loadings. With 7 mol % diethyl zinc and the model *p*-anisaldehyde, the solvent tetrahydrofuran

Table 1. Optimization of the Zinc Catalyzed Allenylation
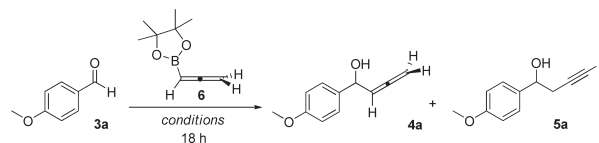
entry	conditions[a]	solvent	temp (°C)	4a:5a[b]	conv[c]
1	None	THF	20		0.5%
2	None	Toluene	20		1%
3	7% Et$_2$Zn	THF	20	30:70	100%
4	20% Et$_2$Zn	THF	20	25:75[16]	100%[d]
5	7% Et$_2$Zn	Heptane	20	92:8	100%
6	7% Et$_2$Zn	DCM	20	84:16	100%
7	7% Et$_2$Zn	IpAc	20	71:29	100%
8	7% Et$_2$Zn	Toluene	20	93:7	100%
9	2% Et$_2$Zn	Toluene	20	93:7	100%
10	13% Et$_2$Zn	Toluene	20	54:46	100%
11	7% Et$_2$Zn	Toluene	−20	97:3	44%
12	7% Et$_2$Zn	Toluene	−10	96:4	100%
13	7% Et$_2$Zn	Toluene	0	95:5	100%
14	7% Et$_2$Zn	Toluene	40	85:15	100%
15	5% Et$_2$Zn	Toluene	0	93:7	100%[e]

[a] Diethyl zinc (mol % to starting aldehyde) was charged to an anhydrous solution of the aldehyde and borolane **6** (1.5 equiv) in the indicated solvent at the indicated temperature. [b] Site selectivity between **4a:5a** determined by HPLC. [c] Molar conversion based on aldehyde. [d] Seventy-four percent isolated yield for **5a**. [e] Ninety-two percent isolated yield for **4a**.

favored the homopropargylic alcohol product and toluene favored the allenyl alcohol. In toluene, low catalyst loadings (7 mol %) favored the allenyl alcohol (93:7) whereas high loadings (100 mol %) favored the homopropargylic alcohol (86:14) (Figure 1). At approximately 15 mol % diethyl zinc, a nearly equal ratio of the homopropargyl and allenyl alcohol can be obtained. The temperature showed a minimal effect on the site selectivity, and the optimal conditions to afford the allenyl alcohol utilized 5 mol % diethyl zinc in toluene at 0 °C.

The optimized conditions for the zinc-catalyzed allenylation with an allenyl borolane proved general for a broad number and types of aldehydes and ketones (Table 2). The methodology afforded > 90:10 site selectivity for the allenylic alcohol for both aldehydes and ketones and generally provided high yields. Numerous functional groups were also tolerated including aryl and aliphatic halides, esters, olefins, and Lewis basic functional groups such as quinolines and carbamates that are typically not compatible with Lewis acid-catalyzed processes. Furthermore, the more electrophilic aldehydes provided higher preference (99:1) for the allenylic alcohol (entries 2−4) in comparison to the electron-rich *p*-anisaldehyde (93:7) (entry 1).

(12) For selected examples, see: (a) Marshall, J. A.; Adams, N. D. *Org. Lett.* **2000**, *2*, 2897–2900. (b) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, *66*, 1373–1379. (c) Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. *J. Am. Chem. Soc.* **2002**, *124*, 1664–1668. (d) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 3694–3695. (e) Marshall, J. A. *J. Org. Chem.* **2007**, *72*, 8153–8166. (f) Poisson, J.-F.; Normant, J. F. *Org. Lett.* **2001**, *3*, 1889–1891. (g) Chemla, F.; Ferreira, F.; Gaucher, X.; Palais, L. *Synthesis* **2007**, 1235–1241. (h) Ma, X.; Wang, J.-X.; Li, S.; Wang, K.-H.; Huang, D. *Tetrahedron* **2009**, *65*, 8683–8689.

(13) (a) Ma, S.-M.; Zhang, A.-B. *Pure Appl. Chem.* **2001**, *73*, 337–341. (b) Marshall, J. A. Synthesis and Reactions of Allenylzinc Reagents. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons Ltd: England, 2006; Ch 10. (c) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565–4567. (d) Poisson, J.-F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553–6560. (e) Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377–11390.

(14) Jogi, A.; Maeorg, U. *Molecules* **2001**, *6*, 964–968.

(15) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Johnson, C. S.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 88–91.
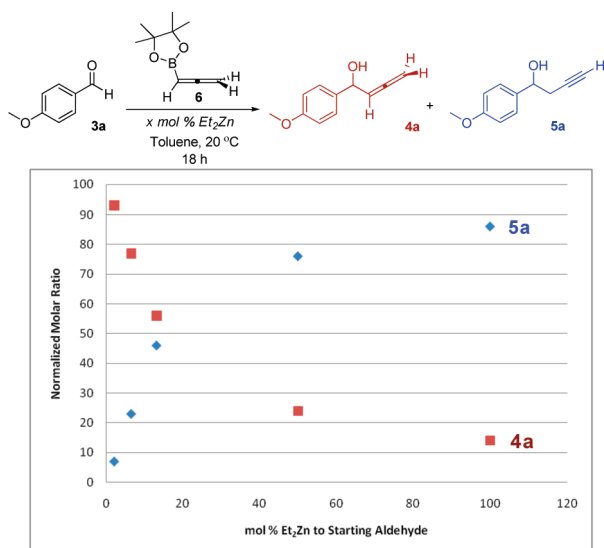
(16) The site selectivity for propargylation is dependant on the addition order and workup conditions. An 80:20 selectivity favoring propargylation with a 78% isolated yield for the alkyne **5a** can be obtained when the aldehyde is charged to a solution of the borolane **6** and diethyl zinc in THF. See Supporting Information for reaction details.

Figure 1. Effect of diethyl zinc loading on site selectivity.

The utility of the generated allenylic alcohols was demonstrated by application to the diastereoselective synthesis of hexahydroisobenzofurans. Rhodium-catalyzed cycloadditions have shown broad versatility for numerous polycyclic ring formations.[17] Although the transfer of chirality from an axial allene stereocenter through an intramolecular [4 + 2] cycloaddition is precedented,[18] the ability to control the diastereoselectivity from an allenylic ether stereocenter is not known. Application of the Rh-catalyzed [4 + 2] cycloaddition to the allenylic ethers **7** and
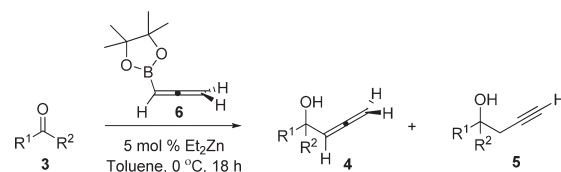
Scheme 2. Application to a [4 + 2] Cycloaddition
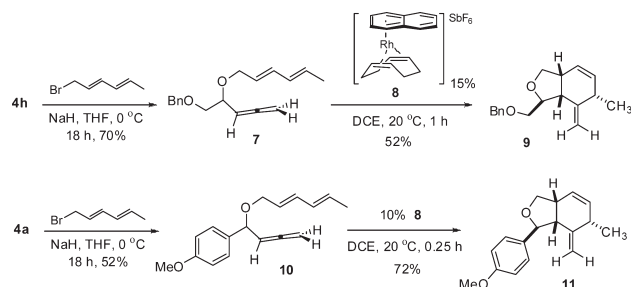
(17) For examples of cycloadditions catalyzed with [(Naphthalene)-Rh-(COD)]BF₄, see: (a) Paik, S.-J.; Son, S. U.; Chung, Y. K. *Org. Lett.* **1999**, *1*, 2045–2047. (b) Wender, P. A.; Williams, T. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4550–4553.

(18) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186–14187.

(19) For selected recent examples of natural products containing a *cis*-fused hexa- and octahydroisobenzofuran, see: (a) Limna Mol, V. P.; Raveendran, T. V.; Parameswaran, P. S.; Kunnath, R. J.; Rajamohanan, P. R. *Can. J. Chem.* **2011**, *89*, 57–60. (b) Chen, B.-W.; Chang, S.-M.; Huang, C.-Y.; Chao, C.-H.; Su, J.-H.; Wen, Z.-H.; Hsu, C.-H.; Dai C.-F.; Wu, Y.-C.; Sheu, J.-H. *J. Nat. Prod.* **2010**, *73*, 1785–1791. (c) Hassan, H. M.; Khanfar, M. A.; Elnagar, A. Y.; Mohammed, R.; Shaala, L. A.; Youssef, D. T. A.; Hifnawy, M. S.; El Sayed, K. A. *J. Nat. Prod.* **2010**, *73*, 848–853.

Table 2. Zinc-Catalyzed Allenylation of Aldehydes and Ketones[a]

entry	product 4	yield 4[b]	4:5[c]
1	**4a**	92%	93:7
2	**4b**	97%	99:1
3	**4c**	92%	99:1
4	**4d**	94%	99:1
5	**4e**	93%	98:2
6	**4f**	81%	92:8[d]
7	**4g**	78%	97:3
8	**4h**	83%	93:7
9	**4i**	95%	95:5
10	**4j**	90%	98:2
11	**4k**	91%	92:8
12	**4l**	87%	95:5

[a] Reactions performed with 1.5 mol equiv borolane **6** to substrate. [b] Isolated yield of the allenyl product. [c] Site selectivity between allenyl and homopropargyl products (**4:5**) deteremined by HPLC and comparison to reference standards. [d] Site selectivity determined by ¹H NMR.

10 (Scheme 2) proceeded with good diastereoselectivity (>4:1) to generate three additional stereocenters and provide a rapid construction of the synthetically valuable hexahydroisobenzofuran core[19] as exemplified by adducts **9** and **11**.[20]

A reasonable rationalization for the site-selective allenylation by the zinc-catalyzed addition to aldehydes and

(20) See Supporting Information for structural and diastereomer assignment of compounds **9** and **11**.

ketones with an allenyl borolane relates to an inversion mechanism for the B/Zn exchange and the addition reaction effectively competing with allenyl-propargyl zinc equilibration. Several studies support a closed transition state for the propargylation with an allenyl zinc intermediate that proceeds through an inversion of the allenyl moiety and first order in zinc.[13,21] Due to the inversion of the propargyl/allenyl moiety of the zinc reagent upon addition to a carbonyl functional group,[13,21] the intermediate for the allenylation of an aldehyde is reasonably the propargyl zinc intermediate **2** (Scheme 3). Accordingly, the B/Zn exchange with the allenyl borolane proceeds with inversion

Scheme 3. Proposed Zinc Equilibration and Site Selectivity for the Allenylation and Propargylation of Aldehydes
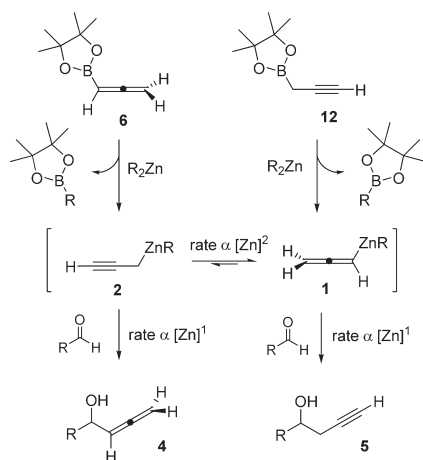
to directly generate the propargyl zinc intermediate **2**.[22] Supporting this double inversion process wherein the allenyl moiety is inverted during the exchange and inverted during the addition, the complementary reaction with the propargyl boronate **12**[23] under the same zinc-catalyzed conditions as for an allenylation proceeded with high selectivity for the homopropargylic alcohol (eq 1). To obtain selectivity for allenylation after the selective formation of the propargyl zinc intermediate **2** by an exchange with the allenyl boronate, the addition to the electrophile must

also effectively compete with propargyl-allenyl zinc equilibration. Otherwise, equilibration to the allenyl zinc species would enable the typical propargylation pathway to be favored.[2,12,13,21] Similar to the proffered bimetallic mechanism for the equilibration of allenyl/propargyl Sn,[24] Pd,[25] and In[2] complexes,[2] the corresponding zinc equilibration has also been proposed as bimolecular in zinc.[26] Since the propargyl/allenyl zinc addition to the electrophile is rationalized as monomeric in zinc, and the equilibration is bimolecular in zinc, low catalyst loadings allow for the propargyl-zinc addition to compete with equilibration (Figure 1). Furthermore, more electrophilic substrates that have been shown to undergo faster additions with an allenyl zinc reagent[15] provide higher site selectivities for the zinc-catalyzed allenylation due to the increased addition rate that enables the addition to more effectively compete with equilibration. Accordingly, the ability to achieve a highly site-selective allenylation with a zinc-catalyzed process was due to a kinetically controlled process as well as the site-selective formation of a propargyl zinc intermediate.
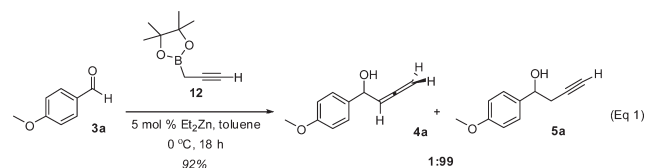
In conclusion, an operationally simple and general zinc-catalyzed allenylation of aldehydes and ketones with an allenyl boronate was developed. High site selectivity for allenylation was rationalized by the B/Zn exchange proceeding with inversion and the addition reaction effectively competing with propargyl/allenyl zinc equilibration. The synthetic utility of the allenylation methodology was demonstrated by application to a rhodium-catalyzed [4 + 2] cycloaddition.

Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C for all products. Preparation of propargyl borolane **12** and reference homopropargylic alcohols for site-selectivity determination. Structural and diastereomer characterization for compounds **9** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) (a) Gaudemar, M. *Bull. Soc. Chim. Fr.* **1962**, 974–987. (b) Gung, B. W.; Xue, X.; Knatz, N.; Marshall, J. A. *Organometallics* **2003**, *22*, 3158–3163. (c) Alvarez, R.; Lera, A. R. de *Organometallics* **2007**, *26*, 2799–2802.

(22) An similar inversion or S_E2' process for a metallo-boron exchange with an allenyl borolane was recently proposed for the transmetallation with a palladium (II) catalyst: Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2011**, *13*, 4858–4861.

(23) Prepared as a 91:9 ratio of propargyl to allenyl boronates **12**:**6**. The exchange with the propargyl borolane **12** was shown to be effectively faster than for the allenyl boronate **6**.

(24) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 6001–6005.

(25) Ogoshi, S.; Nishida, T.; Shinagawa, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 7164–7165.

(26) Guijarro, A. Dynamic Behavior of Organozinc Compounds. In *The Chemistry of Organozinc Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons Ltd: England, 2006; Ch 6.