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Mild and General Zinc-Alkoxide-Catalyzed Allylations of Ketones with Allyl Pinacol Boronates

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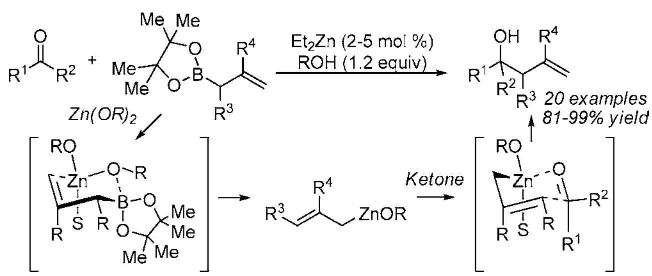
ABSTRACT



A general and efficient zinc-alkoxide-catalyzed allylation of a diverse array of ketones with allyl boronates is presented. The methodology is effective with 2 mol % of catalyst and with relatively short reaction times. Studies of the key exchange process are presented, which support a cyclic transition state for the boron to zinc exchange.

The allylation of ketones[1] has emerged as one of the fundamental methods for the synthesis of versatile tertiary homoallylic alcohol building blocks.[2] In this context, several Barbier-type processes[3] and catalytic examples have been reported utilizing stoichiometric amounts of allyl stannanes[4] and silanes.[5] Although direct allylations with allyl boronates of aldehydes[6] and ketones bearing a coordinating functional group[7] have been reported, only recently have general methodologies been realized with Cu,[8] In,[9] Ir,[10] Ni,[11] and chiral diol catalysts.[12] Recently, we reported the zinc-

(1) For a recent review of asymmetric allylation of ketones, see: Hatano, M.; Ishihara, K. *Synthesis* **2008**, *11*, 1647.
(2) For selected recent reviews on the allylation of aldehydes, see: (a) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, p 965. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.
(3) For selected examples, see: (a) Nair, V.; Ros, S.; Jayan, C. N.; Viji, S. *Synthesis* **2003**, *16*, 2546. (b) Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron* **2001**, *57*, 9453. (c) Kim, H. Y.; Choi, K. I.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Cho, Y. S. *Synth. Commun.* **2003**, *33*, 1899.
(4) For selected recent examples of allylation of ketones employing allyl stannes, see: (a) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew Chem., Int. Ed.* **2002**, *41*, 3697. (b) Yasuda, M.; Hirata, K.; Nishino, M.; Yamamoto, A.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13442. (c) Kim, J. G.; Walts, K M.; Garcia, I. F.; Kwiatkowski, D.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 12580. (d) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743.
(5) For selected recent examples of allylation of ketones employing allyl silanes, see: (a) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. (b) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556. (c) Burns, N. Z.; Hackman, B. M.; Ng, P. Y.; Powelson, I. A.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3811.
(6) For a selected example, see: Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913.
(7) For selected allylation examples of α- and β-hydroxy ketones, see: (a) Wang, Z.; Meng, X.-J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 1945. (b) Kabalka, G. W.; Narayana, C.; Reddy, N. K. *Tetrahedron Lett.* **1996**, *37*, 2181.
(8) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.
(9) (a) Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5909. (b) Schneider, U.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13824.
(10) Barker, T. J.; Jarvo, E. R. *Org. Lett.* **2009**, *11*, 1047–1049.
(11) Zhang, P.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12550.

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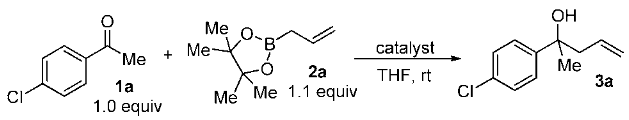
catalyzed propargylations of aldehydes based on a boron−zinc exchange mechanism wherein the zinc alkoxide product from the addition can participate in an exchange with the boronate reagent to regenerate the active nucleophile.[13] Although related catalytic cycles have been proffered for the zinc-catalyzed allylation of hydrazones[14] and copper-catalyzed allylation of ketones,[8] the extension to the zinc-catalyzed allylation of ketones has been elusive. Herein, we report a general and mild zinc-alkoxide-catalyzed allylation of ketones with allyl boronates.

Initial exploration of the process was performed by evaluating selected Lewis acids for the allylation of 4-chloroacetophenone **1a** with allyl boronate **2a** (Table 1). In

Table 1. Survey of Catalysts for the Allylation of *p*-Chloroacetophenone **1a** with Allyl Pinacol Boronate **2a**[a]



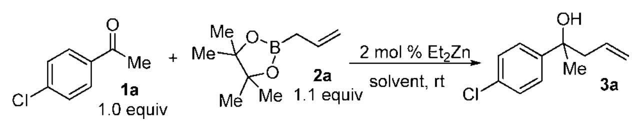
entry	catalyst	additive (equiv)	time (h)	convn[b] (%)
1	none	none	18	0
2	$InCl_3$ (100 mol %)	none	18	4
3	CuBr (100 mol %)	none	48	0
4	$Sc(OTf)_3$ (10 mol %)	none	48	0
5	$ZnCl_2$ (10 mol %)	none	20	12
6	$ZnBr_2$ (100 mol %)	none	48	55
7	$ZnEt_2$ (10 mol %)	none	2.5	40
8	$ZnEt_2$ (10 mol %)	EtOH (1.25)	2.5	97
9	$ZnEt_2$ (2 mol %)	none	2.5	3
10	$ZnEt_2$ (2 mol %)	EtOH (0.02)	2	99[c]
11	$ZnEt_2$ (2 mol %)	EtOH (1.0)	2.5	99[d]
12	none	EtOH (1.0)	2.5	0

[a] Typical reaction conditions: ketone **1** (3 mmol), catalyst and additive, allyl boronate **2** (1.1 equiv), 4 mL of THF. [b] Molar % conversion as determined by HPLC analysis. [c] Isolated yield (92%). [d] Isolated yield (97%).

contrast to indium(III) chloride, copper bromide and scandium triflate, which provided poor conversions for the model system, employing stoichiometric zinc bromide proceeded in moderate conversion (entry 6, 55% conversion). Considering that the zinc reagent could also be operating via an exchange process, the reaction was attempted with diethyl zinc as it has precedence for promoting the B/Zn exchange with other organoboronates.[13,15] The corresponding reaction with catalytic amounts of diethyl zinc (10 mol %, entry 7) proceeded to 40% conversion. Considering that zinc fluorides[14] and zinc hydroxides are competent for the exchange with allyl boronates,[16] we felt that the use of zinc alkoxides as a catalyst might be better suited for the B/Zn exchange and promote the turnover of the zinc from the tertiary alcohol product to generate a catalytic process. An initial experiment for the allylation with an in situ generated diethoxide zinc catalyst generated from diethyl zinc (10 mol %) and excess ethanol (1.25 equiv) proceeded to complete conversion within 2.5 h. This effect is more evident when 2 mol % of diethyl zinc is utilized, which proceeds to complete conversion within 2.5 h when 1 equiv of ethanol is utilized in the reaction (97% isolated yield, entry 10). However, the corresponding reaction without the alcohol additive led to poor conversion (3% conversion, entry 9). As a control experiment, a reaction with 1 equiv of ethanol and without diethyl zinc proceeds with no conversion (entry 12).

The effects of solvent and alcohol additives in the model system were studied (Table 2). The allylation was found to

Table 2. Survey of Additives and Solvents for the Zinc-Catalyzed Allylation of *p*-Chloroacetophenone **1a** with Allyl Pinacol Boronate **2a**[a]



entry	additive (equiv)	solvent	time (h)	convn[b] (%)
1	EtOH (1)	THF	2.5	99[c]
2	EtOH (1)	toluene	22	89
3	EtOH (1)	DCM	22	74
4	EtOH (1)	MeCN	22	1
5	EtOH (1)	MTBE	22	97
6	EtOH (1)	EtOAc	22	4
7	none	EtOH	22	99[d]
8	none	H_2O	18	3
9	H_2O (2)	THF	18	4
10	*t*BuOH (1)	THF	18	97

[a] Typical reaction conditions: ketone **1** (3 mmol), catalyst and additive, allyl boronate **2** (1.1 equiv), 4 mL of THF. [b] Molar % conversion as determined by HPLC analysis. [c] Isolated yield (97%). [d] Isolated yield (99%).

perform well in several solvent systems. In particular, toluene, dichloromethane, or methyl *tert*-butyl ether (MTBE) provided the desired product in ≥74% molar conversions. Noteworthy, the reaction also proceeds well when ethanol is employed as the solvent, providing the product in complete conversion and 99% yield. However, excess moisture led to low yields in this process (2 equiv of water, entry 9). The allylation does not appear to be affected by the alcohol additive, as the reaction with the sterically demanding *tert*-butanol additive provides the product in 97% conversion.

After establishing the optimized conditions, the effect of different substitution patterns on the ketone substrate (Table

(12) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660.

(13) 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.

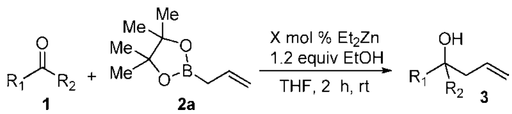
(14) Fujita, M.; Nagano, T.; Schneider, U.; Hamada, T.; Ogawa, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2914.

(15) For a recent review, see: Knochel, P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. In *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Vol. 1, pp 251−346.

(16) For the zinc fluoride exchange with allyl trimethoxysilanes, see: Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3927.

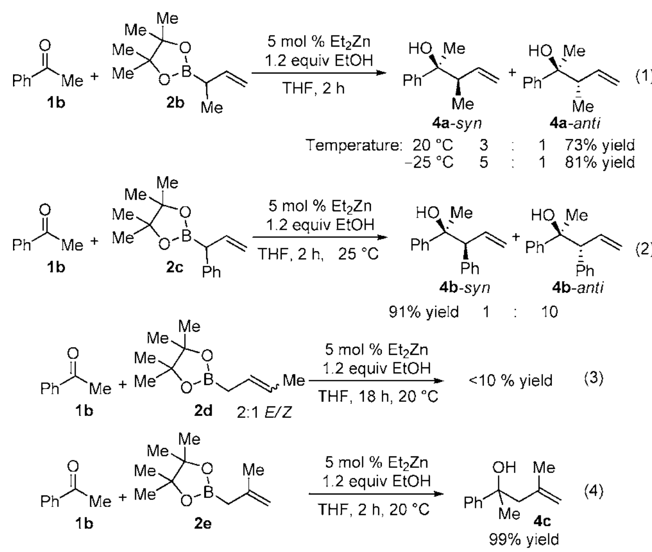
3) was explored. The methodology performs well with a diverse array of functional groups including both electron-deficient and rich aromatic acetophenones providing the desired products in >90% isolated yields with 2 mol % of the zinc catalyst within 2 h at ambient temperature. Even an unprotected phenol (**1i**) and aniline (**1h**) substrates are tolerated in the chemistry, providing the homoallylic substrates in 92 and 96% yield, respectively. Apparently, the allylation of the carbonyl effectively competes with protonolysis of the allyl zinc species with either the ethanol additive or the phenol substrate. The allylation is competent with ethyl (**1c**), chloromethyl (**1e**), and β-chloroethyl (**1d**) substrates, providing the corresponding products in 91−96% isolated yields. It should be noted that no observable intramolecular cyclizations with the appended chloromethyl and chloroethyl side chains of **2d** and **2e** were observed. Unsaturated ketones, in particular, substrates **1o** and **1p**, perform well in the parent methodology, providing access to the 1,2-addition products (96 and 81% yields). Also, an α-keto ester (**1q**) is a competent substrate for the allylation, allowing access to this important class of compounds (92% isolated yield).

Table 3. Survey of Ketones for the Zinc-Catalyzed Allylations with Allyl Pinacol Boronate **2a**[a]



entry	substrate	product	Et_2Zn (time)	yield[b]
1	**1b**	**3b**	2% (2 h)	91%
2	**1c**	**3c**	2% (2 h)	93%
3	**1d**	**3d**	2% (2 h)	96%
4	**1e**	**3e**	5% (2 h)	91%
5	**1f**	**3f**	2% (2 h)	96%
6	**1g**	**3g**	2% (2 h)	91%
7	**1h**	**3h**	2% (2 h)	96%
8	**1i**	**3i**	2% (2 h)	92%
9	**1j**	**3j**	2% (2 h)	96%
10	**1k**	**3k**	2% (2 h)	99%
11	**1l**	**3l**	2% (2 h)	88%[c]
12	**1m**	**3m**	2% (2 h)	96%
13	**1n**	**3n**	2% (0.2 h)	81%
14	**1o**	**3o**	5% (2 h)	93%
15	**1p**	**3p**	2% (2 h)	86%
16	**1q**	**3q**	2% (2 h)	92%

[a] Typical reaction conditions: ketone **1** (3 mmol), diethyl zinc (2 mol % 0.06 mmol), ethanol (1.2 equiv), allyl boronate **2** (1.1 equiv), 4 mL of THF. [b] Isolated yield. [c] 96% assay yield determined by ^{1}H NMR.



The allylation with a series of substituted allyl boronates (eqs 1−4) was also explored. The allylation was found to be competent with the α-methyl-substituted boronate **2b** (eq 1), in which good selectivity is obtained by performing the reaction at −25 °C, providing the *syn*-product **4a** in 5:1 dr and in good yield. The selectivity reverses with the corresponding phenyl-substituted boronate, providing the product in 91% yield and 10:1 diastereoselectivity favoring the *anti*-product **4b** (eq 2). Interestingly, the chemistry fails to proceed to any significant conversion with a terminally methyl-substituted boronate **2d**. However, the 2-methylallyl boronate **2e** performs well in the allylation, providing access to the corresponding homoallyl alcohol **4c** in near quantitative yield (eq 4).

In order to elucidate the effect of the alcohol additive with the parent methodology, the reaction between the boronate reagent and the zinc catalyst was studied. The zinc−boron exchange process and the stability of the allyl pinacol boronate **2a** under typical reaction conditions (Figure 1) were

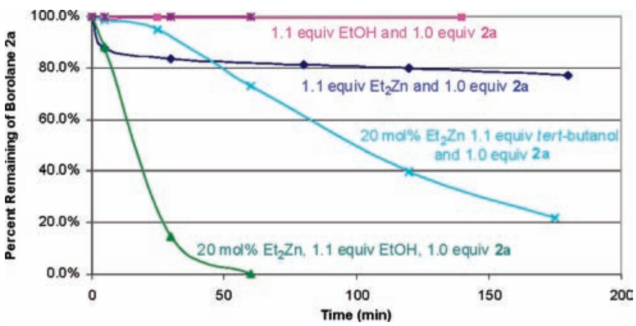
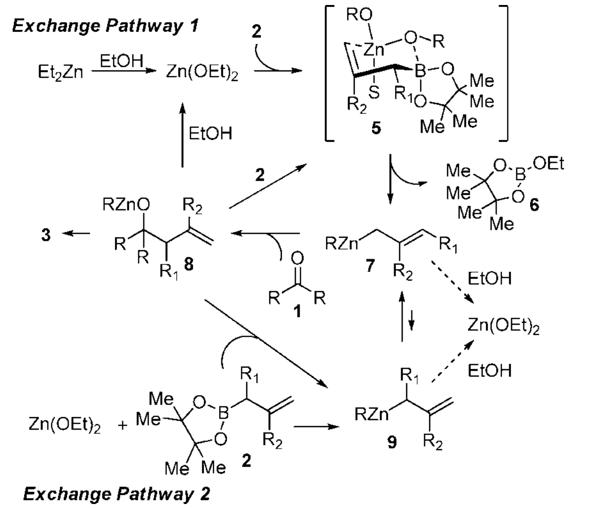


Figure 1. Monitoring of the consumption of allyl pinacol boronate **2a** by GC under various reaction conditions.

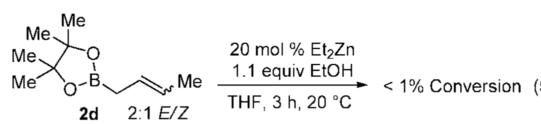
studied by monitoring the consumption of **2a** by GC analysis. The allyl boronate **2a** is stable in the presence of 1.1 equiv of ethanol over 2.3 h at ambient temperature. However, treatment of the boronate **2a** with 1.1 equiv of diethyl zinc afforded partial consumption of the boronate over a 3 h period. ^{1}H NMR studies of the zinc reagent show that diethyl zinc is quickly converted to the alkoxide species when treated with excess ethanol (5 equiv). Under the typical reaction conditions with catalytic zinc (20 mol %) and the presence of 1.1 equiv of ethanol, the boronate **2a** is rapidly consumed within 60 min. Accordingly, the allylation of the ketone must be considerably faster than the corresponding protonolysis in order to provide excellent yields while only employing a slight excess of the boronate. Interestingly, the corresponding experiment with *tert*-butanol (20 mol % of diethyl zinc and 1 equiv of **2a**) shows a slower rate of consumption of the boronate **2a**, which is either an artifact of the slower exchange process with the zinc *tert*-butoxide or subsequent protonolysis.

There are two reported mechanisms for the boron to zinc exchange process (Scheme 1), and each can be differentiated by whether the substituents on the allyl group are inverted or retained during the exchange process with the metal. Kobayashi proposed a cyclic transition structure for the boron to zinc allyl exchange with zinc fluorides,[12] wherein the allyl group is inverted upon the transfer to the zinc metal. The substitution pattern of the allyl group is retained upon the addition to the ketone via a double overall inversion process. Alternately, the allyl group can be transferred directly to the zinc metal[17] without inversion to form **9** that then undergoes an isomerization to form the less sterically encumbered zinc reagent, which is more consistent with a type 1 allylation process.[18] To differentiate between the two proposed ex-

Scheme 1. Exchange Pathways for the Allylation of Ketones Catalyzed by Zinc Alkoxides



change processes, the reactivity of boronate **2d** with the zinc alkoxide catalyst was studied (eq 5). Treatment of allyl boronate **2d** with 20 mol % of zinc alkoxide led to less than 1% consumption of the allyl boronate **2d** over a 3 h period. However, the unsubstituted counterpart **2a** is consumed within 1 h under identical conditions. The lack of reactivity of boronate **2d** in the zinc alkoxide process is consistent with the cyclic exchange process (pathway 1, Scheme 1) as the increased steric requirements of the allyl group and the zinc metal would hinder the exchange in transition state **5**. This effect should not be present if the allyl is transferred through a noninversion process via pathway 2 (Scheme 1).



(5)

In conclusion, the zinc-alkoxide-catalyzed allylation of ketones provides an operationally simple method for the preparation of synthetically useful homoallylic tertiary alcohols. Although the allyl boronate was found to be unstable with the alcohol additive under the reaction conditions, the allylation of the ketones effectively competes with protonolysis and thus renders this process practical. The effect of the allyl boronate substituent is consistent with an inversion exchange mechanism.

Supporting Information Available: Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.; Pericas, M. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1098.

(18) (a) Carreira, E. M.; Kvaerno, L. *Classics In Stereoselective Synthesis*; Wiley-VCH: Weinheim, Germany, 2009; pp 153−185. (b) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.