ORGANIC LETTERS

2010
Vol. 12, No. 1
88−91

Zinc Catalyzed and Mediated Propargylations with Propargyl Boronates

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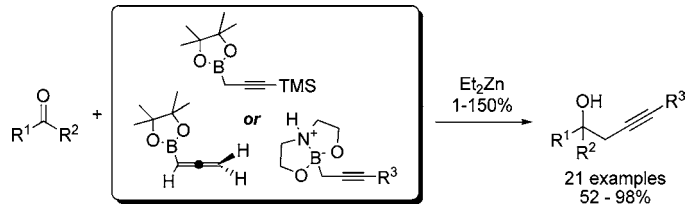
Received October 25, 2009

ABSTRACT



The utility of allenyl and propargyl boronates for the propargylation of aldehydes and ketones mediated by zinc is presented. The reaction is catalytic in zinc with allenyl or propargyl borolanes. The propargylation with crystalline and air-stable propargyl diethanolamine boronates was also achieved. A catalytic cycle is proposed, and preliminary mechanistic studies are discussed.

Organozinc additions to carbonyl species are valuable synthetic methods for the construction of C−C bonds.[1] Zinc mediated propargylations with allenylzinc complexes have shown significant synthetic utility[2] due to the high stereo-, regio-, and chemoselectivities intrinsic to organozinc chemistry.[1,3] Allenylzinc compounds are commonly prepared through oxidative addition with zinc metal or transmetalation.[1,2,4] A particularly useful approach is the Pd/Zn exchange developed by Tamaru and Marshall.[2,5] Pioneered by the work of Zakharkin and Okhlobystin and Thiele and co-workers,[6] the boron−zinc exchange provides a more general entry into the organo-zinc functional group.[1] In particular, the B/Zn exchange has been developed for the preparation of vinyl, aryl, alkynyl, and allylic zinc intermediates.[7] Typically, allenyl or propargyl boranes rapidly react with aldehydes with inversion to furnish the respective homopropargylic or

(1) For general reviews of organozinc chemistry, see: Knochel P.; Leuser, H.; Gong, L.-Z.; Perrone, S.; Kneisel, F. F. *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Whiley-VCH: Weinheim, 2005; pp 251−346.

(2) For 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.

(3) (a) Poisson, J.-F.; Normant, J. F. *Org. Lett.* **2001**, *3*, 1889–1891. (b) Chemla, F.; Ferreira, F.; Gaucher, X.; Palais, L. *Synthesis* **2007**, 1235–1241.

(4) Hameury, T.; Guillemont, J.; Hijfte, L. V.; Bellosta, V.; Cossy, J. *Org. Lett.* **2009**, *11*, 2397–2400.

(5) (a) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, M.; Kimura, *Angew. Chem., Int. Engl. Ed.* **1996**, *35*, 878–880. (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812–3813. (c) Marshall, J. A.; Mullhearn, J. J. *J. Org. Chem.* **2006**, *71*, 4840–4844.

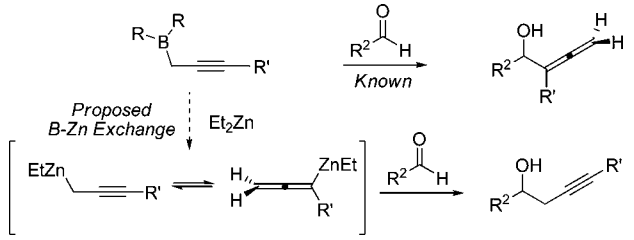
(6) (a) Zakharkin, L. I.; Okhlobystin, O. Y. *Z. Obshch. Khim.* **1960**, *30*, 2134–2138. (b) Thiele, K.-H.; Zdunneck, P. *J. Organomet. Chem.* **1965**, *4*, 10–17. (c) Thiele, K.-H.; Engelhardt, G.; Kohler, J.; Arnstedt, M. *J. Organomet. Chem.* **1967**, *9*, 385–393.

(7) For reviews, see: (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824. (c) Tejedor, D.; Lopez-Tosco, S.; Cruz-Acosta, F.; Mendez-Abt, G.; Garcia-Tellado, F. *Angew. Chem., Int. Engl. Ed.* **2009**, *48*, 2090–2098. For additional examples, see: (d) Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colat, G.; Maseras, F.; Pericas, M. A. *Angew. Chem., Int. Engl. Ed.* **2008**, *47*, 1098–1101. (e) Fujita, M.; Nagano, T.; Schneider, U.; Hamada, T.; Ogawa, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 2914–2915.

10.1021/ol902457m
Published on Web 12/01/2009

allenylic alcohols.[8] Recently, allylic pinacol boronates were demonstrated to be significantly deactivated for direct reaction with carbonyl species, and the development of In,[9] Sn,[10] and Zn[7e] catalyzed allylations with these reagents has shown significant utility. If propargyl pinacol boronates demonstrate a similar deactivation, then a B/Zn exchange can be employed to generate the allenylzinc intermediate in situ useful for a propargylation (Scheme 1).[5,11] Herein, we

Scheme 1. Proposed Complementary Propargylation with Propargyl Borolanes



report the zinc catalyzed and mediated propargylations of aldehydes and ketones with propargyl pinacol boronates and diethanolamine (DEA) boronates.

The background reaction of *p*-anisaldehyde with propargyl borolane **2**[12] required three days for high conversion and proceeded with low selectivity for the allenyl product (Table 1, entries 1 and 2). Addition of stoichiometric CuBr, $ZnBr_2$, or $InBr_3$ increased the rate of the addition and reversed the regioselectivity to favor the complementary homopropargylic product. Further rate acceleration with higher regioselectivity for propargylation was obtained with diethylzinc (entry 6). Interestingly, the role of diethylzinc is catalytic. Complete conversion within 30 min and >100:1 regioselectivity were achieved with catalyst loadings as low as 1 mol % to aldehyde (entry 14). At 0.5 mol % of diethyl zinc, the reaction required 20 h for complete conversion, and the background reaction competed to afford a lower regioselectivity (entry 15). The in situ generated $Zn(OiPr)_2$ catalyst afforded results identical to diethylzinc (entry 16).

(8) For selected examples of propargylations and allenylations with boron reagents, see: (a) Brown, H. C.; Khire, U. R.; Narla, G. *J. Org. Chem.* **1995**, *60*, 8130–8131. (b) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483–486. (c) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878–879. (d) Hernandez, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 4089–4091.

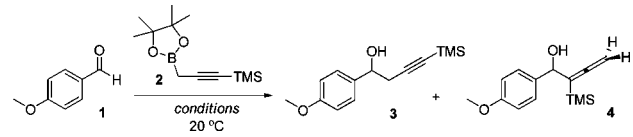
(9) (a) Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 5909–5912. (b) Schneider, U.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13824–13825.

(10) (a) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481–8490. (b) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236–4241.

(11) For selected examples of regioselective TMS−propyne additions to carbonyl species, see: (a) Corey, E. J.; Kirst, H. A. *Tetrahedron Lett.* **1968**, *9*, 5041–5043. (b) Han, Y.; Huang, Y.-Z. *Tetrahedron Lett.* **1994**, *35*, 9433–9434. (c) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 3369–3372. (d) Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042–13043. (e) Masuyama, Y.; Yamazuki, R.; Ohtsuka, M.; Kurusu, Y. *Synlett* **2006**, 1750–1752. (f) Vrancken, E.; Alouane, N.; Gerard, H.; Mangeney, P. *J. Org. Chem.* **2007**, *72*, 1770–1779.

(12) Hoffmann, R. W.; Brinkmann, H.; Frenking, G. *Chem. Ber.* **1990**, *123*, 2387–2394.

Table 1. Optimization of the Zinc Mediated Propargylation

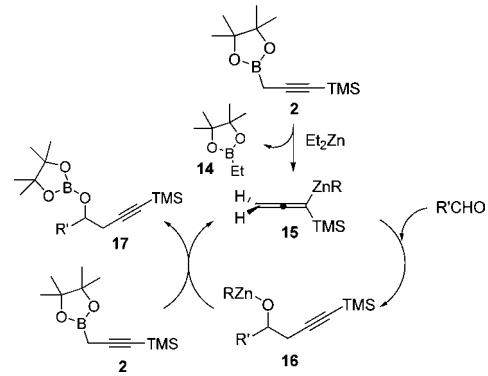


entry	conditions[a]	solvent	time[b]	**3**:**4**[c]	yield[d]
1	none	toluene	3 days	1:2	84%[e]
2	none	THF	20 h	1:2	31%[f]
3	100% $CuBr{\cdot}SMe_2$	THF	20 h	2:1	68%[g]
4	100% $ZnBr_2$	THF	20 h	6:1	79%
5	100% $InBr_3$	THF	20 h	46:1	86%
6	100% Et_2Zn	THF	30 min	>100:1	98%
7	55% $ZnEt_2$	THF	30 min	>100:1	99%
8	9% $ZnEt_2$	THF	30 min	>100:1	97%
9	9% $ZnEt_2$	toluene	30 min	>100:1	97%
10	9% $ZnEt_2$	CH_2Cl_2	30 min	>100:1	96%
11	9% $ZnEt_2$	MTBE	30 min	>100:1	96%
12	9% $ZnEt_2$	EtOAc	30 min	>100:1	93%
13	2% $ZnEt_2$	THF	30 min	>100:1	96%
14	1% $ZnEt_2$	THF	30 min	>100:1	96%[h]
15	0.5% $ZnEt_2$	THF	20 h	33:1	90%[h]
16	9% $Zn(OiPr)_2$	THF	30 min	>100:1	97%

[a] Mole percent to aldehyde. 1.55 equiv of borolane **2** to aldehyde. [b] Time until complete conversion or 20 h. [c] Regioselectivity **3**:**4** determined by HPLC. [d] HPLC assay yields. [e] 86% converison. [f] 31% conversion. [g] 68% conversion. [h] Isolated yield.

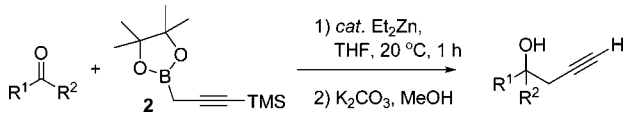
Either the TMS protected or deprotected homopropargylic alcohol can be isolated in high yield. The product of the propargylation is the pinacol borate complex **17** (Scheme 2). This borate complex is effectively degraded by treatment

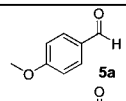
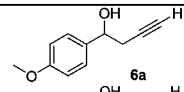
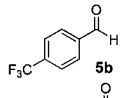
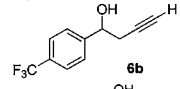
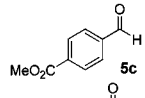
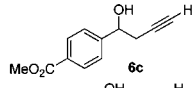
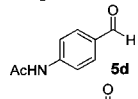
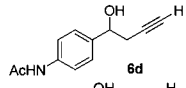
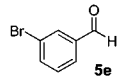
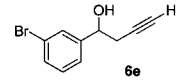
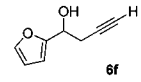
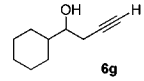
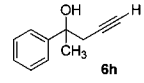
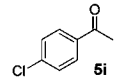
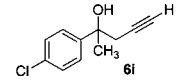
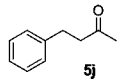
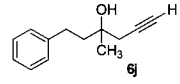
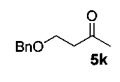
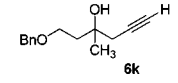
Scheme 2. Proposed Mechanism for the Zinc Catalyzed Propargylation with Propargyl Borolanes



with diethanolamine or under the TMS- deprotection conditions with methanolic potassium carbonate. The latter two-step zinc catalyzed propargylation and deprotection sequence proved general for a variety of aldehydes and ketones (Table 2). High yields were obtained within 30 min for both electron-deficient and -rich aldehydes utilizing 2 mol % of diethylzinc (entries 1−7). Reactions with ketones were

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



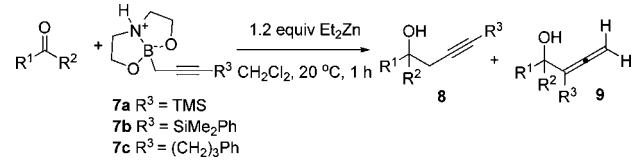
entry	substrate	product	Et_2Zn[b]	yield[c]
1	 5a	 6a	2%	99%
2	 5b	 6b	2%	96%
3	 5c	 6c	2%	98%
4	 5d	 6d	2%	91%
5	 5e	 6e	2%	93%
6	 5f	 6f	2%	97%
7	 5g	 6g	2%	85%
8	 5h	 6h	5%	89%
9	 5i	 6i	5%	95%
10	 5j	 6j	5%	95%
11	 5k	 6k	5%	97%

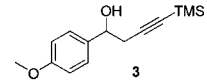
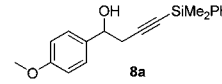
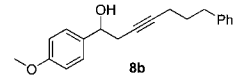
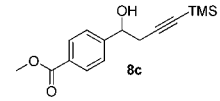
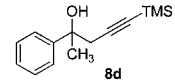
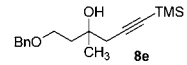
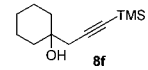
[a] Reactions performed with 1.5 mol equiv of borolane **2** to substrate. [b] Mole percent Et_2Zn (1.1 M in toluene) to substrate. [c] Isolated yields.

slightly slower and required 5 mol % of diethylzinc for high yields within 1 h (entries 8−11). The method tolerated aryl halides, esters, and acetamide functional groups.

Significant interest has focused on derivatizing organoboronic acids or esters to the crystalline diethanolamine-based[13] or *N*-methyl-iminodiacetic acid (MIDA)[14] complexes to facilitate the isolation of the organoboron compounds and increase the stability of these reagents to air and moisture. The propargyl borolane **2** is moisture sensitive, so the use of the air-stable and crystalline diethanolamine (DEA) derivative was explored. The background reaction between anisaldehyde and propargyl DEA boronate **7a** proceeded in low regioselectivity (~1:1) and yield (46%) after 2 days at 60 °C. Utilizing stoichiometric diethylzinc, the reaction between anisaldehyde and the diethanolamine reagent **7a** afforded a high yield and regioselectivity for the homopropargylic alcohol **3** (Table 3). This zinc mediated propargylation of methyl *p*-formylbenzoate also proceeded in high yield (87%), and higher yields (94−98%) were obtained for ketones. The reaction with the dimethylphenylsilyl analogue **7b** to the parent DEA boronate **7a** furnished a similar yield and regioselectivity. Although the aliphatic TMS analogue **7c** afforded a high yield for the propargylation, the reaction proceeded with no regioselectivity.

Table 3. Zinc Mediated Propargylations with Propargyl DEA Boronate **7**[a]



Substrate	R^3	product	**8:9**[b]	yield[d]
5a	**7a**	 3	>20:1	88%
5a	**7b**	 8a	>20:1	90%
5a	**7c**	 8b	1.1:1	92%
5c	**7a**	 8c	>20:1	87%
5h	**7a**	 8d	>20:1	94%
5k	**7a**	 8e	>20:1	98%
Cyclo-hexanone	**7a**	 8f	>20:1	95%

[a] Reactions performed with 1.2 mol equiv of DEA boronate **7** to substrate. [b] Regioselectivity determined by HPLC or ^1H NMR. [c] Isolated yields.

To explore the zinc mediated propargylation with more acidic substrates, the reaction with a β-ketoester and amide substrate was explored.[15] Low conversion was observed with catalytic or stoichiometric diethylzinc at ambient temperature.

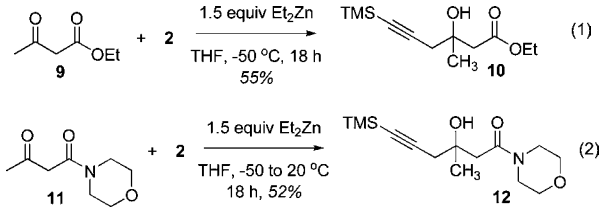
(13) Brown, H. C.; Prasad, J. V. N. V. *J. Org. Chem.* **1986**, *51*, 4526–4530, and references therein.

(14) (a) Mancilla, T.; Carrillo, L.; De La Paz Reducindo, M. *Polyhedron* **1996**, *15*, 3777–3785, and references therein. (b) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717. (c) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466–468. (d) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14084–14085.

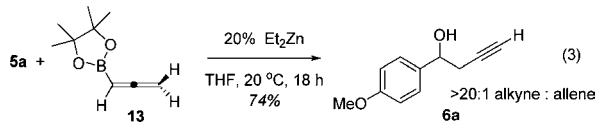
(15) For examples of zinc mediated propargylation to β-ketoamides, see: Taniguchi, M.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 645–653.

(16) *Organozinc Reagents: A Practical Approach*; Knochel, P., Joned, P., Eds.; Oxford Univ. Press.: Oxford, 1999.

Moderate yields with reasonable conversions were obtained by pretreating the propargyl borolane **2** with diethylzinc at −50 °C prior to addition of the substrate (eqs 1 and 2).



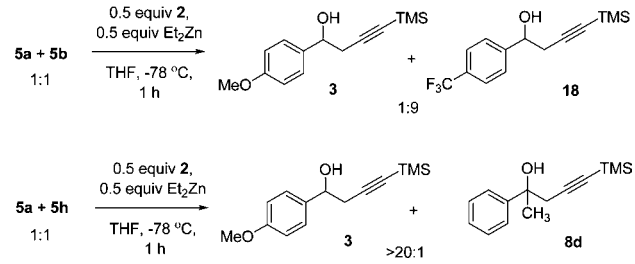
Allenyl and propargylzinc complexes are known to rapidly interconvert,[16] and the reaction with aldehydes typically favors the propargyl product. Since a similar equilibrium is established after a B/Zn exchange with the allenyl or propargyl borolane, the propargylation with the allenyl pinacol boronate **13** was attempted. The background reaction between the allenyl borolane **13** and anisaldehyde was slow and proceeded in less than 5 mol % conversion in 18 h. With 20 mol % diethylzinc, the propargylation afforded directly the terminal homopropargylic alcohol **6a** in 74% and >20:1 regioselectivity (eq 3).



A reasonable rationalization for the catalytic effect of zinc for the propargylation of carbonyl species relates to the facile B/Zn exchange of propargyl borolanes with both alkyl and alkoxy zinc intermediates (Scheme 2). Direct reaction of the allenyl or propargyl borolane with the electrophile is expected to afford the propargyl and allenyl products, respectively, due to an inversion mechanism through a Zimmerman−Traxler type transition state typical with trivalent boron reagents.[8,17] The observation that with diethylzinc both the propargyl and allenyl borolanes afford the propargyl products indicates a B/Zn exchange mechanism wherein the active nucleophile is an allenylzinc intermediate. Accordingly, the first operation in the catalytic cycle is the generation of the allenylzinc intermediate **15**. Control experiments with the propargyl borolane **2** and diethylzinc showed complete exchange to furnish ethyl borolane **14** in <1 h at ambient temperature.[18] After the addition to the aldehyde, the zinc alkoxide **16** participates in another B/Zn exchange with the propargyl borolane reagent to regenerate the allenylzinc intermediate **15** and complete the catalytic cycle. This exchange with an alkoxy zinc complex can be reasonably proffered based on the examples from Kobayashi et al. who previously demonstrated that zinc hydroxide is competent for the B/Zn exchange with allylic borolanes,[7e] and $Zn(OiPr)_2$ showed similar reactivity as diethylzinc for this propargylation (Table 1, entry 16). The low catalytic activity with DEA propargyl borolane reagents and β-ketoester or amide substrates is reasonably rationalized by a competitive protonolysis of the zinc intermediates by the relatively acidic reagent or substrate.

The competition experiments between different aldehydes and a ketone were conducted to probe the relative reactivity of the propargylation toward the substrate (Scheme 3). The competition between *p*-trifluoromethyl and *p*-methoxybenzaldehyde with substoichiometric amount of the reagents at −78 °C showed a 9:1 preference for reaction with the more electron-deficient aldehyde. Similary, the competition between the former less reactive *p*-methoxybenzaldehyde and acetophenone strongly favored reaction with the aldehyde. Additionally, the reactions demonstrate the facile B/Zn exchange between the propargyl borolane and diethylzinc under cryogenic conditions.

Scheme 3. Competition Experiments[a]



[a] Product ratios determined by HPLC.

In conclusion, we demonstrated the zinc catalyzed and mediated propargylation of aldehydes and ketones with propargyl boronates. The reaction showed broad substrate generality, and both the allenyl and propargyl borolane reagents can be employed, indicative of zinc mediated propargylation. The method was also developed to use the crystalline and air-stable DEA propargyl boronates.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For examples, see: (a) Wang, K. K.; Liu, C. *J. Org. Chem.* **1985**, *50*, 2578–2580. (b) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483–486. (c) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236–1240. (d) Hernandez, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 4089–4091. (e) Paton, R. S.; Goodman, J. M.; Pellegrinet, S. C. *Org. Lett.* **2009**, *11*, 37–40.

(18) See Supporting Information.