Tetrahedron Letters, Vol. 33, No. 26, pp. 3717-3720, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Preparation and Reactions of 1,1-Zinc, Boron and 1,1-Copper, Boron Alkenyl Bimetallics

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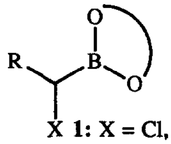
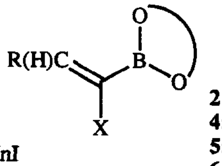
Key Words: Zinc, Boron Bimetallics, d^1-Reagents, Functionalized alkenyl coppers, Functionalized boronic esters

Summary: Pinacol α-iodoalkenylboronates 8, readily prepared by the hydroboration of 1-iodoalkynes, were converted to 1,1-bimetallics of boron and zinc or copper which react with a wide range of electrophiles affording polyfunctional boronic esters. After H_2O_2 oxidation (30% H_2O_2, sat. aq. NaOAc), polyfunctional ketones were produced in good to excellent yields.

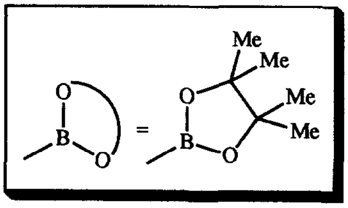
α-Haloalkylboronic esters 1 represent a very useful class of boron intermediates for organic synthesis.[1] Whereas α-halo*alkenyl*boronic esters 2 have been known for several years,[2] they have found comparatively few synthetic applications.[3] Recently, we have reported that α-iodo- or α-bromoalkylboronic esters readily insert zinc dust in THF affording 1,1-bimetallics[4] of boron and zinc 3. We have now found that α-iodoalkenylboronic esters 2 (X = I) react with zinc dust in dry N,N-dimethylacetamide (DMA)[5] and furnish 1,1-boron, zinc alkenylbimetallics 4. After a transmetallation to the 1,1-boron, copper[4] bimetallics 5, these reagents react with a wide range of electrophiles leading to boronic esters 6 which can be oxidized (30% H_2O_2, aq. sat. NaOAc, EtOH:THF 1:1, 25 °C, 0.1 - 1 h) providing various types of polyfunctional ketones 7 (Table I). The (Z)-α-iodoalkenylboronic esters 8 were prepared by the hydroboration of 1-iodoalkynes 9 with $HBBr_2{\cdot}Me_2S$ (Aldrich)[2,6] in CH_2Cl_2 (0 °C to 40 °C, then 25 °C, 2 h) followed by the conversion of the intermediate dibromoboronic ester to

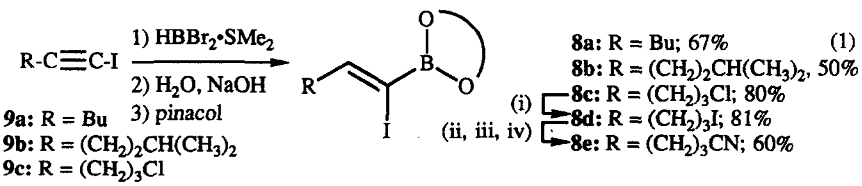


1: X = Cl, Br, I
3: X = ZnBr or ZnI



2: X = Br, I
4: X = ZnI
5: X = Cu(CN)ZnI
6: X = E





R-C≡C-I
9a: R = Bu
9b: R = $(CH_2)_2CH(CH_3)_2$
9c: R = $(CH_2)_3Cl$

8a: R = Bu; 67% (1)
8b: R = $(CH_2)_2CH(CH_3)_2$, 50%
8c: R = $(CH_2)_3Cl$; 80%
8d: R = $(CH_2)_3I$; 81%
8e: R = $(CH_2)_3CN$; 60%

(i) NaI, $CH_3COC_2H_5$, 80 °C, 24 h; (ii) Zn, THF, 50 °C, 3 h; (iii) $CuCN{\cdot}2\,LiCl$; 0 °C, 5 min.; (iv) p-$TolSO_2CN$ (0.7 equiv.), -60 °C to 0 °C, 30 min.

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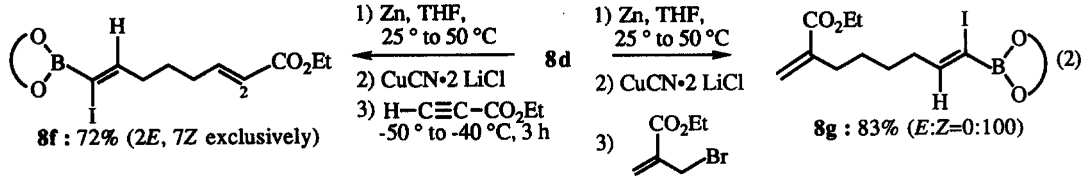
*Present address: Philipps-Universität Marburg; Fachbereich Chemie; Hans Meerwein Str.; D-3550-Marburg Germany the corresponding 1-iodoalkenylboronic acid (NaOH, ice, AcOEt, 0 °C, 3 min) and esterification with pinacol (1.2 equiv.; $MgSO_4$, 1:1 ether:hexane, 25 °C, 1 h, 50-80% overall yield).[7] The 1-iodoalkenylboronic ester **8d** was obtained from **8c** by a Finkelstein reaction (NaI (6 equiv.), $CH_3COC_2H_5$, 80 °C, 24 h, 81%) and **8e** was prepared from **8d** by forming chemoselectively the corresponding alkylzinc iodide in THF (no insertion in the alkenyl iodide was observed in this solvent), treatment with CuCN•2 LiCl[8] and coupling with p-$TolSO_2CN$ (-60 °C to 0 °C, 30 min, 60 %).[9]

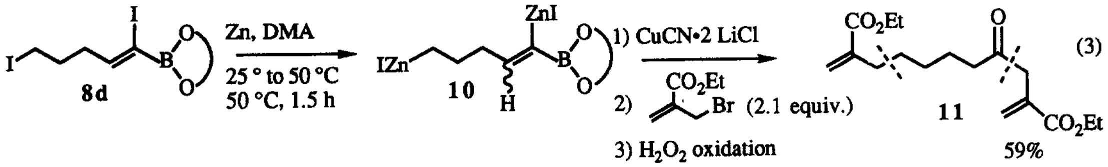


8f : 72% (2*E*, 7Z exclusively)

8g : 83% (*E*:Z=0:100)

(2)

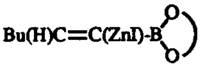
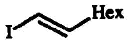
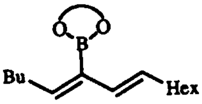
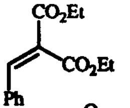
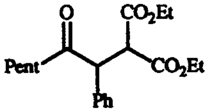
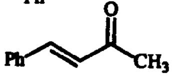
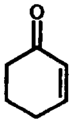
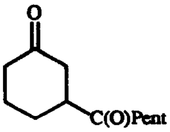
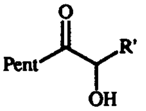
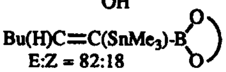
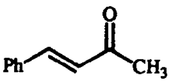
Similarly, the polyfunctional α-iodoalkenylboronic esters **8f** and **8g** were obtained in respectively 72% and 83% yield as pure Z-isomer (eq. 2). The zinc insertion to α-iodoalkenylboronic esters does not occur stereoselectively, and the pure (Z)-α-iodoalkenylboronic ester **8a** is converted to an *E*/*Z* mixture of alkenylzinc iodides **4a** (82:18 as determined by hydrolysis). The iodolysis of **4a** provides the (*E*)-α-iodoalkenylboronic ester **8a** as the major isomer (*E*:*Z* = 82:18). After the transmetallation of **4a** to **5a** with CuCN•2 LiCl and addition of Me_3SnCl (0.67 equiv., -40 °C to 25 °C, 2 h) a *E*/*Z* mixture of the alkenylstannanes **6b** (*E*:*Z* = 82:18); entry 12 of Table I)[10] is obtained. Interestingly, the coupling of **4a** with (*E*)-1-iodooctene[11] (0.58 equiv.) in the presence of $Pd(dba)_2$ (1 mol %)[12] and PPh_3 (4 mol %) provides only the (*E*,*E*)-diene **6a** (THF, 20 °C (exothermic to 35 °C), 1 h; 77%; entry 1). The reagents **5** are efficient acyl anion equivalents (d^1-reagents)[13]. Thus, the Michael addition of **5a** to diethyl benzylidenemalonate (entry 2), benzylideneacetone (entry 3), cyclohexenone (entry 4), ethyl propiolate (entry 5) and ethyl α-(bromomethyl)acrylate (entry 7) affords after H_2O_2-oxidation[14] a variety of 1,4-dicarbonyl compounds in excellent yields. In the case of the addition of **5a** to nitrostyrene the desired 1,4-adduct was contaminated by the eliminated product **7d**. The chromatographed reaction mixture was treated with DBU[15] in CH_2Cl_2 (25 °C, 5 min.) furnishing only **7d** in 69% yield (entry 5). The coupling of **5a** or **5c** with 1-iodohexyne gives after oxidation the corresponding acetylenic ketones **7g** (86%) and **7n** (87%); see entries 8 and 16. The reaction of **5a** with aldehydes in the presence of $BF_3•OEt_2$ provides a new approach to α-hydroxyketones (entries 9-11). Polyfunctional 1,1-bimetallics of type **4** or **5** containing a chloride or cyanide functionality react well with electrophiles and lead after oxidation to polyfunctional ketones such as **7m-o** (entries 15-17).



(3)

It was possible to prepare the polymetallic zinc reagent **10** by treating **8d** with an excess of zinc dust in DMA (40 °C, 2 h). After transmetallation to the copper compound, addition of ethyl α-(bromomethyl)acrylate (2.1 equiv.) and H_2O_2 oxidation, the unsaturated ketodiester **11** was isolated in 59% overall yield (eq. 3). Finally, we have prepared the Diels-Alder adduct **12a** from the reaction of **6a** and diethyl acetylenedicarboxylate (2 eq, $PhCH_3$, 110 °C, 3.5 h, 67%)[16] as well as the new 1,2-diboronic ester **12b** obtained by the reaction of **8a** (0.7 eq) with $(RO)_2BCH_2ZnI$[4a] in the presence of $Pd(dba)_2$ (1 mol %) and PPh_3 (4 mol %) (THF, 40 °C, 12 h) followed by purification by

Table I. Products of Type **6** or **7** Obtained by the Reaction of α-Metallated Alkenylboronic Esters of Copper or Zinc of Type **4** or **5** with Electrophiles

Entry	1,1-Bimetallic **4** or **5**	Electrophile	Reaction Conditions[a]	Product **6** or **7**	Yield (%)[b]
1	 $Bu(H)C{=}C(ZnI){-}B(O_2)$ **4a**		(i)	 **6a**	77
2	 $R(H)C{=}C(Cu(CN)ZnI){-}B(O_2)$ **5a**, R=Bu		(ii)	 **7a**	94
3	**5a**		(iii)	$PentC(O)CHPhCH_2C(O)CH_3$ **7b**	88
4	**5a**		(iv)	 **7c**	76
5	**5a**	$PhCH{=}CHNO_2$	(v)	$PentC(O)C(Ph){=}CH_2$ **7d**	69
6	**5a**	$H{-}C{\equiv}C{-}CO_2Et$	(vi)	$PentC(O)CH{=}CHCO_2Et$ **7e**	91
7	**5a**	$BrCH_2C(CO_2Et){=}CH_2$	(vii)	$PentC(O)CH_2C(CO_2Et){=}CH_2$ **7f**	73
8	**5a**	$Bu{-}C{\equiv}C{-}I$	(viii)	$PentC(O)C{\equiv}C{-}Bu$ **7g**	86
9	**5a**	PhCHO	(ix)	 **7h:** R'=Ph	76
10	**5a**	BuCHO	(ix)	**7i:** R'=Bu	74
11	**5a**	c-HexCHO	(ix)	**7j:** R'=c-Hex	87
12	**5a**	Me_3SnCl	(x)	 $Bu(H)C{=}C(SnMe_3){-}B(O_2)$ E:Z = 82:18 **6b**	89
13	**5b**, $R{=}(CH_3)_2CH(CH_2)_2$	$BrCH_2C(CO_2Et){=}CH_2$	(vii)	$(CH_3)_2CH(CH_2)_3C(O)CH_2C(CO_2Et){=}CH_2$ **7k**	85
14	**5b**		(iii)	$(CH_3)_2CH(CH_2)_3C(O)CHPhCH_2C(O)CH_3$ **7l**	73
15	**5c**, $R{=}Cl(CH_2)_3$	$BrCH_2C(CO_2Et){=}CH_2$	(vii)	$Cl(CH_2)_4C(O)CH_2C(CO_2Et){=}CH_2$ **7m**	66
16	**5c**	$Bu{-}C{\equiv}C{-}I$	(viii)	$Cl(CH_2)_4C(O)C{\equiv}C{-}Bu$ **7n**	87
17	**5e**, $R{=}NC(CH_2)_3$	$BrCH_2C(CO_2Et){=}CH_2$	(vii)	$NC(CH_2)_4C(O)CH_2C(CO_2Et){=}CH_2$ **7o**	60

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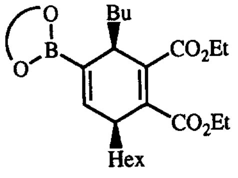
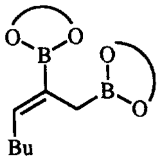
[a] (i) $Pd(dba)_2$ (1 mol %), PPh_3 (4 mol %), 20 °C to 35 °C, 1 h; (ii) 25 °C, 10 h, then H_2O_2 oxidation; (iii) Me_3SiCl (2.3 equiv.), -78 °C to 25 °C, 12 h, H_2O_2 oxidation; then Bu_4NF (0.5 equiv.); (iv) Me_3SiCl (2.3 equiv.), -78 °C to 25 °C, 12 h; (v) -78 °C to 0 °C, 1 h, H_2O_2 oxidation, flash chromatography then DBU (0.57 equiv.), CH_2Cl_2, 25 °C, 10 min.; (vi) -80 °C to -40 °C, 3 h, then H_2O_2 oxidation; (vii) -78 °C to 0 °C, 0.5 h, then H_2O_2 oxidation; (viii) -30 °C, 17 h, then H_2O_2 oxidation; (ix) $BF_3{\cdot}OEt_2$ (2.0 equiv.), -10 °C, 15 h, then H_2O_2 oxidation; (x) -78 °C to 25 °C, 2 h.

[b] Isolated yields of analytically pure compounds. Satisfactory spectral data (IR, ^1H- and ^{13}C-NMR, high-resolution mass spectra) were obtained for all compounds.

vacuum distillation (bp: 110 °C, 0.01 mmHg; 86% yield). In conclusion, we have shown that 1,1-alkenylbimetallics of boron and zinc (or copper) can be efficient building blocks for the preparation of new polyfunctional boron compounds as well as versatile d^1-reagents.



12a (67%)



12b (86%)

Acknowledgments
We thank the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society and the University of Michigan (Office of the Vice President for Research) for the support of this work. We thank J. Magano for some preliminary experiments.

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7. Typical procedure: Preparation of (Z)-pinacol 5-chloro-1-iodo-1-pentenylboronate **8c**: A three-necked flask equipped with a thermometer, an addition funnel and a stirring bar was charged under argon with 5-chloro-1-iodo-1-pentyne **9c** (6.85 g, 30 mmol) in dry CH_2Cl_2 (20 mL) and cooled to 0 °C. $HBBr_2{\bullet}SMe_2$ (8.42 g, 36 mmol) was then added. The reaction mixture was allowed to reach 25 °C and an exothermic reaction took place (35°-40 °C). The reaction mixture was stirred 2 h at 25 °C and poured into a mixture of ice (200 g) and NaOH (3.0 g, 75 mmol) and stirred for 3 min. Ethyl acetate was added (100 mL) and the aqueous layer was washed with AcOEt (2x75 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated. The resulting oil was dissolved in ether (30 mL) and hexane (10 mL) and stirred for 1 h with pinacol (4.25 g, 36 mmol) and $MgSO_4$ (7 g). After filtration, the organic layer was worked up as usual. The crude oil was purified by flash chromatography (hexane:ether, 95:5) affording pure **8c** (8.51 g, 80% yield).
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10. ^1H NMR-shifts ($CDCl_3$) of the vinylic and the two allylic protons of the *E*/*Z* isomers of **6b**: *E*-isomer (major): $\delta(H) = 6.27$ (t, 1H, $J = 6$ Hz); $\delta(CH_2) = 2.18$ (q, 2H, $J = 6$ Hz); Z-isomer (minor): $\delta(H) = 6.98$ (t, 1H, $J = 6$ Hz); $\delta(CH_2) = 2.03$ (q, 2H, $J = 6$ Hz).
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14. Typical procedure. Preparation of 1-chloro-5-oxo-6-undecyne **7n**. A 25 mL, three-necked flask equipped with a magnetic stirring bar, a thermometer and an addition funnel was charged with zinc dust (900 mg, 13.5 mmol) and flushed with Ar. The zinc dust was activated in dry DMA (2 mL) with 1,2-dibromoethane (300 mg) and TMSCl (0.1 mL) as reported previously.[8] The iodide **8c** (2.0 g, 5.4 mmol) in dry DMA (1 mL) was added. An exothermic reaction was observed (25 ° to 35 °C) and the reaction mixture was stirred at 40-45 °C for 0.5-1 h. The completion of the reaction was monitored by GLC analysis of reaction aliquots. Dry THF (10 mL) was added and the excess zinc dust was allowed to settle for 1 h. The clear green solution was transferred via syringe to a THF (5 mL) solution of CuCN (485 mg, 5.4 mmol) and LiCl (459 mg, 10.8 mmol) at -60 °C. The reaction mixture was allowed to warm to 0 °C for 5 min. and cooled to -30 °C and 1-iodohexyne (675 mg, 3.25 mmol) was added. After stirring 17 h at this temperature, the reaction mixture was worked up as usual (extraction with ether) and the resulting crude oil was dissolved in 1:1 EtOH:THF (20 mL), cooled to 0 °C and sat. aq. NaOAc (5 mL) and 30% H_2O_2 (5 mL) was successively added. The reaction mixture is worked up after 10 min. and purified by flash chromatography (ether:hexane, 1:9) affording analytically pure **7n** (569 mg, 87% yield).
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(Received in USA 13 March 1992)