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On the mechanism and origin of the stereoselectivity in iodo-deboronation and chloro-deboronation of hindered alkenyl boronate esters using either ICl–NaOMe or ICl–pyridine

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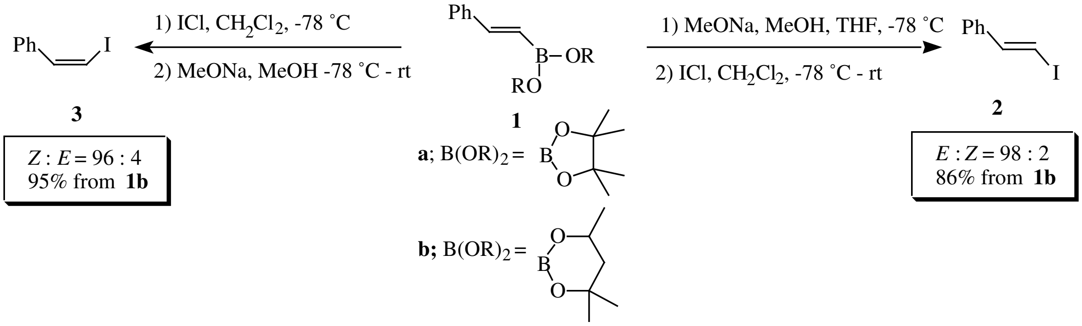
Abstract—Conversion of hindered alkenyl boronate esters into the corresponding iodoalkene, or alkenyl chloride can be carried out stereoselectively using ICl. In the presence of NaOMe, direct reaction of ICl is favoured yielding the *E*-iodoalkene, however, the reaction with ICl followed by NaOMe can be used to give different major alkenyl iodide and chloride products, depending upon reaction temperature, ICl source and alkenyl boronate stereoelectronics.

The stereocontrolled synthesis of alkenyl iodides from alkenyl boron derivatives has been known for many years.[1] However, hydrolytically stable, hindered diol-derived alkenyl boronate esters, such as those derived from pinacol require the application of iodine monochloride and sodium methoxide in order to convert them to iodoalkenes (Scheme 1).[2] This process is a particularly useful one since it can be carried out with very high levels of stereocontrol, allowing either inversion or retention of the original alkenyl boronate stereochemistry,[2,3] simply achieved by controlling the order of addition of the reagents, for example, as outlined in Scheme 1. *E*-Iodoalkene **2** is produced from reaction of *E*-alkenyl boronate ester **1a** by treatment with NaOMe, followed by ICl, while initial addition of ICl, followed by addition of NaOMe yields *Z*-iodoalkene **3**. Herein, we provide a new insight into the mechanisms involved in these processes, showing that there is greater complexity than originally envisaged. We also report the use of a new, mild reagent for certain iodo-deboronation and chloro-deboronation reactions, that is, iodine monochloride–pyridine complex.[4]



Scheme 1.

Keywords: Alkenyl boronate; Boronate esters; Iodo-deboronation; Chloro-deboronation; Iodine-monochloride.

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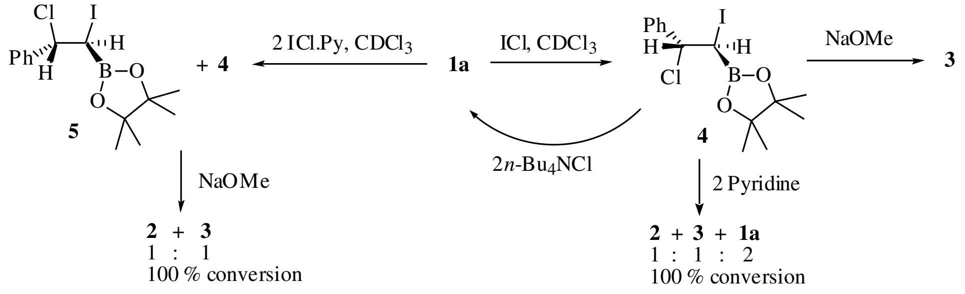
The iodo-deboronation processes outlined in Scheme 1 are applicable to other hindered esters besides pinacol. Hence, hexylene glycol ester **1b**[5] also undergoes smooth conversion to either iodoalkenes **2** or **3**, with both high stereoselectivities and yields.

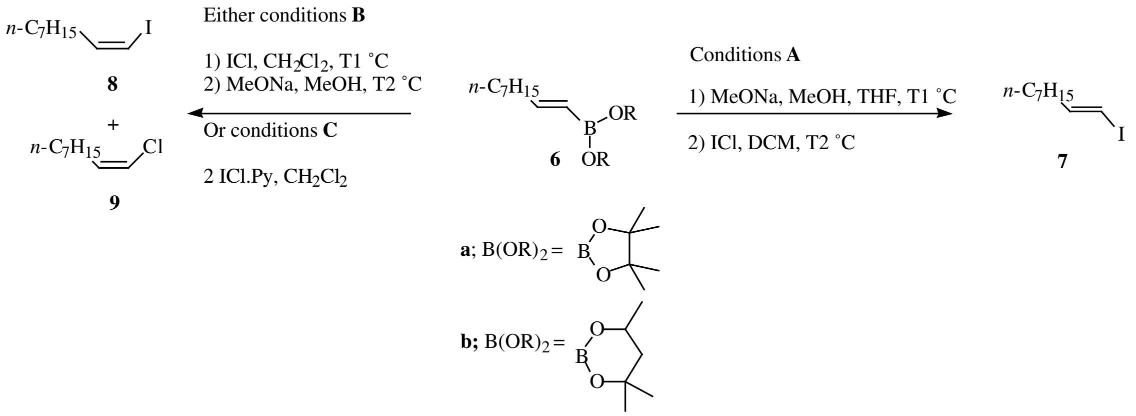
The mechanism of iodo-deboronation of alkenyl boronates **1**, with either retention or inversion of the alkenyl boronate geometry has been previously described by us[2] and was based upon the following: (1) addition of ICl to boronate **1a** (followed by ^{1}H NMR) resulted in the formation of a single diastereoisomer, assumed to be **4** on the basis of an *anti*-addition of ICl via an iodonium ion intermediate,[6] hence, elimination with methoxide results in inversion of alkene geometry to give **3**; (2) conversion of boronate **1a** to alkenyl iodide **2** was presumed to occur as described by Brown et al. when using iodine-hydroxide conditions.[1] However, following problems associated with clean iodo-deboronation of a substrate, which contained an *N*-Boc protecting group,[7] and production of *Z*-alkenyl chloride by-products from *E*-alkylalkenyl boronates (vide infra),[8] we examined alternative electropositive sources of iodine for achieving iodo-deboronation of alkenyl boronates, including the readily prepared ICl–pyridine complex[4] and obtained some unexpected results that have led us to re-examine the mechanisms operating in Scheme 1 and in related iodo-deboronation processes.

The reaction of *E*-boronate **1a** with ICl can be followed by ^{1}H NMR and results in the formation of an intermediate initially presumed to be ICl adduct **4**, which we have found can be isolated[9] as a single diastereoisomer and confirms our previous findings.[2] Indeed, subsequent treatment of ICl adduct **4** with sodium methoxide results in the rapid and efficient formation of the *Z*-iodoalkene **3** (Scheme 2). However, the formation of the corresponding *E*-iodoalkene **2** from **1a** could not be studied by ^{1}H NMR due to the high rate of reaction, that is, initial treatment of boronate **1a** with sodium methoxide, followed by ICl addition provides alkenyl iodide **2** too quickly to allow the observation of any intermediates. In contrast, replacing ICl with ICl–pyridine complex[4] resulted in a slower reaction, which could be followed by NMR. Two addition products (1:1 ratio) were observed; one identical to that ascribed to the *anti*-addition product **4**, and the other being isomeric and presumed to be the diastereoisomer of **4**, that is, the formal *syn*-addition product **5**.[10] Treatment of this 1:1 mixture of diastereoisomers with NaOMe gave both the *E*-and *Z*-iodoalkenes **2** and **3**, respectively, as a 1:1 mixture of iodoalkene stereoisomers (Scheme 2).

Although there is precedent for the *syn*-addition of dihalogen compounds to carbon multiple bonds,[11] in the present case, we were doubtful that such a process was operating on these alkenyl boronate substrates **1**. However, it was noteworthy that 2 M equiv of ICl–pyridine were required for the complete conversion of boronate **1a** to the 1:1 diastereoisomeric mixture of **4** and **5** (Scheme 2), perhaps suggesting that either chloride ion, or pyridine were essential to assist the reaction. The effect of chloride ion was directly tested by addition of tetra-*n*-butylammonium chloride to the ICl addition product **4**, which completely reversed the ICl addition reaction, resulting in a clean conversion back to the boronate **1a**. This shows that it must be the iodonium ion, which is coordinated and controlled by chloride ion concentration since the ICl adduct **4** undergoes complete elimination of ICl to regenerate the starting boronate **1a**. Chloride must cause an *anti*-periplanar elimination of ICl from adduct **4** by direct attack on iodine, rather than causing S_N2-mediated epimerisation of diastereoisomer **4** to **5**. Indeed, the addition of pyridine to adduct **4**, results in attack at both iodine, and boron, which not only regenerates ICl–pyridine, causing both diastereoisomer epimerisation and elimination, but also results in the formation the starting material **1a** and both alkenyl iodides **2** and **3**. Hence, the alternative suggestion that the mechanism of the ICl addition reaction initially involves formation of *anti*-addition product **4**, followed by an equilibrium-controlled conversion to the *syn*-addition product **5** by S_N2 inversion via chloride ion does not explain why 2 M equiv of ICl–pyridine are required for complete conversion of alkenyl boronate **1a**, since the S_N2 equilibration would merely require catalytic chloride ion, which is not the case. The alternative explanation for the effect of chloride ion is to intercept the expected intermediate iodonium ion formed by the addition of I^+ to alkenyl boronate **1a**, that is, producing an iodonium ion, which exists as a stable ion pair with chloride ion and probably further stabilised by pyridine, since ICl alone rapidly adds across the alkenyl boronate (to give **4**). Such ion-paired intermediates, especially involving iodide-iodonium ions have been inferred previously in related *syn*-addition reactions.[11] In the present



Scheme 2.



Scheme 3.

case, we propose that the iodonium ion is relatively stable and fails to react further unless excess chloride is added (or other nucleophiles, e.g., pyridine), which results in both opening of the iodonium ion ring and S_N2-mediated epimerisation at the chloride-substituted benzylic centre, resulting in a 1:1 mixture of diastereoisomers **4** and **5**.

In order to examine the mechanism of both ICl and ICl–pyridine-based additions to non-styrenic alkenyl boronates, we examined the same reactions using boronates **6a** and **b**.[12] These esters behaved like the styrenic boronate esters **1** with ICl alone under conditions A for conversion of the boronate to the *E*-iodide **7**, that is, with retention of stereochemistry (Scheme 3), providing iodide **7** with highest stereoselectivity at lower temperatures, albeit with lower conversion (Table 1, entries 1–4). The preferable conditions involve ester **6b** at −78 °C, treated with base, followed by iodine monochloride (entry 3).

To our surprise, the converse reaction to derive *Z*-iodide **8** from either ester **6a** or **b** did not behave like the styrene system. The formation of *Z*-chloride **9** competes substantially with iodide **8** formation. In fact, *Z*-chloride **9** can be the major product depending upon the reaction conditions and ester used (see Table 1). For clean conversion of boronate **6a** to the *Z*-alkenyl iodide **8**, the ideal conditions involved treatment with ICl at room temperature, followed by the addition of methoxide at room temperature (Table 1, entry 7). Use of lower temperatures resulted in an increasingly selective reaction for the formation of the chloride **9** (Table 1, entries 5 and 6). Interestingly, use of ICl–pyridine complex resulted in a highly selective reaction for the formation of chloride **9**, with both esters **6a** and **b** (Table 1, entries 8 and 13). The ester **6b** behaved similarly, though possessing somewhat greater stability, it required higher temperature reaction conditions to provide complete conversion to the *Z*-iodide **8** (see entries 9–12, Table 1). The most efficient conditions for the conversion of either ester **6a** or **b** to the *Z*-iodide **8** involve conditions B (Table 1, entry 7), that is, using the pinacol ester **6a** at room temperature for both the ICl addition and methoxide elimination steps.

Table 1. Reaction conditions and product distribution for Scheme 3

Entry	Substrate	Reaction conditions[a]	Temperatures *T*1, *T*2	Product ratio[b] **7**[c]:**8**[d]:**9**[e]	Conversion[b] (isolated yield)[f]
1	**6a**	A	−78 °C, −78 °C to RT	100:0:0	25
2	**6a**	A	RT, RT	94:6:0	79 (46)
3	**6b**	A	−78 °C, −78 °C to RT	100:0:0	73 (44)
4	**6b**	A	RT, RT	93:7:0	100 (47)
5	**6a**	B	−78 °C, −78 °C	0:16:84	100
6	**6a**	B	−78 °C, RT	0:69:31	100
7	**6a**	B	RT, RT	0:94:6	100 (65)
8	**6a**	C	RT	0:7:93	100
9	**6b**	B	−78 °C, −78 °C	0:17:83	100
10	**6b**	B	RT, RT	0:37:63	100
11	**6b**	B	40 °C, 40 °C	0:60:40	100
12	**6b**	B[g]	70 °C, 70 °C	0:76:24	100 (64)
13	**6b**	C	RT	0:5:95	100 (48)

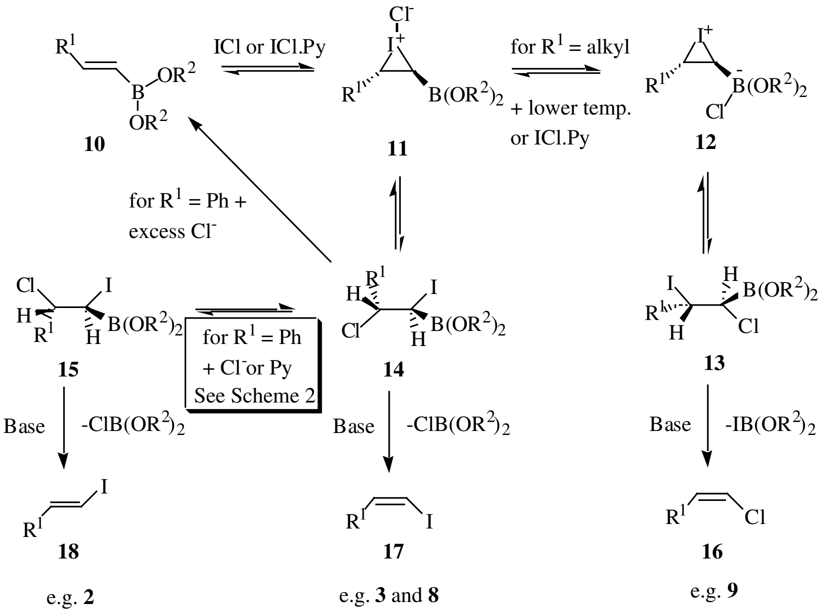
[a] For example procedures, see Ref. 13.

[b] Determined by ^{1}H NMR.

[c,d,e] Structure assignments were in accordance with Ref. 14.

[f] Isolated yield of major product after purification by silica gel chromatography.

[g] 1,2-Dichloroethane used as solvent.



Scheme 4. General scheme for the conversion of hindered vinyl boronate esters into the corresponding *E*- and *Z*-alkenyl iodides and the *Z*-alkenyl chloride by reaction with ICl or ICl–pyridine followed by base.

It is clear from these results (Table 1), that the lack of benzylic stabilisation in esters **6** results in lower susceptibility of the intermediate iodonium ion towards chloride ion pairing[15] (i.e., in **11**, Scheme 4), resulting in rapid *anti*-addition of ICl to give **14** or **13**, with the regiochemistry being heavily temperature controlled. The thermodynamically preferred regiochemistry involves attack of chloride ion away from boron to give **14**, whereas lower temperatures may favour formation of the boronate–chloride complex **12** when an alkyl group assists with iodonium ion stabilisation (Scheme 4). Formation of complex **12** provides a boronate-assisted chloride ion delivery to the alpha-position, eventually resulting in the formation of chloride **16** upon base-mediated elimination of **13**. These results are also related to the effect of using ICl–pyridine since pyridine seems to stabilise iodonium ion **11**. When R^1 is alkyl, the presence of pyridine assists formation of complex **12** and hence formation of chloride **13**, whereas when R^1 is phenyl, regioselective addition of chloride occurs to give **14**, which either undergoes elimination to give **17**, or can undergo interconversion to diastereoisomer **15**, causing formation of the *E*-iodide **18** upon elimination. The overall mechanistic processes occurring are summarised in Scheme 4.

Further developments of the use of ICl–amine complexes and application of alkenyl iodides for coupling reactions in synthesis will be reported in due course.

Acknowledgements

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9. ICl adduct **4**: δ_H (400 MHz, $CDCl_3$) 1.22 (12H, m, 4 × Me), 3.70 (1H, d, *J* 12 Hz, C*H*IB), 5.09 (1H, d, *J* 12 Hz, PhC*H*Cl) and 7.16–7.43 (5H, m, Ph); all other spectroscopic and analytical properties were commensurate with the structure assigned.
10. Compound **5**: δ_H (400 MHz, $CDCl_3$) 1.03 (6H, s, 2 × Me), 1.09 (6H, s, 2 × Me), 4.38 (1H, d, *J* 11 Hz, =C*H*IB), 6.12 (1H, d, *J* 11 Hz, PhC*H*Cl) and 7.20–7.42 (5H, m, Ph).
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12. Preparation of boronates **6a** and **b** was carried out as for **1b**[5b] starting from 1-nonyne.

13. Example experimental methods: Conditions A: A solution of boronate **6a** or **b** (0.50 g, 1.98 mmol) in THF (15 cm^3) under Ar at temperature *T*1 was treated with NaOMe (0.5 M soln in MeOH, 4.76 cm^3, 2.38 mmol). After 30 min, ICl (1.0 M soln in DCM, 2.38 cm^3, 2.38 mmol) was added. After 2 h, while warming to room temperature, the reaction was diluted with Et_2O (40 cm^3), washed with 5% aq $Na_2S_2O_5$ (50 cm^3), water (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and evaporated to yield the crude product. Purification was performed by SiO_2 column chromatography.

    Conditions B: A solution of boronate **6a** or **b** (0.50 g, 1.98 mmol) in DCM (15 cm^3) under Ar at temperature *T*1 was treated with ICl (1.0 M soln in DCM, 2.38 cm^3, 2.38 mmol). After 4 h, the reaction temperature was adjusted to *T*2 before the addition of NaOMe (0.5 M soln in MeOH, 4.76 cm^3, 2.38 mmol). After 30 min, the mixture was diluted with Et_2O (40 cm^3), washed with 5% aq $Na_2S_2O_5$ (50 cm^3), water (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and evaporated to yield the crude product. Purification was performed by SiO_2 column chromatography.

    Conditions C: A solution of boronate **6a** or **b** (0.50 g, 1.98 mmol) in DCM (15 cm^3) under Ar at temperature *T*1 was treated with ICl·Py (0.96 g, 3.97 mmol). After 4 h, the mixture was diluted with Et_2O (40 cm^3), washed with 5% aq $Na_2S_2O_5$ (50 cm^3), water (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and evaporated to yield the crude product. Purification was performed by SiO_2 column chromatography or distillation.
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15. Related effects have been inferred previously,[3c] especially where excess Br_2, ICl or IBr were required for complete conversion of catechol esters to the corresponding halides.