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Coupling Reaction of 4-Cyclopentene-1,3-diol Monoacetate and Lithium Alkenylborates and Its Application to Chiral Synthesis of Prostaglandin Intermediates

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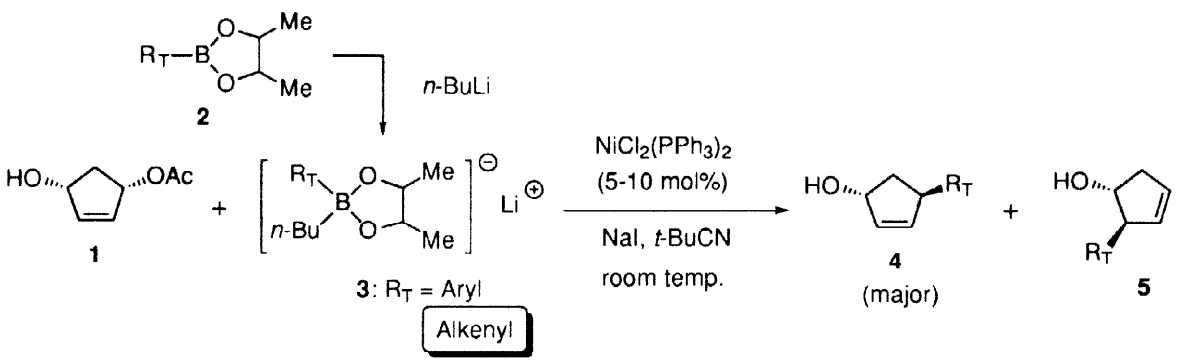
Abstract: Lithium alkenylborates couple with the monoacetate of 4-cyclopentene-1,3-diol under the nickel catalyst regioselectively and stereospecifically to afford *trans* 1,3-isomers in good yields. Moreover, an unexpectedly high level of regio-selectivity is observed with the alkenylborates possessing the prostaglandin (PG) ω-chain structure. The present reaction is successfully applied to the asymmetric synthesis of PG intermediates **9**, **15**, **16**.

In the preceding communication, the coupling reaction of the monoacetate of 4-cyclopentene-1,3-diol and lithium arylborates was presented. The coupling is catalyzed by the nickel complex and proceeds probably through a π-allylnickel intermediate. Although consideration of the classical intermediate and the results of a similar reaction by Stille[1] had suggested difficulty in attaining regio-control and the preliminary results were indeed as we had predicted, finding of the effect provided by *t*-BuCN and NaI led to selective production of the 1,3-isomer. In addition, other synthetic advantages along with this selectivity are (1) a small excess of the borate suffices for the complete reaction and (2) both enantiomers of **1** are easily available with >95% ee.[2] To expand the reaction, we examined coupling of **1** and alkenylborates. We found that the regio-enhancer (*t*-BuCN and NaI) is also successful with alkenylborates (Scheme 1). Moreover, an unexpectedly high level of regioselectivity is observed with a series of alkenylborates. Herein we report these results and its application to asymmetric synthesis of prostaglandin (PG) intermediates.



Scheme 1

Alkenyl groups chosen for the investigation are listed in Table 1. The corresponding boronate esters **2a-e** were prepared from the iodides **6a-e** through lithiation and **2f** from the acetylene **8** through hydroboration using $HBBr_2$, as indicated in Scheme 2. The requisite lithium borates **3a-f** were prepared *in situ* by addition of *n*-BuLi at 0 °C for 30 min in THF. Coupling was examined by using the racemic monoacetate **1** (i.e., *rac*-**1**)[4]

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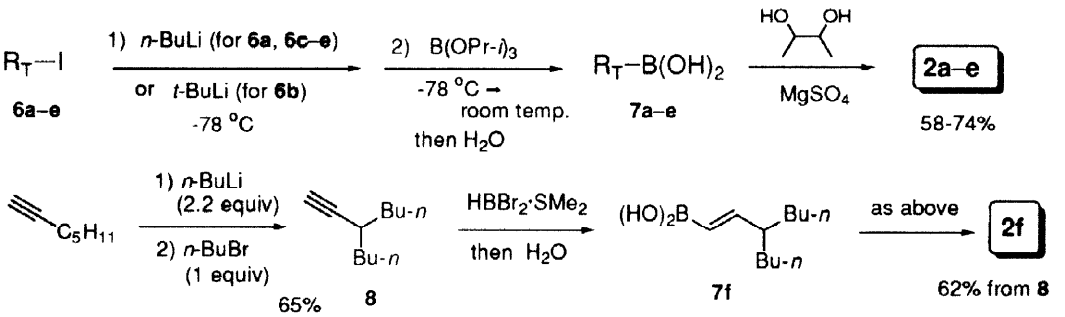
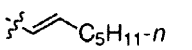
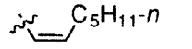
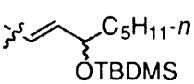
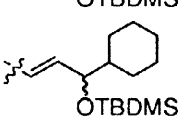
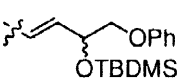
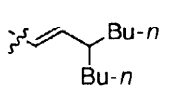
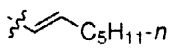


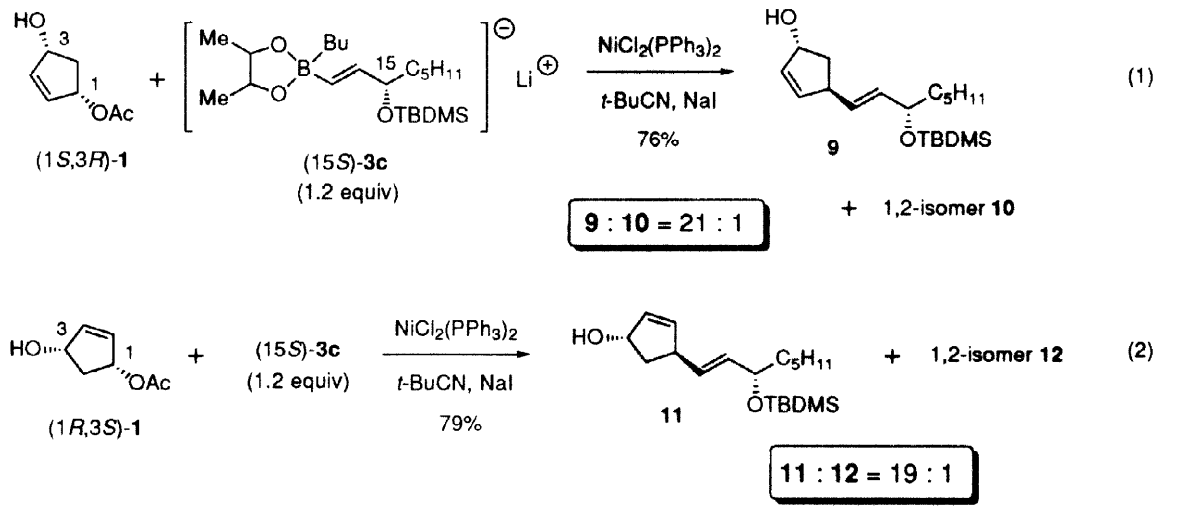
Scheme 2: for **a–f**, see Table 1.

and borates **3a-f** (1.2-1.8 equiv) under the standard conditions established for the arylborates with the regio-enhancer (*t*-BuCN (2-5 equiv) + NaI (0.5-1 equiv)) at room temperature for several hours. Results are summarized in Table 1. For simple *trans* and *cis* alkenylborates **3a,b**, the regio-enhancer indeed effected the regio-selectivity to produce the 1,3-isomers **4a,b** as the major products in good yields (entries 1, 2) and the level of the selectivity is similar to that obtained with arylborates. Fortunately, both isomers were easily purified by chromatography on silica gel. Next, borate **3c**, which is a diastereomeric mixture, was examined. Surprisingly, higher selectivity was observed (entry 3). The major product **4c** is the intermediate for synthesis of PGs and the ^{1}H NMR is consistent with that reported by Marino.[5] Such high selectivity was also recorded for borates **3d** and **3e** (entries 4, 5), both of which are useful intermediates for the PG analogue synthesis. On the other hand, borate **3f**

Table 1. Coupling of *rac*-1 and its MOM ether with the alkenylborates 3a-f[a]

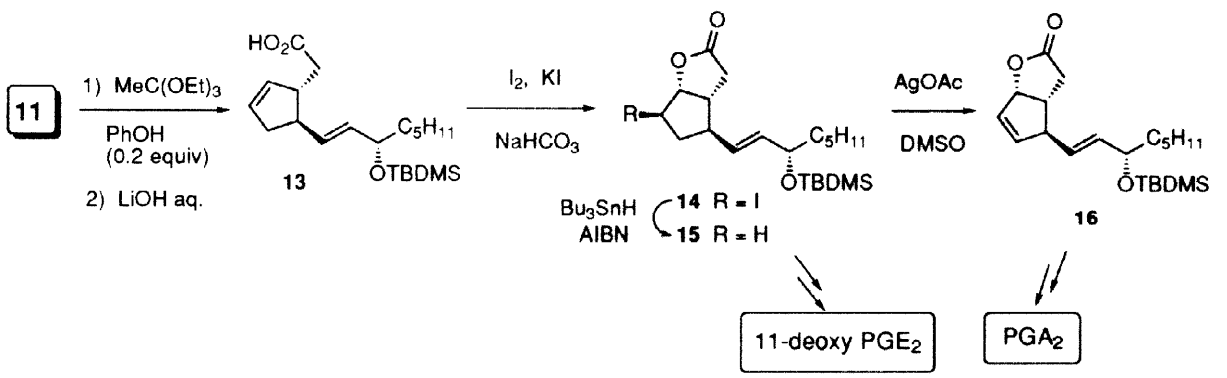
entry	substrate[b]		R$_T$ of **2–7**	yield,%	ratio of **4** : **5**[c,d] with enhancer	ratio of **4** : **5**[c,d] no enhancer
1	*rac*-**1**	**a**		89	6 : 1	3 : 1
2	*rac*-**1**	**b**		85	5 : 1	1.3 : 1
3	*rac*-**1**	**c**		67	15 : 1	5.4 : 1
4	*rac*-**1**	**d**		85	15 : 1	5.5 : 1
5	*rac*-**1**	**e**		80	17 : 1	8 : 1
6	*rac*-**1**	**f**		85	6 : 1	2.5 : 1
7	MOM ether of *rac*-**1**	**a**		87	6 : 1[d]	

[a] Reactions were carried out with $NiCl_2(PPh_3)_2$ (10 mol%) in the presence or absence of the regio-enhancer [*t*-BuCN (2-5 equiv) + NaI (0.5-1 equiv)]. [b] Racemic substrates were used. [c] Ratios were determined by ^{1}H NMR (300 MHz) spectroscopy. [d] Ratio given in entry 7 is for the MOM ethers of **4a** and **5a**.



provided a similar ratio to the simple alkenylborates **3a** (entries 6 and 1). To check the influence of the free hydroxyl group present in **1**, coupling of the MOM ether of *rac*-**1** and borate **3a** was carried out under the same conditions. Comparable regio-selectivity and reactivity to that obtained with *rac*-**1** (entries 7 and 1) were observed. Different from the case of **1**, however, separation of both MOM isomers by chromatography was unsuccessful in our hand; thus we found no synthetic advantage to use of the MOM ether of **1**. In conclusion, the regio-enhancer actually raised the 1,3-/1,2-isomer ratio in the alkenyl coupling, as well as the preceding aryl borates. In addition, *a series of borates corresponding to the PG ω chain and its analogues showed an unexpectedly high level of selectivity*, which is much higher than that reported in the palladium-catalyzed coupling of cyclopentadiene monoepoxide and alkenylstannanes of similar alkenyl groups.[1] As for the monoacetate **1**, the hydroxyl group did not destroy the borates during the reaction and had no influence on the regioselectivity and reactivity.

An additional chiral center of the alkenylborates **3c–e** might be responsible for the highly regioselective production of **4c–e**. To clarify this, (15*S*)-stereoisomer (PG numbering) of **2c** was prepared from TBDMS ether of (*S*,*E*)-1-iodo-3-hydroxy-1-octene[6] (>99% ee) according to the procedure of Scheme 2 [(1) *n*-BuLi, -78 °C; $B(OPr\text{-}i)_3$, -78 °C → room temp.; NH_4Cl aqueous (78%); (2) 2,3-butanediol, $MgSO_4$ (74%)] and converted into (15*S*)-borate **3c** (*n*-BuLi, 0 °C, 15 min). Results of the coupling with (1*S*,3*R*)-**1**[2a,b] (>95% ee by MTPA method) and (1*R*,3*S*) -**1**,[2d,f] (95% ee) are shown in eqs 1 and 2, respectively. Somewhat higher ratios were observed for both combinations. These results and that of entry 6 of Table 1 indicate that the bulky silyloxy group worked cooperatively with the regio-enhancer. Product **9** is the enantiomerically enriched **4c**, the key intermediate of the PG_1 series,[5] while the diastereoisomer **11** was successfully transformed into **15** and **16** from which 11-deoxy PGE_2[7] and PGA_2[8] have been synthesized previously. Thus, Johnson-Claisen rearrangement of



Scheme 3

11 followed by hydrolysis afforded **13** which, upon iodolactonization with KI_3 and $NaHCO_3$, furnished lactone **14** in 47% yield from **11**. Finally, reaction of **14** with Bu_3SnH and AIBN furnished lactone **15** ($[\alpha]^{21}_D$ = +4.4 (*c* 0.95, $CHCl_3$) in 80% yield, while reaction with AgOAc afforded **16** ($[\alpha]^{21}_D$ = +159 (*c* 0.85, $CHCl_3$); lit.[8b] $[\alpha]^{22}_D$ = +161.5 (*c* 2.8, $CHCl_3$)) in 82% yield.

In summary, we confirmed that the regio-selective coupling reaction of **1** under the nickel catalyst in the presence of the regio-enhancer can be extended to alkenylborates **3**, among which the borates possessing the PG ω-chain structure showed high selectivity. Requirement of only a small excess of borates and easy separation of the 1,2-isomers, these synthetic advantages are also observed in the alkenyl coupling. Although precise rolls of *t*-BuCN and NaI are not yet elucidated, applicability of the regio-enhancer to a wide variety of aryl- and alkenylborates may suggest something new intermediates.[9,10] Studies concerning mechanistic aspect of the coupling are now under investigation.[11]

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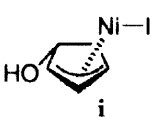
9. The regioselectivity might be explained by assuming a catalytic cycle involving a kinetically produced π-allyl-like intermediate such as **i**, in which nickel is near to the carbon which had OAc group: (1) formation of [Ni(0)-I]$^-$ from Ni(0) and iodide anion (cf. ref. 10); (2) reaction of [Ni(0)-I]$^-$ with acetate **1** to produce **i**; (3) ligand exchange of **i** with borate **3** and reductive elimination to furnish **4** and Ni(0) before changing into the thermodynamically stable π-allyl intermediate(s). Electron donating *t*-BuCN conceivably accelerates the above step(s).



i

10. Formation of [Pd(0)-X]$^-$ (X = Cl, Br, I): see, Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338-1339.
11. ^1H NMR (300 MHz, $CDCl_3$) data of **4a**: δ 0.90 (t, *J* = 7 Hz, 3 H), 1.1-1.5 (m, 7 H), 1.78-1.97 (m, 4 H), 3.47 (q, *J* = 7 Hz, 1 H), 4.85-4.91 (m, 1 H), 5.22 (ddt, *J* = 8, 15, 1 Hz, 1 H), 5.44 (dt, *J* = 15, 7 Hz, 1 H), 5.82 (br s, 2 H); **4b**: δ 0.91 (t, *J* = 7 H, 3 H), 1.2-1.5 (m, 6 H), 1.6 (br s, 1 H), 1.85 (ddd, *J* = 5, 7, 14 Hz, 1 H), 2.01 (ddd, *J* = 2.5, 8, 14 Hz, 1 H), 2.08 (dq, *J* = 1, 7 Hz, 2 H), 3.78-3.89 (m, 1 H), 4.86-4.94 (m, 1 H), 5.09 (tt, *J* = 1.5, 10 Hz, 1 H), 5.38 (ddt, *J* = 1, 10, 7 Hz, 1 H), 5.80 (dd, *J* = 2, 5.5 Hz, 1 H), 5.87 (dt, *J* = 2, 5.5 Hz, 1 H); **9**: δ - 0.003 (s, 3 H), 0.02 (s, 3 H), 0.87 (s, 12 H), 1.18-1.56 (m, 8 H), 1.6 (br s, 1 H), 1.82-2.04 (m, 2 H), 3.49 (q, *J* = 7 Hz, 1 H), 3.99 (q, *J* = 6 Hz, 1 H), 4.84-4.94 (m, 1 H), 5.35 (dd, *J* = 7, 15 Hz, 1 H), 5.42 (dd, *J* = 6, 15 Hz, 1 H), 5.86 (s, 2 H); **11**: δ -0.01 (s, 3 H), 0.01 (s, 3 H), 0.86 (s, 12 H), 1.20-1.56 (m, 8 H), 1.76 (br s, 1 H), 1.82-2.02 (m, 2 H), 3.46 (q, *J* = 6 Hz, 1 H), 3.99 (q, *J* = 7 Hz, 1 H), 4.83-4.92 (m, 1 H), 5.34 (dd, *J* = 7, 16 Hz, 1 H), 5.41 (dd, *J* = 6, 16 Hz, 1 H), 5.80-5.89 (m, 2 H).