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A novel C–C bond formation reaction with 1-methoxymethylindolylborate†

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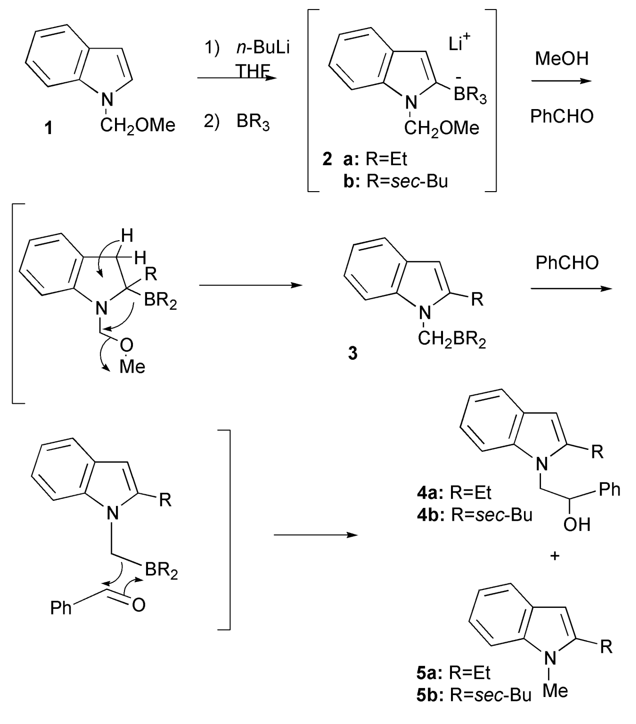
The reaction of 1-methoxymethylindolylborates 2 with electrophiles in the presence of benzaldehyde enabled the novel construction of tri-substituted indoles in a 'one-pot' procedure.

The intramolecular migration reaction of an alkyl group from boron to carbon is a familiar characteristic of organoboron chemistry,[1] with the intramolecular alkyl migration reaction in 1-methyltrialkylindolylborates leading to 2-alkyl-1-methylindoles being a prime example.[2] Another unique feature is boron isomerisation in organoboron compounds under thermal conditions,[3] which has been recently applied to the stereoselective construction of three adjacent carbon stereocenters.[4] During our continuing studies of indolylborate chemistry,[5] we have previously reported the formation of 2-alkyl-1-methylindoles **5** from the reaction of 1-methoxymethylindolylborates **2** with MeOH, in which the intermediary formation of alkylboranes **3** through a novel cascade of alkyl–boryl migration steps was taken as the key reaction feature.[6] To our knowledge, such a cascade of alkylboryl migration processes has hitherto been unknown. Thus, we were intrigued by the idea as to whether operation of **3** in ordinary organoboron chemistry might enable the construction of more elaborate indole derivatives in a novel 'one-pot' procedure from **1**.



Scheme 1

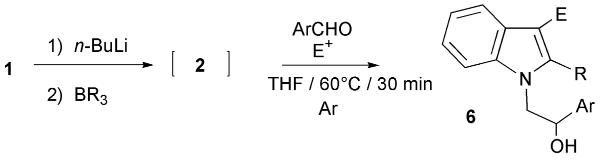
Table 1 Reaction of **2** with MeOH and benzaldehyde

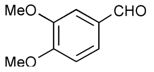
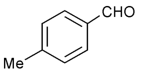
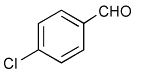
R	MeOH (equiv.)	PhCHO (equiv.)	Yield (%)[a]	
			4	**5**
Et	1.5	1.5	49	10
	1.5	2.0	58	10
	2.0	2.0	52	5
	2.0	3.0	49	8
sec-Bu	1.5	2.0	15	40

[a] All yields are based on **1**.

Therefore, we undertook the reaction of *in situ* generated **3** with benzaldehyde as an initial experiment. Methanol and benzaldehyde were added to a THF solution of **2**, generated from **1** *in situ*, at 0 °C, and the mixture was then gradually warmed to room temperature and stirred for 20 h (Scheme 1). This was found to provide alcohol **4** along with the formation of a small amount of 2-alkyl-1-methylindole **5** from **1** in a 'one-pot' manner (Table 1). The reaction outcome could be rationalized by the steps in a queuing cascade as shown in Scheme 1; (1) initial protonation at the C3 of the indole ring in **2** promotes alkyl migration from the boron to the C2 of the indole ring, (2) boron migration leads to **3**, and (3) subsequent C–C bond formation between the C–B bond of **3** and benzaldehyde provides **4**.

Table 2 Reaction of **2** with electrophiles and substituted benzaldehydes



R	ArCHO	Condition[a]	Yield (%) of **6**[b]
Et	PhCHO	A	65% (**6a**) E = $–CH_2CH{=}CH_2$
	PhCHO	B	65% (**6a**) E = $–CH_2CH{=}CH_2$
		B	30% (**6b**) E = $–CH_2CH{=}CH_2$
		B	50% (**6c**) E = $–CH_2CH{=}CH_2$
		B	60% (**6d**) E = $–CH_2CH{=}CH_2$
sec-Bu	PhCHO	B	53% (**6e**) E = $–CH_2CH{=}CH_2$[c]
Et	PhCHO	C	20% (**6f**) E =
Et	PhCHO	D	27% (**6g**) E =[c]
sec-Bu	PhCHO	D	45% (**6h**) E =

[a] Condition; A: allyl bromide, B: $PdCl_2(Ph_3P)_2$ (0.05 equiv.)–allyl acetate, C: $PdCl_2(Ph_3P)_2$ (0.05 equiv.)–butadiene monoxide, D: $Pd_2(dba)_3·CHCl_3$ (0.05 equiv.) + Ph_3P (0.2 equiv.)–methyl 4-bromocrotonate. [b] Yields are based on **1**. [c] Two diastereoisomers in a 1 : 1 ratio.

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† Electronic supplementary information (ESI) available: selected spectral data for compounds **4a**, **6a**, **6e** (a pair of diastereoisomers) and **6g**. See http://www.rsc.org/suppdata/cc/b1/b109880b/

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Simply heating a mixture of **2a** with allyl bromide and benzaldehyde in THF under an argon atmosphere at 60 °C for 0.5 h provided **6a** in 65% yield.

This initial success led to the examination of the further reaction of **2** with π–allyl palladium complexes, as electrophiles, in the presence of substituted benzaldehydes (Table 2). First, allyl acetate (2 equiv.) in the presence of a catalytic amount of $PdCl_2(Ph_3P)_2$ was subjected to reaction with **2** in the presence of substituted benzaldehydes (2 equiv.) to produce **6a–e**, in which the reaction of **2a** using 3,4-dimethoxybenzaldehyde produced **6b** in lower yield. Also, the palladium catalyzed reaction of **2** with butadiene monoxide and methyl 4-bromocrotonate in the presence of benzaldehyde at 60 °C for 30 min afforded **6f–h**, respectively. The reaction of **2b** with π–allyl palladium complexes and benzaldehyde afforded **6e** and **6h**, as a pair of diastereoisomers in a 1 : 1 ratio.

We have demonstrated, though preliminary experiments, the first examples of a 'one-pot' procedure for the formation of substituted indoles **4** and **6** based on the reaction of indolylborates **2**, generated *in situ* from **1**, with electrophiles and benzaldehydes. The alkylborane intermediates **3**, stemming from the novel cascade of intramolecular alkyl–boryl migration steps in **2**, can be considered to be useful synthetic intermediates, and we are currently exploring this chemistry for the preparation of more elaborate indoles in a 'one-pot' manner.

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