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Baylis–Hillman chemistry: a one pot cross-coupling/allylboration reaction

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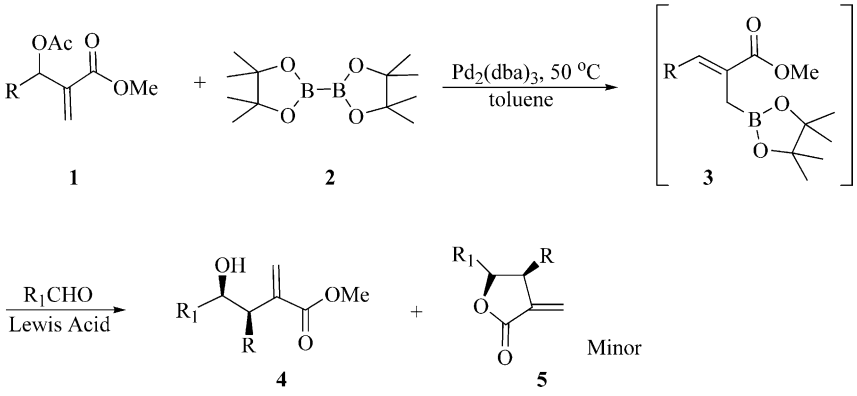
Abstract—A one pot sequential cross-coupling/allylboration is described. Baylis–Hillman acetate adducts couple with bis(pinacolato)diboron to form substituted allylboronates, which react with aldehydes in the presence of a silica supported BF_3 catalyst to form highly functionalized homoallylic alcohols in excellent yields.

The allylboration reaction is used in numerous synthetic applications.[1] Allylboron reagents are useful because they can be used to generate homoallylic alcohols in high yields and with excellent stereoselectivity via six-membered cyclic chair transition states.[2] However, allylboron reagents can be moisture sensitive and substituted allylboronates are unreactive.[3]

In a continuation of studies involving organoboron reactions,[4] we recently reported the cross-coupling reaction of Baylis–Hillman[5] adducts **1** and bis(pinacolato)diboron, **2**, in the presence of a palladium catalyst to produce 3-substituted-2-alkoxycarbonyl allylboronates **3**.[6] The new reaction is unique in that additional base or ligand is not required. The yields of the reaction are good but some loss is experienced due to the moisture sensitivity of the allylboronate intermediates. This study was initiated in an effort to maximize product yields by avoiding isolation of the sensitive boron intermediates using a one-pot protocol (Scheme 1).

In a preliminary study using *p*-nitrobenzaldehyde, the reaction successfully produced the corresponding homoallylic alcohols (Table 1, entry 1). However the synthesis required relatively long reaction times because of the low reactivity of the intermediate allylboronates due to



Scheme 1.

Keywords: Baylis–Hillman; Allylboration; Boronate esters; Cross-coupling.
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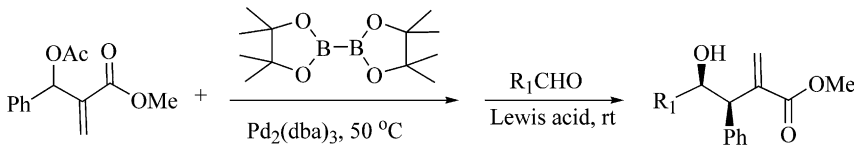
Table 1. Synthesis of homoallylic alcohols from various aldehydes and Baylis–Hillman adducts[a]



Entry	R	Time (h)	Yield[b] (%)
1	*p*-Nitrophenyl	192	74[c]
2	*p*-Nitrophenyl	62	48[d]
3	*p*-Nitrophenyl	48	81[e]
4	*p*-Nitrophenyl	24	83
5	*p*-Trifluoromethylphenyl	24	84[f]
6	Phenyl	48	67
7	*p*-Methoxyphenyl	48	62[c,g]
8	*p*-Cyanophenyl	20	81[f]
9	*p*-Chlorophenyl	24	78
10	Pentafluorophenyl	24	87

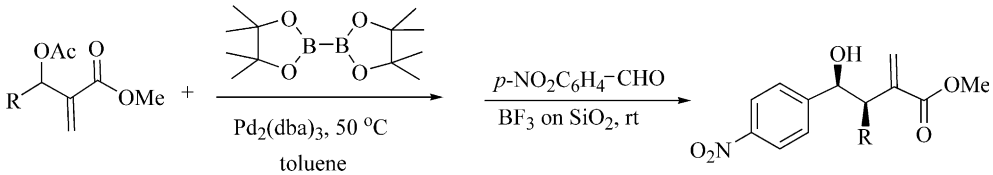
[a] Unless otherwise noted, silica supported BF_3 (100 mg) was used as the Lewis acid.
[b] Isolated yield.
[c] No Lewis acid used.
[d] $Sc(OTf)_3$ (10 mol %) was used.
[e] $BF_3{\cdot}Et_2O$ (30 mol %) was used.
[f] 7% and 12% of corresponding cyclized product **5** was isolated in entries 5 and 8, respectively.
[g] Reaction temperature was 90 °C.

the low nucleophilicity of these reagents.[7] Several reports have appeared describing Lewis acid catalyzed addition reactions involving allylsilanes, allyltin reagents, and more recently allylboron reagents.[8,9] Consequently, we examined the effect of various Lewis acids on the new in situ allylboration reaction. Kennedy and Hall observed that $Sc(OTf)_3$ was effective in accelerating allylboration reactions, but the effect was modest in this case (Table 1, entry 2). We did find that $BF_3{\cdot}Et_2O$ was a useful catalyst. To increase the utility of the reaction, a solid Lewis acid (silica supported BF_3) was prepared and used. This easily handled, heterogenous catalyst[10] can easily be prepared from readily available materials.

In a typical reaction, the corresponding Baylis–Hillman acetate adduct **1** (1 mmol) and bis(pinacolato)diboron, **2**, (1.1 mmol) were dissolved in toluene. The palladium catalyst (3 mol %) was then added and the mixture stirred for 3 h under a nitrogen atmosphere at 50 °C. [For Baylis–Hillman adducts derived from aliphatic aldehydes, the time was increased to 6 h.] After cooling to 0 °C, the aldehyde (1.2 mmol) and silica supported BF_3 catalyst[11] (100 mg) were added and the mixture stirred at room temperature for the indicated time. The mixture was then filtered to remove the solid catalyst. The filtrate was concentrated under reduced pressure and homoallylic alcohol **4** was isolated by silica gel chromatography using hexane/ethyl acetate as eluent.

The results demonstrate that substituents on the aromatic ring of the aldehyde play an important role. The presence of an electron-withdrawing group increases the reaction yields whereas electron-donating groups decrease the yields. *p*-Methoxybenzaldehyde produced

Table 2. Synthesis of homoallylic alcohols from various Baylis–Hillman adducts and *p*-nitrobenzaldehyde[a]



Entry	R	Time (h)	Yields[b] (%)
1	*p*-Tolyl	24	80
2	*p*-Chlorophenyl	24	73
3	*p*-Methoxyphenyl	24	84
4	1-Naphthyl	36	68
5	*o*-Chlorophenyl	24	69
6	2-Furyl	24	56
7	Octyl	20	64

[a] Silica supported BF_3 (100 mg) was used as the Lewis acid.
[b] Isolated yield.

trace amounts of the corresponding homoallylic alcohol at room temperature but acceptable yields were obtained when the reaction was carried out at 90 °C (Table 1, entry 7). In some cases a minor amount of cyclized product **5** was formed (Table 1, entries 5 and 8), however, it is easily separated from the desired product using column chromatography.

Several reactions were carried out using Baylis–Hillman adducts **1** derived from reactions of aromatic, heteroaromatic, and aliphatic aldehydes with *p*-nitrobenzaldehyde (Table 2). Baylis–Hillman adducts derived from aromatic aldehydes gave very high yields of the corresponding homoallylic alcohols. Heteroaromatic (Table 2, entry 6). Aliphatic aldehydes (Table 2, entry 7) also produced good yields. Steric factors were found to affect the reaction yields. For example, Baylis–Hillman adducts derived from 1-napthaldehyde and *ortho*-chlorobenzaldehyde produced somewhat lower yields (Table 2, entries 4 and 5). The homoallylic alcohols **4** formed as the syn isomers. The stereochemistry was determined by converting the homoallylic alcohol obtained from the phenyl derivative (Table 1, entry 6) into the corresponding known cyclized product **5** and comparing the spectral data with those reported in the literature.[12,13] Cyclization was achieved under mild acid conditions (PTSA, CH_2Cl_2) at room temperature.

In conclusion, an efficient and mild synthetic method for preparing highly functionalized homoallylic alcohols **4** from Baylis–Hillman acetate adducts **1** has been developed. A solid Lewis acid, silica supported BF_3, effectively catalyzes the allylboration reaction. The experimental procedure is simple and the conversion occurs at room temperature. The catalytic reaction proceeds with a remarkably high regio- and stereo selectivity.

Acknowledgements

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13. The NMR data for 4-hydroxy-2-methylene-3,4-diphenylbutyric acid methyl ester (Table 1, entry 6): ^{1}H NMR ($CDCl_3$): δ 7.35–7.24 (m, 10H), 6.23 (s, 1H), 5.81 (s, 1H), 5.26 (d, J = 7 Hz, 1H); 4.31 (d, J = 7 Hz, 1H), 3.56 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.9, 147.4, 142.0, 141.0, 138.6, 129.2, 128.5, 128.2, 127.8, 127.2, 127.0, 126.8, 75.7, 54.3, 51.9. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.28, H, 6.32.