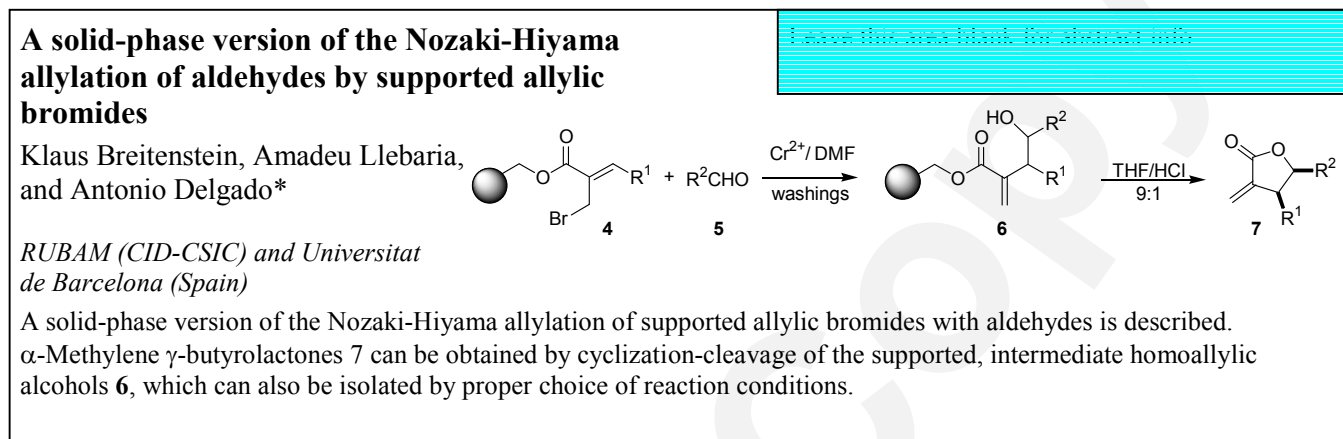


## Graphical Abstract

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Review

# A solid-phase version of the Nozaki-Hiyama allylation of aldehydes with supported allylic bromides

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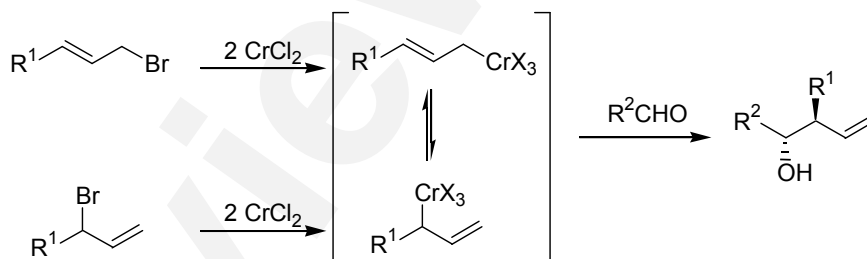
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**Summary:** A solid-phase version of the Nozaki-Hiyama allylation of supported allylic bromides with aldehydes is described.  $\alpha$ -Methylene  $\gamma$ -butyrolactones **7** can be obtained by cyclization-cleavage of the supported intermediate homoallylic alcohols **6**.

**Keywords:** allylation, chromium, solid phase, lactones.

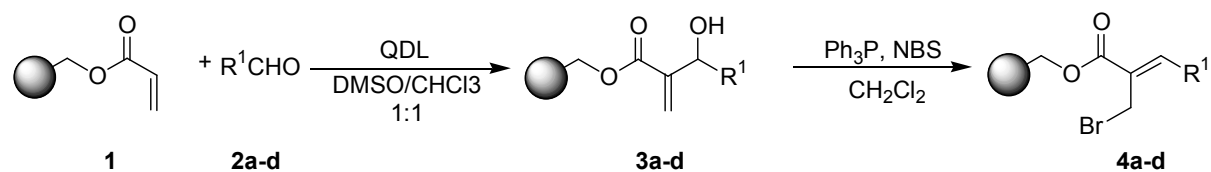
Over the last few years, combinatorial chemistry has emerged as a powerful tool in organic synthesis. As a result, the development of new methodology as well as the adaptation of already existing ones to make them amenable to parallel synthesis has become a very active research topic.<sup>1</sup> Solid phase synthesis is still one of the methods of choice when planning a combinatorial approach, due mainly to the easy separation of reagents and the immobilized substrate during the workup process.<sup>2</sup>

In the course of our research on new aldehyde allylation protocols,<sup>3-6</sup> we were interested in the development of a solid phase version of the well known Cr-promoted Nozaki-Hiyama reaction (Scheme 1).<sup>7</sup>



Scheme 1. Stereo- and regioselectivity of the Nozaki-Hiyama reaction

Allylic halides **4a-d** were chosen as suitable models to test our solid phase approach. They were synthesized from acrylic acid PS-Wang resin **1**<sup>8,9</sup> and aldehydes **2a-d** by a combination of Baylis-Hillman reactions<sup>10</sup> followed by allylic bromination (NBS, Ph<sub>3</sub>P, CH<sub>2</sub>Cl<sub>2</sub>)<sup>11</sup> of the intermediate alcohols **3a-d**<sup>12</sup> (Scheme 2).

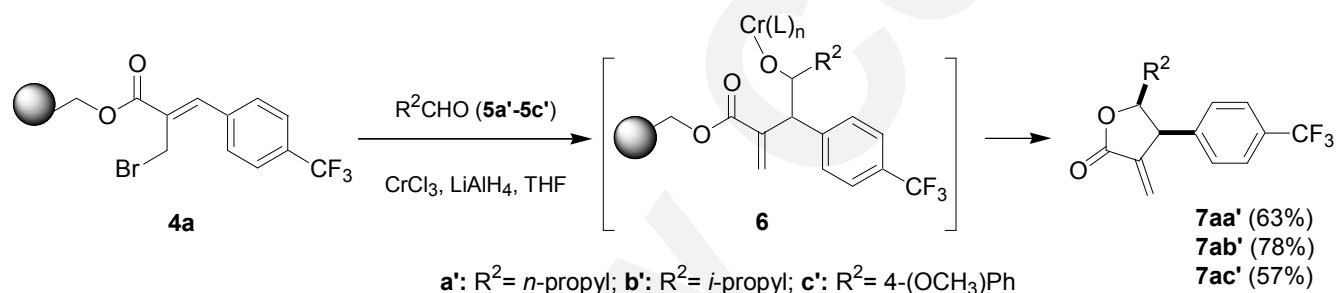


QDL: 3-Quinuclidinol; **a**:  $R^1 = 4-(CF_3)Ph$ ; **b**:  $R^1 = 4-(F)Ph$ ; **c**:  $R^1 = Ph$ ; **d**:  $R^1 = n\text{-propyl}$

Scheme 2. Synthesis of solid-supported allylic bromides **4a-d**

As also observed in control reactions in the solution phase, bromination took place with allylic rearrangement. However, the regioselectivity of this step was not essential for the overall process, due to the well-known regioconvergence of the Nozaki-Hiyama allylation reaction (see Scheme 1).<sup>7</sup>

With allylic halides **4a-d** in hand, we carried out the Nozaki-Hiyama reaction by condensation of **4a** in THF with different aldehydes in the presence of *in situ* generated  $Cr^{2+}$  (freshly prepared from  $CrCl_3$  and  $LiAlH_4$  in THF), following a classical procedure (Scheme 3).<sup>13,14</sup>

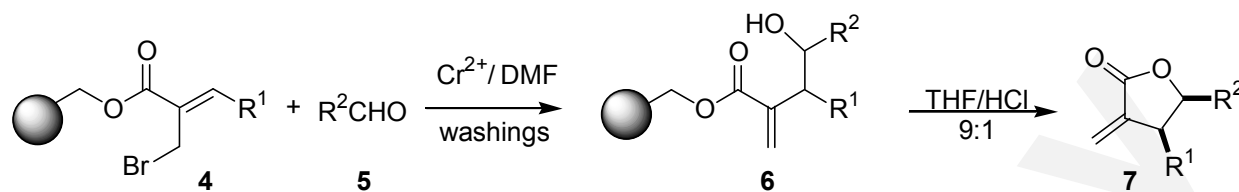


Scheme 3. Reaction of solid-supported **4a** with different aldehydes in the presence of *in situ* generated  $Cr^{2+}$  in THF (for experimental details, see ref 14)

Under these conditions, “premature” cleavage of adducts **6** was observed, since the putative homoallylic alcohol intermediates spontaneously underwent intramolecular transesterification-cleavage to give the corresponding *syn* lactones **7aa'-7ac'** as the only products.<sup>15,16</sup> However, this drawback could be avoided by carrying out the allylation directly with  $CrCl_2$  in DMF.<sup>17,18</sup> Under these experimental conditions, no lactones were detected in the filtrates. Moreover, although traces of Cr by-products were present in the washed resins, these could be properly characterized by gel-phase <sup>13</sup>C NMR, where the resonance peak at around 25 ppm of the starting  $CH_2Br$  group was no longer present and resonances attributable to the  $R^2$  side chains could be observed. A series of resin-bound allylic alcohols **6** were obtained in this way (Table 1). In order to test the reactivity of resin bound allylic alcohols **6**, cyclization-cleavage to lactones **7** was investigated for comparative purposes. After several unsuccessful attempts under basic conditions ( $KOtBu$ ) or in the presence of a Lewis acid ( $BF_3 \cdot Et_2O$ ), treatment with THF/conc.HCl mixture (9:1) afforded lactones **7**,<sup>17</sup> albeit in lower yields than in the “one-pot” protocol depicted in Scheme 3 (compare with entries 1-3, Table). However, despite the lower overall yields, this

two-step protocol has the advantage of keeping the allylation adducts **6** anchored on the solid support for further synthetic manipulations.

Table 1



entry	Resin	R <sup>1</sup>	Aldehyde	R <sup>2</sup>	Lactone	Yield(a)
1	4a	4-(CF <sub>3</sub> )Ph	5a'	<i>n</i> -propyl	7aa'	48
2	4a	4-(CF <sub>3</sub> )Ph	5b'	<i>i</i> -propyl	7ab'	51
3	4a	4-(CF <sub>3</sub> )Ph	5c'	4-(CH <sub>3</sub> O)Ph	7ac'	42
4	4b	4-(F)Ph	5a'	<i>n</i> -propyl	7ba'	45
5	4b	4-(F)Ph	5c'	4-(CH <sub>3</sub> O)Ph	7bc'	31
6	4b	4-(F)Ph	5d'	allyl	7bd'	36
7	4c	Ph	5a'	<i>n</i> -propyl	7ca'	42
8	4c	Ph	5c'	4-(CH <sub>3</sub> O)Ph	7cc'	37
9	4c	Ph	5d'	allyl	7cd'	54
10	4d	<i>n</i> -propyl	5a'	<i>n</i> -propyl	7da'	35
11	4d	<i>n</i> -propyl	5c'	4-(CH <sub>3</sub> O)Ph	7dc'	35
12	4d	<i>n</i> -propyl	5d'	allyl	7dd'	41

(a) overall yield from resin **4**

In summary, a solid-phase version of the Nozaki-Hiyama allylation of allylic bromides with aldehydes is presented. Although  $\alpha$ -methylene  $\gamma$ -butyrolactones **7** are formed in acceptable yields by spontaneous cyclization-cleavage from the resin, the intermediate supported homoallylic alcohols **6** can be isolated by proper choice of conditions. Further studies to exploit the synthetic potential of resins **6** will be addressed in the near future and will be reported elsewhere.

### Acknowledgment

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10. General procedure for the Baylis-Hillman reaction: 1.54 g of resin **1**<sup>9</sup> (1.0 mmol/g) was suspended in 13.5 ml of DMSO/CHCl<sub>3</sub> (1:1 mixture) in a 25 ml screw-cap bottle. 3-Quinuclidinol (QDL, 574 mg, 4.51 mmol) was weighed directly into the bottle followed by 7.50 mmol of aldehyde **2a-d**. The bottle was capped and agitated for cycles of 24 h by mounting it on an incubation tube rotor. After each cycle the reagent solution was removed by inverse filtration and the resin was washed successively with DMSO/CHCl<sub>3</sub> 1:1, MeOH, and DMSO/CHCl<sub>3</sub> 1:1. At the end of the reaction, the reagent mixture was removed by filtration, the resin was washed successively with DMF, MeOH, DMA, CH<sub>2</sub>Cl<sub>2</sub>, and MeOH on a filter funnel, and dried under vacuum. The approximate loading was estimated based on resin weight increase. Aldehydes **2a-d** required 3 cycles for complete reaction, weight increase of resins **3a-d** was higher than 98 % of the theoretical loading. For a similar protocol and a general overview of Baylis-Hilman reactions, see: Patra, A.; Roy, A. K.; Joshi, B. S.; Roy, R.; Batra, S.; Bhaduri, A. P. *Tetrahedron* **2003**, *59*, 663-670, and references therein.
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13. See reference 7a.
14. General procedure for Nozaki-Hiyama reaction of **4a** with aldehydes **5a'-5c'** with *in situ* cyclization-cleavage: A solution of aldehyde **5** (1 mmol) in THF (6 ml) was added to resin **4a** (285 mg, approximate loading 0.80 mmol/g) in 1 ml THF. The slurry was treated with the previously formed Cr<sup>2+</sup> salt, prepared as described in ref 7a. After agitating at rt for 18h, the resin was successively washed with THF, MeOH and CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were evaporated to dryness and the residue was flash chromatographed (hexanes/Et<sub>2</sub>O 4:1) to give lactones **7** (see Scheme 3). **7aa'**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 0.75 (t, 3H); 0.95 (m, 2H); 1.15 (m, 1H); 1.40 (m, 1H); 4.34 (dt, 1H, *J*=7.8; *J'*=2.5); 4.67 (m, 1H); 5.54 (d, 1H, *J*=2.4); 6.41 (d, 1H, *J*=2.4); 7.21 (d, 2H, *J*=7.7); 7.56 (d, 2H, *J*=7.7); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): 13.5 (CH<sub>3</sub>), 19.0 (CH<sub>2</sub>), 34.4 (CH<sub>2</sub>), 49.1 (CH), 80.9 (CH), 123.8 (CF<sub>3</sub>), 124.7 (CH<sub>2</sub>), 125.6 (CH), 129.3 (CH), 129.8 (C-CF<sub>3</sub>), 138.7 (C<sub>q</sub>), 141.8 (C<sub>q</sub>), 169.9 (CO); **7ab'**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 0.67 (d, 3H, *J*=6.6 Hz); 1.02 (d, 3H, *J*=6.6 Hz); 1.58 (m, 1H); 4.23 (m, 2H); 5.58 (d, 1H, *J*=1.6); 6.35 (d, 1H, *J*=1.6); 7.28 (d, 2H, *J*=8.1); 7.57 (d, 2H, *J*=8.1); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): 18.0 (CH<sub>3</sub>); 18.3 (CH<sub>3</sub>); 28.7 (CH); 48.9 (CH); 86.7 (CH); 123.9 (CF<sub>3</sub>); 124.2 (CH<sub>2</sub>); 125.7 (CH); 128.9 (CH); 130.1 (C-CF<sub>3</sub>); 140.2 (C<sub>q</sub>); 142.8 (C<sub>q</sub>); 170.1 (CO); **7ac'**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 3.65 (s, 3H); 4.68 (dt, 1H, *J*=8.2, *J'*=2.8); 5.56 (1H, d, *J*=2.8); 5.81 (d, 1H, *J*=8.2); 6.53 (1H, d, *J*=2.8); 6.63 (m, 2H); 6.71 (m, 2H); 6.86 (d, 2H, *J*=7.9); 7.34 (d, 2H, *J*=7.9); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): 51.7 (CH); 55.2 (CH<sub>3</sub>); 82.0 (CH); 113.6 (CH); 124.2 (CF<sub>3</sub>); 125.1 (C-CF<sub>3</sub>); 125.3 (CH); 127.1 (CH); 129.7 (CH); 137.6 (C<sub>q</sub>); 140.7 (C<sub>q</sub>); 159.5 (C<sub>q</sub>); 170.3 (CO).
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16. The Cr catalytic version of the Nozaki-Hiyama reaction (Furstner, A.; Shi, N. Y. *J. Am. Chem. Soc.* **1996**, *118*, 12349-12357) was tried in order to prevent spontaneous cyclization-cleavage by trapping the reactive Cr-alkoxide intermediate as the corresponding silyl ether. Unfortunately, all attempts were unsuccessful and lactones **7** were also obtained from the filtrates in high yields.
17. General procedure for the synthesis of resins **6** and lactones **7** from Nozaki-Hiyama reaction of resins **4** with aldehydes **5**: Anhydrous CrCl<sub>2</sub> (200 mg, 1.63 mmol) was added portionwise under a stream of Ar over a slurry of resin **4** (200 mg, approximate loading 0.80 mmol/g) in dry DMF (10 ml). After agitating at rt for 18 h, the resin was washed with DMF, MeOH, and CH<sub>2</sub>Cl<sub>2</sub> (3 cycles) and dried under vacuum. Resins **6** were checked by <sup>13</sup>C NMR (see text) and their loadings (weight gain) were estimated between 0.75 and 0.80 mmol/g, depending on the resin. Resins were stirred in a mixture of THF/2*N* HCl (9:1) for 30 min at rt and washed with CH<sub>2</sub>Cl<sub>2</sub> and MeOH. The combined filtrates were evaporated and the remaining residues were flash-chromatographed (hexanes/Et<sub>2</sub>O 4:1) to give lactones **7** (see Table).
18. The use of CrCl<sub>2</sub> to avoid spontaneous lactonization has already been reported (see ref 15c).