



Carbohydrates in asymmetric synthesis: enantioselective allylation of aldehydes

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ABSTRACT

An enantioselective metal-mediated addition of allylic bromides to carbonyl compounds was achieved in the presence of the inexpensive and easily accessible carbohydrates saccharose and β -cyclodextrin. The desired products were obtained in moderate to excellent yields and with up to 93% enantiomeric excess.

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The synthesis of enantiomerically enriched homoallylic alcohols is an important goal in organic synthesis. This is mainly because homoallylic alcohols are versatile intermediates that can be converted to a wide variety of synthetically useful compounds.¹ In this context, the enantioselective allylation of aldehydes plays a major role in the field, and many different systems have been developed to achieve this goal.² For example, chiral Lewis acids based on metals such as Ti,³ In,⁴ B,⁵ Cr,⁶ and Rh⁷ have proven to afford homoallylic alcohols in high ee's.

On the other hand, carbohydrates and their derivatives have recently emerged as an important tool for stereoselective synthesis and as a chiral pool for the design of chiral ligands. Carbohydrates are particularly useful in this context, mainly due to their availability, several stereocenters, and weak coordination sites.^{8,9} However, despite all these new advances, the application of simple carbohydrates in stereoselective synthesis is still scarcely studied.

Herein, we wish to disclose our results in the enantioselective allylation of aldehydes, using simple, inexpensive, and readily available carbohydrates, for example, saccharose **1** and β -cyclodextrin **2** as chiral promoters for the enantioselective addition of in situ generated allylmetal reagents to aldehydes (Fig. 1).

Our survey has started by choosing benzaldehyde as the aldehyde of choice for optimization studies.¹⁰ A number of reaction conditions were examined, and the results are depicted in Table 1. When the reaction was carried out in the presence of different amounts of saccharose **1** as the chiral promoter and zinc powder as the metal, at room temperature, only moderate results were achieved for the desired homoallylic alcohol, even when **1** was used in up to 2 equiv (entries 1–4). Lowering the reaction temperature to 0 °C showed some improvement in the ee of **4**. For example, when the reaction was carried out using 1.2 equiv of **1**, the ee

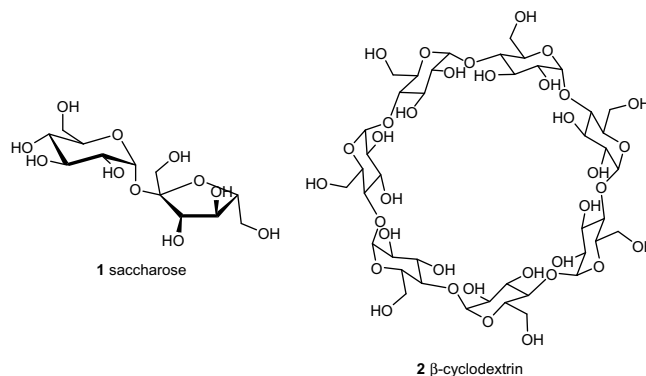


Figure 1. Structures of saccharose and β -cyclodextrin.

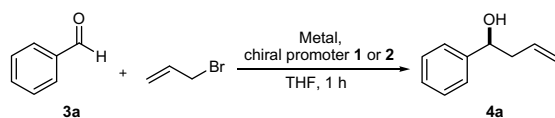
of the product had increased to 55%, although the yield was still low (entry 6). Next, we sought to examine the influence of the metal in the reaction outcome; and indium and tin were used in the enantioselective allylation, in the presence of 1.2 equiv of saccharose. When indium was used, quite disappointing results were achieved, since the homoallylic alcohol was obtained in low yield and negligible enantiomeric excess (entry 8). On the other hand, tin has proved to be much more efficient, furnishing product **4** in 71% ee when the reaction was carried out at room temperature and in 81% ee when the temperature was reduced to 0 °C (entries 9–10).

Furthermore, β -cyclodextrin **2** was also examined as the chiral promoter for the allylation of benzaldehyde (entries 11–16). Quantities of 0.5 and 1.0 equiv of **2** were used in the presence of zinc, indium, or tin as the metal. Again, indium furnished disappointing result with very low conversion and ee. When tin was used as the metal, the product was obtained in high yields, but with almost no enantioselectivity. Gratifyingly, when zinc was employed, better

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Table 1
Allylation of benzaldehyde in the presence of carbohydrate **1** or **2**



Entry	Promoter (equiv)	Metal	Temperature (°C)	Yield ^a (%)	ee ^b (%)
1	1 (0.5)	Zn	rt	15	11
2	1 (1.0)	Zn	rt	14	14
3	1 (1.2)	Zn	rt	23	21
4	1 (2.0)	Zn	rt	18	28
5	1 (1.0)	Zn	0	28	41
6	1 (1.2)	Zn	0	26	55
7	1 (2.0)	Zn	0	17	42
8	1 (1.2)	In	rt	14	3
9	1 (1.2)	Sn	rt	19	71
10	1 (1.2)	Sn	0	25	81
11	2 (0.5)	Zn	rt	17	62
12	2 (1.0)	Zn	rt	56	70
13	2 (0.5)	Zn	0	36	90
14	2 (1.0)	Zn	0	36	23
15	2 (0.5)	Sn	0	84	5
16	2 (0.5)	In	0	8	11

Absolute configuration *R* was determined by comparison with the Ref. 11.

^a Yields determined by GC.

^b Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column.

results were achieved and an ee of 90% of **4** was obtained in the presence of 1 equiv of **2**, at 0 °C (entry 13).

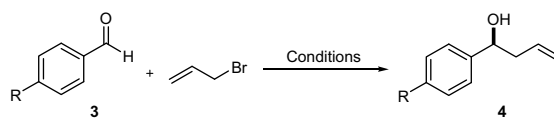
Worth to mention is that no special conditions such as inert atmosphere or dried solvents are required for the allylation reaction, since all reactions were carried out in an open vessel, using ACS grade THF. The only special care that must be taken in consideration is regarding the reaction time, since a decrease in the ee was observed when the reaction was maintained for 4 h, in an attempt to increase the yield of product **4**.

After all the experimentation described in Table 1, we decided to extend the study to a broader range of substituted aromatic aldehydes and we choose to evaluate those conditions that furnished the best results for the allylation of benzaldehyde, which are using **1** (1.2 equiv) as the chiral promoter and either zinc (condition **A**) or tin (condition **B**) as the metal, and using **2** (1.0 equiv) and zinc as the metal (condition **C**).

Thus, the reaction was first performed using saccharose as the agent responsible for the chiral induction, under conditions **A** and **B** (Table 2). With condition **A**, using zinc as the metal, high levels of enantioselection were achieved with *p*-anisaldehyde and *p*-chlorobenzaldehyde, although the yield for the former was only moderate, while for the latter very good conversion was observed (entries 1 and 3). Reaction with *p*-tolualdehyde resulted in somewhat lower ee of the corresponding product (entry 2). By changing to conditions **B**, that used tin as the metal, only moderate yields and enantioselectivity were observed for all aldehydes tested (entries 4–6). On the other hand, the employment of condition **C**, with β -cyclodextrin **2** as the chiral agent and zinc as metal, a very high ee of 93% was achieved by reaction with *p*-anisaldehyde, in 91% yield (entry 7). Lower levels of enantioselectivity were achieved with *p*-chloro- and *p*-tolualdehyde (72% and 63%, respectively; entries 8 and 9).

In conclusion, we have described the enantioselective allylation of substituted benzaldehydes in the presence of simple, inexpen-

Table 2
Enantioselective allylation of substituted benzaldehydes



Entry	Condition ^a	Metal	R	Yield ^b (%)	ee ^c (%)
1	A	Zn	OMe	60	87
2	A	Zn	Me	70	75
3	A	Zn	Cl	88	85
4	B	Sn	OMe	67	16
5	B	Sn	Me	61	66
6	B	Sn	Cl	81	68
7	C	Zn	OMe	91	93
8	C	Zn	Me	67	72
9	C	Zn	Cl	75	63

Absolute configurations *R* were determined by comparison with the Ref. 11.

^a Condition **A**: saccharose (1.2 equiv), Zn (1 equiv); condition **B**: saccharose (1.2 equiv), Sn (1 equiv); condition **C**: β -cyclodextrin (1 equiv), Zn (1 equiv).

^b Yields determined by GC.

^c Enantiomeric excesses were determined by chiral HPLC on a Chiralcel OD column.

sive, and readily available carbohydrates. The reaction proceeds in short reaction times, under simple operational conditions; and the homoallylic alcohols are obtained in useful levels of enantiomeric excess.

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References and notes

- (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701; (b) Hornberger, K. R.; Hamblet, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894; (c) Felpin, F. X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192; (d) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243; (e) de Fátima, A.; Pilli, R. A. *Tetrahedron Lett.* **2003**, *44*, 8721.
- For reviews, see: (a) Denmark, S. E.; Fu, J.-P. *Chem. Rev.* **2003**, *103*, 2763; (b) de Fátima, A.; Robello, L. G.; Pilli, R. A. *Química Nova* **2006**, *29*, 1009.
- Kii, S.; Maruoka, K. *Tetrahedron Lett.* **2001**, *42*, 1935.
- (a) Lu, J.; Ji, S.-J.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 159; (b) Teo, Y. C.; Tan, K.-T.; Loh, T. P. *Chem. Commun.* **2005**, 1318; (c) Haddad, T. D.; Hirayama, L. C.; Taynton, P.; Singaram, B. *Tetrahedron Lett.* **2008**, *49*, 508.
- Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.
- Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248.
- Padwa, A.; Wang, Q. *J. Org. Chem.* **2006**, *71*, 7391.
- (a) Diéguez, M.; Pàmies, O.; Ruiz, A.; Díaz, Y.; Castellón, S.; Claver, C. *Coord. Chem. Rev.* **2004**, *248*, 2165; (b) Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Rev.* **2004**, *104*, 3189.
- (a) Diéguez, M.; Claver, C.; Pàmies, O. *Eur. J. Org. Chem.* **2007**, 4621; (b) Boysen, M. M. K. *Chem. Eur. J.* **2007**, *13*, 8648–8659.
- Typical experimental procedure*: To a 25 mL round-bottomed flask were added saccharose (0.1–5.0 mmol), zinc powder (1.2 mmol), allyl bromide (1.2 mmol), benzaldehyde (1.0 mmol), and the solvent (6 mL). The mixture was stirred vigorously for 1 h at room temperature, and quenched with 4 mL of a dilute HCl solution. The aqueous layer was extracted with hexane (10 mL \times 3). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum to afford the homoallylic alcohol.
- Denmark, S. E.; Coe, D. M.; Pratt, N. P.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.