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(2-Benzyloxyphenyl)acetyl (BnPAc): A Participating Relay Protecting Group for Diastereoselective Glycosylation and the Synthesis of 1,2-*trans* Glycosyl Esters

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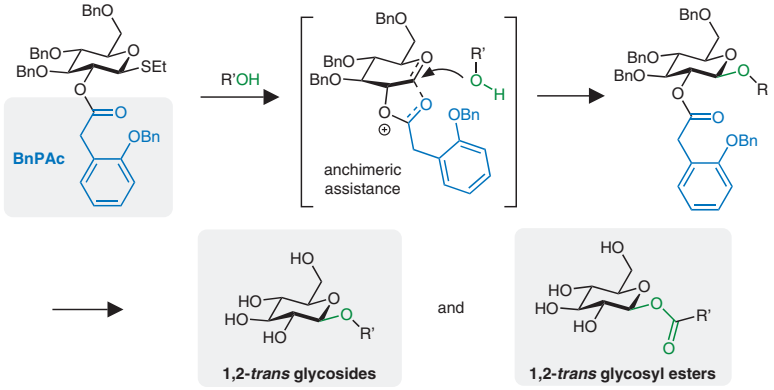

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Abstract The (2-benzyloxyphenyl)acetyl group has been identified as a new protecting group for hydroxyl functions. Various alcohols could be easily protected with high yields, and deprotection was achieved by a relay approach using Pd/H_2 in combination with 1,8-bis(dimethylamino)naphthalene, conditions that are orthogonal to ester groups. The new protecting group is stable in glycosylation reactions demonstrating an effective neighboring group participation leading to the exclusive formation of 1,2-*trans* glycosides and glycosyl esters.

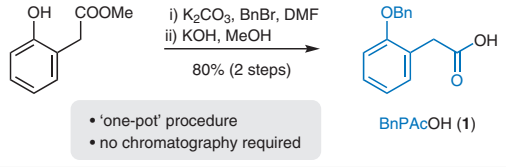
Key words protecting groups, relay deprotection, neighboring group participation, anchimeric assistance, glycosides, glycosyl esters

Protecting groups (PGs) are crucial for the synthesis of complex and multifunctional organic compounds. Especially in the field of carbohydrate chemistry, the use of PGs and protecting group patterns for the differentiation of multiple hydroxyl groups in regard to chemo- and regioselectivity plays a pivotal role.[1,2] Routinely, in oligosaccharide synthesis there are only a few commonly used persistent PGs (acetyl, benzyl, or benzoyl groups); whereas a variety of temporary PGs depending on the structure of the target molecule and the type of the persistent PGs are applied.[3] The requirements for an ideal PG are: (i) simple introduction with readily available, inexpensive reagents, (ii) high stability during chemical transformations and purification steps, and (iii) selective and efficient deprotection under mild conditions without affecting other functional groups.[4] Although a vast number of PGs has been reported,[4,5] only few have found wide application, mostly due to the fact that many groups only partly meet the above-mentioned requirements. As a consequence, there is still a continuous need for the development of new PGs in carbohydrate chemistry.

Relay cleavage is a valuable tool for designing new PGs. In relay cleavage PGs have an auxiliary group that is stable under a wide range of conditions. Cleavage is initiated by a chemical transformation of this group leading to a readily cleavable form or even resulting in spontaneous deprotection under mild conditions. Although relay deprotection lengthens the cleavage process by an extra step of activation, this is compensated by the added measure of orthogonality to other functional and protecting groups.[4] Based on this principle a variety of PGs has been introduced so far, including AZMB,[6] AMPA,[7] APAc,[8] POMB,[9] CAMB,[10] NPAc,[11] PAC,[12] and TMBPP.[13] However, deprotection by hydrogenolysis is represented only rarely within the class of relay protecting groups, even though it is one of the most efficient and thereby common methods for deprotection, considering the wide application of benzyl protection.[4,5] Hydrogenolysis has been described for the removal of the PAC group and its advancement, the TMBPP (3-[2-(benzyloxy)-4,6-dimethylphenyl]-3,3-dimethylpropanoyl) group, which has furthermore been shown to be an efficient neighboring participating group in glycosylation reactions. However, the use of TMBPP leads to failures in coupling reactions with bulky acceptors of low reactivity.[13] Moreover, the reagent required for the introduction of TMBPP either needs to be prepared in three steps from an expensive intermediate or four steps from readily available compounds.

Herein, we introduce (2-benzyloxyphenyl)acetyl as a new participating protecting group that can be cleaved in the presence of either esters or benzyl ethers.

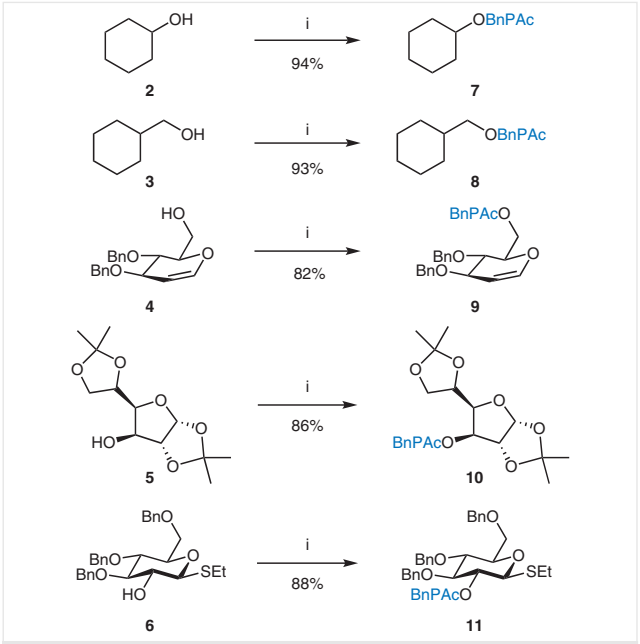
(2-Benzyloxyphenyl)acetic acid (BnPAcOH (**1**), Scheme 1) was prepared as a reagent for the introduction of BnPAc starting by reacting commercially available and inexpensive methyl 2-(2-hydroxyphenyl)acetate with benzyl bromide in the presence of potassium carbonate in DMF, followed by saponification of the methyl ester with potassium hydroxide in methanol. Notably, **1** can be obtained without purification of the benzylated intermediate and without any chromatography in 80% yield.



Scheme 1 Synthesis of (2-benzyloxyphenyl)acetic acid

BnPAc protection of different alcohols **2–6** was readily achieved by reaction with BnPAcOH (**1**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 (General Procedure A).[14] Esters **7–11**[15–19] were obtained in good yields (82–94%, Scheme 2).

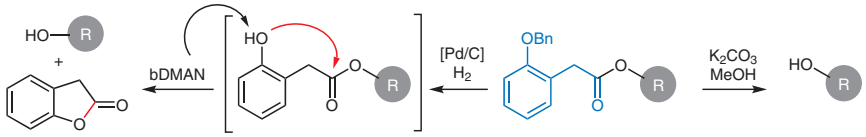
Removal of the BnPAc group was accomplished either by using a relay approach (General Procedure **B1**) applying catalytic hydrogenation in combination with 1,8-bis(dimethylamino)naphthalene (bDMAN)[20] or by reaction with K_2CO_3 in methanol (General Procedure **B2**).[21] Compounds **7**, **8**, and **10** were deprotected using procedure **B1** affording the corresponding alcohols **2**, **3**, and **5**, respectively, and benzofuran-2(3*H*)-one as byproduct formed by intramolecular cyclization of the intermediate (2-hydroxyphenyl)acetyl group leading to final deprotection (Table 1).[8] As compound **9** is sensitive to hydrogenolysis, procedure **B2** was applied to obtain **4**[22] in 90% without affecting the glucal double bond (Table 1, entry 3).



Scheme 2 Introduction of BnPAc. *Reagents and conditions*: i. BnPAcOH (**1**), EDC, DMAP, CH_2Cl_2.

After having established a simple method for the introduction and two orthogonal procedures for the removal of BnPAc, we tested its applicability in diastereoselective glycosylation reactions exploiting the neighboring group participation (anchimeric assistance) of BnPAc (Scheme 3, a). Thioglycoside **11** was activated with NIS and TfOH[23] and reacted with phenylethanol (Scheme 3, b) and glucosyl acceptor **14** (Scheme 3, c), leading exclusively to the formation of β-glucosides **12**[24] and **15**[25] in yields of 88% and 91%, respectively. Simultaneous deprotection of the BnPAc- and Bn-protected glucoside **12** was achieved in a single step by catalytic hydrogenation followed by reaction with bDMAN (procedure **B1**) to obtain glucoside **13**[26] in 84% yield. Selective cleavage of the BnPAc-protected OH-group of **15** in the

Table 1 Removal of BnPAc

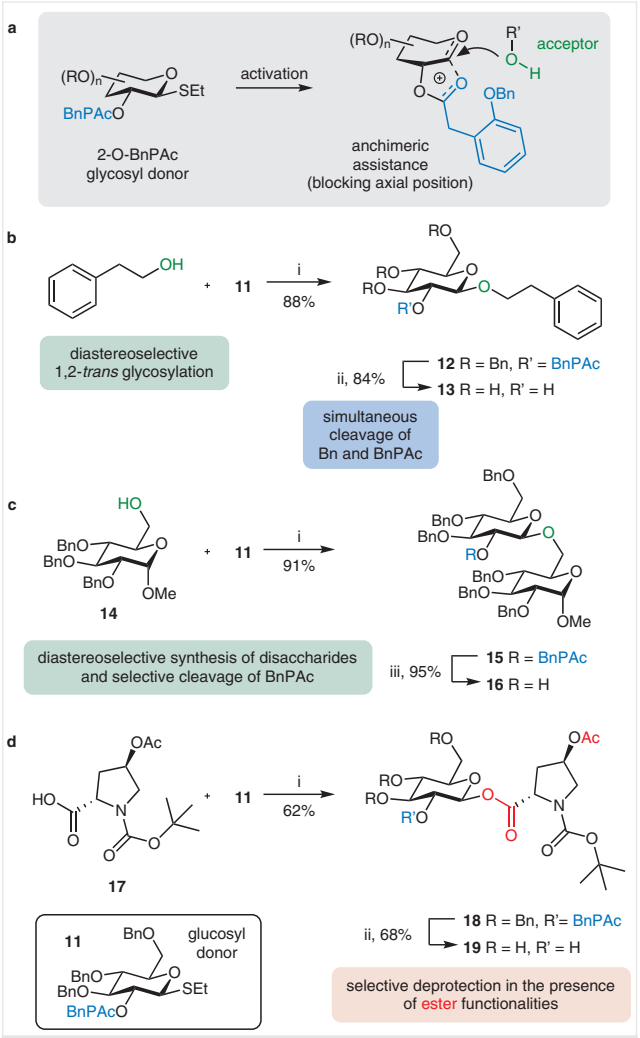


Entry	Substrate	Procedure	Cleavage conditions	Yield (%)
1	**7**	**B1**	[Pd/C], H_2; then bDMAN[a]	>99[b]
2	**8**	**B1**	[Pd/C], H_2; then bDMAN[a]	>99[b]
3	**9**	**B2**	K_2CO_3, MeOH	90
4	**10**	**B1**	[Pd/C], H_2; then bDMAN[a]	63

[a] bDMAN = 1,8-bis(dimethylamino)naphthalene.
[b] Determined by GC-MS.

presence of the benzyl groups was carried out applying procedure **B2** to afford disaccharide **16**[27] (95%).

Encouraged by these results, we proceeded to perform a glycosylation reaction with glucosyl donor **11** and the protected amino acid **17** as acceptor leading to the formation of glucosyl ester **18**[28] with complete β-diastereoselectivity. Relay deprotection of **18** enabled the simultaneous removal of BnPAc and the benzyl groups, leading to **19**[29] in 68% yield. Notably, ester functionalities and the *tert*-butyloxycarbonyl (Boc)-protected amine were not affected (Scheme 3, d).



Scheme 3 Diastereoselective glycosylation using the 2-*O*-BnPAc-glucosyl donor **11**. (a) Anchimeric assistance of BnPAc; (b) BnPAc and benzyl ethers can be deprotected simultaneously; (c) selective deprotection of BnPAc in the presence of benzyl ethers; (d) synthesis of an amino acid glucosyl ester. *Reagents and conditions*: i. NIS/TfOH, CH_2Cl_2; ii. [Pd/C], H_2, then bDMAN; iii. K_2CO_3, MeOH.

In summary, BnPAc is a stable protecting group that can easily be introduced in high yields and either cleaved by a relay approach using catalytic hydrogenation followed by reaction with 1,8-bis(dimethylamino)naphthalene or by Zemplén transesterification using K_2CO_3 in methanol. BnPAc was furthermore shown to provide efficient anchimeric assistance in glycosylation reactions leading to the formation of 1,2-*trans* glycosides with complete diastereoselectivity. Its cleavage under hydrogenolytic conditions, moreover, enables the synthesis of glycosides in the presence of ester functionalities or 1,2-*trans* glucosyl esters. Hence, we are convinced that the BnPAc group represents a valuable tool, especially in the field of carbohydrate chemistry.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610255.

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(14) **General Procedure A: Introduction of BnPAc**
Alcohol (0.5 mmol, 1 equiv), BnPAcOH (0.6 mmol, 1.2 equiv), and DMAP (0.05 mmol, 0.1 equiv) were dissolved in dry CH_2Cl_2 (3 mL) and the mixture cooled to 0 °C. After addition of EDCI (0.6 mmol, 1.2 equiv), the reaction mixture was stirred at r.t. until completion of the reaction. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl (2 × 10 mL), saturated $NaHCO_3$ solution (2 × 10 mL), and brine (10 mL). The aqueous phases were extracted with CH_2Cl_2 (5 mL) after each washing step. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (gradient elution hexanes/EtOAc) to yield the desired product.
(15) **(2-Benzyloxyphenyl) Acetic Acid, Cyclohexyl Ester 7**
Starting from cyclohexanol (100 mg, 0.1 mmol) and following general procedure A BnPAc ester **7** was obtained as a white solid (306 mg, 94%). For analytical data see Supporting Information.

(16) **(2-Benzyloxyphenyl) Acetic Acid, Cyclohexylmethyl Ester 8**
Starting from cyclohexyl methanol (114 mg, 0.1 mmol) and following general procedure A BnPAc ester **8** was obtained as a white solid (315 mg, 93%). For analytical data see Supporting Information.

(17) **(2-Benzyloxyphenyl) Acetic Acid, 3,4-di-*O*-Benzyl Glucuronal Ester 9**
Starting from 3,4-di-*O*-benzyl glucuronal (200 mg, 0.61 mmol) and following general procedure A BnPAc ester **9** was obtained (276 mg, 82%). For analytical data see Supporting Information.

(18) **(2-Benzyloxyphenyl) Acetic Acid, 1,2,5,6-Diisopropylidene Glucosyl Ester 10**
Starting from diacetone-D-glucose (50 mg, 0.19 mmol) and following general procedure A BnPAc ester **10** was obtained (80 mg, 86%). For analytical data see Supporting Information.

(19) **Ethyl 3,4,6-Tri-*O*-benzyl-2-*O*-[(2-benzyloxyphenyl)acetyl]-1-thio-β,D-glucoside (11**)
Starting from ethyl 3,4,6-tri-*O*-benzyl-1-thio-β,D-glucoside (4.4 g, 9 mmol) and following general procedure A glucosyl donor **11** was obtained as a white solid (5.2 g, 88%). For analytical data see Supporting Information.

(20) **General Procedure B1: Deprotection of BnPAc via Catalytic Hydrogenation**
To a solution of the respective BnPAc-protected compound (0.07 mmol, 1 equiv) in dry ethanol (1.5 mL) one small tip of a spatula of Pd/C was added under an argon atmosphere. The argon balloon was changed for a H_2 balloon, and the reaction mixture was stirred for 3–6 h at r.t. The reaction mixture was filtered through a syringe filter, proton sponge (1 equiv) was added to the filtrate, and the reaction solution was heated up to 80 °C until completion of the reaction (4–8 h). The reaction mixture was concentrated, and the residue was purified either by flash chromatography (gradient elution hexanes/EtOAc) or by preparative HPLC (H_2O/MeCN) to yield the corresponding product.

(21) **General Procedure B2: Deprotection of BnPAc via basic hydrolysis**
To a solution of the respective BnPAc-protected compound in dry methanol K_2CO_3 (0.5 equiv) was added. The reaction mixture was stirred for 16 h at room temperature. In some cases, further addition of 0.5 equiv NaOMe was necessary for completion of the reaction. The reaction mixture was filtered, concentrated and the residue was purified by flash chromatography (gradient elution hexanes/EtOAc) or by preparative-HPLC (H_2O/MeCN) to obtain the desired product.

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(23) **General Procedure C: Glycosylation with Donor 11**
To a solution of the acceptor (680 µmol, 2.5 equiv) and glucosyl donor **11** (200 mg, 272 µmol, 1 equiv) in dry CH_2Cl_2 (5 mL) molecular sieves (3 Å, 100 mg/mL) were added, and the reaction mixture was stirred for 2 h at r.t. After cooling to –10 °C, *N*-iodosuccinimide (133 mg, 544 µmol, 2 equiv), followed by trifluoromethanesulfonic acid (5 µL, 54 µmol, 0.2 equiv) were added, and stirring was continued for 16 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and Na_2SO_3 solutions (1:1, 1 mL), then the reaction solution was diluted with CH_2Cl_2 (4 mL) and filtered through Celite®. The filtrate was washed with water (5 mL) and brine (3 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes/EtOAc gradient elution) to obtain the desired product.

(24) **2-Phenylethyl 3,4,6-Tri-*O*-benzyl-2-*O*-[(2-benzyloxy-phenyl)acetyl]-β,D-glucoside (12)**
General procedure C; starting from phenylethanol (83 mg, 0.68 mmol) and glucosyl donor **11** (200 mg, 0.27 mmol) **12** was obtained as a white solid (90 mg, 88%). For analytical data see Supporting Information.

(25) **Methyl 2,3,4,9,10,12-Hexa-*O*-benzyl-8-*O*-[(2-benzyloxy-phenyl)acetyl]-α,D-gentiobioside (15)**
General procedure C; starting from glucosyl donor **11** (60 mg, 0.08 mmol) and acceptor **14** (93 mg, 0.2 mmol) **15** (83 mg, 91%) was obtained. For analytical data see Supporting Information.

(26) **2-Phenylethyl-β,D-glucoside (13)**
Starting from compound **12** (36 mg, 0.05 mmol) and following general procedure B1 **13** was obtained as a white solid (12 mg, 84%). Analytical data matched those reported in the literature.[30]

(27) **Methyl 2,3,4,9,10,12-Hexa-*O*-benzyl-α,D-gentiobioside (16)**
Starting from compound **15** (50 mg, 0.04 mmol) and following general procedure **B2 16** was obtained as a white solid (37 mg, 95%). For analytical data see Supporting Information.

(28) ***trans*-*N*-(*tert*-Butoxycarbonyl)-4-acetoxy-L-proline, 3,4,6-Tri-*O*-benzyl-2-*O*-[(2-benzyloxyphenyl) Acetyl]-β,D-glucosyl Ester (18)**
General procedure C; starting from glucosyl donor **11** (100 mg, 0.14 mmol) and acceptor **17** (57 mg, 0.21 mmol) **18** (80 mg, 62%) was obtained. For analytical data see Supporting Information..

(29) ***trans*-*N*-(*tert*-Butoxycarbonyl)-4-acetoxy-L-proline, β,D-Glucosyl Ester (19)**
Starting from compound **18** (35 mg, 0.04 mmol) and following general procedure B1 **19** was obtained as a colourless solid (11 mg, 68%).

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