


 Cite this: *Chem. Commun.*, 2023, 59, 7052

 Received 20th April 2023,  
 Accepted 16th May 2023

DOI: 10.1039/d3cc01931d

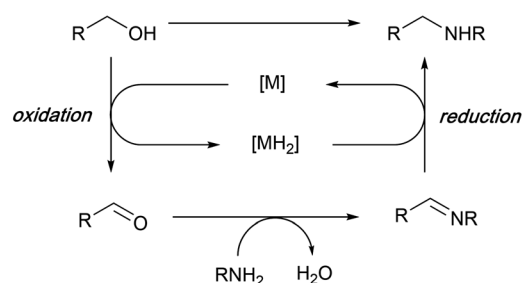
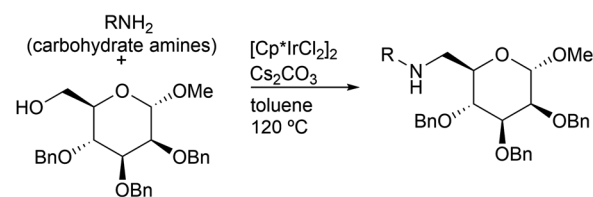
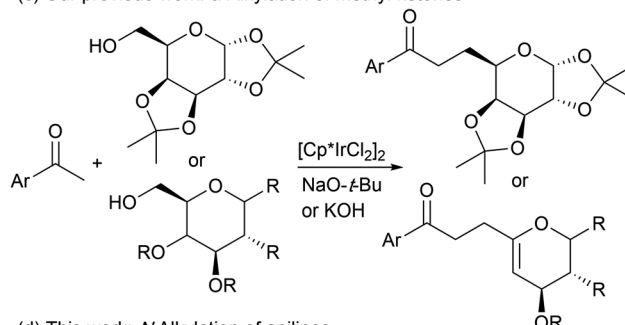
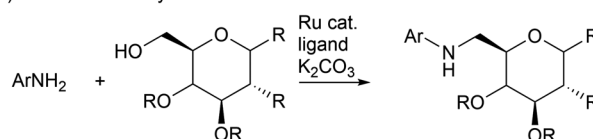
rsc.li/chemcomm

# Ruthenium-catalysed *N*-alkylation of anilines with primary carbohydrate alcohols via borrowing hydrogen strategy†

 Kouki Tsuge,<sup>a</sup> Shunnichi Kubota,<sup>a</sup> Kana Sakamoto,<sup>a</sup> Kenji Kitayama<sup>b</sup> and Takahiro Nishimura<sup>id</sup>\*<sup>a</sup>

**Ruthenium-catalysed *N*-alkylation of anilines with sugar derivatives proceeded via the borrowing hydrogen strategy. Primary carbohydrate alcohols were successfully applied to *N*-alkylation of aniline derivatives to give the corresponding aminosugars in high yields.**

Transition-metal-catalysed *N*-alkylation of amines via the borrowing hydrogen strategy is a desirable process for the formation of carbon–nitrogen bonds, enabling alcohols to be employed directly as alkylating agents (Scheme 1a).<sup>1</sup> A variety of catalytic systems based on the late-transition metals have been developed for the *N*-alkylation of amines by using simple alcohols.<sup>2–5</sup> Biomass-derived alcohols, such as ethylene glycol, 1,3-propanediol, isohexides, and so on, have also been recognized as important reaction partners in the borrowing hydrogen strategy.<sup>6</sup> However, carbohydrate alcohols have been scarcely used for the direct *N*-alkylation reaction. In this respect, in 2011, Cumpsty and Martín-Matute reported the first example of *N*-alkylation of alkylamines derived from sugars with primary carbohydrate alcohols catalysed by an Ir(III) complex, where amine-linked pseudodisaccharides are successfully synthesized in a single step through borrowing hydrogen strategy (Scheme 1b).<sup>7</sup> In this context, we recently reported  $\alpha$ -alkylation of methyl ketones with primary carbohydrate alcohols as alkylating agents (Scheme 1c).<sup>8</sup> The reaction is efficiently catalysed by an Ir(III) complex in the presence of a strong base. During our studies on the catalytic functionalization of sugar derivatives,<sup>8,9</sup> it was found that a ruthenium complex was effective in catalyzing the borrowing hydrogen reaction between anilines and sugars (Scheme 1d). Here we describe that a ruthenium/dppf type ligand complex efficiently

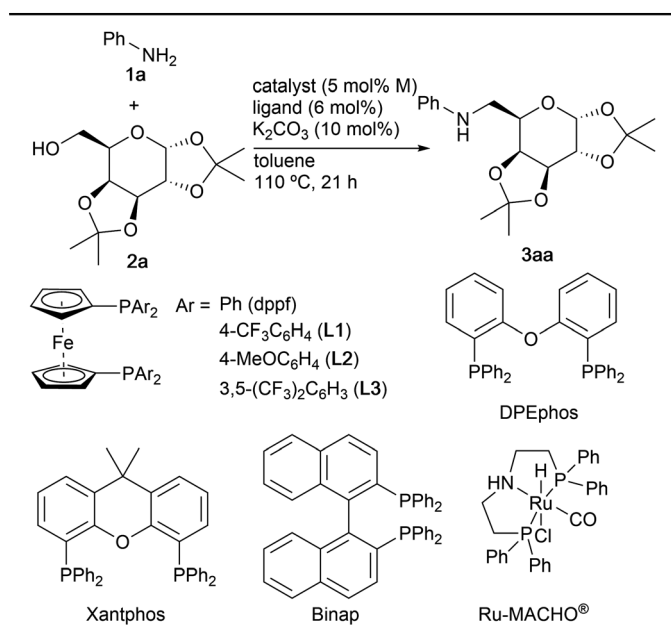
 (a) *N*-Alkylation through borrowing hydrogen strategy

 (b) Ir-catalysed *N*-alkylation of carbohydrate amines

 (c) Our previous work:  $\alpha$ -Alkylation of methyl ketones

 (d) This work: *N*-Alkylation of anilines


Scheme 1 Borrowing hydrogen reactions.

<sup>a</sup> Department of Chemistry, Graduate School of Science, Osaka Metropolitan University, Sumiyoshi, Osaka 558-8585, Japan. E-mail: tnishi@omu.ac.jp

<sup>b</sup> Daicel Corporation, Grand Front Osaka Tower-B, 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

 † Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3cc01931d>


**Table 1** Ruthenium-catalysed *N*-alkylation of aniline **1a** with galactopyranose **2a**<sup>a</sup>

Entry	Catalyst	Ligand	Yield <sup>b</sup> (%)
1	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	dppf	31
2	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	—	0
3 <sup>c</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	dppf	0
4	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	L1	69
5	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	L2	6
6	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	L3	0
7	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	DPEphos	15
8	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	Xantphos	6
9	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	Binap	0
10 <sup>d</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	L1	76
11 <sup>de</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	L1	45
12 <sup>df</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	L1	53
13 <sup>dg</sup>	[RuCl <sub>2</sub> ( <i>p</i> -cymene)] <sub>2</sub>	L1	87 (82) <sup>h</sup>
14	[RuCl <sub>2</sub> (benzene)] <sub>2</sub>	L1	7
15 <sup>cd</sup>	Ru <sub>3</sub> (CO) <sub>12</sub>	—	0
16 <sup>d</sup>	Ru <sub>3</sub> (CO) <sub>12</sub>	—	0
17 <sup>d</sup>	Ru-MACHO <sup>®</sup>	—	0

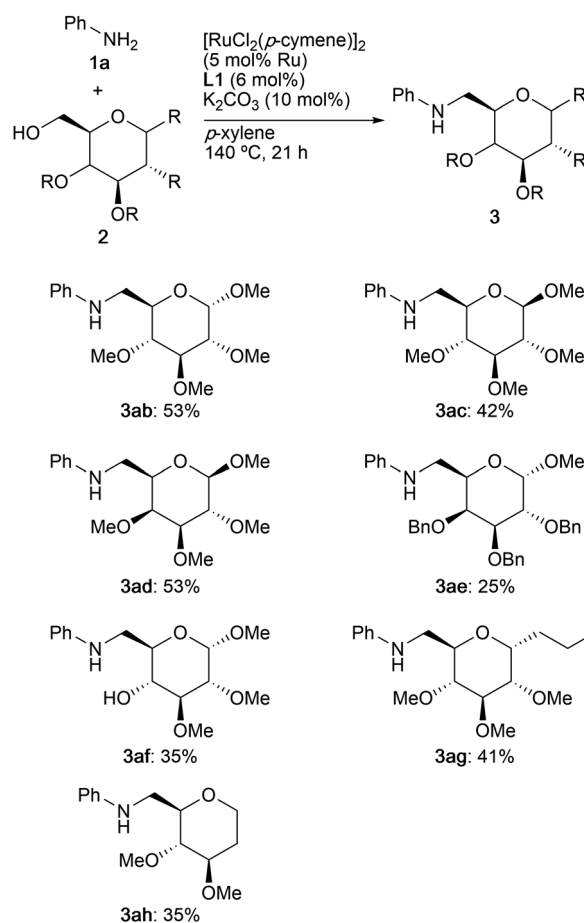
<sup>a</sup> Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.0050 mmol, 5 mol% of Ru), and base (10 mol%) in toluene (0.30 mL) at 110 °C for 21 h. <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Without K<sub>2</sub>CO<sub>3</sub>. <sup>d</sup> Performed with **1a** (0.20 mmol) and **2a** (0.24 mmol). <sup>e</sup> With Na<sub>2</sub>CO<sub>3</sub> instead of K<sub>2</sub>CO<sub>3</sub>. <sup>f</sup> With Cs<sub>2</sub>CO<sub>3</sub> instead of K<sub>2</sub>CO<sub>3</sub>. <sup>g</sup> At 140 °C in *p*-xylene. <sup>h</sup> Isolated yield.

catalyses *N*-alkylation of anilines with primary carbohydrate alcohols, providing a new method for the synthesis of aminosugar derivatives.<sup>10</sup> Aminosugars possess potential properties that take part in a variety of biological functions, and therefore, the development of the synthesis of the aminosugars is important for the understanding of their functions.<sup>11</sup>

Our initial studies focused on the *N*-alkylation of aniline (**1a**) with 1,2:3,4-di-*O*-isopropylidene- $\alpha$ -D-galactopyranose (**2a**) in the presence of ruthenium complexes directed toward the catalytic synthesis of aminosugar **3aa** (Table 1).<sup>12</sup> Treatment of **1a** (1.2 equiv.) with **2a** (1.0 equiv.) in the presence of [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol% of Ru), dppf (6 mol%), and K<sub>2</sub>CO<sub>3</sub> (10 mol%) in toluene, which is one of the reaction conditions

reported by Williams and co-workers,<sup>2c</sup> at 110 °C for 21 h gave alkylated product **3aa** in 31% yield (entry 1). The ligand and base were necessary to obtain **3aa** (entries 2 and 3). The aryl groups on dppf ligands significantly influenced the reactivity. The use of ligand **L1** substituted with *p*-(trifluoromethyl)phenyl groups improved the yield of **3aa** up to 69% (entry 4). In contrast, methoxy-substituted **L2** diminished the yield (entry 5), and ligand **L3** inhibited the reaction, probably due to the bulkiness (entry 6). DPEphos, Xantphos, or Binap were not effective in catalyzing the present reaction (entries 7–9). The use of a slight excess (1.2 equiv.) of alcohol **2a** toward aniline (**1a**) improved the yield up to 76% (entry 10). Na<sub>2</sub>CO<sub>3</sub> and Cs<sub>2</sub>CO<sub>3</sub> were less effective than K<sub>2</sub>CO<sub>3</sub>, thus giving **3aa** in 45 and 53% yields, respectively (entries 11 and 12). The reaction in *p*-xylene at 140 °C gave **3aa** in 87% yield (entry 13). The catalytic activity of [RuCl<sub>2</sub>(benzene)]<sub>2</sub> was quite low (entry 14). Ru<sub>3</sub>(CO)<sub>12</sub><sup>2d</sup> and Ru-MACHO<sup>®2j</sup> did not work as catalysts (entries 15–17).

Scheme 2 summarizes the results obtained for the reaction of several primary carbohydrate alcohols. The reactions of *O*-methylated  $\alpha$ -glucose **2b**,  $\beta$ -glucose **2c**, and  $\beta$ -galactose **2d** with aniline (**1a**) gave the corresponding sugars **3ab–3ad** in 42–53%



Scheme 2 Scope of carbohydrate alcohols. Reaction conditions: **1a** (0.10 mmol), **2** (0.12 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.0025 mmol, 5 mol% of Ru), **L1** (6 mol%) and K<sub>2</sub>CO<sub>3</sub> (10 mol%) in *p*-xylene (0.15 mL) at 140 °C for 21 h.



yields. Alcohol **2e** having benzyl ether moieties and **2f** with a free hydroxy group reacted with **1a** to give *N*-alkylated products **3ae** and **3af** in 25% and 35% yields, respectively. The reaction of *C*-glycoside **2g** and deoxyglucose **2h** also proceeded to give the corresponding aminosugars **3ag** and **3ah**.

A variety of aniline derivatives **1** participated in the reaction with carbohydrate alcohol **2a** as summarized in Scheme 3. *N*-Alkylation of anilines having electron-donating and -withdrawing substituents (**2a–2m**) at the *o*-, *m*-, and *p*-positions proceeded to give the corresponding aminosugars in 18–97% yields, where anilines substituted with electron-withdrawing groups displayed the low reactivity. In particular, the loss of the catalytic activity was observed in reaction of *p*-bromoaniline (**1f**). Dimethyl (**1n**) and dimethoxyanilines (**1o** and **1p**) reacted with **2a** to give aminosugars **3na**, **3oa**, and **3pa**, respectively, in high yields. Modest yields were observed for 3,4,5-trifluoroaniline (**1q**), 5-methoxy-1-naphthylamine (**1r**), and 6-methyl-2-aminopyridine (**1s**). In sharp contrast, *N*-methylaniline or aliphatic amines such as *n*-butylamine and piperidine were not alkylated under the present reaction conditions.

In summary, we have developed ruthenium-catalysed *N*-alkylation of anilines with primary carbohydrate alcohols. A variety of aniline derivatives were applied to the reaction to give

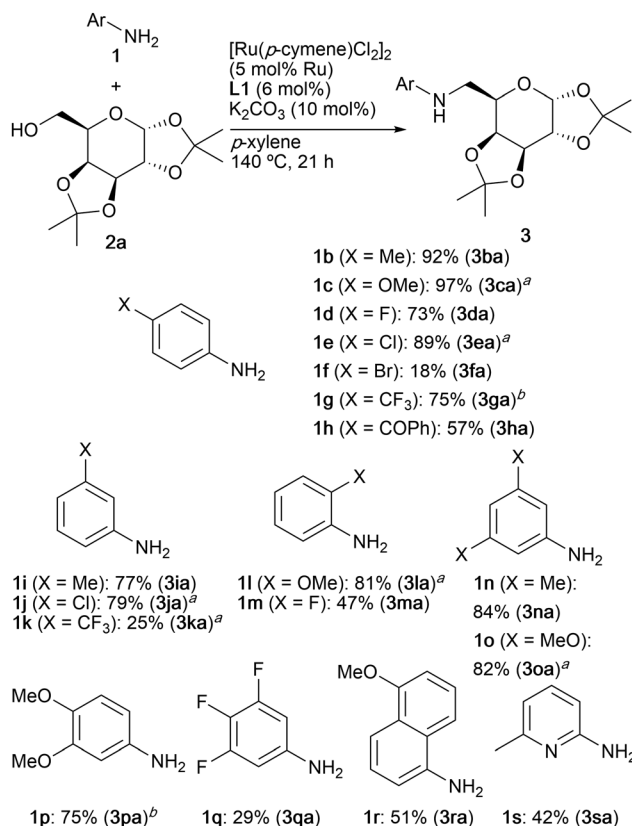
the corresponding aminosugars in high yields. Several *O*-protected sugar derivatives could be used as alkylating agents for *N*-alkylation of aniline derivatives.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- For selected recent reviews, see: (a) E. Podyacheva, O. I. Afanasyev, D. V. Vasilyev and D. Chusov, *ACS Catal.*, 2022, **12**, 7142; (b) B. G. Reed-Berendt, D. E. Latham, M. B. Dambatta and L. C. Morrill, *ACS Cent. Sci.*, 2021, **7**, 570; (c) T. Irrgang and R. Kempe, *Chem. Rev.*, 2019, **119**, 2524; (d) B. G. Reed-Berendt, K. Polidano and L. C. Morrill, *Org. Biomol. Chem.*, 2019, **17**, 1595; (e) A. Corma, J. Navas and M. J. Sabater, *Chem. Rev.*, 2018, **118**, 1410; (f) Q. Yang, Q. Wang and Z. Yu, *Chem. Soc. Rev.*, 2015, **44**, 2305; (g) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853; (h) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (i) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555.
- For selected examples using Ru catalysts, see: (a) Y. Watanabe, Y. Tsuji and Y. Ohsugi, *Tetrahedron Lett.*, 1981, **22**, 2667; (b) M. H. S. A. Hamid and J. M. J. Williams, *Chem. Commun.*, 2007, 725; (c) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766; (d) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell and M. Beller, *Chem. – Asian J.*, 2007, **2**, 403; (e) R. N. Monrad and R. Madsen, *Org. Biomol. Chem.*, 2011, **9**, 610; (f) A. B. Enyong and B. Moasser, *J. Org. Chem.*, 2014, **79**, 7553; (g) S. P. Shan, X. Xiaoke, B. Gnanaprakasam, T. T. Dang, B. Ramalingam, H. V. Huynh and A. M. Sayad, *RSC Adv.*, 2015, **5**, 4434; (h) M. Kaloglu, *Inorg. Chim. Acta*, 2019, **498**, 119163; (i) A. E. Putra, Y. Oe and T. Ohta, *Eur. J. Org. Chem.*, 2013, 6146; (j) O. Ogata, H. Nara, M. Fujiwhara, K. Matsumura and Y. Kayaki, *Org. Lett.*, 2018, **20**, 3866; (k) M. Maji, K. Chakrabarti, B. Paul, B. C. Roy and S. Kundu, *Adv. Synth. Catal.*, 2018, **360**, 722; (l) X.-J. Yu, H.-Y. He, L. Yang, H.-Y. Fu, X.-L. Zheng, H. Chen and R.-X. Li, *Catal. Commun.*, 2017, **95**, 54; (m) S. Agrawal, M. Lenormand and B. Martín-Matute, *Org. Lett.*, 2012, **14**, 1456; (n) S. Demir, F. Coskun and I. Özdemir, *J. Organomet. Chem.*, 2014, **755**, 134; (o) Ö. Ulu, N. Gürbüz and I. Özdemir, *Tetrahedron*, 2018, **74**, 645; (p) S. N. R. Donthireddy, P. M. Illam and A. Rit, *Inorg. Chem.*, 2020, **59**, 1835; (q) R. Savela, D. Vogt and R. Leino, *Eur. J. Org. Chem.*, 2020, 3030; (r) F.-L. Yang, Y.-H. Wang, Y.-F. Ni, X. Gao, B. Song, X. Zhu and X.-Q. Hao, *Eur. J. Org. Chem.*, 2017, 3481; (s) V. R. Jumde, L. Gonsalvi, A. Guerriero, M. Peruzzini and M. Taddei, *Eur. J. Org. Chem.*, 2015, 1829; (t) K. O. Marichand and J. M. Takacs, *ACS Catal.*, 2016, **6**, 2205; (u) R. Ramachandran, G. Prakash, M. Nirmala, P. Viswanathamurthi and J. G. Malecki, *J. Organomet. Chem.*, 2015, **791**, 130; (v) S. Gayathri, P. Viswanathamurthi, R. Bertani and P. Sgarbossa, *ACS Omega*, 2022, **7**, 33107; (w) F. V. Rossi, J. T. Starr, D. P. Uccello and J. A. Young, *Org. Lett.*, 2020, **22**, 5890.
- For pioneering examples using Rh catalysts, see: (a) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpeny, *J. Chem. Soc., Chem. Commun.*, 1981, 611; (b) N. Tanaka, M. Hatanaka and Y. Watanabe, *Chem. Lett.*, 1992, 575; (c) C. Liu, S. Liao, Q. Li, S. Feng, Q. Sun, X. Yu and Q. Xu, *J. Org. Chem.*, 2011, **76**, 5759.
- For pioneering examples using Ir catalysts, see: (a) K. Fujita, Z. Li, N. Ozeki and R. Yamaguchi, *Tetrahedron Lett.*, 2003, **44**, 2687; (b) K. Fujita, Y. Enoki and R. Yamaguchi, *Tetrahedron*, 2008, **64**, 1943; (c) R. Kawahara, K. Fujita and R. Yamaguchi, *J. Am. Chem. Soc.*, 2010, **132**, 15108; (d) F. Cami-Kobeci, P. A. Slatford, M. K. Whittlesey and J. M. J. Williams, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 535; (e) O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden and J. M. J. Williams, *Chem. Commun.*, 2010, **46**, 1541; (f) B. Blank, M. Madalska and R. Kempe, *Adv. Synth. Catal.*, 2008, **350**, 749.
- For selected examples of catalytic *N*-alkylation by use of transition-metal catalysts other than Ru, Rh, and Ir, see: (a) R. Martínez,



Scheme 3 Scope of anilines **1**. Reaction conditions: **1** (0.10 mmol), **2a** (0.12 mmol),  $[\text{RuCl}_2(\text{p-cymene})_2]$  (0.0025 mmol, 5 mol% of Ru), ligand (6 mol%), and  $\text{K}_2\text{CO}_3$  (10 mol%) in *p*-xylene (0.15 mL) at 140 °C for 21 h. <sup>a</sup>0.20 mmol scale reaction. <sup>b</sup>For 48 h.



- D. J. Ramón and M. Yus, *Org. Biomol. Chem.*, 2009, 7, 2176; (b) A. Martínez-Asencio, D. J. Ramón and M. Yus, *Tetrahedron Lett.*, 2010, 51, 325; (c) M. Peña-López, P. Piehl, S. Elangovan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2016, 55, 14967; (d) S. Rösler, M. Ertl, T. Irrgang and R. Kempe, *Angew. Chem., Int. Ed.*, 2015, 54, 15046; (e) M. Vellakkaran, K. Singh and D. Banerjee, *ACS Catal.*, 2017, 7, 8152.
- 6 (a) N. K. Gupta, P. Reif, P. Palenicek and M. Rose, *ACS Catal.*, 2022, 12, 10400; (b) S. Hameury, H. Bensalem and K. de Oliveira Vigier, *Catalysts*, 2022, 12, 1306.
- 7 I. Cumpstey, S. Agrawal, K. E. Borbas and B. Martín-Matute, *Chem. Commun.*, 2011, 47, 7827.
- 8 K. Tsuge, S. Kubota, K. Sakamoto, K. Kitayama and T. Nishimura, *Adv. Synth. Catal.*, 2023, 365, 971.
- 9 K. Sakamoto, M. Nagai, Y. Ebe, H. Yorimitsu and T. Nishimura, *ACS Catal.*, 2019, 9, 1347.
- 10 For a review of the synthesis of aminosugar derivatives, see: R. Sangwan, A. Khanam and P. K. Mandal, *Eur. J. Org. Chem.*, 2020, 5949.
- 11 L. Cipolla and F. Peri, *Mini-Rev. Med. Chem.*, 2011, 11, 39.
- 12 For an example of the synthesis of **3aa** by *N*-arylation of 6-amino-6-deoxy-1,2:3,4-di-*O*-isopropylidene- $\alpha$ -*D*-galactopyranose, see: K. B. Pal, M. Mahanti and U. J. Nilsson, *Org. Lett.*, 2018, 20, 616.

