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Highly Efficient Selective Benzylation of Carbohydrates Catalyzed by Iron(III) with Ag₂O and Bromide Anion as Co-catalysts

Bo Ren,^[a] Jian Lv,^[a] Yu Zhang,^[a] Jun Tian,^[a] and Hai Dong*^[a]

Abstract: It was firstly reported a green regioselective benzylation method with both mild reaction temperature and high reaction efficiency (short reaction time). With the use of 0.6 equiv. of Ag₂O and 0.1 equiv. of TBABr as co-catalysts, an iron(III)-catalyzed benzylation can proceed to completion at 40 °C in 2 - 3 hours with high regioselectivities and isolated yields. The mechanism was proposed involving the principle on enhanced basicity of Ag₂O by soft anions.

Regioselective protections play important roles in carbohydrate chemistry where well-designed selective protection and deprotection strategies remain fundamental to the synthesis of saccharide building blocks.1 Selective benzylation is one of the most important protection methods, in which organotin species used to be the most widely used reagents in order to obtain good selectivities.² Recently, several environment-friendly methods have been developed to substitute the traditional organotin methods, including the use of oranoboron,³ organotin⁴ and organoiron⁵ as catalysts, all of which with their respective advantages and shortcomings. For example, the alkylations where K_2CO_3 is used as a base require high reaction temperatures (70 – 90 °C) (Figure 1a).^{4a-c,5} Temperature sensitive substrates may not tolerate in high temperature conditions. For the alkylations where Aq₂O is used as a base, although the reactions can proceed at mild temperature (r.t. -40°C), their reaction efficiencies are quite poor (24 - 48 hours' reaction time) (Figure 1b).^{3,4d} To the best of our knowledge, a regioselective alkylation method with both mild reaction temperature and high reaction efficiency (short reaction time) has never been reported. In the present study, under the guidance of the principle on enhanced basicity of Ag₂O by the coordination of soft anions to silver, we firstly developed a regioselective benzylation with both mild reaction temperature and high efficiency (Figure 1c). With the use of 0.6 equivalents of Ag₂O and 0.1 equivalents of tetrabutylammonium bromide (TBAB) as co-catalysts, an iron(III)-catalyzed benzylation can proceed to completion at 40 °C in 2 - 3 hours in comparison with all previous reported methods. All used reagents are associated with lower toxicity and environment-friendly.

Initially, reports of a variety of Ag₂O-mediated selective protections caught our attention due to their efficiency and environmental benefits.⁶ A large amount of Ag₂O (More than stoichiometric amount) are usually used in these methods. It was also reported that a catalytic amount of potassium iodide (KI) could largely improve reactivities in some Ag₂O-mediated protections.^{6c,d} Based on this, we used to try to develop a selective benzylation of carbohydrates with the use of Ag₂O and bromide anion. Although we finally failed to develop the method due to poor selectivities, the origin of the improved reactivity by

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KI in Ag₂O-mediated reactions was disclosed, and a principle of the enhanced basicity of Ag₂O through the coordination of soft anion to silver was proposed.7 The enhanced basicity of Ag₂O depends on the initial additive amount of anions and remains unchanged until Ag₂O is depleted. In the proposed mechanism, AgOH is formed with the deprotonation of hydroxyl group by strong base AgO⁻. It is well known that AgOH cannot exist stably under normal circumstances and instead immediately decomposes into Ag₂O and water once it forms. Thus, we start to suspect that excess amounts of Ag₂O have been used in all previous reports. A little more than 0.5 equivalents of Ag₂O may be only required in Ag₂O-mediated reactions since Ag₂O is partially recycled. Strong basicity is often worried to be the major cause of poor selectivities in selective protections. For Ag₂Omediated reaction, however, the basicity during the whole process can be enhanced and controlled by the addition of soft anions, which may lead to improved reaction efficiency without causing poor selectivity. Consequently, highly regioselective protections with both mild temperature and high efficiency could be developed through the assistance of 0.6 equivalents of Ag₂O and a catalytic amount of bromide anion.

a) Adv. Synth. Catal. 2014, 356, 1735; Chem. Eur. J. 2016, 22, 2481



Figure 1 Comparison of the present method with previous reported methods.

Ye's group reported a Ag₂O-mediated selective acylation and sulfonylation method where 1.5 equivalents of Ag_2O and 0.2 equivalents of KI were used.^{6c} We firstly started our study based on this method to test if the reaction requires only 0.6 equivalents of Aq₂O and 0.1 equivalents of NaBr practically. It is proposed that NaOH be able to be used instead of NaBr since bromide anions would form with the depletion of NaOH. Thus, benzoylation and sulfonylation of methyl pyranoside 1, 3, 5, 7, 9 and 11 were tested with 0.6 equivalents of Ag₂O and 0.1 equivalents of NaOH or NaBr (Entries 1 - 4 in Table 1). It can be seen, similar results to Ye's report were obtained, supporting our conjecture. Then we turned our attention to Taylor's alkylation. Taylor's method gives excellent selectivities where 1.1 equivalents of Ag₂O were used.³ Its shortcoming is the longer reaction time (48 h). We hypothesized that 0.6 equivalents of Ag₂O be enough for the reaction and the addition of 0.1 equivalents of bromide anion be able to shorten the reaction time largely. However, the experimental results did not support our hypothesis. The addition of bromide caused poor

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selectivities, which might be due to that the basicity did not play a key role in the formation of the organoboron intermediate proposed by Taylor³ and instead accelerated the direct benzylation. Without the addition of bromide, organoboroncatalyzed benzylation of compounds 7, 9, 11, 14, 18, 20, 22, 24 and 26 was performed with 0.8 equiv. of Ag₂O, leading to excellent isolated yields (Entries 3 - 9 in Table 1). Base on this, we suspected that organotin/organoiron-catalyzed alkylations should be improved by the addition of 0.6 equivalents of Ag₂O and 0.1 equivalents of bromide since basicity plays an important role in the formation of the stannylene intermediate^{4b} and the organoiron intermediate⁵ proposed by us.

formed by the coordination of two deprotonated hydroxyl groups to a tin atom, strong bacisity should favor the formation of this intermediate. Consequently, the reaction can be improved by the addition of Ag₂O and bromide anion. Fortunately, the hypothesis was supported this time (Entries 1 - 4 in table 2). The organotincatalyzed alkylation can proceed to completion at 40 °C in 2 - 3 hours through the use of 0.6 equivalents of Ag₂O and 0.1 equivalents of bromide as co-catalysts. Good isolated yields (88-95%) for benzylations of compounds 7, 11, 14, 20, and 22 were obtained.

Table 2 Selective benzylation of carbohydrates with Ag₂O and bromide anion as co-catalysts.

Table 1	Selective protections wi	ith reduced amounts of .	Ag ₂ O.	Entry	Substrate	Major Product	Isolated Yields 9
Entry	Substrate	Major Product	Isolated Yields %		TBSO.	TBSO.	
1	Ph O O D B	$R_{3}O$ R_{1}	2a : ^a 85, ^b 85 2b : ^a 77 ^b 70	1		HO DOH BNO 13 OMe	^a 88 ^b 94
1	HO HO_{R_2} 1: R ₁ = OMe, R ₂ = H 3: R ₁ = H, R ₂ = OMe	H $\dot{O}_{R_2}^{\downarrow}$ 2a: R ₁ = OMe, R ₃ = Ts 2b: R ₁ = OMe, R ₃ = Bz 4: R ₂ = OMe, R ₃ = Bz	4 : ^a 80, ^b 75	2		BnO R1 HO R2	15 : ^a 85, ^b 85
2	Ph 0 0 HO 5 HO Me	Ph O HO HO 6a: R = Ts 6b: R = Bz	6a : ^b 92 6b : ^b 72	3	11: $R_1 = OMe, R_2 = H$ 14: $R_2 = OMe, R_1 = H$ Ph O OH HO 20 OMe	15: $R_1 = OMe$, $R_2 = H$ 16: $R_2 = OMe$, $R_1 = H$ Ph O OH BnO 21 OMe	^a 90 ^b 92
3		HO R ₃ O BOUL	8 : °70 10 : °78	4	HO OBn HO OMe OBn 22 OH	HO OBn BnO OBn 23 OBn 23	^a 95 ^b 91
	R_{OMe}^{+} 7: $R_1 = H, R_2 = OH$ 9: $R_2 = H, R_1 = OH$	8: $R_2 = OH, R_3 = Bz$ 10: $R_1 = OH, R_3 = Bz$ 13: $R_2 = OH, R_3 = Bn$	13 : ^d 86	5	HO DO 24 BnO OMe	HO BnO BnO BnO OMe	^b 93
4		$R_{30} \rightarrow R_{1}$	12: °95	6	ноОн но	Bn0OH H0、	^b 90
4	HO _{K2} 11: R ₁ = OMe, R ₂ = H 14: R ₂ = OMe, R ₁ = H	$\begin{array}{c} 12: \ R_1 = OMe, \ R_3 = Bz \\ 1 & 15: \ R_1 = OMe, \ R_3 = Bn \\ 16: \ R_2 = OMe, \ R_3 = Bn \end{array}$	15 : 70 16 : ^d 76	7	HO OH HO 28 OMe	HO BnO OMe	^b 91
5		HO $R_3 O R_2$	17 : ^d 83 19 : ^d 60	8		$HO OH OH OH R_1$	31 : ^b 88
	9: R ₁ = H, R ₂ = ÕMe 18: R ₁ = OMe, R ₂ = H	17: R ₂ = OMe, R ₃ = Bn 19: R ₁ = OMe, R ₃ = Bn			30: $R_1 = H$, $R_2 = OMe$ 32: $R_2 = H$, $R_1 = OMe$	31: R ₁ = H, R ₂ = OMe 33: R ₂ = H, R ₁ = OMe	33 : 89
6	Ph O OH HO 20 OMe	Ph O OH Bno 21 OMe	^d 84	9	Ph O O HO R1 HO HO R2	Ph O BnO HOR2	35: [▶] 60, °66
7	HO OBn HO OBn 22	HO OBn BnO OBn OBn 23	^d 90		34: R ₁ = OMe, R ₂ = H 36: R ₁ = SPh, R ₂ = H Ph	35: R ₁ = OMe, R ₂ = H 37: R ₁ = SPh, R ₂ = H Ph	37: ^b 73, ^c 82
8	HO BnO BnO BnO BnO BnO BnO	HO OBn BnO 25 BnO Ma	^d 78	10			39: ⁶ 63, °73
	ONIC	ONE			ΗÒR	- HO _R	41: ⁶ 4, ^c 74

Reaction conditions: ^a Substrate (100 mg), CH₂Cl₂ (1 mL), NaOH (0.1 eq.), Ag₂O (0.6 eq.), TsCl/BzCl (1.2 eq.), rt, 24 h. ^b NaBr (0.1 eq.) instead of NaOH in condition a. ° MeCN (1 mL) instead of CH2Cl2 in condition b. d substrate (100 mg), MeCN (1 mL), organoboron (0.1 eq.), Ag₂O (0.8 eq.), BnBr (1.5 eq.), 40°C, 24 - 48 h.

Based on the mechanism studies of organotin-mediated selective protection,⁸ we used to develop an organotin-catalyzed alkylation method^{4b,c} where the reaction proceeded at 80 °C for 3 hours. A proposed mechanism suggest that a dioxlane five or six membered ring stannylene intermediate plays an important role in the catalysis process. Since the stannylene intermediate is

Reaction conditions: ^a substrate (100 mg), MeCN (1mL), Me ₂ SnCl ₂ (0.1
eq.), Ag ₂ O (0.6 eq.), TBAB (0.1 eq.), BnBr (1.5 eq.), 40 °C, 2 - 3 h. ^b
Substrate (100 mg), MeCN (1 mL), Fe(dibm) ₃ (0.1 eq.), Ag ₂ O (0.6 eq.),
TBAB (0.1 eq.), BnBr (1.5 eq.), 40° C, 2 - 3 h. ^c Similar conditions to b
except for longer reaction time (8 h.).

39: R₁ = OMe, R₂ = H

41: $R_1 = SPh, R_2 = H$

38: R₁ = OMe, R₂ = H

40: R₁ = SPh, R₂ = H

We developed an iron(III)-catalyzed selective alkylation method just few months ago.⁵ A resemble dioxlane five or six membered COMMUNICATION

ring intermediate where iron atom displaced with tin atom has been proposed to play an important role in the catalysis process.⁵ Apparently, strong basicity should also favor the formation of this intermediate. It is therefore easy to conclude that the iron(III)-catalyzed selective alkylation may proceed at a mild temperature for a short time when Ag₂O and bromide are used as co-catalysts. In order to confirm this, compounds 7, 11, 14, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38 and 40 were benzylated using iron(III)-catalyzed method where 0.6 equivalents of Ag₂O and 0.1 equivalents of TBAB were used as co-catalysts instead of 1.5 equivalents of K₂CO₃ (Table 2). It can be seen that good isolated yields (66-94%) were obtained for all cases after the reactions proceeded at 40 °C for 2 hours. However, the cis-diols appear lower reactivity and require longer reaction times (Entries 9 - 10 in Table 2).



Figure 2. A proposed mechanism for iron(III)-catalyzed benzylation with $\mbox{Ag}_2\mbox{O}$ and TBABr as co-catalysts

A mechanism was proposed in Figure 2. The cyclic dioxolanetype intermediate formed by tin or iron catalyst with two adjacent hydroxyl groups plays key roles for the benzylation selectivity. The resulted regioeslectivity by intrinsic reactivities of diols, including 1,2-diols, 1,3-diols, cis-diols, and trans-diols, has been fully discussed in our previous studies.^{8b} In the present systems, the regioselectivity should rely not only on the conditions but also to some favorable intrinsic relative reactivity of diols, notably diols exhibiting the axial-equatorial relationship (cisdiols). Ag₂O turns into a strong base after the coordination of bromide to silver, which favors the formation of this cyclic intermediate. Meanwhile, Ag₂O as a Lewis acid can also activate the leaving of bromide from the benzylation reagent. Ag₂O is partially recycled in the catalytic process through the decomposing of AgOH. Consequently, the whole reaction can be performed under mild condition with high efficiency through the addition of catalytic amount of Ag₂O and TBAB.

In conclusion, by the mechanism analysis on the enhanced basicity of Ag_2O by the coordination of soft anions to silver, we proposed that Ag_2O be partially recycled in Ag_2O -mediated protections. Some of these protections may be highly improved in reaction efficiency through the addition of bromide anion if strong basicity favors these reactions. The conjecture was then supported by tests in four types of Ag_2O -mediated protections. Finally, a green regioselective benzylation method with both mild temperature and high reaction efficiency (short reaction time) were firstly developed in this study. With the use of 0.6 equivalents of Ag_2O and 0.1 equivalents of bromide anions as co-catalysts, both the organotin-catalyzed benzylation and the iron(III)-catalyzed benzylation can proceed to completion at 40

°C in 2 - 3 hours. Good isolated yields were obtained in all cases. This directly translates into high regioselectivities.

Experimental Section

General Preparation method for Fresh Ag₂O: A stoichiometric amount of saturated sodium hydroxide solution was added dropwise to a silver nitrate aqueous solution (10 mL, 0.2 M) to form a large amount of precipitate. After being filtered, washed with deionized water for three times, washed with ethanol and dried at 40 °C, solid silver oxide was obtained as brown powder.

General procedure of Ag2O-mediated organotin/Fe (III)-catalyzed selective benzylation: Substrates (100 mg) were allowed to react with BnBr (1.5 equiv.) in dry acetonitrile (1 mL) at 40 oC for 2 - 3 h in the presence of Ag2O (0.6 equiv.), TBAB (0.1 equiv.) and Me2SnCl2/Fe(dibm)3 (0.1 equiv.). The reaction mixture was filtered and directly purified by flash column chromatography (hexanes/EtOAc = 3:1 to 1:1) to afford the pure products.

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Keywords: silver catalysis • iron(III) catalysis • Ag₂O • regioselective benzylation • green

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