Theses of doctoral (PhD) dissertation

Coupling reactions of anhydro-aldose tosylhydrazones

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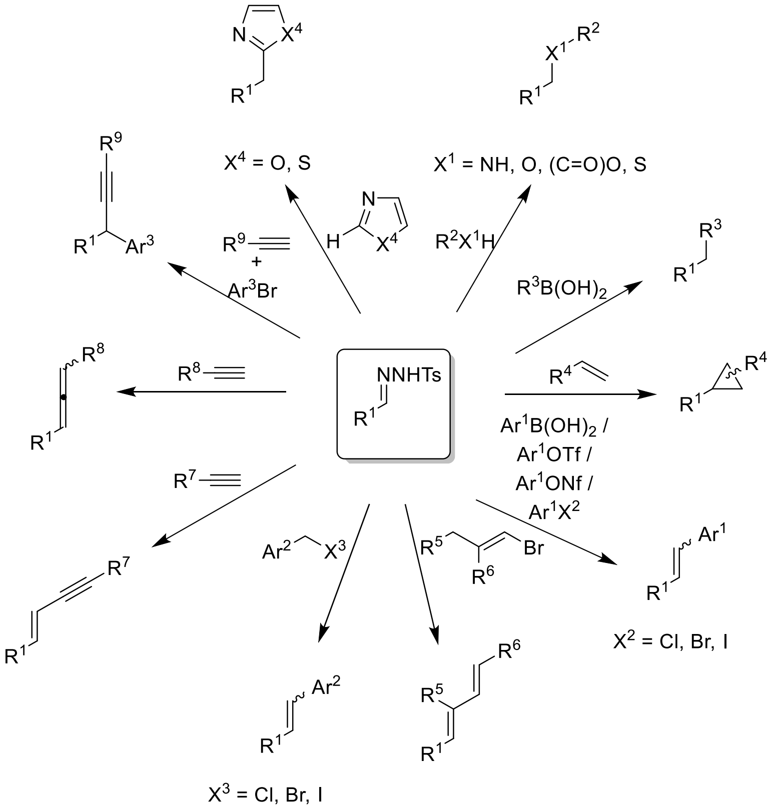
1. Introduction and objectives

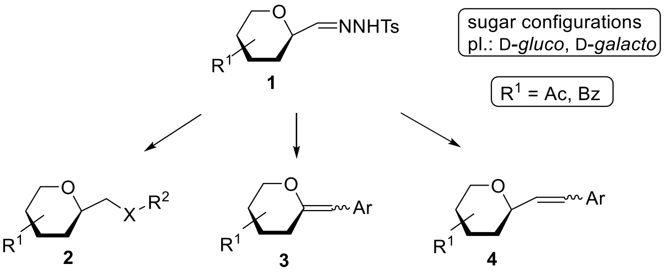
Metal-catalysed and metal-free coupling reactions have fundamentally changed the way how complex organic molecules are assembled nowadays. Couplings of carbohydrates are not frequent because the subtituents easily eliminate. Functional and protecting group intolerance of most of the necessary orgametallic reagents is another drawback.

In the last decade *N*-tosylhydrazones emerged as partners in both metal-catalysed and metal-free coupling reactions. Synthetic utility of these compounds as carbene precursors is very large (Scheme 1). Tosylhydrazones can be easily prepared from aldehydes or ketones, however, tosylhydrazones of anhydro-aldoses are not readily available, and their preparation needs special methods. Our group has elaborated a simple synthetic procedure for this type of compounds: reduction of glycosyl cyanides with *in situ* trapping of the intermediate imine by tosylhydrazine.



Scheme 1 Synthetic utilities of *N*-tosylhydrazones

Based on this background our aim was the examination of metal-free and Pd-catalysed coupling reactions of anhydro-aldose tosylhydrazones **1** (Scheme 2), which is a new field in carbohydrate chemistry. We envisaged to investigate the coupling reactions of tosylhydrazones **1** with alcohols, phenols, carboxylic acids and thiols under metal-free conditions to get glycopyranosylmethyl compounds **2**. Another goal of our work was to study the Pd-catalyzed couplings of tosylhydrazones **1** with aryl and benzyl halides to give substituted *exo*-glycals **3** and ω-*C*-glycosyl styrenes **4**. The low hydrolytic stability of natural *O*-glycosidic bonds reduces the applicability of carbohydrate-type molecules as drug candidates. The replacement of the glycosidic oxygen with other atoms, such as S, N, and C may result in hydrolytically more stable moieties, thus the planned transformations may open simpler and shorter ways for the syntheses of glycomimetic compounds.



R^2 = alkyl, heteroalkyl, aryl, heteroaryl, sugar
X = O, C(=O)O, S

Scheme 2 Planned transformations of anhydro-aldose tosylhydrazones

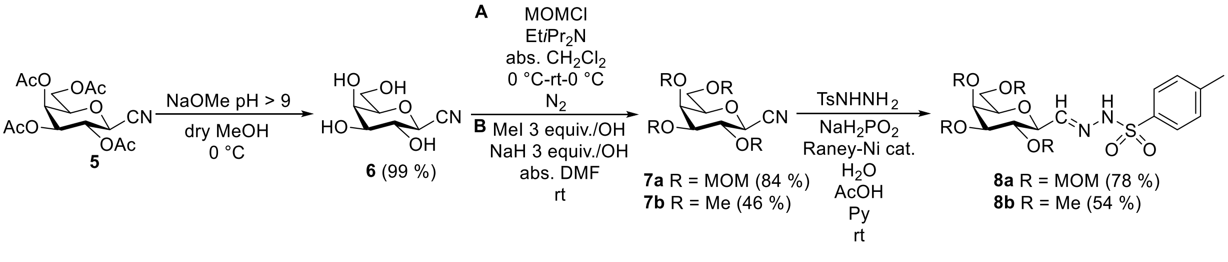
2. Applied methods

In the course of our synthetic work, macro, semi micro and micro methods of modern preparative organic chemistry were applied. Reactions were monitored by thin-layer chromatography. Products of the reactions were purified by column chromatography and/or by crystallization. New compounds were characterized by their physical property (optical rotation) and their structures were elucidated by 1D- and 2D-, ^{1}H- and ^{13}C-NMR methods as well as mass spectrometry.

3. New results of the dissertation

3.1. Synthesis of *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazones with ether type protecting groups

Galactopyranosyl cyanide **5** was deacetylated under Zemplén conditions to give the deprotected **6**, which was reacted with MOMCl (method **A**) to yield the *O*-permethoxymethylated compound **7a**. Reaction of **5** with methyl-iodide (method **B**) resulted in cyanide **7b**. Reduction of compounds **7** in the presence of tosylhydrazine furnished tosylhydrazones **8** in good to moderate yields.

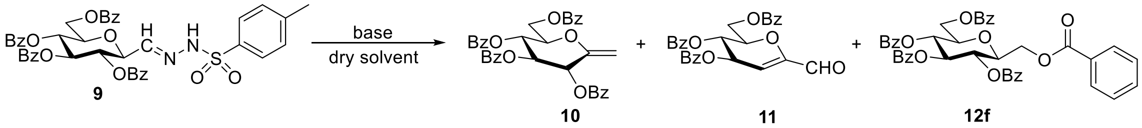


Scheme 3 Synthesis of *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazones with ether type protecting groups

3.2. Examination of the generation of *C*-glucosylmethylene carbenes

Generation of *C*-glucosylmethylene carbene from tosylhydrazone **9** was studied in the presence of various bases to result in *exo*-glucal **10**. The best results were achieved in the presence of K_3PO_4 in 1,4-dioxane at reflux temperature or with LiO*t*Bu at 110 °C in a sealed tube (Table 1). Based on these results coupling reactions were mainly performed under these reaction conditions.

Table 1 Generation of *C*-glucosylmethylene carbenes



Entry	Base (equiv.)	dry Solvent	Yield (%)		
			10	**11**	**12f**
1	NaH (10)	1,4-dioxane	72	-	-
2	K_2CO_3 (1.5)	1,4-dioxane	21	5	16
3	K_2CO_3 (5)	1,4-dioxane	26	6	9
4	K_2CO_3 (10)	1,4-dioxane	25	9	5
5	LiO*t*Bu (1.5)	1,4-dioxane	50[a]	-	-
6	LiO*t*Bu (5)	1,4-dioxane	24	-	-
7	$(n\text{-Bu})_4NF$ (5)	1,4-dioxane	44	+	14
8	K_3PO_4 (3)	1,4-dioxane	46	-	-
9	K_3PO_4 (5)	1,4-dioxane	70	-	-
10	K_3PO_4 (5)	PhF	10	-	-
11	K_3PO_4 (5)	PhF	29[b]	-	-

[a] Performed in a sealed tube, 110 °C, Ar

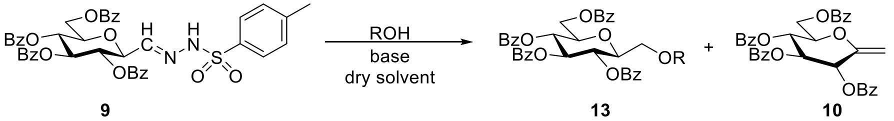
[b] Performed in a sealed tube, 100 °C

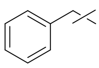
3.3. Metal-free coupling reactions – Formation of C-O bonds

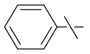
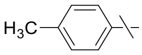
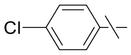
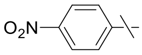
3.3.1. Synthesis of β-D-glucopyranosylmethyl ethers

Tosylhydrazone **9** was reacted with alcohols and phenols under UV-irradiation, microwave or conventional thermic activation. Coupling of compound **9** with alcohols failed, except 1,1,1,3,3,3-hexafluorpropanol which provided ether **13a** in moderate yield. Reactions with phenols resulted in the corresponding ethers **13b**,**d**,**e** in low and moderate yields. E*xo*-glucal **10** was isolated as a by-product in these experiments (Table 2).

Table 2 Coupling of *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone with alcohols and phenols



Entry		R	ROH (equiv.)	Base (equiv.)	dry Solvent	T (°C)	t (h)	Yield (%)	
								13	**10**
1		CH_3CH_2-		K_3PO_4 (5)	ethanol	78	3	Decomposition	
2		$(CH_3)_3C$-	20	K_3PO_4 (10)	1,4-dioxane	80	3	-	28
3			20	LiO*t*Bu (1.2)	PhF	100[a]	0.25	-	42
4			20	LiO*t*Bu (1.2)	PhF	100[a]	0.25	-	+
5	**a**	$(CF_3)_2CH$-	20	LiO*t*Bu (1.2)	1,4-dioxane	110[b]	0.5	35	28
6			20	LiO*t*Bu (1.2)	PhF	100[a]	0.25	25	5

7	**b**		35	K_3PO_4 (10)	1,4-dioxane	101	1	-	-
8			33	LiO*t*Bu (1.5)	1,4-dioxane	110^b	1	25	45
9			20	LiO*t*Bu (1.5)	1,4-dioxane	25^c	1.5	8	33
10	**c**		5	K_3PO_4 (2)	1,4-dioxane	110^b	0.5	+	42
11			20	LiO*t*Bu (1.2)	1,4-dioxane	110^b	0.5	+	55
12	**d**		20	K_3PO_4 (5)	1,4-dioxane	110^b	1	20^d	-
13			20	LiO*t*Bu (1.2)	1,4-dioxane	101	0.5	30	13^d
14			20	LiO*t*Bu (1.2)	PhF	100^b	17.5	39	-
15			2	K_2CO_3 (3.5)	PhF	155^a	0.3	17	+
16	**e**		20	K_3PO_4 (10)	1,4-dioxane	110^b	0.5	28	-
17			20	LiO*t*Bu (1.2)	1,4-dioxane	110^b	0.5	34	+

[a] MW (150 W 100 °C, 200 W 155 °C)

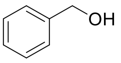
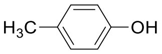
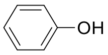
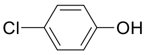
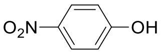
[b] Performed in a sealed tube

[c] Irradiation with mercury vapour lamp (250 W, λ_{max}=365 nm)

[d] Yields were calculated on the basis of the ^1H NMR spectra of the worked-up reaction mixtures

The acidity of the reagents and the yield of the reactions showed a good correlation. Reactions in the presence of alcohols and phenols with p*K*a > 10 failed (Table 3, entries 1–4), but resulted in products **13a**,**b**,**d**,**e** with low and moderate yields (Table 3, entries 5–8) when p*K*a < 10.

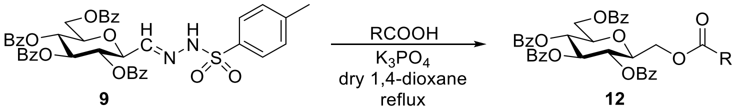
Table 3 Comparison of the acidity (p*K*a) of the investigated alcohols and phenols and its influence on the yields

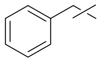
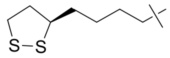
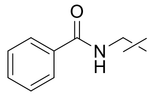
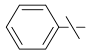
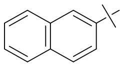
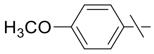
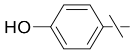
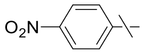
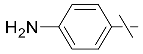
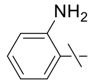
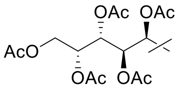
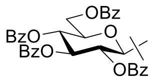
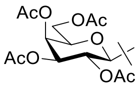
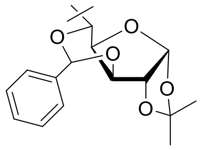
Entry	ROH	ROH (equiv.) (number of compounds)	Yield (%) (number of compounds)	p*K*a
1	$(CH_3)_3COH$	20 (**9**)	-	17.0
2	CH_3CH_2OH	20 (**9**)	-	15.5
3		20 (**9**)	-	14.4
4		20 (**9**)	in trace (**13c**)	10.3
5		20 (**9**)	25 (**13b**)	9.9
6		20 (**9**)	30 (**13d**)	9.4
7	$(CF_3)_2CHOH$	20 (**9**)	35 (**13a**)	9.3
8		20 (**9**)	34 (**13e**)	7.2

3.3.2. Synthesis of β-D-glycopyranosylmethyl esters

The coupling reactions of tosylhydrazone **9** and carboxylic acids resulted in esters **12**. Aliphatic esters **12a–e** were prepared in poor (**12a**,**e**) to moderate (**12b–d**) yields (Table 4, entries 1–6). The aromatic **12f–l** and sugar esters **12m–p** were isolated in low (**12f**,**h**), moderate (**12g**,**i–l** and **12m**,**o**) and good (**12n**,**p**) yields (Table 4, entries 7–18).

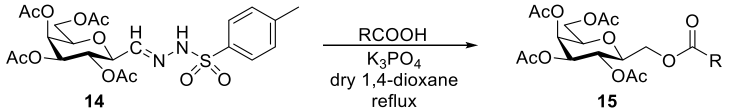
Table 4 Coupling of *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone with carboxylic acids

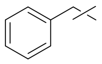
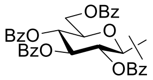


Entry		R	RCOOH (equiv.)	K_3PO_4 (equiv.)	Yield (%) **12**
1	**a**	CH_3-	20	10	31
2	**b**	CH_3CH_2-	20	10	49
3	**c**		20	10	58
4			2	2	39
5	**d**		5	5	39
6	**e**		5	5	28
7	**f**		40	20	22
8	**g**		20	10	37
9	**h**		20	25	29
10	**i**		20	20	43
11	**j**		20	25	51
12			5	9	33
13	**k**		3	8	36
14	**l**		20	15	51
15	**m**		5	5	48
16	**n**		5	4	60
17	**o**		5	3	58
18	**p**		5	5	66

Experiments were extended to the D-*galacto* configured tosylhydrazone **14**. The corresponding aliphatic β-D-galactopyranosylmethyl esters **15a–c** were obtained in low (**15b**,**c**) and moderate (**15a**) yields, the sugar ester **15d** was isolated in good yield (Table 5).

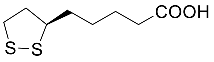
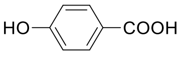
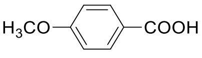
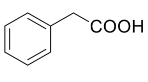
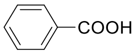
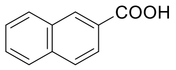
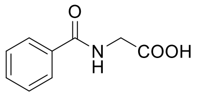
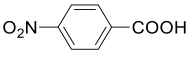
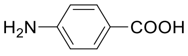
Table 5 Coupling of *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazone with carboxylic acids

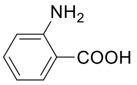
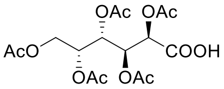
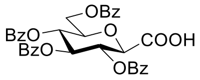
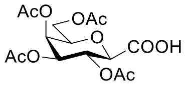
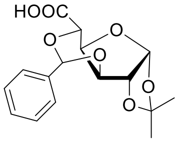


Entry		R	RCOOH (equiv.)	K_3PO_4 (equiv.)	Yield (%) **15**
1	**a**	CH_3-	20	10	51
2	**b**	CH_3CH_2-	5	4	30
3	**c**		2	2	25
4	**d**		5	3	75

The correlation of the acidity of the reagents and the yields was also examined. Carboxylic acids with pK_a > 3 gave esters in low to moderate yields (**12a–j**, **15a–c**, Table 6, entries 1–10), however with pK_a < 3 furnished the coupled products in moderate and good yields (**12k–p**, **15d**, Table 6, entries 11–16).

Table 6 Comparison of the acidity (pK_a) of the investigated carboxylic acids and its influence on the yields

Entry	RCOOH	RCOOH (equiv.) (number of compounds)	Yield (%) (number of compounds)	pK_a
1	CH_3CH_2COOH	20 (**9**) 5 (**14**)	49 (**12b**) 30 (**15b**)	4.9
2	CH_3COOH	20 (**9**) 20 (**14**)	31 (**12a**) 51 (**15a**)	4.8
3		5 (**9**)	39 (**12d**)	4.8
4		20 (**9**)	43 (**12h**)	4.6
5		20 (**9**)	29 (**12i**)	4.5
6		20 (**9**) 2 (**14**)	58 (**12c**) 21 (**15c**)	4.3
7		20 (**9**)	22 (**12f**)	4.2
8		20 (**9**)	37 (**12g**)	4.2
9		5 (**9**)	28 (**12e**)	3.6
10		20 (**9**)	51 (**12j**)	3.4
11		3 (**9**)	36 (**12k**)	2.5

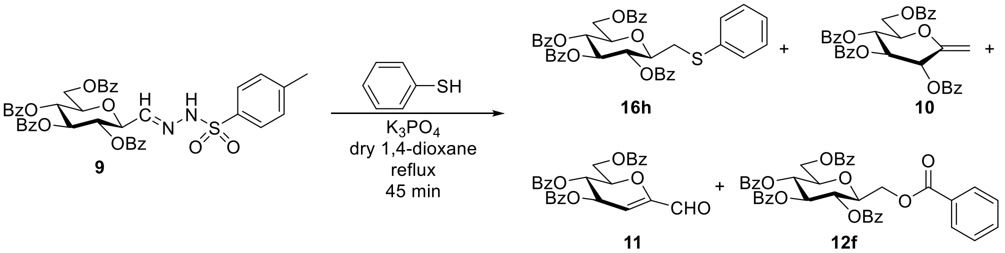
12		20 (**9**)	51 (**12l**)	2.2
13		5 (**9**)	48 (**12m**)	2.3–2.6
14		5 (**9**) 5 (**14**)	60 (**12n**) 75 (**15d**)	
15		5 (**9**)	58 (**12o**)	
16		5 (**9**)	66 (**12p**)	

3.4. Metal-free coupling reactions – Formation of C-S bonds

Synthesis of β-D-glycopyranosylmethyl sulfides

Coupling reactions of tosylhydrazone **9** with thiols was optimized with thiophenol (Table 7). The best reagent and base ratios were 20 : 10, 5 : 2 és 2 : 2, which provided sulfide **16h** in good yields (Table 7, entries 1, 5 and 7). So these conditions were employed in the following transformations.

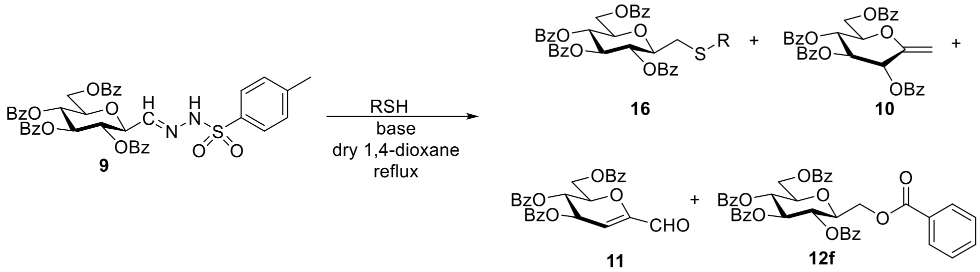
Table 7 Optimization of the reaction conditions and the coupling of *C*-(β-D-glucotopyranosyl)formaldehyde tosylhydrazone with thiophenol

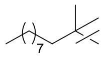
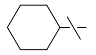
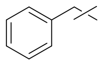
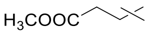
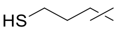
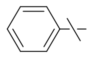
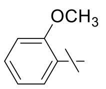
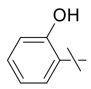
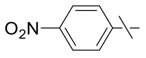


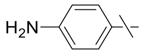
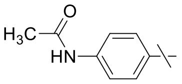
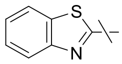
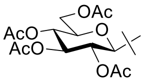
Entry	Reaction conditions		Yield (%)			
	PhSH (equiv.)	K_3PO_4 (equiv.)	**16h**	**10**	**11**	**12f**
1	20	10	70	3	-	-
2	10	10	40	23	-	-
3	2	10	33	18	-	-
4	5	5	44	13	+	-
5	5	2	76	+	+	+
6	4	2	53	12	-	+
7	2	2	72	-	+	-
8	1	1,5	59	-	+	-

Next, analogous reactions with other thiols were performed. The couplings gave the corresponding aliphatic sulfides **16a–g** in low (**16b**,**c**,**f**) and moderate (**16a**,**d**,**e**,**g**) yields (Table 8, entries 1–13), while low (**16l**), moderate (**16k**) and good (**16h–j**,**m**,**n-I**) yields were achieved in the case of aromatic and heteroaromatic sulphides **16h–n** (Table 8, entries 14–26). However, the reactions failed with sugar thiols (Table 8, entry 27).

Table 8 Coupling of *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone with thiols



Entry		R	RSH (equiv.)	Base (equiv.)	Yield (%)	
					16	**10**
1	**a**	CH_3CH_2-	20	K_3PO_4 (10)	51	-[a]
2			20	LiO*t*Bu (1.2)	53[b]	3
3	**b**	$CH_3CH_2CH_2$-	20	K_3PO_4 (10)	29	-[a]
4	**c**		20	K_3PO_4 (10)	17	+[a,d]
5	**d**		20	K_3PO_4 (10)	39	-
6			5	K_3PO_4 (2)	22[c]	11[c,d]
7			20	LiO*t*Bu (1.2)	27[b,c]	36[c]
8	**e**		20	K_3PO_4 (10)	44	+[d]
9			20	LiO*t*Bu (1.2)	34[c]	17[d]
10	**f**		20	K_3PO_4 (10)	23	+
11	**g**		20	K_3PO_4 (10)	37	+[a,d]
12			0.5	K_3PO_4 (2)	7	5[d]
13			20	LiO*t*Bu (1.2)	42[c]	-
14	**h**		20	K_3PO_4 (10)	70	+[a,d]
15			5	K_3PO_4 (2)	76	+[a,d]
16	**i**		20	K_3PO_4 (10)	69	+
17			5	K_3PO_4 (2)	64	+[a]
18			2	K_3PO_4 (2)	55	-
19			5	LiO*t*Bu (1.2)	63[b]	+
20	**j**		20	K_3PO_4 (10)	68	-
21			5	K_3PO_4 (2)	64	
22	**k**		5	K_3PO_4 (6)	54	-

23	**l**		20	K_3PO_4 (10)	23	-
24	**m**		5	K_3PO_4 (2)	65	-
25	**n-I**		5	K_3PO_4 (2)	70[e]	-
26			2	K_3PO_4 (2)	51[b,e]	-
27			20	K_3PO_4 (10)	Complex reaction mixture	

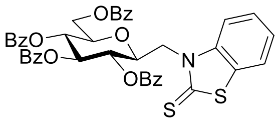
[a] Compound **11** was detected in the mixture

[b] Performed in a sealed tube, 110°C

[c] Yields were calculated on the basis of the ^{1}H NMR spectra of the worked-up reaction mixtures

[d] Compound **12f** was detected in the mixture

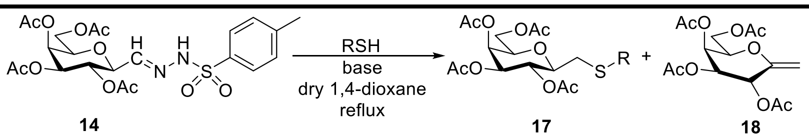
[e] Compound **16n-II** was also isolated in a 10 % yield



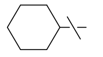
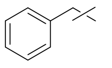
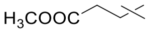
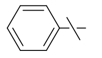
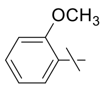
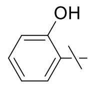
16n-II

The experiments were extended to *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazone **14**, as well. Aliphatic sulfides **17a–e** were isolated in low (**17a**,**b**,**d**) and moderate (**17c**,**e**) yields, while aromatic sulfides **17f–h** were obtained in moderate (**17h**) and good (**17f**,**g**) yields (Table 9).

Table 9 Coupling of *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazone with thiols



14 **17** **18**

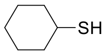
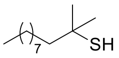
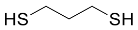
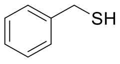
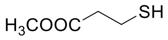
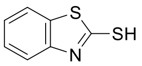
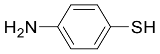
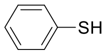
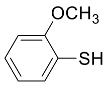
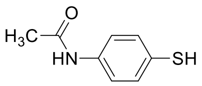
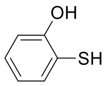
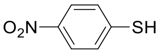
Entry		R	RSH (equiv.)	Base (equiv.)	Yield (%)	
					17	**18**
1	**a**	CH_3CH_2-	20	K_3PO_4 (10)	16	25
2	**b**	$CH_3CH_2CH_2$-	20	K_3PO_4 (10)	30	+
3	**c**		20	K_3PO_4 (10)	51[a]	+
4			5	K_3PO_4 (2)	36	+
5	**d**		20	K_3PO_4 (10)	27	-
6	**e**		20	K_3PO_4 (10)	39	+
7			20	LiO*t*Bu (1.2)	55[b]	-
8	**f**		20	K_3PO_4 (10)	62	+
9			5	K_3PO_4 (2)	77	+
10	**g**		20	K_3PO_4 (10)	60	+
11	**h**		20	K_3PO_4 (10)	51	-

[a] Yields were calculated on the basis of the ^{1}H NMR spectra of the worked-up reaction mixtures

[b] Perfomed in a sealed tube, 110 °C

The acidity of the thiols and the yields of the transformations were in good correlations. Thiols with pK_a > 9 provided the coupled products in low to moderate yields (**16a–g**, **17a–e**, Table 10, entries 1–7), whereas the more acidic aromatic thiols pK_s < 7 yielded the coupled products in moderate and good yields (**16h–n**, **17f–h**, Table 10, entries 8–14).

Table 10 Comparison of the acidity (pK_a) of the investigated thiols and its influence on the yields

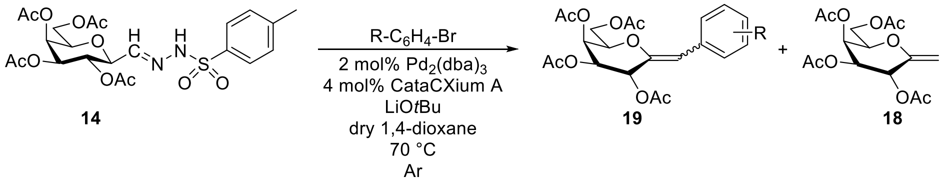
Entry	RSH	RSH (equiv.) (number of compounds)	Yield (%) (number of compounds)	pK_a
1		20 (**9**) 5 (**14**)	39 (**16d**) 36 (**17c**)	10.7
2	CH_3CH_2SH	20 (**9**) 20 (**14**)	51 (**16a**) 16 (**17a**)	10.5
3	$CH_3CH_2CH_2SH$	20 (**9**) 20 (**14**)	29 (**16b**) 30 (**17b**)	10.2
4		20 (**9**)	17 (**16c**)	10.0
5		20 (**9**)	37 (**16g**)	9.9 and 10.5
6		20 (**9**) 20 (**14**)	44 (**16e**) 27 (**17d**)	9.4
7		20 (**9**) 20 (**14**)	23 (**16f**) 39 (**17e**)	9.3
8		5 (**9**)	70 (**16n**)	6.9
9		20 (**9**)	23 (**16k**)	6.9
10		5 (**9**) 5 (**14**)	76 (**16h**) 77 (**17f**)	6.6
11		5 (**9**) 20 (**14**)	64 (**16i**) 60 (**17g**)	6.1
12		5 (**9**)	65 (**16l**)	6.1
13		20 (**9**) 20 (**14**)	68 (**16m**) 51 (**17h**)	6.0
14		5 (**9**)	54 (**16j**)	4.7

3.5. Palladium-catalyzed coupling reactions – Formation of C-C bonds

3.5.1. Synthesis of substituted *exo*-glycals

The Pd-catalyzed couplings of tosylhydrazones **8b** and **14** with aryl halides were optimized in the Department of Chemistry, University of Rostock. Transformation of the *O*-permethylated tosylhydrazone **8b** gave the corresponding *exo*-galactals in good yields (Ph: 61 %, 4-CH_3Ph: 75 %). Compound **14** was reacted with aryl halides in the presence of $Pd_2(dba)_3$, CataCXium A and LiO*t*Bu in 1,4-dioxane, at 70 °C to give the corresponding aryl substituted *exo*-galactals **19a–c** in low (**19b**,**c**) and moderate (**19a**) yields (Table 11).

Table 11 Pd-catalyzed coupling of *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazone with aryl bromides

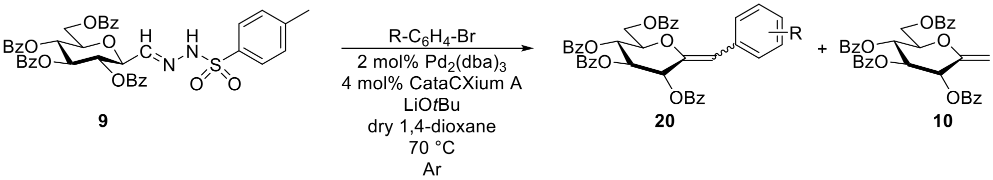


Entry		R	R-C_6H_4-Br (equiv.)	LiO*t*Bu (equiv.)	Yield (%)[a]		
					19	**19**: *E*:*Z*	**18**
1	**a**	H	3	2.2	44	1:3	22
2	**b**	4-CH_3O	3	2.2	21	1:4	16
3	**c**	4-Cl	6	2.2	6	1:3	2

[a] Yields were calculated on the basis of the ^1H NMR spectra of the worked-up reaction mixtures

The reactions were extended to D-*gluco* tosylhydrazone **9**, and substituted *exo*-glucals **20a–g** were prepared in low (**20a**,**c–e**,**g**) and moderate (**20b**,**f**) yields (Table 12).

Table 12 Pd-catalyzed coupling of *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone with aryl bromides



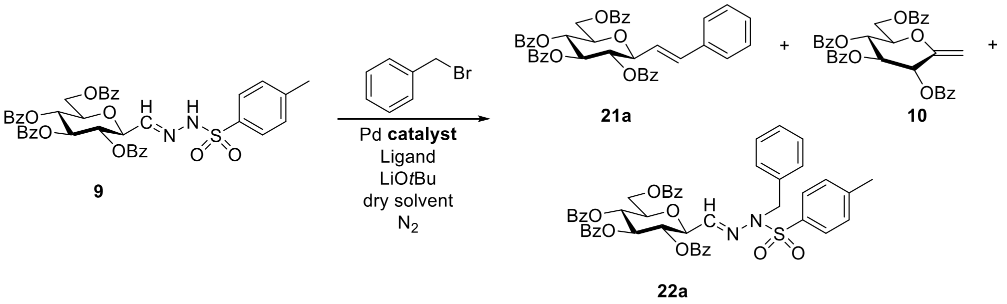
Entry		R	R-C_6H_4-Br (equiv.)	LiO*t*Bu (equiv.)	Yield (%)		
					20	**20**: *E*:Z	**10**
1	**a**	H	3	2.2	24[a]	1:2	36[a]
2	**b**	4-CH_3	6	2.2	41[a]	1:2	19[a]
3	**c**	4-CH_3O	3	2.2	11	1:2	27
4	**d**	4-F	6	2.2	32[a]	1:2	16[a]
5	**e**	4-NO_2	6	1.5	33	1:2	24
6	**f**	4-CN	6	2.2	46	1:2	4
7	**g**	3-CN	6	1.5	20	1:2	+

[a] Yields were calculated on the basis of the ^1H NMR spectra of the worked-up reaction mixtures

3.5.2. Synthesis of ω-(*C*-glycopyranosyl)styrenes

This type of coupling was optimized with tosylhydrazone **9** and benzyl bromide. The best conditions ($Pd_2(dba)_3$ catalyst, P(2-furil)$_3$ ligand, LiO*t*Bu base, 1,4-dioxane, 70 °C) was applied in the following experiments (Table 13, entries 7–9).

Table 13 Optimization of the Pd-catalyzed coupling of *C*-(β-D-glucopyranosyl)formaldehyde tosylhydrazone with benzyl bromide

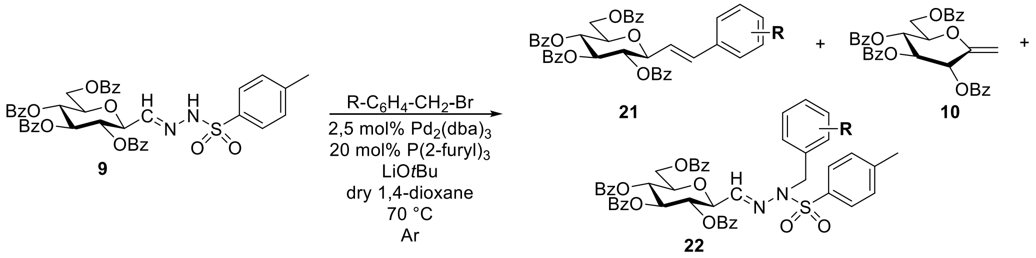


E.	Pd catalyst (mol%)	Ligand (mol%)	BnBr (equiv.)	LiO*t*Bu (equiv.)	dry Solvent	T (°C)	Yield (%)		
							21a	**10**	**22a**
1	Pd(OAc)$_2$ (5)	XPhos (20)	1	3	1,4-dioxane	70	3	15	4
2	Pd(OAc)$_2$ (5)	P(2-furyl)$_3$ (20)	1	3	1,4-dioxane	70	25	+	-
3	Pd(OAc)$_2$ (5)	CataCXium A (20)	1	3	1,4-dioxane	70	3	4	1
4	Pd(OAc)$_2$ (5)	DPPF (20)	1	3	1,4-dioxane	70	24	2	1
5	Pd(OAc)$_2$ (5)	DPPP (20)	1	3	1,4-dioxane	70	3	7	+
6	$Pd_2(dba)_3$ (2.5)	P(2-furyl)$_3$ (20)	1	3	1,4-dioxane	101	4	-	-
7	$Pd_2(dba)_3$ (2.5)	P(2-furyl)$_3$ (20)	1	3	toluene	80	32	2	3
8	$Pd_2(dba)_3$ (2.5)	P(2-furyl)$_3$ (20)	3	1.5	1,4-dioxane	70	22	-	-
9	$Pd_2(dba)_3$ (2.5)	P(2-furyl)$_3$ (20)	6	1.5	1,4-dioxane	70	48	11	-

[a] Yields were calculated on the basis of the ^{1}H NMR spectra of the worked-up reaction mixtures

Transformation of tosylhydrazone **9** with substituted benzyl bromides gave the corresponding styrenes **21a**–**k** in low (**21c**,**d**,**k**) and moderate (**21a**,**b**,**e**–**j**) yields (Table 14).

Table 14 Pd-catalyzed coupling of *C*-(β-D-glucotopyranosyl)formaldehyde tosylhydrazone with benzyl bromides

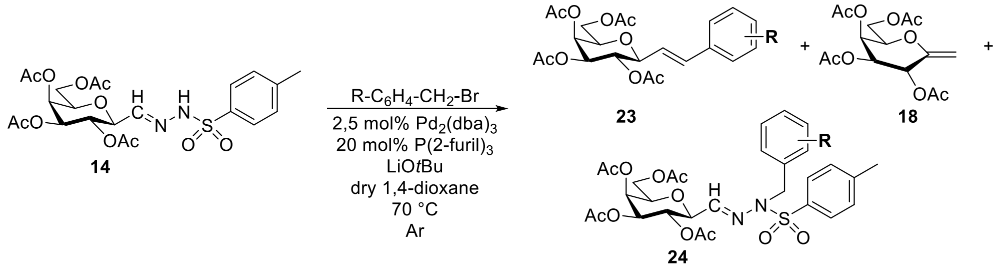


Entry		R	R-C_6H_4-CH_2-Br (equiv.)	LiO*t*Bu (equiv.)	Yield (%)		
					21	**10**	**22**
1	**a**	H	6	1.5	48	11	-
2	**b**	4-CH_3	6	1.5	40	6	11
3	**c**	3-CH_3	6	1.5	17[a]	26[a]	-
4	**d**	3-CH_3O	6	1.5	10	-	31
5	**e**	4-Cl	6	1.5	40	5	14
6	**f**	3-Cl	6	1.5	42	6	-
7	**g**	4-Br	6	1.5	54	4	-
8	**h**	4-Br	6	1.5	41[a]	11[a]	5
9	**i**	2-Br	6	1.5	36[a]	20[a]	2
10	**j**	4-NO_2	6	1.5	39[a, b]	+	16[a]
11	**k**	4-CN	6	1.5	27	16[a]	17[a]

[a] Yields were calculated on the basis of the ^1H NMR spectra of the worked-up reaction mixtures
[b] *E*:*Z* = 1:1

The experiments were extended to the D-*galacto* tosylhydrazone **14**. Coupling reactions provided the ω-*C*-galactosyl styrenes **23a–e** in moderate (**23c**,**e**) and good (**23a**,**b**,**d**) yields (Table 15).

Table 15 Pd-catalyzed coupling of *C*-(β-D-galactopyranosyl)formaldehyde tosylhydrazone with benzyl bromides



Entry		R	$R\text{-}C_6H_4\text{-}CH_2\text{-}Br$ (equiv.)	Li*Ot*Bu (equiv.)	Yield (%)		
					23	**18**	**24**
1	**a**	H	6	1.5	59	5	-
2	**b**	$4\text{-}CH_3$	3	2.2	55[a]	7[a]	-
3	**c**	$3\text{-}CH_3$	6	1.5	25	3	7
4	**d**	3-Cl	6	1.5	59	3	-
5	**e**	4-Br	6	1.5	31	1	9

[a] Yields were calculated on the basis of the ^{1}H NMR spectra of the worked-up reaction mixtures

4. Possible application of the resultes

This work is a basic research in carbohydrate chemistry whereby the applicability of anhydro-aldose tosylhydrazones in coupling reactions was explored. In comparison to the existing synthetic pathways, the methods elaborated represent new, alternative and simpler ways to form β-D-glycopyranosylmethyl ethers, esters and sulfides, substituted *exo*-glycals and ω-(*C*-glycosyl)styrenes, thereby opening a new possibility to get such kinds of glycomimetics.

Conferences

Lectures and posters related to the theses:

Lectures:

1. T. Kaszás, M. Tóth, L. Somsák:
   Some new reactions of anhydro-aldose tosylhydrazones
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2. M. Tóth, B. Szőcs, T. Kaszás, E. K. Szabó, T. Docsa, P. Gergely, L. Somsák
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6. B. Szőcs, T. Kaszás, E. K. Szabó, M. Tóth, T. Docsa, P. Gergely, L. Somsák:
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   26th International Carbohydrate Symposium, Madrid, Spain, July 22-27, **2012**, P399, poster

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List of publications related to the dissertation

Foreign language scientific articles in international journals (3)

1. **Kaszás, T.**, Ivanov, A., Tóth, M., Ehlers, P., Langer, P., Somsák, L.: Pd-catalyzed coupling reactions of anhydro-aldose tosylhydrazones with aryl bromides to produce substituted exo - glycals.
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   Rev. Roum. Chim. 58 (4-5), 335-345, 2013. ISSN: 0035-3930.
   IF: 0.393

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Total IF of journals (publications related to the dissertation): 8,473

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

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