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Tuning the Chemoselectivity of Silyl Protected Rhamnals by Temperature and Brønsted Acidity: Kinetically Controlled 1,2-Addition vs Thermodynamically Controlled Ferrier Rearrangement

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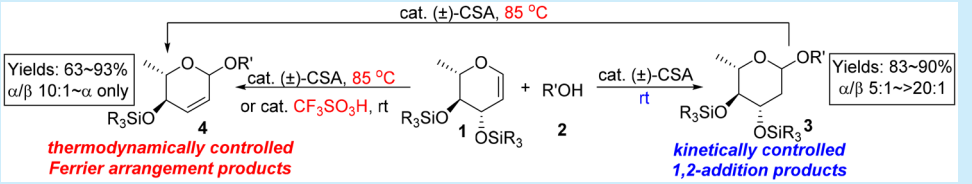
Supporting Information

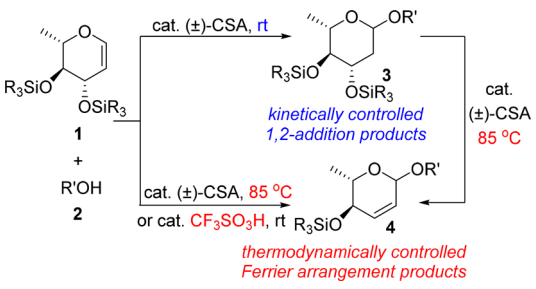


ABSTRACT: An acidity- and temperature-dependent chemoselective glycosylation of silyl-protected rhamnals with alcohols has been revealed. The reaction undergoes a 1,2-addition pathway with (±)-CSA as the catalyst at rt, affording kinetically controlled 2-deoxyl rhamnosides. In contrast, only thermodynamically controlled 2,3-unsaturated rhamnosides are formed via Ferrier rearrangement when elevating reaction temperature to 85 °C or using CF_3SO_3H instead. This tunable glycosylation allows facile and practical access to both 2-deoxyl and 2,3-unsaturated rhamnosides with excellent yields and high α-stereoselectivity.

1,2-Glycals, a kind of important synthon, have attracted increasing attention due to its easy preparation, good stability, and ready functionalization into different chemo-, regio-, and stereovarieties. They thus have been broadly employed in the synthesis of a large number of carbohydrates and other useful chiral compounds.[1] The coupling reaction between 1,2-glycals and alcohols under acidic conditions enables the preparation of 2-deoxy glycosides through 1,2-addition.[2] The 2-deoxy sugars are important structural frames found in many bioactive natural products[3] and drug molecules,[4] such as the anthracycline antibiotic daunorubicin,[4b] the anticancer drug doxorubicin,[4c] and so on. Interestingly, the reaction of 1,2-glycals with hydroxyl compounds can also lead to 2,3-unsaturated glycosides via Ferrier rearrangement pathway under certain acidic conditions.[5] The olefinic moiety in the pyran or furan rings of 2,3-unsaturated glycosides can be further diversified, and they are consequently served as important chiral intermediates in organic synthesis. Although various catalytic systems have been developed to construct either 2-deoxy glycosides[2,6] or 2,3-unsaturated glycosides,[5,7] there are only a few studies[8] on the chemoselectivity for the glycosylation of 1,2-glycals with nucleophiles which has two competing reaction pathways, 1,2-addition and Ferrier rearrangement, as well as influential factors on the selectivity.

Herein, we report an acidity- and temperature-dependent chemoselective glycosylation of silyl protected rhamnals with various alcohol acceptors (Scheme 1). 2-Deoxyl rhamnosides **3**, which are key scaffolds in a wide spectrum of bioactivities,[9] were predominantly formed via the kinetic 1,2-addition pathway when a relatively weaker acid ((±)-CSA) and lower reaction temperature (rt) were applied. In contrast, a stronger acid (CF_3SO_3H) or higher reaction temperature (85 °C) only provided 2,3-unsaturated rhamnosides **4**, versatile intermediates in organic synthesis,[10] via a thermodynamic Ferrier rearrangement pathway. This tunable glycosylation is facile and practical for the synthesis of both 2-deoxyl and 2,3-unsaturated rhamnosides with excellent yields and high α-stereoselectivity. In addition, the kinetic addition products **3** can be converted to the rearranged products **4** via glycals **1** when heated with catalytic amounts of (±)-CSA.

Scheme 1. Acidity- and Temperature-Dependent Chemoselective Glycosylation of Rhamnals



Our study commenced by using bulky silyl TBDPS protected rhamnal **1a** as a glycosyl donor and menthol **2a** as an acceptor in the presence of various acid catalysts at rt (Table 1). No reaction took place when thiourea (pK_a 8.5)[11a]

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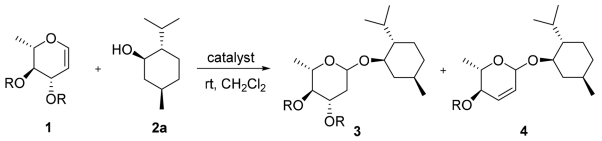
Table 1. Catalyst Screening for Chemoselective Rhamnosylation of Different Donors 1a−1e with Acceptor 2a[a]



R= TBDPS, TIPS, TBS, Ac, Bn

entry	R	cat.	compd 3: yield/%[b] (α/β)[c]	compd 4: yield/%[b] (α/β)[c]	donor recovery /%[b]
1		Thiourea	**3aa**: 0	**4aa**: 0	100
2		CH_3CO_2H	**3aa**: 0	**4aa**: 0	100
3	 1a	(±)-CSA	**3aa**: 88 (18:1)	**4aa**: 9 (15:1)	3
4		$TsOH·H_2O$	**3aa**: 75 (9:1)	**4aa**: 23 (14:1)	2
5		CF_3SO_3H	**3aa**: 0	**4aa**: 85 (16:1)	0
6		CH_3CO_2H	**3ba**: 0	**4ba**: 0	100
7	 1b	(±)-CSA	**3ba**: 70 (2.8:1)	**4ba**: 23 (>20:1)	6
8		CF_3SO_3H	**3ba**: 0	**4ba**: 92 (10:1)	4
9	 1c	(±)-CSA	**3ca**: 0	**4ca**: 0	0
10	 1d	(±)-CSA	**3da**: 38 (1.5:1)	**4da**: 30 (>20:1)	0
11		CF_3SO_3H	**3da**: 41 (7.5:1)	**4da**: 8 (>20:1)	0
12	 1e	(±)-CSA	**3ea**: 54 (1.3:1)	**4ea**: 23 (>20:1)	0
13		CF_3SO_3H	**3ea**: 59 (1:1)	**4ea**: 21 (5.5:1)	0

[a]Reaction of donor **1**, acceptor **2a** (1.2 equiv), and catalyst (0.1 equiv) in DCM at rt under Ar atmosphere. [b]Isolated yield. [c]Determined by ^{1}H NMR spectra of the reaction mixture.

or acetic acid (pK_a 4.76)[11b] was used as an acid catalyst, and the glycal donor **1a** was recovered completely (entries 1−2). When (±)-CSA (pK_a 1.17)[11c] was taken as the acid catalyst, to our delight, the 1,2-addition product, 2-deoxy rhamnoside **3aa**, was obtained as the major product in 88% yield with excellent anomeric α-selectivity (α/β 18:1). Meanwhile, a small amount of 2,3-unsaturated glycoside **4aa** from the competing Ferrier rearrangement was also observed (9%, α/β 15:1) (entry 3). Interestingly, when the reaction was treated with catalytic amounts of $TsOH·H_2O$ (pK_a −2.8),[11d] the yield of the addition product **3aa** decreased (from 88% to 75%, entries 3 and 4) while that of **4aa** increased remarkably (from 9% to 23%, entries 3 and 4). More interestingly, when strong acid CF_3SO_3H (pK_a −14)[11c] was employed, the Ferrier rearranged product **4aa** could be obtained in 85% yield (α/β 16:1) without any formation of **3aa** detected (entry 5). Further exploration was conducted on different silyl protected donors **1b** and **1c** with menthol **2a**. For TIPS-protected glycal **1b**, none of the addition product **3ba** or rearranged product **4ba** was observed with AcOH as the acid catalyst (entry 6). As expected, when using (±)-CSA as the catalyst, the 1,2-addition product **3ba** could be obtained as the major product (70%, α/β 2.8:1) with the rearranged product **4ba** as the minor product (23%, α/β> 20:1, entry 7). When a catalytic amount of CF_3SO_3H was applied, the rearranged product **4ba** was formed in 92% yield (α/β 16:1) with no formation of **3ba** (entry 8). Unfortunately, the reaction of TBS-protected glycal **1c** with menthol **2a** led to complex mixtures under the current acidic catalyst system (entry 9), presumably due to the acidic lability of TBS protecting group. The outcomes of the above experiments (entries 1−8) suggest that the silyl protected rhamnal donors tend to undergo 1,2-addition to provide 2-deoxyglycosides under the catalysis of an appropriate acid (such as (±)-CSA). However, the competing Ferrier rearrangement would progressively become the prevailing reaction pathway with the increase of the acidity of the catalyst. When the acid strength reaches a certain threshold (for example, CF_3SO_3H, pK_a −14), only Ferrier rearrangement occurs with no 1,2-addition product observed. It should be noted that this interesting phenomenon is only observed from the silyl protected glycal donors (**1a** and **1b**) while other rhamnal donors, such as the acyl or benzyl protected one (**1d** and **1e**), does not show this acidity-dependent behavior (entries 10−13).

After exploring the effect of catalyst acidity on the rhamnosylation, we next investigated the effect of the reaction temperature. Various rhamnals **1a−1e** were reacted with **2a** in the catalysis of (±)-CSA at different temperatures (Table 2). It was observed that the increase of the reaction temperature led to the sharp decrease of the ratio of the addition product **3aa** to the rearranged product **4aa** using the TBDPS-protected glycal **1a** as the substrate (entries 1−7). When the temperature rose to 85 °C, **4aa** could be gained in excellent yields with high α-selectivity without any **3aa** observed (entry 7). The TIPS-protected glycal **1b** behaved similar to the case where low temperature favors 1,2-addition and high temperature favors Ferrier rearrangement (entries 8−11). To our surprise, no such behavior was observed on acyl or benzyl protected glycal **2c** or **2d** (entries 12−15). It seems that the bulky silyl protecting groups at C3 and C4 play significant roles in both the acidity- and temperature-dependent chemoselectivity for the glycosylation of rhamnals with acceptors, probably due to the steric hindrance and stereoelectronic characteristics of the bulky silyl groups. It has been reported that bulky silyl protecting groups on glycosyl donors have great impact on the glycosylation, such as enhancing the reactivity of donors[12] and contributing the stereoselectivity for anomers,[13] by conformational change or restriction. In our case, the silylation of the hydroxyl groups in rhanmals probably induces a distinctive difference in the activation energy of the two pathways and, as a result, leads to the chemoselectivity between the 1,2-addition and Ferrier rearrangement pathway.

Based on the above findings, we hypothesized that the glycosylation of 3,4-silyl protected rhamnals with hydroxyl compounds could undergo two competing pathways to deliver different products. When a relatively weaker acid is used as the catalyst at lower temperature, the 1,2-addition reaction prevails, leading to the kinetically controlled product 2-deoxy

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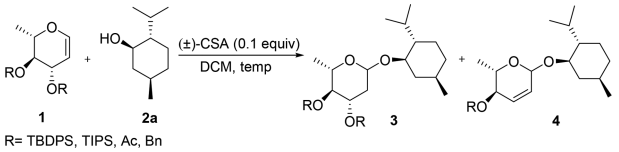
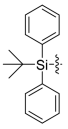
Table 2. Investigation of the Effect of Temperature on Chemoselective Rhamnosylation[a]

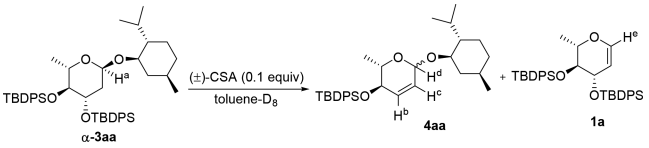


entry	R	temp (°C)	compd **3**: yield/%[b] (α/β)[c]	compd **4**: yield/%[b] (α/β)[c]	donor recovery/ %[b]
1		0	**3aa**: 72 (1.4:1)	**4aa**: 2 (n.d.)	26
2		10	**3aa**: 94 (3:1)	**4aa**: 4 (n.d.)	2
3		25	**3aa**: 89 (18:1)	**4aa**: 10 (15:1)	1
4	 1a	30	**3aa**: 82 (20:1)	**4aa**: 15 (>20:1)	3
5		35	**3aa**: 77 (>20:1)	**4aa**: 22 (>20:1)	1
6		40	**3aa**: 73 (>20:1)	**4aa**: 22 (>20:1)	5
7[d]		85	**3aa**: 0	**4aa**: 90 (>20:1)	0
8		-10	**3ba**: 89 (2.4:1)	**4ba**: 5 (5:1)	6
9	 1b	0	**3ba**: 82 (5.5:1)	**4ba**: 14 (10:1)	4
10		25	**3ba**: 69 (12:1)	**4ba**: 23 (>20:1)	8
11[d]		85	**3ba**: 0	**4ba**: 95 (>20:1)	5
12	 1d	25	**3da**: 38 (1.5:1)	**4da**: 30 (>20:1)	0
13[d]		85	**3da**: 48 (4:1)	**4da**: 51 (16:1)	0
14	 1e	25	**3ea**: 54 (1.3:1)	**4ea**: 13 (>20:1)	0
15[d]		85	**3ea**: 32 (1.4:1)	**4ea**: 25 (10:1)	0

[a]Reaction of donor **1**, acceptor **2a** (1.2 equiv), and (±)-CSA (0.1 equiv) in DCM at rt under Ar atmosphere. [b]Isolated yield. [c]Determined by ^{1}H NMR spectra of the reaction mixture. [d]1,2-DCE was used as solvent.

rhamnoside **3**. In contrast, a stronger acid catalyst or higher reaction temperature favors the pathway of Ferrier rearrangement, resulting in the thermodynamically more stable product 2,3-unsaturated rhamnosides **4**. To confirm our hypothesis, variable-temperature ^{1}H NMR experiments were carried out to monitor the transformation of **3aa** into **4aa** in an NMR tube in the presence of 0.1 equiv of (±)-CSA in toluene-D8 (Scheme 2 and Figure 1). After being placed at 40 °C for 1 h, **3aa** started to convert into **4aa** (Figure 1b). More **4aa** was formed after the mixture was placed at 60 °C for 1 h. It should be noted that 3,4-silyl protected glycal **1a**, the key elimination

Scheme 2. Investigation of the Transformation of α-3aa into 4aa through Variable-Temperature ^{1}H NMR Experiments



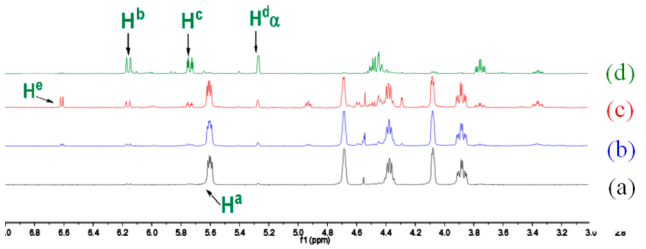


Figure 1. Crude ^{1}H NMR spectra (in toluene-D8) of the transformation of α-**3aa** into **4aa** at different temperatures: (a) rt (black), (b) 40 °C for 1 h (blue), (c) 60 °C for 1 h (red), (d) 85 °C for 2 h (green).

intermediate for the conversion of **3aa** to **4aa**, was also detected during the variable-temperature ^{1}H NMR experiments (Figure 1b and c). When the temperature was further elevated to 85 °C, most of α-**3aa** was transformed into **4aa** in 2 h (Figure 1d). The results provide strong support for our assumption that 2-deoxy rhamnosides **3** from 1,2-addition are the kinetic products and are favored under kinetic control, while 2,3-unsaturated rhamnosides **4** from Ferrier rearrangement are the thermodynamic products and are favored under thermodynamic control.

To examine the generality of our observation, various acceptors **2a**−**2h** were subjected to the glycosylation under the kinetically controlled conditions of 0.1 equiv of (±)-CSA in DCM at rt (Table 3, condition A). The reaction between **1a** and different nonsugar acceptors **2b**−**2d**, regardless of primary or second alcohol, steroidal or terpenoidal alcohol, performed well and gave the corresponding kinetically controlled α-2-deoxyl rhamnosides **3ab**−**3ad** in excellent yields (entries 1−3, condition A). The sugar-based acceptors **2e**−**2h**, including glucosyl, galactosyl, and rhamnosyl ones, were also smoothly coupled with **1a** to furnish the oligosaccharides **3ae**−**3ah** in a chemoselective manner with excellent yields and high α-selectivity (entries 4−7, condition A). In all cases, the kinetically controlled adducts **3** were obtained as the major products (yields: 83−90%) with only a small ratio of thermodynamic products **4** (ratio of **3**/**4**: 7:1−36:1) observed, demonstrating the usefulness of our findings in the synthesis of 2-deoxy rhamnosides and oligosaccharides.

The glycosylations of **1a** with **2a**−**2h** were also evaluated under the thermodynamically controlled conditions (Table 3, conditions B and C). With the treatment of 0.1 equiv of (±)-CSA in 1,2-DCE at 85 °C, 2,3-unsaturated rhamnosides/disaccharides **4** were formed in excellent yields with high α-selectivity via the thermodynamically favored Ferrier rearrangement, without formation of the addition products **3** (entries 1−7, condition B). Gratifyingly, this catalytic system tolerated a number of commonly employed protecting groups, such as isopropylidene acetals, bulky silyl ethers, benzoates, and allyl ethers. When CF_3SO_3H was used as the catalyst, the Ferrier rearrangement was still the dominant reaction pathway, affording the corresponding **4** as major products (entries 1−

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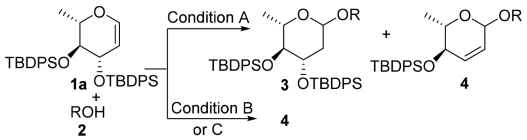
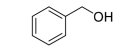
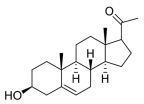
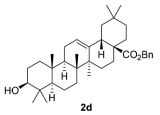
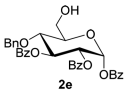
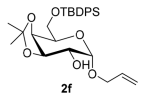
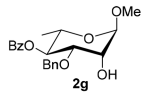
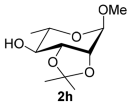
Table 3. Rhamnosylation of 1a with Various Hydroxyl Acceptor 2 under Kinetic and Thermodynamic Control



entry	ROH	results of condition A[a] compd **3**: yield/%[d] (α/β)[e]	ratio of **3**/**4**[e]	results of condition B[b] or C[c] compd **4**: yield/%[d] (α/β)[e]
1[f]	 **2b**	**3ab**: 93 (10:1)	**3ab**/**4ab**: 36:1	**4ab**: 89 (14:1)[b] 85 (10:1)[c]
2	 **2c**	**3ac**: 90 (>20:1)	**3ac**/**4ac**: 15:1	**4ac**: 93 (>20:1)[b] 80 (16:1)[c]
3	 **2d**	**3ad**: 89 (>20:1)	**3ad**/**4ad**: 11:1	**4ad**: 90 (>20:1)[b] 82 (18:1)[c]
4	 **2e**	**3ae**: 90 (5:1)	**3ae**/**4ae**: 21:1	**4ae**: 76 (only)[b] 64 (9:1)[c]
5	 **2f**	**3af**: 83 (>20:1)	**3af**/**4af**: 7:1	**4af**: 83 (20:1)[b] 63 (14:1)[c]
6	 **2g**	**3ag**: 84 (>20:1)	**3ag**/**4ag**: 7.6:1	**4ag**: 84 (>20:1)[b] 80 (15:1)[c]
7	 **2h**	**3ah**: 87 (>20:1)	**3ah**/**4ah**: 11:1	**4ah**: 87 (>20:1)[b] 68 (18:1)[c]

[a]Condition A: reaction of donor **1a**, acceptor **2** (1.2 equiv), and (±)-CSA (0.1 equiv) in DCM at rt under Ar atmosphere. [b]Condition B: reaction of donor **1a**, acceptor **2** (1.2 equiv), and (±)-CSA (0.1 equiv) in 1,2-DCE at 85 °C under Ar atmosphere. [c]Condition B: reaction of donor **1a**, acceptor **2** (1.2 equiv), and CF_3SO_3H (0.1 equiv) in DCM at rt under Ar atmosphere for 1 min. [d]Isolated yield. [e]Determined by ^1H NMR spectra of the reaction mixture. [f]Reaction of **1a** and **2b** was also carried out on a 1 mmol scale of **1a**. Under condition A, yield of **3ab** was 91% (α/β 10:1) and ratio of **3ab**/**4ab** was 30:1. Under conditions B and C, the yield of **4ab** was 88% (α/β 15:1) and 82% (α/β 10:1), respectively.

7, condition C). However, compared with the outcomes from condition B, the yields and diastereoselectivity of **4** are lower, presumably due to the undesired side reactions (such as deprotection and hydrolysis) caused by the harsh acidic conditions.

In conclusion, we have developed a chemoseletive glycosylation of rhamnals by controlling the acidity and the reaction temperature. By using (±)-CSA as the catalyst at lower temperature, the 1,2-addition reaction prevails and gives the kinetic adducts as the major products. The Ferrier rearrangement products are formed when strong acid catalyst CF_3SO_3H or elevated temperature is employed. The protecting groups on the glycals are also proven to affect the chemoselectivity, and the bulky silyl group TBDPS gives the best result. The reactions of TBDPS-protected rhamnals with alcohol acceptors under kinetic or thermodynamic conditions proceed efficiently to afford the corresponding products in good to excellent yields with high stereoselectivity and should therefore have widespread applications in the synthesis of rhamnosides and disaccharides. To the best of our knowledge, it is the first time it has been disclosed that the chemoselectivity of 1,2-rhamnals can be regulated by the change of reaction temperature and Brønsted acidity of acid catalysts via introducing bulky silyl protecting groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00009.

Experimental details, ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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