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Palladium-Catalyzed Glycal Imidate Rearrangement: Formation of α- and β-*N*-Glycosyl Trichloroacetamides

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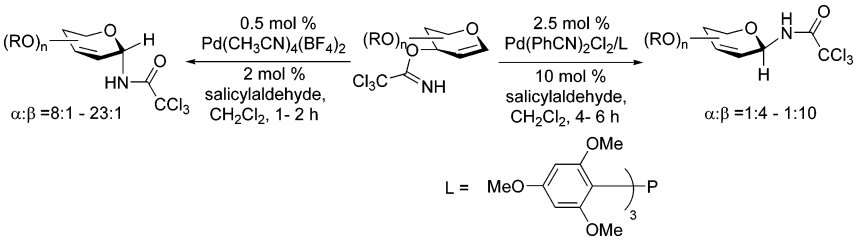
ABSTRACT



A novel palladium(II)-catalyzed stereoselective synthesis of α- and β-*N*-glycosyl trichloroacetamides has been developed. The α- and β-selectivity at the anomeric carbon depends on the nature of the palladium–ligand catalyst. While the cationic palladium(II) promotes the α-selectivity, the neutral palladium(II) favors the β-selectivity.

The stereoselective synthesis of α- or β-*N*-glycosyl amides has recently received considerable attention since the recognition of glycoproteins is important in a variety of biochemical processes such as cell−cell recognition, cellular transport, adhesion for the binding of pathogens to cells, and metastasis.[1] Early work on the synthesis of glycosyl amides employed the reaction of glycosyl amines with activated carboxylic acid derivatives.[2] Although this method is still frequently used, drawbacks of this methodology include hydrolysis of the starting glycosyl amines as well as anomerization of the protected glycosyl azides upon reduction.[3] In an alternative strategy, the glycosyl amides can be produced by treatment of isothiocyanates with the appropriate acids.[4] In recent years, glycosyl amides have also been made via Staudinger reduction of glycosyl azides.[5] Although this approach gives the desired glycosyl amides in good yields, the α/β-selectivity at the anomeric carbon is poor. DeShong and several research groups, who recognized the challenge of this approach, developed a stereoselective synthesis of α-*N*-glycosyl amides from glycosyl azides using isoxazoline intermediates.[6] We report herein a novel method for the stereoselective synthesis of α- and β-*N*-glycosyl amides involving Pd(II)-catalyzed glycal imidate rearrangement. In our approach, the nature of the palladium−ligand complex

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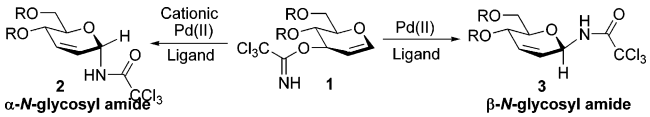
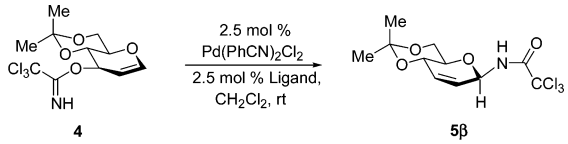
Scheme 1



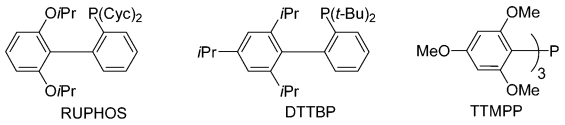
controls the anomeric selectivity (Scheme 1). The cationic Pd(II), which promotes ionization of the glycal imidate **1** by coordinating to the imidate nitrogen,[7] results in the formation of α-*N*-glycosyl trichloroacetamide **2**. In contrast, use of neutral Pd(II) promotes a concerted-type mechanism to provide *β*-*N*-glycosyl trichloroacetamide **3**.[8] Although the allylic imidate rearrangement is pioneered by Overman,[9] there is no report on utilizing this method in carbohydrate synthesis to control the α- and *β*-selectivity of the glycosyl amide at the anomeric carbon.

Treatment of glucal imidate **4** with 2.5 mol % of $Pd(PhCN)_2Cl_2$ in CH_2Cl_2 at 25 °C for 2 h provided a 1:1 mixture of α- and *β*-*N*-glycosyl trichloroacetamide **5** in 60% yield (Table 1, entry 1). It was anticipated that the anomeric selectivity would depend on the ligand on palladium. Accordingly, glucal imidate **4** was treated with a preformed solution of $Pd(PhCN)_2Cl_2$ and Ph_3P, and **5** was isolated in 83% yield with α:*β* = 1:2 (entry 2). With the use of RUPHOS and DTTBP as the phosphine ligands,[10] the anomeric selectivity was slightly improved, favoring the *β*-anomer (entries 3 and 4). Employing TTMPP as the phosphine ligand led to an improvement of both the yield and the *β*-selectivity (entry 5). However, it took 16 h for the reaction to go to completion. Gratifyingly, it was found that addition of 10 mol % of salicylaldehyde significantly shortened the reaction time to 4 h (entries 6 and 7), and the desired *N*-glycosyl trichloroacetamide **5** was obtained in good yield with excellent *β*-selectivity. Thus, the combination of the bulky phosphine ligand and salicylaldehyde increased both the yield and the *β*-selectivity as well as shortened the reaction time. We also examined whether temperature affected the selectivity; increasing or decreasing the reaction temperature only decreased the *β*-selectivity. This is the first example wherein a bulky phosphine ligand is employed to control the stereoselectivity at the anomeric carbon in the allylic imidate rearrangement.

Table 1. Pd(II)-Catalyzed Formation of *β*-*N*-Glycosyl Trichloroacetamide[a]



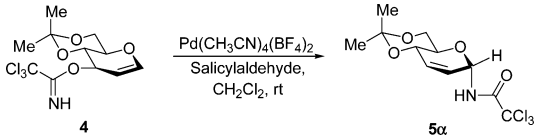
entry	phosphine ligand	additive	time	yield[b]	α:*β*[c]
1	none	none	2 h	60%	1:1
2	Ph_3P	none	16 h	83%	1:2
3	RUPHOS	none	16 h	77%	1:3
4	DTTBP	none	25 h	73%	1:4
5	TTMPP	none	16 h	89%	1:7
6	DTTBP	10 mol % of salicylaldehyde	4 h	70%	1:7
7	TTMPP	10 mol % of salicylaldehyde	4 h	86%	1:9
8	none	10 mol % of salicylaldehyde	1 h	71%	1:2



[a] All reactions were carried out in CH_2Cl_2 (0.2 M) with 2.5 mol % of Pd(II)/ phosphine ligand. [b] Isolated yield. [c] ^1H NMR ratio.

When cationic palladium,[11] $Pd(CH_3CN)_4(BF_4)_2$, was employed in the reaction, the desired α-*N*-glycosyl trichloroacetamide **5** was obtained in 73% yield as the major anomer (Table 2, entry 1). Addition of 10 mol % of salicylaldehyde

Table 2. Pd(II)-Catalyzed Formation of α-*N*-Glycosyl Trichloroacetamide[a]



entry	palladium	salicylaldehyde	time	yield[b]	α:*β*[c]
1	2.5 mol %	none	45 min	73%	9:1
2	2.5 mol %	10 mol %	1 h	80%	14:1
3	0.1 mol %	0.4 mol %	2 h	78%	9:1
4	0.5 mol %	2 mol %	1 h	82%	13:1

[a] All reactions were carried out in CH_2Cl_2 with $Pd(CH_3CN)_4(BF_4)_2$ and salicylaldehyde (1:4) except for entry 1. [b] Isolated yield. [c] ^1H NMR ratio.

significantly increased the α-selectivity (entry 2).[12] Decreasing the catalyst loading still maintained the yield and the selectivity (entries 3 and 4). Thus, switching to the cationic palladium reverses the anomeric selectivity, favoring the α-anomer.[13]

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To assess the feasibility of this palladium reaction for the synthesis of β-*N*-glycosyl trichloroacetamides, glycal imidates incorporating cyclic ketal protecting groups were investigated (Figure 1). The desired products **6**−**10** were

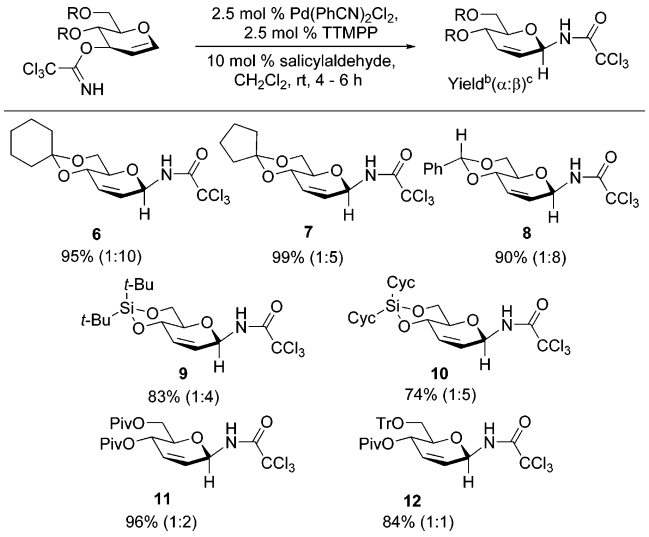

Figure 1. Stereoselective formation of β-*N*-glycosyl trichloroacetamides. All reactions were performed with 2.5 mol % of $Pd(PhCN)_2Cl_2$/TTMPP and 10 mol % of salicylaldehyde. [b] Isolated yield. [c] ^{1}H NMR ratio.

obtained with good β-selectivity. The deactivating effect of 4,6-acetal protecting groups on these glycal imidates restricts them in the *tag* conformations, thus limiting ionization to favor β-anomers.[14] In contrast, glycal imidates incorporating acyclic protecting groups gave a mixture of α- and β-*N*-glycosyl trichloroacetamides such as **11** and **12**.

In the formation of α-*N*-glycosyl trichloroacetamides, a number of glycal imidates incorporating a variety of cyclic and acyclic protecting groups were examined (Figure 2). The desired glycosyl amides **6**−**13** were obtained with excellent α-selectivity. These results suggest that the cationic palladium−salicylaldehyde complex was responsible for the observed α-selectivity at the anomeric center and the protecting groups on the glycal imidates had little effect on the selectivity.

The proposed mechanism for Pd(II)-catalyzed formation of α- and β-*N*-glycosyl trichloroacetamides is outlined in Figure 3. In the case of the cationic palladium, the $Pd(CH_3CN)_4(BF_4)_2$−salicylaldehyde complex coordinates to the imidate nitrogen of **4** to form **14** which subsequently undergoes ionization to generate allylic cation **15**. Regioselective addition of trichloroamide to the α-face of **15** followed by displacement of the amide from palladium

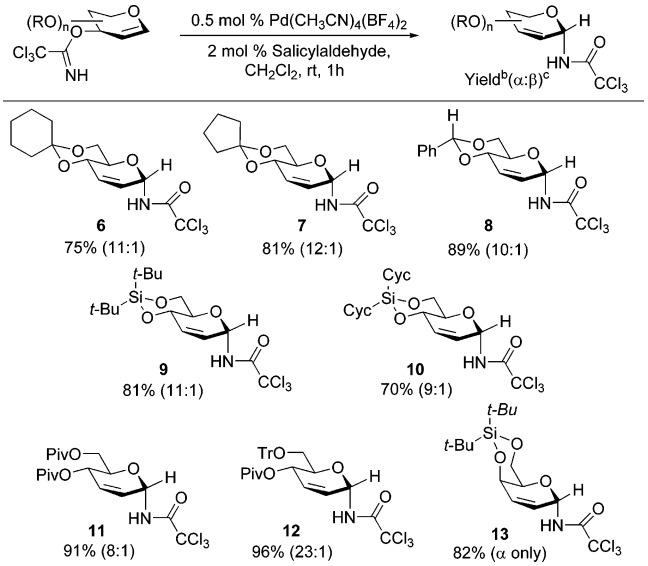

Figure 2. Stereoselective formation of α-*N*-glycosyl trichloroacetamides. All reactions were performed with 0.5 mol % of $Pd(CH_3CN)_4(BF_4)_2$ and 2 mol % of salicylaldehyde. [b] Isolated yield. [c] ^{1}H NMR ratio.

provides α-anomer **5**.[7b] In contrast, use of the $Pd(PhCN)_2Cl_2$−TTMPP−salicylaldehyde complex promotes a cyclization-induced rearrangement.[8] In this pathway, the palladium catalyst coordinates to the double bond of **4** to form π-complex **16**, which is activated toward nucleophilic attack by the imidate nitrogen. Subsequent cyclization of **16** provides σ-complex **17**. Grob-like fragmentation followed by dissociation releases β-anomer **5**.

The glycosyl urea is found in nature as a structural unit of glycocinnamoylspermidine antibiotics.[15] There are several methods reported for the construction of glycosyl urea.[16] To demonstrate the utility of the 2,3-unsaturated glycosyl

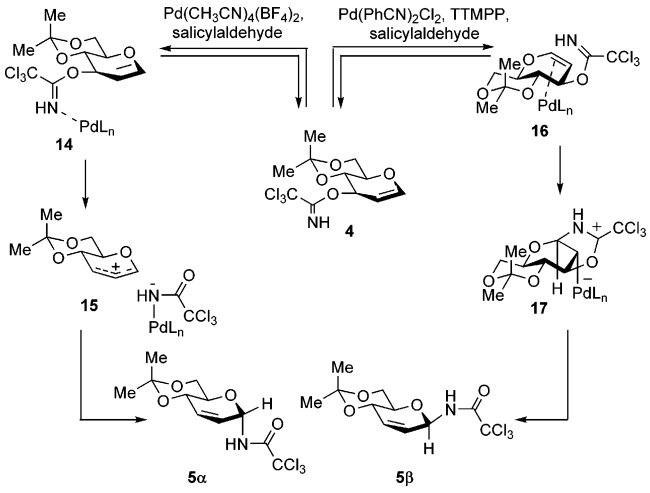

Figure 3. Proposed mechanism for the α-/β-selectivity.

(13) We also investigated whether the glycal imidate rearrangement could be catalyzed by a Lewis acid. Accordingly, treatment of **4** with 0.5 mol % of TMSOTf in CH_2Cl_2 at 0 °C only resulted in decomposition.

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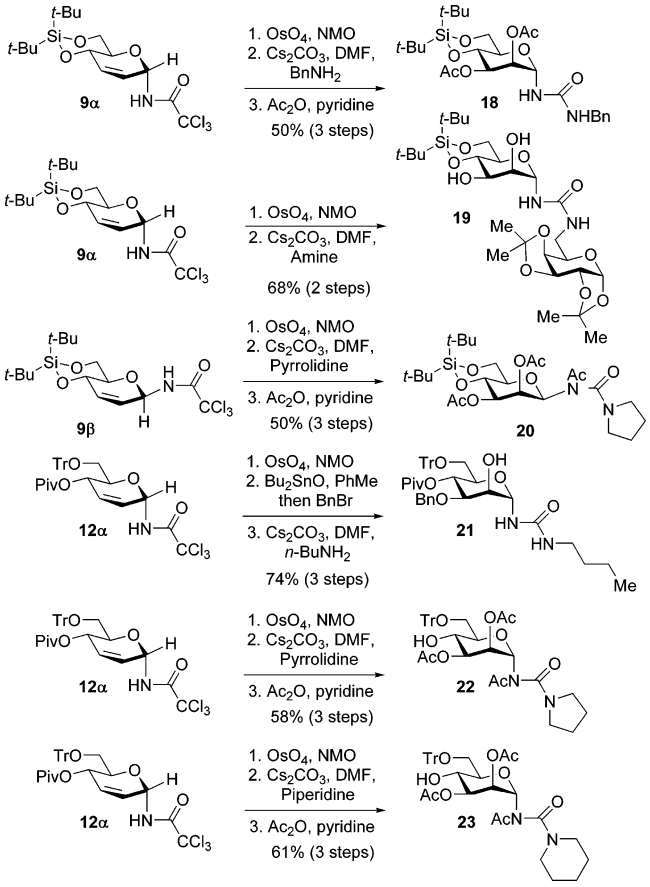
Scheme 2



amide products, both the α- and *β*-*N*-glycosyl trichloroacetamides were transformed into the corresponding glycosyl ureas **18**−**23** by dihydroxylation of *N*-glycosyl trichloroacetamides and subsequent treatment with Cs_2CO_3 and amines in DMF (Scheme 2).[17] The diol and triol intermediates of certain glycosyl ureas were acylated to ease the purification process.

In summary, a novel method for palladium(II)-catalyzed stereoselective formation of α- and *β*-*N*-glycosyl trichloroacetamides has been developed. The α- and *β*-selectivity at the anomeric carbon depends on the nature of the palladium−ligand catalyst. While the cationic palladium−salicylaldehyde complex promotes the α-selectivity, the neutral palladium−ligand catalyst favors the *β*-selectivity. Because of its substrate tolerance and mild conditions, this palladium method is applicable to a wide range of glycal imidates. The resulting *N*-glycosyl trichloroacetamides were further transformed into glycosyl ureas.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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