Reductive Samariation of Anomeric 2-Pyridyl Sulfones with Catalytic Nickel: An Unexpected Improvement in the Synthesis of 1,2-*trans*-Diequatorial C-Glycosyl Compounds

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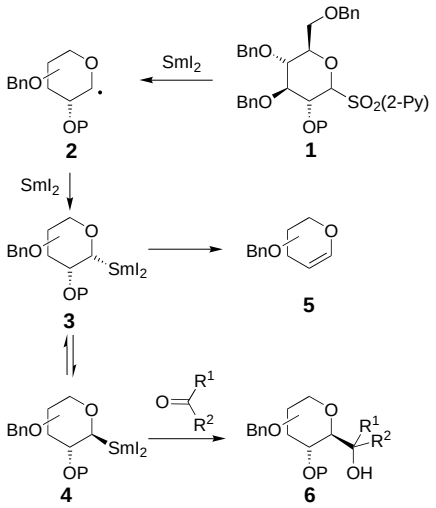
Dedicated to Professor Pierre Sinaÿ on the occasion of his 62nd birthday

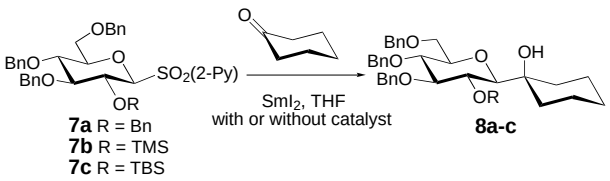
A direct method for the synthesis of C-glycosyl compounds derived from neutral hexoses was recently developed by our group. This procedure, which consists in the reductive samariation of anomeric 2-pyridyl sulfones in the presence of carbonyl compounds (Barbier procedure), yields exclusively 1,2-*trans* C-glycosyl compounds in the hexopyranosyl series, typically the α-C-mannopyranosyl or β-C-glucopyranosyl compounds.[1–3] In the mechanistic rationale formulated earlier, we proposed that the anomeric radical **2**, which results from the first electron transfer, is further reduced to a kinetic α-oriented organosamarium **3** which, in the *gluco* series, either *syn*-eliminates to glucal **5** or anomerizes to the β-species **4** (Scheme 1). The latter species does not *trans*-eliminate, as it is stable enough at room temperature to react



Scheme 1. Previous mechanistic proposal for the coupling of anomeric 2-pyridyl sulfones with carbonyl compounds mediated by samarium diiodide. 2-Py = 2-pyridyl; P = protecting group.

with the carbonyl compound. In the *manno* series, efficient constructions of carbon-linked dimers, mimics of biologically relevant disaccharides, were developed from this procedure.[4] With the glucopyranosyl and, more drastically, with the galactopyranosyl series, the *C*-glycosylation was not efficient enough to be integrated into a synthetic plan.[1b] The major drawback was a too high level of the competing β-elimination (elimination/C–C bond formation in an approximately 1/1 ratio), that could only be minimized in the *gluco* series by using a bulky protecting group at *O*-2 (*tert*-butyldimethylsilyl, P in **1**). We now report an unexpected solution to this problem by incorporating catalytic amounts of nickel(II) iodide (1 mol%) with the reducing agent. Such catalysis by transition metals of some samarium diiodide mediated reactions was introduced by Namy and Kagan.[5]

Treatment of a solution of sulfone **7a** and cyclohexanone (2 equiv) in THF at 0 °C with a freshly prepared THF solution of SmI_2 containing 1 mol% of nickel(II) iodide, afforded, after a standard workup, the C-glycosyl derivative **8a** in an isolated 94% yield (Equation 1 and Table 1, entry 1). As determined



(1)

Table 1. SmI_2-induced coupling of glucopyranosyl sulfones **7** with cyclohexanone. 2-Py = 2-pyridyl.

Entry	Pyridyl sulfone	Conditions[a]	C-Glycoside (yield)[b]	Elimination (yield)[b]
1	**7a**	0 °C, 1% NiI_2	**8a** (94%)	none
2	**7a**	0 °C	**8a** (36%)	**9** (22%)
3	**7a**	25 °C	**8a** (39%)	**9** (51%)
4	**7a**	0 °C, 1% $CuCl_2$	**8a** (30%)	**9** (64%)
5	**7a**	0 °C, 1% $FeCl_3$	**8a** (79%)	**9** (17%)
6	**7a**	25 °C, 1% NiI_2	**8a** (60%)	**9** (40%)
7	**7b**[c]	25 °C	**8b** (44%)	**9** (37%)
8	**7c**[c]	25 °C	**8c** (57%)	**9** (21%)

[a] For the reaction conditions, see also the Experimental Section. [b] Yields of isolated products after chromatography on silica gel. [c] Results taken from ref. [1].

by ^{1}H NMR analysis, this was the only detectable product of the crude reaction mixture. The absence of the elimination reaction is remarkable and the effect of the nickel catalysis is highlighted by the results obtained in the same reaction under identical conditions without NiI_2, which provided the same coupling product **8a** (36%) along with the elimination product tri-*O*-benzyl-D-glucal (**9**, 22%) and the starting sulfone **7a** (27%) (Table 1, entry 2). Complete conversion of sulfone **7a** only occurred at room temperature (Table 1, entry 3). In a limited study, nickel iodide appears to be the most useful transition metal catalyst to prevent or minimize the competing elimination reaction. Copper(II) chloride has no effect (Table 1, entry 4), whereas the Fe^{III} salt stands as a usable catalyst, although less efficient (Table 1, entry 5). Earlier, we observed that the competing elimination with sulfones in the *gluco* series could be partly suppressed by substituting the trimethylsilyl group at O2 in **7b** by the bulkier *tert*-butyldimethylsilyl group in **7c** (Table 1, entries 7 and 8).[1] The nickel catalyst not only modifies the rate of the reductive process[5b] but also the product distribution and, apparently, the overall mechanism.

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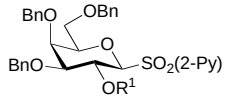
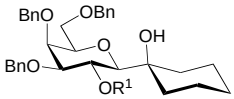
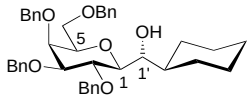
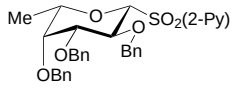
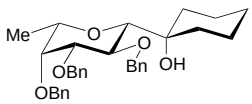
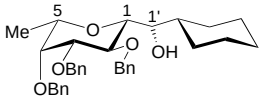
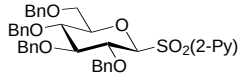
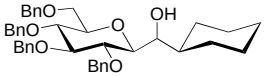
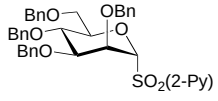
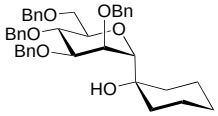
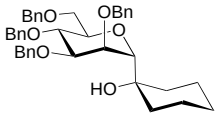
The new procedure was also successful with the D-galactopyranosyl and L-fucopyranosyl 2-pyridyl sulfones **10** and **16**. These results are presented in Table 2. Addition of the nickel catalyst resulted in an improvement of the *C*-glycosylation reaction in the *galacto* series from 52 to 80% (Table 2, entries 1 and 2) with a concomitant decrease in the elimination reaction (tri-*O*-benzyl-D-galactal, **12**). Similarly, the L-fucosyl sulfone **16** provided a 96% yield of the C-fucosyl derivative **17** (Table 2, entry 5; 2% of the elimination product di-*O*-benzyl-L-fucal, **18**).

A series, in which sulfones **10**, **16**, and **7** coupled with cyclohexane carbaldehyde, also proceeded smoothly (Table 2), to provide the corresponding β-C-glycosyl products in **15**, **19**, and **20**, respectively (80–82% yield). These results are significant in that a strong increase in the reactivity of SmI_2 makes the Barbier reaction of simple alkyl iodides and aldehydes problematic due to the competing Oppenauer reaction with the aldehyde.[5b] For products **15** and **19**, only one diastereomer could be detected by ^{1}H NMR analysis, which showed H1 ($\delta = 3.37$ (**15**) and 3.33 (**19**)) with a large value (9.3–9.5 Hz) for the $J(1,2)$ coupling constant (hexose atom numbering, see Table 2) and a small value (<1 Hz) for the $J(1,1')$ coupling constant, characteristic of an *R* center at C1′ in **15** ("D series") and an *S* center at C1′ in **19** ("L series").[6–8] The mannopyranosyl sulfone **21** provided the corresponding C-glycosyl compounds **22** and **23** (Table 2, entries 8 and 9) in yields similar to those obtained without NiI_2.[1]

The utility of this new procedure has been demonstrated in a fast synthesis of C-glycosyl dimers using aldehyde **27**, obtained by the five-step sequence of reactions shown in Scheme 2.[9] The 1,6-C-linked disaccharides **28**–**31** were all provided in good yields (83 to 89%, Table 3, entries 1–4). The addition of the organosamarium reagents to the carbonyl group of aldehyde **27** occurred with a high facial selectivity, to produce the C-glycosyl compounds **29**, **30**, and **31** with a diastereomeric ratio of about 95:5. The major isomers of the diequatorial compounds **28**, **29**, and **30** showed, in their

Table 2. SmI_2-induced C-glycoside formation with catalytic nickel at 0 °C.[a]

Entry	Pyridyl sulfone	Carbonyl compound	C-Glycoside (yield)[b]	Elimination (yield)[b]
				
1	**10**, $R^1 = Bn$	cyclohexanone	**11** (80%)	**12** (15%)
2[c]	**10**, $R^1 = Bn$	cyclohexanone	**11** (52%)	**12** (40%)
3[c,d]	**13**, $R^1 = TMS$	cyclohexanone	**14** (25%)	**12** (35%)
				
4	**10**, $R^1 = Bn$	cyclohexanecarbaldehyde	**15** (82%; >95:5)	**12** (16%)
				
5	**16**	cyclohexanone	**17** (96%)	**18** (2%)
				
6	**16**	cyclohexanecarbaldehyde	**19** (80%; >95:5)	**18** (14%)
				
7	**7**	cyclohexanecarbaldehyde	**20** (82%; n.d.)[e]	**9** (16%)
				
8	**21**	cyclohexanone	**22** (83%)	**9** (11%)[f]
				
9	**21**	cyclohexanecarbaldehyde	**23** (87%; n.d.)	**9** (8%)

[a] 2-Py = 2-pyridyl. [b] Yields of isolated products after chromatography on silica gel; second values refer to the diastereomeric ratio as determined by ^{1}H NMR. [c] Reaction performed without NiI_2 at 25 °C. [d] Results taken from reference [1b]. [e] Not determined due to severe overlap in the ^{1}H NMR spectrum. [f] The protonation product, 1,5-anhydro-2,3,4,6-tetra-*O*-benzyl-D-*manno*-hexitol, was also formed (2%).

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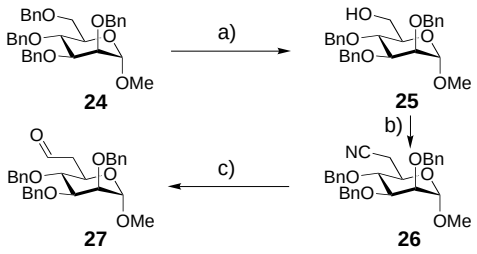

Scheme 2. Synthesis of aldehyde **27**. a) 1) Ac_2O/CF_3COOH (4/1), 25 °C, 1 h, 88 %; 2) MeONa, MeOH, 25 °C, 12 h, 96 %; b) 1.4 equiv PPh_3, 4 equiv I_2, imidazole, toluene, 70 °C, 1 h, 85 %; 2) 1.4 equiv Bu_4NCN, DMF, 0 to 25 °C, 3 h, 94 %; c) 3 equiv DIBAL-H, CH_2Cl_2, −78 °C, 0.5 h, 80 %. DIBAL-H = diisobutylaluminum hydride.

Table 3. SmI_2-induced C-glycosyl dimer formation with catalytic nickel at 0 °C.

Entry	Pyridyl sulfone[a]	C-Dimer (yield)[b,c]	Diastereomer ratio[d]
1	**7**	**28** (83 %)	n.d.[e]
2	**10**	**29** (85 %)	≈ 95:5
3	**16**	**30** (89 %)	94:6
4	**21**	**31** (88 %)	95:5

[a] For the reaction conditions, see the Experimental Section. [b] Yields of isolated products (both diastereomers at C7) after chromatography on silica gel. [c] The asymmetric center drawn at C7 is that of the major isomer. [d] Diastereomeric ratio at C7 as determined by HPLC analysis. [e] Not determined due to severe overlap.

^{1}H NMR spectra, large values (9.0 to 9.5 Hz) for the J(8,9) and J(9,10) coupling constants (tridecopyranoside atom numbering, see Table 3), which indicates an equatorial C7-C8 carbon–carbon bond with a chair conformation for the C8-C13 tetrahydropyran ring. As seen above with **15** and **19**, the small values (< 1–1.3 Hz) for the J(7,8) coupling constants in all three cases are diagnostic of an *R* center at C7 in **28** and **29** ("β-D series") and an *S* center at C7 in **30** ("β-L series").[6–8] The *S* center at C7 of the major isomer in **31** has been assigned, on the basis of our previous work in the *manno* series.[4b, 4c] These observations showed that the facial discrimination establishing the configuration of the exocyclic asymmetric center is exclusively controlled by the asymmetry of the C-glycosyl donor.

In summary, we have extended the reductive samariation protocol to the highly selective synthesis of 1,2-*trans* diequatorial C-glycosyl compounds at synthetically useful levels. The results obtained in these new conditions suggest a possible mechanism in which, during the samariation step, the intermediate anomeric radical is reduced primarily under the control of steric factors by a bulky catalytic species containing low-valent nickel (Figure 1).[10–12] Work is in progress to delineate a precise mechanism for this transformation and to apply this method to the construction of bioactive compounds.

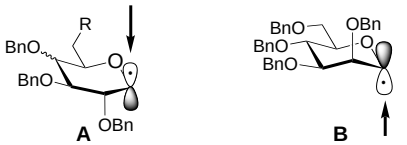

Figure 1. Possible reduction mechanism of the anomeric radical from the *gluco*, *galacto*, or *fuco* series (A) and *manno* series (B) by a catalytic complex containing low-valent nickel under the steric control of the substituent at position 2.

Experimental Section

8a: A solution of NiI_2 in THF (0.01 M, 1 mL) was added to a solution of SmI_2 in THF (0.1 M, 10 mL) under Ar. This solution (1.03 mL, 94 μmol of SmI_2) was cooled to 0 °C and added to a stirred solution of pyridyl sulfone **7a** (25 mg, 37.5 μmol) and cyclohexanone (12 μL, 116 μmol) in THF (0.5 mL) at 0 °C under Ar. After stirring at 0 °C for 0.5 h, saturated aq. NH_4Cl was added. The reaction mixture was extracted twice with CH_2Cl_2. The combined organic phases were washed twice with water, dried with Na_2SO_4, and evaporated to dryness. Flash chromatography (cyclohexane/EtOAc, 6/1) gave **8a** (22 mg, 94 %) as the only product. $[\alpha]_D^{20} = +3$ ($c = 2$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.37–7.19$ (m, 20 H; 4 Ph), 5.05, 4.98, 4.86, 4.82, 4.73, 4.63, 4.62, 4.57 (8 × d, 8 H, $J = 11$ Hz; CH_2Ph), 3.81, 3.74 (2 × t, 2 H, $J \approx 9$ Hz; H-2,3), 3.69–3.70 (m, 2 H; H-6,6′), 3.64 (dd, 1 H, $J(4,5) = 9.7$, $J(3,4) = 8.8$ Hz; H-4), 3.44 (ddd, 1 H, $J(4,5) = 9.7$, $J(5,6) = J(5,6') = 3.2$ Hz; H-5), 3.30 (br s, 1 H; OH), 3.15(1d, 1 H, $J(1,2) = 9.2$ Hz; H-1), 1.73–1.45 (m, 10 H; 5 CH_2); MS (ES): $m'z = 645$ [M+Na]; HR-MS (ES) for $C_{40}H_{46}NaO_6$ [M+Na]: calcd: 645.3192; found: 645.3198.

29: The procedure for the preparation of **8a** was followed with sulfone **10** (25 mg, 37.5 μmol) and aldehyde **27** (27 mg, 56.7 μmol, 1.5 equiv) and provided C-linked disaccharide **29** (32 mg, 85 %). ^{1}H NMR ($CDCl_3$, 250 MHz, atom numbering of a tridecopyranoside): $\delta = 7.40–7.22$ (m, Ph), 4.99–4.42 (m, 14 H; CH_2Ph), 4.67 (d, 1 H, $J(1,2) = 1.9$ Hz; H-1), 4.17 (t, 1 H, $J(8,9) = J(9,10) = 9.5$ Hz; H-9), 4.02 (d, 1 H, $J(10,11) = 3$ Hz; H-11), 3.88 (dd, 1 H, $J(3,4) = 9.2$, $J(2,3) = 3.2$ Hz; H-3), 3.81 (dd, 1 H, $J(1,2) = 1.9$, $J(2,3) = 3.2$ Hz; H-2), 3.68 (t, 1 H, $J(4,5) = 9.5$ Hz, $J(3,4) = 9.2$ Hz; H-4), 3.63 (dd, 1 H, $J(9,10) = 9.5$, $J(10,11) = 3$ Hz; H-10), 3.62–3.53 (m, 3 H; H-12,13,13′), 3.28 (s, 3 H; CH_3), 3.135 (dd, 1 H, $J(8,9) = 9.5$, $J(7,8) = 1.3$ Hz; H-8), 2.27 (ddd, 1 H, $J = 14$, 11.2, 2.2 Hz; H-6), 1.62 (ddd, 1 H, $J = 14$, 10.2, 2.8 Hz; H-6′); MS (ES): $m/z = 1023$ [M+Na]; HR-MS (ES) for $C_{63}H_{68}NaO_{11}$: calcd: 1023.4659; found: 1023.4652.

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[6] It is now well documented that the value for the $J(1,1')$ coupling constant for **15** and **19** (atom numbering in Table 2) or the $J(7,8)$ coupling constant for **28**, **29**, and **30** (atom numbering in Table 3), which reflect the most populated conformer in the *exo*-anomeric conformation, indicates the nature of the asymmetric center at C7, with small values (1.7–2.8 Hz) for an *R* center and large values (6.4–9.0 Hz) for an *S* center in the β-D-*gluco*[7] or the β-D-*galacto* series.[8]

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Formation of Optically Active Aromatic α-Amino Acids by Catalytic Enantioselective Addition of Imines to Aromatic Compounds**

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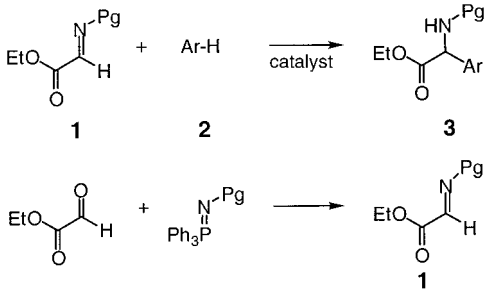
Optically active α-amino acids are vital to life as building blocks of peptides, proteins, and many other natural products. Amino acids are also applied extensively as food additives, pharmaceuticals, and agrochemicals. Furthermore, amino acids are widely used in organic synthesis as targets, and as constituents for reagents and/or catalysts in asymmetric synthesis.

The synthesis of optically active nonproteinogenic α-amino acids is an interesting and important research field which has received much attention[1] and the application of asymmetric catalysis towards formation of these compounds from simple starting materials is a fundamental challenge.

Recently, catalysts have been developed for enantioselective addition reactions to imines, including processes such as the ene[2], Mannich-type,[3] allylation,[4] and aza-Diels–Alder reactions.[5] Reports on the catalytic enantioselective addition of imines to aromatics are very few, and, according to our knowledge, only one example of the addition of an imine to indole and pyrrole systems has been reported.[6] Recently, several catalytic asymmetric Strecker reactions have emerged for the synthesis of optically active, natural, as well as unnatural, aromatic and aliphatic α-amino acids.[7]

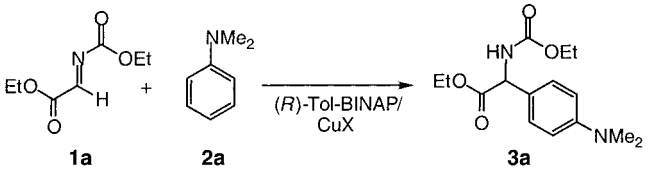
In this paper we present the development of a catalytic enantioselective addition reaction of imines **1** to electron-rich aromatic compounds **2** leading to protected optically active aromatic α-amino acids **3**[8] (Scheme 1). An advantage of this reaction is that **1** is prepared by an aza-Wittig reaction[9] and used directly without further purification (Scheme 1).



Scheme 1. Top: Addition of imines **1** to electron-rich aromatic compounds **2** to form protected aromatic α-amino acids **3**. Bottom: Synthesis of the protected imine starting materials **1**. Pg = protecting group.

The combination of $CuClO_4$ and (*R*)-Tol-BINAP catalyzed the reaction of the α-imine ester **1a** with *N,N*-dimethylaniline (**2a**) in THF at room temperature to give the protected aromatic α-amino acid **3a** in 81% yield and with 14% *ee* (see Equation (1) and Table 1, entry 1). Lowering the reaction temperature to $-78\,^{\circ}C$ caused a substantial improvement in

Table 1. Optimisation results for the reaction of imine **1a** and *N,N*-dimethylaniline (**2a**) with (*R*)-Tol-BINAP/CuX as the catalyst.



Entry	CuX	Cat. concentration [mol%]	Solvent	*T* [°C]	Yield[a] [%]	*ee* [%]
1	$CuClO_4$	10	THF	RT	81	14
2	$CuClO_4$	10	THF	−78	81	87
3	$CuClO_4$	10	CH_2Cl_2	−78	82	85
4	$CuClO_4$	5	THF	−78	78	93
5	$CuPF_6$	5	THF	−78	75	96
6	$CuPF_6$	1	THF	−78	79	81
7[b]	$CuPF_6$	5	THF	−78	76	93

[a] Yield of isolated products. [b] Large scale reaction with 8.0 mmol of starting material.

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