Catalytic synthesis of **5**: Imine (0.57 mmol) and acid chloride (0.57 mmol) were combined in 10 mL of $CH_3CN$ and stirred for 15 min. To this solution was added $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol %) in 10 mL of $CH_3CN$. The reaction mixture was transferred to a 100 mL reaction bomb and left to stir at room temperature for 30 min. 790 Torr of CO was then added to the reaction mixture, and it was allowed to stir at 55 °C for 24 h. The resulting solution was filtered through celite, redissolved in $CHCl_3$, then washed with dilute HCl, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, followed by drying over $Na_2SO_4$. After filtration, the solvent was removed in vacuo, and the resultant material dissolved in diethyl ether and cooled to −40 °C. The imidazoline **5** was then collected as a white precipitate.

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# Synthesis of a Trisaccharide Library by Using a Phenylsulfonate Traceless Linker on Synphase Crowns**

Takashi Takahashi,* Hitoshi Inoue, Yuichi Yamamura, and Takayuki Doi

The development of novel linkers and linkage strategies has become essential in solid-phase synthesis for the discovery of new drugs and materials. In recent years, many efficient linkers were developed.[1] Traceless linkers are advantageous in that the original functional group of the linker does not remain in the product.[2] We have reported a phenylsulfonate traceless linker,[3] which acts as a leaving group under nucleophilic-displacement reaction conditions.[4, 5] With this linker a diversity of products can be obtained, because various functional groups can be introduced at the final stage in a solid-phase synthesis. Herein, we report a high-speed synthesis of a functionalized trisaccharide library utilizing the phenylsulfonate linker on Synphase Crowns.[6, 7]

The synthetic strategy is illustrated in Scheme 1. The trisaccharide derivatives **I**, **II**, and **III** which have various functional groups **Z** at the 6 position of their glucose unit could be synthesized from solid support **4**, which consists of a

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[*] Prof. Dr. T. Takahashi, H. Inoue, Y. Yamamura, Prof. Dr. T. Doi
Department of Applied Chemistry
Graduate School of Science and Engineering
Tokyo Institute of Technology
2-12-1 Ookayama, Meguro, Tokyo 152-8552 (Japan)
Fax: (+81) 3-5734-2884
E-mail: ttakashi@o.cc.titech.ac.jp

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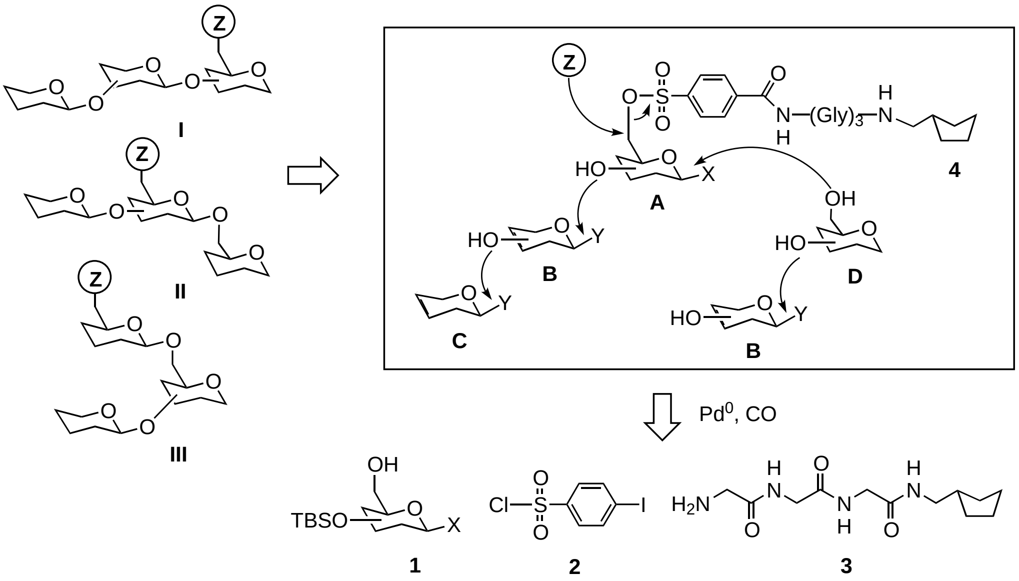
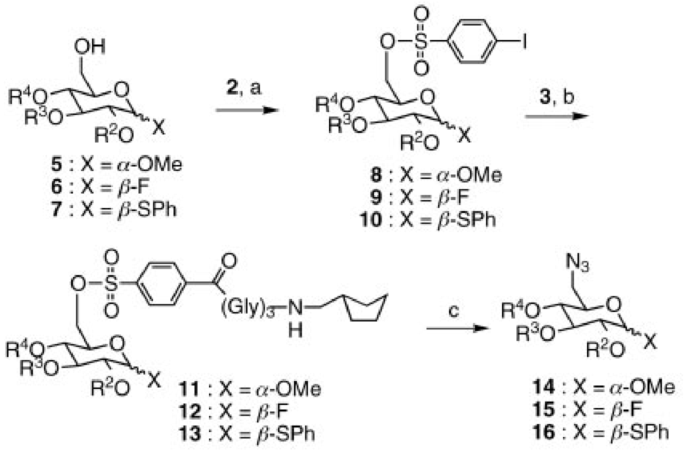


Scheme 1. Synthesis of an oligosaccharide library by using a phenylsulfonate traceless linker. TBS = *tert*-butyldimethylsilyl.

glucose unit **A** linked by a sulfonate linker at the 6 position. 1) Glycosylation of the supported glycosyl acceptor **4** (unit **A**) with glycosyl donor **B** followed by glycosylation of the **B** unit of the produced disaccharide with glycosyl donor **C** and displacement of the sulfonate linker of the **A** unit with a nucleophile **Z** lead to the trisaccharide **I**. 2) Glycosidation of the supported glycosyl donor **4** (unit **A**) with glycosyl acceptor **D** followed by glycosylation of either the **A** or the **D** unit with donor **B** (two-directional glycosylation)[8] and displacement with **Z** lead to the trisaccharide **II** or **III.** Sulfonylation of monosaccharide **1** at the 6 position with 4-iodobenzenesulfonyl chloride (**2**), which can be regarded as a precursor for an activated ester, was followed by Pd$^0$-catalyzed carbonylative amidation with support **3**.[9] This support, which can be easily handled, consists of aminomethyl crown residues that are distinguishable by the tagging stems clipped to them and a tripeptide spacer (Gly-Gly-Gly) to maintain a suitable distance between the reaction site and the solid support. In this strategy, it is feasible that the diversity of the oligosaccharide library could increase in a combinatorial fashion through variation of the position of the glycosylation and the number of nucleophiles. To synthesize each compound, in the pure form, in the library of trisaccharides, the crown residues were clipped with Transtems and were utilized in a split-and-mix method because the crown residues can be identified as and when necessary by "reading" the radiofrequency tags.[6]

We optimized the reaction conditions of the Pd$^0$-catalyzed carbonylative amidation with support **3**.[10] Methyl glycosides **5**, glycosyl fluorides **6**, and thioglycosides **7** were converted into the precursors **8**–**10**, respectively, by sulfonylation with **2** (Scheme 2). The products were carbonylated and amidated with **3**,[9] the yields were determined by HPLC with integration of the peak area of the corresponding 6-azido-6-deoxymonosaccharide. For methylglycoside **8a** coupling at 40 °C gave, after cleavage, **14a** in 46 % yield (Scheme 2, entry 1).[3, 11] When this carbonylation was carried out at room temperature or at 80 °C (entries 2 and 3, respectively), the yield decreased. The reactions with **8b** and glycosyl fluoride **9e**, both of which have a TBS group at the 3 position, were successful (entries 4 and 5, respectively). The attachment of thioglycoside **10e** onto **3** resulted in decomposition, whereas the attachment of triply benzoyl-substituted thioglycoside **10h** was successful. In the light of these results, we chose to use the glycosyl fluorides **9e**–**g** as solid-supported glycosyl donors.

A 44-member trisaccharide library was synthesized as follows: carbonylative amidation of methyl glycosides **8b**–**d** and glycosyl fluorides **9e**–**g** was carried out in parallel under the conditions given above to afford six different solid-supported monosaccharides, **11b**–**d** and **12e**–**g**. The three



| Entry | Substrate | $T$[°C] | Product, yield [%] |
|---|---|---|---|
| 1 | **8a** | 40 | **14a**, 46 |
| 2 | **8a** | RT | **14a**, 8 |
| 3 | **8a** | 80 | **14a**, 35 |
| 4 | **8b** | 40 | **14b**, 48 |
| 5 | **9e** | 40 | **15e**, 38 |
| 6 | **10e** | 40 | **16e**, 0 |
| 7 | **10h** | 40 | **16h**, 35 |

|  | R$^2$ | R$^3$ | R$^4$ |
|---|---|---|---|
| **a** | Bn | Bn | Bn |
| **b** | Bn | TBS | Bn |
| **c** | Bn | Bn | TBS |
| **d** | TBS | Bn | Bn |
| **e** | Bz | TBS | Bn |
| **f** | Bz | Bn | TBS |
| **g** | Bz | Bn | Bn |
| **h** | Bz | Bz | Bz |

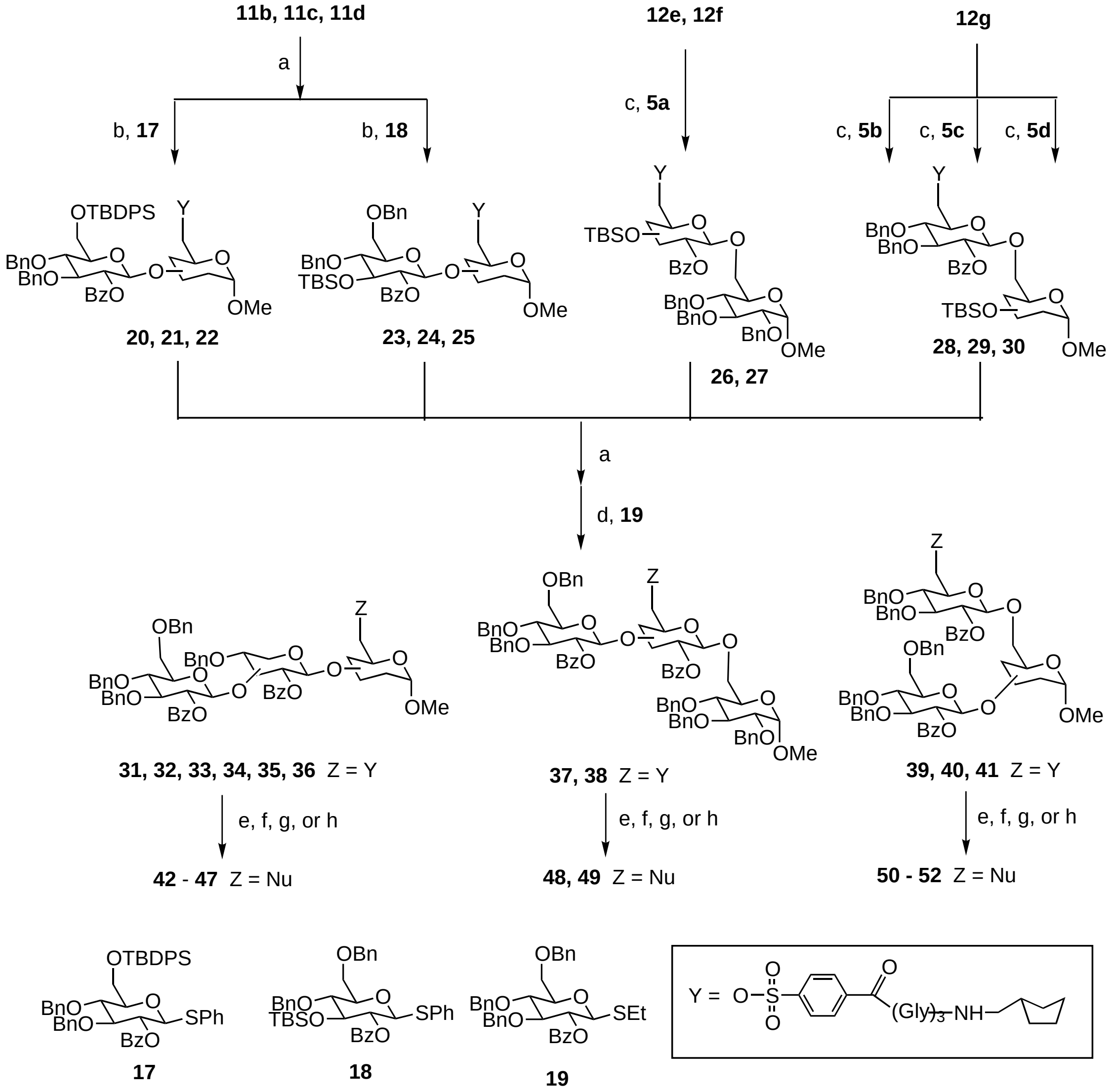
Scheme 2. Attachment of glycosides by Pd$^0$-catalyzed carbonylative amidation. a) py, CH$_2$Cl$_2$; b) ArI (0.5 M), [Pd(PPh$_3$)$_4$] (0.01 M), NEt$_3$ (0.5 M), CO (10 atm), DMF, 40 °C, 24 h; c) NaN$_3$, DMF, 60 °C, 12 h; Bn = benzyl, Bz = benzoyl, py = pyridine.

solid-supported methylglycosides **11b–d**, which differ in the position of the TBS group, were mixed, selectively deprotected and divided into two equal fractions (Scheme 3). Using DMTST[12] as an activator, one fraction was treated with the glycosyl donor **17**, which has a TBDPS group at the 6 position, and the other was treated with the glycosyl donor **18**, which has a TBS group at the 3 position, to provide the six disaccharides **20–25**.[13] Subsequently, the two solid-supported glycosyl fluorides **12e** and **12f** were placed in a single vial and treated with glycosyl acceptor **5a** and $[Cp_2Zr(OTf)_2]$[14] to afford the two disaccharides **26** and **27** (Scheme 3). Next, the solid-supported glycosyl fluoride **12g** was divided into three portions, which were treated with glycosyl acceptor **5b**, **5c**, and **5d**, respectively, in parallel to provide the disaccharides **28–30** (Scheme 3).

The eleven prepared silyl-protected disaccharides **20–30** were combined. Deprotection of the silyl group and glycosylation of all the solid-supported disaccharides with glycosyl donor **19** in a single vial[15] afforded the solid-supported trisaccharides **31–41**[16] (Scheme 3).

Finally, the crown compounds were sorted by means of their radiofrequency tags,[6] and nucleophilic displacement—cleavage with sodium azide, sodium iodide, cesium acetate, and sodium borohydride—furnished the desired 44 functionalized trisaccharides **42–52**.[3, 17] These reactions were performed in parallel to give each trisaccharide as a pure product, not as a mixture of trisaccharides (Table 1). The purities of the desired trisaccharides were determined by high-performance liquid chromatography (HPLC) and the structures of the respective major products in all the reactions were characterized by mass spectrometry and NMR spectroscopy after preparative HPLC.[18, 19]

In summary, we have demonstrated a solid-phase synthesis of a functionalized trisaccharide library by using a phenyl-



Scheme 3. Synthesis of a 44-member trisaccharide library by glycosylation of a sulfonate-linked solid support followed by displacement with nucleophiles. a) 2 M HCl in MeOH/THF (1:1), RT; b) glycosyl donor **17** (TBDPS = *tert*-butyldiphenylsilyl) or **18** (0.2 M), DMTST (0.2 M), MS-4Å, $CH_2Cl_2$, RT, 24 h, repeated twice for improving the yield; c) glycosyl acceptor **5** (0.2 M), $[Cp_2Zr(OTf)_2]$ (0.2 M), MS-4Å, $CH_2Cl_2$, RT, 24 h; d) glycosyl donor **19** (0.2 M), NIS (0.2 M), TfOH (0.05 M), MS-4Å, $CH_2Cl_2$, RT, 24 h;[16] e) $NaN_3$ (0.1 M), DMF, 60 °C, 12 h; f) NaI (0.1 M), DMF, 60 °C, 12 h; g) CsOAc (0.1 M), [18]crown-6 (0.02 M), DMF, 60 °C, 12 h; h) $NaBH_4$ (0.1 M), DMSO, 60 °C, 12 h. DMTST = dimethyl(methylsulfanyl)sulfonium triflate, NIS = *N*-iodosuccinimide, Tf = trifluoromethanesulfonate.

Table 1. Nucleophilic displacement and cleavage to afford a 44-member trisaccharide library.[a]

| Components | | | Trisaccharides | Nu = $N_3$ | Nu = I | Nu = OAc | Nu = H |
|---|---|---|---|---|---|---|---|
| **11b** | **17** | **19** | Glcβ1 →6Glcβ1 →3(6-Nu)Glcα-OMe **42** | 55 | 52 | 49 | 50 |
| **11c** | **17** | **19** | Glcβ1 →6Glcβ1 →4(6-Nu)Glcα-OMe **43** | 66 | 70 | 65 | 65 |
| **11d** | **17** | **19** | Glcβ1 →6Glcβ1 →2(6-Nu)Glcα-OMe **44** | 51 | 48 | 48 | 46 |
| **11b** | **18** | **19** | Glcβ1 →3Glcβ1 →3(6-Nu)Glcα-OMe **45** | 66 | 61 | 60 | 62 |
| **11c** | **18** | **19** | Glcβ1 →3Glcβ1 →4(6-Nu)Glcα-OMe **46** | 54 | 52 | 49 | 46 |
| **11d** | **18** | **19** | Glcβ1 →3Glcβ1 →2(6-Nu)Glcα-OMe **47** | 71 | 68 | 70 | 65 |
| **12e** | **5a** | **19** | Glcβ1 →3(6-Nu)Glcβ1 →6Glcα-OMe **48** | 83 | 81 | 81 | 75 |
| **12f** | **5a** | **19** | Glcβ1 →4(6-Nu)Glcβ1 →6Glcα-OMe **49** | 50 | 51 | 44 | 43 |
| **12g** | **5c** | **19** | (6-Nu)Gluβ1 →6Gluα(Gluβ1 →4)-OMe **50** | 65 | 66 | 63 | 66 |
| **12g** | **5b** | **19** | (6-Nu)Gluβ1 →6Gluα(Gluβ1 →3)-OMe **51** | 84 | 79 | 81 | 78 |
| **12g** | **5d** | **19** | (6-Nu)Gluβ1 →6Gluα(Gluβ1 →2)-OMe **52** | 92 | 90 | 88 | 90 |

[a] Purities [%] of the trisaccharides **42**–**52** in the crude products. Glc = D-glucoside.

sulfonate traceless linker. In this study, an efficient strategy for diversification, Pd$^0$-catalyzed carbonylative amidation to immobilize monosaccharides, glycosylation at various positions of the solid-supported glycosyl acceptors, and cleavage from the sulfonate linker with four nucleophiles has been developed.

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[16] Glycosylation of a typical disaccharide produced a trisaccharide with 45% conversion (with DMTST) and with 83% conversion (with NIS/TfOH). Two further cycles of the glycosylation under the latter conditions completely consumed the disaccharide on the solid support.

[17] Sodium borohydride in DMSO reduced **11a** to methyl 2,3,4-*O*-tribenzyl-6-deoxy-α-D-glucopyranoside in 70% conversion and 88% purity; see: J. D. Prugh, A. A. Deana, *Tetrahedron Lett.* **1982**, *23*, 281–284.

[18] β configuration of the glycosidic linkages in all products was assumed on the basis of the known anchoring effect of an adjacent benzoate group in solid-phase syntheses; selected spectral data for **45** (Nu = OAc): $^1$H NMR ($CDCl_3$, 270 MHz): $\delta = 1.96$ (s, 3H, acetyl), 3.09 (dd, 1H, $J = 3.6, 9.6$ Hz, H-2), 3.19 (s, 3H, methoxy), 3.28 (dd, 1H, $J = 7.9, 8.9$ Hz, H-4), 3.51–3.86 (m, 10H), 4.07 (d, 1H, $J = 12.2$ Hz, benzyl), 4.13–4.58 (m, 15H), 4.74 (d, 1H, $J = 10.6$ Hz, benzyl), 4.85 (d, 1H, $J = 7.9$ Hz, H-1′), 5.02 (d, 1H, $J = 11.2$ Hz, benzyl), 5.10 (d, 2H, $J = 8.9, 8.9$ Hz, 2 benzyl), 5.25 (dd, 1H, $J = 7.9, 8.9$ Hz, H-2′), 5.29 (dd, 1H, $J = 7.9, 8.9$ Hz, H-2″), 6.96–7.65 (m, 41H, aromatic), 7.75 (d, 2H, $J = 7.3$ Hz, aromatic), 7.94 (d, 2H, $J = 7.3$ Hz, aromatic); $^{13}$C NMR ($CDCl_3$, 67.8 MHz): $\delta = 20.8$, 54.9, 63.1, 68.1, 69.1 (2 ×), 73.2, 73.4, 73.5, 74.0, 74.6, 74.8, 74.9, 75.0, 75.1 (3 ×), 75.5, 76.3, 78.1, 78.2, 79.8, 80.9, 83.0, 97.3, 100.5 (2 ×), 127.2, 127.3, 127.4, 127.5, 127.7, 127.8, 127.9, 128.09, 128.14, 128.17, 128.24, 128.3, 128.4, 128.6, 129.7, 129.8, 132.8, 133.2, 137.5, 137.7, 138.0, 138.2, 138.3, 138.4, 138.6, 164.2, 165.2, 170.6; IR (KBr):$\tilde{\nu} = 3029$, 2867, 1732, 1452, 1266, 1070 cm$^{-1}$; MS (ESI-TOF) calcd for $C_{84}H_{86}O_{19}$: 1416.6 [$M^+$+$NH_4$], found: 1416.6; **48** (Nu = $N_3$): $^1$H NMR ($CDCl_3$, 270 MHz): $\delta = 3.12$ (s, 3H, methoxy), 3.25–3.84 (m, 14H), 4.03 (br d, 1H, $J = 8.9$ Hz, H-6), 4.09 (d, 1H, $J = 11.2$ Hz, benzyl), 4.25 (d, 1H, $J = 7.9$ Hz, H-1″), 4.29 (d, 1H, $J = 10.2$ Hz, benzyl), 4.41–5.09 (m, 14H), 5.06 (d, 1H, $J = 11.2$ Hz, benzyl), 5.19 (dd, 1H, $J = 7.2, 7.9$ Hz, H-2″), 5.25 (dd, 1H, $J = 8.2, 9.2$ Hz, H-2′), 6.90–7.60 (m, 41H, aromatic), 7.78 (d, 2H, $J = 7.8$ Hz, aromatic), 7.91 (d, 2H, $J = 7.3$ Hz, aromatic); $^{13}$C NMR ($CDCl_3$, 67.8 MHz): $\delta = 51.4$, 54.8, 67.6, 69.0, 69.1, 73.2, 73.4, 73.8, 74.5, 74.8, 75.1, 75.4, 75.5, 76.3, 77.3, 77.9, 78.8, 79.6, 81.8, 82.8, 97.7, 100.1, 100.5, 127.3, 127.4, 127.5, 127.6, 127.8, 127.9, 128.0, 128.10, 128.14, 128.2, 128.3, 128.4, 128.5, 129.5, 129.6, 129.8, 133.0, 133.2, 137.4, 137.6, 137.8, 138.0, 138.1, 138.2, 138.8, 163.9, 165.4; IR (KBr): $\tilde{\nu} = 2966$, 2812, 2072, 1715, 1439, 1255, 1087 cm$^{-1}$; MS (ESI-TOF) calcd for $C_{82}H_{83}N_3O_{17}$: 1399.6 [$M^+$+$NH_4$] found: 1399.7.

[19] Removal of the protecting groups (benzoyl and benzyl) of two samples **45** (Nu = OAc) and **48** (Nu = $N_3$) (10 mg cleaved from the three crown compounds; NaOMe, THF/MeOH; $Pd(OH)_2$/C, MeOH/$H_2O$) afforded the corresponding free trisaccharides detected by $^1$H NMR spectroscopy (400 MHz) and mass spectrometry (ESI-TOF) in quantitative yields. None of the problems mentioned by one of the referees (loss of the product or incomplete hydrogenolysis) was observed.