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Synthesis of SL0101 Carbasugar Analogues: Carbasugars via Pd-Catalyzed Cyclitolization and Post-Cyclitolization Transformations

Mingde Shan and **George A. O'Doherty***
Department of Chemistry, West Virginia University, Morgantown, WV 26506

Abstract

A general approach to the stereoselective synthesis of 5a-carbasugars has been developed. The route mimics our palladium catalyzed glycosylation/post-glycosylation approach to carbohydrates in that it also utilizes a highly regio- and stereospecific palladium catalyzed allylation and post-glycosylation reaction sequence for the installation of either D- or L-cyclitols. This cyclitolization/post-cyclitolization sequence was used for the enantioselective synthesis of a cyclitol analogue of SL0101, its D-sugar enantiomer as well as several acetylation pattern analogues.

The p90 ribosomal S6 kinase (RSK) is a family of serine/threonine kinases that have been identified as a promising target for anti-cancer study.1 Among the four RSK isoforms (RSK1-4), RSK1 and RSK2 are the most closely linked to cancer cell growth.1 Therefore, inhibitors of RSK1-2 have the potential to be chemotherapies of human cancers. So far, several small molecules have been recognized to inhibit RSK1-2.1 Among them, SL0101 and its analogues with different acetylation patterns were initially discovered by Smith, Hecht and Lannigan to be the first specific inhibitors of RSK1-2 (Figure 1).2

Not long after the discovery, Prof. Hecht reported a total synthesis of SL0101.3 And later, additional analogues were synthesized and screened for RSK2 inhibitory activities.4 As part of a larger effort aimed at understanding the structural details behind SL0101's risk inhibition, we also reported a synthetic approach to SL0101 and its analogues (**1**-**3**) via a Pd-catalyzed glycosylation5 and subsequent post-glycosylation transformations (Scheme 1).6 In contrast to the other routes to SL0101, our route also provided access to the D-sugar enantiomer of SL0101, allowing us to gauge the role of the sugar in its structure activity relationship (SAR).

In this same vein, we turned our attention to the synthesis of carbasugar analogues of SL0101, as part of a continuing effort to search for more potent analogues of SL0101 (Figure 1). Carbasugars have been known as sugar mimics, in which the ring oxygen of the sugar moiety was replaced with a methylene group.7 This substitution imparts stability to acid and enzymatic hydrolysis and thus provides substantially improved bio-stability. While,

George.ODoherty@mail.wvu.edu .

Supporting Information Available: Complete experimental procedures and spectral data for all new compounds can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

the carbasugar motif has been used by both man8 and nature9 a unified strategy for their synthesis was lacking.

In this regard, we were particularly interested in developing a practical and general approach to carbasugar synthesis, which mimics our Pd-catalyzed glycosylations (**7a** to **8a**) and post-glycosylation approach (**8a** to **9a**) (Scheme 1). Because our palladium glycosylations reaction uses the double bond to stablize the carbocation intermediate (via a β-Pd-π-allyl intermediate), the ring oxygen is not needed. For our proposed cyclitolization reaction variant to work as well the electron-withdrawing *C*-4 ketone must direct the incoming nucleophile to the *C*-1 sugar position.

The desire for this transformation preforced the use of a Boc-enone **7b** instead of a Boc-pyranone **7a** in an analogous Pd-catalyzed cyclitolization (**7b** to **8b**), which would install the carbasugar glycosidic bond in **8b**. In turn, suitable post-cyclitolization transformations (**8b** to **9b**) could be used to install the remaining carbasugar functionality. Herein we describe our successful efforts to expand our de novo approach to carbohydrates to include the synthesis of carbasugars. In addition, we demonstrate its utility in the synthesis of novel SL0101 carbasugar analogues and their enantiomers.

Recently, we developed a stereo-divergent synthesis of either enantiomer of the required Boc-enones from D-quinic acid. Thus, both α-L-Boc-enone **7b** and α-D-Boc-enone (*ent*)-**7b** were prepared in 12 and 11-steps from quinic acid **10** (Scheme 2).10 Although the route was a little long, it provided ample quantities of the two enantiomeric D- and L-Boc-enones for our methodological and medicinal chemistry studies (vide infra).

Our carbasugar studies began with our investigations of the palladium(0)-catalyzed cyclitolization. In practice, α-D-Boc-enone ((*ent*)-**7b**) was treated with BnOH in CH_2Cl_2 in the presence of 10 mol% $Pd(PPh_3)_2$ at 0 °C for 12 hours. As a result, the reaction afforded glycosylated enone **11** in a reasonable 60% yield (Scheme 3).

In order to construct the sugar functionality, we next turned our attention to the post-cyclitolization transformation. In particular, we hope to develop a practical way to the *manno/rhamno*-stereochemistry since the sugar moiety in SL0101 and its analogues are *rhamno*-sugars. In analogy to our pyranones chemistry, we first explored the Luche type 1,2-reduction of the α,β-unsaturated ketone. Unfortunately, these conditions ($NaBH_4/CeCl_3$ at −78 °C) gave the allylic alcohol with only a 1.5:1 diastereoselectivity, which is poor in comparison to the pyranone chemistry (dr > 20:1). After screening a variety of reducing agents, we found $LiAlH_4$ reduction at −78 °C resulted in a reasonable diastereoselectivity of 11:1 to afford allylic alcohol **12** with 85% yield. The minor diastereomer could be removed by silica gel chromatography. To install the cisdiol, allylic alcohol **12** was then dihydroxylated at 0 °C upon Upjohn condition (OsO_4/NMO)11 which afforded triol **13** in 90% yield with complete stereocontrol (Scheme 4).

With this proof of concept established, we decided to next investigate the Pd-cyclitolization with phenolic and enolic nucleophiles, because the aglycone of SL0101 is an enolic nucleophile. For this purpose, a number of phenol/enol nucleophiles with different substitution patterns were chosen for testing (Table 1). It turned out that the Pd-cyclitolization worked very well with reasonable to excellent yields even for those phenols/enols either with sterically demanding substituents or highly electron deficient. With the phenol/enol nucleophiles, there is the added issue of *O*- vs *C*-allylation and/or accompanied Claisen rearrangements.12 Thus, we were delighted to see that for this cyclitolization, this appeared not to be a problem. It is also worth mentioning that the Pd catalyst loading could be lowered to 5 mol% with the reaction times remaining in the 0.5 to 2 hour range.

We next turned our attention to the synthesis of SL0101 carbasugar glycoside analogues, by examining the Pd-cyclitolization reaction with a suitably protected SL0101 aglycon **15** (Scheme 5). In practice, reaction between flavonol **15** and α-D-Boc-enone **7b** went smoothly in CH_2Cl_2 in the presence of 5 mol% Pd-catalyst at 0 °C in half an hour to afford desired glycosylated enone **16** in 84% yield.

To install the remaining SL0101 functionalities in the carbasugar, we explored the post-cyclitolization transformation. Although we were concerned about the ketone functionality in the aglycon, this turned out not to be a problem. Thus, reduction of the glycosylated enone **16** with $LiAlH_4$ at −78 °C afforded allylic alcohol (89%, dr 11:1) which was acylated to give allylic acetate **17** in 93% yield (Scheme 6). Dihydroxylation of the olefin furnished a diol **18** as a single diastereomer (73%), which was then debenzylated via hydrogenolysis with Pd/C to afford one of our desired carbasugar glycoside analogues of SL0101, the *C*-4 monoacetate **6** in 68% yield.

In order to achieve the diacetate carbasugar glycoside analogues of SL0101, we thought a selective *C*-2 acylation could be carried out on diol **18** via orthoacetate formation and kinetic hydrolysis. This was successfully used in our synthesis of SL0101 (Scheme 7). To our surprise, when diol **20** was reacted with trimethyl orthoacetate at 0 °C in the presence of catalytic amount of *p*-toluenesulfonic acid followed by the hydrolysis by using 90% aqueous acetic acid furnished a mixture of 2,4-diacetate **19** and 3,4-diacetate **20** in a 1.5:1 ratio. This result stood in contrast to the completely regioselective acylation of the axial hydroxy group in the synthesis of SL0101,5 indicating a significantly less rigid chair conformation for this *rhamno*-carbasugar versus the *rhamno*-sugar. This is presumably due to the loss of anomeric effect. After separation of these two regioisomers on silica gel chromatography, **19** and **20** were per-debenzylated with H_2 upon Pd/C producing the other two desired SL0101 carbasugar analogues, the *C*-2,*C*-4 diacetate **5** (63%) and the *C*-3,*C*-4 diacetate **4** (75%), respectively.

The synthesis of the enantiomeric carbasugar glycoside analogues (*ent*-**4**, *ent*-**5** and *ent*-**6**), was accomplished by simply switching the α-L-Boc-enone **7b** to α-D-Boc-enone (*ent*)-**7b**. A Pd-catalyzed cyclitolization of kaempferol **15** with Boc-enone (*ent*)-**7b** afforded 85% yield of enone (*ent*)-**16** in the same conditions as before, which after same sequence of post-cyclitolization transformation, carbasugar glycoside analogues of SL0101, *C*-4 monoacetate (*ent*)-**6** was obtained (Scheme 8).

By a similar orthoacetate formation and kinetic hydrolysis with 90% acetic acid, the diol (*ent*)-**18** was converted to a mixture of diacetate (*ent*)-**19** and (*ent*)-**20** in about a 1:1 ratio. Global debenzylation of these two precursors by hydrogenation afforded enantiomeric carbasugar glycoside of SL0101, *C*-2,*C*-4 diacetate (*ent*)-**5** and *C*-3,*C*-4 diacetate (*ent*)-**4** (Scheme 9).

In conclusion, six SL0101 carbasugar glycoside analogues in either enantiomeric form have been synthesized successfully. The formation of the key glycosidic bond features a highly regio- and stereospecific Pd-catalyzed cyclitolization. The functionalities on the sugar moieties have been established via corresponding post-cyclitolization transformations. Further applications of this new methodology along with the associated medicinal chemistry studies, will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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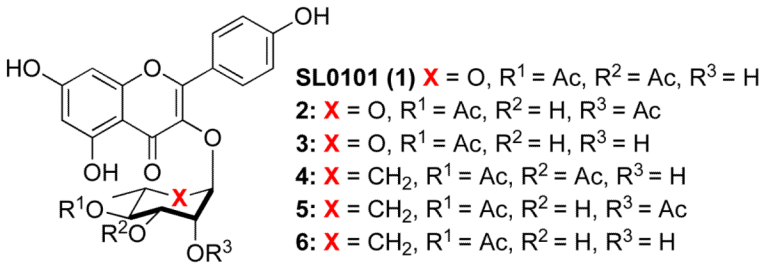
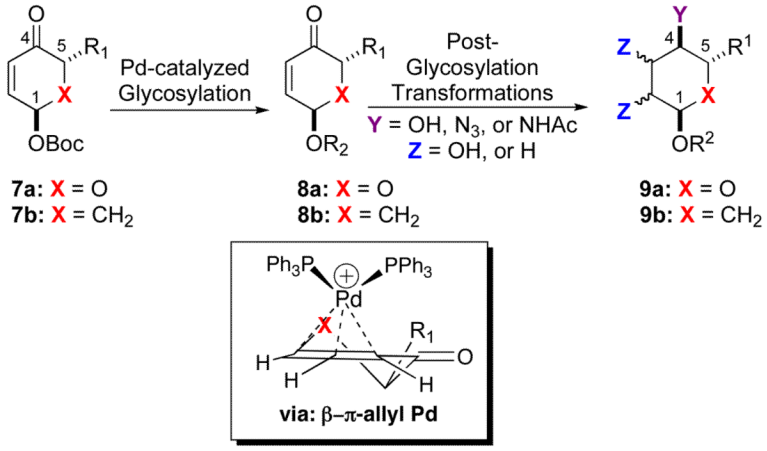
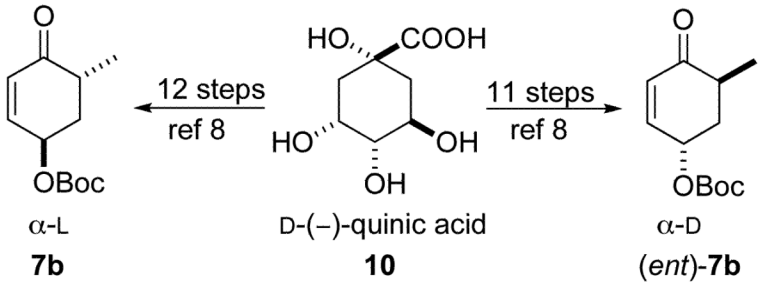


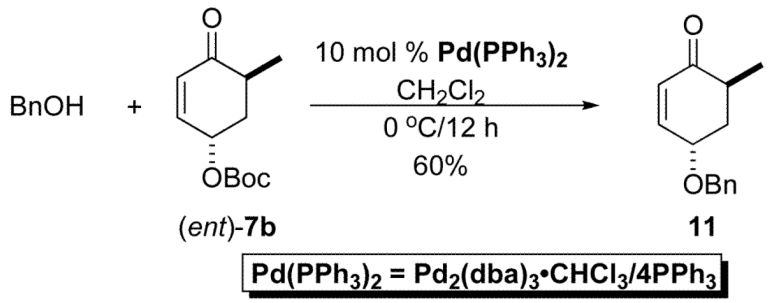
Figure 1.
RSK2 inhibitors SL0101 and its analogues



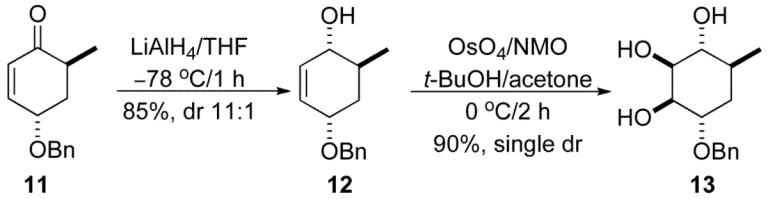
Scheme 1.
De Novo Approach to normal sugar and carbasugar



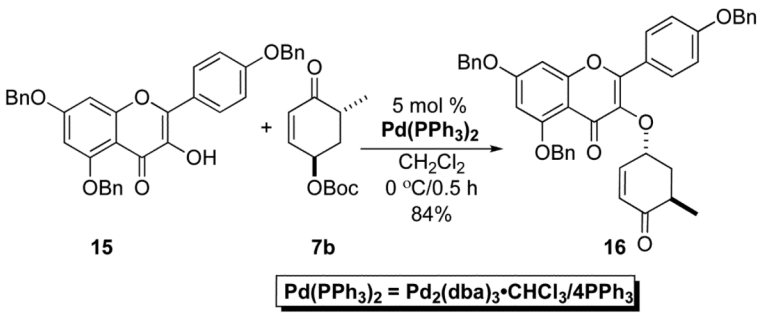
Scheme 2.
Synthesis of two α-Boc-enones from quinic acid



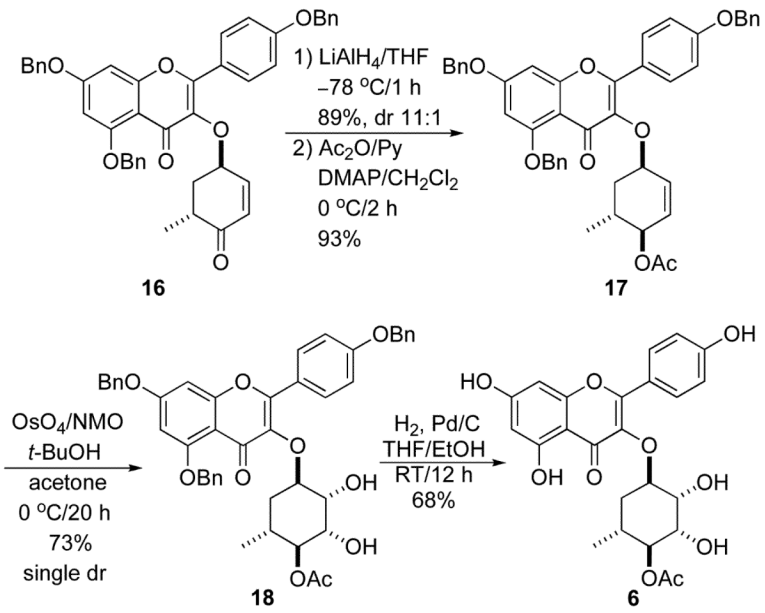
Scheme 3.
Pd-Cyclitolization for α-Boc-enones with BnOH



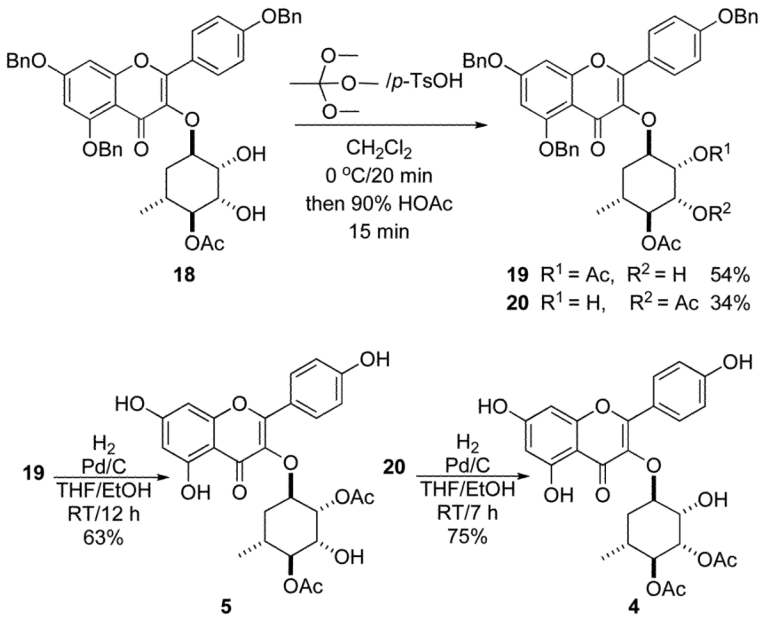
Scheme 4.
Post-cyclitolization transformation



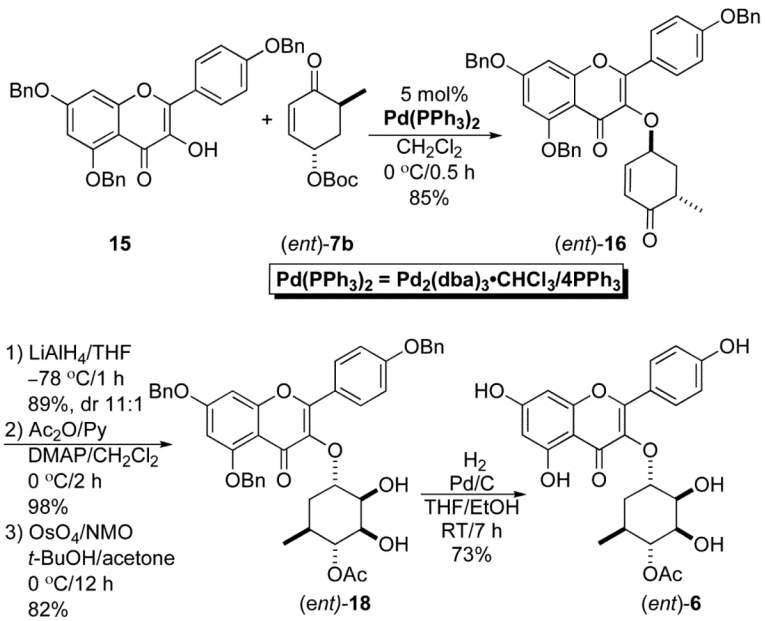
Scheme 5.
Pd-Cyclitolization for kaempferol with α-L-Boc-enone



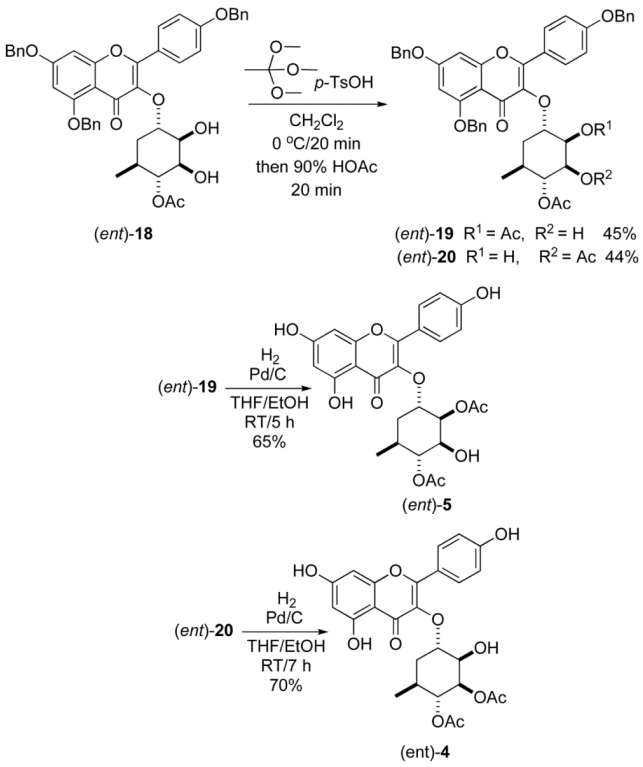
Scheme 6.
Synthesis of SL0101 5a-carbasugar α-L-glycoside **4**



Scheme 7.
Synthesis of SL0101 5a-carbasugar α-L-glycoside **5** & **6**



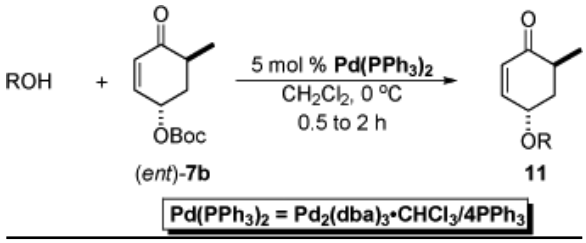
Scheme 8.
Synthesis of (*ent*)-**6**



Scheme 9.
Synthesis of (*ent*)-**5** & (*ent*)-**4**

Table 1

Pd-cyclitolization of phenols and enol with α-D-Boc-enone



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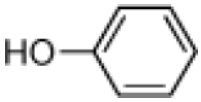
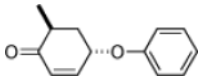
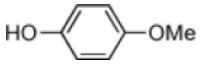
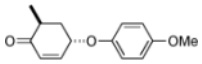
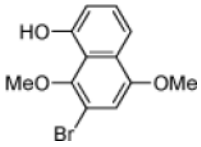
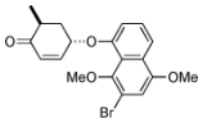
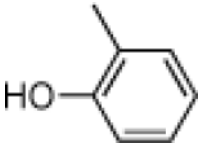
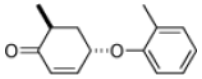
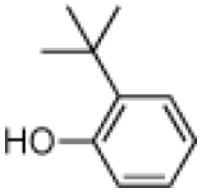
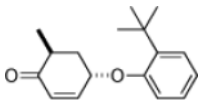
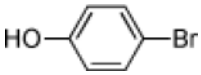
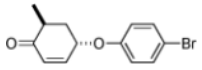
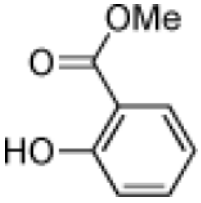
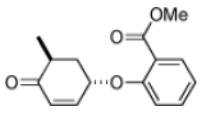
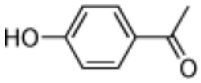
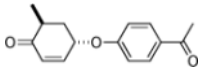
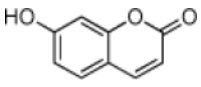
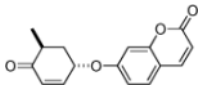
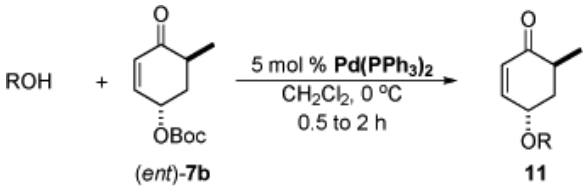
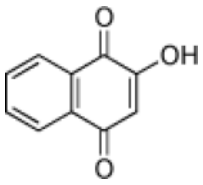
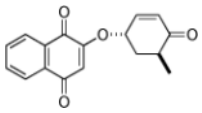
a			88%
b			96%
c			86%
d			89%
e			88%
f			76%
g			66%
h			84%
i			98%



Pd(PPh$_3$)$_2$ = Pd$_2$(dba)$_3$•CHCl$_3$/4PPh$_3$

entry	ROH	products	yield
j			83%