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Carboxybenzyl Group as an *O*-Nucleophile in the C−H Allylic Oxidation: Total Synthesis of (−)-Castanospermine

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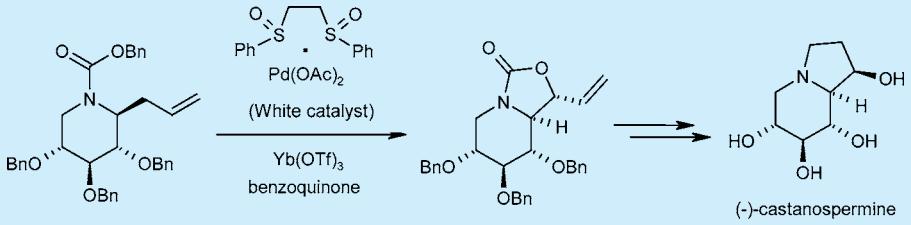
Supporting Information



ABSTRACT: The first palladium-mediated C−H allylic oxidation with a Cbz group acting as an *O*-nucleophile is reported. It was found that this transformation is promoted by rare-earth metal triflates: $Yb(OTf)_3$ or $Sc(OTf)_3$. A possible catalytic cycle is proposed. This reaction was applied in the synthesis of a D-xylose derived oxazolidinon, a versatile intermediate used further in the stereoselective synthesis of unnatural (−)-castanospermine. Cyclization of the key intermediate with PhSeBr afforded the desired bicyclic scaffold. In an alternative route, hydroboration/oxidation followed by DPPA-mediated cyclization was used.

Iminosugars, i.e. polyhydroxylated cyclic (or bicyclic) structures containing the nitrogen atom in the ring(s), are continuing to attract the attention of the scientific community due to their interesting biological properties.[1] Many of these products are potent glycosidase inhibitors and also exhibit antiviral activity.[2] Numerous methodologies for the effective synthesis of various mono- and polycyclic iminosugars have been proposed.[3]

(+)-Castanospermine is preeminent among the bicyclic, naturally occurring iminosugars, and its synthesis has been accomplished by many groups.[4] There is, however, only one reported synthesis of (−)-castanospermine.[5] As a consequence, the biological activity of this particular stereoisomer remains unknown. Therefore, (−)-castanospermine is an interesting synthetic target.

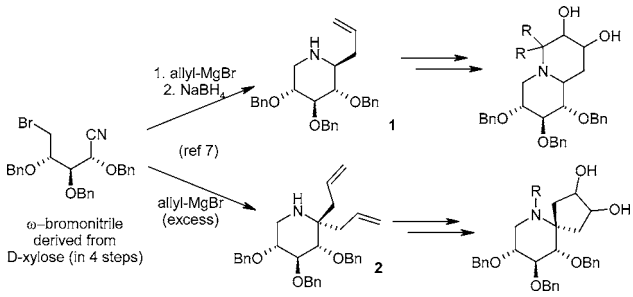
Synthesis of sugar mimics is one of the main research areas in our laboratory.[6] Recently, we put forward a methodology that enables a facile preparation of the precursors of some novel iminosugars: 2-allylpiperidine **1** and 2,2-diallylpiperidine **2**, from the D-xylose-derived *ω*-bromonitrile (Scheme 1).[7]

We also envisaged that, after oxidation of the allylic position, piperidine **1** might be transformed into (−)-castanospermine (Scheme 2). The standard approach for executing such a transformation requires the use of selenium or chromium reagents.[8] Other transition metals were also explored in the context of the C−H allylic oxidation,[9] but the only general methodology, which can be applied to a wide variety of compounds, has been elaborated by the White group. During the past decade, White's Pd-catalyst (Scheme 3a) has established its position as a powerful tool for the allylic C−H oxidation.[10]

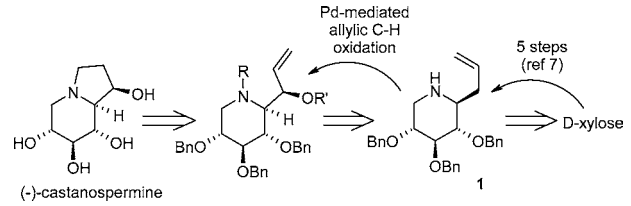
The catalyst's versatility is best reflected by the fact that it can mediate intramolecular reactions[11] including macrocyclizations, equally well as intermolecular ones.[12] It is particularly interesting and useful in the synthesis of polyoxygenated derivative, an idea accomplished with much success by the White group itself.[13]

Encouraged by these facts, we decided to take advantage of this catalytic system to install an oxygen function at the allylic

Scheme 1. Synthesis of Allyl-Substituted Piperidines (Previous Work)



Scheme 2. Retrosynthetic Analysis of (−)-Castanospermine



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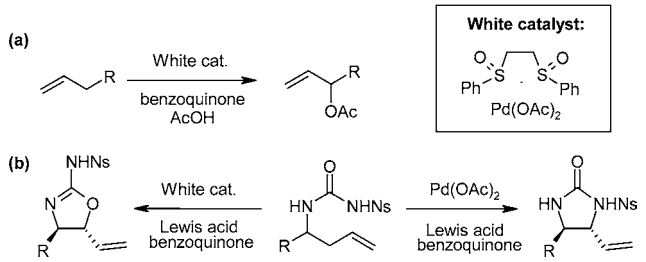
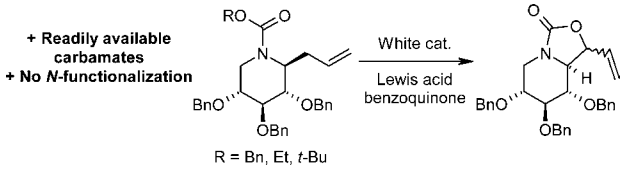
Scheme 3. C−H Allylic Oxidation Methodology by White



position of compound **1**. Since an intermolecular variant would more likely suffer from poor diastereoselectivity than an intramolecular one, we initially opted for White's *N*-nosyl urea methodology (Scheme 3b). Although it seemed suitable for our purposes, we were wondering if it would be possible to use much more available carbamates (such as Cbz- or Boc-) instead of *N*-nosyl ureas (Scheme 4). In such a case, the lack of

Scheme 4. Carbamates as *O*-Nucleophiles in C−H Allylic Oxidation (This Work)

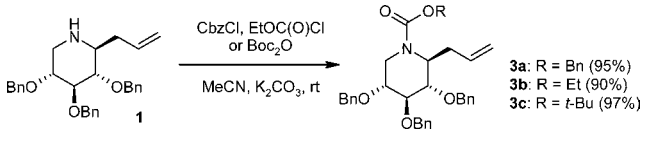


a nucleophilic nitrogen would eliminate the risk of *N*-functionalization. As a result of the process, an oxazolidinone scaffold would be formed. It can be regarded as a masked *β*-amino alcohol, a moiety found in compounds of medicinal importance.[14]

A related C−H oxidation was reported by Shimamoto and Ohfune,[15] who generated the benzylic cations from the L-tyrosine derivatives by treatment with $K_2S_2O_8/CuSO_4$ and trapped them with the oxygen atom of a Boc-group. There are some reports on the use of carbamates as *O*-nucleophiles in intramolecular reactions involving "classical" leaving groups.[16] A Tsuji−Trost-type approach leading to 5-vinyl-oxazolidinones has been also developed.[17] We have found no reports on the use of an oxygen atom of a carbamate as a nucleophile in the allylic C−H oxidation.

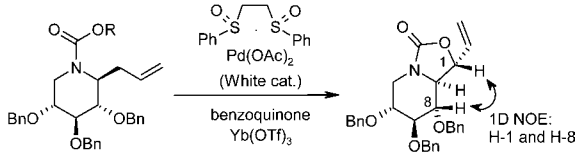
To verify this novel approach, we transformed **1** into carbamates **3a**, **3b**, and **3c** (Scheme 5) and subjected them to the oxidative conditions as reported in Table 1.

Scheme 5. Synthesis of Carbamates 3a, 3b, and 3c



It turned out that the reaction leading to **4** proceeded best with **3a** in the presence of catalytic amounts of $Yb(OTf)_3$ (entry 1). In the case of ethyl carbamate **3b**, the time of the reaction was much longer and full conversion required a substantially higher loading of the catalyst (entry 8), whereas conversion of the *t*-Bu carbamate was as fast as in the case of **3a**, but the yield was much lower (entry 11; a complicated mixture of products was formed).

Table 1. Optimization of the Reaction Conditions[a]



3a: R = Bn; **3b**: R = Et; **3c**: R = *t*-Bu

4

entry	substrate	cat. load. (mol %)	$Yb(OTf)_3$ (mol %)	time (h)	yield[b] (%)
1	**3a**	10	10	4	71
2[c]	**3a**	0	50	15	0
3[d]	**3a**	0	10	8	16
4[e]	**3a**	10	0	4	69
5[c,f]	**3a**	10	0	15	21
6[c]	**3a**	20	0	15	6
7[c,g]	**3a**	20	20	15	0
8	**3b**	20	30	20	47
9[d]	**3b**	10	10	24	29
10[c,g]	**3b**	20	50	20	0
11	**3c**	10	10	4	30
12[c,g]	**3c**	20	20	20	0

[a]All reactions were carried out in dioxane (0.2 M) at 75 °C under air, with 2 equiv of BQ, until total consumption of the starting material, unless otherwise stated. [b]Isolated yields. [c]Full conversion was not achieved. [d]$Pd(OAc)_2$ (10 mol %) was used as a catalyst. [e]$Sc(OTf)_3$ (10 mol %) was used as a promoter. [f]$Zn(OTf)_2$ (10 mol %) was used. [g]Reaction carried out in the presence of molecular sieves 4 Å.

The presence of a Lewis acid was crucial; without it, only traces of **4** were isolated (entry 6).[18] Under the oxidative conditions, but without the White catalyst, the reaction did not proceed at all (entry 2).

When $Pd(OAc)_2$ was used instead of the White catalyst (entry 3, Table 1), the Wacker oxidation product (methyl ketone) was isolated as the main product (42%), along with only small amounts (16%) of the desired compound.

Notably, when the reaction was conducted analogously to entry 1 (Table 1), but with 10 mol % of $Sc(OTf)_3$ instead of $Yb(OTf)_3$ (entry 4), **4** was obtained in similar yield (69%). Use of $Zn(OTf)_2$ was much less successful and yielded the desired product in only 21% yield (entry 5, 26% conversion).

In all cases, oxazolidinone **4** was formed as a single diastereoisomer. The configuration of the new stereogenic center was confirmed by 1D-NOE (Table 1). Formation of the *anti*-product is in accordance with White's observations regarding intramolecular C−H oxidations.[11f,13a]

In the case of **3a**, monobenzyl hydroquinone ether was isolated as the major byproduct in 35% yield. Moreover, the reaction did not proceed in the presence of molecular sieves 4 Å (entries 7, 10, 12), which indicated that water may be involved in the process.

Based on these observations and the mechanistic aspects already discussed by White, we have proposed a possible catalytic cycle leading to **4** (Scheme 6). The oxophilic Lewis acid additive is probably promoting the reaction by enhancing the susceptibility of *π*-allyl-Pd(BQ) species to undergo the S_N2-type cyclization.[19] As proposed by White, the Lewis acid binds through a benzoquinone molecule.[12b] The role of water is, at this moment, unclear. We suppose, that it is somehow involved in the removal of a benzyl moiety, because the former steps, i.e. C−H oxidation and S_N2-type cyclization, do not require a water molecule to proceed.

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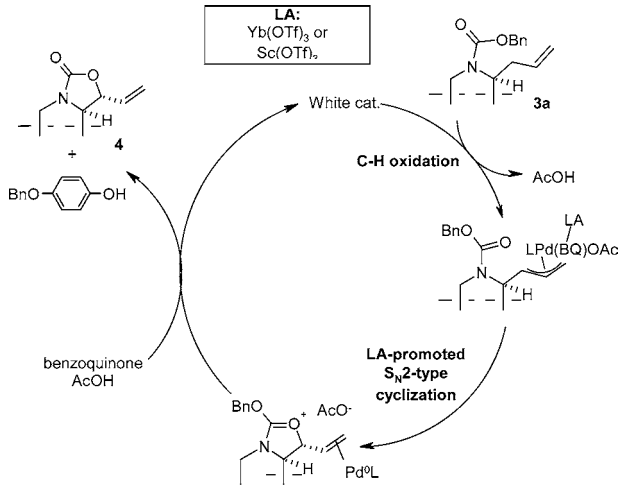
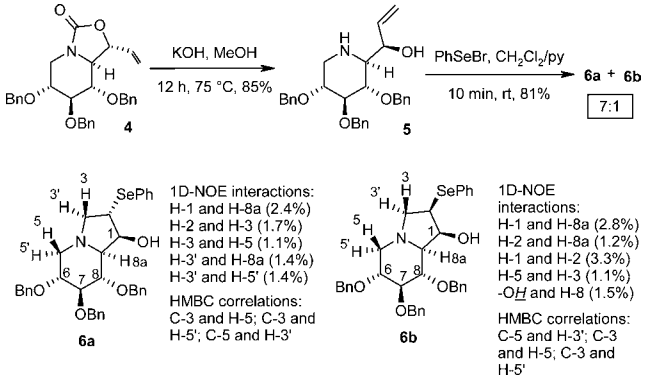
Scheme 6. Possible Catalytic Cycle Leading to 4



Once the conditions of this late-stage oxidation were optimized, we turned our attention to the final steps of the synthetic route. Methanolysis of **4** afforded *β*-amino alcohol **5** in very good yield (Scheme 7). Treatment of the latter with phenylselenyl bromide[20] afforded two bicyclic isomeric products: **6a** and **6b** (as a separable mixture) in a 7:1 ratio.

Scheme 7. Selenium-Mediated Cyclization to the Core of (−)-Castanospermine



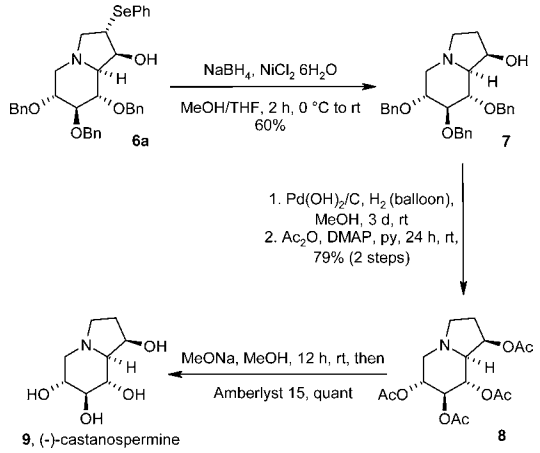
The five-membered structure of the newly formed ring was confirmed by the ^{13}C-HMBC and 1D-NOE experiments. Only the major product was used in the next step.

The subsequent deselenylation of **6a** turned out to be not as straightforward as expected. Standard procedures with tin and silicon hydrides (*n*-Bu_3SnH, Ph_3SnH, $(TMS)_3SiH$ in toluene, 80−110 °C) under free radical conditions (AIBN as initiator) suffered from very low conversions. Only a rarely used methodology, involving in situ produced nickel boride,[21] furnished the desired alcohol **7** (Scheme 8).

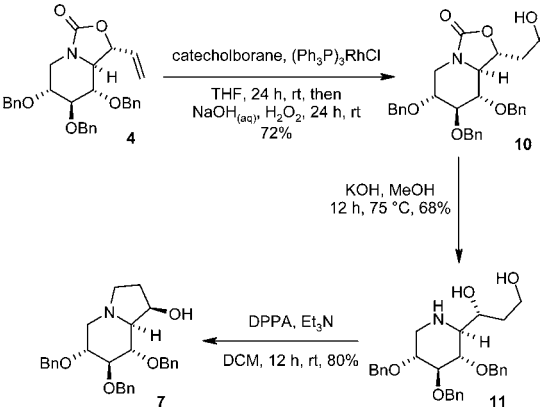
The subsequent hydrogenation over $Pd(OH)_2/C$ yielded, after acetylation−deacetylation, the title alkaloid **9**. All spectral and physical data matched those reported for (−)- and (+)-castanospermine (see Supporting Information). This compound was also characterized as tetraacetate **8**.

In an alternative approach, compound **4** was subjected to a hydroboration/oxidation procedure (Scheme 9). The use of BH_3·THF gave a complicated mixture of products, whereas 9-BBN did not react at all, even at elevated temperatures. Only rhodium-catalyzed hydroboration with catecholborane afforded

Scheme 8. Synthesis of (−)-Castanospermine



Scheme 9. DPPA-Mediated Cyclization to the Core of (−)-Castanospermine



the desired alcohol **10**. Subsequently, **11** was formed by a standard procedure and finally cyclized to **7** by treatment with diphenyl phosphoryl azide (DPPA).

In summary, we have presented a novel approach for Pd-mediated C−H allylic oxidation. In this transformation, promoted by $Yb(OTf)_3$ or $Sc(OTf)_3$, simple carbamates (most notably the Cbz group) serve as *O*-nucleophiles to generate an oxazolidinone scaffold. Further studies of the applicability of the described process are currently in progress.

This reaction was used as a key, late-stage step in the synthesis of unnatural (−)-castanospermine. Starting from D-xylose, the whole synthetic route was accomplished in only 11 steps. To our knowledge, this is the second reported approach to the title compound and appears to be much more efficient.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, full characterization, copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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