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Tandem Prins/pinacol reaction for the synthesis of oxaspiro[4.5]decan-1-one scaffolds†

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A novel Lewis acid catalyzed Prins/pinacol cascade process has been developed for the synthesis of 7-substituted-8-oxaspiro[4.5]decan-1-ones in good yields with excellent selectivity. This is the first example of the synthesis of oxaspirocycles from aldehydes and 1-(4-hydroxybut-1-en-2-yl)cyclobutanol through a cascade of Prins/pinacol rearrangement. This method is applicable to a wide range of aldehydes such as aromatic, aliphatic, heteroaromatic, and α,β-unsaturated aldehydes.

Cascade reactions are important transformations as they provide structural complexity and diversity in a single step process.[1] 'Prins cyclization' is a very useful reaction for the stereoselective construction of oxygen containing heterocycles.[2] In particular, Prins cascade reaction is a versatile strategy for the synthesis of fused or bridged tetrahydropyran scaffolds[3] and it has been successfully employed in the total synthesis of natural products.[4] Recently, we reported the synthesis of fused five- and six-membered oxacycles in high yields with excellent diastereoselectivity through a tandem Prins cyclization.[5] On the other hand, the oxaspirocycles are frequently found in various natural products and biologically active molecules (Fig. 1).[6] These complex structures possess a well-defined three-dimensional spatial arrangement, which exhibits specificity of action with enzymes and biological receptors.[7] Recently, a multi-component Prins cyclization has been reported for the synthesis of dioxaspirodecanes.[8] However, to date, there are only a few reports on the synthesis of spirocycles through a Prins/pinacol reaction.[9]

Following our interest in Prins spirocyclization[10] we herein report a novel cascade reaction for the stereoselective synthesis of oxaspirocycles through a Prins/pinacol sequence. The required starting material was easily prepared from commercially available homopropargylic alcohol as depicted in Scheme 1.

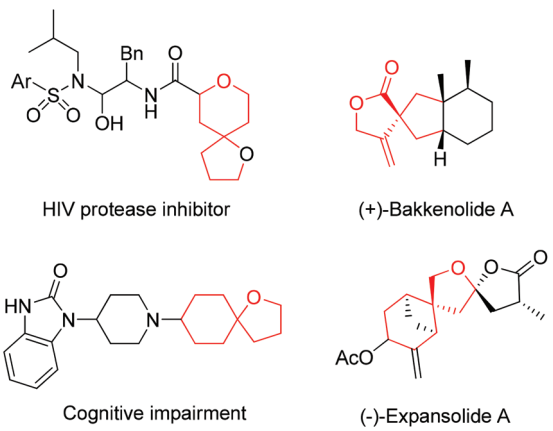
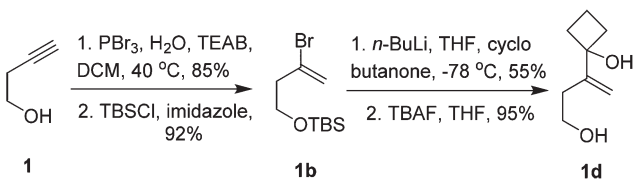


Fig. 1 Biologically active oxaspirocyclics.



Scheme 1 Preparation of the starting material (**1d**).

At first, we attempted the Prins/pinacol reaction of **1d** with 4-bromobenzaldehyde in the presence of a Lewis acid. To optimize the reaction conditions, several acid catalysts were screened and the results are presented in Table 1. Of the various acids tested, both $BF_3{\cdot}OEt_2$ and TMSOTf were found to be equally effective for this conversion (entries a and b,

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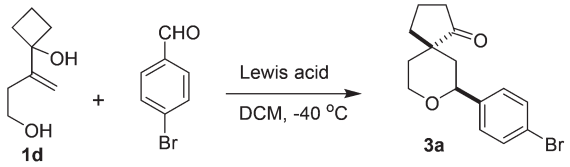
† Electronic supplementary information (ESI) available: Detailed procedures and spectroscopy data for novel compounds, NOESY spectra of product **3m** and copies of ^{1}H NMR and ^{13}C NMR spectra of novel compounds. See DOI: 10.1039/c4ob01188k

Table 1 Screening the catalysts in the formation of **3a**[a]



Entry	Catalyst	mol%	Time (min)	Yield[b] (%)
a	$BF_3{\cdot}OEt_2$	10	25	85
b	TMSOTf	10	30	83
c	$SnCl_4$	10	40	65
d	$Yb(OTf)_3$	10	50	20
e	$InCl_3$	10	30	50
f	Benzoic acid	10	50	10
g	CSA	10	50	30
h	$InBr_3$	10	45	55
i	$Sc(OTf)_3$	10	50	40

[a] Reaction was performed on the 0.5 mmol scale with respect to olefin. [b] The yield of the pure product after column chromatography.

Table 1). In addition, 10 mol% $SnCl_4$ also afforded the desired product **3a** in moderate yield (entry c, Table 1). Other Lewis acids ($InBr_3$, $InCl_3$, $Sc(OTf)_3$, $Yb(OTf)_3$) and Brønsted acids (CSA, benzoic acid) were found to be inferior for this reaction. Next, we examined the effect of solvents such as tetrahydrofuran, dichloromethane, and toluene. Of these, dichloromethane appeared to give the best results. Under optimized conditions, the reaction of **1d** with 4-bromobenzaldehyde in the presence of 10 mol% of $BF_3{\cdot}OEt_2$ afforded the corresponding oxaspirocycle **3a** in 85% yield as a single diastereomer.

Inspired by the above result, we extended this method to other aromatic aldehydes such as 4-cyanobenzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 2,4-dichlorobenzaldehyde, 2,4,5-trifluorobenzaldehyde, 4-tolualdehyde, benzaldehyde and 4-isopropylbenzaldehyde (entries a–h and l, Table 2). In all cases, the corresponding 7-aryl-8-oxaspirocycles were obtained in good to excellent yields (Table 2). This method works not only with aromatic aldehydes but also with aliphatic aldehydes such as 3-methylbutanal and pivalaldehyde (entries i and n, Table 2). In the case of aliphatic aldehydes, the corresponding 7-alkyl-8-oxaspirocycles were obtained in slightly lower yield than the aromatic counterpart.

Furthermore, a sterically hindered pivalaldehyde also reacted well with 1-(4-hydroxybut-1-en-2-yl)cyclobutanol (**1d**) to furnish the respective oxaspirocycle in good yield (entry n, Table 2). The efficacy of this approach was also tested by performing the reaction with heteroaromatic aldehydes like 4-bromo-thiophene-3-carboxaldehyde (entry k, Table 2). This method is effective even with acid sensitive cinnamaldehyde to provide the respective oxaspirocycle in good yield (entry m, Table 2). Next the reaction was performed with substituted cyclobutanol to produce the 2,4,6-trisubstituted tetrahydropyran derivative. Accordingly, treatment of 1-(4-hydroxy-6-phenylhex-1-en-2-yl)cyclobutanol (**2d**) with 2,4,5-trifluoro-

Table 2 Synthesis of 7-substituted-8-oxaspiro[4.5]decan-1-one scaffolds

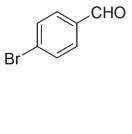
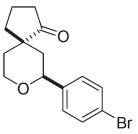
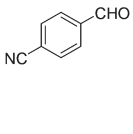
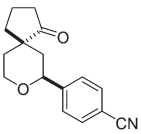
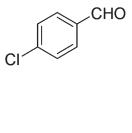
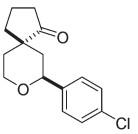
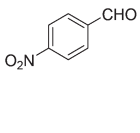
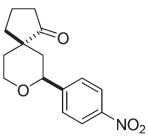
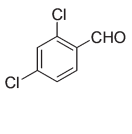
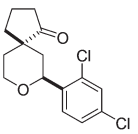
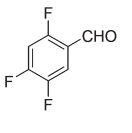
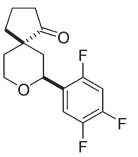
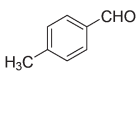
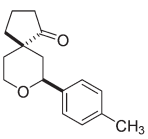
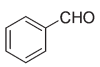
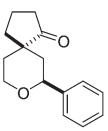
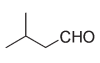
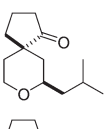
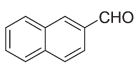
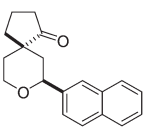
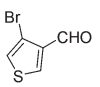
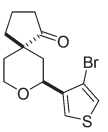
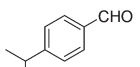
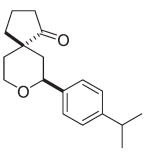
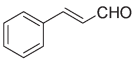
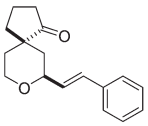
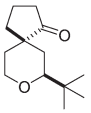
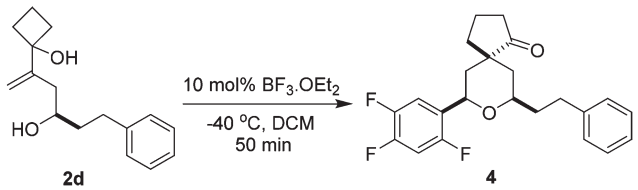
Entry	Aldehydes	Product (**3**)[a]	Time (min)	Yield[b] (%)
A			25	85
B			20	78
C			30	86
D			25	80
E			30	86
F			20	82
G			35	78
H			30	85
I			30	78
J			25	88
K			35	80
L			30	82

Table 2 *(Contd.)*

Entry	Aldehydes	Product (3)[a]	Time (min)	Yield[b] (%)
M			30	78
N			30	75

[a] All the products were characterized by NMR, IR and mass spectroscopy. [b] The yield of the pure product after chromatography.



Scheme 2 Synthesis of 7,9-disubstituted-8-oxaspiro[4.5]decan-1-one.

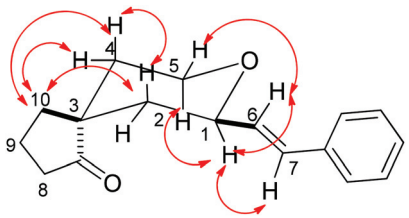


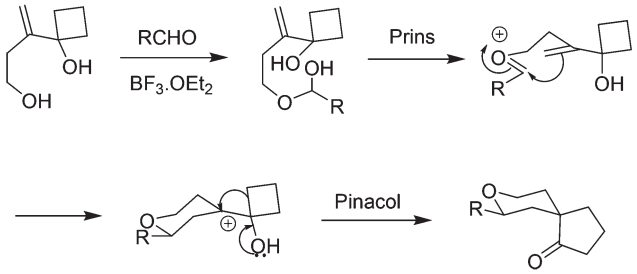
Fig. 2 Characteristic nOe cross-correlations of **3m**.

benzaldehyde under similar conditions gave the 7-phenethyl-9-(2,4,5-trifluorophenyl)-8-oxaspiro[4.5]decan-1-one (**4**) in 78% yield (Scheme 2).

The relative stereochemistry of **3m** was established by extensive NMR experiments including nuclear Overhauser effect spectroscopy (NOESY). The assignments were made with the help of NOESY experiments (Fig. 2). The nOe correlations between H_{4e}/H_{10}, H_{4a}/H_{10}, H_{2a}/H_{10}, H_{1a}/H_6, H_{1a}/H_7 and H_{5e}/H_6 confirm the structure as shown in Fig. 2.

A plausible mechanism for a Prins/pinacol cascade is proposed in Scheme 2. The reaction is assumed to proceed through the formation of an oxocarbenium ion that is generated *in situ* from the homoallylic diol (**1d**) and aldehyde under acidic conditions. Thus formed oxocarbenium ion is attacked by an internal olefin resulting in the formation of a carbocation, which is simultaneously terminated by a pinacol 1,2-shift to give the desired oxaspirocycle **3** as depicted in Scheme 3.

Finally, the reaction was performed on a 1 gram scale using the present reaction conditions. To our delight, the results are consistent with the small scale reaction (0.5 mmol).



Scheme 3 A possible reaction pathway.

In summary, we have developed a novel cascade process for the stereoselective synthesis of 7-substituted-8-oxaspiro[4.5]-decan-1-one derivatives through a Prins/pinacol reaction. This method offers several advantages such as high yields, excellent selectivity and compatibility with various aldehydes, which make it attractive for the synthesis of oxaspirocycles.

Experimental

General

All reactions were carried out under a nitrogen atmosphere. Commercial reagents were used as received, unless otherwise stated. ^{1}H NMR spectra were recorded on a 300 MHz or 500 MHz spectrometer using $CDCl_3$ as a solvent. ^{13}C NMR spectra were recorded on 75 MHz and 125 MHz spectrometers using $CDCl_3$. TMS was used as an internal reference for ^{1}H NMR analysis. All the compounds were purified by column chromatography on silica gel (60–120 mesh) using the hexane–ethyl acetate mixture as the eluent. Mass analysis was carried out using an *APCI* mass spectrometer.

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