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Domino Prins Cyclization of Enynols: Stereoselective Synthesis of Bicyclic Vinyl Fluorides

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A fluoride-induced termination of Prins cyclization has been observed using a tethered alkyne and stoichiometric amounts of $AgSbF_6$ and found to generate a novel series of 6-fluoro-1-aryl-hexahydro-1*H*-isochromene derivatives in good yields with excellent selectivity. This is the first report of the synthesis of fluoro-substituted oxabicycles. In this tandem process, three reactions occur in one-pot to leading to installation of three contiguous stereocenters.

Introduction

Fluorine-containing molecules play an important role in agrochemicals, pharmaceuticals, biomedical imaging agents, and chemically resistant materials due to their unique physical and chemical properties.[1] Among them, monofluoroalkenes[2] are of particular interest because of their potential applications in medicinal chemistry and materials science.[3–5] More specifically, the fluorooctahydro-1*H*-isochromene ring is a core structure of different sesquiterpenes like artemisin derivatives[6] as shown Figure 1.

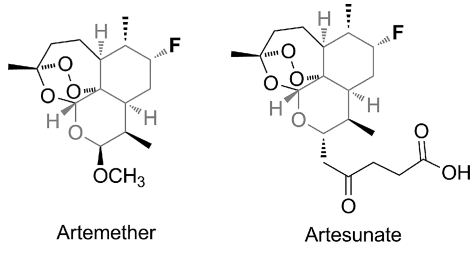

Figure 1. Biologically active fluoro-containing natural product derivatives.

Generally speaking, fluoro-substituted tetrahydropyrans are prepared by Prins cyclization.[7] Recently, a domino Prins cyclization has become a popular strategy for the stereoselective synthesis of fused or bridged oxacycles.[8] It is a highly diastereoselective process, in which the geometry of the olefin determines the stereochemical outcome of the reaction. It is also a cascade process, in which the Prins cyclization can be terminated by tethered nucleophiles. Consequently, different nucleophiles have been used to intramolecularly terminate the Prins cyclization thus producing unique fused or bridged oxacycles.[9,10] Inspired by this cascade process, we recently reported a novel series of oxacycles from homoallylic substrates bearing pendant nucleophiles such as hydroxy, thiol, sulfonamide, alkene and arene groups.[11] However, there are no reports of Prins cyclization termination with pendent alkyne moieties leading to functionalized oxabicycles.

Results and Discussions

In this article, we report a novel strategy for stereoselective synthesis of fluorooxabicycles from (*E*/*Z*)-oct-3-en-7-yn-1-ol and aldehydes through the application of a sequential Prins/alkynylation/fluorination domino process.

In this process, $AgSbF_6$ plays a dual role as i) a catalyst first activating the terminal alkyne, and ii) secondly, as a source of fluoride ion that traps the transient vinyl cation; fulfilling these two roles, $AgSbF_6$ readily enables vinyl fluoride production. In a test reaction, we attempted cross-coupling of (*E*)-oct-3-en-7-yn-1-ol (**1a**) with 4-nitrobenzaldehyde (**2**) in the presence of 1.1 equiv. $BF_3{\cdot}OEt_2$. The reaction was initially carried out in dichloroethane at –10 °C and then the temperature was slowly raised to 25 °C. After 12 h stirring at the same temperature, corresponding fluorohexahydro-1*H*-isochromene **3a** was obtained in 30% yield (Table 1, Entry a). To identify conditions that might enhance the yield the reaction was performed using various reagents such as HBF_4, InF_3, $AgSbF_6$ and $AgBF_4$. The use of 1.1 equiv. of $AgSbF_6$ in dichloroethane gave the desired

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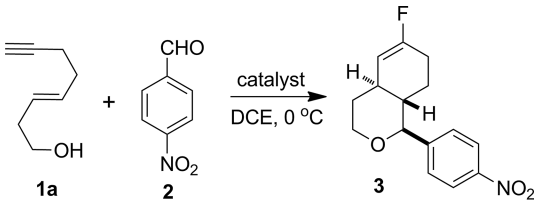
product **3a** in 90% yield with complete *trans*-selectivity (Table 1, Entry e). $AgBF_4$ was equally effective at enabling this conversion (Table 1, Entry m). Next, we examined the influence of different solvents such as dichloroethane, acetonitrile, tetrahydrofuran, benzene, toluene, 1,4-dioxane, and nitromethane on reaction efficiency. Of these, dichloroethane gave the best results in terms of conversion. The structure and relative stereochemistry of products were established on the basis of extensive NMR studies.[12]

Table 1. Screening different promoters and solvents for the formation of **3a**.[a]



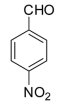
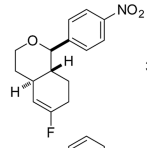
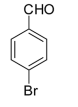
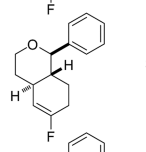
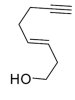
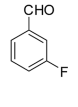
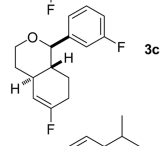
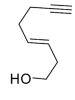
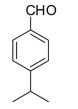
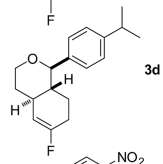
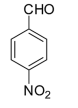
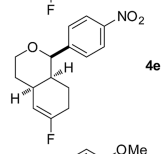
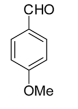
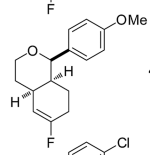
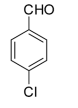
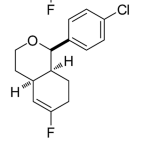
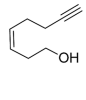
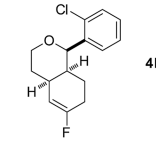
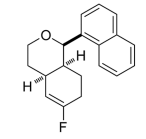
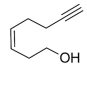
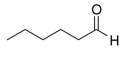
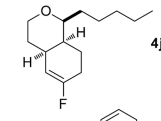
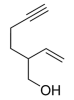
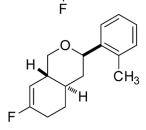
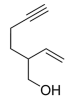
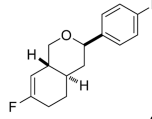
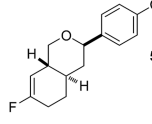
Entry	Catalyst (1.1 equiv.)	Solvent	Yield (%)[b]
a	$BF_3{\cdot}Et_2O$	DCE	30
b	HBF_4	DCE	10
c	InF_3	DCE	35
e	$AgSbF_6$	DCE	90
f	$AgSbF_6$	THF	40
g	$AgSbF_6$	toluene	65
h	$AgSbF_6$	benzene	60
i	$AgSbF_6$	acetonitrile	35
j	$AgSbF_6$	nitromethane	30
k	$AgSbF_6$	dioxane	20
l	$AgBF_4$	DCE	75

[a] Reaction was performed for 12 h. [b] Isolated yield.

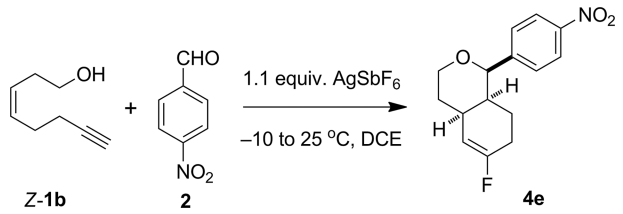
Inspired by these reaction optimization results, we extended this method to different aldehydes; the results of these efforts are exemplified in Table 2. Interestingly, several aromatic aldehydes such as benzaldehyde, 3-fluoro-, and 4-isopropyl benzaldehydes reacted effectively with (*E*)-oct-3-en-7-yn-1-ol to afford the respective aryl-substituted *trans*-fluorohexahydro-1*H*-isochromene derivatives **3b**–**3d** in good to excellent yields (Table 2, Entries b–d).

Furthermore, the coupling of (*Z*)-oct-3-en-7-yn-1-ol (**1b**) with *p*-nitrobenzaldehyde (**2**) in the presence of 1.1 equiv. of $AgSbF_6$ in dichloroethane at –10 to 25 °C over the course of 9 h gave corresponding *cis*-fluorohexahydro-1*H*-iso-

Table 2. Synthesis of fluorooxabicycles using Prins/yne cyclization chemistry.

Entry	Enynol	Aldehyde	Product		Yield (%)	*trans:cis*
a				**3a**	90	100:0
b				**3b**	86	100:0
c				**3c**	82	100:0
d				**3d**	85	100:0
e				**4e**	86	0:100
f				**4f**	85	0:100
g				**4g**	81	0:100
h				**4h**	81	0:100
i				**4i**	82	0:100
j				**4j**	75	0:100
k				**5k**	85	90:10
l				**5l**	82	86:14
m				**5m**	88	92:8

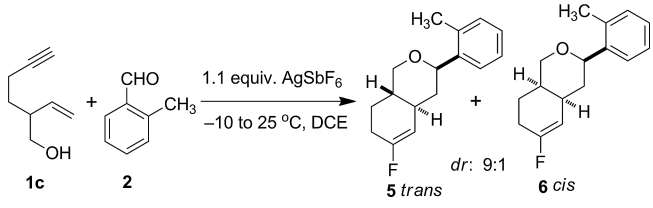
chromene (**4e**) exclusively in 86% yield (Scheme 1, Table 2, Entry e).



Scheme 1. Prins/yne cyclization of (*Z*)-oct-3-en-7-yn-1-ol with *p*-nitrobenzaldehyde.

Similarly, other aromatic aldehydes such as 4-methoxy-, 4-chloro-, and 2-chlorobenzaldehydes also participated well in this cascade process. Furthermore, a sterically hindered 1-naphthaldehyde gave the anticipated product in fair to good yield (Table 2, Entry i). This method was successful not only with aromatic aldehydes but also with aliphatic aldehydes. However, the aliphatic aldehyde *n*-hexanal, afforded the corresponding *n*-pentyl fluorohexahydro-1*H*-isochromene in lower yield than its aromatic counterpart (Table 2, Entry j). On the basis of data in Table 2, it is evident that the geometry of the olefin controls the stereoselectivity of the reaction.

Inspired by the results obtained with oct-3-en-7-yn-1-ol, we extended this approach to a branched homoallylic alcohol 2-vinylhex-5-yn-1-ol (**1c**). Accordingly, treatment of **1c** with *o*-tolualdehyde in the presence of 1.1 equiv. of $AgSbF_6$ in dichloroethane at –10 °C to room temperature over the course of 6 h gave corresponding fluoro-hexahydro-1*H*-isochromene as a mixture of **5** and **6** in 85% yield (Scheme 2, Table 2, Entry k). Similarly, other aromatic aldehydes like 3-fluorobenzaldehyde, *p*-chlorobenzaldehyde reacted perfectly with 2-vinylhex-5-yn-1-ol (**1c**) under the present conditions to provide respective fluoro-hexahydro-1*H*-isochromene derivatives with high *trans*-selectivity (Table 2, Entries l–m).

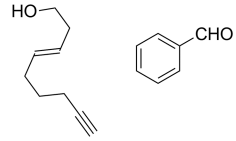
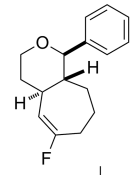
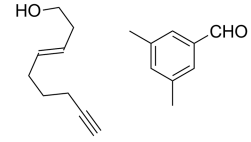
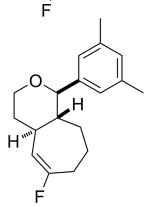
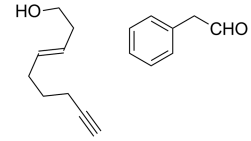
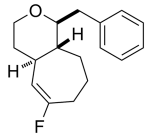
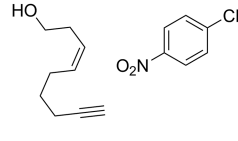
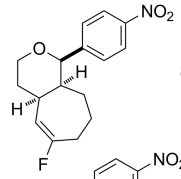
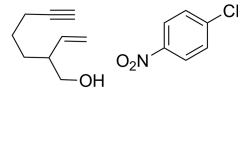
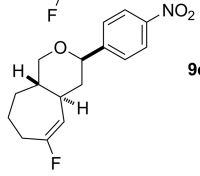
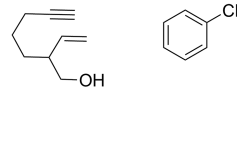
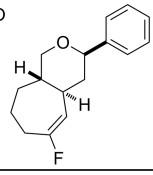


Scheme 2. Prins/yne cyclization of 2-vinylhex-5-yn-1-ol (**1b**) with *o*-tolualdehyde.

The scope of the reaction was further illustrated with (*E*/*Z*)-non-3-en-8-yn-1-ol and the results are presented in Table 3.

Accordingly, the cross coupling of (*E*)-nonenynol (**1d**) with various aldehydes such as benzaldehyde, 3,5-dimethylbenzaldehyde and phenylacetaldehyde furnished respective *trans*-fused fluorooctahydrocyclohepta[*c*]pyran derivatives **7a–c** in good yields with high selectivity (Table 3, Entries a–c), whereas the use of *cis*-nonenynol (**1e**) afforded *cis*-fused

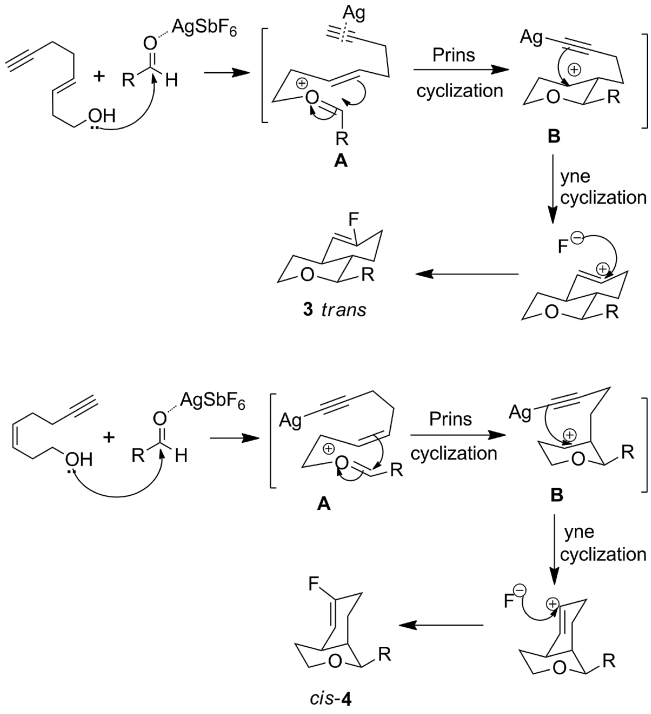
Table 3. Synthesis of fluorooxabicycles via Prins/yne cyclization chemistry.

Entry	Enynol	Aldehyde	Product	Yield (%)[a]	*trans:cis*[b]
a				**7a** 82	100:0
b				**7b** 81	100:0
c				**7c** 75	100:0
d				**8d** 84	90:10
e				**9e** 85	86:14
f				**9f** 80	87:13

[a] Yield determined on basis of pure products obtained following column chromatography. [b] Ratio was determined on the basis of ^{1}H NMR data analysis of crude product mixture.

product **8d** as a major diastereomer (Table 3, Entry d). However, the use of branched enynol, 2-vinylhept-6-yn-1-ol (**1f**) gave *trans*-fused product **9** as a major isomer (Table 3, Entries e and f).

A plausible mechanism for this cascade process is proposed in Scheme 3. The reaction likely proceeds through an oxocarbenium ion formed upon convergence of the aldehyde and enynol. In this reaction, $AgSbF_6$ activates the aldehyde thus facilitating the formation of oxonium ion **A**, which is then attacked by an internal olefin to generate carbocation **B**. Subsequent activation of the alkyne C–H bond by Ag^I generates the silver acetylide, simultaneous carbocation attack installs the bicyclic vinyl cation. Finally, nucleophilic attack of fluoride ion at the vinyl cation center affords the desired product (Scheme 3).



Scheme 3. A plausible reaction pathway.

Conclusions

In summary, we have demonstrated a highly efficient and stereoselective approach for the synthesis of bicyclic vinyl fluorides from enynols and aldehydes employing 1.1 equiv. of $AgSbF_6$. This method provides direct access to bicyclic vinyl fluorides in good yields. The salient features of this method include: i) high conversions, ii) mild reaction conditions, iii) high selectivity, and iv) operational simplicity.

Experimental Section

Typical Procedure for Domino Prins Cyclization: To a stirred solution of an enynol (**1a**–**1f**) (0.5 mmol) and aldehyde **2** (0.525 mmol) was added 1.1 equiv. of $AgSbF_6$ in dichloroethane at –10 °C and the temperature was slowly raised to room temperature for the specified time (8–10 h). After completion of the reaction as indicated by TLC, the mixture was quenched with saturated $NaHCO_3$ solution (0.5 mL), diluted with water (2–3 mL) and extracted with dichloromethane (2 × 5 mL). The combined organic phases were washed with brine (3 × 2 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100–200 mesh) using EtOAc/hexane gradients to afford the pure products (see Tables 2 and 3).

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[12] The stereochemistry of **3c** and **4e** was assigned on the basis of nOe studies (see Supporting Information).

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