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BF_3·OEt_2-Promoted Propargyl Alcohol Rearrangement/[1,5]-Hydride Transfer/Cyclization Cascade Affording Tetrahydroquinolines

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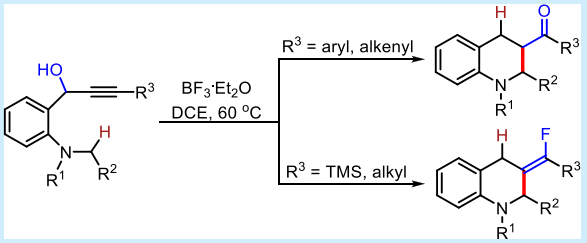
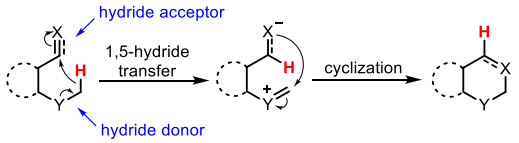
Supporting Information

ABSTRACT: An efficient BF_3·OEt_2-mediated propargyl alcohol rearrangement/[1,5]-hydride transfer/cyclization cascade for the synthesis of tetrahydroquinoline derivatives has been described. The substituents adjacent to triple bonds play an important role in the formation of ketones (via [1,3]-hydroxyl shift) or alkenyl fluorides which are products of formal *trans*-carbofluorination of internal alkynes. This method provides a rapid access to diverse heterocycles in moderate to excellent yields.



As one of the most valuable skeletons and building blocks, tetrahydroquinoline can be found in many natural products and drugs with strong antibacterial and anti-inflammatory biological activities.[1] Over the past years, [1,5]-hydride transfer/cyclization cascade reactions proved synthetically powerful for the construction of structurally diverse complex molecules, especially tetrahydroquinoline derivatives.[2] The hydride transfer process usually requires hydride donors and hydride acceptors. The typical hydride donor is a C(sp^3)−H moiety adjacent to a tertiary amine or an ethereal oxygen (Scheme 1).[3] In most cases, electron-deficient alkenes were used as hydride acceptors in [1,5]-hydride transfer/cyclization cascade reactions to construct a tetrahydroquinoline skeleton.[4] Besides activated alkenes, aldehydes,[5] ketones,[6] imines,[7] allenes,[8] and so on can also serve as different types of hydride acceptors.

Scheme 1. [1,5]-Hydride Transfer/Cyclization Cascade



hydride acceptor: activated alkenes, alkynes, ketones, imines, etc.
X, Y = C, O, N, etc.

In recent years, alkynes also served as hydride acceptors in this cascade reaction.[9] For example, Barluenga et al. reported a Fischer carbene-activated [1,5]-hydride transfer/cyclization process for the efficient synthesis of 1,2-hydroquinolynyl carbene complexes (Scheme 2a).[10] In addition, Liang et al. reported a platinum-catalyzed [1,5]-hydride transfer/cyclization reaction, in which the hydroxyl moiety was protected with an acetyl and a [1,3]-OAc shift was involved in this process (Scheme 2b).[11] In 2012, Gong et al. reported a transition-metal-free [1,5]-hydride transfer/cyclization process of terminal alkynes,[12] which was promoted by Brønsted acid and pyridine-*N*-oxide, to give 2,3-dihydroquinolinones (Scheme 2c). Herein, we will report a propargyl alcohol rearrangement/[1,5]-hydride transfer/cyclization cascade promoted by Lewis acid BF_3·Et_2O (Scheme 2d). The current method provided a straightforward and convenient one-step synthetic route toward a variety of tetrahydroquinoline derivatives.

Our study was initiated by examining the [1,5]-hydride transfer/cyclization with the easily prepared propargyl alcohol **1a** being the model substrate in the presence of Lewis acids (Table 1). To our delight, the desired tetrahydroquinoline derivative **2a** was obtained in 78% yield with 3.0 equiv of BF_3·OEt_2 as a Lewis acid in 1,2-dichloroethane (DCE) at 80 °C (entry 1). In this reaction, **3a** was obtained in 7% yield which probably was formed via Meyers−Schuster rearrangement reaction[13] of propargyl alcohol **1a**. When anhydrous $Yb(OTf)_3$ or $FeCl_3$ was employed as a Lewis acid, the reaction was messy and only a trace amount of **2a** was observed (entries 2 and 3). Other Lewis acids, including $AlCl_3$, $ZnCl_2$, and $CuCl_2$, were also tested, but no desired product **2a** was obtained (entries 4−6). Brønsted acids such as *p*-toluenesulfonic acid (TsOH), trifluoroacetic acid (TFA), and camphorsulfonic acid (CSA) were also screened, however, mainly leading to **3a** in modest yields (entries 7−9). With BF_3·OEt_2 as the Lewis acid of choice, different solvents have been investigated, and we found that nonchlorinated solvents, such as 1,4-dioxane, dimethyl sulfoxide (DMSO), acetonitrile, tetrahydrofuran, and toluene,

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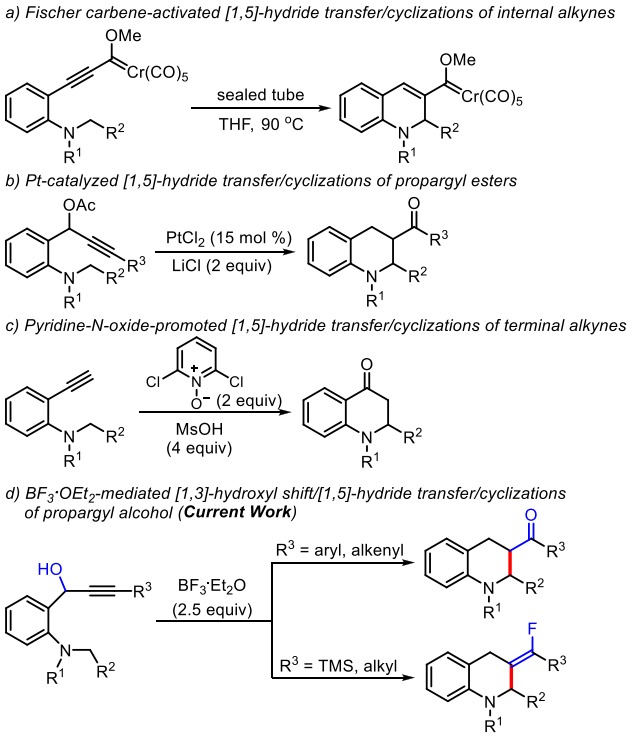
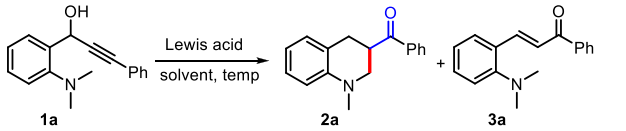
Scheme 2. Alkynes as Hydride Acceptors in [1,5]-Hydride Transfer/Cyclization Cascade toward the Synthesis of Tetrahydroquinolines



all led to lower yields compared to DCE (entries 10−14). Employing dichloromethane and chloroform instead of DCE, the reaction gave slightly lower yields for the desired product (entries 15 and 16). The amount of Lewis acid was also checked, and a slightly higher conversion of **1a** was observed when the Lewis acid was decreased to 2.5 equiv (entry 17). When 2 equiv of $BF_3{\cdot}OEt_2$ were used, the GC yield of product **2a** was 72% (entry 18). However, further decreasing the amount of $BF_3{\cdot}OEt_2$ to 1.5 equiv resulted in lower selectivity for the target product (entry 19), while low conversion of **1a** was observed when the amount of $BF_3{\cdot}OEt_2$ was decreased to a catalytic amount (entry 20). Then, we also screened the reaction temperature (entries 21−23). When the reaction was conducted at 60 °C, **2a** was obtained in 91% yield (entry 23). Consequently, 2.5 equiv of $BF_3{\cdot}OEt_2$ as the Lewis acid and 1,2-dichloroethane as solvent at 60 °C were chosen as the optimized conditions.

With the optimal reaction conditions in hand, a wide range of functional groups were then evaluated to investigate their influence on the overall reactivity and to establish the reaction scope with respect to the aromatic rings connecting directly to hydride acceptors (Scheme 3). Excellent yields were obtained in the reaction including *para*-alkyl-substituted substrates (**2b**, **2c**) and an electron-donating naphthalene ring (**2h**, **2i**). Electron-withdrawing substituents such as F (**2d**), Br (**2e**), Cl (**2f**) in the *para* position were also well-tolerated, and the corresponding products were obtained in moderate-to-good yields. A *meta*-CH_3-substituted product (**2g**) was smoothly furnished in 87% yield when the reaction was conducted in 1.5 h. Furthermore, substrates with a larger conjugate structure proceeded smoothly under the optimized conditions to afford **2j** and **2k** in 62% and 80% yield, respectively. It was gratifying to note that substrates with an electron-withdrawing group

Table 1. Optimization of Reaction Conditions[a]



entry	Lewis acid	solvent	temp (°C)	**2a** (%)[b]	**3a** (%)[b]
1	$BF_3{\cdot}OEt_2$	DCE	80	78	7
2	$Yb(OTf)_3$	DCE	80	<5	<5
3	$FeCl_3$	DCE	80	<5	45
4	$AlCl_3$	DCE	80	<5	50
5	$ZnCl_2$	DCE	80	<5	45
6	$CuCl_2$	DCE	80	<5	46
7	TsOH	DCE	80	<5	66
8	TFA	DCE	80	<5	64
9	CSA	DCE	80	<5	67
10	$BF_3{\cdot}OEt_2$	dioxane	80	34	18
11	$BF_3{\cdot}OEt_2$	DMSO	80	<5	<5
12	$BF_3{\cdot}OEt_2$	MeCN	80	35	8
13[c]	$BF_3{\cdot}OEt_2$	THF	80	<5	32
14	$BF_3{\cdot}OEt_2$	toluene	80	34	<5
15[c]	$BF_3{\cdot}OEt_2$	$CHCl_3$	80	69	<5
16[c]	$BF_3{\cdot}OEt_2$	DCM	80	77	7
17[d]	$BF_3{\cdot}OEt_2$	DCE	80	81	<5
18[e]	$BF_3{\cdot}OEt_2$	DCE	80	72	8
19[f]	$BF_3{\cdot}OEt_2$	DCE	80	46	12
20[g]	$BF_3{\cdot}OEt_2$	DCE	80	<5	<5
21[d]	$BF_3{\cdot}OEt_2$	DCE	rt	<5	46
22[d]	$BF_3{\cdot}OEt_2$	DCE	40	67	21
23[d]	$BF_3{\cdot}OEt_2$	DCE	60	91 (83)	<5

[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **1a** (0.5 mmol, 1.0 equiv), Lewis acid (1.5 mmol, 3.0 equiv), in DCE (1 mL) at 80 °C under Ar for 1.5−2 h. [b]Yields were determined by GC analysis with dodecane as an internal standard. The value in parentheses is the isolated yield. [c]The reaction was run in sealed reaction tube. [d]$BF_3{\cdot}OEt_2$ (2.5 equiv). [e]$BF_3{\cdot}OEt_2$ (2.0 equiv). [f]$BF_3{\cdot}OEt_2$ (1.5 equiv). [g]$BF_3{\cdot}OEt_2$ (30 mol %).

(bromo) and electron-donating group (methyl) in the *meta* or *para* position to the nitrogen atom also give rise to the desired products in typically excellent yields (**2l**−**2n**). Unfortunately, substrates with a *para* methoxy group and thiophene group led to only an *α,β*-unsaturated ketone. Various heterocycles derived from different cyclic or acyclic amines were also investigated to demonstrate the substrates scope of this methodology. Substrates containing aza-cycle scaffolds with different ring sizes, (**1o**−**1q**) and 5,6,7,8-tetrahydroisoquinoline (**1r**), successfully give rise to the desired fused products in moderate to good yields, generally with the *anti*-products being preferred. Although the two diastereomers can be isolated by column chromatography, they can convert to each other under the reaction conditions (see Supporting Information (SI) for the detailed discussion). When ethereal oxygen containing substrates, with *N,N*-dimethyl group in **2a** being substituted by methoxy or allyloxy, were subjected to the standard conditions, the reactions were messy resulting in a complicated inseparable mixture (see SI for the details).

Subsequently, a variety of substrates with aliphatic substitution on the alkyne moiety were subjected to the above reaction conditions (Scheme 4). Unexpectedly, exoalkenyl fluoride **4** resulted as a major product, which is a formal *trans*-carbofluorination product of the internal alkyne. Substrate with TMS-substitution (**1s**) afforded 77% **4s** with

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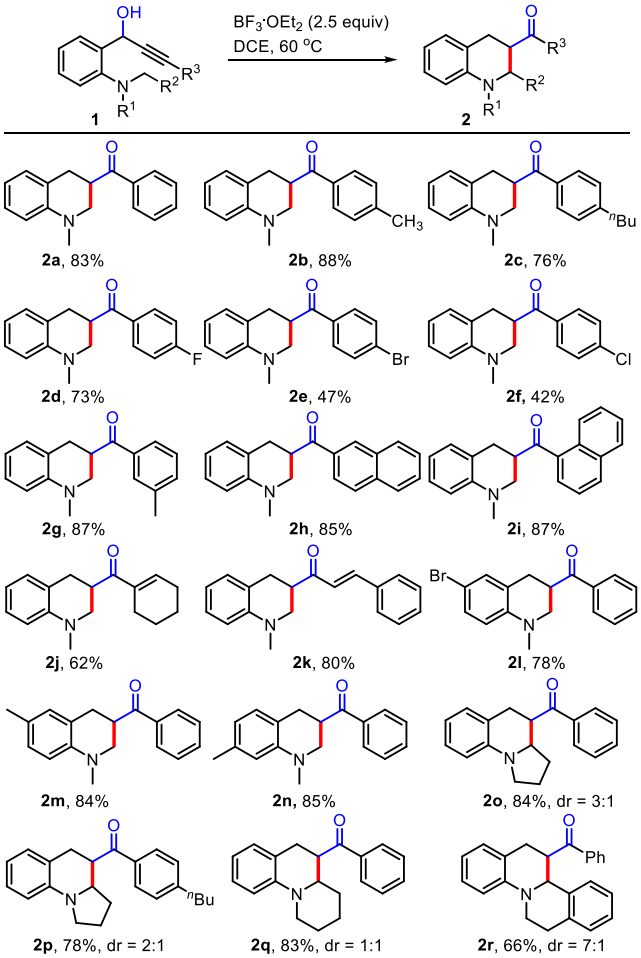
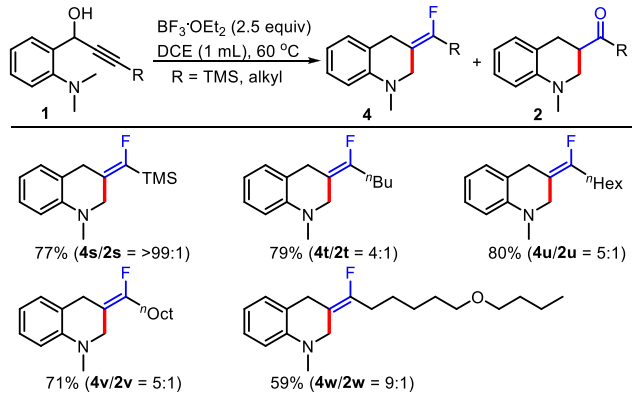
Scheme 3. BF_3·OEt_2-Promoted [1,3]-Hydroxyl Shift/[1,5]-Hydride Transfer/Cycloaddition[a,b]



[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **1** (0.5 mmol, 1.0 equiv), BF_3·OEt_2 (1.25 mmol, 2.5 equiv), in DCE (1 mL) at 60 °C under Ar for 1.5−2 h. [b]All yields were the isolated yields.

Scheme 4. BF_3·OEt_2-Promoted [1,5]-Hydride Transfer/Cycloaddition[a,b]

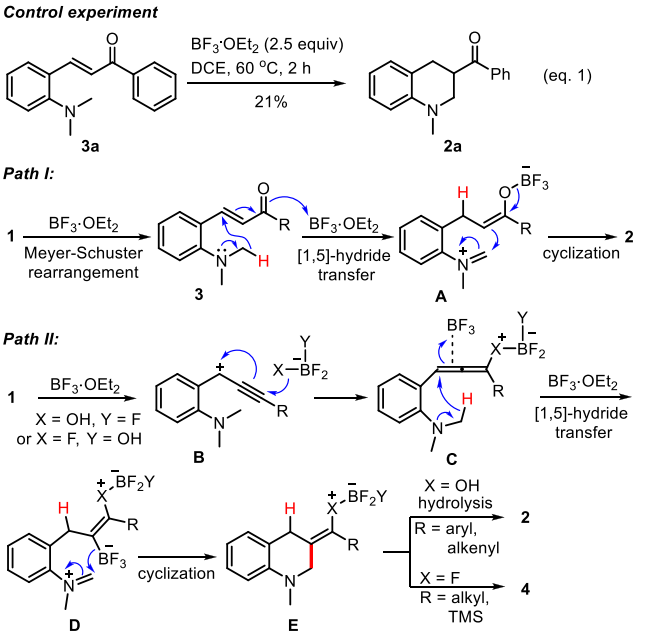


[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **1** (0.5 mmol, 1.0 equiv), BF_3·OEt_2 (1.25 mmol, 2.5 equiv), in DCE (1 mL) at 60 °C under Ar for 1.5−2 h. [b]All yields were the isolated yields of alkene-form and keto-form products.

high selectivity. Propargylic alcohols **1t**−**1w** led to similar outcomes for the formation of an alkenyl fluoride **4** product with moderate results, along with a minor amount of **2** being isolated in these reactions. The stereochemistry of alkenyl fluoride was determined by NOE measurement of compound **4w**.

Based on previous studies,[11,14] a plausible reaction pathway is postulated in Scheme 5 (Path I), which involves a Lewis acid

Scheme 5. Control Experiment and Proposed Mechanism



induced 1,3-hydroxyl shift (Meyer−Schuster rearrangement) leading to an α,β-unsaturated ketone (**3**). Then, coordination of a Lewis acid to the carbonyl oxygen forms a complex which undergoes a [1,5]-hydride shift to afford the zwitterionic intermediate **A**. Finally, Mannich cyclization afforded the desired tetrahydroquinoline (**2**). However, when α,β-unsaturated ketone (**3a**) was subjected under standard conditions (eq 1), only a 21% yield of **2a** was obtained, which indicates the presence of other possible reaction pathways. Moreover, the formation of **4** cannot be explained through this pathway. Therefore, an alternative pathway is proposed (Path II) in which the Meyer−Schuster rearrangement product is bypassed. First, reaction of propargyl alcohols with Lewis acid may lead to propargyl cation intermediate **B**, which undergoes an S_N1' nucleophilic attack leading to allenyl-boron complex **C**.[15] Then the hydrogen on the methyl group adjacent to the nitrogen atom migrates in a [1,5]-fashion to the most electrophilic carbon of allene, affording zwitterionic intermediate **D**. Afterward, intermediate **D** undergoes Mannich cyclization affording the intermediate **E**. The formation of product **2** or **4** as major products is dependent on the substituted group on the alkyne. When the alkyne is substituted by an aromatic group, the nucleophilic S_N1' attack of OH^- is favored due to its higher nucleophilicity compared with fluoride. Accordingly, the intermediate **E** will be hydrolyzed to give the keto product **2**. However, when the alkyne is substituted by the alkyl group, the nucleophilic S_N1' attack of F^- is favored due to the higher steric demand of alkyl substitution and the alkenyl fluoride **4** will be the dominant product.[16] For the highly steric hindered

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TMS-substituted substrate, only the alkenyl fluoride was identified.

We have demonstrated a mild, efficient, and versatile method for construction of tetrahydroquinoline derivatives from easily available propargyl alcohols with an *ortho*-amino substituted phenyl group. A plausible reaction mechanism involving a $BF_3{\cdot}OEt_2$-promoted propargyl alcohol rearrangement/[1,5]-hydride transfer/internal imino-aldol cyclization tandem process is proposed. The formation of keto-products or alkenyl fluoride is dependent on the substitution mode of the alkyne. [1,5]-Hydride transfer/cyclization resulting in *trans*-carbofluorination of the internal alkyne is responsible for the formation of the alkenyl fluoride. Further studies to expand the reaction scope and elucidate the mechanism are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01153.

Experimental procedures, spectral and analytical data, copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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