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Lewis Acid Catalyzed Cyclization of Propargylic Alcohols with 2-Vinylphenol

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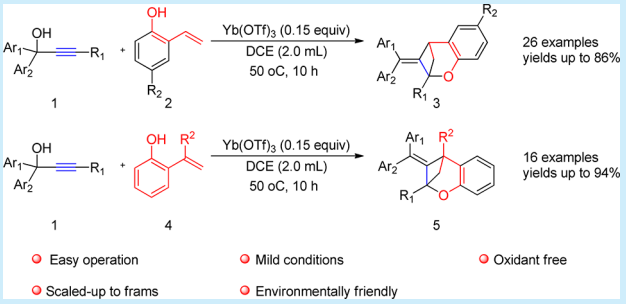
Supporting Information

ABSTRACT: An unprecedented Lewis acid catalyzed, protection-free, and high-efficiency synthesis of valuable 3,4-dihydro-2*H*-2,4-methanochromans via cycloaddition of propargylic alkynols with 2-vinylphenol is described. This cycloaddition protocol, which tolerates a wide variety of functional groups, provides practical, versatile, and atom-economical access to a new class of appealing bridged-ring products in satisfactory yields. Compared with the reported reaction conditions for bridged-ring skeletons synthesis, the present reaction conditions are neutral, mild, and without any additives.



The 2-oxabicyclo[3.1.1]heptanes represent an important class of bridged-ring compounds because they are the key structural motifs in a wide array of biologically and pharmacologically relevant natural products.[1] For example, compound **a** (Figure 1), which contains a bridged-ring system,

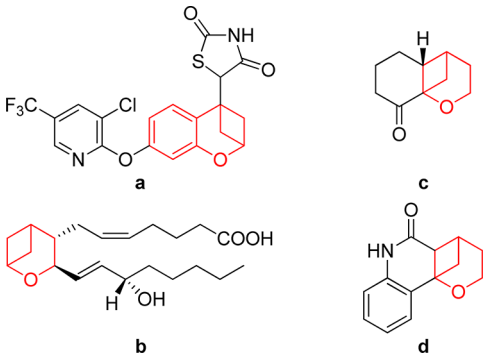


Figure 1. Selected examples bearing the 2-oxabicyclo[3.1.1]heptane.

was identified as an effective pharmaceutical agent for the treatment of Type 2 diabetes mellitus, lipid disorders, and obesity.[1d] Deoxygenated analogue **b** showed good potential in preventing platelet aggregation and vasoconstriction.[1b] Bicyclic molecules **c** and **d** were identified as effective building blocks in organic synthesis.[1a,c,e,f] Therefore, versatile, convenient, and efficient methods for the synthesis of bridged rings are highly desirable.

Recently, the direct metal-catalyzed functionalization of C−H bonds in various carbocycles and heterocycles has been the focus of a significant number of research initiatives[2] due to the fundamental scientific appeal and its potential utility in organic synthesis. In particular, the employment of oxygen-containing coupling partners for the construction of structurally diverse oxygen-containing compounds, such as furans,[3] benzofurans,[4] furanones,[5] chromenes,[6] and isoquinolones,[7] has been widely investigated. Remarkably, almost all of these transformations were achieved by [3 + 2] or [4 + 2] tandem cyclization to afford five- or six-membered rings, but it is worth noting that a direct Lewis acid catalyzed pathway to construct oxygen-containing bridged rings is still an extremely attractive yet challenging task, and few approaches to oxygen-containing bridged rings have been reported. Herein, we set out to develop a new type of Lewis acid catalyzed cyclization between alkynols with 2-vinylphenol to synthesize functionalized 3,4-dihydro-2*H*-2,4-methanochromans.

This work originated from our previous observation on Lewis acid catalyzed [4 + 3] cyclization of alkynols and azides to synthesize indole azepines.[8] The initial exploration began by employing the alkynol substrate **1j** with 2-vinylphenol **2a** as the model substrates to optimize the reaction conditions. The product **3j** was obtained in 67% yield in the presence of $Zn(OTf)_2$ (20 mol %) in DCE at 40 °C for 6 h (Table 1, entry 1). Different Lewis acid catalysts were tested in this system, which could also catalyze the cyclization to furnish the desired product in 36−71% yields (entries 2−6). A subsequent investigation on the effect of temperature revealed that the

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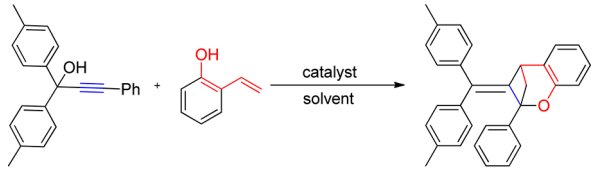
Table 1. Optimization of the Reaction Conditions of 1j with 2-Vinylphenol[a,b]



1j 2a 3j

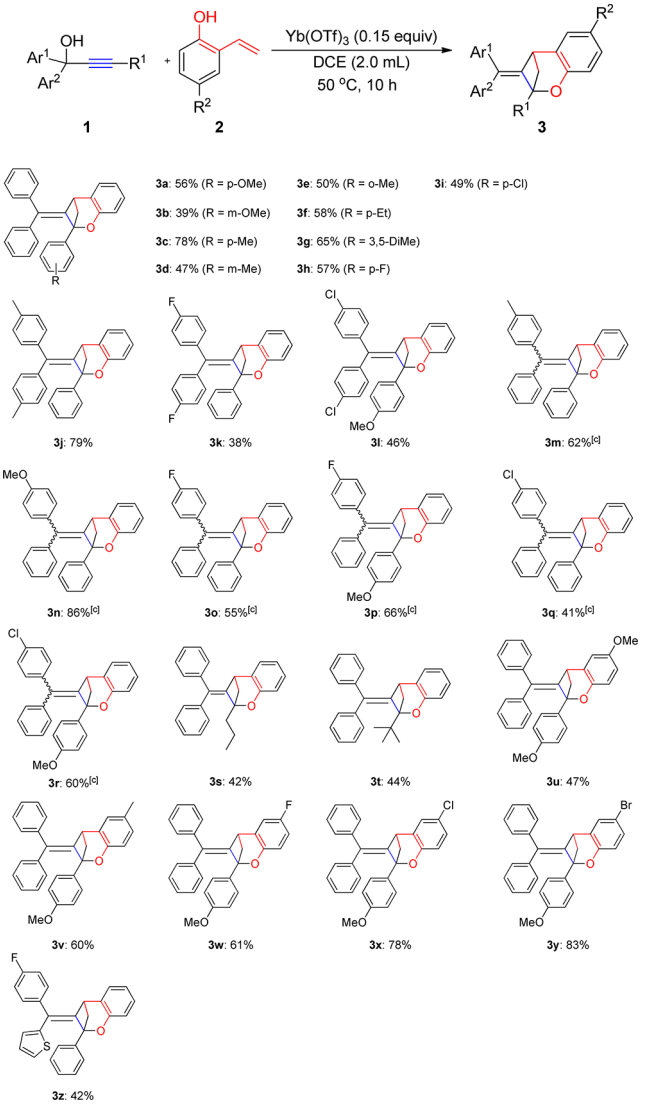
entry	catalyst (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)
1	$Zn(OTf)_2$ (20)	DCE	40	6	67
2	$Al(OTf)_3$ (20)	DCE	40	6	56
3	$Y(OTf)_3$ (20)	DCE	40	6	61
4	$Bi(OTf)_3$ (20)	DCE	40	6	59
5	$In(OTf)_3$ (20)	DCE	40	6	36
6	$Yb(OTf)_3$ (20)	DCE	40	6	71
7	$Yb(OTf)_3$ (20)	DCE	50	6	73
8	$Yb(OTf)_3$ (20)	DCE	60	6	68
9	$Yb(OTf)_3$ (20)	DCE	70	6	62
10	$Yb(OTf)_3$ (20)	DCE	80	6	55
11	$Yb(OTf)_3$ (20)	DCE	50	8	74
12	$Yb(OTf)_3$ (20)	DCE	50	10	82
13	$Yb(OTf)_3$ (20)	DCE	50	12	69
14	**$Yb(OTf)_3$ (15)**	**DCE**	**50**	**10**	**79**
15	$Yb(OTf)_3$ (10)	DCE	50	10	67
16	$Yb(OTf)_3$ (15)	CH_2Cl_2	50	10	66
17	$Yb(OTf)_3$ (15)	CH_3NO_2	50	10	17
18	$Yb(OTf)_3$ (15)	1,4-dioxane	50	10	32
19	$Yb(OTf)_3$ (15)	THF	50	10	29

[a]Unless otherwise noted, all reactions were performed with **1j** (0.1 mmol) and 2-vinylphenol **2a** (2.0 equiv) in solvent (2.0 mL). [b]Yields are given for isolated products.

reaction gave the best result at 50 °C (entries 7−10). Other adjustments indicated that 10 h was the most suitable for this transformation, which gave 82% yield of the product (entries 11−13). Decreasing the catalyst loading to 15 mol % slightly reduced the yield to 79% (entries 14 and 15). Various representative solvents such as CH_2Cl_2, CH_3NO_2, 1,4-dioxane, and THF proved to be less effective (entries 16−19). Ultimately, the optimal reaction conditions were eventually finalized with the use of **1j** (0.1 mmol) and 2-vinylphenol **2a** (2.0 equiv) in the presence of $Yb(OTf)_3$ (15 mol %) in DCE (2.0 mL) at 50 °C for 10 h.

Under the standard reaction conditions, the scope of this transformation was then explored by employing a variety of propargylic alcohols to react with **2**. It is noteworthy that substrates containing substituents of diverse electron-rich (OMe, Me, Et, **3a−g**) or electron-deficient character (F, Cl, **3h,i**), at any position of the benzene ring (R^1), were compatible with this protocol and were easily converted to the corresponding bridged-ring products **3a−i** in moderate to good yields (39−78%, Scheme 1). Regarding symmetrical propargylic alcohols containing either electron-donating or electron-withdrawing groups on the aromatic rings (Ar^1, Ar^2), the annulation proceeded smoothly to give the corresponding single diastereomeric products in 38−79% yields (**3j−l**). The structure of **3j** was further elucidated by X-ray crystal structure analysis (see the Supporting Information). When the unsymmetrical propargylic alcohols were tested, the reaction also participated in the process and generated anticipated products **3m−r** with yields ranging from 41% to 86%. Remarkably, alkyl-

Scheme 1. Transformation of Propargylic Alcohols to 3,4-Dihydro-2*H*-2,4-methanochromans[a−c]



[a]Unless otherwise noted, all reactions were performed with **1** (0.1 mmol) and **2** (2.0 equiv) in the presence of $Yb(OTf)_3$ (15 mol %) in DCE (2.0 mL) at 50 °C for 10 h. [b]Yields are given for isolated products. [c]The olefin isomer *E*/*Z* ratios of **3m−r** are 1:1, which are assigned by integral area of ^1H NMR spectra.

substituted (R^1) tertiary propargylic alcohols (**1s**, **1t**) were suitable substrates for this reaction and afforded the desired products in moderate yields. In addition, substituents with different electronic natures (OMe, Me, F, Cl, Br) on the aromatic ring of **2** also participated well in the reaction, leading to the efficient formation of corresponding products **3u−y** in satisfactory yields. The reaction of heteroaryl-substituted (R^1) propargylic alcohol **1z** with substrate **2a** afforded the product **3z** in 42% yield.

Next, we sought to investigate the scope with respect to the 2-(prop-1-en-2-yl)phenol. The reaction of 2-(prop-1- en-2-yl)phenol **4** with various propargylic alcohols proceeded well, allowing the facile synthesis of 4-methyl-3,4-dihydro-2*H*-2,4-methanochromans in generally good to excellent yields (Scheme 2). The substrates bearing electron-donating or electron-withdrawing groups on the aromatic ring (R^1) reacted smoothly to deliver the corresponding products **5a−h** in 50−

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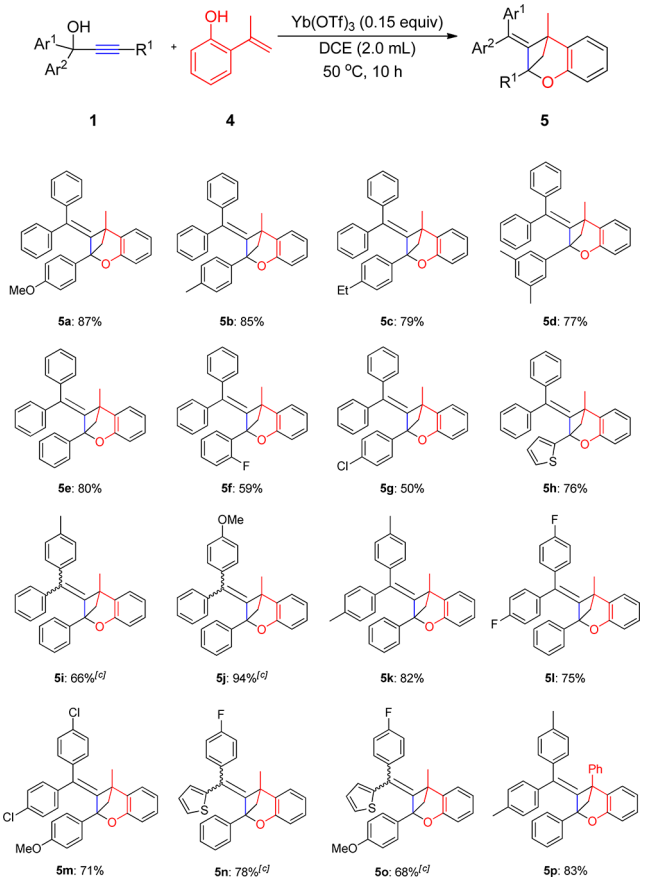
Scheme 2. Transformation of Propargylic Alcohols to 4-Methyl-3,4-dihydro-2*H*-2,4-methanochromans[a−c]



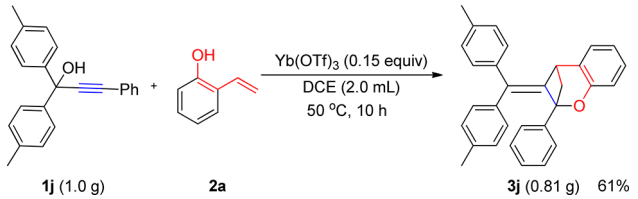
[a]Unless otherwise noted, all reactions were performed with **1** (0.1 mmol) and **4** (2.0 equiv) in the presence of $Yb(OTf)_3$ (15 mol %) in DCE (2.0 mL) at 50 °C for 10 h. [b]Yields are given for isolated products. [c]The olefin isomer *E*/*Z* ratios of **5i,j,n** and **5o** are 1:1, 1:1, 1:1, and 1:1, respectively, which are assigned by integral area of ^{1}H NMR spectra.

87% yields. Moreover, different unsymmetrical propargylic alcohols were suitable substrates for this cyclization reaction, affording the desired products **5i,j** with yields ranging from 66% to 94%. Propargylic alcohols bearing electron-rich (Me) or electron-deficient (F, Cl) substituents on the aromatic rings (Ar^1, Ar^2) were also found to be compatible with the reaction and led to the expected products in moderate to good yields (**5k−m**). The reactions of heteroaryl-substituted (R^1) tertiary propargylic alcohols were well implemented to form the desired products **5n,o** in 68−78% yields. The 2-(1-phenylvinyl)phenol was employed in the reaction, which afforded the desired product **5p** in 83% yield.

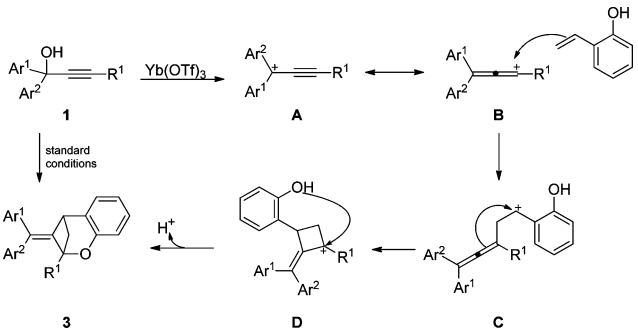
It was noteworthy that our developed reaction system could be scaled up to gram quantities. The desired product **3j** was obtained in a moderate yield of 61% under the standard conditions (Scheme 3).

A plausible mechanism based on the literature[9−13] is proposed in Scheme 4. Initially, propargylic alcohol **1** converts to propargyl cation species **A** in the presence of $Yb(OTf)_3$, which could resonate with resonance-stabilized **B**. Nucleophilic attack of 2-vinylphenol **2** onto the intermediate **B** forms intermediate **C**. Subsequent intramolecular nucleophilic addition of intermediate **C** to the carbocation site produces

Scheme 3. Scale-up Experiment



Scheme 4. Proposed Mechanism for the Formation of 3,4-Dihydro-2*H*-2,4-methanochromans



intermediate **D**. Finally, intermediate **D** undergoes an intramolecular nucleophilic attack and the release of a proton to furnish the desired product **3**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01875.

Experimental details and NMR data (PDF)
Crystallographic data for **3j** (CIF)

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Notes

The authors declare no competing financial interest.

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