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Lewis Acid Catalyzed [4 + 3] Cycloaddition of Propargylic Alcohols with Azides

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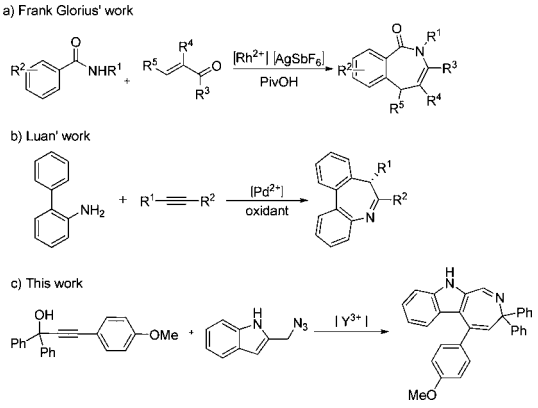
Supporting Information

ABSTRACT: An unprecedented Lewis acid catalyzed [4 + 3] cycloaddition reaction is described that provides a straightforward route to polycyclic products containing an imine-based indole azepine scaffold, starting from readily available internal tertiary alkynols and azides. This cycloaddition protocol provides efficient and atom-economical access to a new class of fascinating imine-containing products in satisfactory yields, which has shown good application in the construction of seven-membered *N*-heterocycles.

Lewis acid catalyzed cycloaddition has attracted considerable attention in the field of large ring skeleton structure synthetic methodology.[1] The cycloaddition of propynols with diverse nucleophiles has provided a powerful method for the construction of seven-membered carbon heterocycles with high efficiency.[2] In particular, employment of nitrogen-containing coupling partners for the construction of structurally diverse *N*-heterocyclic compounds has been widely investigated.

Azepines represent an important class of seven-membered *N*-heterocycles as the key structural motifs in a wide array of biologically and pharmacologically relevant natural products.[3−6] They have also been identified as effective early biosynthetic precursors and could regulate gene expression.[7−10] Classical methods for the synthesis of azepines rely on the use of catalysts such as Rh or Pd via a cyclization reaction. In 2013, the Glorius group reported a novel method employing amides with α,β-unsaturated aldehydes or ketones to construct azepine derivatives (Scheme 1a).[11] Very recently, Luan and co-workers disclosed a Pd-catalyzed transformation of alkynes to azepines (Scheme 1b).[12] Nevertheless, the high cost of catalysts, complicated operation, or the use of an extra oxidant impose restrictions on application in synthetic chemistry. Due to the significance and wide applications of such compounds in organic chemistry, the search for new reliable synthetic approaches for the preparation of azepines from readily available starting materials is still attractive to researchers. Still, a direct Lewis acid catalyzed pathway for the construction of larger rings is an extremely attractive yet challenging task. Herein, we report a novel and direct Lewis acid catalyzed [4 + 3] cyclization of alkynols with azides to synthesize indole azepines. Compared to traditional catalytic systems, our developed reaction system avoids the use of costly catalyst and extra oxidant.

Scheme 1. Summary of Present Studies and Our New Anticipation toward Seven-Membered Compounds



Our initial investigation[13] focused on the reaction of the alkynol substrate **1a** with 2-(azidomethyl)-1*H*-indole **2a** in the presence of $Zn(OTf)_2$ (20 mol %) in toluene at 80 °C (Table 1, entry 1). To our delight, expected product **3a** was obtained in 55% yield after 6 h. Notably, it was found that a number of other Lewis acids also worked and gave product **3a** in 36−61% yield (entries 2−6), indicating that this cycloaddition is proposed to occur through a nucleophilic substitution pathway. A subsequent investigation on the effect of temperature showed that this transformation was most efficiently conducted at 120 °C (entries 7−10). Prolonging the reaction time to 10 h generated the desired product **3a** in 76% yield (entries 11−13). The yield was slightly reduced to 75% by decreasing the catalyst

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Table 1. Optimization of the Reaction Conditions of 1a with 2a[a]

1a 2a 3a

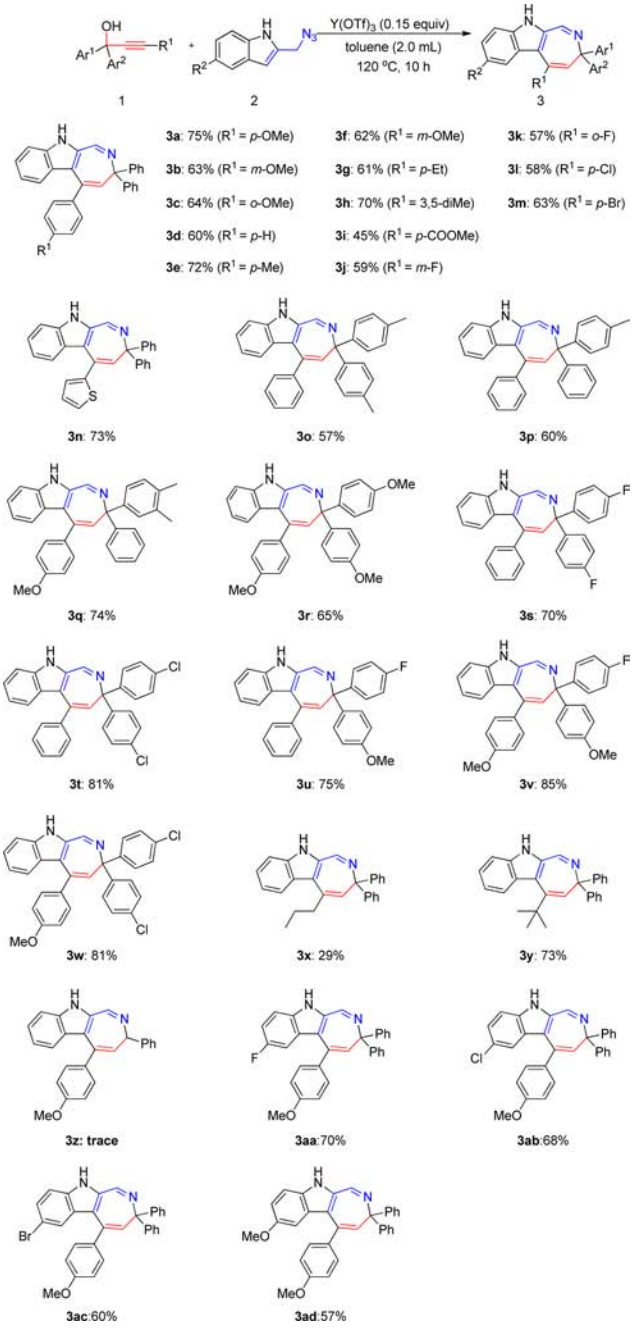
entry	catalyst (mol %)	solvent	temp (°C)	t (h)	yield[b] (%)
1	$Zn(OTf)_2$ (20)	toluene	80	6	55
2	$Al(OTf)_3$ (20)	toluene	80	6	41
3	$Yb(OTf)_3$ (20)	toluene	80	6	43
4	$Bi(OTf)_3$ (20)	toluene	80	6	45
5	$In(OTf)_3$ (20)	toluene	80	6	36
6	$Y(OTf)_3$ (20)	toluene	80	6	61
7	$Y(OTf)_3$ (20)	toluene	100	6	63
8	$Y(OTf)_3$ (20)	toluene	110	6	65
9	$Y(OTf)_3$ (20)	toluene	120	6	68
10	$Y(OTf)_3$ (20)	toluene	130	6	59
11	$Y(OTf)_3$ (20)	toluene	120	8	71
12	$Y(OTf)_3$ (20)	toluene	120	10	76
13	$Y(OTf)_3$ (20)	toluene	120	12	70
14	**$Y(OTf)_3$ (15)**	toluene	**120**	**10**	**75**
15	$Y(OTf)_3$ (10)	toluene	120	10	68
16	$Y(OTf)_3$ (15)	DCE	120	10	66
17	$Y(OTf)_3$ (15)	CH_3NO_2	120	10	55
18	$Y(OTf)_3$ (15)	1,4-dioxane	120	10	32
19	$Y(OTf)_3$ (15)	CH_3CN	120	10	59

[a]Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol) and **2a** (2.0 equiv) in the presence of $Y(OTf)_3$ (15 mol %) in toluene (2.0 mL). [b]Yields are given for isolated products.

loading to 15 mol % (entries 14 and 15). Various representative solvents such as DCE, CH_3NO_2, CH_3CH, and 1,4-dioxane did not result in any improvement in the yield (entries 16−19). Ultimately, the optimal conditions for the generation of **3a** were determined to be **1a** (0.1 mmol) and **2a** (2.0 equiv) in the presence of $Y(OTf)_3$ (15 mol %) in toluene at 120 °C for 10 h.

Under the standard reaction conditions, the scope of this transformation was then investigated by employing a variety of tertiary propargylic alcohols (**1a−1y**). Substrates bearing substituents of varying electron-rich (OMe, Me, Et, **3a−3h**) or electron-deficient character (COOMe, F, Cl, Br, **3i−3m**), at any position of the aromatic ring (R^1), were tolerated, giving the desired [4 + 3] cycloaddition products **3a−3m** in moderate to good yields (45−75%, Scheme 2). The structure of **3h** was further identified by X-ray crystal structure analysis (Figure 1; see the Supporting Information). It is noteworthy that halo-substituted alkynol substrates worked smoothly and furnished the corresponding halo-substituted indole azepines in moderate yields, which might have potential applications in various cross-coupling reactions (**3l−3m**). Additionally, the substrates bearing electron-donating and/or electron-withdrawing groups on the aromatic rings (Ar^1, Ar^2) were also found to be compatible with this protocol and generated corresponding products in moderate to good yields (**3o−3w**). Various asymmetric tertiary alkynol were also studied (**3p**, **3q**, **3u**, and **3v**). They participated in the [4 + 3] cycloaddition to give the corresponding indole azepines in moderate yields. Remarkably, when alkyl-substituted (R^1) tertiary propargylic alcohols (**3x**,**3y**) were employed, the anticipated [4 + 3] cycloaddition proceeded smoothly to generate the products in good yields. Next, we sought to investigate the scope with

Scheme 2. Transformation of Propargylic Alcohols to Indole Azepines[a,b]



[a]Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol) and **2a** (2.0 equiv) in the presence of $Y(OTf)_3$ (15 mol %) in toluene (2.0 mL) at 120 °C for 10 h. [b]Yields are given for isolated products.

respect to **2a**. The substrates bearing electron-withdrawing (F, Cl, Br) or electron-donating (OMe) groups on the aromatic rings performed well and gave the desired products in moderate to satisfactory yields (**3aa−3ad**). However, secondary propargylic alcohol **1z** and alkyl-substituted (Ar^1, Ar^2 = alkyl) tertiary propargylic alcohols failed to afford the corresponding products under the optimal conditions. This might be attributed to the reason that one aryl group or two alkyl groups could not stabilize the carbocation intermediate **B** generated by propargylic alcohol substrates (see Scheme 3).

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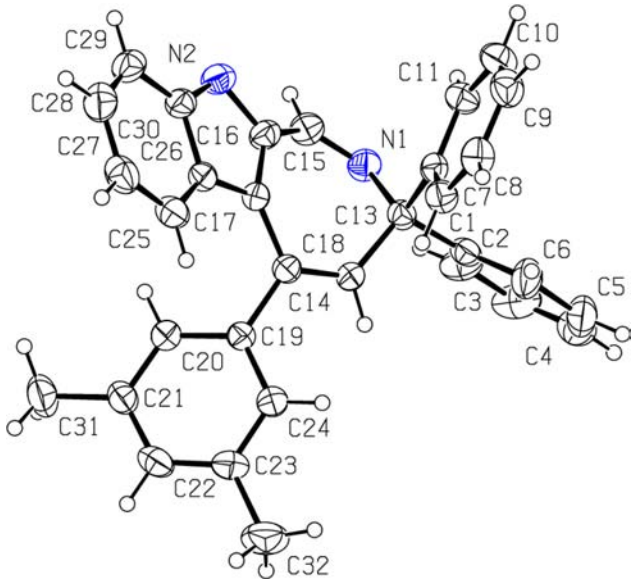
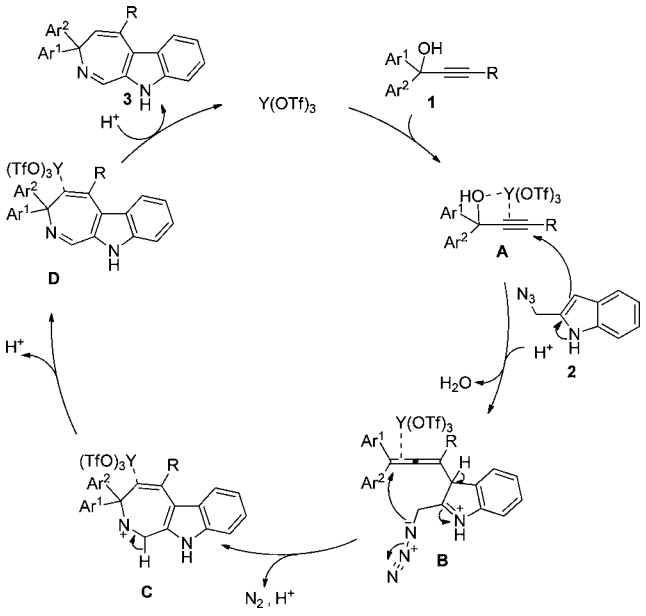


Figure 1. X-ray structures of **3h**. Thermal ellipsoids are shown at 30% probability.

Scheme 3. Proposed Mechanism for the Formation of Indole Azepines



A plausible mechanism was then proposed on the basis of literature[14−16] (Scheme 3). Initially, propargylic alcohol **1** converts to intermediate **A** in the presence of $Y(OTf)_3$. The attack of 2-(azidomethyl)-1*H*-indole **2** onto the C−C triple bond of intermediate **A** generates intermediate **B**, which could be converted into intermediate **C** through an intramolecular nucleophilic attack, followed by the release of a proton and a molecule of nitrogen gas. Finally, the desired product **3** was afforded by protonation with the regenerated catalyst.

In conclusion, a novel Lewis acid catalyzed [4 + 3] cycloaddition of propargylic alcohols with azides was achieved for building a seven-membered N-heterocyclic architecture that contained an indole azepine scaffold. This cycloaddition protocol is applicable to a wide range of propargylic alcohols and azides and results in the efficient preparation of imine-containing azepine derivatives in moderate to high yields. Significantly, this protocol provides a straightforward approach to construct the complex polycyclic skeleton through a [4 + 3] cycloaddition process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03657.

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

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Notes

The authors declare no competing financial interest.

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