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DABCO-Mediated [4 + 4]-Domino Annulation: Access to Functionalized Eight-Membered Cyclic Ethers

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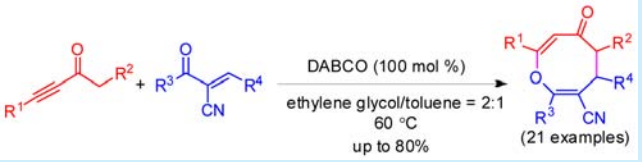
Supporting Information

ABSTRACT: DABCO-mediated [4 + 4] domino annulation reactions of ynones and α-cyano-α,β-unsaturated ketones were discovered. The domino process affords an alternative route to eight-membered cyclic ethers in good yields under mild conditions.



Eight-membered cyclic ethers occur widely in natural products that have intriguing biological activities (Figure 1). For example, Integrastatin A displays inhibitory activity

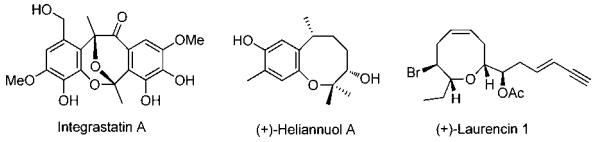
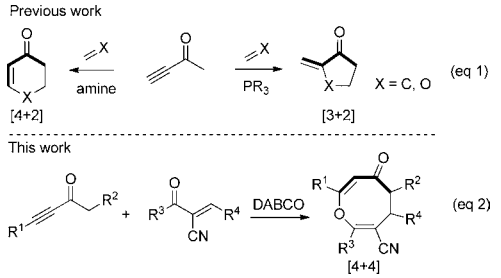


Figure 1. Examples of eight-membered ethers possessing biological activities.

against HIV-1 integrase at micromolar concentrations and has thus been an attractive target for therapeutic development.[1] (+)-Heliannuol A is a naturally occurring sesquiterpenoid exhibiting strong allelopathic activity.[2] (+)-Laurencin 1 is a red algae metabolite which was first isolated from methanol extracts of *Laurencia glandulifera*.[3] Thus, a number of synthetic methods have been devised for the synthesis of this structural motif over the past decades, such as (1) ring-closing metathesis,[4] (2) Lewis acid promoted acetal−alkene cyclizations,[5] (3) intramolecular amide enolate alkylation,[6] (4) retro-Claisen rearrangement,[7] (5) reductive desulfurization of the thioethers,[8] and others.[9] However, some drawbacks of these methods are unsatisfactory yields, poor stereoselectivities, tedious processes for purification, and costly catalysts. On the other hand, these synthetic methods are mainly concentrated on the intramolecular cyclization. Therefore, a new synthetic approach to this class of useful molecules is still highly desirable.

Lewis base catalyzed domino reactions have become a fast growing field owing to convenience and efficiency.[10] DABCO is widely used as a Brønsted base or Lewis base in domino reactions.[11] Ynones have participated in organocatalytic domino reactions mainly in two ways (Scheme 1, eq 1): (a) in phosphine catalyzed processes, where ynones were used as three-carbon synthons (C3) for [3 + 2]-annulation;[12] (b) in nitrogen-containing catalyst promoted processes, where ynones could be used as four-carbon synthons (C4) for [4 + 2]-annulation instead.[13]

Scheme 1. Lewis Base Catalyzed Domino Reactions of Ynones



During our ongoing investigation on phosphine- and nitrogen-containing Lewis base catalyzed domino cyclization reactions of ynones,[14] we report herein a 1,4-diazabicyclo-[2.2.2]octane (DABCO) promoted [4 + 4]-cycloaddition reaction of ynones and α-cyano-α,β-unsaturated ketones under mild conditions furnishing a series of highly functionalized eight-membered cyclic ethers in good yields (Scheme 1, eq 2).

To validate the feasibility of the cyclic addition reaction, we investigated the reaction of 4-phenylbut-3-yn-2-one (**1a**) with (*E*)-2-benzoyl-3-(4-bromophenyl)acrylonitrile (**2a**) in the presence of 100 mol % DABCO in ethanol at 40 °C;[14b] after 24 h, the desired product was isolated in 24% yield (see Supporting Information S-Table 1). When the reaction was performed at 60 °C, a higher yield could be achieved. Attempts to improve the yield by employing other nitrogen-containing Lewis bases turned out to be unavailing. The use of DBU and DMAP failed to give any product; Et_3N, TMEDA, and DIPEA relative to DABCO gave lower yields. The solvent effect was also examined by screening CH_3CN, DMSO, isopropanol, toluene, and $CHCl_3$, of which toluene and $CHCl_3$ were found to be suitable as the medium. Changing the ratio of the substrates in ethanol and toluene improved the yield to 53%

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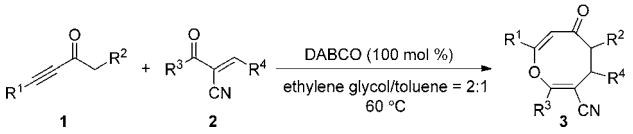
and 52%. When the 1,3-propanediol was used, this reaction provided a low yield; however, using ethylene glycol as the solvent, a moderate yield of 57% was obtained. In order to improve the yield, a mixture solvent (ethylene glycol/toluene = 2:1) was used, the best yield was obtained at 78%, when the reaction was performed at a higher temperature (110 °C) or in another solvent mixture (ethylene glycol/$CHCl_3$ = 2:1), no better result could be obtained. Although catalytic transformation was realized in some cases, 100 mol % DABCO was needed to obtain a satisfactory conversion and yield. It should be noted that no positive results were observed when more DABCO was employed. Meanwhile, when tertiary phosphine catalysts were used, no desired product was detected. Optimized reaction conditions were determined using 100 mol % of DABCO as a catalyst in a solvent mixture (ethylene glycol/toluene = 2:1) solution at 60 °C for 24−48 h. In addition, the structure and stereochemistry of **3a** were characterized by a combination of NMR, HRMS spectra, and single-crystal X-ray analysis (see Supporting Information S-Figure 1).[15]

With the optimized reaction conditions in hand, we continued our investigation of the reaction with the substrate scope (Table 1). Generally, the present DABCO-mediated [4 + 4]-annulation reaction served as an efficient approach toward functionalized eight-membered cyclic ethers. In addition, a set of functional groups, such as halide, methoxyl, and trifluoromethyl groups, were compatible with the system, furnishing the desired products with moderate to good yields (Table 1, entries 1−12). Interestingly, substrate **2** bearing a α-naphthyl or β-naphthyl group could react smoothly to deliver the corresponding product with a moderate yield (52% and 51% respectively), while a 2-furyl or 2-thienyl decorated α,β-unsaturated ketone was not a good candidate for this transformation (Table 1, entries 15−16). Substituted phenyls on R^3 were accommodated in this transformation and provided the desired products in medium yields (Table 1, entries 17−18). Furthermore, several ynones were also probed and good yields were obtained (Table 1, entries 19−20). The substituents R^2 were not limited to hydrogen (Table 1, entries 21−22), when R^2 was methyl group, the product was obtained as a single *trans*-isomer in 73% yield, and **3t** was isolated in 80% yield when two methyl groups were introduced. It was worth noting that R^4 was also suitable to the alkyl group; when R^4 was a cyclohexyl group, the desired product was produced in a slightly low yield of 33%. However, R^1 was limited to a phenyl group. When the reaction was conducted with substrate **1v** (R^1 = *n*-butyl), no reaction occurred. On the other hand, for the Michael acceptors, a CN group played a key role in the reactions, when CN was replaced by other electron-withdrawing groups, such as carbonyls or sulfonyls (see Supporting Information), no corresponding products were obtained.

To demonstrate the practicality of our method, we performed this [4 + 4]-annulation reaction on a gram scale. When **1a** and **2a** were used under the optimal reaction conditions, the reaction proceed smoothly to afford desired product **3a** in 67% yield (Scheme 2). In addition, **3a** could also be further reduced using $NaBH_4$ under mild conditions to generate the corresponding alcohol **4a** with a good yield and diastereoselectivity (62%, dr = 7:1) (Scheme 2).

To gain insight into the mechanism of the present reaction, several control experiments were conducted (Scheme 3). When **1a** was mixed with DABCO in the presence of 50 equiv of D_2O in $CHCl_3$, a H/D exchange at the α-position of carbonyl was detected, while no exchange was found in the absence of DABCO, unveiling its potential role as a base in the transformation (Scheme 3, eq 1). However, when the reaction was conducted with K_2CO_3 instead of DABCO, only a 22% yield of the product was generated, suggesting that DABCO likely acted in a role beyond a base. On the other hand, D-substituted product **D-3a** was furnished under the standard conditions with $CHCl_3$ as solvent in the presence of D_2O, which demonstrated that a carbon anion possibly existed at these positions.

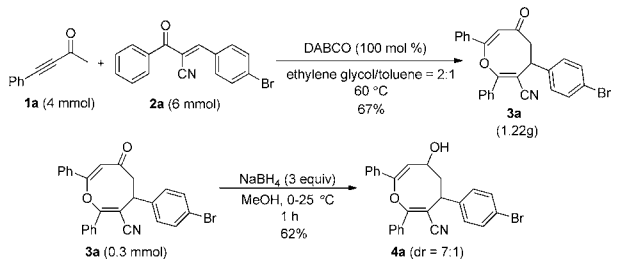
Table 1. Substrate Scope[a]



entry	R^1	R^2	R^3	R^4	time (h)	3, yield/%[b]
1	Ph	H	Ph	4-BrC_6H_4	24	**3a**, 78
2	Ph	H	Ph	3-BrC_6H_4	24	**3b**, 67
3	Ph	H	Ph	2-BrC_6H_4	24	**3c**, 78
4	Ph	H	Ph	4-MeC_6H_4	48	**3d**, 51
5	Ph	H	Ph	3-MeC_6H_4	48	**3e**, 49
6	Ph	H	Ph	2-MeC_6H_4	48	**3f**, 69
7	Ph	H	Ph	C_6H_5	20	**3g**, 60
8	Ph	H	Ph	4-ClC_6H_4	12	**3h**, 76
9	Ph	H	Ph	4-FC_6H_4	12	**3i**, 59
10	Ph	H	Ph	4-$MeOC_6H_4$	48	**3j**, 36
11	Ph	H	Ph	2,4-$Cl_2C_6H_3$	24	**3k**, 66
12	Ph	H	Ph	4-$CF_3C_6H_4$	24	**3l**, 57
13	Ph	H	Ph	α-naphthyl	48	**3m**, 52
14	Ph	H	Ph	β-naphthyl	48	**3n**, 51
15	Ph	H	Ph	2-furyl	48	–
16	Ph	H	Ph	2-thienyl	48	–
17	Ph	H	4-BrC_6H_4	4-BrC_6H_4	12	**3o**, 56
18	Ph	H	4-Me C_6H_4	4-BrC_6H_4	24	**3p**, 53
19	4-Me C_6H_4	H	Ph	4-BrC_6H_4	24	**3q**, 59
20	4-FC_6H_4	H	Ph	4-BrC_6H_4	24	**3r**, 64
21	Ph	Me	Ph	4-BrC_6H_4	48	**3s**, 73
22	Ph	di-Me	Ph	4-BrC_6H_4	24	**3t**, 80
23	Ph	H	Ph	cyclohexyl	48	**3u**, 33
24	*n*-Bu	H	Ph	4-BrC_6H_4	48	–

[a]Reactions were performed using **1a** (0.5 mmol), **2a** (0.75 mmol), DABCO (0.5 mmol) in 3 mL of solvent (EG/Toluene = 2:1) at 60 °C. [b]Isolated yields. EG = ethylene glycol.

Scheme 2. Gram-Scale DABCO-Mediated [4 + 4]-Annulation and Further Transformation of 3a



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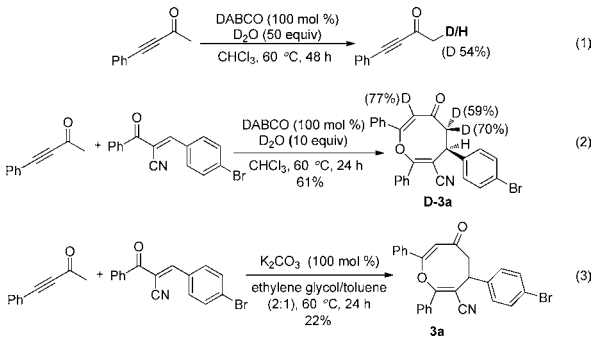
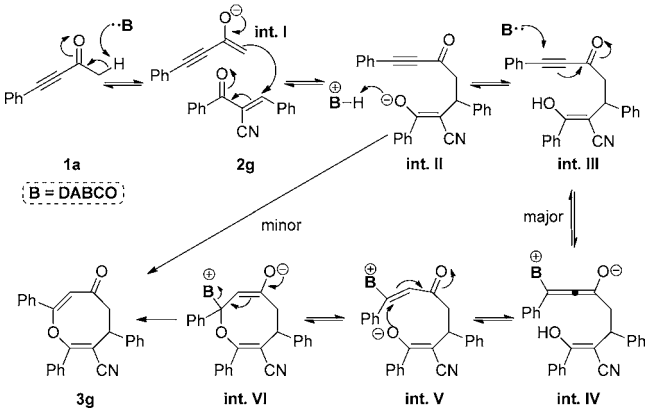
Scheme 3. Control Experiments



On the basis of these results in the current study and previous reports,[13,14,16] a plausible mechanism for this domino reaction is illustrated in Scheme 4. Initially, 4-phenylbut-3-yn-2-

Scheme 4. Proposed Mechanism



one (**1a**) was deprotonated by DABCO to generate enolate **int. I** which underwent conjugate nucleophilic addition to α,β-unsaturated ketone **2g** delivering **int. II**; in this step, DABCO was just used as as a base. Subsequent protonation of **int. II** gave **int. III**, which underwent the second Michael addition with DABCO generating zwitterionic **int. IV**. A further 1,7-hydrogen shift, intramolecular nucleophilic addition, and finally release of DABCO afforded the product **3g**. Another possible pathway includes a simple 8-*endo*-dig cyclization from **int. II** by direct intramolecular nucleophilic addition to produce **3g**; however, based on the experiments result, this pathway was not a main route, because an inorganic base could not give a satisfactory yield as presented above.[17]

In conclusion, we have developed a DABCO mediated domino reaction of ynones **1** with activated α,β-unsaturated ketones **2** to construct highly substituted eight-membered cyclic ethers in moderate to good yields. A broad substrate scope has been successfully employed in this reaction. From the synthetic point of view, this protocol provides an extremely simple and atom-economic alternative to synthesize medium cyclic ethers. Readily available starting materials, mild reaction conditions, and an inexpensive catalyst make this reaction valuable in synthetic chemistry. We expect that this method could be potentially applied to the synthesis of eight-membered cyclic ethers in natural products. Further studies on elaborating the reaction mechanism are underway 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.5b02498.

Experimental details, characterization data for new compounds, copies of NMR spectra, X-ray crystal structure of **3a** (CIF)

Crystallographic data for **3a** (PDF)

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Notes

The authors declare no competing financial interest.

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(15) CCDC 969392 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data via www.ccdc.cam.ac.uk/services/structure_deposit/cif.
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(17) We thank the reviewers for their comments on the mechanism, and one alternative process is also plausible and could not be ruled out: the reaction might initiate with a nucleophilic attack of DABCO on ynone, generating a zwitterionic intermediate which could undergo a 1,3-proton shift. After addition to the α,β-unsaturated ketone, the **Int. V** is directly obtained.

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