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The Dual Role of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in the Synthesis of Terminal Aryl- and Styryl-Acetylenes via Umpolung Reactivity

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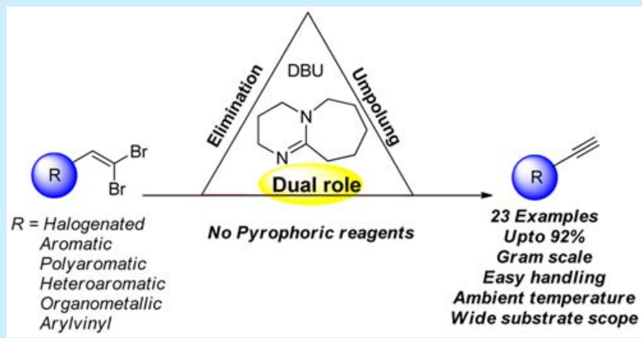
Supporting Information

ABSTRACT: The dual role of the bicyclic amidine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was demonstrated in a synthesis of terminal aryl- and styryl-acetylenes. Mechanistically, a tandem process involving elimination/Umpolung/protonation occurs in a single step to generate terminal aryl- and styryl-acetylenes from geminal dibromoalkenes. The key to the success of this transformation lies in the organobase-mediated generation of the acetylide from the 1-bromoalkynes at room temperature. The unique characteristics of DBU as an inherently safer reagent make it an attractive alternative to previous systems wherein required pyrophoric reagents and nonambient temperatures remain unsolved issues. The procedure does not work for the synthesis of alkyl-acetylenes.



Advances in synthetic organic chemistry have revealed a number of reagent systems with a dual role;[1] however, in a single transformation, it represents a unique challenge. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU,**1**), a non-nucleophilic base generally used for dehydrohalogenation, has exhibited versatile reactivity (Figure 1). Møller et al.[2] first discovered the superiority of **1** over related bases, and its nucleophilic character was later explicated by Bertrand's group;[3] it has since played a pivotal role in organo nucleophilic catalysis.[4]

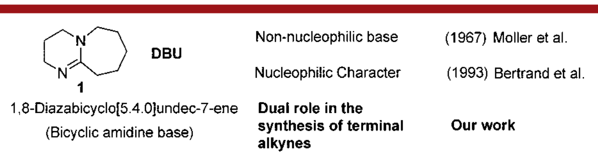
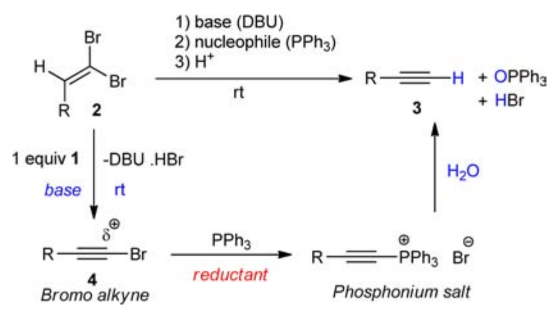


Figure 1. Structure of DBU and its characteristics.

Because the nucleophilic attack of DBU on a bromoalkyne has never been demonstrated, we wished to explore the sequential reactivity of DBU followed by triphenylphosphine on 1,1-dibromoalkene **2**[5,6] to access a terminal alkyne **3**[7] (Scheme 1).

The utility of alkynes has been demonstrated in transformations such as couplings,[8−11] cycloadditions,[12,13] and metathesis[14] for assembling synthetic materials and molecules of medicinal value. Traditionally, terminal alkynes are prepared by a Corey−Fuchs reaction[15] using geminal dibromoalkenes in the presence of a strong base (Scheme 2). More recently, Hu et al.[16] described modified conditions in the presence of triphenyl phosphine as a stoichiometric reductant in combination with excessive tetrabutylammonium fluoride trihydrate (TBAF·3H_2O) as a base. Because of the importance of alkynes as versatile building blocks in organic synthesis, a mild and practical protocol for their preparation is highly desirable.

Scheme 1. Designed Pathway to Terminal Alkynes at Ambient Temperature



On the basis of the basic reactivity of DBU at ambient temperature, we envisioned a sequential elimination reaction of **2** with **1** (1 equiv),[17] followed by a nucleophilic attack on the resulting 1-bromoalkyne intermediate **4** by 1 mol of phosphine

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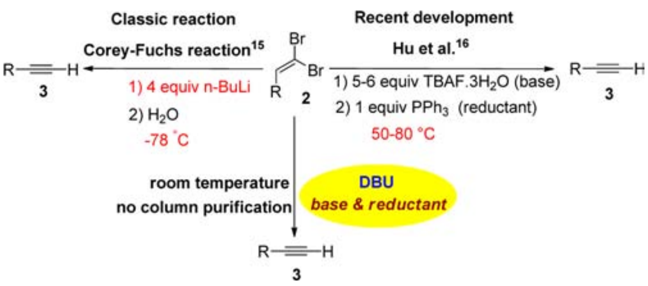
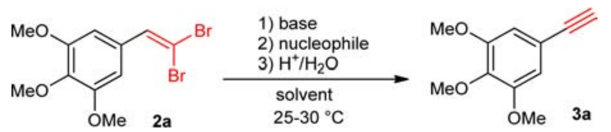
Scheme 2. Prior Art To Generate Terminal Alkynes from Geminal Dibromoalkenes



to generate an alkynyl phosphonium salt via addition/elimination (Scheme 1). A subsequent workup would furnish the desired alkyne **3** and triphenylphosphine oxide in the presence of water.

Thus, we set out to investigate the reactivity of alkene **2a**, a highly electron-rich substrate containing multiple electron-donating groups; the results are summarized in Table 1.

Table 1. Optimization Study[a]



entry	DBU (equiv)	nucleophile (1 equiv)	solvent	t (h)	3a[b]
1	1	PPh_3	DMSO/H_2O	48	19
2	2	PPh_3	DMSO/H_2O	24	33
3	2.0	PPh_3	DMSO/H_2O	4	31
4	2.0	PPh_3	DMSO/H_2O	24	35
5	2.0	PPh_3	THF/H_2O	48	27
6	2.0	PPh_3	CH_3CN/H_2O	16	58
7	3.0	–	DMSO/H_2O	24	39
8	4.0	–	DMSO/H_2O	48	59
9	4.0	–	CH_3CN/H_2O	48	64
10	4.0	–	DMSO	19	72
11	4.0	–	CH_3CN	16	92
12	4.0	–	neat	1	10

[a]Reaction conditions: **2a** (1.0 equiv, 1 mmol), base **1**, PPh_3 (1.0 equiv, 1 mmol), solvent/H_2O (2 mL/3 mmol) or solvent (2 mL) at ambient temperature. [b]Isolated yields, %.

Another incentive for choosing the electron-rich compound **2a** is that elimination and nucleophilic reactions on such a system are notoriously difficult and challenging tasks. The initial experiment was conducted using base **1** and triphenylphosphine as a nucleophile. The protonation requires that, at the final stage of the reaction (Scheme 1), a stoichiometric amount of H_2O be present along with the organic solvents (Table 1, entries 1−6). The results revealed the formation of the expected alkyne **3a**, albeit in low yields. Unreacted triphenylphosphine and the byproduct triphenylphosphine oxide complicated the purification, which could also explain the low isolated yields. Surprisingly, with an increased molar quantity of DBU in DMSO, we observed alkyne formation prior to the addition of the triphenylphosphine nucleophile (entry 7). This formation of alkyne **3a** might be attributable to the dual character of DBU **1** as a base and nucleophile. We then explored the DBU nucleophilicity by simply loading an excess of this reagent (entries 7−9). Notably, switching the nucleophile from triphenylphosphine to DBU **1** resulted in the formation of **3a** in low yields, which might be attributable to the attenuated nucleophilicity of DBU **1** by protonation in the presence of water. To rule out the protonation of **1** and to allow it to function as a free nucleophile, we next conducted the reaction in the absence of H_2O (entries 10−11). A remarkable improvement in the conversion of **2a** to **3a** was realized in the presence of 4.0 equiv of DBU **1** in anhydrous CH_3CN as the solvent (entry 11).[18] Moreover, an exothermic reaction was observed when the reaction was conducted under neat conditions (entry 12), resulting in a poor yield (10%), likely due to decomposition of the reaction mixture. Nevertheless, DBU was established as the sole reagent for the success of this transformation. This finding suggested that triphenylphosphine was not necessary, as anticipated for the nucleophilic reaction (Scheme 1).

We next probed the scope and generality of the protocol with an assortment of 1,1-dibromoalkenes comprising electron-rich **2a**−**2g**, electron-deficient **2h**−**j**, polyaromatic **2l**−**n**, halogenated **2o**−**s**, heteroaromatic **2s**−**u**, arylvinyl (styryl) **2v**, and organometallic **2w** substituents to afford the corresponding alkynes **3a**−**w** (Table 2). Notably, the presence of an electronegative substituent such as a nitro group in alkenes **2h** and **2i** increased the reaction rate to furnish the desired alkynes in 4 h (Table 2). Significantly, halogenated substrates **2o**−**s**, including the sterically hindered 1,6-disubstituted compound **2r**, underwent the sequential transformation smoothly and cleanly to afford the desired alkyne in good yields. In addition, heteroaromatic compounds such as pyrrole **2t** and benzofuran **2u** were well tolerated and resulted in the production of the alkyne in good yields. Importantly, the present method is amenable to 1-chloro-2-ethynyl quinoline **3s**, which could not be obtained using the previously discussed methods. In addition, aryl-vinyl-substituted geminal dibromoalkene **2v** efficiently reacted under these conditions to provide the corresponding α,β unsaturated alkyne **3v**. The synthetic utility of the present system was further illustrated to access organometallic ferrocene **3w**,[19] albeit with a prolonged reaction time. In contrast, the alkylated dibromoalkene **3x** did not react, which further highlights the preferred selectivity of DBU in such transformations.

Next, we sought to evaluate the scalability of the reaction. To this end, the synthesis of electron-rich alkyne **3a** (eq 1, Scheme 3) and an electron-poor alkyne (eq 2, Scheme 3) were demonstrated on the gram scale under optimized conditions, further demonstrating the robustness of the protocol upon scale-up.

To confirm the unprecedented nucleophilic reaction in this particular transformation, we performed a control experiment. The isolated 1-bromoalkyne **4a** intermediate generated during this process was treated with 2 equiv of **1** in CH_3CN to afford **3a** in 87% yield (Scheme 4). This finding further confirms the nucleophilic role of DBU, as indicated by the complete conversion of **4a** to **3a**. The conformation of alkyne **3a** was also observed by ^1H NMR analysis of the reaction mixture in CD_3CN.[20]

On the basis of the outcome of these studies, a possible mechanism was deduced. In the first step, base **1** promoted the dehydrobromination of dibromoalkene **2** to generate bromoalkyne **4**, as shown in Scheme 5. The subsequent nucleophilic attack on **4** with another molecule of DBU gave the intermediate acetylide **5** and *N*-bromo DBU (**1a**). Eventually, **5** was protonated upon aqueous workup to provide alkyne **3**.

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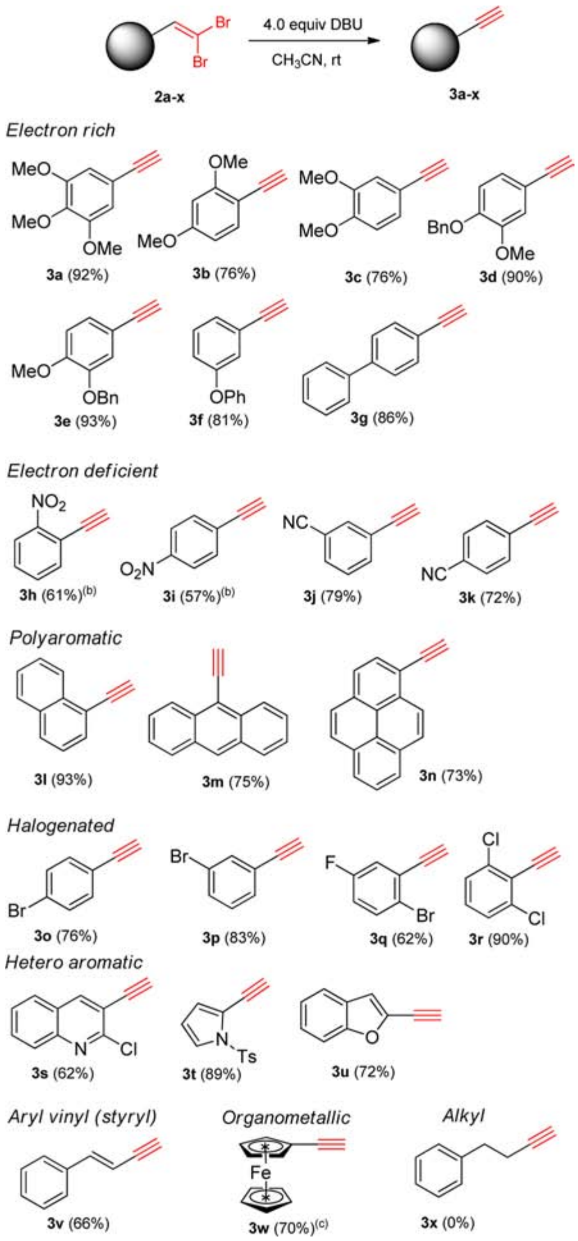
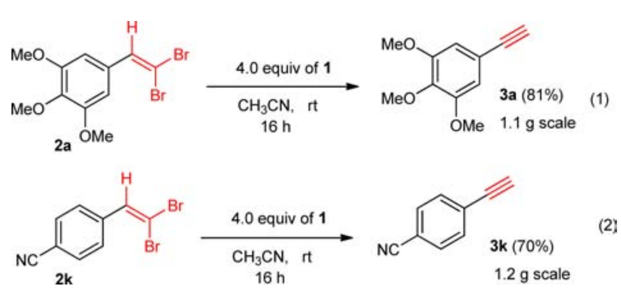
Table 2. Substrate Scope of Alkynes[a]



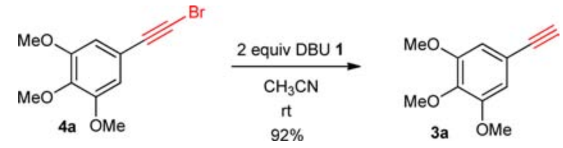
[a]Reaction conditions: **2a** (1.0 equiv, 1 mmol), **1** (4.0 mmol), dry CH_3CN (2 mL) at ambient temperature for 16 h. Isolated yields are given in parentheses. [b]Reaction time 4 h, [c]Reaction time 48 h.

Scheme 3. Scale-up Experiment of Electron-Poor and Electron-Rich Substances

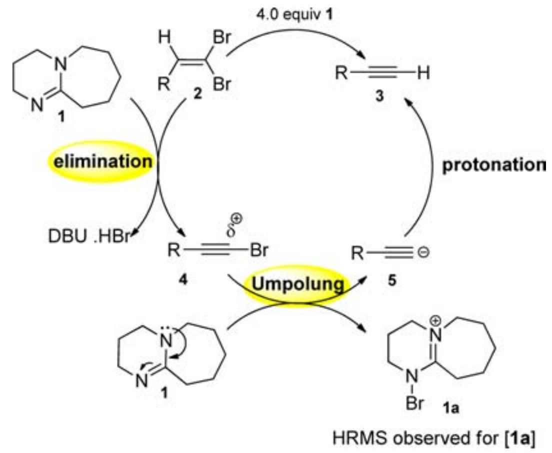


The byproducts generated via this mechanism are soluble in acidic aqueous solution, thereby avoiding column purification,

Scheme 4. Control Experiment



Scheme 5. Plausible Mechanism



which is unlikely to be the case when triphenylphosphine is used as a nucleophile. The presence of a peak corresponding to **1a** in the HRMS spectrum of the reaction mixture further supports this proposed mechanism.[20]

In summary, the dual role and distinctive reactivity of DBU **1** as a base and as a nucleophile in a single reaction has been highlighted. The presented method features numerous advantages: (i) it is simple; (ii) it avoids the use of pyrophoric reagents or other reagents, such as phosphines, that complicate the purification process; (iii) it obviates column chromatography; and (iv) it is safer and greener than previous protocols. In general, the protocol is sufficiently mild to tolerate a wide range of functional groups. We believe this protocol will find applicability in synthetic organic chemistry, especially in the fine and polymer chemical industries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02398.

Complete experimental procedures and characterization data for unknown starting materials and all known products (PDF)

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Notes

The authors declare no competing financial interest.

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(20) See the Supporting Information for the complete details of the experiment.

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