Organocatalytic hetero [4+2] cycloaddition reactions of 2-(1-alkynyl)-2-alkene-1-ones: metal-free access to highly substituted 4*H*-pyrans†

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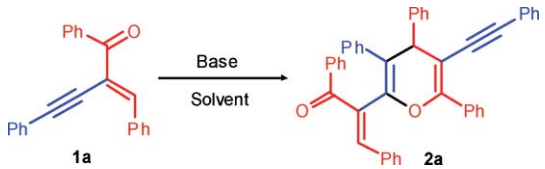
Highly substituted 4*H*-pyrans can be smoothly synthesized from readily available 2-(1-alkynyl)-2-alkene-1-ones by DBU- or *n*-Bu_3P catalyzed hetero-[4+2] cycloaddition reactions, in which 2-(1-alkynyl)-2-alkene-1-ones act as both heterodiene and heterodinenophile.

The development of new tandem reactions for constructing highly functionalized substituted pyrans from easily available acyclic starting materials has been stimulated by their appearance in many bioactive natural products and important pharmaceuticals as well as useful building blocks in organic synthesis.[1–3] Among many strategies towards highly substituted pyrans,[4] the hetero-Diels–Alder reactions of α,β-unsaturated ketones (as heterodiene) with electron-rich carbon–carbon unsaturated bonds (as heterodienophiles) are considered as a straightforward method for the synthesis of highly substituted 4*H*-pyrans.[5] However, the alkynes except ynamides[6] are low reactive, which has limited their use in the [4+2] cycloaddition reaction. In 2000, Trost reported a ruthenium-catalyzed intramolecular [4+2] cycloaddition of yne-enones leading to bicyclic 4*H*-pyrans.[7] Very recently, Koyama developed a nickel-catalyzed [4+2] cycloaddition of enones with alkynes, which can provide highly substituted pyrans in good yields.[8] In the context of our ongoing effort to develop methods towards heterocycles,[9] we reported herein a novel organocatalytic hetero-Diels–Alder of 2-(1-alkynyl)-2-alkene-1-ones[10] leading to full substituted multi-functionalized 4*H*-pyrans, in which the enone moieties act as the heterodienes and the electron-deficient alkyne moietes act as the heterodienophiles.

During our study of the DBU-catalyzed nucleophilic addition of nucleophiles to 2-(1-alkynyl)-2-alkene-1-ones,[9f] we happened to find that poly-functionalized 4*H*-pyran **2a** was formed when occasionally mixing the base and electron-deficient 1,3-conjugated yne-enone **1a** without adding the nucleophiles. Then, a series of reaction conditions were screened and the results were summarized in Table 1. After some attempts, we were pleased to find that the hetero-[4+2] cycloaddition reaction of **1a** under DBU (20 mol%) in DMF (2.5 mL) at 0 °C for 11 h afforded 91% yield of **2a** (Table 1, entry 10). Other inorganic bases such as *t*BuOK, K_2CO_3, KOH and Cs_2CO_3 were tested and most of them except Cs_2CO_3 were less effective. No reaction occurred when Et_3N, DABCO or DMAP were used as catalyst (Table 1, entries 4–6). Solvent effect was also studied (Table 1, entries 12–17). Lower catalyst loading (10 mol%) results in a lower yield (Table 1, entry 11). The reaction did not occur at 100 °C without the catalyst (Table 1, entry 18).

Table 1 Screening reaction conditions for hetero-Diels–Alder reaction of **1a**[a]



Entry	Base (mol%)[c]	Conditions	Yield (%)[b]
1	*t*BuOK (50)	THF, 40 °C, 30 h	48
2	K_2CO_3 (20)	THF, 40 °C, 24 h	Complicated
3	KOH (20)	THF, 40 °C, 24 h	66
4	Et_3N (20)	DMF, 40 °C, 24 h	0
5	DABCO (20)	DMF, 40 °C, 24 h	0
6	DMAP (20)	DMF, 40 °C, 48 h	0
7	Cs_2CO_3 (20)	DMF, 40 °C, 30 h	80
8	DBU (20)	DMF, 40 °C, 6 h	81
9	DBU (50)	DMF, 40 °C, 3 h	70
10	DBU (20)	DMF, 0 °C, 11 h	91
11	DBU (10)	DMF, 0 °C, 11 h	81
12	DBU (20)	DMSO, 40 °C, 6 h	77
13	DBU (20)	MeOH, 40 °C, 24 h	68
14	DBU (20)	CH_2Cl_2, 40 °C, 48 h	27
15	DBU (20)	Toluene, 40 °C, 12 h, then 100 °C, 24 h	67
16	DBU (20)	CH_3CN, 40 °C, 9 h	76
17	DBU (20)	DMA, 40 °C, 12 h	81
18	—	DMF, 100 °C, 24 h	0

[a] The reactions were carried out by using 1a (0.5 mmol) in solvent (2.5 mL). [b] Isolated yield. [c] DBU = 1.8-diazabicycl-[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo-[2.2.2.]-octane, DMAP = *N*, *N*-4-dimethylaminopyridine.

With the optimized conditions in hand, we determined the scope of the electron-deficient conjugated yne-enones **1**, and the results were summarized in Table 2. Generally, introduction electron-withdrawing groups to the conjugated yne-enones will increase the reactivity and lead to high yields. For example, the reaction of **1c** with an electron-withdrawing nitro group at *para*-position of phenyl ring (R^3) was consumed completely within 4 h to give **2c** in 91% yield, in contrast, only 60% yield of **2b** could be obtained from the corresponding **1b** after 62 h (Table 2, entries 1 *vs.* 3). The structure of **2b** was further confirmed by single crystal X-ray diffraction (Fig. 1).[11] Introduction an electron-donating methoxy group at *para*-position of R^2 also decreased the reactivity, for example, the cycloaddition of **1i** gave 51% yield of **2i** and 35% of **1i** was recovered after 60 h under the catalysis of 20 mol% of DBU (Table 2, entries 9 *vs.* 11). The reaction of aldehyde **1l** was slow to

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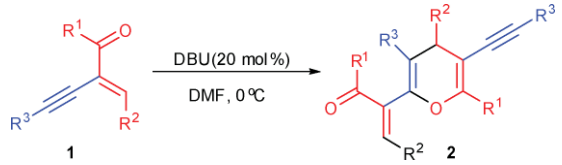
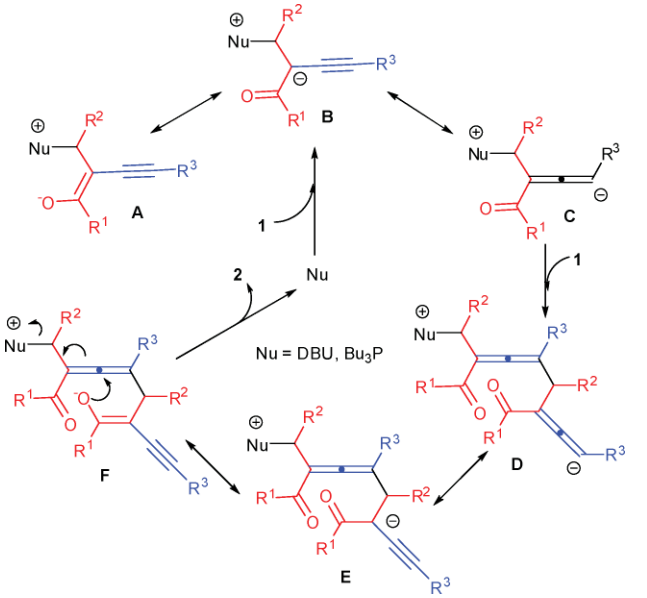
Table 2 Efficient synthesis of highly substituted functionalized 4*H*-pyrans[a]



Entry	Ketone **1** $R^1/R^2/R^3$	Time/h	**2** Yield (%)[b]
1	Ph/Ph/4-$MeOC_6H_4$ (**1b**)	62	**2b** (60)
2[c]	**1b**	22	**2b** (76)
3	Ph/Ph/4-NO_2Ph (**1c**)	4	**2c** (91)
4[c]	Ph/Ph/n-C_4H_9 (**1d**)	2	**2d** (60)
4	4-ClC_6H_4/Ph/Ph (**1e**)	15	**2e** (94)
5	Me/Ph/Ph (**1f**)	38	**2f** (88)
6	Me/4-$MeOC_6H_4$/Ph (**1g**)	60	**2g** (45[d])
7[c]	**1g**	22	**2g** (82)
8	Me/Ph/4-$NO_2C_6H_4$ (**1h**)	1	**2h** (80)
9	Me/4-$MeOC_6H_4$/1-naphthyl (**1i**)	60	**2i** (51[e])
10[c]	**1i**	22	**2i** (60)
11	Me/Ph/1-naphthyl (**1j**)	60	**2j** (75)
12	CO_2Me/Ph/Ph(**1k**)	3	**2k** (80)
13	H/Ph/1-naphthyl (**1l**)	60	**2l** (50)
14	MeO/Ph/Ph (**1m**)	96	**2m** (0)

[a] Unless otherwise specified, the reactions was carried out with enynes **1** (0.5 mmol) and DBU (20 mol%) at 0 °C in DMF (2.5–3 mL). [b] Isolated yields. [c] 20 mol% of *n*-Bu_3P was used instead of DBU and the reaction was run at rt. [d] 37% of **1g** was recovered. [e] 35% of **1i** was recovered.

give **2l** in 50% yield. The ester **1m** could not undergo hetero-[4+2] reaction to give the corresponding cycloadduct. Interestingly, It was found that *n*-Bu_3P was a more effective catalyst than DBU to give the corresponding products in higher yields. For example, the reaction of **1g** could not be complete after 60 h to give a 45% yield under the catalysis of DBU (Table 2, entry 6), however, the reaction proceeded smoothly to produce **2g** in 82% yield in the presence of 20 mol% of *n*-Bu_3P (Table 2, entry 7).



Scheme 1 Plausible mechanism of organocatalytic hetero [4+2] cycloaddition.

A plausible mechanism for this organocatalytic hetero-Diels–Alder cycloaddition was depicted in Scheme 1. A nucleophlic addition of the catalyst Nu (Nu = DBU or Bu_3P) to conjugated yne-enones **1** would produce zwitterionic intermediates with three resonance structures, *i.e.*, enolate **A**, propargylic carbanions **B** and allenyl carbanions **C**. Subsequent Michael–addition of allenyl carbanions **C** to another molecular of **1** would give new zwitterionic intermediates also with three resonance structures, *i.e.*, allenyl carbanions **D**, propargylic carbanions **E** and enolates **F**. Intramolecular nucleophlic substitutition (S_N2') of intermediates **F** would produce the 4*H*-pyran products and regenerate the catalyst.

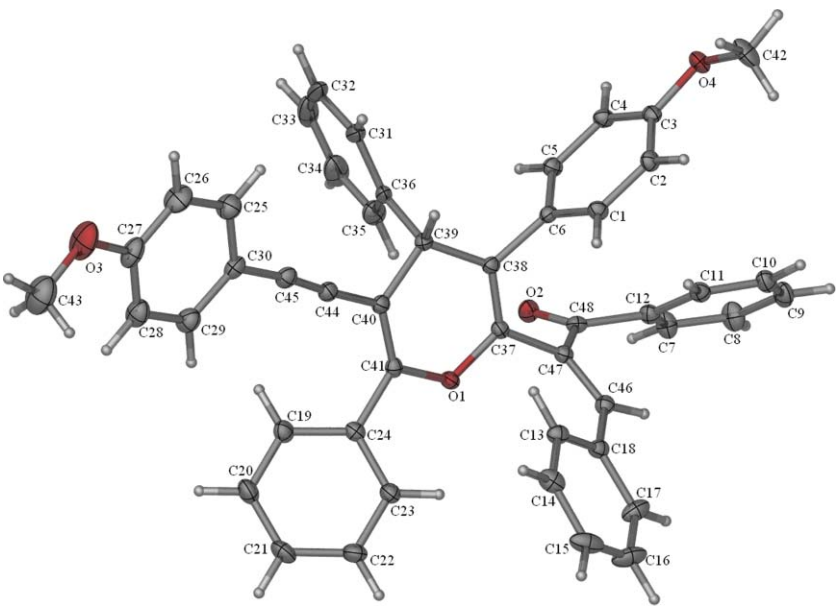


Fig. 1 ORTEP representation of compound **2b**.

In conclusion, we have developed an organocatalytic hetero-[4+2] cycloaddition reaction of readily available 2-(1-alkynyl)-2-alkene-1-ones, which provided a general, efficient and metal-free access to poly-functionalized 4*H*-pyrans in good yields under mild conditions. The electron-deficient alkyne moiety of one molecular of yne-enone plays the role of heterodinenophile component and enone moiety of the other yne-enone plays the role of heterodiene component. Studies on coupling of electron-deficient conjugated yne-enones with other nucleophiles and electrophiles are ongoing in this laboratory.

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11 CCDC 738752 (**2b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge form The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.