Chinese Chemical Letters 34 (2023) 107751

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Stereoselective construction of azepine-containing bridged scaffolds *via* organocata-lytic bicyclization of yne-allenone esters with nitrones

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ARTICLE INFO

Article history:
Received 24 April 2022
Revised 11 August 2022
Accepted 16 August 2022
Available online 23 August 2022

Keywords:
Bicyclization
Diastereoselectivity
Organocatalysis
Bridged heterocycles
YNE–allenone esters
Nitrones

ABSTRACT

A new organocatalytic double annulation cascade involving scission/recombination of N-O bonds of nitrones is reported for the first time, and used to produce a range of hitherto unprecedented tricyclic bridged-fused benzo[*d*]azepines bearing three stereogenic centers with moderate to good yields and complete diastereoselectivity. A quinine-catalyzed reaction of yne–allenone esters with nitrones worked well and provided a convergent and regioselective pathway to access these three-dimensional scaffolds from the planar conjugated system. Density functional theory (DFT) calculations have been applied to understand the key process for forming diradical intermediates.

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Developing new reactions and strategies to construct polycyclic bridged architectures is one of the most impacting frontiers of organic synthesis, considering that advances in this direction will improve efficiency in accessing natural products with various rings, substituents and stereochemistry [1–9]. This is also important to advance pharmaceutical chemistry because the new skeletons developed, whether they are found in nature or not, will expand the chemical space of drug discovery and other fields as well. In line with these findings, we think that developing reactions for the synthesis of bridged azepines and their derivatives with high stereoselectivity is a required technology. This can be understood, on the one hand, by the existence of such a skeleton in natural products with biological activities, exemplified by hunterine A [7], subincanadine F [7], Ibogamine [8], and cephalocyclidin A [9] (Fig. 1), and on the other hand, by the potential of using these molecules for downstream studies in chemical biology and medicinal chemistry. Unfortunately, synthesizing this medium-sized skeleton remains a formidable challenge with conventional cyclization or cycloaddition strategies due to unfavorable transannular interactions and entropic and/or enthalpic factors [10–15].

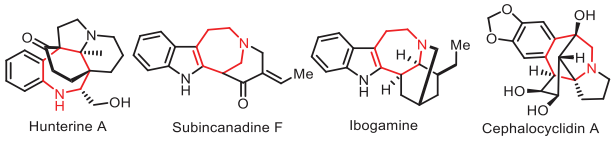

Fig. 1. Azepine-containing bridged natural products.

Nitrones, well recognized as versatile 1,3-dipoles endowed with nucleophilic and electrophilic sites, are competent reactants [16] and often serve as three-atom building units for many important aza-heterocyclic molecules [17–20]. Generally, nitrones are widely applied in various cycloadditions to access aza-heterocycles [21–27]. Remarkably, the N-O bond cleavage of nitrones has become a powerful tool for the synthesis of valuable nitrogen-containing compounds that are cumbersome to prepare by other methods and thus have attracted widespread attention from chemists [28–33]. Strategies for N-O bond cleavage of nitrones often include the well-developed Kinugasa reaction (Scheme 1a, path i) [34,35], transition-metal-catalyzed C-H bond functionalization (Scheme 1a, path ii) [36–40], [3,3]-rearrangement of allenes [41–45] or ketenes (Scheme 1a, path iii) [46,47] and metal-catalyzed oxygen migration (Scheme 1a, path iv) [48–50]. Despite these advances, the continuous development of new methodologies capable

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https://doi.org/10.1016/j.cclet.2022.107751
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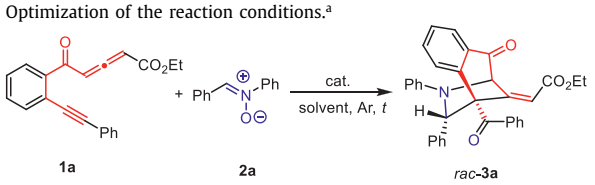
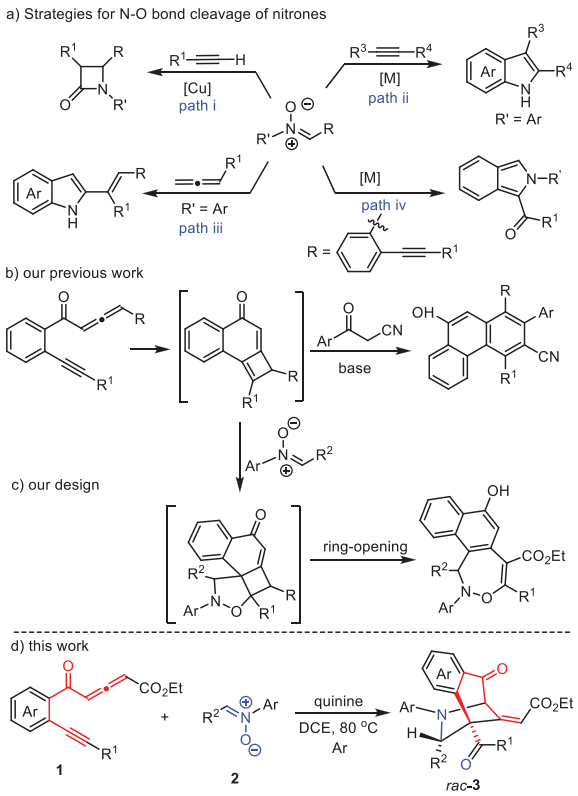
Table 1
Optimization of the reaction conditions.[a]



1a 2a *rac*-3a

Entry	Cat. (mol%)	Solvent	*t* (°C)	Yield (%)[b]
1	Quinine (5)	DCE	70	49
2	Quinine (5)	DCE	80	55
3	Quinine (5)	DCE	90	50
4	Quinine (10)	DCE	80	63
5	Quinine (15)	DCE	80	58
6	Quinine (10)	CH_3CN	80	N.R.
7	Quinine (10)	Toluene	80	N.R.
8	Quinine (10)	THF	80	N.R.
9	DBU (10)	DCE	80	20
10	Et_3N (10)	DCE	80	39
11	DABCO (10)	DCE	80	12
12	Pyridine (10)	DCE	80	36
13[c]	Quinine (10)	DCE	80	48
14[d]	Quinine (10)	DCE	80	47
15	–	DCE	80	34

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.26 mmol, 1.3 equiv.), catalyst (0.02 mmol, 10 mol%), 4 Å MS (50 mg), dry solvent (2 mL), under Ar conditions for 48 h.
[b] Isolated yield based on **1a**.
[c] Under air conditions.
[d] Without 4 Å MS.



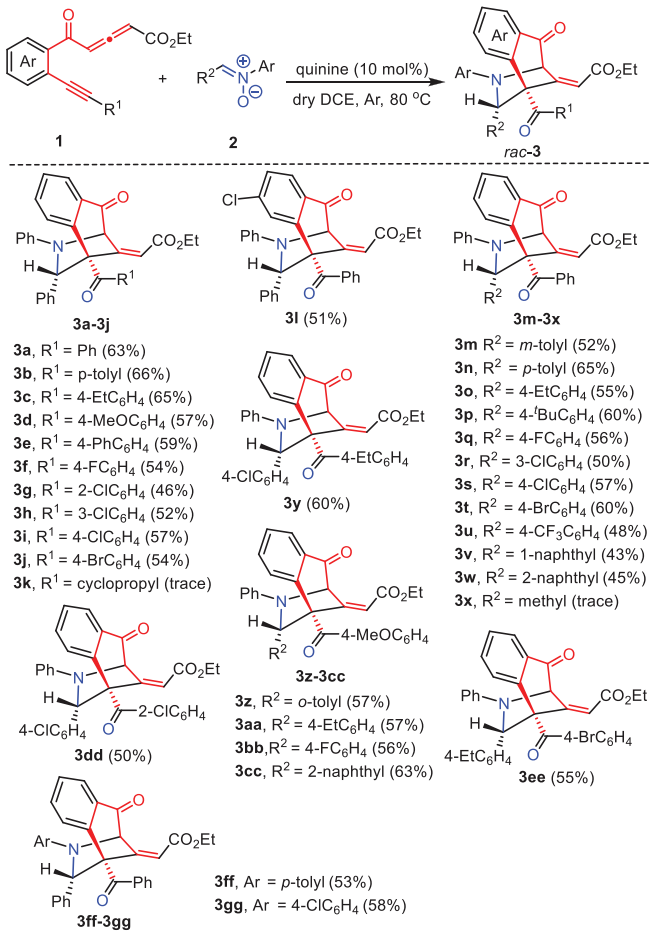
Scheme 1. Synthesis of bridged benzo[*d*]azepines.

of N-O bond cleavage of nitrones is still of great synthetic importance.

Very recently, we synthesized yne–allenone esters containing multiple reactive sites and found that such substrates could enable rapid intramolecular [2 + 2] cycloaddition to generate highly reactive cyclobutene intermediates for *in situ* applications [51–56]. For instance, a base-promoted naphthannulation reaction between yne–allenone esters and β-ketonitriles generated polycyclic aromatic hydrocarbons with good yields (Scheme 1b) [53]. During this project, we conceived that base-promoted [2 + 2]/[3 + 2] cyclization of yne–allenone esters with nitrones may allow a new double annulation process to access naphtho[1,2-*d*][1,2]oxazepines (Scheme 1c). Interestingly, instead of the expected targets, the reaction proceeded in a completely different direction to provide azepine-containing bridged scaffolds bearing an all-carbon quaternary stereocenter with excellent stereoselectivity by employing quinine as the base promoter (Scheme 1d). Of note is that the present transformation enabled a successive double annulation cascade involving N-O bond cleavage of nitrones, furnishing a wide range of hitherto unreported 1,4-methanobenzo[*d*]azepines with excellent diastereoselectivity and (*Z*)-selectivity of exocyclic double C-C bonds. During this process, a double annulation cascade can be realized in one pot, with 100% atom utilization and good functional group tolerance as well as complete diastereoselectivity. Intrigued by this bicyclization reaction, we have also performed preliminary theoretical calculations to elucidate the reaction mechanism. Herein, we elaborate on this attractive transformation of yne–allenone esters with nitrones.

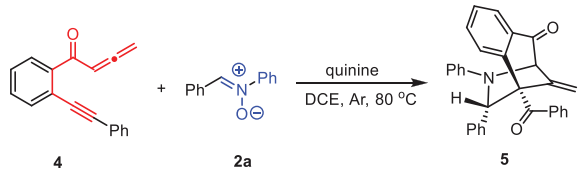
Initially, yne-allenone ester **1a** and nitrone **2a** were chosen as the model substrates to establish the optimal conditions. As shown in Table 1, the reaction of **1a** with **2a** worked smoothly in the presence of 4 Å MS in dry DCE at 70 °C under argon conditions by using quinine (5 mol%) as the base catalyst, delivering bridged 1,4-methanobenzo[*d*]azepine **3a** in 49% yield and with excellent stereoselectivity (Table 1, entry 1). We then examined the effect of reaction temperature on the efficiency of the transformation and found that increasing the reaction temperature to 80 °C facilitated the reaction process, giving 55% yield (entry 2). Further elevating the temperature did not improve the yield (entry 3). After that, the quinine loading was investigated. Changing the quinine loading from 5 mol% to 10 mol% is beneficial for this transformation, resulting in a higher yield of 63% (entry 4). A lower conversion was detected when the loading of quinine was increased to 15 mol% (entry 5). Next, a brief screening of various solvents revealed that the solvent exerted a profound influence on the reaction outcome. With other aprotic solvents being the reaction medium, such as CH_3CN, toluene and tetrahydrofuran (THF), the reaction process was completely suppressed (entries 6–8). Different bases, such as DBU, Et_3N, DABCO, and pyridine, were also screened, and all these bases gave unsatisfactory results regarding the yield of **3a** compared with quinine (entries 9–12 *vs.* entry 4). Finally, the reaction was carried out under air conditions, and a decline in the yield was observed (entry 13). A similar outcome was detected without 4 Å MS (entry 14). These inferior results were due to water reacting with yne–allenone ester to give 1-naphthol derivatives, thereby inhibiting the conversion of **1** into **3**. Thus, the removal of water from the reaction system is crucial to improve the yield of **3**. Without quinine, the reaction could work to access product **3a**, albeit with a relatively low yield (34%, entry 15), revealing that quinine was not involved in the N-O cleavage of nitrones but could accelerate the conversion of **1a** into **3a**.

With the optimized conditions in hand (Table 1, entry 4), we set out to investigate the generality of the quinine-promoted N-O cleavage strategy to construct bridged-fused benzo[*d*]-azepines by examining a variety of yne–allenone esters and nitrones. As depicted in Scheme 2, the scope with respect to yne–allenone esters **1** was first evaluated by adopting nitrone **2a** as a representative substrate. To our delight, yne–allenone esters **1** bearing both electron-donating and electron-withdrawing groups linked by the arylalkynyl moiety did not hamper the reaction process. Various substituents, such as methyl (**1b**), ethyl (**1c**), methoxy (**1d**), phenyl

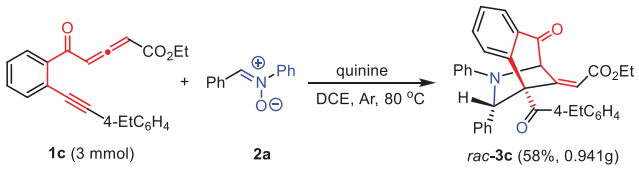


Scheme 2. Substrate scope for the synthesis of **3**. Reaction conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.26 mmol, 1.3 equiv.), quinine (0.02 mmol, 10 mol%), 4 Å MS (50 mg), DCE (2 mL), under Ar conditions.

(**1e**), fluoro (**1f**), chloro (**1 g-1i**), and bromo (**1j**), at different positions (*othro*, *meta*, or *para*) of the phenyl ring were examined in this catalytic system, and all these cases worked well, leading to the highly stereoselective formation of unprecedented bridged 1,4-methanobenzo[*d*]azepines **3b–3j** in acceptable yields with (*Z*)-selectivity of its exocyclic double C-C bond. It is found that this transformation seems sensitive to the steric bulkiness of the R^1 substituents because the sterically crowded *o*-chlorophenyl analogue **1g** worked sluggishly to access **3g** in a moderate yield. However, cyclopropyl-substituted **1k** resulted in severe decomposition, leading to a trace amount of product **3k**, which failed to be isolated. This outcome demonstrates that aryl group-stabilized yne–allenone esters prove to be good precursors. Moreover, a chloro–functionality (**1l**) was introduced into the C4 position of the internal arene ring of substrate **1** and then employed to react with **2a**, enabling a similar annulation process to give product **3l** with a moderate yield and high stereoselectivity. Next, a careful survey of the possible variation in both substituents of nitrones was investigated (Scheme 2). Nitrones carrying alkyl (methyl **2b**, **2c** and **2n**, ethyl **2d** and *t*–butyl **2e**), halo (fluoro **2f**, chloro **2g**, **2h** and bromo **2i**) and trifluoromethyl **2j** at the *ortho*-, *meta*- or *para*-position of the phenyl ring proximal to the imine unit were all accommodated, stereoselectively delivering the corresponding products **3m-3u**, **3z-3bb** and **3dd-3ee** with comparable efficiency. Indeed, essentially a single (*Z*)-stereoisomer was detected in these cases. Of these groups, a strong electron-withdrawing trifluoromethyl group also exhibited good compatibility, as evident by the correspond-



Scheme 3. Limitation of catalytic annulation.



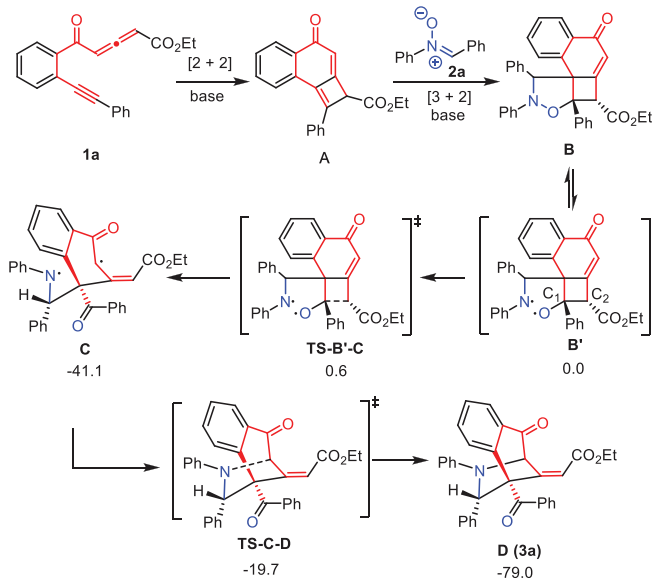
Scheme 4. Synthetic potential of this protocol. Reaction conditions: **1c** (3 mmol, 1.0 equiv.), **2a** (3.9 mmol, 1.3 equiv.), quinine (0.3 mmol, 10 mol%), 4 Å MS (750 mg), DCE (30 mL), under Ar conditions.

ing product **3u** being obtained, albeit with a relatively lower yield (48%). Notably, the sterically encumbered 1- and 2-naphthyl counterparts (**2k** and **2l**) were adopted to prove the validity of this double annulation, furnishing the corresponding bridged products **3v-3w** and **3cc** in acceptable yields. However, methyl-substituted nitrone **2m** failed to undergo this process. Subsequently, representative methyl (**2o**) and chloro (**2p**) groups located at the *para*-position of the arene ring relative to the nitrogen heteroatom of nitrones were tested, and both substrates were converted into products **3ff** and **3gg** in satisfactory yields and excellent stereoselectivity, indicating that different electronic properties of substrates have a negligible effect on the reactivity.

Unfortunately, the reaction between yne–allenone **4** and **2a** did not give the expected product **5** under the standard conditions, even elevating the reaction temperature to 120 °C (Scheme 3), showing that the ester anchored on the allene unit was the key factor for the success of this protocol, probably because such group with strong electron-withdrawing nature could stabilize C-centered radical species to accelerate radical cross coupling (See proposed mechanism).

This reaction system was further demonstrated by its synthetic utility through the amplification reaction for the generation of **3c** on a 3.0 mmol scale (58%, Scheme 4). The structural elucidation and attribution of the relative stereochemistry of the resulting bridged cyclic products have been fully characterized by NMR and HRMS. Furthermore, in the case of product **3n**, the stereostructure was determined by X-ray crystallographic analysis (CCDC: 2043024, see Supporting information).

Combining the above observations and the computational studies on the key process for producing diradical species, a reasonable mechanism for forming product **3a** is proposed in Scheme 5. Initially, in the presence of the base, intramolecular [2+2] cycloaddition of yne–allenone ester **1a** gives cycloadduct **A**, followed by 1,3-dipolar cycloaddition with nitrones to form a transient intermediate **B** [57]. Since the nitrogen-oxygen bond of the resulting isoxazolidine ring is known to be very weak [58–60], such chemical bond is readily cleaved to diradical intermediate **C** [61–64]. To prove this, we conducted density functional theory (DFT) calculations to examine the possibility of producing diradical intermediates. When the structure containing four-membered and five-membered ring **B** was optimized, the O-N bond distance of the five-membered isoxazolidine was calculated to be 1.449 Å, meaning that the O-N bond of isoxazolidine is very weak, almost in a broken form compared with the equilibrium bond length of the O-N bond of 1.36 Å. This result is also consistent with the reported results in the literatures [61–64]. The four-membered ring of species **B** undergoes a process



Scheme 5. Proposed mechanism for forming product **3a.**

of C_1-C_2 bond cleavage to generate the intermediate **C**, which only needs to overcome a small energy barrier of 0.6 kcal/mol and is exothermic by 41.1 kcal, being very easy to occur. The following intramolecular radical cross coupling of **C** affords the desired product **D** (**3a**), which is exothermic by 38.1 kcal/mol with an energy barrier of 21.4 kcal/mol. Clearly, the whole process for forming the experimental product **3a** is not difficult to occur, supporting the plausible feasibility of our proposed reaction mechanism.

In summary, starting from preformed yne–allenone esters and easily available nitrones, we have established a new and attractive double annulation cascade for the regio- and diastereoselective synthesis of unprecedented bridged 1,4-methanobenzo[*d*]azepines bearing three stereocenters with moderate to good yields. This reaction proceeded through a successive [2+2]/[3+2] bicyclization, N-O bond cleavage of isoxazolidine and nucleophilic substitution sequence, featuring the complete control of regio- and stereochemistry and good compatibility with different types of substituents as well as 100% atom utilization. It opened new avenues for the streamlined synthesis of structurally complex three-dimensional molecules with all-carbon quaternary centers evolved from the planar conjugated system. Further applications of the N-O bond cleavage of nitrones are underway in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

We are grateful for financial support from the National Natural Science Foundation of China (Nos. 21871112 and 21971090).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107751.

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