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Stereoselective synthesis of bicyclo[3.n.1]alkenone frameworks by Lewis acid-catalysis†

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An intermolecular cyclization of alkynyl enones with cyclic ketones for the synthesis of bicyclo[3.n.1]alkenones is reported. This protocol exhibits a high functional group tolerance and provides access to a variety of bicyclic systems found as skeletons in many natural products.

Bicyclo[3.n.1]- and [4.n.1]-alkenones as privileged structural subunits¹ are widely present in numerous bioactive natural products, such as (+)-ingenol,² clusianone,³ and enaimeone A⁴ (Fig. 1). Additionally, such bridged skeletons can also be used as versatile cyclic precursors for the synthesis of complex molecules.⁵ Consequently, considerable research efforts have been devoted to develop methodologies for the synthesis of bicyclo[3.2.1] and [3.3.1] molecular skeletons and related structural motifs *via* intra- or intermolecular approaches.^{1a-d,6} In particular, α,α' -annulations of cyclic ketones (*via* enamine formation) with the appropriate C3-synthons ((*E*)-2-nitroallylic acetates,⁷ α -nitrocycloalkanones,⁸ Fischer carbene complexes,⁹ allenyl esters,^{5c,10} or/and activated enones^{6b,8,11}) into these frameworks, have recently attracted significant attention.

Electron-deficient 1,3-conjugated alkynyl enones are useful building-blocks for a variety of rather complex structural

motifs (Scheme 1). Generally, alkynyl enones are good Michael acceptors, which can undergo tandem reactions with different nucleophiles, leading to various acyclic and cyclic targets.¹²

For example, the base-catalysed intermolecular cyclization of 2-(1-alkynyl)-2-alken-1-one **1** with 2-aminomalonates¹³ to access structurally diverse heterocyclic compounds was reported by Zhang and co-workers. The reaction was postulated to proceed *via* a 1,2-allene intermediate (Scheme 1a). Recently, our group reported a highly diastereoselective intermolecular annulation of alkynyl enones **1** with enamines formed *in situ*, demonstrating the versatility of alkynyl enones (Scheme 1b).¹⁴ One of the key features of this transformation was the excellent catalytic activity of indium salts which allowed for a wide variety of alkynyl

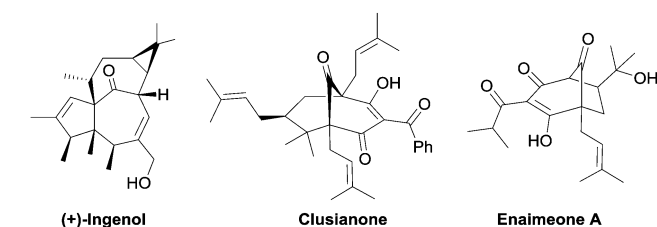


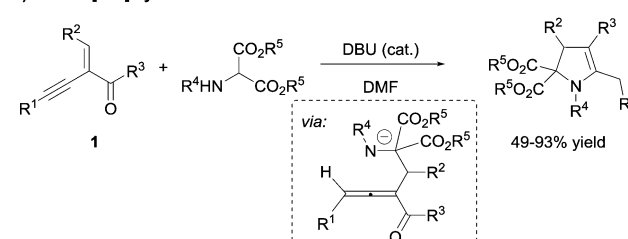
Fig. 1 Bioactive natural products containing the bicycloalkenone scaffold.

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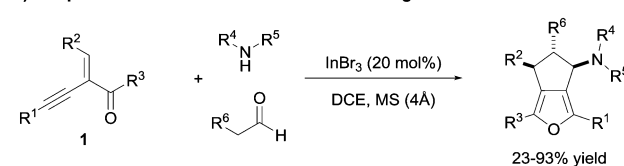
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† Electronic supplementary information (ESI) available: Experimental details and spectral data. CCDC 1569101. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc06400d

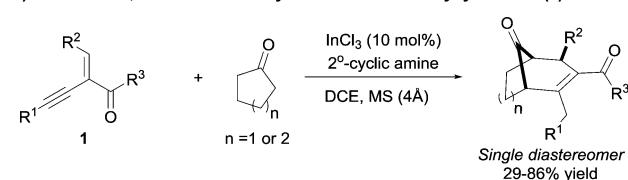
a) Formal [3+2] cycloaddition of **1** with 2-aminomalonates¹³



b) Our previous work: annulation of **1** with *in situ*-generated enamines¹⁴



c) This work: α,α' -annulation of cyclic ketones with alkynyl enones (**1**)

Scheme 1 Synthetic utility of 2-(1-alkynyl)-2-alken-1-ones **1**.

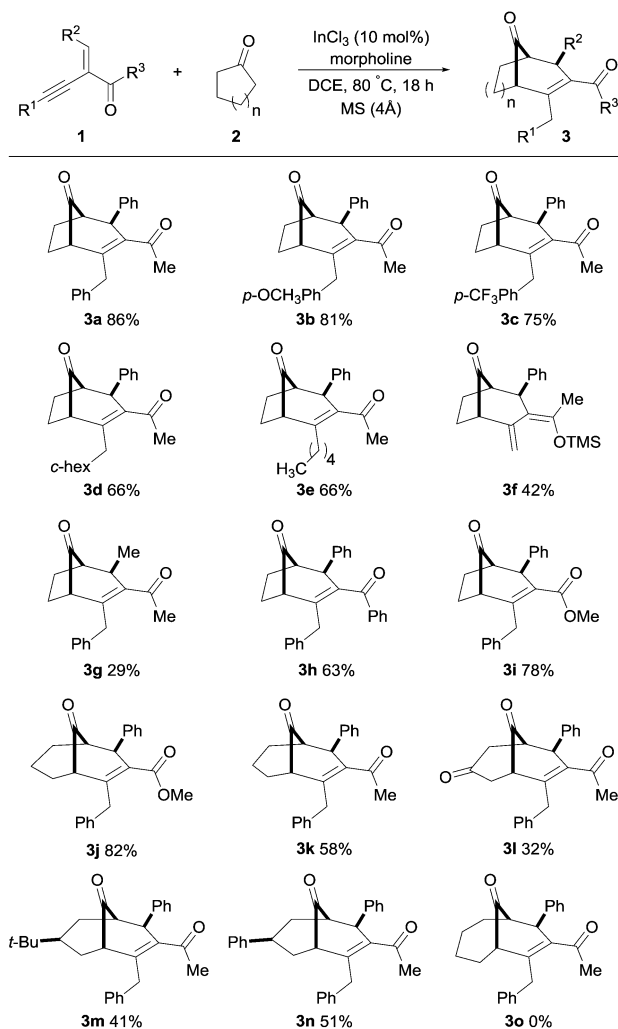
enones, aldehydes, and amines as substrates. Herein, we report on the extension of this methodology for the synthesis of bicyclo[3.2.1] and [3.3.1] molecular skeletons from alkynyl enones, possibly *via* allene intermediates¹²ⁱ (Scheme 1c).

The initial study of alkynyl enone **1a** with cyclopentanone and morpholine was performed; the desired bicyclo[3.2.1]-alkenone product **3a** was obtained in 61% yield as a single diastereomer along with the alkyne hydroamination product **4a** in 17% yield using InBr₃ (Table 1, entry 1). We observed an improved yield of **3a** (84%) and a reduced amount of the alkyne hydroamination side-product when molecular sieves (4 Å) were used, and by decreasing the solvent volume from 2 mL to 1 mL (entries 2 and 3). Other solvents were slightly less efficient (entries 4–6). It should be noted that product **3a** was also formed in the absence of a catalyst, albeit in lower yield and with more side-products (entry 7). Employing different triflate-based metal salts like AgOTf and InOTf₃ yielded **3a** in 76 and 35% yield respectively (entries 8 and 9). The use of ZnCl₂ led to a moderate yield of the desired product **3a** (62%, entry 10). Gratifyingly, the yield of product **3a** increased when InCl₃ was used as a catalyst (entry 11). A similar result was also obtained with only 10 mol% of InCl₃; product **3a** was obtained in 90% yield (entry 12). Further decreasing the catalyst loading to 5 mol% resulted in a lower yield of **3a** (entry 13). A Brønsted acid as catalyst resulted in a lower yield and a complex reaction mixture (entry 14). Screening of various amines and loadings did not improve the yield of **3a**. We speculate that amine is not fully deliberated under the reaction, preventing the use of a catalytic amount of the amine. Additional screening data can be found in the ESI†

With the optimal conditions for the synthesis of bicyclo[3.2.1]alkenone **3a** established, we further explored the substrate

scope of this transformation with a variety of alkynyl enones **1** and cyclic ketones **2** (Scheme 2).

Gratifyingly, a broad range of alkynyl enones **1** reacted to give the corresponding bicyclo[3.2.1] and [3.3.1] molecular skeletons **3** as single diastereomers in moderate to good yields. As expected, electron-donating and electron-withdrawing substituents at the R¹ position had no significant effect on the outcome of the reaction; **3b** and **3c** were obtained in 81 and 75% respectively. The use of cyclohexyl- and linear alkane-substituted alkynyl enones with cyclopentanone furnished **3d** and **3e**, both in 66% yield. It was interesting to find that when a TMS-substituted enynone was used as substrate, an intramolecular rearrangement of the TMS-group from carbon to oxygen (Brook rearrangement) was observed, resulting in product **3f** in 42% yield. Moreover, methyl-substitution at the R² position furnished product **3g** in a lower yield, whereas phenyl-substitution at the R³ position had a small negative effect on the outcome (**3h**, 63%). Furthermore, a methoxy-substituent in the R³ position furnished the bicyclo[3.2.1] and [3.3.1] molecular skeletons **3i**



Scheme 2 Substrate scope with respect to various alkynyl enones and cyclic ketones. Compounds **3j–3n** were synthesized using pyrrolidine in place of morpholine, see the ESI† for full experimental details.

Table 1 Screening of reaction conditions^a

Entry	Catalyst (mol%)	Solvent (mL)	Yield 3a ^b [%]	Yield 4a ^b [%]
1 ^c	InBr ₃ (20)	DCE (2.0)	61	17
2	InBr ₃ (20)	DCE (2.0)	84	2
3	InBr ₃ (20)	DCE (1.0)	89	6
4	InBr ₃ (20)	EtOAc (1.0)	74	4
5	InBr ₃ (20)	CH ₃ CN (1.0)	79	9
6	InBr ₃ (20)	CH ₂ Cl ₂ (1.0)	85	2
7	None	DCE (1.0)	39	16
8	AgOTf (20)	DCE (1.0)	76	9
9	InOTf ₃ (20)	DCE (1.0)	35	9
10	ZnCl ₂ (20)	DCE (1.0)	62	6
11	InCl ₃ (20)	DCE (1.0)	91	3
12	InCl₃ (10)	DCE (1.0)	90 (86)^d	4
13	InCl ₃ (5)	DCE (1.0)	74	4
14	TsOH·H ₂ O (20)	DCE (1.0)	57	12

^a Reaction conditions: **1** (0.10 mmol), **2** (0.15 mmol), morpholine (0.20 mmol), catalyst (0–20 mol%), solvent (1.0–2.0 mL), activated molecular sieves 4 Å (45 mg), 80 °C for 18 h. ^b The yields were determined by ¹H NMR analysis with 1,3,5-trimethoxy benzene as an internal standard. ^c Without molecular sieves. ^d Isolated yield.



and **3j** in high yields, thus showing the versatile nature of this transformation.

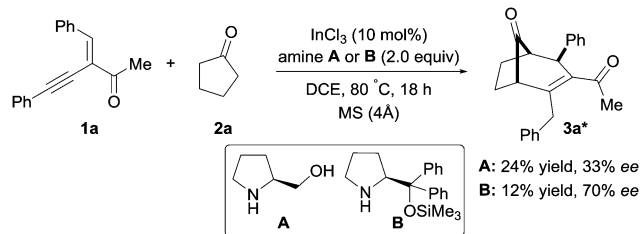
Next, we examined the scope of this transformation with a variety of cyclic ketones to provide bicyclo[3.3.1]alkenones. It was found that the transformation with cyclohexanone derivatives provided products **3j–3n** in higher yields when pyrrolidine was used in place of morpholine. Cyclohexanone gave the corresponding product **3k** in moderate yield (58%, 33% with morpholine), whereas 1,4-cyclohexanedione resulted in product **3l** in a lower yield, 32%. We were pleased to see that the substituted cyclic ketones (4-*tert*-butyl and 4-phenylcyclohexanone) furnished desymmetrization products **3m** and **3n** as single diastereomers in good yields. The structure and stereochemistry of product **3n** was established by single-crystal X-ray analysis,¹⁵ and other derivatives were assigned by analogy. Unfortunately, cycloheptanone and cyclooctanone furnished only hydroamination products, and no desired products were observed.

The generality of this transformation was further investigated by using cyclic 2-(1-alkynyl)-2-alken-1-ones with cyclic ketones (Scheme 3). The five- and six-membered alkynyl enones with cyclopentanone and cyclohexanone furnished the corresponding polycyclo[3.2.1] and [3.3.1]alkenones (**3p–3s**) in high yields (52–73%, Scheme 3).

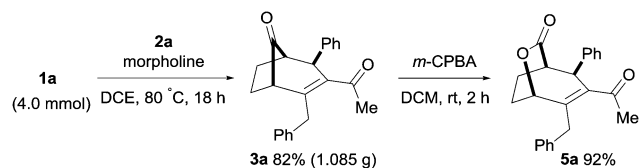
Next, we evaluated the feasibility of this reaction with α -substituted chiral amines (Scheme 4 & ESI[†]). In the presence of the secondary chiral amine **A**, product **3a** was formed in 24% yield and 33% ee (Scheme 4). Compared to amine **A**, the use of TMS-protected diphenyl prolinol **B** displayed a better enantioselectivity but a poor reactivity (Scheme 4).

Furthermore, the bicyclo[3.2.1]alkenone product **3a** was isolated in 1.08 g upon performing the transformation on a larger scale (4.0 mmol, Scheme 5). The ring-strained bicyclo[3.2.1]keto compounds are highly reactive and can undergo a selective Baeyer–Villiger oxidation in the presence of *m*-CPBA in DCM at room temperature. As a result, lactone product **5a** was obtained in 92% yield from the bicyclo[3.2.1]alkenone **3a** (Scheme 5). The lactone functionality of compound **5a** is useful as a synthetic intermediate for natural product synthesis and found in a number of bioactive natural products.¹⁶

A plausible mechanism for this transformation is shown in Scheme 6. The regioselective nucleophilic addition of the *in situ*-generated enamine produces intermediate **B** from the



Scheme 4 Performing the reaction with chiral amines **A** and **B**.

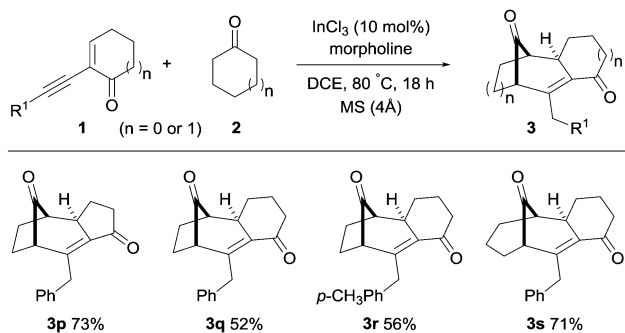


Scheme 5 Synthesis of **3a** on a 4.0 mmol scale and subsequent oxidation of **3a**. See the ESI[†] for full experimental details.

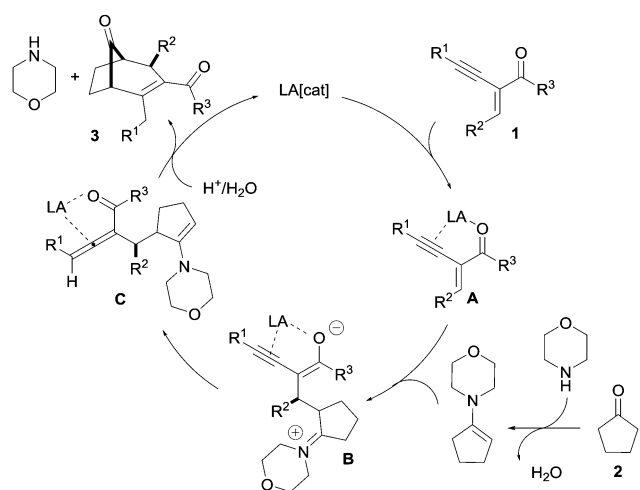
activated intermediate **A**. The alkyne hydroamination product **4**, as well as the 1,2-allenyl ketone intermediate **C**, were observed during the reaction. Based on these results, one can envisage that the 1,2-allenyl ketone intermediate **C** was formed by a rearrangement of intermediate **B** through Lewis acid alkyne activation. From intermediate **C**, the desired product **3** can be formed *via* an intramolecular enamine addition at the allene carbon followed by hydrolysis. Our efforts to lower the amount of the cyclic amine remain fruitless.

In summary, we have developed a Lewis acid-catalysed intermolecular α,α' -annulation of enamines (generated *in situ*) with alkynyl enones, providing an easy access to bicyclo[3.2.1]alkenones. The corresponding products can be obtained in high yields under benign reaction conditions.

Desymmetrization products can be achieved with meso-cyclic ketones as substrates. Furthermore, the reaction is scalable and the bicyclo[3.2.1]alkenone product can undergo a selective Baeyer–Villiger oxidation. The use of an indium Lewis acid catalyst



Scheme 3 Synthesis of polycyclo[3.2.1]alkenones with cyclic alkynyl enones and cyclic ketones. See the ESI[†] for full experimental details.



Scheme 6 Plausible mechanism.



reduced the formation of side-products (alkyne hydroamination and aza-Michael addition).

Conflicts of interest

There are no conflicts to declare.

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