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Catalyst-Controlled Cascade Synthesis of Bridged Bicyclic Tetrahydrobenz[*b*]azepine-4-ones

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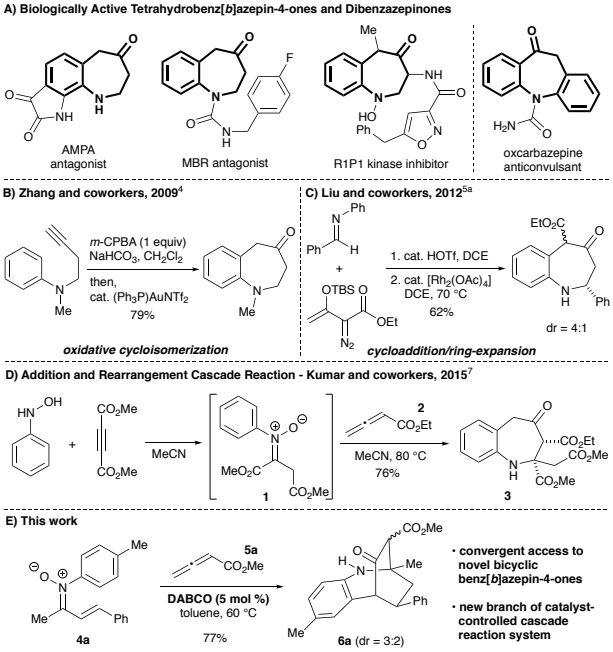
A catalyst-controlled cascade reaction has been developed for the synthesis of bridged bicyclic tetrahydrobenz[*b*]azepin-4-ones from *N*-arylnitrones and allenes. This method expands the accessible structural diversity of a synthetically challenging heterocyclic scaffold and tunes a catalyst-sensitive process in a new direction.

Tetrahydrobenz[*b*]azepin-4-ones are found in a variety of biologically active molecules that exhibit therapeutic properties (Scheme 1A).[1] Structurally similar oxcarbazepine is one of several anticonvulsant dibenzazepinone drugs.[2] Due to the reactivity of the second arene ring, dibenzazepinones can be accessed through Friedel-Crafts reactions, palladium-catalyzed C–N bond formation, and ring-expansion methods.[3] In contrast, routes to tetrahydrobenz[*b*]azepin-4-ones are more limited despite the presence of this scaffold in biologically active compounds. Recently, Zhang and coworkers reported an elegant solution to this synthetic challenge with the development of an oxidative Au-catalyzed cycloisomerization of homopropargylic anilines (Scheme 1B).[4] Cyclization and ring-expansion strategies have also been investigated for the preparation of these medium-sized heterocycles (Scheme 1C).[5] An alternative appealing convergent approach towards the synthesis of tetrahydrobenz[*b*]azepin-4-ones is the cascade reaction of *N*-arylnitrones and allenes. Tufariello, Blechert, and Padwa each observed benz[*b*]azepin-4-ones in product mixtures and as intermediates in early reports of these cascade transformations.[6] In 2015, Kumar and coworkers determined that when nitrone **1** is accessed via hydroamination, benzazepines **3** can be isolated after treatment with allenes **2** (Scheme 1D).[7] We wondered if further catalytic manipulation of this cascade process could expand the structural diversity of the accessible benz[*b*]azepin-4-one products beyond dimethyl-acetylene dicarboxylate-derived nitrones and to include more complex three-dimensional structures. Recently, while studying the preparation of dihydropyrido[1,2-a]indoles via a catalyst-controlled cascade reaction of nitrones and allenes, we observed that the use of hydrogen-bond-donor catalysts with nucleophilic amine functionalities gave bridged bicyclic tetrahydrobenz[*b*]azepin-4-ones as a byproduct.[8] Herein we report that bridged bicyclic tetrahydrobenz[*b*]azepin-4-ones **6** can be easily constructed from nitrones **4** and allenes **5** using a simple Lewis base catalyst, 1,3-diazabicyclo[2.2.2]octane (DABCO) (Scheme 1E). This catalyst selectively steers the versatile cascade process that we have previously tuned for the synthesis of dihydrocarbazoles, dihydropyridoindoles, and 3-functionalized indoles towards these novel, medium-sized heterocyclic compounds.[8,9] The scope of this transformation for the preparation of **6** and the relationship of this branch of the cascade system to previously reported pathways is discussed. This new method expands the structural diversity of accessible tetrahydrobenz[*b*]azepin-4-one scaffolds and further advances our understanding of nitrone and allene cascade reactions.[10]



Scheme 1. Strategies towards the synthesis of tetrahydrobenz[*b*]azepin-4-ones and a new convergent route to bridged bicyclic derivatives via cascade reaction catalyst tuning.

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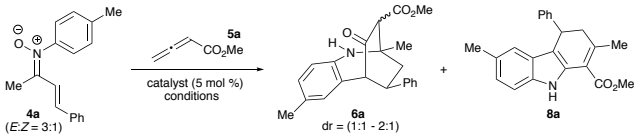
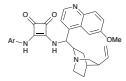
† Electronic Supplementary Information (ESI) available: General information, experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

Optimization of the synthesis of tetrahydrobenz[*b*]azepin-4-one **6a** from nitrone **4a** and allene **5a** was achieved by deconstructing a squaramide catalyst and examining solvent effects (Table 1). The study was initiated using squaramide **7** because this hydrogen-bond donor catalyst had previously been observed to give a chalcone-derived bicyclic benz[*b*]azepin-4-one as a byproduct of an alternative branch of our tunable cascade system.[8] When a mixture of **4a** and **5a** was treated with squaramide **7**, **6a** was isolated in 74% yield (Table 1, entry 1). Removal of the hydrogen-bond donor portion of **7** established that quinine was an equally efficient catalyst for the synthesis of **6a** (Table 1, entry 2). Further simplification of the catalyst structure showed that DABCO is a better catalyst than quinine for the formation of **6a** at shorter reaction times and a solvent screen showed that DABCO is most effective as a catalyst in either toluene or THF at 60 °C for 3 h (Table 1, entries 3 – 9). In all cases, **6a** was isolated as a mixture of diastereomers, which were characterized as having stereochemical distinction at the β-ketoester functionality.[11] Surprisingly, when MeOH was used as the solvent for the cascade reaction, dihydrocarbazole **8a** was formed in 68% yield (Table 1, entry 6).[9a] Further exploration of alternative amine bases as catalysts for the formation of **6a** indicated that reactivity trends did not correlate to pKa values (Table 1, entries 10 – 13).[12] While quinuclidine was demonstrated to be a superior catalyst to DABCO for the formation of **6a**, inferior yields to DABCO were observed for other substrates.[12] The optimization data described in Table 1 suggested that DABCO was the optimal catalyst for the formation of bicyclic benz[*b*]azepin-4-ones **6** from nitrones **4** and allenoates **5** and the conditions given in Table 1, entry 4 were used to further investigate reaction scope.

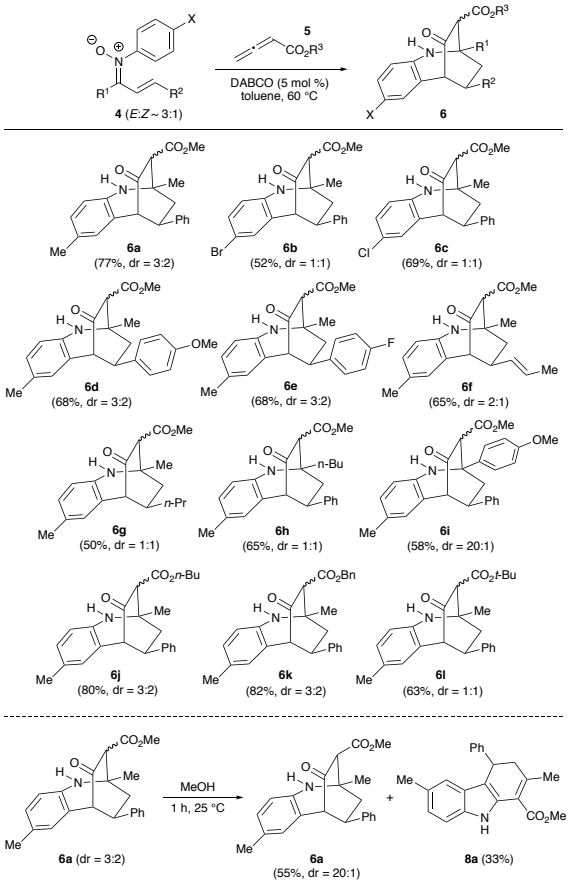
Table 1. Optimization of the cascade synthesis of bicyclic benz[*b*]azepine-4-one **6a**.



Entry[a]	Catalyst	Solvent	Time (h)	% Yield **6a** (**8a**)
1	 **7**[b]	C_6F_6	18	74[c]
2	quinine	toluene	18	73[c]
3	DABCO	toluene	18	57
4	DABCO	toluene	3	83
5	DABCO	*i*-PrOAc	3	68
6	DABCO	MeOH	3	(68)
7	DABCO	THF	3	83
8	DABCO	MeCN	3	73
9	DABCO	DCE	3	80
10	DBU	toluene	3	56
11	quinuclidine	toluene	3	92
12	DMAP	toluene	3	68
13	imidazole	toluene	3	56
14	DABCO	toluene	3[d]	66
15	DABCO	toluene	3[e]	50

[a] Conditions: **4a** (1 equiv), **5a** (3 equiv), 0.12 M, 60 °C. [b] Ar = 3,5-$(F_3C)_2(C_6H_3)$. [c] % ee = trace. [d] 80 °C. [e] 25 °C. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. DMAP = 4-dimethylaminopyridine.

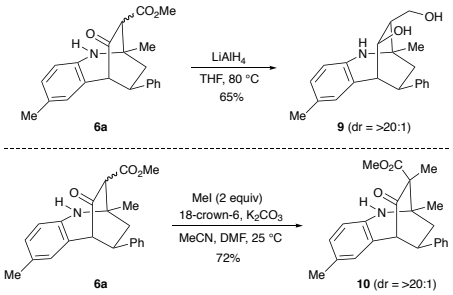
The scope of the bicyclic benz[*b*]azepine-4-one synthesis was investigated with respect to the structure of nitrone **4** and the ester group of allene **5**. As shown in Scheme 2, the cascade reaction tolerates alkyl- and halogen-substituents at the *N*-aryl functionality of nitrone **4** (see **6a** – **6c**). An X-ray crystallography study of bicyclic benz[*b*]azepin-4-one **6b** verified the proposed structure of products.[13] Longer chain alkyl groups are tolerated at the R^1-position of **4**, as well as aryl-, alkyl-, and alkenyl-substituents at the R^2-position (see **6d** – **6h**). Chalcone-derived nitrone **4i** was also shown to undergo formation of corresponding **6i**. The ester-substituent of allene **5** was varied to give **6j** – **6l**. These studies indicated that the cascade synthesis of benz[*b*]azepin-4-ones **6** is tolerant of a variety of nitrones and allenes with different carbon frameworks. In all cases, except for **6i**, the bicyclic benz[*b*]azepin-4-ones were isolated as mixtures of diastereomers. Treatment of **6a** with MeOH resulted in an increase in the diastereomeric ratio with concomitant formation of dihydrocarbazole **8a**. Further derivatization studies were then pursued to determine if the diastereomeric ratio of **6** could also be improved via transformation of the β-ketoester group.



Scheme 2. Scope of bicyclic benz[*b*]azepine-4-one cascade synthesis. Reaction conditions: 4 (1 equiv), 5 (3 equiv), DABCO (5 mol %), 0.12 M, toluene, 60 °C, 3 h.

The reactivity of the β-ketoester functionality of **6a** was tested under reduction and alkylation conditions. As shown in Scheme 3, reduction of **6a** with $LiAlH_4$ gave diol **9** in good yield and as a single diastereomer. An X-ray crystallography study of **9** verified the illustrated relative stereochemistry.[13] Similarly, methylation of **6a** gave bicyclic benzazepinone **10** as a single diastereomer. These results showed that bicyclic benz[*b*]azepin-4-one cascade products **6** can undergo simple reductions and

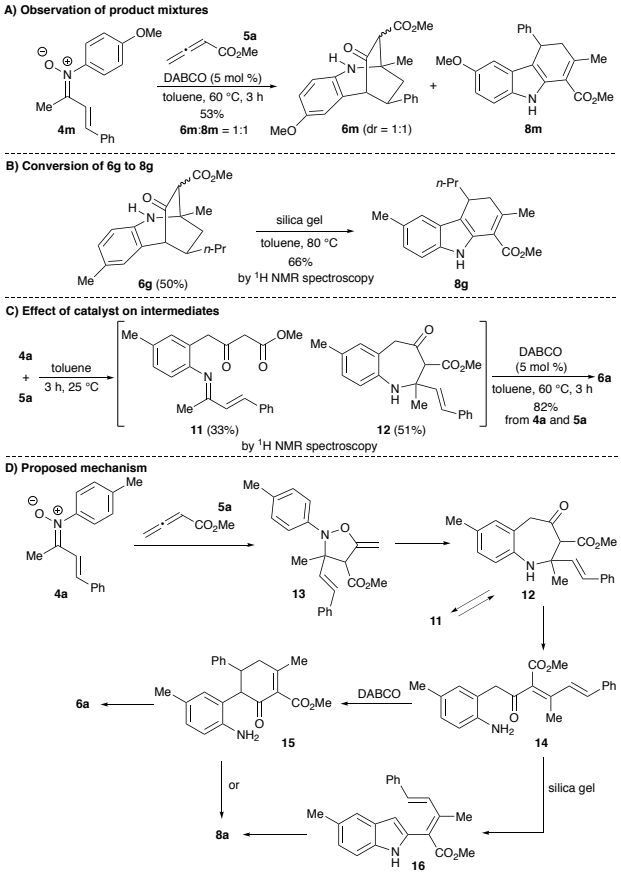
alkylations to eliminate the acidic proton of the β-ketoester functionality and access a single diastereomer of these novel heterocycles.



Scheme 3. Derivatization of bicyclic benz[*b*]azepine-4-one **6a**.

Investigation of a nitrone with an electron-rich *N*-aryl group under the optimal conditions described in Table 1 resulted in the formation of a mixture of products that provided initial insight into the reaction pathway for this branch of the cascade system. As shown in Scheme 4A, when nitrone **4m** was treated with **5a** and subjected to reaction conditions a mixture of bicyclic benz[*b*]azepin-4-one **6m** and dihydrocarbazole **8m** was isolated. This observation initially suggested that the formation of **6** may proceed along a similar reaction pathway to the formation of **8**.[9a] To determine if **6** could be converted to **8** under optimal conditions for the formation of **8**, **6g** was treated with silica gel and heated in toluene (Scheme 4B).[9a] A 66% conversion to **8g** was observed by ^{1}H NMR spectroscopy, which supported our hypothesis that the reaction pathways could be related. To provide information regarding the effect of DABCO on the intermediates of the cascade reaction, nitrone **4a** was treated with allene **5a** in toluene to give a mixture of **11** and **12** as previously observed for related transformations (Scheme 4C).[8,9c,14] The addition of 5 mol % DABCO to this mixture converted both **11** and **12** to bicyclic benz[*b*]azepin-4-one **6a**. Based on these experiments, we propose the mechanism illustrated in Scheme 4D for the formation of **6a**. An initial [3+2] cycloaddition of **4a** and **5a** followed by a formal [3,3]-rearrangement of exomethylene isoxazoline **13** could give benzazepinone **12** as previously proposed by our group and others.[6,9a,14] Compound **12** could then undergo a reversible retro-Mannich ring-opening to form **11** or a retro-Michael ring-opening to form **14**.[14] Under Lewis acidic conditions, we previously proposed that **14** undergoes condensation to form indole **16** and electrocyclization to form the dihydrocarbazole **8a**.[9a] In the presence of DABCO, indole condensation appears to be disfavoured, allowing for cyclization to form **15** and a second conjugate addition to form **6a**. In the presence of an aniline with increased nucleophilicity, or in the presence of a protic solvent, **15** can alternatively undergo condensation to give dihydrocarbazole **8a**.

In summary, a catalyst-controlled cascade reaction has been discovered for the synthesis of bridged bicyclic benz[*b*]azepin-4-ones **6**. This new method provides a route to synthetically challenging tetrahydrobenz[*b*]azepin-4-ones and provides the opportunity to access new bridged bicyclic examples of these heterocyclic compounds. Our previous investigations of cascade reactions of *N*-arylnitrones and allenes that produced dihydrocarbazoles or dihydropyridoindoles provided a strategy for deconstructing hydrogen-bond donor catalyst **7** to enable construction of bridged bicyclic benz[*b*]azepin-4-ones **6** as the sole N-heterocyclic product of this cascade system.[8,9] Future studies will be aimed at showing that increased mechanistic insight into this versatile system will continue to achieve catalyst-control of new cascade processes.



Scheme 4. Proposed mechanism and relationship to dihydrocarbazole cascade synthesis.

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Conflicts of interest

There are no conflicts to declare.

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11 See Supporting Information for details.

12 See Supporting Information for an expanded Table 1.

13 CCDC 1886668 contains the supplementary crystallographic data for compound **6b** and CCDC 1886326 contains the supplementary crystallographic data for compound **9**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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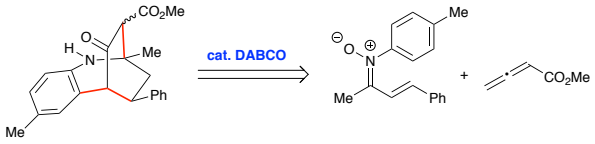

A new cascade reaction provides convergent access to novel bridged bicyclic medium-sized N-heterocycles.