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DBU-Catalyzed Desymmetrization of Cyclohexadienones: Access to Vicinal Diamine-Containing Heterocycles

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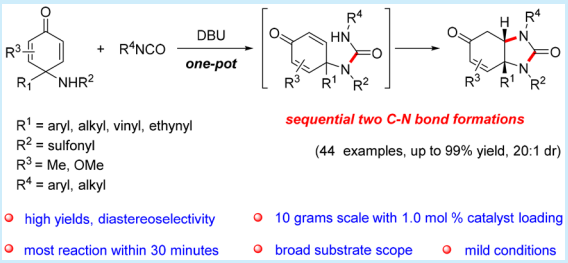
Supporting Information

ABSTRACT: A DBU-catalyzed desymmetrization strategy between cyclohexadienones and isocyanates was discovered, affording a series of vicinal diamine-containing heterocycle derivatives in moderate to good yields and excellent diastereoselectivity under mild conditions. Furthermore, this reaction could be performed on a 10 g scale using 1.0 mol % of catalyst loading.



Nitrogen heterocycles that contain vicinal amines are privileged structural motifs found in a wide range of pharmaceutical and bioactive molecules (Figure 1).[1] For

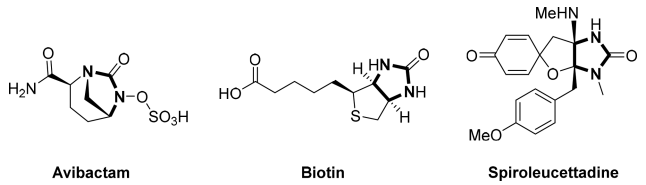
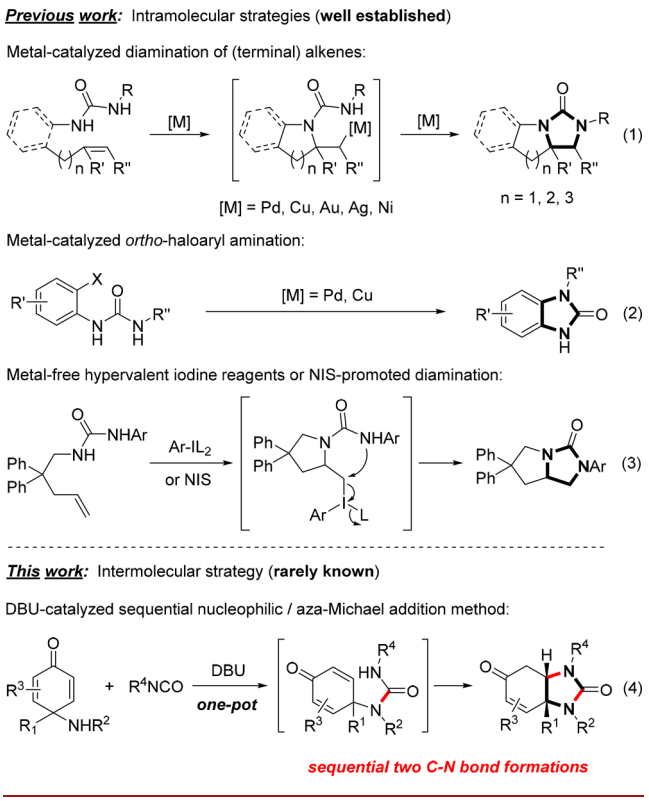


Figure 1. Examples of vicinal diamine-containing heterocycles possessing pharmaceutical and biological activities.

example, Avibactam, which is the first non-β-lactam β-lactamase inhibitor to be introduced for clinical use, is a broad-spectrum serine β-lactamase inhibitor with activity against class A, class C, and some class D β-lactamases.[1a] Biotin is a water-soluble B-vitamin, also called vitamin B_7. Formerly known as vitamin H or coenzyme R, biotin is also very important in the synthesis of fatty acids, isoleucine, and valine and in gluconeogenesis.[1b] Spiroleucettadine was originally isolated from the bright yellow *Leucetta* calcareous sponge in 2004, and the disclosure was met with keen interest by the natural products and synthetic communities due to its antibacterial activity (minimum inhibitory activity, MIC < 6.25 g/mL against *Enterococcus durans*).[1c,d] Thus, a number of synthetic methods have been achieved for the synthesis of this complex polycyclic structural motif over the past decades. First is the metal-catalyzed diamination of (terminal) alkenes (Scheme 1, eq 1);[2] notably, the Muñiz,[3] Shi,[4] and Chemler[5] groups have successively employed sulfonylamides and diaziridinones as nitrogen sources, in combination with Pd, Cu, and other metal catalytic systems, to realize the more challenging diamination of olefins. Second is the metal-catalyzed *ortho*-haloaryl amination (Scheme 1, eq 2).[6] The third is metal-free hypervalent iodine reagents or

Scheme 1. Selected Examples of Vicinal Diamine-Containing Heterocycle Synthesis and the Diagram of Our Work



NIS-promoted amination (Scheme 1, eq 3)[7] and others.[8] However, despite their potential applications in approaches to

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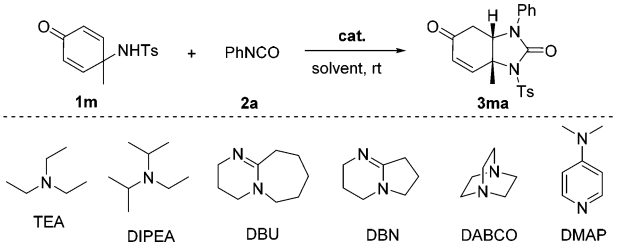
vicinal diamine-containing heterocycles, some drawbacks of these methods are ineluctable, such as harsh conditions, limited substrate scope, tedious processes for purification, and costly catalysts. On the other hand, these synthetic methods are mainly concentrated on the intramolecular cyclization. Therefore, a new synthetic approach to this class of useful molecules is still underdeveloped and highly desirable.

Due to the development of desymmetrization of cyclohexadienones[9] and our ongoing investigation on organocatalytic sequential annulation domino reaction,[10] we would like to address this challenge and report a DBU-catalyzed intermolecular sequential nucleophilic/aza-Michael addition strategy under mild conditions (Scheme 1, eq 4). This protocol allows the diastereoselective construction of a broad range of vicinal diamine-containing heterocycles in high yields from readily available cyclohexadienones and isocyanates.

To validate the feasibility of the cyclization reaction, our initial investigations began with 4-methyl-*N*-(1-methyl-4-oxocyclohexa-2,5-dien-1-yl)benzenesulfonamide **1m** and isocyanatobenzene **2a** in CH_2Cl_2 at room temperature under the catalysis of Et_3N (Table 1, entry 1), and we were pleased to find that bicyclic

Table 1. Optimization of the Reaction Conditions[a]



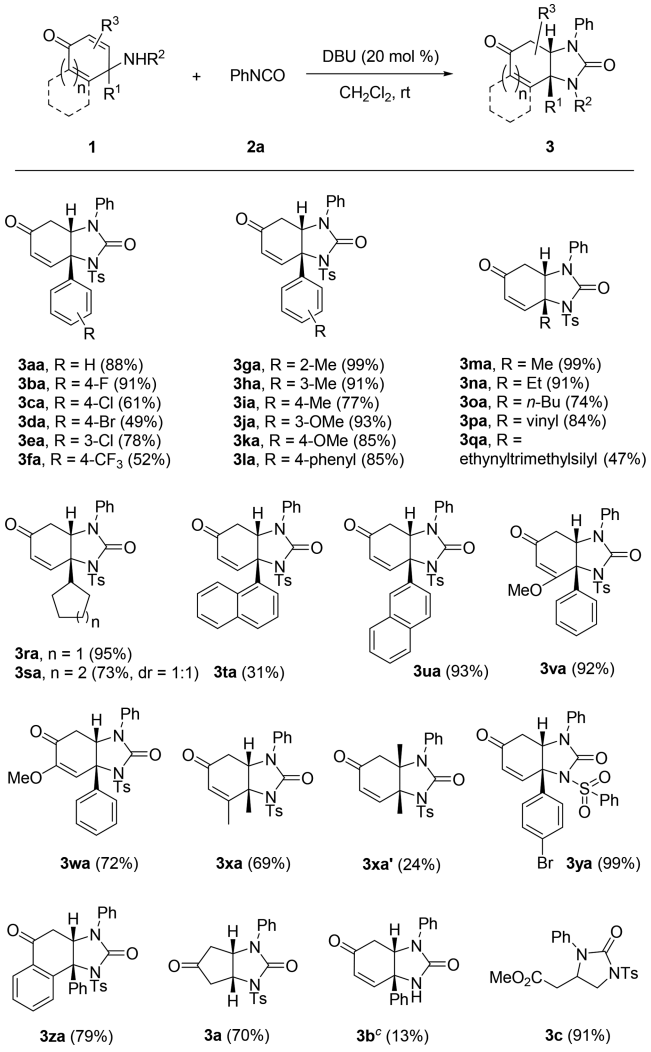
entry	cat.	solvent	time (h)	yield (%)[b]
1	Et_3N	CH_2Cl_2	24	91
2	K_2CO_3	CH_2Cl_2	3.5	93
3	DBU	CH_2Cl_2	0.5	99
4	DIPEA	CH_2Cl_2	50	94
5	DBN	CH_2Cl_2	3.5	86
6	DABCO	CH_2Cl_2	24	96
7	DMAP	CH_2Cl_2	120	89
8	DBU	toluene	0.6	82
9	DBU	THF	0.6	89
10	DBU	$CHCl_3$	0.5	95
11	DBU	CH_3CN	120	53
12	DBU	CH_3CH_2OH	120	14
13	none	CH_2Cl_2	24	0

[a]Unless otherwise noted, reactions of **1m** (0.10 mmol) and **2a** (0.12 mmol) were carried out with 20 mol % of catalyst loading in 1.0 mL of solvent. [b]Isolated yields.

vicinal diamine-containing heterocycle **3ma** was formed in 91% yield after 24 h. Attempts to improve the yield and decrease the reaction time by employing other organic or inorganic base catalysts turned out to be pleasing. The use of DBN and DMAP failed to give better results (Table 1, entries 5 and 7), but to our delight, we quickly found that K_2CO_3, DBU, DIPEA, and DABCO relative to Et_3N gave positive results. Considering that it had the shortest reaction time and highest yield, we chose the DBU as the best catalyst (Table 1, entries 2, 3, 4, and 6). After that, a routine solvent screening process was carried out using toluene, THF, $CHCl_3$, CH_3CN, and ethanol as solvent, and no better results were obtained (Table 1, entries 8−12). As usual, the blank control experiment without DBU catalyst showed that the desired cyclization process could not be achieved.

With the optimized reaction conditions in hand, we subsequently continued our investigation of the reaction with the substrate scope (Scheme 2). The reaction was applicable to a

Scheme 2. Substrate Scope for the Cyclization Reaction of Various Cyclohexadienones and Phenyl Isocyanate 2a[a,b]



[a]Unless otherwise noted, reactions of **1** (0.10 mmol) and **2a** (0.12 mmol) were carried out in 1.0 mL CH_2Cl_2. [b]Isolated yields. [c]Reaction on 0.20 mmol for 48 h.

wide range of different substituents on the starting materials. Generally, the substrate with electron-rich substituents at the position of the benzene ring delivered yields higher than that with electron-deficient aryl substituents (**3aa**−**3la**) (Scheme 2). Variation of the alkyl substituent from methyl to butyl was tolerated, and the corresponding cyclized products **3ma**, **3na**, and **3oa** were obtained in good yield. Substrates **1p** and **1q**, which contain vinyl or ethynyl side chains, also worked well, and the desired products **3pa** and **3qa** were isolated in 84 and 47% yields. Further investigation showed that substrate **1** bearing cyclopentyl, cyclohexanyl, and naphthyl groups (α or β position) (**3ra**−**3ua**) was also efficient for the transformation. Then the methoxyl-substituted cyclohexadienone substrates **3va** and **3wa** resulted in good yields. However, substrate **1x** with the

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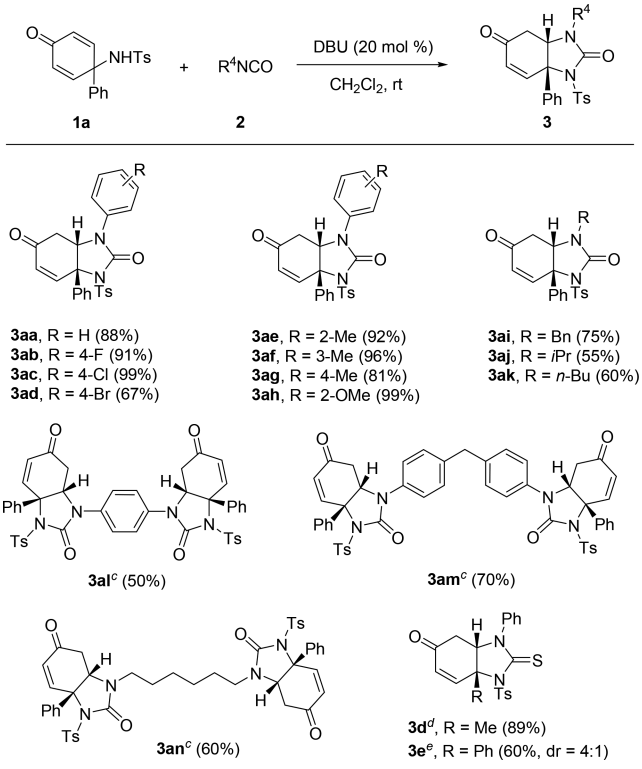
methyl-substituted group showed unsatisfactory chemoselectivity, although the total yields of **3xa** and **3xa′** were very good (93%). The protecting group of the sulfamide functional group could also be changed (**3ya**). Interestingly, substrate **1z**, derived from 4-methoxynaphthalen-1-amine, also smoothly delivered the tricyclic product **3za** in 79% yield under the optimized conditions. Notably, five-membered ring substrate **1** offered an opportunity to construct bicycle imidazole scaffolds with two contiguous chiral centers, albeit with moderate yield (**3a**). Moreover, the N-free product could be obtained with 13% yield (**3b**). The simple unsaturated electron-deficient olefins bearing a nitrogen nucleophile also adapted to the process with good yield (**3c**). In addition, the structure and stereochemistry of **3ia** were characterized by a combination of NMR, HRMS spectra, and single-crystal X-ray analysis (see Supporting Information (SI), Figure S1). It should be noted that only a single diastereomer was obtained in all cases, except for **3sa**.

Encouraged by these results, we surveyed the scope of isocyanates **2** with **1a** as a counterpart (Scheme 3). To our delight, various isocyanates bearing either electron-rich or electron-deficient aryl substituents at the *para* and *meta* position of the aromatic ring were well-tolerated, producing the desired products in good to high yields (**3ab**−**3ah**). In addition, the incorporation of various alkyl substituents in the substrate showed satisfactory yields (**3aj**−**3ak**). Furthermore, the diisocyanates **2l**, **2m**, and **2n** were also suitable for this reaction, delivering the corresponding bimolecular products with moderate to good yields. The isothiocyanate also adapted to the process with good yields with a slight change on reaction conditions (**3d** and **3e**).

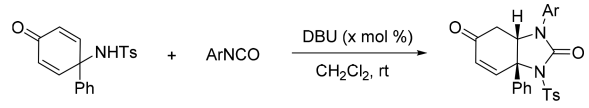
Scheme 3. Substrate Scope for the Cyclization Reaction of Cyclohexadienones 1a and Various Isocyanates[a,b]



[a]Unless otherwise noted, reactions of **1a** (0.10 mmol) and **2** (0.12 mmol) were carried out in 1.0 mL of CH_2Cl_2. [b]Isolated yields. [c]Reactions of **1a** (0.10 mmol) and **2** (0.05 mmol) were carried out in 1.0 mL of CH_2Cl_2. [d]40 °C for 30 h. [e]40 °C for 5 days.

To display the potential applicability of this protocol, we performed the reaction on a multigram scale (the same catalyst concentration as the optimized reaction conditions). We were delighted to find that when the catalyst loading was decreased to 1.0 mol %, the reaction still smoothly proceeded at 25 mmol scale to provide **3ac** in 12.13 g with 98.5% yield (Table 2, entry 5).

Table 2. Cyclization Reaction on a Multigram Scale

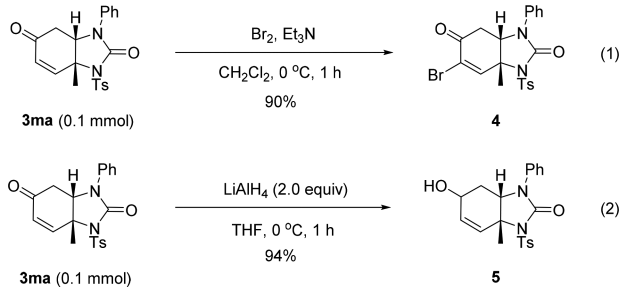


entry	scale (mmol)	x	time	3ac	yield (%)[a]
1	0.1	20	10 min	0.049 g	99.5
2	1.0	10	10 min	0.492 g	99.5
3	5.0	5	40 min	2.42 g	98
4	10.0	2.5	3 h	4.85 g	98.5
5	25.0	1	4 h	12.13 g	98.5

[a]Isolated yields.

The vicinal diamine-containing bicyclic products also serve as useful precursors to other interesting compounds. For example, the bromination of **3ma** went smoothly and delivered corresponding product **4** in 90% yield (Scheme 4, eq 1). Moreover, product **5** could also be obtained from **3ma** via a $LiAlH_4$ reduction strategy in 94% yield (Scheme 4, eq 2).

Scheme 4. Further Transformation of Product 3ma



We further investigated the asymmetric version of this new domino reaction using several commonly used chiral amine catalysts (see SI), and the enantioselective version of this reaction was carried out by utilizing the catalyst **1** at room temperature (25 °C) in dichloromethane. When substrates **3m** and **2a** were used, the corresponding product **3ma** was obtained in 50% yield and 15% ee; unfortunately, when **1a** and **2a** were used, no reaction took place.

In conclusion, we have developed a DBU-catalyzed intermolecular sequential nucleophilic/aza-Michael addition strategy between cyclohexadienones and isocyanates, which provides a rapid, efficient, and selective route to vicinal diamine-containing heterocycle derivatives in good to excellent yields. This reaction could be performed on a 10 g scale using 1.0 mol % of catalyst loading. From the synthetic point of view, the broad substrate scope, mild reaction conditions, and an inexpensive catalyst make this protocol valuable in synthetic chemistry.

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Further studies on asymmetric versions of the reaction are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02158.

Experimental details, characterization data for new compounds, NMR spectra, and X-ray crystal structure of **3ia** (PDF)

Accession Codes

CCDC 1816081 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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