ChemPubSoc Europe

DOI: 10.1002/chem.201601626

CHEMISTRY
A European Journal
Communication

Dual Organocatalysis |*Hot Paper*|

A Catalyst-Enabled Diastereodivergent Aza-Diels–Alder Reaction: Complementarity of *N*-Heterocyclic Carbenes and Chiral Amines

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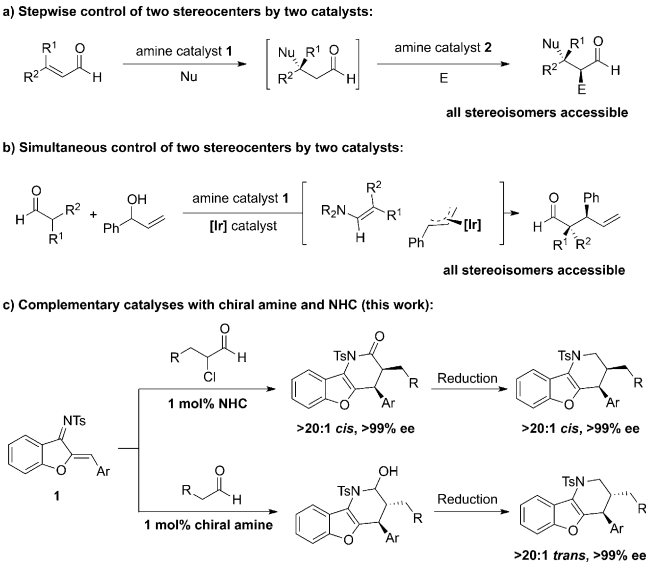
Abstract: Highly efficient and diastereodivergent aza-Diels–Alder reactions have been developed to access either diastereomeric series of benzofuran-fused δ-lactams and dihydropyridines in nearly perfect stereoselectivity (d.r. >20:1, >99% *ee* for all examples). The complementarity of *N*-heterocyclic carbene and chiral amine as the catalyst was demonstrated for the first time, together with an excellent level of catalytic efficiency (1 mol% loading).

The efficient generation of structural diversity in organic compounds is an important goal in chemistry and chemical biology.[1] In the field of catalytic method development, the modulation of the catalyst to realize chemo-, regio-, or diastereodivergent transformations from the same starting materials has gained much significance and prominence in recent years.[2] In such transfomations where multiple stereocenters are created, it is undoubtedly more attractive to be able to access all the stereoisomers in pure form rather than getting a mixture or simply one of the diastereomeric series. The identification of catalysts that enable such divergent reactivities, however, is highly challenging and "requires creativity and insight".[3] The use of two different catalysts for the control of stepwise formation of two stereogenic centers (Scheme 1 a)[4] and the simultaneous formation of two stereocenters by the act of two catalysts working independently[5] (Scheme 1 b) have been elegantly demonstrated. More examples have also been reported in which the alternation of the chiral ligand or catalyst structure could also result in diastereodivergent reactions.[6] Herein we present an alternative method in which two different classes of catalysts (NHC and chiral amine) promote the Diels–Alder reactions of azadiene and aldehyde with exquisite stereoselectivity and complementary diastereocontrol (Scheme 1 c).

During the past few decades, both chiral amines and carbenes have been developed into powerful and versatile catalysts for the synthesis of a diverse range of chiral compounds.[7] The construction of heterocycles through aza-Diels–Alder reaction,[8] in particular, was realized with both catalytic systems in excellent level of stereoselectivity. While chiral amines catalyze the reaction between simple aldehydes with enone/azadienes to produce the lactol/hemiaminal as the initial product,[9] the analogous NHC-catalyzed procedures utilize functionalized aldehydes and produce lactone/lactams directly.[10] The choices of diastereocontrol in these two series, although not compared directly, are complementary in most known systems. Our group has become interested in NHC-catalyzed cyclization reactions as a means to access chemical structural diversity for biological screening. Very recently we have reported that aurones related to **1** (Scheme 1 c) can undergo divergent reactivities to generate either 7-membered-ring lactones or spirocyclic heterocycles in high stereoselectivity by the use of different NHC catalysts.[11,12] We also became interested in the efficient generation of both diastereomeric series of the benzofuran-fused heterocycles bearing multiple stereocenters to further enhance the diversity of this important class of pharmacologically active compounds.[13] Herein, we present our development of the first highly diastereodivergent and enantioselective aza-DA reactions by employing chiral amine or NHC catalytic systems. Along with the excellent stereoselectivity, the superb catalytic efficiency in this report also highlights the great potential of our system in synthesis.



Scheme 1. Diastereodivergent reactions enabled by the dual catalytic system.

We initiated our studies by examining the reaction of azadiene **1 a** with α-chloroaldehyde **2 a** using different NHC cata-

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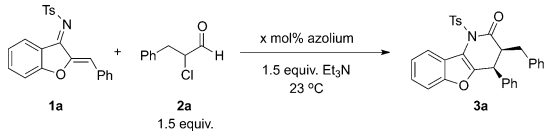
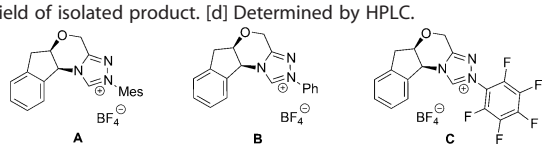
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201601626.

Table 1. Optimization of *cis*-aza-DA of **1a** and **2a**.[a]



Entry	Azolium (%)	Solvent	Time	d.r.[b]	Yield[c] [%]	*ee*[d] [%]
1	**A** (10)	CH_2Cl_2	<10 min	>20:1	96	>99
2	**B** (10)	CH_2Cl_2	<10 min	>20:1	95	>99
3	**C** (10)	CH_2Cl_2	<10 min	>20:1	95	84
4	**A** (5)	CH_2Cl_2	20 min	>20:1	96	>99
5	**A** (2)	CH_2Cl_2	90 min	>20:1	96	>99
6	**A** (1)	CH_2Cl_2	4 h	>20:1	96	>99
7	**A** (1)	THF	5 h	>20:1	95	>99
8	**A** (1)	Et_2O	5 h	>20:1	93	>99
9	**A** (1)	toluene	5 h	>20:1	95	>99

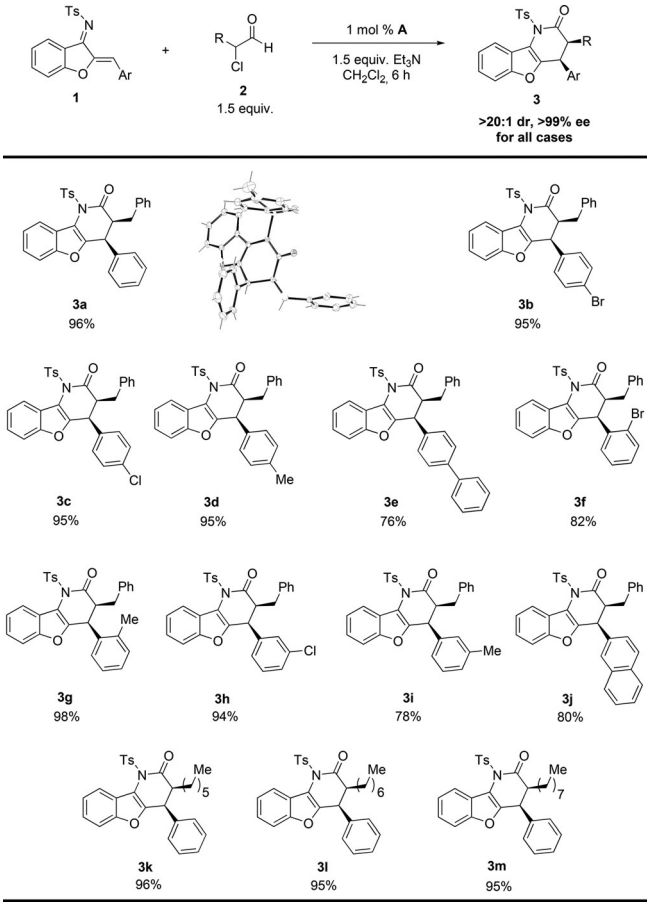
[a] Unless noted otherwise, **1a** (0.05 mmol), **2a**, azolium salt and NEt_3 were allowed to stir in solvent (1.0 mL) at 23 °C for the give period of time. [b] Determined by ^1H NMR analysis of the crude reaction mixture. [c] Yield of isolated product. [d] Determined by HPLC.



lysts; representative results are listed in Table 1. The use of various azolium salts including **A**, **B**, and **C** at 10 mol% loading with NEt_3 as the base all led to the formation of **3a** in excellent yield as a single *cis*-isomer in less than 10 min (entries 1–3). In terms of the enantioselectivity, however, catalyst **A** and **B** proved to be superior (>99% *ee*) than **C** (84% *ee*, entry 3). Lowering the catalyst loading was then examined using **A** (entries 4–6). The reaction efficiency was soon discovered to be extremely high. Even with 1 mol% **A**, the reaction went to completion in 4 h to yield **3a** in excellent yield, diastereo- and enantioselectivity (entry 6). Screening of various solvents showed that the reaction was similarly efficient and selective in a range of solvents (entries 6–9). Finally, the conditions in entry 6 was adopted to examine the substrate scope of this catalytic system, as the use of CH_2Cl_2 as the solvent showed consistently higher reactivity for all the substrates examined (Scheme 2).

The substrate scope of this catalytic system turned out to be very broad. The easily accessible *N*-tosyl azadienes **1** bearing *ortho*-, *meta*- or *para*-substituents of both electron-poor and electron-rich characters at the aryl rings could be well-tolerated to yield the corresponding dihydropyridinones (**3a**–**3j**) in uniformly perfect diastereo- and enantioselectivity.[14] It is particularly noteworthy that the sterically challenging *ortho*-substituted substrates underwent reaction with similar level of efficiency to yield **3f**–**3g** in high yields.

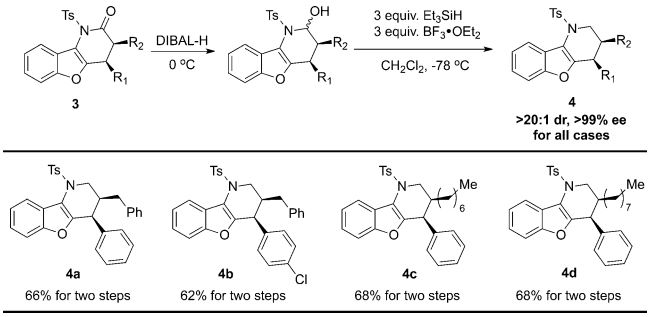
Furthermore, various α-chloroaldehydes bearing different linear alkyl substituents participated in the reaction similarly well (**3k**–**3m**). Compared to the previously reported NHC-catalyzed aza-DA reactions,[10] the greatly improved efficiency in our system may be due to the driving force of aromatization in benzofuran formation.[11,12]



Scheme 2. Scope of the NHC-catalyzed *cis*-selective Diels–Alder reaction. Unless noted otherwise, **1** (0.10 mmol), **2**, azolium salt, and NEt_3 were added to CH_2Cl_2 (1.0 mL) and allowed to stir at 23 °C for 6 h.

The relative and absolute configuration of **3a** was unambiguously assigned by single-crystal X-ray diffraction analysis. Considering a similar reaction mechanism for the formation of **3**, and in connection with the same NMR characters for all the products, the other dihydropyridinones **3** were assigned to have the same relative and absolute configuration.

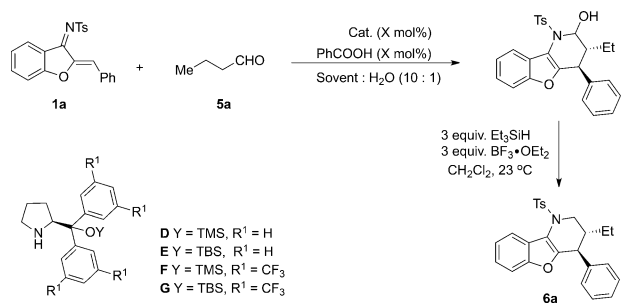
The resulting multisubstituted dihydropyridinones provide many possibilities for further transformations. For example, reduction of the lactam moiety in **3** yielded the corresponding *cis*-tetrahydropyridine **4** in good yields without any erosion of diastereo- and enantiopurity (Scheme 3).



Scheme 3. Access to *cis*-tetrahydropyridine.

Aiming at accessing the *trans*-series of the benzofuran-fused heterocycles, we turned our attention to the investigation of the reaction of **1a** with butyraldehyde (**5a**) catalyzed by the readily available α,α-diphenylprolinoltrimethylsilyl ether **D**[15] and benzoic acid at 20 mol% loading, typically for enamine catalysis (Table 2). The aza-DA reaction proceeded smoothly to reach completion within less than one hour. The hemiaminal moiety was directly reduced with $Et_3SiH/BF_3{\cdot}Et_2O$ in DCM at ambient temperature to yield the desired tetrahydropyridine **6a** in a high yield of 97% with 93% *ee* (entry 1). The addition of water led to an acceleration of the aza-DA reaction; higher selectivity was also observed when a mixed solvent of DCM and H_2O (10:1) was used (entry 2). This is consistent with previous reports in chiral amine-catalyzed aza-DA reactions that water is helpful for the hydrolysis of the intermediate to release the catalyst and thus facilitate catalytic turnover.[9]

Table 2. Optimization of *trans*-aza-DA of **1a** and **5a**.[a]



Entry	Catalyst (mol%)	Solvent	Time [h]	d.r.[b]	Yield [%][c]	*ee* [%][d]
1[d]	**D** (20)	CH_2Cl_2	1	>20:1	97	93
2	**D** (20)	CH_2Cl_2	1	>20:1	96	>99
3	**E** (20)	CH_2Cl_2	1.5	>20:1	95	>99
4	**F** (20)	CH_2Cl_2	24	>20:1	96	>99
5	**G** (20)	CH_2Cl_2	72	>20:1	96	>99
6	**D** (20)	CH_3CN	0.5	>20:1	96	>99
7	**D** (20)	THF	2	>20:1	95	>99
8	**D** (20)	dioxane	2	>20:1	97	>99
9	**D** (20)	toluene	0.5	>20:1	95	>99
10	**D** (10)	toluene	1	>20:1	97	>99
11	**D** (5)	toluene	1.5	>20:1	96	>99
12	**D** (2)	toluene	3	>20:1	96	>99
13	**D** (1)	toluene	4	>20:1	93	>99

[a] Reaction conditions: **1a** (0.05 mmol), **5a** (0.075 mmol) and amine catalyst and benzoic acid were allowed to stir in the listed solvent (0.5 mL) and H_2O (0.05 mL) at ambient temp. [b] Determined by HPLC (Chirapak Daicel IC). [c] Yield of isolated product. [d] Without water.

The popular analogous catalysts **E**–**G** were examined next. The bulkier silyl ethers **E** led to similar enantioselectivity but with slightly lower catalytic activity (entry 3). The secondary amines **F** and **G** with strong electron-withdrawing substituents on the aryl rings produced similar enantioselectivity and yield, but with much lower catalytic activity, so that 24 and 72 h were needed for the reaction to reach completion (entries 4 and 5). Using the optimal catalyst **D**, different commonly used solvents were examined (entries 6–9). While all the solvents resulted in excellent yield and enantioselectivity, toluene turned out to be the optimal choice with the highest reaction rate. The test of lower catalyst loading to 10%, 5%, 2%, and 1% was attempted next (entries 10–13). To our excitement, complete conversion could be achieved in a few hours even with 1 mol% catalyst loading (entry 13). Similar to the reactions shown in Scheme 2, it is believed that the aromatization of the starting material serves as a strong driving force for the aza-DA reaction to proceed in high efficiency.

Having established the optimal reaction conditions, we explored the scope of this *trans*-selective aza-DA reaction. Various azadienes **1** were treated with aldehydes **5** in the presence of **D** (1 mol%) and benzoic acid (1 mol%) in a mixture of toluene and H_2O (10:1) at room temperature, followed by reduction using $Et_3SiH/BF_3{\cdot}Et_2O$ to yield the tetrahydropyridines **6**. For the reactions with butyraldehyde, a wide range of *ortho*-, *meta*-, or *para*-substituents could be present at the aryl rings of ketimine **1**. Excellent diastereo- and enantioselectivity was observed throughout the substrates, although relative lower yield was obtained for the *ortho*-bromo-substituted product **6g**, which was probably due to steric hindrance. Other aldehydes, including the linear and branched aliphatic and benzylic aldehydes, could all be applied smoothly in the aza-DA reaction with **1** to yield **6i**–**6l** in excellent yields and stereoselectivities. The relative and absolute configuration of **6b** was unambiguously assigned by single-crystal X-ray diffraction analysis and the configuration of all other products was assigned to be the same by analogy.

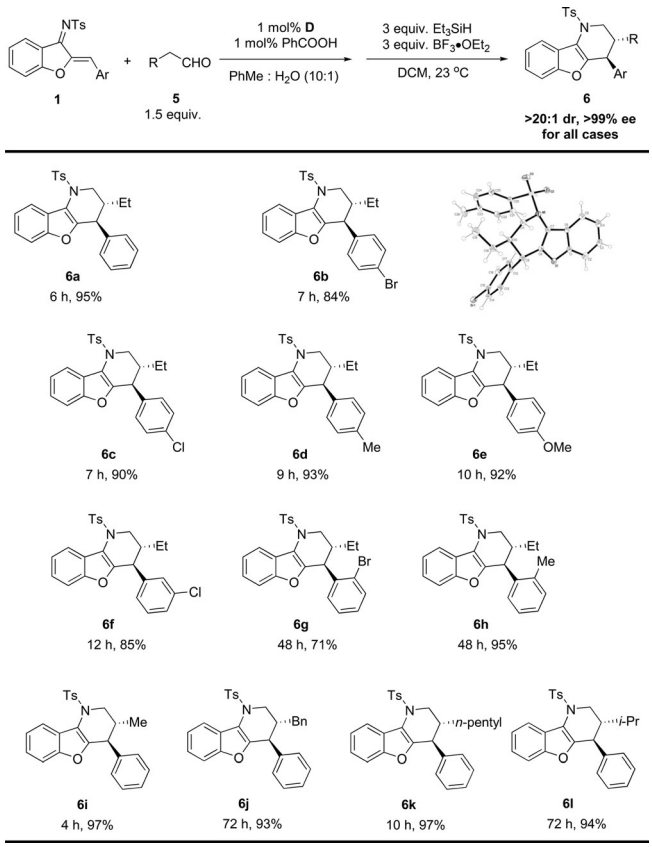
It is important to note that the products shown in Scheme 3 and Scheme 4 are the two diastereomeric series of benzofuran-fused tetrahydropyridines. Thus, by utilizing either readily available NHC or chiral amine catalyst, we were able to access all the possible isomers of this class of compounds. The high level of catalytic efficiency and stereoselectivity makes this method highly attractive in asymmetric synthesis.

We propose the reaction pathways in Scheme 5 to account for the diastereodivergency of our catalytic systems. Based on the literature precedents in chiral NHC and amine catalysis, the formation of NHC-containing (*Z*)-enol **I** followed by a concerted [4+2] cycloaddition through TS **A** should lead to the formation of the *cis*-series of the products. On the other hand, enamine **II** should be formed with the (*E*)-configuration; the reaction of **II** with **1** will then result in the formation of the *trans*-products through TS **B**.

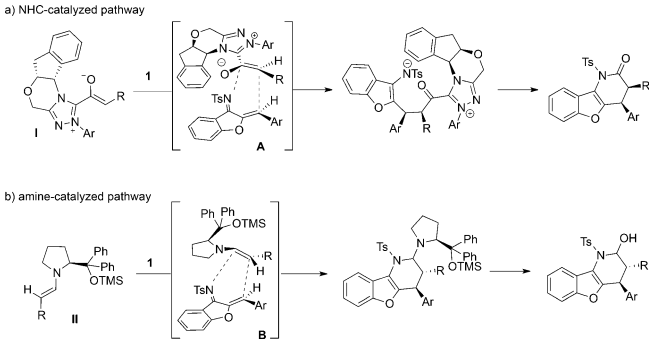
In conclusion, we have developed highly efficient catalytic aza-DA reactions to access either diastereomeric series of the benzofuran-fused lactams and tetrahydropyridines. The complementarity of chiral amine and NHC catalysts is demonstrated for the first time, which made it possible to achieve such diastereodivergent and highly stereoselective transformations. It is believed that this strategy should prove general for substrates beyond the azadienes included in this report. Studies on further applications are currently underway.

Experimental Section

NHC-catalyzed *cis*-DA reaction: The substrate **1** (0.10 mmol), triazolium salt **A** (0.001 mmol) were added in a 4 mL vial. The mixture



Scheme 4. Scope of the chiral amine-catalyzed *trans*-selective Diels–Alder reaction. Unless noted otherwise, the reactions of **1** (0.15 mmol) and **5** (0.225 mmol) in the presence of 1 mol% of **D** and PhCOOH were allowed to stir in toluene (1.5 mL) and H_2O (0.15 mL) (10:1) at ambient temperature. The hemiaminal was then reduced with $Et_3SiH/BF_3{\cdot}Et_2O$ in CH_2Cl_2 at ambient temperature.



Scheme 5. Rationale for divergent reactivity.

was taken into glovebox, where anhydrous CH_2Cl_2 (1.0 mL), α-chloroaldehydes **2** (0.15 mmol), and NEt_3 (21 μL, 0.15 mmol) were added using a micropipette. The reaction mixture was taken outside the glovebox, and the reaction mixture was allowed to stir at ambient temperature for 6 h. The crude reaction mixture was directly purified by silica gel column chromatography with hexanes/ethyl acetate (5:1) as eluent to afford the desired product **3**.

Chiral amine-catalyzed *trans*-DA reaction: The reaction was carried out with substrate **1** (0.15 mmol) and aldehyde **5** (0.225 mmol) in the presence of catalyst **D** (0.0015 mmol) and benzoic acid (0.0015 mmol) in a mixture of toluene and H_2O (1.65 mL, 10:1) at room temperature. After the reaction was complete, the mixture was concentrated and the residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate = 10:1) to afford the corresponding hemiaminal compound. To an anhydrous dichloromethane solution of the hemiaminal compound was added triethyl silane (52.3 mg, 0.450 mmol) and $BF_3{\cdot}Et_2O$ (56 μL, 0.45 mmol) in one portion. The reaction mixture was stirred at 0 °C for 5 min and then at room temperature until the reaction was complete (monitored by TLC). The reaction was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexanes/ethyl acetate = 15:1) to yield the final product **6** as a while solid.

Acknowledgements

We are grateful for the generous financial support from Singapore National Research Foundation (R-143-000-477-281 and R-143-000-606-281) and the Ministry of Education of Singapore (R-143-000-605-112).

Keywords: chiral amines · Diels–Alder cycloaddition · diastereodivergence · enantioselectivity · N-heterocyclic carbenes

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Received: April 7, 2016
Published online on June 17, 2016