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Organocatalytic enantioselective hetero-Diels–Alder reaction of aldehydes and *o*-benzoquinone diimide: Synthesis of optically active hydroquinoxalines

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ABSTRACT

A highly enantioselective inverse electron demand hetero-Diels–Alder reaction of *o*-benzoquinone diimide and aldehydes has been developed by secondary amine catalysis, giving a facile protocol to access a variety of chiral hydroquinoxalines under mild conditions.

Quinoxalines and related compounds represent a prominent class of pharmaceutical molecules, and the investigation on these intriguing structures has captured continuing interest of researchers worldwide.[1] Compounds with quinoxaline cores are used as HIV antiviral agents,[2] antagonists of the selective human A_3 adenosine receptor,[3] antagonists of 5-HT3 receptors,[4] growth inhibitors of *Trypanosoma cruzi*,[5] etc. Moreover, quinoxalines including 3,4-dihydroquinoxalinone and 1,2,3,4-tetrahydroquinoxaline are also promising targets for asymmetric synthesis as they show various types of biological activity such as in blocking or reversing activation of bradykinin (BK) receptors, in the management of pain and inflammation, as well as in the treatment of disorders mediated by BK.[6] However, few successful examples of enantioselective synthesis of the functionalized hydroquinoxalines have yet been reported. In 2006, Lectka and co-workers reported an elegant asymmetric inverse electron demand hetero-Diels–Alder reaction (HDAR) of acyl chlorides[7] and *o*-benzoquinone diimides to deliver the chiral quinoxalinones.[7c] Although perfect ee values were observed by the catalysis of Lewis bases derived from cinchona alkaloids, the reaction condition was somewhat harsh (−78 °C) and metal triflates must be used as co-catalysts to activate the electrophilic *o*-benzoquinone diimides.[7c,d]

Recently, our group has developed an asymmetric inverse electron demand aza-Diels–Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes[8] and aldehydes by employing the small organic molecule as catalyst, which is often nontoxic, environmentally friendly, and stable under aerobic and aqueous reaction conditions.[9] A diversity of chiral piperidine derivatives and other valuable compounds could be efficiently prepared from the hemiaminal cycloadducts.[10] Encouraged by the excellent stereoselectivity observed in the reaction, we envisaged that another direct asymmetric HDAR of *o*-benzoquinone diimides[7c] and aldehydes could be carried out through the same catalytic mechanism, giving a facile strategy to access chiral hydroquinoxalines.

Since the required *o*-benzoquinone diimide **2a** were easily accessible by benzoylation of commercial available *o*-phenylenediamine and subsequent oxidation,[7c] we immediately started our investigation on the proposed reaction. In the initial screen, we conducted the HDAR under the previous established conditions: *o*-benzoquinone diimide **2a** (1.0 equiv), butyraldehyde (2.0 equiv), benzoic acid (10 mol %), and the catalyst α,α-diphenylprolinol *O*-TMS ether **1** (10 mol %) in a mixture of CH_3CN and H_2O (10:1) at room temperature.[10] To our delight, this HDAR reaction smoothly proceeded without the metal-activation of *o*-benzoquinone diimide **2a**. The desired hemiaminal **4a** was isolated as a relatively stable compound with excellent stereoselectivity and good yield (Table 1, entry 1, dr >99:1, 97% ee). Moreover, we found that water is also crucial for the transformation efficiency in this HDAR.[10] The expected product could not be obtained when anhydrous acetonitrile was employed (entry 2). Encouraged by the promising results, we undertook more detailed study. It was found that the solvent

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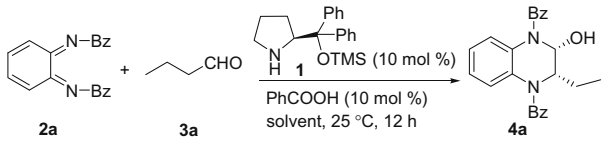
Table 1
Optimization of the organocatalytic HDAR of the *o*-benzoquinone diimide **2a** and butyraldehyde **3a**[a]



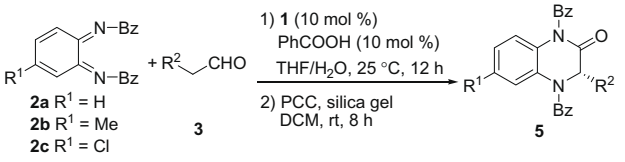
Entry	Solvent	Concentration (M)	Yield[b] (%)	ee[c] (%)
1	MeCN/H_2O	0.1	71	97
2	MeCN	0.1	<10	ND[d]
3	Diox/H_2O	0.1	83	>99
4	THF/H_2O	0.1	89	>99
5	toleune/H_2O	0.1	55	98
6	MeOH/H_2O	0.1	49	>99
7	THF/H_2O	0.07	81	>99
8	THF/H_2O	0.2	89	>99

[a] Reaction conditions: **2** (0.1 mmol), **3** (0.2 mmol), **1** (0.01 mmol), benzoic acid (0.1 mmol), organic solvent/H_2O (10:1), at 25 °C for 12 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis, dr >99:1.
[d] Not determined.

had an obvious effect on the outcome of the reaction. While the high stereoselectivity remained unchanged, lower yields were obtained in toluene and MeOH (entries 3 and 4); nevertheless, more satisfactory yields could be attained in a mixture of Diox/H_2O or THF/H_2O (entries 5 and 6). The reaction concentration also did not affect the stereoselectivity (entries 7 and 8), but the dilute conditions slightly slowed the rate of the reaction.

Subsequently, the scope of this asymmetric HDAR was evaluated under the optimized reaction condition with *o*-benzoquinone diimide **2a**. Since the hemiaminal **4** was not stable enough for further analysis,[11] PCC (pyridinium chlorochromate) oxidation was employed to give the more stable quinoxalinones **5**. As shown in Table 2, a variety of aldehydes **3a–e** bearing simple linear or branched α-substituted alkyl groups were well tolerated and excellent enantioselectivities were generally obtained (Table 2, entries 1–5). In addition, aldehydes **3f–h** with heteroatom bearing substituents were also employed, and provided the corresponding quinoxalinone products in good yield and with outstanding optical purity (entries 6–8). Not surprisingly, poor regioselectivity was observed when unsymmetrical *o*-benzoquinone diimides **2b** and **2c** were employed in the reaction with butyraldehyde **3a**, and mixtures were isolated.

Table 2
Asymmetric inverse electron demand hetero-Diels–Alder reactions of *o*-benzoquinone diimide **2a** and aldehyde **3a-h**[a]



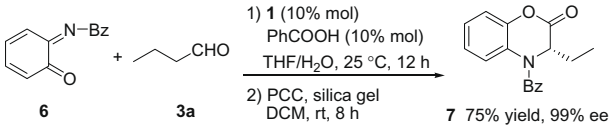
Entry	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	H	Et (**3a**)	**5a**–85	98
2[d]	H	Me (**3b**)	**5b**–82	94
3[e]	H	*i*-Pr (**3c**)	**5c**–90	99[f]
4[e]	H	$PhCH_2$ (**3d**)	**5d**–78	99
5	H	*n*-Pent (**3e**)	**5e**–92	99
6[d]	H	$BnO(CH_2)_2$ (**3f**)	**5f**–82	96
7[d]	H	$PhSCH_2$ (**3g**)	**5g**–63	95
8[d]	H	$NO_2(CH_2)_2$ (**3h**)	**5h**–79	95

[a] Reaction conditions (unless otherwise noted): for HDAR: **2a** (0.1 mmol), **3** (0.2 mmol), **1** (0.01 mmol), benzoic acid (0.01 mmol), THF/H_2O (10:1, 1 mL), at 25 °C for 12 h; for PCC oxidation: PCC (3 equiv), silica gel (65 mg), at 25 °C for 8 h.
[b] Isolated yield for two steps.
[c] Determined by chiral HPLC analysis.
[d] At 15 °C for 24 h.
[e] 4 equiv of aldehyde was added.
[f] The absolute configuration of **5c** was determined by the comparison of the specific rotation with known compound.[7c] The other products were assigned by analogy.

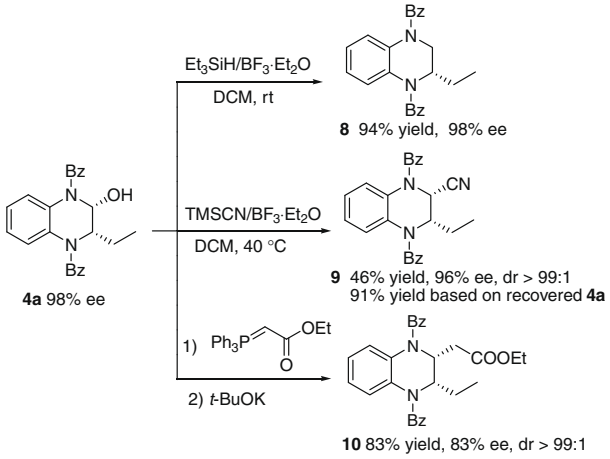
In addition, *o*-benzoquinone imide **6** instead of *o*-benzoquinone diimide **2a** was also tested with butyraldehyde **3a** under the same catalytic conditions (Scheme 1). The expected hemiacetal was produced with good isolated yield and excellent enantioselectivity. After PCC oxidation, 1,4-benzoxazinone **7**, which is another scaffold for biologically active molecules as well as an α-amino acid precursor,[7b] was smoothly obtained without any racemization (99% ee).

As an illustration of the versatility of this methodology, the asymmetric HDAR product hemiaminal **4a** could be readily converted into other useful chiral hydroquinoxalines. Apart from PCC oxidation to afford quinoxalinone **5a**, the hydroxyl group of **4a** was smoothly removed by reduction with $Et_3SiH/BF_3{\cdot}Et_2O$ at ambient temperature, affording substituted 1,2,3,4-tetrahydroquinoxaline **8** with preserved ee value (Scheme 2, 98% ee, dr >99:1). The hydroxyl group of **4a** was replaced with a cyano group using $TMSCN/BF_3{\cdot}Et_2O$ to give compound **9**, which could be used for the synthesis of various 1,2,3,4-tetrahydroquinoxaline-2-carboxylic acid derivatives; while only moderate yield could be obtained due to the low reaction conversion. Furthermore, **4a** could be easily transformed to chiral 1,2,3,4-tetrahydroquinoxaline-2-acetic acid ester **10** by successive Wittig reaction-intramolecular aza-Michael addition; unfortunately, some racemization was detected in the final product **10** (82% ee, dr >99:1).[12,13]

In summary, we have developed a highly enantioselective organocatalytic inverse electron demand hetero-Diels–Alder reaction of *o*-benzoquinone diimide and aliphatic aldehydes catalyzed by a chiral secondary amine.[14] This reaction was carried out under



Scheme 1. Synthesis of 1,4-benzoxazinone via asymmetric inverse electron demand HDAR.



Scheme 2. Synthetic transformations of the chiral hemiaminal **4a**.

mild conditions and a number of enantioenriched hydroquinoxalines could be prepared from the hemiaminal adducts. An optically pure 1,4-benzoxazinone was also prepared through a similar HDAR of *o*-benzoquinone imide and butyraldehyde. We anticipate that these new HDARs will have great potential in the field of medicinal chemistry.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.013.

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