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Chiral Bisguanidine-Catalyzed Inverse-Electron-Demand Hetero-Diels−Alder Reaction of Chalcones with Azlactones

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Abstract: A new type of C_2-symmetric chiral bisguanidine was designed as a highly efficient catalyst in the inverse-electron-demand hetero-Diels−Alder reaction of chalcones with azlactones for the first time. A wide variety of γ,δ-unsaturated δ-lactone derivatives with α-quaternary-β-tertiary stereocenters were obtained in high yields (up to 88%) with excellent enantioselectivities (up to 99% ee). Hydrogen bonds were considered to be crucial for the activation and stereoinduction of the reaction. In all cases, the major was HDA adducts, which were obtained as a single diastereomer along with little amount of Michael addition products.

The inverse-electron-demand hetero-Diels−Alder (IEDDA) reaction[1] has been demonstrated to be one of the most powerful strategies for construction of six-membered oxygenated heterocycles.[2] Cinnamaldehyde and activated enones have been successfully identified for IEDDA reactions with electron-rich olefins,[3] while simple α,β-unsaturated ketones, such as chalcones, have usually been used as classical Michael acceptors rather than dienes.[4] To date, few examples of catalytic asymmetric IEDDA reactions of chalcones have been reported.[1c] Azlactones, as versatile reactants,[5a] have been employed as Michael donors in the synthesis of potentially bioactive α,α-disubstituted α-amino acids.[5b−d] It was rationalized that Michael addition involving chalcones and azlactones was prone to occur (Scheme 1, route a). However, we found that an unexpected IEDDA reaction of chalcones and azlactones[6] occurred preferentially in the presence of a new type of C_2-symmetric chiral bisguanidine, affording chiral γ,δ-unsaturated δ-lactones with a quaternary stereocenter (Scheme 1, route b).

Chiral guanidines,[7] because of the characteristics of high pK_a values and hydrogen-bonding activation, have been shown to be efficient catalysts for enantioselective reactions. Initially, the reaction of chalcone **3a** and azlactone **4a** was carried out with chiral guanidine[7d] catalyst **1a** at 0 °C in THF. Unexpectedly, the major product was cyclic adduct **5a**, which was obtained as a single diastereomer in 45% yield and 13% ee along with a 5% yield of the Michael addition products **6** (Table 1, entry 1). Encouraged by this interesting result, we synthesized and evaluated a number of chiral guanidines. Enhanced enantioselectivities were obtained using bisguanidines with achiral or chiral linkers (Table 1, entries 2−4). Chiral guanidine **2c** derived from (*S*,*S*)-1,2-diphenylethylenediamine gave δ-lactone **5a** in 61% yield with 82% ee (Table 1, entry 4). Fortunately, 73% yield with 96% ee was obtained when the reaction temperature was decreased to −20 °C and THF/$CHCl_3$ was used as solvent (Table 1, entries 5 and 6). To understand the pathway for obtaining cyclic adduct **5a**,[8] Michael products **6a** and **6a′** were isolated and resubjected to the reaction system; neither could perform intramolecular nucleophilic addition to give **5a**, which suggested that the cyclic adduct **5a** was obtained via the IEDDA reaction of the chalcone at the C4 and C5 positions of the azlactone (Scheme 1, route b).

Under the optimized conditions, a series of chalcone derivatives were examined. As summarized in Table 2, both electron-deficient and electron-rich chalcones (Table 2, entries 1−15 and 17−23) as well as heterocyclic examples (Table 2, entries 16, 24, and 25) underwent the IEDDA reaction smoothly, giving the corresponding δ-lactones in good yields (40−88%) with excellent enantioselectivities (89−99% ee). Generally, chalcones with electron-withdrawing groups on the aromatic substituents exhibited higher reactivity than those with electron-donating groups. In all cases, only a single diastereomer of **5** was obtained.

The scope of the IEDDA reaction of chalcone **3a** with various azlactones was also surveyed. As shown in Table 3, regardless of the electronic nature and steric hindrance of the R^3 substituent on the aromatic ring of **4**, high yields and excellent enantioselectivities (92−97% ee) were obtained (Table 3, entries 1−5). Furthermore, azlactones derived from other amino acids were also tolerated (Table 3, entries 6 and 7). To further evaluate the synthetic potential of the catalytic system, the reaction was conducted on a gram scale to afford **5a** with similar results (1.511 g, 70% yield, 93% ee). In addition, chiral

Scheme 1. Two Possible Base-Catalyzed Reactions of Chalcones with Azlactones

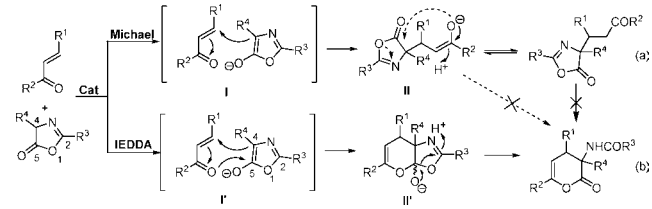
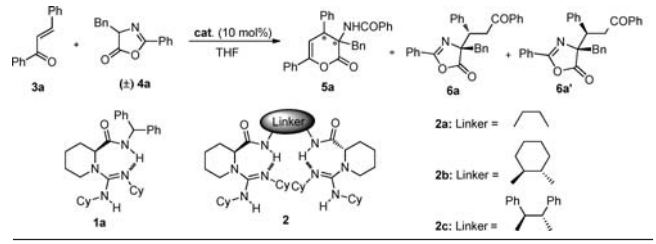


Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	T (°C)	yield (%) 5a[b,c]	yield (%) 6a and 6a′[b]	ee of 5a (%)[d]
1	**1a**	0	45	5	−13
2	**2a**	0	30	20	25
3	**2b**	0	65	18	30
4	**2c**	0	61	13	82
5[e]	**2c**	−20	78	6	89
6[e,f]	**2c**	−20	73	8	96

[a] Unless otherwise noted, all of the reactions were carried out with guanidine (10 mol %), **3a** (0.2 mmol), and **4a** (0.1 mmol) in THF (1.0 mL) for 48 h. [b] Isolated yield. [c] Only a single diastereomer of **5a** was obtained. [d] Determined by chiral HPLC analysis. [e] For 72 h. [f] THF/$CHCl_3$ [1/1 (v/v)] was used as the solvent.

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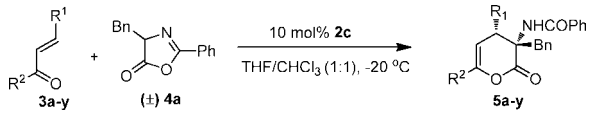
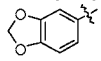
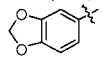
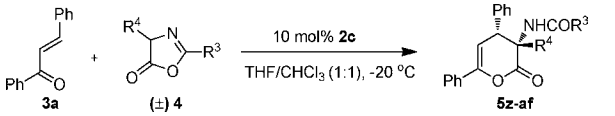
Table 2. Scope of the Asymmetric IEDDA Reaction of Chalcones[a]



entry	R^1	R^2	t (h)	yield (%)[b,c]	ee (%)[d]
1	Ph	Ph	72	73 (**5a**)	96
2	2-ClC_6H_4	Ph	72	75 (**5b**)	90
3	3-ClC_6H_4	Ph	72	78 (**5c**)	92
4[e]	4-ClC_6H_4	Ph	72	75 (**5d**)	94
5	3,4-$Cl_2C_6H_3$	Ph	72	88 (**5e**)	89
6	4-FC_6H_4	Ph	72	78 (**5f**)	94
7	4-BrC_6H_4	Ph	72	80 (**5g**)	94
8	3-BrC_6H_4	Ph	72	88 (**5h**)	93
9	3-MeC_6H_4	Ph	84	65 (**5i**)	94
10	4-MeC_6H_4	Ph	84	68 (**5j**)	95
11	3-$PhOC_6H_4$	Ph	96	64 (**5k**)	98
12	4-PhC_6H_4	Ph	72	68 (**5l**)	94
13	1-naphthyl	Ph	96	40 (**5m**)	90
14	2-naphthyl	Ph	72	70 (**5n**)	94
15		Ph	96	40 (**5o**)	99
16	4-pyridine	Ph	96	62 (**5p**)	90
17	Ph	4-FC_6H_4	72	67 (**5q**)	92
18	Ph	4-BrC_6H_4	72	65 (**5r**)	90
19	Ph	3-MeC_6H_4	84	80 (**5s**)	95
20	Ph	4-MeC_6H_4	84	73 (**5t**)	96
21	Ph	2-naphthyl	72	72 (**5u**)	94
22	Ph		96	50 (**5v**)	92
23	Ph	cinnamyl	72	70 (**5w**)	95
24	Ph	2-furyl	84	55 (**5x**)	91
25	Ph	2-thienyl	84	65 (**5y**)	92

[a] All of the reactions were carried out with 10 mol % **2c**, **3** (0.2 mmol), and **4a** (0.1 mmol) in 1.0 mL of THF/$CHCl_3$ [1/1 (v/v)] at −20 °C for 72−96 h. [b] Isolated yield. [c] Only a single diastereomer was obtained. [d] Determined by chiral HPLC analysis. [e] The absolute configuration was (3*S*,4*R*), as determined by X-ray analysis.[9]

Table 3. Scope of the Asymmetric IEDDA Reaction of Azlactones[a]



entry	R^3	R^4	*t* (h)	yield (%)[b]	ee (%)[c]
1	2-ClC_6H_4	Bn	72	76 (**5z**)	95
2	3-ClC_6H_4	Bn	72	78 (**5aa**)	92
3	4-ClC_6H_4	Bn	72	80 (**5ab**)	95
4	3-MeC_6H_4	Bn	84	71 (**5ac**)	97
5	3-$MeOC_6H_4$	Bn	96	68 (**5ad**)	93
6	Ph	CH_3	84	76 (**5ae**)	92
7	Ph	$MeS(CH_2)_2$	84	78 (**5af**)	90
8[d]	Ph	Bn	72	70 (**5a**)	93
9[e]	Ph	Bn	72	70 (**5a**)	93

[a] Unless otherwise noted, all of the reactions were carried out with 10 mol % **2c**, **3a** (0.2 mmol), and **4** (0.1 mmol) in 1.0 mL of THF/$CHCl_3$ [1/1 (v/v)] at −20 °C for 72−96 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was carried out on a 5 mmol scale. [e] The catalyst was recovered in 85% yield and reused on a 4.25 mmol scale of **4a**.

catalyst **2c** was recovered from the reaction mixture and reused without any loss of catalytic activity or enantioselectivity (Table 3, entries 8 and 9).

On the basis of the X-ray structures[9] of guanidine **2c** and product **5d**, a bifunctionally activated transition state for the IEDDA reaction of chalcone **3a** with azlactone **4a** is proposed.[8] As shown in Figure 1,

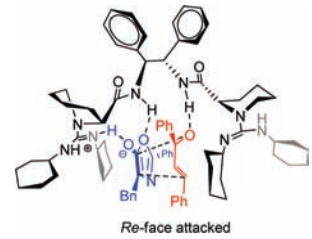


Figure 1. Proposed transition state for the IEDDA reaction of chalcone **3a** with azlactone **4a**.

the N−H moiety of the amide could act as a Brønsted acid to activate the chalcone and lower its LUMO energy through a hydrogen bond. Azlactone **4a** could be enolized and recognized by the guanidine moiety, associating with the N−H proton of the amide on the other side via dual intermolecular hydrogen bonds. The enolized azlactone could attach only from the *Re* face of the chalcone to form the major (3*S*,4*R*) product, in accordance with the experimental results.

In conclusion, the first catalytic enantioselective IEDDA reaction of chalcones with azlactones has been realized using a novel C_2-symmetric chiral bisguanidine as a catalyst. It performed well over a wide range of substrates, affording chiral γ,δ-unsaturated δ-lactones containing a quaternary stereocenter in high yields (up to 88%) with excellent enantioselectivities (up to 99% ee). Hydrogen bonds were considered to be crucial for the activation and stereoinduction of the reaction. More endeavors to understand the mechanism of the reaction are underway.

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Supporting Information Available: Experimental procedures, spectral and analytical data for catalysts and products, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For details, see the Supporting Information.
(9) CCDC 763202 (**2c**), CCDC 763200 (**5d**), and CCDC 778528 (**6a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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