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Remote Asymmetric Oxa-Diels−Alder Reaction of 5-Allylic Furfurals via Dearomatizative Tetraenamine Catalysis

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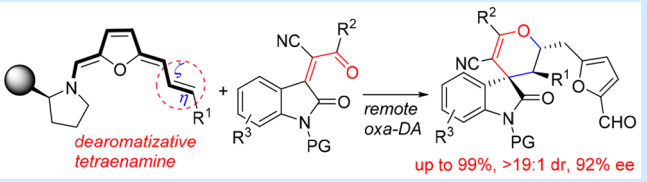
Supporting Information

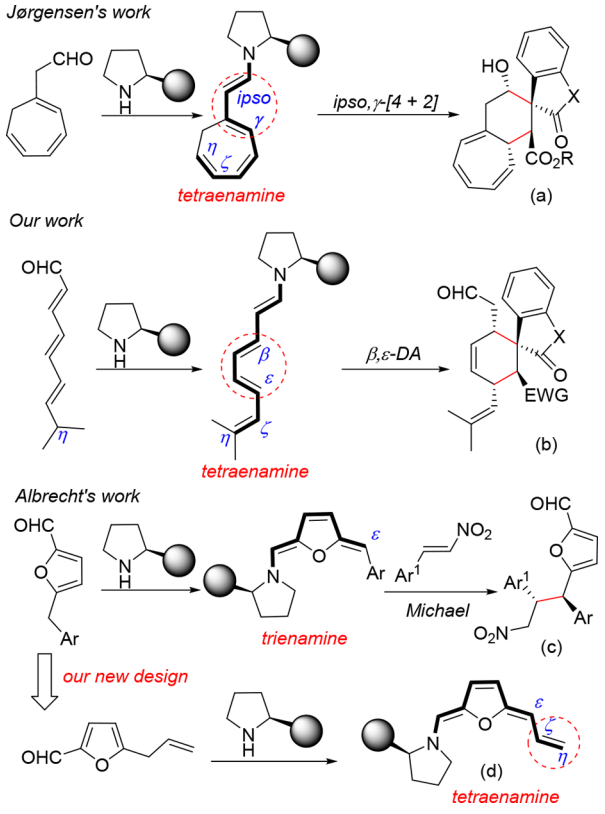
ABSTRACT: A previously unreported activation mode is developed through the generation of dearomatizative tetraenamine species between 5-allylic furfurals and a bifunctional amine-thiourea catalyst. The very remote ζ,η-alkenes perform as effective HOMO-raised dienophiles in inverse-electron-demand oxa-Diels−Alder cycloadditions with isatin-derived oxadiene substrates, delivering multifunctional spirocyclic oxindoles incorporating a dihydropyran skeleton in moderate to high yields with good to excellent enantio- and diastereoselectivity.



The development of remote functionalization reactions with high levels of stereocontrol has attracted considerable attention, but it has particular challenges in asymmetric catalysis.[1] Based on the principle of vinylogy, the electronic effect of functional groups can be transmitted to some remote sites through the conjugated π-systems.[2] The construction of a new stereogenic center located at five (γ-site) or even seven (ε-site) bonds away from the chiral center of the amine catalyst was realized via dienamine or trienamine catalysis, respectively.[3] These results prompted speculation whether tetraenamine catalysis, which could activate farther positions, could be achieved similarly in high stereoselectivity. The Jørgensen group reported the first example of tetraenamine catalysis with 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde, which underwent *ipso*,γ-regioselective [4 + 2] cycloadditions with activated alkenes (Scheme 1a).[4] Our group disclosed the in situ formed tetraenamine intermediates from 2,4,6-trienal substrates with η,η-disubstitutions and amine catalysts, proceeding in β,ε-regioselective Diels−Alder (DA) reactions (Scheme 1b).[5] However, the remote ζ,η-C=C bonds in neither case participated in the above reactions. Therefore, the remote tetraenamine catalysis has not been actually achieved, probably due to the decreased reactivity. Besides, the existence of multiple potential reaction sites and the long distance from the terminal double bonds to the stereodifferentiating catalysts undoubtedly render the regio- and stereocontrol in such a mode extremely challenging.

The furans are ubiquitous as key structural motifs in a variety of natural products or biologically active molecules.[6] The furan ring also represents a perfect heteroaromatic backbone through which the electronic effect could be effectively transmitted.[7] Based on this feature, our group successfully developed amine-catalyzed asymmetric remote Friedel−Crafts reactions of furan derivatives with excellent regio- and enantioselectivity.[8] Recently, the Albrecht group reported an elegant asymmetric remote Michael reaction of 5-benzyl furfurals via dearomatizative trienamine catalysis, albeit with moderate stereoselectivity

Scheme 1. Diverse Remote Enamine Activation Modes



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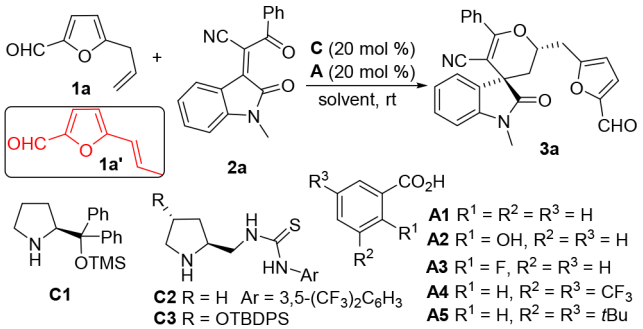
(Scheme 1c).[9,10] With the continuing efforts toward developing remote activation modes, we envisaged that dearomatizative tetraenamine species would be generated between 5-allyllic furfural substrates and amine catalysts via an inducing strategy[11] (Scheme 1d). Such a substitution pattern would render the remote ζ,η-C=C bonds more reactive, for example, as potential dienophile partners in cycloaddition reactions. Moreover, the relatively rigid tetraenamine backbone also might be helpful for the challenging remote stereocontrol.

While initial attempts with readily available 5-allyl furfural **1a** and a number of electrophiles resulted in limited success,[12] to our gratification, the isatin-derived oxodiene[13] **2a** showed good reactivity with **1a** in toluene at room temperature under the catalysis of α,α-diphenylprolinol *O*-silyl ether **C1** and benzoic acid **A1**. As expected, the remote ζ,η-terminal C=C bond of **1a** severed as a dienophile counterpart in an inverse-electron-demanded oxa-DA cycloaddition version,[14] delivering the spirooxindole product[15] **3a** in 82% yield, but with low stereoselectivity (Table 1, entry 1). It should be pointed out that substrate **1a′** with a conjugated system did not work under the identical conditions, demonstrating that the positioned ζ,η-C=C bond is crucial for the formation of the dearomatizative tetraenamine species.[11] By using a bifunctional amine **C2** with a thiourea moiety, both reactivity and stereoselectivity were significantly enhanced (entry 2), whereas **C3** with a bulky substitution gave lower enantioselectivity (entry 3). The acid additives were investigated as well (entries 4−7), and **A5** with *t*-butyl groups further improved the reactivity (entry 7). Then different solvents were screened (entries 8−10), and a slightly higher ee value was obtained in Et_2O, albeit with lower reactivity (entry 10). Consequently, the mixture of toluene and Et_2O was tested, also at lower temperatures (entry 11−15). It was found that the best results were obtained under the catalysis of **C2** and **A5** in toluene and E_2O (1:4) at 0 °C (entry 15). Remarkably, the reaction still proceeded well at lower catalyst loadings, giving the cycloadduct in comparable data by extending the reaction time (entries 16 and 17). Furthermore, similar good results were attained at a larger scale in toluene, though a longer time was required to achieve a high conversion (entry 18).

With the optimized reaction conditions in hand, the scope and limitations of the tetraenamine-mediated asymmetric oxa-DA reaction were explored. The results are summarized in Table 2. First, isatin-derived oxadienes **2** with a variety of *N*-protecting groups were employed in the reactions with **1a**. All of them, even the one with a free NH moiety, gave the corresponding cycloadducts in moderate to good yields with high enantio- and diastereoselectivity (Table 2, entries 1−7). In addition, oxadienes **2** with different substituents on the oxindole ring, including electron-donating and -withdrawing groups, were compatible with the cycloadditions, delivering products **3h−m** in good to excellent yields, whereas slightly lower enantioselectivity was observed for the latter ones (entries 8−13). The oxadienes **2** possessing diverse aryl and heteroaryl groups were investigated, giving the desired products **3n−q** in satisfactory results (entries 14−17). Unfortunately, the oxadienes **2** bearing alkyl substitutions failed to undergo the cycloadditions. However, furfural substrates (**1b** and **1c**) with a methyl and a phenyl group on the terminal double bond, respectively, were applied in the reactions, providing the cycloadducts **3r** and **3s** with three continuous stereogenic centers in good yields with high levels of stereoselectivity (entries 18 and 19).

Table 1. Screening Conditions of Oxa-Diels−Alder Reaction of Furfural 1a and Oxadiene 2a[a]



entry	cat.	acid	solvent	*t* (h)	yield (%)[c]	dr[b]	ee (%)[d]
1	**C1**	**A1**	toluene	16	82	3:1	28
2	**C2**	**A1**	toluene	12	94	>19:1	88
3	**C3**	**A1**	toluene	6	94	>19:1	80
4	**C2**	**A2**	toluene	12	58	>19:1	86
5	**C2**	**A3**	toluene	12	97	>19:1	88
6	**C2**	**A4**	toluene	12	90	>19:1	87
7	**C2**	**A5**	toluene	5	94	14:1	87
8	**C2**	**A5**	DCM	48	90	>19:1	80
9	**C2**	**A5**	THF	36	47	10:1	82
10	**C2**	**A5**	Et_2O	36	80	19:1	91
11	**C2**	**A5**	toluene/Et_2O (1:1)	6	82	>19:1	88
12[e]	**C2**	**A5**	toluene/Et_2O (1:1)	12	86	>19:1	90
13[e]	**C2**	**A5**	toluene/Et_2O (1:2)	12	72	>19:1	91
14[e]	**C2**	**A5**	toluene/Et_2O (1:4)	12	80	>19:1	91
15[f]	**C2**	**A5**	**toluene/Et_2O (1:4)**	**20**	**85**	**>19:1**	**92**
16[e,g]	**C2**	**A5**	toluene/Et_2O (1:4)	48	91	>19:1	92
17[h]	**C2**	**A5**	toluene	72	98	>19:1	88
18[e,i]	**C2**	**A5**	toluene	80	88	>19:1	89

[a]Unless noted otherwise, the reactions were carried out with **1a** (0.075 mmol), **2a** (0.05 mmol), amine **C** (20 mol %), and acid **A** (20 mol %) in solvent (1.0 mL) at room temperature. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Determined by ^1H NMR analysis. [e]At 4 °C. [f]At 0 °C. [g]With 10 mol % of catalyst. [h]With 5 mol % of catalyst. [i]At a 1.0 mmol scale.

Further transformations have been conducted with cycloadduct **3a**. The cyano group was smoothly hydrogenated and subsequently protected as an *N*-Boc derivative in the presence of Raney Ni and $(Boc)_2O$. The aldehyde group was also reduced to the corresponding alcohol simultaneously to afford product **4** (Scheme 2). Nevertheless, further attempts to chemoselectively reduce the enolate ether functionality were not successful, probably due to the crowded structure.

Based on the X-ray structure of the enantiopure cycloadduct **3a**, we proposed a plausible catalytic transition state to rationalize the stereoselectivity of the present oxa-DA reaction. As shown in Scheme 3, the bifunctional amine reacted with furfural **1a** to form the dearomatizative tetraenamine intermediate, and the hydrogen-bonding activated oxadiene **2a** approached the *Si*-face of ζ,η-C=C bond in an *endo*-selective [4 + 2] cycloaddition pattern to afford the observed chiral product **3a**.[14f,16]

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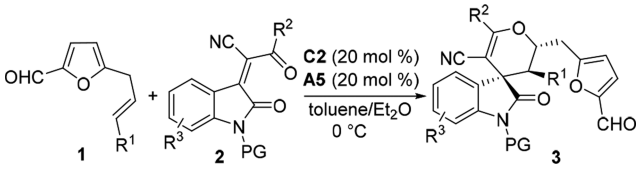
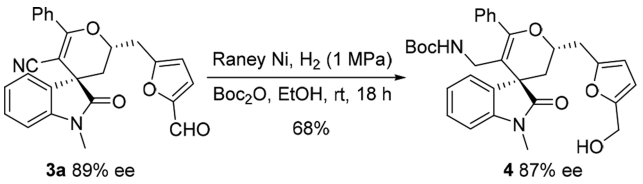
Table 2. Substrate Scope and Limitations of Oxa-Diels–Alder Reaction of Furfurals 1 and Oxadienes 2[a]



entry	R^1	PG	R^2	R^3	t (h)	yield (%)[b]	ee (%)[c]
1	H	Me	Ph	H	20	**3a**, 85	92[d]
2	H	Bn	Ph	H	18	**3b**, 76	87
3	H	allyl	Ph	H	12	**3c**, 80	89
4[e]	H	MOM	Ph	H	6	**3d**, 78	89
5[f]	H	Ph	Ph	H	7	**3e**, 72	82
6	H	Boc	Ph	H	10	**3f**, 61	83
7[f]	H	H	Ph	H	21	**3g**, 83	91
8	H	Me	Ph	5-Me	12	**3h**, 88	90
9[e,f]	H	Me	Ph	5,7-Me_2	10	**3i**, 94	89
10	H	Me	Ph	5-MeO	20	**3j**, 89	92
11[f,g]	H	Me	Ph	5-Cl	7	**3k**, 84	85
12[e,f]	H	Me	Ph	5-I	10	**3l**, 95	80[i]
13[e]	H	Me	Ph	7-CF_3	6	**3m**, 89	83
14[f]	H	Me	4-MeC_6H_4	H	72	**3n**, 96	86
15[e,h]	H	Me	4-BrC_6H_4	H	24	**3o**, 80	80
16	H	Me	2-naphthyl	H	24	**3p**, 76	92[i]
17	H	Me	2-furyl	H	24	**3q**, 72	86[i]
18	Me	Me	Ph	H	18	**3r**, 94	91[d]
19	Ph	Me	Ph	H	36	**3s**, 99	84

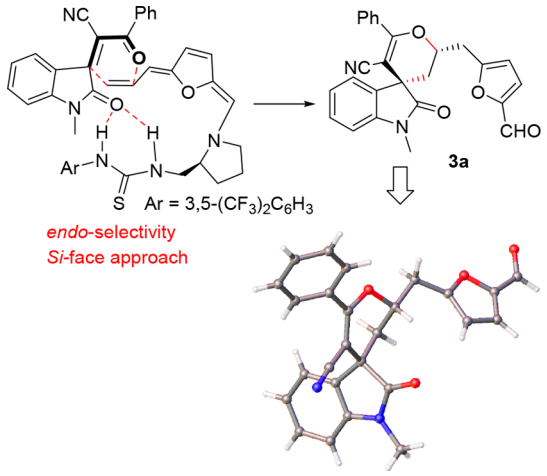
[a]Unless noted otherwise, the reactions were carried out with **1** (0.15 mmol), **2** (0.1 mmol), catalyst **C2** (20 mol %), and acid **A5** (20 mol %) in a mixture of toluene and Et_2O (2.0 mL, 1:4) at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase; in general, dr > 19:1 by ^1H NMR analysis. [d]The absolute configuration of enantiopure **3a** (CCDC 1811840) was determined by X-ray analysis. The other products were assigned by analogy. The relative configuration of **3r** (CCDC 1811841) was confirmed by X-ray analysis. [e]In toluene. [f]At 4 °C. [g]dr = 7:1. [h]At rt. [i]Determined after conversion to a 1,3-dithioketal derivative.

Scheme 2. Transformations of Cycloadduct 3a



In conclusion, we have developed an unprecedented remote activation mode, through generating dearomatizative tetraenamine species between 5-allylic furfural substrates and a chiral bifunctional amine-thiourea catalyst. The HOMO-raised remote ζ,η-C=C bonds smoothly participated in inverse-electron-demand oxa-Diels–Alder cycloaddition reactions with isatin-derived oxadienes exclusively, and a spectrum of multifunctional spirocyclic oxindoles incorporating a dihydropyran skeleton were obtained in moderate to high yields with good to high stereoselectivity. The success of this tetraenamine mode provides an efficient strategy for asymmetric remote activation, though reaction patterns and substrate limitations require further exploration. Meanwhile, these chiral scaffolds with high molecular and stereogenic complexity might find further application in organic synthesis and medicinal chemistry in the future.

Scheme 3. Proposed Catalytic Transition State for the Asymmetric Oxa-Diels–Alder Reaction



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03942.

Complete experimental procedures and characterization of new products; NMR spectra and HPLC chromatograms (PDF)

Accession Codes

CCDC 1811840–1811841 contain 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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