

Cu(I)-Catalyzed Asymmetric Multicomponent Cascade Inverse Electron-Demand Aza-Diels–Alder/Nucleophilic Addition/Ring-Opening Reaction Involving 2-Methoxyfurans as Efficient Dienophiles

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S Supporting Information

ABSTRACT: An unprecedented multicomponent cascade asymmetric inverse-electron-demand Diels–Alder/nucleophilic addition/ring-opening reaction involving 2-methoxyfurans as efficient dienophiles was successfully developed with Cu(I)/^tBu-Box complex as the catalyst. A diverse array of tetrahydropyridazines containing unexpectedly stable γ -hydroxyl ester moiety was obtained in generally good yield with exclusive regioselectivity and excellent stereoselectivity.

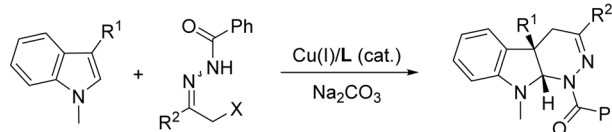
The catalytic asymmetric inverse-electron-demand Diels–Alder (IEDDA) reaction¹ has been recognized as one of the most powerful protocols featured in the preparation of highly functionalized and enantioenriched six-membered carbocycles and heterocycles, which are embedded in many biologically active natural products and pharmaceuticals. In the last few years, the asymmetric IEDDA reaction has witnessed intensive development promoted by various chiral Lewis acid catalysts² or organocatalysts.³ Considerable efforts in reactivity and stereoselectivity have been made with numerous electron-rich vinyl ethers, enecarbamates, vinyl indoles, or cyclopentadienes as dienophiles.^{2,3} With catalytic asymmetric dearomatization (CADA) strategy,⁴ You pioneered utilizing electron-rich indoles as dienophiles in an elegant organocatalyzed asymmetric IEDDA-type reaction to afford bridged indoline scaffolds.⁵ Subsequently, Sun⁶ and our group⁷ identified indoles as efficient 2π -components in chiral phosphoric acid and Cu(I)/Phosferrox complex catalyzed IEDDA reaction with in situ-formed arylimines and azoalkenes, respectively. While significant progress has been achieved with indoles as aromatic dienophiles, furans have received much less attention in this kind of synthetic transformation. In general, furans have been widely employed as dienes in normal electron-demand [4 + 2] Diels–Alder reactions⁸ with alkenes, alkynes, or allenes, [4 + 3] annulation⁹ with 2-oxyallyl cations, or vinylcarbenoids. The dienophilic behavior of furans was sporadically addressed only in non-symmetric transformations.¹⁰ Therefore, developing asymmetric reaction with furans as dienophiles is challenging probably due to the strongly enophilic nature and multiselectivity issues such as chem-, regio-, and stereoselectivity.

While investigating the behavior of furans in azoalkene-involved IEDDA reaction, we observed a novel Cu(I)-catalyzed

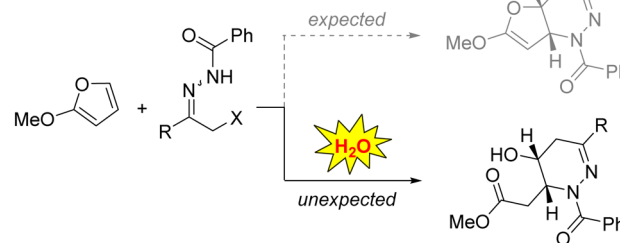
asymmetric multicomponent cascade IEDDA/nucleophilic addition/ring-opening reaction (Scheme 1). Replacing indole

Scheme 1. IEDDA Reaction of Indole with Azoalkene and Multicomponent Cascade IEDDA/Nucleophilic Addition/Ring-Opening of 2-Methoxyl Furan with Azoalkene

Previous work



This work



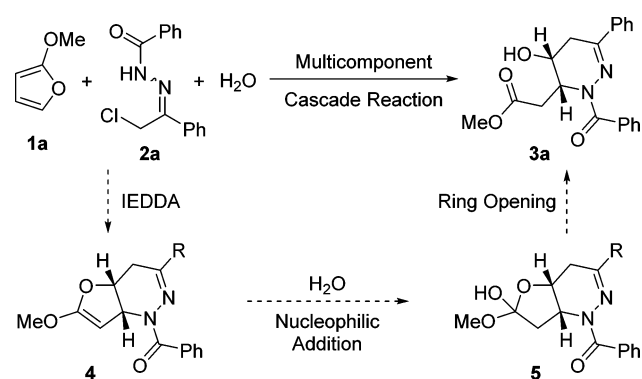
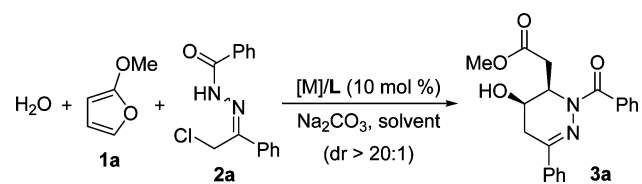
with 2-methoxyfuran did not produce the anticipated bicyclic heterocycle. Instead, the cycloadduct was further attacked by water as the nucleophile, followed by tetrahydrofuran ring-opening, leading to highly unexpected but biologically attractive tetrahydropyridazine derivatives¹¹ bearing γ -hydroxyl ester moiety (Scheme 2). Enantioenriched functionalized γ -hydroxyl esters are versatile building blocks¹² with two distinct functional groups for further synthetic manipulations. Notably, methodologies for those molecules containing γ -hydroxyl ester moiety are almost unknown due to the propensity of γ -hydroxyl ester to lactonize spontaneously.¹³

Our initial study began with the uncatalyzed reaction of 2-methoxy furan **1a** and α -chloro *N*-benzoyl hydrazone **2a** as azoalkene¹⁴ surrogate in the presence of Na_2CO_3 as the base. A heterocycle was obtained as a single isomer in moderate yield with exclusive regioselectivity and high diastereoselectivity (Table 1, entry 1). To our surprise, the product was finally

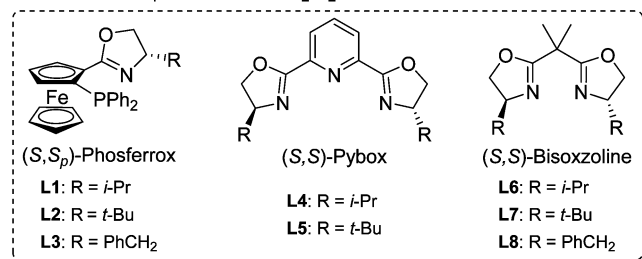
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Scheme 2. Plausible Reaction-Pathway Leading to 3a

Table 1. Catalyst Screening and Optimization of the Reaction Condition^a

Entry	[M]	ligand	Solvent	T (°C)	time (h)	yield ^b (%)	ee ^c (%)
1	-	-	CH ₂ Cl ₂	0	24	60	-
2	CuBF ₄	L1	CH ₂ Cl ₂	0	12	65	9
3	CuBF ₄	L2	CH ₂ Cl ₂	0	12	74	70
4	CuBF ₄	L3	CH ₂ Cl ₂	0	12	55	15
5	CuBF ₄	L4	CH ₂ Cl ₂	0	12	35	43
6	CuBF ₄	L5	CH ₂ Cl ₂	0	12	30	61
7	CuBF ₄	L6	CH ₂ Cl ₂	0	12	85	34
8	CuBF ₄	L7	CH ₂ Cl ₂	0	12	80	93
9	CuBF ₄	L8	CH ₂ Cl ₂	0	12	80	16
10	Cu(OTf) ₂	L7	CH ₂ Cl ₂	0	12	79	81
11	CuBF ₄	L7	THF	0	12	50	12
12	CuBF ₄	L7	PhMe	0	12	26	3
13	CuBF ₄	L7	MeCN	0	12	43	79
14	CuBF ₄	L7	CH ₂ Cl ₂	-20	20	76	95
15	CuBF ₄	L7	CH ₂ Cl ₂	-40	36	78	98



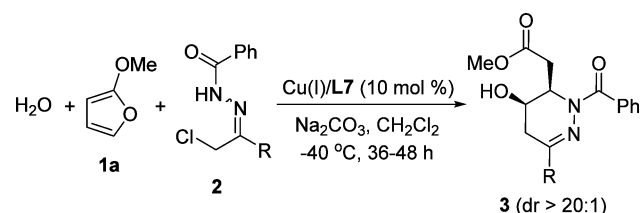
^aReaction conditions for entries 2–15: H₂O/1a/2a = 1.5:1.5:1, [1a] = 0.15 mmol/mL, CuBF₄ = Cu(MeCN)₄BF₄. For entry 1, the incidental water in the reaction system participated in the cascade reaction as a nucleophile. ^bIsolated yield. ^cEe was determined by HPLC analysis, and >20:1 dr was determined by the crude ¹H NMR.

identified as a three-component coupling adduct tetrahydropyridazine 3a bearing unexpectedly stable γ -hydroxy ester moiety. The structure was further validated by X-ray structure analysis of its analog. This intriguing result not only revealed that 2-methoxy

furan did serve as a dienophile in this IEDDA reaction with azoalkene but also indicated that incidental water in the reaction system must participate in the reaction as a nucleophile, attacking the C=C bond of intermediate 4 followed by subsequent tetrahydrofuran ring-opening of 5 to deliver the heterocyclic 3a (Scheme 2). The cascade IEDDA/nucleophilic addition/ring-opening reaction prompted a detailed study of asymmetric variant of this protocol. Inspired by the above observation, water (1.5 equiv) was added to facilitate the reaction in the subsequent investigation. We first screened different ferrocene-based chiral P,N-ligand L1–L3 in this novel multicomponent cascade reaction combined with the Lewis acid Cu(MeCN)₄BF₄, which exhibited high catalytic activity and excellent asymmetric induction in the previous indole-involved IEDDA reaction with azoalkene.⁷ The cascade reaction proceeded smoothly delivering the cycloadduct in accepted yields albeit with unsatisfied (up to 70%) enantioselectivity (Table 1, entries 2–4). To further improve the enantioselectivity, other commonly used chiral ligands were tested in the reaction. The chiral Cu(I)/PYBOX complex promoted the reactions only in moderate yield with pretty low enantioselectivity (entries 5 and 6). When the Cu(I)/(S,S)-tBu-BOX complex was chosen as the chiral catalyst, the unfavored background reaction was suppressed, efficiently affording the adduct 3a in 80% yield with 93% ee (entry 8). The Cu(II) metal source could also catalyze the reaction but did not provide a better result (entry 10). Further solvent effect study of this cycloaddition with Cu(I)/(S,S)-tBu-BOX identified CH₂Cl₂ as the best one in terms of yield and enantioselectivity, while toluene and THF exhibited a deleterious effect for this reaction (entries 8 and 11–13). Remarkably, the cascade reaction occurred readily at reduced temperature, and 98% ee with full conversion was achieved at –40 °C (entry 15).

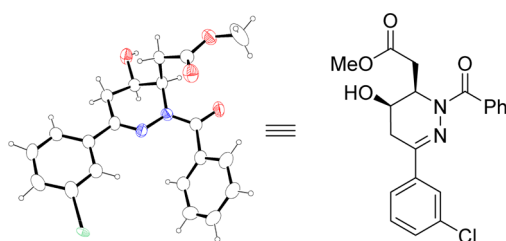
Using the optimized experimental condition, the substrate scope of the current cascade three-component reaction with respect to α -halogeno-N-benzoyl hydrazone was then examined. The representative results were tabulated in Table 2: Regardless of the electron property (electron-rich, -neutral, or -deficient) and the substituent pattern (*para*-, *meta*-, or *ortho*-position) on the aromatic ring of α -chloro or α -bromo N-benzoyl hydrazones, tetrahydropyridazines 3 containing free γ -hydroxyl ester moiety were obtained in good yield with high diastereoselectivity and excellent enantioselectivity (Table 2, entries 1–10). Fused-ring aromatic 2-naphthyl hydrazone 2k was also a suitable candidate for this cascade three-component transformation, affording the desired adduct 3k in good yield with 96% ee (entry 11). Alkyl-substituted hydrazone was not tolerated in this catalytic system, affording a racemic adduct probably due to the competitive background reaction. Remarkably, alkenyl-substituted cinnamyl hydrazone 2l was a viable heterodiene precursor in this cascade multicomponent reaction, leading to the corresponding adduct 3l in good yield with excellent stereoselectivity control (entry 12). The absolute configuration of the heterocyclic tetrahydropyridazine 3c was unequivocally determined as (3R,4R) by X-ray diffraction analysis, and those of other adducts were tentatively proposed on the basis of these results (Figure 1).

Encouraged by the excellent results achieved with various α -halo-N-benzoyl hydrazones as the heterodienes, we then investigated the cascade multicomponent reaction of an array of 2-alkoxy furans with respect to the scope of enophiles. As shown in Table 3, variation of the ether group from methoxy to ethoxy, propoxy, or isopropoxy has negligible influence on this reaction, and the desired cycloadducts were separated in good yield with similarly exclusive regioselectivity and high levels of

Table 2. Substrate Scope of Hydrazone 2 in Cu(I)-Catalyzed Asymmetric Multicomponent Cascade Reaction^a

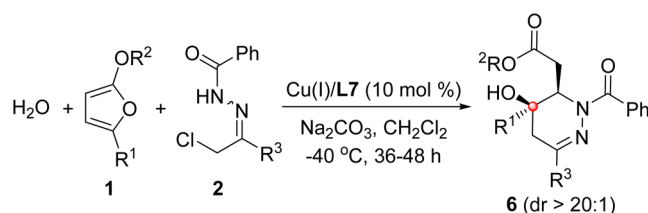
entry	R	prod.	yield ^b (%)	ee ^c (%)
1	Ph (2a)	3a	78	98
2	<i>p</i> -Br-C ₆ H ₄ (2b)	3b	77	93
3 ^d	<i>m</i> -Cl-C ₆ H ₄ (2c)	3c	65	94
4 ^d	<i>o</i> -Cl-C ₆ H ₄ (2d)	3d	55	93
5 ^d	<i>p</i> -F-C ₆ H ₄ (2e)	3e	75	91
6 ^d	<i>o</i> -F-C ₆ H ₄ (2f)	3f	63	97
7 ^d	<i>p</i> -Me-C ₆ H ₄ (2g)	3g	78	98
8 ^d	<i>m</i> -Me-C ₆ H ₄ (2h)	3h	69	97
9 ^d	<i>o</i> -Me-C ₆ H ₄ (2i)	3i	60	90
10 ^d	<i>m</i> -OMe-C ₆ H ₄ (2j)	3j	75	98
11 ^d	2-naphthyl (2k)	3k	70	96
12	PhCH=CH (2l)	3l	68	92

^aReaction conditions: H₂O/1a/2 = 1.5:1.5:1, [1a] = 0.15 mmol/mL. ^bIsolated yield. ^cDr was determined by the crude ¹H NMR, and ee was determined by HPLC analysis. ^dUsing α -bromo *N*-benzoyl hydrazone.

Figure 1. X-ray structure of (3*R*,4*R*)-3c.

diastereo-/enantioselectivity (Table 3, entries 1–6). Subsequently, we turned our attention to the more challenging 5-substituted 2-methoxy furans as dienophiles, leading to the efficient construction of an O-substituted quaternary stereogenic center that is adjacent to a tertiary N-substituted stereogenic center within the heterocyclic product. This category of transformation has received scarce attention even in non-asymmetric examples, probably due to the strongly steric hindrance. To our delight, 5-alkyl-substituted 2-methoxy furans worked well in this transformation. The length of the tested linear alkyl group had little effect on the reactivity and stereoselectivity of this reaction, and 2-methoxy furans with primary ethyl and *n*-pentyl group at 5-position afforded high reactivity and excellent stereoselectivity (entries 7–10). Sterically bulky 5-isobutyl 2-methoxy furan also proved to be a viable dienophile, providing the corresponding heterocycle 6k in good yield and acceptable enantioselectivity (entry 11).

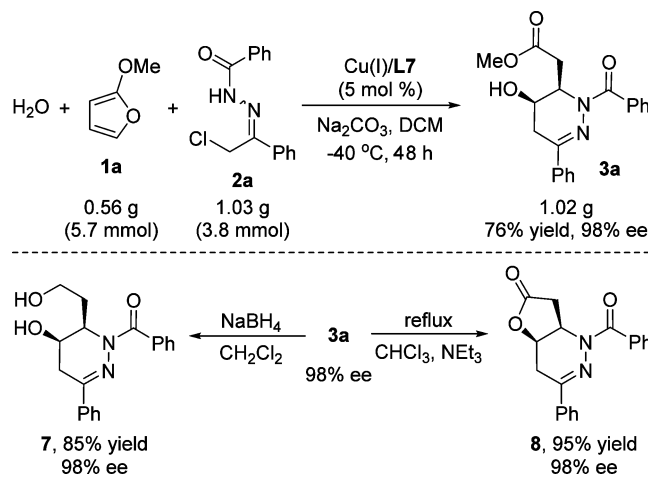
To further probe the potential scalability of this newly developed methodology, a gram scale synthesis of enantio-enriched tetrahydropyridazine was carried out with 5 mol % catalyst loading. The multicomponent reaction proceeded smoothly delivering 3a in synthetically acceptable yield and 98% ee (Scheme 3). Upon treatment with NaBH₄, the ester moiety in 3a was reduced successfully to afford the chiral diol 7. The lactonization of γ -hydroxyl ester moiety can be easily realized

Table 3. Substrate Scope of 2-Alkoxy Furans 1 in the Cu(I)-Catalyzed Asymmetric Multicomponent Cascade Reaction^a

entry	1			prod.	yield ^b (%)	ee ^c (%)	
	R ¹	R ²	R ³				
1	H	1b	Et	Ph	6a	70	98
2 ^d	H	1b	Et	<i>p</i> -Me-C ₆ H ₄	6b	75	97
3 ^d	H	1b	Et	<i>m</i> -MeO-C ₆ H ₄	6c	75	96
4	H	1b	Et	<i>p</i> -Br-C ₆ H ₄	6d	73	97
5	H	1c	Pr	Ph	6e	76	95
6	H	1d	<i>i</i> -Pr	Ph	6f	72	91
7	C ₂ H ₅	1e	Me	Ph	6g	68	94
8	<i>n</i> -C ₅ H ₁₁	1f	Me	Ph	6h	70	92
9 ^d	<i>n</i> -C ₅ H ₁₁	1f	Me	<i>p</i> -Me-C ₆ H ₄	6i	65	93
10	<i>n</i> -C ₅ H ₁₁	1f	Me	<i>p</i> -Br-C ₆ H ₄	6j	63	94
11	<i>i</i> -Bu	1g	Me	Ph	6k	64	84

^aReaction conditions: H₂O/1/2 = 1.5:1.5:1, [1] = 0.15 mmol/mL. ^bIsolated yield. ^cDr was determined by the crude ¹H NMR, and ee was determined by HPLC analysis. ^dUsing α -bromo *N*-benzoyl hydrazone.

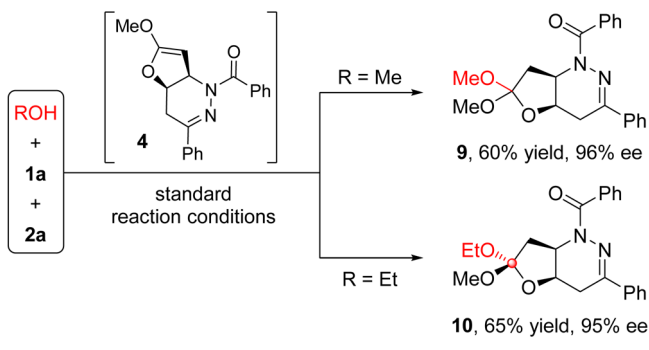
Scheme 3. Scale-Up of Catalytic Asymmetric Cascade Three-Component Reaction and Synthetic Transformation



under reflux in CHCl₃ in good yield without loss of enantioselectivity, which provides a facile and more atom-economy means for the direct and stereoselective construction of biologically important fused butyrolacton, merely sacrificing a methyl group compared with our previous work.¹⁵

To gain some light on the mechanism of this three-component reaction, several experiments were subsequently performed to validate the key intermediate 4. The attempts to isolate the intermediate failed, probably due to the instability of the enol ether 4.¹⁶ Then, other nucleophiles instead of H₂O were employed under the standard reaction conditions to trap the active intermediate (Scheme 4): Dimethyl ortho ester 9 was generated in 60% yield and 96% ee with methanol as the third partner. Intriguingly, the mixed methyl and ethyl ortho ester 10 was isolated in good yield and excellent enantioselectivity with a

Scheme 4. Experiment To Confirm the Intermediate 4 with Other Trapping Agents (MeOH or EtOH) as the Nucleophile Instead of H₂O



high diastereoselective manner employing ethanol as the nucleophile (see SI for details), which not only confirmed the key intermediate but also indicated that the diastereoselectivity of the nucleophilic addition is exclusively controlled by the stereoconfiguration generated in the first IEDDA step.

In conclusion, we have developed a novel copper-catalyzed asymmetric three-component cascade IEDDA/nucleophilic addition/ring-opening reaction involving 2-methoxyfurans, azoalkene, and water. To our knowledge, this is the first example of utilizing furans as dienophiles in a catalytic asymmetric Diels–Alder reaction. A wide variety of tetrahydropyridazines containing stable γ -hydroxyl ester moiety were obtained in generally good to high yield with exclusive regioselectivity and excellent stereoselectivity. Further applications of this multi-component cascade reaction in organic synthesis and elucidating the origin of the asymmetric inductions and the detailed mechanism are currently underway in our lab.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01008.

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Notes

The authors declare no competing financial interest.

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- (16) When 2-methyl furan **11** was used as dienophile under standard reaction conditions, the expected IEDDA product **12** was isolated as a stable compound in good yield and high enantioselectivity.

