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Iron-catalyzed cascade C-C/C-O bond formation of 2,4-dienals with donor-acceptor cyclopropanes: access to functionalized hexahydrocyclopentapyrans†

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Iron-catalyzed cascade C-C and C-O bond formation of 2,4-dienals with donor-acceptor cyclopropanes (DACs) has been developed to furnish hexahydrocyclopentapyrans. Optically active DACs can be coupled stereospecifically (>97% ee). Chirality transfer, use of ironcatalysis and substrate scope are the salient practical features.

Pyrans are the structural constituents of a broad spectrum of natural products, exhibiting interesting biological and medicinal properties (Fig. 1). The development of effective synthetic methods for the construction of these structural scaffolds would thus be valuable.2 Cascade C-C and C-heteroatom bond formation represents a powerful synthetic tool for the conversion of simple substrates into complex molecules with structural diversity.³ In this context, $\alpha, \beta, \gamma, \delta$ -unsaturated aldehydes allow the construction of C-C and C-O bonds, leaving the unsaturated C=C for further modifications.⁴ Precisely, 2,4-dienals in the presence of Lewis acid can convert into an oxyallyl cation, which can be trapped by suitable carbon or heteroatom nucleophiles in an interrupted iso-Nazarov process to construct valuable organic parallels (Scheme 1a). In addition, 4π -conrotatory cyclization of 2,4-dienals may give 1,3-dipolar species that can be explored in a cascade fashion as an effective 1,3-synthon. Despite these advances, selective coupling at the C2-C3 backbone is quite challenging due to the competing 1,2- and 1,4-additions in 2,4dienal.⁶ Furthermore, DAC has emerged as a versatile building block for the construction of five-membered cyclic scaffolds.^{7,8}

The cycloaddition of aldehydes with DAC has been achieved using Sn(OTf)2-catalysis to provide tetrahydrofurans.8c Later, a stoichiometric amount of FeCl3 was used for the reaction of heterocumulenes with DACs to provide 2-pyrrolidines, where the chirality transfer was not consistently observed. 8d Recently,

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the coupling of ketenes with DAC has been shown utilizing InBr₃-EtAlCl₂ dual catalysis to yield cyclopentanones. 8f Herein, we present an iron-catalyzed stereospecific cascade C-C and C-O bond formation of 2,4-dienal with DAC to give functionalized hexahydrocyclopentapyran derivatives (Scheme 1b). Excellent chirality transfer, use of iron-catalysis, cascade C-C and C-O bond formation for the construction of the bicyclic ethers and substrate scope are the important practical features.

First, we commenced the optimization studies with dimethyl 2-phenylcyclopropane-1,1-dicarboxylate 1a and 4-phenylhepta-2,4-dienal 2a as the model substrates (Table 1 and Table S1, ESI†). To our delight, the coupling occurred to furnish the cyclic scaffolds 3a and 4a in 31% and 27% yields, respectively, when the substrates were stirred with 10 mol% FeCl3 in 1,2dichloroethane for 4 h at room temperature. Subsequent screening of the solvent, quantity (20 mol%) of Lewis acid and temperature led to the production of 3a in 78% yield along with a trace amount of 4a in toluene at 60 °C, whereas THF, CH₃CN and HFIP afforded a mixture of 3a and 4a in moderate yields. Lewis acids such as Sc(OTf)3, Yb(OTf)3, Cu(OTf)2, Zn(OTf)2 and CoCl₂ yielded inferior outcomes. A control experiment confirmed that in the absence of the Lewis acid, the formation of the cycloadduct was unsuccessful.

Having optimized the reaction conditions, the scope of the procedure was examined, engaging a series of substituted DACs 1b-t with 2a as the standard substrate (Scheme 2). The 2-tolyl DAC 1b underwent reaction to furnish 3b in 72% yield, whereas 1c with an electron withdrawing 3-CF₃ substituent delivered 3c in 76% yield. Furthermore, the 4-substituted DACs viz., methyl

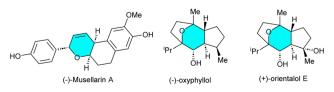
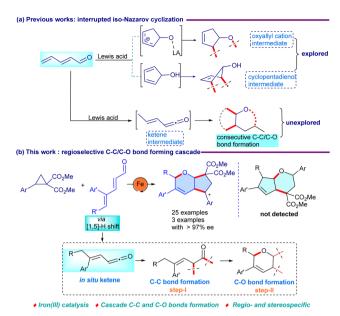


Fig. 1 Examples of biologically important pyran scaffolds

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Scheme 1 Cascade cyclization of dienals with D-A cyclopropane.

Table 1 Optimization of the reaction conditions^{ab}

Ph CO ₂ Me	+ Ph 0	Lewis acid solvent, temp time Ph	* Et Ph
1a	2a	3a	4a

Entry		Solvent	Yield ^b		
	Lewis acid		3a	4a	
1	FeCl ₃	(CH ₂ Cl) ₂	31	27	
2^c	$FeCl_3$	Toluene	45	52	
3^d	$FeCl_3$	Toluene	57	22	
4^e	$FeCl_3$	Toluene	78	Trace	
5^f	$FeCl_3$	Toluene	72	Trace	
6	_	Toluene	n.d.	n.d.	

^a Reaction conditions: 1a (0.1 mmol), 2a (0.12 mmol), Lewis acid (10 mol%), solvent (1.5 mL), 4 h, room temperature. ^b Isolated yield. ^c FeCl₃ (0.5 equiv). ^d FeCl₃ (20 mol%). ^e FeCl₃ (20 mol%), 60 °C, 2 h. f FeCl₃ (20 mol%), 80 °C, 2 h.n.d. = not detected.

1d, fluoro 1e, bromo 1f, tert-butyl 1g, nitro 1h and cyano 1i groups reacted to furnish the target scaffolds 3d-i in 64-78% yields, which suggested that electron donating and withdrawing groups were well compatible. In addition, 2-pyrenyl 1j and thienyl 1k substrates conveyed the target products 3j and 3k (X-ray, CCDC = 2298985, see ESI†) in 73% and 77% yields, respectively. Under these conditions, the ester functionality of the DACs was varied, and the linear diethyl variant 1l gave 3l in 72% yield, whereas bulkier iso-propyl 1m and benzyl 1n gave no desired cycloadduct due to the steric effect. Similarly, cyclohexyl bearing 1m was an unsuccessful substrate, which suggests that the electrophilicity of the cyclopropyl carbon is crucial for the coupling. Also, no cycloaddition was observed when the phenyl ring of DAC was altered with a heterocyclic 4-pyridyl 1p, indicating the complexation of the catalyst with

Scheme 2 Substrate scope of D-A cyclopropanes. a Reaction conditions: 1b-t (0.1 mmol), 2a (0.12 mmol), FeCl₃ (20 mol%), toluene (1.5 mL), 60 °C, 2 h. b Isolated yield. n.d. = not detected.

the active N-atom of pyridyl. However, the natural productderived DACs such as (\pm) - α -tocopherol **1q** and cholesterol **1r** successfully reacted to produce the scaffolds 3q and 3r in 77% and 76% yields, respectively. Moreover, terpenoid derived DACs 1s and 1t underwent coupling to afford the bicyclic ethers 3s (d.r. 1:0.45) and 3t (d.r. 1:0.35) in 80% and 81% yields, respectively.

Next, the diversification of 2,4-dienals 2b-i was investigated utilizing dimethyl 2-phenylcyclopropane-1,1-dicarboxylate 1a as the standard substrate (Scheme 3). The presence of aliphatic substituents at the C-5 position of the 2,4-dienals, such as methyl 2b, iso-propyl 2c and iso-butyl 2d, led to the production of the target cyclic ethers 3u-w in 61-76% yields. In addition, aliphatic trans,trans-2,4-hexadienal 2e and trans,trans-2,4nonadienal 2f were amenable, furnishing 3x and 3y in 83% and 86% yields, respectively. Intriguingly, 2-naphthyl substituted 2g installed at the C-5 position of the 2,4-dienal performed excellently delivering 3z in 78% yield, whereas the thiophenyl 2h yielded 3aa in a trace amount. Furthermore, a

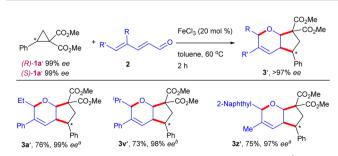
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Scheme 3 Substrate scope of 2,4-dienals. a,b a Reaction conditions: 1a (0.1 mmol), **2b-i** (0.12 mmol), FeCl₃ (20 mol%), toluene (1.5 mL), 60 °C, 2 h. ^bIsolated yield. n.d. = not detected.

biphenyl derivative 2i failed to give the desired cycloadduct 3ab. This might be ascribed to the restriction in H-shift at the C-5 position by the large terminal biphenyl group, which hinders all cis C-C double bond formation that plays a key role in the reaction.

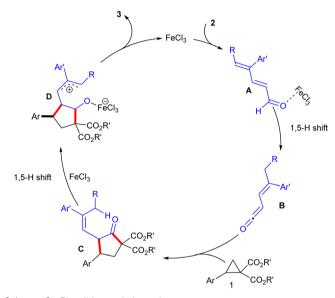
To get an insight into the reaction pathway, the coupling of the optically pure DACs (R)-1a' and (S)-1a' was examined as the representative examples (Scheme 4). The coupling of dienal 2a with (R)-1a' produced 3a' in > 99% ee, whereas 2c and 2g underwent coupling with (S)-1a' and (R)-1a' to yield 3v' and 3z' in 98% and 97% ee, respectively. These results suggest that the coupling is regio- and stereospecific with excellent chirality transfer. In addition, the coupling of 1a and 2a occurred efficiently in the presence of the radical scavengers, 2,2,6,6-tetra-methylpiperidine-1-oxyl (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT), which suggested that the radical pathway might not be involved (Scheme 5). Thus, FeCl₃-catalyzed⁹ [1,5]-H shift^{10a-c} of 2,4-dienal 2 may deliver the ketene B, which can couple with DAC 1 stereospecifically to furnish the cyclic scaffold C (Scheme 6).8 In another [1,5]-H shift, the allylic intermediate D may undergo a nucleophilic attack on the C-5 center to give the target bicyclic ether 3. 10d

To demonstrate the synthetic utility, a scale-up of the reaction was investigated using 3 mmol of 1a with 2a as the representative



Scheme 4 Stereospecificity experiments. ${}^{a}(R)$ -1 ${\bf 1a}'$ is used. ${}^{b}(S)$ -1 ${\bf 1a}'$ is

Preliminary mechanistic investigation.



Plausible catalytic cycle.

substrate to produce 3a in 62% yield (Scheme 7a). In addition, Krapcho decarboxylation of 3a using LiCl afforded the monoester 6 in 67% yield (d.r. 1:0.25) (Scheme 7b).

In summary, we have described the iron-catalyzed cascade C-C and C-O bond formation of 2,4-dienals with DACs to furnish functionalized bicyclic cyclopentapyran derivatives. The use of iron-catalysis, excellent chirality transfer and substrate scope are the important practical features.

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Scale-up and synthetic transformation.

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Conflicts of interest

There are no conflicts to declare.

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