ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2024, **60**, 2788

Received 25th December 2023,
Accepted 8th February 2024

DOI: 10.1039/d3cc06261a

rsc.li/chemcomm

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 iron-catalysis 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).[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, α,β,γ,δ-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).[5] 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 2,4-dienal.[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 $FeCl_3$ was used for the reaction of heterocumulenes with DACs to provide 2-pyrrolidines, where the chirality transfer was not consistently observed.[8d] Recently, the coupling of ketenes with DAC has been shown utilizing $InBr_3$–$EtAlCl_2$ 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% $FeCl_3$ in 1,2-dichloroethane 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, CH_3CN 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 $CoCl_2$ 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-CF_3 substituent delivered **3c** in 76% yield. Furthermore, the 4-substituted DACs *viz.*, methyl

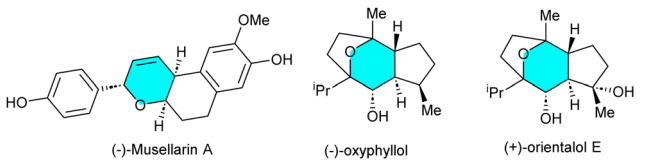

Fig. 1 Examples of biologically important pyran scaffolds.

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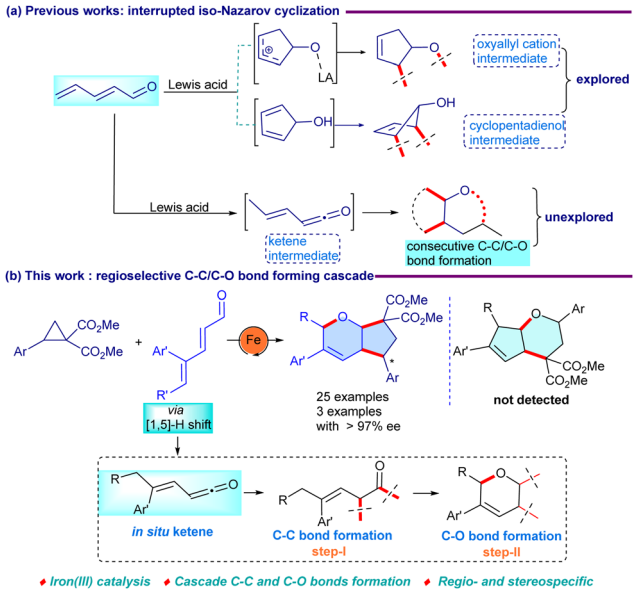
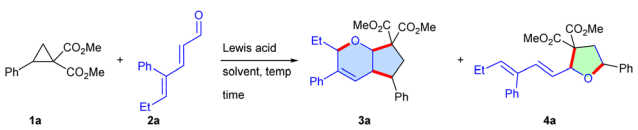
† Electronic supplementary information (ESI) available. CCDC 2298985. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3cc06261a



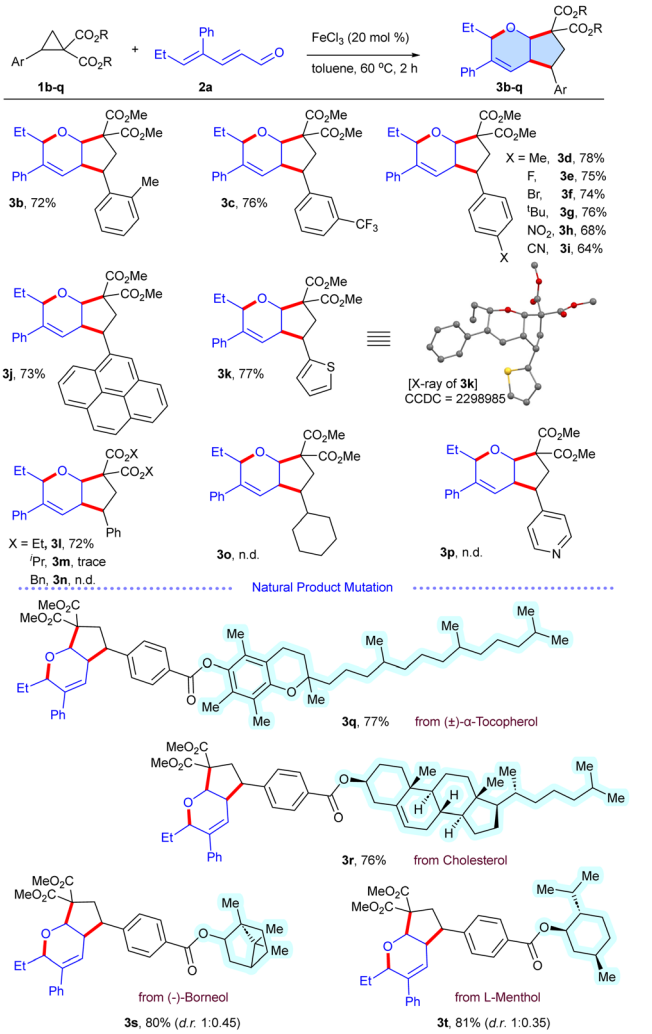
Scheme 1 Cascade cyclization of dienals with D–A cyclopropane.

Table 1 Optimization of the reaction conditions[ab]



Entry	Lewis acid	Solvent	Yield[b] 3a	4a
1	$FeCl_3$	$(CH_2Cl)_2$	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.

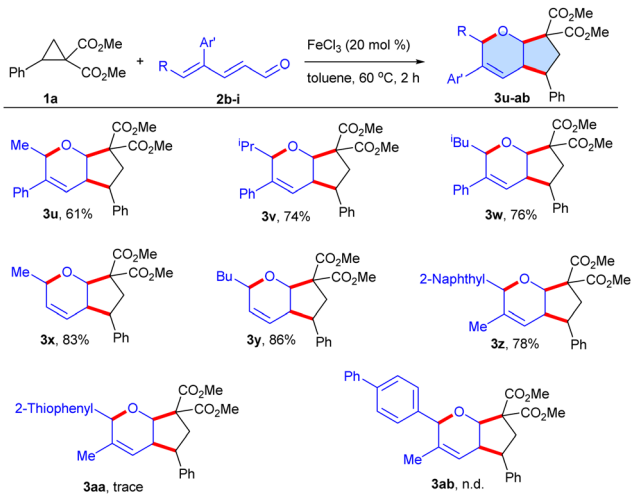
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), Lewis acid (10 mol%), solvent (1.5 mL), 4 h, room temperature. [b] Isolated yield. [c] $FeCl_3$ (0.5 equiv). [d] $FeCl_3$ (20 mol%). [e] $FeCl_3$ (20 mol%), 60 °C, 2 h. [f] $FeCl_3$ (20 mol%), 80 °C, 2 h.n.d. = not detected.



Scheme 2 Substrate scope of D–A cyclopropanes.[a,b] [a] Reaction conditions: **1b–t** (0.1 mmol), **2a** (0.12 mmol), $FeCl_3$ (20 mol%), toluene (1.5 mL), 60 °C, 2 h. [b] Isolated yield. 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 the active N-atom of pyridyl. However, the natural product-derived DACs such as (±)-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*-2,4-nonadienal **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

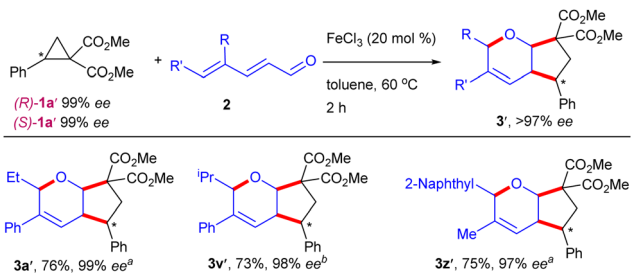


Scheme 3 Substrate scope of 2,4-dienals.[a,b] [a] Reaction conditions: **1a** (0.1 mmol), **2b–i** (0.12 mmol), $FeCl_3$ (20 mol%), toluene (1.5 mL), 60 °C, 2 h. [b] Isolated yield. n.d. = not detected.

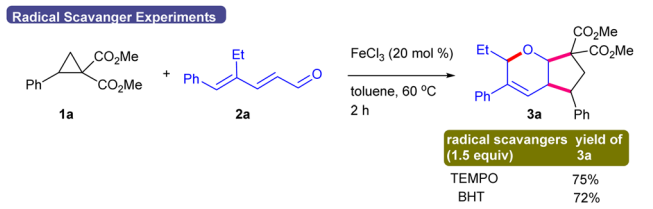
biphenyl derivative **2i** failed to give the desired cycloadduct **3ab**. This might be ascribed to the restriction in H-shift at the C-5 position by the large terminal biphenyl group, which hinders all *cis* C–C double bond formation that plays a key role in the reaction.

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, $FeCl_3$-catalyzed[9] [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).[8f] 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]

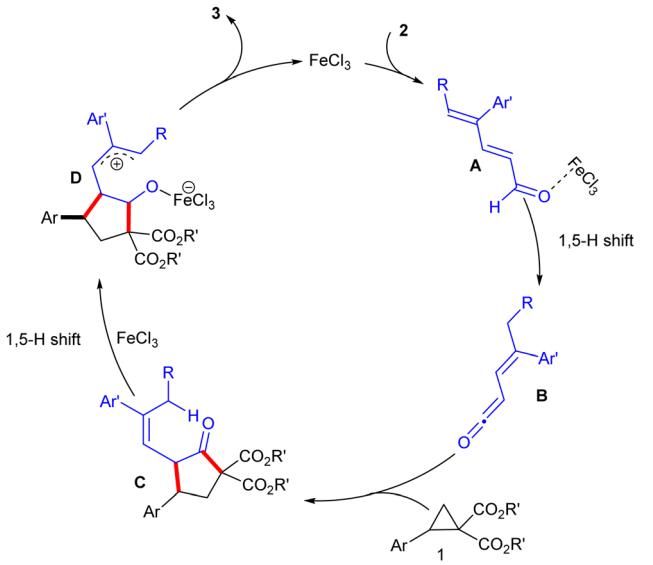
To demonstrate the synthetic utility, a scale-up of the reaction was investigated using 3 mmol of **1a** with **2a** as the representative



Scheme 4 Stereospecificity experiments. [a] (*R*)-**1a′** is used. [b] (*S*)-**1a′** is used.



Scheme 5 Preliminary mechanistic investigation.

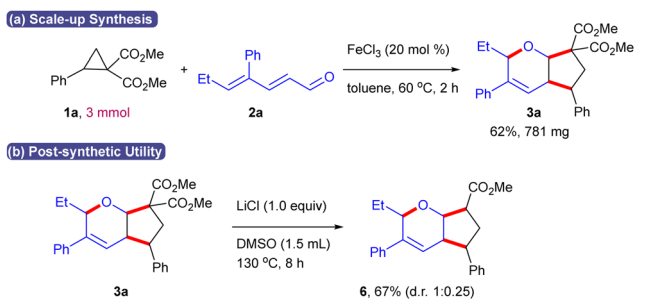


Scheme 6 Plausible catalytic cycle.

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.

We thank CSIR (02(0458)/21/EMR-II) for the financial support and CIF and NECBH (BT/CoE/34/SP28408/2018), and DST-FIST (SR/FST/CS-II/2017/23c) for NMR, mass and X-ray analyses. M. M. acknowledges the CSIR for the fellowship and T. P.



Scheme 7 Scale-up and synthetic transformation.

thanks SERB for the J. C. Bose Fellowship (JCB/2022/000037). We also thank Mr Sandeep Kumar for solving the X-ray crystallography.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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