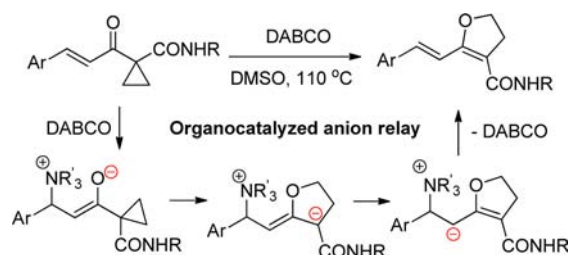


Organocatalyzed Anion Relay Leading
to Functionalized 2,3-DihydrofuransMengru Li,[†] Shaoxia Lin,[†] Zhiyong Dong,[†] Xintong Zhang,[‡] Fushun Liang,^{*,†,‡} and
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ABSTRACT



A DABCO-mediated organocatalyzed anion relay cascade based on 1-cinnamoylcyclopropanecarboxamides has been developed and applied in the construction of 2,3-dihydrofurans with the original alkene and amide functionalities intact. In the aza-oxy-carbanion relay process, DABCO provides both the electron source and sink. The enolate anion-triggered ring opening of the cyclopropane is ascribed to the key step in the anion relay cascade.

The dihydrofuran ring system is widely found in the molecular skeleton of naturally occurring and biologically active substances (e.g., clerodin, azadirachtin, and austocystin A).^{1,2} 2,3-Dihydrofurans are also versatile building blocks in organic transformation, e.g. in the synthesis of highly functionalized tetrahydrofurans with high

stereoselectivity.³ To date, a few synthetic methods have been documented toward 2,3-dihydrofurans, such as [3 + 2] annulations of 1,3-dicarbonyl compounds with appropriate olefins,^{4,5} cyclization of α -ketosulfides of benzothiazole or α -ketopolyfluoroalkanesulfones with

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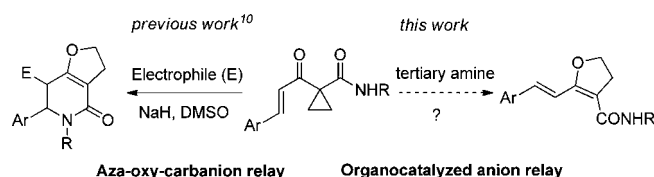
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aldehydes,⁶ and the transition-metal-catalyzed reactions of α,β -unsaturated enones, vinyl ethers, or aldehydes with varied diazo compounds.⁷ Dihydrofurans can also be obtained by the ring enlargement of suitably substituted cyclopropanes, catalyzed by Lewis acids, metals, or strong oxidizing agents,⁸ which has become a complementary but powerful approach.

Anion relay chemistry (ARC) has been demonstrated as an effective protocol for diversity-oriented construction of natural and unnatural molecules of higher complexity, and tremendous progress has been made.⁹ The group of Smith III has presented a variety of elegant Brook-rearrangement-based anion relay reactions over the past decade. Recently, we reported a Michael addition-initiated aza-oxy-carbanion relay by the reaction of 1-cinnamoylcyclopropanecarboxamides with selected electrophiles (Scheme 1, left pathway).¹⁰ In continuation of this work, we wish to explore the possibility of an organocatalyzed anion relay cascade (Scheme 1, right pathway).¹¹ As a result, a new concept of an organocatalyzed anion relay cascade is established and has been applied in the construction of functionalized 2,3-dihydrofurans.

Scheme 1



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Initially, the model reaction of 1-cinnamoyl-*N*-benzylcyclopropanecarboxamide **1a** was examined under basic conditions (Table 1).¹² No reaction occurred by the utilization of Et₃N as the base in DMSO at 110 °C, and the substrate may be retractable quantitatively (entry 1). In the reaction with DBU (1.2 equiv) as the base, substrate **1a** decomposed completely within 0.5 h (entry 2). To our delight, DABCO (1.0 equiv) gave the expected (*E*)-*N*-benzyl-2-(4-methylstyryl)-4,5-dihydrofuran-3-carboxamide **2a** in 90% yield under otherwise identical conditions (entry 3).¹³ The amount of DABCO could be reduced to be 0.2 equiv without significantly sacrificing the yield (entry 4). A further decrease of the amount of DABCO to 0.1 equiv or lowering the temperature to 90 °C may lead to dramatically decreased yields (entries 5 and 6). Other solvents, such as DMF, toluene, DCE, MeCN, and THF proved to be inferior to DMSO (entries 7–11).

Table 1. Optimization of the Reaction Conditions^a

entry	base (equiv)	solvent	<i>t</i> (°C)	time (h)	2a yield (%) ^b
1	Et ₃ N (1.0)	DMSO	110	12	n.r.
2	DBU (1.2)	DMSO	110	0.5	0
3	DABCO (1.0)	DMSO	110	3	90
4	DABCO (0.2)	DMSO	110	3	89
5	DABCO (0.1)	DMSO	110	4	67
6	DABCO (0.2)	DMSO	90	3.5	45
7	DABCO (0.2)	DMF	110	1	76
8	DABCO (0.2)	toluene	110	12	5
9	DABCO (0.2)	DCE	reflux	12	0
10	DABCO (0.2)	MeCN	reflux	12	0
11	DABCO (0.2)	THF	reflux	12	0

^a Reactions were carried out with **1a** (1.0 mmol) and the base in solvent (4.0 mL). ^b Isolated yield.

Under the optimized conditions (Table 1, entry 4), a range of reactions were carried out with various substrates **1** (Table 2). The substituents R¹ on substrates **1** may be

(12) In the cases of tertiary amine as the base, the intramolecular aza-Michael addition is inhibited. See: (a) Reference 10. (b) Li, Y.; Xu, X.; Tan, J.; Liao, P.; Zhang, J.; Liu, Q. *Org. Lett.* **2010**, *12*, 244. (c) Liu, J.; Lin, S.; Ding, H.; Wei, Y.; Liang, F. *Tetrahedron Lett.* **2010**, *51*, 6349.

(13) The C=C double bond in all the products is in (*E*)-conformation, which were assigned based on the ¹H NMR spectra and single-crystal data. Also refer to: Sonye, J. P.; Koide, K. *Org. Lett.* **2006**, *8*, 199.

Table 2. DABCO-Catalyzed Anion Relay Leading to Functionalized 2,3-Dihydrofurans^a



entry	1	R ¹	R ²	R ³	2	yield (%) ^b
1	1b	4-MeOC ₆ H ₄	Bn	H	2b	76
2	1c	3,4-OCH ₂ OC ₆ H ₃	Bn	H	2c	86
3	1d	C ₆ H ₅	Bn	H	2d	94
4	1e	2-ClC ₆ H ₄	Bn	H	2e	90
5	1f	4-ClC ₆ H ₄	Bn	H	2f	91
6	1g	3-NO ₂ C ₆ H ₄	Bn	H	2g	92
7	1h	4-pyridyl	Bn	H	2h	43
8	1i	2-thienyl	Bn	H	2i	86
9	1j	2-furyl	Bn	H	2j	84
10	1k	<i>t</i> -Bu	Bn	H	2k	0
11	1l	4-MeC ₆ H ₄	4-	H	2l	89
12	1m	4-MeC ₆ H ₄	MeC ₆ H ₄ CH ₂ -2-	H	2m	92
13 ^c	1n	4-MeC ₆ H ₄	Ph	H	2n	83
14 ^c	1o	4-MeC ₆ H ₄	4-MeOC ₆ H ₄	H	2o	82
15 ^c	1p	4-MeC ₆ H ₄	4-ClC ₆ H ₄	H	2p	86
16	1q	4-MeC ₆ H ₄	Bn	Me	2q	84

^a Reactions were carried out on a 1.0 mmol scale in DMSO (4.0 mL) for 1–5 h with DABCO (0.2 equiv) as the catalyst unless otherwise noted. ^b Yield of isolated product. ^c 1.2 equiv of DABCO was used.

either electron-rich or -deficient aryl groups (entries 1–6), and heteroaryls such as the 4-pyridyl, 2-thienyl, and 2-furyl group (entries 7–9). However, when R¹ equals an alkyl group such as *tert*-butyl, the reaction was inert, presumably due to the steric effect (entry 10).¹⁴ The scope of the R² group on the N-atom of the amide group was also investigated. Substituent R² may be either alkyls (entries 1–12) or aryls (entries 13–15). It should be noted that 1.2 equiv of DABCO was used in the reactions with *N*-aryl substituents.¹⁵ Substrate **1q** containing a methyl group on the cyclopropyl ring afforded the trisubstituted 2,3-dihydrofuran **2q** in 84% yield (entry 16). The structure of **2n** was confirmed by X-ray single crystal diffraction (Figure 1).¹⁶ All the above results indicated the efficiency of the organocatalyzed anion relay cascade.

In the following work, we further extended the scope of the organocatalyzed anion relay reaction by varying the

(14) Substrates **1** with other types of alkyl substituents such as methyl, *n*-butyl, etc. on the β-position of the unsaturated enone moiety were not easy to prepare.

(15) The *N*-aryl amides display relatively stronger acidity than the corresponding *N*-alkyl counterparts, and the *N*-aryl amide functionality might consume a certain amount of DABCO.

(16) CCDC 946390 (**2n**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information.

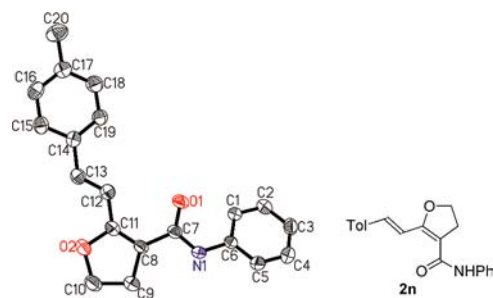
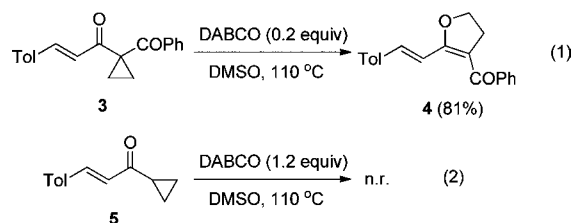


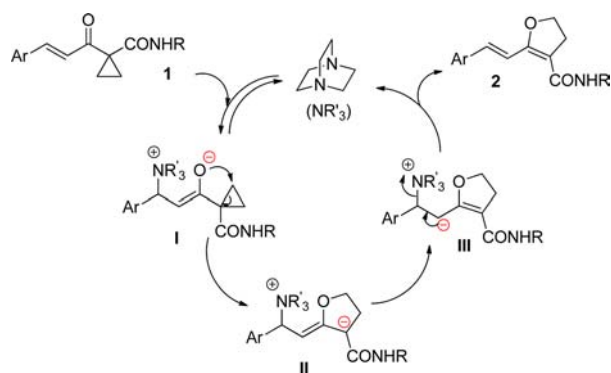
Figure 1. ORTEP drawing of **2n**.

amide group to other types of functionalities (Scheme 2). The reaction of pent-4-ene-1,3-dione **3** in the presence of 0.2 equiv of DABCO proceeded smoothly, affording the desired product, (*E*)-(2-(4-methylstyryl)-4,5-dihydrofuran-3-yl)(phenyl)methanone (**4**), in 81% yield (eq 1). However, the reaction of 1-cyclopropyl-3-(*p*-tolyl)prop-2-en-1-one **5** did not occur, with the substrate intact (eq 2).

Scheme 2. Further Scope Extension



Scheme 3. Proposed Organocatalyzed Anion Relay Mechanism



On the basis of all the results described above, along with our previous work,¹⁰ an organocatalyzed anion relay mechanism for the formation of functionalized 2,3-dihydrofuran was proposed, as depicted in Scheme 3.

(17) For a minireview on conjugate additions-triggered tandem transformation, see: (a) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. For a recent review on organocatalytic asymmetric aza-Michael addition, see: (b) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058.

Initially, intermolecular Michael addition by DABCO generates the enolate anion **I**.¹⁷ Then, an oxyanion-triggered 1,3-sigmatropic carbon rearrangement takes place, giving the tertiary carbanion **II**, which is stabilized by the adjacent C=C double bond and the electron-withdrawing amide group. Exocyclic double-bond migration gives rise to the secondary carbanion **III**. A rapid elimination of DABCO (to complete the catalytic cycle) delivers the final product **2**. In the reaction, DABCO tunes the reactivity as a chemical switch and causes the ring opening of cyclopropane to occur. From the electron point of view, DABCO provides both an electron source and sink.

In summary, an organocatalyzed anion relay chemistry has been developed based on doubly electron-withdrawing

group activated cyclopropanes. The tertiary amine-mediated anion relay cascade not only provides a novel method for the ring opening of the cyclopropanes^{8,18} but also an efficient strategy toward highly functionalized 2,3-dihydrofurans. Further work on anion relay cascades and the application in the construction of various fused heterocycles is in progress.

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Supporting Information Available. Experimental details and characterization for all new compounds and crystal structure data (CIF file). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.