Organic LETTERS

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Organocatalytic Cloke–Wilson Rearrangement: DABCO-Catalyzed Ring Expansion of Cyclopropyl Ketones to 2,3-Dihydrofurans

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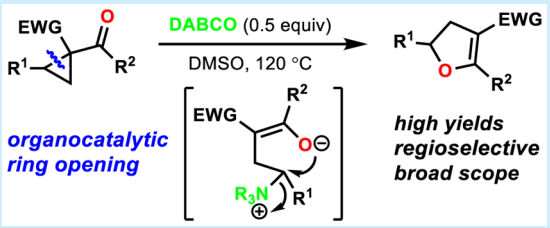
Supporting Information

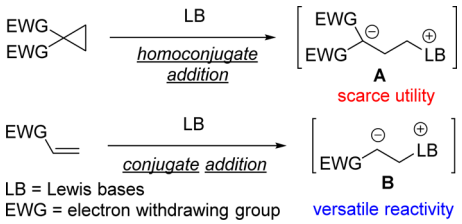
ABSTRACT: An organocatalytic Cloke–Wilson rearrangement of cyclopropyl ketones to 2,3-dihydrofurans is exploited utilizing the homoconjugate addition process. With 1,4-diazabicyclo[2.2.2]octane as the catalyst, the rearrangement in DMSO at 120 °C proceeded in generally high yields, exclusive regioselectivity, and a broad substrate scope. An examination of the mechanism including stereochemical analysis and intermediate isolation supports an S_N1-type ring opening of the mechanism.



Cyclopropanes[1] have been used as versatile building blocks in organic synthesis due to their remarkable reactivity that originates from the intrinsic ring strain. Lewis acid and transition-metal catalysis have been extensively applied to the ring opening of cyclopropanes;[1l,m] however, organocatalytic strategies for the activation of cyclopropanes are less well developed. Extant approaches include N-heterocyclic carbene (NHC) catalysis,[2] urea catalysis,[3] iminium activations,[4] and enamine activations.[5] Whereas these tactics mostly rely on a specific substituent pattern on the cyclopropane ring, the activation of general electrophilic cyclopropanes under Lewis base catalysis by means of direct nucleophilic ring opening remains an underutilized approach.[6]

As early as 1975, Danishefsky and co-workers[7] reported the homoconjugate addition of electrophilic cyclopropanes with Lewis bases (e.g., piperidine, pyridine) to afford zwitterionic adducts **A** (Scheme 1); however, this type of species has been

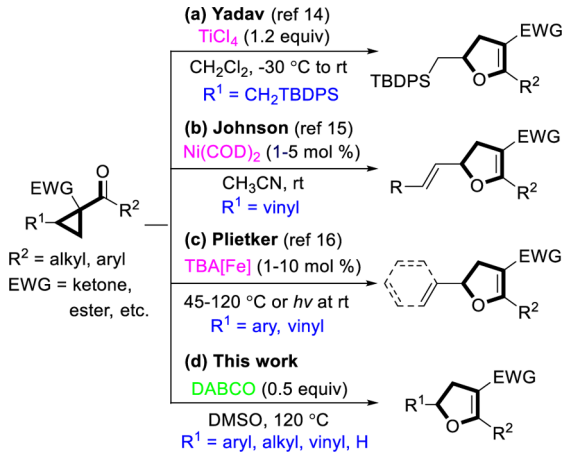
Scheme 1. Zwitterions Generated from Lewis Bases and Electrophilic Cyclopropanes or Alkenes



rarely engaged in reaction discovery.[6,8] This stands in striking contrast with the homologous intermediates **B** generated from the conjugate addition of Lewis bases to electrophilic alkenes, by which a myriad of transformations have been engendered.[9] Therefore, it would be rewarding to explore transformations utilizing the homoconjugate addition process.

Ring-enlargement of cyclopropanes constitutes a powerful tool for accessing structurally diverse carbo- and heterocycles.[1n] Analogous to the vinylcyclopropane–cyclopentene (VCP–CP) rearrangement,[10] the isomerization of cyclopropyl imines, aldehydes, and ketones, namely the Cloke–Wilson rearrangement,[11] delivers heterocycles of 2-pyrrolines and 2,3-dihydrofurans, respectively. As this transformation is substrate-dependent and often requires a high temperature,[12] considerable efforts have been aimed at developing mild and general conditions.[13] Notably, Yadav and co-workers[14] in 2001 disclosed $TiCl_4$-mediated silicon-assisted rearrangement of (*tert*-butyldiphenylsilyl)methylcyclopropyl ketones at a low temperature (Scheme 2, eq a). In 2006, the Johnson group[15] realized mild Ni-catalyzed rearrangement of vinyl cyclopropyl

Scheme 2. Cloke–Wilson Rearrangement under Mild Conditions



Received: March 17, 2017

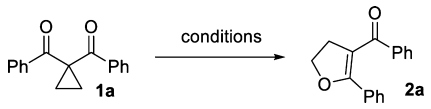
DOI: 10.1021/acs.orglett.7b00805
Org. Lett. XXXX, XXX, XXX–XXX

ketones resting upon a Ni–π-allyl intermediate (eq b). Recently, Plietker and co-workers[16] also demonstrated mild thermal or photochemical Cloke–Wilson rearrangements for vinyl and aryl cyclopropyl ketones catalyzed by TBA[Fe] (eq c). Inspired by these reports, and stemming from our interest in Lewis base catalysis,[17] we envisioned that an organocatalytic strategy for the Cloke–Wilson rearrangement might be possible by utilizing the homoconjugate addition process (*vide infra*). This hypothesis is reminiscent of the Heine rearrangement,[18] which proceeds in a similar pathway. Herein, we report an organocatalytic DABCO-catalyzed Cloke–Wilson rearrangement of cyclopropyl ketones in generally high yields, complete regioselectivity, and a broad substrate scope (eq d).

1,1-Dibenzoylcyclopropane (**1a**) was chosen as the model substrate for an initial investigation (Table 1). Inspired by the Heine reaction, we first examined the standard Heine conditions (NaI in refluxing acetone) and modifications (entries 1–5), which however, were ineffective for the rearrangement. Phosphines have been shown by Morgan and co-workers[19] to catalyze the Heine reaction. For the current system, it was found that PBu_3 and PCy_3 were able to catalyze the Cloke–Wilson rearrangement in low yields, while dppb, dppe, and PPh_3 were incompetent (entries 6–10). Gratifyingly, nucleophilic amines turned out to be superior. In the presence of DABCO (20 mol %), the rearrangement of **1a** in DMSO at 120 °C completed in 15 h, resulting in the isolation of desired 2,3-dihydrofuran **2a** in 75% yield (entry 11). DMAP and DBU were also effective albeit with lowered yields (entries 12 and 13). Among several common solvents examined, DMF and acetonitrile gave yields of 74% and 34%, respectively, whereas THF and 1,4-dioxane inhibited the reaction (entries 14–17). It was found that a lowered reaction temperature (80 °C) decreased the yield substantially (53%) (entry 18). Extending the period of time hardly influenced the yield (entry 19); however, increasing the loading of DABCO to 50 mol % upgraded the yield to 85%, and 1.0 equiv increased that to 93% (entries 20 and 21). In view of the practicality, we established the standard conditions by using 50 mol % of DABCO as the catalyst in DMSO at 120 °C.

Success at identifying the organocatalytic Cloke–Wilson rearrangement prompted us to probe its scope using a range of cyclopropyl ketones (Table 2). Cyclopropanes **1a–c** with germinal diketones readily converted into 2,3-dihydrofurans

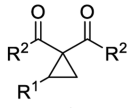
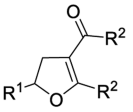
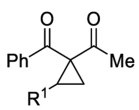
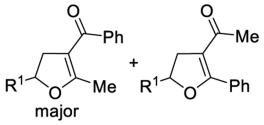
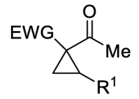
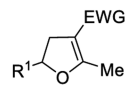
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	temp (°C)	time (h)	yield[b] (%)
1	NaI	acetone	reflux	24	trace
2	NaI	DMSO	120	24	trace
3	ZnI_2	DMSO	120	24	trace
4	MgI_2	DMSO	120	24	trace
5	none	DMSO	120	24	
6	PBu_3	DMSO	120	48	18
7	PCy_3	DMSO	120	48	10
8	dppb	DMSO	120	24	trace
9	dppe	DMSO	120	24	trace
10	PPh_3	DMSO	120	24	trace
11	DABCO	DMSO	120	15	75
12	DMAP	DMSO	120	15	28
13	DBU	DMSO	120	15	44
14	DABCO	DMF	120	15	74
15	DABCO	acetonitrile	reflux	15	34
16	DABCO	THF	reflux	15	trace
17	DABCO	1,4-dioxane	reflux	15	trace
18[c]	DABCO	DMSO	80	15	53
19	DABCO	DMSO	120	24	75
20[d]	DABCO	DMSO	120	15	85
21[e]	DABCO	DMSO	120	15	93

[a]Under N_2 atmosphere, the catalyst (20 mol %) was added to a solution of **1a** (0.2 mmol) in the specified solvent (2.0 mL) in a Schlenk tube (25 mL), and the mixture was heated. [b]Isolated yield. [c]Substrate **1a** was recovered in 36% yield. [d]50 mol % catalyst loading. [e]1.0 equiv of DABCO was used.

Table 2. Substrate Scope of DABCO-Catalyzed Cloke–Wilson Rearrangement of Cyclopropyl Ketones[a]

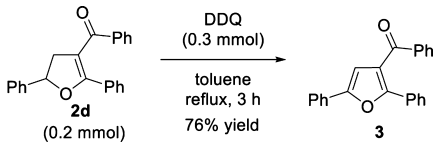
entry	substrates **1**		**2**	yield[b] (%)
				
1	**1a**	R^1 = H	R^2 = Ph	**2a**	85
2	**1b**	R^1 = H	R^2 = 4-$CH_3C_6H_4$	**2b**	94
3	**1c**	R^1 = H	R^2 = 4-$CH_3OC_6H_4$	**2c**	88
4	**1d**	R^1 = Ph	R^2 = Ph	**2d**	94(85[c])
5	**1e**	R^1 = Ph	R^2 = 4-$CH_3C_6H_4$	**2e**	99
6	**1f**	R^1 = Ph	R^2 = CH_3	**2f**	93
7	**1g**	R^1 = Ph	R^2 = 4-$CH_3OC_6H_4$	**2g**	76
8	**1h**	R^1 = 4-ClC_6H_4	R^2 = Ph	**2h**	77
9	**1i**	R^1 = 4-ClC_6H_4	R^2 = 4-$CH_3C_6H_4$	**2i**	84
10	**1j**	R^1 = 4-ClC_6H_4	R^2 = 4-$CH_3OC_6H_4$	**2j**	64
11	**1k**	R^1 = 4-ClC_6H_4	R^2 = CH_3	**2k**	87
12[d]	**1l**	R^1 = -CH=CH_2	R^2 = CH_3	**2l**	57
13	**1m**	R^1 = -CH=CH_2	R^2 = Ph	**2m**	76
14	**1n**	R^1 = -CH=CH_2	R^2 = 4-$CH_3OC_6H_4$	**2n**	60
15	**1o**	R^1 = Me	R^2 = Ph	**2o**	72
16	**1p**	R^1 = Me	R^2 = 4-$CH_3C_6H_4$	**2p**	49
				
17	**1q**	R^1 = H	**2q**/**2q'** (1.6:1)		72
18[e]	**1r**	R^1 = Ph	**2r**/**2r'** (1.3:1)		86
19[e]	**1s**	R^1 = -CH=CH_2	**2s**/**2s'** (1.3:1)		77
20	**1t**	R^1 = Me	**2t**/**2t'** (1.2:1)		42
				
21	**1u**	EWG = CO_2Et, R^1 = Ph		**2u**	93
22	**1v**	EWG = CO_2Et, R^1 = 4-ClC_6H_4		**2v**	87
23	**1w**	EWG = CO_2Et, R^1 = 4-$OCH_3C_6H_4$		**2w**	79
24[d]	**1x**	EWG = CO_2Et, R^1 = -CH=CH_2		**2x**	61
25[f]	**1y**	EWG = CONHPh, R^1 = -CH=CH_2		**2y**	46

[a]Typical procedure: under N_2 and at 120 °C, to a solution of **1** (0.2 mmol) in DMSO (2.0 mL) was added DABCO (0.1 mmol), and the mixture was stirred for 15–48 h. [b]Isolated yield. [c]Scaled-up yield of **2d** (1.10 g). [d]1.0 equiv of DABCO was used. [e]Both diastereomers of substrates gave the same results. [f]Acrylonitrile (1.0 equiv) was used as the additive with toluene as the solvent.

DOI: 10.1021/acs.orglett.7b00805
Org. Lett. XXXX, XXX, XXX–XXX

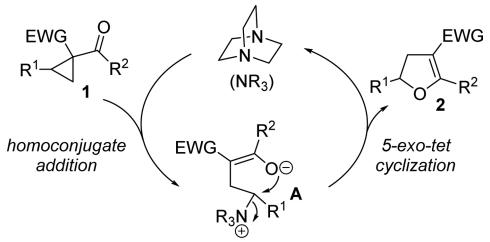
2a–c in 85–94% yields (entries 1–3). Cyclopropyl ketones with an extra substituent were then tested, whose rearrangement would pose a regioselectivity issue. Intriguingly, when a series of aryl-, vinyl-, or alkyl-substituted cyclopropyl ketones (**1d–p**) were treated, the corresponding trisubstituted 2,3-dihydrofurans **2d–p** were generated in good to excellent yields, with a C–O bond forming solely on the sterically hindered carbon (entries 4–20). Of interest is that the regioselectivity is opposite to that of the Heine rearrangement that occurs at the less hindered position.[19] The product structure was unequivocally established by X-ray crystallography (for **2d**, see the Supporting Information). Subsequent investigation was extended to cyclopropanes bearing different geminal carbonyls. Substrates **1q–t**, which carry geminal acetyl and benzoyl groups, produced a pair of 2.3-dihydrofurans in 42–86% yields (ratios 1.2:1–1.6:1) favoring acetyl-rearranged products (entries 17–20). However, cyclopropyl ketones **1u–y** with a germinal ester or amide group underwent highly selective rearrangements toward the ketone, furnishing products **2u–y** in 46–93% yields (entries 21–25). Collectively, the DABCO-catalyzed Cloke–Wilson rearrangement is general for a broad range of substrates which include aryl-, alkyl-, vinyl-, and nonsubstituted cyclopropyl ketones (both aromatic and aliphatic) that are geminally activated by a ketone, ester, or amide substituent. As 2,3-dihydrofurans are ubiquitous substructures in natural products and biologically active molecules,[20] this reaction accordingly offers a practical access to this class of heterocycles under mild metal-free conditions. To demonstrate the practicality, a scaled-up synthesis of 2,3-dihydrofuran **2d** (85% yield, 1.10 g scale) was carried out (Table 2, entry 4), and the elaboration of the product to a furan derivative **3** by DDQ oxidation was exemplified in Scheme 3.

Scheme 3. Synthesis of Furan 3



For the mechanism, a stepwised pathway is proposed to rationalize the DABCO-catalyzed Cloke–Wilson rearrangement (Scheme 4). Initial nucleophilic attack of DABCO on

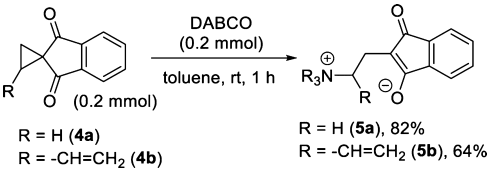
Scheme 4. Possible Mechanism for DABCO-Catalyzed Cloke–Wilson Rearrangement of Cyclopropyl Ketones



cyclopropanes **1**, in the form of the homoconjugate addition, produces the enolate intermediate **A**, which undergoes a favorable 5-*exo-tet* cyclization to furnish the product and release the catalyst. The regioselective ring opening may be ascribed to the highly polarized C–C bond rendered by the electron-donor substituent R^1 of the donor–acceptor (D–A) cyclopropanes.[1k]

The proposed mechanism could be supported by intermediate isolation from structurally similar substrates. It was found that cyclopropyl ketones **4** with a spiro backbone readily reacted with DABCO in toluene at room temperature, producing zwitterionic intermediates **5** in good yields as yellow precipitates (Scheme 5). Attempts to engage these inter-

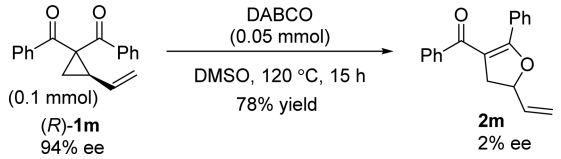
Scheme 5. Zwitterions Formation from Cyclopropanes 4



mediates in further ring closure, however, were unsuccessful despite prolonged reaction at a higher temperature (DMSO, 2 days, 180 °C).[21] Nevertheless, such intermediates support the step of regioselective ring opening of the proposed mechanism.

Originally, we assumed that the ring opening of the DABCO-catalyzed Cloke–Wilson rearrangement may proceed in an S_N2 manner as shown in the literature;[22] however, stereochemical analysis with an optically active substrate disfavors this pathway.[23] Under the standard conditions, it was found that enantioenriched (*R*)-**1m** (94% ee) converted into 2,3-dihydrofurane **2m** in 78% yield yet with almost complete loss of the stereochemical integrity (2% ee) (Scheme 6). With this result, it is apparent that an S_N1-type ring opening process is responsible for the DABCO-catalyzed Cloke–Wilson rearrangement.

Scheme 6. DABCO-Catalyzed Cloke–Wilson Rearrangement of Enantioenriched 1m



In conclusion, our efforts to explore the utility of the homoconjugate addition have led us to the discovery of an organocatalytic Cloke–Wilson rearrangement of cyclopropyl ketones to 2,3-dihydrofurans. The established conditions (DABCO, DMSO, 120 °C) are compatible with a broad range of substrates giving good yields and complete regioselectivity, which may constitute a mild and general protocol for the Cloke–Wilson rearrangement of cyclopropyl ketones. Based on the results of intermediate isolation and stereochemical analysis using an optically active substrate, an S_N1-type ring opening mechanism is proposed for the rearrangement. Future efforts focus on applying the current reaction in target-oriented synthesis and exploiting new reactivities based on the homoconjugate addition process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00805.

Experimental procedures, analytical data, NMR spectra, and crystallographic information (PDF)

DOI: 10.1021/acs.orglett.7b00805
Org. Lett. XXXX, XXX, XXX–XXX

X-ray data for compound **2d** (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (Nos. 21402149, 21602167), the Natural Science Basic Research Plan in Shaanxi Province of China (Nos. 2015JQ2050, 2016JQ2019), the China Postdoctoral Science Foundation (Nos. 2014M550484, 2015T81013, 2015M580830), and the Shaanxi Province Postdoctoral Science Foundation is gratefully acknowledged. Dedicated to Professor Yuhai Tang on the occasion of his 60th birthday.

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DOI: 10.1021/acs.orglett.7b00805
Org. Lett. XXXX, XXX, XXX−XXX