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Retro Reactions

DBU-Catalyzed Ring-Opening and Retro-Claisen Fragmentation of Dihydropyranones**

Anton Axelsson,[a][‡] Emmelie Hammarvid,[a] Martin Rahm,*[a] and Henrik Sundén*[a][‡‡]

Abstract: We present a general protocol for the formal Michael addition of acetone to α,β-unsaturated esters and amides, a transformation difficult to perform using current methods. The protocol comprises of an amidine catalyzed relay ring-opening and fragmentation of 3,4-dihydropyranones. The reaction proceeds under mild conditions, has a broad substrate scope and the products can be isolated in good to excellent yields. The method can be applied to homochiral substrates with total preservation of chiral information, generating products in high optical purity. Kinetic experiments supported by quantum chemical modeling indicate a mechanism in which the catalyst takes a bifunctional role, acting both as a Brønsted base and as a hydrogen-bond donor.

Introduction

The Michael reaction is one of the most well-known and important reactions in synthetic organic chemistry.[1] During the last three decades, a variety of catalytic methods for asymmetric Michael additions have been developed.[2] Despite the progress, some issues remain unsolved. For example, in reactions with unactivated Michael acceptors, such as α,β-unsaturated esters or amides, poor reactivity is observed due to low electrophilicity.[3] In addition to problematic electrophiles, some nucleophiles have also proven challenging in asymmetric Michael reactions. Acetone is a notorious example of a difficult nucleophile. Direct Michael addition of acetone is possible only with highly activated electrophiles such as nitroolefins and a thiourea-based catalyst or by indirect methods using RAMP/SAMP auxiliaries.[4] Here, we describe the DBU catalyzed ring-opening/retro-Claisen fragmentation of dihydropyranones for the formal addition of acetone to unactivated Michael acceptors. The protocol is highly modular and allows for the asymmetric synthesis of both oxohexanoates and oxohexanamides.

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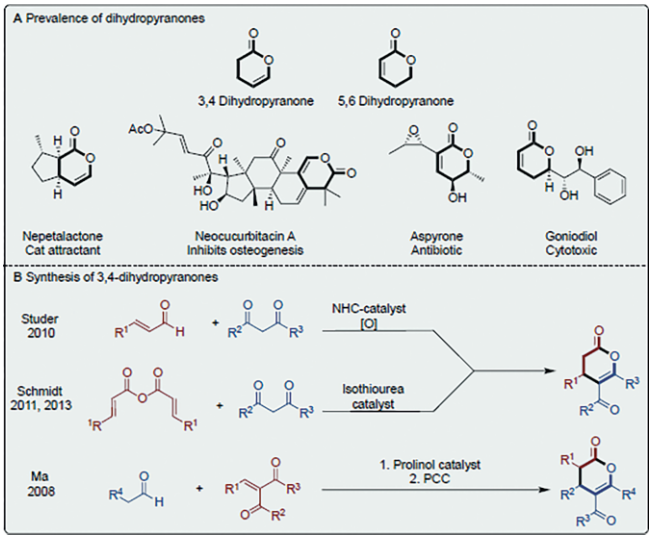
The dihydropyranone is an intriguing structural moiety that is found in several natural products and biologically active molecules (Scheme 1A).[5] For instance, the cat attractant Nepetalactone and osteogenenesis inhibitor Neocucurbitacin A, isolated from catnip and *Luffa operculta* respectively, both contain a 3,4-dihydropyranone moiety.[6] The 5,6-dihydropyranone scaffold is also prevalent in natural products, as seen in the antibiotic Aspyrone and the cytotoxic Goniodiol.[7] Furthermore, the 5,6-dihydropyranone moiety has proven a useful synthon for further manipulation[8] and a valuable intermediate for the synthesis of natural products.[9]



Scheme 1. Structure, biological activity, and synthesis of dihydropyranones.

Unfortunately, the corresponding valorization of 3,4-dihydropyranones remains scarce, despite several potential sites for further manipulation. This is surprising considering the recent surge in organocatalytic methods yielding 3,4-dihydropyranones.[10] For example, in a pioneering report from Studer et al.

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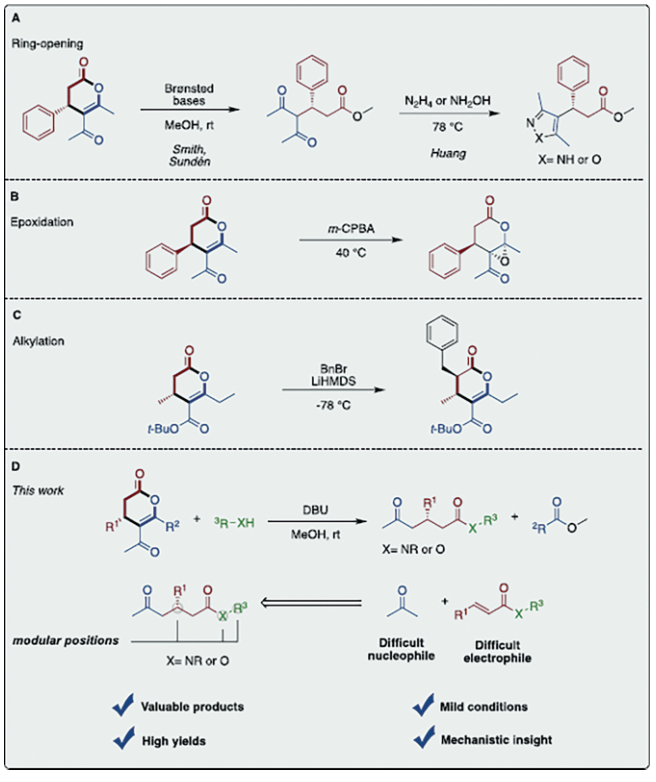
enals were shown to react with 1,3-carbonyls via oxidative *N*-heterocyclic carbene (NHC) catalysis yielding 3,4-dihydropyranones (Scheme 1B).[11] Since then, a plethora of NHC-catalyzed reactions yielding homochiral dihydropyranones has been reported based on both oxidative[12] and redox neutral pathways.[13] Lately, several strategies that use oxygen as oxidant has been reported.[13e,14] Other organocatalytic methods toward the dihydropyranones involve activation of anhydrides with isothioureas, as reported by Smith and co-workers,[15] and enamine catalysis-oxidation sequences as reported by Ma et al.[16]

Clearly, the discovery of new general methods for derivatization of 3,4-dihydropyranones would be beneficial. While some reactions already have been reported, these are often single substrate examples. For instance, both Smith et al. and our group have observed facile ring-opening with methanol when using Brønsted bases (Scheme 2A).[14a,15b] Huang et al. have shown that it is possible to extend this type of reaction by treating the acyclic ester with either hydrazine or hydroxylamine, yielding pyrazoles or isoxazoles respectively.[14c] A diastereoselective epoxidation of the enol double bond using *m*-CPBA with only slight erosion of enantiopurity was developed by Chi and co-workers (Scheme 2B).[12c] Diastereoselective alkylation of the corresponding lithium enolate with benzyl bromide has been reported by Evans et al. (Scheme 2C).[17] Recently, an oxidative ring contraction of dihydropyranones was reported.[18]



Scheme 2. Reactivity of dihydropyranones.

Intrigued by the potential of the 3,4-dihydropyranones as starting points for further synthesis, we set out to expand on the synthetic utility of this neglected synthon. Here, we describe our efforts towards developing a formal addition of acetone to unactivated Michael acceptors by ring-opening and fragmentation of 3,4-dihydropyranones (Scheme 2D).[19]

Results and Discussion

Reaction Optimization and Scope

While examining the ring-opening of dihydropyranone **1**, a striking difference in reactivity was observed upon a slight variation of reaction conditions (Table 1). Treatment with equimolar amounts of NHC precatalyst **4** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol yielded the ring-opened diketone **3** in 95 % yield, as previously reported.[14a] However, usage of slightly higher loadings of DBU (15 mol-%) in the absence of **4** yielded compound **2** in 89 % isolated yield. A stoichiometric amount of methyl acetate was also detected in the crude reaction mixture by ^{1}H NMR, suggesting that **2** is formed via a retro-Claisen fragmentation of the 1,3-diketone of compound **3**.[20] Fascinated by the difference in reactivity, we optimized the reaction further with respect to oxoester **2**. As it turns out, both the structurally related guanidine base 1,5,7-triazabicyclo[4.4.0]-dec-5-ene (TBD) and potassium hydroxide are capable of mediating the reaction, yielding **2** in slightly lower yields than DBU (Table 1, entries 2–3). Weaker bases such as nucleophilic 1,4-diazabicyclo[2.2.2]octane (DABCO), non-nucleophilic triethylamine and potassium carbonate does not allow for the formation of **2**, and yields **3** as the sole product in > 90 % yield (Table 1, entries 4–6). Dihydropyranone **1** is stable in methanol in the absence of base, and no ring-opening is observed after 1 h.

Our attempts to replace methanol as solvent was accompanied by drastically reduced yields (Table 1). When acetonitrile or toluene was used together with 5 equiv. of MeOH this resulted in selective formation of **3** over **2**. Protic nucleophilic solvents also proved challenging. With water or 2-propanol as the reaction solvent the retro-Claisen reaction was impeded, yielding the diketone-carboxylic acid or isopropyl ester in > 90 % yield respectively (Table 1, entries 9–10). When ethanol was used as a solvent the corresponding 5-oxoester could be obtained, albeit in approximately 10 % yield after 24 h, leaving **3** as the main product (ca 90 % yield, Table 1, entry 11).

Having identified mild conditions for the synthesis of 5-oxo-hexanoates, we proceeded to evaluate the scope of the reaction with respect to the dihydropyranones (Scheme 3). The reaction works well with electron-donating substituents on the phenyl ring (**5**, **6**, **11**) and 4-tolyl-substituted 5-oxo-hexanoate **6** could be isolated in 80 % yield. The reaction also proceeds smoothly with dihydropyranones with electron-withdrawing substituents (**7**–**9**). For example, fluorinated 5-oxo-hexanoate **8** was obtained in 81 % yield. Bulky substituents at the 2-position are tolerated, and 9-anthracenyl (**10**) and 2-methoxyphenyl (**11**) substituted 5-oxo-hexanoates could be isolated in 64 % and 77 % yield respectively. Alkyl substitution at the 5-position is possible, and methyl-substituted **12** could be isolated in 84 % yield.

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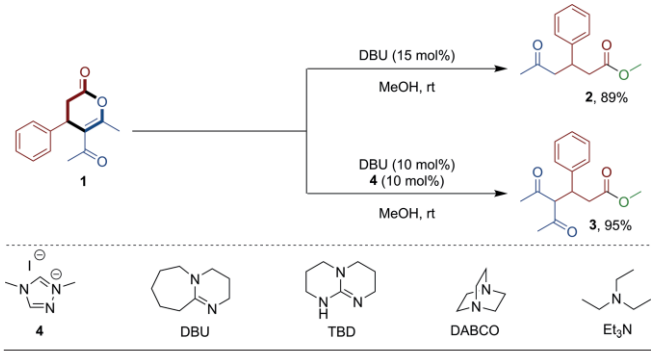
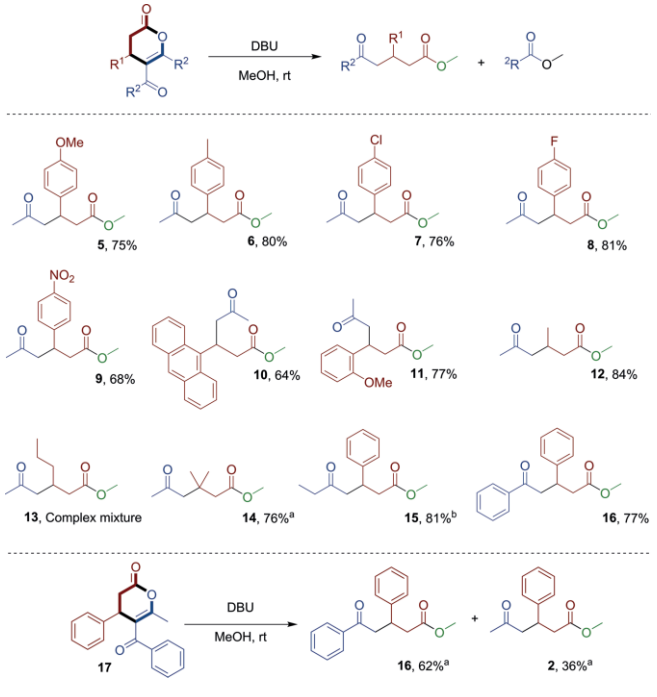
Table 1. Screening of reaction conditions.



Entry	Deviation from standard conditions	Yield (**2**, %)[a]
1.	None	89[b]
2.	TBD instead of DBU	83
3.	KOH instead of DBU	84
4.	DABCO instead of DBU	0
5.	Et_3N instead of DBU	0
6.	K_2CO_3 instead of DBU	0
7.[c]	MeCN instead of MeOH	0
8.[c]	PhMe instead of MeOH	0
9.[d]	Water instead of MeOH	0
10.[d]	IPA instead of MeOH	0
11.[d]	EtOH instead of MeOH	≈ 10 %

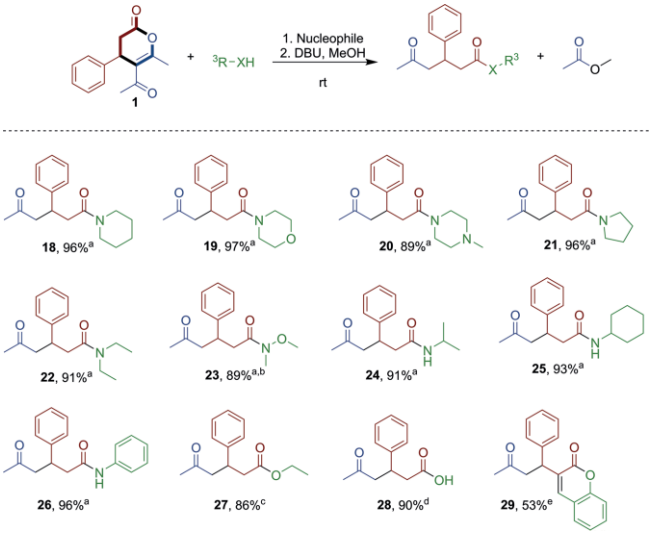
[a] **1** (0.12 mmol), base (0.15 equiv.) solvent (0.4 mL), stirred at ambient temperature for 24 h. Yield determined by ^{1}H NMR using 1,2,4,5-tetramethylbenzene as internal standard. [b] Isolated yield. [c] 5 equivalents of MeOH added. [d] Based on the corresponding carboxylic acid, isopropyl ester or ethyl ester as the product respectively.



Scheme 3. Scope with respect to the dihydropyranone. Dihydropyranone (1.0 equiv.), DBU (0.15 equiv.), MeOH stirred at ambient temperature, isolated yield. [a]Using DBU (0.25 equiv.) for 48 h. [b]Performed at 70 °C.

Dihydropyranones with larger alkyl groups in the 5-position reacts considerably slower. For example, a propyl-substituted dihydropyranone yielded a mixture of **13** and the corresponding diketone, which proved difficult to separate. Dimethylated dihydropyranones are tolerated by the reaction but required slightly higher loadings of DBU (25 mol%). With the latter modification product **14**, which represents the formal total synthesis of the plant hormone abscisic acid,[21] could be obtained in 76 % yield. Introducing longer alkyl substituents in the 3- and 4-positions results in sluggish reactions. However, by increasing the reaction temperature to 70 °C, 5-oxo-heptanoate **15** could be isolated in 81 % yield. In contrast, dihydropyranones with aromatic substituents in the 3- and 4-position readily react at room temperature and **16** could be isolated in 77 % yield. Lastly, the reaction of dihydropyranone **17**, which may yield two different products, was investigated. Product **16** and **2** were formed in a 1.7:1 under the developed reaction conditions.

Next, we investigated if the ring-opening of dihydropyranones could be performed with nucleophiles other than methanol. As it turns out, it is possible to obtain a wide range of amides in excellent yields (Scheme 4) by reacting dihydropyranone **1** with an amine, followed by the addition of methanol and DBU. Cyclic amines are well suited for the transformation as shown in Scheme 4. For example, piperidine, morpholine, 1-methylpiperazine, and pyrrolidine could be used to synthesize compounds **18**–**21** in 96 %, 97 %, 89 %, and 96 % yield, respectively.



Scheme 4. Scope with respect to the nucleophile. [a]**1** (1.0 equiv.), amine (1.1–2.0 equiv.) 2–12 h. Then MeOH and DBU (0.15 equiv.), stirred at ambient temperature. Isolated yield. [b]The corresponding hydrochloride salt was used as nucleophile and was neutralized with an equimolar amount of DBU in DCM. [c]Performed in EtOH at 70 °C.[d] **1** (1 equiv.), $KOH_{(aq)}$ as nucleophile (2.1 equiv.). [e]Salicylaldehyde (1.5 equiv.) as nucleophile using 1.5 equiv. of DBU.

Acyclic secondary amines proved viable nucleophiles and the use of diethylamine yielded amide **22** in 91 % yield. The developed procedure also proved suitable for the construction of synthetically useful Weinreb amides exemplified with the synthesis of compound **23**, obtained in 89 % yield. Several primary amines can also be used as reagents (**24**–**26**). For ex-

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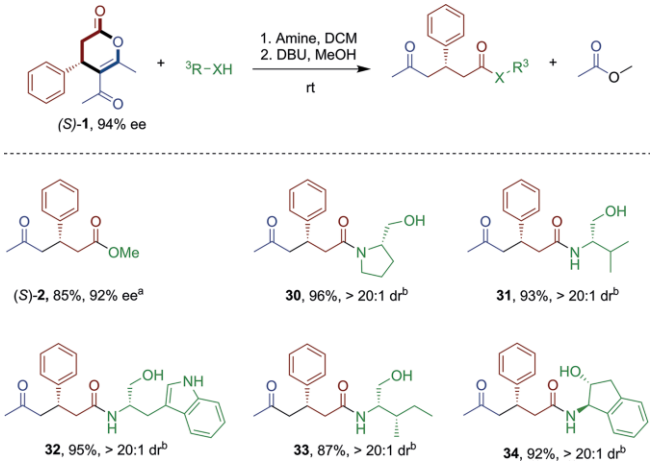
ample, cyclohexylamine and aniline derived amides **25** and **26**, which could be isolated in 93 % and 96 % yield, respectively. It was also discovered, contrary to the optimization results (Table 1, entry 11) that the corresponding ethyl ester can be obtained by using ethanol as the solvent and heating the reaction to 70 °C, yielding **27** in 86 % yield. Attempts to access isopropyl or *tert*-butyl esters in a similar manner were unsuccessful. It is also possible to obtain the carboxylic acid product by using aqueous KOH as the nucleophile, and **28** was obtained in 90 % yield. Using salicylaldehyde as the nucleophile together with a stoichiometric amount of DBU yielded substituted coumarin **29** in 53 % yield. Presumably via acylation, aldol condensation, and retro-Claisen fragmentation. It is worth noting that compound **29** is only one 4-hydroxyl substituent on the coumarin motif away from the anticoagulant warfarin.[22]

We also investigated the possibility of obtaining these valuable products in optically pure form (Scheme 5). By relying on our aerobic oxidative protocol for the synthesis of dihydropyranones, (*S*)-**1** could be obtained in good yield and 94 % *ee* on gram-scale.[14a] Treatment of (*S*)-**1** with DBU under standard conditions gave (*S*)-**2** in 85 % yield with almost complete preservation of enantiomeric excess (92 % *ee*, Scheme 5). Chiral amino alcohols are also viable reaction partners and (*S*)-prolinol, (*S*)-valinol, (*S*)-tryptophanol, and (*S*)-isoleucinol could be used to synthesize the corresponding 5-oxo-hexanamides in 87–96 % yield. An indanol based amino alcohol also proved a competent nucleophile yielding product **34** in 92 % yield. All reactions proceeded with excellent chemo- and diastereoselectivity without noticeable racemization.



Scheme 5. Synthesis of homochiral products. [a](*S*)-1 (1.0 equiv.), MeOH and DBU (0.15 equiv.), stirred at ambient temperature. Isolated yield. [b](*S*)-1 (1.0 equiv.), amino alcohol (1.0–1.4 equiv.), dichloromethane, stirred overnight. Then MeOH and DBU (0.15 equiv.), stirred at ambient temperature. Isolated yield. Diastereomeric ratio (*dr*) determined by ^{1}H NMR of crude reaction mixture.

Investigation of the Reaction Mechanism

To gain further insight into the reaction mechanism, the reaction was monitored using a gas chromatograph equipped with a flame ionization detector (GC-FID). The concentration profile of a reaction shown in Figure 1. The reaction used 0.3 equiv. of DBU to achieve greater conversion during the experiment. In the shown experiment, the ring-opening of **1** to **3** was complete within minutes at 297 K,[23] while the transformation of **3** to **2** was considerably slower. Plotting ln[**3**] vs. time showed that the reaction is of the first order with respect to **3** (R^2 = 0.99, see Figure S2 in ESI). Overall, the reaction follows first-order kinetics since the reaction order in **3** is one and the reaction is performed under pseudo-first-order conditions, with [MeOH] >> [**3**], the concentration of DBU is constant and that the reaction of **1** → **3** is essentially irreversible and considerably faster than **3** → **2**.[24]

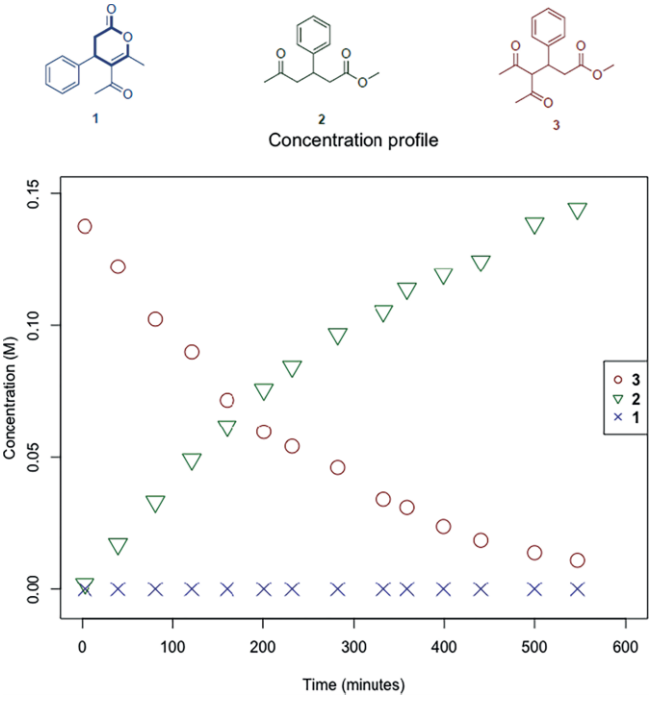


Figure 1. Example concentration profile for the reaction of **1** yielding **2**. The ring-opening of **1** to yield **3** is very rapid, while the retro-Claisen fragmentation of **3** to give **2** is considerably slower. The experiment was run with 0.3 equiv. of DBU as catalyst.

To study the retro-Claisen fragmentation in greater detail the reaction of pre-formed **3** into **2** was studied at three different loadings of DBU (0.15, 0.30 and 0.45 equiv.). Plotting ln[**3**] vs. time once again produced straight lines (Figure S3 in ESI), which enabled us to determine the apparent rate (slope=k_{obs}) for the different reactions. We then used log-log plots to elucidate the reaction order in DBU.[25] Plotting ln(rate) vs. ln[DBU] gave a straight line (R^2 = 0.99) with a slope of 1.6 (Figure S4 in ESI), indicating that the reaction is of the 1.6th order in DBU.

A normal kinetic isotope effect (KIE, k_H/k_D) of 2.3 was measured by running the reaction in MeOH and [D_4]MeOH (Scheme 6). As a rule of thumb, deuterated hydrogen bonds are weaker than their protonated counterpart.[26] A KIE of this size suggests a primary effect, i.e. that a bond to hydrogen is directly involved in the rate-determining step. The measured value is too large to be caused by several secondary KIEs.[27]

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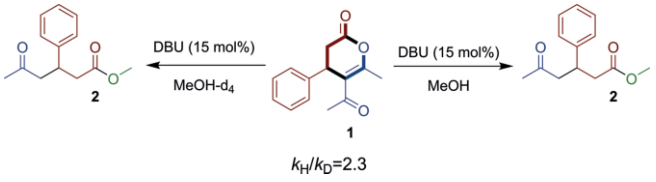
The observed kinetics (Figure 1) indicates that the rate-determining step should be part of the retro-Claisen fragmentation.



Scheme 6. Determination of kinetic isotope effect.

The commonly accepted view is that *C–C* bond breakage is rate-determining for retro-Claisen fragmentations under alkaline conditions.[28] Combined, knowledge of a primary KIE and a reaction order above 1 with respect to DBU made us wonder if both DBU and the corresponding acid ($DBUH^+$) could be involved in the retro-Claisen reaction.

Two different mechanisms that allow for our combination of experimental observations are proposed. In both situations, $DBUH^+$ acts as a hydrogen-bond donor (HBD) (path A and B, cf. Figure 2). Protonated amines are known to be strong HBDs.[29] With HBD parameter values of $\alpha \approx 5$ they are, for example, considerably stronger than alcohols (for aliphatic alcohols, $\alpha \approx 2.7$.[30])

In our proposed mechanisms, the DBU-catalyzed ring-opening of dihydropyranone **1** with methanol to yield **3** occurs first, which completes within minutes at room temperature (Figure 2). The mechanism for the retro-Claisen fragmentation begins with the deprotonation of methanol by DBU. The formed methoxide then adds in a nucleophilic 1,2-addition to one of the ketones in **3**. And here is where the two mechanisms diverge, yielding either an anionic hemiacetal in which $DBUH^+$ is coordinated to the ketone (in path A) or to the anionic hemiacetal via hydrogen bonding (in path B). We distinguish between these two complexes by naming them **35** (in path A) and **37** (in path B). It is possible that **35** and **37** are in equilibrium, but for clarity, they are drawn as separate catalytic cycles.

In path A, **35** collapses into the hydrogen-bonded enolate **36** and methyl acetate. Proton transfer between $DBUH^+$ and the enolate subsequently yields product **2** and regenerates DBU, completing the catalytic cycle. A similar mechanism has previously been suggested in ring-opening polymerization reactions.[31] In path B, **37**, instead collapses to **38**, a complex different from **36** in that it lacks an explicit hydrogen bond to $DBUH^+$. In path B it is instead the formed methyl acetate **39**, which is hydrogen-bonded. Dissociation of complex **39** and subsequent protonation of enolate **38** yields product **2** and regenerates DBU.

The type of mechanisms we are considering (A and B, cf. Figure 2) are both able to explain the observed first-order dependence in **3** and the 1.6th order dependence in DBU, the primary KIE and the sensitivity towards steric encumbrance close to the 1,3-diketone moiety (cf. products **13**–**15** and **27**). So, how can we determine which mechanism that is governing?

We used Density Functional Theory (DFT) calculations to evaluate the effect of the catalyst and which of the two considered pathways is more likely. The calculations were performed

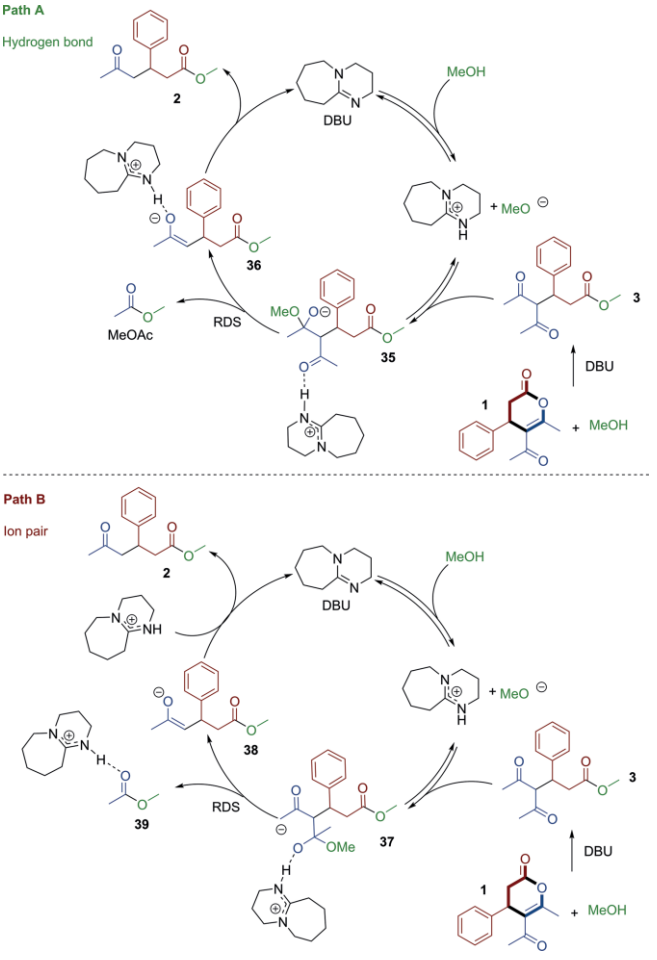


Figure 2. Two proposed mechanism for the ring-opening and fragmentation of dihydropyranones. Both options are in agreement with experimental data. RDS = rate-determining step.

using the Gaussian 16 package, revision B.01.[32] Geometry optimizations and frequency analyses were performed at the ωB97X-D/6-311+G(2d,p) level of theory. Final single-point energies were computed using the larger 6-311++G(2df,2pd) basis set. Implicit consideration of solvent effects in methanol was included through the Solvation Model based on Density (SMD) method in all calculations.[33] The dispersion-corrected and range-separated hybrid functional ωB97X-D has previously been successfully used together with Pople-style basis sets to model organocatalytic reactions were hydrogen bonding is important, including hydrogen bonding involving amine superbases such as DBU.[34]

The transformation of **1** into **2** was chosen as a model reaction in our calculation. We considered three different mechanisms – path A in which $DBUH^+$ coordinates to the ketone (Figure 3, green line), path B where $DBUH^+$ coordinates to the anionic hemiacetal (Figure 3, blue line) and path C, in which $DBUH^+$ takes no part (Figure 3, red line).

The calculated difference in Gibbs energy (ΔG^0) for the first step, the exergonic ring-opening of **1** to yield **3**, is –10.3 kcal/mol. The value agrees with observations showing that the concentration of **1** is close to zero throughout the reaction (Figure 1). Formation of the anionic hemiacetals (**35**, **35^C**, or **37**)

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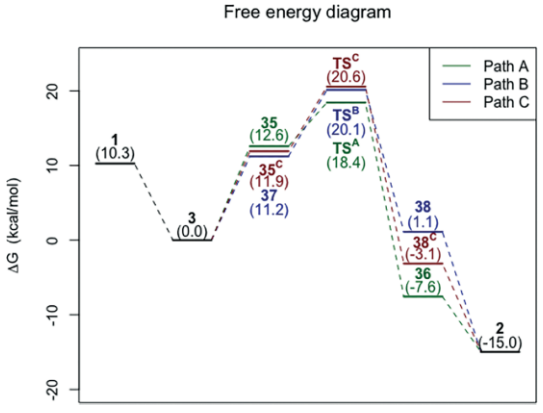

Figure 3. Computed free energy (298.15 K, 1 M) diagram for path A–C. A superscript C (X^C) denotes the corresponding structures without coordination of DBUH+. Energies relative to the 1,3-diketone **3** and free MeOH are shown in kcal/mol.

are significantly endergonic relative to **3**. The ion-paired structure **37** calculates as 0.7 kcal/mol Lower in energy compared to the uncoordinated **35^C** and 1.4 kcal/mol below hydrogen-bonded **35**. The former energy difference is an estimate of the hydrogen bond strength between the hemiacetal and $DBUH^+$. Because we are relying on implicit models to account for solvation effects, we must stress that the estimate is approximative. Our calculations are sensitive to the solvation energy of $DBUH^+$. More accurately estimates of solvation effects, in general, would require explicit consideration of solvent molecules. Such calculations would ideally rely on molecular dynamics simulations, which we consider outside the scope of the current work.

The third step is where the rate-determining *C–C* bond cleavage takes place. Transition state TS^A calculates as lowest in free energy at $\Delta G^{\ddagger}$ = 18.4 kcal/mol. Which is arguably in part due to the hydrogen bonding interaction with $DBUH^+$ (Figure 3). TS^B calculates as second to lowest, at $\Delta G^{\ddagger}$ = 20.1 kcal/mol. Finally, TS^C, which correspond to no $DBUH^+$-coordination, is predicted to lie highest at $\Delta G^{\ddagger}$ = 20.6 kcal/mol. The competing transition states are predicted to lie close in energy, and near, in fact, to the accuracy of the used DFT method (the estimated average error of the ωB97X-D functional for predicting general reaction barriers is ≈ 1.5 kcal/mol)[35,33c] However, error cancellation is expected to play an important role when comparing the relative energies of such similar transition states. To verify our predictions the transitions state energies were re-calculated using the M06-2X-D3 DFT functional with similar results (see Table S20 in the ESI).[36] We note that the identified lowest reaction barrier of ≈ 18 kcal/mol is in good qualitative agreement with experiment, as it infers a reasonable reaction rate near room temperature (reaction time ≈ 24 h).

Conformational sampling is one possible source of error. In addition to the rate-determining steps outlined in Figure 3, we have carefully evaluated a large number of other competing possibilities, including several that have been suggested for related processes (for a discussion see ESI S18–S21). These include considering synchronous protonation of the enolate/*C–C* bond breakage, synchronous deprotonation of the neutral hemiacetal/*C–C* bond breakage, intramolecular proton transfer, formation of acyl ammonium species by a Lewis base mechanism as suggested by Wolf et al. for a related process,[37] and a cyclic TS as suggested in Lewis acid-catalyzed retro-Claisen reactions.[38] The alternatives mentioned calculate as distinctly higher in free energy (typically $\Delta G^{\ddagger}$ > 30 kcal/mol, see Figure S10). The proposed dual role of DBU, as both a strong base and a potent HBD, represent a new mode of activation for retro-Claisen processes.

The *C-C* bond breakage step, e.g. **35** → **36**, is exergonic relative the anionic hemiacetal in all three cases, but to what extent varies considerably (Figure 3). Our calculations for this step might be less exact due to the separate implicit solvation treatment of the formed $DBUH^+$–ester complex. Fortunately, the step is inconsequential for determining the governing reaction mechanism. In the final step, all three competing mechanisms proceed via protonation of the formed enolate to yield the product (**2**) and regenerate DBU. Relative to **3**, the overall process is thermodynamically downhill by ≈ 15 kcal/mol. We should also add that our results do not demand that the coordination of $DBUH^+$ is constant during the reaction, i.e. **35** might form, rearrange to **37** and react via TS^A. The situation is analogous with a reaction under Curtin–Hammet control.[39] Although paths A, B, and C are deemed energetically possible our computational study supports pathway A (Figure 3) as the main reaction path. How can the conclusion be explained?

One way to rationalize the outcome is by analyzing the intermediates directly before and after the transition states. In path A, coordination of $DBUH^+$ destabilizes the anionic hemiacetal but stabilizes the enolate as compared to path C, while the opposite is true for path B. We note that the stabilization of **36** in path A (≈ 4.5 kcal/mol compared to path C) is considerably larger than the stabilization of **37** in path B (≈ 0.7 kcal/mol compared to path C). Hence, the only clearly favorable interaction between $DBUH^+$ and the substrate is found in path A. Moreover, it is worth noting that the length of the *C–C* bond being broken in the rate-determining transition state varies as path A (2.06 Å) < path C (2.10 Å) < path B (2.13 Å), in agreement with the Hammond postulate (Figure 4).[40]

Another possible reason for the energetic ordering of the transition states can be gleaned from their optimized geometries. A closer look at the hydrogen bonds in TS^A and TS^B shows that the *O–H–N* bond angle is close to the calculated optimal linear rearrangement ($\angle_{OHN}$ = 177°) in TS^A, while in TS^B the hydrogen bond is more skewed ($\angle_{OHN}$ = 163°). At the same time, the *O–H* distances in TS^A and TS^B are very similar (1.78 Å vs. 1.77 Å). The *O–N* distance is slightly shorter in TS^B compared to in TS^A (2.81 Å vs. 2.77 Å). An additional aspect that favors path A is interactions between $DBUH^+$ and the phenyl ring. In the favored TS^A, $DBUH^+$ and the phenyl ring adopts a slipped stacked conformation that lowers the energy by ≈ 1.3 kcal/mol (see comparison with unstacked TS^D in Figure S10 the ESI). However, path A remains the favored mechanism even without the interactions associated with the slipped stacked conformation shown in Figure 4. This is because the lost interaction (mainly dispersion) is partly compensated by stronger hydrogen bonding in TS^D ($D_{O\text{-}H}$ = 1.73 Å in TS^D vs. $D_{O\text{-}H}$ = 1.78 Å in TS^A, Figure S10 in the ESI).

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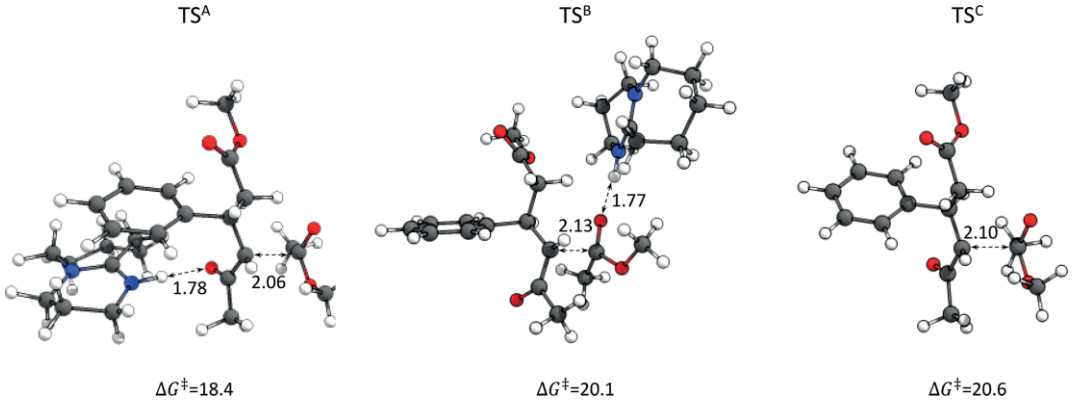

Figure 4. Optimized structures and selected distances of TS^A, TS^B, and TS^C (in Å) together with Gibbs energy reaction barriers (298K, 1 M, in kcal/mol).

Summary

We have presented a method for the formal addition of acetone to unactivated Michael acceptors. Until now, the use of acetone and unactivated Michael acceptors have been plagued by low selectivity and low reactivity, respectively. Our method consists of DBU-catalyzed ring-opening and retro-Claisen fragmentation of 3,4-dihydropyranones and produces 5-oxo-hexanoates and 5-oxo-hexanamides in good to excellent yields. The reaction is compatible with a wide range of nucleophiles, providing access to esters, carboxylic acids, and secondary, tertiary, and Weinreb amides. The synthetic approach enables access to chiral 5-oxo-hexanoates and stereoselective functionalization of chiral amino alcohols under mild conditions.

Kinetic studies have revealed that the initial ring-opening is rapid and completes within minutes at ambient conditions, while the cleavage of the *C–C* bond in the corresponding 1,3-diketone is slower. The breakage of the *C–C* bond proceeds in first order with respect to the 1,3-diketone and with a reaction order above 1 with respect to the DBU catalyst. These observations, together with a measured primary kinetic isotope effect, have led us to propose a mechanism in which DBU acts both as a Brønsted base and a hydrogen-bond donor. A quantum chemical investigation supports the mechanism and suggests that $DBUH^+$ lowers the activation barrier for the *C–C* bond scission by coordinating to the ketone (Figure 3, path A). Our method provides access to valuable compounds from readily available and previously overlooked starting materials.

Experimental Section

Representative Procedure for the Synthesis of 5-Oxo-hexanoates: A pear-shaped flask, equipped with a magnetic stirrer, was charged with 5-acetyl-6-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-2-one **1** (30.4 mg, 0.13 mmol) and methanol (0.45 mL). The heterogeneous mixture was gently stirred and DBU (3.0 mg, 0.020 mmol) was added and the mixture turned homogeneous within one minute. The mixture was stirred at ambient temperature and monitored via ^{1}H NMR. When the reaction had reached completion (typically within 24 h), the crude reaction mixture was purified using the automatic flash system from Biotage (Isolera One) with a 100 % heptane followed by dichloromethane/methanol solvent mixture (20 mL/min, 100 % heptane, 100 % DCM → 2 % methanol → 4 % methanol → 5 % methanol → 10 % methanol in dichloromethane). The product **2** was obtained as a clear oil that slowly solidified into a white solid (25.7 mg, 0.12 mmol, 89 %).

Note: The reaction is sensitive to any traces of Brønsted acids. **1** is prone toward hydrolysis, especially if exposed to "wet" solvents or ambient atmosphere for a prolonged period of time. The product of the hydrolysis is the corresponding carboxylic acid, which seriously impedes the reaction. To avoid hydrolysis, **1** should be stored at –18 °C and time spent at temperatures above –18 °C should be kept to a minimum.

Representative Procedure for the Synthesis of 5-Oxo-hexanamides: A pear-shaped flask, equipped with a magnetic stirrer, was charged with 5-acetyl-6-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-2-one **1** (36.2 mg, 0.16 mmol) and cyclohexylamine (17.2 mg, 0.17 mmol, 1.1 equiv.) (1.0–2.0 equiv. of amine used for the reported examples). The mixture was gently stirred overnight. Methanol (0.52 mL) and DBU (3.6 mg, 0.023 mmol) were added and the mixture is stirred at ambient temperature and monitored via ^{1}H NMR. When the reaction had reached completion (typically within 24 h), the crude reaction mixture was purified using the biotage with a 100 % heptane followed by dichloromethane/methanol solvent mixture (20 mL/min, 100 % heptane, 100 % DCM → 2 % methanol → 4 % methanol → 5 % methanol → 10 % methanol in dichloromethane). The product **24** was obtained as a white solid (42.1 mg, 0.15 mmol, 93 %). For solid or less nucleophilic amines dichloromethane (0.6 M) was used as a solvent in the first step, followed by removal of volatiles under reduced pressure before the addition of methanol and DBU. More information about the variations can be found in the characterization section of each compound.

Note: Excess of amine impedes the *C-C* bond scission of the 1,3-diketone, possibly via the formation of the corresponding enaminone. If a reaction does not react reach full conversion repeating the reaction with lower loadings of the amine might prove fruitful.

Gram-Scale Synthesis 1: To a 200 mL round-bottomed flask was added 1,4-dimethyl-4-H-1,2,4-trizole iodide **4** (174.2 mg, 0.77 mmol), tetrahydrofuran (70 mL), DBU (115.2 mg, 0.76 mmol), and 3,3′,5,5′-tetra-*tert*-butyl-[1,1′-bi(cyclohexylidene)]-2,2′,5,5′-tetraene-4,4′-dione (**S1**,310.1 mg, 0.76 mmol). The dark brown mixture is stirred at ambient temperature for 5 minutes. Pentane-2,4-dione (1136.1 mg, 11.35 mmol) and cinnamaldehyde (1.00 g, 7.57 mmol) were added and the mixture was stirred for 5 minutes. To the stirring mixture was added iron(II)phthalocyanine (431.8 mg, 0.76 mmol) and the mixture was stirred overnight (18 h). The volatiles were removed under reduced pressure and the crude mixture was purified using

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manual flash-chromatography using ethyl acetate/petroleum ether (40 °C–60 °C) 1:3 as the eluent. The product 5-acetyl-6-methyl-4-phenyl-3,4-dihydro-2*H*-pyran-2-one **1** was obtained as a white powder (1.390 g, 6.04 mmol, 80 %).

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Keywords: Michael addition · Organocatalysis · Oxygen heterocycles · Retro-claisen · Synthetic methods

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