Formal Addition of Acetone to Unactivated Michael Acceptors via Ring-Opening and Retro-Claisen Fragmentation of Dihydropyranones

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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 (30 examples, with up to 97 % yield). 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 indicates that the reaction is of second order with respect to the catalyst. The kinetic isotope effect has been determined to be 2.3, which supports a mechanism in which the catalyst takes a bifunctional role, acting both as a Brønsted base and as a hydrogen bond donor. The findings presented here enables a rapid entry to compounds previously considered difficult to access and highlights the dual functionality of amidine superbases as catalysts.

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.2–6 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.7,10 In addition to problematic electrophiles, some nucleophiles have also proven challenging in asymmetric Michael reactions. Acetone is a notorious example of a difficult nucleophile, which suffers from both low enantioselectivity and the need for highly activated electrophiles such as nitroolefins.11,16 A method for selective addition of acetone to either α,β-unsaturated esters or amides lacks precedent in the literature. Here, we describe a method for the formal addition of acetone to unactivated Michael acceptors by ring-opening and fragmentation of 3,4-dihydropyranones.

The dihydropyranone is an intriguing structural moiety that can be found in several natural products and biologically active molecules (Scheme 1 A).17–20 For instance, the cat attractant Nepetalactone and anticancer Neocucurbitacin B, isolated from catnip and Luffa opercula respectively, both contain a 3,4-dihydropyranone moiety.21,22 The 5,6-dihydropyranone scaffold is also prevalent in natural products, as seen in the antibiotic Asyprone and the cytotoxic Goniodiol.23,24 Furthermore, the 5,6-dihydropyranone moiety has proven a useful synthon for further manipulation25–26 and a valuable intermediate for the synthesis of natural products.27–28

Unfortunately, the corresponding valorization of 3,4-dihydropyranones remain scarce, despite several potential sites for further manipulation. Which is surprising considering the recent surge in organocatalytic methods yielding 3,4-dihydropyranones.29 For example, in a pioneering report from Studer et al. enals were shown to react with 1,3-carbonyls via oxidative N-heterocyclic carbene (NHC) catalysis yielding 3,4-dihydropyranones (Scheme 1 B).30 Since then, a plethora of NHC-catalyzed reactions yielding homochiral dihydropyranones have been reported based on both oxidative31–33 and redox neutral pathways.34–38 Lately, several strategies that uses oxygen as oxidant has been reported.39–41 The latter approaches represents an important step towards making 3,4-dihydropyranones valuable starting material for further functionalization.32–44

Scheme 1. Structure, biological activity and synthesis of dihydropyranones
Scheme 2. Reactivity of dihydropyranones

Other organocatalytic methods toward the dihydropyranones involve activation of anhydrides with isothioureas, as reported by Smith and coworkers, and enamine catalysis-oxidation sequences as reported by Ma et al.

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 Bronsted bases (Scheme 2 A). 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. A diastereoselective epoxidation of the enol double bond using m-CPBA with only slight erosion of enantiopurity was developed by Chi and coworkers (Scheme 2 B). Diastereoselective alkylation of the corresponding lithium enolate with benzyl bromide has been reported by Evans et al. (Scheme 2 C).

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 2, D).

RESULT AND DISCUSSION

Reaction optimization and scope

While examining the ring-opening of dihydropyranone 1, a striking difference in reactivity was observed upon 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 diketoester 3 in 95 % yield, as previously reported. However, usage of slightly higher loadings of DBU (15 mol%) in 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 1H NMR, suggesting that 2 is formed via a retro-Claisen fragmentation of the 1,3-diketone of compound 3. Fascinated by the difference in reactivity, we optimized the reaction further with respect to ketoester 2. As it turns out, both the structurally related guanidine base 1,5,7-triazabi-cyclo[4.4.0]dec-5-ene (TBD) and potassium hydroxide is capable of mediating the reaction, yielding 2 in slightly lower yields than DBU (Table 1, entry 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 (Table 1, entry 4–6).

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

Table 1. Screening of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard conditions</th>
<th>Yield (2, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>None</td>
<td>89</td>
</tr>
<tr>
<td>2.</td>
<td>TBD instead of DBU</td>
<td>83</td>
</tr>
<tr>
<td>3.</td>
<td>KOH instead of DBU</td>
<td>84</td>
</tr>
<tr>
<td>4.</td>
<td>DABCO instead of DBU</td>
<td>0</td>
</tr>
<tr>
<td>5.</td>
<td>Et3N instead of DBU</td>
<td>0</td>
</tr>
<tr>
<td>6.</td>
<td>K2CO3 instead of DBU</td>
<td>0</td>
</tr>
<tr>
<td>7.</td>
<td>MeCN instead of MeOH</td>
<td>0</td>
</tr>
<tr>
<td>8.</td>
<td>PhMe instead of MeOH</td>
<td>0</td>
</tr>
<tr>
<td>9.</td>
<td>Water instead of MeOH</td>
<td>0</td>
</tr>
<tr>
<td>10.</td>
<td>IPA instead of MeOH</td>
<td>0</td>
</tr>
<tr>
<td>11.</td>
<td>EtOH instead of MeOH</td>
<td>~10%</td>
</tr>
</tbody>
</table>

| 8 | (0.12 mmol), base (0.15 eq.) solvent (0.4 mL), stirred at ambient temperature for 24h. Yield determined by 1H NMR using 1,2,4,5-tetramethylbenzene as internal standard. | 9 | Isolated yield. | 5 equivalents of MeOH added. | 6 | Based on the corresponding carboxylic acid, isopropyl ester or ethyl ester as the product respectively. |
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 benzyl 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 is possible, and methyl substituted 12 could be isolated in 84% yield. Dihydropyranones with larger alkyl groups in the 5-position react considerably slower. For example, a propyl substituted dihydropyranone yielded a mixture of 13 and the corresponding diketone, which proved difficult to separate. Dimethylated dihydropyranones is tolerated by the reaction but required slightly higher loadings of DBU (25 mol%).

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 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 17–20 in 96%, 97%, 89% and 96% yield, respectively. Acyclic secondary amines proved viable nucleophiles and the use of diethylamine yielded amide 21 in 91% yield. The developed procedure also proved suitable for the construction of synthetically useful Weinreb amides exemplified with the synthesis of compound 22, obtained in 89% yield.

**Scheme 3. Scope of dihydropyranones**

Dihydropyranone (1.0 eq.), DBU (0.15 eq.), MeOH stirred at ambient temperature, isolated yield.

**Scheme 4. Scope with respect to the nucleophile.**

Dihydropyranone (1.0 eq.), DBU (0.15 eq.), MeOH stirred at ambient temperature, isolated yield. *Using DBU (0.25 eq.) for 48h.

*Performed at 70 °C.

Several primary amines can also be used as reagents (23–25). For example, cyclohexylamine and aniline derived amides 24 and 25, which could be isolated in 93% and 96% yield, respectively. Lastly, it was 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 26 in 86% yield. Attempts to access iso-propyl or tert-butyl esters in a similar manner were unsuccessful.

We also investigated the possibility of obtaining these valuable products in optically pure form. By relying on our aerobic oxidative protocol for synthesis of dihydropyranones, (S)-1 could be obtained in good yield and 94% ee on gram scale. Treatment of (S)-1 with DBU under standard conditions gave (S)-2 in satisfying 85% yield and 92% ee (Scheme 5). Chiral aminoaacloids are also viable reaction partners and

**Scheme 5. Synthesis of homochiral products.**

(S)-1 (1.0 eq), MeOH and DBU (0.15 eq.), stirred at ambient temperature. Isolated yield. *Using DBU (0.25 eq.) for 48h.

*Performed at 70 °C.
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 aminoalcohol also proved a competent nucleophile yielding product 31 in 92% yield. All reactions proceeded with excellent chemo- and diastereoselectivity without noticeable racemization.

**Kinetic investigation of the reaction mechanism**

In the retro-Claisen fragmentation, a 1,3-diketone reacts to form a ketone and an ester. If the diketone is symmetric only one set of products can form. However, if the diketone is asymmetric, the possibility of forming two different ketones and two different esters arises. Up until this point, we have only discussed dihydropyranones that yield symmetrical diketones when ring-opened (Scheme 3-5). In contrast, a dihydropyranone like 32 yields an asymmetric diketone when ring-opened (Scheme 6). Thus, it can react via two different hemiacetals (33 and 35), to yield two different ketones (15 and 2) and either methyl acetate or methyl benzoate, respectively. When 32 was subjected to the developed conditions, product 15 and 2 was formed in a 1.7:1 ratio.

The low selectivity may seem surprising when considering the stability of the two enolates (34 and 36), since aromatic ketones generally are more acidic than aliphatic ones. One way to approximate the relative stability of the two enolates is to consider the pKa values of two pairs of structurally related ketones (in DMSO): acetone vs. acetoephene (ΔpK_a = 1.8) and pentan-3-one vs. propiophenone(ΔpK_a = 2.7) The comparison implies that 34 is between 60 and 500 times (10^ΔpK_a) more thermodynamically favored compared to 36. Since 34 and 36 are structurally more similar to pentan-3-one and propiophenone than they are to acetone and acetoephene, the true value is probably closer to 500 than it is to 60. The difference between the stability of 34 and 36 and the observed selectivity (1.7:1) indicates that the cleavage of the C–C bond is not under thermodynamic control.

Steric effects (methyl vs. phenyl) in the formation of hemiacetals 33 and 35 is an alternative explanation for the observed selectivity. To estimate these effects, we used the Taft steric parameter, E_s, which is derived from the rate of hydrolysis of substituted esters. E_s is defined as E_s = log(kMe/kM) , where kMe is the rate of hydrolysis for the ester of interest and kM is the corresponding reference rate of the methyl ester. Because the addition of water to the protonated ester is rate determining in these reaction, the Taft parameter should be a valid indicator of the steric effect in the formation of the two hemiacetals.

The Taft steric substituent constant for a phenyl group is −2.55. The value implies that formation of acetal 33 should be approximately 350 times (10^-(2.55)) faster than formation of 35. The value is far from the observed selectivity of 1.7:1. Clearly, the rate of formation for the anionic hemiacetal is not the determining factor behind the observed selectivity.

To gain further insight into the reaction mechanism, we performed a series of kinetic experiments. 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 eq. 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, while the transformation of 3 to 2 was considerably slower. The significant difference in rates made it practical to study the kinetics of the retro-Claisen fragmentation of the 1,3-diketone moiety in more detail.

The consumption of 3 was monitored at different loadings of DBU (0.1, 0.2 and 0.3 eq.). Plotting ln[3] against time shows a linear dependence (R^2 > 0.97, see ESI Figure S2), implicating a first-order reaction with respect to 3. The fact that we observe first-order reaction kinetics is not surprising because the reaction is performed under pseudo-first order conditions, with [MeOH]>>[3] and the concentration of DBU being constant.

To evaluate the reaction order with respect to DBU we used the normalized time scale method developed by Bures. The Bures method relies on time resolved concentration profiles of reactions, each with a different concentration of catalyst. The time axis is in the approach normalized by [cat]^n, where n equals the reaction order in catalyst. The method exploits the fact that the
catalyst concentration remains constant during the course of a reaction, which enables one to factorize out [cat]$^n$ from the integrated rate expression. In other words, when the temporal concentration of the reaction is plotted against time$^{n}$[cat]$^n$ where $n$ equals the reaction order, the lines superimpose. When we apply the normalized time scale method, the overlap is considerably better for $n=2$ (Figure 2, right graph) than for $n=1$ (Figure 2, left graph), revealing that the reaction is of the second order with respect to DBU.

A normal kinetic isotope effect (KIE, $k_H/k_D$) of 2.3 was measured by running the reaction in MeOH and MeOH-d$_4$ (Scheme 7). 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. The observed kinetics (Figure 1), indicates that the rate determining step should be part of the retro-Claisen fragmentation. The commonly accepted view is that C–C bond breakage is rate determining for retro-Claisen fragmentations under alkaline conditions. Combined, knowledge of a primary KIE and kinetics of the second order with respect to DBU made us wonder if both DBU and the corresponding acid (DBUH$^+$) could play roles in the retro-Claisen reaction.

We have envisioned two different mechanisms that allow for our combination of experimental observations. In both situations DBUH$^+$ acts as a hydrogen bond donor (HBD) (path A and B, c.f. Figure 3). Protonated amines are known to be strong HBDs. With HBD parameter values of $\alpha \sim 5$ they are, for example, considerably stronger than alcohols. Aliphatic alcohols such as methanol have HBD parameter values of $\alpha \sim 2.7$. 

Scheme 7. Determination of kinetic isotope effect.

The two considered mechanisms begin in the same way. In the first step, which is very rapid, DBU acts as a Brønsted base to catalyze the ring-opening of 1 to 3 (Figure 3). In the second step of both mechanisms, DBU again functions as a Brønsted base yielding an anionic hemiacetal. The difference between path A and B comes about in the third step, in which DBUH$^+$ is coordinated to either the ketone (in path A) or the anionic hemiacetal via hydrogen bonding (in path B). We distinguish between these two complexes by naming them 37 (in path A) and 39 (in path B).

In path A, 37 collapses into the hydrogen bonded enolate 38 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.

In path B, 39, instead collapses to 40, a complex different from 38 in that it lacks an explicit hydrogen bond to DBUH$^+$. In path B it is instead the formed methyl acetate 41 which is hydrogen bonded. Dissociation of complex 41 and subsequent protonation of enolate 40 yields product 2 and regenerates DBU.

Quantum chemical investigation of reaction mechanisms

The type of mechanisms we are considering (A and B, c.f. Figure 3) are both able to explain the observed first order dependence in 3 and the second order dependence in DBU, the primary KIE and the sensitivity towards steric encumbrance close to the 1,3-diketone moiety (c.f. products 13, 14, 15 and 25). 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 catalyzed pathways is more likely. The calculations were performed using the Gaussian 16 package, revision B.01. Geometry optimizations and frequency analyses were performed at the ωB97X-D/6-311+G(2d,p) level of theory.
energy of DBUH$^+$. More accurately estimates to 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$^2$ 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 5). TS$^2$ calculates as second to lowest, at $\Delta G^\ddagger=20.1$ kcal/mol. Finally, TS$^1$, 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). 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).

Conformational sampling is one possible source of error. In addition to the rate determining steps outlined in Figure 4, we have carefully evaluated a large number of other competing possibilities. 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 as suggested by Wolff et al. for a related process, and a cyclic TS as suggested in Lewis acid catalyzed retro-Claissen reactions. The alternatives mentioned calculates as distinctly higher in free energy (typically $\Delta G^\ddagger>30$ kcal/mol, see figure S10). 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 ~24h).

The $C$–$C$ bond breakage step, e.g. $37 \rightarrow 38$, is exergonic relative the anionic hemiacetal in all three cases, but to what extent varies considerably (Figure 4). Our calculations for this step might be less exact due to the separate implicit
Figure S10

Figure 5. Optimized structures and selected distances of TS\(^A\), TS\(^B\) and TS\(^C\) (in Å) together with Gibbs energy reaction barriers (298K, 1M, in kcal/mol).

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. Overall, our computational study supports pathway A (Figure 3) as more probable. 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 38 in path A (~4.5 kcal/mol compared to path C) is considerably larger than the stabilization of 39 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 5).\(^{30}\)

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 (\(\angle_{OHN} = 177^\circ\)) in TS\(^A\), while in TS\(^B\) the hydrogen bond is more skewed (\(\angle_{OHN} = 163^\circ\)). 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 mechanisms even without the interactions associated with the slipped stacked conformation shown in Figure 5. Which is because the lost interactions (mainly dispersion) is partly compensated by a stronger hydrogen bonding in TS\(^D\) (\(D_{O,H} = 1.73\) Å in TS\(^D\) vs. \(D_{O,H} = 1.78\) Å in TS\(^A\), Figure S10 in the ESI).

**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-dihydropyranoles 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, and primary, secondary and Weinreb amides. The synthetic approach enables access to chiral 5-oxo-hexanoates and stereoselective functionalization of chiral aminoalcohols 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 proceed in first order with respect to the 1,3-diketone and in second order 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, in analogy to bifunctional thioureas. 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 and highlights the possibility of using organic superbases as bifunctional catalysts.
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