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# Aliphatic Ketone Claisen Rearrangement: Troubleshooting the Transetherification Step by Identifying a Stable Acid Catalyst

Veera K. Bruce,[a] Kaveh Farshadfar,[b] Aino Rolig,[a] Kari Laasonen,[b] and Petri M. Pihko*[a]

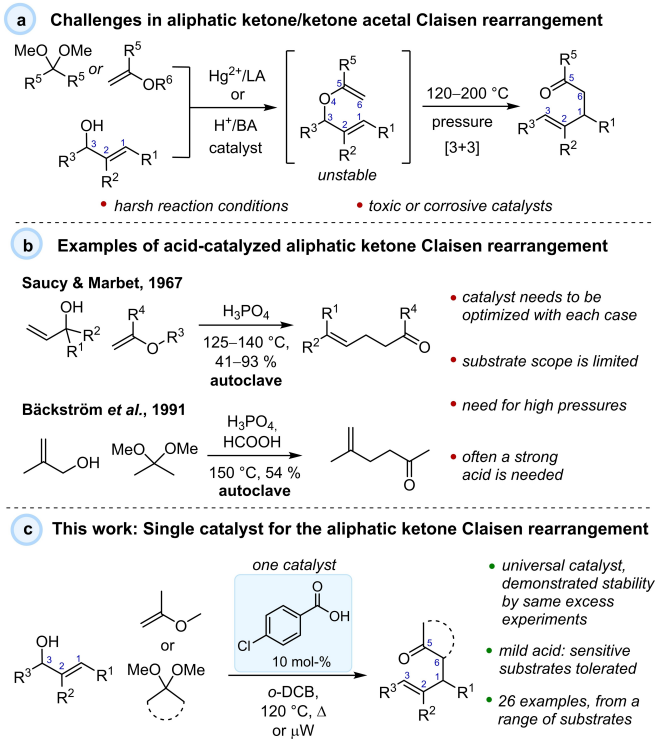
After optimization for retention of catalytic activity, 4-chlorobenzoic acid emerged as the optimal catalyst for the aliphatic ketone Claisen rearrangement. The optimal catalyst enables a one-pot, metal-free, catalytic protocol from allylic alcohols to γ,δ-unsaturated ketones. The optimized process tolerates a range of substrates, including substituents with acid-labile protecting groups. Reaction monitoring and DFT studies of the aliphatic ketone Claisen process agree that the ultimate rearrangement step typically has the highest activation barrier.

## Introduction

The aliphatic Claisen rearrangement is a well-established method for the synthesis of γ,δ-unsaturated carbonyl compounds, such as esters (Johnson-Claisen),[1] carboxylic acids (via silyl ketene acetals, Ireland-Claisen)[2] or amides (Eschenmoser-Claisen).[3] In contrast, the corresponding γ,δ-unsaturated ketones are less commonly accessed via the Claisen rearrangement.[4] While the Johnson-Claisen variant readily proceeds under mild carboxylic acid catalysis with ortho esters, typical literature conditions for promoting the corresponding Claisen rearrangement with ketone acetals/enol ethers include strong acids, such as $H_3PO_4$[5,6] and the use of autoclaves or high pressures (Scheme 1).[7,8] For a limited range of allylic alcohols, Daub and co-workers reported success with mild carboxylic acid catalysts.[7e–f] Alternatively, the aliphatic Claisen rearrangement reactions to give ketones can be promoted by $Hg^{2+}$ salts under milder conditions, but the toxicity of $Hg^{2+}$ is an obvious deterrent.[9]

Even with mild acids, the aliphatic ketone Claisen rearrangements suffer from the lack of universal catalyst. Faulkner and Johnson concluded in 1973 that *"there is no way to predict the best acid catalyst"* for ketone Claisen reactions with unsaturated ketone acetals.[7a] Baeckström and Li[10,11] reported that the Claisen reactions with allylic alcohols and 2,2-dimethoxypropane required separate optimization for each substrate. We hypothesized that catalyst decay might lie behind these erratic results. Surprisingly, typical experimental optimization workflows in organic synthesis do not systematically address the issue of catalyst decomposition.

Herein we show that 4-chlorobenzoic acid emerges as an optimal, stable, and universal catalyst for the ketone Claisen rearrangement. A wide range of allylic alcohol classes are tolerated, providing the γ,δ-unsaturated ketones in up to quantitative yields.




**Scheme 1.** Acid catalyzed aliphatic ketone Claisen rearrangement.

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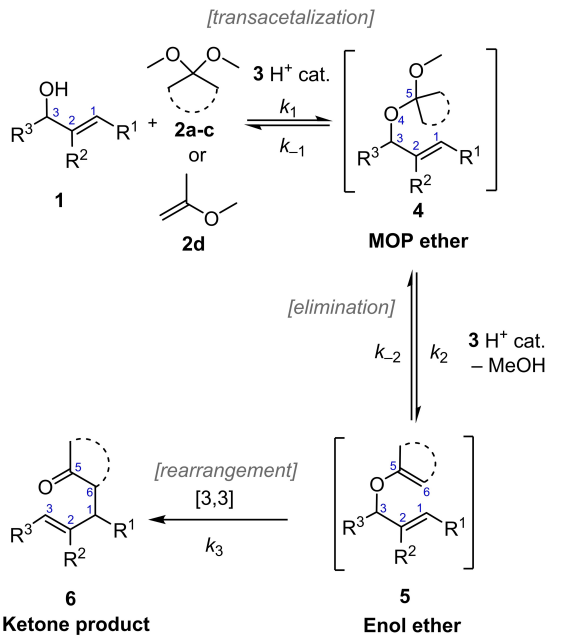
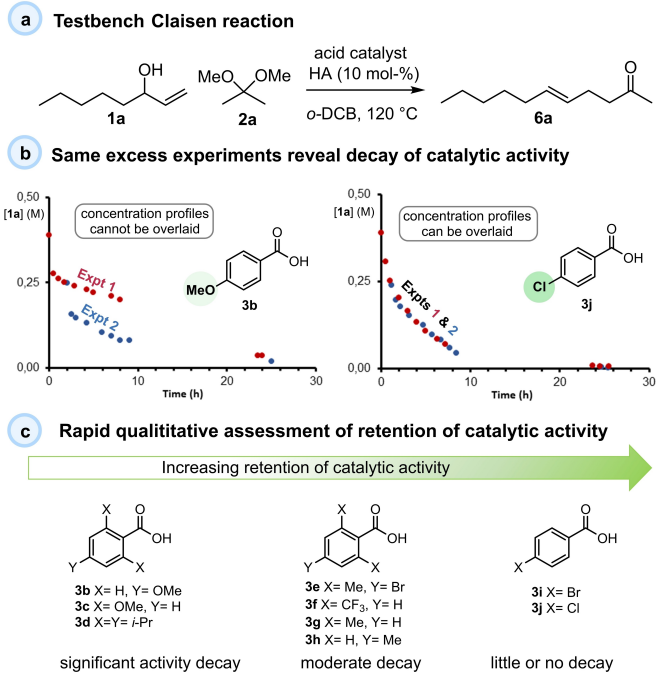



**Scheme 2.** Steps of the aliphatic ketone Claisen rearrangement.




**Scheme 3.** Optimization of the catalysts for the ketone Claisen rearrangement. (a) Test reaction. (b) Examples of same excess experiments with two benzoic acids, **3b** and **3j**. Typical initial conditions: for catalyst **3b**, experiment 1 (red dots) **1a** (0.39 M), **2a** (1.17 M), **3b** (0.039 M); experiment 2 (blue dots) **1a** (0.20 M), **2a** (0.98 M), **3b** (0.039 M). (c) Observed trends with different benzoic acids in the transacetalization -Claisen rearrangement sequence.

## Results and Discussion

### Experimental Results and Discussion

The aliphatic ketone Claisen rearrangement is believed to involve three distinct steps: (1) transacetalization to give the mixed methoxypropyl ether (MOP ether),[12] (2) elimination of methanol to give the enol ether and (3) the [3,3]-sigmatropic rearrangement (Scheme 2).[6] The first transacetalization reaction quickly establishes equilibrium following the elimination reaction. The first two steps are known to be acid catalyzed, but it is uncertain whether the acid catalyst participates in the last rearrangement step. Hydrogen bonding urea and thiourea-based catalysts are known to accelerate the sigmatropic rearrangement step, but the range of substrates amenable to such catalysts is generally limited.[13,14]

Instead of optimizing conversion at a certain endpoint, we decided to optimize for catalyst stability. We used 1-octen-3-ol (**1a**) and 2,2-dimethoxypropane (**2a**) as the substrates for the screens (Scheme 3). After initial preliminary tests with stronger acids, which generally resulted in significant decomposition and erratic results, we progressed to systematic screens for catalyst stability. In these screens, we focused on weaker substituted benzoic acids (**3a**–**3j**, see Scheme 3). The rationale for using benzoic acids was that a wide range of substituted benzoic acids is readily available, assisting in systematic optimization.

For simplicity, the extent of catalyst decay was evaluated by qualitatively plotting the consumption of **1a** (monitored by GC, see the SI for details) under two different initial concentrations of **1a** and **2a** but same excess of **2a**.[15] The same excess method enables visual identification of catalysts that maintain their turnover rates over time: the reaction profiles can be overlaid if the catalytic activity is not decaying during the experiments.[15] As shown in Scheme 3b, different benzoic acids gave very different results in these experiments. 4-Bromobenzoic acid (**3i**) and 4-chlorobenzoic acid (**3j**) were generally the best catalysts (Scheme 3c), demonstrating only slight (**3i**) or no observable activity decay (**3j**). (For details and more examples, please see the Supporting Information (SI)). Catalyst **3j** also led to the highest conversion to product (80%).

We note that neither simple p$K_a$ trends nor steric effects can readily explain why **3j** emerged as the optimal catalyst in this study.[16] Control experiments with **3b** indicated that esterification of the catalyst with either methanol (generated from **2a**) or with **1a** cannot be detected under the reaction conditions (see the SI), indicating that esterification is not the reason for decaying catalytic activity. Nevertheless, we noted that replacing 2,2-dimethoxypropane **2a** with 2-methoxypropene **2d** accelerated the consumption of allyl alcohol (**2a** $t_{1/2} \approx 2$ h, **2d** $t_{1/2} \approx 0.5$ h) and raised the conversion to product **6a** to 85%, providing a set of optimized conditions for further elaboration.

After identifying the optimal catalyst, the catalytic Claisen rearrangement with **3j** was screened with variety of

allyl alcohol classes (see Figure 1). The reactions between the allyl alcohols **1a–j** and 2-methoxypropene **2d** in 1,2-dichlorobenzene (*o*-DCB) were run at 120 °C under thermal conditions without pressure (reflux, open flask). The yields with *class 1* alcohols with $R^3$ substituents varied between 40% to quantitative (Scheme 4). Interestingly, alcohols with phenyl and *p*-methoxyphenyl groups as $R^3$ substituents led to low yields (**6f**, **6g**) but a *p*-trifluoromethylphenyl group was well tolerated (**6h**). Both Boc-protected amines (**6d**) and allylic benzyl ethers (**6i**) survived the reaction conditions.

Under the new catalytic conditions, only *class 1a* alcohols gave acceptable yields of the ketone products at 120 °C under thermal, open flask conditions (see Scheme 4). With other allylic alcohol classes, the reactions typically stopped at the enol ether intermediate **5** and they were characterized by decomposition. To overcome the apparently higher activation barriers with the *class 2* and *3* alcohols, we anticipated that microwave conditions might facilitate safe heating under pressure without loss of volatile reagents.

To our delight, Claisen rearrangements with **3j** as the catalyst in a sealed microwave tube at 120 °C led to excellent conversions with all alcohol classes (Scheme 5). The low yield with **6f** under thermal (open flask conditions, see Scheme 4) was improved to 98% in 1 mmol scale in the microwave conditions (Scheme 5). The stability of four

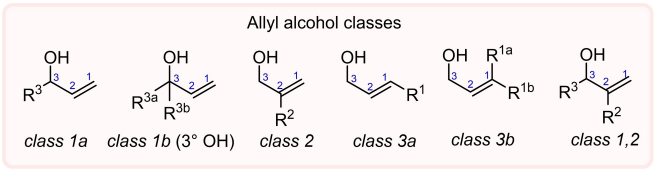
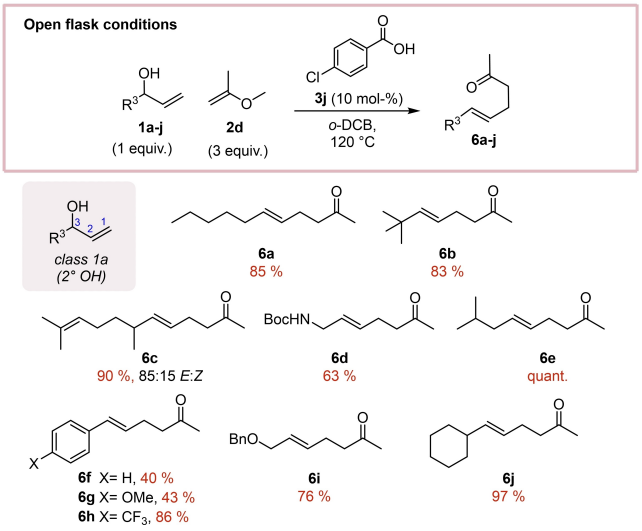
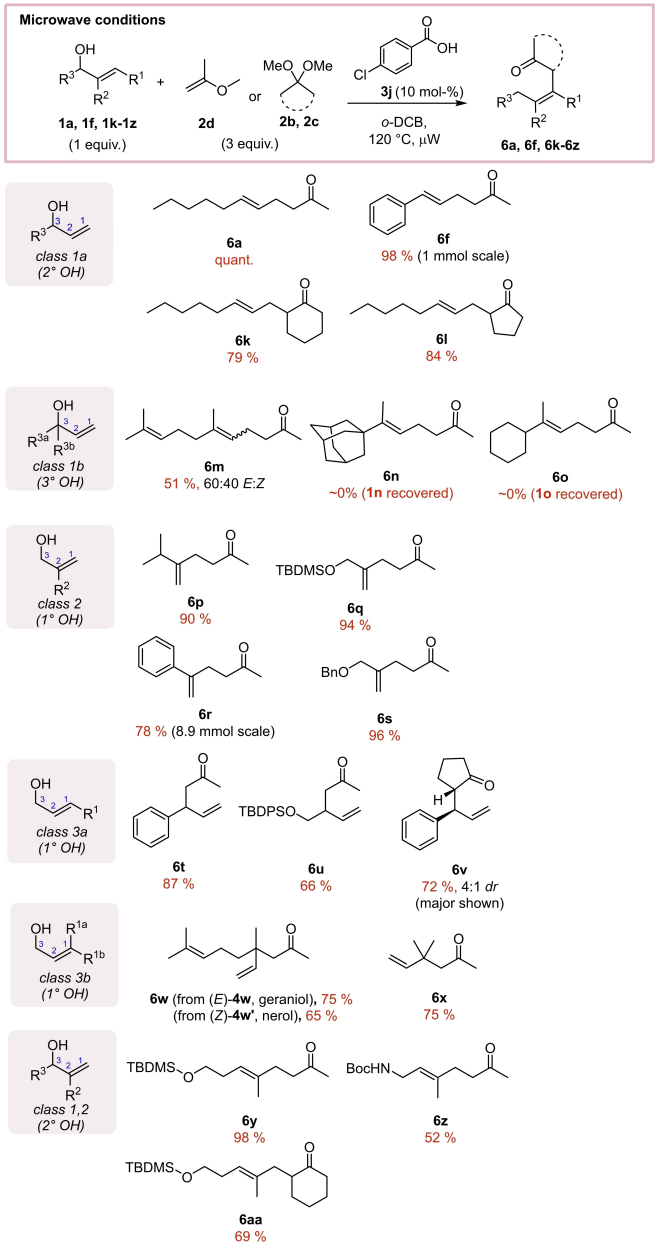



**Figure 1.** Classification of allylic alcohols by their substituent patterns in this study.




**Scheme 4.** Substrate scope of the ketone Claisen rearrangement for *Class 1a* allylic alcohols: thermal conditions.




**Scheme 5.** Substrate scope of the ketone Claisen rearrangement under microwave conditions.

different protecting groups were explored, and silyl- or benzyl-protected alcohols (**6q**, **6s**, **6u**, **6y**, **6aa**) and Boc-protected amines (**6z**, see also **6d** in Scheme 4) survived the conditions, although the silyl- and benzyl-protected alcohols generally gave better yields. The reaction could also be readily scaled up to 8.9 mmol scale (**6r**, 78% yield).

Limitations of the method include highly hindered tertiary alcohols **1n** and **1o** (*class 1b*): their exposure to the reaction conditions resulted in the recovery of the starting materials. However, the reaction with less hindered *class 1b* substrate linalool **1m** led to **6m** in 51% yield. Cyclic ketones could also be readily accessed using 1,1-dimethoxycyclo-

pentane **2b** or 1,1-dimethoxycyclohexane **2c** (for products, see **6k**, **6i**, **6v** and **6aa** in Scheme 5).[17]

The reactivity difference between *class 1* and *class 2* substrates can be illustrated by reaction progress curves with **1a** (*class 1*) and **1p** (*class 2*) as substrates under the standard thermal conditions (o-DCB, 120 °C). While the reaction with **1a** proceeds cleanly to afford almost quantitative conversion to **6a** (via MOP ether **4a** and enol ether **5a**), with **1p**, the reaction gives successively **4p** and then the enol ether **5p**, but its conversion to **6p** is slow under these conditions (Scheme 6).

## Computational Results and Discussion

The reaction pathway was also investigated by density functional theory (DFT), employing the SMD/wB97XD/def2-TZVP//SMD/M06-2X/6-31G(d) level of theory in *o*-DCB (for details, see the SI). Figure 2 illustrates the energy profile for 1-octen-3-ol (**1a**) substrate at 120 °C (393 K). Catalyst **3j** serves as the acid-base catalyst in the steps preceding the Claisen rearrangement (Figure 2), but all attempts at locating a TS where **3j** assists the final Claisen rearrangement step resulted in TSs that were higher in energy than those without **3j**. The computed mechanism highlights the dual role of the carboxylate/carboxylic acid in synchronous proton transfer events in both $TS_{1a-4a}$ and $TS_{4a-5a}$.[6,12] The MOP ether intermediate **4a** is the most stable species prior to the product **6a**, which is consistent with experimental data (Scheme 6) indicating a rapid buildup of **4a** in the reaction mixture. Finally, **5a** undergoes a Claisen rearrangement to yield the final product **6a**. Generally, the ultimate Claisen rearrangement step has the highest barrier (see Table 1).[18] In addition, the barrier for the rearrangement of **5p** (*class* 2), $TS_{5p-6p}$ has a barrier that is 1.2 kcal/mol higher in energy than the corresponding $TS_{5a-6a}$. This result is in good agreement with the experimental results (Scheme 6) which clearly show that the reactivity difference between substrates **1a** and **1p** is due to the ultimate Claisen rearrangement step.

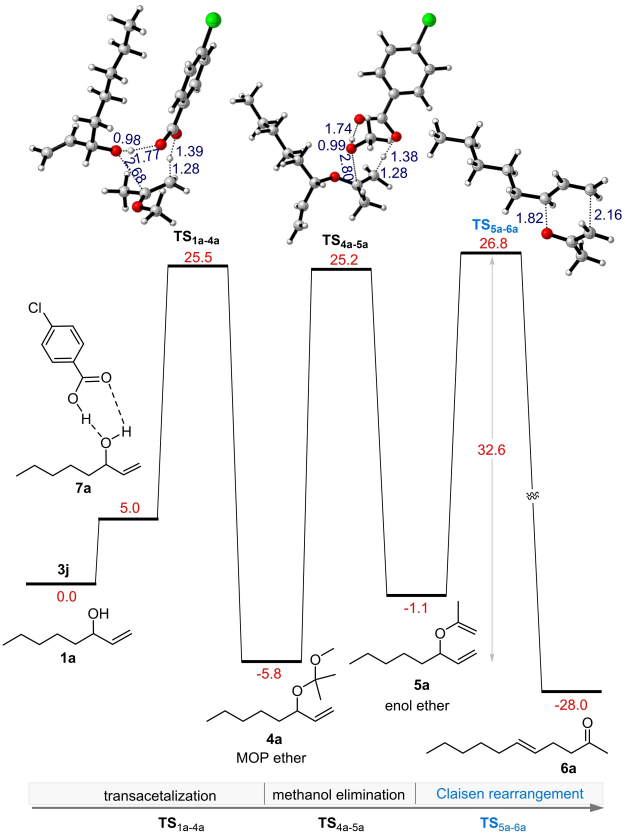
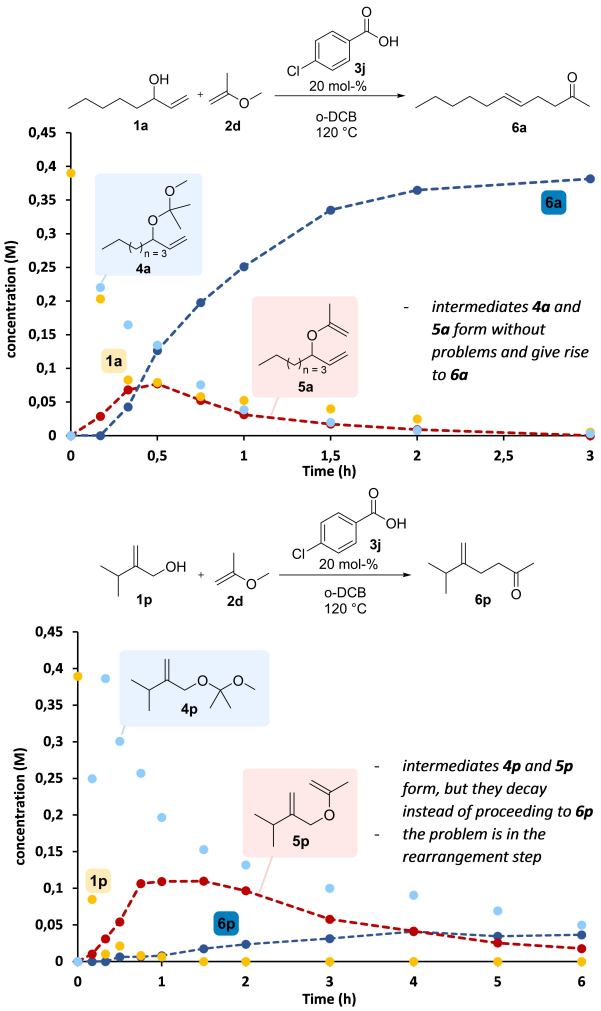



**Figure 2.** Computational free energy profile (at 120 °C) for the acid-catalyzed transetherification-Claisen rearrangement sequence starting from **1a** and **2d**. 2-methoxypropene and methanol side product are omitted from the profile for clarity, but they are included in the free energy calculations. The relative free energies are given in kcal/mol (in red). Selected distances (Å) are annotated in blue.




**Scheme 6.** Reaction progress curves for the reactions with **1a** and **1p**.

**Table 1.** The calculated free energies at 120 °C for the transition states ($TS_{1-4}$), ($TS_{4-5}$) and the final Claisen rearrangement step ($TS_{5-6}$), and stationary points for selected substrates.

| Class | Substrate | μW | $TS_{1-4}$ | **4** | $TS_{4-5}$ | **5** | $TS_{5-6}$ | **6** |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | no | 25.4 | −5.8 | 25.2 | −1.1 | 26.8 | −28.0 |
| 2 | **1p** | yes | 23.7 | −5.2 | 24.5 | −0.6 | 28.5 | −24.5 |
| 2 | **1r** | yes | 24.6 | −6.5 | 24.8 | −0.8 | 26.6 | −25.5 |
| 3a | **1t** | yes | 24.4 | −4.7 | 25.9 | −1.4 | 29.6 | −14.6 |
| 3b | **1x** | yes | 25.8 | −6.0 | 25.2 | −0.5 | 31.0 | −17.2 |
| 1,2 | **1z** | yes | 26.0 | −2.4 | 32.0 | 3.0 | 31.4 | −20.0 |

## Conclusions

In conclusion, we report that 4-chlorobenzoic acid is a stable, general catalyst for the aliphatic Claisen rearrangement to give γ,δ-unsaturated ketones. Importantly, the most viable catalyst was identified by monitoring decay of catalytic activity with different catalysts. The new catalytic protocol tolerates a wide range of allylic alcohols as substrates under either open flask conditions or under microwave heating.

## Supporting Information Summary

Supporting Information includes: Experimental procedures, optimization and same excess experiments, characterization data, and computational details, and copies of NMR spectra and GC chromatograms (PDF), XYZ coordinates of computed structures (ZIP) and FAIR data, including the primary NMR FID files, for compounds **1b–1z, S1a–S1c, 6a–6aa, S6a–S6c, 4a, 4p, 5a, 5p** (ZIP).

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## *Conflict of Interests*

The authors declare no conflict of interest.

## *Data Availability Statement*

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Claisen rearrangement · Acid catalysis · Reaction optimization

[1] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741–743.
[2] C. M. McFarland, M. C. McIntosh in *The Claisen Rearrangement: Methods and Applications* (Eds.: M. Hiersmann, U. Nubbemeyer), VCH, Weinheim, **2007**, pp. 117–210.
[3] A. E. Wick, D. Felix, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, *47*, 2425–2429.
[4] a) K. Maruoka, H. Ichikawa in *The Claisen Rearrangement: Methods and Applications* (Eds.: M. Hiersmann, U. Nubbemeyer), VCH, Weinheim, **2007**, pp. 45–85; b) P. Wipf in *Comprehensive Organic Synthesis*, Vol. 5 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 827–873; c) S. J. Rhoads, R. N. Raulins, *Org. React.* **2011**, *22*, 1–252; d) F. E. Ziegler, *Chem. Rev.* **1988**, *88*, 1423–1452; e) A. M. M. Castro, *Chem. Rev.* **2004**, *104*(6), 2939–3002.
[5] R. Marbet, G. Saucy, *Helv. Chim. Acta* **1967**, *50*(7), 2095–2100.
[6] G. Saucy, R. Marbet, *Helv. Chim. Acta* **1967**, *50*(7), 2091–2095.
[7] For examples of aliphatic Claisen rearrangement to give ketones, seea) J. D. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1973**, *24*, 553–563; b) P. Baeckström, L. Li, *Tetrahedron* **1991**, *47*(32), 6521–6532; c) A. Srikrishna, P. Kumar, *Tetrahedron Lett.* **2000**, *56*, 8189–8195; d) D. S. Reddy, *Org. Lett.* **2004**, *6*(19), 3345–3347; e) G. W. Daub, M. A. McCoy, M. G. Sanches, J. S. Carter, *J. Org. Chem.* **1983**, *48*(22), 3876–3883; f) G. W. Daub, S. R. Lunt, *Tetrahedron Lett.* **1983**, *24*(41), 4397–4400; g) W. Daub, M. G. Sanchez, R. Cromer, L. L. Gibson, *J. Org. Chem.* **1982**, *47*(4), 743–745. For additional examples and discussion, see the Supporting Information. We use the term "aliphatic ketone Claisen rearrangement" herein as a broad class of aliphatic Claisen rearrangements that proceed via enol ether intermediate such as **5** and gives γ,δ-unsaturated ketones as products.
[8] For examples of aliphatic Claisen rearrangement to give aldehydes, see a) G. Buchi, J. D. White, *J. Am. Chem. Soc.* **1964**, *84*(14), 2884–2887; b) H. Yamamoto, H. L. Sham, *J. Am. Chem. Soc.* **1979**, *101*(6), 1609–1611; c) S. A. Bal, P. Helquist, *Tetrahedron Lett.* **1981**, *22*(40), 3933–3936; d) K. Yu, Z. Yang, C. Liu, S. Wu, X. Hong, X. Zhao, H. Ding, *Angew. Chemie.* **2019**, *131*(25), 8644–8648. For additional examples and discussion, see the Supporting Information.
[9] For examples of $Hg^{2+}$ salt promoted vinyl ether formation see a) W. H. Watanabe, L. E. Conlon, *J. Am. Chem. Soc.* **1957**, *79*, 2828–2833; b) A. W. Burgstahler, I. C. Nordin, *J. Am. Chem. Soc.* **1961**, *83*(1), 198–206; c) G. Buchi, J. D. White, *J. Am. Chem. Soc.* **1964**, *84*(14), 2884–2887; d) H. Yamamoto, H. L. Sham, *J. Am. Chem. Soc.* **1979**, *101*(6), 1609–1611; e) S. A. Bal, P. Helquist, *Tetrahedron Lett.* **1981**, *22*(40), 3933–3936; f) K. Yu, Z. Yang, C. Liu, S. Wu, X. Hong, X. Zhao, H. Ding, *Angew. Chem. Int. Ed.* **2019**, *58*(25), 8556–8560; g) S. A. Snyder, D. S. Treitler, A. P. Brucks, W. A. Sattler, *J. Am. Chem. Soc.* **2011**, *133*(40), 15898–15901.
[10] P. Baeckström, L. Li, *Tetrahedron* **1991**, *47*(32), 6521–6532.

[11] P. Baeckström, L. Li, I. Polec, C. R. Unelius, W. R. Wimalasiri, *J. Org. Chem.* **1991**, *56*(10), 3358–3362.
[12] For examples of the transacetalization to get the MOP-ethers see a) N. B. Lorette, W. L. Howard, *J. org. Chem.* **1960**, *25*, 521–525; b) P. H. Dussault, K. R. Woller, *J. Chem. Soc., Chem. Commun*. **1992**, *60*(2), 2024; c) J. Choutka, R. Pohl, K. Parkan, *ACS Omega* **2018**, *3*(7), 7875–7887.
[13] D. P. Curran, L. H. Kuo, *Tetrahedron Lett.* **1995**, *36*(37), 6647–6650.
[14] C. Uyeda, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*(29), 9228–9229.
[15] For an overview, see: C. D. T. Nielsen, J. Burés, *Chem. Sci.* **2019**, *10*, 348–353. We use the term "decaying catalytic activity" instead of "catalyst decay" since we cannot completely rule out inhibition by the intermediates and/or the products as a rationalization of the differences between the acid catalysts. The temporal resolution of the experiments is not sufficient to reliably pinpoint the origin of the decay at this time.
[16] Previously, reaction progress monitoring has been used to in reaction optimization to obtain the rates and to predict the optimal catalyst from the rate data. See: A. Yada, T. Matsumura, Y. Ando, K. Nagata, S. Ichinoseki, K. Sato, *Synlett.* **2021**, *32*, 1843–1848. DOI: 10.1055/a-1304-4878.
[17] During the preparation of this manuscript, a transacetalization-Claisen rearrangement was reported with **2c** and *class 3a*-type substrates using a solid acid catalyst. See: K. Kobayashi, C. Negoro, J. Takaishi, K. Masuda, S. Kobayashi, *Org. Chem. Front.* **2024**, *11*, 1990–1995https://doi.org/10.1039/D3QO01889J.
[18] For an earlier DFT study, see: T. R. Ramadhar, R. A. Batey, *Comput. Theor. Chem.* **2011**, *976*, 167–182. The computed barriers of the Claisen rearrangement step are in general agreement with the results reported herein.

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