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Steering Reaction Pathways: From Benzyl Claisen Rearrangements to Powerful Ionic Shifts

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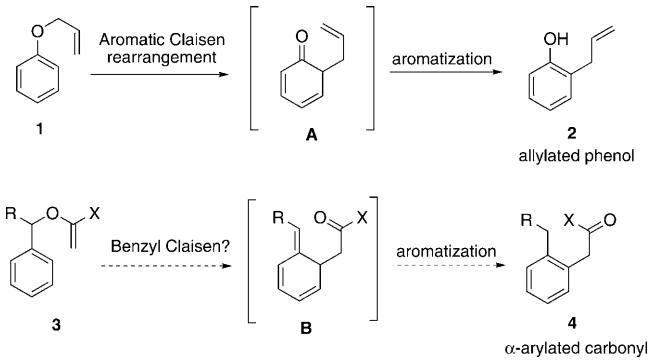
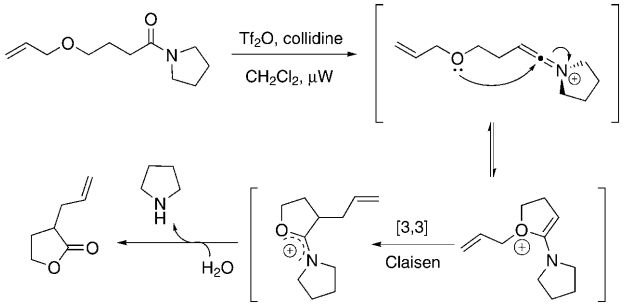
The aromatic Claisen rearrangement is originally the skeletal rearrangement of allylphenyl ethers **1** into *o*- (or *p*-) allylated phenols **2** (Scheme 1).[1] This transformation, assumed to proceed through a dearomatized cyclohexadienone **A**, was originally reported by Claisen nearly 100 years ago and is arguably a "textbook reaction" in organic chemistry.[2] Intriguingly, the analogous rearrangement of benzylvinyl ethers **3** is much less developed. Presumably, the energetic barrier associated with generation of the considerably less-stabilized triene intermediate **B** is too high, and various literature reports actually document the unfeasibility of this process as a general transformation, particularly if R = H (**3a**).[3] This is a remarkable fact, given that the potential products arising from rearrangement of **3** would be the valuable α-(*ortho*-alkyl)arylated carbonyl derivatives **4**.[4,5,6]



Scheme 1. Aromatic Claisen rearrangement and proposed benzyl Claisen variant.

Our group has recently reported a novel "Claisen-like" rearrangement of keteniminium salts that allows direct and stereoselective access to challenging substituted lactones.[7] As depicted in Scheme 2, this process initially converts simple ω-allyloxyamides into keteniminium ion intermediates, thus triggering an unusual cascade of nucleophilic attack and sigmatropic rearrangement events that lead to the final products. We were eager to address the challenge of developing a "benzyl variant" of this reaction because it could potentially lead to synthetically useful α-arylated lactones.[8,9] We describe, herein, our preliminary results in this endeavor, as well as the mechanistic exploitation of a side result that permits us to advance our method beyond strictly pericyclic reaction pathways.



Scheme 2. Aliphatic Claisen rearrangement and proposed mechanism; Tf = trifluoromethanesulfonyl.

We initially explored the rearrangement of the readily available benzyloxyamide **5a** (Scheme 3). Unsurprisingly (see above), this proved a difficult transformation although the desired product could be detected from the very first attempts. After reaction optimization (not shown), we were pleased to obtain the α-arylated lactone **6a**, with an *ortho*-methyl substituent, in moderate yield. We then proceeded to examine the scope of the reaction (Scheme 3). Since the starting benzyloxyamides are easily accessible by simple benzylation of the corresponding hydroxyl derivatives,[10] a broad range of substrates could be prepared. The rearrangement proved to be tolerant to the presence of varied substituents on the aromatic ring, affording the desired α-arylated lactones **6a–6e** in moderate yields. Indeed, the transformations in Scheme 3 conceptually represent rare metal-free α-arylation reactions of lactones,[11] delivering compounds with peculiar aromatic substitution patterns that would not be straightforward to prepare by other routes.

Interestingly, the methyl mandelate derivatives **5f–5i** ($R_2 = CO_2Me$, Scheme 3) smoothly rearranged to α-arylated lactones **6f–6i** in very good to excellent yields.[4d] We presume that the introduction of an electron-withdrawing substituent at the benzylic position (R in compounds **3**,

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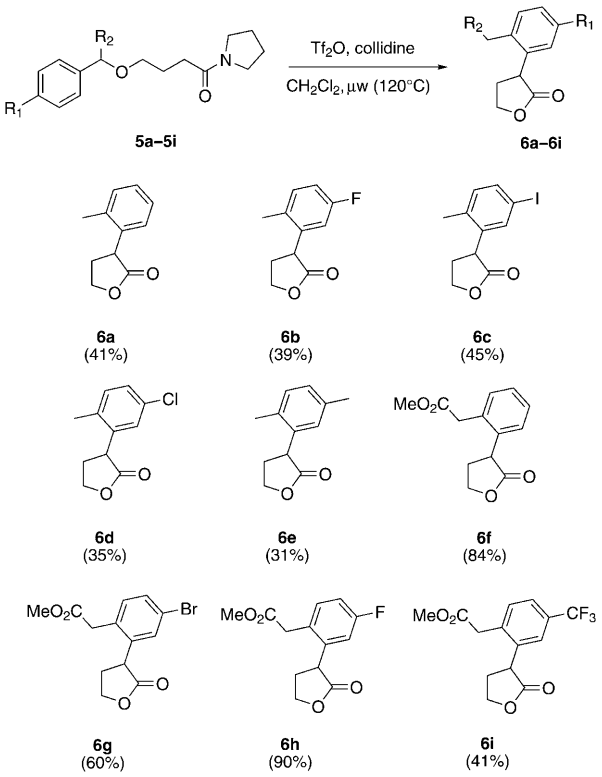
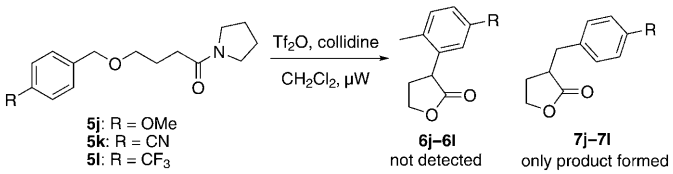


Scheme 3. Scope of the benzyl Claisen rearrangement.



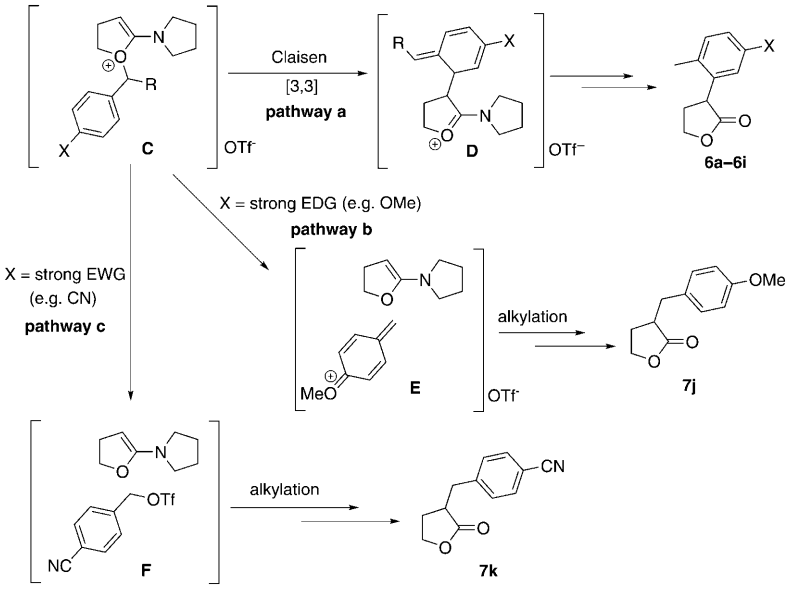
Scheme 4. Formation of α-benzylated lactone products.

Scheme 1) renders the energetics of the rearrangement more favorable through conjugative stabilization of intermediate **B** (see Scheme 1). Importantly, not only is the ester function well tolerated by the rearrangement conditions, but the products thus obtained contain two chemo-differentiated carboxylate moieties for further elaboration.

In addition to the α-arylated lactones, most of the crude reaction mixtures always displayed the presence of the corresponding α-benzylated lactones as side products. In particular, substrates **5j**–**5l** (Scheme 4) afforded the benzylic transfer adducts **7j**–**7l** as the only rearranged products of the reaction. Although this was somewhat anticipated in the case of the electron-rich *para*-methoxy benzyl moiety of **5j**, we were surprised to observe a similar phenomenon for the electron poor **5k** and **5l**. Our working mechanistic hypothesis to accommodate these observations is summarized in Scheme 5. After keteniminium formation, intramolecular nucleophilic attack to the benzyl-vinyl oxonium intermediate **C** takes place. Intermediate **C** can undergo a charge-accelerated "Claisen-like" [3,3] sigmatropic rearrangement,[7] delivering the α-arylated lactone products via the putative dearomatized species **D** (Scheme 5, pathway a). On the other hand, the observed formation of "benzyl-transfer" products suggests the dissociation of the benzylic moiety from the oxonium intermediate **C**, generating two fragments **E**, the recombination of which could account for product **7j** (Scheme 5, pathway b). An alternative mechanistic scenario might explain the formation of such products from electron-poor benzyl moieties **7k**–**7l** as proceeding through an uncharged electrophile of the type depicted in **F** (Scheme 5, pathway c).

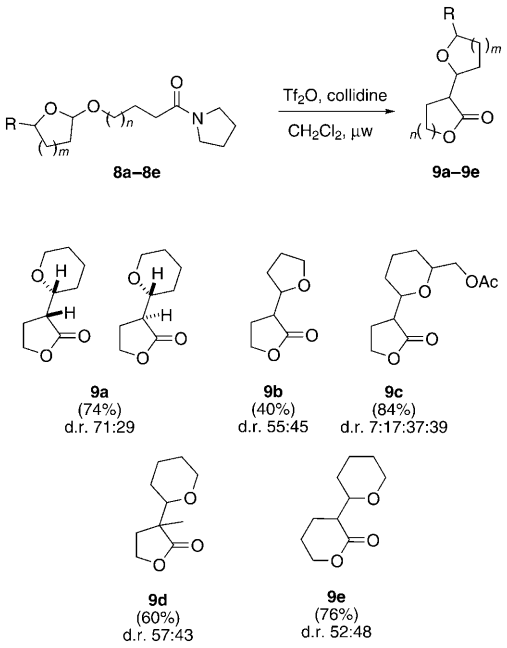
The formation of such benzyl-transfer products **7j**–**7l** was particularly informative. Since our mechanistic rationale (Scheme 5) assumes that they are formed through non-pericyclic, ionic manifolds, it was tempting to speculate whether this could be further explored by designing substrates with even stronger positive charge stabilization ability (see Scheme 5, pathway b). Analogous cationic transfers were reported by the groups of Fürstner and Yamamoto during their elegant independent studies of metal-catalyzed rearrangements of enynes.[12,13]

Aiming to influence the reaction pathway in a similar manner, we chose the simple THF- and THP-protected hy-



Scheme 5. Working mechanistic hypothesis; EDG = electron-donating group, EWG = electron-withdrawing group.

droxylamides **8a** and **8b** as challenging probes. Pleasingly, upon submission to our reaction conditions, these substrates smoothly rearranged to the corresponding adducts **9a–9b** in moderate to very good yields (Scheme 6).

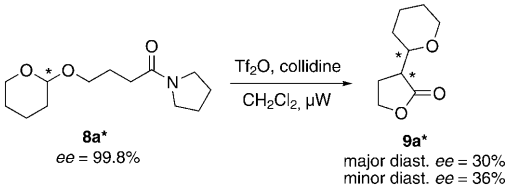


Scheme 6. Ionic O–C shift of THF and THP substrates.

As depicted in Scheme 6, the introduction of a methyl substituent α to the carbonyl (**8d**) did not affect the efficiency of the reaction, leading to the generation of the corresponding lactone **9d** with a quaternary centre in 60% yield, albeit with low diastereocontrol. Additionally, both an increase of the length of the tethered chain (**9e**) and introduction of substituents on the migrating moiety (**9c**) are well tolerated.

This interesting reaction effectively converts what might be seen as trivial THF- and THP-protected alcohols into otherwise powerful cationic oxacycle donors through an essentially irreversible C–C bond-formation step. The efficiency of the THP shift is even more noteworthy, considering that the rearrangement of THP derivatives was shown not to proceed at all in the systems previously reported by Fürstner/Yamamoto, which are analogous to the reactions reported herein.[12] Presumably, in those cases facile elimination to dihydropyran (or dihydrofuran, in the case of THF) takes place before rearrangement can occur. In contrast to such a scenario, we have seldom observed minute amounts of cyclic enol ethers in the reaction mixtures, indicating that in our system the O–C shift uniquely outperforms elimination of the migrating moiety.

The facility with which these rearrangements take place raises additional mechanistic questions. In particular, it suggests that the dissociation–recombination events occur at a very high rate or that at least the recombining fragments merge at a rate that is competitive with diffusion away from a solvent cage. If that is indeed the case, then opportunities for observing "chiral memory" phenomena may be within reach.[14] In an encouraging preliminary experiment, when enantiomerically enriched (99.8% enantiomeric excess (*ee*)) **8a*** was employed as a substrate (Scheme 7), the major diastereoisomer of **9a*** was formed upon rearrangement with 30% *ee*.[15]



Scheme 7. Preliminary results for chirality transfer in the O–C shift.

In summary, we have developed a benzyl-Claisen variant of our keteniminium rearrangement. The efficiency of this reaction draws decisively from the compelling ability of keteniminium intermediates to undergo cascade rearrangements and delivers α-arylated lactone products under metal-free conditions. In addition, we have used mechanistic insight collected during later studies to design unprecedented O–C shifts that proceed in high yields, are amenable to "chiral memory" phenomena, and further highlight the unique features of our system. The ability, documented herein, to completely steer the rearrangement pathway from pericyclic to cationic purely by design raises exciting prospects for future developments. These, including more detailed mechanistic studies and exploration of additional reaction modes, are underway and will be reported in due course.

Acknowledgements

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Keywords: chirality · Claisen rearrangement · ionic shift · lactones · rearrangement

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[15] This result does not rule out possible alternative mechanistic scenarios including bimolecular direct transfer and/or stereospecific nucleophilic displacement. Further mechanistic investigations may allow a more clear distinction between pathways.

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