Olefination of Aromatic Carbonyls via Site-Specific Activation of Cycloalkanone Ketals

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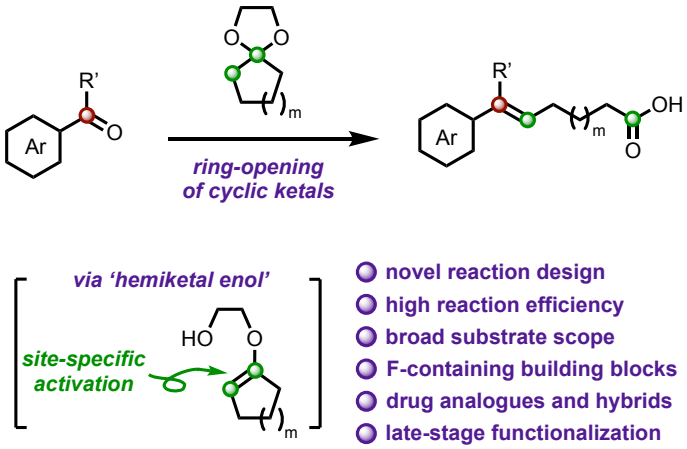
Abstract: Skeletal editing is an important strategy in organic synthesis as it modifies the carbon backbone to tailor molecular structures with precision, enabling access to compounds with specific desired properties. Skeletal editing empowers chemists to transform synthetic approaches of target compounds across diverse applications from drug discovery to materials science. Herein, we introduce a new skeletal editing method to convert readily available aromatic carbonyl compounds into valuable unsaturated carboxylic acids with extended carbon chains. Our reaction setup enable a cascade reaction of enolization-[2+2]cycloaddition-[2+2]cycloreversion between aromatic carbonyl compounds and ketals of cyclic ketones to generate un-saturated carboxylic acids as ring-opening products. Through a simple design, our substrates are specifically activated to react at predetermined positions to enhance selectivity and efficiency. This practical method offers convenient access to versatile organic building blocks as well as provides fresh insights into manipulating traditional reaction pathways for new synthetic applications.



One-Sentence Summary: A simple substrate design allows site-specific activation of cyclic ketones for olefination reaction of aromatic carbonyl compounds.

Main Text:

The concept of skeletal editing holds significant importance in organic synthesis.(*1*) By strategically modifying the carbon backbone while retaining other key functional groups, researchers can intricately tailor the molecular architecture to achieve desired properties and reactivity.(*2*) Cyclic ketones, readily available synthetic precursors, have been one of the primary targets for skeletal editing as they can lead to a plethora of complex molecules with applications in materials and pharmaceutical industries.(*3*) Typical skeletal editing strategies on cyclic ketones include well-established transformations such as (i) ring-expanding heteroatom insertion, e.g. Baeyer-Villiger oxidation,(*4*) Schmidt reaction(*5*) or Beckmann rearrangement;(*6*) (ii) ring-expansion, e.g. Büchner–Curtius–Schlotterbeck reaction(*7*) or Dowd-Beckwith reaction;(*8*) or (iii) ring-contraction, e.g. Favorskii(*9*) or Wolff(*10*) rearrangements (Figure 1). On the other hand, ring-open reactions of cyclic ketones have been relatively less explored comparing to the other aforementioned skeletal editing strategies. Most known transformations in this chemical space are limited in substrate scope, e.g the Halle-Bauer reaction on non-enolizable ketones,(*11*) the retro-Claisen reaction on 1,3-dicarbonyl compounds,(*12*) the Norrish type-I homolytic cleavage(*13*) or ring-opening reactions of strained cyclic ketones such as cyclobutanones.(*14*) A direct ring-opening reaction of cyclic ketones is challenging to develop as it is often complicated by multiple possible processes such as aldol reaction or Claisen-Schmidt reaction.(*15*) Herein, we report the development of a new ring-opening reaction to convert a wide range of cyclic ketone ketals and aromatic carbonyl compounds into valuable unsaturated carboxylic acids with extended carbon chains. Through a simple reaction design, our cyclic ketone framework is specifically activated at predetermined position to enhance selectivity and efficiency. This provides convenient access to fluorine-containing scaffolds or analogues of pharmaceuticals and is also applicable to late-stage modification of bio-relevant frameworks.

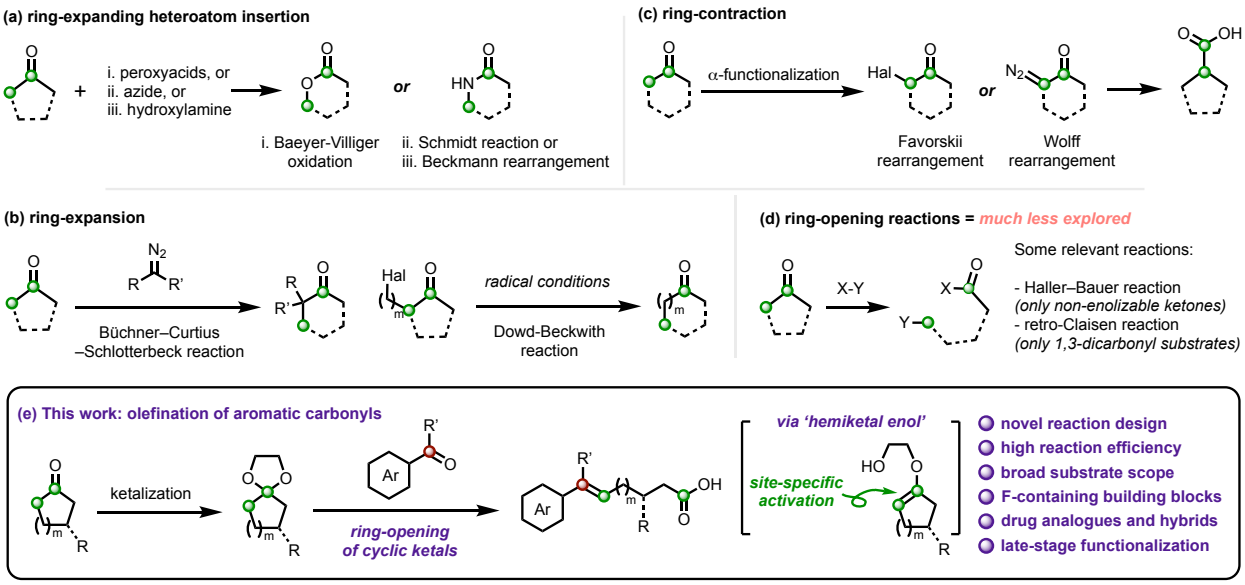
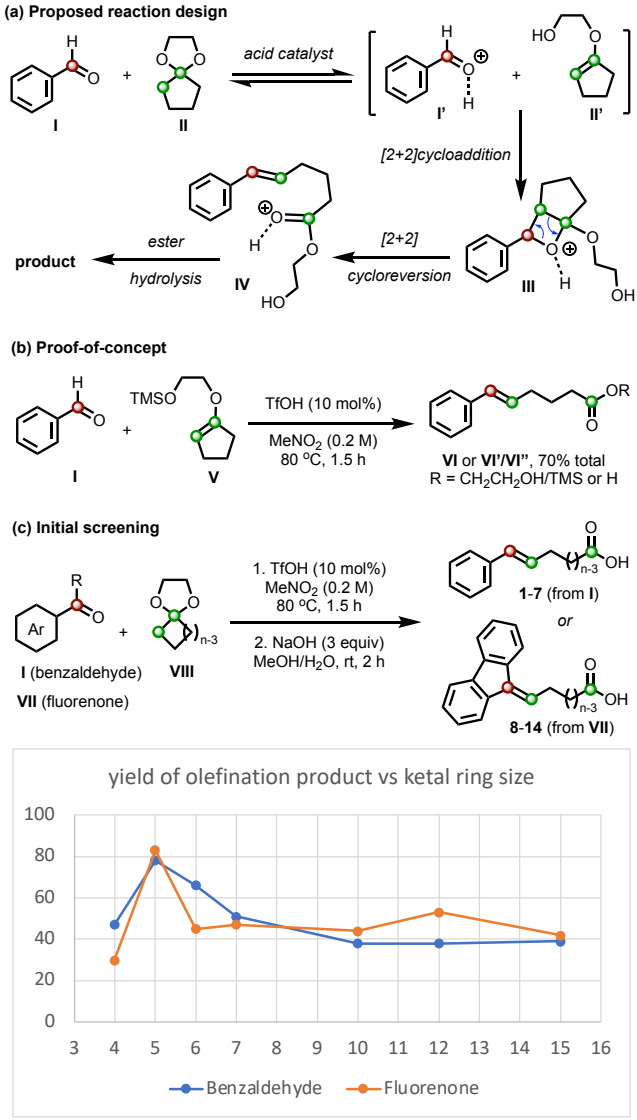


Fig. 1. Traditional skeletal editing reactions of cyclic ketones and a new design for the ring-opening reaction.

Based on our earlier works on olefination of carbonyl compounds,(*16-20*) we envisioned that ketals of cyclic ketones **II** could be suitable substrates for a Brønsted acid catalyzed cascade enolization/[2+2]cycloaddition/[2+2]cycloreversion sequence with another carbonyl compound **I** to form the corresponding ring-opening ester products (Scheme 1a). Oxetanium **III** is a frequently

encountered intermediate in carbonyl chemistry.(*16-22*) Key to this cascade sequence is the enolization of the cyclic ketal under acidic conditions, which releases a 'hemiketal enol ether' reactive intermediate **II'** for a [2+2]cycloaddition reaction(*23*) specifically at the newly created C-C double bond. The reason why we chose to use cyclic ketals of diols is that they are often more tolerant of acidic conditions than non-cyclic ketals of mono-ols. Our substrate design and reaction setup evade side aldol-type reactions and suspend any potential reversible processes as the ester products are energetically stable.



Scheme 1. (a) Reaction design; (b) Proof-of-concept; (c) Initial screening of cyclic ketone ketals with different ring sizes.

Gratifyingly, our proof-of-concept reaction with the silyl protected enol ether **V**, to mimic the reactive intermediate **II'** in Scheme 1a, met with immediate success to produce a mixture of ethylene glycol ester products **VI/VI'** and its hydrolyzed acid derivative **VI''** with high total efficiency (Scheme 1b). To explore the reactivity of aromatic carbonyl counterpart, we also carried out an initial screening between benzaldehyde **I** or fluorenone **VII** and of cyclic ketone ketals of different ring sizes **VIII**. As illustrated in Scheme 1c, most medium ring size reacted well with

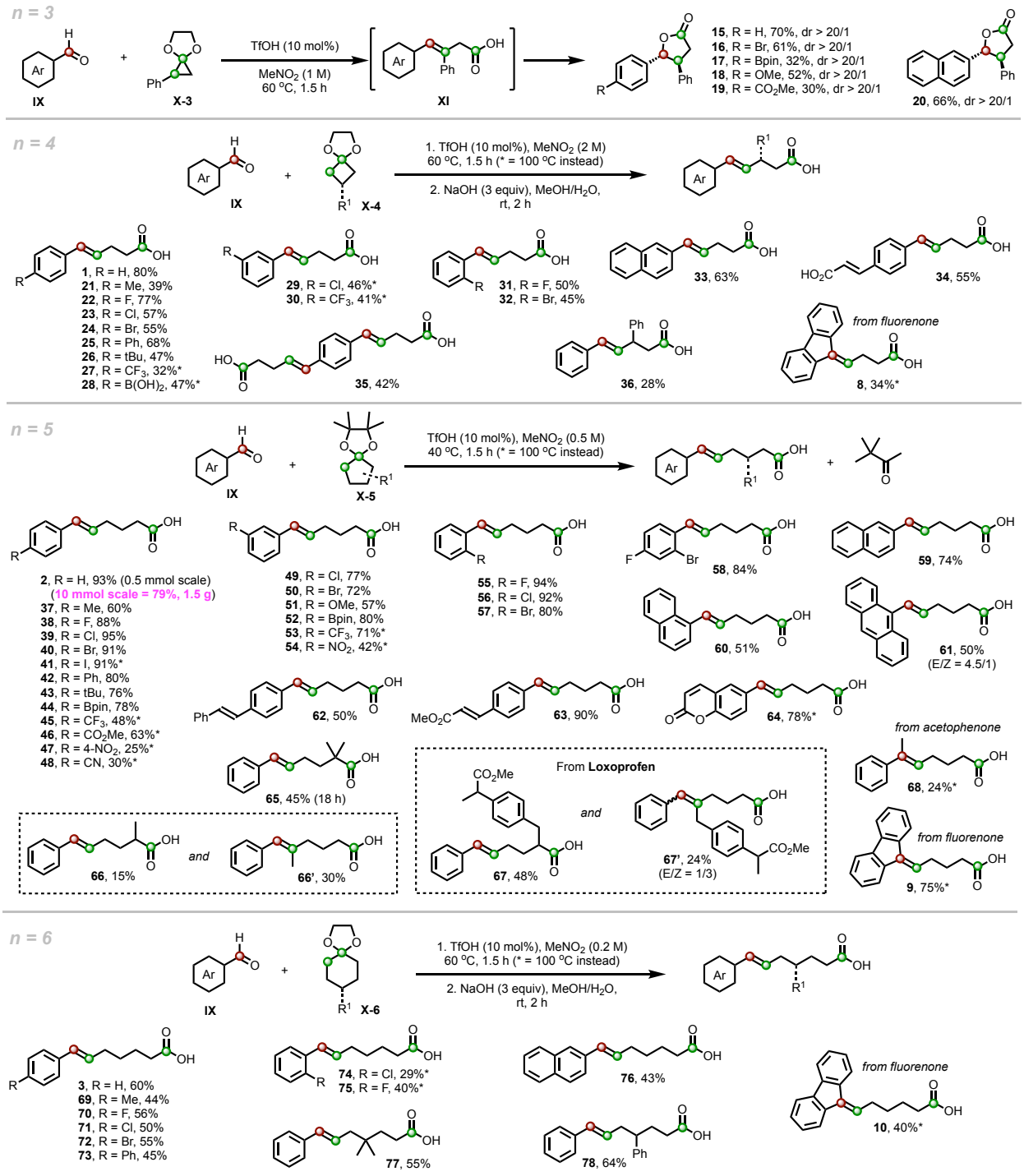
benzadehyde **I** to give carboxylic acid derivatives in good to high yields after ester hydrolysis, but the reaction efficiencies were only moderate with large ring sizes. Fluorenone **VII** displayed the same trend of reactivity towards these ketals. Interestingly, all products (**VI**-**VI'**/**VI''** and **1**-**7**, Scheme 1b-c) were formed as *E*-isomers exclusively. These results further confirmed our reaction hypothesis in Scheme 1a and encouraged us to fully develop this ring-opening cascade reaction of cyclic ketone ketals as a novel method for olefination of aromatic carbonyl compounds.

After extensive optimization studies with a range of different Brønsted acid catalysts, solvents and protecting diols for the ketals, we were able to settle the optimal conditions for each ring-size as illustrated in Scheme 2 (see pages S6-9 of the SI for further details). An extended substrate scope investigation was carried out for ketals of cyclobutanone, cyclopentanone and cyclohexanone, the three most frequently encountered members of this family. Ethylene glycol ketals of cyclobutanones **X-4** reacted smoothly with aromatic aldehydes **IX** to give γ,δ-unsaturated carboxylic acids **1** and **21**-**35** in moderate to excellent yields. Substituted ketal gave product **36** with low yield. Since the reaction with fluorenone to form product **8** was relatively inefficient, we did not investigate any other aromatic ketones.

For cyclopentanones, we opted to use pinacol ketals **X-5** instead of ethylene glycol ketals, as these precursors are more stable. Furthermore, they reacted with aromatic carbonyl compounds to directly form the desired δ,ε-unsaturated carboxylic acids and pinacolone by-product, via the pinacol-rearrangement, without the need of a hydrolysis step. Most reactions with **X-5** led to good to excellent efficiencies and a diverse range of functional groups were tolerated (**2** and **37**-**65**, Scheme 2). Compound **2** could be produced on gram-scale with high yield. Substituted cyclopentanone ketals also reacted quite well to produce mixtures of regio- and stereo-isomers (**66**-**67**). While fluorenone gave high yield of product **9**, the same reaction with acetophenone resulted in low yield of product **68** due to side aldol-type processes of the acetophenone precursor.

X-6, ethylene glycol ketals of cyclohexanones reacted with aromatic compounds with similar reactivity and efficiency to **X-4**, ketals of cyclobutanones, to give ε,ζ-unsaturated carboxylic acids **3** and **69**-**76** in moderate to good yields. The significant difference is that substituted six-membered ring substrates (**77**-**78**, Scheme 2) worked better than substituted four-membered ring substrate (**36**), which can be attributed to the less detrimental steric effect in the formers. It should also be noted that the five-membered ketone ketals worked better than the four- and six-membered analogues, which is consistent with the trend of reactivity we observed earlier in Scheme 1c.

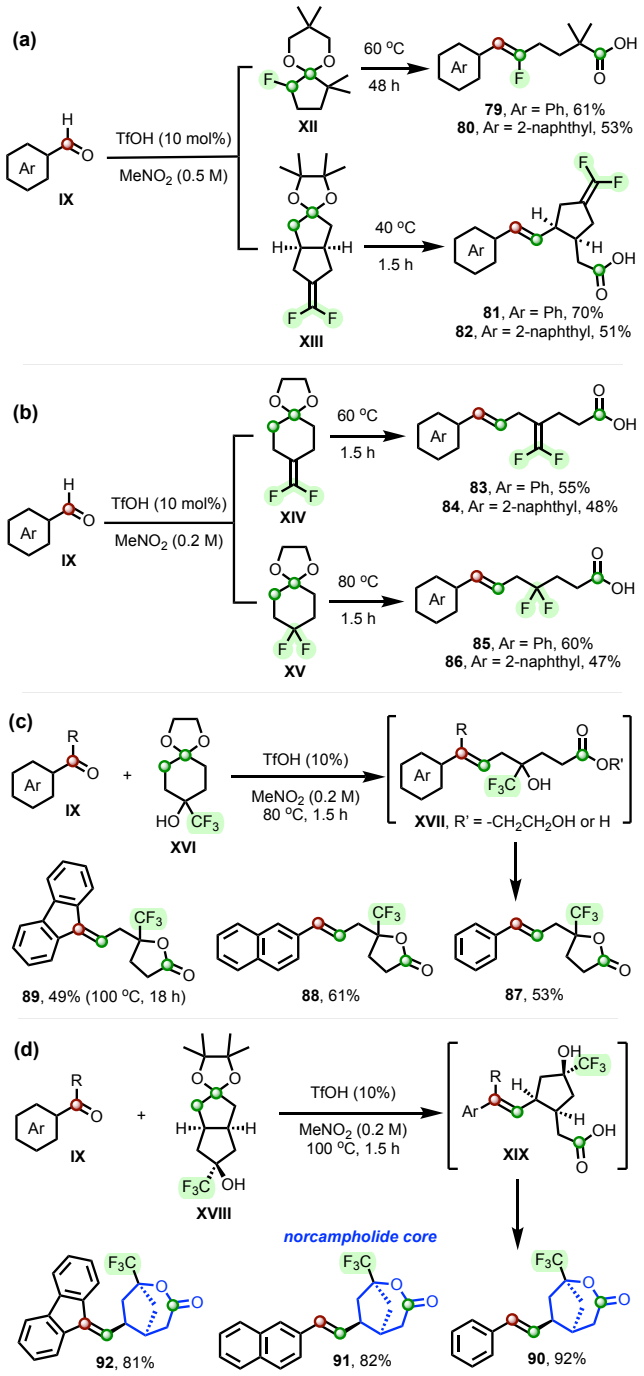
Cyclopropanones and their ketals would be interesting substrates for this newly developed transformation.(*24*) However, these highly strained compounds are generally unstable and difficult to handle. Nevertheless, we were able to identify a stable phenyl-substituted ketal substrate (**X-3**, Scheme 2) for this investigation. **X-3** reacted well with a selected number of aromatic aldehydes to give 4,5-diaryl lactones **15**-**20** in moderate to good yields with excellent diastereoselectivity. Presumably, these products formed via the hydrolactonization(*25*) of the β,γ-unsaturated carboxylic acid intermediates **XI**. This represents a novel formal pathway for [3+2]cycloaddition reaction between cyclopropenone ketals and benzaldehydes, which is being fully investigated in our laboratory and will be reported in due course.



Scheme 2. Extended substrate scope with n = 3, 4, 5, 6; see the SI for experimental details.

The cyclic ketone precursors can be easily functionalized into substituted derivatives, and these substituents are transferred to the carboxylic acid products in these ring-opening olefination reactions. Thus, we subsequently exploited our newly developed methods on fluorinated cyclic ketone ketals to produce a range of fluorinated unsaturated carboxylic acids (Scheme 3). Fluorinated cyclopentanone ketal **XII**, produced from the α-fluorinated parent ketone, reacted smoothly with benzaldehyde and 2-naphthaldehyde to produce vinyl fluoride products **79** and **80**

in good yields. Similarly, 1,1-difluoro olefin **XIII** reacted to afford monocyclic products **81** and **82** in good and moderate yields (Scheme 3a).

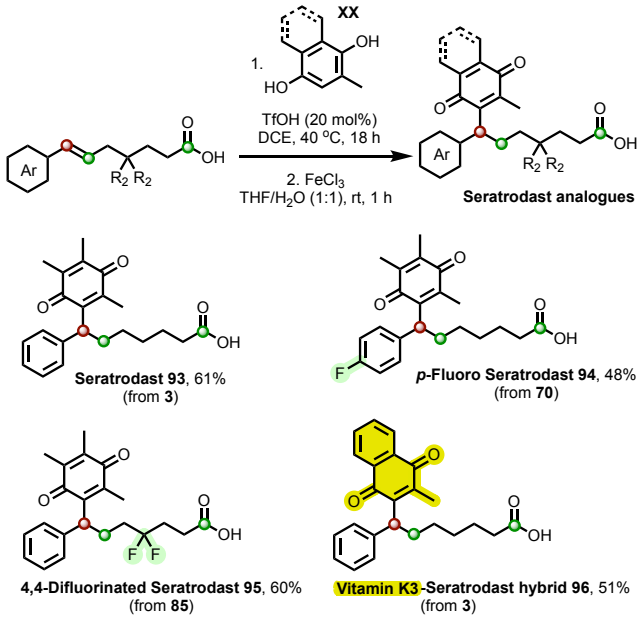


Scheme 3. Ring-opening olefination reactions with fluorinated substrates.

Fluorine-containing ketals of cyclohexanones **XIV**-**XV** also worked smoothly with benzaldehyde and 2-naphthaldehyde under our reaction conditions to produce the corresponding fluorinated unsaturated carboxylic acids **83**-**84** in moderate to good yields (Scheme 3b). When there was an extra alcohol moiety on the ketal precursor **XVI**, the reactions with aromatic aldehydes or ketone **IX** directly led to the formation of fluorinated lactone products **87**-**89** (Scheme 3c). When the same

strategy was applied to the tetrahydropentalene dione derived precursor **XVIII**, a range of products bearing the trifluoromethyl norcampholide framework were obtained in high to excellent yields (**90-92**, Scheme 3d). All of these are valuable novel fluorine-containing building blocks for synthetic applications.(*26*)

The *trans*-unsaturated carboxylic acids formed in Scheme 2 and Scheme 3 can also be used for many synthetic applications. As an illustration of their synthetic value, we used some of the previously obtained ε,ζ-unsaturated carboxylic acids to produce analogues of Seratrodast, an anti-asthmatic drug.(*27*) Thus, in a simple two-step one-pot process, these carboxylic acids were coupled with hydroquinone **XX** followed by an oxidation reaction with iron(III) chloride to achieve Seratrodast **93**, *p*-fluoro Seratrodast **94**, 4,4-difluoro Seratrodast **95** and Vitamin K3-Seratrodast hybrid **96** in moderate to good overall yields (Scheme 4).

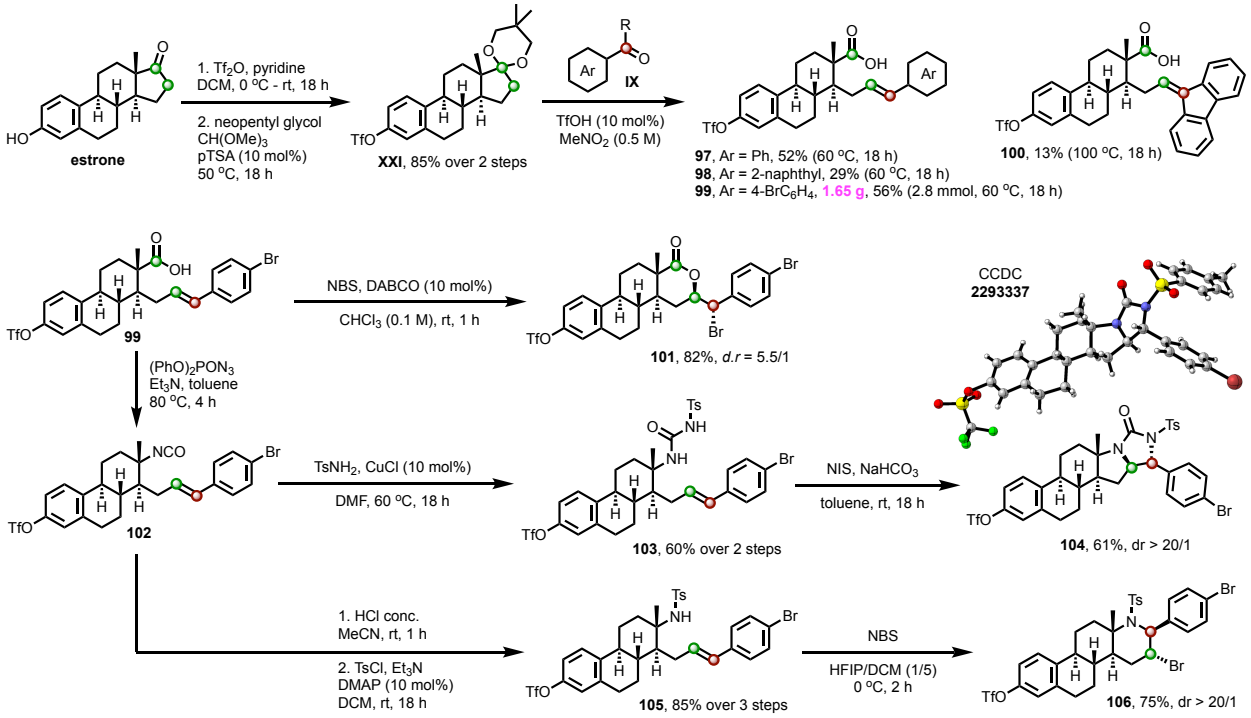


Scheme 4. A representative synthetic application of unsaturated carboxylic acid products.

The simple setup and relatively mild reaction conditions of our newly developed ring-opening olefination protocol render it highly suitable for late-stage functionalization of cyclic ketone containing natural products or biologically relevant organic compounds. In a preliminary demonstration of such potential application, we used the steroid estrone as a cyclopentanone-containing precursor. Cyclic ketal **XXI** was produced in high yield from estrone in a two-step sequence consisting of a triflation and ketal formation with neopentyl glycol (Scheme 5). It was then converted to a range of different unsaturated carboxylic derivatives **97-100** using our ring-opening olefination protocol with aromatic carbonyl compounds. Product **99** was produced on gram-scale with good efficiency.

Synthetic utilities of estrone-derived product **99** were further demonstrated in Scheme 5. Treatment of **99** with *N*-bromosuccinimide in the presence of DABCO catalyst afforded bromolactonization product **101** in high yield with good diastereoselectivity. Conversion of the carboxylic acid group to the isocyanate moiety (**102**), followed by copper(I)-catalyzed urea formation (**103**) with tosylamide and *N*-iodosuccinimide promoted oxidative cycloaddition reaction led to pentacyclic product **104** in good yield and excellent diastereoselectivity. The structure of **104** was confirmed by XRD analysis. Additionally, isocyanate **102** could be converted to tosylamide derivative **105**,

which was treated with NBS to obtain tetracyclic amine **106** in high yield and excellent diastereoselectivity (Scheme 5).



Scheme 5. Late-stage functionalization of a biologically relevant framework.

In conclusion, this work introduced a novel skeletal editing approach that transforms aromatic carbonyl compounds into unsaturated carboxylic acids with extended carbon chains via ring-opening reactions of cyclic ketone ketals. The developed method harnesses the power of cascade reactions involving enolization, [2+2]cycloaddition and [2+2]cycloreversion, which were made possible by an innovative substrate design for site-specific C-C bond activation. This method provides convenient access to interesting fluorine-containing organic scaffolds or analogues of pharmaceuticals and is also applicable to late-stage modification of biologically relevant frameworks.

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Supplementary Materials

Experimental procedures and methods, characterization data and NMR spectra.