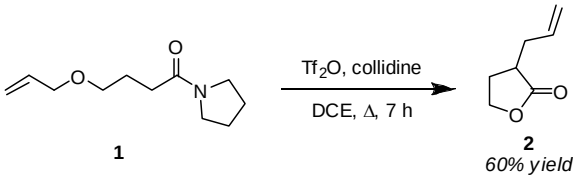
2.2.7 Research Area "Electrophilic Activation of Amides / Pericyclic Reactions of Keteniminium Derivatives" (N. Maulide)

Involved: C. Madelaine, D. Petkova, V. Valerio, M. Winzen

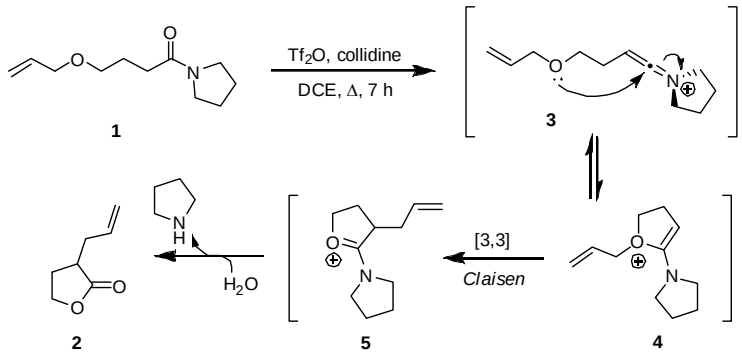
Objective: The selective activation of amides by interaction with suitable electrophilic reagents allows access to novel reactivity manifolds and opens up intriguing perspectives in synthesis. In particular, the *in situ* preparation of keteniminium salts for subsequent [2+2] cycloadditions is a well-known transformation, although the chemistry of those intermediates is scarcely explored beyond four-membered ring formation.

The aim of this project is the development of new pericyclic cascade transformations of keteniminium salts generated *via* electrophilic activation of amides.

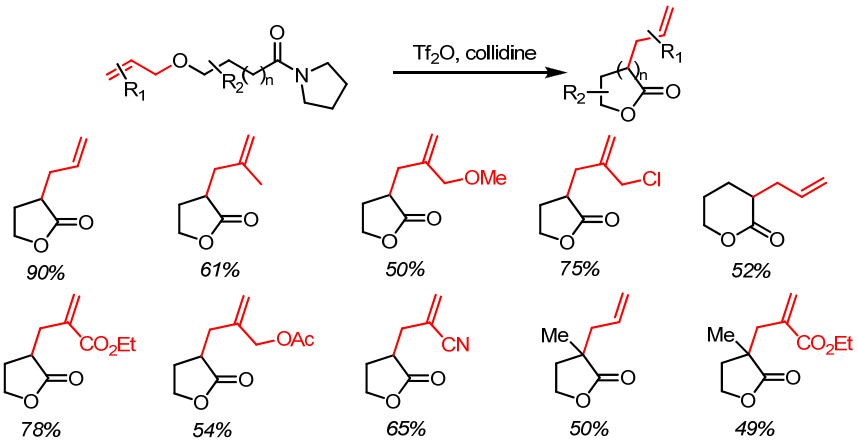
Results: This area of research is predicated on our original observation that electrophilic activation of the γ-alkoxyamide **1** under the typical conditions for generation of an intermediate keteniminium salt (triflic anhydride and a base) did not lead to the anticipated [2+2] cycloadduct. Instead, we were surprised to observe the *exclusive* formation of α-allyl butyrolactone **2**.



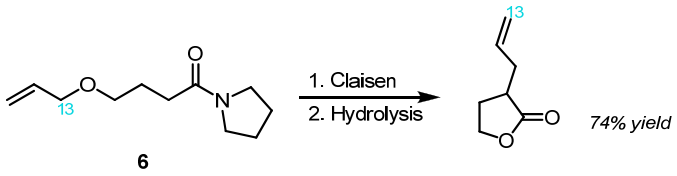
Mechanistically, we assume the reaction to proceed as depicted below. Accordingly, after initial activation of the amide carbonyl by the electrophilic reagent, elimination to form keteniminium **3** probably takes place. The enhanced electrophilicity of this intermediate then triggers an unusual ether nucleophilic addition step, which may be reversible. This step, however, generates a vinyl-allyl-oxonium **4** which is ideally poised to undergo a [3,3]-sigmatropic rearrangement. Such a reorganization should lead to the stabilized carbenium ion **5**, hydrolysis of which then accounts for the formation of lactone **2**.



We have developed this transformation into a general synthesis of γ-butyro- and δ-valerolactones. As shown, the mild conditions of this rearrangement tolerated a variety of functional groups, including ester, nitrile and halide moieties. The selective activation of the amide functional group of the starting materials in the presence of the latter moieties highlights the chemoselectivity of this procedure.

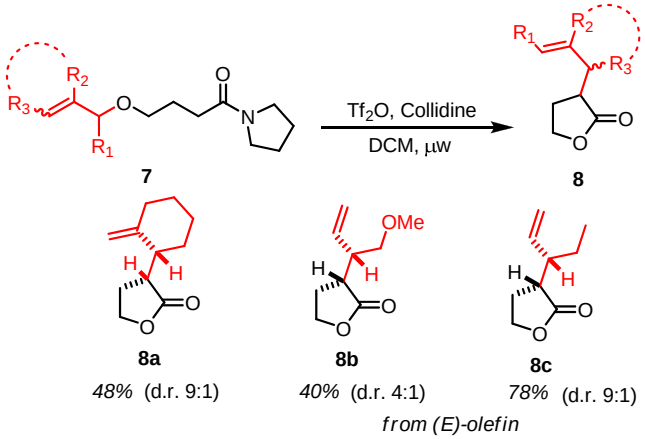


Allylic inversion was unambiguously established through rearrangement of the ^{13}C-labelled amide **6**.



6

This unequivocal result suggested opportunities for preparation of diastereoenriched lactones with challenging reaction patterns. Indeed, when the readily available (*E*)-amides **7a** and **7b-c** were employed in the reaction, high diastereoselectivities for the formation of products **8a** and **8b-c** were observed.



7 **8**

8a *48%* (d.r. 9:1)

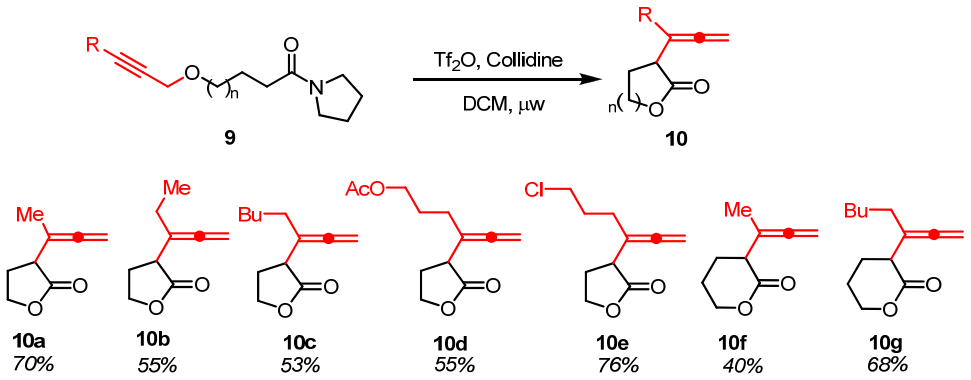
8b *40%* (d.r. 4:1)

8c *78%* (d.r. 9:1)

from (E)-olefin

In addition, subjection of propargyl ether-containing amides **9** to the reaction conditions resulted in smooth rearrangement to α-allenyl lactones **10** in moderate to very good yields. As before, the reaction tolerated a broad variety of functional groups, including

esters and halides. It is particularly noteworthy that none of the lactones **10** were known in the chemical literature prior to our studies.



In summary, we have developed a novel Claisen-like rearrangement of keteniminium intermediates generated through electrophilic amide activation. Future work will focus on the broadening of the concepts presented herein to more complex cascade rearrangements.

Publications resulting from this research area: 355

External funding: Deutsche Forschungsgemeinschaft; Alexander von Humboldt Foundation (stipend to C. Madelaine)

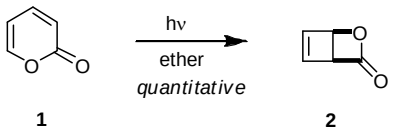
Cooperations: L. Veiros (Lisbon, PT)

2.2.8 Research Area "Stereoselective Synthesis of Cyclobutenes" (N. Maulide)

Involved: D. Audisio, F. Frébault, M. Luparia, M. T. Oliveira, U. Specht, E. Wöstefeld

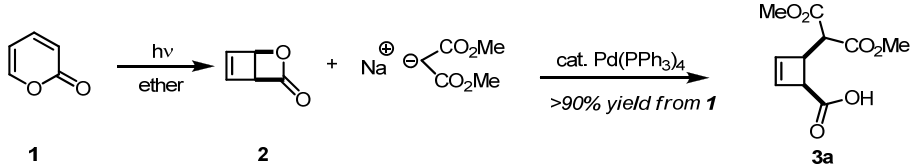
Objective: The preparation of small rings has been a pervasive topic in organic synthesis ever since chemists realized the potentialities and fascinating properties associated with their inherent ring strain. Furthermore, the number of isolated natural products which contain, embedded in their core structure, a cyclopropane or cyclobutane does not cease to grow. Nevertheless, there is a serious lack of general methodologies for the preparation of optically active functionalized cyclobutane derivatives. This is even more so when one considers cyclobut**e**nes, uniquely attractive building blocks due to the synthetic versatility associated with the presence of the additional carbon-carbon double bond embedded in the four membered ring.
The aim of this project is the development of new strategies for the stereoselective preparation of versatile cyclobutene building blocks starting from 2-pyrone.

Results: 2-Pyrone **1** is known to undergo photomediated isomerization to the unstable oxabicyclo[2.2.0]hexane **2**. Historically, this reaction has been the subject of considerable scrutiny, since it still constitutes the surest path to the synthesis of the elusive anti-aromatic compound cyclobutadiene (*via* decarboxylation of **2**).



1 **2**

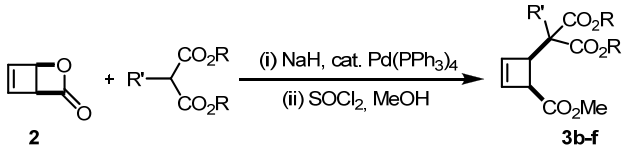
This project has its origins on our realization that compound **2** is, structurally, an allylic ester susceptible of ionization by a suitable zero-valent, electron-rich transition metal. We have achieved the first catalytic, stereoselective transformations of **2** that suggest a versatile synthesis of functionalized cyclobutenes in only two operations from 2-pyrone. In preliminary experiments, we found that treatment of **2** with sodium dimethylmalonate in the presence of 5 mol% $Pd(PPh_3)_4$ led to a nearly quantitative yield of the *cis*-cyclobutene carboxylic acid **3a** as a single diastereomer. The structure of **3a** was confirmed unequivocally by X-ray analysis.



1 **2** **3a**

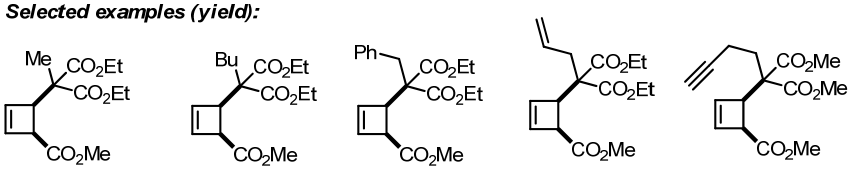
Following optimization of the reaction conditions, the scope for this transformation was evaluated. As depicted below, a variety of active methylene compounds could be used

as nucleophilic partners. The corresponding cyclobutene carboxylic acids (or the derived methyl esters) were formed in good to excellent yields.



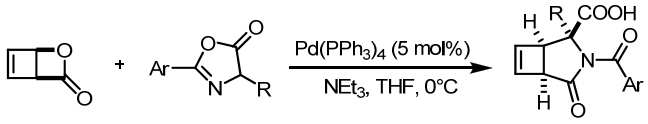
2 3b-f

Selected examples (yield):



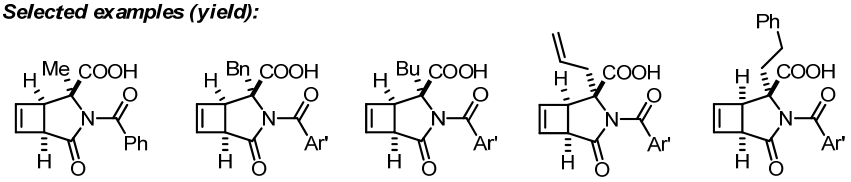
3b (80%) **3c** (74%) **3d** (83%) **3e** (76%) **3f** (88%)

In addition, we found that azlactones of the general structure **4** also function as competent nucleophiles in this process. Incidentally, the products obtained were not the expected alkylated acids but rather the rearranged azabicycles **5**. The structure of **5a** was confirmed unambiguously by X-ray analysis.



1 4 5

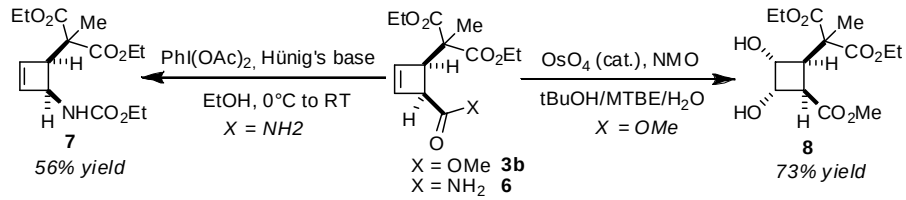
Selected examples (yield):



5a 57% **5b** 46% **5c** 57% **5d** 56% **5e** 47%

Ar' = (p-NO2)C6H4

The adducts formed through this simple reaction sequence proved amenable to a variety of transformations, exploiting the latent reactivity of the functional groups generated. For instance, the strained cyclobutene double bond of **3b** could be easily dihydroxylated in good yield, affording the tetrasubstituted cyclobutane **8** with complete control of all four stereogenic centers. Aiming at biologically relevant scaffolds, the amide derivative **6** smoothly underwent Hofmann rearrangement to the novel constrained, fully protected cyclobutene-γ-amino acid **7**.



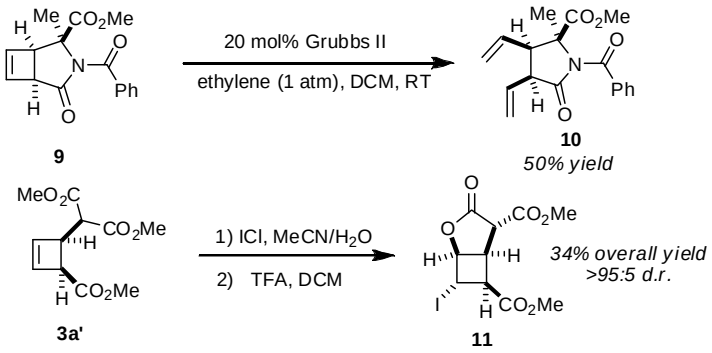
7 *56% yield*

X = OMe **3b**
X = NH_2 **6**

8 *73% yield*

Other manipulations further showcase the synthetic advantage deriving from the cyclobutene double bond and hint at potential applications of this method in total synthesis. Thus, ROM/CM of azabicycle **9** under an atmosphere of ethylene (1 atm) promoted by Grubbs' second generation catalyst afforded the diastereopure pyrrolidinone **10**, reminiscent of kainic and domoic acid derivatives.

On the other hand, a two-step halolactonization of triester **3a'** led to compound **11**, possessing the core structure of Pestalotiopsin A. It is testament to the power of this approach that synthetically relevant compounds can be derived from 2-pyrone in no more than three straightforward synthetic operations.



In summary, we have developed a new and concise synthesis of functionalized cyclobutenes. The overall process reported here combines the efficiency of clean, highly efficient photochemical reactions with the powerful selectivity that can be imparted by metal catalysis and should find broad applications in synthesis. Current and future work will focus on broadening the scope of this and other related methodologies.

Publications resulting from this research area: 310, 311

External funding: Deutsche Forschungsgemeinschaft; Alexander von Humboldt Foundation (stipend to M. Luparia)

Cooperations: R. Goddard, W. Thiel (Mülheim/Ruhr, DE)

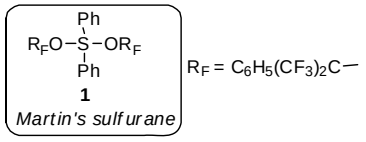
2.2.9 Research Area "Sulphur Chemistry Revisited / New Ylide Transfer Reactions" (N. Maulide)

Involved: X. Huang

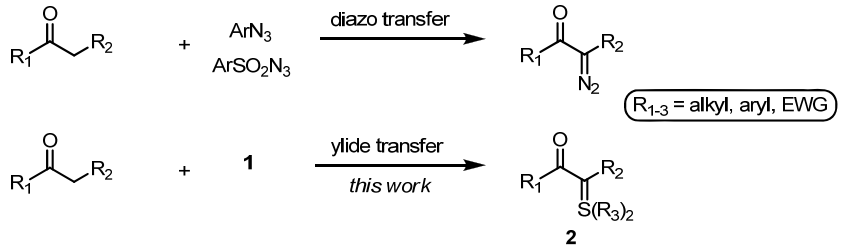
Objective: Sulfur ylides occupy a prominent place among so-called "textbook reagents" in organic chemistry. Their use as connective reagents for the preparation of small rings (the *Corey-Chaykosvky* reactions) and in cascade cyclizations is well established in the literature. Recently, they have garnered interest as potential carbene donors for metal complexes, presenting clear advantages when compared to the diazo compounds that are almost ubiquitously employed in that role. Nevertheless, their synthesis is still a multi(≥ 2)step procedure and applications in transition metal catalysis remain limited.

The aim of this project is the development of a new concept of "ylide transfer" to carbonyl derivatives and heteroaromatic compounds that directly delivers sulfur ylides in a single step.

Results: Martin's sulfurane **1**, named after the scientist who first prepared it in 1971, is widely used as a reagent for dehydration of alcohols in organic synthesis.

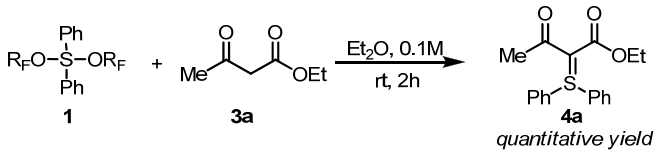


We speculated that **1** might behave as an ylide transfer reagent to suitable carbonyl derivatives, thus yielding diphenylsulfonium ylides (**2**, R^3=Ph) in a single step.

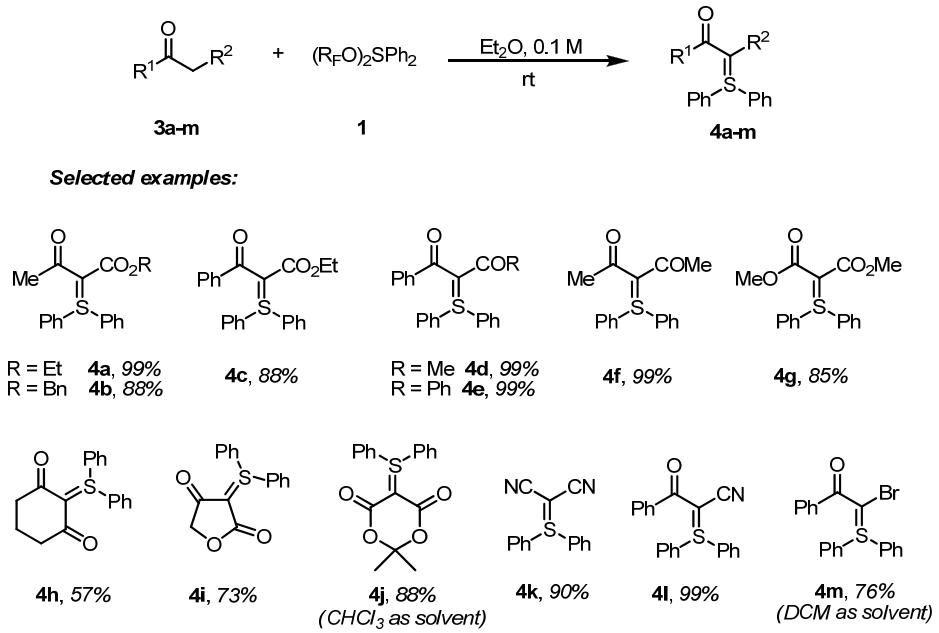


If successful, this would constitute an interesting novel concept of "ylide transfer", the long-awaited analogue of the well-known "diazo transfer" family of reactions.

In initial experiments, we were delighted to find that **1** reacts with ethyl acetoacetate **3a** to afford the sulfur ylide **4a** in quantitative yield (structure confirmed by X-ray analysis). The striking simplicity of this reaction stimulated us to investigate it further.

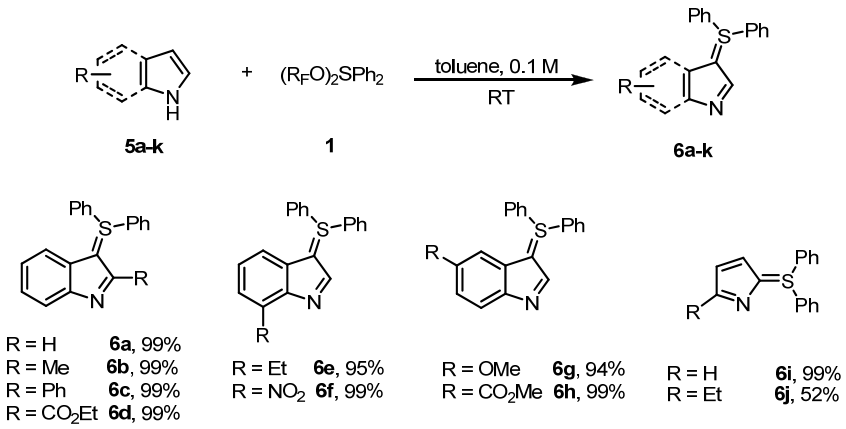


Additional experiments verified the generality of this observation. As displayed below, different active methylene compounds **3a-m** successfully underwent the reaction, affording the corresponding sulfur ylides **4a-m** in excellent yields. Notably, this transfer process was successful with β-ketoesters, β-diketones and even diesters.



Dimethylmalonate **3g** afforded the corresponding ylide **4g** in very high yield. Cyclic diketones and diesters **3h-j** also responded well to this reaction, as did nitriles **4k-l**. The α-bromoketone **3m** merits special notice, as related compounds have been accessed only by cumbersome bromination/deprotonation of the corresponding, non-halogenated ylides. In contrast, ylide **4m** is directly available from bromoacetophenone in a single step using this procedure.

We further speculated that **1** might be capable of "Friedel-Crafts-like" dearomatization of suitable heterocycles. In the event, we discovered that indoles **5** reacted smoothly with **1** within 2 hours at room temperature, affording the corresponding indole-3-sulfonium ylides in excellent yields. As can be seen, this reaction appears to possess a broad scope. Indoles **5a-h** bearing a notable scope of substituents ranging from electron-donating to electroneutral and strong electron-withdrawing were perfectly tolerated. Moreover, considerable flexibility is allowed regarding the substituent locus. All the ylides **6a-h** were obtained in quantitative yields.



In addition, pyrrole **5i** and its derivative **5j** also performed competently in this reaction. As might be expected, pyrrole 2-sulfonium ylides **6i-j** were obtained as the exclusive regioisomers. The robustness of this reaction is further apparent from the ease of scale-up: indole derivative **5d** was easily converted to the corresponding sulfonium ylide (**6d**) on a multigram scale.

In summary, we have developed a new ylide transfer reaction. This process allows a direct, operationally simple synthesis of sulfur ylides from active methylene compounds and heteroaromatics and provides a powerful sulfur equivalent to the well-known diazo transfer reactions. The readily available sulfurane **1** and its exquisite reactivity under particularly mild conditions were decisive to achieve this goal. Indeed, **1** appears uniquely suited to direct, high-yielding syntheses of sulfur ylides and the reactions described herein should find broad applications in synthesis. Further work focuses on detailed study of the fascinating structures of the ylides synthesized and their applications in catalysis.

Publications resulting from this research area: 325

External funding: none

Cooperations: R. Goddard (Mülheim/Ruhr, D)