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Tandem Cyclopropanation/Vinylogous Cloke−Wilson Rearrangement for the Synthesis of Heterocyclic Scaffolds

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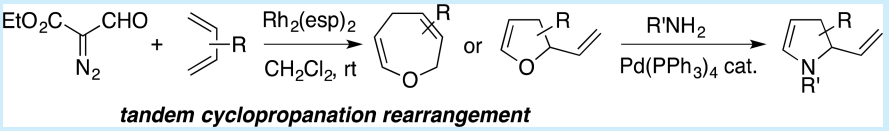
Supporting Information



tandem cyclopropanation rearrangement

ABSTRACT: Cyclopropanation of 1,3-dienes with ethyl 2-formyldiazoacetate under rhodium catalysis results in either a tandem cyclopropanation/Cloke−Wilson rearrangement or a vinylogous variant, depending on the diene used. These adducts may be subjected to an oxygen to nitrogen substitution with various amines under palladium catalysis. The substrate scope and mechanistic reasoning is presented.

The ring strain inherent in cyclopropanes has been exploited for decades to prepare compounds of a value-added nature. Simple ring opening of a donor−acceptor cyclopropane (a homo-Michael addition) results in linear compounds, while reaction with dipolar species can result in hetero- or carbocylic products.[1] Perhaps one of the most well established processes is the vinylcyclopropane rearrangement, which results in five-membered-ring products.[2] A much less studied variant of this (a hetero-vinylcyclopropane rearrangement) is the so-called Cloke−Wilson rearrangement (Scheme 1). In 1929, Cloke reported that treatment of cyclopropyl phenyl ketone with ammonium chloride resulted in the formation of a dihydropyrrole.[3] In 1947, Wilson was able to rearrange cyclopropane carboxaldehyde to dihydrofuran.[4] Since these initial discoveries, there have been notable advancements, including organocatalysis,[5] DYKAT,[6] silicon promotion,[7] and transition metal catalysis.[8] Herein we report a tandem cyclopropanation/Cloke−Wilson rearrangement as well as a rarer but not unprecedented[9] vinylogous variant (a retro-Claisen rearrangement) to form seven-membered oxacycles.

The discovery of the title reactions came about during exploration of a route to the kainoids (such as kainic acid). The original plan was to cyclopropanate cyclopentadiene **1** with ethyl 2-formyldiazoacetate (**2**) to produce **3**, which would be subjected to an aza-Cloke−Wilson rearrangement to produce **6** (if cyclopentadiene itself were used), which we deemed a possible synthetic precursor to the target kainoids. We were surprised to observe that the cyclopropane was not isolable but formed a new product in situ, which we first assigned to a Cloke−Wilson product such as **8a**. However, extensive NMR analysis showed that the product was in fact 2,5-dihydrohydrooxepine **5**, the product of a vinylogous Cloke−Wilson reaction. With this interesting lead result in hand, we sought to explore this rich new chemistry in terms of substrate scope and mechanistic hypothesis.

Our study commenced with the treatment of a variety of readily available butadienes with **2**. As noted in the initial discovery, the products were 2,5-dihydrooxepines **5**. Figure 1 shows the results. The catalyst of choice for this transformation rapidly emerged as $Rh_2(esp)_2$.[10] While other catalysts did promote this reaction, the yields were much poorer (see the Supporting Information for a table of catalyst screening results). The yields are modest but acceptable given the rapid formation of molecular complexity.

The less than optimal yields may be due to the formation of diastereomers during the cyclopropanation stage (Scheme 2). While one diastereomer (**7b**) would be well-positioned to undergo rearrangement, the other (**7a**) would not. At this stage this is merely a hypothesis, as we have never been able to isolate products derived from **7a**. In addition, the diazo species has been reported to be prone to facile dimerization.[11]

We were surprised to see a different reactivity pattern emerge when aryl-substituted butadienes were employed. Rather than the vinylogous manifold of reactivity, a tandem cyclopropanation/Cloke−Wilson process occurred. Figure 2 shows the results. The most electron-rich butadienes (yielding **4b** and **4d**) underwent spontaneous rearrangement to the dihydrofurans, while the others required treatment with a Lewis acid such as $Sc(OTf)_3$.

Interestingly, the dihydrooxepines from Figure 1 were rearranged to their dihydrofuran counterparts upon treatment with a Lewis acid (Figure 3), likely via a 1,3-oxygen migration involving an allyl cation. Several things are worthy of note. The bicyclic dihydrooxepines underwent this process in exceedingly high yields, likely because of the favorable strain relief in going from a seven-membered ring to a five-membered ring. When a mixture of regioisomers **5d** and **5e** was subjected to the reaction conditions, only **5d** underwent rearrangement. This is

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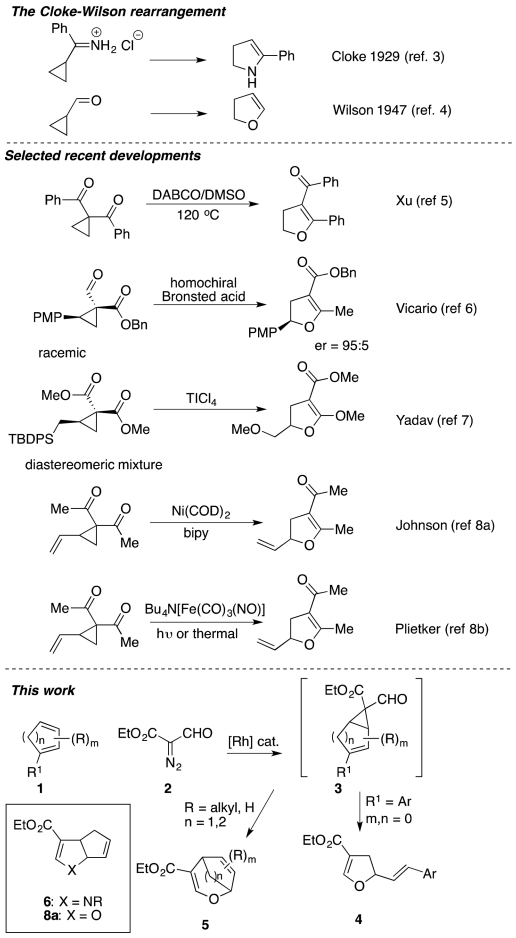
Scheme 1. Tandem Cyclopropanation/Cloke–Wilson and Vinylogous Cloke–Wilson Rearrangements



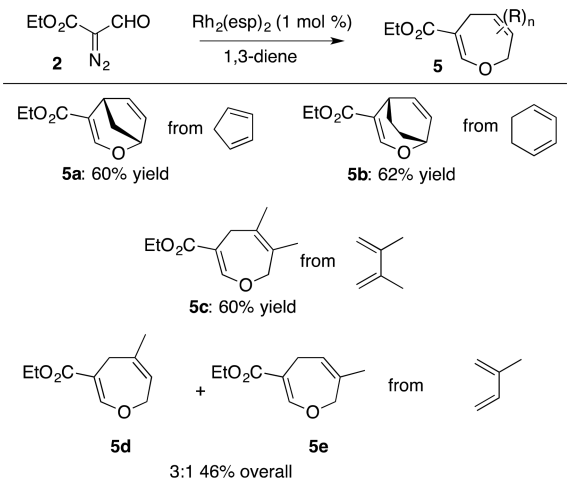
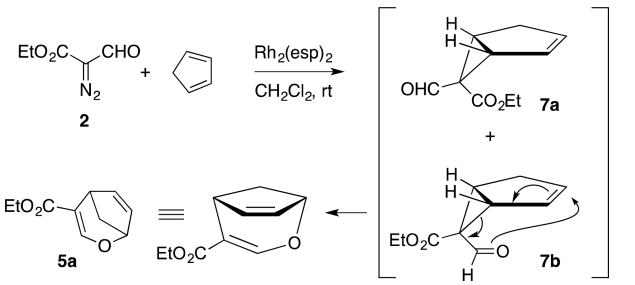


Figure 1. Tandem cyclopropanation/vinylogous Cloke–Wilson rearrangement with simple 1,3-butadienes.

Scheme 2. Mechanistic Hypothesis



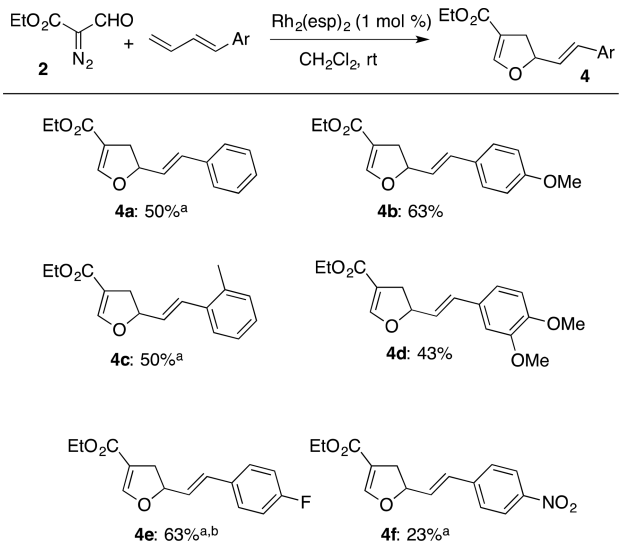


Figure 2. Tandem cyclopropanation/Cloke–Wilson rearrangement with 1-aryl-1,3-butadienes. Notes: [a]Isolated with unrearranged cyclopropane; rearrangement was effected by treatment with 5 mol % $Sc(OTf)_3$ at 40 °C in CH_2Cl_2. [b]Isolated with a small amount of an unknown byproduct.

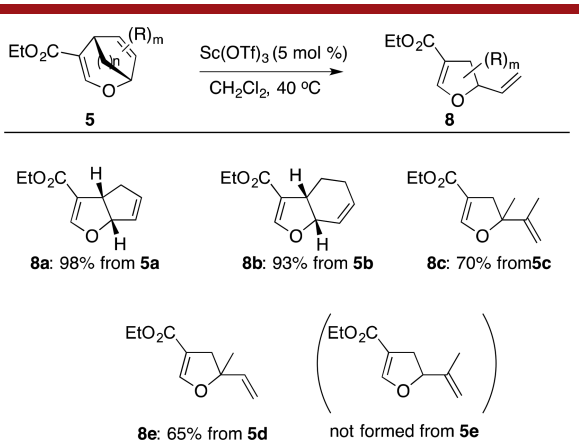


Figure 3. Rearrangement of dihydrooxepines to dihydrofurans.

likely due to the fact that **5d** may form a 3° carbocation while **5e** would require a higher-energy 2° cation.

Inspired by a report by the Ma group,[12] we sought to perform an oxygen to nitrogen transposition to access aza-heterocycles. The Ma communication reported only a single example as a mechanistic study, so this is (to the best of our knowledge) an unexplored reaction. We subjected the dihydrofurans from Figures 2 and 3 to the conditions detailed by Ma and were delighted with the results, which are shown in Figure 4. We limited this study to the use of benzylamine except for a single case where *p*-anisidine was employed successfully. Ma's paper provides a reasonable mechanism that involves a π-allyl intermediate.

In order to improve the efficiency of the processes described above, we sought ways to shorten the number of steps involved (Figure 5). To this end, $Sc(OTf)_3$ was added directly to the cyclopropanation reaction mixture. Indeed, the 1,3-rearrange-

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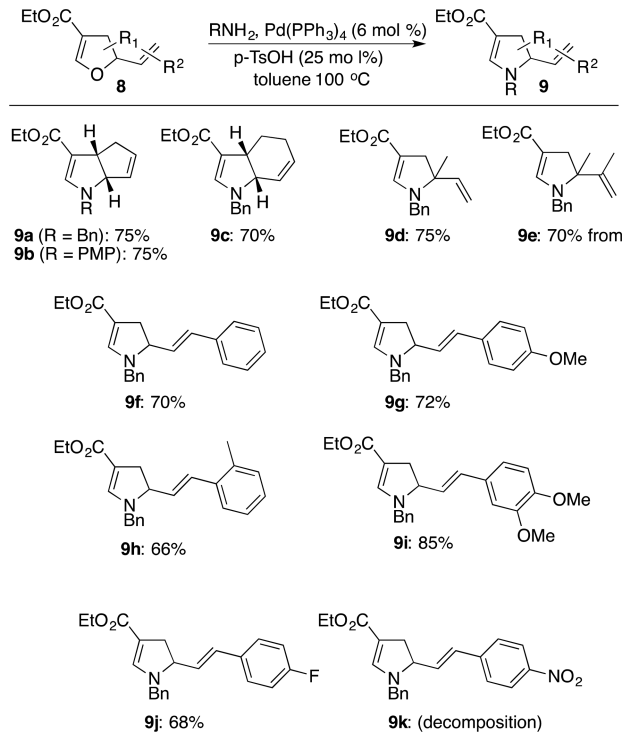

Figure 4. Conversion to dihydropyrroles.

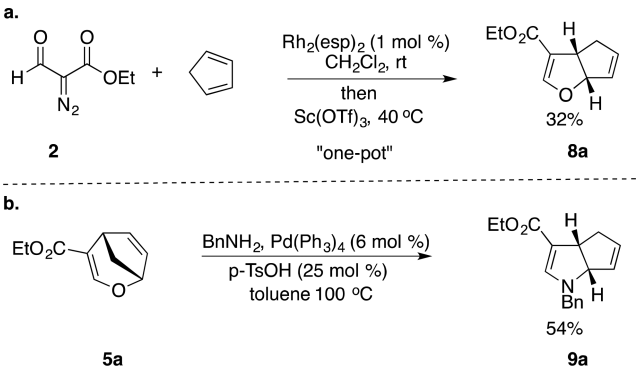

Figure 5. (a) "One-pot" cyclopropanation/vinylogous Cloke–Wilson rearrangement/1,3-allylic migration. (b) Direct conversion of dihydrooxepine to dihydropyrrole.

ment was effected, but the overall yield was inferior. Also, when the oxygen to nitrogen transposition was attempted on oxepine **5a**, rearrangement was concurrent with nitrogen insertion. The yield for the one-step process was similar to that for the sequential reactions.

In summary, we have described a tandem cyclopropanation/Cloke–Wilson rearrangement as well as the associated vinylogous Cloke–Wilson rearrangement to provide access to dihydrooxepine and dihydrofuran scaffolds. Moreover, the dihydrofurans were converted to dihydropyrroles via a relatively unknown palladium-catalyzed oxygen to nitrogen transposition. Further development of these reactions as well as their application to target-oriented synthesis is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03361.

Full experimental details and spectroscopic data for all new compounds (PDF)

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Author Contributions

The manuscript was written through contributions from both authors. Both authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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