Lewis Base Catalysis Based on Homoconjugate Addition: Rearrangement of Electron-Deficient Cyclopropanes and Their Derivatives

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Abstract
Cyclopropane is one of the most reactive functionalities owing to its intrinsic ring strain. Transition-metal catalysis and Lewis acid catalysis have been extensively used in ring openings of cyclopropanes; however, Lewis base-catalyzed activation of cyclopropanes remains largely unexplored. Upon nucleophilic attack with Lewis bases, cyclopropanes undergo ring cleavage in a manner known as homoconjugate addition to form zwitterionic intermediates, which have significant potential for reaction development but have garnered little attention. Here, we present a brief overview of this area, with an emphasis on our recent efforts on Lewis base-catalyzed rearrangement reactions of electron-deficient cyclopropanes using the homoconjugate addition process.

1 Introduction
Cyclopropanes are important motifs in organic chemistry because they exist as essential cores in many natural products and important drugs; they also serve as versatile building blocks in organic synthesis. The ring-opening reactions of cyclopropanes have emerged as powerful tools for the construction of molecular architectures, especially

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1 Introduction
Cyclopropanes are important motifs in organic chemistry because they exist as essential cores in many natural products and important drugs; they also serve as versatile building blocks in organic synthesis. The ring-opening reactions of cyclopropanes have emerged as powerful tools for the construction of molecular architectures, especially
for various carbo- and heterocycles. Whereas the release of ring strain of cyclopropanes (~27 kcal/mol) provides a thermodynamic driving force, nonactivated cyclopropanes are kinetically rather inert toward ring opening. Therefore, many creative catalytic strategies and a range of substrates with specific substitution patterns have been devised to achieve effective and selective activation of cyclopropanes.

In particular, donor–acceptor cyclopropanes (DACs) are a privileged class of substrates that have been extensively exploited for their ring-opening reactions, especially under Lewis acid catalysis. In principle, the bonding of a Lewis acid to the acceptor (usually a geminal ester) of a DAC provides an electron-withdrawing force for the C–C bond cleavage, generating an intermediate A for subsequent functionalization (Scheme 1a). In an opposite way, a Lewis base can supply a lone pair of electrons to induce nucleophilic attack for the ring opening of an electron-deficient cyclopropane, in a process known as ‘homoconjugate addition’, with formation of a zwitterionic intermediate B (Scheme 1b). However, this species has seldom been used in reaction discovery in the context of Lewis base catalysis. This stands in striking contrast with the homologous intermediate C generated by the conjugate addition of a Lewis base to an electron-deficient alkene (Scheme 1c), through which numerous transformations have been engendered.

The history of homoconjugate addition of Lewis bases or bases with electron-deficient cyclopropanes or alkenes can be traced back to the 1970s, when the Hanafusa group and Danishefsky groups reported ring openings of highly electron-deficient cyclopropanes with pyridine or piperidine to afford stable zwitterionic adducts 1 and 2, respectively (Schemes 2a and 2b). In 2006, Kuznetsova and co-workers reported that 1,1-dinitrocyclopropanes underwent a homoconjugate addition with a range of Lewis bases to form similar zwitterions 3 (Scheme 2c).

However, catalytic transformations based on the homoconjugate addition were not realized until 2014, when Liang and co-workers demonstrated a DABCO-catalyzed annihilation reaction of cyclopropanecarboxamides 4 with electron-deficient alkenes to afford γ-lactams 5 (Scheme 3). The annihilation is believed to proceed by the steps of homoconjugate addition, alkylation, proton transfer, and, finally, cyclization. Inspired by these precedents and as part of our interest in Lewis base catalysis, in the past three years our group has focused on Lewis base catalysis using the homoconjugate addition process. In this Synpacts, we summarize
several types of Lewis base-catalyzed rearrangement reactions of electron-deficient cyclopropanes.\textsuperscript{15d–g} These transformations are complementary to those catalyzed by Lewis acids or transition metals, and they highlight the significant promise of homoconjugate addition processes in the development of new reactions.

2  DABCO-Catalyzed Cloke–Wilson Rearrangement of Cyclopropyl Ketones

As a heteroatom variant of the vinylcyclopropane–cyclopentene rearrangement,\textsuperscript{16} Cloke–Wilson rearrangements\textsuperscript{17} of cyclopropyl ketones or aldehydes deliver 2,3-dihydrofurans, whereas those of imines give 2-pyrrolines. However, this type of rearrangement suffers from the limitations of a narrow substrate scope and the need for harsh conditions, such as high temperatures. Therefore, considerable efforts have been devoted to improving the efficiency of the reaction. Notable examples\textsuperscript{18} include a TiCl\textsubscript{4}-mediated silicon-assisted Cloke–Wilson rearrangement,\textsuperscript{18a} a Ni-catalyzed rearrangement based on a Ni–π-allyl intermediate,\textsuperscript{18b} and TBA[Fe]-catalyzed thermal or photochemical Cloke–Wilson rearrangements.\textsuperscript{18c} An enantioselective Cloke–Wilson rearrangement has also been realized by using a chiral phosphoric acid catalyst.\textsuperscript{19} Recently, Piotrowski and Kerr\textsuperscript{20} reported an interesting Rh-catalyzed tandem cyclopropanation/Cloke–Wilson rearrangement and its vinylcyclic variant, depending on the diene substrate used. Because of our interest in homoconjugate addition, we proposed that an organocatalytic Cloke–Wilson rearrangement using a homoconjugate addition process might be possible.\textsuperscript{15d}

Screening of the conditions indicated that with the use of 50 mol% of DABCO in DMSO at 120 °C, the desired organocatalytic Cloke–Wilson rearrangement of cyclopropyl ketones preceded with high efficiency (Scheme 4). A wide array of unsubstituted and aryl-, alkyl-, or vinyl-substituted cyclopropyl ketones 6 containing either aromatic or aliphatic ketone moieties were found to be suitable substrates, giving the corresponding dihydrofuran products 7 in good to excellent yields. Notably, the rearrangement of trisubstituted cyclopropanes showed exclusive regioselectivity, with C–O bond forming exclusively on the sterically hindered carbon. Various electron-withdrawing groups, including ketones, esters, and amides, were also well tolerated. However, when the substrate carried two different ketone groups, e.g. acetyl and benzoyl, its rearrangement produced a pair of dihydrofurans, favoring the acetyl-rearranged product (7q–t).

A plausible mechanism for the DABCO-catalyzed Cloke–Wilson rearrangement is shown in Scheme 5. Homoconjugate addition of DABCO to the cyclopropane 6 generates an enolate intermediate 8, which undergoes a favorable 5-exo-tet cyclization\textsuperscript{21} to form the 2,3-dihydrofuran 7 with regeneration of the catalyst.

The proposed intermediates 8 can be isolated from the reactions of the structurally similar substrates 6z and 6z′ with DABCO (Scheme 6a). For trisubstituted cyclopropanes, the C–C bond bearing an electron-donor substituent can be more polarized,\textsuperscript{22} which might account for the regioselective ring cleavage. It was also found that the enantioenriched substrate (R)-6m (94% ee) rearranged with loss of stereochemical integrity, suggesting an S_N1-type ring opening in the mechanism (Scheme 6b).
2 Hydroxylamine-Mediated Tandem Cloke-Wilson/Boulton-Katritzky Reaction of Cyclopropyl Ketones

During our investigations of the Cloke–Wilson rearrangement, we found that hydroxylamine as a Lewis base delivered an interesting reactivity.\textsuperscript{15e} When cyclopropyl ketone 6d was treated with 20 mol% of NH₂OH at 110 °C in DMSO, the desired Cloke–Wilson product 7d was obtained in 77% yield along with isoxazole 9a in 12% yield (Scheme 7, entry 1). With a stoichiometric amount of NH₂OH, 9a was obtained in 66% yield as the sole product (Scheme 7, entry 2). Evidently, a tandem Cloke–Wilson/Boulton–Katritzky\textsuperscript{22} reaction mediated by NH₂OH had taken place in one pot. In this reaction, NH₂OH served as both a catalyst for the upstream Cloke–Wilson rearrangement and as a reactant in the downstream Boulton–Katritzky reaction. This reaction therefore presents a new sustainable strategy\textsuperscript{23} by recycling the catalyst as a reactant. The strategy might not only have potential in improving the atom efficiency of tandem reactions, but might also circumvent the concern regarding the use of large catalyst loadings that is often encountered in organocatalysis, because all the catalyst material is incorporated into the final product.

Under optimized conditions (in DMSO at 130 °C with 2.0 equiv of NH₂OH·HCl and 2.4 equiv of K₂CO₃ added in two portions), the tandem Cloke–Wilson/Boulton-Katritzky reaction showed a broad substrate scope. Cyclopropyl ketones 6 with various substituents (R¹ = aryl, vinyl, alkyl, or H; R² = aliphatic, aromatic) all worked well in the reaction, producing the desired isoxazoles 9 in good to excellent yields (Scheme 8).

In contrast to hydroxylamine, hydrazine failed to promote a similar tandem reaction to generate the corresponding pyrazoles. However, when DABCO was employed as a catalyst,\textsuperscript{15d} the desired pyrazoles were obtained in excellent yields in a one-pot process (Scheme 9). This result, however, corroborates the dual role of hydroxylamine as both catalyst and reactant in the Cloke–Wilson/Boulton–Katritzky reaction.

A plausible mechanism for the Cloke–Wilson/Boulton–Katritzky tandem reaction is shown in Scheme 10. First, NH₂OH as a catalyst triggers a Cloke–Wilson rearrangement of cyclopropyl ketone 6 to form dihydrofuran 7. Subsequently, in a Boulton–Katritzky reaction,\textsuperscript{24} NH₂OH acts as a
reactant, condensing with 7 to give oxime 11, which is deprotonated by a base and then undergoes cyclization to produce intermediate 12. Finally, fragmentation followed by protonation delivers the desired isoxazole 9. The Cloke–Wilson rearrangement should be faster than the downstream Boulton–Katritzky reaction, as evidenced by the isolation of intermediate 7d in an appreciable yield when 20 mol% of hydroxylamine was employed (Scheme 7).

4 Phosphine-Catalyzed Rearrangement of Vinylcyclopropyl Ketones To Form Cycloheptenones

Phosphine catalysis\(^\text{25}\) has attracted much attention owing to its unique and versatile reactivity, particularly for the construction of carbo- and heterocycles. Phosphine-catalyzed annihilations mainly utilize electron-deficient alkenes, alkynes, or allenes as substrates.\(^\text{26}\) These precursors serve as useful C\(_1\) to C\(_4\) synthons for building various cyclic structures, especially five- or six-membered rings. In continuation of our exploration of the utility of homoconjugate addition, we proposed that electron-deficient vinylcyclopropanes 14 might be used as possible C\(_3\) synthons under phosphine catalysis to provide access to medium-sized ring structures (Scheme 11).\(^\text{15c}\)

Initially, the reaction of vinylcyclopropane 14a with PPh\(_3\) in CDCl\(_3\) at 40 °C was examined by NMR. This reaction clearly afforded the zwitterion 15a, presumably through the proposed ring opening followed by a double-bond migration (Scheme 11a). However, when 1,1-diacetyl-2-vinylcyclopropane (14b) was employed, we were pleased to observe an unprecedented phosphine-catalyzed rearrangement of the vinylcyclopropyl ketone to a cycloheptenone. A survey of the conditions suggested that reaction in toluene
at 110 °C with 20 mol% of PBu₃ offered the optimal results, producing cycloheptenone 15b in 85% yield as a pair of keto–enol tautomers (keto/enol = 1:2) (Scheme 11b).

A variety of vinylcyclopropyl ketones 14 worked well in this rearrangement under the optimized conditions (Scheme 12). Substitution at either an internal or external position of the alkene (R¹ and R²) was feasible, as well as substitution on the acetyl fragment (R³). Thus, the rearrangement allows a controlled synthesis of 2-, 3-, or 4-substituted cycloheptenones. In addition, substrates with an amide or ester group (EWG = CONHR, CO₂R) were also compatible, producing the desired products in good yields. Because cycloheptenones are synthetically challenging units that occur in many natural products and biologically active molecules, this rearrangement should offer mild access to this type of medium-sized carbocycle.

A plausible mechanism for the phosphine-catalyzed rearrangement of vinylcyclopropyl ketones is shown in Scheme 13. First, regioselective attack by PBu₃ on the vinylcyclopropyl ketone 14b through homoconjugate addition forms intermediate 16. In addition, substrates with an amide or ester group (EWG = CONHR, CO₂R) were also compatible, producing the desired products in good yields. Because cycloheptenones are synthetically challenging units that occur in many natural products and biologically active molecules, this rearrangement should offer mild access to this type of medium-sized carbocycle.

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5 Phosphine-Catalyzed Rearrangement of Alkylidenecyclopropyl Ketones To Form Poly-substituted Furans and Dienones

Alkylidenecyclopropanes (ACPs)⁷d are extremely versatile building blocks in organic synthesis due to their unique structure and high ring strain (~38.8 kcal/mol). Whereas transition metals and Lewis acids have been largely used for the activation of ACPs, organocatalyzed ring openings of ACPs are scarce. Inspired by the rearrangement of electron-deficient vinylcyclopropanes, we extended our investigation to electron-deficient ACPs 18 under phosphine catalysis (Scheme 14). We proposed that an attack by a phosphine on an ACP 18 might generate the allylic phosphonium species 19 through cleavage of the distal C–C bond. Such intermediates can be regarded as homologues of the well-studied phosphine–allene adducts 20, which exhibit tremendous reactivity in phosphine-catalyzed annihilations. We speculated that intermediates 19 might also possess significant promise for reaction development. Inspired by the palladium-catalyzed rearrangements of alkylidenecyclopropyl ketones reported by Ma and co-workers, we attempted a phosphine-catalyzed ring opening of alkylidenecyclopropyl ketones, which led to the discovery of three types of substrate-controlled rearrangement reaction (see below).¹⁵g

With a catalytic amount of (4-MeOC₆H₄)₃P (20 mol%) in DMSO at 120 °C, alkylidenecyclopropyl ketones 21 bearing a geminal electron-withdrawing group (R² = EWG) readily rearranged to afford the trisubstituted furans 22 in good yields. Substrates with various electron-withdrawing groups and aliphatic or aromatic ketone groups on the cyclopropyl ring, as well as a range of substituents on the alkene, were well tolerated (Scheme 15).

### Scheme 13
Proposed mechanism for the phosphine-catalyzed rearrangement of vinylcyclopropyl ketones to cycloheptenones

### Scheme 14
Adducts of phosphines with electron-deficient ACPs or allenes

### Scheme 15
Phosphine-catalyzed rearrangement of alkylidenecyclopropyl ketones to 1,2,3-trisubstituted furans

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Notably, when the R2 substituent was switched from an EWG to an aryl group, the corresponding alkylidenecyclopropyl ketones 23 rearranged selectively to produce 1,2,4-trisubstituted dienones 24 (Scheme 16). This reaction was best carried out in refluxing DCE with PBu3 (20 mol%), which was compatible with an array of substrates, giving high yields and high stereoselectivities. Of note, this transformation had previously been realized through transition-metal catalysis only.31

Furthermore, when the alkene group of the ACP was substituted with an aryl group, thus preventing diene formation, the rearrangement was further diverted toward the construction of fully substituted furans with high chemoselectivity (Scheme 17). It is noteworthy that this reaction stands in contrast to the Pd(PPh3)4-catalyzed counterpart reported by Ma and co-workers.30b Under the optimized conditions, a range of alkylidenecyclopropyl ketones undergoes an intramolecular SN2 displacement to give a dihydrofuran intermediate to ensue three distinct rearrangements, depending on the substituent pattern. In Path A, when R2 is an electron-withdrawing group, the phosphonium species 19 undergoes an intramolecular S_N2 displacement to give a dihydrofuran 22' that isomerizes to a trisubstituted furan 22. In Path B, replacement of the EWG with aryl group increases the basicity of the corresponding dienolate 19, thereby promoting an intramolecular 1,4-proton transfer to give intermediate 27. Subsequent 1,4-elimination regenerates the catalyst and produces the diene 24' that isomerizes to the thermodynamically more stable diene 24. In Path C, installation of an aryl group (R1 = aryl) on the alkene blocks the aforementioned 1,4-proton transfer, leading to an intramolecular S_N2' substitution to furnish dihydrofuran 26', which isomerizes to the fully substituted furan 26. These rearrangements are complementary to their previously reported transition-metal-catalyzed counterparts,30b1 demonstrating the versatile reactivity permitted by phosphine-catalyzed ring opening of ACPs.

**Scheme 16** Phosphine-catalyzed rearrangement of alkylidenecyclopropyl ketones to 1,2,4-trisubstituted dienones

**Scheme 17** Phosphine-catalyzed rearrangement of alkylidenecyclopropyl ketones to fully substituted furans

**Scheme 18** Proposed mechanism for the phosphine-catalyzed divergent rearrangements of alkylidenecyclopropyl ketones
6 Conclusion and Outlook

Although homoconjugate addition of electron-deficient cyclopropanes with Lewis bases was reported as early as the 1970s, it has rarely been used in reaction development. This is opposite to the conjugate addition, which has been widely used in Lewis base catalysis. In this Synfacts, we have summarized our recent findings on the Lewis base-catalyzed annulations of electron-deficient cyclopropanes and their derivatives through a homoconjugate addition process. The established reactions offer efficient syntheses of dihydrofurans, isoxazoles, pyrazoles, cycloheptenones, furans, or dienes. Although there are few examples, the diverse reactivity of zwitterionic intermediates generated by homoconjugate addition is striking. A particularly attractive application is the use of vinylicyclopropanes to access medium-sized rings under phosphine catalysis. Challenges going forward include the intermolecular annihilations of the intermediates with suitable coupling partners. For example, Lewis base-catalyzed [3+n]-annulations of electron-deficient cyclopropanes are still absent, yet evidently offer significant opportunities. Consequently, Lewis base-catalyzed ring opening of cyclopropanes through homoconjugate addition will continue to garner attention and interest, because investigations in this context will enrich the fields of Lewis base catalysis and cyclopropane chemistry.

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