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Evidence for Heterolytic Cleavage of a Cyclic Oxonium Ylide: Implications for the Mechanism of the Stevens [1,2]-Shift†

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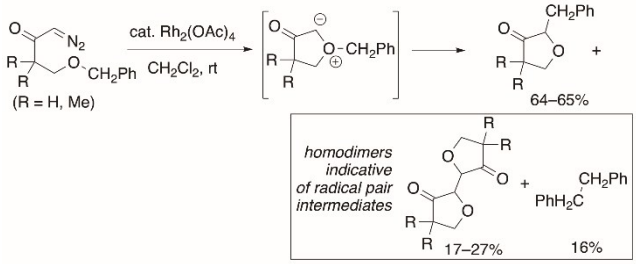
Formation and rearrangement of several oxonium ylides containing cyclopropylcarbinyl migrating groups were studied. Efficient ring-contraction by [1,2]-shift to form cyclopropane-substituted cyclobutanones was observed, with no competing cyclopropane fragmentation. Substitution with the hypersensitive mechanistic probe (*trans*,*trans*-2-methoxy-3-phenylcyclopropyl)methyl led to cyclopropane fragmentation via an apparent heterolytic pathway, providing the first evidence for ion pair intermediates from ylide cleavage, and suggesting a possible alternative heterolytic mechanism for the Stevens [1,2]-shift.

Oxonium ylides are versatile intermediates suitable for the construction of a variety of complex targets.[1] Typically they are generated via nucleophilic trapping of metallocarbenes by ethers, usually in an intramolecular process to limit alternative metallocarbene reactivity. The resulting cyclic ylides can undergo a variety of subsequent transformations, including [2,3]-sigmatropic rearrangement,[2] Stevens [1,2]-shift,[3] sequential electrophilic/nucleophilic trapping,[4] or fragmentation.[5]

Among these pathways, the Stevens [1,2]-shift entails an unusually complex mechanistic odyssey. Concerted migration of one of the ylide substituents from heteroatom to carbon is symmetry-forbidden,[6] leading to various alternative stepwise mechanistic proposals. In the context of the corresponding ammonium ylides, Ollis and co-workers provided strong evidence for migration via homolysis and radical pair recombination.[7] The observation of homodimeric side-products in some oxonium ylide examples suggested that a similar mechanism was in effect for these intermediates (Scheme 1).[8]

Based upon the assumption that [1,2]-shifts of oxonium ylides proceed through a homolytic mechanism, we were interested in the fate of a cyclopropyl-substituted migrating group in such a process. The cyclopropylcarbinyl radical is a well-known radical clock, with its rearrangement to the 3-butenyl radical occurring at a rate of 1 x 10^8 s^{-1} at 25 °C.[9] To the best of our knowledge, Stevens rearrangement of cyclopropylcarbinyl-substituted oxonium ylides has not been examined,[10] and its competence as a migrating group and the fate of the cyclopropane ring were of interest to us.[11]



Scheme 1 Evidence of radical pairs in oxonium ylide [1,2]-shifts

Diazoketone **1a** was selected for initial study, with the expectation that metallocarbene **2a** would generate cyclic oxonium ylide **3a**, whose rearrangement would afford [1,2]-shift products **6a** and/or **7a** (Scheme 2) Observation of **7a** would offer strong evidence for the intermediacy of a radical pair consisting of tetrahydrofuranone radical **4a** and cyclopropylcarbinyl radical **5a**. In the event, treatment of **1a** with $Cu(hfacac)_2$[‡] in dichloroethane (DCE) at reflux furnished carbene dimer **8a** (mixture of *E/Z* isomers) as the sole isolable product. Exclusive formation of products derived from **2a** suggests slow rearrangement of oxonium ylide **3a**, with preferential reaction via the metallocarbene side of the equilibrium.[12]

We imagined that the rate of oxonium ylide rearrangement could be affected by the degree of radical stabilization on the migrating group, and therefore prepared 1-phenylcyclopropylcarbinyl substrate **1b**. Treatment of this compound with $Cu(hfacac)_2$ in DCE at reflux provided the [1,2]-shift product **6b** in good yield, with none of the carbene dimer **8b**. Also notable were the isolation of minor amounts of bis(tetrahydrofuranone) **9**, and the absence of any homoallyl migration product **7b**. As noted earlier, observation of homo-

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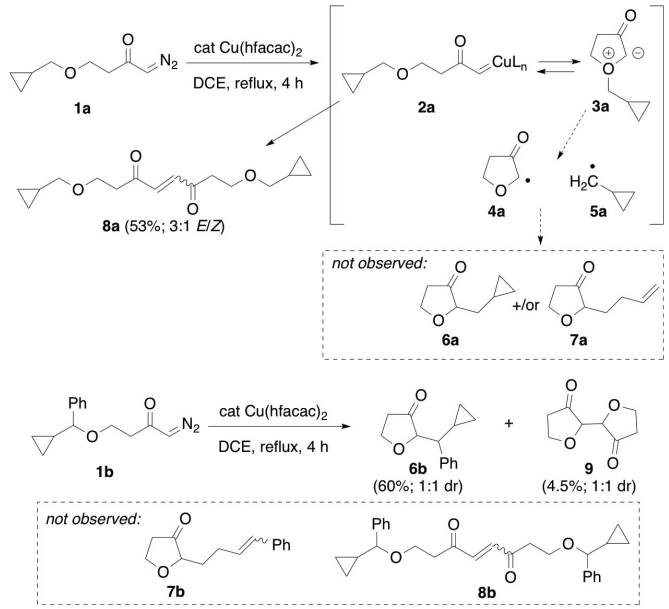
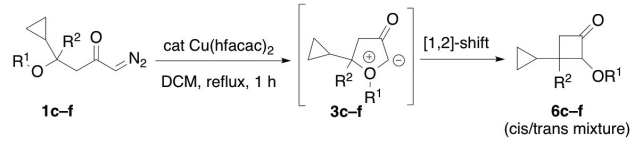


Scheme 2 Attempted oxonium ylide formation/rearrangement of cyclopropylcarbinyl ethers

dimers such as **9** is a compelling indicator for radical intermediates. Formation of **6b** to the exclusion of **7b** is consistent with reports that the 1-phenylcyclopropylcarbinyl radical undergoes *reversible* ring-opening, with the equilibrium favoring the ring-closed form.[13]

The notable difference in the behavior of **1a** and **1b** points to the sensitivity of the migrating center to stabilizing substituents, prompting us to examine substrate **1c**, in which the cyclopropyl-substituted migrating group was now *endocyclic* in the intermediate ylide **3c** (Table 1). [1,2]-Shift of this group would entail a net ring-contraction to afford cyclobutanone **6c**.[14] A range of reaction conditions were surveyed (see ESI), with the optimal ones ($Cu(hfacac)_2$ in DCM at reflux) furnishing cyclobutanones **6c** in 80% yield and as a 6:1 ratio of *cis*:*trans* diastereomers.* Treatment of substrate **1c** with rhodium catalyst also generated the cyclobutanones **6c** with 73% yield and with a dr of 2.2:1 (entry 2). Successful ring-contraction of **1c** shows that the presence of a strongly stabilizing aryl group is not required for the intermediate

Table 1 Cyclobutanones by cyclopropyl-directed ring-contraction of oxonium ylides

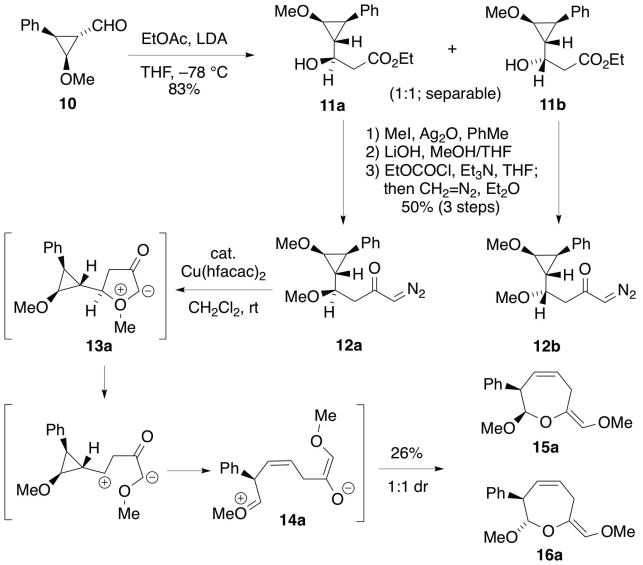


Entry	Substrate	R^1	R^2	Catalyst	Yield **6** (*cis*:*trans*)[a]
1	**1c**	Me	H	$Cu(hfacac)_2$	80 (6:1)
2	**1c**	Me	H	$Rh_2(OAc)_4$	73 (2.2:1)
3	**1d**	Me	Me	$Cu(hfacac)_2$	50 (1.4:1)
4	**1e**	Et	H	$Cu(hfacac)_2$	70 (6:1)
5	**1f**	*i*-Pr	H	$Cu(hfacac)_2$	78 (4.8:1)

[a]Yields given are for isolated product after purification. Ratios were determined ^{1}H NMR analysis via integration of ether O–C–H resonances.

oxonium ylide to undergo cleavage and [1,2]-shift; in this case the adjacent ring methylene was sufficient for clean rearrangement. Several other cases were also studied, varying the degree of substitution on the migrating carbon (**1d**) or the oxygen substituent (**1e**,**f**). In all cases the cyclobutanones were formed efficiently, though in varying ratios of diastereomers. No products of cyclopropane fragmentation were seen in any of these cases.

The absence of any products of cyclopropylcarbinyl–homoallyl rearrangement for substrates **1c**-**f** provoked uncertainty on our part as to whether [1,2]-shift by the corresponding ylides **3** occurred via radical intermediates. Isolation of **9** from the reaction of **1b** suggests that at least some of that reaction proceeds through a homolysis manifold, but other pathways such as heterolysis or metal-assisted migration might also be available.[12b,15] We therefore turned to the hypersensitive mechanistic probe described by Newcomb and co-workers, wherein alternative cyclopropane cleavage pathways are expected depending upon the intervention of a radical or cationic center at the cyclopropylcarbinyl position (Scheme 3).[16] Aldehyde **10** was subjected to aldol addition, and the resulting hydroxyester diastereomers **11a**,**b** were separated and subjected to 3 successive steps to afford substrates **12a**,**b**,# which were then subjected to the standard conditions for ylide formation and rearrangement. In the event, **12a** afforded a complex mixture of products from which the only isolable components were diastereomeric tetrahydrooxepines **15a** and **16a**.§ These products are presumed to result from ring closure through the carbonyl oxygen of zwitterion **14a**, which results from heterolytic cyclopropane fragmentation of ylide **13a**. None of the corresponding homolytic fragmentation products (resulting from cleavage adjacent to the phenyl group) were isolated, nor were any cycloheptanones (the product of attack through the enolate carbon of **14a**). Preferential cyclization to afford **15a** and **16a** rather than cycloheptanones may be due to a preference by the oxocarbenium ion intermediate to react



Scheme 3 Preparation and rearrangement of hypersensitive mechanistic probe **12a**

with the harder oxygen nucleophile.[17] It should be noted that **15a** and **16a** can form only from the (*Z*)-isomer of **14a**, and to whatever extent fragmentation affords the (*E*)-alkene, numerous uncharacterizable pathways are expected to predominate.[16b,18] This stereospecific reactivity, together with the lability of oxepines **15a** and **16a**,[§§] is likely responsible for the low mass balance for this transformation.

The connectivity of **15a** and **16a** was determined via HMBC analysis, in which clear evidence was seen for cyclopropane fragmentation adjacent to the methoxy group rather than the phenyl (see ESI). The relative stereochemical configurations of these isomers was assigned based upon the vicinal coupling constants of the adjacent methine protons on C2 and C3 of the oxepine ring, as well as NOE correlations that clearly showed an (*E*)-geometry in each case for the exocyclic enol ether moieties.

In the case of this sensitive mechanistic probe, the only identifiable pathway for cyclopropane fragmentations proceeds through apparent ionic intermediates, offering the first evidence for ion pair intermediates from cleavage of oxonium ylides. The heterolytic fragmentation pathway may intervene in the mechanism of the corresponding Stevens [1,2]-shift. This result, in conjunction with prior examples involving apparent homolytic mechanisms, suggests that the reaction manifold is quite sensitive to the structure of the migrating group.[19] In particular, oxonium or sulfonium ylide substrates possessing anomeric acetal migrating carbons[3,20] seem well suited to heterolysis, suggesting a careful re-examination of those examples for solvent and substituent effects. Continuing efforts in this regard are ongoing and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Subsequent to the original report,[8] we have found that soluble Cu(II) catalysts are superior to Rh(II) catalysts for oxonium ylide formation from diazo precursors.

* Cyclobutanone stereoisomers were assigned via TROESY analysis. See ESI for details.

#The relative configuration of the carboxylic acid precursor to diastereomeric diazoketone **12b** was determined via X-ray crystallographic analysis (see ESI).

§ Methoxy diastereomer **12b** furnished an intractable mixture of many products under analogous conditions to those applied to **12a**.

§§ The presence of hydrolytically sensitive enol ether and acetal functionalities in **15a** and **16a** render them sensitive to decomposition during chromatography on silica gel.

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Evidence for heterolytic cleavage of a cyclic oxonium ylide: implications for the mechanism of the Stevens [1,2]-shift

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In contrast to prior evidence for a homolytic mechanism, a cyclopropylcarbinyl-substituted oxonium ylide furnished cleavage products consistent with a zwitterionic intermediate.