ORGANIC CHEMISTRY

# Interrupted carbonyl-olefin metathesis via oxygen atom transfer

Jacob R. Ludwig[1], Rebecca B. Watson[1]*, Daniel J. Nasrallah[1]*, Joseph B. Gianino[2], Paul M. Zimmerman[1], Ren A. Wiscons[1], Corinna S. Schindler[1]†

**Some of the simplest and most powerful carbon-carbon bond forming strategies take advantage of readily accessible ubiquitous motifs: carbonyls and olefins. Here we report a fundamentally distinct mode of reactivity between carbonyls and olefins that differs from established acid-catalyzed carbonyl-ene, Prins, and carbonyl-olefin metathesis reaction paths. A range of epsilon, zeta-unsaturated ketones undergo Brønsted acid–catalyzed intramolecular cyclization to provide tetrahydrofluorene products via the formation of two new carbon-carbon bonds. Theoretical calculations and accompanying mechanistic studies suggest that this carbocyclization reaction proceeds through the intermediacy of a transient oxetane formed by oxygen atom transfer. The complex polycyclic frameworks in this product class appear as common substructures in organic materials, bioactive natural products, and recently developed pharmaceuticals.**

Carbonyl and olefin functionalities generally react together through carbonyl-ene (*1*–*5*) or Prins (*5*–*10*) pathways upon activation with strong Brønsted or Lewis acids. Both pathways can be accessed from similar substrates **1**, depending on the choice of catalyst and conditions (Fig. 1A). Upon coordination to a carbonyl, Lewis acids can induce a change in polarization that enhances reactivity. Different Lewis acids can subtly alter the charge distribution in the resulting Lewis acid–substrate complex (*11*–*14*) to generate a continuum between a stepwise mechanism involving carbocationic intermediate **2** and a concerted mechanism via a six-membered transition state **3** (I, Fig. 1A) (*3*). The carbonyl-ene reaction can proceed through either route to generate homoallylic alcohol **4** upon addition of an electrophilic carbonyl to an alkene with concomitant transfer of an allylic hydrogen atom. In comparison, the Prins reaction proceeds through intermediate carbocation **2** that is subsequently captured by an exogenous nucleophile to provide the corresponding alcohol **5** (II, Fig. 1A) (*5*). In a further modulation of the reactivity between carbonyls and olefins, we have recently reported an iron(III)-catalyzed carbonyl-olefin ring-closing metathesis reaction of substrate **1** to provide cyclohexene product **7** (III, Fig. 1A) (*15*). Mechanistic studies supported a concerted, asynchronous [2+2]-cycloaddition reaction that does not rely on carbocation intermediates to form oxetane **6**, which subsequently fragments in an asynchronous, concerted retro-[2+2]-cycloaddition to provide the corresponding cyclopentene and -hexene metathesis products (*16*). In this context, Lewis acid activation opens access to intermediate oxetanes that are otherwise restricted to photochemical [2+2] cycloadditions such as the Paternò-Büchi reaction (*17*–*19*).

We herein report that these fundamental acid-mediated transformations between carbonyls and olefins can be expanded to include an additional mode of reactivity (IV, Fig. 1A). This transformation resembles the carbonyl-olefin metathesis reaction in that it also proceeds via an oxetane (**8**); however, its fragmentation pathway is interrupted to result in the formation of an intermediate carbocation. This interrupted carbonyl-olefin metathesis path relies on Brønsted acid activation of carbonyl and olefin functionalities to yield a complex, carbocyclic framework **9** (*20*, *21*) upon formation of two carbon-carbon bonds. Whereas this multiple bond–forming process selectively yields the tetrahydrofluorene product **9**, the presence of a Brønsted acid has previously been reported to be detrimental to many Lewis acid–catalyzed carbonyl-ene and Prins reactions, resulting in undesired polymerization and isomerization of olefins (*22*). Furthermore, this interrupted carbonyl-olefin metathesis reaction provides access to tetrahydrofluorene product **9** in a single synthetic transformation, whereas current strategies rely on multistep sequences and precious metal–catalyzed cycloisomerizations (*23*, *24*). Tetrahydrofluorenes represent key structural elements in materials science (**10**) (*25*) and are ubiquitous core structures in biologically active natural products (**11**) (*26*). Additionally, tetrahydrofluorenes are found in recently developed pharmaceuticals [Merck's ERβ agonist **12** (*27*) and ledipasvir **13** (*28*), part of Harvoni, Gilead's two-component treatment against hepatitis C].

During our investigations into the iron(III)-catalyzed carbonyl-olefin metathesis reaction, we discovered a complementary mode of reactivity of aryl ketone **14**, depending on the choice of iron(III) catalyst (Fig. 1B). Specifically, when **14** was converted under the optimal reaction conditions developed for carbonyl-olefin metathesis using 5 mole % (mol %) iron(III) chloride ($FeCl_3$) in dichloroethane, the desired metathesis product **16** was obtained in 71% yield. We initially postulated that iron(III) triflate [$Fe(OTf)_3$] could function as a stronger Lewis acid catalyst to further improve the yield of the carbonyl-olefin metathesis product **16**. However, subjecting the same aryl ketone **14** to 10 mol % $Fe(OTf)_3$ resulted in the formation of a new product, in 55% yield, that was identified as tetrahydrofluorene **17**. We hypothesized that this new compound likely arose from an intermediate carbocation that subsequently underwent Friedel-Crafts alkylation with the pendant aromatic ring to form the tricyclic core. This outcome is in stark contrast to the reactivity observed in $FeCl_3$-catalyzed carbonyl-olefin metathesis, which proceeds via an asynchronous, concerted mechanism and does not involve carbocations as essential intermediates. As such, this result indicated that altering the catalytic system, which we ultimately discovered to be Brønsted acid catalyzed, provides access to a distinct reaction pathway relying on carbocation intermediates. The combined importance of the tetrahydrofluorene products obtained along with the distinct reactivity observed upon Brønsted acid catalysis of aryl ketone **14** prompted us to further optimize this reaction, explore the substrate scope, and investigate the reaction mechanism of this transformation.

Thorough optimization involved the evaluation of various Lewis and Brønsted acids, solvents, and reaction times and ultimately led to the following optimal reaction conditions: 5 mol % triflic acid (TfOH) at 80°C in degassed benzene (see supplementary materials for details).

Initial efforts to explore the scope of this transformation focused on investigating the effect of varying the olefin substitution (Fig. 2A). The trisubstituted olefins **18** and **19** provided the corresponding tetrahydrofluorene product in 85 and 86% yield, respectively. Phenyl-substituted olefin **20** and exocyclic olefins **21** to **23** proved to be viable substrates, with the latter leading to spirocyclic tetrahydrofluorene products. Specifically, piperidine **23** bearing a para-trifluoromethyl phenylsulfonylamide underwent efficient cyclization in 87% yield, demonstrating the potential for the incorporation of heteroatoms into the polycyclic scaffold. Aryl ketones **24** and **25**, incorporating either a 1,2-di-substituted olefin or a 1,1-di-chlorinated olefin, failed to undergo the desired transformation, suggesting that two carbon-based substituents are required to increase the nucleophilicity of the olefin.

The optimized reaction conditions for the formation of tetrahydrofluorenes proved general for various electronically and sterically differentiated aryl ketone substrates (Fig. 2B). Electron-rich aryl ketones bearing hydroxyl, methoxy, or dioxole functionalities underwent the desired transformation in good to excellent yields (**17**, **26**, **27**, **31**, **32**, **36**, and **42**, Fig. 2B). Specifically, di- and trimethoxy–substituted aryl ketones **26** and **42** provided the desired products in 78 and 90% yield, respectively. A silyl-protected phenol underwent the desired cyclization with advantageous in situ deprotection to result in 92%

[1]Department of Chemistry, University of Michigan, Ann Arbor, MI, USA. [2]Advanced Materials and Systems Research, BASF, Wyandotte, MI, USA.
*These authors contributed equally to this work.
†Corresponding author. Email: corinnas@umich.edu

yield of **27**; subjection of the corresponding unprotected phenol also afforded efficient conversion to the desired tetrahydrofluorene **27** in 71% yield. Aryl ketones bearing electron-neutral *tert*-butyl, methyl, naphthyl, or phenyl substitution at the aromatic moiety provided the corresponding products in up to 94% yield (**28**, **37**, **43**, and **46**, Fig. 2B). Electron-deficient aryl ketones bearing chlorine or fluorine substitution reacted to form **41** and **47** in 66 and 88% yield, respectively. The para position of the aromatic subunit was thoroughly investigated and found to be widely electronically tolerant (**27** to **29**, **32**, **33**, **35**, **37**, **39** to **41**, **44**, **46**, and **47**, Fig. 2B). Similarly, substitution at the meta and ortho positions of the aromatic subunit led to the desired tetrahydrofluorene products; however, in the case of meta-substituted substrates, a mixture of regioisomers **34** and **36** was observed. The optimized reaction conditions also proved efficient for heteroaromatic ketones, resulting in the formation of benzothiophene **30** in 73% yield and thiophene **38** in 57% yield. Aryl ketones that contained heteroatoms distal from the reactive sites proved viable substrates for the desired transformation, resulting in the corresponding tetrahydrofluorene products in up to 59% yield (**29**, **33**, and **35**, Fig. 2B).

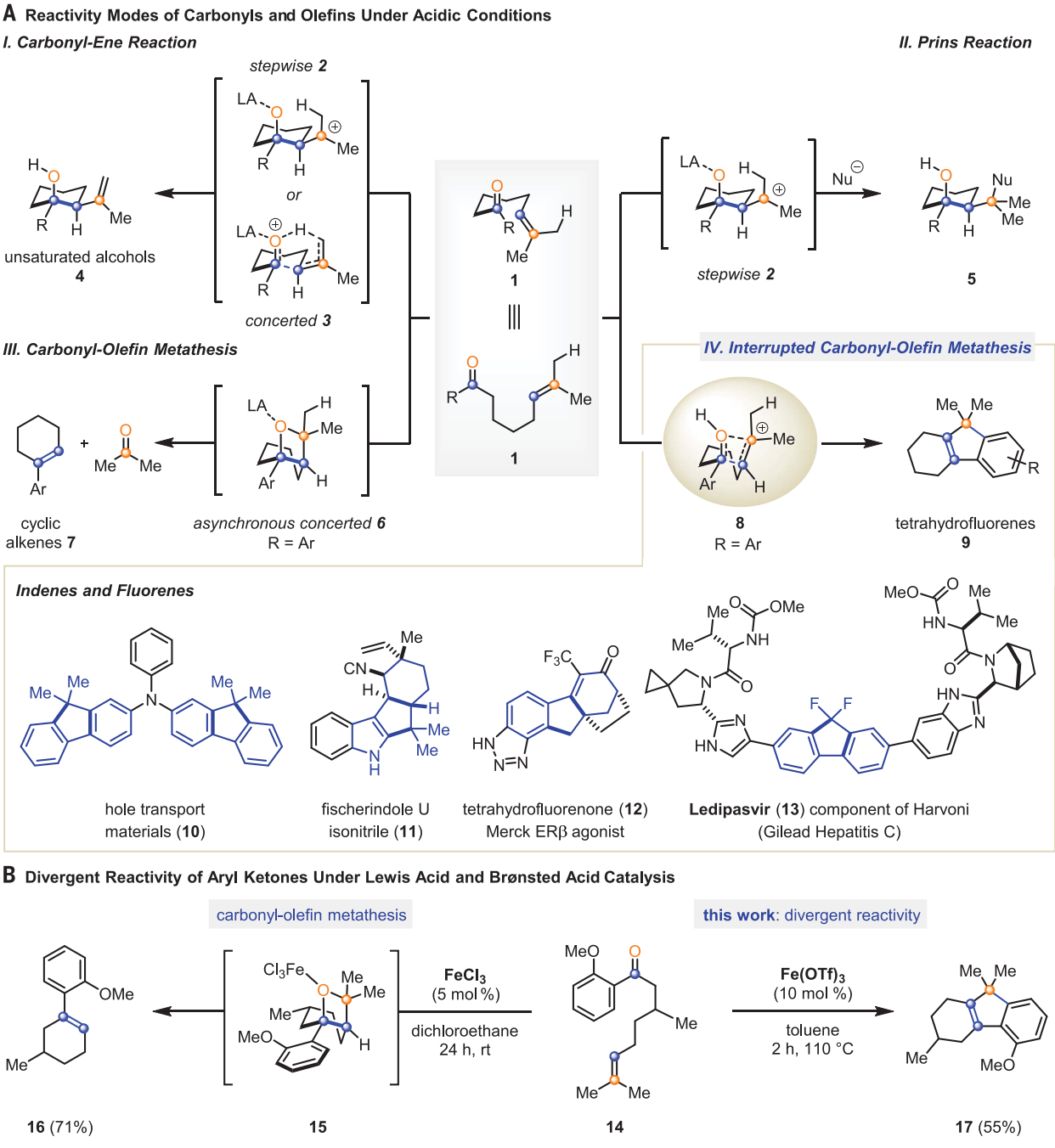


**Fig. 1. Chemistry of carbonyls and olefins.** (**A**) Fundamental acid-catalyzed reactivity modes between carbonyls and olefins. (I) Carbonyl-ene reaction. (II) Prins reaction. (III) Carbonyl-olefin metathesis.; (IV) This work: interrupted carbonyl-olefin metathesis. The importance of the products accessible in this reactivity mode is showcased below. LA, Lewis acid; R, hydrogen, alkyl, or aryl; Me, methyl; Nu, nucleophile; Ar, aryl. (**B**) Complementary reactivity modes of aryl ketone **14** are accessible depending on the choice of iron(III)-derived Lewis acid catalyst. The use of $FeCl_3$ leads to the formation of the carbonyl-olefin metathesis product **16,** whereas $Fe(OTf)_3$ results in tetrahydrofluorene **17**. rt, room temperature.

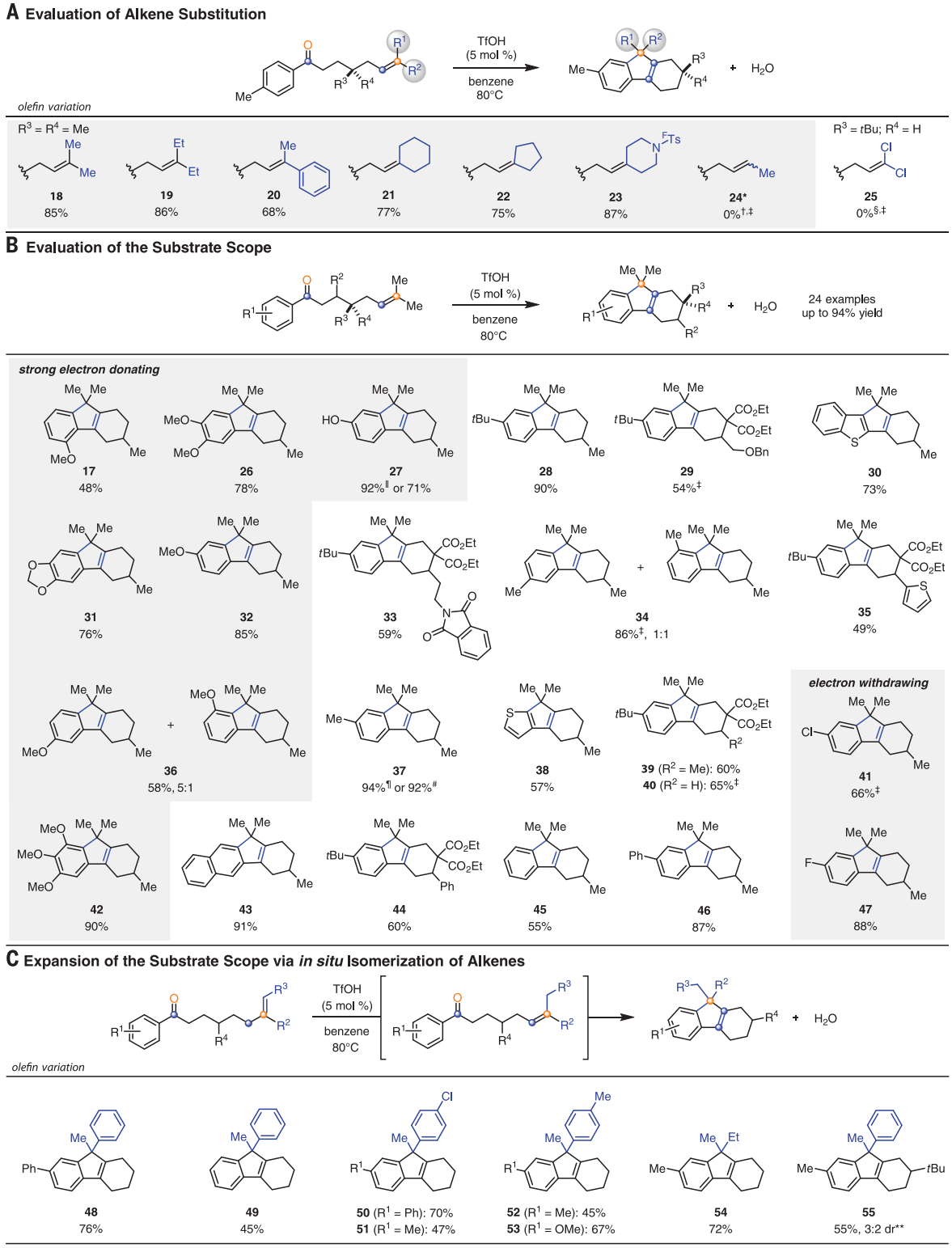


**Fig. 2. Substrate scope.** Conditions: Ketone (1.0 equivalent; 0.02 M), TfOH (5 mol %) in benzene at 80°C. See supplementary materials for additional experimental details. (**A**) Variation of the alkene substitution. Et, ethyl; $^{F}$Ts, (4-(trifluoromethyl)phenyl)sulfonyl; *t*Bu, *tert*-butyl. (**B**) Variation of the aryl ketone and carbon tether. Bn, benyl; Ph, phenyl. (**C**) In situ isomerization of alkenes to expand substrate scope. Footnotes: *4.3:1 mixture of *E* and *Z* alkenes. †81% of starting material **24** is recovered. ‡Percent yield and percent conversion determined by $^{1}$H nuclear magnetic resonance (NMR) using dimethyl terephthalate or mesitylene as an internal standard. §98% of starting material **25** is recovered. ||Starting material TBS (*tert*-butyldimethylsilyl) protected. ¶Percent yield determined by gas chromatography using dodecane as an internal standard. #Reaction run on a 10.2-mmol scale. **Percent yield and diastereomeric ratio (dr) determined by $^{1}$H NMR using dimethyl terephthalate as an internal standard.

Advantageously, benzyl ether **29** and phthalimide **33** can be deprotected to provide handles for further elaboration. *Tert*-butyl–substituted aromatic substrates bearing distinct functionalities along the carbon backbone resulted in the formation of the desired products **39**, **40**, and **44** in up to 65% yield, whereas the substrate bearing minimal substitution also proved viable, providing the desired tetrahydrofluorene **45** in 55% yield. Taken together, the substrate scope suggests that the electronics of the aryl ketone and sterics on the substrate tether do not alter the efficiency of this transformation. The optimized reaction conditions also proved amenable to gram-scale synthesis of **37**.

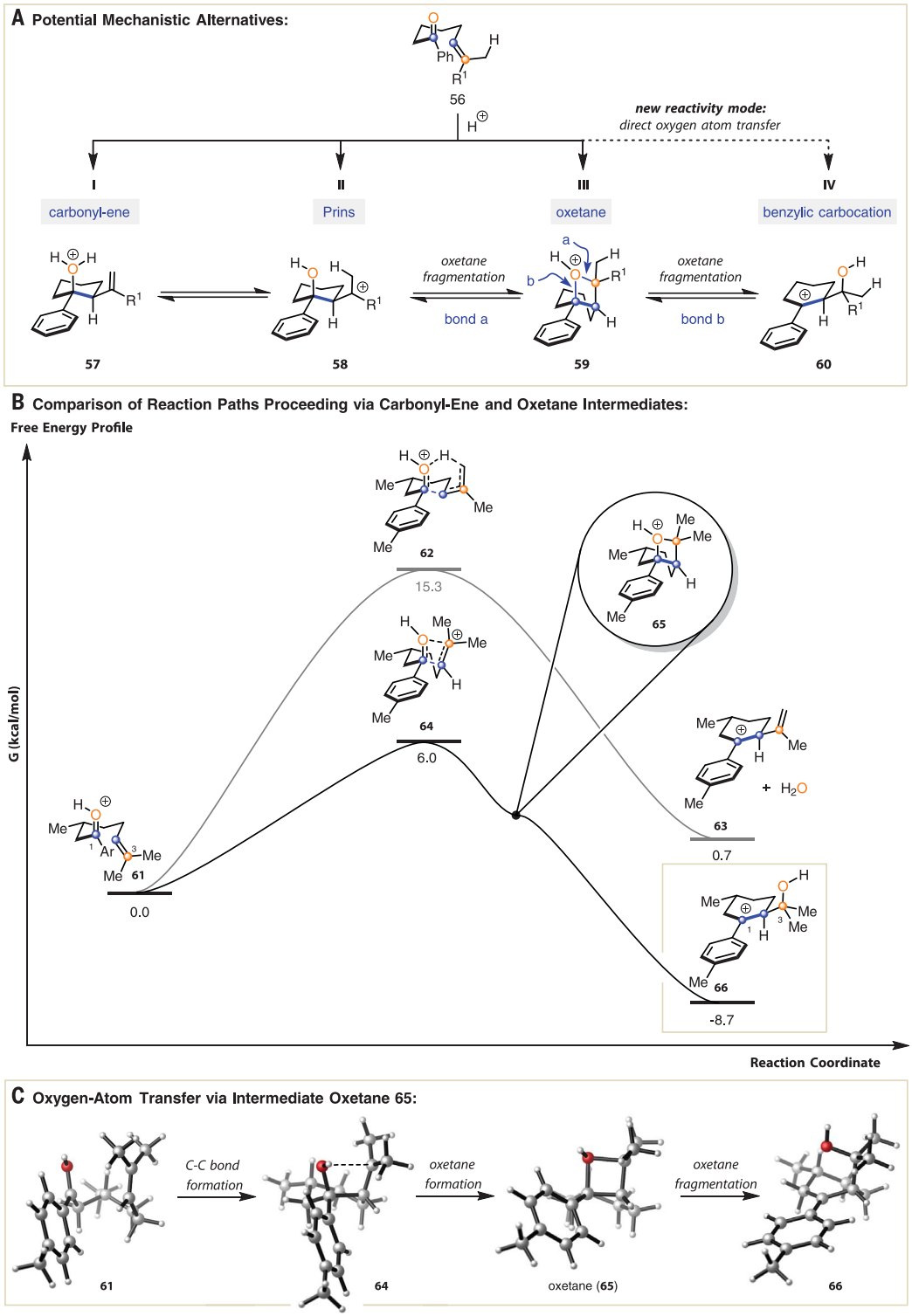


**Fig. 3. Mechanistic investigations.** (**A**) Possible mechanistic alternatives in the Brønsted acid–catalyzed formation of tetrahydrofluorenes from aryl ketones. (**B**) Density functional theory studies of the reaction pathway comparing carbonyl-ene reactivity to a pathway relying on a transient oxetane. G, free energy. (**C**) Three-dimensional representations of intermediates and transition states.

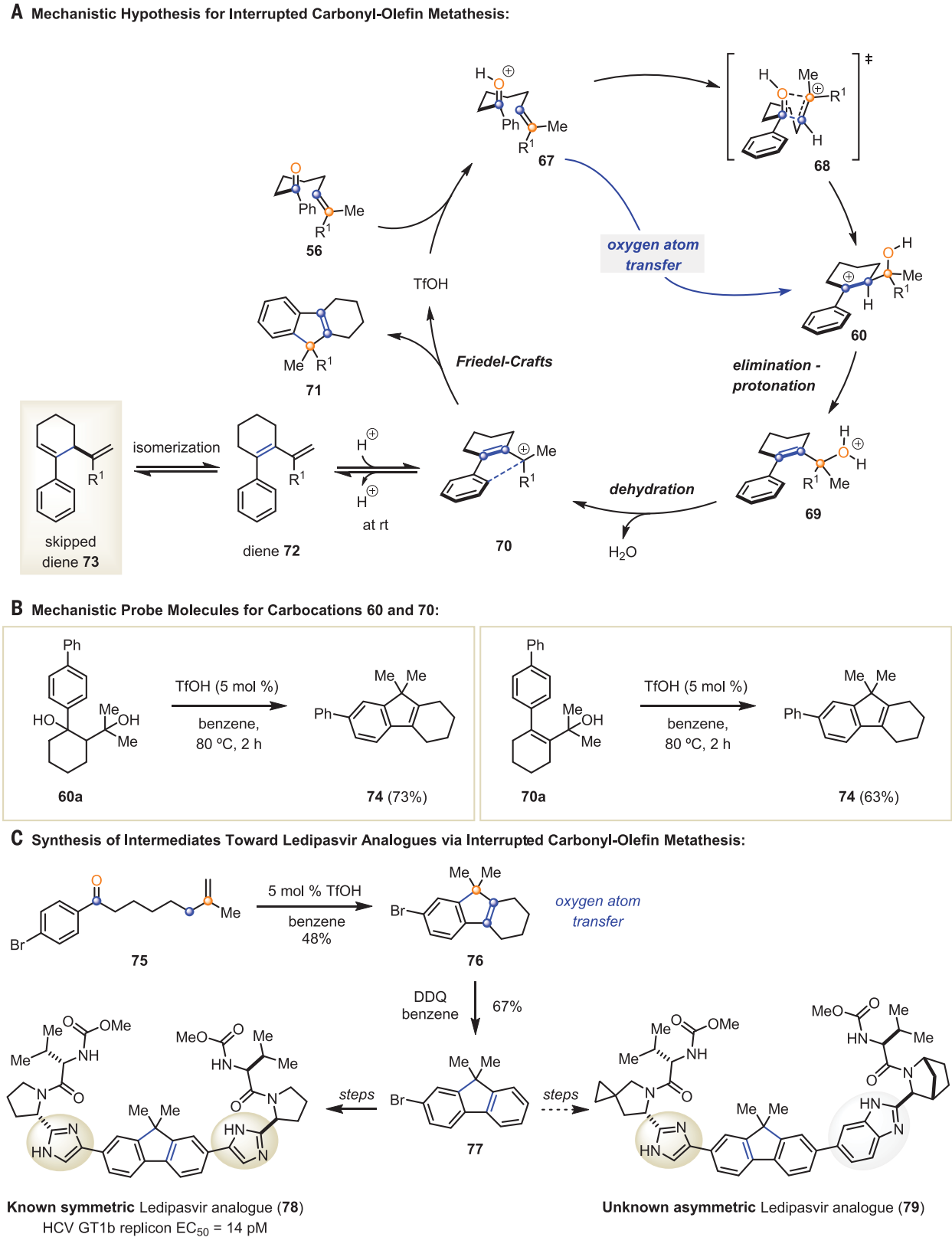


**Fig. 4. Proposed mechanism and application.** (**A**) Mechanistic hypothesis for interrupted carbonyl-olefin metathesis reaction. (**B**) Investigation of mechanistic probe molecules. (**C**) Synthesis of intermediates to access known and new ledipasvir analogs. HCV, hepatitis C virus.

Subsequent efforts focused on further expanding the scope of this transformation to include 1,1-disubstituted alkenes that are readily accessible via Wittig olefination or hydroarylation strategies (Fig. 2C). Isomerization of these alkenes in situ under Brønsted acid catalysis results in the corresponding 1,2,2-trisubstituted analogs that subsequently enable facile access to tetrahydrofluorene products bearing distinct substitution at the central five-membered ring. Specifically, aryl ketones bearing electron-rich and neutral substituents proved viable substrates in the isomerization-cyclization sequence and provided the corresponding tetrahydrofluorene products in up to 76% yield (**48** to **55**, Fig. 2C). Varying the electronics of the alkene itself was tolerated with both electron-poor (**50** and **51**) and -neutral (**52** and **53**) styrene derivatives, which underwent the desired transformation in up to 70% yield. This in situ isomerization-cyclization sequence is not only limited to terminal styrene derivatives but also tolerates the alkene-bearing aliphatic substituents (**54**). Modest diastereoselectivity (3:2 diastereomeric ratio) was observed for tetrahydrofluorene **55**, demonstrating the potential for this mode of reactivity to be used in the development of stereoselective methods.

On the basis of the literature precedent of transformations between carbonyls and olefins, we initially considered a mechanistic hypothesis relying on a carbonyl-ene reaction to form alcohol **57** upon nucleophilic addition between the carbonyl and olefin functionalities of **56** (Fig. 3A). However, this initial mechanistic hypothesis proved inconsistent with experimental data (supplementary materials), and other potential mechanistic alternatives were evaluated. In addition to a concerted carbonyl-ene reaction path (I, Fig. 3A), intermediate carbocation **58** could result from a nucleophilic addition between the carbonyl and olefin moieties in **56**, in accordance with established Prins reactivity (II, Fig. 3A). A third alternative would be the formation of oxetane **59** in analogy to the recently established carbonyl-olefin metathesis reaction proceeding via the asynchronous, concerted formation of intermediate oxetanes (III, Fig. 3A). Intermediates **57**, **58**, and **59** could also interconvert in reversible transformations. Finally, Brønsted acid catalysis of aryl ketone **56** could give rise to a fourth intermediate, benzylic carbocation **60**, as the product of a direct oxygen atom transfer relying on the initial formation of oxetane **59** (IV, Fig. 3A). Unlike in carbonyl-olefin metathesis, which proceeds via a retro-[2+2]-cycloaddition of oxetane **59**, this fragmentation is interrupted to result in carbocation **60** (fragmentation of bond b in **59**).

These distinct mechanistic scenarios were subsequently investigated computationally (unrestricted B97-D density functional and 6-31+G* basis set) to determine the viability of their transition states and corresponding minimal-energy pathways. The quantum chemical simulations based on the growing string method (*29*) revealed two possible reaction paths (see supplementary materials for computational details): (i) a concerted carbonyl-ene pathway via transition state **62**, following the initial mechanistic hypothesis (Fig. 3B), and (ii) a single-elementary step pathway passing through transition state **64** and oxetane **65** (Fig. 3B) (*30*). The latter path was found to have an energy barrier 9.3 kcal/mol lower than that of the carbonyl-ene reaction, which suggests that it is the preferred reaction path. This lower-energy pathway yields benzylic carbocation intermediate **66** and constitutes a direct oxygen atom transfer between two carbons (C-1 and C-3 in **66**, Fig. 3B). Electronically, conversion of **61** to **66** is enabled by an asynchronous, concerted path that is best conceptualized as two distinct transitions connected by an unstable oxetane intermediate **65**. Figure 3, B and C, highlights the asynchronous nature of this path by showing the transition state **64** as the highest-energy point, which forms oxetane **65** and subsequently fragments through an energetically favorable ring-opening to result in benzylic carbocation intermediate **66**. The second electronic change in this reaction path is barrierless, due to the instability of the protonated oxetane **65** when compared to its fragmentation product **66**.

This Brønsted acid–catalyzed mode of reactivity complements the previously established Lewis acid–catalyzed carbonyl-olefin metathesis reaction that relies on intermediate oxetanes. However, under Brønsted acid catalysis, fragmentation of the transient oxetane interrupts the carbonyl-olefin metathesis pathway and results in a new reactive intermediate, benzylic carbocation **66**. As such, the transience of **65** suggests a direct oxygen atom transfer that represents a distinct reactivity mode between carbonyls and olefins to provide benzylic carbocations (Fig. 3A, pathway IV).

Taking into account the experimental and computational results obtained, we propose the following reaction mechanism for the Brønsted acid–catalyzed interrupted carbonyl-olefin metathesis reaction (Fig. 4A). Protonation of aryl ketone **56** initiates intramolecular oxygen atom transfer via transition state **68** to form intermediate benzylic carbocation **60**. Elimination and subsequent protonation of the resulting allylic alcohol provides **69**, which can then undergo dehydration to produce carbocation **70**. This highly stabilized allylic carbocation undergoes a final Friedel-Crafts alkylation to form the tetrahydrofluorene product **71**. This hypothesis was subsequently tested by the independent synthesis of two probe molecules—specifically, tertiary alcohols **60a** and **70a** (Fig. 4B). Diol **60a** and allylic alcohol **70a** are both able to undergo a Friedel-Crafts alkylation to provide tetrahydrofluorene product **74** upon treatment with TfOH, which supports carbocations **60** and **70** as potential intermediates. However, at lower reaction temperatures, Friedel-Crafts alkylation does not proceed and carbocation **70** is quenched via elimination to result in diene **72**. Further isomerization of diene **72** provides an experimentally observed skipped diene **73** as a shunt product (supplementary materials). Alternative pathways for the formation of skipped diene **73** were investigated computationally but were found to be higher in energy. Upon exposure to the optimized reaction conditions, skipped diene **73** reengages in the reaction pathway to give rise to the tetrahydrofluorene product exclusively (see supplementary materials for experimental details).

The tetrahydrofluorene products obtained in our one-step, multiple bond–forming transformation can be readily oxidized to the corresponding fluorene compounds in up to 99% yield using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (supplementary materials). The synthetic value of this cyclization-oxidation sequence has been demonstrated in the synthesis of a key fluorene intermediate toward a biologically active ledipasvir analog (Fig. 4C) (*28*). Importantly, the interrupted carbonyl-olefin metathesis reaction enables rapid entry to aromatic fluorene moieties bearing distinctive substitution patterns that are difficult to access with currently available synthetic methods. Specifically, symmetric and asymmetric analogs are accessible using the same fluorene core. Under the optimized reaction conditions, aryl ketone **75** yields tetrahydrofluorene **76**, which upon subsequent oxidation results in fluorene **77**. This intermediate (**77**) can be further advanced to known symmetric ledipasvir derivative **78**, with a hepatitis C virus GT1b replicon $EC_{50}$ (median effective concentration) value of 14 pM, or an unknown asymmetric analog **79** (*28*).

The developed interrupted carbonyl-olefin metathesis reaction complements the repertoire of well-established reactions between carbonyls and olefins and provides entry into the formation of complex, polycyclic tetrahydrofluorenes in a single synthetic step relying on TfOH as an inexpensive catalyst.

## REFERENCES AND NOTES


1. K. Alder, F. Pascher, A. Schmitz, *Br. Dtsch. Chem. Ges. B Ser.* **76**, 27–53 (1943).
2. M. L. Clarke, M. B. France, *Tetrahedron* **64**, 9003–9031 (2008).
3. K. Mikami, M. Shimizu, *Chem. Rev.* **92**, 1021–1050 (1992).
4. C.-Y. Ho, K. D. Schleicher, T. F. Jamison, *Synlett* **2009**, 2565–2582 (2009).
5. B. B. Snider, in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, Eds. (Pergamon, 1991), vol. 2, pp. 527–562.
6. O. Kriewitz, *Ber. Dtsch. Chem. Ges.* **32**, 57–60 (1899).
7. H. J. Prins, *Chem. Weekblad* **16**, 1510–1526 (1919).
8. E. Arundale, L. A. Mikeska, *Chem. Rev.* **51**, 505–555 (1952).
9. C. Olier, M. Kaafarani, S. Gastaldi, M. P. Bertrand, *Tetrahedron* **66**, 413–445 (2010).
10. I. M. Pastor, M. Yus, *Curr. Org. Chem.* **11**, 925–957 (2007).
11. L. M. Stephenson, M. Orfanopoulos, *J. Org. Chem.* **46**, 2200–2201 (1981).
12. H. Kwart, M. Brechbiel, *J. Org. Chem.* **47**, 5409–5411 (1982).
13. B. B. Snider, E. Ron, *J. Am. Chem. Soc.* **107**, 8160–8164 (1985).
14. D. A. Singleton, C. Hang, *J. Org. Chem.* **65**, 895–899 (2000).
15. J. R. Ludwig, P. M. Zimmerman, J. B. Gianino, C. S. Schindler, *Nature* **533**, 374–379 (2016).
16. J. R. Ludwig *et al.*, *J. Am. Chem. Soc.* **139**, 10832–10842 (2017).
17. E. Paternò, *Gazz. Chim. Ital.* **39**, 237–250 (1909).
18. G. Büchi, C. G. Inman, E. S. Lipinsky, *J. Am. Chem. Soc.* **76**, 4327–4331 (1954).
19. J. A. Porco Jr., S. L. Schreiber, in *Comprehensive Organic Synthesis*, B. M. Trost, I. Fleming, Eds. (Pergamon, 1991). vol. 5, pp. 151–192.
20. The formation of a related tetrahydrofluorene has previously been described as a by-product in 38% yield using catalytic

$Bi(OTf)_3$. However, the reaction was assumed to proceed following a carbonyl-ene reaction path and subsequent Friedel-Crafts alkylation. See (*21*).
21. P. Tremel *et al*., *New J. Chem.* **39**, 7453–7458 (2015).
22. B. B. Snider, *Acc. Chem. Res.* **13**, 426–432 (1980).
23. G. Lemière *et al*., *Angew. Chem. Int. Ed.* **45**, 7596–7599 (2006).
24. S. M. Wilkerson-Hill, C. M. Lavados, R. Sarpong, *Tetrahedron* **72**, 3635–3640 (2016).
25. A.-H. Zhou, F. Pan, C. Zhu, L.-W. Ye, *Chemistry* **21**, 10278–10288 (2015).
26. Z. Lu, M. Yang, P. Chen, X. Xiong, A. Li, *Angew. Chem. Int. Ed.* **53**, 13840–13844 (2014).
27. M. L. Maddess *et al*., *Org. Process Res. Dev.* **18**, 528–538 (2014).
28. J. O. Link *et al*., *J. Med. Chem.* **57**, 2033–2046 (2014).
29. P. M. Zimmerman, *J. Comput. Chem.* **36**, 601–611 (2015).
30. Attempts to probe the Prins reaction pathway computationally did not support a tertiary carbocation but instead implicated benzylic carbocation **66** via a transition state resembling an oxetane (**64**).

## ACKNOWLEDGMENTS

**Funding:** This work was supported by the NIH National Institute of General Medical Sciences (R01-GM118644), the David and Lucile Packard Foundation, and the Alfred P. Sloan Foundation (fellowships to C.S.S.). J.R.L. and R.B.W. thank the National Science Foundation for predoctoral fellowships. P.M.Z. thanks the National Science Foundation (CHE-1551994). **Author contributions:** J.R.L., R.B.W., D.J.N., and C.S.S. devised the experiments and prepared the manuscript for publication. D.J.N. conducted the theoretical investigations. J.B.G. performed initial experiments, P.M.Z. provided guidance in theoretical investigations, and R.A.W. conducted x-ray crystallographic studies. **Competing interests:** The authors declare no competing interests. **Data and materials availability:** The supplementary materials contain complete experimental and spectral details for all new compounds and all reactions reported herein. Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under reference CCDC-1584828.

## SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/361/6409/1363/suppl/DC1
Materials and Methods
Figs. S1 to S7
Tables S1 to S4
References (*31*–*64*)
NMR Spectra

20 December 2017; accepted 25 July 2018
10.1126/science.aar8238

# Interrupted carbonyl-olefin metathesis via oxygen atom transfer

Jacob R. Ludwig, Rebecca B. Watson, Daniel J. Nasrallah, Joseph B. Gianino, Paul M. Zimmerman, Ren A. Wiscons and Corinna S. Schindler

*Science* **361** (6409), 1363-1369.
DOI: 10.1126/science.aar8238

**Two ways out of an oxetane**

Oxetanes are highly reactive four-membered rings that contain three carbon atoms and an oxygen atom. Recently, they were implicated as transient intermediates in Lewis acid–catalyzed intramolecular metathesis reactions of ketones with olefins. Ludwig *et al.* now report that by replacing the Lewis acid with a strong Brønsted acid, they can change the course of the oxetane ring-opening. In a so-called interrupted metathesis, the oxygen atom migrates and then departs through dehydration, while the remaining carbon framework cyclizes to form tetrahydrofluorene compounds.

*Science*, this issue p. 1363