Chemical Science



Catalytic Activation of a Single C-F Bond in Trifluoromethyl Arenes

Journal:	Chemical Science
Manuscript ID	SC-EDG-09-2015-003415.R1
Article Type:	Edge Article
Date Submitted by the Author:	14-Oct-2015
Complete List of Authors:	Dang, Hester; University of Washington, Chemistry Whittaker, Aaron; University of Washington, Chemistry Lalic, Gojko; University of Washington, Chemistry

SCHOLARONE[™] Manuscripts

Journal Name



COMMUNICATION

Catalytic Activation of a Single C-F Bond in Trifluoromethyl Arenes

Hester Dang, Aaron M. Whittaker, and Gojko Lalic*

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Synthetic methods for the direct transformation of $ArCF_3$ to $ArCF_2R$ would enable efficient diversification of trifluoromethyl arenes and would be of great utility in medicinal chemistry. Unfortunately, the development of such methods has been hampered by the fundamental properties of C-F bonds, which are exceptionally strong and become stronger with increased fluorination of the carbon atom. Here, we describe a method for the catalytic reduction of $ArCF_3$ to $ArCF_2H$ through a highly selective activation of a single C-F bond. Mechanistic studies reveal separate reaction pathways for the formation of $ArCF_2H$ and $ArCH_3$ products and point to the formation of an unexpected intermediate as the source of the unusual selectivity for the mono-reduction.

Fluorinated organic molecules play an important role in the pharmaceutical^{1, 2} and agrochemical industries.³ Fluorine atoms are commonly introduced into organic molecules in an effort to manipulate the physical and chemical properties of these compounds, without making drastic changes to their overall structure.4, 5 Trifluoromethylation of arenes is one of the most commonly used methods for fluorination of organic molecules, and can be accomplished using one of the numerous synthetic methods developed over the last two decades.⁶⁻⁹ This relatively small structural change results in increased bioavailability, lipophilicity, and metabolic stability of aromatic compounds,^{10, 11} and often leads to an improved pharmacological profile. As a result of the favorable pharmacological properties imparted by trifluoromethylation, trifluoromethyl arenes are extensively used in medicinal chemistry and are present in a number of prescription drugs, including Prozac, Celebrex, and Januvia

Difluoroalkyl arenes ($ArCF_2R$) are analogues of $ArCF_3$ that hold great potential for applications in medicinal chemistry. Difluoroalkyl substituents have a similar effect on the pharmacokinetic properties of arenes as CF_3 substituent.¹² Moreover, they offer a greater structural and functional

diversity, which is often critical in the optimization of bioactive lead compounds.¹³ To fully exploit the potential of $ArCF_2R$ in medicinal chemistry, transformations that would enable their synthesis directly from $ArCF_3$ precursors are needed (Scheme 1a).¹⁴⁻²⁰ Direct mono-functionalization of $ArCF_3$ would be the most efficient strategy for diversification of this important class of compounds, and would effectively leverage the reliable access to $ArCF_3$ provided by synthetic methods developed in the last two decades.⁶⁻⁹

Unfortunately, selective functionalization of a single C-F bond in ArCF₃ remains one of the great unmet challenges in organic chemistry. The problems associated with the selective C-F functionalization become evident when we consider the fundamental properties of C-F bonds in ArCF₃. The C-F bond is the strongest single bond to carbon, with a bond dissociation energy (BDE) of 109 kcal/mol in CH₃-F.²¹ Even a relatively weak C-F bond in benzyl fluoride has a BDE of 99 kcal/mol (Scheme 1b).²² Not surprisingly, any transformation involving the activation of such strong bonds is difficult to accomplish, despite the significant progress made in the field of C-F bond activation.²³⁻²⁵ Furthermore, with increased fluorination of a carbon atom, C-F bonds become stronger and shorter, and thus less reactive (Scheme 1b).²⁶⁻²⁸ As a result, selective functionalization of a single C-F bond in ArCF₃ poses an additional selectivity challenge: the product of the C-F functionalization (ArCF₂R) is inherently more reactive than the starting material (ArCF₃). Overcoming this selectivity problem has proven to be particularly difficult. Only reported examples of the selective monofunctionalization of ArCF3 are based on single electron transfer reactions achieved bv electrochemistry²⁹ or alkali earth metal reduction.^{30, 31} So far, no catalytic methods for functionalization of a single C-F bond in a trifluoromethyl group have been reported in the literature.

^a. Address here. Department of Chemistry, University of Washington, Seattle, Washington 98195, United States

⁺ Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available:

Journal Name

Scheme 1. Selective Activation of a single C-F Bond in ArCF₃

a) Potential	C-F	
Ar-CF ₃	functionalization	Ar-CF ₂ R
b) Challenges		r – ri, aryı, aryı
	H ₃ C—F	HF ₂ C—F
BDE (kcal/mol) bond length (Å)	109 1.385	128 1.332
	PhCH ₂ —F	PhF ₂ C—F
BDE (kcal/mol)	99	~115

In this report, we describe the discovery of a transition metalcatalyzed activation of a single C-F bond in $ArCF_3$ that results in the selective formation of $ArCF_2H$. We present the results of mechanistic studies that provide insight into the source of the unusual selectivity and the results of our exploration of the substrate scope.

We recently discovered that the reduction of 4-(4-MePh)C₆H₄CF₃ (1) to $4-(4-MePh)C_6H_4CH_3$ (2) can be accomplished at room temperature using just 1 mol % of palladium(II) acetate as a catalyst, in the presence of triphenylsilane and potassium *tert*-butoxide (Table 1, entry 1). We also found that replacing potassium tert-butoxide with sodium *tert*-butoxide abolishes the reactivity. Even at a higher temperature reduction products (ArCH₃ and ArCF₂H) are obtained in low yields (Table 1, entry 2). However, the addition of a copper co-catalyst restores the reactivity, and leads to the formation of 4-(4-MePh)C₆H₄CF₂H as the major product of the reaction (Table 1, entry 3). Considering that known methods for catalytic reduction of ArCF₃ using Lewis acid catalysis, early transition metal catalysis or late transition metal catalysis, produce only the fully reduced $ArCH_3$ products,³²⁻³⁸ we were intrigued by the unusual selectivity of our reduction reaction and decided to pursue the development of a synthetic method for the selective mono-reduction of ArCF₃.

In the initial experiments we confirmed that both copper and palladium catalysts were necessary for the observed selectivity. Furthermore, we found that in the absence of both catalysts, starting material is fully recovered. Our initial attempts to optimize the reaction focused on improving the conversion of the starting material. We achieved complete conversion of 4-(4-MePh) $C_6H_4CF_3$ by increasing the catalyst loading and modifying the ratio of the two catalysts (Table 1, entry 4). However, these changes did not improve the yield and instead decreased the selectivity. We also explored modifying the palladium catalyst with various classes of ligands and found that phosphine and *N*-heterocyclic carbene (NHC) ligands completely inhibited the reaction. The presence of amines, diamines, amides, and amino alcohols had a small, but consistently positive effect on selectivity. The greatest improvement was observed in the presence of 5 mol % of 2pyridone (Table 1, entry 5). To facilitate further reaction optimization, we decided to focus on gaining a better understanding of the reaction mechanism and the source of the observed selectivity.

1. The Discove	ery and	Initia	I Op	otimization	of
F₃ + Ph₃SiH	<mark>yst, base</mark> ⊃MF	Ar— <mark>C</mark> 2	H ₃ +	Ar—CF ₂ H 3	
catalyst	base	2	3	conversion	
Pd(OAc) ₂ 1 mol %	KO <i>t</i> -Bu	94%	0%	100%	
Pd(OAc) ₂ 1 mol %	NaO <i>t</i> -Bu	8%	7%	-	
Pd(OAc) ₂ 1 mol % & SIPrCuCl 1 mol %	NaO <i>t</i> -Bu	12%	52%	90%	
Pd(OAc) ₂ 3 mol % & SIPrCuCl 20 mol %	NaO <i>t</i> -Bu	15%	51%	100%	
Pd(OAc) ₂ 3 mol % & SIPrCuCl 20 mol % & 2-pyridone 5 mol %	NaO <i>t</i> -Bu	3%	56%	100%	
	1. The Discove F ₃ + Ph ₃ SiH $\frac{catal}{r}$ catalyst Pd(OAc) ₂ 1 mol % Pd(OAc) ₂ 1 mol % Pd(OAc) ₂ 1 mol % SIPrCuCl 1 mol % SIPrCuCl 20 mol % & SIPrCuCl 20 mol % & SIPrCuCl 20 mol % & SIPrCuCl 20 mol %	1. The Discovery and F ₃ + Ph ₃ SiH $\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} $	1. The Discovery and Initia F ₃ + Ph ₃ SiH $\xrightarrow[DMF]{DMF}$ Ar $\xrightarrow[C]{2}$ catalyst base 2 Pd(OAc) ₂ 1 mol % KOt-Bu 94% Pd(OAc) ₂ 1 mol % NaOt-Bu 8% Pd(OAc) ₂ 1 mol % NaOt-Bu 12% SIPrCuCl 1 mol % NaOt-Bu 12% Pd(OAc) ₂ 3 mol % & SIPrCuCl 20 mol % NaOt-Bu 15% Pd(OAc) ₂ 3 mol % & SIPrCuCl 20 mol % NaOt-Bu 3%	1. The Discovery and Initial Operators F_3 + Ph ₃ SiH $\xrightarrow{\text{catalyst, base}}$ DMF $Ar \xrightarrow{\text{cH}_3} + 2$ catalyst base 2 3 Pd(OAc) ₂ 1 mol % KOt-Bu 94% 0% Pd(OAc) ₂ 1 mol % NaOt-Bu 8% 7% Pd(OAc) ₂ 1 mol % NaOt-Bu 12% 52% Pd(OAc) ₂ 3 mol % & SIPrCuCl 20 mol % NaOt-Bu 15% 51% Pd(OAc) ₂ 3 mol % & SIPrCuCl 20 mol % NaOt-Bu 3% 56% & SIPrcuCl 20 mol % NaOt-Bu 3% 56%	1. The Discovery and Initial Optimization F ₃ + Ph ₃ SiH $\xrightarrow{\text{catalyst, base}}$ $Ar \xrightarrow{\text{CH}_3}$ + $Ar \xrightarrow{\text{CF}_2H}$ 2 3 conversion Pd(OAc) ₂ 1 mol % KOt-Bu 94% 0% 100% Pd(OAc) ₂ 1 mol % NaOt-Bu 8% 7% - Pd(OAc) ₂ 1 mol % NaOt-Bu 12% 52% 90% $Pd(OAc)_2$ 3 mol % & SIPrCuCl 20 mol % NaOt-Bu 15% 51% 100% $Pd(OAc)_2$ 3 mol % & SIPrCuCl 20 mol % NaOt-Bu 3% 56% 100%

Monodefluorination Reaction.

a) Reaction conditions: Ph₃SiH (4 equiv), base (5 equiv), DMF, 25 °C, 1 h. b) Reaction performed at 45 °C for 11 h then 60 °C for 17 h. c) Reaction performed at 45 °C for 2 h, followed by 60 °C for 17 h. Ar = 4-(4-CH₃Ph)C₆H₄; SIPr = *N*,*N'*bis(2,6-diisopropylphenyl)imidazolin-2-ylidene; DMF = *N*,*N*-dimethylformamide. All yields were determined by GC using an internal standard.

Our first hypothesis was that ArCF₂H is an intermediate in the formation of ArCH₃ and that high selectivity can be achieved only at a low conversion or with a low mass balance. However, the results of experiments in which we closely monitored the progress of the reaction shown in entry 3 of Table 1 contradicted this hypothesis. We found that the conversion of the starting material reached 90% and stopped after 11 hours at 45 °C. At this point, most of the fully reduced ArCH₃ 2 had already been formed (11%), while almost no ArCF₂H 3 (4%) was present in the reaction mixture (see ESI for details). At the same time point, the major component of the reaction mixture was intermediate X, which over the next 18 hours was converted into $ArCF_2H$ 3 (Scheme 2). Over the same period, essentially no more 2 was formed (12% vs 11%). The same observations were made when the reaction was performed in the presence of 2-pyridone (Table 1, entry 5) (see ESI for details). The only difference is that 2-pyridone inhibits the formation of 2. Overall, the results of these experiments suggest that the formation of ArCH₃ and ArCF₂H occurs through two independent reaction pathways, and that ArCF₂H and intermediate X are not intermediates in the formation of ArCH₃ (Scheme 2). Encouragingly, this finding suggested that, at least in principle, high yields of ArCF₂H can be obtained with high selectivity.

Our next goal was to determine the structure of intermediate **X**. The analysis of the reaction mixture by mass spectrometry suggested aldehyde **4** as the intermediate (Scheme 3). Furthermore, a reaction performed in DMF-d7 solvent resulted in the formation of the mono-deuterated intermediate (mass increased by 1 amu), indicating that the formyl group of ArCF₂CHO is likely derived from DMF. From the reaction mixture containing intermediate **X** as the major species, we were also able to isolate the 2,4-dinitrophenyl hydrazone of 4-(4-MePh)C₆H₄CF₂CHO (**5**) in 50% yield and characterize it by x-

ray crystallography (Scheme 3). On the other hand, attempts to establish the presence of the aldehyde in the reaction mixture by in situ methods were not successful.



^a Reaction conditions shown in Table 1, entries 3 or 5; Ar = $4 - (4 - MePh)C_6H_4$

For example, in situ analysis of the reaction mixture by 1 H and ¹³C NMR indicated no presence of ArCF₂CHO. Furthermore, a significant amount of the aldehyde could be identified in the mass spectrum only if the sample was exposed to air and silica gel. Overall, these results are consistent with the idea that intermediate X is a hemiacetal or a hemiaminal of ArCF₂CHO 4, or a silylated version of the two, and that the aldehyde is revealed only in the presence of a protic acid (MeOH or moisture).

Based on the hypothesis that intermediate ${f X}$ is a silylated hemiacetal or a hemiaminal, we speculated that the relatively slow conversion of intermediate X to the aldehyde before decarbonylation to the difluoromethyl arene may be responsible for the low yield of the desired product. We reasoned that decomposition of the intermediate could be facilitated by the presence of a mild Brønsted acid. Indeed, we found that if 1 equivalent of tert-butanol was added to the reaction mixture after full conversion of the 4-(4-MePh)C₆H₄CF₃ is achieved, there was a dramatic increase in both the rate of the reaction and in the yield of ArCF₂H. The complete conversion of intermediate X was achieved in 2 hours at 60 °C, and ArCF₂H 3 was obtained in 95% yield (Scheme 4). Similar results can be accomplished using phenol as an acid. Addition of an acid at the beginning of the reaction resulted in significantly lower yields.



This journal is © The Royal Society of Chemistry 20xx

Scheme 3. Structure of Intermediate X

To gain more information about the mechanism of decarbonylation and the role of the acid we performed isotope labeling experiments. We found that the hydrogen atom in ArCF₂H 3 is derived from tert-butanol, and not from the silane or from DMF (via intermediate X) (Scheme 4b) (see ESI for details). Based on these results, we favor the mechanism of decarbonylation that involves a difluorobenzyl anion intermediate, akin to the haloform reaction. It is interesting to note that the presence of the two intermediates (intermediate X and difluorobenzyl anion) in this transformation provides a great opportunity for the development of other transformations of ArCF₃.



Ar = $4 - (4 - MePh)C_6H_4$

Scheme 4. The Role of Brønsted Acid

Finally, we were interested in the fate of the fluoride removed from the ArCF₃ and the mechanism of C-F activation. In a crude reaction mixture we were not able to identify any silyl fluoride, which we expected to be the major byproduct of the reaction. Instead, the only fluoride-containing byproduct was KF. In a control experiment, we found that Ph₃SiF reacts with KOt-Bu under the reaction conditions to produce KF and Ph₃SiOt-Bu, which further complicates interpretation of our findings in the context of the mechanism of the C-F activation.

The general understanding of the catalytic C-F activation by transition metals suggest that ArCF₂H would be more reactive than $ArCF_3$.^{21, 39} However, in our reaction, we found that the opposite is true. With 4-(4-MePh)C₆H₄CF₂H as the substrate, only ~36% conversion is achieved at the time necessary for the full conversion of ArCF₃ 1 (2 h at 45 °C) (Scheme 5). One mechanistic hypothesis that accounts for this unusual order of reactivity (ArCF₃ > ArCF₂H) is C-F activation by a single electron transfer: ArCF₃ are better electron acceptors than ArCF₂H,²⁹ although the difference in energy of $\sigma^{*}_{\mbox{\tiny C-F}}$ orbitals is often too small to allow good selectivity.^{40, 41} This mechanism would also explain why intermediate **X** is resistant to further reduction. Furthermore, mixtures of silanes and alkoxides have previously been implicated in single electron chemistry.^{42, 43} However, it is important to note that the presence of transition metal catalysts is essential for C-F activation. In the absence of transition metals, we can fully recover the starting material, in agreement with the observations made by Grubbs and Stoltz.⁴³ Scheme 5. C-F activation of ArCF₂H



After exploring the mechanism of the mono-defluorination reaction, we turned our attention to further the reaction optimization and the exploration of the substrate scope. In the process, we found that SIPrCuCl could be replaced by significantly less expensive and commercially available CuF_2 or CuBr, with CuF_2 generally providing superior selectivity. Other copper(I) and copper(II) salts gave significantly lower yields of the desired product and/or significantly lower selectivity. We also found that consistently better selectivity could be obtained using KOSiMe₃ instead of NaOt-Bu.



Table 2. Optim	nized Reaction	Conditions	and Substrate	Scope
----------------	----------------	------------	---------------	-------

 $^{\it o}$ Ratio of $ArCF_2H$ and $ArCH_3.$ See Supporting Information for a detailed description of experimental procedure.

The optimized reaction conditions shown in Table 2, were used in mono-reduction of several trifluoromethyl arenes. We found that the reaction can be accomplished in the presence Journal Name

of amines, ethers, and acetals with several biphenyl and aryl substrates. Reducible groups, such as aryl halides, nitro arenes, or nitriles are reduced under the reaction conditions. Orthosubstituted trifluoromethyl arenes provided low yields of the desired products.

Conclusions

We have discovered a combination of palladium and copper catalysts that allows selective activation of a single C-F bond in trifluoromethyl arenes under relatively mild conditions. This discovery allowed the development of a method for selective reduction of $ArCF_3$ to $ArCHF_2$. More importantly, the unique mechanism of the reaction and the unusual source of the selectivity provide new opportunities for the development of useful transformations based on selective C-F activation.

Acknowledgement

Financial support by NSF (NSF CAREER award #1254636) is gratefully acknowledged. We gratefully acknowledge Sarah E. Flowers for assistance with X-ray crystallography.

Notes and references

- 1 K. L. Kirk, J. Fluorine. Chem., 2006, 127, 1013-1029.
- 2 K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881-1886.
- 3 P. Jeschke, ChemBioChem, 2004, 5, 570-589.
- 4 B. E. Smart, J. Fluorine Chem., 2001, 109, 3-11.
- 5 K. L. Kirk, Curr. Top. Med. Chem., 2006, 6, 1447-1456.
- 6 C. Alonso, E. Martínez de Marigorta, G. Rubiales and F. Palacios, Chem. Rev., 2015, 115, 1847-1935.
- 7 Z. Jin, G. B. Hammond and B. Xu, Aldrichimica Acta, 2012, 45, 67-83.
- 8 G. Shi, C. Shao, S. Pan, J. Yu and Y. Zhang, Org. Lett., 2015, 17, 38-41.
- 9 M. Shang, S.-Z. Sun, H.-L. Wang, B. N. Laforteza, H.-X. Dai and J.-Q. Yu, Angew. Chem., Int. Ed., 2014, 53, 10439-10442.
- 10 G. Gerebtzoff, X. Li-Blatter, H. Fischer, A. Frentzel and A. Seelig, *ChemBioChem*, 2004, **5**, 676-684.
- B. K. Park and N. R. Kitteringham, Drug Metab. Rev., 1994, 26, 605-643.
- G. D. Diana, P. Rudewicz, D. C. Pevear, T. J. Nitz, S. C. Aldous, D. J. Aldous, D. T. Robinson, T. Draper and F. J. Dutko, *J. Med. Chem.*, 1995, **38**, 1355-1371.
- 13 N. A. Meanwell, J. Med. Chem., 2011, 54, 2529-2591.
- 14 For examples of catalytic methods that can be used to prepare ArCF₂R from other precursors, see ref. 12-17.
- 15 Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **134**, 1494-1497.
- 16 P. S. Fier and J. F. Hartwig, J. Am. Chem. Soc., 2012, **134**, 5524-5527.
- 17 Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, J. Am. Chem. Soc., 2014, **136**, 1230-1233.

4 | J. Name., 2012, 00, 1-3

This journal is © The Royal Society of Chemistry 20xx

Journal Name

- K. Fujikawa, Y. Fujioka, A. Kobayashi and H. Amii, *Org. Lett.*, 2011, *13*, 5560-5563.
- 19 J.-B. Xia, C. Zhu and C. Chen, J. Am. Chem. Soc., 2013, 135, 17494-17500.
- 20 P. Xu, S. Guo, L. Wang and P. Tang, Angew. Chem., Int. Ed., 2014, 53, 5955-5958.
- 21 J. Burdeniuc, B. Jedlicka and R. H. Crabtree, *Chem. Ber.*, 1997, **130**, 145-154.
- 22 Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Taylor and Francis Group, LLC, Boca Raton, 2007.
- 23 M. F. Kuehnel, D. Lentz and T. Braun, *Angew. Chem., Int. Ed.*, 2013, *52*, 3328-3348.
- 24 H. Amii and K. Uneyama, Chem. Rev., 2009, 109, 2119-2183.
- 25 T. A. Unzner and T. Magauer, *Tetrahedron Lett.*, 2015, *56*, 877-883.
- 26 J. A. Pople, L. Radom and W. J. Hehre, J. Amer. Chem. Soc., 1971, 93, 289-300.
- 27 K. B. Wiberg and P. R. Rablen, J. Am. Chem. Soc., 1993, 115, 614-625.
- 28 D. O'Hagan, Chem. Soc. Rev., 2008, 37, 308-319.
- 29 Y. Yamauchi, T. Fukuhara, S. Hara and H. Senboku, *Synlett*, 2008, 438-442.
- 30 H. Amii, Y. Hatamoto, M. Seo and K. Uneyama, J. Org. Chem., 2001, 66, 7216-7218.
- S. Utsumi, T. Katagiri and K. Uneyama, *Tetrahedron*, 2012, 68, 1085-1091.
- 32 C. Douvris and O. V. Ozerov, Science, 2008, 321, 1188-1190.
- 33 R. Panisch, M. Bolte and T. Müller, J. Am. Chem. Soc., 2006, 128, 9676-9682.
- T. Stahl, H. F. T. Klare and M. Oestreich, J. Am. Chem. Soc., 2013, 135, 1248-1251.
- 35 K. Fuchibe and T. Akiyama, J. Am. Chem. Soc., 2006, **128**, 1434-1435.
- 36 K. Fuchibe, Y. Ohshima, K. Mitomi and T. Akiyama, Org. Lett., 2007, 9, 1497-1499.
- 37 S. Sabater, J. A. Mata and E. Peris, Nat. Commun., 2013, 4.
- 38 W. Zhao, J. Wu and S. Cao, Adv. Synth. Catal., 2012, 354, 574-578.
- 39 T. L. Gianetti, R. G. Bergman and J. Arnold, J. Am. Chem. Soc., 2013, 135, 8145-8148.
- P. Clavel, G. Lessene, C. Biran, M. Bordeau, N. Roques, S. Trévin and D. d. Montauzon, J. Fluorine. Chem., 2001, 107, 301-310.
- 41 J. H. Stocker and R. M. Jenevein, *Chem. Commun.*, 1968, 934-935.
- 42 A. Fedorov, A. A. Toutov, N. A. Swisher and R. H. Grubbs, *Chem. Sci.*, 2013, *4*, 1640-1645.
- 43 A. A. Toutov, W.-B. Liu, K. N. Betz, A. Fedorov, B. M. Stoltz and R. H. Grubbs, *Nature*, 2015, *518*, 80-84.