Homogeneously-Catalyzed Reductive Routes to Fluoroölefin Refrigerants

Alexandre Sicard

Thesis submitted to the University of Ottawa in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Chemistry

Center for Catalysis Research and Innovation
Department of Chemistry and Biomolecular Sciences, University of Ottawa

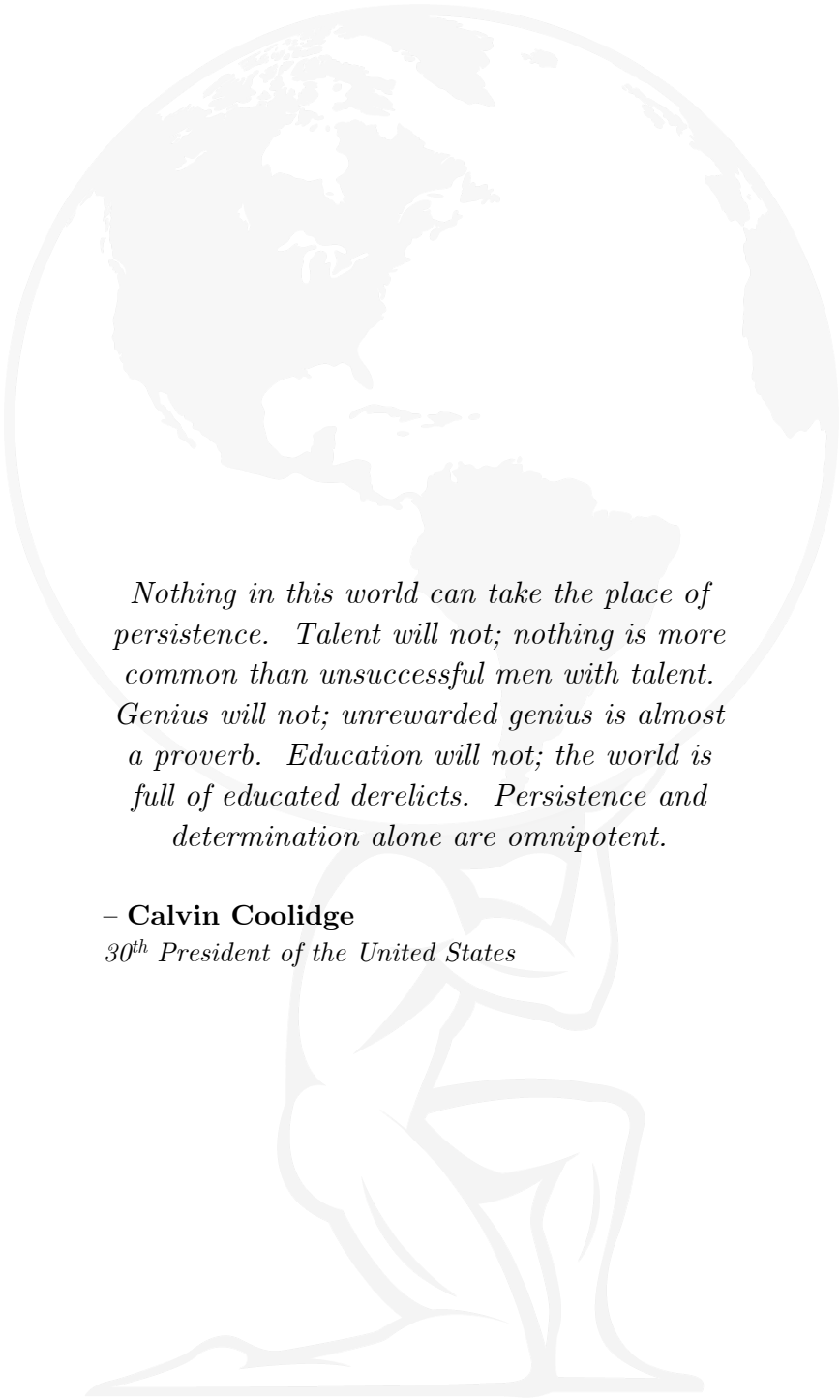
© Alexandre Sicard, Ottawa, Canada, 2021

Abstract

The fluororefrigerant industry has been subject to a near century-long history of disruptive innovations brought-upon by a combination of chemical and physical criteria imposed by both regulators and end-users. End-users take for granted that fluororefrigerants should be paragons of safety, exhibiting no traces of toxicity or flammability, while regulators enact ever-stricter limitations on global warming and ozone-depleting potentials. HFOs (HFO = hydrofluoroölefin) are a class of compounds with the potential to achieve the ideal balance of health, safety, and environmental impact, but they are limited both in number and in preparative methods. This thesis contains contributions which address both of these limitations. First, a Ni-catalyzed hydrodefluorodimerization (HDFD) reaction was developed (Chapter 3), which couples a head-tail dimerization of vinylidene difluoride (VF2) with a silane reduction step to form the new product $CHF_2CH_2CF{=}CH_2$ (**1363pfy**), a process believed to proceed *via* β-fluoride elimination from a metallacyclopentane to furnish isolable $L_nNi(F){-}CF_2CH_2CF{=}CH_2$ products. Next, two different hydrodefluorination (HDF) protocols were developed, the first of which utilizes alkylphosphines as organocatalysts in conjunction with hydrosiloxane reducing agents to convert hexafluoropropylene (HFP) to either $CF_3CF{=}CHF$ (**1225ye**) or $CF_3CF{=}CH_2$ (**1234yf**) in high yield (Chapter 4), and the second of which utilizes cheaply-available Cr or Cu naphthenates in conjunction with phosphite ligands and hydrosiloxane reductants to carry out the aforementioned transformation

(Chapter 5). Both of these HDF methods can also be used to synthesize rare olefins starting from commonplace starting materials; the Cr-catalysts were found uniquely capable of carrying out the difficult mono-hydrodefluorination of chlorotrifluoroethylene (CTFE) to an *E/Z*-mixture of CFCl=CHF (**1122a**), a potential new refrigerant candidate, while the alkylphosphine catalysts were used to synthesize the new hydrofluorovinyl ether *(E/Z)*-CHF=CF(OCF_3) starting from perfluoro(methyl vinyl ether). Not only are these novel olefins worthy of investigation as refrigerants, but the HDFD and HDF methodologies can possibly render a whole host of new models that were previously inaccessible by traditional methods, models which might address the shortcomings of the current HFO lineup. Moreover, these methods leverage the catalysis body of homogeneous catalysis knowledge to solve problems in a particular sector of organofluorine chemistry that has previously been ignored by practitioners of this art.

For my parents.



Nothing in this world can take the place of persistence. Talent will not; nothing is more common than unsuccessful men with talent. Genius will not; unrewarded genius is almost a proverb. Education will not; the world is full of educated derelicts. Persistence and determination alone are omnipotent.

– **Calvin Coolidge**
30th President of the United States

Acknowledgements

ALONG the lengthy and arduous journey of the Ph.D student, it is impossible not to have amassed a lengthy list of debts owed to certain important individuals who provided critical assistance of all sorts and without whom the title work would never have come to fruition. First and foremost, I have come to find that there is no greater gift which Fortune can bestow than that of great parents, and this is the reason for which I—like countless graduate students before me—dedicate this document to them, for its existence is by no small measure the result of their tireless support over my entire life. Without them (and my younger brother) standing behind me, I should not have trodden this path with so sure a footing, and I address this not only to them or to the readers of this thesis, but to my future self, lest he ever forgets the source from whence was drawn the industry and conscientiousness that enabled this achievement to be realized.

Next, I must express a deep and undying gratitude to my supervising professor, Prof. R. Tom Baker, who has nurtured my academic growth since my undergraduate days, and who provided me with an environment in which to continuously learn and improve. I should add that he met my seemingly endless stream of harebrained ideas with equal measures patience and interest, prompting where potential existed and cautioning where there was none. I now understand that my experience of unfettered academic freedom to dive headlong into whatever wild goose chases took my fancy—regardless of whether or not I actually returned with a goose in hand for our troubles—is a rare one.

In reference to the aforementioned working environment, I would be remiss in writing these Acknowledgements without mention of the fine members of the Baker Group over my decade of tenure therein. Though the character of this group has changed over the years as its members have come and gone, I will never forget the standard and expectation of excellence and scientific rigor that was instilled in me from my first day as an undergraduate. I especially thank Nicholas Andrella, whose academic journey in the Baker Lab started concurrently with mine and who has been a dear friend ever since. Other early and influential group members Kaitie Giffin and Matt Leclerc are worthy of mention, along with my undergraduate apprentices Angeli Reyes and Nathalie Rowlinson. The latter is most recognized for her contributions to the final two chapters in this document, and was an instrumental part in taking this work past the finish line. Our group has hosted several postdoctoral fellows over the years, but among these I am most indebted to Behnaz Ghaffari, who provided much-needed relief from the strain of lab duties, industry deliverables, and thesis work that all collided in my final year. But beyond yeoman service, our entire group has been fortunate to receive the benefit of her guidance and experience, and will continue to do so after I take my leave.

From further afield, none of the work described in this document would have been possible without the courageous participation of our industry partners at Arkema Inc. who not only provided us with funding, but with countless loans of fluorochemicals which were (and continue to be) screened for interesting chemistry by our group. Beyond the funding and in-kind, my many fruitful conversations with Lucy Clarkson and Jessica

DeMott enriched my work with a broader perspective often missed in the academy. Jessica in particular has been an engaging counterpart, having joined me with a lively interest in rabbit-hole after rabbit-hole as we examined the possible avenues for solutions to problems in this field. I often left these sessions bristling with newfound ideas and renovated motivation, and this periodic replenishment of the well proved more useful than I can faithfully convey here.

I also need to thank all of my other friends in the Chemistry Department who are too many to name but who have made my time here memorable and enjoyable, especially my peers in the Newman, Organ, and Fogg labs. They were always open to the exchange of ideas (and on the not-so-rare occasion, chemicals) and I wish them all the greatest success in their future endeavors. I am particularly indebted to Daniel Luis do Nascimento for his assistance provided in an olefin metathesis project (not featured here, for it never crossed the chasm from theory to reality). I also need to thank my thesis committee for their patience in critically reading this document, for evaluating the scientific credibility of its contents, and for providing constructive commentary. A doctoral thesis is not a small thing to review, and I can only hope that this document conveys its messages without putting undue strain on its readership.

Table of Contents

Abstract ii

Acknowledgements vi

Chapters in Summary xii

List of Abbreviations xiii

List of Schemes xv

List of Charts xix

List of Figures xx

List of Tables xxi

List of Compounds xxii

Published Work xxiii

1. A Personal Statement 1

1.1 Setting the Record Straight 1

1.1.1 The man who tamed explosions 4

1.1.2 The man who conjured the cold electric 8

1.1.3 Midgley's Legacy 16

1.2 References 22

2. The Field of Fluororefrigerants 24

2.1 Introduction 24

2.2 Fluorinated Refrigerants and their Syntheses: Past to Present 28

2.3 Refrigerant Characterization 31

2.4 ASHRAE Nomenclature and Safety Designations 37

2.5 EPA Regulations Regarding ODP and GWP 43

2.6 The Ideal Refrigerant 46

2.7 The difficulty (and opportunity) in developing drop-in replacements 49

2.8 Fundamental Synthetic Tools 56

2.9 Fluorination Fundamentals 58

2.10 Relevance to the Present Work 64

2.11 References 66

3. The Hydrodefluorodimerization (HDFD) Reaction 68

3.1 Introduction 68

3.2 Prior Art 71

3.3 This work: Coordination chemistry of VF2 101

3.4 Early hydrodefluorodimerization 104

3.5 Perfecting Ni(cod)$_2$ 106

3.6 Attempts to apprehend the metallacycle 111

3.7 Optimization of the HDFD Reaction 113

3.8 DFT Studies 114

3.9 Concluding Remarks 120

3.10 Experimental Section 121

3.10.1 Preparation of 1,3-di(1-adamantyl)imidazolium tetrafluoroborate (IAd·HBF_4) *123*
3.10.2 Preparation of 1,3-di(1-adamantyl)imidazol-2-ylidene (IAd) *124*
*3.10.3 [$L_2Ni(\eta^2\text{-}CF_2{=}CH_2)$] complexes (**2.1a-g**) (NMR scale) General Procedure* *124*
*3.10.4 [$(P(n\text{-}Bu)_3)_2Ni(\eta^2\text{-}CF_2{=}CH_2)$] (**2.1a**)* *125*
*3.10.5 [$(P(i\text{-}Bu)_3)_2Ni(\eta^2\text{-}CF_2{=}CH_2)$] (**2.1b**)* *125*
*3.10.6 [$(P(n\text{-}Pr)_3)_2Ni(\eta^2\text{-}CF_2{=}CH_2)$] (**2.1c**)* *125*
*3.10.7 [(dibpe)Ni($\eta^2\text{-}CF_2{=}CH_2$)] (**2.1d**)* *125*
*3.10.8 [(dibpp)Ni($\eta^2\text{-}CF_2{=}CH_2$)] (**2.1e**)* *126*
*3.10.9 [(dcyppe)Ni($\eta^2\text{-}CF_2{=}CH_2$)] (**2.1f**)* *126*
*3.10.10 [(dppf)Ni($\eta^2\text{-}CF_2{=}CH_2$)] (**2.1g**)* *126*
*3.10.11 [(DPEphos)Ni($\eta^2\text{-}CF_2{=}CH_2$)] (**2.1h**)* *126*
*3.10.12 [(IAd)Ni($CF_2CH_2CF{=}CH_2$)(μ-F)]$_2$ (**2.2a**)* *127*
*3.10.13 [($PCyp_3$)Ni($CF_2CH_2CF{=}CH_2$)(μ-F)]$_2$ (**2.2b**) (NMR scale)* *128*
*3.10.14 [($P(t\text{-}Bu)_2(n\text{-}Bu)$)Ni($CF_2CH_2CF{=}CH_2$)($\mu$-F)]$_2$ (**2.2c**) (NMR scale)* *128*
*3.10.15 [(IAd)($P(i\text{-}Bu)_3(\eta^2\text{-}CF_2{=}CH_2$] (**2.1i/2.1i'**) (NMR scale)* *128*
*3.10.16 CHF_2–CH_2–$CF{=}CH_2$ (**1363pfy**) (NMR scale)* *129*
3.11 References 130

4. Alkylphosphine-mediated Hydrodefluorination 135

4.1 Introduction 135
4.2 Prior Art 138
4.2.1 The origins of alkylphosphines *138*
4.2.2 Phosphines as organocatalytic nucleophiles *141*
4.2.3 Phosphines as reducing agents *145*
4.2.4 Phosphine-Organofluorine Chemistry *148*
4.3 Reactivity with hexafluoropropylene (HFP) 159
4.4 Reactivity with perfluoro(methyl vinyl ether) (PMVE) 166
4.5 Mechanistic Considerations 168
4.6 Conclusion and Future Outlook 171
4.7 Experimental Section 172
General Procedures *172*
*4.7.1 Observation of compounds **4.1*** *173*
*4.7.2 Observation of compounds **4.1'** and **4.2*** *174*
*4.7.3 Observation of compound **4.3*** *174*
4.7.4 Generalized NMR tube HDF procedure *175*
*4.7.5 Generation of (E/Z)-**E1225ye** from PMVE* *175*
4.8 References 176

5. Metal ethylhexanoate-catalyzed hydrodefluorination 181

5.1 Introduction 181
5.2 Prior Art 182
5.3 The present work 214
5.4 Mechanistic Considerations 230
5.5 Conclusion 236
5.6 Experimental Section 237
5.6.1 General Procedures *237*
5.6.2 NMR tube screening conditions *238*
5.6.3 Isomerization of F-4M2P to F-2M2P *239*
*5.6.4 HDF of F-2M2P to **1567mcftc*** *240*

*5.6.5 HDF of PFCP to **c1427yz*** *240*
*5.6.6 HDF of PFCP to **c1436zz*** *241*
*5.6.7 HDF of PFCP to **c1445yzf*** *241*
*5.6.8 HDF of CTFE to **1122a*** *241*
5.7 References 243

6. Future Perspectives 249

6.1 New Molecules 250
6.2 New Regulations 256
6.3 New Methods 259
6.4 Intervening Work 262
6.5 Final Thoughts 264
6.6 References 267

A-I **270**

A-II **288**

A-III **299**

A-IV **312**

Chapters in Summary

CHAPTER 1. The title subject in retrospect; Biographical sketch of T. M., Jr. as industry pioneer; Major innovations by T. M.—antiknock fuel, fluorocarbon refrigerants; The spirit of the inventor and the discovery/invention axis; Restoring the name of T. M. and the reputation of his works.

CHAPTER 2. Introduction to refrigerants; Four generations; ASHRAE, nomenclature; Safety issues re: flammability, toxicity; Environmental issues re: ODP, GWP; Strategic zeotropic/azeotropic blending; Standard synthetic techniques; The order of C–Cl bond fluorination by HF or SbF_x; Statement of the present subject & relevance to the foregoing.

CHAPTER 3. Statement of the subject; Introduction to fluorinated metallacycles, their syntheses—Ni, Zn, Cu, Co, Fe, Au; Prior coördination chemistry of VF2; *This work:* Synthesis of π-VF2 complexes with phosphines; Expansion to NHC ligands, new μ-F dimeric C_4-containing product; Utilization of same for catalytic HDFD reaction—new olefin 1363pfy; Development of a suitable $Ni(cod)_2$ synthesis; Failed attempts to apprehend proposed intermediate; HDFD optimization—HDFD vs. HDF; DFT studies in partnership with R. P. Hughes—β-F vs β-H elim. pathways; Experimental, NMR data.

CHAPTER 4. The HDF reaction and justification therefor; Introduction to organophosphines in catalysis as nucleophiles, reductants; phosphine reactivity with fluorocarbons, ylides *vs.* fluorophosphoranes, and other work by D. Burton; *This work:* observation of P-fluorophosphoranes from PR_3 and HFP; Thermolysis of same to form $[PF_2]$ products and HFOs; turnover of P–F intermediates with hydrosiloxanes; Application to conversion of PMVE to E1225ye; Experimental, NMR data.

CHAPTER 5. Introduction to metal-catalyzed HDF; Cu hydride catalysts, their HDF reaction mechanisms, DFT; *This work:* Replacement of isolated $[PPh_3CuH]_6$ with air-stable precatalysts; Replacement of costly phosphine ligands with polymer-additive phosphites; Application to the HDF of perfluoroölefins—HFP, *F*-2M2P, PFCP; New Cr-catalyst, application to CTFE HDF; Experimental, NMR data.

CHAPTER 6. Future predictions; Resurgence of C_2 models; Resurgence of C–Cl bonds; Emergence of iodocarbon additives; Fluorinated ethers; Restrictions on HFCs incl. 404A, 410A; Difficulty in replacing latter; Future of homogeneous catalysis for refrigerants; Closing remarks.

List of Abbreviations

18-C-6	18-Crown-6 [CAS 17455-13-9]
2-EH	2-Ethylhexanoate(–1)
acac	Acetylacetonate(–1)
ACS	The American Chemical Society
ASHRAE	The American Society of Heating, Refrigeration, and Air-Conditioning Engineers
bipy	2,2'-Bipyridine [CAS 36145-03-6]
CFC	Chlorofluorocarbon
CFSE	Crystal field stabilization energy
CFO	Chlorofluoroölefin
cod	1,5-Cycloöctadiene [CAS 111-78-4]
COP	Coefficient of performance
CPME	Cyclopentyl methyl ether [CAS 5614-37-9]
CTFE	Chlorotrifluoroethylene, C_2F_3Cl [CAS 79-38-9]
dcpe	1,2-Bis(dicyclohexylphosphino)ethane [CAS 23743-26-2]
dcppe	1,2-Bis(dicyclopentylphosphino)ethane [CAS 111848-16-9]
DFT	Density functional theory
dibpe	1,2-Bis(diisobutylphosphino)ethane
dibpp	1,3-Bis(diisobutylphosphino)propane
DMAP	4-(Dimethylamino)pyridine [CAS 1122-58-3]
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether [CAS 166330-10-5]
dppe	1,2-Bis(diphenylphosphino)ethane, 'diphos,' [CAS 1663-45-2]
dppf	1,1'-Bis(diphenylphosphino)ferrocene [CAS 12150-46-8]
EEA	European Environmental Agency
EPA	Environmental Protection Agency
***F*-2M2P**	Perfluoro(2-methyl-2-pentene), [CAS 1584-03-8]
***F*-4M2P**	Perfluoro(4-methyl-2-pentene), [CAS 2070-70-4]
FC	Fluorocarbon
GWP	Global warming potential
HCFC	Hydrochlorofluorocarbon
HCFO	Hydrochlorofluoroölefin
HDF	Hydrodefluorination
HDFD	Hydrodefluorodimerization
HFC	Hydrofluorocarbon
HFO	Hydrofluoroölefin
HFP	Hexafluoropropylene, C_3F_6 [CAS 116-15-4]
HSE	Health, Safety, and Environment
IAd	1,3-Di(1-adamantyl)imidazol-2-ylidene [CAS 131042-77-8]
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidene [CAS 244187-81-3]
ItBu	1,3-Di(*tert*-butyl)imidazol-2-ylidene [CAS 157197-53-0]
JSRAE	Japanese Society for Refrigerating and Air Conditioning Engineers
KPI	Key performance indicator
LFL	Lower flammability limit (usually expressed in vol. % or kg/m^3)
MTBE	Methyl *tert*-butyl ether [CAS 1634-04-4]

Nap	Naphthenate(–1)
NHC	N-heterocyclic carbene
NMR	Nuclear Magnetic Resonance
O_h	Octahedral
***o*-TTP**	Tri(*o*-tolyl)phosphite [CAS 2622-08-4]
ODP	Ozone depletion potential
OEM	Original equipment manufacturer
OTf	Trifluoromethanesulfonate(–1), triflate(–1)
PEL	Permissible exposure limit (usually expressed in ppm)
PFCP	Perfluoro(cyclopentene) [CAS 559-40-0]
PMHS	Poly(methylhydrosiloxane) [CAS 63148-57-2]
PMVE	Perfluoro(methyl vinyl ether) [CAS 1187-93-5]
***p*-TTP**	Tri(*p*-tolyl)phosphite [CAS 620-42-8]
SBM	Sigma-bond metathesis
S_NV	Nucleophilic vinylic substitution
SIPr	1,3-Bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene [CAS 244187-81-3]
St	Stearate(–1)
tdame	1,1,1-Tris(diphenylarsinomethyl)ethane [CAS 40169-66-2]
TEHP	Tri(2-ethylhexyl)phosphite [CAS 301-13-3]
Terpy	2,2':6',2"-terpyridine [CAS 1148-79-4]
TES-H	Triethylsilane [CAS 617-86-7]
TFE	Tetrafluoroethylene [CAS 116-14-3]
THF	Tetrahydrofuran [CAS 109-99-9]
TIDP	Tri(isodecyl)phosphite [CAS 25448-25-3]
TIPS-H	Triïsopropylsilane [CAS 6485-79-6]
TMDS	1,1,3,3-Tetramethyldisiloxane [CAS 3277-26-7]
tmeda	*N,N,N',N'*-tetramethylethylenediamine [CAS 110-18-9]
TMSOTf	Trimethylsilyl trifluoromethanesulfonate [27607-77-8]
TOP	Tri(oleyl)phosphite [13023-13-7]
tripod	1,1,1-Tris(diphenylphosphinomethyl)ethane [CAS 22031-12-5]
VF	Vinyl fluoride [CAS 75-02-5]
VF2	Vinylidene difluoride, [CAS 75-38-7]
VF3	Trifluoroethylene [CAS 359-11-5]
VLT	Very low temperature (usually in reference to –40°C to -101°C in refrigeration)
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene [CAS 161265-03-8]
τ_{atm}	Atmospheric lifetime (in years)

List of Schemes

Scheme 2.9.1: Fluorination orders of chloroethanes 62
Scheme 3.2.1: Formation and manipulations of octafluoronickelacyclopentanes by Stone et al. [6] ... 73
Scheme 3.2.2: Preparation of a five-coördinate perfluoronickelacylopentane by Stone et al. [10] 74
Scheme 3.2.3: Synthesis of phosphite-ligated perfluoro- and hydrofluoro-nickelacyclopentanes and their hydrogenolysis to C_4 HFCs [12] 75
Scheme 3.2.4: C_a–F abstractions from PEt_3 perfluoronickelacycle by BF_3 [15] 76
Scheme 3.2.5: Preparation and of C_a–F abstractions of PS-ligated metallacycle by TMSOTf [16] 77
Scheme 3.2.6: Formation of anionic metallacycles with a PS thiolate ligand [17] 78
Scheme 3.2.7: Formation and reactions of metallacycles containing a PN amine or amide ligand [18] 78
Scheme 3.2.8: Formation and C_a–F activation of SIPr-ligated three-coördinate metallacycle by Lewis or Brønsted acids [19] 79
Scheme 3.2.9: Formation of isomeric VF3-derived nickelacyclopentanes with a variety of ligands ordered based on cone angle (ϑ) [20] 80
Scheme 3.2.10: Reactions of VF3-derived metallacycles with Brønsted and Lewis acids, and the product distributions thereof [20] 81
Scheme 3.2.11: Synthesis of heteroleptic TFE/ethylene metallacycles and Ni-catalyzed cotrimerization of TFE/ethylene (Ogoshi et al.) [21] 82
Scheme 3.2.12: Cotrimerization of ethylene, TFE, and aldehydes catalyzed by $Ni(cod)_2$ with IPr (Ogoshi et al.) [21] 83
Scheme 3.2.13: Reductive heterodimerization of TFE and aldehydes with Et_3SiH catalyzed by $Ni(cod)_2$ with P(*t*-Bu)$_3$ (Ogoshi et al.) [23] 84
Scheme 3.2.14: Cotetramerization of TFE/HFP, ethylene, and alkynes with or without styrene catalyzed by nickel (Ogoshi et al.) [24] 86
Scheme 3.2.15: Synthesis and reactions of octafluorobutyldizinc dimer prepared from 1,4-diïodoperfluorobutane (Vicic et al.) [26] 88
Scheme 3.2.16: Derivatization of the MeCN-metallacycle with various nitrogen ligands, and reactions of the complexes thereof (Vicic et al.) [27, 28] 89
Scheme 3.2.17: Synthesis of Ni(III) and Ni(IV) metallacycles bearing the Tp ligand (Sanford et al.) [29] 90
Scheme 3.2.18: Synthesis of half-sandwich Co metallacycle (Stone et al.) [30] 90
Scheme 3.2.19: Early syntheses and reactivity studies of Fe perfluorometallacycles [12, 31–33] 92
Scheme 3.2.20: Hypothesized pathways to 338pcc and 347pcc from $Fe(CO)_4$ metallacycle and formation of bisphosphine adducts thereof [34] 93
Scheme 3.2.21: Ligand substitution and spontaneous α-elimination from Fe carbonyl metallacycles, and justification of HFC-347pcc formation [34] 95
Scheme 3.2.22: Formation of perfluororuthenacycles from either $[Ru(CO)_3(PPh_3)_2]$ or $[RuCl_2(PPh_3)_4]$ [35, 36] 96
Scheme 3.2.23: Formation of a cationic perfluorocobaltacycle starting from Vicic's octafluorobutyldizinc reagent (Vicic et al.) [37] 97
Scheme 3.2.24: Formation of perfluorinated auracycles and open chain μ-$(CF_2)_4$-dimers (Gil-Rubio et al.) [39] 98

Scheme 3.2.25: Formation of PPh_3-ligated π-complex of VF2 (Stone et al.) [40] 98
Scheme 3.2.26: Formation of various π-complexes of VF2 using chelate ligands (Hoberg & Guhl) [41] 99
Scheme 3.2.27: Reactivity of a cationic μ-CO methyliridium dimer with various hydrofluoroethylenes (Cowie et al.) [42] 100
Scheme 3.3.1: Formation of π-VF2 complexes 3.1a–h with Ni and phosphine ligands..... 102
Figure 3.3.1: ORTEP representation of the molecular structure of complex 3.1h. Ellipsoids are set at the 30% probability level, and hydrogen atoms are omitted. 102
Scheme 3.3.2: Formation of Breslow-type adducts between free NHCs and VF2..... 103
Scheme 3.3.3: Formation of compound 2.2a from VF2 and proposed intermediate metallacycle 104
Figure 3.3.2: ORTEP representation of the molecular structure of complex 3.2a. Ellipsoids are set at the 30% probability level, and hydrogen atoms are omitted. 104
Scheme 3.4.1: Hydrodefluorodimerization of VF2 to HFO-1363pfy 105
Scheme 3.6.1: Attempts to apprehend the VF2 metallacycle with co-ligands 112
Scheme 4.2.1.1: General types of hydrophosphination reactions [7–12] 139
Scheme 4.2.1.2: Cyclic phosphine architectures exclusively from PH_3 [13–16]..... 141
Scheme 4.2.2.1: Generalized mechanism for the Rauhut-Currier reaction [21–23]..... 142
Scheme 4.2.2.2: Examples of cross Rauhut-Currier reactions [24, 25]..... 142
Scheme 4.2.2.3: Phosphine-catalyzed conjugate addition [26]..... 143
Scheme 4.2.2.4: Phosphine-catalyzed conjugate addition to methyl propiolate [28] 144
Scheme 4.2.2.5: Phosphine-catalyzed Morita-Baylis-Hilman reaction [29–32]..... 145
Scheme 4.2.3.1: Assorted phosphine-mediated reductions [33–36] 146
Scheme 4.2.3.2: Wittig reaction of an MBH adduct [42] 147
Scheme 4.2.3.3: The first reported catalytic Wittig reaction [43] 148
Scheme 4.2.3.4: Catalytic Staudinger reduction [44]..... 148
Scheme 4.2.4.1: Generation and Wittig reaction of $[PPh_3{=}CF_2]$ [46] 149
Scheme 4.2.4.2: Base-free Wittig reaction of trifluoromethyl ketones [49]..... 150
Scheme 4.2.4.3: Wittig reaction and generation of chlorofluoromethylene ylide [51]..... 151
Scheme 4.2.4.4: CF_2: generation and cyclopropanation from $[PPh_3CF_2Br]^+$ [53] 151
Scheme 4.2.4.5: $Ph_3P{=}CHF$ generation and Wittig reaction from $[PPh_3CHFI]^+$ [54] 152
Scheme 4.2.4.6: Reactivity of aliphatic ylides with fluorocarbons [57–59] 153
Scheme 4.2.4.7: Reactivity of phosphines with fluoroölefins [62] 154
Scheme 4.2.4.8: HDF of fluoroölefins by phosphonium salt hydrolysis [66] 155
Scheme 4.2.4.9: Single-component HDF of fluoroarenes by PEt_3 [69, 70]..... 157
Scheme 4.2.4.10: HDF of β-trifluoromethylstyrenes with 2° diaminophosphine [71]..... 158
Scheme 4.3.1: Reactivity of PR_3 with HFP at 50°C and 70°C..... 162
Scheme 4.4.1: Reactivity of P(*i*-Bu)$_3$ and TMDS with PMVE at 50°C..... 167
Scheme 4.5.1: Proposed mechanism for phosphine-catalyzed HDF of HFP/PMVE 171
Scheme 5.2.1: Hydrodefluorination of HFP to HFC-263fb mediated by Rh (Braun et al.) [5, 6] 183
Scheme 5.2.2: Hydrodefluorination of HFP to 1225ye/1234yf mediated by Ru (Whittlesey et al.) [5, 6]..... 184
Scheme 5.2.3: Hydrozirconation/elimination of HFP using $[(Cp^*)_2ZrH_2]$ (Jones et al.) [8] 185
Scheme 5.2.4: Hydrodefluorination of various fluoroölefins using $[(Cp^*)_2HfH_2]$ (Jones et al.) [9]..... 186
Scheme 5.2.5: HDF of PFCB and PFCP using $[(Cp^*)_2ZrH_2]$ (Jones et al.) [10]..... 187
Scheme 5.2.6: Reduction pathway for PFCP by $[(Cp^*)_2ZrH_2]$ compared with the expected insertion/elimination pathways [10]..... 189

Scheme 5.2.7: Proposed α-elimination pathway for formation of vinylic hydrodefluorinated products, formation of [Zr] vinyl species, and full reduction of HFP [10, 11] 190
Scheme 5.2.8: Use of [Cp_2TiF_2] and Ph_2SiH_2 to hydrodefluorinate various fluoroölefins [12] 192
Scheme 5.2.9: DFT-determined pathway for hydrotitanation/elimination mechanism of HFP by [Cp_2TiH] (T = 298 K, 1 bar in THF) [15] 192
Scheme 5.2.10: DFT calculations for HDF of HFP by SBM and S_NV pathways with [Cp_2TiH] (T = 298 K, 1 bar in THF) [15] 193
Scheme 5.2.11: HDF of HFO-1243zf using *β*-diketiminatoiron(II) hydride catalyst (Holland et al.) [16] 194
Scheme 5.2.12: Use of Red-Al® as a catalyst-free reducing agent for *β,β*-difluorostyrenes [18] 195
Scheme 5.2.13: Use of Cp_3Ln catalysts to hydrodefluorinate HFP with $LiAlH_4$ [19] 195
Scheme 5.2.14: Use of Cp_3Ln catalysts to hydrodefluorinate 1225zc with $LiAlH_4$ [19] 196
Scheme 5.2.15: Use of Cp_3Ln catalysts to hydrodefluorinate VF3 with $LiAlH_4$ [19] 197
Scheme 5.2.16: Use of Cp_3Ln catalysts to hydrodefluorinate CTFE with $LiAlH_4$ [19] 197
Scheme 5.2.17: HDF of HFP using NHC-Alane reagent [20] 197
Scheme 5.2.18: HDF of HFP using various alane reagents with or without diglyme catalyst [21] 198
Scheme 5.2.19: HDF of HFP using $(i\text{-}Bu)_2AlH$/diglyme (major products) [21] 198
Scheme 5.2.20: HDF of 1225zc using alanes/diglyme [21] 199
Scheme 5.2.21: HDF of VF3 using alanes/diglyme [21] 199
Scheme 5.2.22: HDF of CTFE using alanes/diglyme [21] 200
Scheme 5.2.23: HDF of BrTFE using alanes/diglyme [21] 200
Scheme 5.2.24: HDF of ITFE using alanes/diglyme [21] 201
Scheme 5.2.25: HDF of HFP using $BH_3{\cdot}SMe_2$ or $AlH_3{\cdot}NEt_3$, and explanations of the origin of selectivity of the $AlH_3{\cdot}NMe_3$ reduction [24] 202
Scheme 5.2.26: Stereoselective HDF of *α*-trifluoromethylstyrenes using LAH [26] 203
Scheme 5.2.27: HDF and hydrogermylation/defluorogermylation of HFOs [31] 204
Scheme 5.2.28: Proposed mechanism of hydrodefluorination/dehydrofluorination of HFC-245cb by ACF/Et_3SiH [32] 205
Scheme 5.2.29: Cu-catalyzed stereoselective HDF of difluorovinyl substrates using B_2nep_2/H_2O as the reductant system [34] 206
Scheme 5.2.30: Cu-catalyzed stereoselective HDF or defluorinative borylation of *β,β*-difluorostyrene derivative [35] 206
Scheme 5.2.31: Cu-catalyzed stereoselective HDF of *β,β*-difluorostyrene derivative [35] 207
Scheme 5.2.32: Proposed mechanisms for Cu-catalyzed HDF/borylation of *β,β*-difluorostyrenes with B_2pin_2 or silane (pin = pinacolato) [35] 208
Scheme 5.2.33: HDF of HFP by $[PPh_3CuH]_6$/TMDS and various ligands [36] 209
Scheme 5.2.34: HDF of various fluoroolefins catalyzed by [PPh_3CuH]/TMDS and either Xantphos (10 mol%) or $P(OEt)_3$ (30 mol%) [36] 211
Scheme 5.2.35: HDF of VF3 to 1132 isomers by [PPh_3CuH] showing ligand-dependent stereoselectivity [36] 212
Scheme 5.2.36: DFT modeling of three TFE hydrocupration pathways for $(PMe_3)_3CuH$ [36] 213
Scheme 5.2.37: DFT modeling of L_2 and L_3 *β*-elimination pathways for [Cu–CF_2CF_2H] showing relative free energies *(and actual energies continued from Scheme 4.2.36 in italic)* [36] 214
Scheme 5.3.1: Common preparations of Stryker's Reagent starting from commercial Cu sources [40–42] 216
Scheme 5.3.2: Reductive methods for PFCP to HFCs or HFOs [58–60] 225
Scheme 5.3.3: Cu-catalyzed HDF of PFCP (NMR scale) 226

Scheme 5.3.4: M(2-EH)$_x$-catalyzed HDF of HFP (NMR scale) 229
Scheme 5.4.1: Potential evolution of active [CuH] catalysts for HDF 232
Scheme 5.4.2: Possible elimination mechanisms leading to 1122a 235

List of Charts

Chart 2.4.1: Tetrafluoropropylene isomers and their ASHRAE names..... 41
Chart 2.8.1: The six most common reactions used to prepare fluorocarbons..... 58
Chart 3.1.1: Possible fluoroölefins of study according to price, precedent, and hazard profile. 69
Chart 3.1.2: Fluorometallacycles and their regioisomers, with proposed VF2 products shown at right. 70
Chart 5.3.1: Possible structures of naphthenic acids represented by the general formula $C_nH_{2n+z}O_2$ [63]. 219
Chart 5.3.2: Chelating nitrogen ligands tested for Cu-Nap-catalyzed HDF of HFP..... 222
Chart 6.1.1: C_2 HFOs and HCFOs, and their normal boiling points..... 252
Chart 6.1.2: C_2 and C_3 HFCs *vs* HFEs and their GWP and τ values 256
Chart 6.1.3: Assorted PFEs and their normal boiling points..... 256

List of Figures

Figure 2.4.1: ASHRAE refrigerant numbering system 38
Figure 2.6.1: Balancing the properties for the ideal halocarbon [14] 47
Figure 2.6.2: The optimal boiling point of refrigerants, with halomethane examples 48
Figure 3.5.1: Precipitated $Ni(cod)_2$ obtained by simple filtration and washing 109
Figure 3.6.1: ORTEP representation of the molecular structure of complex 2.2b 112
Figure 3.8.1: DFT/B3LYP-D3/LACV3P** calculations of the energetics of metallacyclopentane formation from VF2. 116
Figure 3.8.2: DFT/B3LYP-D3/LACV3P** calculated structures of Ia-IVa and V. 117
Figure 3.8.3: DFT/B3LYP-D3/LACV3P** calculations of the energetics of β-F elimination from metallacyclopentanes IIIa and IVa and β-H elimination from IVa 118
Figure 3.8.4: DFT/B3LYP-D3/LACV3P** calculated β-F elimination transition structures VI and VIII and products VII and IX. 120
Figure 4.5.1: $^{19}F\{^{1}H\}$ NMR (471 MHz) comparing P–F signal in complex 4.1c with and without added $Ti(O^{i}Pr)_4$ 170
Figure 6.1.1: Relation of A1-rated HCFOs to HFOs 251
Figure 6.4.1: Potential observation by ^{19}F NMR (282 MHz) of head-tail metallacycles containing both IAd and DMAP 264

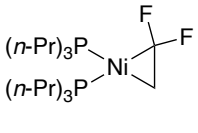
List of Tables

Table 2.3.1: Classifications of halogenated hydrocarbons used in this text 37
Table 2.4.1: Halocarbon molecular fragments and corresponding letter designations 40
Table 2.5.1: ODP, GWP, and atmospheric lifetimes of common CFCs and HCFCs 45
Table 2.5.2: ODP, GWP, and atmospheric lifetimes of common HFCs 45
Table 2.6.1: Selected single-compound refrigerants and their physical characteristics 49
Table 2.7.1: Common non-HFO refrigerant blends, boiling points, and applications 53
Table 2.7.2: Common HFO refrigerant blends, boiling points, and applications 54
Table 3.5.1: $Ni(cod)_2$ syntheses in assorted ethereal solvents 109
Table 3.6.1: Catalytic VF2 HDFD runs 114
Table 4.3.1. Trialkylphosphine-mediated hydrodefluorination of HFP using TMDS as the terminal reductant 164
Table 4.3.2. Trialkylphosphine-mediated hydrodefluorination of HFP using PMHS as the terminal reductant 166
Table 4.4.1. Trialkylphosphine-mediated hydrodefluorination of PMVE using TMDS as the terminal reductant 168
Table 5.3.1: HDF of HFP catalyzed by $Cu(O_2CR)_2$ and various ligands 221
Table 5.3.2: HDF of HFP using $Cu(Nap)_2$ and various phosphite ligands at 70^oC 223
Table 5.3.3: HDF of CTFE using $Cr(2\text{-}EH)_3$ and various alkylphosphite ligands 230

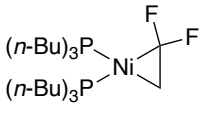
List of Compounds

NOTE: Small fluorocarbon HCFCs, HFCs, HFOs, &c. are excluded. See ***Appendix-IV***.

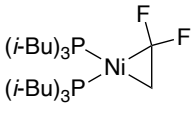
*Compounds **3.1***



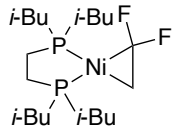
3.1a



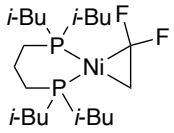
3.1b



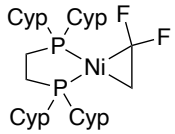
3.1c



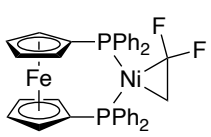
3.1d



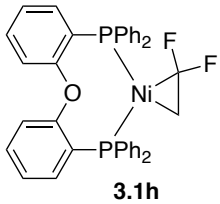
3.1e



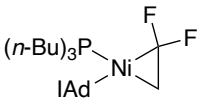
3.1f



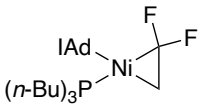
3.1g



3.1h

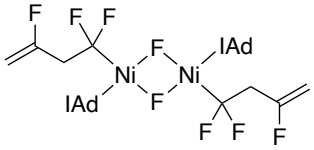


3.1i

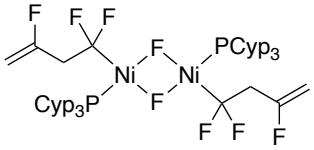


3.1i'

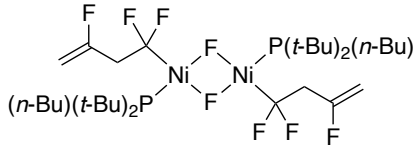
*Compounds **3.2***



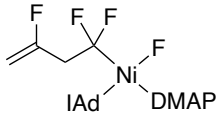
3.2a



3.2b

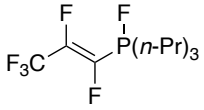


3.2c

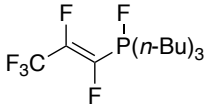


3.2d

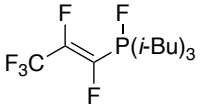
*Compounds **4.1***



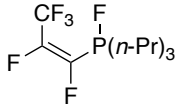
4.1a



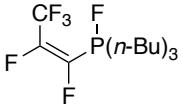
4.1b



4.1c

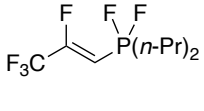


4.1a'

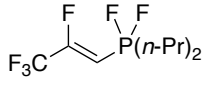


4.1b'

*Compounds **4.2***

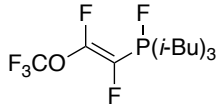


4.2a



4.2b

*Compound **4.3***



Published Work

1. Process for catalytic hydrodefluorodimerization of fluoroölefins, R. T. Baker and Alexandre J. Sicard (2020), United States Patent 10,882,802 B2
2. Fluorocarbon Refrigerants and their Syntheses: Past to Present, Alexandre J. Sicard & R. Tom Baker, *Chem. Rev.* **2020**, *120*(17), 9164-9303
3. Safe and Expeditious Preparation of $Ni(cod)_2$ for Same-Day High-Throughput Screening, Alexandre J. Sicard & R. Tom Baker, *OPR&D* **2020**, *24*(12), 2950-2952

Note to the reader:

There have also been written a set of completed manuscripts that are awaiting submission pending clearance from our industrial partner. As these works contain inventions for which patents are currently being filed, the manuscripts have been withheld from public view by the author (along with this thesis) until the patent applications have been disclosed. The manuscripts are listed on the following page, along with their intended journals.

4. Nucleophilic hydrodefluorination of fluorinated olefins mediated by common trialkylphosphines, Alexandre J. Sicard, Nathalie Rowlinson, and R. Tom Baker, *Adv. Synth. Catal.* **202x**, xx, xxxx
5. Economical and scalable hydrodefluorination reactions catalyzed by Cu-based wood preservatives, Alexandre J. Sicard, Behnaz Ghaffari, Nathalie Rowlinson, and R. Tom Baker, *ACS Catal.* **202x**, xx, xxxx
6. Coordination Chemistry of Vinylidene Difluoride with Nickel and Ensuing Catalytic Hydrodefluorodimerization Reaction, Alexandre J. Sicard, Bulat M. Gabidullin, Russell P. Hughes, and R. Tom Baker, *JACS* **202x**, xx, xxxx
7. Catalytic Olefin Hydrodefluorination as an Emerging Route to Next-Generation Fluororefrigerants: A Review, Alexandre J. Sicard & R. Tom Baker, *ACS Catal.* **202x**, xx, xxxx

1

CHAPTER ONE

1. A Personal Statement

PRIOR to the body of this thesis, I wish to, in addition to the words of acknowledgement ascribed earlier, provide the reader with a brief statement on what might be described as 'lessons-learned' in a more philosophical sense, more abstractly related to chemistry *qua* chemistry. Any student will have, throughout their scholastic apprenticeship, inadvertently received lessons from a variety of teachers (both living and deceased) on the philosophical underpinnings of their craft. Unlike the attributions outlined in the *Acknowledgements* section, which are specific and relevant to the author, the foregoing tells a story whose lessons are of general interest to any reader of this thesis seeking an answer to the question: *"What motivates the pursuit of science and engineering?"* In this spirit, I offer the following:

1.1 Setting the Record Straight

When interviewed about the aforementioned scholarly journey, I am confident that any specialist can easily point to a particular figure (or perhaps several) in his field as a

source of inspiration, whether in the capacity of direct mentorship or in the background as a historical personage of great accomplishment in the art. For example, students of the poetic and dramatic literatures have Wordsworth and Chekhov; the physics and math students can pore over the theorems of Feynman and Turing; the business students can look to such titans as Carnegie and Rockefeller, and enlightened economics students can study the collected works of Milton Friedman and Thomas Sowell (the less-enlightened ones perhaps preferring Keynes or Krugman). It is true that chemistry too, like any other field, has its celebrated heroes. From our first year we might learn such names as Dalton, Boyle, Pasteur, Curie, Nobel, Perkin, and Pauling, to name a few. Eventually, as we settle into our respective fields of expertise, we hear of more specific chemists of note, such as Woodward or Werner, depending on where we sit on the organic/inorganic axis. At a level more granular still, we have such subdisciplines as organofluorine chemistry, about which no discussion would be complete without mention of Moissan and Swarts. If asked about my own sources of inspiration, however, I would point to none other than Thomas Midgley Jr., the 20th-century chemist, engineer, and industrialist credited with the creation of the very field that has so deeply engaged my interest (and which constitutes the subject of this thesis). For that reason, throughout the pages of this chapter will be found several of his passages quoted *in extenso*.

This subsection is so-titled because the man in question has, in my view, been subject to much unfair treatment in retrospect. Midgley and his legacy have fallen prey to that pernicious habit which so pervades writers and commentators of the 21st-century—

namely, the imposition of modern-day sensibilities on historical personages, and the subsequent condemnation of (inevitably all) such figures when they, having lived as people of their respective decade or century, fail to have upheld the norms and standards of the 21st century (nay, the year to date, for the rules and norms now seem to morph on an annual rather than on a decennial basis, and with ever stricter enforcement). Perform a simple internet search of Thomas Midgley Jr., and you will find him portrayed predominantly in a negative light, but for what transgression? Among Midgley's many inventions were tetraëthyllead (the key component of leaded gasoline, and first synthetic octane-booster), and chlorofluorocarbons (CFCs, the first refrigerants, but more significantly, the first commercial organofluorine compounds). These two inventions so stir the ire of modern-day environmental zealots that a dislike of the compounds themselves has morphed into a condemnation of the man himself, as though he set out intentionally to produce inventions with environmental harm in mind, rather than to provide clever and functional solutions to the problems of the day—solutions taken for granted by those who have long since forgotten the original problems. The posthumous recasting and consequent denunciation of historical persons (whether perpetrated against Midgley or anyone else) constitutes at best, in my view, intellectual ignorance, and at worst, willful academic malpractice. I wish therefore, to put forward hereinbelow a thorough defense of this man in a small effort to restore his good name in the annals of chemistry not only as a brilliant chemist and engineer, but as an *inventor's inventor*.

1.1.1 The man who tamed explosions

In search of a more complete picture of Midgley the man, one should look no further than his biographical memoir penned by Charles F. Kettering, who first employed Midgley (then age 27) at the Dayton Engineering Laboratories Company in 1916 (Dayton, Ohio).[1] In the fifteen years following his employment by Kettering, Midgley went on to produce his most successful inventions, eventually giving way to a famous 1944 ACS Presidential Address titled *"Accent on Youth,"* where he demonstrated that the preponderance of commercially-successful inventions to be found in the United States Patent Office were reported by inventors under the age of 45,[2] a finding which prompted him to the conclusion that *"it would seem foolish to increase the time required for formal education beyond what it now is, since such increases would definitely encroach upon the most valuable years for actively prosecuting research and development."* Midgley's first foray into industrial research is one of his best-known—the study of engine knock, which at the time was widely believed to have been blamed on the advent of battery ignition and self-starter engines. Midgley demonstrated its origin as a result of preïgnition, and that the physical phenomenon of "knocking" came directly from abrupt pressure spikes in the cylinder following the initiating spark—but how to address the issue? Surely the automotive engineers could not do away with the self-starting engine and return to the days of manual cranks. Instead, Midgley decided that this particular challenge had to be confronted in terms of the fuel, as opposed to the engine mechanics. His first (admittedly rather whimsical) solution involved coloring the fuel red so that it might absorb more

radiant heat, thereby allowing the vapors to evaporate more quickly and evenly in the cylinder, and allowing for a knock-free combustion. His first choice of tincture was iodine, simply owing to its ease of availability and solubility in hydrocarbon media. His theory appeared initially to be vindicated by the observation that indeed, the iodine-doped fuel was effectively knock-proof, but whether or not this observation was due to its vermillion coloration had yet to be demonstrated. Substituting soluble aniline red dye for iodine gave no appreciable knock resistance, while colorless ethyl iodide suppressed knock as effectively as did I_2, and so the conclusion was that suppressant effect must have arisen from some chemical property inherent to iodine itself rather than its coloration. Kettering then recalls Midgley having stated: *"No one knows anything about this problem. We must outline a whole series of experiments and find out if it is physics or chemistry."* This was an important question, and a timely one; by then, the United States was hurling itself full-force into World War I, and engine knock was emerging as a key hindrance in the development of faster fighter planes. Cyclohexane (rumored—though apparently falsely—to have been used by the German *Luftstreitkräfte*) emerged as a much more smoothly-combusting aviation fuel, and thus it was called-for in larger quantities than were available at the time. Midgley then threw himself at the problem of hydrogenating benzene to cyclohexane on large scale, an infamously grinding pursuit, as the hydrogenation catalysts of the era could be easily foiled by the inevitable presence of sulfur heterocycles in the BTEX fraction. The best he was able to achieve was a 70/30 cyclohexane/benzene eutectic, which the allied Air Forces happily accepted by the barrel. This first-ever

synthetic aviation fuel proved to be a winning formula both on *terra firma* and *in caelum*, but after the war, it became obvious for economic reasons that the average American could not be expected to run his automobile on Midgley's 70/30 blend, and thus the quest for a practical and economical antiknock fuel resumed apace.

In an I&EC article titled *From the Periodic Table to Production*, Midgley, writing as an executive of the Ethyl Gasoline Corporation (Detroit, Mich.), notes that the early examples of antiknock agents were determined by a more sporadic method, which arose from the basic discovery that elemental iodine in minute quantities dramatically reduced a fuel's propensity to knock.[3] From this observation it followed that oil-soluble iodine compounds acted similarly, aniline and its homologs showed varying activity depending on the hydrocarbyl substituents on nitrogen, and Br_2, CCl_4, acids, and nitrates all tended to *increase* knock, while selenium oxychloride was extremely effective in preventing it. Midgley then changed course from his Edisonian gallivant to what he termed a more rational 'fox hunt,' whereupon *"predictions began fulfilling themselves instead of fizzling. Diethyl selenide was prepared and worked as expected; diethyl telluride next fulfilled our predictions, and seemingly our wildest dreams of success had been realized."* Of course, any reader well-read (or God forbid, *well-practiced*) in the art of tellurium chemistry would shudder at the idea of having to endure the distinct aroma of Et_2Te at the pump on a regular basis. Midgley himself later admitted: *"there are, however, good reasons for not using tellurium compounds."* Moving on to the carbon group, tetraëthyltin showed a marked antiknock effect, which prompted the team to move further down to discover that

tetraëthyllead was by far the most effective antiknock agent. The hunt was over, fox in hand.

Of course, discovering the utility of Et_4Pb was merely the first phase of a protracted bench-to-pilot project which involved first the optimization and commercialization of the tedious process of extracting bromine from seawater; Br_2 was required in large quantities for the manufacture of EtBr—the source of ethyl in *Ethyl*—and ethylene dibromide—the coädditive to *Ethyl* which prevented the formation of Pb deposits—but elemental bromine was not yet widely available at the time. In another of his IE&C articles titled *Problem + Research + Capital = Progress,* Midgley states:[4] *"bromine was then an expensive chemical used primarily for making photographic plates and headache powders. The principal known reservoir of bromine is the sea. But there are only approximately 67 parts of bromine in a million parts of sea water. Could it be extracted commercially?"* This is the phase which Mr. Kettering termed *"the typical 'shirt-losing era' of a new industry."* According to Midgley, the Ethyl Gasoline Corporation (Detroit, Mich.) spent $500,000 (ca. $6.4M in today's terms) to acquire the *S. S. Ethyl*—a vessel designed to mine bromine out of seawater. Despite being relatively unsuccessful, this pursuit led to the formation of a jointly-owned subsidiary with Dow Chemical, which managed to optimize the process so that at the time of writing of Midgley's IE&C article, the Ethyl Dow Chemical Company was producing over 1.5 million pounds of bromine each month from sea water using a plant built on the North Carolina coast. Of course, this demonstrates the truth of the matter which is that the work does not stop with a

discovery, but rather, that the discovery is the first step in a long quest filled with blind-alleys and dead-ends before finally, after much toil and drudgery, a viable product can be unveiled to the market. I will end this sketch of the *Ethyl* portion of Midgley's career with a passage from this last IE&C article, which I believe makes the point very clearly:

"It should be evident to anyone who knows all the facts, that the discovery of Ethyl and the benefactions it has brought were possible only because of the American way of business, only because courageous corporate executives had the foresight to invest large sums of money and continue backing an idea through periods when less astute minds might have dropped it. They would not have done this had they not believed in the end they would make a profit from it for their stockholders. They would not have been able to do it had they not previously made large sums of money for their corporations from other ventures, which allowed them to finance this one. They would not have been able to do it had there been any law against their taking the chance of losing the money put into it. For it must be remembered, that with only slightly different circumstances the whole project of Ethyl might have been written off at one time as a $3,000,000 flop." [4]

1.1.2 The man who conjured the cold electric

Of course, Midgley did not rest on his laurels following the invention of octane-boosting fuel-additives; he went straight back to work on an altogether unrelated problem which was put forth to him by Kettering *via* a prior discussion with Lester Keilholtz, who was at that time the Chief Engineer at the Frigidaire Corporation (Dayton, Ohio). In *From the Periodic Table to Production*, Kettering is quoted issuing the following challenge: *"Midge, I was talking with Lester Keilholtz last night and we came to the*

conclusion that the refrigeration industry needs a new refrigerant if they ever expect to get anywhere," following which, Midgley recalls: *"What we wanted was obvious—a nontoxic, non-flammable refrigerant. On leaving Keilholtz I expressed myself as very doubtful that we would be able to find a single substance suited to the task but that there might be some hope of greatly reducing the existing hazards by using mixtures where non-flammable but toxic materials would be mixed with nontoxic, flammable compounds to give a mixture substantially non-flammable and considerably less toxic than the refrigerants then commonly employed."* It is important to note that at the time, such compounds as SO_2, NH_3, Et_2O, C_3H_8, and CH_3Cl were commonly employed as refrigerants, all of which carry substantial hazards in terms of toxicity and/or flammability. The engineers at Frigidaire recognized this obvious danger early, and Midgley's team was charged with its solution. Once again, a major problem in a mechano-electrical industry was being resolved by chemists. The idea-gathering phase of Midgley and his associates A. L. Henne and Robert MacNary went as follows:

"The desired combination of properties was a boiling point between 0° and -40^oC, stability, nontoxicity, and non-flammability. International Critical Tables gave us a partial summary of the volatile organic compounds. The now proved mistake that carbon tetrafluoride boiled at -15^oC struck us in the face and started us thinking about fluorine. No one could doubt at that time that it was terribly toxic, probably too toxic to use even with isobutane. Perhaps we could add some chlorine compound with beneficial results. Henne suggested chlorofluorides as a class to be investigated further. And so the discussion ran." [3]

The zeroing-in on fluorine also had a theoretic basis; just as Midgley used periodic trends to predict success in *Ethyl*, so too did he use them to predict which elements would best fulfill the requirements of Keilholtz et al. at Frigidaire. Obviously, the inert gases fulfilled the toxicity/flammability requirements, but they are far too low in boiling point to have been seriously considered. This left the remaining non-metals, on which Midgley notes: *"Flammability decreases from left to right. Toxicity (in general) decreases from the heavy elements at the bottom to the lighter elements at the top. These two desiderata focus on fluorine."* We take such trends for granted now, but in Midgley's day, the very idea of organofluorine compounds being potentially nontoxic was so unimaginable as to have escaped any consideration by the Frigidaire engineers. This, of course, followed from the knowledge that fluorine itself is an outstandingly reactive and toxic gas, and that these properties (as well as the toxicity of inorganic fluorides) were estimated to commutate to its organic derivatives. Upon checking the heats of formation, Midgley confirmed that they increased from iodine to fluorine, and deduced correctly that organofluorine compounds should exhibit a high degree of stability. The team was certainly wary of using gaseous hydrofluoric acid early on, so they instead opted for classical Swarts fluorinations, a method calling for antimony trifluoride as the source of nucleophilic fluorine. This was a rare compound at the time, as Midgley recalls: *"I called one of the chemical supply houses by telephone and ordered five 1-ounce bottles of antimony trifluoride. I believe this was all there was in the country at the time."* Indeed, the stakes were high to obtain valuable data from so little a sample of this rare salt.

The first organofluorine compound synthesized and tested for ideal refrigerant properties was fluorodichloromethane (HCFC-**21**), a few grams of which was made from $CHCl_3$ and one of the five bottles of SbF_3 and immediately tested by placing a guinea pig under a bell jar containing it. Midgley recounts that the guinea pig, upon exposure to the HCFC, *"didn't suddenly gasp and die. In fact it wasn't even irritated. Our predictions were fulfilled."* The reader should note that a great deal of good fortune was involved in the transpiring of this first result, for upon synthesizing a second batch from another of the five SbF_3 bottles, and repeating the experiment with the guinea pig, the animal suffered considerable irritation—but why? In fact, 4/5 of the SbF_3 bottles were significantly contaminated by a double salt of crystallization containing oxygen, likely due to moisture exposure. A sniff-test of the product sample rendered from these other SbF_3 bottles immediately revealed the problem; the impure SbF_3, under Swarts conditions, converted some of the $CHCl_3$ to phosgene, which contaminated the resulting HCFC and accounted for the animal's respiratory irritation. All that was needed was a simple caustic scrub of the $CHCl_2F$ to render a product which, once again, produced no ill effects on inhalation. Consider for a moment how fortunate Midgley and his technicians were to have, as a first foray into chlorofluoro-compounds, used the one SbF_3 bottle of five which was pure enough to render HCFC uncontaminated by phosgene, for had they used one of the other four bottles, the irritation would likely have been blamed on the fluorocarbon, and the whole organofluorine project would have been abandoned as a "failed hunch."

The molecular candidates for refrigeration advanced beyond HCFC-**21**, eventually landing on $CFCl_3$ (CFC-**11**) and CF_2Cl_2 (CFC-**12**). Midgley co-authored an IE&C article in 1930 with his associate Albert L. Henne where he first charts the problems with the common refrigerants of the day in terms of their various practical properties.[5] The authors point out that though *"it is accepted that the substitution of halogen for hydrogen in general increases toxicity,"* they were surprised to find that *"the substitution of fluorine for hydrogen on a carbon atom which is already linked to one or more halogen atoms greatly reduces toxicity."* The reader might compare, for example, the non-toxicity of CFC-**11** with the toxicity of $CHCl_3$. In this article, Midgley and Henne discuss the factors which contributed to their arrival at CFC-**12** as the *ideal* refrigerant. For one, it is outstandingly non-toxic, a feat which Kettering recalls was demonstrated by Midgley himself on stage in a demonstration where he filled his lungs with CFC-**12** and blew out a candle standing in front of him, simultaneously proving non-toxicity and non-inflammability.[1] Animal tests where test subjects were placed in an environment containing air diluted with 20% of CFC-**12** exhibited only mild symptoms of oxygen deprivation.[5] No long-term effects after the test concluded were observed, with the animals recovering from the mild symptoms within minutes. Interestingly, CFC-**12** was shown to be less fatal to animals than carbon dioxide in high (at least 30% v/v) concentrations.

Second, its boiling point of -30°C was squarely within the ideal range of -40 to 0°C, and its vapors (if pure and dry) were stable for at least 30 days at 175°C. It showed

satisfactorily little corrosion at this temperature of stainless steels, aluminum, copper, Monel® metal, tin, and tin-lead solders. It was, however, unsatisfactory with bronze, brasses, or magnesium alloys, and zinc, magnesium, and water all eventually attacked the C–Cl bonds at high temperatures. Finally, the production scheme for CF_2Cl_2 was devised without great difficulty (especially compared to the struggles with *Ethyl*), owing mainly to the prior art from Swarts, who demonstrated the high fluorinating ability of $SbF_3/SbCl_5$ mixtures. Product purification was also simple: *"Since each fluorine substitution lowers the boiling point of the resulting compound by about 52°C., it becomes a relatively simple matter to extract any desired substitution product by fractional distillation, thus removing it from the reaction field as it is formed."*

Midgley, for his part, did not cease to ponder on issues of air-conditioning. In his view, the advent of air-conditioning would have no less a significant impact on human flourishing than high-performance fuels. This sentiment is presented in an IE&C article titled *Synthetic Weather*, published in September of 1935. According to Midgley, *"air-conditioning implies the creation of an atmospheric environment which is comfortable; comfort, in turn, implies a psychological condition closely associated with psychology. This environment is referred to as the comfort zone which has been aptly described as being not too hot, not too cold, not too dry, and not too damp."* Thus, he proceeded from focusing on chemistry to thinking about the psychology, architecture, and economics of air-conditioning, even going so far as to chart the desirable inside conditions according to varying outside temperatures. He defines the requirements of year-round air-conditioning

as including cooling, dehumidification, heating, humidification, cleaning, deodorizing, and circulating. He also describes the *Frigidaire House*—a purpose-built dwelling designed to render the most comfortable indoor environment, and which was exhibited at the *Century of Progress* (Chicago, 1934). Finally, as Kettering recalls in his biographical memoir of Midgley, the organofluorine project (like the earlier antiknock project) contributed to the war effort during World War II, where Freon was used as a nontoxic vehicle for dispersing insect repellents in confined spaces.

In a 1938 article titled *Man-Made Molecules*, Midgley discusses the great progress made at the hands of science, and holds it as evidence that man's greatest strength is not merely an ability to adapt to his surroundings, but to adapt the surroundings themselves to suit his need.[6] From the building of fires to the cooking of food, man has experimented with altering the molecular constitution of his surroundings to suit the requirements of his survival, whether through the consumption of food free of parasites, or through the building of stronger, more durable shelter to protect from nature's elements. Though chemistry itself is a relatively novel pursuit, Midgley urges us to consider that around ten thousand years ago, so-called *alchemists* were pursuing the reduction of metal oxides, though they knew not then that they were in fact proto-metallurgists. He urges us to consider advances in the pharmaceutical industry, and its implications for human health and longevity. The ability to produce, for example, what he terms "*hormone-like substances*" which have never before existed in nature push the boundary of biology far beyond the wildest dreams of the early alchemists and witch-doctors. The ability to live

under so-called "synthetic weather" conditions of optimal humidity, temperature, and barometric pressure is just another example of man perfecting his own environment. We take for granted that when the terrain is too rocky, we can carpet it in smooth tarmac; when the outdoor temperature varies wildly, we can insulate the walls of our shelters with a synthetic urethane foam; when our soil is too poor to cultivate, we can enrich it with fertilizer so as to render ample crop yields; when our air is tepid, we can condition it to the ideal temperature and humidity; and when our bodies begin to fail us, we can extend their lifespan further with various medicaments. The rapid development of COVID-19 vaccines is just another example of man's ingenious use of science and technology to thwart any threat to his survival, both natural and otherwise. This, I assert, answers our question at the beginning of this section as to what motivates the pursuit of science and engineering. In this spirit, I will conclude this section with an entreaty from *Man-Made Molecules*:

"Through the medium of man-made molecules man has the means of altering his environment as he chooses. What that choice shall be is not for the chemist alone to decide. Steel may be used for building and transportation or for guns and shells, high explosives for mining and construction or for the killing of women and children, and the same tools that make dyes will make poison gases. May I therefore ask you to join with me and with chemistry, in the name of the man whose memory we honor here, in doing all within our power to see that these man-made molecules are applied exclusively to the pursuit of happiness? Thus may we comply with God's edict in Genesis that Man shall be in His likeness and have dominion over all the earth." [6]

1.1.3 Midgley's Legacy

The foregoing two subsections should by now have persuaded the reader of Midgley's inventive prowess which should have cemented his position among the historical greats of chemistry, as befitting a winner of the Perkin, Priestley, and Gibbs Medals.[7,8] We have just heard of a man who, in a single lifetime, contributed to motor fuels, refrigerant gases (along with aerosol propellants, foam expanding agents, &c.),[9] and, though unmentioned in this biographic sketch, a decade of work on natural,[10–14] synthetic,[15–24] and vulcanized[25] rubbers and their molecular constituents spanning a decade of publications. Most chemists of note across history become associated with a particular and singular body of work which represents their most significant contribution to the art. Midgley's legacy can be associated with *three* bodies of work,[i] and were it not for his untimely death in 1944 (aged 55) due to a rare and acute case of polio,[ii] who knows what other unlikely and unrelated subdisciplines of chemistry might have been radically disrupted by his inventive mind? Of course, such things are best left unthought, such is the sadness they cause.

[i] Though most sources separate Midgley's work into three main bodies, his obituary, penned by T. Boyd, lists *four* contributions. These include the work done on the effective and economical extraction of bromine from seawater, in addition to antiknock, refrigeration, and rubbers.

[ii] According to Boyd's obituary, Midgley, good-humored despite being deprived of the use of his legs by the disease, computed that the statistical probability of a man his age contracting polio is "substantially equal to the chances of drawing a certain individual card from a stack of playing cards as high as the Empire State Building," going on to say that "nevertheless, it was my tough luck to draw it."

All the more criminal, then, that he should be posthumously slandered by modern day—and usually young—members of the academy and society, so jejune of intellect and opinion, and yet so cocksure of both! Though the case has been made first by K. R. Williams,[26] and then by Viana and Porto[27] that Midgley's expansive and nonlinear thinking which led to the aforementioned inventions (especially regarding the development of refrigerants) should be taught as part of a chemical education curriculum with a focus on the philosophy of science, a short and (in this author's opinion) sardonic rebuke[28] (to Williams' original article) was published by Kauffman which calls Midgley a 'two-time environmental loser.' Kauffman is far from alone; one article[29] describes Midgley as "the most environmentally disastrous person of all time," another[30] calls him "the most harmful inventor in history," and another[31] goes so far as to call him "arguably the most dangerous man of all time,"—at this 'argument,' no doubt the great despots of the 20th century are laughing in their graves. Of course, these are internet sources penned by non-scientists using that particularly hyperbolic and overly dramatized fishbait style which is characteristic of such periodicals. Though the perspectives offered by these pieces are barren of nuance, their target audience (namely the ever-growing group of ersatz 'internet-intellectuals') prefers it that way; their arrogant presumption of their own superior intellect to all who came before them leaves no room for nuanced thinking, and so they treat Midgley as just another among a long line of great historical personages to be put before the millennial firing squad for the grave sin of having lived in a prior age and having exhibited great competence while doing so. It is the unfortunate truth that many

among the younger generation will come across these online articles long before having been exposed to Kettering's biography, Boyd's obituary, or any papers written by the man himself in JACS and I&EC, and will therefore entertain a far worse opinion of him than he deserves. It is still more unfortunate that they think their thirst for knowledge can be quenched by this vile blackwater, while they will never have drunk of the crystal-clear well awaiting as a reward for those who choose to dig for it.

While I am certain that this document is unlikely to sway the minds of such people who regard the aforementioned websites as credible primary sources, I can at least attempt to convey to my readers here what *should* be (and once was) Midgley's legacy, if I may be first indulged a brief tangent. In the sciences, I have come to find that we are driven by one of two primary motives: *discovery* and *invention*. I separate these because they manifest themselves very differently and are unevenly distributed among the various subdisciplines of STEM. For instance, a *discoverer* is much more likely to take up biology, that they may be let alone to spend years, for example, studying the elusive mating habits of some obscure poisonous Amazonian frog. These scientists are animated by a curiosity about how that which already exists has come to be, and why it works. It is only natural, then, that they should be drawn to the natural world; to the animate, rather than the inanimate. Of course, discoverers more interested in the *inanimate* are fewer, and they traditionally end up in the physics and geology departments. We see discovery-oriented people in the chemistry department as well, traditionally well-situated among the physical, physical-organic, physical-inorganic, computational, and other subdisciplines primarily

concerned with the elucidation of reaction mechanisms rather than the synthetic applications of chemical reactions. The latter, of course, is the domain of the *inventors*.

Chemists motivated by the spirit of invention are more motivated by the creation of something new rather than the study of that which already exists. While they may have some interest in reaction mechanisms, this is only insofar as it enables the creative process. The inventor needs only know enough about the mechanism to optimize the reaction so that it is fit for purpose, whatever that purpose may be. Once functional and optimized, he can move on to another invention, while his discovery-oriented friends spend the ensuing years examining every step and aspect under the microscope. While it is certainly true that a greater knowledge of reaction mechanisms can give rise to incremental improvements, by the time such knowledge is apprehended, the original inventor is likely to have already lost interest, burying himself neck-deep into some other problem. Of course, this is not to say that any one of us is all or nothing, for none among us are entirely motivated by invention or discovery on a mutually-exclusive basis. This heterogeneity is what makes chemistry as a discipline unique in STEM. It is difficult to be an inventor in biology or physics, for each is concerned with the natural world *as it already is*. It is equally difficult to be a discoverer in engineering, for by definition engineers are concerned with the creation of new and unnatural things: bridges, buildings, freeway ramps, &c. Only chemistry provides an environment which when taken as a whole is constituted of equal parts invention and discovery. It is therefore the only natural home for a *scientist* motivated predominantly by *invention*.

Midgley proved a fundamental axiom of invention, which is that an absolute knowledge of the background theory is not essential to the creation of something new or the utilization of an existing tool on empirical grounds. A child walking to the park need not be familiar with the physics of the wheel in order to independently arrive at the conclusion that he can more easily carry his toys in a rolling wagon than in his own arms. Likewise, Midgley did not (nor need to) possess the knowledge of free-radical chemistry necessary to explain why heavier alkyl chalcogenides and iodides suppressed engine knock; and yet, a large and very profitable industry was built around his antiknock formula. His legacy should be that he embodied the spirit of the inventor in its raw, undistilled form. Most other scientists would, upon having invented an antiknock formula, spend the remainder of the careers studying every mechanistic aspect of engine knock. But Midgley did not dwell; far from it, he went on to solve the altogether unrelated problem of refrigeration. Nor, once this was solved, did he dwell on the study of Swarts fluorination or trends in refrigeration performance relating to molecular structure—such trends having been reported-on later by his colleague A. L. Henne.[32] Instead, Midgley had by that time moved on and taken a lively interest in synthetic rubbers, funding the work substantially by himself, and continuing on even in his semi-invalid state when he was unable to participate in the laboratory.

In these past passages, it has hopefully been demonstrated that to simply look upon Midgley as a malicious environmental menace as so many people do is a libelous misrepresentation and a miscarriage of history. While I contributed this section with the

primary goal of restoring Midgley's good name, it can just as easily be seen as a long and protracted acknowledgement. In that spirit I must offer my deepest thanks to Thomas Midgley, Jr. for not only paving the roads taken throughout my own research, but for sparking in me the inventive motive, and the grit to persist against all resistance in pursuit of my goals. The resolute and robust spirit of the inventor that constitutes his memory and legacy should stand as an inspiration to all who enter into the STEM fields. I will end this section as Boyd began his obituary; with some lines of verse that culminated Midgley's famous 1944 "Accent on Youth" ACS Presidential Address:[2]

"When I feel old age approaching and it isn't any sport,
And my nerves are growing rotten, and my breath is growing short,
And my eyes are growing dimmer, and my hair is turning white,
And I lack the old ambitions when I wander out at night,
Then, though many men my senior may remain when I am gone,
I'll have no regrets to offer just because I'm passing on.
Let this epitaph be graven on my tomb in simple style,
'This one did a lot of living in a mighty little while.'"



1.2 References

(1) Kettering, C. F. *Biographical Memoir of Thomas Midgley Jr. (1889-1944)*; National Academy of Sciences of the United States of America, 1947. [http://www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/midgley-thomas.pdf]

(2) Midgley, T. Presidential Address: Accent on Youth. *Chem. Eng. News* **1944**, *22*, 1646–1649.

(3) Midgley, T. From the Periodic Table to Production. *Ind. Eng. Chem.* **1937**, *29*, 241–244.

(4) Midgley, T. Problem + Research + Capital = Progress. *Ind. Eng. Chem.* **1939**, *31*, 504–506.

(5) Midgley, T.; Henne, A. L. Organic Fluorides as Refrigerants. *Ind. Eng. Chem.* **1930**, *22*, 542–545.

(6) Midgley, T. Man-Made Molecules. *Ind. Eng. Chem.* **1938**, *30*, 120–122.

(7) Priestley Medal Award to Thomas Midgley, Jr. *News Ed. Am. Chem. Soc.* **1941**, *19*, 1021–1024.

(8) Midgley, T. Willard Gibbs Medal. A Critical Examination of Some Concepts in Rubber Chemistry. *Ind. Eng. Chem.* **1942**, *34*, 891–896.

(9) Freon Marks Quarter of a Century. *Chem. Eng. News* **1956**, *34*, 396–397.

(10) Midgley, T.; Henne, A. L. Natural and Synthetic Rubber. I. Products of the Destructive Distillation of Natural Rubber. *J. Am. Chem. Soc.* **1929**, *51*, 1215–1226.

(11) Midgley, T.; Henne, A. L. Natural and Synthetic Rubber. VI. The Pyrolysis of Natural Rubber in the Presence of Metallic Oxides. *J. Am. Chem. Soc.* **1931**, *53*, 203–204.

(12) Midgley, T.; Henne, A. L.; Renoll, M. W. Natural and Synthetic Rubber. VII. Fractional Precipitation of Natural Rubber. *J. Am. Chem. Soc.* **1931**, *53*, 2733–2737.

(13) Midgley, T.; Henne, A. L.; Shepard, A. F. Natural and Synthetic Rubber. IX. The Products of the Destructive Distillation of Ebonite. *J. Am. Chem. Soc.* **1932**, *54*, 2953–2960.

(14) Midgley, T.; Henne, A. L.; Shepard, A. F. Natural and Synthetic Rubber. XIV. A Structural Formula for Ebonite. *J. Am. Chem. Soc.* **1934**, *56*, 1326–1328.

(15) Midgley, T.; Henne, A. L. Natural and Synthetic Rubber. II. Reduction of Isoprene by Na-NH3. *J. Am. Chem. Soc.* **1929**, *51*, 1293–1294.

(16) Midgley, T.; Henne, A. L. Natural and Synthetic Rubber. III. Dimethyloctadiene. *J. Am. Chem. Soc.* **1922**, *51*, 1294–1296.

(17) Midgley, T.; Henne, A. L. Natural and Synthetic Rubber. IV. 4-Methyl-4-Octene by Isoprene Ethylation. *J. Am. Chem. Soc.* **1930**, *52*, 2075–2077.

(18) Midgley, T.; Henne, A. L. Natural and Synthetic Rubber. V. Tetramethyloctadiene. *J. Am. Chem. Soc.* **1930**, *52*, 2077–2078.

(19) Midgley, T.; Henne, A. L.; Shepard, A. F. Natural and Synthetic Rubber. VIII. Products of the Destructive Distillation of Sodium Rubber. *J. Am. Chem. Soc.* **1932**, *54*, 381–386.

(20) Midgley, T.; Henne, A. L.; Renoll, M. W. Natural and Synthetic Rubber. X. Constituents of the Rubber Hydrocarbon. *J. Am. Chem. Soc.* **1932**, *54*, 3343–3348.

(21) Midgley, T.; Henne, A. L.; Renoll, M. W. Natural and Synthetic Rubber. XI. Constituents of the Milled Rubber Hydrocarbon. *J. Am. Chem. Soc.* **1932**, *54*, 3381–3383.

(22) Midgley, T.; Henne, A. L. The Separation and Identification of Sol Rubber Hydrocarbons. *J. Phys. Chem.* **1932**, *36*, 2880–2884.
(23) Midgley, T.; Henne, A. L.; Shepard, A. F.; Renoll, M. W. Natural and Synthetic Rubber. XIII. The Molecular Weight of Sol Rubber. *J. Am. Chem. Soc.* **1934**, *56*, 1325–1326.
(24) Midgley, T.; Henne, A. L.; Leicester, H. M. Natural and Synthetic Rubber. XVI. The Structure of Polystyrene. *J. Am. Chem. Soc.* **1936**, *58*, 1961–1963.
(25) Midgley, T.; Henne, A. L.; Shepard, A. F. Natural and Synthetic Rubber. XII. Reversible Vulcanization, by Organo-Metallic Derivatives. *J. Am. Chem. Soc.* **1934**, *56*, 1156–1157.
(26) Williams, K. R. Refrigeration - From Ice Man to Ozone Hole. *J. Chem. Educ.* **2000**, *77*, 1540–1541.
(27) Viana, H. E. B.; Porto, P. A. Thomas Midgley, Jr. and the Development of New Substances: A Case Study for Chemical Educators. *J. Chem. Educ.* **2013**, *90*, 1632–1638.
(28) Kauffman, G. B. Midgley—A Two-Time Environmental Loser. *J. Chem. Educ.* **2002**, *79*, 559.
(29) Phillips, T. Thomas Midgley, Jr. may have been the most environmentally disastrous person of all time https://www.popsci.com/humans-thomas-midgley-excerpt/ (accessed Jul 12, 2021).
(30) Larsen, N. Thomas Midgley, The Most Harmful Inventor in History https://www.bbvaopenmind.com/en/science/research/thomas-midgley-harmful-inventor-history/.
(31) Schleien, D. Meet Thomas Midgley Jr., Arguably The Most Dangerous Man Of All Time https://medium.com/climate-conscious/meet-thomas-midgley-jr-arguably-the-most-dangerous-man-of-all-time-2ae66b1cc101 (accessed Jul 12, 2021).
(32) Henne, A. L.; Renoll, M. W. Fluoro Derivatives of Ethane and Ethylene. IV. *J. Am. Chem. Soc.* **1936**, *58*, 887–889.

2

CHAPTER TWO

2. The Field of Fluororefrigerants

2.1 Introduction

THE title of this chapter refers to a review article of the same name which was written over a period of several years going back to the beginning of my doctoral research. For as long as I have been a member of the Baker research group, presentations given by my colleagues both past and present have always included a requisite slide justifying to the audience the need for the work. These slides often made connection between our work and, for example, the fluoropolymer industry (in the case of the fluorocarbene project), pharmaceuticals and agrochemicals (in the case of our Cu-mediated fluoroalkyl transfer projects) or refrigerants, blowing agents, and propellants (in the case of our other fluorine projects). Most members of a general audience (scientific or otherwise), though unaware of the niche of organofluorine chemistry, *are* aware of the existence of its fruits, including non-stick cookware, air-conditioning, and insulation foam, and so such associations served their purpose well in a presentation setting. Descriptions of refrigerants in such presentations have rarely strayed far beyond mentioning such standard-bearers as R-**12**,

R-**22**, or R-**134a** (see ***Section 2.3*** for a description of this numbering system, and ***Appendix A-IV*** for a list of compounds and their numbers). Occasionally, R-**1234yf** or R-**1234ze** might be invoked as objects of desire (whether as products or precursors), though until only recently, they had not featured in any of our publications. Upon digging a little deeper into the compounds used as justification for my own work, **1234yf** included, I found that there was very little information available in the academic literature on their industrial synthesis, their uses, or their developmental history. I found that though these compounds are oft-cited in the current literature among our peers as motive for their work, they are only mentioned in passing. There might be some brief note about the hazards of HF or of pentavalent antimony in the introduction, but beyond that, readers are left with little else useful to which to compare the findings at hand. I decided early on that if the core of my project in the Baker group would be to improve upon the current paradigm of small fluorocarbon synthesis, then it follows that I should have a firm grasp of that paradigm at the outset. In the absence of a clear road to such an end, I decided to pave it myself by writing a review article that I would have wished for when I began my own journey.

It must also be stressed that *Fluorocarbon Refrigerants and their Syntheses* is in many ways an atypical *Chemical Review*. Its bibliography is almost entirely comprised of patents and patent applications, with only a precious few academic articles scattered throughout to add some mechanistic or theoretical color. Though the patent literature is vast, there are good reasons why most graduate students avoid visiting that particular

well—and indeed when they do, it is usually motivated by a desperate thirst indeed. Where academic articles are written to deliver their contents in as clear and concise a way as possible, patents and patent applications do the opposite; one could argue that as legal documents, they were never explicitly designed to be used as reference materials. Especially for the past few decades, they have been written in a tortured, almost obscurantist language, and in such a way that until you reach the *Examples* section, it might not be entirely clear to the reader what the authors actually invented, so impressionistic a picture the *Claims* paint. That they are not designed as reference tools does not, however, preclude their usefulness as such, and it is my hope that this Review can be used as a more accessible portal to the wealth of information that exists in nearly a century's worth of intellectual property disclosures on fluororefrigerant production.

The nature of this research topic incurs as a consequence the necessity to present each work at a resolution not common in *Chemical Reviews*, as patents often read so similarly as to seem identical from afar. I endeavored to present each report with a focus on originality and usefulness, which meant occasionally identifying details which would seem otherwise superfluous (especially in a review article), but without which the core novelty of the patent would be lost, along with all credit due their inventors. Given the evolutionary path of the field of refrigerants, I wrote the Review in roughly chronological order, with increasing compound specificity from section to section. Where possible I grouped compounds of interest (and their syntheses) together so that if a reader is, for example, interested in hydrogenative syntheses of HFC-**134a**, they need not read the entire

section on hydrogenative syntheses of hydrofluoroethanes to find every example. Also discussed in brief within the text is the turbulent regulatory environment within which refrigerant manufacturers operate. Though the chemical industry at large is typically subject to strict regulations, the effect these have had on the refrigerant industry is especially acute.

The introductory pages of the Review also contain a summary of the American Society for Heating, Refrigeration, and Air-Conditioning Engineers (ASHRAE) nomenclature for refrigerants: an alphanumeric system taking into account the number of double bonds, carbon atoms, fluorine atoms, and hydrogen atoms in the molecule, with declensions to account for isomeric variance. The ubiquity of this nomenclature (especially in patents) renders it essential learning for any prospective practitioner of this art. It will also be an essential preface for readers of this thesis, as I will be making use of ASHRAE names throughout. The word-wise economies to be gained by this decision will be made inescapably evident to the reader as the document progresses.

Lastly, the aforementioned review in its full and comprehensive form is itself nearly doctoral thesis-length. Thus, to save readers of this document from so great a demand as reading *Fluorocarbon Refrigerants and their Synthesis* in its entirety—an undertaking for which I express an undying gratitude to my peer reviewers at *Chemical Reviews*—I have taken *verbatim* only those parts which are explicitly germane to the novel works presented in this thesis—namely, Sections 2.2–2.6. In many ways, the Review stands alone as an independent supplement to this thesis, but nonetheless is a recommended accompaniment

for readers who are more deeply interested in the field of fluororefrigerants at large but who would otherwise be deterred by a literature so heavily patent-centric.

2.2 Fluorinated Refrigerants and their Syntheses: Past to Present

The field of fluoro-organic chemistry has received unprecedented levels of attention from the organic chemistry community in recent years. The discipline's increased favor in recent times can be explained principally by the increase in the number of pharmaceutical and agricultural agents containing fluorinated substituents, and the commensurately emergent interest in the installation of such substituents by late-stage reactions. These reactions, however interesting from the point of view of the medicinal chemist, have curried little favor from the organofluorine *process chemist* tasked with developing new routes to small (C_1–C_4) fluorocarbons for such applications as those reflected in the title of this review. This disparity is attributable substantially to the high costs (and often poor atom-economy) of these new and fashionable fluorinating (or fluoroalkylating) agents, which cannot be borne by original halocarbon manufacturers or their customers; unlike active pharmaceutical ingredients, refrigerants are highly commoditized bulk products and their buyers are price-sensitive above all else. For this reason, the methods to be outlined herein (as published primarily in the patent literature) make no mention of such modern fluorochemical implements as [R^FCu], *XtalFluor*®, or *SelectFluor*®. Another important point that separates refrigerants (as well as blowing agents, foam expanding agents, and fluorinated working fluids—for the purposes of this

review, all of these applications are considered germane) from all other applications of fluoroorganic chemistry is their unique naming system, which will be described in detail prior to any discussion of refrigerant chemistry. The ASHRAE nomenclature is the simplest shorthand for small fluorinated molecules and is used generally by practitioners of the art, and therefore will be used almost exclusively in this review to refer to the compounds of interest. Section 2.4 is dedicated to introducing the reader to this system; for further assistance, the reader may conveniently refer to ***Appendix A–IV*** at the end of this thesis.

The Review is structured in order to separate refrigerants by both their *type* (CFC, HCFC, *etc.*) and their carbon-count. Within each subsection, the methodologies are presented to the reader in rough chronological order, in keeping with a time-oriented organization. The reader should note that the *entire* body of work performed by this industry spanning from the 1930s to present is in excess of that which is reasonably presentable in a single introductory chapter, and as such, I have summarized and tabulated the various methodologies (and catalyst preparations) from the patent literature, minimizing or omitting redundancies for the sake of sensible brevity and convenience. Still, among those examples presented, the reader will no doubt find consistencies from one system to the next, and in so-doing give grounds to this concision.

The scope of the Review includes all synthetic work targeted towards the preparation of C_1-C_4 compounds having at least one carbon-fluorine bond. In this regard, this article is *comprehensive*. It is *not* meant to be a comprehensive review of the

preparation of C_1-C_4 *halocarbons* (including chlorocarbons and hydrochlorocarbons), though they are relevant as starting materials for fluorocarbon synthesis and will thus be discussed in brief. Furthermore, this is not intended to be a review on halocarbon *blending*, though this practice is of massive importance to the industry, and will be visited briefly in Section 2.7. A less-comprehensive introduction to the field can also be found in a chapter of *Modern Fluoroorganic Chemistry* by Kirsch[1].

Another important aspect to the study of fluoro-refrigerants is that the primary source of information is the patent literature rather than common academic periodicals, an observation readily explainable by the relative diseconomies posed by this chemistry when conducted on a small (laboratory) scale. In light of the commercial origin of many of these references, the authors have opted to include in textual references not only the names of the authors involved, but the organizations they represent, so that the reader may better understand the important industrial players. The predominance of industrial practice in this sector is easily explained; for the same reason that purely academic labs would rarely (if ever) undertake the task of crude petroleum reforming, so too would they recoil from the pursuit of fluorination using anhydrous HF or SbF_5 at high temperatures and pressures. Another reason could simply be a general lack of interest on the part of academic researchers in using conditions they would deem to be excessively forcing in order to synthesize compounds which may be (in most cases) procured commercially in substantial volume and with little difficulty. The wide availability of many such compounds feeds a misconception in the academic community that their syntheses need

not be further improved or optimized, while in fact, it is just these syntheses which stand to receive the greatest benefit from even the most minor of improvements, with percentage-points of additional yield accounting for potentially tens of millions of dollars in savings annually by the original manufacturer. Such incremental improvements to pre-existing reactions, though scarcely found in the academic literature, are rich and diverse in the patent literature, and together tell a compelling story of the deceptively complex evolution of a relatively simple group of molecules, and all concomitant challenges faced thereby. These challenges, and the development of solutions thereto, constitute the foundation of the Review.

2.3 Refrigerant Characterization

For our purposes here, we will divide fluoro-refrigerants into four "generations" reflecting the relative order in which they gained popularity. This generational separation is also useful as a way to distinguish the refrigerants by their environmental performance, as will be discussed further in the chapter. It is worthwhile to note that, though they are outside the scope of this thesis, non-fluorinated gases have been used as refrigerants in the past. Herein, these legacy models will be referred to as *"zeroth-generation"* refrigerants, a classification which includes all non-fluorinated gases used in applications where fluoro-gases are now used. A subset of the zeroth-generation refrigerants is comprised by the so-named "natural refrigerants" which include such naturally-occurring atmospheric molecules as carbon dioxide (R-**744**), ammonia (R-**717**), nitrous oxide (R-

744a), and sulfurous anhydride (R-**764**). Other notable zeroth-generation refrigerants are isobutane (R-**600a**), propane (R-**290**), ethylamine (R-**631**), and ethyl ether (R-**E170**). The reader may immediately note that the aforementioned molecules have properties which would, for obvious reasons, be undesirable in many refrigeration applications. For instance, one can imagine the dangers of a leaky ethyl ether refrigerator in a kitchen equipped with a natural-gas range, or the toxicity hazards that would result from an air-conditioner leaking SO_2 or NH_3 into one's home ventilation.

The first-generation refrigerants are comprised of molecules known collectively as the *chlorofluorocarbons* (CFCs); these are perhaps the most well-known (and historically notorious) refrigerants, as they were the first fluorinated gases to be manufactured in significant quantities. Members of this class are renowned for being outstandingly non-toxic, however, it is their environmental impact[2] that afforded them their notoriety in popular culture, namely in the depletion of atmospheric ozone at the Earth's poles. Due to this effect, the EPA has issued legislation which prohibits their use except in very specific situations. Notwithstanding, the reader should not allow the popular defamation of CFCs to overshadow their historical importance to the development and advancement of the field of organofluorine chemistry, and more broadly, of human civilization. Consider, for example, the reliance of human settlements in forbiddingly hot climates on the ability to preserve food and water for extended periods of time—a feat not possible without the ability to electrically conjure the cold.

The parameter known as *ozone-depleting potential* (ODP) arises from the evolution of chlorine radicals in the upper levels of the atmosphere, which *catalytically* convert two equivalents of ozone to three equivalents of molecular oxygen. Once this effect was recognized and finally accepted,[3] regulating bodies pressured manufacturers towards refrigerant models in which *some* C–Cl bonds were replaced by C–H bonds. These models together comprise the second-generation refrigerants, known as *hydrochlorofluorocarbons* (HCFCs). Though CFCs and HCFCs were originally first prepared nearly in parallel, the popularity of the latter only arose much later for the aforementioned reason. The impact of HCFCs on atmospheric ozone is significantly lower than that of the CFCs. For example, dichlorodifluoromethane (CFC-**12**) has an assigned ODP value of 1.00, while chlorodifluoromethane (HCFC-**22**) has an ODP of only 0.05—a 95% improvement afforded by merely substituting a *single* chlorine atom with hydrogen!

With the continuing interest of developing models that have *zero* ODP, the third-generation *hydrofluorocarbons* (HFCs) came into existence, which replaced *all* C–Cl bonds with C–H bonds. This push gave rise to the proliferation of 1,1,1,2-tetrafluoroethane (HFC-**134a**), one of the most ubiquitous fluorocarbons ever produced. This model has no impact on atmospheric ozone (ODP 0), but acts somewhat as a greenhouse gas (*global warming potential*—GWP—1,430) owing to the combination of C-F bonds which absorb in the infra-red region, and a resistance to degradation that affords such compounds a long atmospheric lifetime. With this discovery, refrigerants now have *two* environmental key performance indicators (KPIs) to minimize: ODP and GWP.

The minimization of these two indices has been met mainly by the fourth-generation *hydrofluoroölefins* (HFOs), which, though technically a subclass of HFCs, possess at least one C=C double bond. The reasoning behind the installation of this double bond is to impart a degree of atmospheric reactivity not present in earlier generations, thereby allowing the oxidized products to fall from the troposphere, preventing any significant build-up over time. Two of the most popular HFOs on the market today are isomers of tetrafluoropropylene (HFO-**1234yf** and HFO-**1234ze**). **1234yf** is a near-drop-in replacement for HFC-**134a**. Unfortunately, the reactivity imparted by the double bond also sacrifices some of the inertness to flame which made their progenitors so attractive for consumer products (ASHRAE Safety Group A2L, with low flammability—see Section 2.5). In a now-famous 2012 study[4] by Mercedes-Benz, HFO-**1234yf** was dispersed in the vicinity of hot components (namely, the exhaust system of the automobile) in a simulated serious head-on collision which severed the refrigerant line. Though **1234yf** ignites only with difficulty under laboratory conditions, the researchers at Mercedes-Benz demonstrated that in the simulated collision, this refrigerant *can indeed* ignite in an engine compartment at higher temperatures, and therefore the manufacturer opted not to transition from **134a** to **1234yf** until their safety concerns were resolved. The authors of the study described "a ball of fire, followed by a cloud of hydrogen fluoride gas" which then etched the car's windshield. The reader should note that only Mercedes-Benz has found any concern with the refrigerant's safety, and that automotive manufacturers within the SAE International group (comprising Audi, BMW, Chrysler/Fiat, Daimler,

Ford, GM, Honda, Hyundai, Jaguar/Land Rover, Mazda, PSA, Renault, and Toyota) have amassed a substantial body of data supporting the safety of **1234yf**. However, according to one **1234yf** manufacturer, Honeywell, the conditions of the Mercedes-Benz test were not realistic, and inflating airbags pose "100 times higher" danger to occupants in a collision than a **1234yf** leak.[5] The questions concerning the test's validity meant that it was not immediately accepted by other vehicle manufacturers, and it should be noted that several (including General Motors) have already incorporated **1234yf** into their modern product lines. Nonetheless, the test has sparked additional debate about the safety of **1234yf** and has spurred additional testing by automakers. The flammability parameter is of utmost importance in the mobile air-conditioner application, and this potential shortcoming continues to be an *Achilles' heel* for manufacturers of HFOs, especially **1234yf**, which is unendingly plagued by safety concerns raised by its flammability.

The flammability parameter can be minimized by blending; for example, the zeotropic R-**448A** blend (marketed by Honeywell as *Solstice*® N40) contains a quintenary mixture of HFCs **32** (26%), **125** (26%), and **134a** (21%) blended with HFOs **1234ze** (7%) and **1234yf** (20%). This blend satisfies the requirements for ASHRAE A1 designation, but has a GWP of 1,273—significantly higher than pure **1234yf** or **1234ze**. Similarly, Chemours markets R-**449A**—a zeotropic quaternary blend containing **134a** (25.7%), **125** (24.7%), and **32** (24.3%) with **1234yf** (25.3%))—as *Opteon*™ XP40 with an ASHRAE A1 safety designation. This product is also sold by Arkema as *Forane*® **449A**. Like R-**448A**,

however, the composition of this blend is *predominantly* HFC, thus the low GWP property of the **1234yf** is sacrificed to some extent in favor of the non-flammability.

The desire to restore this non-flammability has also led manufacturers to revisit the C–Cl bond in their products (for blowing agents in particular), as the short atmospheric lifetimes of these compounds appear to minimize any negative impact borne by the chlorine atoms towards ozone concentrations. Thus, two currently popular models are *hydrochlorofluoroölefin* isomers of chlorotrifluoropropylene (HCFO-**1233zd** and HCFO-**1233xf**), both of which are non-flammable and are classified in safety group A1. Most current research in this field is focused on optimizing the syntheses of existing HFOs/HCFOs or developing new models within these classes to use as environmentally benign refrigerants and blowing agents. All other classes of compounds not belonging to any specific category, as well as their abbreviations, are located in Table 1. Despite the regulations around their production, CFCs and HCFCs are still useful for specific industrial applications, and in particular are often intermediates to HFOs or HCFOs. Thus, despite their highly-restricted commercial sale to non-industrial end-users, CFCs and HCFCs are still of great industrial interest, and their syntheses are foundationally worth studying for any practitioner of organofluorine chemistry.

Table 2.3.1: Classifications of halogenated hydrocarbons used in this text

Compound Class	Abbreviation
Chlorofluorocarbon	CFC
Hydrochlorofluorocarbon	HCFC
Hydrofluorocarbon	HFC
Hydrochlorocarbon	HCC
Hydrofluoroölefin	HFO
Hydrochlorofluoroölefin	HCFO
Chlorofluoroölefin	CFO
Hydrochloroölefin	HCO
Perfluorocarbon/Perfluoroölefin	FC

2.4 ASHRAE Nomenclature and Safety Designations

Most patents and marketing materials describe small fluorinated molecules using a system of nomenclature devised by the ASHRAE. This taxonomy is designed to act as a non-proprietary shorthand so as to obviate any ambiguity concerning the contents of a refrigerant product regardless of its manufacturer of origin. Please consult ***Appendix A-IV*** for a comprehensive list of ASHRAE numbers for compounds of C_1 through C_3 used in this text.

In most marketing materials, major OEMs typically substitute a brand name in place of the "R-" abbreviation as a way to distinguish their own products from those of competing manufacturers. For example, Du Pont originally marketed CFC-**12** under the brand name *Freon® 12*. The marketing of this product was so successful that the reader will likely recognize the term *Freon®* which—after having been entrenched in the public vernacular—is often used by laymen as a catch-all synonym for any "refrigerant gas." This

section will instruct the reader on the identification of fluorinated compounds by their ASHRAE number (Figure 1). Figures first showing these new compounds will denote the ASHRAE number beneath their structure. Details concerning the naming convention are available in literature published directly by ASHRAE, but an equally useful and abridged version has been published in a letter by Deiters[6], the contents of which are hereto briefly summarized.

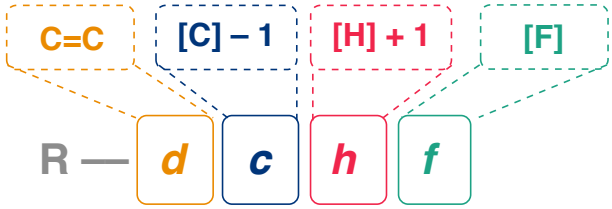


Figure 2.4.1: ASHRAE refrigerant numbering system

All refrigerants are assigned a four-figure *R-number* composed of variables *d, c, h,* and *f,* representing (respectively) the number of double bonds, the number of carbon atoms less one, the number of hydrogen atoms plus one, and the number of fluorine atoms. If any number ends up being zero, it is deleted, unless it follows a nonzero number. Consider the example of chlorodifluoromethane—$CHClF_2$; with no double bonds, one carbon atom (less one gives zero), one hydrogen atom (plus one gives two) and two fluorine atoms, the R-number is 22. The compound is a hydrochlorofluorocarbon, so it is fully abbreviated as HCFC-**22**. Suppose that a bromine atom was substituted for the chlorine atom; the name must be amended to reflect this, and thus a B-number is appended to the R-number as originally assigned; therefore, $CHBrF_2$ is R-**22B1**. The same applies for iodo-congeners, only instead of R-**22B1** it would be R-**22I1**. If the compound is cyclic, the

letter *c* is added *before* the R-number, such as for perfluorocyclobutane—C_4F_8—which is called FC-**c318**. Alternatively, the number can follow the prefix *cyclo*, as in *cyclo*-**318**. With an increasing number of carbons there arises the issue of constitutional isomerism. The R-numbering system has undergone two evolutions to deal with this added complication. First, for two-carbon refrigerants, the letters *a*, *b*, or *c* are simply added to the end of the R-number as the compound becomes less symmetrical (with *a*, *b*, and *c* moving in order from most to less symmetrical); the most symmetrical isomer is not accompanied by any letter. For example, there are two isomers of tetrafluoroethane; the symmetrical isomer CHF_2–CHF_2 is known as HFC-**134**, while the (more common) unsymmetrical isomer CF_3–CH_2F is known as HFC-**134a**. Occasionally there are additional isomeric possibilities which complicate matters; these situations often bring some ambiguity as there is sometimes disagreement among practitioners as to the symmetry order. For example, chlorodifluoroethane has three constitutional isomers: CHF_2–CH_2Cl, CHClF–CH_2F, and $CClF_2$-CH_3. Most readers would likely agree that the third isomer is decidedly the least symmetrical (HCFC-**142b**), with all of the halogens on one carbon, but which of the first two is the least symmetrical? By distribution of mass, the second is more asymmetric, but by dipole moment, the verdict falls to the first. In cases such as this, it is best to derive consensus from industrial marketing materials, in which the first isomer is commonly named HCFC-**142a**, and the second HCFC-**142**. Where ethers are concerned, a capital letter *E* is affixed to the beginning of the number. For smaller molecules, the same number may be used, as the positioning of the oxygen is

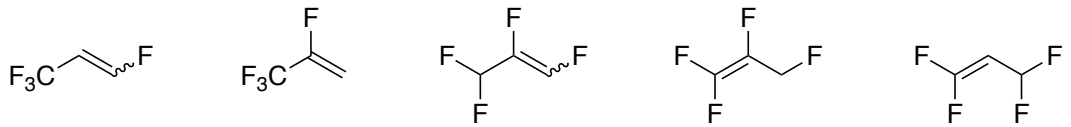
inferred. For example, CF_3OCHF_2, possessing the same number of carbons, hydrogens, and fluorines as **125** is simply named **E125**. The reader may notice that throughout the course of this review, some refrigerants have R-numbers that seem to defy the conventions laid out herein; the explanation for this deviation is that the names were assigned prior to the standardization of naming by ASHRAE, with their original monikers remaining in industrial use. Higher haloalkanes (C_3 and beyond) are more complex and possess far too many constitutional isomers for their nomenclature to be assigned simply on the basis of rudimentary symmetry arguments; therefore, different letters are suffixed to the R-number which describe specific C_1 fragments present in the molecule. These fragments are described in Table 2, along with their associated letter designations.

Table 2.4.1: Halocarbon molecular fragments and corresponding letter designations

Fragment	Designation		
CCl_2	a	$CHCl_2$	n
CClF	b	CH_2Cl	o
CF_2	c	CHF_2	p
CHCl	d	CH_2F	q
CHF	e	CHClF	r
CH_2	f	CH_3	s
CCl_3	j	C	t
CCl_2F	k	CCl	x
$CClF_2$	l	CF	y
CF_3	m	CH	z

For example, recall the aforementioned tetrafluoropropylene isomers which comprise the most popular HFOs today, of which there are seven in total (accounting for *cis/trans* isomerism). In the ASHRAE system, the *Z/E* letters are appended (in brackets)

at the end of the R-number to denote *cis* and *trans*, respectively. The five isomers (*cis/trans* isomerism not included) and their R-numbers are shown in Chart 1.



HFO-**1234ze** HFO-**1234yf** HFO-**1234ye** HFO-**1234yc** HFO-**1234zc**

Chart 2.4.1: Tetrafluoropropylene isomers and their ASHRAE names

The R-number/letter designations as stated here are functional through the 300s, but not the 400s, as R-400-series refrigerants are reserved for zeotropic blends of gases (R-**410A**, *e.g.* which corresponds to a 50/50 blend of difluoromethane (HFC-**32**) and pentafluoroethane (HFC-**125**)). Similarly, R-500-series refrigerants are normally reserved for azeotropic blends. The reader will no doubt observe that the letter suffix found in some R-400- or 500-series refrigerants is capitalized (*e.g.* R-**404A**). This is because the letter is added merely as a means to distinguish two or more blends with the same components in different ratios. Refrigerants with numbers in the 600s and 700s are reserved for legacy refrigerants, with the exception of propane, which is named R-**290** as per the normal convention. All blended refrigerants (as they may contain components belonging to varying classes) will simply be referred to using the R-prefix; the same convention is used for legacy refrigerants of the zeroth generation.

Nomenclature is just one of the functions of ASHRAE, but more importantly, the society is concerned with sustainability and safety in the field of heating, ventilation, and air-conditioning. ASHRAE has divided refrigerants into safety groups in terms of two key metrics: flammability and toxicity, with the verdict of the former being determined by the rate of flame propagation and the lower flammability limit (LFL) as determined by ASTM E681-04,[7] and the verdict of the latter being determined by permissible exposure limit (PEL). There are two toxicity groups: group A and group B, delimited by a PEL of 400 ppm, above which is the former group and below which is the latter. Formerly, there were two groups for flammability: Class 1 and Class 2, delimited by an LFL of 0.10 $kg \cdot m^{-3}$, below which is the former group and above which is the latter. More recently, a third group has been added as a sub-group to Class 2 in order to account for refrigerants having intermediate flammability (characteristic of many modern HFOs and some HFCs). Qualification for this intermediate group, known as Class 2L, is determined by fulfilling the criteria for Class 2, yet having a burning velocity of less than 10 $cm \cdot s^{-1}$. ASHRAE has defined many other standards that pertain to the deployment of refrigeration systems, however since these have more to do with refrigerant selection and mechanical compatibility rather than preparation, they are beyond the scope of this introduction.

2.5 EPA Regulations Regarding ODP and GWP

Owing to the ozone-depleting activity of first- and second-generation refrigerants, the EPA (under force by the Montreal Protocol) issued a ruling in 1992 requiring the gradual phaseout of Class I ozone-depleting substances by the year 2000,[8] Class I comprises eight groups of substances including assorted CFCs, brominated CFCs, and some HCFCs. Class II ozone-depleting substances are characterized by an ODP of less than 0.2, and are subject to a later phase-out than members of Class I; their usage must be reduced to at least 99.5% below baseline levels as of 2020, with culmination of the phaseout in 2030 in accordance with the Clean Air Act. The HCFC allowances first target the members of Class II with the highest ODP (HCFC-**141b**, HCFC-**142b**, and HCFC-**22**), and their production or import as refrigerants is to be prohibited as of the year 2020 (10 years in advance of the total HCFC ban in 2030).[9] The inclusion or exclusion of refrigerants in these classes is determined by a particular trend in their composition as it pertains to its behavior in the atmosphere: the greater the number of chlorine atoms, the more Cl radicals can be formed, and thus the higher the ODP value. A less obvious observation is that the greater the number of C–F bonds, the more potent a greenhouse gas the compound will be in the atmosphere, resulting in a higher GWP value. GWP is a function of the IR cross-section of the molecule, and thus models bearing fewer C–F bonds have attenuated activities as greenhouse gases. ODP and GWP values for various common CFC, HCFC, and HFC refrigerants are shown in Tables 3 and 4. The degradation pathways for CFCs and HFCs differ, with the former most easily losing Cl

radicals and the latter decomposing by C–H abstraction by hydroxyl radicals in the atmosphere. These alkyl radicals immediately react with O_2 to give acyl radicals, which can react with NO to liberate CO_2 and fluoromethyl-radicals which eventually leave the atmosphere as alcohols or acids.[10] Unfortunately, the addition of more C–F bonds renders the molecules resistant to degradation by this pathway, leading to suppressed reaction rates with atmospheric hydroxyl radicals, and thereby increasing atmospheric lifetime. This has led to the United States, Canada, and Mexico proposing an amendment to the Montreal Protocol requiring the downward regulation of HFC production and consumption to 15% of baseline by 2046.[11] In general, HFCs are more tolerated by regulatory bodies because of their lack of impact on atmospheric ozone, and thus they continue to be popular, especially considering their significantly lower cost of production than HFOs. HFOs in particular are characterized as having properties similar to HFCs, but with extremely short atmospheric lifetimes; HFO-**1234yf**, for example, has a lifetime of *ca.* 6 days (*cf.* 14 years for HFC-**134a**).[12] The main degradation product is the relatively innocuous trifluoroacetic acid.

Table 2.5.1: ODP, GWP, and atmospheric lifetimes of common CFCs and HCFCs

Formula	R-Number	ODP	GWP (100 yr)	τ_{atm} (years)
$CFCl_3$	CFC-**11**	1.000	4,750	45.0
$CBrClF_2$	CFC-**12B1**	7.100	1,890	16.0
CCl_2F_2	CFC-**12**	1.000	10,890	100.0
$CBrF_3$	CFC-**13B1**	16.000	7,140	65.0
$CHCl_2F$	HCFC-**21**	0.010	151	1.7
$CHClF_2$	HCFC-**22**	0.050	1,810	12.0
$CCl_2F–CClF_2$	CFC-**113**	0.800	6,130	85.0
$CClF_2–CClF_2$	CFC-**114**	1.000	10,040	300.0
$CClF_2–CF_3$	CFC-**115**	0.440	7,370	1,700.0
$CHCl_2–CF_3$	HCFC-**123**	0.020	77	1.3
$CHClF–CF_3$	HCFC-**124**	0.020	609	5.8
$CCl_2F–CH_3$	HCFC-**141b**	0.120	725	9.3
$CClF_2–CH_3$	HCFC-**142b**	0.070	2,310	17.9
CFC-**12**/-**114**	R-**400**	1.000	11,000	-

Table 2.5.2: ODP, GWP, and atmospheric lifetimes of common HFCs

Formula	R-Number	ODP	GWP (100 yr)	τ_{atm} (years)
CHF_3	HFC-**23**	0	14,760	270.0
CH_2F_2	HFC-**32**	0	675	4.9
CH_3F	HFC-**41**	0	92	2.4
$CHF_2–CF_3$	HFC-**125**	0	3,500	29.0
$CH_2F–CF_3$	HFC-**134a**	0	1,430	14.0
$CF_2H–O–CF_2H$	HFC-**E134**	0	6,310	26.0
$CF_3–CH_3$	HFC-**143a**	0	4,470	52.0
$CHF_2–CH_3$	HFC-**152a**	0	124	1.4
$CH_2F–CH_3$	HFC-**161**	0	12	0.2
$CF_3–CHF–CF_3$	HFC-**227ea**	0	3,220	42.0
$CF_3–CH_2–CF_3$	HFC-**236fa**	0	9,810	240.0
$CH_2F–CF_2–CHF_2$	HFC-**245ca**	0	693	6.2
$CHF_2–CH_2–CF_3$	HFC-**245fa**	0	1,030	7.6
125/**143a**/**134a**	R-**404**	0	3,900	-
32/**125**	R-**410**	0	2,100	-

Of the compounds on the second list, it may be said that they are superior to the first and second-generation candidates (due to their lack of ODP), but many of them

retain the high GWP afforded by the increase in the number of fluorine atoms (cf. CHF_3 at 14,760 vs. CH_3F at 92). Of those surveyed here, HFC-**134a** is undoubtedly the most popular, alongside its blend R-404, as its GWP and atmospheric lifetime are reasonable. Another good candidate is HFC-**152a**, which has a 91% lower GWP than **134a**, and an atmospheric lifetime of less than two years. In fact, **152a** has been touted as a suitable alternative automotive refrigerant to replace the former model under SNAP.[13] Its only drawback is its high C–H to C–F bond ratio, which leads to flammability concerns (safety group A2), especially in vehicle air-conditioner units.

Finally, OEMs must constantly monitor the changing requirements imposed by EPA-like federal agencies in other countries to ensure product compliance. This includes (non-exhaustively) the European Environment Agency (EEA, European Union), the Department for Environment (United Kingdom), the Environmental Assessment Agency (Canada), and Ministry of the Environment (Japan), for example.

2.6 The Ideal Refrigerant

The development of ideal halocarbons from an HSE perspective is a compromise between the three elements of hydrogen, chlorine, and fluorine. This can be visualized using a triangle as depicted by Calm (Figure 2.6.1).[14] Simply, if one desires low (or no) flammability, this can be achieved by increasing the number of fluorine and chlorine atoms. Doing so, however, compromises the environmental property of GWP (in the case of fluorine) and ODP (in the case of chlorine). Eliminating C–F bonds altogether lowers

GWP, but increase ODP and toxicity. Eliminating all halogens altogether minimizes toxicity and environmental impact, but maximizes flammability. Eliminating hydrogen atoms completely (first-generation) minimizes flammability and toxicity but maximizes atmospheric impact. Thus, the HSE performance indices are at continual odds with one another. Calm and Didion observe that when the ratio of hydrogen to halogen is at least 0.5, the resulting compound will be at least marginally flammable.[15]

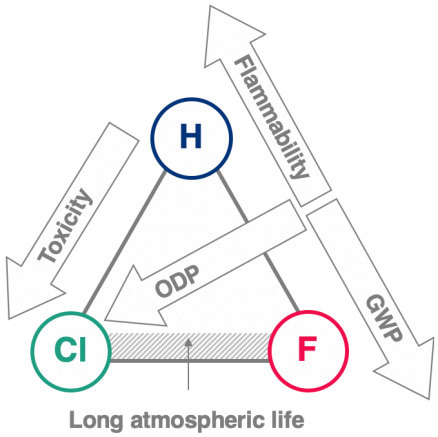


Figure 2.6.1: Balancing the properties for the ideal halocarbon [14]

Furthermore, the ideal refrigerant also possesses a certain set of thermophysical properties. The simplest trend in popularity is observed for boiling point (at atmospheric pressure, Figure 2.6.2).[16] The ideal boiling point range for refrigerants is between –45 and 0°C, and most popular refrigerant gases clearly follow this trend; even legacy models (such as methyl chloride, bp. -24.2^{o}C, and SO_2, bp. -10°C) fall well within this range.

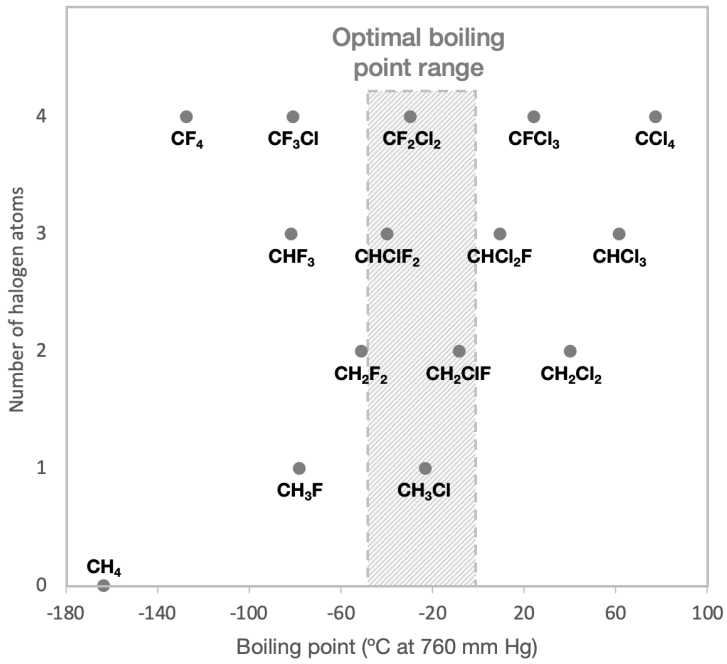


Figure 2.6.2: The optimal boiling point of refrigerants, with halomethane examples

Though there have been tabulated countless thermophysical performance indicators for halocarbons, their suitability for refrigeration can be expressed most succinctly by their *coefficient of performance (COP)*, which is simply the ratio of the amount of heat removed by the system over the amount of work performed to remove said heat. COP is usually measured in kW/kW terms for small units, but in larger chiller installations, it is expressed in terms of kW per refrigeration ton (where one refrigeration ton is 12,000 BTU/h). In other words, one refrigeration ton is the amount of heat required to melt 1 ton (2000 lbs.) of ice in 24 h. When referred to in kW/ton terms, the COP is also called the *specific power*. The ideal refrigerant maximizes the physical properties

contributing to COP, while minimizing flammability, environmental impact, and toxicity (Table 2.6.1).

Table 2.6.1: Selected single-compound refrigerants and their physical characteristics

Name	Formula	bp. (°C)	Vapor pressure	Safety Group
CFC-**12**	CF_2Cl_2	–29.8	84.7 psia @ 21°C	A1
HCFC-**22**	CF_2HCl	–41	137 psia @ 21°C	A1
HCFC-**142b**	$CF_2Cl–CH_3$	–9.2	45 psia @ 21°C	A2
HFC-**32**	CF_2H_2	–51.7	199.7 psia @ 21°C	A2L
HFC-**23**	CF_3H	–84	663.7 psia @ 21°C	A1
HFC-**152a**	$CHF_2–CH_3$	–24.7	77.7 psia @ 21°C	A2
HFC-**134a**	$CF_3–CH_2F$	–27	96.3 psia @ 21°C	A1
HCFO-**1233zd*(E)***	$CF_3–CH=CHCl$	21	22 psia @ 30°C	A1
HCFO-**1233xf**	$CF_3–CCl=CH_2$	14	22.9 psia @ 25°C	A1
HFO-**1234yf**	$CF_3–CF=CH_2$	–28.3	88 psia @ 21°C	A2L
HFO-**1234ze*(E)***	$CF_3–CH=CHF$	–19	72.3 psia @ 25°C	A2L
HFO-**1336mzz*(Z)***	$CF_3–CH=CH–CF_3$	33.4	8.77 psia @ 20°C	A1

2.7 The difficulty (and opportunity) in developing drop-in replacements

As this thesis is being submitted in fulfillment of a degree in chemistry, and the aforementioned review was published in *Chemical Reviews*, little mention has been made of the concurrent development of actual refrigeration equipment. However, such OEMs are naturally the largest end-user of the products whose syntheses in which we are interested. When making the case for the utility of a new chemical invention, it is essential to identify the end-user(s) who could derive potential value therefrom. At the outset, the reader should note that not just any low-boiling gas can be charged into a domestic refrigerator or air-conditioner. These units are manufactured to a specification determined by their designated refrigerant charge, which is often an azeotropic (or near-azeotropic) blend of other refrigerants designed to attain a balance of thermophysical properties

targeted to the application of that particular unit. The demands of large-scale centrifugal chillers, for instance, are different than those in mobile air-conditioners in automobiles, just as the demands for an ultra-low-temperature freezer (such as those in which the Pfizer/BioNTech COVID-19 vaccine is stored) tasked with maintaining a stable internal temperature of –80°C are different than the demands for a conventional household refrigerator tasked with stably maintaining +4°C. In short, there is no such thing as a 'one-size fits all' refrigerant, and to market a new model as a 'drop-in' replacement for a previous model, the new model must mimic the thermophysical properties of its predecessor almost perfectly in order for the compressor to discharge its duties efficiently. This means that the market for such products is filled with niche applications and potential for new entrants with unique core value propositions. There exists an entire subdiscipline in the chemical refrigeration field involving the development of new binary, ternary, quaternary, and even quintenary blends of existing compounds which collectively offer properties suitable for a target end-user, but which cannot be fulfilled by any of the constituent compounds in their pure form. In a 'best of both worlds' approach, blends can be used to combine desirable characteristics of each component compound. For instance, HFO-**1234ze** is partially-flammable (A2L), but when blended with 42% HFC-**134a**, the resulting zeotrope (R-450A) is non-flammable (A1). Referring to the aforementioned R-450A, the HFO component **1234ze** offers low-GWP, while the HFC component **134a** imparts non-flammability; the combination of the two results in a refrigerant with less flammability than pure **1234ze** and lower GWP than pure **134a**

(GWP_{100} = 547, *cf.* 1,430 for **134a**). Often, refrigerant blends are devised to mimic the properties of a single compound which is being replaced for environmental or safety reasons. For example, the blend R-508B (comprised of 46% HFC-**23** and 54% FC-**116**) was designed as a chlorine-free replacement for CFC-**13** in VLT cascade refrigeration units. Entire composition-of-matter patents are filed containing pages of such tabulated blends well in advance of their entry into the market. Name-wise, blended refrigerants either fall into the 400-series or the 500-series; this category of ASHRAE nomenclature is designed to separate azeotropes (500s) from zeotropes (400s).

The 400s often contain 3 or more constituents, and are susceptible to a property known as *temperature glide*. Pure compounds and azeotropes have a single definite boiling point, but zeotropes have a boiling *range*, from the bubble point (the point at which a refrigerant blend begins to boil) and the dew point (the point at which the last droplet boils away). This range is what is known as the *glide* of the refrigerant. Usually when referring to the normal boiling point of blends, the bubble point is referenced. High-glide refrigerants can have temperature differentials across the circulating coils such that if the air inlet is nearest the coldest region of the coil, unwanted frost builds up much more rapidly. Excess frosting ultimately requires a full system shutdown in order to defrost, lowering uptime. Furthermore, high-glide refrigerant blends can leak heterogeneously; this is to say that depending on where the leak occurred, a greater proportion of the lower-boiling constituent can escape, thereby altering the blend ratio and decreasing overall performance. However, high-glide refrigerants also have a potential operational benefit in

that their lower bubble point allows for the design of a system with a higher dew point temperature which reduces overall energy consumption. There are both zeotropes with a gentle glide (such as R-404A) and zeotropes with a high-glide (such as R-407A) available commercially, depending on the end-use case. There are several other factors to consider here, and as this is not an engineering-centered thesis, the reader is encouraged to refer to a useful practical guide[17] for more information on dealing with high-glide blends.

Table 2.7.1 shows a list of the most common non-HFO refrigerant blends, their constituent compounds, safety rating, replacements (if any), and their applications. The majority of these blends are HFC based, and are designed around the easy replacement of HCFC-**22** with non-ozone-depleting alternatives. This problem has been largely well-addressed by the market, with such offerings as R-427A or R-417A offering similar properties and in many cases requiring no oil changes on retrofitting. However, with the move to low-GWP options, there are increasingly demands to replace HFC-**134a** (and blends thereof) with HFO-based blends. Herein awaits the opportunity for improvement, as many HFO blends that have been put forth which include HFOs among their constituency still contain HFCs in order to mitigate the flammability of the former and achieve the coveted A1 safety rating. As mentioned before, they represent a compromise between the non-flammable HFCs which have a nonzero GWP and the moderately-flammable HFOs which have a near-zero GWP. Table 2.7.2. includes these latest-generation HFO-based blends.

Table 2.7.1: Common non-HFO refrigerant blends, boiling points, and applications

Name	Components	n bp.	Safety	Replaces	Applications
R-502	**22** (48.8%) **115** (51.2%)	–45.1°C	A1		Broad range low- and medium-temp. refrigeration systems including food service and ice machines
R-507A	**125** (50%) **143a** (50%)	–46.7°C	A1	R-502	Supermarket display cases, ice machines
R-508B	**23** (46%) **116** (54%)	–87.4°C	A1	**13**	Low-stage of low-temp. cascade systems
R-401A	**22** (53%) **152a** (13%) **124** (34%)	–33°C	A1	**12**	Medium-temp. commercial refrigeration systems
R-401B	**22** (61%) **152a** (11%) **124** (28%)	–34°C	A1	**12**	Low-temp. commercial and transport refrigeration systems, air-conditioning, dehumidification
R-404A	**125** (44%) **143a** (52%) **134a** (4%)	–46.5°C	A1	R-502	Broad range medium- and low-temp. refrigeration systems
R-407A	**32** (20%) **125** (40%) **134a** (40%)	–45.3°C	A1	**22**	Supermarket refrigeration, cold transport, food processing
R-407C	**32** (23%) **125** (45%) **134a** (42%)	–43.9°C	A1	**22**	Residential/commercial air-conditioners, non-flooded evaporator chillers
R-408A	**125** (7%) **143a** (46%) **22** (47%)	–44.9°C	A1	R-502	Broad range low- and medium-temp. refrigeration systems
R-409A	**22** (60%) **124** (25%) **142b** (15%)	–34°C	A1	**12**	Broad range medium- and low-temp. refrigeration systems
R-410A	**32** (50%) **125** (50%)	–51.7°C	A1	**22**	Residential and light commercial air-conditioning systems, heat pumps, dehumidifiers, and chillers. *Not a drop-in **22** retrofit.*
R-417A	**125** (46.6%) **134a** (50%) **600** (3.4%)	–38.4°C	A1	**22**	Residential and commercial air-conditioning systems including food service
R-427A	**32** (15%) **125** (25%) **143a** (10%) **134a** (50%)	–43.2°C	A1	**22**	Residential and commercial air-conditioning systems and heat pumps
R-438A	**32** (8.5%) **125** (45%) **134a** (44.2%) **600** (1.7%) **601a** (0.6%)	–42.3°C	A1	**22**	Residential and commercial air-conditioning systems

Table 2.7.2: Common HFO refrigerant blends, boiling points, and applications

Name	Components	n bp.	Safety	Replaces	Applications
R-513A	**1234yf** (56%) **134a** (44%)	–29.2°C	A1	**134a**	Medium-temp. chillers, air-conditioners, and heat pumps; ice rinks
R-514A	**1336mzz** (74.7%) **1130** (25.3%)	+29.1°C	B1	**123**	Low-pressure centrifugal chillers for commercial and industrial applications
R-515B	**1234ze** (91%) **227ea** (9%)	–18.9°C	A1	**134a**, **124**	Medium- and high-temp. commercial refrigeration systems
R-448A	**32** (26%) **125** (26%) **134a** (21%) **1234ze** (7%) **1234yf** (20%)	–46.1°C	A1	R-404A, **22**	Low- and medium-temperature refrigerant for supermarket applications and ice rinks
R-449A	**32** (24.3%) **125** (24.7%) **1234yf** (25.3%) **134a** (25.7%)	–46.0°C	A1	R-404A, R-507, R-407	Supermarkets, food service, cold storage, and other low- and medium-temp. commercial applications
R-449C	**125** (20%) **134a** (29%) **32** (20%) **1234yf** (31%)	–44.5°C	A1	**22**, R-407C	Residential and commercial air-conditioning, retrofit of existing systems
R-450A	**134a** (42%) **1234ze** (58%)	–23.4°C	A1	**134a**	Medium-temp. heat-pumps, chillers, vending machines, beverage dispensers, and CO_2 cascade systems
R-452A	**32** (11%) **125** (59%) **1234yf** (30%)	–47.0°C	A1	R-404A, R-507A	Refrigerated trucks, vans, containers, and other low- and medium-temp. commercial and industrial refrigeration
R-454A	**32** (35%) **1234yf** (65%)	–48.3°C	A2L	R-404A	Supermarkets, food service, cold storage, and other low- and medium-temp. commercial applications
R-454B	**32** (68.9%) **1234yf** (31.1%)	–50.9°C	A2L	R-410A	Residential and light-commercial chillers and air-conditioning, window-units, and portable units
R-455A	**1234yf** (75.5%) **32** (21.5%) CO_2 (3%)	–52°C	A2L	R-404A	Commercial low-temperature refrigeration, cold rooms, walk-ins
R-459A	**32** (68%) **1234yf** (26%) **1234ze** (6%)	–45.9°C	A2L	R-404A, R-407, **22**	Supermarkets, food service, and other commercial low-temp. refrigeration; heat pumps/water heaters
R-466A	**32** (49%) **125** (11.5%) **13I1** (39.5%)	–51.7°C	A1	R-410A	Stationary residential and commercial air-conditioning systems
R-470A	**1234ze** (44%) **125** (19%) **32** (17%) CO_2 (10%) **134a** (7%) **227ea** (3%)	–62.5°C	A1	R-410A	Low- and medium-temperature residential and commercial refrigeration systems, drop-in retrofit

As can be seen by the above table, the market has certainly provided end-users with options to replace pure-HFC blends with reduced-GWP HFC blends, and even some of these retain the A2L partial-flammability rating. Thus far, the blend that remains the most difficult to replace is R-410A, which—originally invented by AlliedSignal but licensed to producers worldwide—is the refrigerant of choice for residential air-conditioners. If you are reading this document and live in Japan, Europe, or North America, the chances are very good that your house or apartment is kept cool by R-410A. A proposed substitute is pure HFC-**32** which, strangely enough, is actually a component of R-410A. The GWP of pure **32** is lower than 410A (675, *cf.* 2,088 for 410A), but the flammability is higher, **32** being an A2L refrigerant. Chemours has proposed R-454B (Opteon™ XL41), which contains a mixture of HFO-**1234yf** and HFC-**32**—both A2L—and has a GWP of 466. While it is not a direct drop-in 410A replacement, Chemours states that 454B can be applied to equipment designed for 410A with only minor modifications. One major OEM (Carrier) has already selected R-454B for use in its new residential and light-commercial solutions.[18] Honeywell has proposed R-466A (Solstice™ N41) containing the iodocarbon **13I1** which—despite being a CFC congener—has an atmospheric lifetime of under one month (*cf.* 77 years for CF_3Br and 640 years for CF_3Cl) owing to the high reactivity of the C–I bond. R-466A has a commensurately reduced GWP of 733 and a safety classification of A1, having recently been also recognized as an "inert gas" by Japan's JSRAE.[19] Finally, Refrigerant Solutions has put forth R-470A as a retrofit replacement for 410A with an A1 safety rating and a GWP of 979. It is a rare hexenary blend whose

major (44%) component is HFO-**1234ze**, along with, interestingly, 10% CO_2. This gas was designed to comply with the European Union's F-Gas Regulations. The foregoing clearly shows that while improvements have been made, OEMs have had to resort to complex and exotic compounds and mixtures to attain properties which were taken for granted with HFC-based solutions. Furthermore, though HFO refrigerants in their pure form have no ODP and negligible GWP, they lag somewhat behind their predecessors in flammability and safety concerns. Simply put, the industry and regulating bodies have yet to coalesce, and there remains plenty of opportunity in the market for new contenders.

2.8 Fundamental Synthetic Tools

Throughout the text, the reader will notice that the synthesis of fluorocarbons is usually carried out using six general reaction types (Chart 2.8.1), and the subsections of each model generation are divided by the transformation used in the key step. The most common manipulation is *fluorination*, which, in the context of this thesis, refers to the exchange of a C–Cl bond for a C–F bond by action of HF, usually in the presence of a catalyst. Sometimes the HF is co-fed with Cl_2 in a process known as *chlorofluorination* which involves the single-step conversion of hydrocarbons to CFCs or HCFCs. This step bypasses the need to isolate such chlorinated materials as are described in ***Section 1.6*** of our review. Fluorination can be a key manufacturing step for all four generations of refrigerant compound. It is also possible to *oxidatively fluorinate* C–H bonds using elemental fluorine.

For compounds either containing hydrogen (HCFCs, HFCs, HFOs) or olefins, a hydrodehalogenation can be used (either using a metal reducing-equivalent in protic media or H_2 over a heterogeneous catalyst). C–Cl bonds are typically reduced before C–F bonds, so hydrodehalogenations are often employed in the synthesis of HCFCs and HFCs. Sometimes in practice, these are referred to as *hydrogenolysis*, especially when conducted at pyrolytic temperatures which usually involve formation of carbene intermediates. For olefinic compounds, *dehydrohalogenation* (also known as *elimination*) steps are employed. These can be carried-out in the traditional way, which is to say in a biphasic mixture of aqueous alkali and halocarbon in the presence of a phase-transfer agent (Aliquat® 336, most commonly), or by thermal cracking in the gas-phase over a heterogeneous catalyst. Thermal dehydrohalogenation is a frequently-encountered side-reaction in gas-phase fluorinations, which are often carried out at cracking temperatures. Sometimes this is beneficial, such as in the direct transformation of saturated hydrochlorocarbons to unsaturated hydrofluoroölefins or hydrochlorofluoroölefins by a single fluorination step.

For C_3 and C_4 products, *Kharasch* or *Prins additions* are often employed. This manipulation involves the addition of a C–X bond to a π-system in the presence of a catalyst (radical initator such as $CuCl_2$ in the case of Kharasch, or Lewis acid such as $AlCl_3$ in the case of Prins) in the liquid-phase. For example, the addition of CCl_4 to olefins is a particularly useful means to install a trichloromethyl group which can be subsequently fluorinated to a trifluoromethyl group.

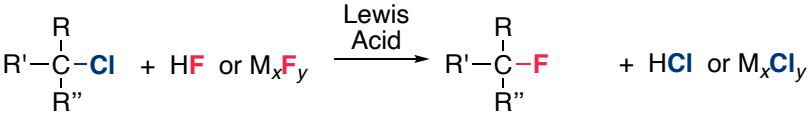
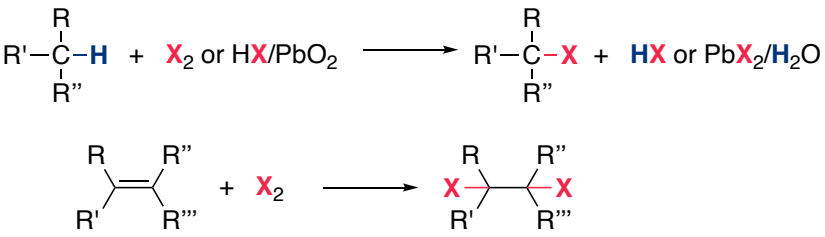
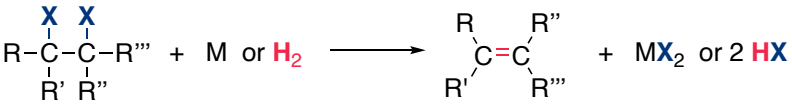
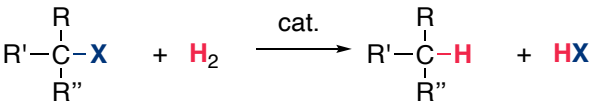
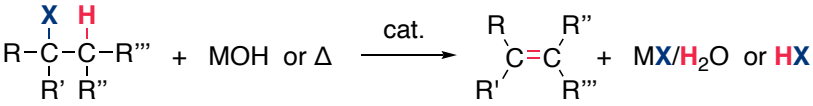
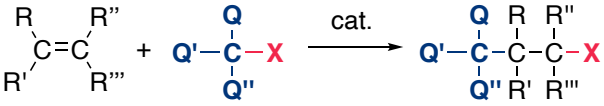
FLUORINATION	
OXIDATIVE HALOGENATION	
DEHALOGENATION	
HYDRODEHALOGENATION	
DEHYDROHALOGENATION	
KHARASCH/PRINS ADDITION	

Chart 2.8.1: The six most common reactions used to prepare fluorocarbons

2.9 Fluorination Fundamentals

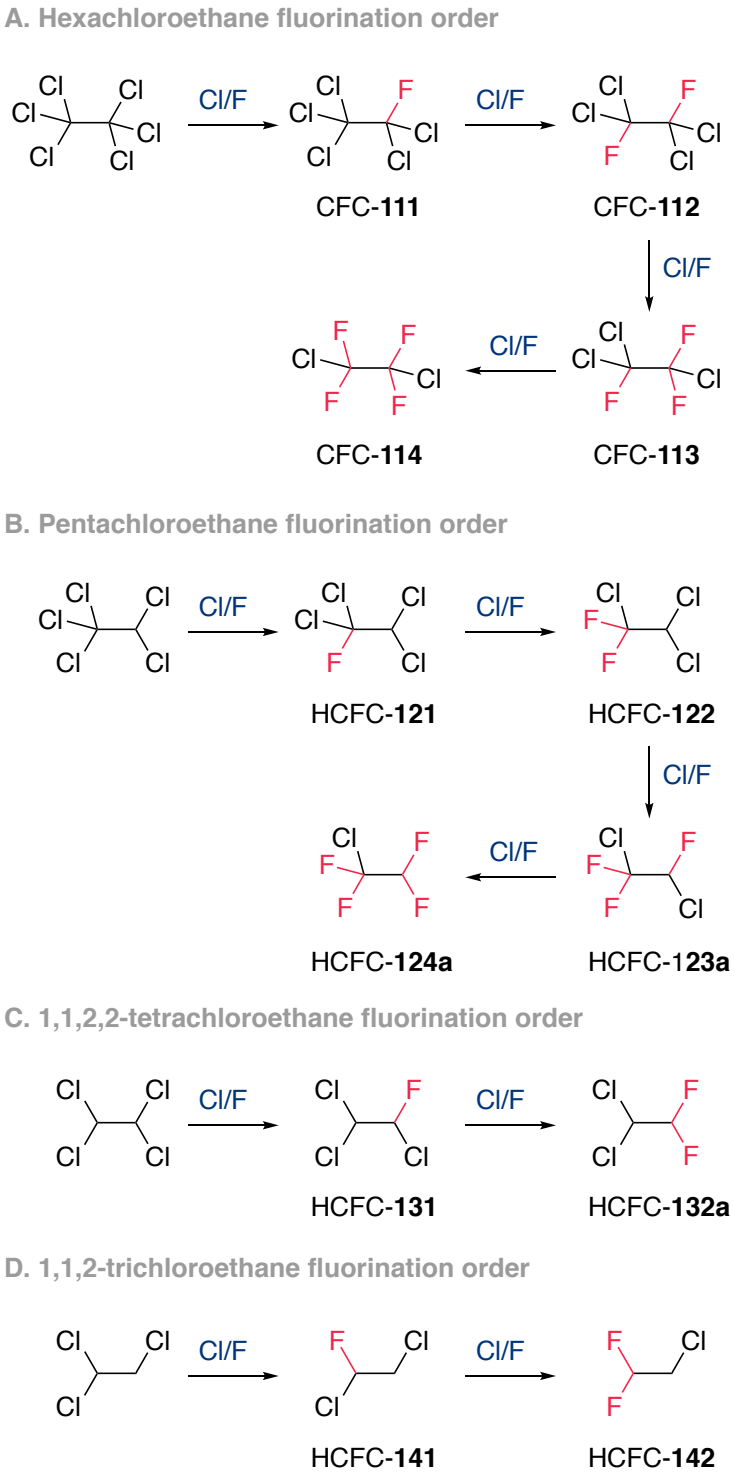
The Swarts Fluorination is by far the most common method of installing C–F bonds and is featured throughout all sections of our review. This type of reaction is commonly referred to as such in honor of its inventor, Belgian chemist Frédéric Jean Edmond Swarts, who first reported the use of pentavalent chlorofluorides of antimony as fluorination catalysts (and trivalent antimony fluorides as stoichiometric reagents) in 1892.[20] SbF_3 is easily synthesized from the chloride and hydrofluoric acid.[21] This is a

suitable juncture then to outline the characteristics (and more importantly, limitations) of these procedures that serve as the framework for most patented innovations pertaining to fluorination. The limitations of Swarts chemistry are bounded by the stability influenced by the presence of a particular number of fluorine atoms in a molecule, especially in a certain ratio to chlorine atoms. These relative product stabilities are discussed in detail by Henne and Midgley,[22] whose report on the matter will be summarized here in brief. They described difluorodichloromethane (CFC-**12**) as being an outstandingly inert molecule, mentioning that *"the fluorine in this molecule is not only quite inert but its presence seemingly strengthens the C–Cl bonds so that the chlorine is much less reactive than in any other similar chlorine compound such as CH_2Cl_2 or CBr_2Cl_2."* Interestingly, the stability of these compounds is not necessarily exclusively proportional to the number of fluorine atoms present in the molecule; for example, fluorides higher than amyl fluoride *"show a tendency to decompose spontaneously to hydrogen fluoride and ethylenic hydrocarbons."* Lighter alkyl fluorides (CH_3F, C_2H_5F, *e.g.*), however, are stable and distil without decomposition. Furthermore, 2° and 3° alkyl fluorides are so susceptible to dehydrofluorination that it is impossible to prepare them in pure form—that is to say, free of olefin/HF. Though the light alkyl monofluorides are sufficiently stable to distil, they are still substantially susceptible to hydrolysis (especially under acidic conditions). The tendency to lose HF also has a marked influence on the toxicity of alkyl monofluorides. According to Henne and Midgley, *"inhalation of a 30% concentration of ethyl fluoride in air (by volume) is needed to produce anesthesia and is*

invariably fatal; death is caused by a severe œdema of the lungs and upper respiratory tract [...] characteristic of hydrogen fluoride burns." Alkyl monofluorides are even less stable when vicinal; ethylene fluoride, for example, spontaneously decomposes at 0°C to two equivalents of HF and one equivalent of butadiene. However, certain functional groups are able to stabilize monofluorides; monofluoroethanol and monofluoroacetic acid are examples. Furthermore, the presence of other halogens on the same carbon dramatically increases the C–F bond stability, especially when the other halogen is also fluorine. For instance, CH_3Cl is more stable than CH_3F, but CH_2ClF is more stable than CH_2Cl_2, and CH_2F_2 is effectively inert. The presence of fluorinated groups adjacent to a halogen can also impart a dramatic stabilizing effect to normally easily activated bonds: 1-Bromo-2,2-difluoroethane, for example, is so resistant to hydrolysis as to require prolonged boiling with mercuric hydroxide to furnish 2,2-difluoroethanol. Henne and Midgley claimed that *"how far along the chain this influence is exerted cannot at present be definitely stated, but in propane derivatives it has been detected two carbon atoms away."*

Beyond being of basic interest as a chemical curiosity, the stabilizing effect of nearby fluorine atoms is of practical synthetic use in determining the order of fluorination of polychlorinated ethanes and propanes (Scheme 2.9.1). For example, in the fluorination of hexachloroethane with an excess of antimony fluorides, the most fluorinated product obtained is 1,2-dichloro-1,1,2,2-tetrafluoroethane (CFC-**114**). However, the use of precise stoichiometric amounts of fluorinating agent gives first pentachloroethyl fluoride (CFC-

111), then tetrachloroethylene difluoride (CFC-**112**), then 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-**113**), and finally CFC-**114**. Two important observations can be made here, the first of which being simply that no CF_3 groups can be formed by fluorination with antimony. Secondly, we can deduce an order of reactivity towards fluorination: $CCl_3 > CFCl_2 > CF_2Cl$. The transition from **112** to **113** is easily accomplished—requiring only room temperature and SbF_3 to proceed—thus illustrating that substitution of a single fluorine on an adjacent carbon is insufficient to impart the outstanding stability mentioned previously. The transition from **113** to **114**, however, requires heating to at least 140°C and the use of stoichiometric quantities of Sb(V) (in the form of SbF_3Cl_2). When fluorinating pentachloroethane similarly, the relative reactivities are as follows: $CCl_3 > CCl_2F > CHClF > CHCl_2$. The final product of the reaction is 1-chloro-1,1,2,2-tetrafluoroethane (HCFC-**124a**)—a compound with anaesthetic properties.[23] 1,1,2,2-tetrachloroethane fluorinates as far as 1,1-dichloro-2,2-difluoroethane (HCFC-**132a**), indicating that $CHClF > CHCl_2$. 1,1,1,2-tetrachloroethane fluorinates as far as 1,2-dichloro,1,1-difluoroethane (HCFC-**132b**), indicating a reactivity order of $CCl_2F > CH_2Cl$. Finally, 1,1,2-trichloroethane fluorinates as far as 1-chloro-2,2-difluoroethane (HCFC-**142**), indicating a reactivity order of $CHCl_2 > CH_2Cl$ and $CHClF > CH_2Cl$. In fact, the authors found it impossible to fluorinate any CH_2Cl group by means of antimony fluorides.



Scheme 2.9.1: Fluorination orders of chloroethanes

The authors sought to complete their theory of vicinal fluoride stabilization by demonstrating that *"reactants capable of transforming a CH_2Cl group into a CH_2F group*

fail to perform that transformation or are at least considerably retarded after the CH_2Cl group has been 'stabilized' by the presence of two fluorine atoms on the adjacent carbon." This was proven simply by using HgF_2 as the fluorinating agent, which fluorinates ethyl chloride with ease, and 1,2-dichloro-2-fluoroethane (HCFC-**141a**) with considerable difficulty yet fails to exert any effect on **142**. Even 1-iodo-2,2-difluoroethane is only fluorinated in poor yields by HgF_2 under prolonged heating at 160°C. It is worthwhile noting that HgF_2 still follows the same empirical reactivity order as shown in the SbF_3 reactions mentioned previously. HgF_2 is a stronger fluorinating agent than SbF_3, as described by Henne and Midgley in the paper[24] directly following their presently discussed study, and is capable of converting methyl chloroform fully to methyl fluoroform (HFC-**143a**). α,α,α-Trichlorotoluene also converts cleanly to α,α,α-trifluorotoluene, indicating that the stabilization in CF_2Cl imparted by the two fluorine atoms is overcome by the reactivity of the benzylic C–Cl bond.

A final observation in the report of Midgley and Henne pertains to the reduction of two-carbon CFCs/HCFCs by ethanolic zinc; the C–F bonds are substantially more resistant to reduction than C–Cl bonds, and the presence of additional C–F bonds renders the saturated compounds more resistant to dehalogenation overall. The authors claim that though it is easy to obtain compounds such as fluorotrichloroethylene and 1,2-dichlorodifluoroethylene by this means, it is difficult to similarly obtain compounds such as chlorotrifluoroethylene or 1,2-chlorofluoroethylene in reasonable yields. Finally, it is exceedingly difficult to obtain tetrafluoroethylene (TFE) by dechlorination of CFC-**114**,

the reaction proceeding only so far as 30-35%. The observations by Henne and Midgley are critical in understanding the impetus behind the progress and innovations of the fluororefrigerant industry as they will be presented here; in particular, the shift from CFCs to HCFCs and ultimately HFCs required the development of reagents and/or catalysts which would overcome the stabilizing effects described by Midgley and Henne in order to prepare, for example, chlorotrifluoroethane (CFC-**13**) or 1,1,1,2-tetrafluoroethane (HFC-**134a**) in a high yield and with good selectivity.

2.10 Relevance to the Present Work

The foregoing should have provided the reader with a suitable foundation with which to assess the novel works being presented herein. It is my hope that this section, though brief and topical compared to the *Chemical Review* from which it is derived, has convinced the reader of the importance of this field as a subset of organofluorine chemistry, despite a chronic underrepresentation in the academic milieu. In particular, the reader should have assimilated that though the proverbial environmental goalposts continue to shift, the strict requirement remains that fluororefrigerants possess no danger to humans (be it by toxicity or by flammability) as enshrined by their CFC progenitors nearly a century ago. The current HFOs available on the market satisfy the environmental requirement, but are plagued by other issues such as high-cost, moderate flammability, and high boiling points, thereby necessitating their formulation in blends with other, lower-boiling and more inert molecules which are less environmentally benign. While this

thesis could not possibly aim to address all of the above concerns, it has been my goal throughout this work to contribute both novel compounds and more economical routes for their synthesis, especially utilizing organometallic catalysis. In ***Chapter 3***, the reader will be introduced to routes to fluorocarbons derived from fluorinated metallacyclopentanes of nickel, and a novel Ni-catalyzed transformation which leverages past technology to furnish a 4th-generation product from vinylidene difluoride (VF2). In ***Chapter 4***, the reader will be introduced to hydrodefluorinative (HDF) routes to HFOs, whereby perfluorinated or otherwise polyhalogenated compounds are selectively reduced to hydrofluoro- or hydrochlorofluoro-derivatives of greater value, with specific focus on obtaining HFO-**1234yf** from HFP using an organophosphine in substoichiometric quantity and a silane as the terminal reductant. ***Chapter 5*** builds on the HDF theme, but this time focuses on [CuH] technology previously developed in our group, and more specifically, the scalability thereof using cheaply-available and air-stable Cu precursors and siloxane reductants. Also in ***Chapter 5*** can be found the début of a novel Cr-based catalyst system which provides unpredecented selectivity for a new and potentially exciting refrigerant candidate—1-chloro-1,2-difluoroethylene, HCFO-**1122a**—starting from readily-available chlorotrifluoroethylene (CTFE). Finally, ***Chapter 6*** contains a forward-looking perspective on the most fertile areas for growth in this industry, along with the potential (and yet largely unrecognized) opportunity for contributions from academic researchers.



2.11 References

(1) Kirsch, P. Part III Applications of Organofluorine Compounds Halofluorocarbons , Hydrofluorocarbons , and Related Compounds. *Mod. Fluoroorg. Chem. Synth. React. Appl.* **2013**.

(2) Sayers, R. R.; Yant, W. P.; Chornyak, J.; Shoaf, H. W. *Toxicity of Dichloro-Difluoro Methane: A New Refrigerant*; 1930.

(3) Stoye, E. The Hole Story. *Chemistry World*. August 28, 2018.

(4) Davis, J. *Mercedes-Benz Independent Study Finds New Refrigerant to Be Dangerous*; Mercedes-Benz Corporate News, 2012.

(5) Ernst, K. Mercedes-Benz investigating refrigerant that caused "ball of fire" https://www.motorauthority.com/news/1081180_mercedes-benz-investigating-refrigerant-that-caused-ball-of-fire (accessed Mar 7, 2020).

(6) Deiters, U. K. Some Remarks on the Nomenclature of Refrigerants. *Fluid Phase Equilib.* **1997**, *132*, 265–270.

(7) (ASTM). *ASTM E681-04: Standard Test Method for Concentration Limits of Flammability of Chemicals (Vapors and Gases)*; West Conshohocken, PA, 2004.

(8) (EPA). FRL-4158-2 Protection of Stratospheric Ozone. *Fed. Regist.* **1992**, *57*, 33754–33798.

(9) EPA. FRL-9917-98-OAR Protection of Stratospheric Ozone: Adjustments to the Allowance System for Controlling HCFC Production, Import and Export, 2015–2019. *Fed. Regist.* **2014**, *79*, 64254–64290.

(10) Good, D. A.; Francisco, J. S. Atmospheric Chemistry of Alternative Fuels and Alternative Chlorofluorocarbons. *Chem. Rev.* **2003**, *103*, 4999–5023.

(11) Stratospheric Protection Division Office of Atmospheric Programs Office of Air and Radiation. Benefits of Addressing HFCs under the Montreal Protocol. *EPA 430-S-15-001* **2015**.

(12) Luecken, D. J.; Waterland, R. L.; Papasavva, S.; Taddonio, K. N.; Hutzell, W. T.; Rugh, J. P.; Andersen, S. O. Ozone and TEA Impacts in North America from Degradation of 2,3,3,3-Tetrafluoropropene (HFO-1234yf), A Potential Greenhouse Gas Replacement. *Environ. Sci. Technol.* **2010**, *44*, 343–348.

(13) (SNAP), E. Transitioning to Low-GWP Alternatives in Passenger Vehicle Air Conditioners. *EPA 430F14021* **2015**.

(14) Calm, J. M.; Didion, D. A. Trade-Offs in Refrigerant Selections: Past, Present, and Future. *Int. J. Refrig.* **1998**, *21*, 308–321.

(15) Calm, J. M. Options and Outlook for Chiller Refrigerants. *Int. J. Refrig.* **2002**, *25*, 705–715.

(16) Atwood, T. CFCs in Transition. *Int. J. Refrig.* **1988**, *11*, 234–238.

(17) Withouse, J. (Parker H. C. *System Considerations for Refrigerant Blends with Temperature Glide*; Form 5-492/22017; Washington, MO, 2017.

(18) Turpin, J. R. R-454B Emerges as a Replacement for R-410A https://www.achrnews.com/articles/143548-r-454b-emerges-as-a-replacement-for-r-410a (accessed May 22, 2021).

(19) (Honeywell Refrigerants). Honeywell Solstice N41 (R-466a) Nonflammable Refrigerant Receives Inert Gas Registration From Japanese Hvac Governing Body [Press Release] https://sustainability.honeywell.com/us/en/news-and-events/news/2021/04/honeywell-solstice-n41-r-466a-nonflammable-refrigerant-receives-inert-gas-registration-from-japanese-hvac-governing-body (accessed May 22, 2021).
(20) Wang, Z. Swarts Reaction. In *Comprehensive Organic Name Reactions and Reagents*; 2010; pp 2744–2747.
(21) Midgley, T. J.; Henne, A. L.; McNary, R. R. Manufacture of Antimony Trifluoride. US 2,024,008, 1931.
(22) Henne, A. L.; Midgley Jr., T. Reactivity and Influence of Fluorine in Aliphatic Compounds. *J. Am. Chem. Soc.* **1936**, *58*, 882–884.
(23) Larsen, E. R.; Ruh, R. P. Chlorofluoromethylfluoroform. US 2,951,102, 1960.
(24) Henne, A. L.; Midgley, T. Mercuric Fluoride, a New Fluorinating Agent. *J. Am. Chem. Soc.* **1936**, *58*, 884–887.

3

CHAPTER THREE

3. The Hydrodefluorodimerization (HDFD) Reaction

3.1 Introduction

THE work described in this section is a continuation of the work developed in my M.Sc research[1]. Though much of the original motive for the work was described in the afore-cited thesis, I found that this story is better told in its entirety, especially considering that the success of the original work is a large part of why I chose to forge ahead in my academic journey and pursue a Ph.D rather than leaving the academy after completing my M.Sc and M.Eng degrees. It was also responsible for curing and solidifying my foundational interest in fluorinated refrigerants, on which this entire thesis is based. For the sake of absolute clarity, where the original work ends and the present work begins will be clearly indicated in the course of this account.

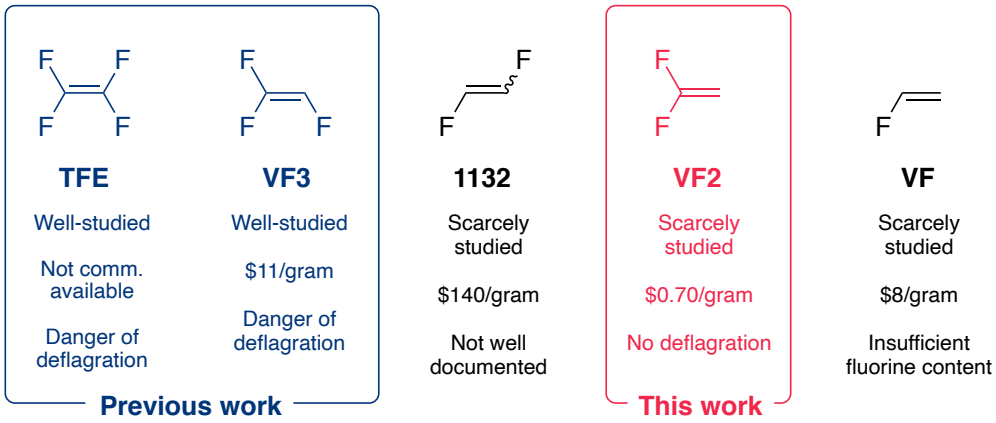


Chart 3.1.1: Possible fluoroölefins of study according to price, precedent, and hazard profile.

The original motive for the project was to expand our group's portfolio of fluoroölefin-derived metallacycles to include vinylidene difluoride (VF2). The decision to use VF2 was mainly based on a natural progression from tetrafluoroethylene (TFE) and trifluoroethylene (VF3), both of which were investigated earlier by past members of the Baker group. In particular, I was influenced by the work of K. Giffin, whose experiments with VF3 demonstrated a sharp departure from the norm in terms of the reactivity of the metallacycles derived therefrom. The presence of hydrogen in such metallacycles introduced two additional facets: the potential for regioisomers (head-tail, head-head, or tail-tail), and the observed ability to undergo β-F elimination (a property not previously observed with perfluoronickelacycles). VF2 thus represents a unique substrate to further probe these properties. Its much stronger dipole than VF3 could, I hypothesized, afford better head-tail regioselectivity, and the existence of $-CH_2-$ groups in its theoretical metallacycle might encourage β-F elimination as did the –CHF– groups in K. Giffin's

work. In addition, there are other more practical reasons why I diverted focus to VF2 instead of VF3, the foremost among which being relative cost and safety. Pure VF3 is notoriously prone to spontaneous polymerization and deflagration events,[2] though it has more recently been found to be stable in certain compositions with HCl[3], HFC-**32**,[4] or HFO-**1132***(E)*.[5] The dangers of pure VF3 also incur a monetary cost, with a 90-gram cylinder selling for nearly $1,000[3]. VF2, by comparison, presents no such hazards or hindrances, and polymer-grade material can be easily handled and shipped at low cost.

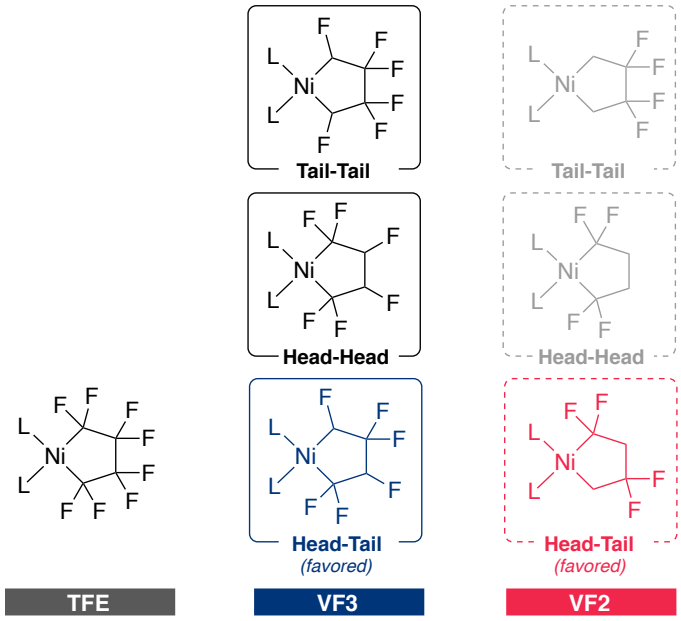


Chart 3.1.2: Fluorometallacycles and their regioisomers, with proposed VF2 products shown at right.

[3] Price in USD, from www.synquestlabs.com (PN 1300-3-05), accurate as of the time of publication

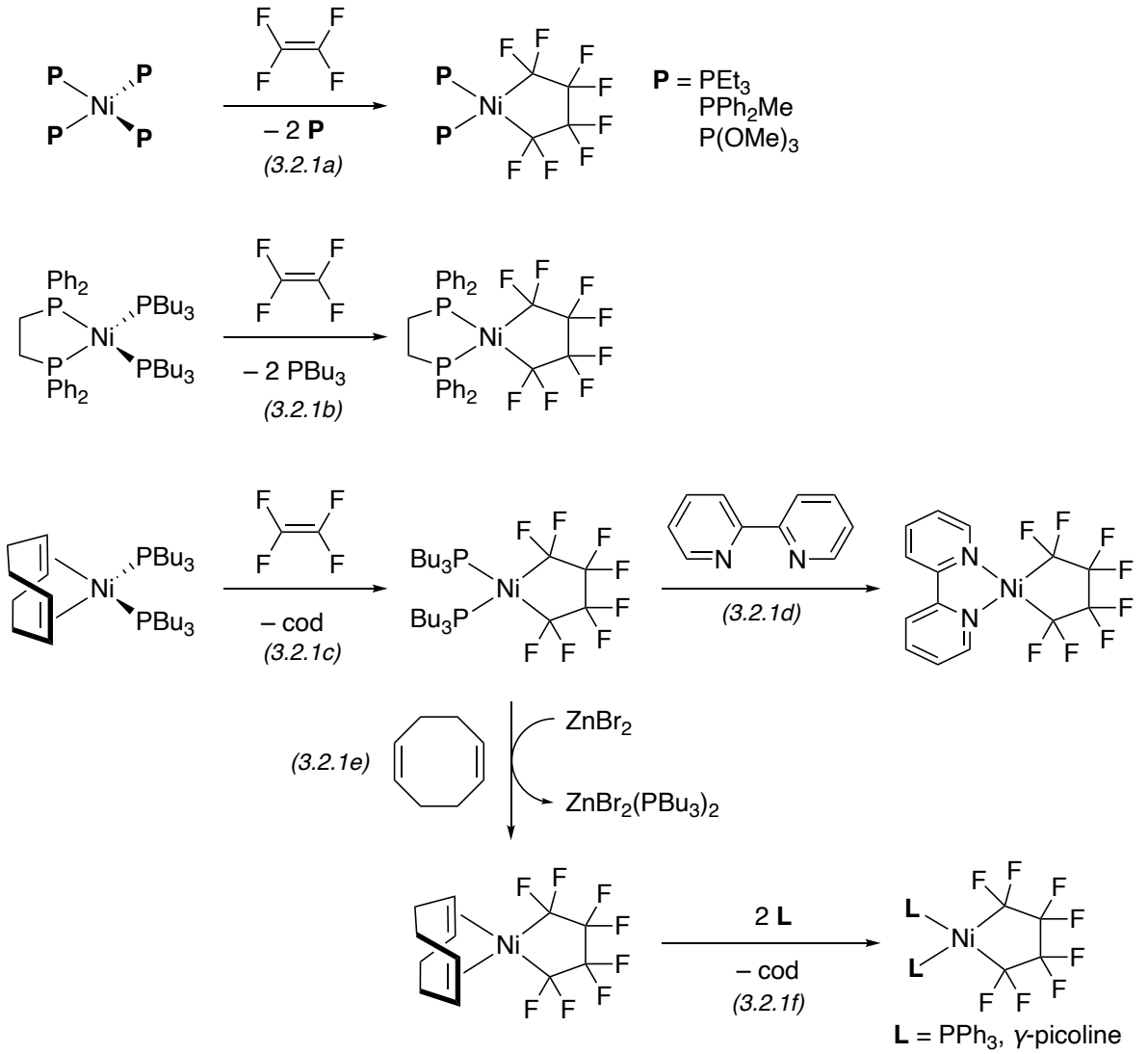
3.2 Prior Art

This section constitutes a comprehensive review of fluorinated metallacycles, provided in order to add context to the findings presented later in this chapter. Fluorinated metallacycles have a long history (dating back to the 1960s), and are best-known to form in reactions between zerovalent nickel and a fluorinated olefin (most commonly tetrafluoroethylene, TFE). Though possessed of a long history, fluorinated metallacycles were treated as little more than academic curiosities until their reactivity with H2 was leveraged subsequently by Baker et al. in the hydrodimerization reaction to be discussed in this section. The hydrodimerization, along with other examined reactions of fluorometallacycles, will be examined here in depth.

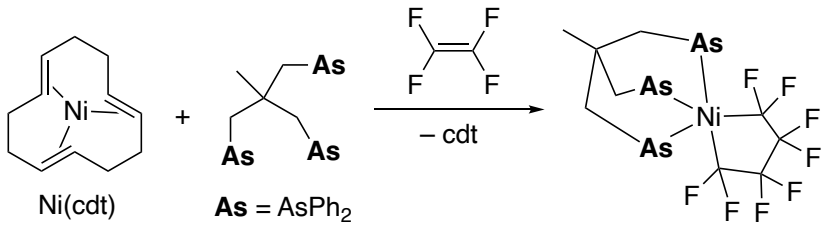
This introduction will begin with homo-nickelacycles (formed from two equivalents of the *same* olefin) and hetero-nickelacycles (formed from two or more equivalents of *different* olefins or other π-systems). Following these, an innovative non-olefin metallacycle precursor developed by Vicic will also be introduced, along with the ensuing non-nickel metallacycles. Finally, the prior reports of coördination chemistry of VF2 will be introduced, including examples on metals other than nickel. This extended prior art will serve as a suitable backdrop against which the reader can view the current work, and will also establish a relative continuum of reactivity between the fluoroölefins ranging from TFE to VF2.

The work done by my current and previous peers regarding metallacycles derived from fluoroölefins builds on the early work by Stone et al.[6] whereby two equivalents of TFE oxidatively cyclize with a zerovalent nickel complex to form perfluorometallacyclopentanes which can then undergo various ligand substitutions (Scheme 3.2.1). Tetrakis-phosphine complexes $Ni(PEt_3)_4$ and $Ni(PPh_2Me)_4$ readily react with TFE with ejection of two equivalents of phosphine to form $[P_2Ni(\varkappa^2\text{-}CF_2)_4]$ complexes, while the tetrakis-trimethylphosphite Ni(0) precursor does so only on prolonged heating (eqn 3.2.1a). Tributylphosphine is selectively displaced from the heteroleptic $(dppe)Ni(PBu_3)_2$ to form $[(dppe)Ni(\varkappa^2\text{-}CF_2)_4]$ (eqn 3.2.1b), while the bis-tributylphosphine derivative is accessible from $[(cod)Ni(PBu_3)_2]$ by selective displacement of cyclooctadiene (eqn 3.2.1c). The PBu_3 in this product can be readily displaced by 2,2'-bipyridyl (eqn 3.2.1d), or—assisted by $ZnBr_2$ as a phosphine-scavenger—cyclooctadiene (eqn 3.2.1e). The resulting cyclooctadiene complex is labile and can be substituted by PPh_3 or γ-picoline (eqn 3.2.1f). The 5-membered metallacycle product is also obtained from Ni(*t*-BuNC)$_4$, but Ni(cdt) only gives a 3-membered $\pi\text{-}C_2F_4$ complex.[7] The $\pi\text{-}C_2F_4$ complex $[(PPh_3)_2Ni(\eta^2\text{-}C_2F_4)]$ (accessible by treatment of the aforementioned $[(cdt)Ni(\eta^2\text{-}C_2F_4)]$ with two equivalents of PPh_3) was also shown to undergo ring-expansion when treated with trifluoroethylene (VF3) to form a product formulated as $[(PPh_3)_2Ni(C_4F_7H)]$.[8] Similarly, tertiary arsine complexes of Ni(0) form products such as $[(PhMe_2As)_2Ni(\varkappa^2\text{-}CF_2)_4]$ when treated with TFE.[9] 5-coordinate pentagonal-bipyramid metallacyclopentanes could be obtained using $MeC(CH_2AsPh_2)_3$ (tdame, the arsine-

congener of tripod) as the ligand (Scheme 3.2.2).[10] The tdame ligand can be displaced by tripod to form the phosphine-congener of the same compound.

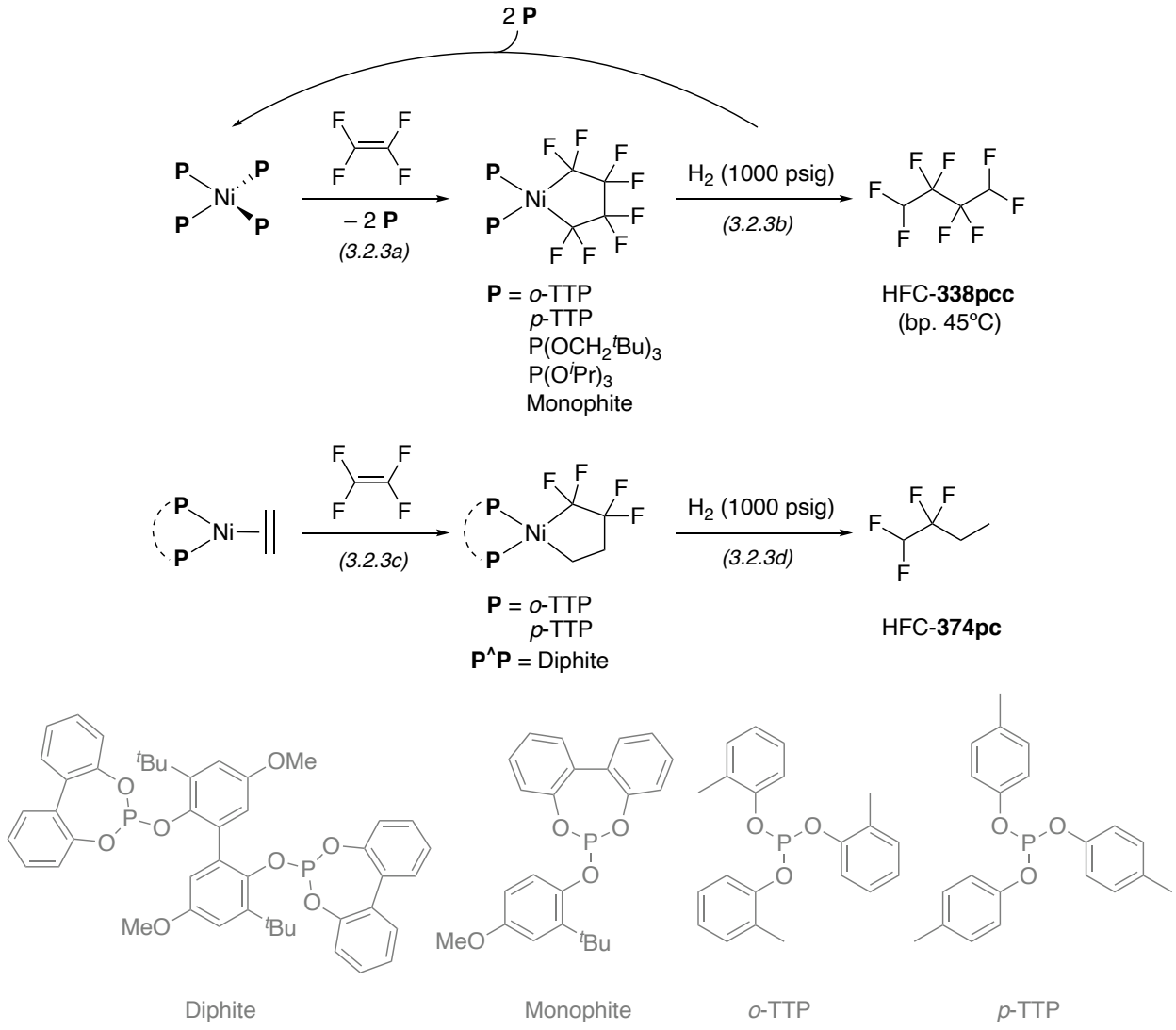


Scheme 3.2.1: Formation and manipulations of octafluoronickelacyclopentanes by Stone et al. [6]



Scheme 3.2.2: Preparation of a five-coördinate perfluoronickelacylopentane by Stone et al. [10]

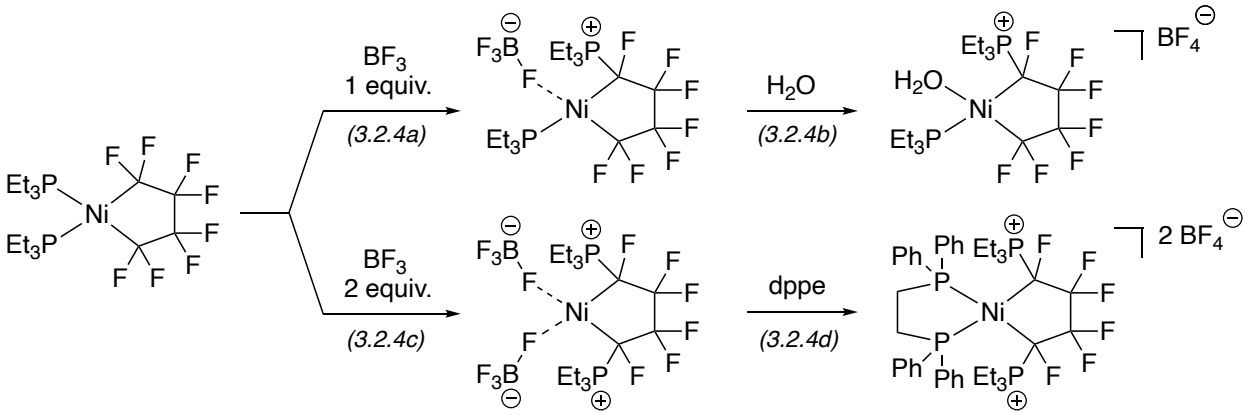
These metallacycles remained academic curios until the 1990s, when Baker et al. (Du Pont) expanded their syntheses to various bulky triaryl- and trialkyl-phosphites (locally available owing to their use as ligands for the Ni-catalyzed hydrocyanation reaction[11], also developed at Du Pont), and leveraged them for a new catalytic transformation: the Ni-catalyzed hydrodimerization of TFE to *1H,4H*-octafluorobutane (HFC-**338pcc**, Scheme 3.2.3).[12,13] Tetrakis(phosphite) nickel(0) complexes react with an excess of TFE as developed by Stone et al. to form perfluoronickelacycles (eqn 3.2.3a) which undergo hydrogenolysis at high pressure to the hydrofluorocarbon (eqn 3.2.3b). A mixed-olefin metallacycle comprising both TFE and ethylene is accessible if the [$L_2Ni(\eta^2$-$C_2H_4)$] precursor is used, which undergoes hydrogenolysis to the more hydrogen-rich HFC-**374pc** (eqns 3.2.3c and 3.2.3d). The hydrodimerization can be conducted catalytically by performing a series of TFE/H_2 cycles on a solution of NiL_4, or by pressurizing an autoclave with both TFE and H_2 simultaneously. HFC-**338pcc** (bp. 45°C) is useful as an inert, non-ozone-depleting precision cleaning solvent or component of a foam expanding agent blend.[14]



Scheme 3.2.3: Synthesis of phosphite-ligated perfluoro- and hydrofluoro-nickelacyclopentanes and their hydrogenolysis to C_4 HFCs [12]

Besides hydrogenolysis and ligand substitution, the study of perfluorometallacyclopentane reactivity has been largely centered on C_α–F bond activation, as first explored by Burch et al. in 1988 (Scheme 3.2.4). BF_3 abstracts an α-fluorine to form an electrophilic ylide intermediate (so-called by the authors) which is rapidly trapped by phosphine ligand migration. This can be done with either one (eqn

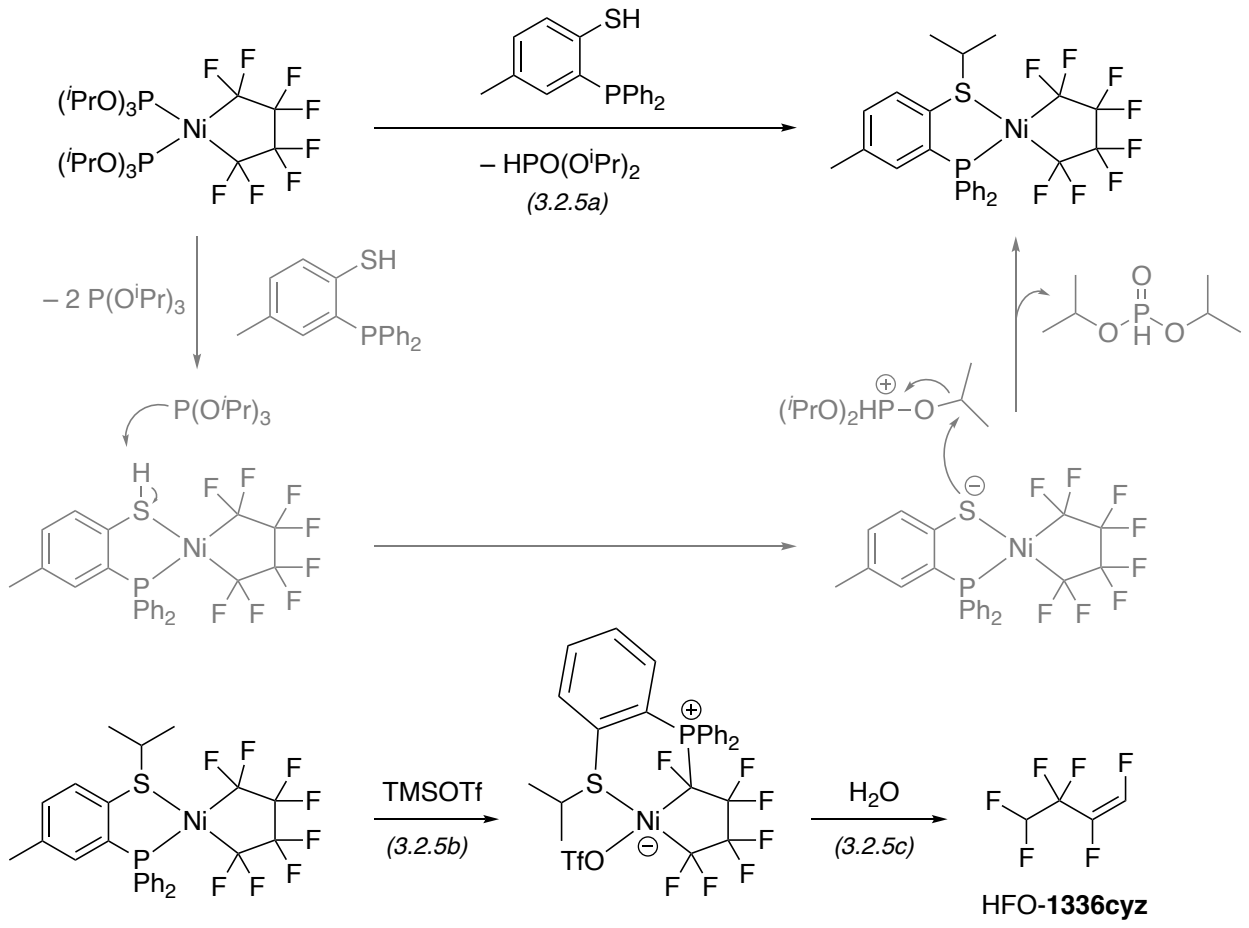
3.4.2a) or two (eqn 3.2.4c) equivalents of BF_3; the mono-abstracted product contains a weakly-bound fluoroborate anion which can be easily displaced into the outer sphere by water (eqn 3.2.4b) while the di-abstracted product (an insoluble purple powder) can coördinate dppe to furnish the bis(fluoroborate) dication (eqn 3.2.4d).[15]



Scheme 3.2.4: C_a–F abstractions from PEt_3 perfluoronickelacycle by BF_3 [15]

In 2013, Giffin (of our group) reported on a unique ligand substitution of the $P(O^iPr)_3$ metallacycle using a PS thiol ligand (Scheme 3.2.5), in which the ejected phosphite deprotonates the coördinated thiol, which attacks the isopropyl of the protonated phosphite to liberate diisopropylphosphite and the neutral isopropyl thioether ligand (eqn 3.2.5a).[16] Subjecting this PS-ligated metallacycle to a fluoride-abstracting Lewis acid (TMSOTf) results in the expected phosphine migration to the *a*-carbon, forming a zwitterionic triflate complex (eqn 3.2.5b) which hydrolyzes to liberate a new organic product 1,2,3,3,4,4-hexafluoro-1-butene (HFO-**1336cyz**, eqn 3.2.5c) and uncharacterized nickel co-products. In a subsequent report (Scheme 3.2.6),[17]

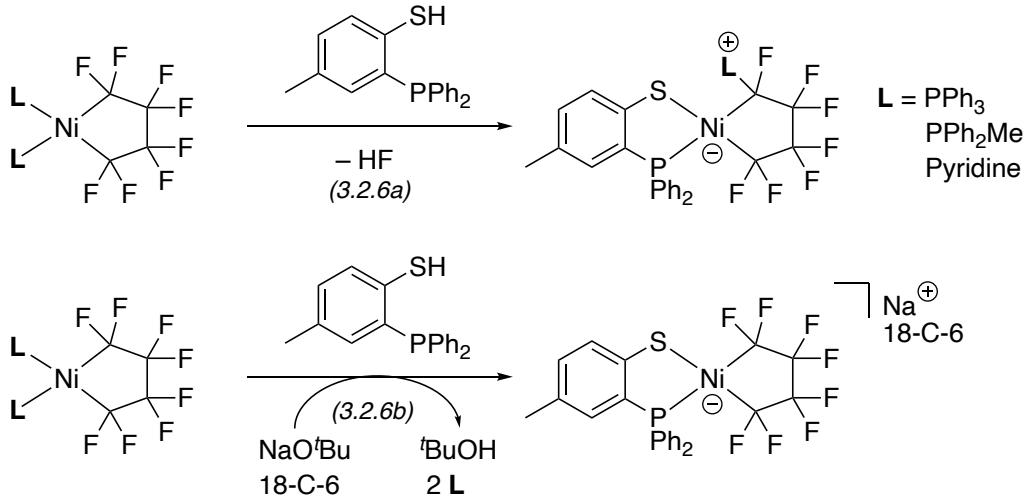
bis(phosphine) metallacycles were treated with the same ligand, and instead of an Arbuzov reaction, the thiol of the ligand acted as a Brønsted acid, abstracting a C_a–F bond and triggering the expected phosphine migration (eqn 3.2.6a). If the ligand is deprotonated with NaOtBu in the presence of 18-crown-6 (18-C-6), then the ate complex is obtained (eqn 3.2.6b).



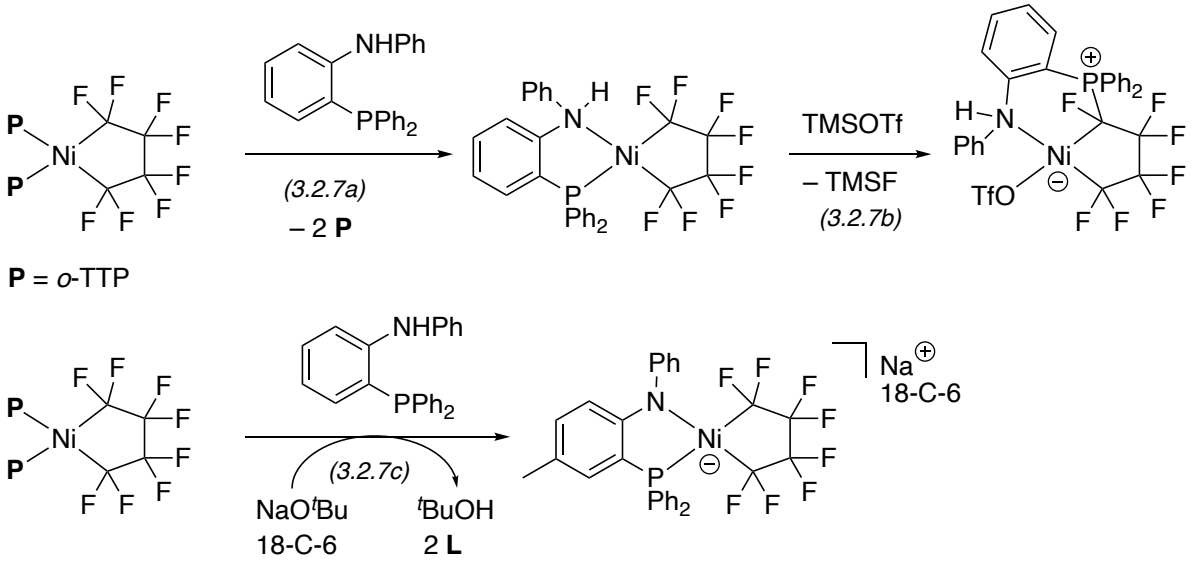
Scheme 3.2.5: Preparation and of C_a–F abstractions of PS-ligated metallacycle by TMSOTf [16]

Similar reactivity was obtained using a PN chelate ligand in a subsequent report (Scheme 3.2.7).[18] The neutral species (prepared by substitution of o-TTP) can undergo ligand migration under treatment with TMSOTf (eqn 3.2.7a) and the coördinated 2º

amine deprotonated by NaOtBu (eqn 3.2.7b). The anionic 18-C-6-complexed sodium salt was obtained when the ligand was previously deprotonated with NaO^{t}Bu in the presence of the crown ether (eqn 3.2.7c).



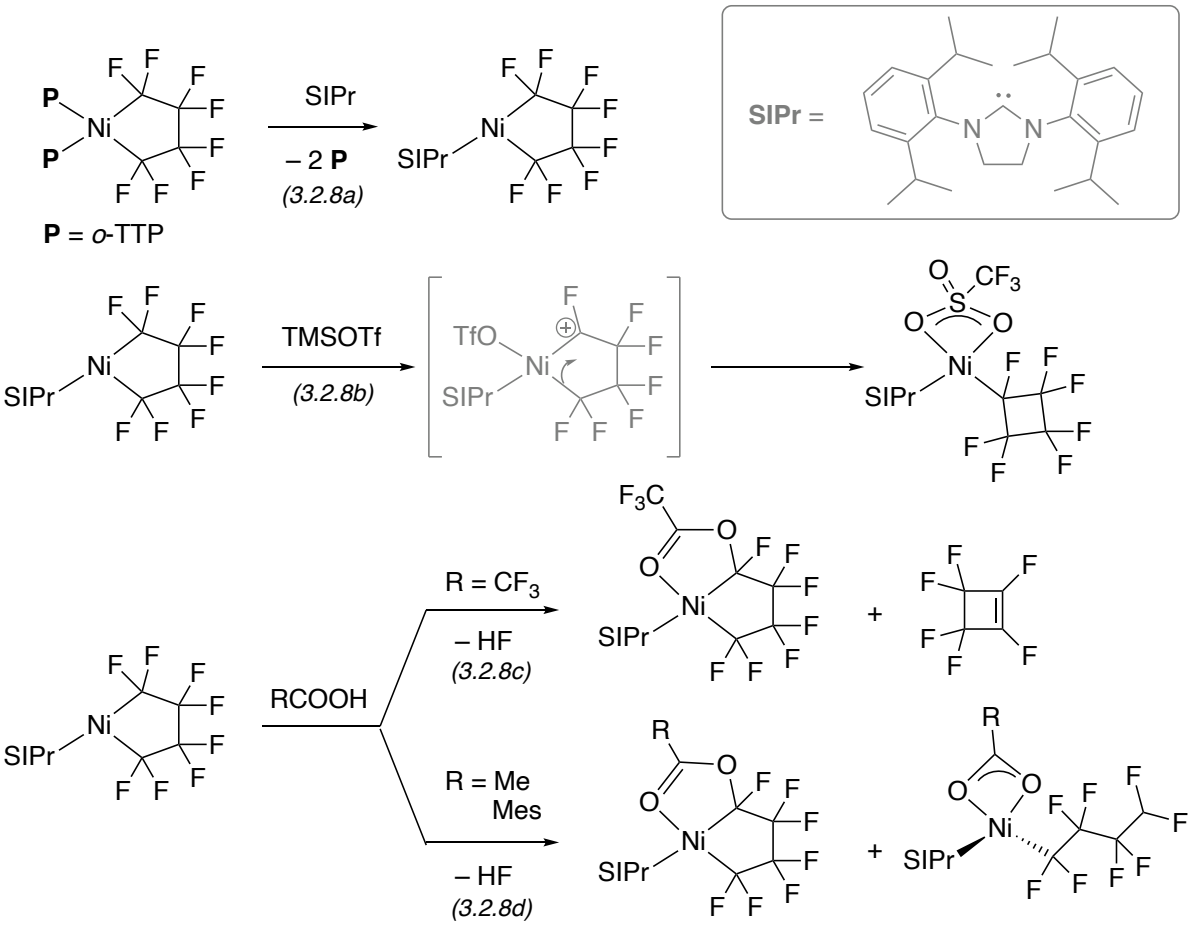
Scheme 3.2.6: Formation of anionic metallacycles with a PS thiolate ligand [17]



Scheme 3.2.7: Formation and reactions of metallacycles containing a PN amine or amide ligand [18]

In 2015, Andrella (of our group) reported on a pseudo-three-coördinate metallacycle prepared by substituting both phosphite ligands of the *o*-TTP-ligated metallacycle with

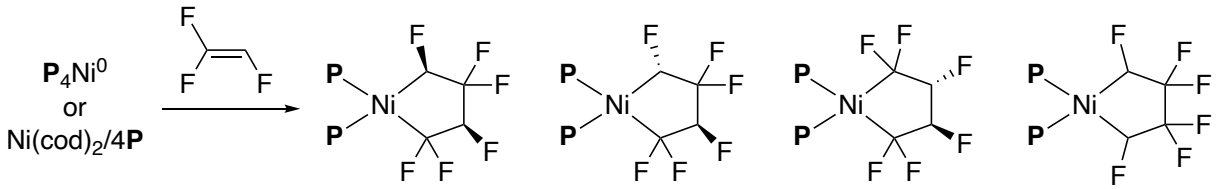
1,3-bis(2,6-diisopropylphenyl)imidazolidine-2-ylidene (SIPr), a bulky N-heterocyclic carbene (NHC) ligand (Scheme 3.2.8, eqn 3.2.8a).[19] The C_α–F bond reacts with TMSOTf as before, but instead of ligand migration, the metallacycle collapses by ring-contraction to a perfluorocyclobutyl complex with a rare κ^2-bound triflate (eqn 3.2.8b). By contrast, Brønsted acids protonate the C_α–F bond with nucleophilic attack of the carboxylate at the incipient cation, with the C=O bond forming an internal chelate.



Scheme 3.2.8: Formation and C_α–F activation of SIPr-ligated three-coördinate metallacycle by Lewis or Brønsted acids [19]

When trifluoroacetic acid is used, the internal chelate is obtained in addition to the β-fluoride elimination product perfluorocyclobutene (eqn 3.2.8c). When an acid with

a lower pKa (acetic) or a greater steric bulk (mesitic), a mixture of C_a–F bond and Ni–C bond activation ensues, with formation of both the internal chelate products and the open-chain *4H*-octafluorobutyl complexes (eqn 3.2.8d). Surprisingly, the latter was stable to heating at 80°C for 12 h. In 2017, Giffin et al. of our group expanded the body of knowledge of metallacycles to include derivatives of trifluoroethylene (VF3).[20] Unlike TFE, which forms symmetrical octafluoronickelacycles, VF3 is an unsymmetrical olefin which produces hydrofluorometallacycles containing both regioisomers and stereogenic centers. A variety of different ligands were employed, and the isomeric distribution trends examined (Scheme 3.2.9); the phosphines with smaller cone angles (ϑ) favored the head-head isomer while smaller cone angles favored the head-tail isomer. In all cases, the *cis*-head-tail was favored over the *trans*-, and the *trans*-head-head isomer was favored over the *cis*. The tail-tail isomers were disfavored in all examples tested.

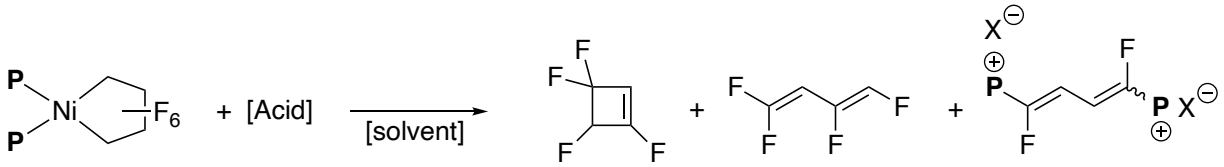


P	θ (deg)	*cis* Head-Tail	*trans* Head-Tail	*trans* Head-Head	Tail-Tail
PPh_3	145	53	25	17	4
o-TPP	141	53	20	21	6
PPh_2Me	136	53	25	20	2
$PPhMe_2$	122	50	21	28	0
PMe_3	118	38	13	49	0

Scheme 3.2.9: Formation of isomeric VF3-derived nickelacyclopentanes with a variety of ligands ordered based on cone angle (ϑ) [20]

With PPh_3 as the ligand, the three-membered metallacycle could be isolated if the reaction was stopped after one hour. When treated with Lewis or Brønsted acids, collapse

of the metallacycles was invariably observed (Scheme 3.2.10), with formation of mixtures favoring either 1,3,3,4-tetrafluorocyclobutene or 1,1,3,4-tetrafluorobuta-1,3-diene, in addition to a small amount of fluorobutadiene-derived vinylphosphonium salts derived from the H-H isomer. Note that in both cases, C_α–F and C_β–F activation has occurred.

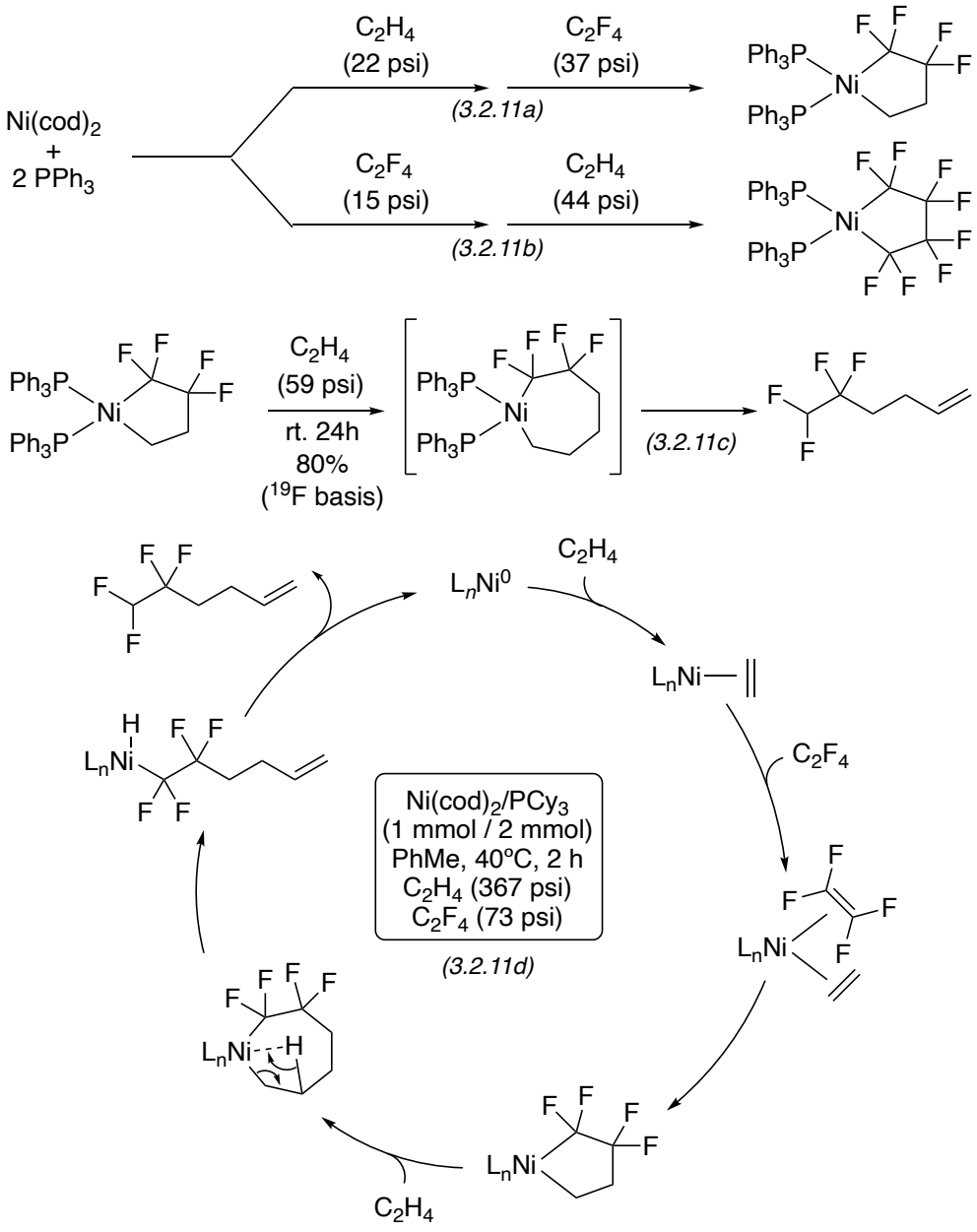


P	[Acid]	(equiv.)	[Solvent]	I	II	III
PPh_2Me	$BF_3 \cdot OEt_2$	1.1	$CDCl_3$	66	3	15
$PPhMe_2$	$BF_3 \cdot OEt_2$	1.1	$CDCl_3$	50	3	20
PPh_2Me	TMSOTf	2.1	CH_2Cl_2	3	45	19
$PPhMe_2$	TMSOTf	2.1	CH_2Cl_2	<1	23	22
PPh_2Me	$PhNMe_2HBr$	1.2	CH_2Cl_2	3	61	5
$PPhMe_2$	$PhNMe_2HBr$	1.2	CH_2Cl_2	4	64	12

Scheme 3.2.10: Reactions of VF3-derived metallacycles with Brønsted and Lewis acids, and the product distributions thereof [20]

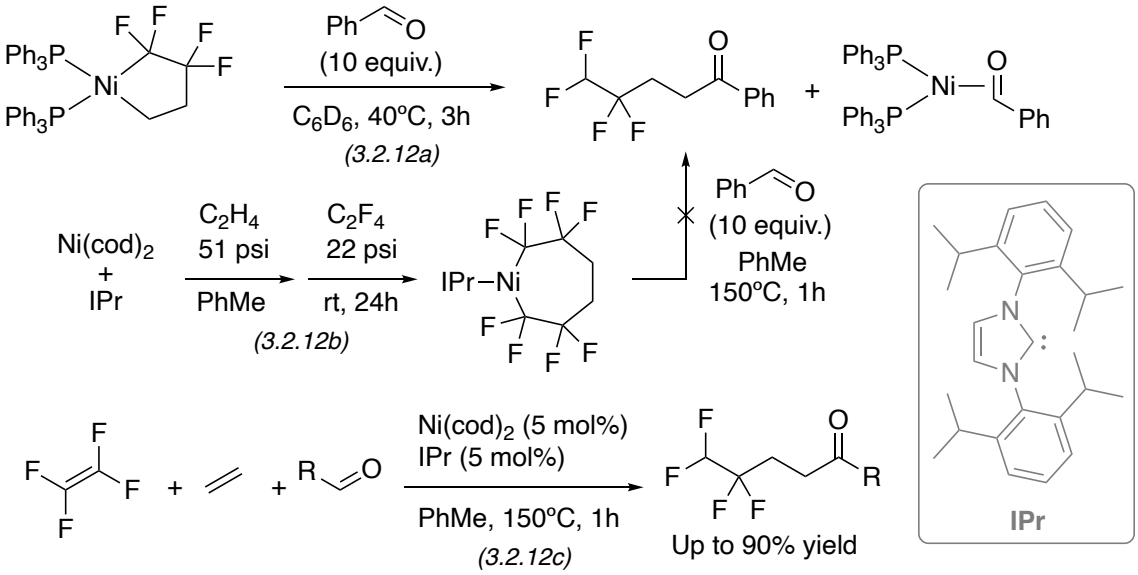
Generation of hydrofluorometallacycles has also been explored extensively by Ogoshi et al. in collaboration with Daikin Industries. Subjecting a mixture of $Ni(cod)_2$ and PPh_3 (2 equiv.) to both ethylene and tetrafluoroethylene in different orders yielded different products (Scheme 3.2.11).[21] If the Ni(0) mixture is first pressurized with ethylene, then with TFE, a heteroleptic metallacyclopentane containing both olefins is obtained (eqn 3.2.11a) but if the order is reversed, only the TFE homo-metallacycle is obtained with no ethylene incorporation (eqn 3.2.11b). Interestingly, if the heteroleptic metallacycle is further pressurized with ethylene, a new C_6 HFC product is liberated, purportedly via β-hydride elimination from an unstable 7-membered metallacycle having incorporated a second equivalent of ethylene (eqn 3.2.11c). This cotrimerization can be

conducted catalytically in nickel (TON = 13) using $Ni(cod)_2/PCy_3$ (1:2 ratio) as long as a large overpressure of ethylene is used (eqn 3.2.11d). Various other 3rd partner-olefins can be used, including $a\beta$-unsaturated ketones and allylstyrene, the latter of which undergoes a cycloaddition during the reaction.



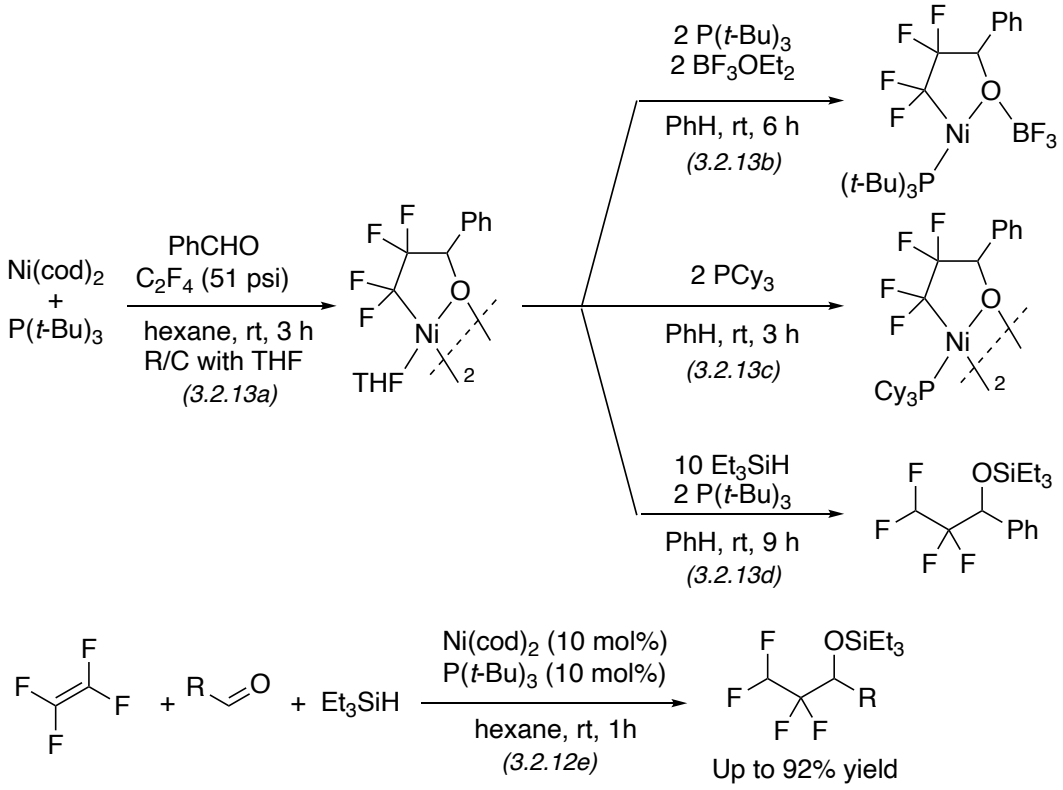
Scheme 3.2.11: Synthesis of heteroleptic TFE/ethylene metallacycles and Ni-catalyzed cotrimerization of TFE/ethylene (Ogoshi et al.) [21]

In another report, Ogoshi et al. examined the use of Ni(0)/IPr (IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene) to cotrimerize three different π-systems comprising ethylene, TFE, and aldehydes (Scheme 3.2.12). First, the PPh_3-ligated heteroleptic ethylene/TFE metallacycle reacts with an excess of benzaldehyde to furnish the 3,3,4,4-tetrafluorobutylated ketone (eqn 3.2.12a). If $Ni(cod)_2$/IPr (1:1 ratio) is allowed to react with ethylene followed by TFE at room temperature for 24 hours, a stable 7-membered heteroleptic metallacycle is obtained (3.2.12b) which does not further react with aldehydes, and which was crystallographically characterized as having a T-shape similar to the SIPr-ligated metallacyclopentane of Scheme 3.2.8. This metallacycle is noteworthy for its stability towards β-elimination despite the proclivity of 7-membered metallacycles to do so.[22] The reaction can be carried out catalytically in nickel with a variety of aldehydes in yields up to 90% (eqn 3.2.12c).



Scheme 3.2.12: Cotrimerization of ethylene, TFE, and aldehydes catalyzed by $Ni(cod)_2$ with IPr (Ogoshi et al.) [21]

Ogoshi et al. also reported that TFE can also be coupled to aldehydes in absence of ethylene using P^{t}Bu$_3$ as the ligand via oxa-nickelacycle intermediates (Scheme 3.2.13).[23] Interestingly, though the initial reaction mixture contains a 1:1 ratio of Ni(cod)$_2$/P(*t*-Bu)$_3$, the obtained fluorinated oxa-nickelacycle obtained on recrystallization from THF is dimeric, and contains only a coördinated THF molecule in place of the phosphine (eqn 3.2.13a).

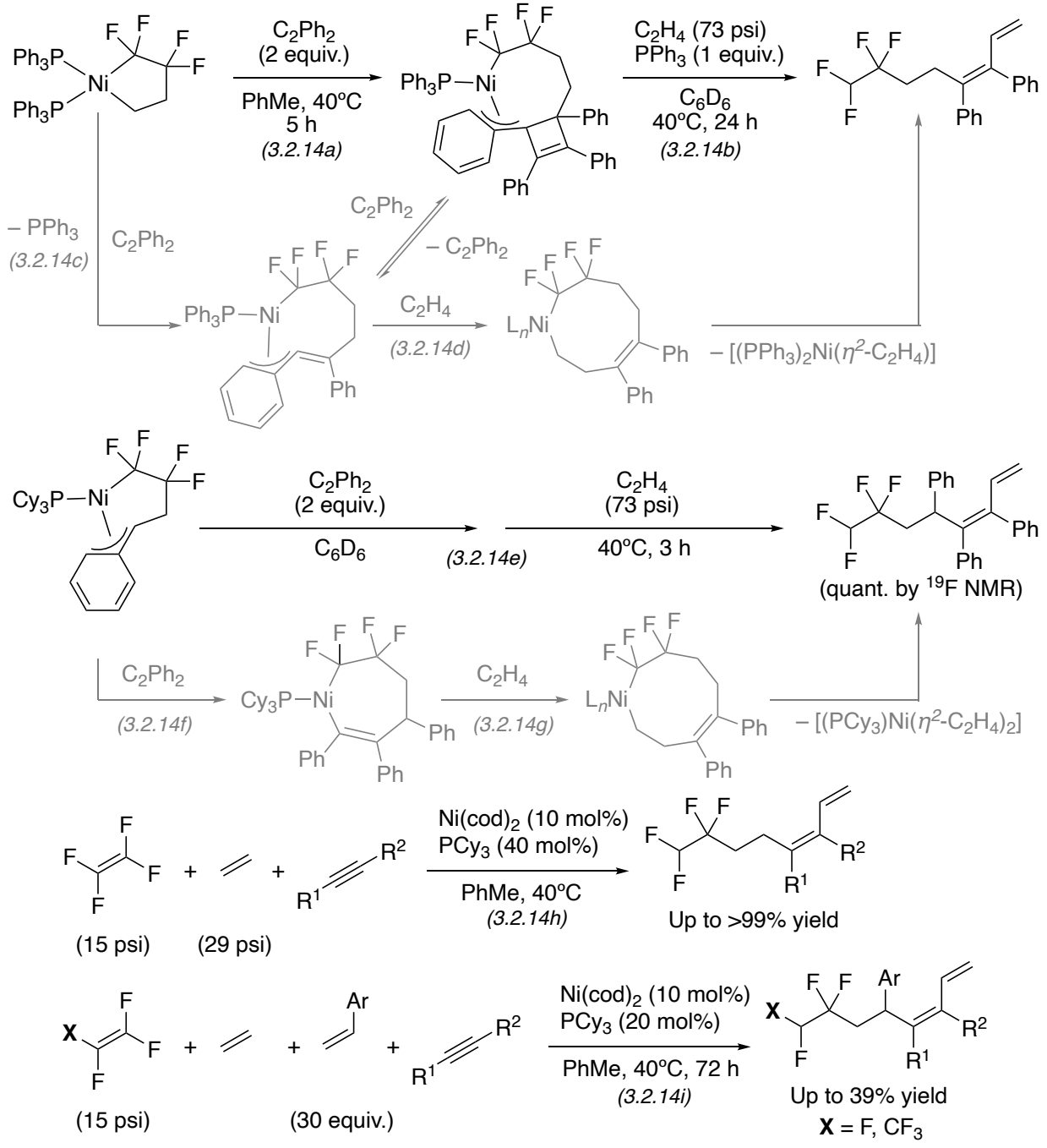


Scheme 3.2.13: Reductive heterodimerization of TFE and aldehydes with Et$_3$SiH catalyzed by Ni(cod)$_2$ with P(*t*-Bu)$_3$ (Ogoshi et al.) [23]

Addition of P(*t*-Bu)$_3$ (2 equiv.) in the presence of BF$_3$·Et$_2$O breaks the dimer (eqn 3.2.13b), while addition of PCy$_3$ (2 equiv.) without acid furnishes phosphine-ligated dimer (eqn 3.2.13c). The oxa-metallacycles can be reduced by addition of triethylsilane,

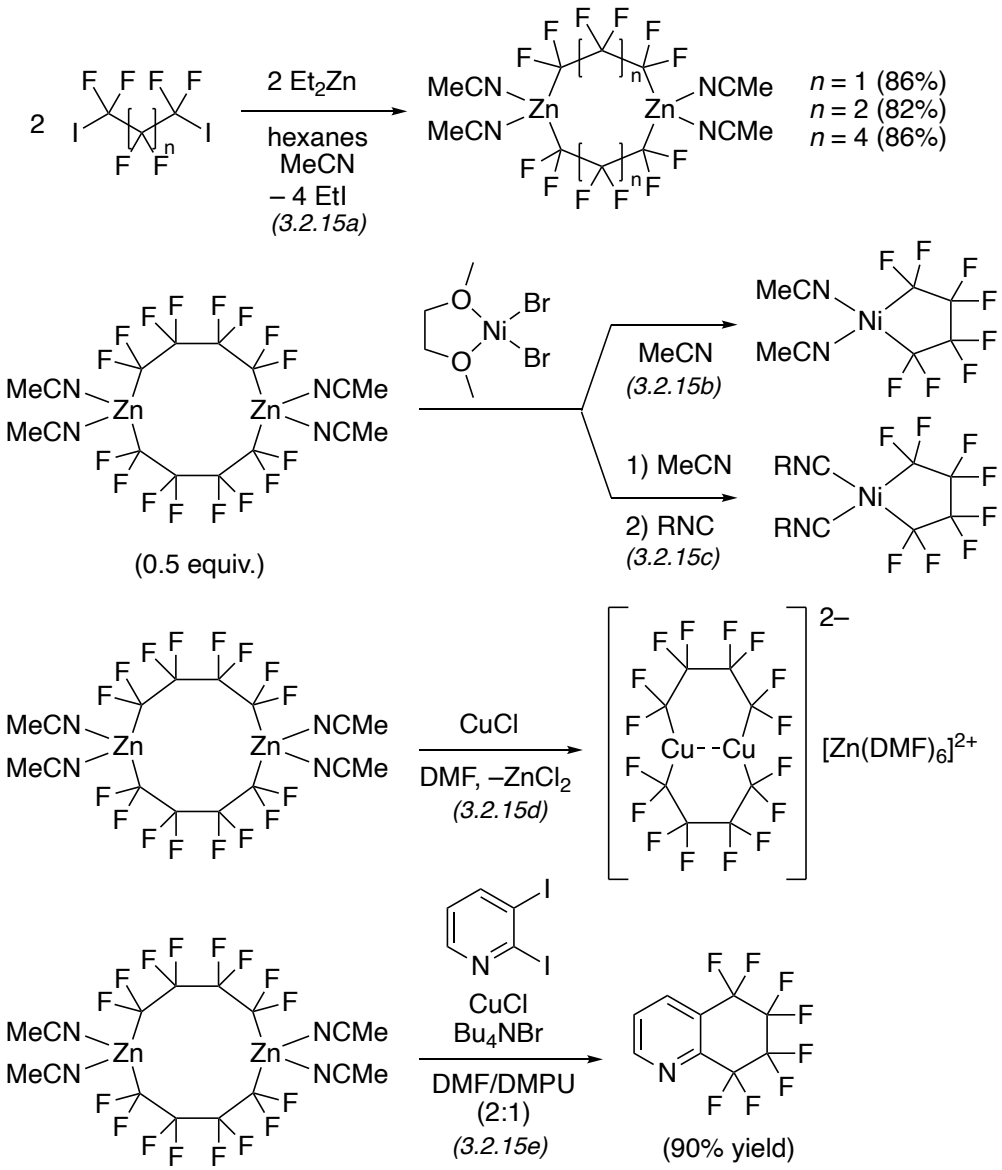
furnishing the hydrosilylated aldehyde coupling product (eqn 3.2.13d), a reaction which can be performed catalytically in nickel with P(*t*-Bu)$_3$ as the ligand at room temperature (3.2.13e). Ogoshi et al. also found that alkynes can be used as substrates for coupling with TFE or hexafluoropropylene (HFP), having reported a unique cross-tetramerization with TFE, ethylene, styrenes, and internal alkynes to chain-extended 1,3-dienes (Scheme 3.2.14).[24] Starting from the PPh_3-ligated TFE/ethylene metallacycle, diphenylacetylene inserts either two equivalents (eqn 3.2.14a) or one equivalent (eqn 3.2.14c). In both cases, the benzylic group binds η^3 to the nickel, but in the former case, this is accompanied by formation of a tetraphenylmetallacyclobutene. The two compounds are in equilibrium with each other, and react with ethylene and PPh_3 to furnish a C_8 chain containing a 1,3-diene (eqn 3.2.14b). This proceeds via the single-equivalent diphenylacetylene insertion product, which inserts ethylene to form a ring-expanded nickelacyclononene, which collapses by β-hydride elimination (3.2.14d). In another example, a mixed TFE/styrene metallacycle could be made[25] with PCy_3 in which the benzylic carbon is similarly bound η^3, and which inserts in sequence diphenylacetylene and ethylene to furnish a similar C_8 chain (eqn 3.2.14e). First, the benzylic metallacycle is ring-expanded by C_2Ph_2 to a metallacycloheptene (eqn 3.2.14f) which is further expanded by ethylene (eqn 3.2.14g) to a nickelacyclononene, which β-hydride eliminates to the octadiene product with liberation of a Ni(0) ethylene adduct. These transformations can be carried out catalytically in nickel, with the former reaction requiring 10 mol% of nickel and 40 mol% of PCy_3, and giving the octadiene products in up to >99% yield (eqn 3.2.14h). The second reaction

can be performed using either TFE or HFP, and furnishes the styrene-inserted octadiene products in up to 39% yield.



Scheme 3.2.14: Cotetramerization of TFE/HFP, ethylene, and alkynes with or without styrene catalyzed by nickel (Ogoshi et al.) [24]

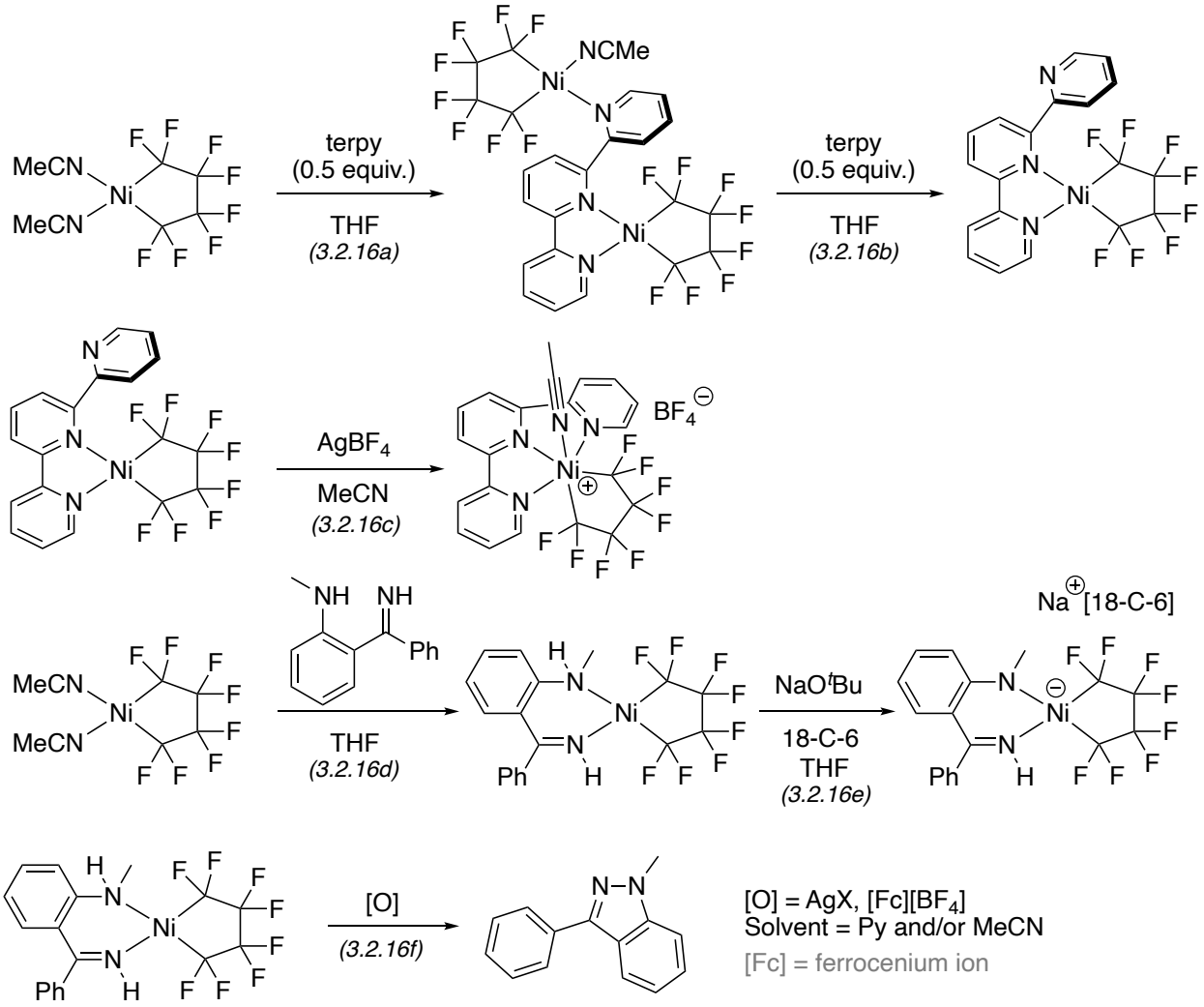
Metallacycles have also been prepared using a specialized zinc bis(fluoroalkyl) dimer prepared by Vicic et al. (Scheme 3.2.15).[26] Terminally diïodinated perfluoropropane, *n*-butane, and *n*-hexane smoothly react with diethylzinc in hexanes with MeCN to furnish the bridged tetrahedral dizinc reagents ligated with MeCN in high yields (eqn 3.2.15a). The dimer derived from $I(CF_2)_4I$ reacts with 2 equivalents of $NiBr_2$(glyme) in MeCN to furnish the acetonitrile-complexed octafluoronickelacyclopentane (eqn 3.2.15b), from which the MeCN ligands can readily be displaced by isonitriles (eqn 3.2.15c). A similar Cu(I) dimer can be prepared by reacting the aforementioned dizinc reagent with CuCl in DMF; this ate complex has a weak Cu-Cu interaction (2.548Å in the solid state) and is accompanied by a DMF-ligated octahedral Zn^{2+} counterion (eqn 3.2.15d). Furthermore, the dizinc reagent can be used as a nucleophile in a Cu-catalyzed Negishi coupling with diïodinated substrates in DMF/DMPU solvent (eqn 3.2.15e). The terminally diïodinated perfluoroalkanes are commercially-available liquids which can be easily handled compared to TFE, which is not commercially-available in laboratory quantities, and—owing to strict transport and usage regulations—is not easily acquired directly from OEMs such as Chemours (USA), AGC (JP), or Daikin (JP). The reagents prepared by Vicic offer a means to study the perfluorometallacycles without the necessity of acquiring, preparing, or generating TFE.



Scheme 3.2.15: Synthesis and reactions of octafluorobutyldizinc dimer prepared from 1,4-diïodoperfluorobutane (Vicic et al.) [26]

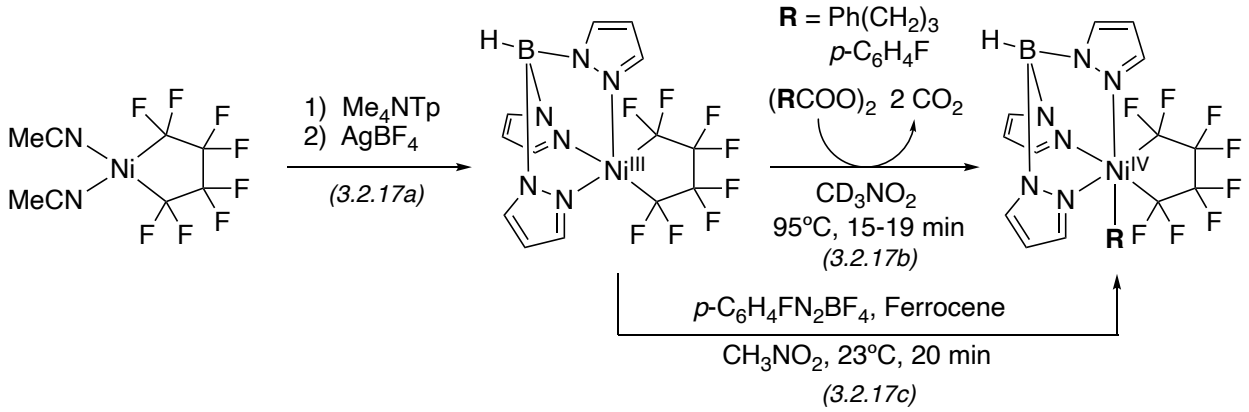
Vicic's MeCN-ligated metallacycle also reacts with terpyridine (terpy, Scheme 3.2.16)[27] in THF to sequentially form a dimeric bis(nickel) species where one of the nickel centers has engaged 2 terpy nitrogens and the other has engaged one, with one remaining MeCN (eqn 3.2.16a). Addition of another 0.5 equivalent of terpy furnishes the monomer containing an uncoördinated pyridine arm (eqn 3.2.16b), which can be oxidized by $AgBF_4$

to an octahedral Ni(III) where the terpy is fully engaged (eqn 3.2.16c). An iminoaniline ligand was also coördinated to the MeCN-metallacycle (eqn 3.2.16d)[28], on which the aniline can be deprotonated by NaO^{t}Bu in the presence of 18-crown-6 to form the ate complex (eqn 3.2.16e) similar to that reported by Giffin in Scheme 3.2.7. The neutral complex can be oxidized with a silver or ferrocenium salt to induce N-N bond formation to the benzopyrazole reductive elimination product (eqn 3.2.16f).



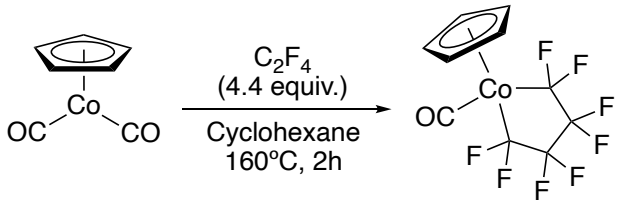
Scheme 3.2.16: Derivatization of the MeCN-metallacycle with various nitrogen ligands, and reactions of the complexes thereof (Vicic et al.) [27, 28]

Sanford et al. used Vicic's MeCN-metallacycle as a starting point for the synthesis of tris(pyrazolyl)borate (Tp^-)-nickel derivatives (Scheme 3.2.17).[29] Oxidation with $AgBF_4$ gave the Ni(III) metallacycle (eqn 3.2.17a), which could be oxidized further with peroxides in nitromethane to furnish alkyl- or aryl-nickel(IV) metallacycles (eqn 3.2.17b). Alternatively, the same product can be furnished with a diazonium salt in the presence of ferrocene (eqn 3.2.17c).



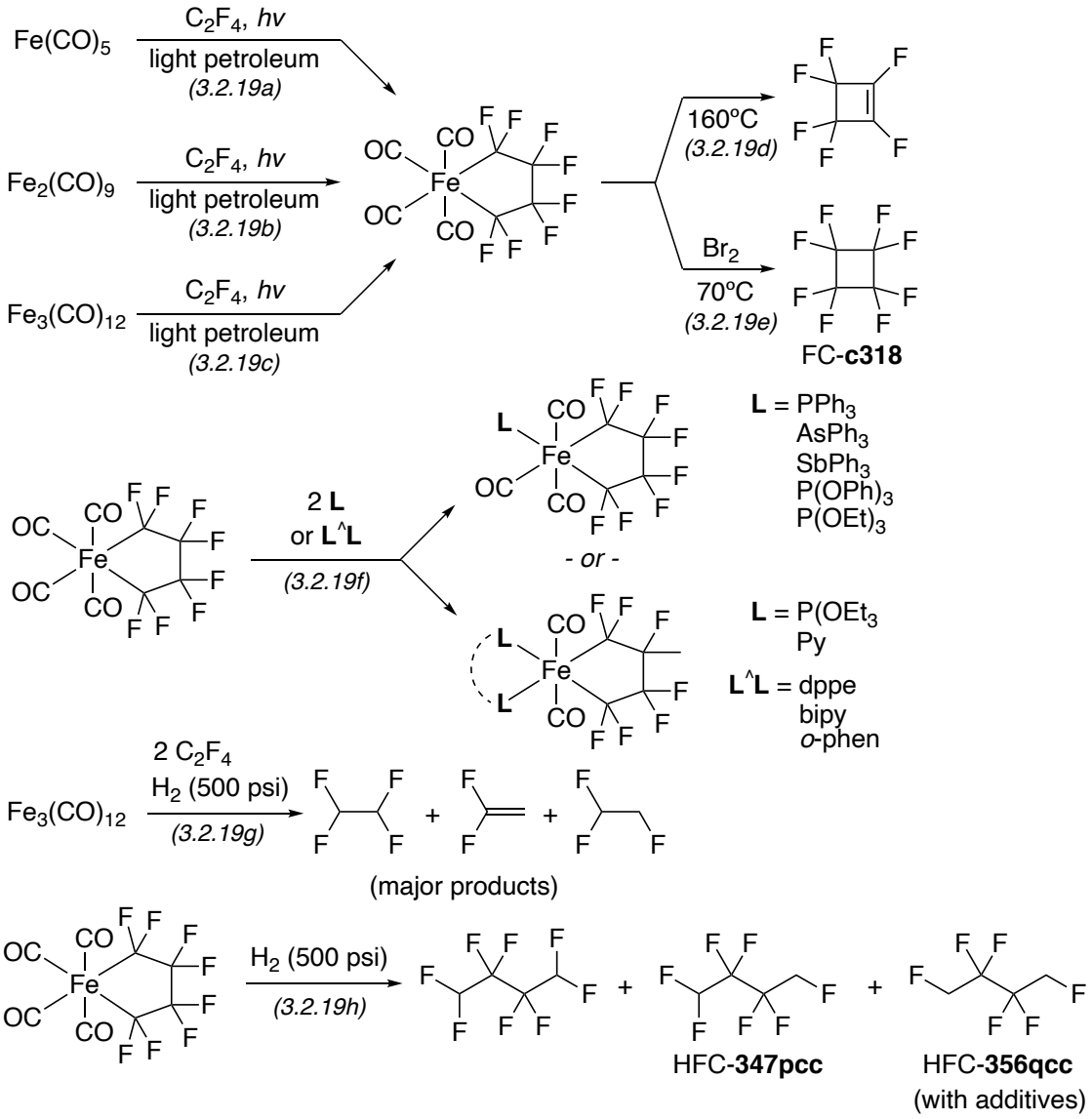
Scheme 3.2.17: Synthesis of Ni(III) and Ni(IV) metallacycles bearing the Tp ligand (Sanford et al.) [29]

Perfluorometallacycles have also been made and studied on metals other than nickel. One of the earliest examples was reported by Stone in 1961, prepared from cyclopentadienylcobalt dicarbonyl and an excess of TFE (Scheme 3.2.18).[30] The compound was sublimable and air-stable, but no further reactivity was reported.



Scheme 3.2.18: Synthesis of half-sandwich Co metallacycle (Stone et al.) [30]

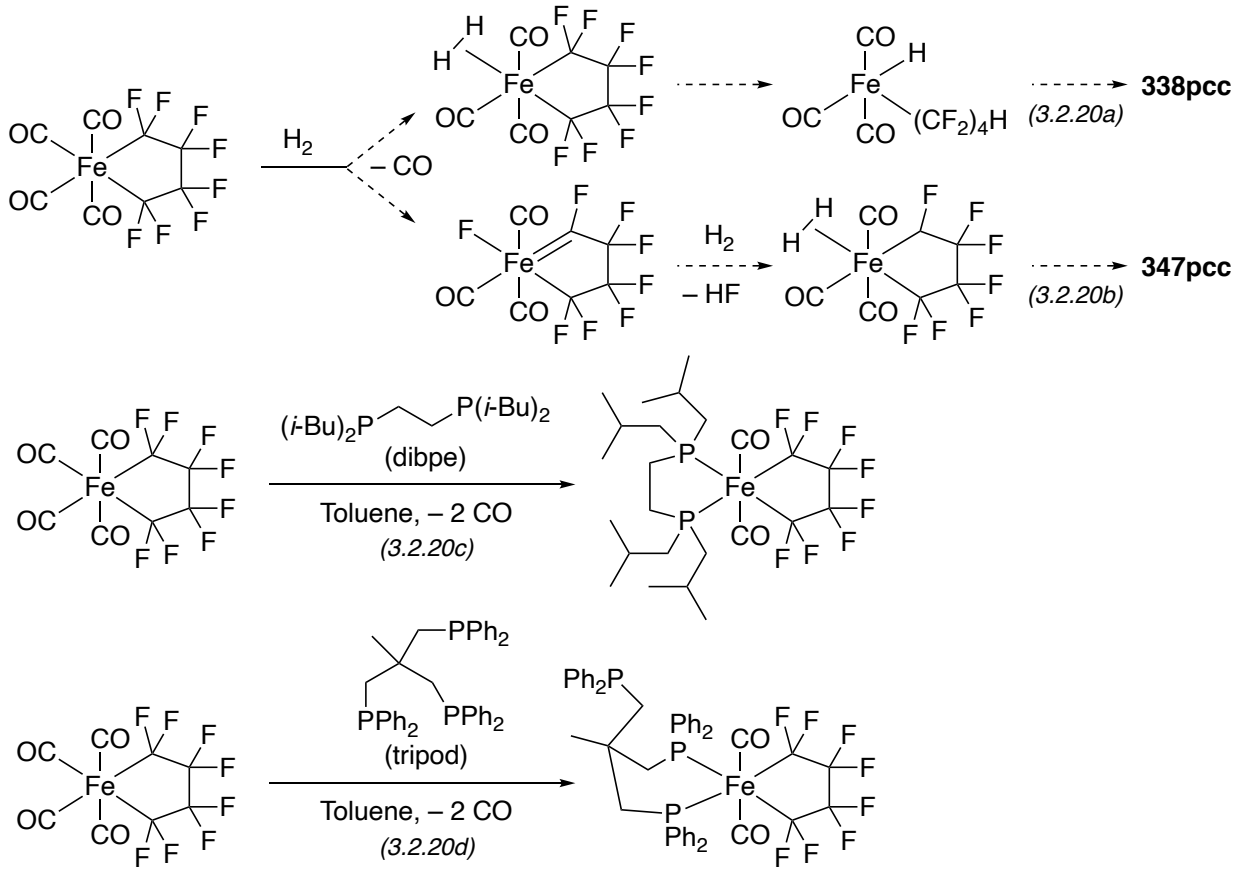
One of the more studied metallacycles is the iron carbonyl derivative, which was originally reported by Wilkinson in 1961 and synthesized from $Fe_3(CO)_{12}$ (eqn 3.2.19c).[31] Alternatively, it can be synthesized from $Fe(CO)_5$ (eqn 3.2.18a)[32] or $Fe_2(CO)_9$ (eqn 3.2.19b), and either pyrolyzed at 160°C to furnish perfluorocyclobutene (eqn 3.2.19e) or oxidized by bromine to liberate perfluorocyclobutane (eqn 3.2.19e).[33] The same report also outlines a series of carbonyl ligand substitutions by either monodentate or bidentate ligands, with the products identified by IR and NMR spectroscopy (eqn 3.2.19f). Given the formation of similar metallacycles to nickel, examples of hydrodimerization catalyzed by iron carbonyls were also included by Baker et al. in the hydrodimerization patent, but the authors found that $Fe_3(CO)_{12}$ primarily hydrogenated and hydrodefluorinated TFE when subjected to 2 equiv. of it in the presence of a large excess of H_2 (eqn 3.2.19g). However, when the preformed tetracarbonyl metallacycle is subjected to the same H_2 pressure, the expected HFC-**338pcc** is formed alongside an unexpected product HFC-**347pcc** (eqn 3.2.19h).[12] The **347pcc** was originally proposed to arise via C_a–F activation and formation of a metallacyclocarbene, the hydrogenolysis of which produces the CH_2F–containing product (*vide infra*). A further hydrogenated product, 1,2,2,3,3,4-hexafluorobutane (HFC-**356qcc**) could be obtained on performing the hydrogenolysis of the metallacycle in the presence of various additives, including Pd/C, Rh/C, $RhCl(PPh_3)_3$, or PPh_3. The Rh/C example contained a significant quantity of perfluorocyclobutene in the liquid phase, and up to 90.5% of the **347pcc** could be obtained using $RuHCl(PPh_3)_3$ as the additive.



Scheme 3.2.19: Early syntheses and reactivity studies of Fe perfluorometallacycles [12, 31–33]

The carbene hypothesis for the **347pcc**/**356qcc** formation was left alone for years until a former student in our group, K. Ghostine, revisited these metallacycles (Scheme 3.2.20).[34] The hypothesis for the formation of the aforementioned **347pcc** and **356qcc** hydrofluorocarbons was the spontaneous *α*-fluoride elimination to a metallacyclocarbene, which could be hydrogenated with elimination of HF to **347pcc** (eqn 3.2.20b) as opposed

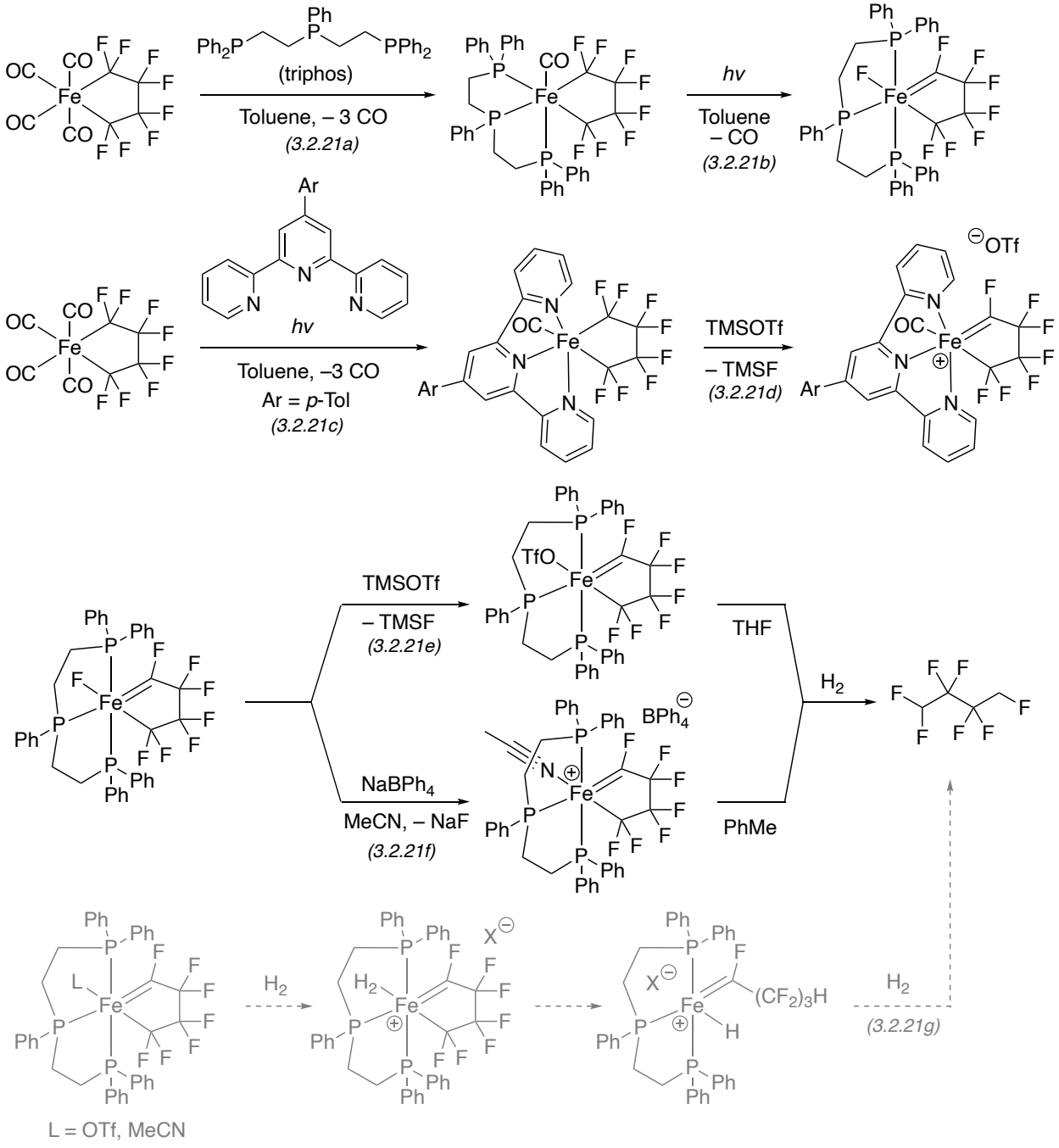
to the expected Fe–C bond hydrogenolysis for 338pcc (eqn 3.2.20a). To probe this hypothesis, a ligand substitution was first performed of the tetracarbonyl metallacycle using the electron-rich bidentate ligand 1,2-bis(diisobutylphosphino)ethane (dibpe, eqn 3.2.20c). This product was stable and isolable. Attempting the tridentate ligand 1,1,1-tris(diphenylphosphinomethyl)ethane (tripod) only gave the disubstituted product with one free uncoördinated phosphine arm which did not react further (eqn 3.2.20d).



Scheme 3.2.20: Hypothesized pathways to 338pcc and 347pcc from $Fe(CO)_4$ metallacycle and formation of bisphosphine adducts thereof [34]

By contrast, meridionally-binding tridentate ligands *do* manage to displace three carbonyls to bind in a κ^3-fashion (Scheme 3.2.21). Linear triphos (bis(2-

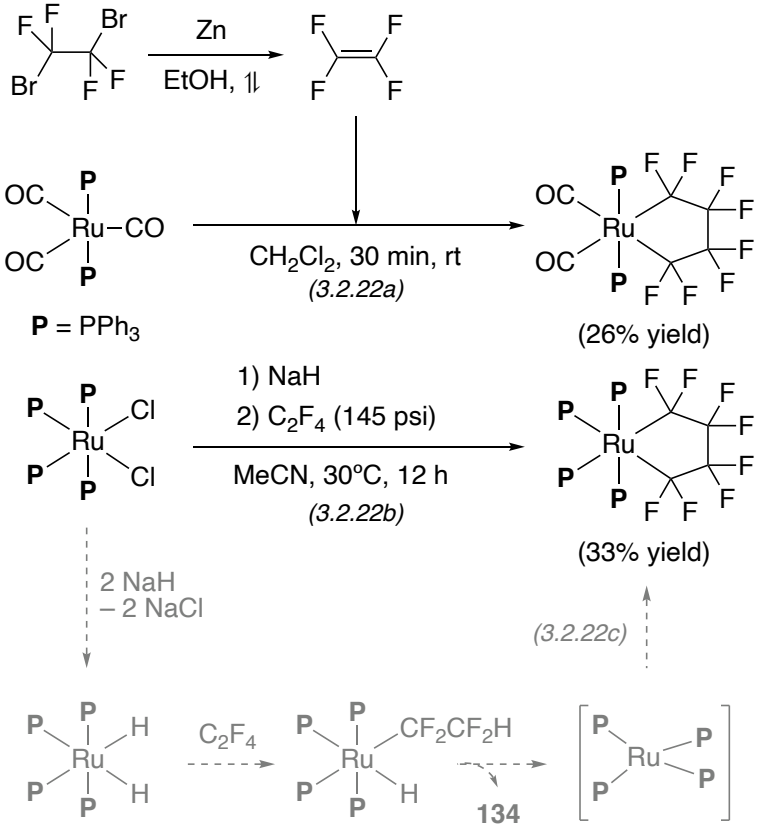
diphenylphosphinoethyl)phenylphosphine) fully coordinates to the tetracarbonyl metallacycle (eqn 3.2.21a), as does terpyridine (terpy, eqn 3.2.21c). The triphos metallacycle readily loses its last carbonyl under photolysis, with the empty site triggering spontaneous *a*-elimination to the metallacyclocarbene iron fluoride (eqn 3.2.21b). The highly deshielded carbenic fluoride was identified by its characteristic downfield ^{19}F NMR signal (111.3 ppm), and the iron fluoride was also identified at –395 ppm. The terpy metallacycle undergoes C_a–F abstraction on treatment with TMSOTf, but unlike the nickelacycles—which the reader will recall underwent ring contraction or ligand migration under similar treatment—formed a stable, cationic, carbonyl-ligated metallacyclocarbene triflate (eqn 3.2.21d). The Fe–F bond can be similarly abstracted from the aforementioned triphos carbene using either TMSOTf (eqn 3.2.21e) or $NaBPh_4$ in MeCN (eqn 3.2.21f). Either of these species readily hydrogenate at low pressures to furnish exclusively HFC-347pcc, allegedly originating from hydrogenolysis of both the Fe=C and Fe–C bonds (eqn 3.2.21g). These findings contribute to the vindication of Baker's original hypothesis that the hypothesis that metallacyclocarbene formation accounts for the overreduced HFC products in the high-pressure hydrogenolysis of $[(CO)_4Fe(\varkappa^2\text{–}(CF_2)_4\text{–})]$.



Scheme 3.2.21: Ligand substitution and spontaneous α-elimination from Fe carbonyl metallacycles, and justification of HFC-347pcc formation [34]

Compared to its first-row congener, the metallacyclopentanes of ruthenium are less-studied (Scheme 3.2.22). Kuwae et al. reacted TFE (generated by reductive debromination of $CF_2Br–CF_2Br$ by zinc in refluxing ethanol and bubbled through the

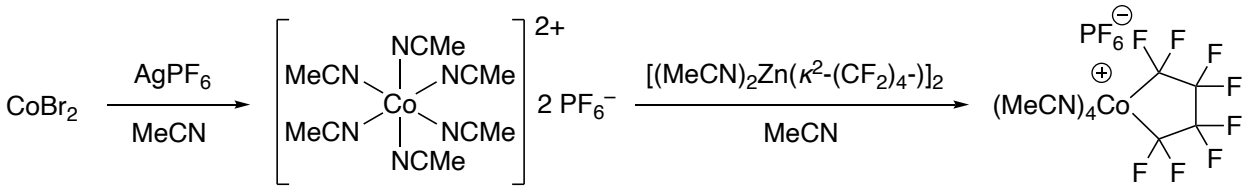
reactive solution) with $[Ru(CO)_2(PPh_3)_3]$ in CH_2Cl_2 at room temperature for 30 minutes to obtain the bisphosphine dicarbonyl metallacycle in 26% yield as an air-stable CH_2Cl_2 solvate (eqn 3.2.22a).[35] Another means to synthesize Ru metallacycles was developed by Gasafi-Martin et al. and entails the reaction of $[RuCl_2(PPh_3)_4]$ with NaH in MeCN in an autoclave, followed by treatment with TFE (145 psi) to form the tetrakis(phosphine) ruthenacycle (eqn 3.2.22b).[36] The pathway is believed to proceed via formation of Ru hydrides, which reduce to Ru(0) on hydrogenation of TFE to HFC-**134** (eqn 3.2.22c).



Scheme 3.2.22: Formation of perfluororuthenacycles from either $[Ru(CO)_3(PPh_3)_2]$ or $[RuCl_2(PPh_3)_4]$ [35, 36]

Fluorometallacycles on other metals can also be synthesized using ready-made fluorinated C_4 building blocks. For example, Vicic used his octafluorobutyldizinc reagent

to transfer a metallacycle to a solvated cobalt(II) cation, forming a cationic Co(III) metallacycle (Scheme 3.2.23).[37]

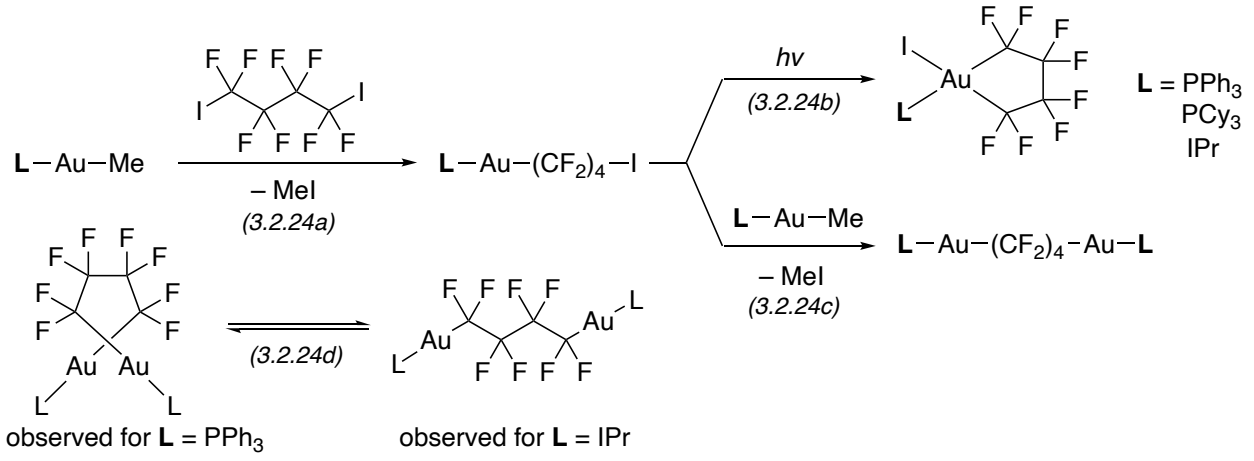


Scheme 3.2.23: Formation of a cationic perfluorocobaltacycle starting from Vicic's octafluorobutyldizinc reagent (Vicic et al.) [37]

In the first example of a discrete perfluorometallacyclopentane of a coinage metal (Scheme 3.2.24)[38], Gil-Rubio et al. found that I–$(CF_2)_4$–I is smoothly aurated with linear LAuMe complexes with elimination of MeI (eqn 3.2.24a). The remaining iodinated chain could then undergo intramolecular oxidative addition to form the Au(III) metallacycle (eqn 3.2.24b). Alternatively, reaction with a second equivalent of LAuMe furnishes the μ-$(CF_2)_4$-digold products (eqn 3.2.24c). Two different folds can interconvert (eqn 3.2.24d), with the crossed-fold favored for small ligands like PPh_3 and PMe_3, and the open-chain fold observed for bulky ligands like IPr or PCy_3. The crossed-fold contains a weak Au···Au interaction (3.039Å for L = PPh_3 in the solid state). The PCy_3 product is a special case, with the crossed-fold observed by ^{19}F NMR in a mixture with the open-chain fold at low temperature 164 K, but no crossed-fold observed at 291 K.

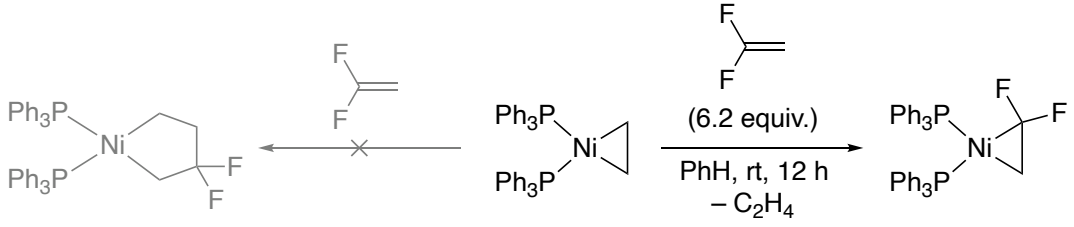
Thus, the field of fluorinated metallacycles has grown highly diverse especially recently, but the emphasis is ever on the perfluorinated models (*i.e.* those derived from either TFE or I–$(CF_2)_4$–I). With growing interest in the applications of such metallacycles to the realm of catalysis[39], there remains an opportunity to explore the reactive tendencies

of metallacycles derived from olefins containing still less fluorine than TFE, particularly if said olefins are more commercially available.



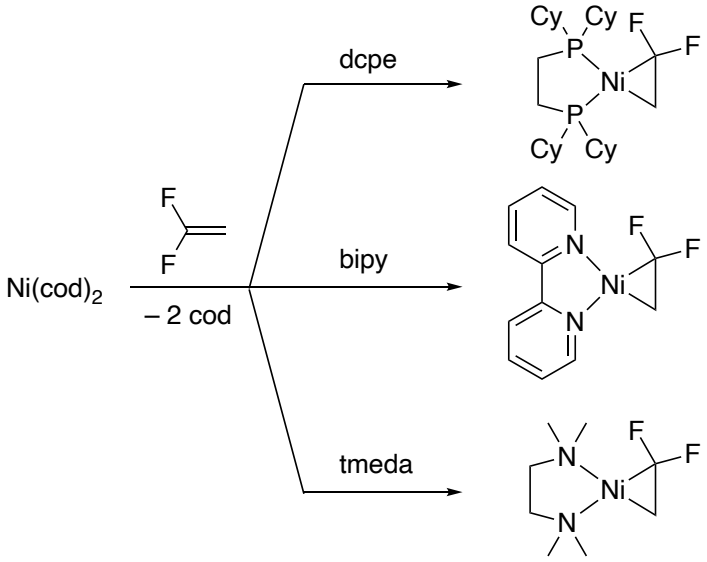
Scheme 3.2.24: Formation of perfluorinated auracycles and open chain μ-$(CF_2)_4$-dimers (Gil-Rubio et al.) [39]

Regarding vinylidene difluoride (VF2), far fewer precedent examples exist in the literature than do for TFE, but the few that do exist sufficiently contribute to the notion that it is an olefin possessed of a very different temperament than TFE or even VF3. Possessing half of TFE's fluorine content, it is substantially less oxidizing, as evidenced by Stone's early example showing that rather than forming a mixed metallacycle (as did TFE in Scheme 3.2.11), VF2 merely displaces ethylene from $[(PPh_3)_2Ni(\eta^2\text{-}C_2H_4)]$, forming the new π-complex $[(PPh_3)_2Ni(\eta^2\text{-}CF_2{=}CH_2)]$ (Scheme 3.2.25).[40]



Scheme 3.2.25: Formation of PPh_3-ligated π-complex of VF2 (Stone et al.) [40]

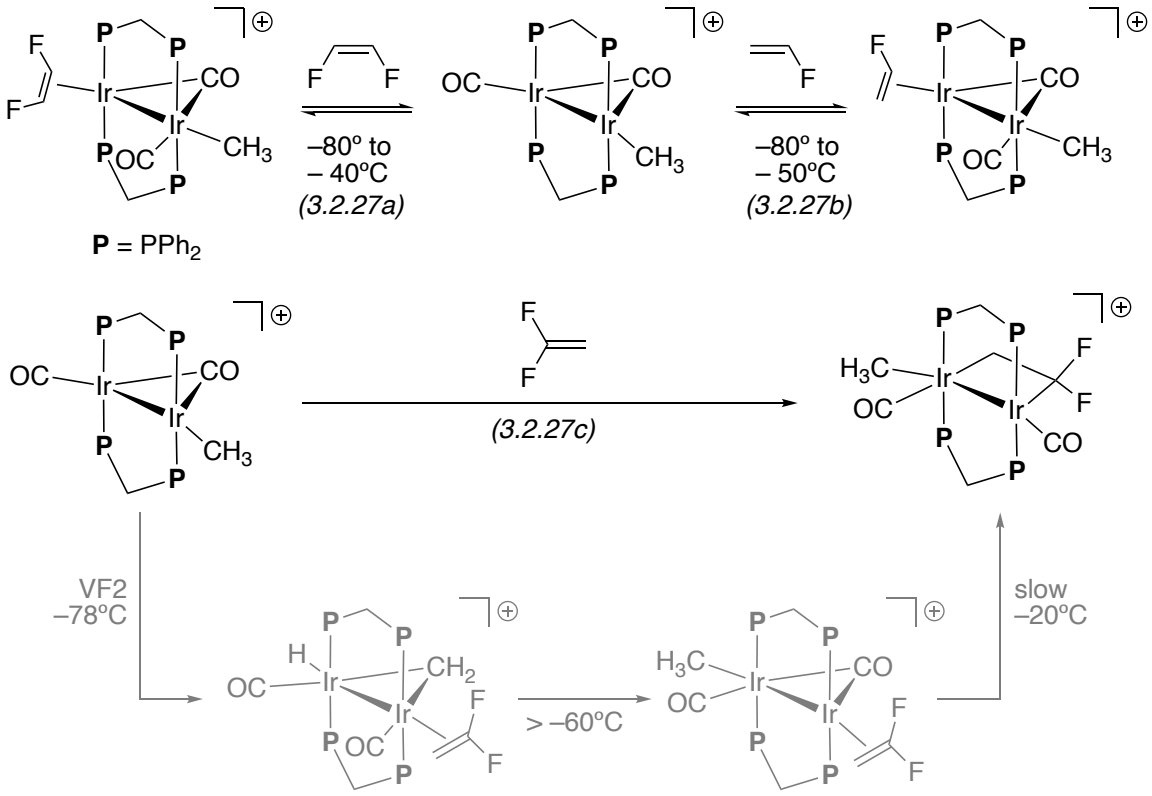
Hoberg and Guhl isolated other π-VF2 complexes using either 1,2-bis(dicyclohexylphosphino)ethane (dcpe), 2,2'-bipyridyl (bipy), or *N,N,N',N'*-tetramethylethylenediamine (tmeda) by displacement of $Ni(cod)_2$ in Et_2O (Scheme 3.2.25).[41]



Scheme 3.2.26: Formation of various π-complexes of VF2 using chelate ligands (Hoberg & Guhl) [41]

Cowie et al. used a unique cationic μ-CO methyliridium(I) dimer to coördinate various fluoroölefins including VF2 (Scheme 3.2.27).[42] At low temperatures, the methyl would shift to the same carbon as the terminal carbonyl, and coördinate the olefin to the other iridium; the same result was observed for both 1,2-difluoroethylene (HFO-**1132**, eqn 3.2.27a) and vinyl fluoride (VF, eqn 3.2.27b). With VF2, the transformations were observed in sequence where at –78°C, both carbonyls were terminal and the C–H of the methyl had oxidatively added to form a μ-methylidene with a terminally coördinated VF2. By heating to greater than 60°C, the methyl shifted to the other Ir, restoring the μ-

carbonyl, and then slowly at –20°C the VF2 replaced the CO as the bridging ligand, forming a diïridacyclobutane complex (3.2.27c).



Scheme 3.2.27: Reactivity of a cationic μ-CO methyliridium dimer with various hydrofluoroethylenes (Cowie et al.) [42]

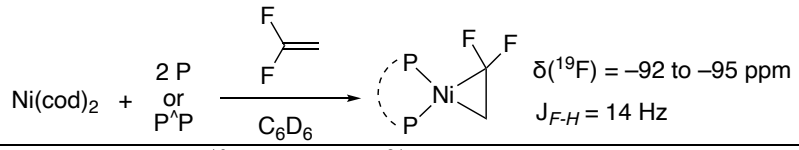
The aforementioned examples clearly demonstrate a lack of metallacyclopentanes derived from VF2, and a much-reduced ability to oxidize low-valent metal centers as compared with TFE and VF3. However, given the dearth of such examples, the original motive of this project was to expand the library of ligands tested to include much more electron-rich phosphines and to examine whether under such conditions, metallacyclopentanes might yet be formed from this olefin.

3.3 This work: Coordination chemistry of VF2

At the outset of the project, it became apparent that given the differences in reactivity between VF2 and TFE, different strategies would be needed than were used for the prior TFE work. The goal was to compare and contrast the behavior of VF2 with TFE and VF3, knowing from the prior art that VF2 has a substantially less oxidizing character than the former two substrates. Thus, I began my studies using several simple but electron-rich alkylphosphines which had recently come into our possession, and which had been manufactured originally and supplied by Cytec Canada (now Solvay). My attempts at furnishing metallacyclopentanes by combining the olefin with a 1:2 ratio of $Ni(cod)_2$ with PPr_3, PBu_3, and $P(i\text{-}Bu)_3$ were frustrated by the formation of simple π-olefin complexes **3.1a–c** of the formulation $[(R_3P)_2Ni(\eta^2\text{-}CF_2{=}CH_2)]$ (Scheme 3.3.1) which were only stable under an atmosphere containing VF2. They could therefore not be isolated in pure form by vacuum stripping, but could be observed and characterized by ^{19}F NMR. I was met with the same result when using chelating bisphosphines of various bite angles such as dibpe, dibpp, dcppe, dppf, and DPEphos, (respectively, **3.1d–h**) but with the latter ligand, solid material (from which I obtained a crystal structure much later-on during my Ph.D research) could be obtained by precipitation from ether (Figure 3.3.1). At this point, concluding that the intransigence of VF2 had to be overcome by a more electron-rich Ni(0) center than could be provided by these simple alkylphosphines,[4]

[4] In addition to the alkyl- and aryl-phosphine ligands mentioned here, typical phosphite ligands from our group's previous work (e.g. $P(O^iPr)_3$, $P(O\text{-}o\text{-}tol)_3$, &c) were also attempted but in these cases the VF2

I leaned back into NHC ligands. In my prior paper[19] with N. Andrella, bulky NHC ligands were shown to give reactive, low-coördinate metallacycles; this, and the growing body of work[39,43,44] from the Ogoshi group at Osaka University, served as precedent that perhaps such ligands might be the tools needed to finally coax some reactivity out of VF2.



Compound	P or P^P	δ(^{19}F) (ppm)	δ(^{31}P) (ppm)	J_{F-H} (Hz)	J_{F-P} (Hz)	J_{P-P} (Hz)
2.1a	P(*n*-Bu)$_3$	–96.4	8.7, 14.0	13	40, 27	31
2.1b	P(*i*-Bu)$_3$	–95.3	8.0, 13.0	14	37, 24	30
2.1c	P(*n*-Pr)$_3$	–96.4	7.5, 12.8	14	40, 26	33
2.1d	dibpe	–92.6	31.9, 36.8	14	50, 41	66
2.1e	dibpp	–94.6	0.7, 4.9	14	46, 37	25
2.1f	dcyppe	–92.0	59.7, 63.1	15	50, 39	57
2.1g	dppf	–94.7	21.3, 24.5	13	43, 28	22
2.1h	DPEphos	–92.5	18.7, 23.0	13	47	br mult

Scheme 3.3.1: Formation of π-VF2 complexes 3.1a–h with Ni and phosphine ligands

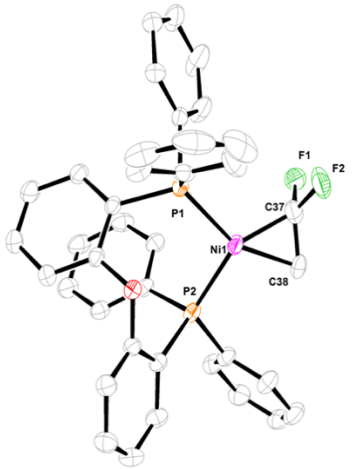
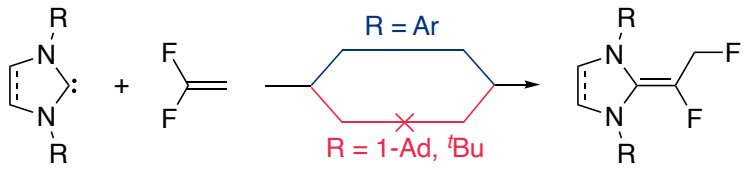


Figure 3.3.1: ORTEP representation of the molecular structure of complex 3.1h. Ellipsoids are set at the 30% probability level, and hydrogen atoms are omitted.

was found to be an insufficiently strong binder to push the equilibrium from NiL_4 to L_2Ni(olefin) + 2L. This led me to the conclusion that for VF2, much more electron-rich P-donors were required.

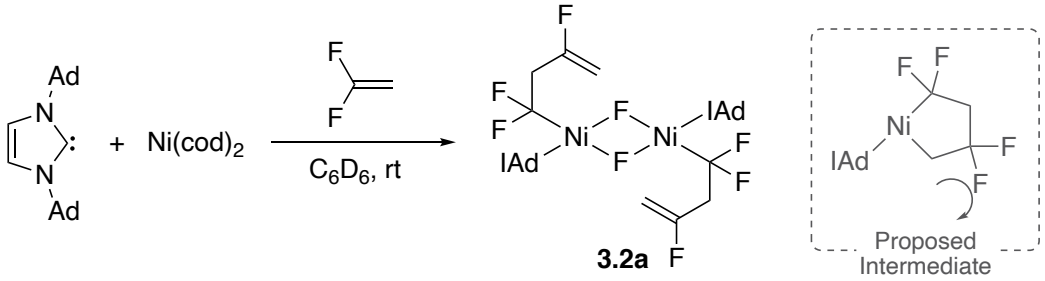


Scheme 3.3.2: Formation of Breslow-type adducts between free NHCs and VF2

There are limitations, however, to the use of free carbenes as co-reagents with fluoroölefins. This is primarily due to their fast and irreversible formation of Breslow-like adducts (Scheme 3.3.2), as first demonstrated first by Ogoshi[45] (and later elaborated on by M. Leclerc of our group[46]). The only free carbenes that appeared to resist this reaction were those with a 1,3-di(tert-alkyl) substitution pattern, of which IAd and ItBu are most common.[5] Upon reaction of a 1:1 ratio of IAd/Ni(cod)$_2$ with VF2 in benzene, there was obtained a dark red-orange solution which was characterized by ^{19}F NMR as containing a product with two signals integrating 2:1, and a nickel fluoride signal at –423 ppm. The presence of four apparent fluorines was encouraging, and suggested that VF2 dimerization had indeed occurred, albeit not to anything resembling a metallacycle. X-ray crystallography provided the definitive answer: a μ-F nickel dimer containing the –$CF_2CH_2CF{=}CH_2$ chain (compound **3.2a**), which may originate from a head-to-tail

[5] Despite having prepared both, I ultimately decided to work with IAd due to the difficulty of isolating large quantities of pure ItBu, of which a large proportion is frequently lost to sublimation during the solvent-stripping step.

metallacycle (Scheme 3.3.3) which had β-fluoride eliminated (a proposal which was much later supported by DFT studies carried out by our collaborator, R. P. Hughes—*vide infra*).



Scheme 3.3.3: Formation of compound 2.2a from VF2 and proposed intermediate metallacycle

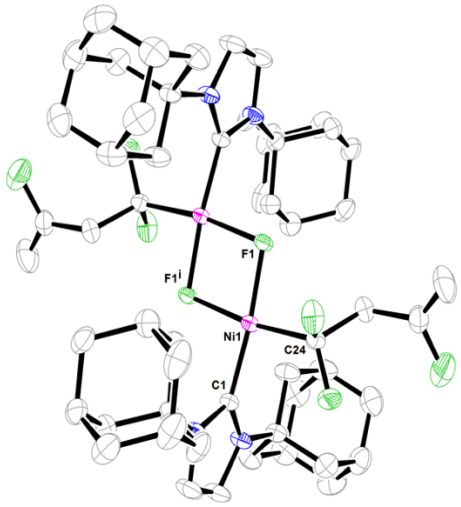
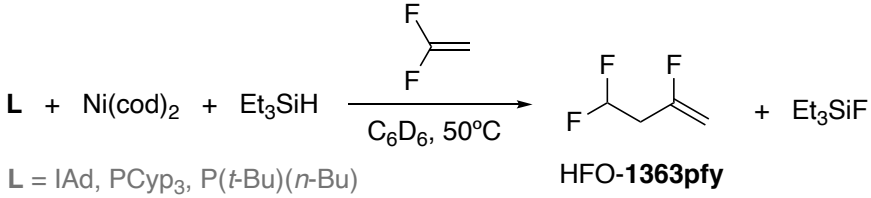


Figure 3.3.2: ORTEP representation of the molecular structure of complex 3.2a. Ellipsoids are set at the 30% probability level, and hydrogen atoms are omitted.

3.4 Early hydrodefluorodimerization



Scheme 3.4.1: Hydrodefluorodimerization of VF2 to HFO-1363pfy

Given the uniqueness of the 1,1,3-trifluorobut-3-enyl fragment, the opportunity to liberate a new fluoroölefin from this intermediate was sought. Unsurprisingly, prolonged heating of the complex failed to give any C–F bond reductive elimination. However, performing the IAd/Ni(cod)$_2$ reaction with VF2 in the presence of Et_3SiH resulted in the formation of Et_3SiF, accompanied by a new organic product: $CHF_2CH_2CF{=}CH_2$, provisionally named HFO-**1363pfy** (Scheme 3.4.1). I found no preparations of this compound anywhere in the academic or patent literatures, C_4-HFO refrigerant candidates themselves being few in number. Furthermore, preliminary studies suggested that this reaction, which I termed the *hydrodefluorodimerization* (HDFD), could be conducted with catalytic quantities of Ni(cod)$_2$. It was here that we decided to seek out an industry partner who could shed some light on the potential industrial utility of such a reaction and compound, and thus was initiated our fruitful relationship with Arkema Inc. In light of the applied direction this project was taking, the first step towards rendering this transformation attractive was to eliminate the NHC ligand. NHC ligands, though ubiquitous in academia (and increasingly so in medicinal chemistry, where money is no object), appear all but absent from commodity chemical processes—and no wonder; imidazolium salt cyclizations tend to be low-yielding (especially in the case of IAd), and their deprotonations inconsistent. Furthermore, in order to obtain a reasonable yield of pure carbene on deprotonation, an extremely pure imidazolium salt is needed, which often necessitates more than one recrystallization. Phosphines, on the other hand, are easily

synthesized on a commercial scale, and especially cheaply-so if they are accessible from PH_3. Fortunately, we were in possession of an assortment of PH_3-derived ligands manufactured by Cytec Canada, any of which could, if functional, be more cost-effective than IAd.

I found that a 1:1 ratio of $PCyp_3/Ni(cod)_2$ reacted the same way with VF2 as $IAd/Ni(cod)_2$, and also gave a catalytically active HDFD system, as did di(*tert*-butyl)-*n*-butylphosphine. It was thus demonstrated that costly NHC ligands are not crucial to the success of the reaction. *The reader should note that this is where the M.Sc research ends, and the new research relevant to the present thesis begins.*

3.5 Perfecting $Ni(cod)_2$

Up to this point, commercial $Ni(cod)_2$ had been used for all of our studies, and at no small expense. Though it is common in the inorganic community for regular users to eventually begin to synthesize their own $Ni(cod)_2$, it is a terribly inconvenient activity, requiring pyrophoric aluminum reducing agents, Schlenk technique verging on the virtuosic, and usually an overnight recrystallization at $-78^{o}C$—easy for those fortunate enough to be in possession of an ultralow-temperature freezer, which we were not. Furthermore, the thermal-instability of $Ni(cod)_2$ in regular glove-box freezers means that month-old samples begin to turn green with paramagnetic impurities, spoiling NMR experiments, causing workup headaches, and leading to potential reproducibility issues in

catalysis. While old samples *can* be restored to their original jonquil glow by recrystallization, this requires either dry ice temperatures (from a toluene-cod mixture), or an impractical excess of solvent (from anhydrous ether). All of this is to say that in order to sustain a $Ni(cod)_2$-based project, the myriad nuisances of its synthesis must be periodically re-lived in order to maintain a steady supply of fresh batches. Motivated by a strong disinclination to subject myself to this Sisyphean routine, I set out to develop a more user-friendly and hassle-free approach to $Ni(cod)_2$ which could be carried out in the glovebox at freezer-accessible temperatures. What follows is the result of that effort.

All $Ni(cod)_2$ syntheses generally follow the same pattern; a solution of anhydrous $Ni(acac)_2$ containing 1,5-COD (usually in excess by at least 50%) is reduced by an alkylaluminum reagent (usually also in slight excess) at low temperatures in either toluene or THF, warmed to room temperature, filtered to remove Ni black, crystallized overnight at $-78^{o}C$, and filtered again. These methods are consistent going back to the days of Wilke,[47,48] who used diethylaluminum ethoxide ('DEALOX') as the reducing equivalent, though $AlEt_3$[49] and DIBAL-H[50,51] are also commonly employed as the metal alkyl. It has been recently demonstrated by Wielandt and Ruckerbauer that the much milder Bu_2Mg can serve the same purpose.[52] Following suit, I too decided to use that same organometallic as a cheap, non-pyrophoric substitute[6] for the more reactive aluminum

[6] I have been informed that upon publication of this manuscript in OPR&D, some commentary was given *via* Twitter taking issue with my claim that $(n\text{-Bu})_2Mg$ is non-pyrophoric. Indeed, alkyl- and dialkylmagnesium reagents *in their pure form* are pyrophoric, but when $(n\text{-Bu})_2Mg$ is used as its commercial 1.0M solution in heptane, it is not; the MSDS of dibutylmagnesium solutions lacks the hazard statement H250 indicating pyrophoricity, and contains instead H260, which states that flammable gases will be

species. Wielandt and Ruckerbauer used (n-Bu)$_2$Mg in THF, the reaction solvent (in which Ni(cod)$_2$ is also moderately soluble), which necessitated on workup a vacuum-stripping step, methanol quench, and several extraction/filtration steps prior to obtaining solid material, tan in color according to the checkers. Given the low solubility of Ni(cod)$_2$ in aliphatic hydrocarbons, I hypothesized that using the commercial heptane solution, it would precipitate from solution as the solvent ratio grew more heptane-rich past the midpoint of the Bu$_2$Mg addition. Furthermore, though our glovebox is equipped with a liquid nitrogen cold-well for low-temperature reactions, not all gloveboxes are so implemented, and seeking the most widely practicable method possible, I opted to try my synthesis at –35°C (easily reached by a conventional glovebox freezer). The final consideration taken was to use strictly anhydrous conditions and high-grade anhydrous Ni(acac)$_2$, as unlike alkylaluminums, which form organic-soluble aluminoxanes upon exposure to trace amounts of moisture, Grignard reagents form insoluble oxide-hydroxides which could contaminate the precipitated Ni(cod)$_2$. Upon attempting the reaction on a 5 mmol scale, my hypotheses were vindicated by the observation of a beautiful bright yellow product which began to form after about the midpoint of the Grignard addition.

---

released in contact with water. Furthermore, I have carried out dozens of trials of this procedure, in one case even quenching the reaction effluent (which contains an excess of unreacted (n-Bu)$_2$Mg) with wet laboratory acetone *in air at room temperature*, and have observed no ignition events. This is in stark contrast to alkylaluminum reagents, which must be very carefully quenched over ice. I conclude therefore that for our purposes here, the use of (n-Bu)$_2$Mg demands no more extraordinary precautions than would be taken for the use of any other commonplace Grignard reagent, and thus feel justified in my claim that this method is possessed of a superior safety profile than the prior art. That being said, users should always observe the necessary precautions and SOPs when removing any air-sensitive material (phosphines, finely-divided metals, metal alkyls, &c) from the glovebox.

Furthermore, I found that the Bu_2Mg could be added rather quickly (in about 10 minutes on a 5 mmol scale), and after only another 10 minutes, a large volume of $Ni(cod)_2$ had precipitated, which could be easily isolated in 75–80% yield by filtration and washing sequentially with pentane and acetone. The product had a physical appearance no different from commercial $Ni(cod)_2$ (Figure 3.5.1)[7] and was pure by ^1H NMR (see ***Appendix A-I***).



Figure 3.5.1: Precipitated $Ni(cod)_2$ obtained by simple filtration and washing

Table 3.5.1: $Ni(cod)_2$ syntheses in assorted ethereal solvents

Example[a)]	**Solvent**	**Yield**[b)]
1	ethyl ether	76%
2	tetrahydrofuran	71%
3	1,4-dioxane	75%
4	isopropyl ether	76%
5	cyclopentyl methyl ether	74%
6	methyl *tert*-butyl ether	83%
7[c)]	methyl *tert*-butyl ether	61%
8[d)]	methyl *tert*-butyl ether	75%

[7] The thereby obtained product, though directly precipitated from the reaction media, was nonetheless possessed of that satisfying microcrystalline shimmer characteristic of recrystallized commercial samples.

[a] Standard conditions: $Ni(acac)_2$ (5 mmol), 1,5-cod (30 mmol), solvent (4 mL), (n-Bu)$_2$Mg (1.0 M in heptane, 11 mmol), $-35 \rightarrow 0$ °C for 20 min under N_2 atmosphere. [b] Isolated yield. [c] According to standard conditions but substituting 0.7M (n-Bu)(s-Bu)Mg for (n-Bu)$_2$Mg. [d] Linearly scaled to 50 mmol of $Ni(acac)_2$.

I carried out this reaction in a series of ethereal solvents and found that similarly good yields could be obtained (Table 3.5.1). Even process-friendly[53] cyclopentyl methyl ether (CPME) can be used. The alternate Grignard (s-Bu)(n-Bu)Mg could also be used as the reducing equivalent, albeit at a slight cost of yield, most likely due to concentration effects.[8] Furthermore, during the acetone washing step, the *sec*-butyl Grignard produces voluminous yellow insoluble matter in the filtrate which can be tedious to clean, and for those reasons this reaction is preferably carried out with the di-n-butyl Grignard. The quality of the $Ni(cod)_2$ remained the same for both Grignard reagents, and for all solvents tested. On a 5 mmol scale, the entire procedure takes only 20 minutes, and is therefore suitable for same-day catalyst screening in applications such as high-throughput experimentation. For larger-scale reactions, this method can be linearly scaled to 50 mmol with no appreciable loss in yield, with *ca.* 10 grams of material obtained after a total prep time of only a couple of hours.[9] Therefore, this improved procedure successfully attends to the apparent diseconomies of using large amounts of $Ni(cod)_2$ for an applied project.

[8] The (s-Bu)(n-Bu)Mg is only available from Aldrich as a more dilute 0.7M solution in hexanes.
[9] NB: this prep time does not include the time needed to cool the aluminum bead bath and reaction vessel in the glovebox freezer to –35°C. In my own practice, I have found it convenient to prepare the $Ni(acac)_2$/1,5-COD solutions the day before, and to place them (and the aluminum beads) in the freezer overnight, such that by next morning, the Grignard addition can be carried out in the quoted time.

This method is not only invaluable for the project at hand, but given the diverse and growing ecosystem of Ni catalysis,[54] should prove useful for the community at large.

3.6 Attempts to apprehend the metallacycle

Prior to engaging the services of our computational collaborator, R. P. Hughes, our initial hypothesis that the trifluorobutenyl fragment arises from a head-tail metallacycle was based on prior experience with other fluoroölefins (Scheme 3.6.1, eqn 3.6.1a). Efforts were made to apprehend this key intermediate using a variety of co-ligands with IAd, which would block the empty coördination site (and presumably also the β-fluoride elimination pathway). First, $Ni(cod)_2$ with a 1:1 ratio of IAd and P(*i*-Bu)$_3$ was tried, but with no success; after 15 minutes, ^{19}F NMR showed a roughly 1:1 mixture of both isomers of heteroleptic π-VF2 complex **3.1i**/**3.1i'** (eqn 3.6.1b). After allowing this mixture to sit overnight at room temperature, the phosphine simply dissociated and gave rise to complex **3.2a** (eqn 3.6.1c). Next, 4-dimethylaminopyridine (DMAP) ligand was tried, with the conviction that this much harder Lewis base would have less affinity for the softer π-VF2 complex than for the metallacycle. The DMAP reaction gave an ill-defined mixture containing multiple Ni fluorides (including **3.2a**), but from which **3.2d** serendipitously crystallized out (eqn 3.6.1d and Figure 3.6.1). More work is ongoing to determine what role the DMAP is playing, and whether other nitrogen-based ligands might be able to arrest the metallacycle, if only briefly enough to observe by ^{19}F NMR.

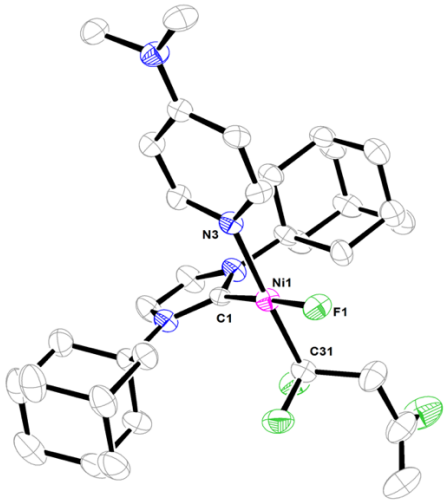
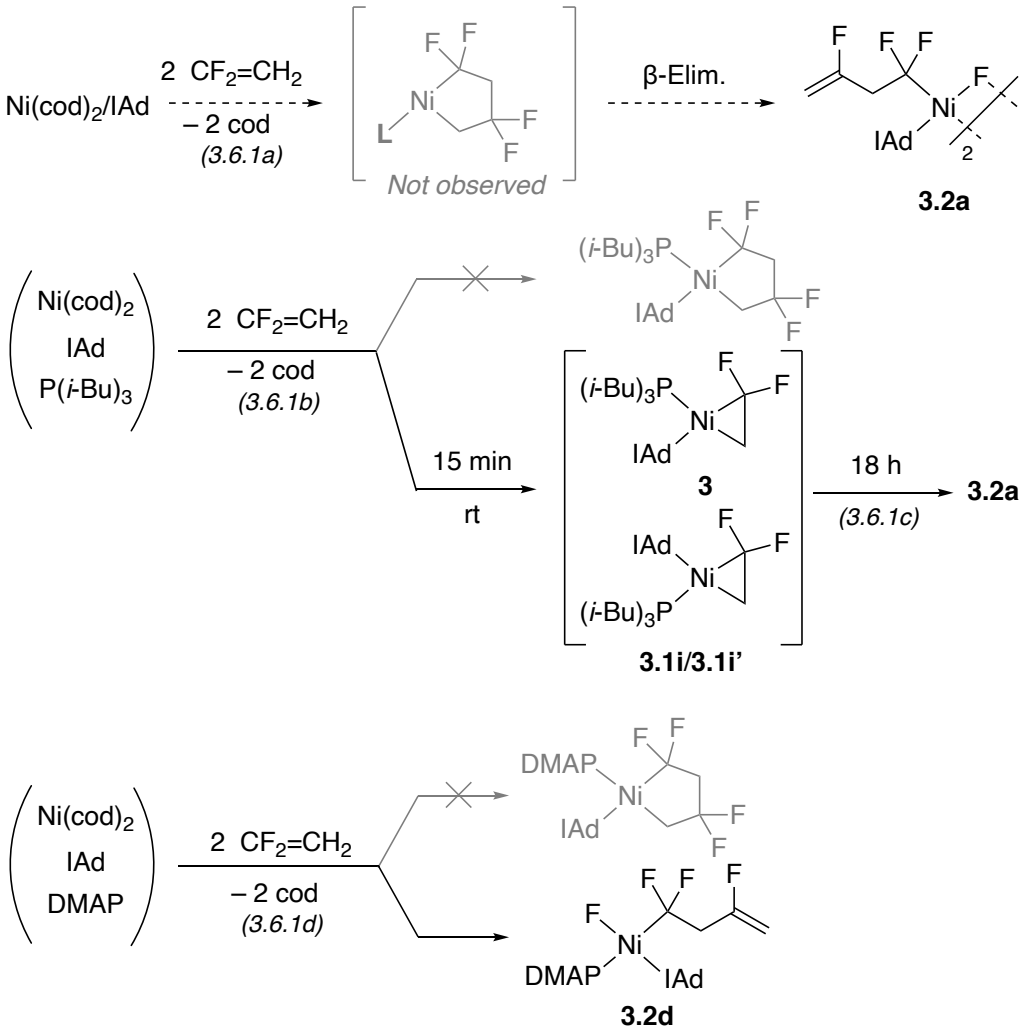


Figure 3.6.1: ORTEP representation of the molecular structure of complex 2.2b



Scheme 3.6.1: Attempts to apprehend the VF2 metallacycle with co-ligands

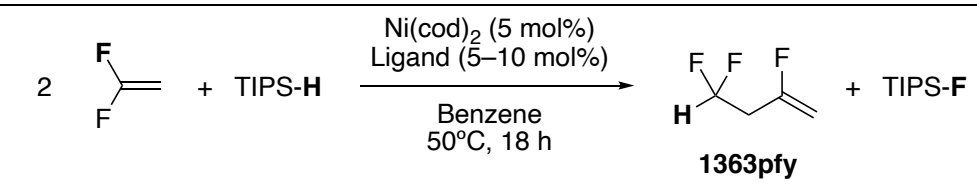
Our inability to observe the formation of the metallacycle would suggest that its lifetime is exceedingly short, and that its collapse *via* β-fluoride elimination is likely to be fast and unimolecular. Given our engagement of an industry partner at this time, efforts to apprehend the metallacycle were paused here in favor of further development and optimization of the aforementioned hydrodefluorodimerization reaction.

3.7 Optimization of the HDFD Reaction

Solutions of 10 mol% $Ni(cod)_2$ and various electron-rich ligands were screened and the selectivity for **1363pfy** determined by ^{19}F NMR (Table 3.6.1). Despite mild standard conditions (50°C for 18 h), a considerable quantity of dark precipitate was observed in runs 1 and 2 which, respectively, generated complexes **3.2a** and **3.2b** *in situ*. Run 3 using $PCyp_3$ was similar both in its performance and its production of precipitated matter, a fault which was not rectified when the ligand loading was increased to 20 mol% (run 4), nor when combined with DMAP (run 5). The greasier P(*t*-Bu)$_2$(*n*-Bu) fared better with regard to solution stability, but suffered a substantial loss in conversion and a slight drop in selectivity when combined with DMAP.[10] In all cases except Run 8, the HDFD reactions were ≥99% selective for **1363pfy**, with ≥95% VF2 conversion on a ^{19}F NMR basis.

[10] The byproduct accounting for 2% of the product mixture in run 8 was HFC-**152a**, the hydrogenation product of VF2.

Table 3.6.1: Catalytic VF2 HDFD runs



Run[a]	Ligand	S / Si / Ni /L	Conv. (%)[b]	1363pfy sel. (%)[b]
1	IAd	40 / 20 / 1 / 1	93	100
2	IAd[c]	40 / 20 / 1 / 1	95	100
3	$PCyp_3$	40 / 20 / 1 / 1	98	100
4	$PCyp_3$	40 / 20 / 1 / 2	99	100
5	$PCyp_3$[c]	40 / 20 / 1 / 1	97	99[d]
6	P(*t*-Bu)$_2$(*n*-Bu)	40 / 20 / 1 / 1	95	100
7	P(*t*-Bu)$_2$(*n*-Bu)	40 / 20 / 1 / 2	98	99
8	P(*t*-Bu)$_2$(*n*-Bu)[c]	40 / 20 / 1 / 1	79	98[e]

[a] Standard conditions based on 2.06 mmol VF2 in benzene (500 µL) at 50 °C for 18 h, see Experimental Section. [b] Based on ^{19}F NMR integrations. [c] With added equiv of DMAP (L / DMAP = 1/1). [d] Balance is byproduct ethyl fluoride (HFC-**161**). [e] Balance is by-product 1,1-difluoroethane (HFC-**152a**).

3.8 DFT Studies

The principal questions raised by these experimental studies involve the regioselective head-to-tail dimerization of VF2 to give a metallacyclopentane intermediate, and subsequent *β*-fluoride elimination to yield the final product. Curiously, *β*-fluorine elimination must be preferred over *β*-hydride elimination in the metallacycle to account for the observed final product. Unfortunately, neither the metallacycle intermediate nor the immediate product of *β*-F elimination can be observed under the reaction conditions. Accordingly, DFT calculations were performed at the B3LYP-D3/LACV3P**/ZPE level.

This choice of functional and basis set gave excellent agreement of metrics with those from the X-ray structure of **3.2a**. The I^{t}Bu ligand was chosen for computational study since its chemistry parallels that of its IAd analogue.

The calculated energetics for the three modes of cyclodimerization of VF2 are shown in Figure 4. Because of the experimental reaction stoichiometry used, calculations were confined to a single I^{t}Bu ligand bound to Ni. In fact, attempts to coordinate a second I^{t}Bu ligand *in silico* led invariably to dissociation of the added NHC. The three isomeric bis(alkene) complexes **Ia-c** (drawn as metallacyclopropanes[55]) are very close in energy, with a low energy transition state (**Id:** 10.2 kcal/mol) for their interconversion via rotation about the Ni-olefin axis.[56] Consequently, access to all three isomeric complexes **Ia-c** is energetically facile under the reaction conditions. All three possible metallacyclopentanes **IIIa-c** are significantly downhill from the starting complexes, with metallacycle **IIIc**, containing two Ni-CH_2 bonds being significantly less stable than **IIIb** with its two Ni-CF_2 bonds. The selectivity for dimerization via **Ia** is clearly kinetic in origin, with the transition state for head-to-tail dimerization (**IIa:** 19.7 kcal/mol) significantly lower in energy than those for head-to-head and tail-to-tail reactions (**IIb, IIc**). The calculated structures of **Ia-IVa** and **V** are illustrated in Figure 3.8.2. As expected, all σ-bonds from Ni to CF_2 are significantly shorter than corresponding bonds to CH_2.[57–59]

Interestingly, the preferred cyclization transition state **IIa** appears to be ambimodal,[60–68] and evolves downhill to a second transition state, leading to a bifurcated

pathway to give the two possible T-shaped metallacycles (**IIIa; IVa**) of the head-to-tail dimerization product. This second transition state corresponds to the Y-shaped transition state **V** for interconversion of the expected T-shaped[69–72] three-coordinate **IIIa** and **IVa**. Therefore, the head-to-tail dimerization produces an essentially equal mixture of rapidly equilibrating T-shaped metallacycles **IIIa** and **IVa**, each of which contains a vacant coordination site providing the option of β-F and β-H elimination reactions.

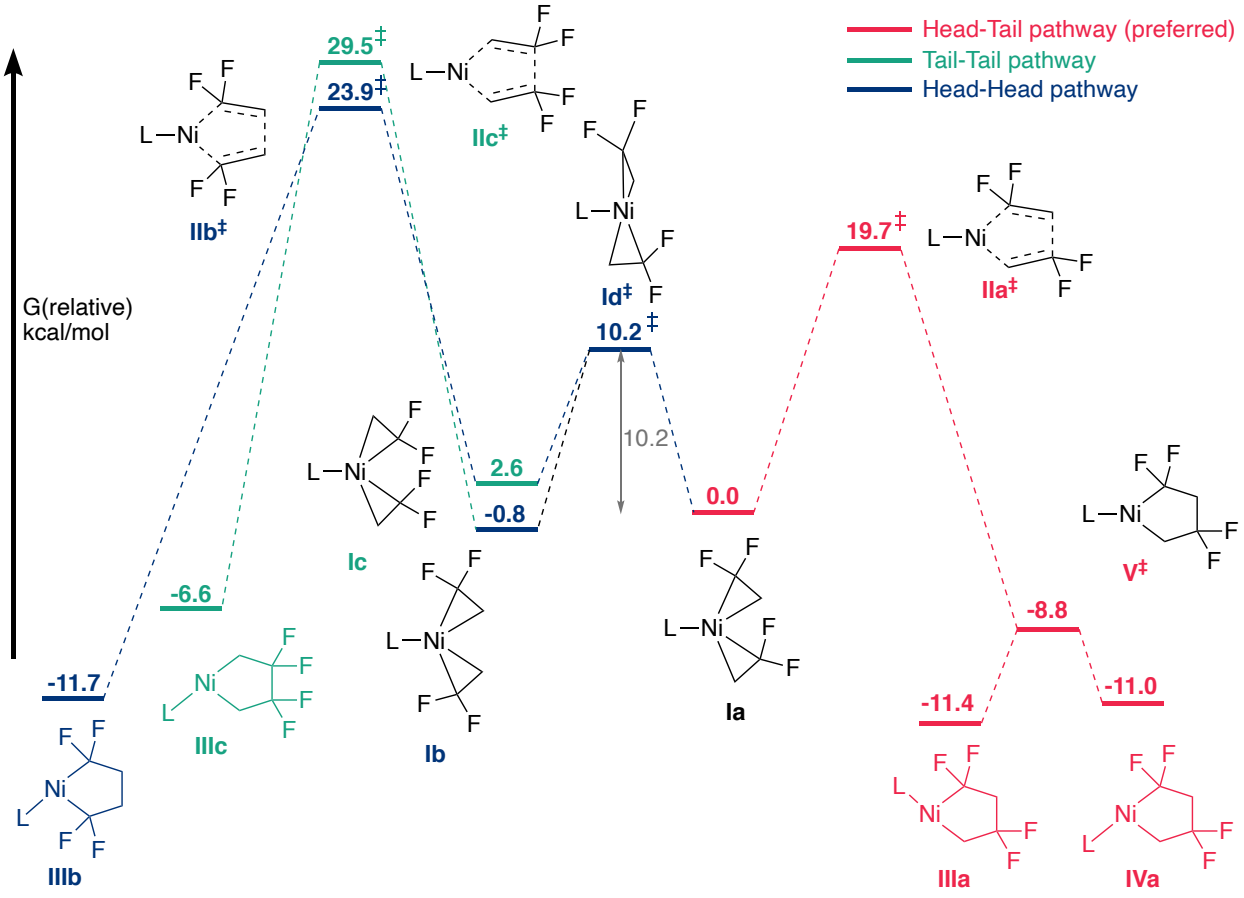


Figure 3.8.1: DFT/B3LYP-D3/LACV3P calculations of the energetics of metallacyclopentane formation from VF2.**[11]

[11] Transition structures are labelled ‡. All G values are rel. to that of **Ia** and are ZPE corrected. L = ItBu

β-Hydrogen eliminations from metallacycles have been addressed in previous computational studies, with the conclusion that such eliminations in metallacyclopentanes are relatively high in energy compared to acyclic analogues or larger metallacycle intermediates, in which β-agostic stabilization is conformationally accessible.[73–75] It is clear from the final product structure described here that β-F elimination must be preferred over the β-H option. The energy landscape for the two possible β-F elimination reactions from metallacycles **IIIa** and **IVa** are shown in Figure 6. Elimination from **IIIa** via transition state **VI** is energetically preferable to the corresponding elimination from **IVa** via transition state **VIII**. Calculated transition structures **VI** and **VIII** and resultant products **VII** and **IX** are shown in Figure 3.8.4.

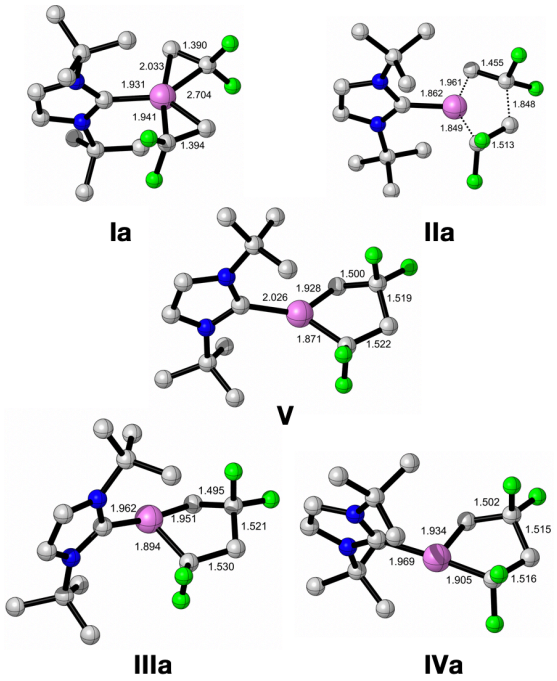


Figure 3.8.2: DFT/B3LYP-D3/LACV3P calculated structures of Ia-IVa and V.**[12]

[12] All hydrogen atoms are excluded for clarity. Distances are in Å.

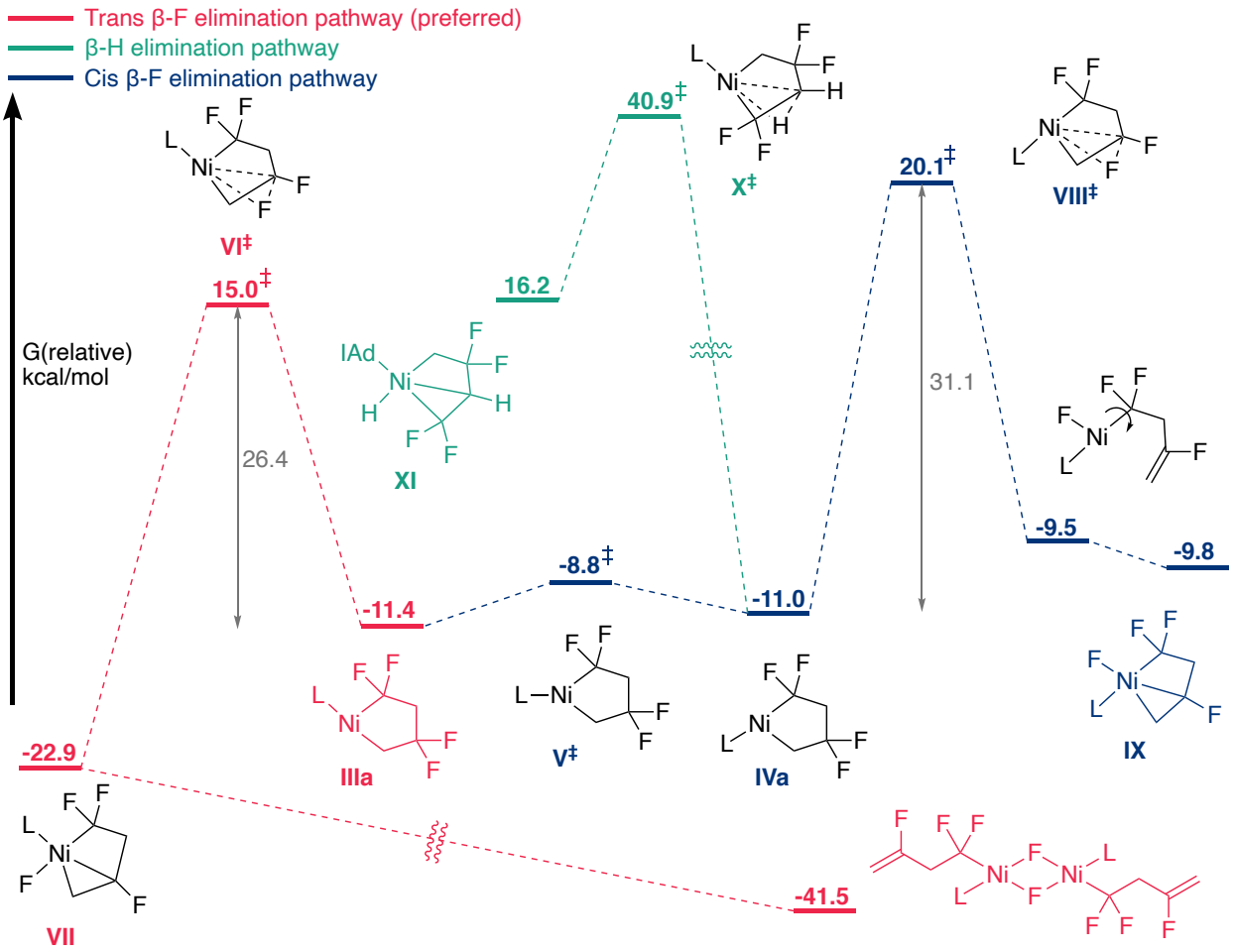


Figure 3.8.3: DFT/B3LYP-D3/LACV3P calculations of the energetics of β-F elimination from metallacyclopentanes IIIa and IVa and β-H elimination from IVa**[13]

At first blush it is surprising that transition state **VIII** is not more dramatically higher in energy than **VI**, since the final elimination product **IX** is that of a formally *trans* β-elimination. However, by virtue of the initial metallacyclic structure these eliminations possess different stereochemical features from many β-elimination reactions. In

[13] L = ItBu. Transition structures are labelled ‡. All G values are relative to that of **Ia** (Figure 3.8.1) and are ZPE corrected.

coordinately unsaturated d^8 complexes the four participating, mutually coplanar, atoms lie in the T-shaped coordination plane, with the migrating atom moving into the vacant *cis* coordination site. In these isomeric T-shaped metallacyclic precursors **IIIa** and **IVa**, the corresponding atoms lie almost *perpendicular* to the T-plane, such that the migrating fluorine in transition states **VI** or **VIII** is moving into a site perpendicular to that plane i.e. *not* the formally vacant site in the "square plane" of coordination. Subsequent reorganization allows **VI** to evolve into **VII** (a net *cis* β-F elimination), or **VIII** into **IX** (a net *trans* β-F elimination). Since isomer **VII**, (strong *trans*-influence CF_2 *trans* to weak *trans*-influence F)[36,53–55] is considerably more stable than **IX**, the Leffler-Hammond postulate[56–58] is consistent with a lower energy for transition state **VI**. We also considered the option of β-H elimination from **IIIa** or **IVa**, although this pathway is inconsistent with the final product structure. The free energy of activation for β-H elimination from **IVa** lies a whopping 49.0 kcal/mol uphill (Figure 6); we speculate that β-F elimination may be preferred to β-H elimination in this system because of participation of the fluorine lone pairs in forming the incipient agostic interaction. Finally, the observed dimeric fluoro-bridged product is significantly downhill from monomers **VII** or **IX** (Figure 3.8.3).

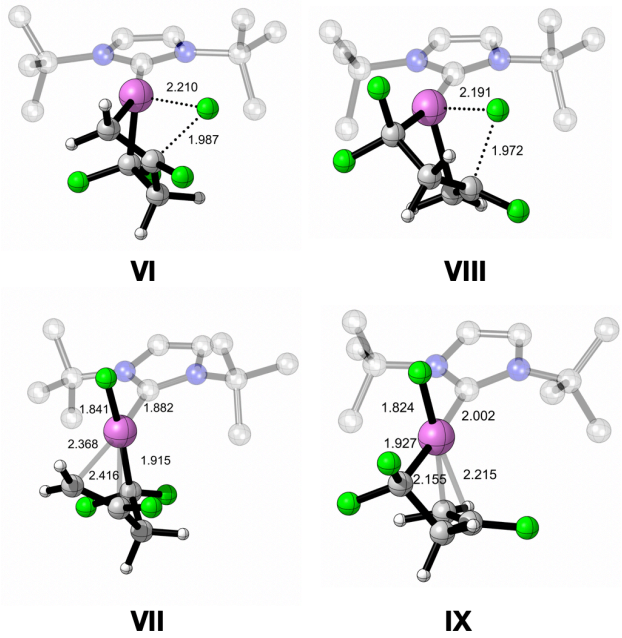


Figure 3.8.4: DFT/B3LYP-D3/LACV3P calculated β-F elimination transition structures VI and VIII and products VII and IX.**[14]

3.9 Concluding Remarks

The goal set out for this project was achieved and even transcended; the metallacycle derived from VF2 has been shown to behave in stark contrast to those derived from TFE or VF3 discussed in the prior art. The β-fluoride elimination pathway offers a unique new method by which fluorinated olefins can be reductively dimerized. The potential broader utility of HDFD prompted us to seek out (and eventually obtain) a patent[76] on this invention. A further study of fluoro-ethylenes and -propylenes of varying substitution patterns is underway.[15] Future practitioners will be able to go through large

[14] Hydrogen atoms on the I^{t}Bu ligand are excluded for clarity. Distances are in Å.
[15] On this, more in the overall concluding remarks found in ***Chapter 6***.

amounts of $Ni(cod)_2$ with impunity, thanks to the rapid and straightforward synthesis of same described earlier. That the catalytic HDFD reaction can also be performed using $RP(t\text{-}Bu)_2$ derivatives based on PH_3[16] eliminates the absolute necessity of deploying expensive NHC ligands where phosphines will do, and where isolable, solid products are not wanted. Opportunities for improvement include (a) the lowering of the catalyst loading to <10%—more relevant the more expensive the ligand—and; (b) identification of additives or alternate ligands to accelerate the reaction such that it can be scaled on a semicontinuous basis at ambient temperature.[17] The HDFD reaction represents the only catalytic reaction to come from homoleptic fluorometallacycles since Baker's 1998 patent, and there remain a great many questions yet to be tackled by more discovery-minded students in the future, as well as a wealth of other commercially-available highly electron-rich ligands to be tested for catalytic activity.

3.10 Experimental Section

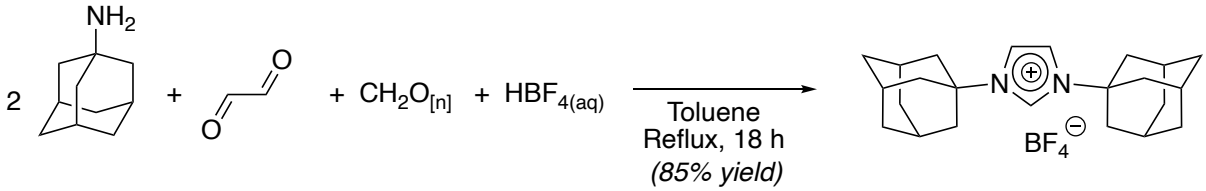
Experiments were conducted under nitrogen using an MBraun glovebox unless otherwise noted. Glassware was dried in an oven set at 120°C for 2 h before use. THF, toluene and ethyl ether were dried on columns of activated alumina using a J. C. Meyer (formerly Glass Contour) solvent purification system and stored over activated 3Å

[16] Further argumentation in favor of PH_3-based phosphines is upcoming in ***Chapter 4***.

[17] I spent a considerable amount of time attempting to carry out the HDFD at ambient pressures in a round-bottomed flask under a slow sparge of VF2. Unfortunately, the reaction was too slow for this to be practical, and the continuous sparge led to unwanted contamination of the product stream by solvent and TIPS-F.

molecular sieves overnight before use. Benzene (>99.5%, TCI America), benzene-d_6 (99.5%, Cambridge Isotope Laboratories), pentane (>99%, Fisher Chemical HPLC grade), cyclohexane (99.5%, anhydrous, Sigma-Aldrich), and toluene-d_8 (99.5%, Cambridge Isotope Laboratories) were dried over activated 3Å molecular sieves overnight before use. Tributylphosphine, triisobutylphosphine, tripropylphosphine, diethylisobutylphosphine, 1,2-bis-(diisobutylphosphino)ethane, 1,2-bis-(dicyclopentylphosphino)ethane, tricyclopentylphosphine, and di(*tert*-butyl)-*n*-butylphosphine were originally manufactured by Cytec Canada (now Solvay) and were used as received. Adamantan-1-amine (97%, Oakwood Chemical), 1,1'-bis(diphenylphosphino)ferrocene (≥97%, Accela ChemBio Inc.), 4-(dimethylamino)pyridine (98%, Fluka), fluoroboric acid (48% in water, Oakwood Chemical), glyoxal (40% in water, Sigma-Aldrich), (Oxybis(2,1-phenylene))bis(diphenylphosphine)—DPEphos—(97%, Ambeed), paraformaldehyde (95%, Sigma-Aldrich), sodium tert-butoxide (97%, Sigma-Aldrich), and triisopropylsilane (98%, Oakwood Chemical) were used as received. Vinylidene difluoride (VF2, polymer grade) was a generous donation from Arkema Inc. (King of Prussia, PA) and was used as received. $Ni(cod)_2$ was freshly prepared using our recently-reported method.[77] NMR spectra were recorded on a Bruker Avance 300 MHz instrument unless otherwise indicated. In ^{19}F spectra containing it, free VF2 was used as an internal chemical shift reference (δ –82.8 ppm). In HDFD reactions, NMR spectra were referenced to triisopropylsilyl fluoride (TIPS-F, δ –185.8 ppm). Isolated products were referenced to $PhCF_3$ (δ –83.5 ppm). ^{31}P NMR spectra were externally referenced to H_3PO_4.

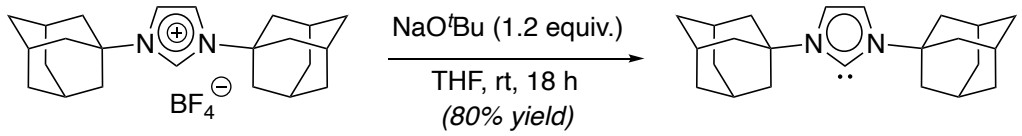
3.10.1 Preparation of 1,3-di(1-adamantyl)imidazolium tetrafluoroborate (IAd·HBF$_4$)



The following is an adaptation of the method previously reported by Bertrand et al.[78] A 250-ml round-bottomed flask was charged with paraformaldehyde (4.00 g, 100 mmol) and toluene (100 ml). The mixture was heated gently until an even suspension was observed, then 1-adamantanamine (15.125 g, 100 mmol) was added and the mixture stirred giving a milky white suspension. The, the flask was placed in an ice bath and a further equivalent of 1-adamantanamine (15.125 g, 100 mmol) was added. After stirring at 0°C for 10 minutes, fluoroboric acid solution (11.5 mL, 48% in H_2O) was added portionwise over 15 minutes, after which the flask was brought to room temperature and glyoxal solution (11.0 mL, 40% in H_2O) added. To the completed reaction (thick with white precipitate) was added another 50 ml of toluene, and then the flask was placed in an aluminum bead-bath (from Lab Armor; Irving, TX) at 110°C overnight with stirring. Upon warming, the thick suspension loosened and eventually gave way to a pale-yellow solution. The next day, the solution appeared dark red with a fine white suspension, which was filtered through a medium-porosity polyethylene fritted funnel (from Chemrus; Holliston, MA), washed first with toluene, then repeatedly with ethyl ether until a free-flowing white powder was obtained on drying under a stream of air. 36.0 grams (85% of

theory) of the title compound were thereby obtained. NMR spectra matched those reported in the literature.

3.10.2 Preparation of 1,3-di(1-adamantyl)imidazol-2-ylidene (IAd)



A 100-ml round-bottomed flask was charged with IAd-HBF$_4$ (2.122 grams, 5 mmol) and NaO^{t}Bu (577 mg, 6 mmol). The solids were suspended in THF (40 ml) and stirred at ambient temperature overnight, after which the reaction was stripped of volatiles under vacuum at 40°C to give an off-white residue. The residue was triturated with ethyl ether and filtered through a pad of Celite® to afford a pale-yellow solution. Removal of the ether under gentle vacuum gave the IAd free carbene as an off-white microcrystalline powder (1.355 grams, 80% of theory), which was stored in the freezer (–35°C) when not in use. NMR spectra matched those reported in the literature.[78]

*3.10.3 [L$_2$Ni(η^2-CF$_2$=CH$_2$)] complexes (**2.1a-g**) (NMR scale) General Procedure*

An NMR tube was charged with Ni(cod)$_2$ (14 mg, 0.05 mmol) and monodentate phosphine (0.1 mmol) or bidentate phosphine (0.05 mmol) dissolved in C_6D_6 (600 µL). The NMR tube was sealed with a gastight rubber septum cap wrapped in parafilm, and VF2 (3.0 ml, ca. 0.12 mmol) injected via a syringe fitted with a 23-gauge needle. (Caution!

Flammable gas!) The tube was then allowed to sit at room temperature for 30 minutes before analysis by NMR.

*3.10.4 [(P(n-Bu)$_3$)$_2$Ni(η^2-CF$_2$=CH$_2$)] (**2.1a**)*

^{19}F NMR (282 MHz., C_6D_6): –96.4 ppm (ddt, J_{F-H} = 13 (t), J_{F-P} = 40 (d), 27 Hz (d)). ^{31}P[^{1}H] NMR (121 MHz.): 8.7, 14 ppm (J_{P-P} = 31 Hz).

*3.10.5 [(P(i-Bu)$_3$)$_2$Ni(η^2-CF$_2$=CH$_2$)] (**2.1b**)*

^{19}F NMR (282 MHz., C_6D_6): –95.3 ppm (ddt, J_{F-H} = 14 (t), J_{F-P} = 37 (d), 24 Hz (d)). ^{31}P[^{1}H] NMR (121 MHz.): 8.0, 13.0 ppm (J_{P-P} = 30 Hz).

*3.10.6 [(P(n-Pr)$_3$)$_2$Ni(η^2-CF$_2$=CH$_2$)] (**2.1c**)*

^{19}F NMR (282 MHz., C_6D_6): –96.4 ppm (ddt, J_{F-H} = 14 (t), J_{F-P} = 40 (d), 27.5 Hz (d)). ^{31}P[^{1}H] NMR (121 MHz.): 7.5 ppm, 12.8 ppm (J_{P-P} = 33 Hz).

*3.10.7 [(dibpe)Ni(η^2-CF$_2$=CH$_2$)] (**2.1d**)*

^{19}F NMR (282 MHz., C_6D_6): –92.6 ppm (ddt, J_{F-H} = 13.5 (t), J_{F-P} = 50 (d), 40.5 Hz (d)). ^{31}P[^{1}H] NMR (121 MHz.): 31.9, 36.8 ppm (J_{P-P} = 65.5 Hz).

*3.10.8 [(dibpp)Ni(η^2-CF_2=CH_2)] (**2.1e**)*

^{19}F NMR (282 MHz., C_6D_6): –94.6 ppm (ddt, J_{F-H} = 14 (t), J_{F-P} = 46 (d), 36.5 Hz (d)). ^{31}P[^{1}H] NMR (121 MHz.): 0.7, 4.9 ppm (J_{P-P} = 25 Hz).

*3.10.9 [(dcyppe)Ni(η^2-CF_2=CH_2)] (**2.1f**)*

^{19}F NMR (282 MHz., C_6D_6): –92.0 ppm (ddt, J_{F-H} = 14.5 (t), J_{F-P} = 49.5 (d), 39 Hz (d)). ^{31}P[^{1}H] NMR (121 MHz.): 59.7, 63.1 ppm (J_{P-P} = 57 Hz).

*3.10.10 [(dppf)Ni(η^2-CF_2=CH_2)] (**2.1g**)*

^{19}F NMR (282 MHz., C_6D_6): –94.7 ppm (ddt, J_{F-H} = 12.5 (t), J_{F-P} = 42.5 (d), 28 Hz (d)). ^{31}P[^{1}H] NMR (121 MHz.): 21.3, 24.5 ppm (J_{P-P} = 21.5 Hz).

*3.10.11 [(DPEphos)Ni(η^2-CF_2=CH_2)] (**2.1h**)*

A 40-ml vial containing a PTFE-coated stir bar was charged with Ni(cod)$_2$ (100 mg, 0.364 mmol), DPEPhos (200 mg, 1 equiv.), and ethyl ether (5 ml). The vial was sealed with a bonded-septum vial and VF2 (45 ml) was added by syringe injection with stirring. After 45 minutes at room temperature, the resulting yellow precipitate was filtered in the glovebox through a medium-porosity fritted funnel, washed with hexanes (3 x 5ml), and dried under a stream of nitrogen to give the title compound as a bright yellow powder (274 mg, 97% of theory). Single crystals for X-ray diffraction were obtained

by carrying out the reaction in benzene without stirring and allowing the reaction mixture to sit overnight under a VF2 atmosphere at room temperature. ^{19}F NMR (292 MHz, C_6D_6) –92.5 ppm (tt, $J_{F-P} = 47$, $J_{F-H} = 13$ Hz). ^{31}P[^{1}H] NMR (121 MHz) 23, (br mult.), 18.7 ppm (br mult.).

*3.10.12 [(IAd)Ni(CF$_2$CH$_2$CF=CH$_2$)(μ-F)]$_2$ (**2.2a**)*

A 40-ml vial containing a PTFE-coated stir bar was charged with Ni(cod)$_2$ (412 mg, 1.5 mmol), IAd (505 mg, 1.5 mmol), and cyclohexane (10 ml). The vial was sealed with a PTFE/silicone bonded-septum cap and the mixture was stirred at room temperature until most of the Ni(cod)$_2$ had dissolved, giving a turbid pinkish-orange solution. To this solution was added VF2 (50 ml) through a syringe fitted with a 23-gauge needle. The color changed yellow-orange, with concomitant formation of some precipitate. Another 30 ml of the gas was charged, and the resulting mixture placed in an aluminum bead-bath heated to 50°C to stir for one hour, whereupon a large amount of orange precipitate formed beneath a dark red-orange supernatant. After cooling to room temperature, the precipitate was filtered in the glovebox through a medium-porosity polyethylene fritted funnel, washed with pentane (10 ml), and dried under a stream of nitrogen. There was thereby obtained 570 mg (73% of theory) of an orange amorphous powder. ^{19}F NMR (292 MHz): –423 (Ni–**F**, br mult.), –71.3 (Ni–C**F$_2$**–, mult.), –87.3 ppm (C**F**=CH$_2$, mult.).

*3.10.13 [(PCyp$_3$)Ni(CF$_2$CH$_2$CF=CH$_2$)(μ-F)]$_2$ (**2.2b**) (NMR scale)*

Performed as for **1a** but using 0.05 mmol of PCyp$_3$ instead of P(*n*-Bu)$_3$. Upon gas charging, the solution turned dark red-orange within minutes. No precipitate was observed. ^{19}F NMR (292 MHz, C_6D_6) –387 (Ni–**F**, br mult.), –87 (–C**F**=CH$_2$, br mult.), –67.8 ppm (Ni–C**F$_2$**–, br mult.). ^{31}P[^{1}H] NMR (121 MHz) 34.6 ppm (br mult.).

*3.10.14 [(P(t-Bu)$_2$(n-Bu))Ni(CF$_2$CH$_2$CF=CH$_2$)(μ-F)]$_2$ (**2.2c**) (NMR scale)*

Performed as for **1a** but using 0.05 mmol of P(*t*-Bu)$_2$(*n*-Bu) instead of P(*n*-Bu)$_3$. Upon gas charging, the solution turned dark red-orange within minutes. No precipitate was observed. ^{19}F NMR (292 MHz, C_6D_6) –387 (Ni–**F**, br mult.), –87 (–C**F**=CH$_2$, br mult.), –67.8 ppm (Ni–C**F$_2$**–, br mult.). ^{31}P[^{1}H] NMR (121 MHz) 34.6 ppm (br mult.).

*3.10.15 [(IAd)(P(i-Bu)$_3$(η^2-CF$_2$=CH$_2$] (**2.1i/2.1i'**) (NMR scale)*

Performed as for **2.1a** but using 0.05 mmol each of Ni(cod)$_2$, P(*i*-Bu)$_3$, and IAd. Upon gas charging, the solution turned bright yellow within minutes, slowly darkening to orange over the course of hours. No precipitate was observed. Products **2.1i**/**2.1i'** were observed by NMR after enough time had elapsed to fully dissolve the Ni(cod)$_2$—*ca.* 15 minutes. The *cis*- and *trans*-complexes (**2.1i** and **2.1i'**, respectively) are assigned as follows: ^{19}F NMR (292 MHz, C_6D_6) –94.6 (**2.1i'**, dt, J_{F-P} = 46, J_{F-H} = 11), –92.7 ppm

(**2.1i**, dt, J_{F-P} = 22, J_{F-H} = 12 Hz). $^{31}P[^{1}H]$ NMR (121 MHz) 9.4 (**2.1i'**, t, J_{P-F} = 46), 15.5 ppm (**2.1i**, t, J_{P-F} = 22 Hz).

*3.10.16 CHF_2–CH_2–CF=CH_2 (**1363pfy**) (NMR scale)*

An 8" NMR tube was charged with $Ni(cod)_2$ (3 mg, 0.012 mmol), IAd (4 mg, 0.012 mmol), Et_3SiH (7 mg, 0.06 mmol), and C_6D_6 (600 μL). The tube was sealed with a gastight rubber septum and wrapped with parafilm. VF2 (3 mL, *ca.* 0.12 mmol) was added by injection through a syringe fitted with a 23-gauge needle. The NMR tube was then placed in an aluminum bead bath heated to 50°C for 2 hours prior to analysis by ^{19}F NMR. **1363pfy**: ^{19}F (282 MHz): –117.0 (2F, dtd, $^{2}J_{F-H}$ = 56, $^{3}J_{F-H}$ = 16, $^{4}J_{F-F}$ = 4.3 Hz), –96.0 ppm (1F, ddt, $^{3}J_{F-H(trans)}$ = 49, $^{3}J_{F-H(cis)}$ = 21, $^{3}J_{F-H}$ = 17 Hz).

3.11 References

(1) Sicard, A. J. Organometallic Manipulations of Fluoroolefins Mediated or Catalyzed by Low-Coordinate Nickel, University of Ottawa, 2016.

(2) Feiring, A. E.; Hulbert, J. D. Trifluoroethylene Deflagration. *Chem. Eng. News* **1997**, *75*, 6.

(3) Antenucci, E. Stable Compositions of Trifluoroethylene. US 9,266,800 B2, 2016.

(4) Fukushima, M. Working Fluid for Heat Cycle, Composition for Heat Cycle System, and Heat Cycle System. US 2020/0079986 A1, 2020.

(5) Maeyama, H.; Sato, K. Refrigeration Cycle Apparatus. JP Appl. 2020-73649 A, 2020.

(6) Cundy, C. S.; Green, M.; Stone, F. G. A. Reactions of Low-Valent Metal Complexes with Fluorocarbons. Part XII. Fluoro-Olefin Reactions of Zerovalent Nickel Complexes. *J. Chem. Soc. A.* **1970**, 1647–1653.

(7) Green, M.; Shakshooki, S. K.; Stone, F. G. A. Reactions of Low-Valent Metal Complexes with Fluorocarbons. Part XVIII t-Butyl Isocyanide-Nickel Complexes. *J. Chem. Soc. A* **1971**, 1971–2828.

(8) Greco, A.; Green, M.; Shakshooki, S. K.; Stone, F. G. A. Ring Expansion Reactions in Organonickel Chemistry. *J. Chem. Soc. D Chem. Commun.* **1970**, No. 20, 1374–1375.

(9) Browning, J.; Green, M.; Stone, F. G. A. Reactions of Low-Valent Metal Complexes with Fluorocarbons. Part XVII. Tertiary Arsine-Nickel Complexes. **1971**, 453–457.

(10) Maples, P. K.; Green, M.; Stone, F. G. A. Reactions of Low-Valent Metal Complexes with Fluorocarbons. Part XXVI. 1,1,1-Tris(Diphenylphosphinomethyl)- and 1,1,1-Tris(Diphenylarsinomethyl)-Ethane. *J. Chem. Soc., Dalt. Trans.* **1973**, 388–392.

(11) Drinkard, W. C.; Lindsay, R. V. J. Hydrocyanation of Olefins Using Selected Nickel Phosphite Catalysts. US 3,496,215, 1970.

(12) Baker, R. T.; Beatty, R. P.; Farnham, W. B.; Wallace, R. L. J. Process for the Manufacture of Selected Halogenated Hydrocarbons Containing Fluorine and Hydrogen and Compositions Provided Therein. US 5,760,282, 1998.

(13) Baker, R. T.; Beatty, R. P.; Sievert, A. C.; Wallace, J. R. L. Process for the Manuacture of Fluorine-Substituted Hydrocarbons. US 6,242,568 B1, 2001.

(14) MInor, B. H.; Sievert, A. C. 1,1,2,2,3,3,4,4-Octafluorobutane Compositions. US 5,705,471, 1998.

(15) Burch, R. R.; Calabrese, J. C.; Ittel, S. D. Fluoroorganometallic Chemistry: Carbon-Fluorine Bond Activation in Perfluorometallacyclopentane Complexes. *Organometallics* **1988**, *7*, 1642–1648.

(16) Giffin, K. A.; Harrison, D. J.; Korobkov, I.; Baker, R. T. Activation of C-F and Ni-C Bonds of [P,S]-Ligated Nickel Perfluorometallacycles. *Organometallics* **2013**, *32*, 7424–7430.

(17) Giffin, K. A.; Korobkov, I.; Baker, R. T. Brønsted Acid-Promoted C-F Bond Activation in [P,S]-Ligated Neutral and Anionic Perfluoronickelacyclopentanes. *Dalt. Trans.* **2015**, *44*, 19587–19596.

(18) Giffin, K. A.; Pua, L. A.; Korobkov, I.; Baker, R. T. Formation and C–F Bond Functionalization of [P,N]-Ligated Perfluoronickelacyclopentanes. *Polyhedron* **2019**, *157*,

458–466.
(19) Andrella, N. O.; Sicard, A. J.; Gorelsky, S. I.; Korobkov, I.; Baker, R. T. A T-Shaped Ni[K2-(CF2)4-] NHC Complex: Unusual Csp3-F and M-CF Bond Functionalization Reactions. *Chem. Sci.* **2015**, *6*, 6392–6397.
(20) Giffin, K. A.; Pua, L. A.; Piotrkowski, S.; Gabidullin, B. M.; Korobkov, I.; Hughes, R. P.; Baker, R. T. Generation of Hydrofluoronickelacycles from Trifluoroethylene and Ni(0): Ligand Effects on Regio-/Stereoselectivity and Reactivity. *J. Am. Chem. Soc.* **2017**, *139*, 4075–4086.
(21) Ohashi, M.; Kawashima, T.; Taniguchi, T.; Kikushima, K.; Ogoshi, S. 2,2,3,3-Tetrafluoronickelacyclopentanes Generated via the Oxidative Cyclization of Tetrafluoroethylene and Simple Alkenes: A Key Intermediate in Nickel-Catalyzed C−C Bond-Forming Reactions. *Organometallics* **2015**, *32*, 1604–1607.
(22) Emrich, R.; Heinemann, O.; Jolly, P. W.; Krüger, C.; Verhovnik, G. P. J. The Role of Metallacycles in the Chromium-Catalyzed Trimerization of Ethylene. *Organometallics* **1997**, *16*, 1996–1998.
(23) Shirataki, H.; Ohashi, M.; Ogoshi, S. Nickel-Catalyzed Three-Component Coupling Reaction of Tetrafluoroethylene and Aldehydes with Silanes via Oxa-Nickelacycles. *European J. Org. Chem.* **2019**, *2019*, 1883–1887.
(24) Kawashima, T.; Ohashi, M.; Ogoshi, S. Nickel-Catalyzed Formation of 1,3-Dienes via a Highly Selective Cross-Tetramerization of Tetrafluoroethylene, Styrenes, Alkynes, and Ethylene. *J. Am. Chem. Soc.* **2017**, *139*, 17795–17798.
(25) Ohashi, M.; Ueda, Y.; Ogoshi, S. Nickel(0)-Mediated Transformation of Tetrafluoroethylene and Vinylarenes into Fluorinated Cyclobutyl Compounds. *Angew. Chemie - Int. Ed.* **2017**, *56*, 2435–2439.
(26) Kaplan, P. T.; Xu, L.; Chen, B.; Mcgarry, K. R.; Yu, S.; Wang, H.; Vicic, D. A. Mild, Safe, and Versatile Reagents for (CF2)n Transfer and the Construction of Fluoroalkyl-Containing Rings. *Organometallics* **2013**, *32*, 7552–7558.
(27) Yu, S.; Dudkina, Y.; Wang, H.; Kholin, K. V.; Kadirov, M. K.; Budnikova, Y. H.; Vicic, D. A. Accessing Perfluoroalkyl Nickel(Ii), (Iii), and (Iv) Complexes Bearing a Readily Attached [C_4F_8] Ligand. *Dalt. Trans.* **2015**, *44*, 19443–19446.
(28) Kosobokov, M. D.; Sandleben, A.; Vogt, N.; Klein, A.; Vicic, D. A. Nitrogen-Nitrogen Bond Formation via a Substrate-Bound Anion at a Mononuclear Nickel Platform. *Organometallics* **2018**, *37*, 521–525.
(29) Bour, J. R.; Ferguson, D. M.; McClain, E. J.; Kampf, J. W.; Sanford, M. S. Connecting Organometallic Ni(III) and Ni(IV): Reactions of Carbon-Centered Radicals with High-Valent Organonickel Complexes. *J. Am. Chem. Soc.* **2019**, *141*, 8914–8920.
(30) Coyle, T. D.; Kings, R. B.; Pitcher, E.; Stafford, S. L.; Teichel, P.; Stone, F. G. A. A Novel Heterocyclic Cobalt Compound. *J. Inorg. Nucl. Chem.* **1961**, *20*, 172–173.
(31) Hoehn, H. H.; Pratt, L.; Watterson, K. F.; Wilkinson, G. Transition-Metal Fluorocarbon Complexes. Part I. Derivatives of Perfluoro-Olefins. *J. Chem. Soc.* **1961**, 2738–2745.
(32) Manuel, T. A.; Stafford, S. L.; Stone, F. G. A. Chemistry of the Metal Carbonyls. VII. Perfloroalkyl Iron Compounds. *J. Am. Chem. Soc.* **1961**, *83*, 249–250.
(33) Fields, R.; Germain, M. M.; Haszeldine, R. N.; Wiggans, P. W. Metal Carbonyl Chemistry. Part IX. Improved Syntheses and Some Reactions of Tetracarbonylcyclo-Octatetramethyleneiron. *J. Chem. Soc. A* **1970**, 1964–1969.

(34) Ghostine, K.; Gabidullin, B. M.; Tom Baker, R. Synthesis and Reactivity of Perfluoroferracyclocarbenes. *Polyhedron* **2020**, *185*, 114587.
(35) Kuwae, R.; Kawakami, K.; Tanaka, T. Dicarbonylbis(Triphenylphosphine)(Fumaronitrile)Ruthenium(0) and Related Complexes. Preparation and Configuration in Solution. *Inorganica Chim. Acta* **1977**, *22*, 39–42.
(36) Gasafi-Martin, W.; Oberendfellner, G.; Von Werner, K. A Facile Synthesis of Metalla-Octafluorocyclopentane Complexes of Ruthenium and Nickel. *Can. J. Chem.* **1996**, *74*, 1922–1924.
(37) Xue, T.; Vicic, D. A. Routes to Acetonitrile-Supported Trifluoromethyl and Perfluorometallacyclopentane Complexes of Cobalt. *Organometallics* **2020**, *39*, 3715–3720.
(38) Portugués, A.; González, L.; Bautista, D.; Gil-Rubio, J. Gold Complexes with Difunctional Perfluoroalkyl Chains: Quantifying the Energy of Aurophilic Interactions in Flexible Open-Chain Complexes. *Angew. Chemie - Int. Ed.* **2020**, *59*, 15220–15225.
(39) Ogoshi, S. Highly Atom Economical Molecular Transformation via Hetero-Nickelacycle. *Bull. Chem. Soc. Jpn.* **2017**, *90*, 1401–1406.
(40) Ashley-Smith, J.; Green, M.; Stone, F. G. A. Reactions of Low-Valent Metal Complexes with Fluorocarbons. Part VII. Bis(Triphenylphosphine)(π-Ethylene)Nickel and Tetrakis(Methyldiphenylphosphine)Nickel. *J. Chem. Soc. A* **1969**, 3019–3023.
(41) Hoberg, H.; Guhl, D. 1,1-Difluorethen-Nickel-Ligand-Komplexe. *J. Organomet. Chem.* **1989**, *373*, 27–30.
(42) Ristic-Petrovic, D.; Anderson, D. J.; Torkelson, J. R.; McDonald, R.; Cowie, M. Olefin Binding in a Binuclear Iridium Complex as a Function of Fluorine Substitution: Ethylene to Tetrafluoroethylene. *Organometallics* **2003**, *22*, 4647–4657.
(43) Iwamoto, H.; Imiya, H.; Ohashi, M.; Ogoshi, S. Cleavage of C(Sp3)-F Bonds in Trifluoromethylarenes Using a Bis(NHC)Nickel(0) Complex. *J. Am. Chem. Soc.* **2020**, *142*, 19360–19367.
(44) Asada, T.; Hoshimoto, Y.; Ogoshi, S. Rotation-Triggered Transmetalation on a Heterobimetallic Cu/Al N-Phosphine-Oxide-Substituted Imidazolylidene Complex. *J. Am. Chem. Soc.* **2020**, *142*, 9772–9784.
(45) Ohashi, M.; Saijo, H.; Shibata, M.; Ogoshi, S. Palladium-Catalyzed Base-Free Suzuki-Miyaura Coupling Reactions of Fluorinated Alkenes and Arenes via a Palladium Fluoride Key Intermediate. *European J. Org. Chem.* **2013**, No. 3, 443–447.
(46) Leclerc, M. C.; Gorelsky, S. I.; Gabidullin, B. M.; Korobkov, I.; Baker, R. T. Selective Activation of Fluoroalkenes with N-Heterocyclic Carbenes: Synthesis of N-Heterocyclic Fluoroalkenes and Polyfluoroalkenyl Imidazolium Salts. *Chem. - A Eur. J.* **2016**, *22*, 8063–8067.
(47) Bogdanović, B.; Kröner, M.; Wilke, G. Übergangsmetallkomplexe, I. Olefin-Komplexe Des Nickels(0). *Justus Liebigs Ann. Chem.* **1966**, *699*, 1–23.
(48) Wilke, G.; Müller, E. W. Metal Complexes. US 4,120,882, 1978.
(49) Schunn, R. A. Bis(1,5-Cyclooctadiene)Nickel(0). *Inorg. Synth.* **1974**, *15*, 5–9.
(50) Lage, M. L.; Bader, S. J.; Sa-Ei, K.; Montgomery, J. Chemoselective Hydrosilylation of Hydroxyketones. *Tetrahedron* **2013**, *69*, 5609–5613.
(51) Wegner, S.; Rutz, C.; Schütte, K.; Barthel, J.; Bushmelev, A.; Schmidt, A.; Dilchert, K.; Fischer, R. A.; Janiak, C. Soft, Wet-Chemical Synthesis of Metastable Superparamagnetic Hexagonal Close-Packed Nickel Nanoparticles in Different Ionic Liquids. *Chem. - A Eur.*

J. **2017**, *23*, 6330–6340.
(52) Wielandt, J. W.; Ruckerbauer, D. Bis(1,5-Cyclooctadiene)Nickel(0). *Inorg. Synth.* **2016**, *35*, 120–125.
(53) Watanabe, K.; Yamagiwa, N.; Torisawa, Y. Cyclopentyl Methyl Ether as a New and Alternative Process Solvent. *Org. Process Res. Dev.* **2007**, *11*, 251–258.
(54) Ogoshi, S. *Nickel Catalysis in Organic Synthesis: Methods and Reactions*, 1st ed.; Wiley-VCH Verlag GmbH & Co.: Weinheim, Germany, 2019.
(55) Stone, F. G. A. Fluorocarbon Metal Compounds - Role Models in Organotransition Metal Chemistry. In *Fluorine Chemistry at the Millenium*; Banks, R. E., Ed.; Elsevier: Amsterdam, 2000.
(56) Curnow, O. J.; Hughes, R. P.; Mairs, E. N.; Rheingold, A. L. Facile Propeller Rotation in Metallacyclopropanes. Synthesis and Dynamic Behavior of New Tetrafluoroethylene-Ruthenium Complexes. Crystal and Molecular Structure of [Ru(H5-C5Me5)Cl(H2-C2F4). *Organometallics* **1993**, *12*, 3102–3108.
(57) Taw, F. L.; Clark, A. E.; Mueller, A. H.; Janicke, M. T.; Cantat, T.; Scott, B. L.; Hay, P. J.; Hughes, R. P.; Kiplinger, J. L. Titanium(IV) Trifluoromethyl Complexes: New Perspectives on Bonding from Organometallic Fluorocarbon Chemistry. *Organometallics* **2012**, *31*, 1484–1499.
(58) Hughes, R. P. Fluorine as a Ligand Substituent in Organometallic Chemistry: A Second Chance and a Second Research Career. *J. Fluor. Chem.* **2010**, *131*, 1059–1070.
(59) Hughes, R. P.; Meyer, M. A.; Tawa, M. D.; Ward, A. J.; Williamson, A.; Rheingold, A. L.; Zakharov, L. N. Does α-Fluorination Affect the Structural Trans-Influence and Kinetic Trans-Effect of an Alkyl Ligand? Molecular Structures of Pd(TMEDA)(CH_3)(RF) and a Kinetic Study of the Trans to Cis Isomerization of Pt(TMEDA)(CH3)2I(RF) [RF = CF2CF3, CFHCF3. *Inorg. Chem.* **2004**, *43*, 747–756.
(60) Yang, Z.; Dong, X.; Yu, Y.; Yu, P.; Li, Y.; Jamieson, C.; Houk, K. N. Relationships between Product Ratios in Ambimodal Pericyclic Reactions and Bond Lengths in Transition Structures. *J. Am. Chem. Soc.* **2018**, *140*, 3061–3067.
(61) Chen, S.; Yu, P.; Houk, K. N. Ambimodal Dipolar/Diels-Alder Cycloaddition Transition States Involving Proton Transfers. *J. Am. Chem. Soc.* **2018**, *140*, 18124–18131.
(62) Chuang, H. H.; Tantillo, D. J.; Hsu, C. P.; Hsu, C. P.; Tantillo, D. J. Construction of Two-Dimensional Potential Energy Surfaces of Reactions with Post-Transition-State Bifurcations. *J. Chem. Theory Comput.* **2020**, *16*, 4050–4060.
(63) Zhang, Z.; Jamieson, C. S.; Zhao, Y. L.; Li, D.; Ohashi, M.; Houk, K. N.; Tang, Y. Enzyme-Catalyzed Inverse-Electron Demand Diels-Alder Reaction in the Biosynthesis of Antifungal Ilicicolin H. *J. Am. Chem. Soc.* **2019**, *141*, 5659–5663.
(64) Yang, Z.; Zou, L.; Yu, Y.; Liu, F.; Dong, X.; Houk, K. N. Molecular Dynamics of the Two-Stage Mechanism of Cyclopentadiene Dimerization: Concerted or Stepwise? *Chem. Phys.* **2018**, *514*, 120–125.
(65) Mandal, N.; Datta, A. Dynamical Effects along the Bifurcation Pathway Control Semibullvalene Formation in Deazetization Reactions. *J. Phys. Chem. B* **2018**, *122*, 1239–1244.
(66) Yu, P.; Chen, T. Q.; Yang, Z.; He, C. Q.; Patel, A.; Lam, Y. H.; Liu, C. Y.; Houk, K. N. Mechanisms and Origins of Periselectivity of the Ambimodal [6 + 4] Cycloadditions of Tropone to Dimethylfulvene. *J. Am. Chem. Soc.* **2017**, *139*, 8251–8258.

(67) Yu, P.; Patel, A.; Houk, K. N. Transannular [6 + 4] and Ambimodal Cycloaddition in the Biosynthesis of Heronamide A. *J. Am. Chem. Soc.* **2015**, *137*, 13518–13523.
(68) Pham, H. V.; Houk, K. N. Diels-Alder Reactions of Allene with Benzene and Butadiene: Concerted, Stepwise, and Ambimodal Transition States. *J. Org. Chem.* **2014**, *79*, 8968–8976.
(69) Andrella, N. O.; Sicard, A. J.; Gorelsky, S. I.; Korobkov, I.; Baker, R. T. A T-Shaped Ni[K2-(CF2)4–] NHC Complex: Unusual Csp3–F and M–CF Bond Functionalization Reactions. *Chem. Sci.* **2015**, *6*, 6392–6397.
(70) Roselló-Merino, M.; Rivada-Wheelaghan, O.; Ortuño, M. A.; Vidossich, P.; Díez, J.; Lledós, A.; Conejero, S. Coordinatively Unsaturated T-Shaped Platinum(II) Complexes Stabilized by Small N-Heterocyclic Carbene Ligands. Synthesis and Cyclometalation. *Organometallics* **2014**, *33*, 3746–3756.
(71) Walter, M. D.; White, P. S.; Brookhart, M. Synthesis, Structure and Computational Studies of a Cationic T-Shaped Pd-Complex. *New J. Chem.* **2013**, *37*, 1128–1133.
(72) Eckert, N. A.; Dinescu, A.; Cundari, T. R.; Holland, P. L. A T-Shaped Three-Coordinate Nickel(I) Carbonyl Complex and the Geometric Preferences of Three-Coordinate D9 Complexes. *Inorg. Chem.* **2005**, *44*, 7702–7704.
(73) Yu, Z. X.; Houk, K. N. Why Trimerization? Computational Elucidation of the Origin of Selective Trimerization of Ethene Catalyzed by $[TaCl_3(CH_3)_2]$ and an Agostic-Assisted Hydride Transfer Mechanism. *Angew. Chemie - Int. Ed.* **2003**, *42*, 808–811.
(74) De Bruin, T. J. M.; Magna, L.; Raybaud, P.; Toulhoat, H. Hemilabile Ligand Induced Selectivity: A DFT Study on Ethylene Trimerization Catalyzed by Titanium Complexes. *Organometallics* **2003**, *22*, 3404–3413.
(75) Huang, X.; Zhu, J.; Lin, Z. β-Hydrogen Elimination of Five-Membered-Ring Metallacycles. Is It Possible? *Organometallics* **2004**, *23*, 4154–4159.
(76) Baker, R. T.; Sicard, A. J. Process for Catalytic Hydrodefluorodimerization of Fluoroölefins. US 10,882,802 B2, 2021.
(77) Sicard, A. J.; Baker, R. T. Safe and Expeditious Preparation of $Ni(Cod)_2$ for Same-Day High-Throughput Screening. *Org. Process Res. Dev.* **2020**, *24*, 2950–2952.
(78) Palazzolo, A.; Naret, T.; Daniel-Bertrand, M.; Buisson, D. A.; Tricard, S.; Lesot, P.; Coppel, Y.; Chaudret, B.; Feuillastre, S.; Pieters, G. Tuning the Reactivity of a Heterogeneous Catalyst Using N-Heterocyclic Carbene Ligands for C−H Activation Reactions. *Angew. Chemie - Int. Ed.* **2020**, *59*, 20879–20884.

4

CHAPTER FOUR

4. Alkylphosphine-mediated Hydrodefluorination

4.1 Introduction

READERS of this document may, at first glance, be bewildered by the existence of such a reaction as hydrodefluorination (HDF, or the reduction of C–F bonds to C–H bonds) and no wonder; consider that each and every fluorine atom in a molecule contributes to its cost, and therefore that the cheap and efficient installation of fluorine atoms (or fluorinated functional groups) continues to be a highly dynamic and popular pursuit both for bulk industrial processes (as we exhaustively covered in Section 1) and for smaller batch fine chemicals such as pharmaceuticals. It then appears paradoxical that alongside practitioners of fluorination there should also exist a contingent of chemists working towards stripping away those costly fluorine atoms and replacing them with humble hydrogens—one is almost tempted to call it a 'value-removing' step. The fundamental idea is explained as follows; elemental fluorine, while inexpensive in principle, is possessed of such outstanding reactivity that reining it in to selectively fluorinate complex organic molecules is no easy task. This isn't to say that such things haven't been

done in certain specific circumstances[1]—F_2 can be (and is) used quite effectively for small and structurally simple molecules—but that to date there remain very good reasons why ordinary practitioners of the art not otherwise specially equipped or trained in the use of fluorine in its elemental form are likely to avoid it. In contrast to the outstanding reactivity and dangers of F_2, highly fluorinated organic compounds are (excepting a few specific cases) relatively inert, inexpensive, and easily handled. It follows that the larger and more fluorous the organic, the more inert the temperament (and the lower the added cost per fluorine atom). We saw examples of this in Section 3.2 where dangerously reactive TFE was replaced with the much more docile $I(CF_2)_4I$ by Vicic for the synthesis and study of perfluorometallacycles. With regards to whether HDF is 'value-removing' or not, I encourage the reader to compare supplier prices of perhaloölefins with their hydrohalo-counterparts; hexafluoropropylene (HFP) is a perfluorinated olefin which can be procured for as little as \$0.15/gram, while its mono-hydrodefluorinated relative—1,2,3,3,3-pentafluoropropylene (HFO-**1225ye**)—sells for nearly \$2/gram from the same supplier.[18] In another case, chlorotrifluoroethylene (CTFE) sells for as little as \$0.39/gram while its mono-hydrodefluorinated product—1-chloro-1,2-difluoroethylene (HCFO-**1122a**)—sells for roughly \$40/gram in its largest pack size. Simply put, it's easier to perfluorinate (or to perhalogenate) something than to partially halogenate it. Broadly speaking, the prices of these compounds rise and fall more in relation with their ease (and scale) of synthesis

[18] Prices from www.synquestlabs.com in USD and accurate as of the time of publication

than with their fluorine content. HFP is inexpensive because it is manufactured by the pyrolysis of chlorodifluoromethane (HCFC-**22**),[2] itself one of the easiest fluorocarbons to manufacture on a large scale (as we already saw in Chapter 2). CTFE is inexpensive because it is made by pyrolytic reductive dehalogenation of the perhalogenated compound 1,1,2-trichloro-1,2,2-trifluoroethane (CFC-**113**).[3] The proposition of hydrodefluorination, therefore, is that if it is difficult to *selectively install* fluorine atoms, it may be less difficult to *selectively remove* them. Furthermore, it may be possible to access exotic organofluorine architectures through hydrodefluorination of cheap and common precursors such as HFP and CTFE—architectures for which there may not yet even exist a 'traditional' synthetic route. As the diversity of available hydrohalogenated olefins increases to meet the demand for new environmentally benign refrigerant models, HDF will constitute a key tool in the organofluorine chemist's arsenal. While kilotons of material are unlikely to ever be manufactured using methodologies discussed in the next two chapters—industrial practitioners preferring to carry out such reactions in the gas-phase over heterogeneous catalysts—the ability to easily and cheaply convert commercial perhalocarbon starting materials to new, higher-value H-containing compounds with conventional laboratory equipment is of imminent value during the gestational phase of development. Once a viable candidate has been identified and its properties ascertained, only then may it be worthwhile for the OEM to develop a suitable manufacturing protocol based on HF (or F_2) in order to bring the new compound to market.

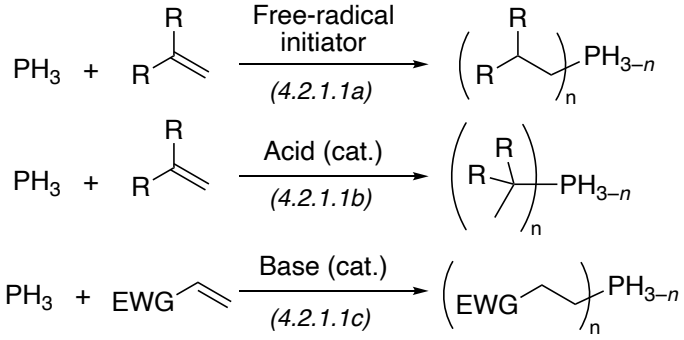
4.2 Prior Art

This chapter is concerned with the HDF of fluorocarbons using main-group nucleophiles, particularly phosphines. For now, we will leave out reports using transition metal catalysts or co-catalysts, as metal-catalyzed HDF will be reviewed independently in Chapter 5. The economics of stoichiometric (or near-stoichiometric) organophosphine reactions will be bolstered by a brief introduction to their syntheses from PH_3. Key to understanding the use of organophosphines as stoichiometric reductants is an accompanying understanding of their reactivity with fluorinated olefins in general, much of which was revealed by the great D. J. Burton—an important organofluorine pioneer whose research will serve as a suitable backdrop for this chapter. For more information on Burton and his illustrious career at the University of Iowa, the reader is encouraged to seek out his chapter in *Fluorine Chemistry at the Millenium.*[4]

4.2.1 The origins of alkylphosphines

Of all of the organophosphines commonly talked-about (whether as ligands, nucleophiles, organocatalysts, &c) all but PPh_3 and PMe_3 are most efficiently derived from the relatively unknown precursor (in laboratory circumstances, in any case)—PH_3. Pure phosphine gas, possessed of both severe toxicity by inhalation (PEL = 0.3 ppm, immediate danger at 50 ppm, LC_{Lo} (human) = 1000 ppm, 5 min)[5] and a tendency to

autoignite in moist air,[6,19] is a chemical implement not for the faint of heart. Indeed, only one primary PH_3 plant exists in North America; situated in Niagara Falls, ON, it has been first operated by American Cyanamid, then Cytec Canada, and currently by Solvay. Despite the difficulties in its handling, and the scarcity of its OEMs, a great number of commodity organophosphines such as PBu_3 and $P(Oct)_3$ are derived from PH_3, typically by olefin hydrophosphination reactions (Scheme 4.2.1.1). Free-radical hydrophosphinations give anti-Markovnikov products (eqn 4.2.1.1a),[7,8] while acid-catalyzed hydrophosphination gives Markovnikov products and tends to favor monosubstitution (eqn 4.2.1.1b).[9,10] PH_3 also has substantial nucleophilic character, and can undergo base-catalyzed Michael-additions to electron-deficient olefins (eqn 4.2.1.1c).[11,12]

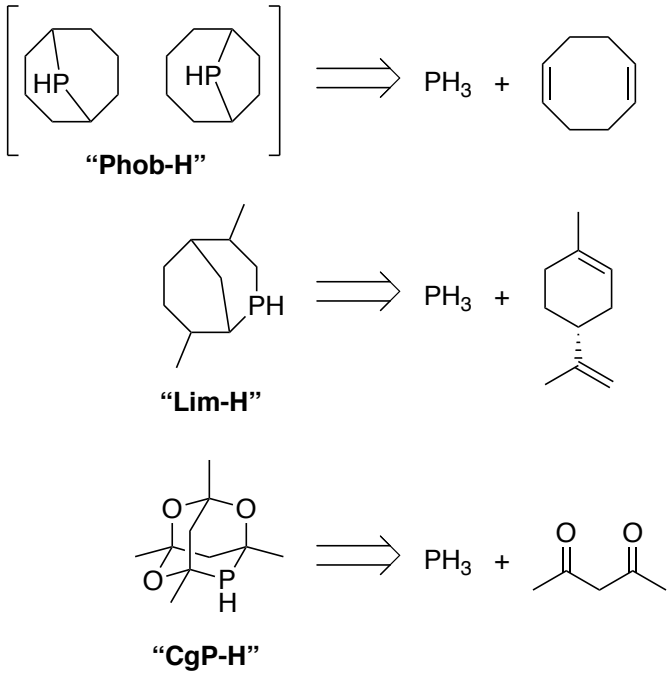


Scheme 4.2.1.1: General types of hydrophosphination reactions [7–12]

[19] Pure PH_3 can ignite in moist air when diluted to as low as 5% in N_2, but impure samples which contain P_2H_4 can ignite at much lower concentrations. Thus, the pyrophoricity risk is paradoxically reduced by using higher-purity material (semiconductor grade 5.5 or greater).

Organophosphine derivatives produced from PH_3 have a marked commercial advantage over those produced by means of P–Cl bonds, *viz.* the low cost and high P-content by weight of PH_3 and the atom-economy afforded by the hydrophosphination reaction. This advantage is of course manifested by their low cost; PBu_3, for example, can be procured for as little as \$0.43/gram (tech. grade 93%) and $P(Oct)_3$ for \$0.70/gram.[20] Of course, the scope of available compounds from PH_3 far exceeds these two mundane examples. A glance at Solvay's Organophosphine Specialties catalog[13] reveals a diverse range of architectures, many of which (such as the *phobane*,[14] *Lim*-,[15] *CgP*[16,17] ligands) cannot be prepared in any other way (Scheme 4.2.1.2). All of this, before launching into the stoichiometric applications of these species, is intended to impress upon the reader the economic advantages to selecting PH_3-derived alkylphosphines.

[20] Products #15-5801 and #15-6655, respectively, from Strem Chemicals (Newburyport, MA); prices in USD available on www.strem.com and accurate as of the time of publication

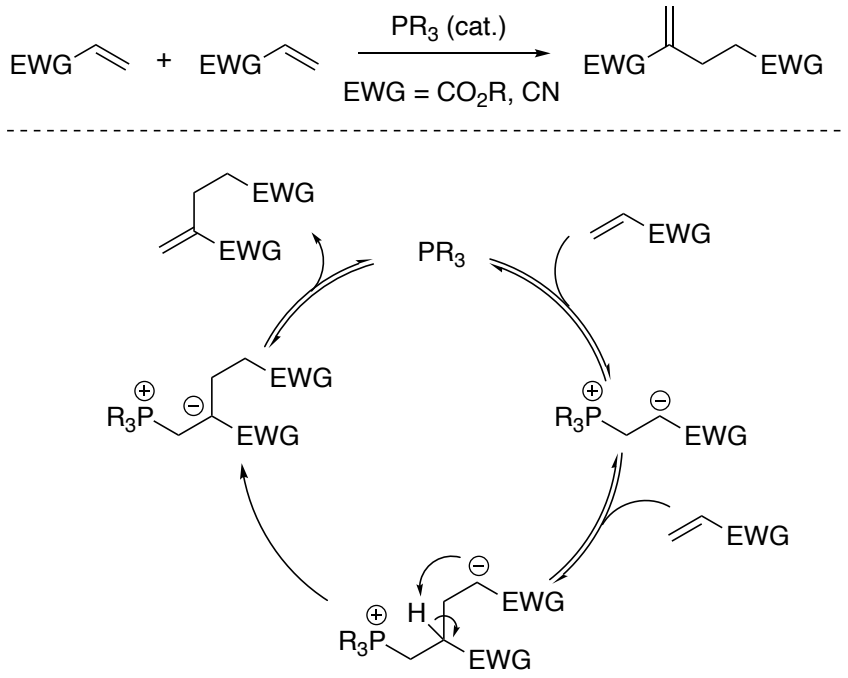


Scheme 4.2.1.2: Cyclic phosphine architectures exclusively from PH_3 [13–16]

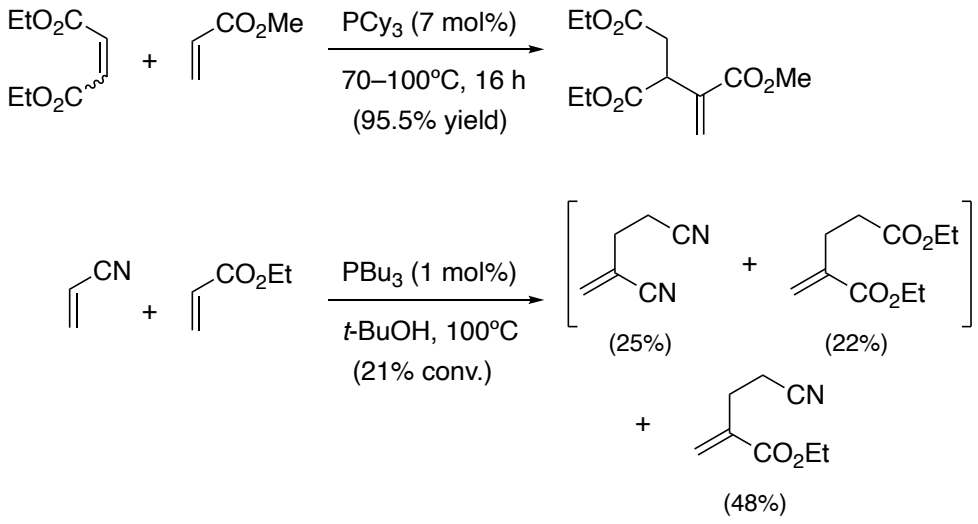
4.2.2 Phosphines as organocatalytic nucleophiles

Perhaps the defining characteristic of organophosphines (other than the spectacle of an occasional lab fire[21]) is their consummate nucleophilicity. Though stoichiometric reactions of organophosphines such as the Wittig olefination[18] have long been known and used, the burgeoning field of organocatalysis has seen the leveraging of the structural and electronic diversity of phosphines for a much wider variety of transformations.[19,20] The majority of these employ some sort of electrophilic π-system as the substrate, such as the phosphine-catalyzed Rauhut-Currier olefin dimerization developed at American Cyanamid (Scheme 4.2.2.1).[21–23] The most characteristic substrates for these dimerizations are acrylonitriles and acrylate esters, which can be cross-coupled (Scheme 4.2.2.2).[24,25]

[21] On this subject, regrettably, your humble author can speak with some experience.



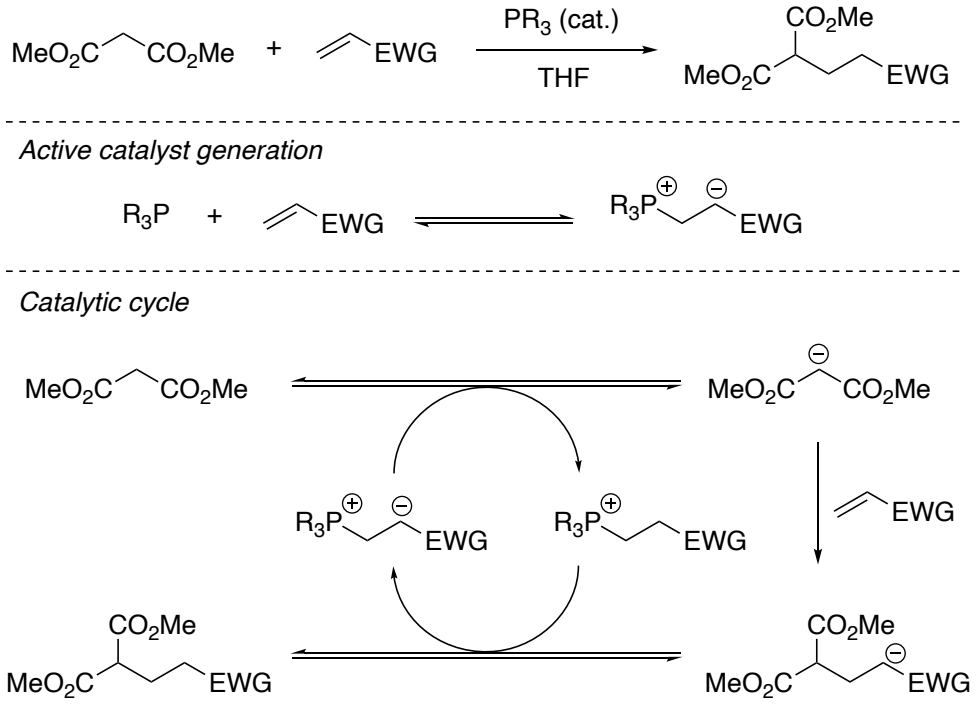
Scheme 4.2.2.1: Generalized mechanism for the Rauhut-Currier reaction [21–23]



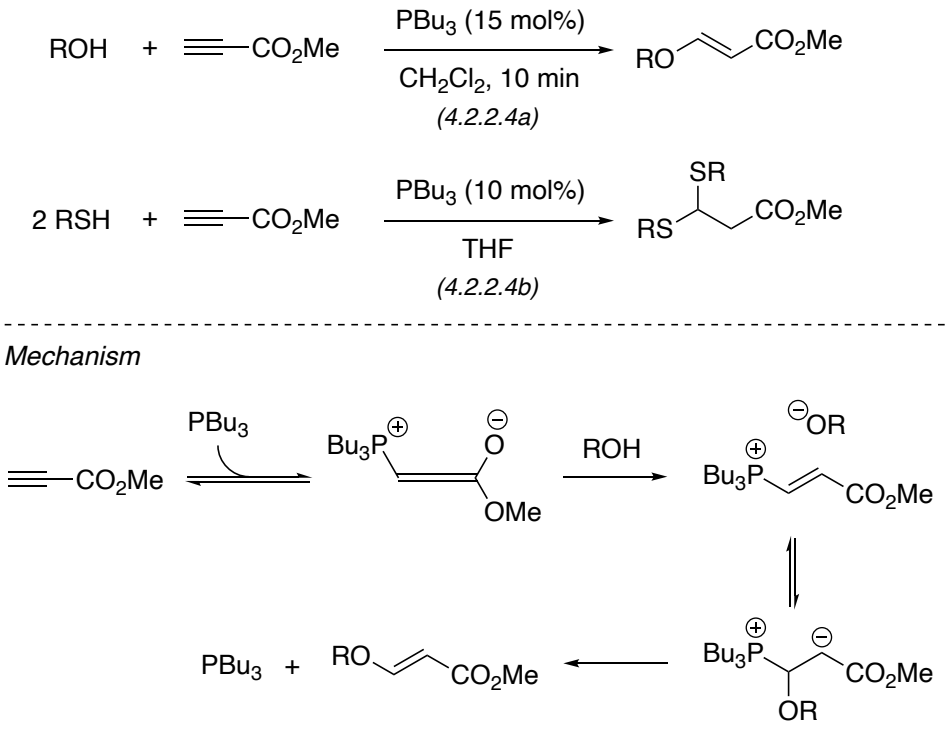
Scheme 4.2.2.2: Examples of cross Rauhut-Currier reactions [24, 25]

Phosphines can also be used to catalyze Michael additions of carbon acids[26] and alcohols[27] to *a*,*β*-unsaturated electrophiles (Scheme 4.2.2.3). Such reactions universally

follow a manifold leading with nucleophilic addition of the phosphine to the π-system, forming the zwitterionic active catalyst. Through a series of proton transfers, the actual nucleophile is deprotonated and undergoes conjugate addition to another equivalent of the electrophile, which subsequently deprotonates the phosphonium salt to regenerate the catalyst. Exemplary nucleophiles for this reaction include nitroalkanes, β-diketonates, β-diesters, alcohols, thiols, &c, while acrylate esters and acrylonitriles constitute the most common electrophiles. Propiolate esters can also be used as electrophiles (Scheme 4.2.2.4), with alcohol (eqn 4.2.2.4a) and thiol (eqn 4.2.2.4b) nucleophiles furnishing vinylic and saturated products, respectively.[28]

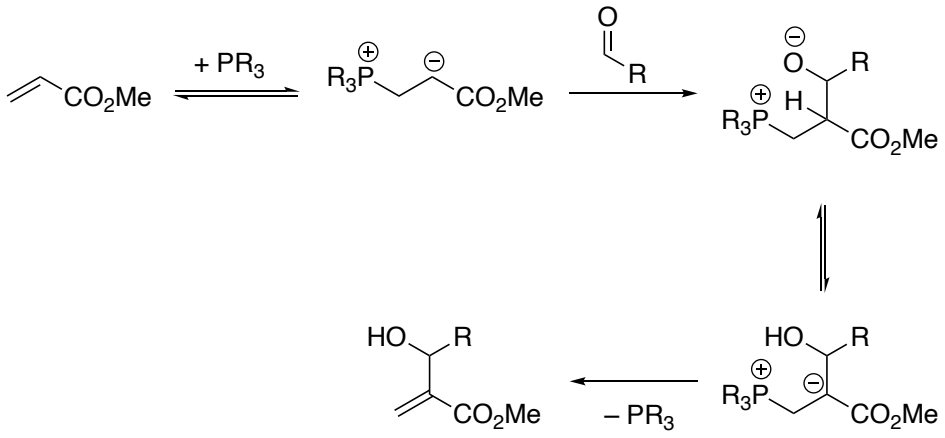


Scheme 4.2.2.3: Phosphine-catalyzed conjugate addition [26]



Scheme 4.2.2.4: Phosphine-catalyzed conjugate addition to methyl propiolate [28]

Not to be omitted in this introductory overview is the ubiquitous Morita-Baylis-Hilman reaction. Well-known to and extensively reviewed by members of the organic community,[29–32] it is one of the most called-upon carbon-carbon bond-forming reactions in the synthetic chemist's toolkit, and though many modern iterations have employed amine bases, it is most classically catalyzed by organophosphines *via* the manifold shown in Scheme 4.2.2.5.



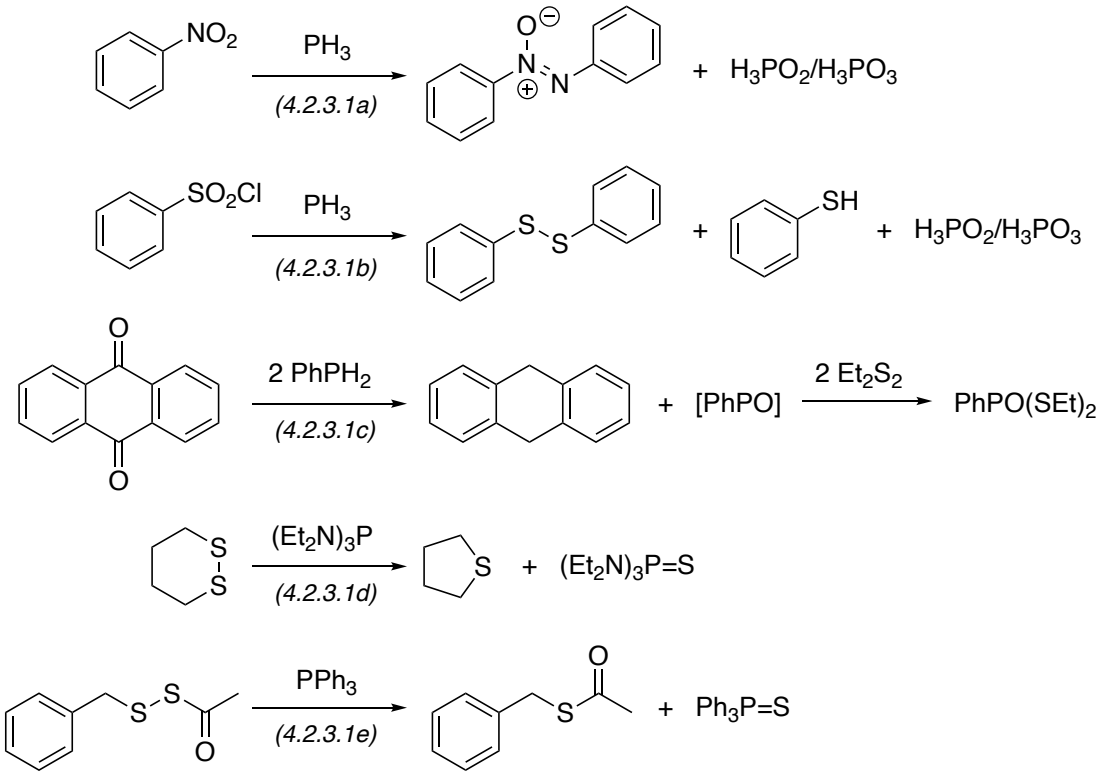
Scheme 4.2.2.5: Phosphine-catalyzed Morita-Baylis-Hilman reaction [29–32]

4.2.3 Phosphines as reducing agents

The sensitivity to air oxidation exemplified by most phosphines suggests that they may have some utility as stoichiometric reductants. Indeed, an early report by Buckler, Epstein, et al.[22] reported on the use of PH_3 itself as a stoichiometric reductant (Scheme 4.2.3.1) for aromatic nitro compounds (eqn 4.2.3.1a) and sulfonyl chlorides (eqn 4.2.3.1b) in alkaline media.[33] Aromatic ketones and thioketones can similarly be reduced with $PhPH_2$ as reported by Tamano and Koketsu, the thereby produced 1° phosphine oxide being converted to the innocuous diethyl phenylphosphonodithioate (eqn 4.2.3.1c).[34] This reactivity of phosphines with sulfur compounds has also facilitated their utility as desulfurization agents. Disulfides are cleanly reduced to sulfides by $(Et_2N)_3P$ at as low as room temperature (eqn 4.2.3.1d),[35] while acetyl benzyl disulfides are reduced to

[22] The same Buckler and Epstein from American Cyanamid Co. who first reported the condensation of PH_3 with acetylacetone to form CgPH

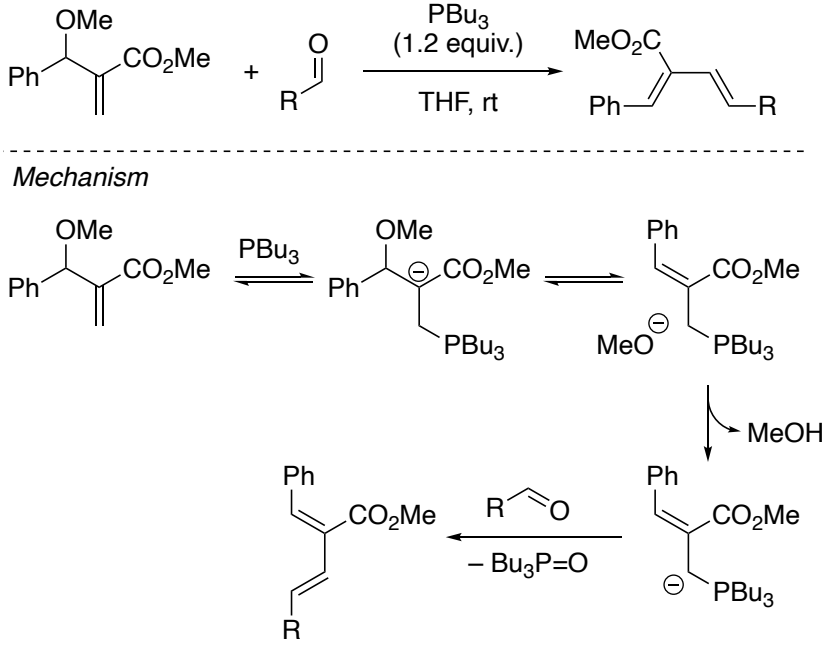
thioesters (eqn 4.2.3.1e).[36] This ability to cleave S–S bonds has been leveraged extensively by the biochemistry community.[37]



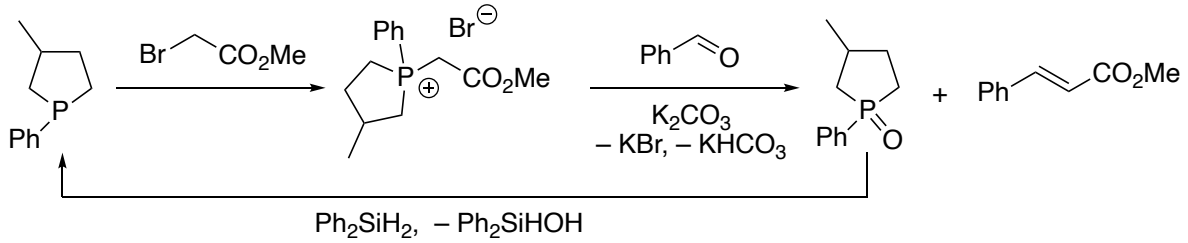
Scheme 4.2.3.1: Assorted phosphine-mediated reductions [33–36]

The Wittig reaction is another well-known and practiced deoxygenative reaction which uses a stoichiometric amount of organophosphine.[38–41] Following from Section 4.2.2, PBu_3 is capable of converting Morita-Baylis-Hilman-adducts into dienes *via* a Wittig reaction (Scheme 4.2.3.2).[42] More germanely to this thesis chapter, there is an increasing interest in carrying out reactions which generate P(V) products in the presence of a suitable alterative terminal reductant, such that the P(III) catalyst can be regenerated and used on a catalytic basis. Wittig reactions, for instance, can be carried out in the

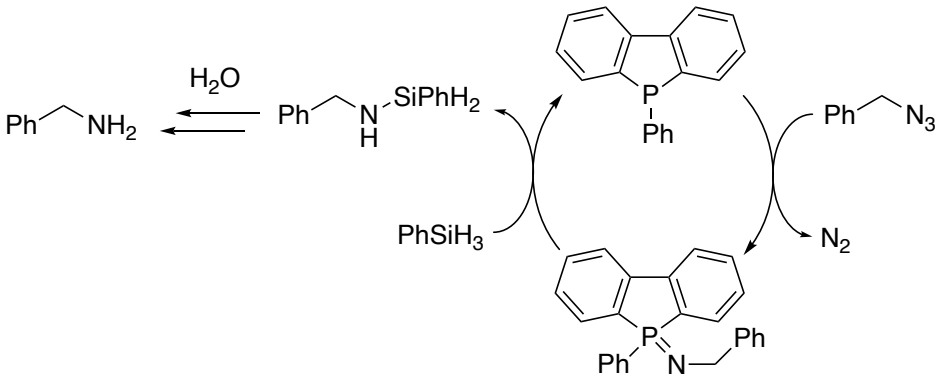
presence of a silane, which selectively regenerates the phosphine nucleophile (Scheme 4.2.3.3).[43] Silanes being of generally lower cost than phosphines (and their waste products more easily dispensed-with than phosphine oxides), Wittig reactions carried out this way have a distinct practical advantage. Furthermore, the air-sensitive P(III) species can be generated *in situ* by action of silane on the P(V) oxide, so that no pyrophoric materials need be handled by the user. Another example of a stoichiometric reaction rendered phosphine-economical is the Staudinger reduction; ordinarily, the P=NR species that results is hydrolyzed on workup to yield phosphine oxide and the reduced RNH_2 species, but van Delft et al. demonstrated that if the reaction is performed in the presence of $PhSiH_3$, the P=NR bond is reduced to RNH[Si] and the phosphine is generated (Scheme 4.2.3.4).[44] The N–Si bond is instead hydrolyzed on workup to yield siloxane byproducts.



Scheme 4.2.3.2: Wittig reaction of an MBH adduct [42]



Scheme 4.2.3.3: The first reported catalytic Wittig reaction [43]



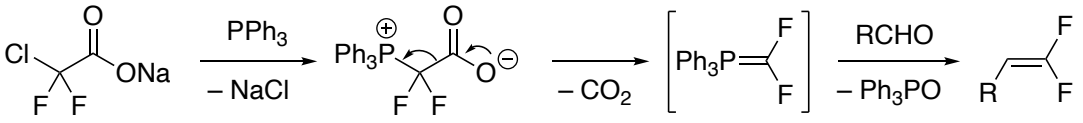
Scheme 4.2.3.4: Catalytic Staudinger reduction [44]

4.2.4 Phosphine-Organofluorine Chemistry

The reactivity of organophosphines with fluorocarbon electrophiles is a topic with which the author has long been well-acquainted,[23] and it is also an area which for a long period of time was associated almost singularly with Donald J Burton. His earliest report on the topic came in 1965, with a Wittig-based methodology for installing the $=CF_2$ group

[23] This is in reference to my undergraduate research in the Baker Lab (2013–2014), the objectives of which were (a) to observe (and isolate) the transient $Ph_3P{=}CF_2$ phosphorane, and; (b) to use *in situ*-generated $Ph_3P{=}CF_2$ as a transferrable "CF_2:" equivalent in order to synthesize transition metal difluorocarbenes. The carbene (generated by debromination of $[PPh_3CF_2Br^+][Br^-]$) was found to rapidly give way to P–F-bonded species, and could never be observed. As for the carbene-transfers, results were mixed; there was some evidence of transfer to $Co_2(CO)_{10}$ by ^{19}F NMR, but yields were low, and the project was shortly abandoned as G. Lee of our group had thereafter developed a superior route from $TMSCF_3$.

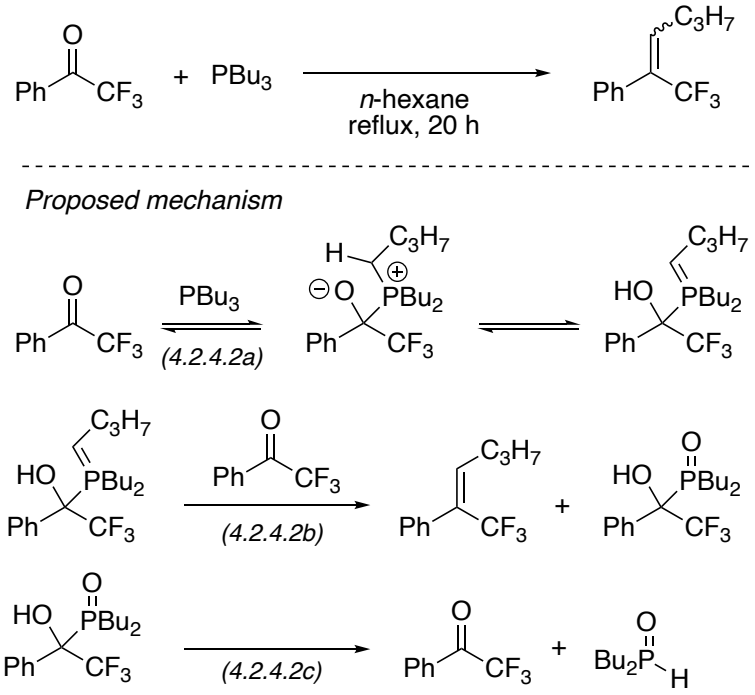
on aryl-fluoroalkyl ketones.[45] The active Wittig reagent was generated *in situ* from the phosphonium salt of PPh_3 and sodium chlorodifluoroacetate—a then already known[46] precursor to difluorocarbene—which spontaneously decarboxylates (Scheme 4.2.4.1). Burton et al. have used this technique extensively to install $=CF_2$ groups on a variety of substrates,[47] and have written a comprehensive treatise on the subject.[48]



Scheme 4.2.4.1: Generation and Wittig reaction of [PPh_3=CF_2] [46]

Along the same lines, Burton reported that trifluoromethyl ketones undergo Wittig-like reactivity with trialkylphosphines to furnish olefins derived from the alkyl groups on the phosphine (Scheme 4.2.4.2).[49] Regular aliphatic ketones and aldehydes are not subject to such reactivity, and thus it appears to be a property inherent to highly electrophilic trifluoromethyl ketones. The authors propose the mechanism to proceed *via* initial nucleophilic attack of the phosphine on the carbonyl carbon, followed by intramolecular proton transfer from the CH_2 *α*-to phosphorus to form the ylide (eqn 4.2.4.2a). This ylide can then undergo a Wittig reaction with another equivalent of ketone to furnish the olefinic product, and an α-hydroxyphosphine oxide (eqn 4.2.4.2b). Burton et al. note that if this were the end of the reaction, yields of no greater than 50% would be expected. That the olefin yields are in many examples >50% suggests that the α-hydroxyphosphine

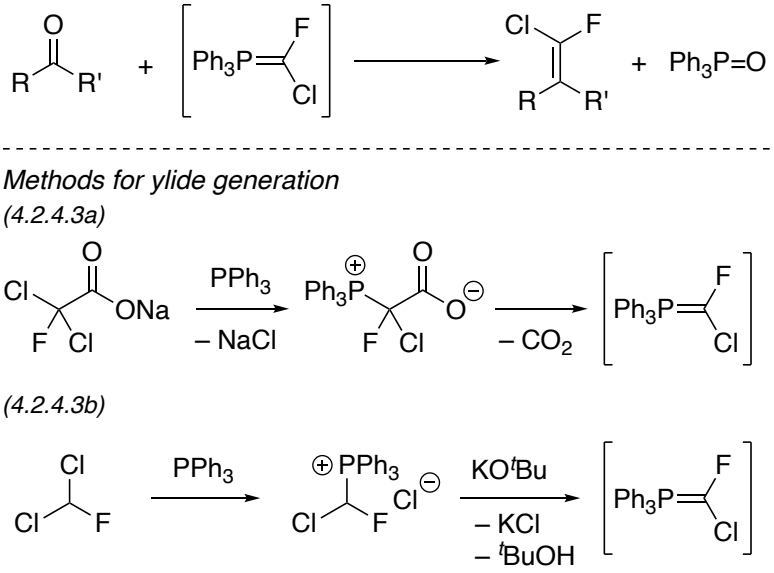
oxides—known to be thermally unstable[50]—can decompose to regenerate the ketone electrophile and release a secondary phosphine oxide (eqn 4.2.4.2c).



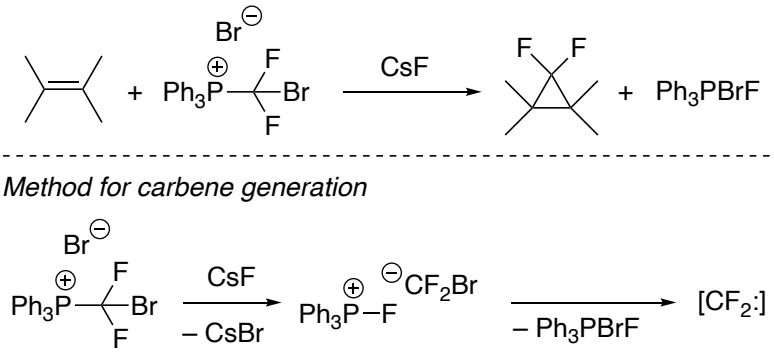
Scheme 4.2.4.2: Base-free Wittig reaction of trifluoromethyl ketones [49]

The mixed chlorofluoromethylene ylide [$Ph_3P{=}CFCl$] has also been generated and used by Burton et al. as a carbene-transfer agent in Wittig transformations (Scheme 4.2.4.3).[51,52] Two different methods were used: the *a*-haloacetate method (eqn 4.2.4.3a) and *via* deprotonation of the phosphonium salt derived from HCFC-**21** (eqn 4.2.4.3b). The halomethane method has also been used to generate difluorocarbene (Scheme 4.2.4.4) whereby the P–CF_2X bond can be substituted by a strong nucleophile such as CsF or NaOMe to eject the CF_2X^- anion, which then ejects X^- to give difluorocarbene.[53] Burton and Greenlimb also reported that Zn(Cu) can be used to deiodinate the phosphonium salt

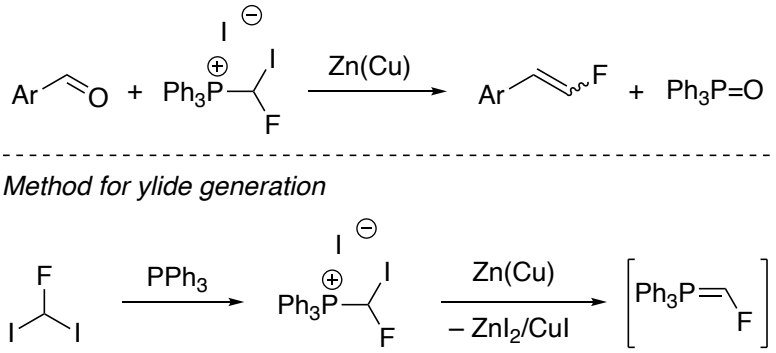
$[PPh_3CHFI^+][I^-]$ to generate the monofluoromethylidene ylide *in situ*, which was also used for Wittig olefinations (Scheme 4.2.4.5).[54,55] Halophosphonium salts also can be dehalogenated to halomethylene olefinating solutions in an equilibrium reaction using another equivalent of triphenylphosphine as reported by Burton et al.[56]



Scheme 4.2.4.3: Wittig reaction and generation of chlorofluoromethylene ylide [51]

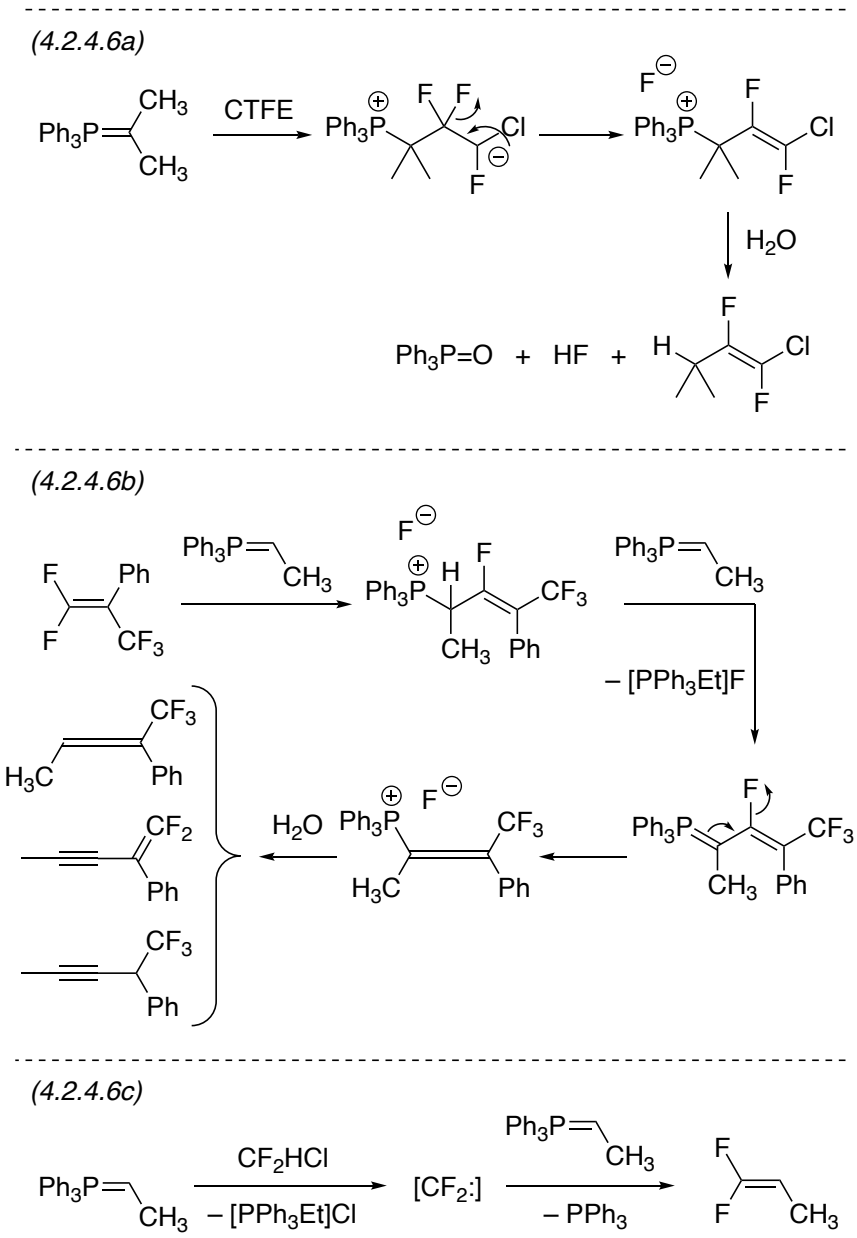


Scheme 4.2.4.4: CF_2: generation and cyclopropanation from $[PPh_3CF_2Br]^+$ [53]



Scheme 4.2.4.5: $Ph_3P{=}CHF$ generation and Wittig reaction from $[PPh_3CHFI]^+$ [54]

Aliphatic phosphorus ylides were shown to be sufficiently nucleophilic to react with terminal difluoroölefins to yield C–F bond-activated chain-extended phosphonium salts (Scheme 4.2.4.6), which hydrolyze with elimination of HF and phosphine oxide to liberate the olefin (eqn 4.2.4.6a).[57] Ylides which contain *a*-hydrogens rearrange to allenic phosphonium salts which hydrolyze to fluorinated acetylene and allene derivatives (eqn 4.2.4.6b). Phosphonium ylides also react with HCFC-**22** in an acid/base reaction to eliminate difluorocarbene, which reacts with another equivalent of ylide to liberate triphenylphosphine and a new terminal difluoroölefin (eqn 4.2.4.6c).[58,59] With regard to the reactivity of fluoromethylene ylides, Burton also found that tris(dimethylamino)phosphine-derivatives are much more reactive than PPh_3-derivatives.[60] This CF_2-chain extension method was also used to prepare fluorinated 1,3-butadienes using *in situ*-generated $[Ph_3P{=}CF_2]$.[61]

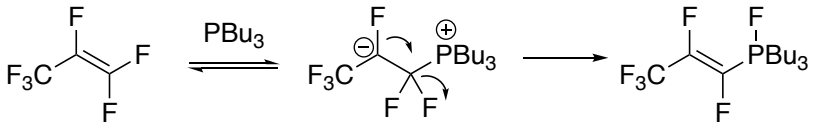


Scheme 4.2.4.6: Reactivity of aliphatic ylides with fluorocarbons [57–59]

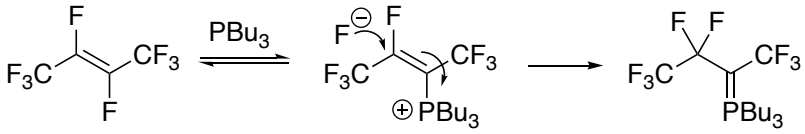
Burton also investigated the reactivity of organophosphine nucleophiles with fluorinated olefins (Scheme 4.2.4.7), finding that nucleophilic attack at terminal fluoroölefins yields a C–F bond-activated vinylphosphonium salt (eqn 4.2.4.7a), whereas nucleophilic attack at cyclic and other internal fluoroölefins gives isolable fluoride-shifted

phosphonium ylides [24] instead (eqn 4.2.4.7b).[62] Another way to isolate bis(fluoroalkyl)phosphonium ylides is by desulfurization of hexafluorothioacetone—originally reported by Middleton with trialkylphosphites[63]—which Burton et al. did with PPh_3 at –78°C *in situ*, forming a competent Wittig reagent for aldehyde olefination.[64] The Bu_3As analog of the perfluorocyclobutylidene was reported later.[65]

(4.2.4.7a)



(4.2.4.7b)

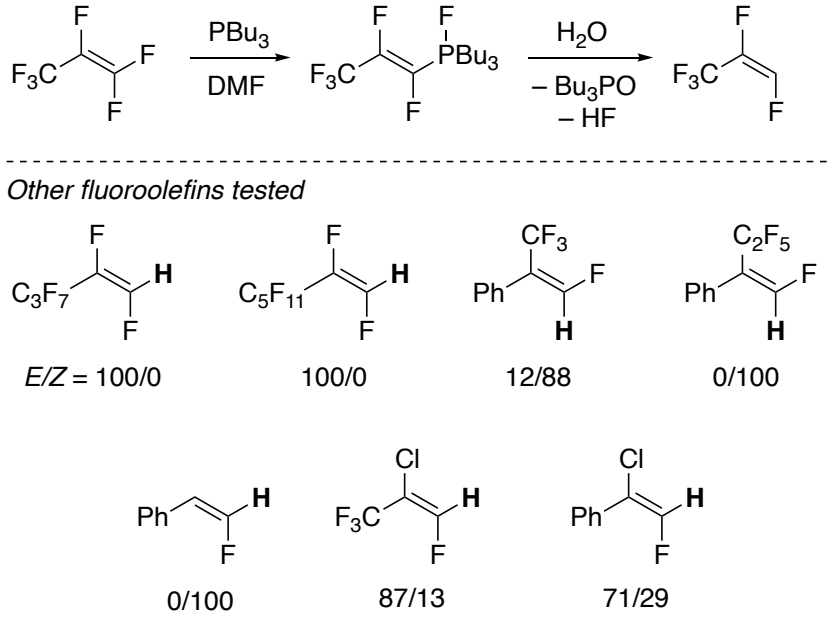


Scheme 4.2.4.7: Reactivity of phosphines with fluoroölefins [62]

Burton subsequently took advantage of the propensity for P-fluorophosphoranes to hydrolyze with elimination of HF and phosphine oxide to carry out a stereoselective hydrodefluorination (HDF) reaction (Scheme 4.2.4.8).[66] First, the P-fluorophosphorane is obtained by reaction of PBu_3 with HFP in DMF, which under aqueous workup gives

[24] In unpublished work carried out in 2019-2020, I prepared perfluorocyclopentylidene-triphenylphosphorane starting from perfluorocyclopentene and PPh_3 as per Burton's method in ref. 62. I had hoped that this previously unreported ylide would be a useful carbene-transfer agent to transition metals. Indeed, when reacted with acidic, oxidizing salts such as $MoCl_5$, WCl_6, or $WOCl_4$, ^{19}F NMR showed a scattering of new fluorocarbene signals, but when a solution of these ill-defined fluorocarbenes was exposed to a test olefin $CF_3CH{=}CH_2$—the objective being self-metathesis to the refrigerant 1336mzz ($CF_3CH{=}CHCF_3$)—no activity was observed even on prolonged heating. Further, there was no evidence whatever of any carbene transfer to salts of Ru^{II}, Co^{I}, or Ni^{0}. This stone-stable temperament is in keeping with Burton's failure to obtain Wittig products using his isolated perfluorocyclobutylidene-phosphorane. After trying for some months, this scheme was finally abandoned.

way to the olefin $CF_3CF{=}CHF$ (HFO-**1225ye**) with 100% *(E)*-selectivity. Unfortunately, the phosphine is fully consumed by such reactions as $Bu_3P{=}O$, and care must be taken of the thereby liberated HF if this is to be done on a large scale. Fluoroölefins other than HFP were also attempted, with similarly good stereoselectivity and yield. *β*-Chloroolefins and fluorinated styrenes were also hydrodefluorinated with moderate selectivity. Hydrolysis of the P-fluorophosphoranes with D_2O also presents a good method for the synthesis of deuterofluoroölefins.

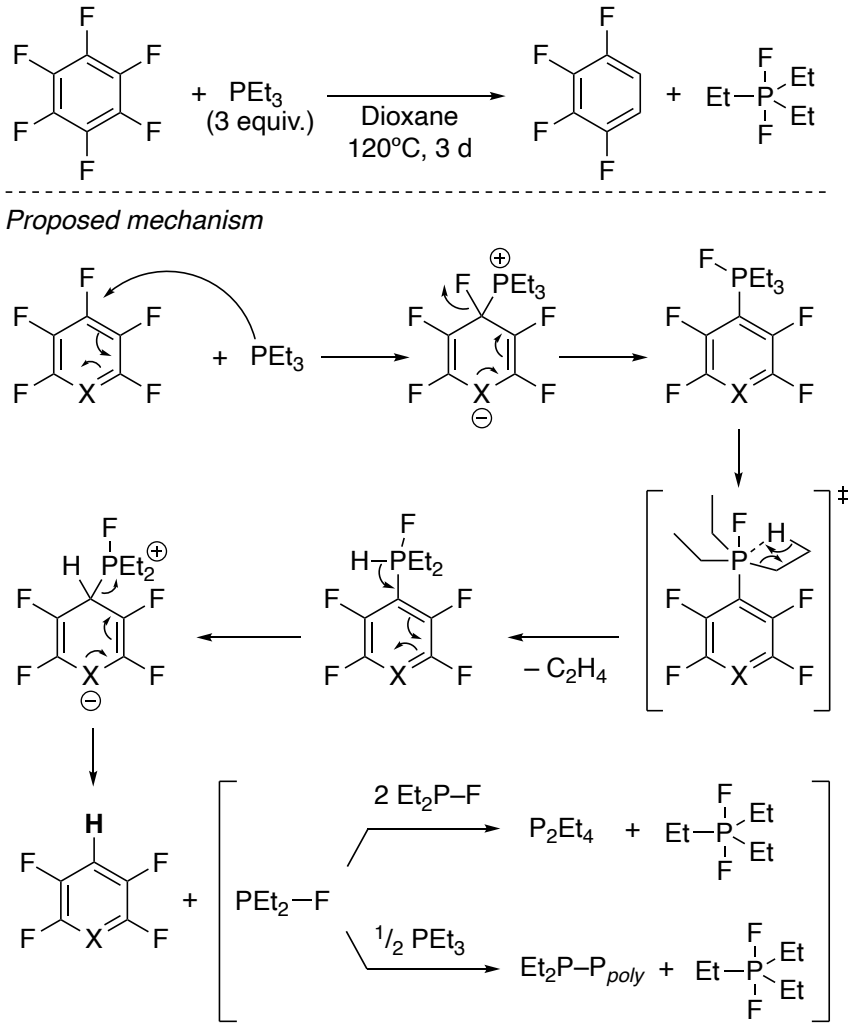


Scheme 4.2.4.8: HDF of fluoroölefins by phosphonium salt hydrolysis [66]

With the aforementioned fluoroölefin HDF reaction (reported in 1980), we have finally arrived at the segment of prior art most germane to the novel works being presented in this chapter. I will leave it to the reader's personal enterprise to seek out the remainder of Burton's numerous contributions to organofluorine chemistry which extend as recently

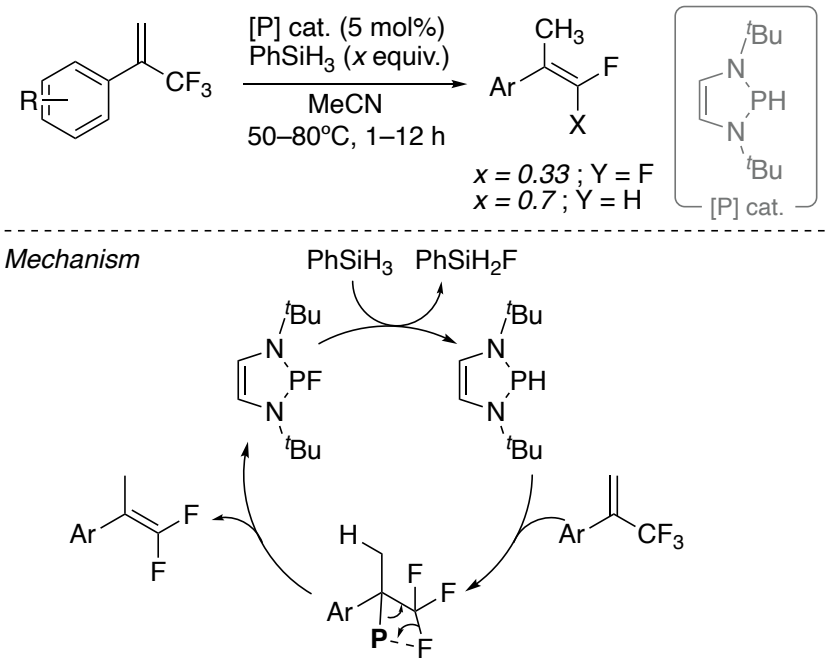
as 2016, and which span far broader a scope than phosphonium salts and ylides. It is worth noting that many of Burton's fluorinated ylide techniques were reprised and used to great effect by Nappa et al. (of Chemours) to synthesize new C_4–C_5 hydrofluoroölefins,[67] breathing new life into these old and scarcely-touched methods.

From here, therefore, we jump forward in time to a 2014 report by García et al., in which PEt_3 was shown to hydrodefluorinate fluoroarenes in the absence of metal, water, silane, or any other extraneous reductant (Scheme 4.2.4.9).[68] In one example, C_6F_6 was converted by an excess (3 equiv.) of PEt_3 to *1H,2H*-C_6F_4 after 3 days in refluxing dioxane. The authors proposed that the phosphine can act as a single-component reductant by forming the expected P–fluorophosphorane, which undergoes β-hydride elimination from one of the ethyl groups to give a hydrofluorophosphorane, the P–H bond of which undergoes *ipso*-substitution at the arene. The resulting Meisenheimer complex then eliminates the Et_2PF. The authors noted that although no 2° fluorophosphines were observed, the major product by ^{31}P NMR was Et_3PF_2, a known disproportionation product of R_2PF compounds.[69] Later experimental and DFT studies confirmed this mechanism.[70] However, like Burton's hydrolytic method, the phosphine is wholly consumed by this reaction, and the disproportionation reactions of the resulting 2° fluorophosphine—which can consume some unreacted 3° phosphine—necessitated an excess of PEt_3.



Scheme 4.2.4.9: Single-component HDF of fluoroarenes by PEt_3 [69, 70]

Finally, Cheng et al. reported this year a 2° diazaphospholene capable of catalyzing the HDF of β-trifluoromethylstyrene derivatives in conjunction with $PhSiH_3$ as the terminal reductant (Scheme 4.2.4.10).[71] The reaction was shown to proceed via hydrophosphination of the fluoroölefin, followed by P–F bond elimination. Depending on the number of equivalents of silane added, the reaction could be tuned to favor the difluoro- or monofluoroölefin product.



Scheme 4.2.4.10: HDF of β-trifluoromethylstyrenes with 2º diaminophosphine [71]

In the Cheng paper, the substrate scope was quite specific and narrowly restricted to styrene derivatives; no small fluoroölefins were attempted. Furthermore, the aminophosphine used is not commercially-available, and must be prepared in-house from PCl_3. Evidently the two ^{t}Bu groups are sufficiently encumbering to prevent the usual disproportionation reactions to which 2º fluorophosphines are susceptible, allowing for a clean turnover of the P–F bond by silane. The last diseconomy of this reaction, as interpreted by this author, is the reliance on $PhSiH_3$—an expensive and highly air-sensitive silane—as the terminal reductant. Even Burton's stoichiometric PBu_3 reductions would be cheaper to carry out. While to date our group has never found any allure in the HDF of fluoroarenes or of fluorinated styrenes, the conversion of small perfluoroölefins to HFOs is an area of interest as a means of supplying new refrigerant candidates. Could

such a method, I wondered, be applied to olefins, given Burton's previous reports of P-fluoro vinylphosphoranes? Could the reactivity of simple, nucleophilic 3º phosphines be combined with Cheng's use of a silane as the terminal reductant? These questions constitute the problem to be solved by this chapter.

4.3 Reactivity with hexafluoropropylene (HFP)

The obvious fluoroölefin targeted by this work is HFO-**1234yf**, the telescoped hydrogenative/dehydrofluorinative synthesis of which from HFP has already been developed and is patented by Arkema Inc.[72,25] It should be noted that the intermediate mono-HDF product HFO-**1225ye** prepared originally by Burton via hydrolysis of the PBu_3-vinylphosphorane was once considered as a refrigerant candidate. With boiling points of –21ºC and –16ºC (*(Z)* and *(E)* isomers, respectively), non-flammability, low acute toxicity, and atmospheric lifetimes of 1–2 weeks, these pentafluoropropylenes had all the promising properties for an HFC-**134a** replacement.[73–75] However, both isomers displayed unfortunate and unforeseen sub-chronic and chronic toxicity hazards which disqualified them shortly after they were proposed.[76,26] However, this toxicity record does not necessarily preclude the pentafluoropropylenes from finding utility in other non-

[25] On this, more details await in Chapter 5.

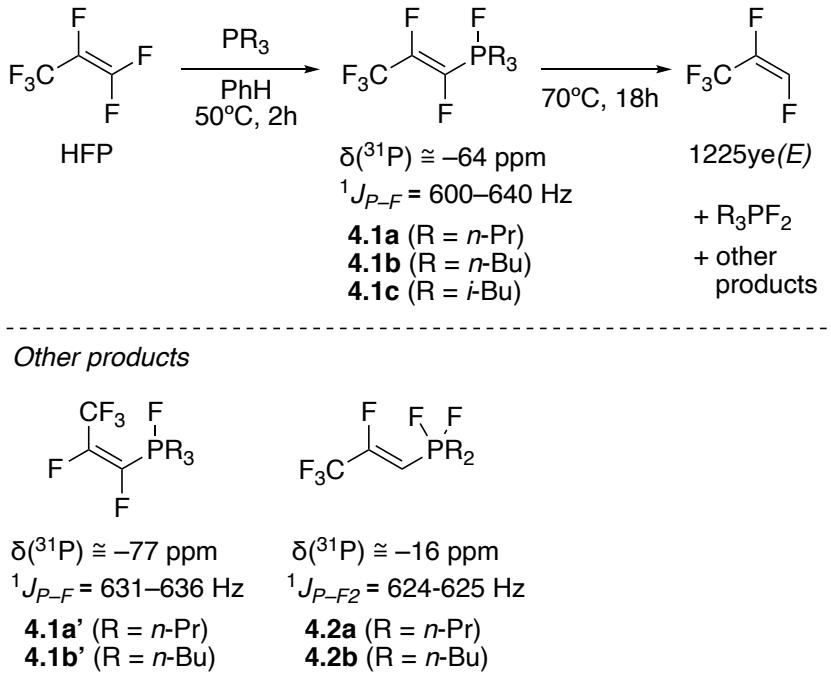
[26] Though in a study done by Mexichem Fluor (ref. 76), no acute toxicity was found in rats even at concentrations >50,000 ppm over 5 days, HFO-1225ye*(Z) did* appear to target the myocardium (cardiac sensitization) after 28 days at 10,000, 25,000 and 50,000 ppm.

refrigeration applications (chemical intermediates, fluoromonomers, electronic etching gases, &c), and therefore their preparation from HFP is not altogether without value. As the Arkema method which produces **1225ye** *en route* to **1234yf** employs a thermal elimination step, the thermodynamic *(Z)*-isomer is obtained. The methodology outlined here, following Burton's results and providing the kinetic *(E)*-isomer, is complementary. The real prize, however, is HFO-**1234yf**, the current favorite among its class. As a near drop-in replacement for HFC-**134a** with a 99.9% lower global warming potential (GWP), it is already seeing widespread adoption by major automakers worldwide.[77] Honeywell claims that global adoption of this refrigerant could cut greenhouse gas emissions by a measure equivalent to 30 million automobiles.[78] There are, however, drawbacks to making the switch from **134a** to **1234yf**, foremost among which being price—the HFO is priced at an up to 10-fold premium over the HFC.[79] This premium arises from its inherently longer and more complex synthesis as compared to **134a**.

I began my foray with an attempt to reproduce the results of Burton with HFP, so that I may get better acquainted with the ^{19}F NMR signatures of the P–fluoro vinylphosphoranes derived therefrom. In keeping with my general philosophy of thrifty lab economics, three simple and widely-available alkylphosphines were used: P(*n*-Pr)$_3$, P(*n*-Bu)$_3$, and P(*i*-Bu)$_3$. The reader may wonder at the absence of PEt$_3$ from this list, given that it was used with success by García, but given its high cost, I opted to substitute it with the much more economical P(*n*-Pr)$_3$, of which our group was already in

possession.[27] The availability and cost of P(*n*-Bu)$_3$ have been discussed earlier (*vide supra*), and P(*i*-Bu)$_3$ was used as a branched alternative in order to offer some steric variety. It was no surprise when, upon injecting HFP into an NMR tube containing benzene solutions of the three phosphines, there emerged clean formation of the expected P-fluoro vinylphosphoranes after heating to 50°C for 2 h (compounds *(Z)*-**4.1a**–**c**, Scheme 4.3.1). Increasing the temperature to 70°C resulted in ^{19}F NMR signals corresponding to HFO-**1225ye*(E)*** and several P–F bonded species, at once vindicating my hypothesis that phosphines can act as single-component HDF agents for fluoroölefins. Besides the pentafluoropropylene and expected R_3PF_2 products, however, there were also observed several interesting side-products. For one, there was evidence of vinylphosphoranes containing *two* P–F bonds (compounds **4.2a**, **4.2b**), which I expect arose from the nucleophilic addition of R_2PF to **1225ye**. Interestingly, no such product was observed in the P(*i*-Bu)$_3$ example. Furthermore, some of the *(E)*-stereoisomer of the HFP-derived vinylphosphoranes **4.1a'** and **4.1b'** was observed, with the stereoselectivity cost likely arising from the higher reaction temperature.

[27] Recently, Cytec-Solvay has begun to distribute their alkylphosphine line through Strem, and though PEt_3 is listed on the Solvay website (as CYTOP®-320), it is not among those that made it into the Strem catalog. P(*n*-Pr)$_3$ (CYTOP®-330, #15-7610), however, is—and can be obtained in laboratory quantities for the quite reasonable price of USD $1.20/gram as of the publication of this document. Furthermore, in a webinar given on the topic of alkylphosphines and their applications, it was suggested by the two Solvay presenters that P(*n*-Pr)$_3$ should be considered as a more cost-effective alternative to PEt_3.



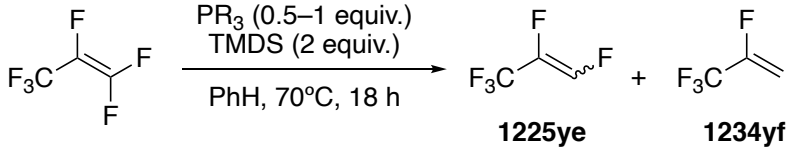
Scheme 4.3.1: Reactivity of PR_3 with HFP at 50°C and 70°C

Having ascertained that the three alkylphosphines are capable of reducing the HFP to **1225ye** directly, reactions were attempted at the same temperature but in the presence of 1,1,3,3-tetramethyldisiloxane (TMDS) as an alternative terminal reductant, in the hopes that the active phosphine could be regenerated. The results are shown in Table 4.3.1. In the first three examples, we already notice an interesting reactivity trend, namely a divergence in selectivity. While 1.0 equiv. of P(*n*-Pr)$_3$ shows a modest selectivity for the second-generation HDF product **1234yf** (ex. 1), P(*n*-Bu)$_3$ is the clear winner, giving same with 95% selectivity (ex. 2). P(*i*-Bu)$_3$, by contrast, inverts the trend and gives a 94% selectivity for the first-generation product **1225ye*(E)*** (ex. 3). In examples 4–6 where the phosphines are deployed substoichiometrically (0.5 equiv.), the conversion is still

quantitative, while the selectivity is inverted for P(*n*-Pr)$_3$ (ex. 4) and maintained at similar levels for P(*n*-Bu)$_3$ and P(*i*-Bu)$_3$ (ex. 4 and 5)—indeed, *improved* in the latter case.

The divergent selectivity was most unexpected, and as yet not fully explainable by the existing data. Electronically speaking, P(*i*-Bu)$_3$ and P(*n*-Bu)$_3$ are approximately equivalent ($^1J_{\text{Se–P}}$ = 683 Hz for (*n*-Bu)$_3$P=Se *vs.* 688 Hz for (*i*-Bu)$_3$P=Se),[80] but where they differ substantially are the cone angles (ϑ = 132° for P(*n*-Bu)$_3$ *vs.* 143° for P(*i*-Bu)$_3$).[81] The intermediate **1225ye** being smaller in size than the parent HFP, however, it is not clear how a smaller cone angle enables the second nucleophilic attack to proceed. Furthermore, if less steric hindrance is better, one would expect P(*n*-Pr)$_3$ to perform better than P(*n*-Bu)$_3$, which it does not. Next, the fate of the phosphine in these examples was probed by ^{31}P NMR, which revealed a mixture of mostly PR_3, contaminated with R_3PO and R_3PF_2, indicating that even in the presence of silane, a substantial fraction of the phosphine was consumed irreversibly. The substoichiometric loading (ca. 4 turnovers in the case of example 6) is in line with the objective, but the question then became how to regenerate the active nucleophile so that it would not be put to waste. One hypothesis is that the phosphine could be further restored by addition of a silane-responsive reduction catalyst, or in other words, a reduction *promoter*.

Table 4.3.1. Trialkylphosphine-mediated hydrodefluorination of HFP using TMDS as the terminal reductant



Ex.[a]	PR_3 (equiv.)	Conv. (%)[b]	HFO Sel. (%)[b]		
			1225ye(*Z*)	1225ye(*E*)	1234yf
1	P(*n*-Pr)$_3$ (1.0)	100	-	23	77
2	P(*n*-Bu)$_3$ (1.0)	100	3	2	95
3	P(*i*-Bu)$_3$ (1.0)	100	-	94	6
4	P(*n*-Pr)$_3$ (0.5)	100	2	82	16
5	P(*n*-Bu)$_3$ (0.5)	100	3	6	91
6	P(*i*-Bu)$_3$ (0.5)	100	-	97	3
7	P(*n*-Pr)$_3$ (0.5)[c]	100	-	68	32
8	P(*n*-Pr)$_3$ (0.5)[c],[d]	100	42	21	37
9	P(*n*-Bu)$_3$ (0.5)[c],[d]	100	14	74	12
10	P(*i*-Bu)$_3$ (0.5)[c]	100	17	82	6
11	P(*i*-Bu)$_3$ (0.5)[c],[d]	100	16	67	17
12	None[c]	56	19	25	-

[a] Standard conditions: Phosphine (0.123 or 0.062 mmol), TMDS (43 µL, 0.246 mmol), benzene, $PhCF_3$ (50 µL of 0.246M solution in benzene) and HFP (3 mL, 0.123 mmol) heated to 70°C for 18 h; [b] ^{19}F NMR yields, HFO basis excluding traces of nonvolatile P–F vinylphosphorane intermediates; [c] with 0.5 equiv. Ti(O*i*Pr)$_4$ added; [d] heated to 70°C for 40 h

There exists a considerable literature precedent for using titanium alkoxides (most commonly the isopropylate) as activators for siloxane terminal reductants such as TMDS or PMHS in the reduction of, for example, amides[82] and phosphine oxides.[83] When reactions were carried out using a mixture of 0.5 equiv. PR_3 and 0.5 equiv. Ti(O*i*Pr)$_4$ (examples 7–11), no P–F bonded species were observed, and the incidence of phosphine

oxide was also greatly reduced, but instead of the expected higher ratio of **1234yf**/**1225ye**, there was observed a larger incidence of **1225ye*(Z)***, even using P(*n*-Bu)$_3$ (ex. 8), suggesting that the titanium species is possessed of additional reactivity independent of the phosphine, leading to the loss of both the selectivity for **1234yf** and the stereoselectivity for **1225ye**, the *(Z)*-isomer of which was only ever observed in reactions containing added Ti(O^{i}Pr)$_4$. A control reaction with only 0.5 equiv. of Ti(O^{i}Pr)$_4$ and no phosphine (ex. 12) shows a low conversion to a roughly 1:1 ratio of (*E*/*Z*)-**1225ye**, supporting this theory.

Next, these HDF experiments were replicated using the more cheaply-available poly(methylhydrosiloxane) (PMHS) in place of TMDS (Table 4.3.2). The HDF of HFP was performed using the two best conditions from Table 4.3.1 (Examples 6 and 9). Three molecular-weight ranges of PMHS were attempted. There was scarcely any difference between the different polymer weights, but the **1234yf**/**1225ye** ratio was not as high as when TMDS was used, despite using 5 hydride equivalents. As with the TMDS examples, ^{31}P NMR showed almost exclusively free phosphine and a small amount of phosphine oxide, with no detectable P–F bonded intermediates, indicating that PMHS is no less capable of turning over such species than TMDS. However, the presence of vinylphosphorane intermediates and the higher proportion of intermediate **2** in examples 1–3 suggest that the polymeric silane is slower at doing so. In summary, the goal of near-total phosphine regeneration was realized, but in practice may need to be carried out in the absence of the fluoroölefin in a sort of separate recycling step.

Table 4.3.2. Trialkylphosphine-mediated hydrodefluorination of HFP using PMHS as the terminal reductant

Ex.	PR_3 (1 eq.)	PMHS MW (g/mol)	Conv. (%)[b]	HFO Sel.[b]	
				1225ye*(E)*	**1234yf**
1	P(*n*-Bu)$_3$	1400-1800[c]	100	18	75
2	P(*n*-Bu)$_3$	1800-2100[d]	100	10	80
3	P(*n*-Bu)$_3$	2100-2400[e]	100	20	74
4	P(*i*-Bu)$_3$	1400-1800[c]	100	76	2
5	P(*i*-Bu)$_3$	1800-2100[d]	100	75	2
6	P(*i*-Bu)$_3$	2100-2400[e]	100	75	2

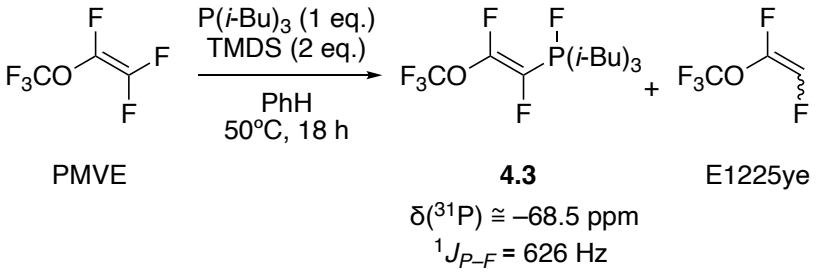
[a] Standard conditions: Phosphine (0.123 or 0.062 mmol), PMHS (37 µL, 5 equiv.), benzene, $PhCF_3$ (50 µL of 0.246M solution in benzene) and HFP (3 mL, 0.123 mmol) heated to 70°C for 18 h; [b] ^{19}F NMR basis, ratio of HFOs excluding 15-18% nonvolatile P–F vinylphosphorane intermediates and <5% *(Z)*-**2**; [c] Kinematic viscosity = 15-25 cSt; [d] Kinematic viscosity = 20-35 cSt; [e] Kinematic viscosity = 30-45 cSt

4.4 Reactivity with perfluoro(methyl vinyl ether) (PMVE)

The successful HDF of HFP using only phosphines led me to pursue reactivity with other terminal fluoroölefins.[28] PMVE is the OCF_3-congener of HFP, and is a common comonomer for the synthesis of Type-3 and Type-5 FKM fluoroelastomers.[84] Perfluorinated vinyl ethers with varying chain-lengths are readily-available and are efficiently synthesized by AGC at commercial scale using the 'PERFECT' direct fluorination process.[85] Hydrofluorovinyl ethers are uncommon, and may be of interest for

[28] Before attempting PMVE, chlorotrifluoroethylene (CTFE) was used as a test substrate. There was some interest in C_2 olefins at the time, particularly the mono-HDF product: 1-chloro-1,2-difluoroethylene (HCFO-1122a—more on this in Chapter 5). Sadly, there was no reactivity between any phosphine tested and CTFE, and thus we moved on to PMVE.

use as fluoromonomers in conjunction with their perfluorinated counterparts. When PMVE was subjected to the same conditions as HFP (2 equiv. TMDS and 1 equiv. phosphine at 50°C), only the P(*i*-Bu)$_3$ vinylphosphorane was observable, along with the mono-HDF product trifluoromethyl 1,2-difluorovinyl ether (**E1225ye**, Scheme 4.4.1). The reaction temperature had to be reduced to 50°C for PMVE, as heating these mixtures any higher resulted in a black/brown heterogeneous reaction mixture, with no identifiable products by NMR.



Scheme 4.4.1: Reactivity of P(*i*-Bu)$_3$ and TMDS with PMVE at 50°C

In all PMVE cases, a high degree of *(E)*-selectivity was observed, albeit less-so than for HFP, indicative of the reduced steric pressure exerted by the OCF_3 of PMVE vs. the CF_3 of HFP. The highest conversion of PMVE was obtained with 1.0 equiv. of P(*n*-Bu)$_3$ (ex. 4). In all examples, trace amounts of *E/Z*-CHF=CHF (HFO-**1132**) were also detected. Addition of 0.5 equiv. Ti(O^{i}Pr)$_4$ (examples 3, 6, 9) lowered the *E/Z* ratio and increased the PMVE conversion relative to the Ti-free examples. As with the HFP examples, no R_3PF_2 or phosphine oxide was observed in any of the Ti-containing reactions.

Unlike with HFP, $Ti(O^iPr)_4$ alone was a very poor catalyst, giving only 12% conversion (ex. 10). The goal of expanding the range of substrates susceptible to phosphine-mediated HDF was achieved, the PMVE→**E1225ye** conversion representing a unique and previously unknown example of such.

Table 4.4.1. Trialkylphosphine-mediated hydrodefluorination of PMVE using TMDS as the terminal reductant

Ex.	PR_3 (equiv.)	Conv. (%)[b)]	HFO Sel. (%)[b),c)]	
			E1225ye*(Z)*	**E1225ye*(E)***
1	P(*n*-Pr)$_3$ (1.0)	80	19	81
2	P(*n*-Pr)$_3$ (0.5)	22	21	79
3	P(*n*-Pr)$_3$ (0.5)[d)]	67	35	65
4	P(*n*-Bu)$_3$ (1.0)	94	23	77
5	P(*n*-Bu)$_3$ (0.5)	32	19	81
6	P(*n*-Bu)$_3$ (0.5)[d)]	54	34	66
7	P(*i*-Bu)$_3$ (1.0)	50	17	83[e)]
8	P(*i*-Bu)$_3$ (0.5)	31	15	85[f)]
9	P(*i*-Bu)$_3$ (0.5)[d)]	50	29	71
10	None[d)]	12	8	4

[a)] Standard conditions: Phosphine (0.123 or 0.062 mmol), TMDS (43 µL, 0.246 mmol), benzene, $PhCF_3$ (50 µL of 0.246M solution in benzene) and PMVE (3 mL, 0.123 mmol) heated to 50°C for 18 h; [b)] ^{19}F NMR basis, excluding nonvolatile P–F vinylphosphorane intermediates; [c)] Traces of *E/Z*-CHF=CHF also observed; [d)] with 0.5 equiv. $Ti(O^iPr)_4$ added; [e)] Mixture contains 22% of **4.3**; [f)] Mixture contains 38% of **4.3**

4.5 Mechanistic Considerations

The Ti- and silane-free HDF (mediated by PR_3) is expected to proceed by a mechanism similar to that described in the García paper,[70] with β-hydride elimination from the P–fluorophosphorane providing the necessary hydride. The observation of R_3PF_2 (the known decomposition product of R_2PF/PR_3 mixtures) in these examples justifies the

initial hypothesis that the phosphine-mediated HDF of fluoroarenes can be commuted to fluoroölefins. The absence of any R_2PH in the ^{31}P NMR spectra suggests that the fluoride turnover happens at the P–F phosphorane step rather than after the β-hydride elimination. The role of the titanium is more nebulous, however. Comparing the ^{19}F NMR spectra of stoichiometric reactions between P(*i*-Bu)$_3$ and HFP with and without Ti(O^{i}Pr)$_4$ suggests an answer; in both cases, the P–F bonded phosphorane intermediate **4.1c** is observed, but in the latter case, the P–F signal at $\delta(^{19}F) = -14.7$ ppm is significantly broadened (Figure 4.5.1), while all other signals remain sharp. This change might suggest an interaction or exchange process between the P–F and the Lewis-acidic Ti(O^{i}Pr)$_4$, which assists the silane in the turnover step. Furthermore, the lack of a substantial R_3PF_2 signal in reactions when Ti(O^{i}Pr)$_4$ is used suggests that it assists the silane in turning over the P(V) difluorophosphorane and restoring the free phosphine. A summary of available pathways according to these proposals can be found in Scheme 4.5.1. The observation that the ideal phosphine for HFP→**1234yf** is P(*n*-Bu)$_3$ (as opposed to the smaller P(*n*-Pr)$_3$) might be explained by intermediate **4.1a** being more susceptible to β-hydride elimination even in the presence of silane, thereby taking the phosphine out of the reaction media as R_3PF_2. Comparing the $^{31}P\{^1H\}$ NMR spectra of examples 2 and 6 in Table 4.3.1 shows that in the P(*n*-Bu)$_3$ case (example 6), there still remains free P(*n*-Bu)$_3$, while in example 2, the phosphine has been fully consumed and there remains only phosphine oxide and (*n*-Pr)$_3$PF$_2$. Therefore, a faster β-elimination (and commensurately shorter lifetime) for P(*n*-Pr)$_3$ might explain the superior performance of the *n*-butyl phosphine over the *n*-propyl.

The unique capability of P(*n*-Bu)$_3$ to perform the HFP→**1234yf** HDF as opposed to P(*i*-Bu)$_3$ is much less explicable. A steric argument is difficult to make as **1225ye**, having fewer fluorine atoms, is less sterically-congested than HFP, and would be expected to have higher reactivity. An electronic argument is also difficult as P(*n*-Bu)$_3$ and P(*i*-Bu)$_3$ are comparably electron-rich. With the data in hand, the origin of the divergence in reactivity remains as yet shrouded in mystery.

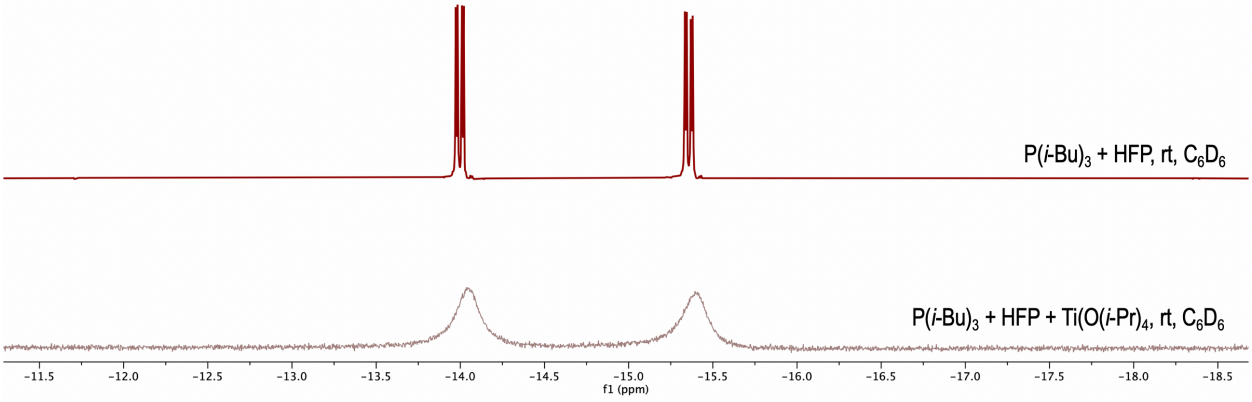
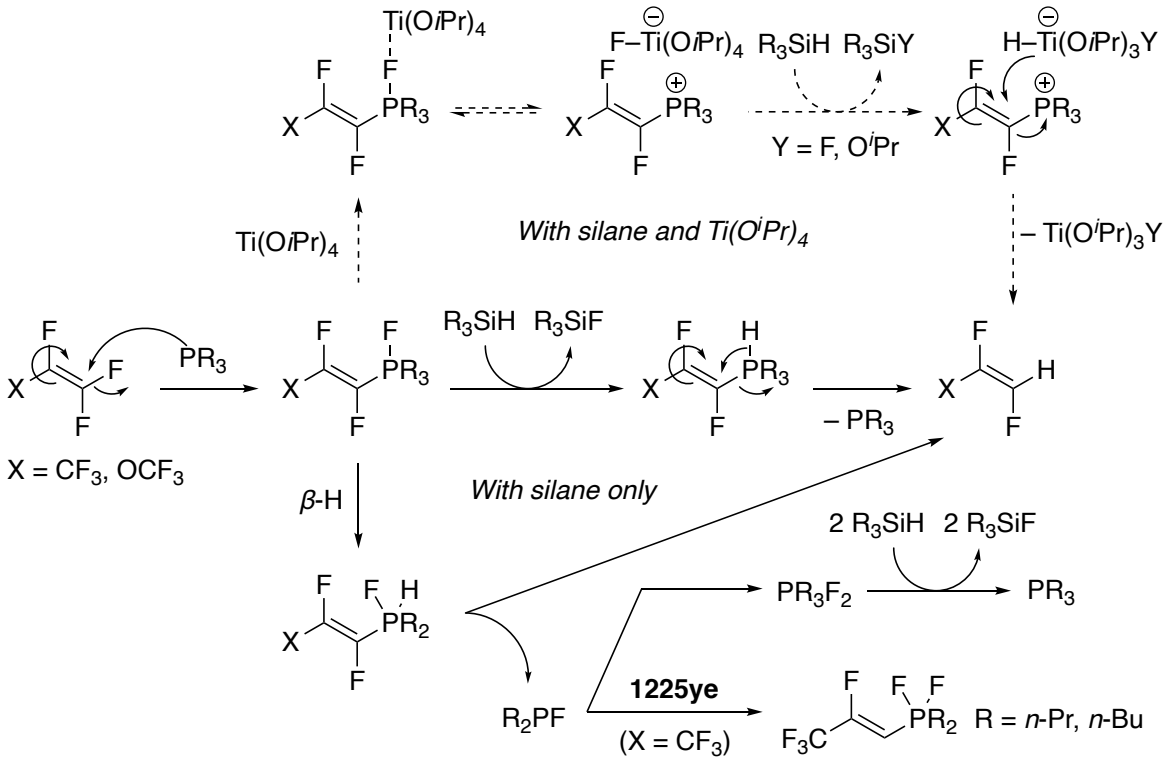


Figure 4.5.1: **^{19}F{^{1}H} NMR (471 MHz) comparing P–F signal in complex 4.1c with and without added Ti(O^{i}Pr)$_4$**



Scheme 4.5.1: **Proposed mechanism for phosphine-catalyzed HDF of HFP/PMVE**

4.6 Conclusion and Future Outlook

A divergent hydrodefluorination method was devised which could render either HFO-**1225ye*(E)*** or HFO-**1234yf** starting from HFP, and also provided a method by which a novel hydrofluoroether **E1225ye** could be synthesized starting from PMVE. In the case of HFP, substoichiometric loadings of phosphine could be used while maintaining >90% selectivity for the target product, and cheaply-available siloxanes can be used as hydride equivalents. The spent phosphine can be regenerated with the aid of $Ti(O^iPr)_4$, however this comes at a cost of selectivity owing to titanium's ability to catalyze the HDF on its own in a stereo-unselective manner. Future work which needs to be done for this project

might include expanding the range of available phosphines which can catalyze this reaction, as well as examining whether the spent phosphine solution from the Ti-free examples can be regenerated post-reaction using additional silane and $Ti(O^iPr)_4$, once the valuable HFO products have already been separated. As far as the author's original intentions for this project, however, it may be considered successful and complete.

4.7 Experimental Section

General Procedures

Experiments were conducted under dry nitrogen using an MBraun glovebox. Glassware was dried in an oven set at 120°C for 2 h before use. Benzene (>99.5%, TCI America, Montgomeryville, PA) and benzene-d_6 (99.5%, Cambridge Isotope Laboratories, Tewksbury, MA) were deoxygenated and dried over 3Å molecular sieves activated at >200°C in a vacuum oven before use. Titanium isopropoxide (97%, Sigma-Aldrich, Oakville, ON), benzotrifluoride (anhydrous ≥99%, Sigma-Aldrich, Oakville, ON), 1,1,3,3-tetramethyldisiloxane (97%, Sigma-Aldrich, Oakville, ON), were used as received. All alkylphosphines were manufactured by Cytec Canada (now Solvay, Niagara Falls, ON) and are distributed by Strem (Newburyport, MA) under the CYTOP® moniker. Perfluoro(methyl vinyl ether) (PMVE, 99%), and hexafluoropropylene (HFP, 98.5%) were used as received from Synquest Laboratories (Alachua, FL). NMR spectra were recorded on a 500 MHz Bruker AvanceIII instrument at room temperature (21–23°C). ^{19}F spectra

were referenced to internal $PhCF_3$ (δ = – 63.5 ppm) and ^{31}P spectra were referenced to external H_3PO_4 (85% aqueous solution, δ = 0 ppm).

*4.7.1 Observation of compounds **4.1***

In the glovebox, an 8 in. NMR tube was charged with the pure phosphine (0.123 mmol), benzotrifluoride (50 μL of 0.246M solution in benzene), and diluted to 600 μL with benzene. The NMR tube was sealed with a fresh (never punctured) rubber septum cap, tightly wrapped with parafilm, and charged with 3 mL of hexafluoropropylene (0.123 mmol) bubbled directly into the solution by injection through a 23-gauge needle. The NMR tube was then immersed to the solvent level in an aluminum bead bath and left to ripen overnight (18 hours), after which it was cooled to RT and analyzed by ^{19}F and ^{31}P NMR.

4.1a: $^{19}F\{^1H\}$ (471 MHz): –18.1 (P–F, ddd, J = 606, 16, 6 Hz), –67.3 (CF_3, dd, J = 23, 10 Hz), –142.0 (CF, mult), –169.0 ppm (CF, mult.). $^{31}P\{^1H\}$ (202 MHz): –64.8 ppm (P–F, dd, J = 606, 8 Hz).

4.1b: $^{19}F\{^1H\}$ (471 MHz): –17.3 (P–F, dd, J = 602, 11 Hz), –67.4 (CF_3, dd, J = 22, 10 Hz), 141.7 (CF, dqd, J = 128, 22, 13 Hz), –169.0 ppm (CF, ddq, J = 128, 11, 10 Hz). $^{31}P\{^1H\}$ (202 MHz): –63.6 ppm (dd, J = 602, 8 Hz).

4.1c: $^{19}F\{^1H\}$ (471 MHz): –14.7 (P–F, ddd, J = 640, 17, 5 Hz), –67.2 (CF_3, dd, J = 21, 10 Hz), –138.6 (CF, dqdd, J = 129, 22, 17, 4 Hz), –165.6 ppm (CF, dqdd, J = 129, 10, 7, 5 Hz). $^{31}P\{^1H\}$ (202 MHz): –64.3 ppm (P–F, ddd, J = 640, 7, 4 Hz).

*4.7.2 Observation of compounds **4.1'** and **4.2***

4.6.2 was repeated and heated to 70°C for another 2 h and analyzed by NMR.

4.1a': $^{19}F\{^{1}H\}$ (471 MHz): –12.7 (P–F, d, J = 636 Hz), –68.4 (CF_3, ddd, J = 22, 11, 6 Hz), –143.3 (CF, dqd, J = 132, 22, 11 Hz), –172.7 ppm (CF, dqdd, J = 132, 11, 10, 4 Hz). $^{31}P\{^{1}H\}$ (202 MHz): –77.7 ppm (P–F, d, 636 Hz)

4.1b': $^{19}F\{^{1}H\}$ (471 MHz): –11.9 (P–F, d, J = 631 Hz), –68.4 (CF_3, ddd, J = 22, 11, 6 Hz), –124.8 (CF, mult.), –142.8 ppm (CF, dqd, J = 132 Hz. $^{31}P\{^{1}H\}$ (202 MHz): –76.3 ppm (P–F, d, 631 Hz)

4.2a: $^{19}F\{^{1}H\}$ (471 MHz): –41.5 (PF_2, d, J = 624 Hz), –67.4 (CF_3, dd, J = 10, 5 Hz), –125.1 ppm (CF, dq, J = 19, 10 Hz). $^{31}P\{^{1}H\}$ (202 MHz): –16.4 ppm (PF_2, tdq, J = 624, 17, 5 Hz).

4.2b: $^{19}F\{^{1}H\}$ (471 MHz): –40.7 (PF_2, d, J = 624 Hz), –67.5 (CF_3, dd, J = 10, 5 Hz), –125.5 ppm (CF, dq, J = 19, 10 Hz). $^{31}P\{^{1}H\}$ (202 MHz): –15.5 ppm (PF_2, tdq, J = 625, 17, 5 Hz).

*4.7.3 Observation of compound **4.3***

The experiment from **1c** was repeated using PMVE in place of HFP.

5: $^{19}F\{^{1}H\}$ (471 MHz): –10.8 (PF, dd, J = 626, 15.5 Hz), –60.4 (OCF_3, dd, J = 6.0, 4.5 Hz), –116.3 (CF, dqd, J = 116.5, 4.5, 1.5 Hz), –152.7 ppm (CF, ddqd, J = 116.5, 15.5, 6 Hz, 3 Hz). $^{31}P\{^{1}H\}$ (202 MHz): –68.5 ppm (PF, d, J = 626 Hz)

4.7.4 Generalized NMR tube HDF procedure

An NMR tube was charged with pure phosphine (0.123 or 0.062 mmol), TMDS (43 μL, 0.246 mmol), benzotrifluoride (50 μL of 0.246 M solution in benzene), and diluted to 600 μL with benzene. The NMR tube was sealed with a fresh (never punctured) rubber septum cap, tightly wrapped with parafilm, and charged with 3 mL of fluorinated gas (0.123 mmol) bubbled directly into the solution by injection through a 23-gauge needle. The NMR tube was then immersed to the solvent level in an aluminum bead bath set to 50°C (PMVE) or 70°C (HFP) and left to ripen overnight (18 hours), after which it was cooled to RT and analyzed by ^{19}F NMR.

*4.7.5 Generation of (E/Z)-**E1225ye** from PMVE*

The general HDF procedure was followed using 3 ml of PMVE and heating to 50°C for 18 h.

E1225ye*(E)*: $^{19}F\{^{1}H\}$ (471 MHz): –60.8 (OCF_3, t, J = 4 Hz), –130.1 (CF, dq, J = 124, 4 Hz), –185.4 ppm (CF, dq, J = 123, 4.5 Hz).

E1225ye*(Z)* $^{19}F\{^{1}H\}$ (471 MHz): –62.0 (OCF_3, d, J = 4.5 Hz), –105.1 (CF, dq, J = 22.5, 4.5 Hz), –177.6 ppm (CF, d, J = 22.5 Hz).

NMR spectra of these examples can be found in Appendix A-II.



4.8 References

(1) Rozen, S. Elemental Fluorine as a "Legitimate" Reagent for Selective Fluorination of Organic Compounds. *Acc. Chem. Res.* **1988**, *21*, 307–312.

(2) Ukihashi, H.; Hisasue, M. Process for Producing Tetrafluoroethylene and Hexafluoropropylene. US 3,459,818, 1969.

(3) Rucker, J. T.; Stormon, D. B. Process for the Production of Chlorotrifluoroethylene by Passing a Mixture of Trichlorotrifluoroethane and Hydrogen through an Unobstructed Iron Tube. US 2,760,997, 1956.

(4) Burton, D. J. The Iowa Connection. In *Fluorine Chemistry at the Millenium*; Banks, R. E., Ed.; Elsevier Ltd, 2000; pp 81–121.

(5) (NIOSH). Phosphine https://www.cdc.gov/niosh/idlh/7803512.html (accessed Jun 24, 2021).

(6) (Voltaix). *Material Safety Data Sheet for Phosphine (PH3)*; North Branch, New Jersey, 1994.

(7) Stiles, A. R.; Rust, F. F.; Vaughan, W. E. The Preparation of Organo-Phosphines by the Addition of Phosphine to Unsaturated Compounds. *J. Am. Chem. Soc.* **1952**, *74*, 3282–3284.

(8) Stiles, A. R. Process for Producing Organic Phosphines. US 2,803,597, 1957.

(9) Brown, H. C. Organic Phosphines. US 2,584,112, 1950.

(10) Sugiya, M.; Watanabe, T.; Sano, N. Highly Pure Monoalkylphosphine and Method for Producing Same. US 5,892,120, 1999.

(11) Hechenbleikner, I.; Rauhut, M. M. Reaction of Phosphine with α,β-Unsaturated Compounds. US 2,822,376, 1958.

(12) Henderson, W. A.; Buckler, S. A. The Nucleophilicity of Phosphines. *J. Am. Chem. Soc.* **1960**, *82*, 5794–5800.

(13) (Solvay). Product List. Phosphorus Specialties, 2018.

(14) Mason, R. F.; Winkle, J. L. Van. Bicyclic Heterocyclic Sec- and Tert-Phosphines. US 3,400,163, 1968.

(15) Crause, C.; Bennie, L.; Damoense, L.; Dwyer, C. L.; Grove, C.; Grimmer, N.; Van Rensburg, W. J.; Kirk, M. M.; Mokheseng, K. M.; Otto, S.; et al. Bicyclic Phosphines as Ligands for Cobalt-Catalysed Hydroformylation. *Dalt. Trans.* **2003**, No. 10, 2036–2042.

(16) Epstein, M.; Buckler, S. A. Substituted 10-Phosphatricyclo[3.3.1.1]Decanes and Methods of Preparing Same. US 3,050,531, 1962.

(17) Epstein, M.; Buckler, S. A. A Novel Phosphorus Heterocyclic System from the Reactions of Phosphine and Primary Phosphines with 2,4-Pentanedione. *J. Am. Chem. Soc.* **1961**, *83*, 3279–3282.

(18) Maercker, A. The Wittig Reaction. In *Organic Reactions*; Denmark, S. E., Ed.; John Wiley and Sons, Inc., 2011; pp 271–377.

(19) Guo, H.; Fan, Y. C.; Sun, Z.; Wu, Y.; Kwon, O. Phosphine Organocatalysis. *Chem. Rev.* **2018**, *118*, 10049–10293.

(20) Xie, C.; Smaligo, A. J.; Song, X. R.; Kwon, O. Phosphorus-Based Catalysis. *ACS Cent. Sci.* **2021**, *7*, 536–558.

(21) Rauhut, M. M.; Currier, H. Preparation of Dialkyl-2-Methylene Glutamates. US 3,074,999, 1963.
(22) Rauhut-Currier Reaction (Rauhut-Currier Dimerization). In *Comprehensive Organic Name Reactions and Reagents*; Wang, Z., Ed.; John Wiley and Sons, Inc., 2010; pp 2307–2310.
(23) Aroyan, C. E.; Dermenci, A.; Miller, S. J. The Rauhut-Currier Reaction: A History and Its Synthetic Application. *Tetrahedron* **2009**, *65*, 4069–4084.
(24) Morita, K.; Kobayashi, T. New Addition Reactions of Acrylic Compounds with Fumaric Acid Esters Catalyzed by Tervalent Phosphorus Compounds. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2732–2732.
(25) McClure, J. D. Triarylphosphine-Catalyzed Dimerization of Acrylonitrile and Related Reactions. *J. Org. Chem.* **1970**, *35*, 3045–3048.
(26) White, D. A.; Baizer, M. M. Catalysis of the Michael Reaction by Tertiary Phosphines. *Tetrahedron Lett.* **1973**, *14*, 3597–3600.
(27) Stewart, I. C.; Bergman, R. G.; Toste, F. D. Phosphine-Catalyzed Hydration and Hydroalkoxylation of Activated Olefins: Use of a Strong Nucleophile to Generate a Strong Base. *J. Am. Chem. Soc.* **2003**, *125*, 8696–8697.
(28) Inanaga, J.; Baba, Y.; Hanamoto, T. Organic Synthesis with Trialkylphosphine Catalysts. Conjugate Addition of Alcohols to α,β-Unsaturated Alkynic Acid Esters. *Chem. Lett.* **1993**, *22*, 241–244.
(29) Basavaiah, D.; Naganaboina, R. T. The Baylis-Hillman Reaction: A New Continent in Organic Chemistry-Our Philosophy, Vision and over Three Decades of Research. *New J. Chem.* **2018**, *42*, 14036–14066.
(30) Wei, Y.; Shi, M. Recent Advances in Organocatalytic Asymmetric Morita-Baylis-Hillman/Aza- Morita-Baylis-Hillman Reactions. *Chem. Rev.* **2013**, *113*, 6659–6690.
(31) Zhong, N. J.; Wang, Y. Z.; Cheng, L.; Wang, D.; Liu, L. Recent Advances in the Annulation of Morita-Baylis-Hillman Adducts. *Org. Biomol. Chem.* **2018**, *16*, 5214–5227.
(32) Kaye, P. T. Applications of the Morita–Baylis–Hillman Reaction in the Synthesis of Heterocyclic Systems. In *Advances in Heterocyclic Chemistry*; Scriven, E. F. V., Ramsden, C. A., Eds.; Elsevier Inc., 2019; Vol. 127, pp 101–152.
(33) Buckler, S. A.; Doll, L.; Lind, F. K.; Epstein, M. Phosphine as a Reducing Agent. *J. Org. Chem.* **1962**, *27*, 794–798.
(34) Tamano, M.; Koketsu, J. Reduction of Aromatic Ketones or Thioketones with Phenylphosphine. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2577–2580.
(35) Harpp, D. N.; Gleason, J. G.; Snyder, J. P. Organic Sulfur Chemistry. I. The Disulfide-Phosphine Reaction. Desulfurization with Tris(Diethylamino)Phosphine. *J. Am. Chem. Soc.* **1968**, *90*, 4181–4182.
(36) Kawamura, S.; Sato, A.; Nakabayashi, T. Reaction of Acetyl Aralkyl Disulfides with Triphenylphosphine. *Chem. Lett.* **1975**, *4*, 1231–1234.
(37) Patel, S. M.; Smith, T. G.; Morton, M.; Stiers, K. M.; Seravalli, J.; Mayclin, S. J.; Edwards, T. E.; Tanner, J. J.; Becker, D. F. Cautionary Tale of Using Tris(Alkyl)Phosphine Reducing Agents with NAD^+-Dependent Enzymes. *Biochemistry* **2020**, *59*, 3285–3289.
(38) Murphy, P. J.; Brennan, J. The Wittig Olefination Reaction with Carbonyl Compounds Other than Aldehydes and Ketones. *Chem. Soc. Rev.* **1988**, *17*, 1–30.

(39) Murphy, P. J.; Lee, S. E. Recent Synthetic Applications of the Non-Classical Wittig Reaction. *J. Chem. Soc. - Perkin Trans. 1* **1999**, No. 21, 3049–3066.
(40) Pommer, H.; Thieme, P. C. Industrial Applications of the Wittig Reaction. *Top. Curr. Chem.* **2005**, *109*, 165–188.
(41) Heravi, M. M.; Ghanbarian, M.; Zadsirjan, V.; Alimadadi Jani, B. *Recent Advances in the Applications of Wittig Reaction in the Total Synthesis of Natural Products Containing Lactone, Pyrone, and Lactam as a Scaffold*; Springer Vienna, 2019; Vol. 150.
(42) Palmelund, A.; Myers, E. L.; Tai, L. R.; Tisserand, S.; Butts, C. P.; Aggarwal, V. K. A New Manifold for the Morita Reaction: Diene Synthesis from Simple Aldehydes and Acrylates/Acrylonitrile Mediated by Phosphines. *Chem. Commun.* **2007**, No. 40, 4128–4130.
(43) O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. Recycling the Waste: The Development of a Catalytic Wittig Reaction. *Angew. Chemie - Int. Ed.* **2009**, *48*, 6836–6839.
(44) Van Kalkeren, H. A.; Bruins, J. J.; Rutjes, F. P. J. T.; Van Delft, F. L. Organophosphorus-Catalysed Staudinger Reduction. *Adv. Synth. Catal.* **2012**, *354*, 1417–1421.
(45) Burton, D. J.; Herkes, F. E. A One-Step Synthesis of β-Phenyl Substituted Perfluoroolefins. *Tetrahedron Lett.* **1965**, *6*, 1883–1887.
(46) Fuqua, S. A.; Duncan, W. G.; Silverstein, R. M. A One-Step Synthesis of 1,1-Difluoro Olefins from Aldehydes. *J. Org. Chem.* **1965**, *30*, 1027–1029.
(47) Herkes, F. E.; Burton, D. J. The Synthesis of β-Substituted Perfluoro Olefins. *J. Org. Chem.* **1967**, *32*, 1311–1318.
(48) Burton, D. J.; Yang, Z. Y.; Qiu, W. Fluorinated Ylides and Related Compounds. *Chem. Rev.* **1996**, *96*, 1641–1715.
(49) Burton, D. J.; Herkes, F. E.; Klabunde, K. J. The Reaction of Trifluoromethyl Ketones and Trialkylphosphines. *J. Am. Chem. Soc.* **1966**, *88*, 5042–5043.
(50) Miller, R. C.; Miller, C. D.; Rogers, W.; Hamilton, L. A. Disubstituted Phosphine Oxides. IV. Addition Reactions with Aldehydes and Ketones. *J. Am. Chem. Soc.* **1957**, *79*, 424–427.
(51) Burton, D. J.; Krutzsch, H. C. The Preparation and Reactions of a Mixed Halogen Ylid. *Tetrahedron Lett.* **1968**, *9*, 71–76.
(52) Burton, D. J.; Krutzsch, H. C. The Synthesis of β-Substituted 1-Chloroperfluoro Olefins. *J. Org. Chem.* **1970**, *35*, 2125–2130.
(53) Burton, D. J.; Naae, D. G. Bromodifluoromethylphosphonium Salts. Convenient Source of Difluorocarbene. *J. Am. Chem. Soc.* **1973**, *95*, 8467–8468.
(54) Burton, D. J.; Greenlimb, P. E. Olefination via Metal Dehalogenation of Phosphonium Salt. *J. Fluor. Chem.* **1973**, *3*, 447–449.
(55) Burton, D. J.; Greenlimb, P. E. Fluoro Olefins. VII. Preparation of Terminal Vinyl Fluorides. *J. Org. Chem.* **1975**, *40*, 2796–2801.
(56) Naae, D. G.; Kesling, H. S.; Burton, D. J. Reversible Equilibrium in Tertiary Phosphine-Fluorohalomethane Reactions. *Tetrahedron Lett.* **1975**, *16*, 3789–3792.
(57) Burton, D. J.; Lee, T. M. The Reaction of Alkylidene Ylides with Fluoroolefins. *J. Fluor. Chem.* **1976**, *8*, 189–192.
(58) Wheaton, G. A.; Burton, D. J. The Reaction of Alkylidenetriphenylphosphoranes with

Chlorodifluoromethane. Synthesis of 1,1-Difluoro-1-Alkenes. *Tetrahedron Lett.* **1976**, *17*, 895–898.

(59) Wheaton, G. A.; Burton, D. J. Ylide-Carbene Chemistry. Synthesis of 1,1-Difluoro-1-Alkenes. *J. Org. Chem.* **1983**, *48*, 917–927.

(60) Hamme, M. J. Van; Burton, D. J. Preparation of Chlorofluoromethylene Olefins via Phosphine Dechlorination of Dichlorofluoromethyltris(Dimethylamino)Phosphonium Chloride. *J. Fluor. Chem.* **1979**, *13*, 407–420.

(61) Burton, D. J.; Inoue, Y.; Headley, J. A. Difluoromethylene Chain-Extension Reactions. Preparation of Fluorinated Alkenes and Alkadienes from Olefin Precursors. *J. Am. Chem. Soc.* **1980**, *102*, 3980–3982.

(62) Burton, D. J.; Seiji, S.; Howells, R. D. The Role of α and β Fluorine in Product Determination of Fluoro Olefin-Tertiary Phosphine Reactions. Ylide vs. Vinylphosphorane Formation. *J. Am. Chem. Soc.* **1979**, *101*, 3689–3690.

(63) Middleton, W. J.; Sharkey, W. H. Fluorothiocarbonyl Compounds. II. Reactions of Hexafluorothioacetone. *J. Org. Chem.* **1965**, *30*, 1384–1390.

(64) Burton, D. J.; Inouye, Y. The in Situ Generation of Ph3P=C(CF3)2. A Facile One Pot Conversion of Aldehydes to Bis-Trifluoromethyl Olefins. *Tetrahedron Lett.* **1979**, *20*, 3397–3400.

(65) Burton, D. J.; Valk, P. D. Vander. Tributylarsonium-2,2,3,3,4,4-Hexafluorocyclobutane Ylide. Preparation and Cleaveage. *J. Fluor. Chem.* **1981**, *18*, 413–416.

(66) Burton, D. J.; Shin-ya, S.; Howells, R. D. A Stereoselective Reduction of Polyfluorinated Olefins. A Facile Conversion of Difluoromethylene Olefins to Fluoromethylene Olefins via Vinyl Phosphoranes and Vinyl Phosphonium Salts. *J. Fluor. Chem.* **1980**, *15*, 543–546.

(67) Yagupolskii, Y. L.; Pavlenko, N. V.; Shelyazhenko, S. V.; Filatov, A. A.; Kremlev, M. M.; Mushta, A. I.; Gerus, I. I.; Peng, S.; Petrov, V. A.; Nappa, M. Alternative Synthetic Routes to Hydrofluoroolefins. *J. Fluor. Chem.* **2015**, *179*, 134–141.

(68) Arévalo, A.; Tlahuext-Aca, A.; Flores-Alamo, M.; García, J. J. On the Catalytic Hydrodefluorination of Fluoroaromatics Using Nickel Complexes: The True Role of the Phosphine. *J. Am. Chem. Soc.* **2014**, *136*, 4634–4639.

(69) Fey, N.; Garland, M.; Hopewell, J. P.; McMullin, C. L.; Mastroianni, S.; Orpen, A. G.; Pringle, P. G. Stable Fluorophosphines: Predicted and Realized Ligands for Catalysis. *Angew. Chemie - Int. Ed.* **2012**, *51*, 118–122.

(70) Facundo, A. A.; Arévalo, A.; Fundora-Galano, G.; Flores-Álamo, M.; Orgaz, E.; García, J. J. Hydrodefluorination of Functionalized Fluoroaromatics with Triethylphosphine: A Theoretical and Experimental Study. *New J. Chem.* **2019**, *43*, 6897–6908.

(71) Zhang, J.; Yang, J.; Cheng, J. Chemoselective Catalytic Hydrodefluorination of Trifluoromethylalkenes towards Mono-/Gem-Di-Fluoroalkenes under Metal-Free Conditions. *Nat. Commun.* **2021**, *12*, 2835.

(72) Takahashi, K.; Shibanuma, T. Process for Producing 2,3,3,3-Tetrafluoropropene. EP 2,292,574 B1, 2015.

(73) Domanski, P.; McLinden, M.; Bell, I.; Linteris, G. *NIST Technical Note 2014. Low-GWP Alternative Refrigerant Blends for HFC-134a*; 2018.

(74) Wuebbles, D. J.; Wang, D.; Patten, K. O.; Olsen, S. C. Analyses of New Short-Lived Replacements for HFCs with Large GWPs. *Geophys. Res. Lett.* **2013**, *40*, 4767–4771.

(75) Raabe, G. Molecular Modeling of Fluoropropene Refrigerants. *J. Phys. Chem. B* **2012**,

116, 5744–5751.

(76) Lindley, A.; Noakes, T. J. *Consideration of Hydrofluoroolefins (HFOs) as Potential Candidate Medical Propellants*; 2010.

(77) Reisch, M. S. Automakers Go HFO https://cen.acs.org/articles/88/i30/Automakers-HFO.html.

(78) (Honeywell Refrigerants). Honeywell Starts Up $300 Million Automotive Refrigerant Production Facility In Louisiana [Press Release] https://www.honeywell.com/en-us/newsroom/pressreleases/2017/05/honeywell-starts-up-300-million-automotive-refrigerant-production-facility-in-louisiana (accessed Apr 22, 2021).

(79) Johnson, A. How Much Is R-1234yf Refrigerant Per Pound in 2020? https://refrigeranthq.com/how-much-is-r-1234yf-refrigerant-per-pound-in-2020/ (accessed Apr 22, 2021).

(80) Bungu, P. N.; Otto, S. Evaluation of Ligand Effects in the Modified Cobalt Hydroformylation of 1-Octene. Crystal Structures of $[Co(L)(CO)_3]_2$ (L = PA-C_5, PCy_3 and $PCyp_3$). *Dalt. Trans.* **2011**, *40*, 9238–9249.

(81) Bilbrey, J. A.; Allen, W. D. Ligand Steric Descriptors. In *Annual Reports in Computational Chemistry*; Elsevier B.V., 2013; Vol. 9, pp 3–23.

(82) Laval, S.; Dayoub, W.; Pehlivan, L.; Métay, E.; Favre-Réguillon, A.; Delbrayelle, D.; Mignani, G.; Lemaire, M. Hydrosiloxane-$Ti(OiPr)_4$: An Efficient System for the Reduction of Primary Amides into Primary Amines as Their Hydrochloride Salts. *Tetrahedron Lett.* **2011**, *52*, 4072–4075.

(83) Coumbe, T.; Lawrence, N. J.; Muhammad, F. Titanium (IV) Catalysis in the Reduction of Phosphine Oxides. *Tetrahedron Lett.* **1994**, *35*, 625–628.

(84) Drobny, J. G. Fluoroelastomer Composition and Properties. *Fluoroelastomers Handb.* **2016**, 17–26.

(85) Okazoe, T. Development of the "PERFECT" Direct Fluorination Method and Its Industrial Applications. *J. Fluor. Chem.* **2015**, *174*, 120–131.

5

CHAPTER FIVE

5. Metal ethylhexanoate-catalyzed hydrodefluorination

5.1 Introduction

This work shares a common objective with the previous chapter—namely, the synthesis of hydrofluoro- and hydrochlorofluoro-olefins from readily-available feedstocks by HDF. This work also follows work which was previously done in our group by N. Andrella[29] concerning the use of [PPh_3CuH] as an HDF catalyst. While there can be no doubt of the significance of Andrella's Cu-catalyzed HDF, the necessity of synthesizing Stryker's reagent and deploying it in such high loading (10 mol%) significantly detracts from its utility to industrial practitioners. In response to a request for a commercial sample of 1,1,4,4,5,5,5-heptafluoro-2-methyl-1-pentene (the fifth-generation HDF product of the thermodynamic dimer of HFP: *F*-2-methyl-2-pentene) from our industrial partner, and this thesis being one of a more applied orientation, I sought a reduction to practice of Andrella's Cu-HDF system which could not only allow us to carry out such a scale-up,

[29] For which a patent (US 10,774,021) was granted in 2020

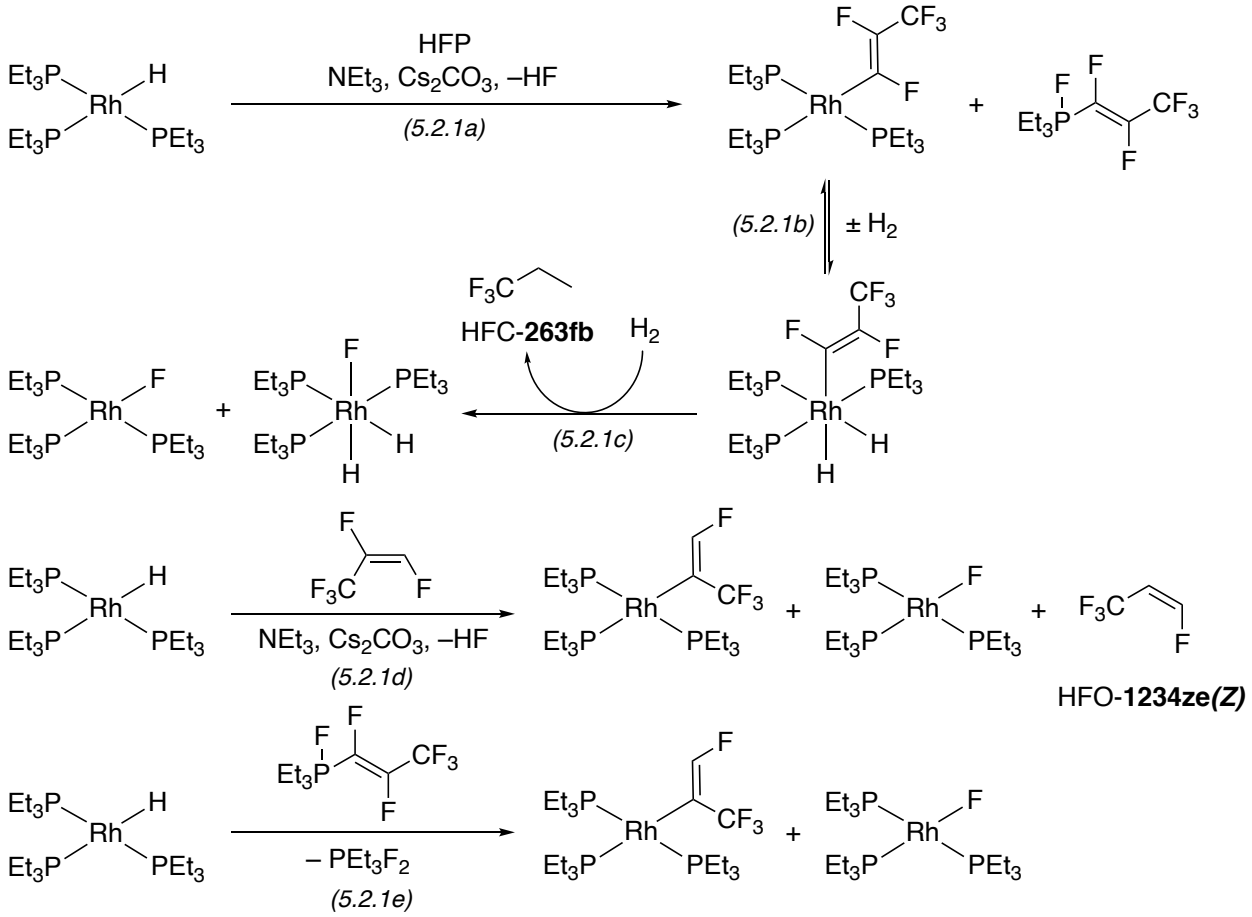
but which could be reasonably practicable by our partner. This optimization was necessary for both reasons of safety[30] and economy, as will be outlined in ***Section 5.3***.

5.2 Prior Art

Since the contributions to be described in ***Section 5.3*** are entirely focused on fluoroolefins (as the core topic of this thesis), then the following review of the prior art will also focus on metal-catalyzed or -mediated hydrodefluorination of olefins. The reader should note that there also exists a body of knowledge concerning hydrodefluorination of arenes or aliphatic fluorocarbons, but on that more can be found elsewhere.[1] This introduction is the complement to that from ***Chapter 4***, which focused on hydrodefluorination using main-group nucleophiles instead of transition metals. An early example of hydrodefluorination was reported by Braun using a Rh(I) hydride reagent (Scheme 5.2.1).[2,3] Insertion/elimination of HFP into the Rh hydride furnishes the *trans*-perfluoropropenyl and a vinylphosphonium fluoride (eqn 5.2.1a) which, on exposure to hydrogen, forms octahedral Rh(III) dihydrides (eqn 5.2.1b) which hydrodefluorinate all sp^2 C–F bonds and hydrogenate the C=C bond to furnish the hydrofluorocarbon 1,1,1-

[30] Prior to arriving at the work presented in this chapter, I spent a great deal of time trying to rein in this reaction as originally published, finding it to be possessed of a rather volcanic temperament. Schemes such as dropwise addition of the silane, fluoroolefin (or both) using syringe pumps were tried, but still resulted in runaway exotherms. A continuous-flow methodology was also attempted, but a cracked PFA line and ruptured syringe later, this idea too was abandoned. It is not possible to carry out the reaction cold, as the fluorous/organic phases fail to mix, leading to no reaction at all (followed by an explosive and sudden reaction upon warming to rt). Ultimately, it was decided that the originally reported system was not fit for purpose, and a gentler catalyst was needed.

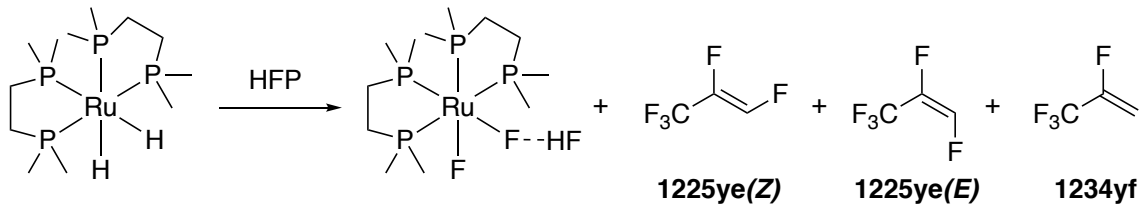
trifluoropropane (HFC-**263fb**, eqn 5.2.1c). Rhodium byproducts include the tris(phosphine)rhodium(III) fluorodihydride and the rhodium(I) fluoride.



Scheme 5.2.1: Hydrodefluorination of HFP to HFC-263fb mediated by Rh (Braun et al.) [5, 6]

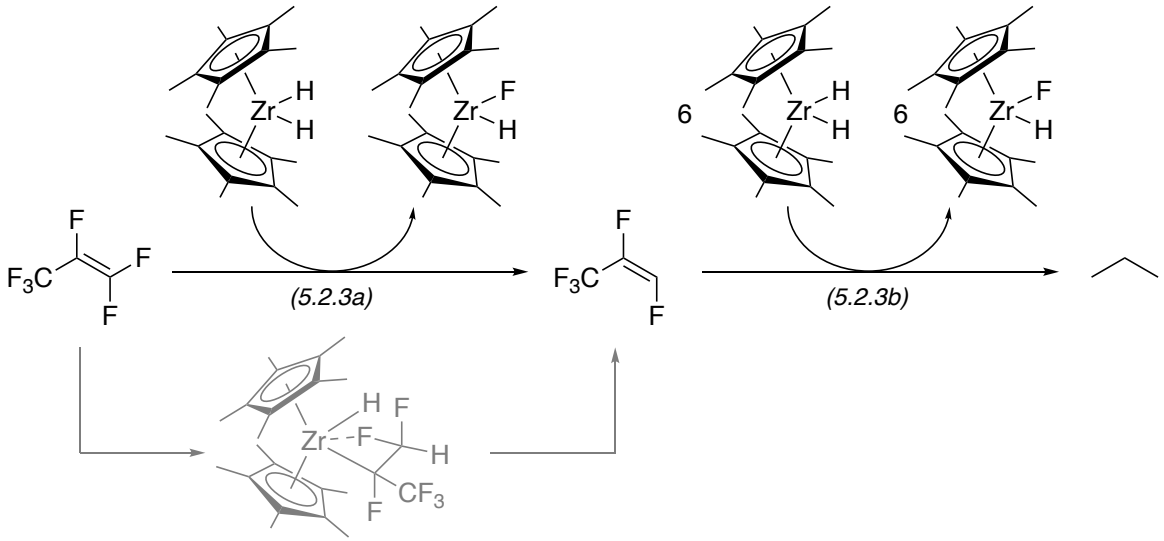
If the hydrofluoroölefin *(E)*-1,2,3,3,3-pentafluoropropylene (HFO-**1225ye*(E)***) was used instead of HFP, then the direction of insertion/elimination reversed, placing the CF_3 α to Rh. By-products included $[(PEt_3)_3RhF]$ (formed as a result of HF reacting with $[(PEt_3)_3RhH]$) and the hydrodefluorinated product HFO-**1234ze*(Z)*** (eqn 5.2.1d). Furthermore, reaction of the vinylphosphonium fluoride (from eqn 5.2.1a) with $[(PEt_3)_3RhH]$ forms the same propenyl as reaction of the Rh(I) hydride with **1225ye*(E)***,

alongside [$(PEt_3)_3RhF$] (eqn 5.2.1e). Another early report by Whittlesey outlined the reaction of *cis*-[$Ru(dmpe)_2H_2$] with HFP, which gives rise to the isolated fluoride-bifluoride product *cis*-[$Ru(dmpe)_2F(F\cdots HF)$] and a mixture of pentafluoropropylenes *(Z)*- and *(E)*-**1225ye** and tetrafluoropropylene (HFO-**1234yf**) in a ratio of 4 : 1 : 3 (Scheme 5.2.2).[4]



Scheme 5.2.2: Hydrodefluorination of HFP to 1225ye/1234yf mediated by Ru (Whittlesey et al.) [5, 6]

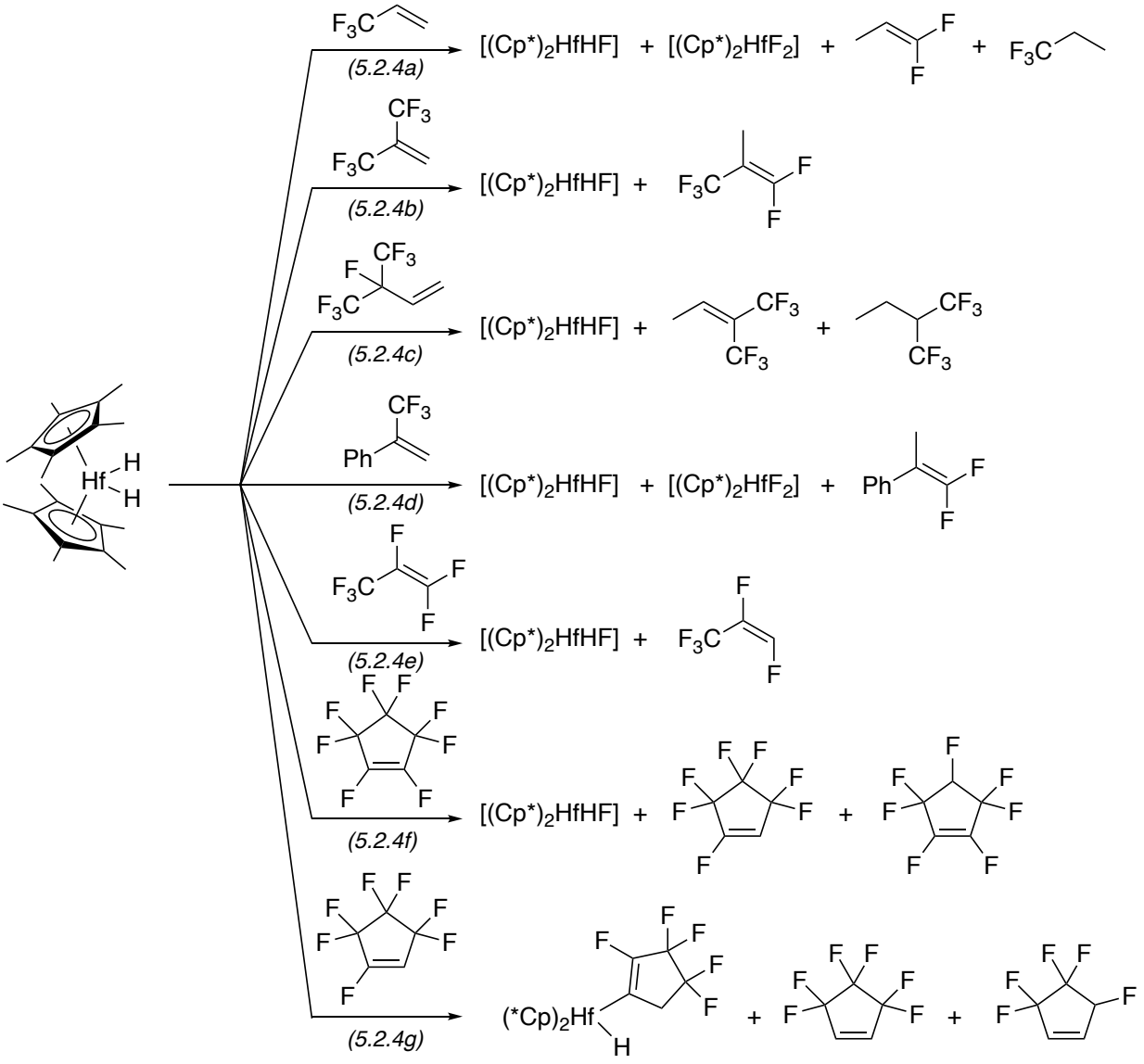
Jones et al. found that decamethylzirconocene dihydride [$(Cp^*)_2ZrH_2$] hydrozirconates HFP and β-fluoride elimination affords **1225ye*(E)*** (Scheme 5.2.3).[5] One equivalent of the zirconocene dihydride hydrodefluorinates one equivalent of HFP (eqn 5.2.3a) and 6 equivalents of the dihydride fully hydrodefluorinates and hydrogenates HFP to propane (eqn 5.2.3b).



Scheme 5.2.3: Hydrozirconation/elimination of HFP using [$(Cp^*)_2ZrH_2$] (Jones et al.) [8]

Jones later compared these results with the behavior of decamethylhafnocene dihydride and a variety of other fluoroölefins (Scheme 5.2.4).[6] The authors observed that the Hf complex exhibited roughly similar reactivity to the Zr congener, but was substantially less reactive. It reacts with 3,3,3-trifluoropropylene to yield a mixture of hydrodefluorinated 1,1-difluoropropylene (HFO-**1252zc**) and hydrogenated HFC-**263fb** (eqn 5.2.4a). Hexafluoroisobutylene also hydrodefluorinated the allylic fluorides to the pentafluoroisobutylene, but no hydrogenation product was observed (eqn 5.2.4b). The heptafluoroisoamylene in eqn 5.2.4c eliminates the allylic fluoride and gives the internal hexafluoroamylene and its hydrogenation product. A similar result is obtained with *α*-trifluoromethylstyrene, but with no hydrogenation (eqn 5.2.4d). HFP gives **1225ye** with selectivity for the *(E)*-isomer (eqn 5.2.4e). Unlike in previous papers, perfluorocyclopentene (PFCP) was also subjected to the metallocene dihydride, and

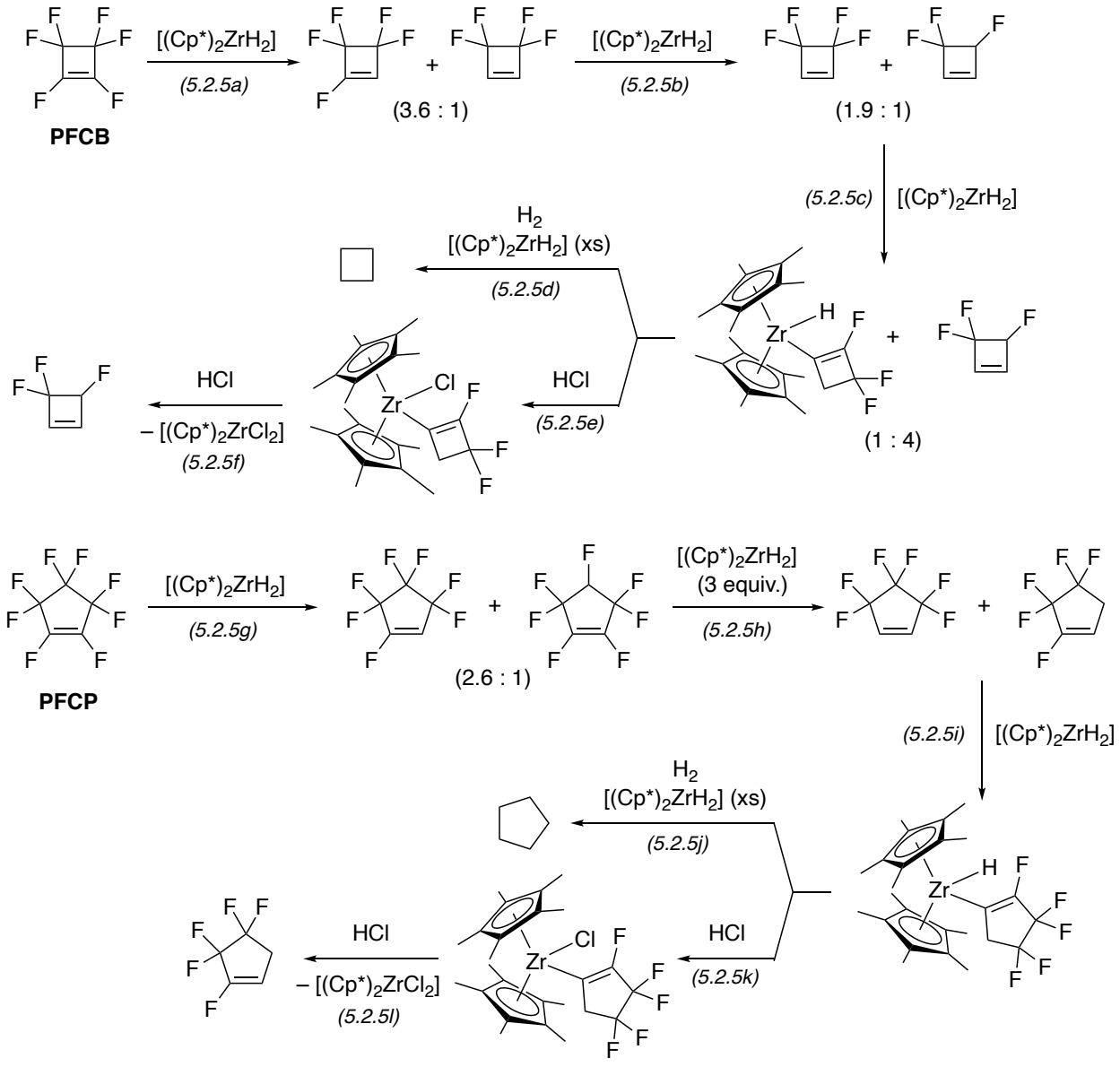
appears to hydrodefluorinate by a different mechanism than the open-chain olefins. Vinylic fluorides tend to be activated rather than allylic, (eqns 5.2.4f and 5.2.4g). This reaction was extremely slow, having been monitored by ^{19}F NMR over a period of weeks.



Scheme 5.2.4: Hydrodefluorination of various fluoroölefins using $[(Cp^*)_2HfH_2]$ (Jones et al.) [9]

The divergent results with PFCP were further examined by subjecting the former $[(Cp^*)_2ZrH_2]$ complex to both PFCP and c-C_4F_6 (PFCB, Scheme 5.2.5).[7] Under the same

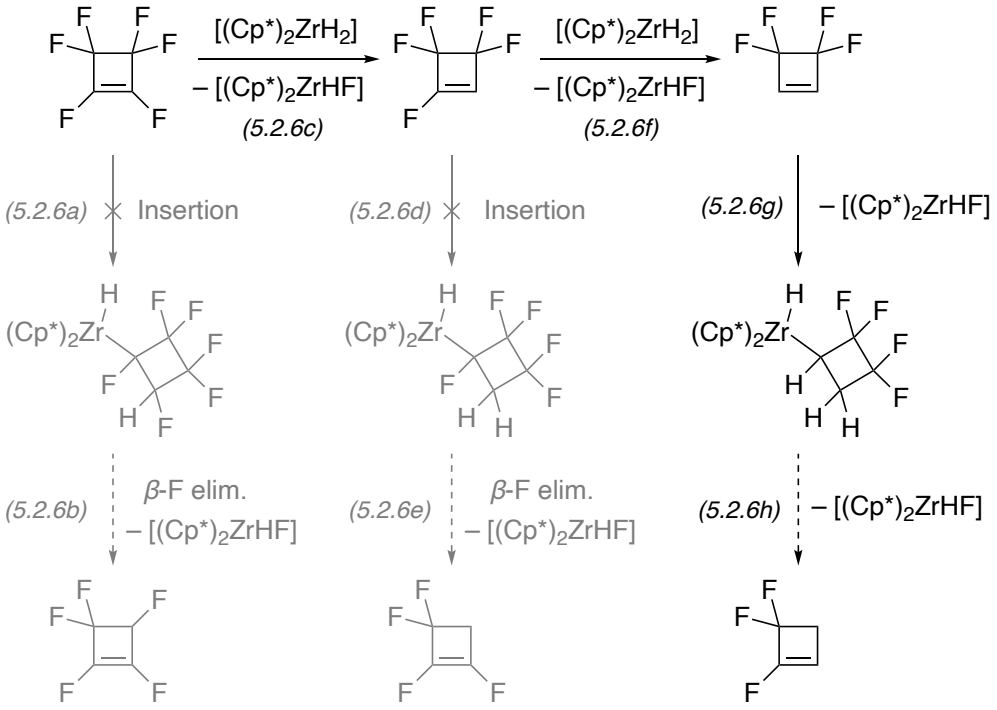
conditions, PFCB was hydrodefluorinated exclusively at the vinylic positions (eqn 5.2.5a) before the allylic positions (eqn 5.2.5b). The 2,2,3,3-tetrafluorocyclobutene slowly converted to the 2,2,3-trifluorocyclobutene *via* a vinylzirconium intermediate (eqn 5.2.5e) which could afford further product on protonolysis (eqn 5.2.5f).



Scheme 5.2.5: HDF of PFCB and PFCP using $[(Cp^*)_2ZrH_2]$ (Jones et al.) [10]

Hydrogenolysis in the presence of excess zirconocene dihydride yields fully reduced cyclobutene (eqn 5.2.5d). The same transformations were carried out stepwise with PFCP (eqn 5.2.5g) which formed predominantly the vinyl C–F hydrodefluorinated product and, interestingly, the homoallylic C–F bond hydrodefluorinated secondary product as the secondary product, which the authors hypothesized to arise from radical C–F bond abstraction by $[(Cp^*)_2Zr^{(III)}H]$. Continuation of the reaction with another 3 equiv. of $[(Cp^*)_2ZrH_2]$ reduced the second vinylic C–F bond to form 3,3,4,4,5,5-hexafluorocyclopentene alongside 1,4,4,5,5-pentafluorocyclopentene (eqn 5.2.5h). Treatment with another equivalent of zirconocene dihydride (eqn 5.2.5i) formed a vinylzirconium species similar to that seen in eqn 5.2.5c, which similarly underwent hydrogenolysis in presence of an excess of zirconocene dihydride and hydrogen to form cyclopentane (eqn 5.2.5j). Alternatively, it undergoes protonolysis by HCl to form first the vinylzirconium chloride (eqn 5.2.5k) and finally zirconocene dichloride with liberated 1,4,4,5,5-pentafluorocyclopentene (eqn 5.2.5l). The reduction of the vinylic C–F bonds is not expected for a reaction which proceeds *via* a hydrozirconation/β-elimination mechanism (Scheme 5.2.6), which should form the insertion product (eqn 5.2.6a) followed by the allylic reduction product from β-fluoride elimination (eqn 5.2.6b). Instead, the vinyl reduction product is observed (eqn 5.2.6c), which itself does not undergo insertion and β-elimination (eqns 5.2.6d and 5.2.6e), but rather further reduces the second vinylic fluoride to 2,2,3,3-tetrafluorocyclobutene (eqn 5.2.6f). This product, having no more vinyl

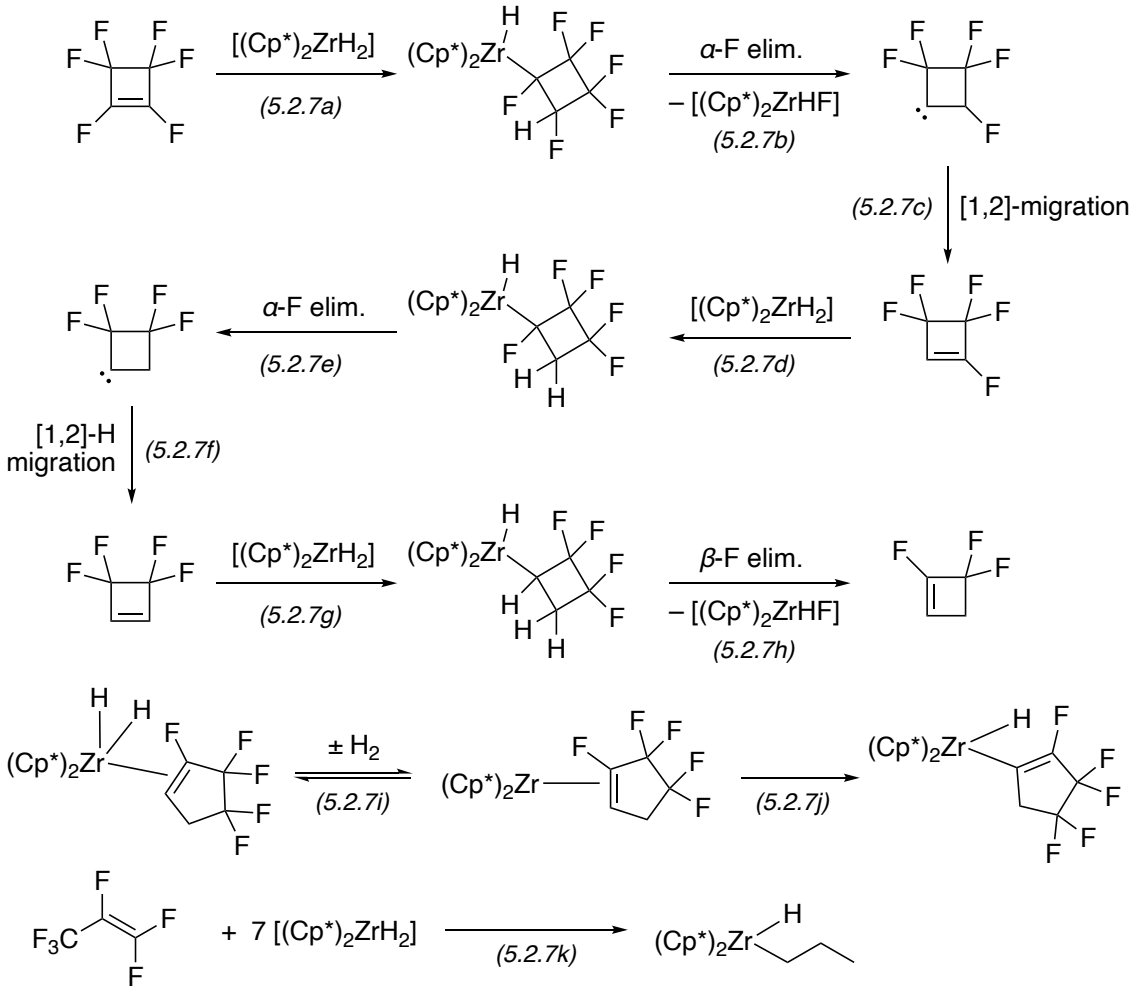
fluorides to reduce, can finally undergo the hydrozirconation (eqn 5.2.6g) and β-fluoride elimination (eqn 5.2.6h) mechanism to 1,4,4-trifluorocyclobutene.



Scheme 5.2.6: Reduction pathway for PFCP by $[(Cp^*)_2ZrH_2]$ compared with the expected insertion/elimination pathways [10]

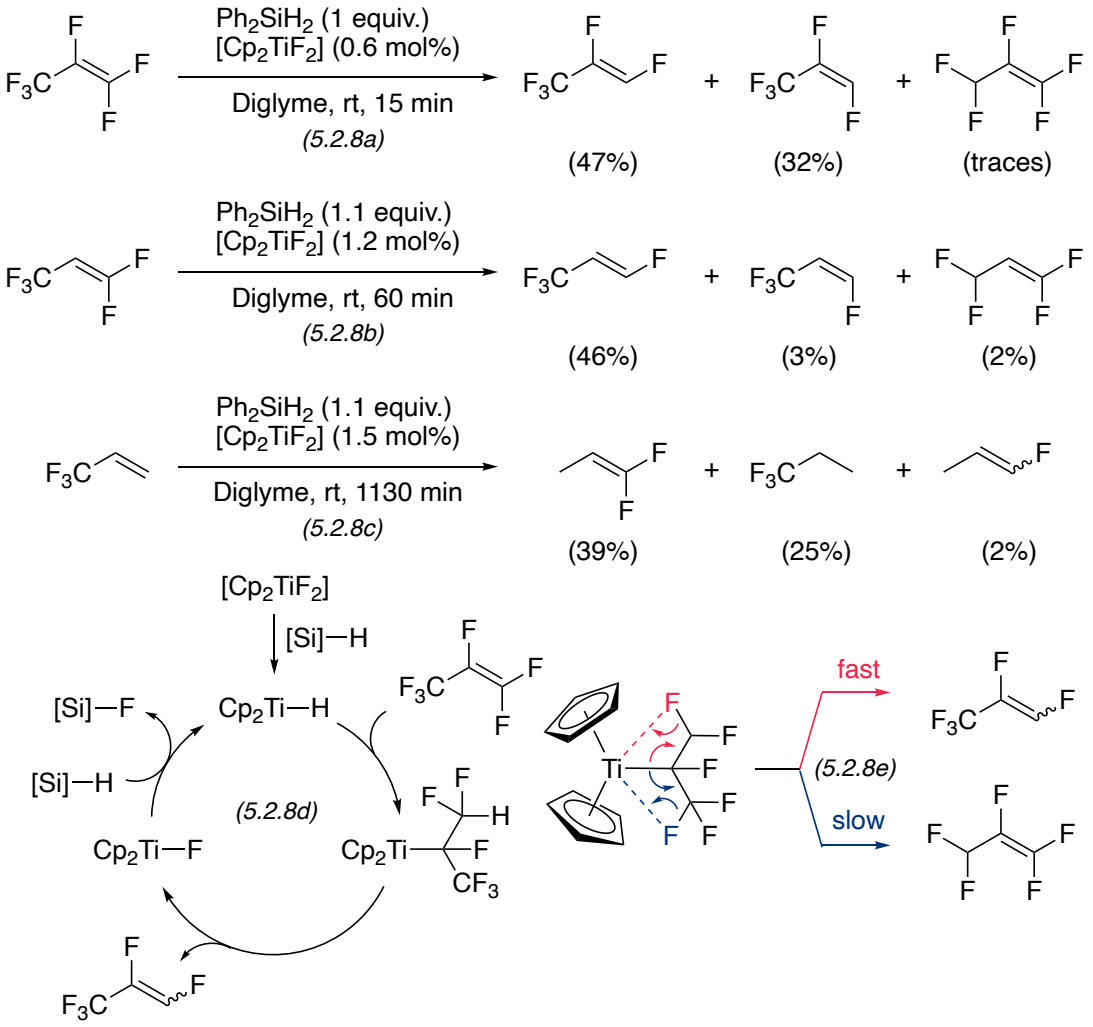
The authors proposed that the vinylic reduction products might still arise from a first hydrozirconation step, but undergo α-fluoride elimination instead of β-fluoride elimination (Scheme 5.2.7). In this scheme, PFCP undergoes a *cis*-insertion (eqn 5.2.7a), followed by α-fluoride elimination to eliminate a cyclic carbene (eqn 5.2.7b) which rapidly undergoes either a [1,2]-fluoride or -hydride shift to restore the olefin, which can undergo these two steps again (eqns 5.2.7d and 5.2.7e) to form a second carbene, which undergoes a [1,2]-hydride shift to form the tetrafluorocyclobutene. The final hydrodefluorination step can then occur via the typical insertion/elimination pathway (eqns 5.2.7g and 5.2.7h)

to form the observed trifluorocyclobutene. These proposals were supported by DFT studies. Formation of the vinyl species was rationalized by elimination of hydrogen to a π-olefin-bound Zr(II) intermediate (eqn 5.2.7i) which undergoes C_{sp2}–H bond activation (eqn 5.2.7j). In another report, Jones found that $[(Cp^*)_2ZrH_2]$ (7 equiv.) rapidly reacts with HFP in 15 min at rt to furnish the fully-reduced *n*-propyl hydride complex (eqn 5.2.7k).[8]

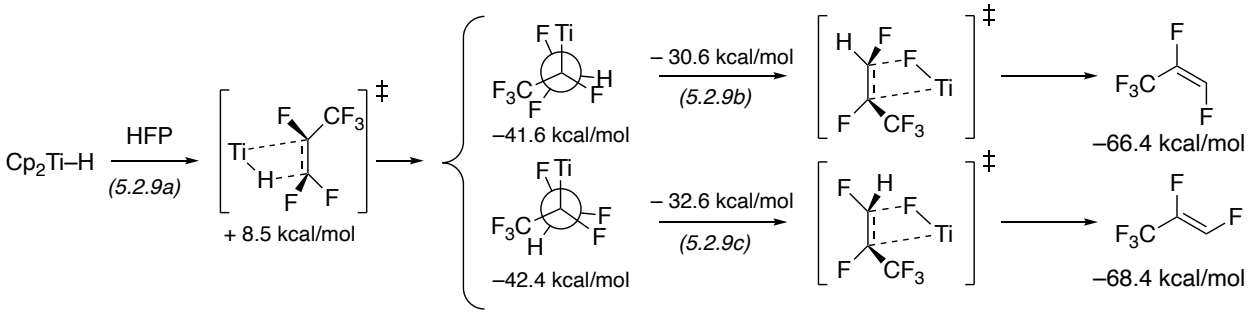


Scheme 5.2.7: Proposed α-elimination pathway for formation of vinylic hydrodefluorinated products, formation of [Zr] vinyl species, and full reduction of HFP [10, 11]

Kühnel and Lentz continued the work on group 4 metallocenes by using titanocene difluoride as an HDF catalyst for open-chain fluoroölefins (Scheme 5.2.8).[9] Titanocene difluoride is known to be reduced by silane to a Ti(III) hydride.[10,11] This [Cp_2TiH] species hydrodefluorinates HFP (eqn 5.2.8a) and 1,1,3,3,3-pentafluoropropene (HFO-**1225zc**) at the terminal position (eqn 5.2.8b). HFO-**1243zf** gives a mixture of HDF product **1262zc** and hydrogenated **263fb** (eqn 5.2.8c). The minor quantity of allylic-HDF product HFO-**1225yc** is formed by slow *β*-fluoride elimination from the *2H*-heptafluoroisopropyl intermediate (eqn 5.2.8e). The catalytic cycle for this HDF reaction is represented by eqn 5.2.8d. Up to 125 turnovers were observed for this catalyst with Ph_2SiH_2, but when the more economical poly(methylhydrosiloxane) (PMHS) was used, the TON dropped to 22, with 60% recovered substrate on workup. The mechanistic pathway for this reaction was studied in depth by Lentz et al. in a subsequent report, where the insertion/elimination (Scheme 5.2.10), sigma-bond metathesis (Scheme 5.2.11), and S_NV (nucleophilic vinylic substitution, Scheme 5.2.12) pathways were compared by DFT calculations done by C. Ehm.[12] The *cis*-hydrotitanation step is irreversible, and has a transition state energy of 8.5 kcal/mol, with the lowest-energy conformer of the inserted product eclipsing the CF_3 and the H. The activation barrier for the *β*-fluoride elimination is +11 kcal/mol from the higher-energy conformer (eqn 5.2.10b) and +9.8 kcal/mol from the lower-energy conformer (eqn 5.2.10c). The *β*-fluoride elimination is irreversible and selectivity-determining.

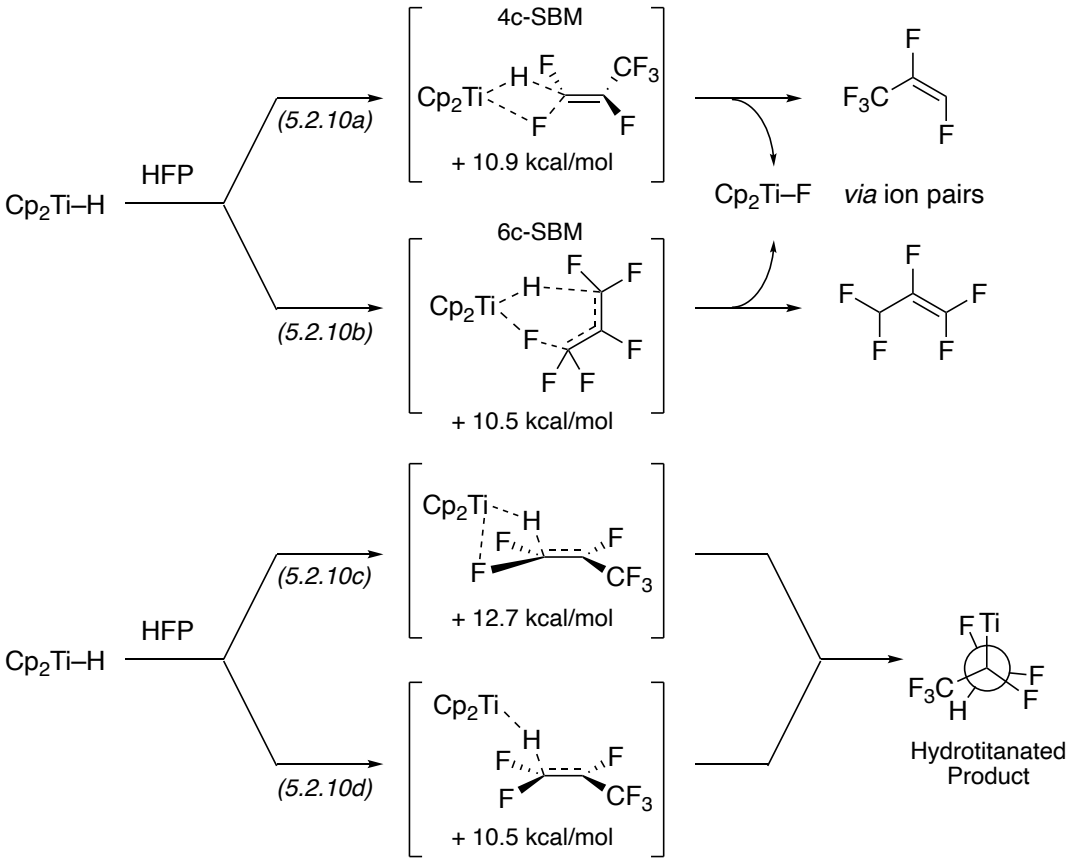


Scheme 5.2.8: Use of $[Cp_2TiF_2]$ and Ph_2SiH_2 to hydrodefluorinate various fluoroölefins [12]



Scheme 5.2.9: DFT-determined pathway for hydrotitanation/elimination mechanism of HFP by $[Cp_2TiH]$ (T = 298 K, 1 bar in THF) [15]

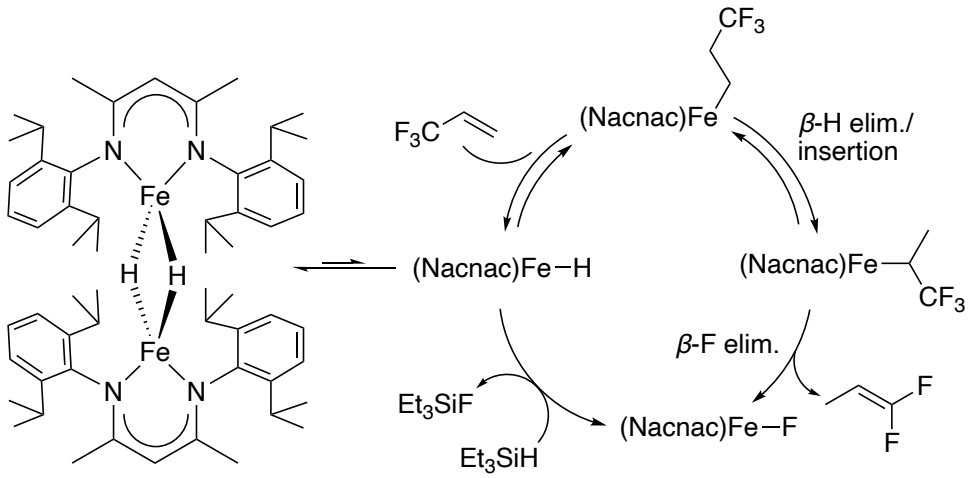
Another mechanism by which the HDF can proceed is σ-bond metathesis (SBM, Scheme 5.2.10), in which the titanocene hydride forms a contact pair with the HFP that gives way to either a 4- (eqn 5.2.10a) or 6-centered TS (eqn 5.2.10b), which proceeds to vinyl- or allyl-hydrodefluorinated products via Ti–F contact pairs. The 6c-SBM TS is slightly lower in energy than the 4c-SBM. The hydride can also attack the fluorovinyl electrophile by an S_NV reaction. The H-addition TS with fluoride contact (eqn 5.2.10c) is higher in energy than the simple H-addition TS (eqn 5.2.10d) by about 2.2 kcal/mol.



Scheme 5.2.10: DFT calculations for HDF of HFP by SBM and S_NV pathways with [Cp_2TiH] (T = 298 K, 1 bar in THF) [15]

In polar media, all three mechanistic pathways are competitive, but the S_NV pathway proceeds unselectively; this pathway can be suppressed by the use of non-polar solvents. The 6c-SBM pathway is favored over the 4c-SBM pathway, and likely accounts for the traces of HFO-**1225zc** formed during the reaction.

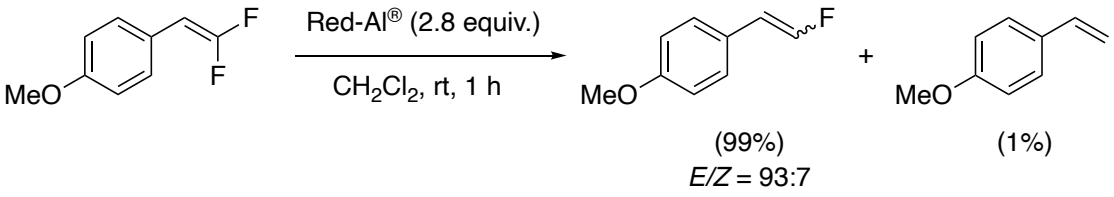
Holland et al. used a β-diketiminate iron(II) catalyst for hydrodefluorinating various substrates, including fluoroölefins (Scheme 5.2.11).[13] The initial insertion may occur with anti-Markovnikov selectivity, but chain-walking gives the Markovnikov product which can β-fluoride eliminate to HFO-1252zc, forming the iron(II) fluoride which can be regenerated by Et_3SiH.



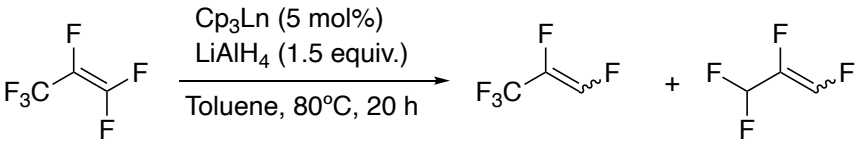
Scheme 5.2.11: HDF of HFO-1243zf using β-diketiminatoiron(II) hydride catalyst (Holland et al.) [16]

Crimmin et al. used zirconocene dichloride as a catalyst for hydrodefluorinating fluoroarenes with a diketiminate-ligated alane as the terminal reductant, but no fluoroölefins were tested.[14] Wu et al. found that Red-Al® (also referred-to as Vitride™)

could be used as a reducing agent for β,β-difluorostyrene derivatives at room temperature in the absence of a catalyst, giving up to 99% selectivity for the desired β-monofluorostyrene with a high *trans*-selectivity (Scheme 5.2.12).[15]



Scheme 5.2.12: Use of Red-Al® as a catalyst-free reducing agent for β,β-difluorostyrenes [18]



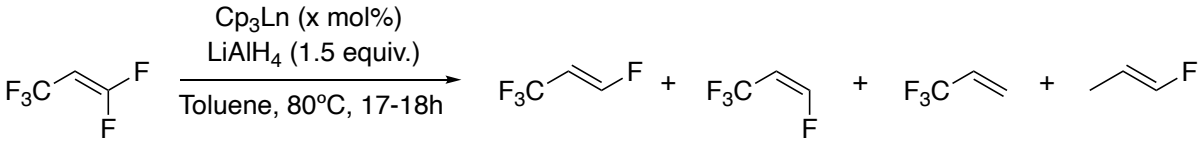
Ln	Conv.	TON	1225ye *(E/Z)*	1234ye *(E/Z)*
Ce	96.9%	24.2	71.1% *(1.6)*	21.6% *(0.29)*
Nd	97.1%	24.8	69.5% (1.6)	23.9% *(0.24)*
Sm	88.4%	20.2	74.8% *(1.7)*	10.4% *(0.33)*
Er	33.9%	9.2	31.9% *(1.5)*	4.7% *(0.24)*
Yb	100%	23.6	81.9% *(2.0)*	14.7% *(0.30)*
Yb*	72.5%	155	64.7% *(1.6)*	6.2% *(0.27)*

* 0.5 mol% catalyst

Scheme 5.2.13: Use of Cp_3Ln catalysts to hydrodefluorinate HFP with $LiAlH_4$ [19]

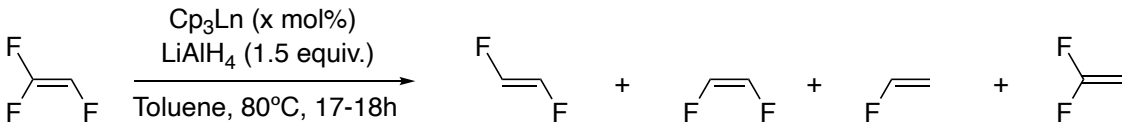
Jaeger and Lentz reported that various tris(cyclopentadienyl)lanthanide complexes catalyze the hydrodefluorination of HFP (Scheme 5.2.13), 1,1,3,3,3-pentafluoropropene (HFO-**1225zc**, Scheme 5.2.14), VF3 (Scheme 5.2.15), and CTFE (Scheme 5.2.16) using $LiAlH_4$ as the terminal reductant.[16] Regarding the HFP examples, Yb gave the highest TON and the highest selectivity for **1225ye**. With 0.5 mol% loading, as many as 155

turnovers were observed. By contrast, with all other olefins tested, Yb performed worse than the others. With **1225zc**, Cp_3Sm was the most competent catalyst, giving 17 turnovers after 17 hours. All catalysts gave predominantly **1234ze**, favoring the *trans* isomer by between 7 and 8-fold. Interestingly, 1-fluoropropylene was observed in small quantities, but no 1,1-difluoropropylene was present. Regarding VF3, the major product was *trans*-1,2-difluoroethylene (HFO-**1132*(E)***), and for this substrate Cp_3Nd was the most competent, giving 77.6% conversion with 16.4 turnovers. The *trans*-selectivity for **1132** was about 10-fold. Minor products included VF and VF2 (<3%). Regarding CTFE, conversions were substantially lower than for the aforementioned olefins. The major product in all cases was 1-chloro-1,2-difluoroethylene (HCFO-**1122a**), with Cp_3Sm topping the range of lanthanides tested (about 30% conversion with 7 turnovers). Minor products included 1-chloro-2-fluoroethylene (HCFO-**1131**, roughly 1:1 ratio of *cis*/*trans*), **1132** (in about the same ratio), and VF.



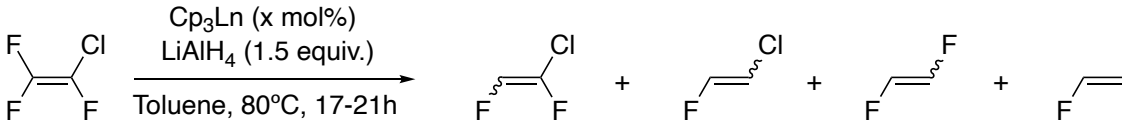
Cat. (mol%)	Conv.	TON	1234ze*(E)*	1234ze*(Z)*	1243zf	1261ze *(E/Z)*
Cp_3Ce (5.7)	79.9%	15.4	66.9%	9.3%	1.7%	1.4% (7.2)
Cp_3Nd (6.3)	87.6%	15.8	73.6%	7.5%	2.5%	2.3% (9.8)
Cp_3Sm (5.6)	86.7%	17.0	73.5%	8.2%	3.0%	1.2% (9.0)
Cp_3Yb (5.8)	27.9%	4.8	22.1%	2.8%	0.1%	2.9% (7.9)

Scheme 5.2.14: Use of Cp_3Ln catalysts to hydrodefluorinate 1225zc with $LiAlH_4$ [19]



Cat. (mol%)	Conv.	TON	1132*(E)*	1132*(Z)*	VF	VF2
Cp_3Ce (4.7)	74.5%	16.3	67.3%	5.7%	1.3%	0.2%
Cp_3Nd (4.8)	77.6%	16.4	69.9%	6.2%	1.3%	0.2%
Cp_3Sm (4.7)	28.6%	6.3	22.4%	2.3%	1.3%	2.7%
Cp_3Yb (4.5)	26.7%	6.0	24.0%	2.1%	0.4%	0.1%

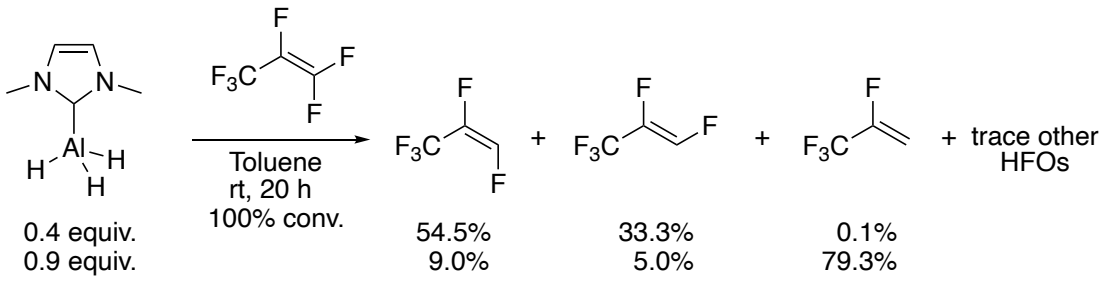
Scheme 5.2.15: Use of Cp_3Ln catalysts to hydrodefluorinate VF3 with $LiAlH_4$ [19]



Cat. (mol%)	Conv.	TON	1122a	1131	1132	VF
Cp_3Ce (5.1)	28.0%	6.6	22.1%	4.0%	1.9%	-
Cp_3Nd (5.1)	22.0%	5.0	18.0%	2.7%	1.2%	0.1%
Cp_3Sm (5.0)	29.8%	7.0	23.0%	3.7%	2.3%	0.4%
Cp_3Yb (4.9)	3.8%	1.1	2.4%	0.7%	0.7%	-

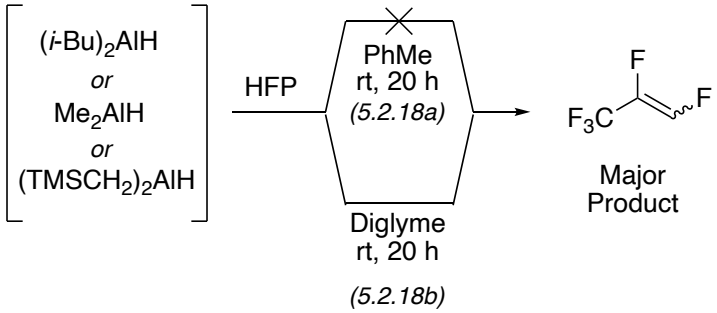
Scheme 5.2.16: Use of Cp_3Ln catalysts to hydrodefluorinate CTFE with $LiAlH_4$ [19]

Lentz and Radius investigated the use of catalyst-free NHC-alane complexes for hydrodefluorination of hexafluoropropylene at room temperature, giving a range of products including predominantly **1225ye** and **1234yf**, among others (Scheme 5.2.17).[17]

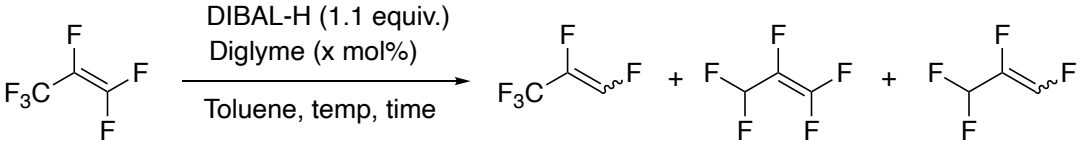


Scheme 5.2.17: HDF of HFP using NHC-Alane reagent [20]

Lentz continued using alanes for HDF, using DIBAL-H in the presence of organocatalytic ethers at rt (Scheme 5.2.18).[18,19] Interestingly, when DIBAL-H, Me_2AlH, or $(TMSCH_2)_2AlH$ are treated with HFP at rt in toluene (or any other non-coördinating solvent), no HDF is observed (eqn 5.2.18a). However, when 11 mol% of ethereal additive is used, >97% conversions are obtained, with 99.8% conversion using diglyme (eqn 5.2.18b). The reaction can be carried out in neat diglyme or toluene containing 11 mol% of diglyme (Scheme 5.2.18). If 1 mol% of diglyme is used, the reaction must be carried out at 100°C for 21h to give >90% conversion. If 11 mol% is used at this temperature, the reaction is 79% converted after only 15 minutes.



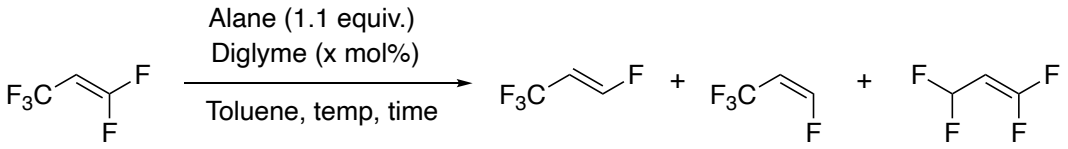
Scheme 5.2.18: HDF of HFP using various alane reagents with or without diglyme catalyst [21]



Diglyme	Temp	Time	1225ye	1225yc	1234ye
11 mol%	25°C	18 h	96%	1.2%	2.4%
1 mol%	100°C	21 h	90.8%	1.1%	1.1%
11 mol%	100°C	15 min	76.0%	2.6%	0.5%

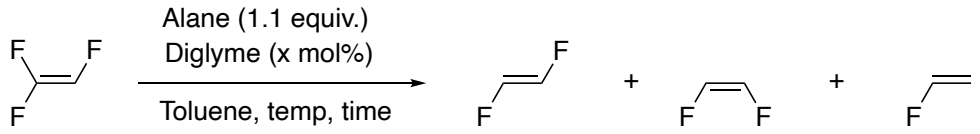
Scheme 5.2.19: HDF of HFP using (i-Bu)$_2$AlH/diglyme (major products) [21]

When HFO-**1225zc** was used as the substrate (Scheme 5.2.20), conversions were lower than with HFP, reaching 59% after 18 h at room temperature, and 87% after 22 h at 100°C. The reactions were highly selective for **1234ze** with a *trans*-selectivity of as high as 13:1. When VF3 was used as a substrate (Scheme 5.2.21), the reactions failed to exceed even 1% conversion with all three alanes tested after as long as 21 h at rt. When CTFE was used as a substrate (Scheme 5.2.22), the major product was the mono-HDF product **1122a**, which was obtained in up to about 60% yield when the reaction was carried out in diglyme at rt overnight.



Alane	x (mol%)	Temp	Time	1234ze*(E)*	1234ze*(Z)*	1234zc
DIBAL-H	12	25°C	18 h	50.8%	4.4%	4.1%
DIBAL-H	12	100°C	22 h	76.7%	5.7%	1.9%
Me_2Al-H	12	25°C	22 h	51.8%	5.3%	1.7%

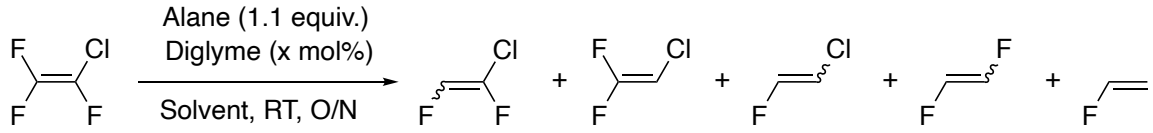
Scheme 5.2.20: HDF of 1225zc using alanes/diglyme [21]



Alane	x (mol%)	Temp	Time	1132*(E)*	1132*(Z)*	VF
DIBAL-H	11	25°C	18 h	0.02%	0.07%	0.05%
Me_2Al-H	8	25°C	21 h	0.04%	0.07%	0.12%
$(TMSCH_2)_2Al$-H	14	25°C	17 h	0.16%	0.03%	-

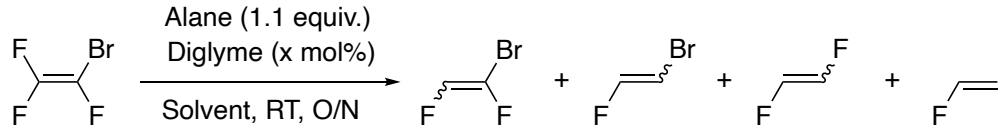
Scheme 5.2.21: HDF of VF3 using alanes/diglyme [21]

When the heavier congeners of CTFE are used, the reactivity profile is altered. With bromotrifluoroethylene (BrTFE, Scheme 5.2.23), the major product remains **1122aBr**, but no **1122** is observed. Up to 77% conversion was achieved. When iodotrifluoroethylene was used (Scheme 5.2.24), scarcely any 1122I was observed, and no 1,2-difluoroethylene or 1,2-iodofluoroethylene. This indicates that predominantly C–I bond reduction occurs first, and the low reactivity of VF3 (Scheme 5.2.21) towards this HDF system ensures a high selectivity for this product. Up to 71.1% conversion was achieved. Gallanes have also been used by Lentz et al. for the same transformations and with similar effectiveness.[20]



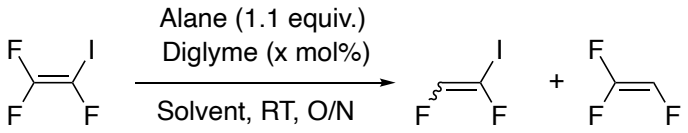
Alane	x (mol%)	Solvent	1122a	1122	1131	1132	VF
DIBAL-H	9.8	Toluene	13.5%	1.5%	1.1%	0.8%	0.8%
DIBAL-H	-	Diglyme	59.9%	3.6%	7.2%	9.4%	1.4%
Me_2Al-H	11	Toluene	20.2%	4.0%	6.5%	1.2%	1.7%

Scheme 5.2.22: HDF of CTFE using alanes/diglyme [21]



Alane	x (mol%)	Solvent	1122aBr	1131Br	1132	VF
DIBAL-H	11	Toluene	48.3%	5.1%	2.6%	0.6%
DIBAL-H	-	Diglyme	61.9%	4.3%	9.9%	1.1%
Me_2Al-H	10	Toluene	27.9%	3.6%	6.4%	1.3%

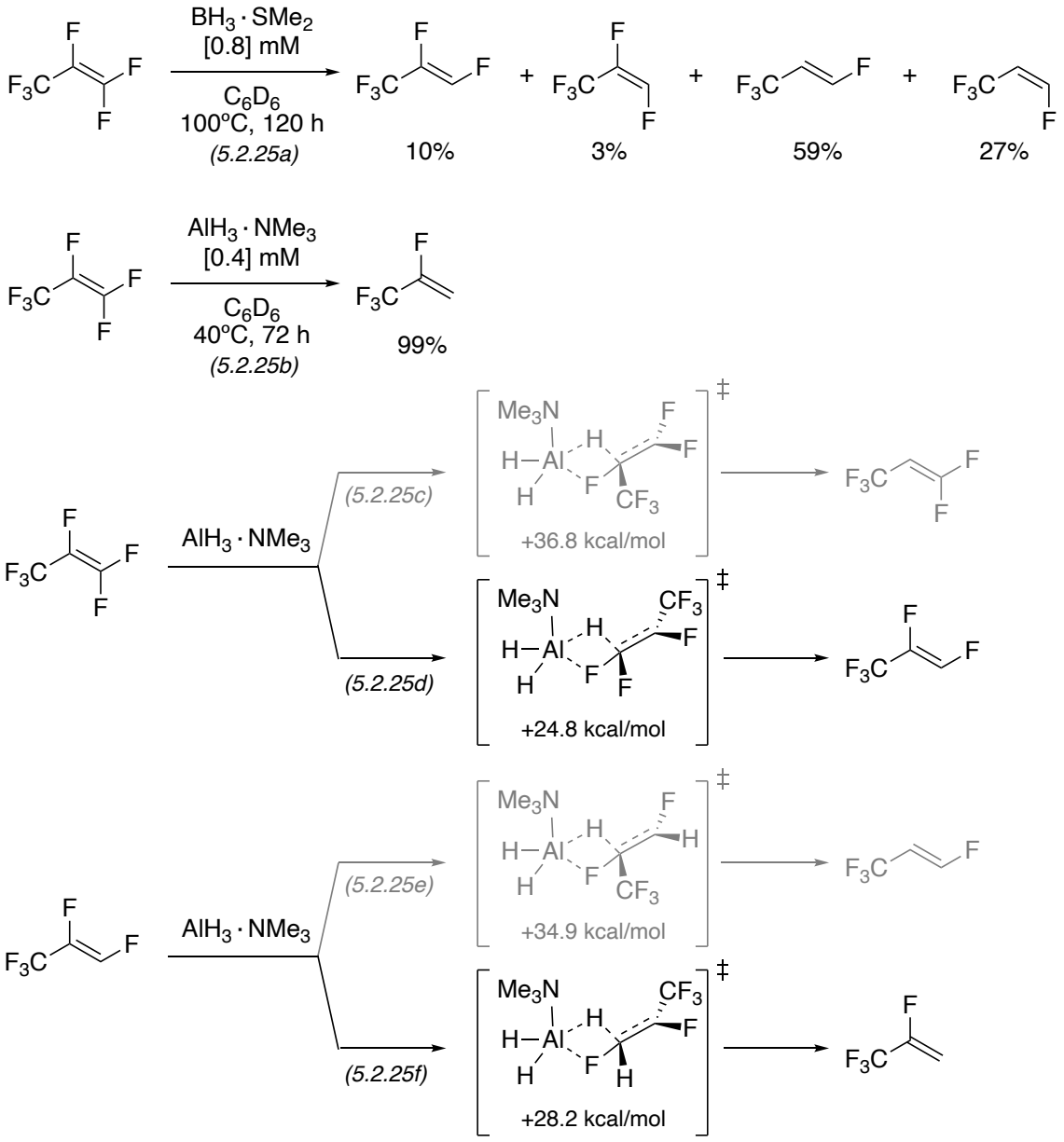
Scheme 5.2.23: HDF of BrTFE using alanes/diglyme [21]



Alane	x (mol%)	Solvent	1122al	1123
DIBAL-H	11	Toluene	0.2%	23.8%
DIBAL-H	-	Diglyme	-	71.1%
Me_2Al-H	10	Toluene	0.4%	14.4%

Scheme 5.2.24: HDF of ITFE using alanes/diglyme [21]

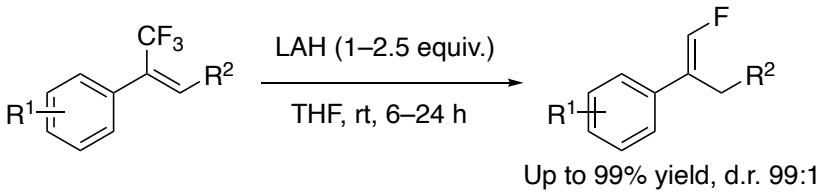
Crimmin et al. compared the HDF activity of BH_3·L and AlH_3·NMe_3 reagents under various conditions (Scheme 5.2.25).[21,22] When borane dimethylsulfide was reacted with HFP at 1 atm pressure and 100°C for 5 days, a mixture containing predominantly HFO-**1234ze** was obtained (eqn 5.2.25a). The reaction was not possible when L = NMe_3 and was ineffective when L = THF. By contrast, when AlH_3·NMe_3 reacts with HFP at 40°C for 3 days, a 99% yield of HFO-**1234yf** was obtained (eqn 5.2.25b). DFT calculations show that the alane reduction proceeds by σ-bond metathesis, with the transition state for hydrodefluorination of HFP at the 2-position (eqn 5.2.25c) being 12 kcal/mol than the hydrodefluorination at the 1-position (eqn 4.2.25d). For **1225ye*(E)***, the TS for the HDF at the 2-position (eqn 5.2.25e) is 6.7 kcal/mol higher than the 1-position (eqn 5.2.25f). For the initial HDF of HFP, the TS leading to the *(E)*-product is 2.8 kcal/mol lower in energy.



Scheme 5.2.25: HDF of HFP using BH_3·SMe_2 or AlH_3·NEt_3, and explanations of the origin of selectivity of the AlH_3·NMe_3 reduction [24]

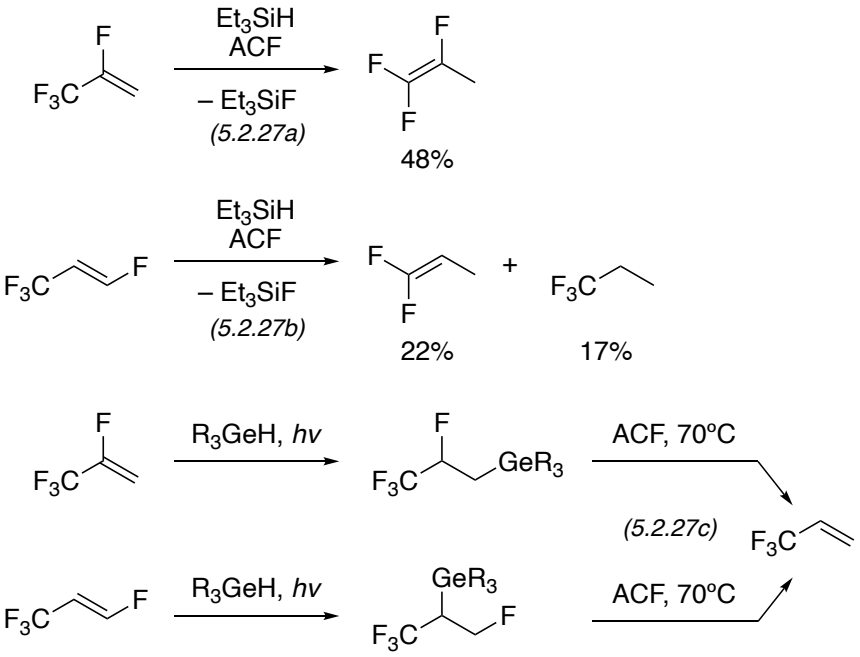
The BH_3 system, by contrast, was too complex to model computationally due to the extremely low-energy barrier of the initial hydroboration. Furthermore, the HDF can be, in principle, carried out by any one of BH_3, BH_2F, or BHF_2, with the concentrations of the latter increasing as the reaction proceeds.

Poisson et al. used $LiAlH_4$ to hydrodefluorinate α-trifluoromethylstyrenes, furnishing the terminal monofluoroölefins in up to 99% yield with as high as 99:1 *E/Z*-selectivity (Scheme 5.2.26).[23]



Scheme 5.2.26: Stereoselective HDF of α-trifluoromethylstyrenes using LAH [26]

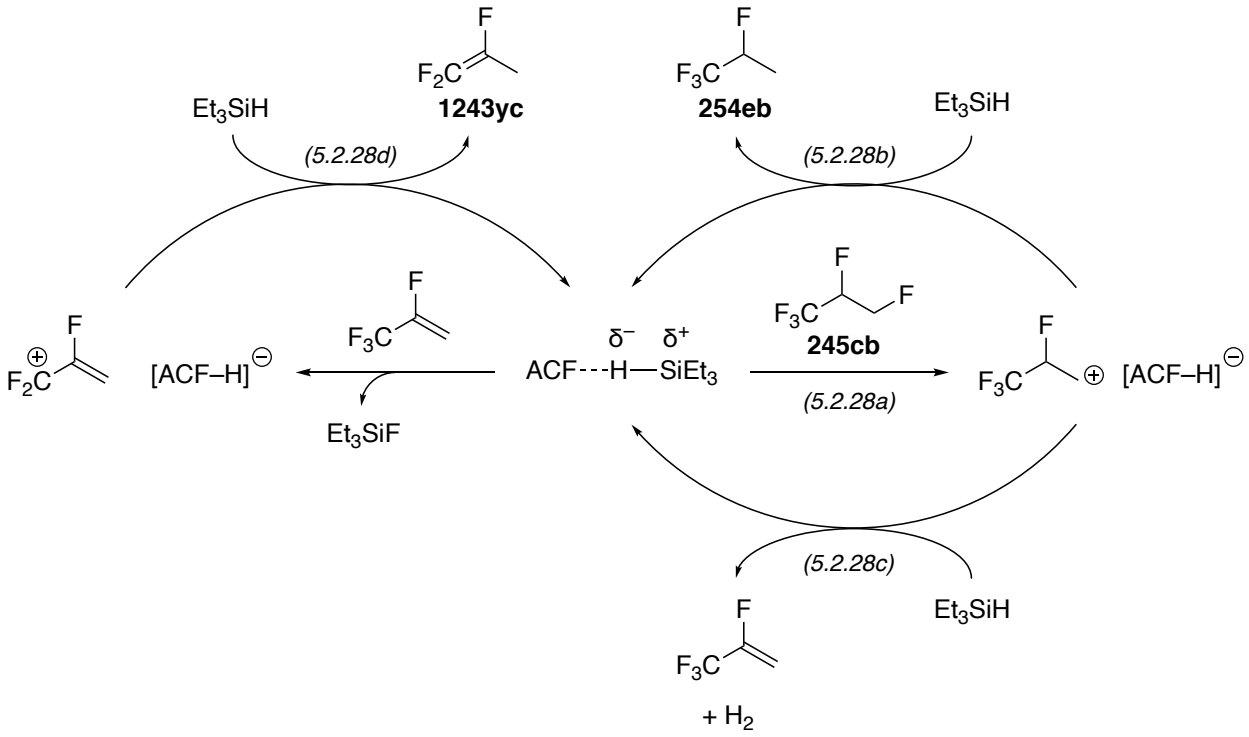
There also exists a considerable body of work surrounding the use of strong Lewis acids to catalyze HDF reactions. It is already known that cationic group IV metallocenes can activate allylic C–F bonds towards, for example, Friedel-Crafts reactions.[24] Silylated chalconium ions were found by Müller to catalyze the HDF of C_{sp3}–F bonds with TON up to >124 in absence of moisture or air.[25] P-based Lewis acids have also been used to this end.[26,27] Kemnitz et al. used acidic aluminum chlorofluoride (ACF) to catalyze hydrogermylation and hydrodefluorination of HFOs **1234yf** and **1234ze** (Scheme 5.2.27).[28] The former reacted with Et_3SiH in the presence of ACF to furnish the mono-HDF product 1,1,2-trifluoropropylene (HFO-**1243yc**, eqn 5.2.27a) and the latter to produce a mixture of HFO-**1252zc** and HFC-**263fb** (eqn 5.2.27b). Reactions of both olefins with 3° germanes under irradiation led to isolable hydrogermylation products which, when subjected to ACF at elevated temperatures, defluorogermylated to HFO-**1243zf** (eqn 5.2.27c).



Scheme 5.2.27: HDF and hydrogermylation/defluorogermylation of HFOs [31]

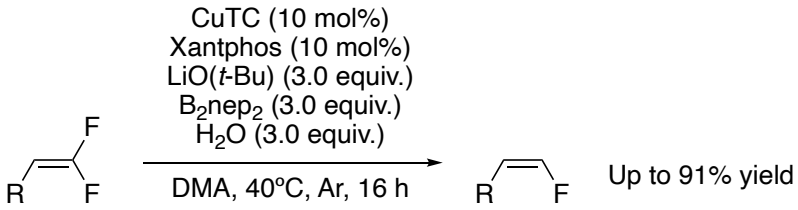
In a subsequent paper, Kemnitz et al. demonstrated that 1,1,1,2,3-pentafluoropropane (HFC-**245cb**) can be tandem dehydrofluorinated and hydrodefluorinated by ACF (Scheme 5.2.28).[29] In absence of silane, the ACF only dehydrofluorinated the **245cb**, but in the presence of Et_3SiH, further reactions ensued which furnished a mixture of hydrogenated and hydrodefluorinated derivatives including HFC-**254eb** and HFO-**1243yc** (eqn 5.2.28b). The authors proposed that reaction proceeds through a silylium ion (generated by interaction of the silane with the ACF) which reacts with the HFC to form an ion pair (eqn 5.2.28a). Further reaction with another equivalent of Et_3SiH gives either form hydrodefluorinated HFC-**254eb** (eqn 5.2.28b) or dehydrofluorinated HFO-**1234yf** (eqn 5.2.28c). The **1234yf** can react further with the

Et_3SiH-ACF ion pair to abstract an allylic fluoride, forming a cationic trifluoroallyl intermediate which can be trapped by further silane (eqn 5.2.28d).



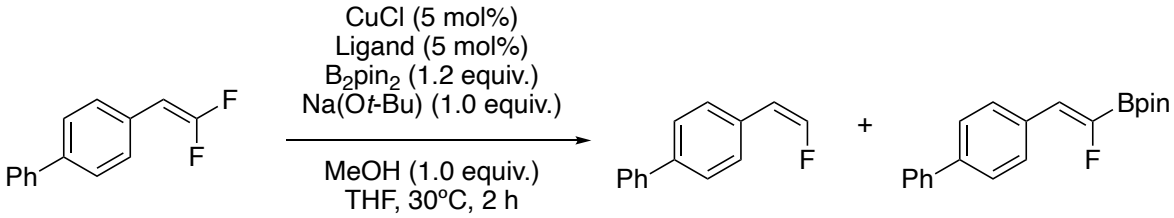
Scheme 5.2.28: Proposed mechanism of hydrodefluorination/dehydrofluorination of HFC-245cb by ACF/Et_3SiH [32]

Another body of work exists for the use of copper catalysts for hydrodefluorination. Cu(I) catalysts are known to hydrodefluorinate fluoroarenes using Me_2PhSiH as the reductant, where the reaction is known to proceed through Cu hydrides.[30] Copper(I) 2-thiophenecarboxylate (CuTC) is also known to selectively mono-hydrodefluorinate 1,1,-difluorovinyl groups using B_2nep_2 as the terminal reductant and water as the hydrogen source instead of silanes (Scheme 5.2.29, nep = neopentylglycolato).[31] The reaction is *cis*-selective, and gives high yields for a variety of aliphatic difluorovinyl substrates, tolerating chlorides, heterocycles, esters, and internal olefins.



Scheme 5.2.29: Cu-catalyzed stereoselective HDF of difluorovinyl substrates using B_2nep_2/H_2O as the reductant system [34]

A similar but simpler system was used by Ito et al. for the hydrodefluorination of *β,β*-difluorostyrenes.[32] The authors observed competing hydrodefluorination and defluorinative borylation reactions (Scheme 5.2.30), finding Xantphos to furnish exclusively HDF, while PPh_3, IPr, dppp, and dppbz all favor the borylation. In all cases, the reaction proceeded with >99% *cis*-selectivity.

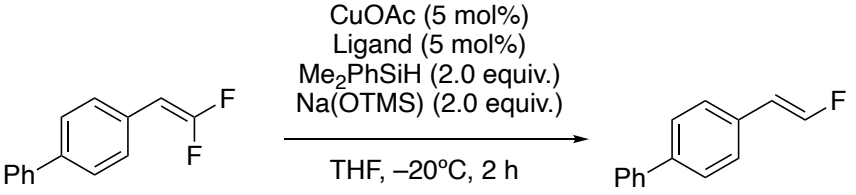


Ligand	HDF product yield	Borylation product yield
Xantphos	96%	0%
None	2%	2%
PPh_3	1%	31%
IPr · HCl	9%	36%
dppp	9%	45%
dppbz	12%	38%

Scheme 5.2.30: Cu-catalyzed stereoselective HDF or defluorinative borylation of *β,β*-difluorostyrene derivative [35]

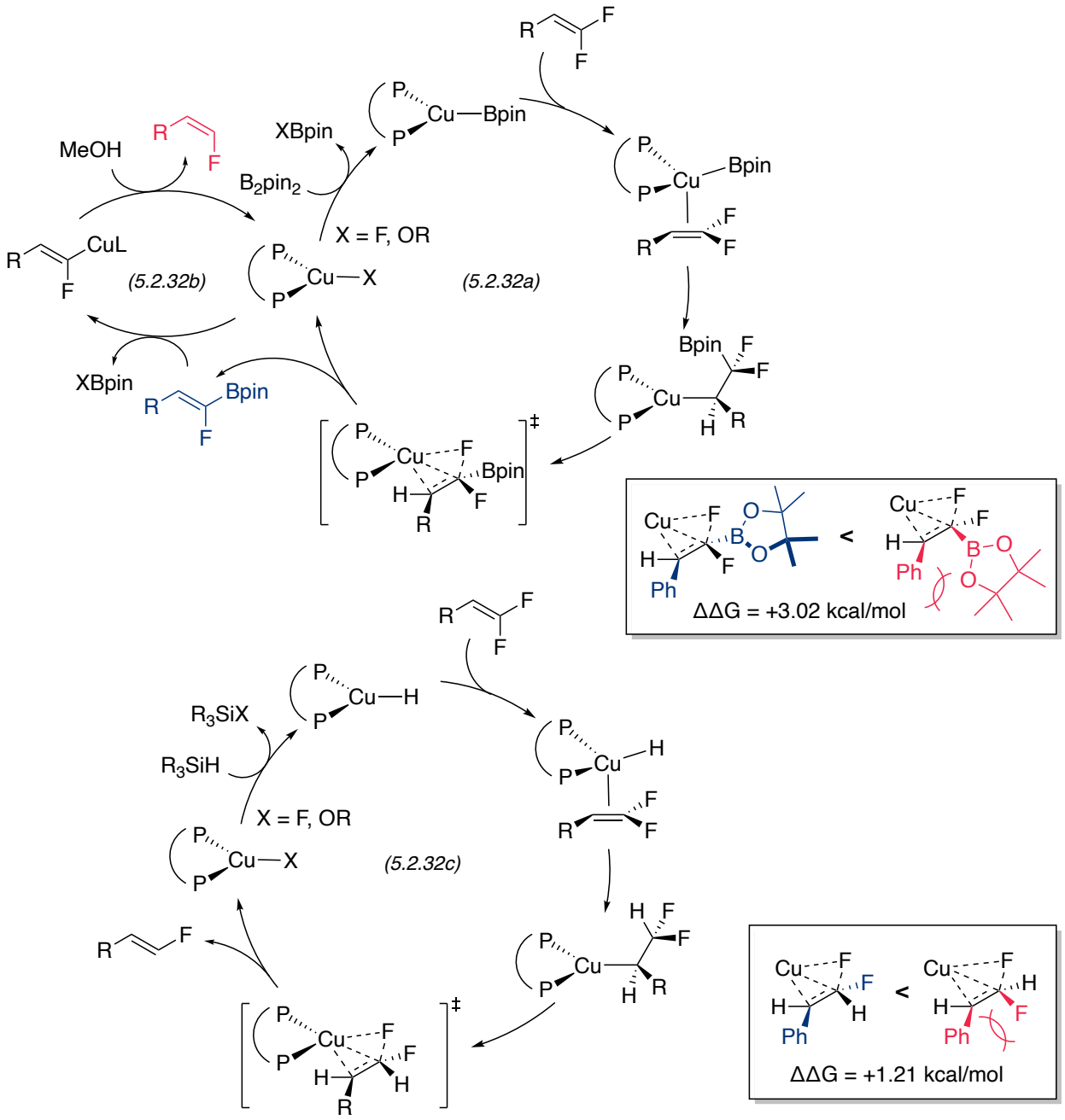
In the same paper, an alternate reaction was performed using a system comprised of copper(I) acetate and a silane as the reducing equivalent, which gave exclusively HDF

with *trans*-selectivity (Scheme 5.2.31). The reaction only worked with phosphine ligands, and gave no conversion with IPr. The highest yield and stereoselectivity were obtained with dppp. The mechanism for the borylation is thought to proceed *via* a conventional cuproborylation of the double bond, followed by *β*-fluoride elimination to eliminate the fluorovinylborate product (Scheme 5.2.32, eqn 5.2.32a). The HDF step is believed to occur by cupration of the resulting vinylborate by L_nCuX, with protonolysis of the resulting vinylcopper species by MeOH furnishing the *cis*-*β*-fluorostyrene (eqn 5.2.32b). The explanation for the *(Z)*-selectivity of the *β*-fluoride elimination can be explained on the basis of minimization of steric repulsion between the Ph and Bpin substituents, with the difference in TS energy amounting to about 3 kcal/mol between *(Z)*-TS and *(E)*-TS (Scheme 5.2.32).



Ligand	HDF product yield	E/Z
dppp	96%	95 : 5
None	0%	-
PPh_3	35%	90 : 10
IPr · HCl	9%	-
dppbz	30%	92 : 8
Xantphos	70%	93 : 7

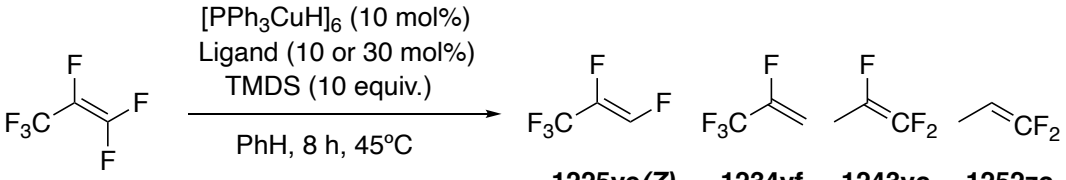
Scheme 5.2.31: Cu-catalyzed stereoselective HDF of *β*,*β*-difluorostyrene derivative [35]



Scheme 5.2.32: Proposed mechanisms for Cu-catalyzed HDF/borylation of β,β-difluorostyrenes with B_2pin_2 or silane (pin = pinacolato) [35]

The HDF with silane is proposed to proceed *via* a Cu hydride species which hydrocuprates the difluorostyrene, followed by an *(E)*-selective β-fluoride elimination (eqn 4.2.32c). The energy difference (+1.21 kcal/mol) comes from Ph/F repulsion.

Andrella et al. (of our group) subsequently reported the use of Stryker's Reagent ($[PPh_3CuH]_6$), an isolable copper(I) hydride, in the presence of other ligand co-additives as a catalyst for HDF of fluoroölefins using 1,1,3,3-tetramethyldisiloxane (TMDS) as the terminal reductant.[33,34] This invention is advantageous particularly for its use of a much lower-energy reducing agent than the prior reports using alanes, boranes, or gallanes. Furthermore, TMDS is a far less expensive silane than the Me_2PhSiH (the former costing as little as \$0.67/gram, compared to \$1.87/gram for the latter[31]) used in the previous report. The use of HFP as a substrate furnished mixtures of HFO products including **1225ye**, **1234yf**, **1243yc**, and **1252zc**, with varying ratios depending on the ligand used (Scheme 5.2.33). All reactions reached 100% conversion.



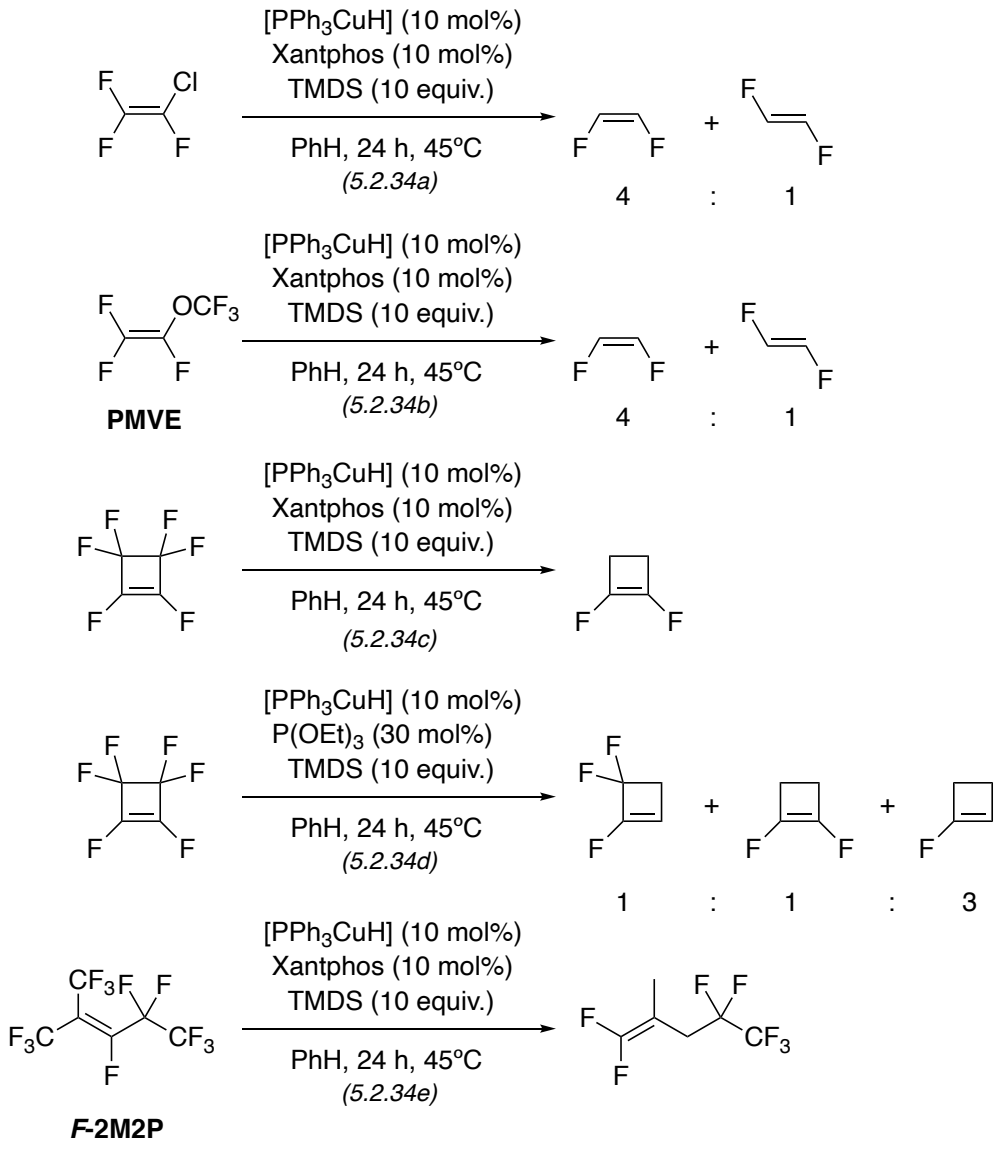
1225ye(*Z*) **1234yf** **1243yc** **1252zc**

Ligand	Selectivity (^{19}F NMR basis)			
None	37%	63%	-	-
PPh_3	40%	60%	-	-
$P(o\text{-Tol})_3$	90%	10%	-	-
tBuXPhos	45%	55%	-	-
PCy_3	43%	57%	-	-
dppe	-	92%	-	8%
dppf	-	25%	-	75%
Xantphos	29%	71%	-	-
$P(OEt)_3$	-	-	29%	71%
$P(OPh)_3$	100%	-	-	-
$P(O\text{-}o\text{-Tol})_3$	97%	3%	-	-

Scheme 5.2.33: HDF of HFP by $[PPh_3CuH]_6$/TMDS and various ligands [36]

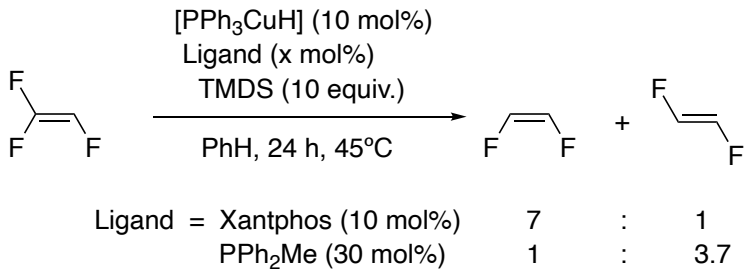
[31] Prices from www.gelest.com in USD and accurate as of the time of publication

Bulky ligands gave decreased catalyst activity, proceeding scarcely further than the first-generation HDF product **1225ye** (only the *(Z)*-isomer of which was observed), but less sterically-hindered ligands such as dppe, dppf, or Xantphos gave second generation HDF product **1234yf** (and in the case of dppf and dppe, some fourth-generation HDF product **1252zc**). The triethylphosphite catalyst was the most active, giving predominantly **1252zc**. With PPh_3, both Me_2PhSiH and poly(methylhydrosiloxane) (PMHS) were also tried with nearly identical results to the TMDS. Being operationally easier and less viscous to handle, TMDS was used for all subsequent experiments. The substrate scope was expanded to include other fluoroölefins in our possession at the time (Scheme 5.2.34). CTFE (eqn 5.2.34a) gave incomplete conversion to to a predominantly *cis*-mixture of **1132** isomers (likely owing to the inability of L_nCuCl to be turned-over by silane). Interestingly, the same result was obtained when perfluoro(methyl vinyl ether) (PMVE) was used as the substrate (eqn 5.2.34b), but with full conversion to **1132** (*E/Z* = 1:4). Two trials were conducted with PFCB, with the Xantphos system giving full conversion to 1,2-difluorocyclobutene (eqn 5.2.34c) and the $P(OEt)_3$ system giving a distribution of products favoring the fifth-generation HDF product 1-fluorocyclobutene (5.2.34d). Next, perfluoro-2-methyl-2-pentene (*F*-2M2P, the thermodynamic dimer of hexafluoropropylene) was attempted, and gave exclusively formation of the fifth-generation HDF product 1,1,4,4,5,5,5-heptafluoro-2-methyl-1-pentene (eqn 5.2.34e).



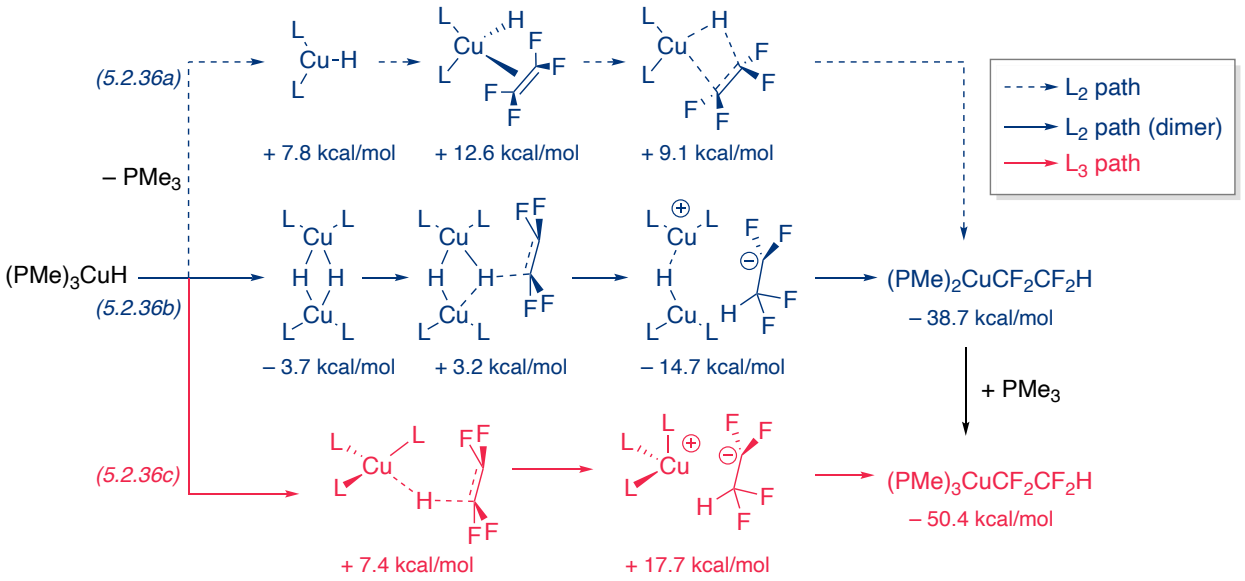
Scheme 5.2.34: HDF of various fluoroolefins catalyzed by [PPh_3CuH]/TMDS and either Xantphos (10 mol%) or $P(OEt)_3$ (30 mol%) [36]

TFE was a poor substrate for HDF by this system, giving incomplete conversion to a mixture of VF3 and hydrogenated product HFC-**134**. VF3, however, furnished isomeric **1132** with ligand-dependent stereoselectivity; the Xantphos system gave a 7-fold *cis*-selectivity and the PPh_2Me system gave a 3.7-fold *trans*-selectivity (Scheme 5.2.35).



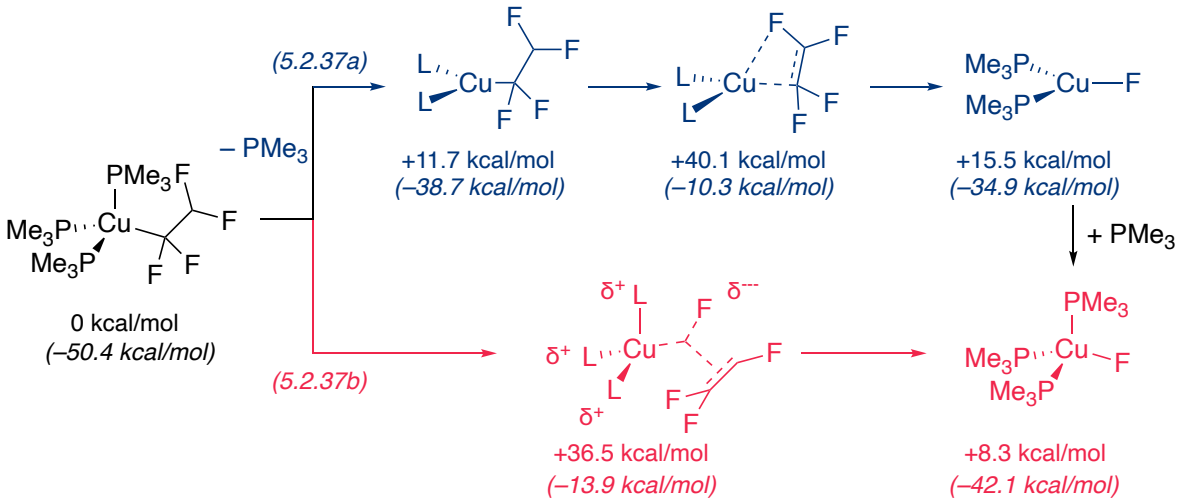
Scheme 5.2.35: HDF of VF3 to 1132 isomers by [PPh_3CuH] showing ligand-dependent stereoselectivity [36]

Extensive DFT modeling was carried out for this system by C. Ehm. The hydrocupration of TFE was examined with L = PMe_3, and three possible pathways were identified (Scheme 5.2.36). The system splits into two L_2 paths and one L_3 path. In the L_2 case (eqn 5.2.36a), the L_2CuH can directly hydrocuprate the TFE *via* its olefin complex, which is endergonic by +12.6 kcal/mol. The TS for the hydrocupration is downhill from the olefin complex by 3.5 kcal/mol. In the L_2 dimer case (eqn 5.2.36b), a thermodynamically downhill $[L_2Cu(\mu\text{-}H)]_2$ dimer forms, one of the hydrides of which undergoes an S_NV (nucleophilic vinylic substitution) reaction along the Burgi-Dunitz trajectory at TFE ($\Delta G^{\ddagger}$ = +3.2 kcal/mol), forming a contact ion pair (CIP) which is –14.7 kcal/mol downhill and which can undergo a barrierless reorientation to the hydrocuprated product. In the L_3 case, a similar S_NV reaction occurs but where the Cu has all three ligands ($\Delta G^{\ddagger}$ = +7.4 kcal/mol) forming a highly endergonic CIP (+17.7 kcal/mol) which reorients to $[L_3CuCF_2CF_2H]$, itself the lowest-energy product. The low-energy dimer-S_NV pathway is only accessible for small phosphines and for sterically unhindered and very electron-poor substrates, while the L_3 S_NV pathway is possible even for bulky phosphines.



Scheme 5.2.36: DFT modeling of three TFE hydrocupration pathways for $(PMe_3)_3CuH$ [36]

The hydrocupration step is irreversible (with deinsertion incurring a barrier of >58 kcal/mol). As with the hydrocupration step, β-fluoride elimination can occur through both an [L_2Cu] or [L_3Cu] pathway (Scheme 5.2.37) and is endergonic, in keeping with experimental results. For the L_2 pathway, the stable L_3 tetrafluoroethyl has to lose one PMe_3 (eqn 5.2.37a) to re-form the L_2 species (+11.7 kcal/mol), which can then undergo a β-fluoride elimination through a tetrahedral TS (+40.1 kcal/mol) to the L_2CuF (+15.5 kcal/mol) which can eventually recoördinate another phosphine to furnish the stable L_3CuF (+8.3 kcal/mol). The L_3 pathway is somewhat stranger (eqn 5.2.37b), with d^{10} Cu unable to accommodate the trigonal bipyramidal TS needed for a conventional β-elimination TS, the TS instead appears more tetrahedral (P–Cu–P bond angles 113(3)^o) with both the leaving fluoride and forming olefin occupying the same coordination site.



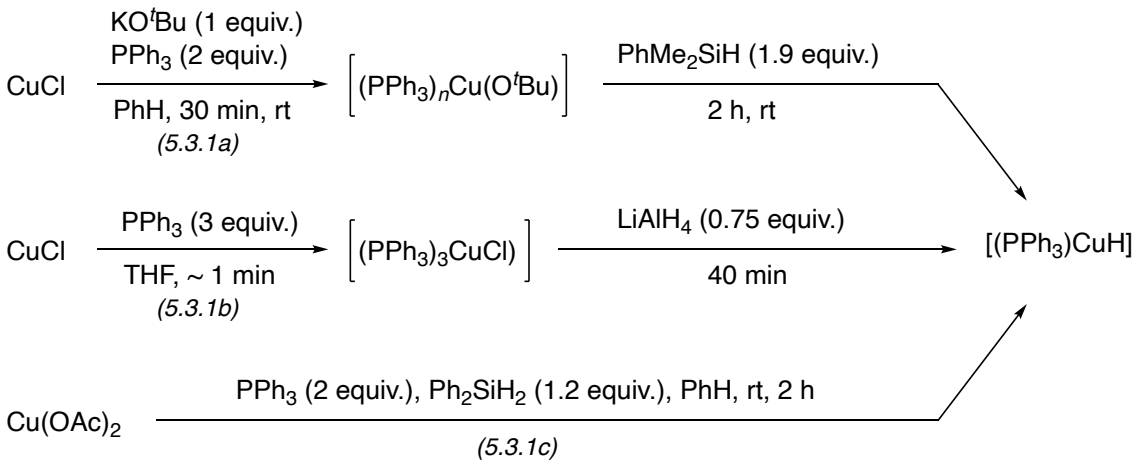
Scheme 5.2.37: DFT modeling of L_2 and L_3 β-elimination pathways for [Cu–CF_2CF_2H] showing relative free energies *(and actual energies continued from Scheme 4.2.36 in italic)* [36]

The ligand-dependent *cis/trans*-selectivity was much more difficult to explain, with the L_3 system showing a greater *trans* preference and the L_2 system favoring the *cis*. The L_2 system (favored by chelate ligands such as Xantphos or dppe) has an unsymmetrical distribution of steric bulk such that the *cis*-TS is favored, while the L_3 system has a more symmetrical distribution where there is no advantage to be gained by *cis*-orientation. The *trans*-preference exhibited by the L_3 system might well be explained by repeated Cu–F insertions/deinsertions. No definitive conclusion has yet been reached, however.

5.3 The present work

I will begin by stating that while the earlier work outlined in Section 5.2 where alanes, boranes, and gallanes are used as reducing equivalents is interesting, none of these are industrially practicable. Aluminum hydrides are energetic species, and their mixtures

with fluoroölefins have been described by the authors as being potentially explosive. Silanes (especially siloxanes), by contrast, are much lower-energy reductants, and can often be handled briefly in air without hazard. Of the silanes examined in the prior art, Ph_2SiH_2 and Me_2PhSiH were ruled out on the basis of cost, and the list candidates were winnowed down to two alkylsilanes (Et_3SiH and (i-Pr)$_3$SiH) and two siloxanes (TMDS and PMHS). Considering that Andrella's Cu system functioned quite well with TMDS and PMHS, and that the former is easier to handle than its polymeric cousin, I focused on the use of TMDS for all subsequent work. A key part of this work was to identify conditions under which the active species could be generated *in situ* from reagents which are compatible with the highly electrophilic fluoroölefin substrates. First, I examined conditions under which Stryker's reagent is normally synthesized (Scheme 5.3.1); one popular method is to start from copper(I) tert-butylate (eqn 4.3.1a) which can either be isolated or generated *in situ* from CuCl/KO^{t}Bu, and which is subsequently reduced by a silane reagent in the presence of PPh_3.[35] Another method is to reduce [$(PPh_3)_3CuCl$] with $LiAlH_4$ (eqn 5.3.1b).[36] The final method, and the preferred one for our purposes, is to reduce $Cu(OAc)_2$ by a silane reagent in the presence of an excess of PPh_3 (eqn 5.3.1c).[37]



Scheme 5.3.1: Common preparations of Stryker's Reagent starting from commercial Cu sources [40–42]

The first two methods were ruled out early owing to incompatibilities of alkoxide bases and aluminum hydrides[32] with fluoroölefins. The third method has been used extensively in our lab to prepare and isolate Stryker's reagent, but it has been our experience that on scaling to >5 grams, long reaction times are required (owing to the very low solubility of $Cu(OAc)_2$ in nonpolar hydrocarbon solvents) and the recrystallization is best carried out overnight for optimal yields. Furthermore, the yields are highest when this reaction is carried out with the more reactive Ph_2SiH_2 than TMDS or PMHS. Nonetheless, this proved the ideal starting point, as it is already quite popular among organic chemistry practitioners who deploy this catalyst to generate it *in situ*, either from the tert-butylate pathway[38] or from the $Cu(OAc)_2$ pathway.[39–41] Hydrated $Cu(OAc)_2$ is substantially cheaper than anhydrous material ($0.22/gram vs

[32] Though Al hydrides can HDF fluoroolefins, such mixtures can be explosive, and are thus not conducive to scale-up work.

$1.52/gram[33]), but as per the reference[37], our in-house syntheses of Stryker's reagent were always performed under moisture-free conditions, and I wished to keep this variable unchanged. My search for a more organic-soluble, anhydrous, and silane-responsive source of Cu(II) landed on copper(II) 2-ethylhexanoate ($Cu(EH)_2$), copper(II) naphthenate ($Cu(Nap)_2$, though often simply referred to as 'Cu-Nap') and copper(II) stearate ($Cu(St)_2$). Before further discussion, this decision deserves clarification with a brief side-note:

Metal 2-ethylhexanoates are lipophilic carboxylate salts based on 2-ethylhexanoic acid (itself an inexpensive and widely-available platform chemical derived from propylene *via* butyraldehyde).[42–44] The material science applications of metal 2-ethylhexanoates are diverse[45], ranging from preparations of nano-powders[46] and sols[47] to metal oxide nanocrystals[48,49] and thin films.[50] There are also numerous applications for specific $M(EH)_x$ in catalysis. Among these, perhaps the best known is $Sn(EH)_2$ (often simply referred to as 'tin octoate'), which is the standard catalyst for ring-opening polymerization of lactones[51], but has also been used for the manufacture of polyurethanes[52], polylactic acid[53], toners[54], and polymeric anti-icing composites[55], to name a few. For this reason, $Sn(EH)_2$ is widely and cheaply available, commonly supplied as a solution in mineral spirits or in 2-ethylhexanoic acid on a % wt. Sn-atom basis, as are most metal 2-ethylhexanoates. For catalysis, these compounds are advantageous for their high

[33] Prices from www.strem.com in USD and accurate as of the time of publication

solubility in organic media, and nearly every metal is available as its 2-ethylhexanoate. Other common examples include $Nd(EH)_3$, which is a preferred Ziegler-Natta precatalyst for the polymerization of butadienes,[56] and $Cr(EH)_3$ which is often used as the Cr-source in ethylene oligomerization and polymerization processes.[57] Close cousins of these compounds can be found in the metal naphthenates. "Naphthenic acid" is not a single discrete molecule, but rather a complex mixture (Chart 5.3.1) of branched, often ring-containing aliphatic carboxylic acids typically containing 10–16 carbons derived from raw petroleum (most commonly from oil sands).[58] The heavier the petroleum from which they derive, the higher the number of carbons. As a direct raw petroleum product, naphthenic acid is extremely inexpensive, and so too their salts, but unlike their 2-EH cousins, these compounds are ill-defined and often contaminated by an excess of naphthenic acid. Nonetheless, metal naphthenates are even less expensive than 2-ethylhexanoates, and so were considered here as candidates. Returning to our original purpose, lipophilic Cu carboxylates were considered as points-of-entry into the Cu-catalyzed HDF reaction. $Cu(EH)_2$ can be purchased as a solvent-free (16-19% wt. Cu) solid for \$3.04/gram, while $Cu(Nap)_2$ can be purchased as a solution in mineral spirits (8% wt Cu) for as little as \$0.12/gram.[34] The latter's low price is accounted-for by its commercial use as a wood preservative[59], in which formulation it can be had for as little as \$35/gallon (68% v/v, 8%

[34] Prices from www.strem.com in USD and accurate as of the time of publication

wt. Cu basis).[35] Copper(II) stearate is useful as a fungicide and algicide for wood and textile products, and thus is also inexpensive and widely available.[60]

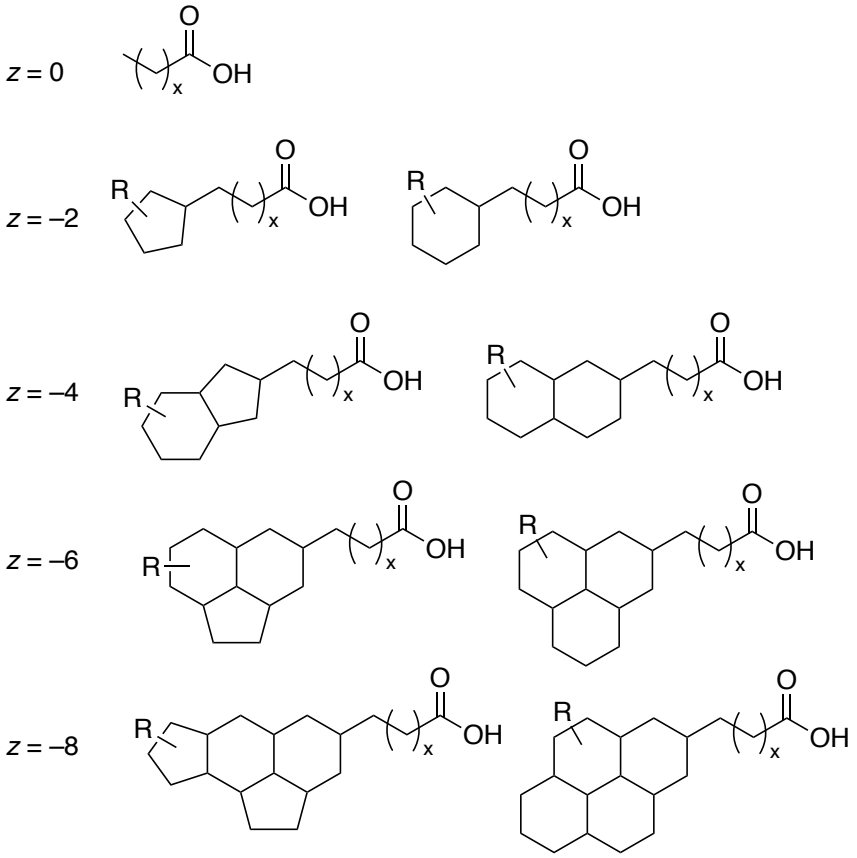


Chart 5.3.1: Possible structures of naphthenic acids represented by the general formula $C_nH_{2n+z}O_2$ [63].

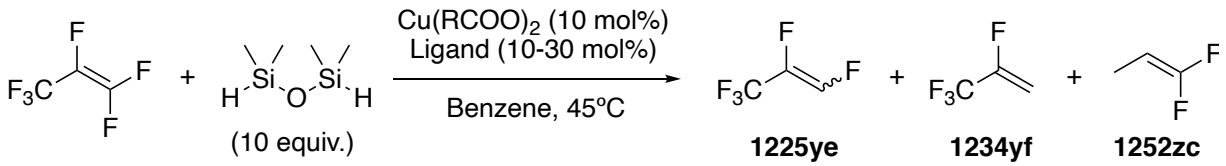
First, Andrella's HDF conditions with HFP were replicated, but substituting the aforementioned Cu soaps for $[PPh_3CuH]_6$ and using 1,2-bis(diphenylphosphino)ethane (dppe) as the ligand (Table 5.3.1). The 2-ethylhexanoate and naphthenate reactions

[35] Price from www.poles.com in USD and accurate as of the time of publication

turned bright yellow within minutes (indicating reduction to Cu^{I}), while the stearate failed to dissolve. After 2 h, $Cu(2\text{-}EH)_2$ had scarcely converted (Table 5.3.1, ex. 1), while $Cu(Nap)_2$ had converted 80% of the starting material to **1225ye** (E/Z = 1.2) with only trace **1234yf** observed and no **1252zc** (Table 5.3.1, ex. 2). After 18 h, the $Cu(2\text{-}EH)_2$ had still converted only 28%, while the $Cu(Nap)_2$ had converted 100% of the HFP to a mixture containing 94% **1234yf** (balance **1252zc**) and only trace **1225ye**. The $Cu(St)_2$ dissolved to a bright yellow solution after 18 h, and was found by ^{19}F NMR to have 100% converted the HFP to a mixture also comprised substantially of **1234yf** with only traces of **1225ye** (Table 5.3.1, ex. 3). Vindicated by this finding that the cheapest available Cu source performed equally as well as the $[PPh_3CuH]_6$, I continued my pursuit with $Cu(Nap)_2$, next examining whether the ligand system could be economized from the quite expensive Xantphos ($17.64/gram[36]) to standard alkyl- or aryl-phosphite ligands. In Andrella's paper, $P(OEt)_3$ was found to work satisfactorily well, so I sought to expand the list of possible phosphites, and to screen specifically those phosphites which have existing commercial applications. Beyond as ligands for catalysis, organophosphites can be used as antioxidant stabilizers for polymers,[61–63] so several examples are commercially available in large quantities and at low cost.

[36] Price from www.strem.com in USD and accurate as of the time of publication

Table 5.3.1: HDF of HFP catalyzed by $Cu(O_2CR)_2$ and various ligands



Ex.[a]	[Cu]	(mol%)	Ligand	TON	t (h)	Conv. (%)[b]	HFO products (% sel.)[b]			
							***(E)*-I**	***(Z)*-I**	**II**	**III**
1	$Cu(2\text{-EH})_2$	10	dppe	0.6	2	6	48	52	-	-
				3.0	18	28	33	65	2	-
2	$Cu(Nap)_2$	10	dppe	8.0	2	80	83	17	trace	-
				21.2	18	100	trace	trace	94	6
3	$Cu(St)_2$	10	dppe	21.6	18	100	trace	trace	92	8
4	$Cu(Nap)_2$	10	$P(OMe)_3$	13.9	18	100	31	32	35	1[c]
5	$Cu(Nap)_2$	10	$P(OEt)_3$	21.4	18	100	2	7	77	12[c]
6	$Cu(Nap)_2$	10	$P(OBu)_3$	23.8	18	100	trace	6	67	22[d]
7	$Cu(Nap)_2$	10	TEHP	30.0	18	100	trace	16	23	58[d]
8	$Cu(Nap)_2$	10	TIDP	27.3	18	100	trace	9	44	41[d]
9	$Cu(Nap)_2$	10	TOP	30.7	18	100	trace	1	39	54[d]
10	$Cu(Nap)_2$	10	TPP	10.2	18	91	57	32	11	-
11	$Cu(Nap)_2$	10	*p*-TTP	5.8	18	58	70	30	-	-
12	$Cu(Nap)_2$	10	TNPP	5.3	18	53	55	45	-	-

Legend: dppe = 1,2-bis(diphenylphosphino)ethane; TEHP = tri(2-ethylhexyl)phosphite; TIDP = triisodecylphosphite (mixture of isomers); TOP = trioleylphosphite; [a] Standard conditions: Under N_2 (glovebox), [Cu], ligand (10 mol% for dppe, 30 mol% for phosphites), TMDS (215 µL, 1.23 mmol, 10 equiv.), benzene (335 µL), $PhCF_3$ (50 µL of 0.246M solution in benzene), and HFP (3 ml, 0.123 mmol) heated to 45°C for the indicated time. [b] ^{19}F NMR basis. [c] Balance 236ea. [d] Balance 236ea and 254eb

All phosphites tested except for $P(OMe)_3$ and $P(OEt)_3$ (Table 5.3.1, ex. 4 and 5) gave substantial overreduction to **1252zc**; it was the major product in the reactions with TEHP and TOP (Table 5.3.1, ex. 7 and 9). The phosphite examples also gave non-negligible quantities of the hydrogenation products of HFP and **1234yf** (HFCs **236ea** and **254eb**, respectively), as well as intermediates of **1252zc** ($CF_3CH{=}CH_2$, **1243zf**, and $CH_3CF{=}CF_2$, **1243yc**). Interestingly, tri*aryl* phosphite ligands produced anemic catalysts which failed to convert all of the HFP. Plain triphenylphosphite (TPP, ex. 10) gave 91%

conversion to almost entirely **1225ye**, in keeping with Andrella's observations in Scheme 5.2.33. *Para*-substituted arylphosphites performed far worse (examples 11, 12), with *p*-TTP (*para*-tritolylphosphite) giving 58% conversion and the more hindered TNPP (tri-*p*-nonylphenylphosphite) giving 53% conversion. Curious about any other possible ligand effects that can be exploited for this HDF reaction, nitrogen-based chelate ligands (Chart 5.3.2) were attempted,[37] but none of them gave any conversion whatever, and several rapidly resulted in Cu mirroring on the NMR tube. Next, a temperature-robustness study of the alkylphosphite-derived catalysts was performed under the same loading as Table 5.3.1, but instead heated to 70°C (Table 5.3.2).

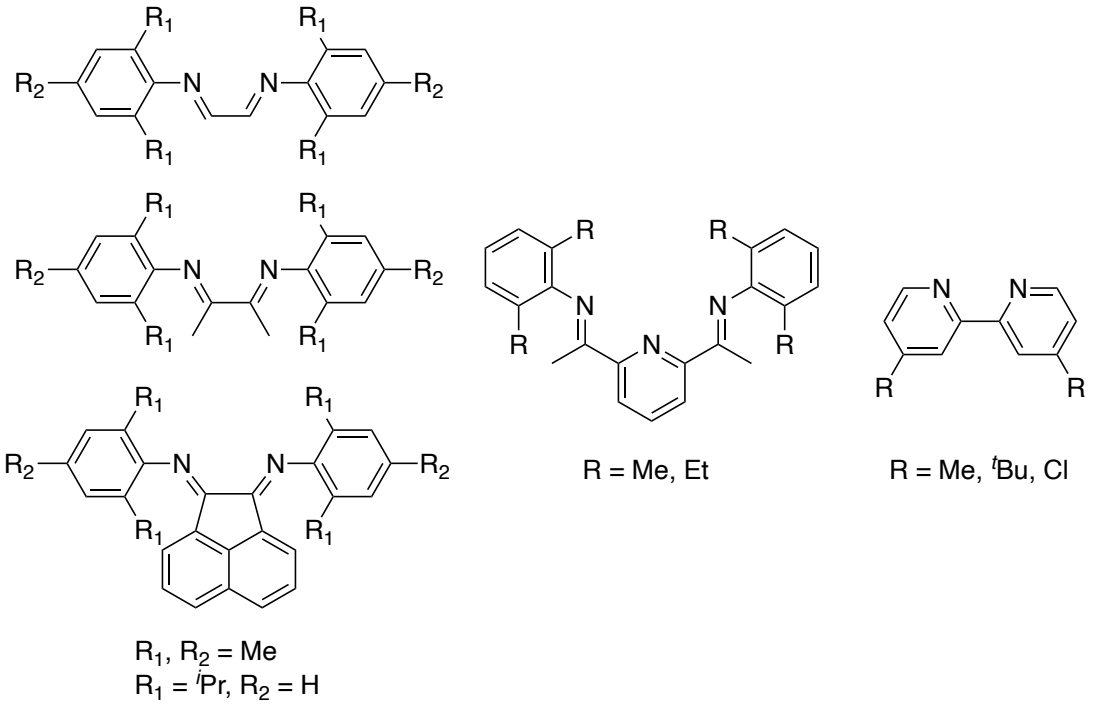


Chart 5.3.2: Chelating nitrogen ligands tested for Cu-Nap-catalyzed HDF of HFP

[37] Standard conditions from Table 5.3.1 were used in all ligand-screening examples

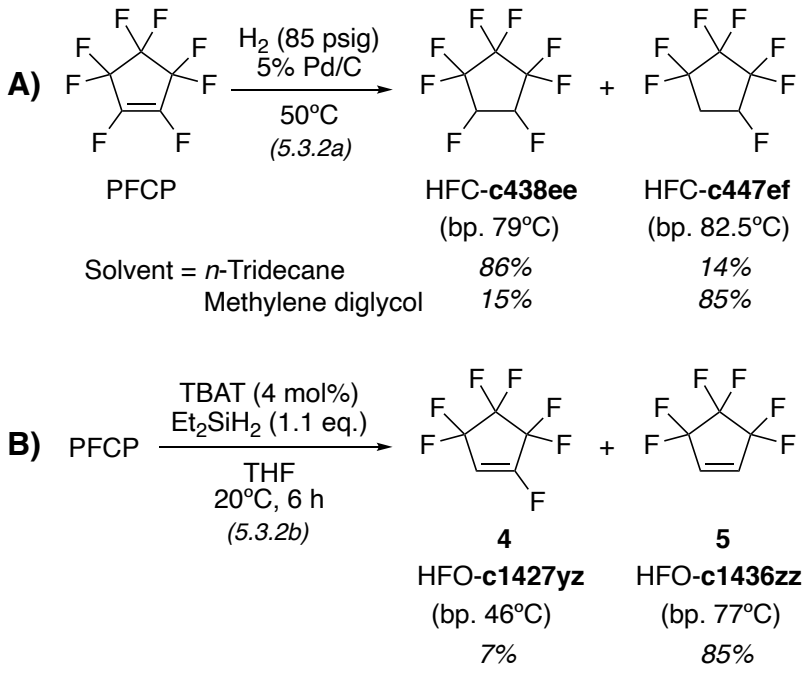
Table 5.3.2: HDF of HFP using $Cu(Nap)_2$ and various phosphite ligands at 70°C

Ex.[a]	$P(OR)_3$	Cu plate	HFO products (% sel.)[b]		
			1225ye *(Z/E)*	**1234yf**	**1252zc**
1	$P(OMe)_3$	Yes	79 (1)	19	trace[c]
2	$P(OEt)_3$	Yes	54 (1.6)	35	4[d]
3	$P(OBu)_3$	Yes	17 (5.2)	56	24[c]
4	TEHP	No	20 (17.5)	18	54[e]
5	TIDP	No	22 (21)	26	63[e]
6	TOP	No	2 (-)[f]	27	64[c]

[a] Standard conditions: Under N_2 (glovebox), $Cu(Nap)_2$ (10 mol%), $P(OR)_3$ (30 mol%), TMDS (215 µL, 1.23 mmol, 10 equiv.), benzene (335 µL), $PhCF_3$ (50 µL of 0.246M solution in benzene), and HFP (3 ml, 0.123 mmol) heated to 70°C for 18 h. [b] ^{19}F NMR basis. 100% conv. unless otherwise specified. [c] Balance 236ea/254eb [d] 95% conv., balance HFP and 236ea/254eb. [e] Balance 236ea/254eb/263fb. [f] Only 1225ye*(Z)* observed

Once again, $P(OMe)_3$ gave the lowest amount of unwanted **1252zc**, but also gave mostly **1225ye** with no *(E/Z)*-selectivity (Table 5.3.2, ex. 1). The reactions using smaller alkylphosphites all plated out Cu mirror (which began to emerge after as little as an hour), while the bulkier, longer-chain 2-ethylhexyl, isodecyl, and oleyl phosphites (Table 5.3.2, ex. 4–6) remained homogeneous, suggesting that the decomposition pathway could be bimolecular. These longer-lived catalysts also gave a lower proportion of **1225ye** with an increasing *(Z)*-preference and a higher proportion of **1252zc** as the phosphite size increased. The usual HFC side products **236ea** and **254eb** still coincided, however with the larger phosphites, $CF_3CH_2CH_3$ (HFC-**263fb**) was also observed. Only the $P(OEt)_3$ system (Table 5.3.2, ex. 2) failed to reach 100% conversion, possibly due to rapid catalyst decomposition at the reaction temperature.

This functional methodology was then applied to another readily-available perfluorinated substrate—perfluorocyclopentene (PFCP). This compound is manufactured by nucleophilic fluorination of its perchloro-congener as per the conventional methods, and is commercially-available from Nippon Zeon Corp. for use as an etching agent.[64] It is related to the company's commercialized non-flammable and non-ozone-depleting solvent *1H,1H,2H*-perfluococyclopentane (HFC-**c447ef**, bp. 82.5°C, marketed as *Zeorora® H*). Although such hydrodefluorinated products are typically prepared by sequential hydrogenation/defluorination[65,66] as with earlier HFO examples (Scheme 5.3.2, eqn 5.3.2a), one example of direct catalytic HDF of PFCP to a cyclic HFO product was reported by Ogoshi et al. This method, however, calls for an expensive and reactive silane (Et_2SiH_2) with tetrabutylammonium triphenyldifluorosilicate (TBAT) as the catalyst (eqn 5.3.2b).[67] It is also possible to HDF PFCP to **5** using stoichiometric $NaBH_4$ or $LiAlH_4$,[68,69] or to dehydrofluorinate the solvent **c447zf** using an amine base at reduced temperature.[70] The boiling points of these various C_5-HFO derivatives make them of potential interest as replacement solvents for current high-GWP HFCs. In order to investigate this line of thinking further, a more direct route to each HFO from PFCP was desired which did not require external cooling or separation from HFC intermediates of similar boiling point.

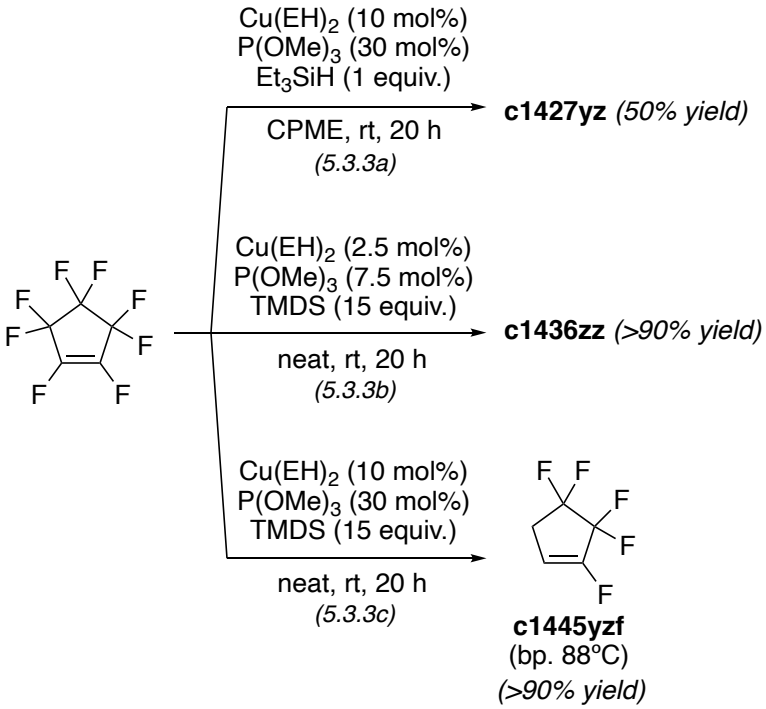


Scheme 5.3.2: Reductive methods for PFCP to HFCs or HFOs [58–60]

Gratifyingly, it was determined that inexpensive Cu carboxylates can catalyze the direct HDF of PFCP to HFOs **c1427yz**, **c1436zz**, and even the 3rd-generation product HFO-**c1445yzf**, with different selectivities depending on the conditions employed (Scheme 5.3.3, eqns 5.3.3a–c respectively). When monitored by ^{19}F NMR, the reaction producing compound **c1445yzf** was shown to proceed *via* allylic HDF of **c1436zz**. Despite the loss of fluorine, the HDF of PFCP to **c1427yz** and **c1436zz** represents a value-add (at current prices[38]) of roughly 20x and 3x, respectively, while **c1445yzf** is not even commercially available. The enhanced solubility of $Cu(EH)_2$ over Stryker's reagent also allowed the reductions to be carried out optionally in neat siloxane. The initial NMR studies were

[38] Based on prices from www.synquest.com and accurate as of the time of publication

conducted with TMDS, however, in order to isolate the target compounds **c1436zz** and **c1445yzf**, an alternate silane was needed, as the fluorosiloxane byproduct $(SiMe_2F)_2O$ (bp. 72°C) cannot be easily separated from the fluorocyclopentenes by distillation. PMHS is the natural alternative, being the polymeric version of TMDS, and is substantially less expensive than the latter (by a factor greater than 4x at current market prices[39]).



Scheme 5.3.3: Cu-catalyzed HDF of PFCP (NMR scale)

Next, we sought to optimize the HDF of *F*-2M2P (the thermodynamic dimer of HFP) that was reported in our previous paper. To begin, the thermodynamic dimer costs nearly 3x as much as the kinetic dimer—*F*-4M2P—and thus, we opted to purchase the

[39] Based on prices from www.gelest.com and accurate as of the time of publication

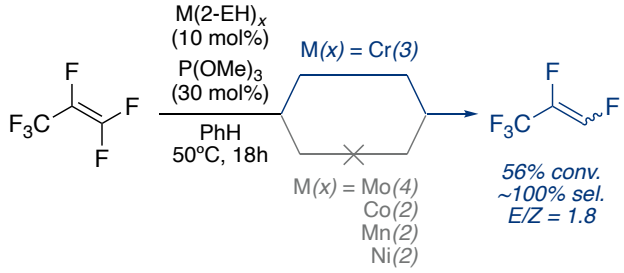
latter and isomerize it in-house. The 1,3-fluoride shift is catalyzed by CsF in MeCN heated to the boiling point of *F*-4M2P,[71,72] and due to the high density of the fluoroolefin, can be easily carried out on a 50-gram scale in a 200ml PTFE-lined stainless-steel autoclave.[40] The fluorous/organic phases separate easily at room temperature, and the thereby-obtained *F*-2M2P was pure enough (>95% by ^{19}F NMR) to use directly for the HDF step without further purification. Furthermore, after opening the isomerization vessel to air, it was found that the CsF/MeCN solution could be recycled, and another batch of *F*-4M2P isomerized under an atmosphere of air using the recycled solution with scarcely any loss in product purity. In order to facilitate an easy product purification by simple distillation, we tested the HDF reaction using $Cu(Nap)_2$ in diglyme and a variety of heavier alkylphosphite ligands with nonvolatile PMHS as the reductant. All ligands tested gave quantitative conversion at room temperature to >90% **1567mcftc** (^{19}F NMR basis) after 2 hours, but TIDP gave the overall cleanest reaction. None of the reaction mixtures gave way to Cu mirroring, even after allowing to sit overnight with the excess of PMHS. Moreover, when carried out under air, the reaction also initiated quickly (turning from dark green to yellow within seconds of *F*-2M2P charging) and catalytic performance was identical to that under N_2, suggesting that unlike with Stryker's reagent, HDF reactions performed using $Cu(Nap)_2$ and higher alkyl phosphites do not require an

[40] Pressure-rated glass round-bottomed flasks or tubes can also be used, but after several runs, I observed substantial fluoride etching of the vessel walls, and therefore recommend that the isomerization be conducted in PTFE-lined equipment to avoid the hazard of structurally-compromised glass under pressure.

inert atmosphere; the optimal TIDP ligand is reportedly less hydrolytically sensitive than lower alkylphosphites like $P(OMe)_3$ or $P(OEt)_3$, with one manufacturer suggesting a shelf-life of up to 4 months following exposure to air.[73]

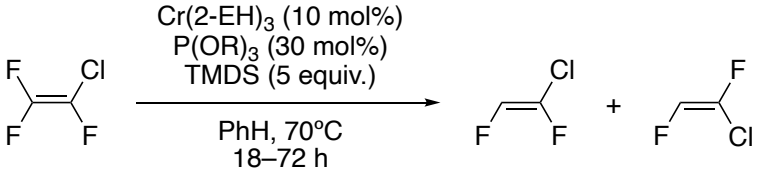
Finally, the success with lipophilic Cu carboxylates prompted a screen of five other base-metal soaps for catalytic activity (Scheme 5.3.4). Prospective reactions were attempted using $P(OMe)_3$ in a 3:1 ratio with the 2-ethylhexanoates of Cr, Mo, Co, Mn, and Ni at 10 mol% loading. Interestingly, the only other metal that showed promise was $Cr(2\text{-EH})_3$, widely used as a soluble precatalyst for Cr-catalyzed ethylene oligomerization. There was obtained exclusively **1225ye** from HFP with incomplete conversion. The specificity of this catalyst for mono-hydrodefluorination prompted us to attempt the HDF of another widely-available fluoromonomer—chlorotrifluoroethylene (CTFE). Prior HDF systems typically give complex mixtures of up to five different HFOs from CTFE, and are thus of limited utility in this application. In our group's previous Cu paper,[33] CTFE consistently underwent C–Cl bond reduction to yield a single turnover's worth of CHF=CHF (HFO-**1132**), while the fate of the catalyst was to precipitate as silane-unresponsive L_nCuCl or to mirror out. However, a small amount of intermediate CFCl=CHF (HCFO-**1122a**) could occasionally be observed in these reactions, suggesting that the reaction manifold leading to **1132** proceeded via initial C–F bond reduction to **1122a**. Intermediate **1122a** is presently being investigated by several OEMs as a potential C_2 refrigerant candidate,[74–77] but owing to a scarcity of manufacturing methods, is not commercially-available in large quantities. A direct route starting from widely-available

CTFE would represent a value add of at least 20x at current market prices, and would thus be highly advantageous for the continued study of **1122a** and its thermophysical properties. To this end, we tested $Cr(2\text{-EH})_3$ with the usual suite of trialkylphosphites under the standard conditions (18 h at 50°C) with a tenfold excess of TMDS (5 equiv.; 10 Si–H equiv.), but obtained zero conversion. However, raising the temperature to 70°C enabled as much as 89% conversion after 18 h (Table 5.3.3, ex. 1) to **1122a** ($E/Z = 1$) with 100% selectivity. The higher alkylphosphites, with the strange exception of TOP (Table 5.3.3, ex. 6), had considerably lower conversions than $P(OMe)_3$, and were only slightly improved after 72 hours. Though with HFP, the $Cr(2\text{-EH})_3$ displayed a small preference for **1225ye*(E)***, there was no such *(E/Z)*-selectivity in any of the CTFE examples.



Scheme 5.3.4: M(2-EH)$_x$-catalyzed HDF of HFP (NMR scale)

Table 5.3.3: HDF of CTFE using Cr(2-EH)$_3$ and various alkylphosphite ligands



1122a*(E)* **1122a*(Z)***

Ex.[a)]	P(OR)$_3$	Temp. (^{o}C)	Time (h)	Conv. (%)[b)]	**1122a*(E)***	**1122a*(Z)***
1	P(OMe)$_3$	70	18	89	45	44
			72	100	49	51
2	P(OEt)$_3$	70	18	33	17	16
			72	60	30	30
3	P(OBu)$_3$	70	18	32	16	16
			72	54	27	27
4	TEHP	70	18	48	24	24
			72	60	30	30
5	TIDP	70	18	33	17	16
			72	38	19	19
6	TOP	70	18	77	37	40
			72	100	47	53
7	None	70	18	12	6	6

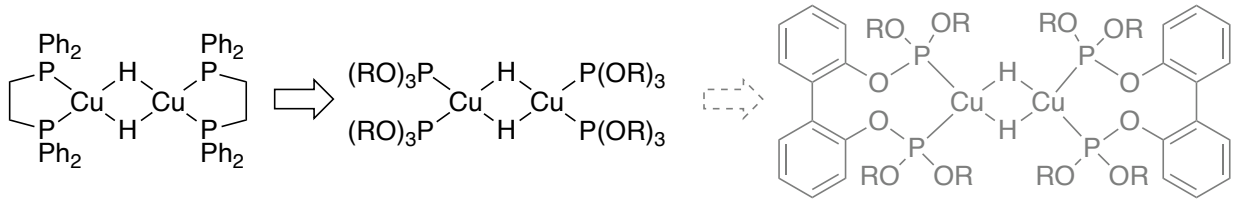
[a)] Standard conditions: Under N_2 (glovebox), [Cr] (10 mol%), P(OR)$_3$ (30 mol%), TMDS (108 µL, 5 equiv.), C_6D_6 (400 µL), $PhCF_3$ (50 µL of 0.246M solution in PhH), and CTFE (3 ml, 0.123 mmol) in an NMR tube. [b)] ^{19}F NMR basis.

5.4 Mechanistic Considerations

Recalling the calculated pathways for the Cu-catalyzed HDF discussed earlier (Schemes ***5.2.36*** and ***5.2.37*** from calculations in the Andrella paper), there are a number of inferences we can make from the empirical data collected here. First, it is important that we consider separately the impact of the ligand on the two steps in the catalytic cycle: Cu–H addition to fluoroölefin, and Cu–F turnover by silane. Disparities in catalytic performance between ligands tested might be due to a diminished capacity to carry out

either (or both) of these steps. From Scheme 5.2.36, we will consider the mechanisms outlined by equations *5.2.36b* and *5.2.36c*, the former being the L_2Cu dimer pathway and the latter being the L_3Cu monomer pathway. It is plainly obvious that the L_3Cu pathway is more energetically demanding, with a TS activation energy of +7.4 kcal/mol *en route* to an intermediate which itself is +17.7 kcal/mol uphill. The L_2Cu dimer pathway, meanwhile, proceeds through a TS which is only +3.2 kcal/mol uphill and forms an ion pair intermediate which is –14.7 kcal/mol *downhill*. It then stands to reason that ligand environments encouraging the copper hydride to adopt the dimeric $[L_2Cu(\mu\text{–}H)]_2$ structure should exhibit a greater activity. The examples from Table 5.3.1 bear this out nicely; entries 3 and 4 using dppe as the sole ligand, for instance, successfully perform two hydrodefluorinations to give >90% yield of **1234yf**. In these cases, the dppe and Cu are present in a 1:1 ratio, virtually ensuring an $[L_2CuH]$ catalyst. The sterically-unhindered $P(OMe)_3$, by contrast, is expected to readily form $[L_3CuH]$ species which are less active, accounting for the poorer performance observed in entry 4. As the phosphite ligands grow in size, however, their HDF performance increases beyond that of dppe, furnishing substantial quantities of the *quadruple*-HDF product **1252zc**. This increased competency cannot *entirely* be laid at the feet of steric hindrance, however. The reader will also recall from ***Section 5.2*** (Scheme 5.2.33) that bulky alkyl*phosphines* ($P(o\text{-tol})_3$, PCy_3, tBuXPhos) were anemic, forming mainly the first-generation HDF product **1225ye**, with no **1252zc** observed. It may be that the ligand influence also contains an electronic component, with electron-deficient phosphites producing a more active Cu hydride; there

is certainly a literature precedent[78,79] (albeit not fluorine-related) for Cu-catalyzed reductions with silane where alkylphosphite ligands greatly outperform their phosphine counterparts. Even with phosphites, however, the positive effect of greater steric hindrance is not without bounds, as the bulkier arylphosphites tested here (Table 5.3.1, examples 11 and 12), as well as the *o*-TTP tested by Andrella (Scheme 5.2.33) were much less active than undecorated $P(OPh)_3$, itself less active than any of the alkylphosphites. The natural conclusion here is that regardless of electronic character, excessively bulky ligands hinder the formation of the active $[L_2Cu(\mu\text{–}H)]_2$ dimer and force the catalyst through the uphill monomer pathway depicted in equation *5.2.36a*. We conclude therefore that to achieve the highest-possible activity, electron-deficient ligands favoring the dimeric L_2Cu pathway are most desirable. Based on the findings here, a logical step further for this project would be to investigate the activity of chelating bisphosphite ligands such as those commonly found in the hydrocyanation and hydroformylation literatures to examine whether the L_2-enforcing chelate and electronic effects can be compounded (Scheme 5.4.1).



Scheme 5.4.1: Potential evolution of active [CuH] catalysts for HDF

With regards to the second step, the *β*-fluoride elimination (Scheme 5.2.37), we see a similar pattern, where the elimination has a relative TS activation energy of +28.4

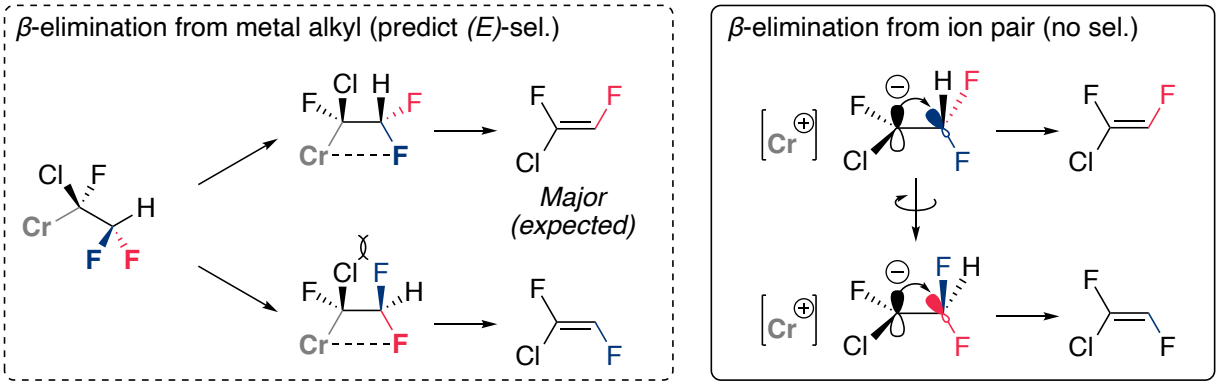
kcal/mol from the L_2CuR^F and +36.5 kcal/mol from the L_3CuR^F. The resulting L_3CuF is, however, more thermodynamically stable than L_2CuF. It is possible, then, that certain ligands which allow for the formation of L_3CuF would render a catalyst more resistant to turnover by silane than those which prefer to maintain L_2CuF; this may also account for the decreased activity of the $P(OMe)_3$ system as compared with the larger alkylphosphites. Finally, all the aforementioned DFT work was done on the reaction of L_nCuH ($L = PMe_3$) with tetrafluoroethylene. It is entirely possible that the energy landscape for HFP (with $L = P(OMe)_3$) looks somewhat different, and that a separate computational study on the latter to inform future studies on the HDF of HFP by Cu would not be imprudent. Finally, the difference between aryl- and alkyl-phosphite ligands is also noteworthy, and cannot be easily explained. One hypothesis is that the L_nCuF is stabilized with $L = (ArO)_3P$ compared to $(AlkO)_3P$, such that turnover is slow, but further experimental evidence (such as attempting to isolate said L_nCuF) is needed before such hypotheses can be made with any degree of confidence.

By contrast, it is not clear that the novel Cr system is possessed of the same mechanistic characteristics as the Cu. For one, Cr(2-EH)$_3$ has *three* opportunities for a κ^2-carboxylate to be replaced by a hydride, and therefore three possible Cr fluorides that can result from reaction of a Cr–H with a fluoroölefin. The catalyst resting state may therefore exist as any permutation of $Cr(2\text{-}EH)_{3-x}F_x$, with or without neutral ligand coördinated. Given that the reaction remains perfectly homogeneous, we may safely rule out the formation of CrF_3, which is expected to have very poor solubility in hydrocarbon

media. It is also noteworthy that the Cr examples were necessarily carried out at higher temperatures than previous examples with Cu; here, no conversion whatsoever was observed at 50°C. Unlike in the former case, here we are contending with the well-documented kinetic inertness of O_h d^3 Cr,[80,41] so the demand for additional energy input should come as no surprise. The increased catalyst activity brought upon by $P(OMe)_3$, however, *is* surprising, as the soft, π-acidic phosphite and hard Lewis-acidic Cr(III) together make for an unconvincing couple. There must be a special effect at play beyond simple σ-donation because a wide variety of alkylamine ligands[42] (traditionally better suitors for Cr(III)) were also attempted and gave activities no better than the ligand-free case (Table 5.3.3, ex. 7). The number of phosphite ligands actually coördinating to the Cr during the catalytic cycle is unknown, the paramagnetic Cr center preventing reliable ^{31}P NMR monitoring. It might be possible to monitor the reaction by mass spectrometry, however, and the number of Cr–O_2CR bonds reduced by silane could be determined by ^{29}Si NMR. With regards to the HDF reaction itself, the complete lack of stereoselectivity in the HDF of CTFE likely rules out a discrete hydrometalation/β-fluoride elimination pathway in which we would expect to see at least a small preference for **1122a*(E)*** (Scheme 5.4.2). By contrast, a mechanism relying on hydride ion addition to the CTFE would

[41] The origins of this stability to ligand exchange can be explained by crystal field theory; in octahedral Cr(III), the three lone electrons are located in the d_{xy}, d_{xz}, and d_{yz} orbitals, which are directed at spaces in-between the point charges of the ligands occupying the vertices of the octahedron. This leaves little space for an approaching ligand to substitute associatively. Dissociative substitution, by contrast, is also energetically costly because the crystal-field stabilization energy (CFSE) is highest for $(t_{2g})^3$ $(-1.2\Delta_{oct})$.
[42] The usual suite of amines (en, tmeda, dmeda, and even Me_3tach) were attempted prior to $P(OMe)_3$.

give a planar [CFCl⁻] carbon which would not be expected to differentiate significantly between rotamers of the adjacent CHF_2, leading to the 50/50 *E*/*Z* mixture of **1122a** observed here. The lack of any change in stereoselectivity even when using more sterically-hindered phosphites either suggests that the actual elimination step is somewhat removed from the environment around the metal, or that the phosphite ligand is not present for that step.



Scheme 5.4.2: Possible elimination mechanisms leading to 1122a

With regards to the oxidation state of the chromium (always a point of contention with this metal), all signs point to a catalytic cycle entirely based around Cr(III). First, none of the spectacular color changes for which Cr is reputed are observed here; the solution retains the original pine green color from the $Cr(2\text{-EH})_3$ even after heating to 70°C for 72 hours. If the metal were performing its usual and theatric oxidation state dance, it would surely have undergone a series of visible costume changes. Second, anhydrous $Cr_2(OAc)_2$ was synthesized and examined for HDF activity under identical conditions, but no reaction with CTFE or HFP was observed, indicating that the catalytic

activity does not arise from a Cr(III)→Cr(II) reduction by the silane. Despite the difficulties in modeling an open-shell system *de novo*, it is likely worthwhile to perform a preliminary DFT study on this system in order to determine the relative energy costs of the hydrometalation *versus* hydride ion transfer, both with and without $P(OMe)_3$.

5.5 Conclusion

Herein has been disclosed a powerful new hydrodefluorination protocol requiring no rigorously air-sensitive synthesis or manipulation, and utilizing only inexpensive commercial materials which are widely-available at a low cost. The utility of this protocol has been demonstrated for the synthesis of assorted hydrofluoroolefins of value, including a new branched C_6 olefin (HFO-**1563mcftc**) derived from the thermodynamic dimer of HFP and three hydrofluoro-derivatives of PFCP (HFOs **c1427yz**, **c1436zz**, and **c1445yzf**). These new products could be easily scaled using our new methodology, which mitigates the thermodynamic challenges relating to the reactions' exothermicity, and isolated using simple vacuum-transfer techniques. We also demonstrated that our group's originally-reported conditions using isolated [PPh_3CuH] to HDF HFP can be replicated with cheap, readily-available $Cu(Nap)_2$ with no loss in performance. Following this, a prospective screen of other base metal precatalysts was performed from which $Cr(2\text{-EH})_3$ emerged as a new candidate, demonstrating moderate performance in the selective mono-HDF of chlorotrifluoroethylene to 1-chloro-1,2-difluoroethylene (HCFO-**1122a**), a reaction which has heretofore never been rendered by *any* HDF system or catalyst. We eagerly continue

pursuit of the development and optimization of this new Cr-based system, along with deeper studies into its mode of action. With these economical HDF protocols in hand, the technique can finally be considered more widely by practitioners of the art as a viable method for the preparation of hydrofluoroölefins on any scale, whether for small refrigerants and solvents as we report here, or for larger, more complex molecules of interest such as agrochemicals or APIs.

5.6 Experimental Section

5.6.1 General Procedures

Experiments were conducted under dry nitrogen using an MBraun glovebox. Glassware was dried in an oven set at 120°C for 2 h before use. Chemicals not packed under inert atmosphere were sparged with nitrogen and then handled in the glovebox. Benzene (>99.5%) and diglyme (>99%) were from TCI America (Montgomeryville, PA) and were deoxygenated and dried over 3Å molecular sieves activated at >200°C in a vacuum oven before use. Cyclopentyl methyl ether (99.9+%, stabilized with 50 ppm BHT, <250 ppm H_2O) was from Alfa-Aesar (Tewksbury, MA) and was dried over activated 3Å molecular sieves before use. Acetonitrile (≥99.9%, Optima™, max 0.01% H_2O) and toluene (≥99.8%, Optima™, max 0.02% H_2O, max 0.05% benzene) were from Fisher Chemical, and were dried on columns of activated alumina using a J. C. Meyer (formerly Glass Contour) solvent purification system and stored under N_2 over activated 3Å molecular sieves. Benzotrifluoride (anhydrous ≥99%), trimethylphosphite (99%), and

triethylphosphite (98%) were used as received from Sigma-Aldrich (Oakville, ON). Tributylphosphite (≥93%), tri(2-ethylhexyl)phosphite (≥90%), triisodecylphosphite (≥95%), and trioleylphosphite (≥98%) were used as received from TCI America (Montgomeryville, PA). 1,1,3,3-tetramethyldisiloxane (98%) and poly(methylhydrosiloxane) (trimethylsilyl terminated, 15-25 cSt, 20-35 cSt, and 30-45 cSt) were used as received from Gelest (Morrisville, PA). Hexafluoropropylene (HFP, 98.5%), perfluoro(4-methyl-2-pentene) (*F*-4M2P, 95%), chlorotrifluoroethylene (CTFE, 99%) and cesium fluoride (99.5%) were from Synquest Laboratories (Alachua, FL). Chromium(III) 2-ethylhexanoate (8–10% Cr in hydro treated middle petroleum distillate), cobalt(II) 2-ethylhexanoate (12% Co in mineral spirits), copper(II) 2-ethylhexanoate (solvent-free, 16–19% Cu), copper(II) naphthenate (8% Cu in mineral spirits), and manganese(II) naphthenate (6% Mn in mineral spirits) were from Strem Chemicals (Newburyport, MA). Copper(II) stearate (98%) was from Ambeed (Arlington Hts, IL), and nickel(II) octanoate (8% Ni in mineral spirits) was from Alfa-Aesar. (Tewksbury, MA). NMR spectra were recorded on a 500 MHz Bruker AvanceIII instrument at room temperature (21–23°C) unless otherwise specified. ^{19}F spectra were referenced to internal $PhCF_3$ (δ = –63.5 ppm), Et_3SiF (δ = –176.7 ppm), or TMDS–F (δ = –130.7 ppm).

5.6.2 NMR tube screening conditions

An 8" NMR tube was charged with the $M(O_2CR)_x$, ligand, silane, $PhCF_3$ (50 µL of a 0.246M solution in benzene), and solvent diluted to 0.6 ml. The tube was sealed with

a rubber septum cap and wrapped several times with parafilm to ensure a tight fit, then it was inverted and the fluorinated gas (3.0 ml, 0.123 mmol) was bubbled upwards through the solution *via* syringe injection through the septum with a 23-gauge needle. The tube was then immersed upright to the solvent level in a heating bath filled with aluminum beads from Lab Armor (Irving, TX) and allowed to ripen at temperature for the specified period of time before analysis by NMR. In the case of a liquid olefin substrate (*F*-2M2P or PFCP), the substrate was added directly to the NMR tube in the glovebox under nitrogen atmosphere unless otherwise stated.

5.6.3 Isomerization of F-4M2P to F-2M2P

In an N_2-filled glovebox, a 200-ml PTFE-lined stainless-steel hydrothermal reactor-style autoclave (rated 290 psi) containing a PTFE-lined stir-bar was charged with dry CsF (250 mg, 1 mol%), MeCN (75 ml), and *F*-4M2P (50 g, 0.17 mol). The reactor was sealed, removed from the glovebox, and immersed to about 40% of its height in a heating bath filled with aluminum beads from Lab Armor (Irving, TX) set to 55°C, and stirred at a temperature range of 55–60°C for 18 hours. After the elapsed time, the reactor was allowed to cool to room-temperature, opened under air, and its contents emptied into a separatory funnel. The denser fluorous phase comprised of >95% pure *F*-2M2P was collected and weighed 42 grams (82% of theory). Losses can be accounted-for by evaporation of the volatile product during workup (bp. 49°C). The CsF/MeCN phase can be discarded, or alternatively reused for another isomerization cycle with no

discernible loss in performance. ^{19}F NMR (471 MHz, neat): –58.8 (3F, mult.), –61.5 (3F, mult.), –84.7 (3F, mult.), –98.9 (1F, mult.), –117.8 ppm (2F, mult.).

5.6.4 HDF of F-2M2P to ***1567mcftc***

Performed as per ***5.5.2***, using *F*-2M2P (0.123 mmol) as the substrate, PMHS (15–25 cSt, 10 equiv.), and Cu-Nap (2.5 mol%) with TIDP (7.5 mol%) in diglyme. ^{19}F{^{1}H} NMR (471 MHz, C_6D_6) for **1567mcftc**: –116.9 (2F, d, $J = 4$), –93.2 (1F, d, $^{2}J = 45$), –92.8 (1F, d, $^{2}J = 45$), –86.4 ppm (3F, s). Spectrum can be found in ***Figure AIII-15***. Comparable performance was obtained when performed under air (***Figure AIII-16***), and when Xantphos (2.5 mol%) was used as the ligand with TMDS the reductant, (***Figure AIII-17***).

5.6.5 HDF of PFCP to ***c1427yz***

A 7" NMR tube was charged with Cu(2-EH)$_2$ (9 mg, 0.025 mmol), P(OMe)$_3$ (9 mg, 0.075 mmol), Et_3SiH (116 mg, 1 mmol), CPME (0.4 mL), and PFCP (0.25 mmol) in that order. The NMR tube was sealed and the mixture allowed to ripen for 20 h at room temperature. ^{19}F{^{1}H} NMR (282 MHz) for **c1427yz**: –131.0 (2F, mult.), –126.6 (1F, ttt, $J = 15$, 12, 4.8 Hz), –120.7 (2F, mult.), –107.4 (2F, mult.).

5.6.6 HDF of PFCP to ***c1436zz***

A 7" NMR tube was charged with $Cu(2\text{-EH})_2$ (2 mg, 2.5 mol%), $P(OMe)_3$ (2 mg, 7.5 mol%), TMDS (503 mg, 3.75 mmol), and PFCP (0.25 mmol) in that order. The NMR tube was sealed and the mixture allowed to ripen for 16 h at room temperature. The resulting reaction mixture contained ~92% of the target product contaminated with intermediate **c1427yz**. $^{19}F\{^1H\}$ NMR (282 MHz) for **c1436zz**: –133.1 (2F, p, J = 3), –110.4 ppm (4F, t, J = 3 Hz).

5.6.7 HDF of PFCP to ***c1445yzf***

A 7" NMR tube was charged with $Cu(2\text{-EH})_2$ (9 mg, 10 mol%), $P(OMe)_3$ (2 mg, 30 mol%), TMDS (503 mg, 3.75 mmol), and PFCP (0.25 mmol) in that order. The NMR tube was sealed and the mixture allowed to ripen for 16 h at room temperature. The reaction mixture showed essentially quantitative conversion to the title product. $^{19}F\{^1H\}$ NMR (282 MHz) for **c1445yzf**: –138.3 (1F, tt, ^3J = 14, ^4J = 14 Hz), –122.2 (2F, dt, J = 14, 2 Hz), –115.2 ppm (2F, q, J = 2 Hz).

5.6.8 HDF of CTFE to ***1122a***

Standard procedure: An 8" NMR tube was charged with $Cr(2\text{-EH})_3$ (7 mg of commercial solution in hydro treated middle petroleum distillate, 8–10% Cr-atom basis, 0.012 mmol), phosphite (0.037 mmol), TMDS (5 equiv.), and C_6D_6 (0.5 mL) containing internal standard $PhCF_3$. The NMR tube was sealed with an airtight rubber septum,

wrapped with parafilm, inverted, and CTFE (3 mL, *ca.* 0.12 mmol) bubbled through the solution using a 23-gauge needle. The NMR tube was then placed upright in an aluminum bead bath (from Lab Armor; Irving, TX) heated to 70°C and allowed to ripen for the time specified in Table 5.3.3 before analysis by NMR. **1122a*(E)***: ^{19}F NMR (282 MHz): –155.7 (1F, dd, J_{F-H} = 72, J_{F-F} = 10 Hz), –105.5 ppm (1F, dd, J_{F-H} = 13, J_{F-F} = 10 Hz). ^{1}H NMR (300 MHz): 5.60 ppm (1H, dd, $^{2}J_{H-F}$ = 13, $^{3}J_{H-F(trans)}$ = 72 Hz). **1122a*(Z)***: ^{19}F NMR (282 MHz): –173.2 (1F, dd, J_{F-H} = 74, J_{F-F} = 132 Hz), –130.5 ppm (1F, d,[43] J_{F-F} = 132 Hz). ^{1}H NMR (300 MHz): 6.46 ppm (1H, d, J_{H-F} = 74 Hz).

[43] This signal overlaps with the –Me_2SiF septet at –130.7 ppm, masking the F–H doublet.

5.7 References

(1) Whittlesey, M. K.; Peris, E. Catalytic Hydrodefluorination with Late Transition Metal Complexes. *ACS Catal.* **2014**, *4*, 3152–3159.

(2) Braun, T.; Noveski, D.; Neumann, B.; Stammler, H. G. Conversion of Hexafluoropropene into 1,1,1-Trifluoropropane by Rhodium-Mediated C-F Activation. *Angew. Chemie - Int. Ed.* **2002**, *41*, 2745–2748.

(3) Noveski, D.; Braun, T.; Schulte, M.; Neumann, B.; Stammler, H. C – F Activation and Hydrodefluorination of Fluorinated Alkenes at Rhodium. *Dalt. Trans.* **2003**, 4075–4083.

(4) Kirkham, M. S.; Mahon, M. F.; Whittlesey, M. K. C-F Bond Activation of Perfluoroalkenes by Ruthenium Phosphine Hydride Complexes: X-Ray Crystal Structures of Cis-Ru(Dmpe)$_2$F(F···HF) and [Ru(Dcpe)$_2$H]+[(CF$_3$)$_2$C=C(O)CF$_2$CF$_3$]-. *Chem. Commun.* **2001**, *168*, 813–814.

(5) Clot, E.; Mégret, C.; Kraft, B. M.; Eisenstein, O.; Jones, W. D. Defluorination of Perfluoropropene Using Cp*2ZrH2 and Cp*2ZrHF: A Mechanism Investigation from a Joint Experimental-Theoretical Perspective. *J. Am. Chem. Soc.* **2004**, *126*, 5647–5653.

(6) Rieth, R. D.; Brennessel, W. W.; Jones, W. D. Activation of Aromatic, Aliphatic, and Olefinic Carbon–Fluorine Bonds Using Cp*$_2$HfH$_2$. *Eur. J. Inorg. Chem.* **2007**, *2007*, 2839–2847.

(7) Kraft, B. M.; Clot, E.; Eisenstein, O.; Brennessel, W. W.; Jones, W. D. Mechanistic Investigation of Vinylic Carbon-Fluorine Bond Activation of Perfluorinated Cycloalkenes Using Cp*$_2$ZrH$_2$ and Cp*$_2$ZrHF. *J. Fluor. Chem.* **2010**, *131*, 1122–1132.

(8) Kraft, B. M.; Lachicotte, R. J.; Jones, W. D. Aliphatic Carbon-Fluorine Bond Activation Using (C$_5$Me$_5$)$_2$ZrH$_2$. *J. Am. Chem. Soc.* **2000**, *122*, 8559–8560.

(9) Kühnel, M. F.; Lentz, D. Titanium-Catalyzed C-F Activation of Fluoroalkenes. *Angew. Chemie - Int. Ed.* **2010**, *49*, 2933–2936.

(10) Lunzer, F.; Marschner, C.; Landgraf, S. (C$_5$H$_5$)$_2$TiF$_2$ and (C$_5$H$_5$)$_2$ZrF$_2$ as Catalyst Precursors for the Dehydropolymerisation of Silanes. *J. Organomet. Chem.* **1998**, *568*, 253–255.

(11) Selvakumar, K.; Rangareddy, K.; Harrod, J. F. The Titanocene-Catalyzed Reduction of Acetamides to Tertiary Amines by PhMeSiH$_2$. *Can. J. Chem.* **2004**, *82*, 1244–1248.

(12) Krüger, J.; Ehm, C.; Lentz, D. Improving Selectivity in Catalytic Hydrodefluorination by Limiting S$_N$V Reactivity. *Dalt. Trans.* **2016**, *45*, 16789–16798.

(13) Vela, J.; Smith, J. M.; Yu, Y.; Ketterer, N. A.; Flaschenriem, C. J.; Lachicotte, R. J.; Holland, P. L. Synthesis and Reactivity of Low-Coordinate Iron(II) Fluoride Complexes and Their Use in the Catalytic Hydrodefluorination of Fluorocarbons.

J. Am. Chem. Soc. **2005**, *127*, 7857–7870.
(14) Yow, S.; Gates, S. J.; White, A. J. P.; Crimmin, M. R. Zirconocene Dichloride Catalyzed Hydrodefluorination of C_{Sp2}-F Bonds. *Angew. Chemie - Int. Ed.* **2012**, *51*, 12559–12563.
(15) Wu, J.; Xiao, J.; Dai, W.; Cao, S. Synthesis of Monofluoroalkenes through Selective Hydrodefluorination of Gem-Difluoroalkenes with Red-Al®. *RSC Adv.* **2015**, *5*, 34498–34501.
(16) Jaeger, A. D.; Lentz, D. Rare Earth Metal Catalyzed C–F Bond Activation. *Zeitschrift fur Anorg. und Allg. Chemie* **2018**, *644*, 1229–1233.
(17) Schneider, H.; Hock, A.; Jaeger, A. D.; Lentz, D.; Radius, U. NHC·Alane Adducts as Hydride Sources in the Hydrodefluorination of Fluoroaromatics and Fluoroolefins. *Eur. J. Inorg. Chem.* **2018**, *2018*, 4031–4043.
(18) Jaeger, A. D.; Ehm, C.; Lentz, D. Organocatalytic C−F Bond Activation with Alanes. *Chem. - A Eur. J.* **2018**, *24*, 6769–6777.
(19) Jaeger, A. D.; Lentz, D. Process for Producing a Fluorinated Alkene. US Appl. 2018/0258017 A1, 2018.
(20) Jaeger, A. D.; Walter, R.; Ehm, C.; Lentz, D. Gallium Hydrides and O/N-Donors as Tunable Systems in C−F Bond Activation. *Chem. - An Asian J.* **2018**, *13*, 2908–2915.
(21) Phillips, N. A.; White, A. J. P.; Crimmin, M. R. Selective Hydrodefluorination of Hexafluoropropene to Industrially Relevant Hydrofluoroolefins. *Adv. Synth. Catal.* **2019**, *361*, 3351–3358.
(22) Crimmin, M. R.; Phillips, N. A. Method of HFO Synthesis. WO 2020/002932 A1, 2020.
(23) Poutrel, P.; Pannecoucke, X.; Jubault, P.; Poisson, T. Stereoselective Synthesis of Terminal Monofluoroalkenes from Trifluoromethylated Alkenes. *Org. Lett.* **2020**, *22*, 4858–4863.
(24) Lanzinger, D.; Höhlein, I. M.; Weiß, S. B.; Rieger, B. Catalytic C-F Activation via Cationic Group IV Metallocenes. *J. Organomet. Chem.* **2015**, *778*, 21–28.
(25) Kordts, N.; Künzler, S.; Rathjen, S.; Sieling, T.; Großekappenberg, H.; Schmidtmann, M.; Müller, T. Silyl Chalconium Ions: Synthesis, Structure and Application in Hydrodefluorination Reactions. *Chem. - A Eur. J.* **2017**, *23*, 10068–10079.
(26) Chitnis, S. S.; Krischer, F.; Stephan, D. W. Catalytic Hydrodefluorination of C−F Bonds by an Air-Stable PIII Lewis Acid. *Chem. - A Eur. J.* **2018**, *24*, 6543–6546.
(27) Waked, A. E.; Chitnis, S. S.; Stephan, D. W. P(V) Dications: Carbon-Based Lewis Acid Initiators for Hydrodefluorination. *Chem. Commun.* **2019**, *55*, 8971–8974.
(28) Meißner, G.; Kretschmar, K.; Braun, T.; Kemnitz, E. Consecutive Transformations of Tetrafluoropropenes: Hydrogermylation and Catalytic C−F Activation Steps at a Lewis Acidic Aluminum Fluoride. *Angew. Chemie - Int. Ed.*

2017, *56*, 16338–16341.
(29) Kervarec, M. C.; Braun, T.; Ahrens, M.; Kemnitz, E. Activation of Pentafluoropropane Isomers at a Nanoscopic Aluminum Chlorofluoride: Hydrodefluorination versus Dehydrofluorination. *Beilstein J. Org. Chem.* **2020**, *16*, 2623–2635.
(30) Lv, H.; Cai, Y. B.; Zhang, J. L. Copper-Catalyzed Hydrodefluorination of Fluoroarenes by Copper Hydride Intermediates. *Angew. Chemie - Int. Ed.* **2013**, *52*, 3203–3207.
(31) Hu, J.; Han, X.; Yuan, Y.; Shi, Z. Stereoselective Synthesis of Z Fluoroalkenes through Copper-Catalyzed Hydrodefluorination of Gem -Difluoroalkenes with Water. *Angew. Chemie Int. Ed.* **2017**, *56*, 13342–13346.
(32) Kojima, R.; Kubota, K.; Ito, H. Stereodivergent Hydrodefluorination of Gem-Difluoroalkenes: Selective Synthesis of (Z)- and (E)-Monofluoroalkenes. *Chem. Commun.* **2017**, *53*, 10688–10691.
(33) Andrella, N. O.; Xu, N.; Gabidullin, B. M.; Ehm, C.; Baker, R. T. Selective Copper Complex-Catalyzed Hydrodefluorination of Fluoroalkenes and Allyl Fluorides: A Tale of Two Mechanisms. *J. Am. Chem. Soc.* **2019**, *141*, 11506–11521.
(34) Baker, R. T.; Andrella, N. O. Process for Preparation of Hydrofluoroalkenes by Selective Catalytic Consecutive Hydrodefluorination. US 10,774,021 B2, 2020.
(35) Chiu, P.; Li, Z.; Fung, K. C. M. An Expedient Preparation of Stryker's Reagent. *Tetrahedron Lett.* **2003**, *44*, 455–457.
(36) Stephens, R. D. Hydrido(Triphenylphosphine)Copper(I). *Inorg. Synth.* **1979**, *19*, 87–89.
(37) Lee, D. W.; Yun, J. Direct Synthesis of Stryker's Reagent from a Cu(II) Salt. *Tetrahedron Lett.* **2005**, *46*, 2037–2039.
(38) Lipshutz, B. H.; Lower, A.; Noson, K. Copper(I) Hydride-Catalyzed Asymmetric Hydrosilylation of Heteroaromatic Ketones. *Org. Lett.* **2002**, *4*, 4045–4048.
(39) Baker, B. A.; Bošković, Ž. V.; Lipshutz, B. H. (BDP)CuH: A "Hot" Stryker's Reagent for Use in Achiral Conjugate Reductions. *Org. Lett.* **2008**, *10*, 289–292.
(40) Zhou, Y.; Bandar, J. S.; Buchwald, S. L. Enantioselective CuH-Catalyzed Hydroacylation Employing Unsaturated Carboxylic Acids as Aldehyde Surrogates. *J. Am. Chem. Soc.* **2017**, *139*, 8126–8129.
(41) Zhou, Y.; Bandar, J. S.; Liu, R. Y.; Buchwald, S. L. CuH-Catalyzed Asymmetric Reduction of α,β-Unsaturated Carboxylic Acids to β-Chiral Aldehydes. *J. Am. Chem. Soc.* **2018**, *140*, 606–609.
(42) Zehner, P.; Ulonska, A.; Paciello, R. Method for Producing Aldehydes and/or Alcohols or Amines. US 6,642,420 B1, 2003.
(43) Smith, E. F. Process for Converting Lower-Boiling Aldehydes into Higher-Boiling Aldehydes. US 2,485,989, 1949.
(44) Lehtinen, C.; Brunow, G. Factors Affecting the Selectivity of Air Oxidation of 2-

Ethyhexanal, an α-Branched Aliphatic Aldehyde. *Org. Process Res. Dev.* **2000**, *4*, 544–549.
(45) Mishra, S.; Daniele, S.; Hubert-Pfalzgraf, L. G. Metal 2-Ethylhexanoates and Related Compounds as Useful Precursors in Materials Science. *Chem. Soc. Rev.* **2007**, *36*, 1770–1787.
(46) Chiang, Y. J.; Wang, S. F.; Lu, C. A.; Lin, H. C.; Wang, L. C.; Ding, Y. Z. Characteristics of Silver Powders Synthesized from Silver 2-Ethylhexanoate and Di-n-Octylamine. *J. Electroceramics* **2013**, *31*, 109–116.
(47) Liu, C.; Tian, Q.; Liao, L. *Sol–Gel Precursor Inks and Films*; Elsevier Inc., 2020.
(48) Epifani, M.; Tang, P. Y.; Genç, A.; Morante, J. R.; Arbiol, J.; Díaz, R.; Wicker, S. The Ethylhexanoate Route to Metal Oxide Nanocrystals: Synthesis of CoO Nanooctahedra from CoII2-Ethylhexanoate. *Eur. J. Inorg. Chem.* **2016**, *2016*, 3963–3968.
(49) Tiseanu, C.; Cojocaru, B.; Parvulescu, V. I.; Sanchez-Dominguez, M.; Primus, P. A.; Boutonnet, M. Order and Disorder Effects in Nano-ZrO2 Investigated by Micro-Raman and Spectrally and Temporarily Resolved Photoluminescence. *Phys. Chem. Chem. Phys.* **2012**, *14*, 12970–12981.
(50) Maruyama, T.; Shionoya, J. Magnesium Oxide Thin Films Prepared by Chemical Vapor Deposition from Magnesium 2-Ethylhexanoate. *Jpn. J. Appl. Phys.* **1990**, *29*, L810–L811.
(51) Bratton, D.; Brown, M.; Howdle, S. M. Tin(II) Ethyl Hexanoate Catalyzed Precipitation Polymerization of ε-Caprolactone in Supercritical Carbon Dioxide. *Macromolecules* **2005**, *38*, 1190–1195.
(52) Schmitz, S.; Hubel, R. Use of Metal Salts of a Carboxylic Acid in the Production of Polyurethane Systems. US 8,841,403 B2, 2014.
(53) Takahashi, Y.; Naotsuka, T.; Tachibana, Y.; Ome, H. Polylactic Acid Resin Composition, Molded Product, and Method of Manufacturing Polylactic Acid Resin Composition. US 9,920,181 B2, 2018.
(54) Hasegawa, K. Toner, and Two-Component Developer and Image Forming Apparatus Using the Toner. US App. 2008/0220360 A1, 2008.
(55) Wang, L.; Wang, V. R. Anti-Icing Composite. US 9,879,153 B2, 2018.
(56) Luo, S.; McCauley, K. M.; Poulton, J. T. Process for Producing Polydienes. US 7,977,437 B2, 2011.
(57) Knudsen, R. D.; Abbott, R. G.; Kreischer, B. E.; Baralt, E. J.; Small, B. L. Methods of Preparation of an Olefin Oligomerization Catalyst. US 7,910,670 B2, 2011.
(58) Rogers, V. V.; Liber, K.; MacKinnon, M. D. Isolation and Characterization of Naphthenic Acids from Athabasca Oil Sands Tailings Pond Water. *Chemosphere* **2002**, *48*, 519–527.
(59) Humphrey, D.; Skewes, B.; McFarling, S. Wood Preservative Formulation. US 10,201,910 B2, 2019.

(60) Nikitin, A. A. Copper Fungicides and Process for Producing Same. US 2,456,727, 1948.
(61) Bobsein, R. L.; Hauger, B. E.; Coutant, W. R.; Rathman, J. Phosphite Additives in Polyolefins. US 7,157,511 B2, 2007.
(62) Habicher, W. D.; Bauer, I.; Pospíšil, J. Organic Phosphites as Polymer Stabilizers. *Macromol. Symp.* **2005**, *225*, 147–164.
(63) Schwetlick, K.; Habicher, W. D. Action Mechanisms of Phosphite and Phosphonite Stabilizers. *Adv. Chem.* **1996**, *249*, 349–358.
(64) Sugawara, M.; Sugimoto, T.; Tanaka, K.; Yamada, T. Gas for Plasma Reaction and Producing Method Therefor. JP 3,960,095, 2007.
(65) Sekiya, A.; Yamada, T.; Watanabe, K. Process for Producing Fluorinated Alkene and Fluorinated Alkane. US 5,847,243, 1998.
(66) Sekiya, A.; Yamada, T.; Uruma, T.; Sugimoto, T. Fluorinated, Saturated Hydrocarbons. US 6,403,846 B1, 2002.
(67) Kikushima, K.; Grellier, M.; Ohashi, M.; Ogoshi, S. Transition-Metal-Free Catalytic Hydrodefluorination of Polyfluoroarenes by Concerted Nucleophilic Aromatic Substitution with a Hydrosilicate. *Angew. Chemie - Int. Ed.* **2017**, *56*, 16191–16196.
(68) Wei, Y.; Liu, Y.; Wong, T.; Lemal, D. M. Extremely Facile Ring Inversion and Rearrangement in Fluorobicyclo[2.1.0]Pentanes. *J. Fluor. Chem.* **2006**, *127*, 688–703.
(69) Feast, W. J.; Perry, D. R. A.; Stephens, R. Fluorocyclopentanes—V. Lithium Aluminum Hydride Reduction of Octafluoro-, 1,2-Dichlorohexafluoro-, and 1-Chloroheptafluoro-Cyclopentene and 1H,2-Chloro-Octafluorocyclohexene. *Tetrahedron* **1966**, *22*, 433–439.
(70) Sugimoto, T. Method for Producing 1H,2H-Perfluorocycloalkene. JP 2019-127466 A, 2019.
(71) Pazenok, S.; Lui, N.; Funke, C. Process for the Preparation of 5-Fluoro-1H-Pyrazoles Starting from Hexafluoropropene. US 9,957,256 B2, 2018.
(72) Pazenok, S. Process for the Preparation of 5-Fluoro-1H-Pyrazoles Starting from Hexafluoropropene. US 10,059,673 B2, 2018.
(73) WESTON® TDP Phosphite Ester. Technical Information. Addivant Corporation 2013.
(74) Taniguchi, T.; Furuta, S. Method for Producing 1-Chloro-1,2-Difluoroethylene. JP Appl. 2015-120670 A, 2013.
(75) Usui, T. Method for Producing 1,2-Dichloro-1,2-Difluoroethane (HCFC-132), Method for Producing 1-Chloro-1,2-Difluoroethylene (HCFO-1122a), and Method for Separating HCFC-132. JP 6,610,625 B2.
(76) Karube, D.; Ohishi, S. Method for Producing 1-Chloro-1,2-Difluoroethylene. US 10,611,710 B2, 2020.
(77) Fukushima, M.; Mitsuoka, H.; Tasaka, M.; Kawaguchi, S.; Ueno, K.; Tanaka, T.;

Okamoto, H.; Otsuka, T.; Kadowaki, Y.; Nogami, T.; et al. Working Fluid for Heat Cycle, Composition for Heat Cycle System, and Heat Cycle System. US 10,787,597 B2, 2020.

(78) Pelšs, A.; Kumpulainen, E. T. T.; Koskinen, A. M. P. Highly Chemoselective Copper-Catalyzed Conjugate Reduction of Stereochemically Labile α,β-Unsaturated Amino Ketones. *J. Org. Chem.* **2009**, *74*, 7598–7601.

(79) Wong, K. C.; Ng, E.; Wong, W. T.; Chiu, P. Copper Hydride Catalyzed Reductive Claisen Rearrangements. *Chem. - A Eur. J.* **2016**, *22*, 3709–3712.

(80) Jiménez, J. R.; Doistau, B.; Poncet, M.; Piguet, C. Heteroleptic Trivalent Chromium in Coordination Chemistry: Novel Building Blocks for Addressing Old Challenges in Multimetallic Luminescent Complexes. *Coord. Chem. Rev.* **2021**, *434*.

6

CHAPTER SIX

6. Future Perspectives

We have now reached the *cadenza* of the thesis, which is to say the passage in which I am charged with the tricky task of prognosticating the direction(s) in which this highly complex and multifaceted industry will proceed forward. Like all subsectors of chemical production, the refrigerant industry and its research pipeline are subject to a number of external and non-scientific forces (rules and regulations originating in government bureaus, tariffs and other barriers to trade, perennial IP litigation, &c.). That most of these barriers to doing business originate in the minds of the scientifically and economically illiterate makes the future industrial environment particularly difficult for a scientist to predict. As such, posterity is seldom kind to such earnestly-attempted divinations, and if events transpire in just the opposite direction as is forecasted here, then the foregoing chapters will hopefully have won enough favor to forgive your humble author's cloudy crystal ball. With the necessary disclaimers out of the way, let us begin with the cast of molecules, present and future.

6.1 New Molecules

Despite a growing acceptance of the two most prominent C_3 olefins **1234yf** and **1234ze**, as well as the C_4 model **1336mzz**, OEMs of air-conditioners, refrigerators, chillers &c. have yet to fully coalesce around a single HFO (or blend thereof) to replace current flag-bearers such as **134a** and its blends, most notably R-404A (*vide ante* in ***Section 2.7***). The very same HSE parameters outlined in ***Section 2.6*** continue to apply, although this author is of the opinion that as of yet, no existing compound perfectly satisfies all requirements, and thus, unless the molecular landscape evolves further, some concessions will have to be made. This could mean a higher tolerance for mild flammability (*e.g.* treatment of A2L refrigerants similarly to A1—*viz.* a loosening of restrictions) or a higher tolerance for a nonzero ODP in the short term in exchange for a lower GWP over the longer term. We have already seen a sort of compromise in the reëmergence of the C–Cl bond in the HCFO foam-expanding agents **1233zd** and **1224yd** (Figure 6.1.1). This is a favorable development, as C–Cl bonds tend to impart a greater resistance to flame than equivalent C–F bonds; indeed, some HCFOs have already been proposed as new Halon substitutes for their fire-extinguishing abilities.[1] Another advantage of Cl-containing models is that they are themselves often produced *en route* to HFOs, and are thus cheaper and easier to manufacture than the latter.[44]

[44] **1233zd** and **1233xf** are respective intermediates to **1234ze** and **1234yf**.

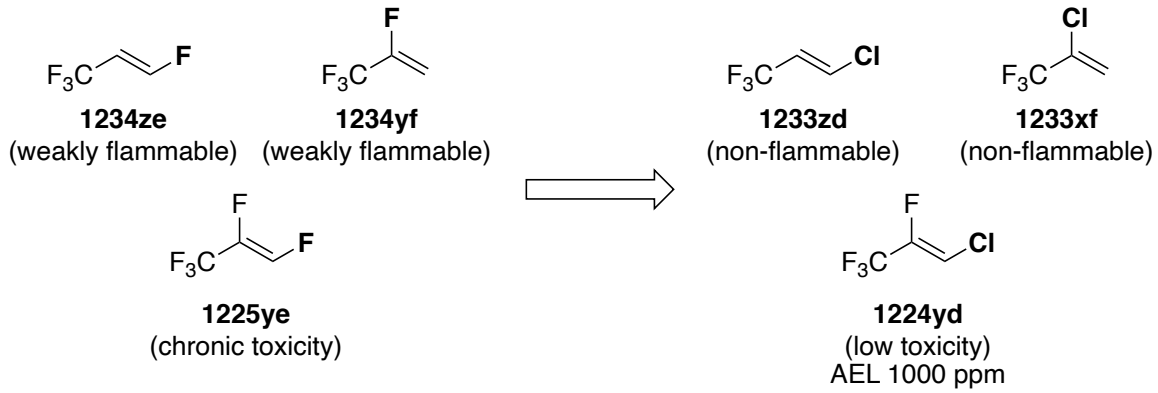


Figure 6.1.1: Relation of A1-rated HCFOs to HFOs

Another growing area of interest is, interestingly, in the realm of C_2 olefins (Chart 6.1.1). It is strange that the industry should have moved directly to fluorinated propylenes before having fully evaluated the fluoroethylene space, and yet recently AGC has championed safe blends containing trifluoroethylene (HFO-**1123**),[2–5,45] notorious—in its pure form—for spontaneous deflagration.[6] Despite this property, **1123** is possessed of low toxicity (LC_{50} >200,000 ppm) and a very low GWP (0.3). Its low boiling point (–59°C) brings it close to R-410A (bp. –51.6°C). However, like the **32** or **1234yf** with which it is blended, **1123** is A2L, meaning it has not totally fulfilled the requirement of non-flammability. Of late, AGC[7] and Daikin[8] have also been independently evaluating synthetic routes to the 1-chloro congener HCFO-**1122a**, which could be another interesting candidate, and which was a late-entry in the work presented in ***Chapter 5***.

[45] Amolea® 370X contains a ratio of 55% **32** and 45% **1123** boiling at –56.8°C and offers a COP of 0.97 (R-410A = 1) with a GWP of 372. Amolea® 370Y2 contains a ratio of 19% **1123**, 55% **32**, and 26% **1234yf** boiling at –53.1°C and also offers a COP of 0.97 with a GWP of 373. Both are possessed of a slight temperature glide (1–2°C) while R-410A has a very low glide (0.1°C).

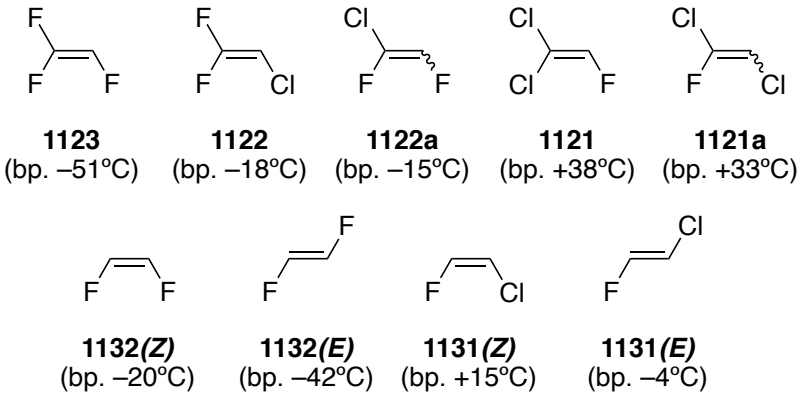


Chart 6.1.1: C_2 HFOs and HCFOs, and their normal boiling points

Of course, it may that not all olefins shown in Chart 6.1.1 are viable candidates. For years, **1123** was never seriously considered due to its deflagration hazard, but through clever blending, the beast within it was tamed, and now a blend thereof is being brought to market. **1122**, despite its attractive boiling point, is not likely to serve as a candidate owing to its reported toxicity and flammability.[9] One report[10,46] mentions, however, that its isomer **1122a** has no flash point, and though there exists currently little information on this compound in the public domain with regard to toxicity or flammability, it deserves a closer look. On the remaining compounds in Chart 6.1.1, the literature is quiet, verging on silent. The high boiling points of **1121**/**1121a** likely rule them out, and though no information could be found to back it up, this author suspects that the high chlorine content would confer an unacceptable degree of toxicity.[47] The 1,2-chlorofluoro

[46] No citation is provided in ref. 10 to back up this statement, however.
[47] It is generally known and accepted that highly chlorinated compounds exhibit toxicity. Even *trans*-1,2-dichloroethylene, commonly deployed as a cleaning solvent, is rated B1.

compounds **1131** are interesting for having been mentioned only in passing at the end of a patent[11,48] by Henne and McNary of Frigidaire Corp. According to their boiling points, the *(Z)*-isomer could conceivably serve as a gaseous foam-blowing agent, while the *(E)*-isomer, having a boiling point of below zero, could serve as a medium-pressure refrigerant, but no affirmative studies on such applications were discovered during the writing of this document. In contrast to the chloro-congeners, refrigerant blends using both **1132*(E)***[12] and **1132*(Z)***[13] have been known since 2015. Manufacturing methods for isomeric **1132** have been disclosed in 2013[14] and 2016[15] by AGC, and more recently in 2021 by Daikin,[16] suggesting a continued interest in this olefin as the fluoroethylenes undergo their nascent revival. Despite being reported 6 years ago by Du Pont, no blends containing **1132** were ever brought to market, and as of the writing of this document, I have been unable to find any data concerning their toxicity, GWP, or flammability, although I expect both isomers to fit soundly in the A2L category.

Besides a potential return to C_2 compounds, another strategy being taken is to craft blends of moderately-flammable refrigerants with fire-extinguishing agents. We have already seen the emergence of CO_2 and CF_3I as blend components in ***Section 2.7***. Field-trials are being undertaken by Trane using Honeywell's new A1-rated Solstice® N41 (R-466A) blend[49] as a replacement for R-410A in rooftop air-conditioners.[17] Note that the

[48] Unfortunately, the authors give no justification, merely stating *verbatim*: "Among these groups we prefer to employ in air cooled household refrigeration compounds in the methane group, and, particularly, dichloro difluoro methane. In the olefin group we may use 1,2 chloro fluoro ethylene."
[49] R-466A consists of 39.5% CF_3I, 49% **32**, and 11.5% **125** with a normal boiling point of –51.7°C

moderate flammability of **32** has been tempered by non-flammable CF_3I and **125**. Though the GWP of R-466A is 733 (*cf.* 675 for HFC-**32**), a mere increase of 8% in GWP over pure **32** is a worthy trade to achieve the coveted A1 safety rating, especially considering its 65% lower GWP and superior heating and cooling capacity relative to R-410A.[18] Given the high cost of iodine, it is yet unclear whether R-466A will be more or less cost-competitive with low-GWP olefin-based offerings already in the market. Nonetheless, the early promise of Honeywell's R-466A is likely to nudge their competitors in this direction.

A group of compounds in which the industry's interest undergoes a periodic revival is the hydrofluoroethers (HFEs). Though they were proposed alongside HFCs some 20 years ago as CFC/HCFC replacements,[19] and their environmental risk assessment carried out shortly thereafter,[20] no refrigerant has ever been brought to market which contains an HFE component, though such compositions have been reported.[21,22] To date, these have mainly seen adoption as inert solvents as part of a wider effort to replace CFC-**113**/**113a** and HCFC-**141b** in the electronics industry,[23–25] or as replacements for perfluorocarbons in fluorous-phase chemistry.[26] Based on kinetic data obtained by Cooper et al. concerning reactivity with ·OH radicals, HFEs having no more than one H atom per carbon are predicted to have *longer* atmospheric lifetimes than HFCs, but the addition of more hydrogen dramatically shortens the lifetime as compared to the equivalent HFC (Chart 6.1.2).[27,28] For example, HFC-**143a** has an atmospheric lifetime of 53.5 years while its ethereal congener CF_3OCH_3 (HFE-**E143a**) has a lifetime of only 5.7 years. Segregated HFEs—that is perfluorocarbyl-hydrocarbyl ethers—such as methyl- or ethyl-

nonafluorobutyl ethers are currently used as precision solvents and are marketed by 3M under the Novec™ moniker. Flanking the hydrofluoroether class are the perfluoroethers (PFEs, Chart 6.1.3). On these, very little has been written, save for some compositions disclosed by Du Pont[21] and Arkema.[29] The study of these compounds is largely limited by the scarcity of methods for their preparation. In particular, **c216E** and **c216E2** have shown promise as arc insulator gases in replacement of the currently-used SF_6.[30,50] Given the provided GWP values and boiling points, only **E143a** would appear to show any immediate promise as a refrigerant, and indeed was disclosed early by ICI as a blend component.[31] Its GWP of 970, however, might appear to current sensibilities as too high to compete with recent aforementioned offerings based around olefinic or iodine-containing components. It may at least be predicted that heavier fluorinated ethers will continue to see adoption as solvents, and more highly-fluorinated ethers could be the subject of increased investigation as insulator gases. Whether the applications of cyclic PFEs will extend beyond specialty electronics uses and see wider deployment as refrigerants or blowing agents, however, can only be determined when their thermophysical and environmental properties are published. Otherwise, the HFE class will remain an academic curiosity of unfulfilled promise.

[50] Though the authors put forth no empirical evidence in support, they claimed that ring strain (particularly on **c216E**) might render cyclic perfluoroethers more susceptible to atmospheric degradation than linear perfluorocarbons.

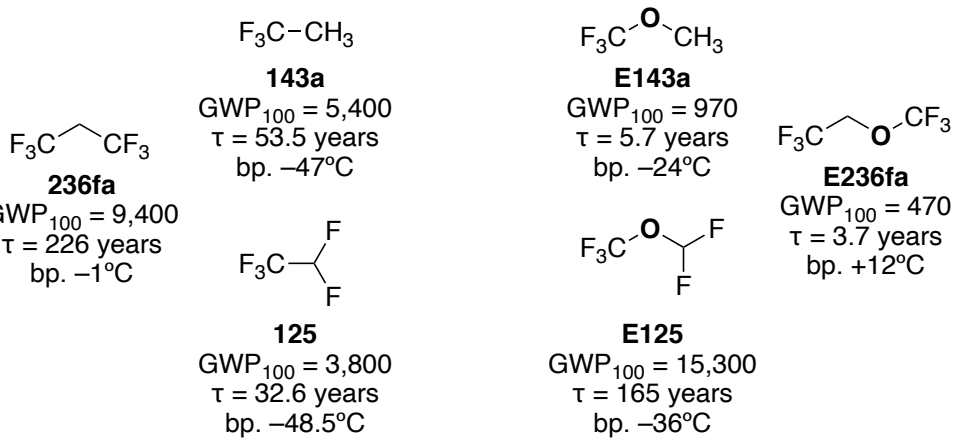


Chart 6.1.2: C_2 and C_3 HFCs *vs* HFEs and their GWP and τ values

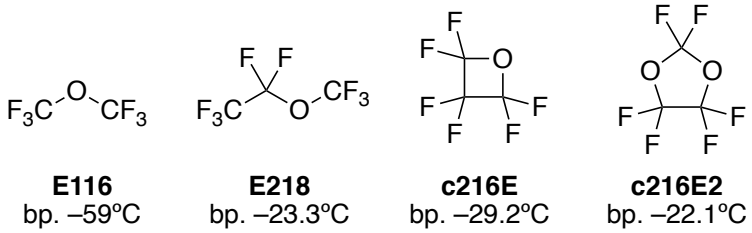


Chart 6.1.3: Assorted PFEs and their normal boiling points

6.2 New Regulations

The regulatory caprices of government bureaucrats and elected officials ensures that what is considered the 'ideal gas' is a target constantly in motion. For example, the recent F-Gas legislation brought about in the European Union[32,51] is likely to cause considerable market distortions in the pricing of new equipment in that region. This is

[51] This regulation was implemented on Jan. 5, 2015, and implies a phase-down of HFC refrigerants by 2030, with particular pressure being exerted on the R-404A, R-507, and R-410A blends. The target for 2030, based on quota allocation, is for high-GWP HFC refrigerants to reach 21% of baseline.

especially the case as R-410A is still without a confirmed and widely-accepted low-GWP replacement save for R-466A, which is still in the field-testing stage. OEMs will be pressured to either stop building R-404A/507 systems or to modify equipment to accept replacements. Concurrent with the declining quotas year-on-year, the supply of virgin refrigerant cylinders (especially 404A) in the EU will continue to dwindle, leading to price inflation. This price inflation might indeed encourage faster adoption of lower-GWP alternatives, and as long as said alternatives are price-competitive with the outgoing blends and can be manufactured at scale sufficiently quickly, then the high prices will be transitory. If not, then the heightened prices of refrigeration gases will exert upward pressure on the prices of refrigeration equipment—prices which will inevitably be borne by the consumer[52]—contributing further to the economic inefficiencies that already plague the EU member states. The OEM community has responded by offering low-GWP options such as Honeywell's Solstice® N41 and AGC's Amolea® X- and Y-series to replace R-410A, for which the more stringently-regulated European market will serve as proving ground.

But North American producers are no safer from the (very *visible*) hand of government policy than their European counterparts. The American Innovation and Manufacturing Act (AIM)[53] passed by the 117th Congress targets a baseline of 15%

[52]It is almost a truism of supply chain dynamics that price inefficiencies incurred in the middle of the chain will ultimately aggregate at the end of the chain—*viz.* at the end-user or consumer.
[53]Bill H.R. 5544, sponsored by Rep. Paul Tonko (D-NY)

production and consumption of certain high-GWP HCFC and HFC gases by the year 2032. Thankfully, the bill makes allowances for specialty applications for which there is no suitable alternative and for which the safety requirements are more stringent (such as metered dose inhalers, semiconductor etching, onboard aerospace fire suppression, military uses, &c.). For instance, the carrier gas of an asthma inhaler is entirely breathed in by the patient during dose administration, and so must carry with it absolutely no toxicity hazard in the volumes dispensed. For this, legacy HFCs like **134a** are truly without substitute. Likewise, fire suppression in aircraft (both civilian and military) requires compounds which are both non-flammable and non-toxic (as they are sprayed within a confined space, exposing any occupants thereof to potentially high local concentrations of the gas). The terms of the AIM act appear slightly gentler than the F-Gas legislation in the EU, but are expected to apply pressure to replace the same cohort of products, albeit over a slightly longer timespan.

The ever-changing regulatory space is just another quirk of our little corner of the chemical industry, and, perhaps thankfully, a thorough and comprehensive examination of same is beyond the scope of this thesis chapter; as with most like matters, we cede that battleground to the lawyers. What *can* be said here is that this unpredictability from region-to-region and decade-to-decade leads to an abnormally large risk borne by refrigerant OEMs. What new models are championed one day by regulators as acceptable alternatives are sure before long to be deemed contraband by those very same regulators. Consider, for example, how much time, effort, and capital were collectively invested into

developing suitable and scalable manufacturing routes for HFC-**134a**—that last $-CH_2Cl$ fluorination being most challenging indeed—with the hopes that this non-ozone-depleting miracle would be the ideal replacement refrigerant. Now that all of the necessary research and development has been done, the parameters optimized, the capacity constructed, and the refrigeration equipment built to match, we are told that this product, now cheaply and widely available to all, is no longer acceptable, and that a new alternative must be put to market within a limited period of time. Within the last two decades, hundreds of millions of dollars have been invested in manufacturing capacity for **1234yf** and **1234ze**, themselves the result of over a decade of development and testing. How much time will pass before the powers that be manage to unearth some new and unforeseen 'problem' with even *these* offerings? Perhaps it is too soon to worry about such a thing, as the age of HFOs is still in its early days, and it is not yet clear that they perfectly fill the shoes of their HFC forebears, though their manufacturers certainly hope so. In any event, we chemists and engineers are ever ready to dutifully return to our labs and drawing boards in order to repeat the cycle anew. *One must imagine Sisyphus happy.*

6.3 New Methods

In this thesis two metal complex-catalyzed fluorochemical synthetic methods were discussed in detail: metalacycle-based reductive olefin dimerization, and hydrodefluorination. While the concept of using transition metals to dimerize and/or

reduce olefins is not new, such techniques have only sparingly been investigated for olefins containing fluorine (or indeed, any other halogen). Nearly all of the past time, effort, and publications devoted to transition metal-catalyzed manipulations of olefins exist squarely in the hydrocarbon realm. Even hydrodefluorination, a reaction which has seen somewhat more sunlight than other metal-haloölefin reactions, is almost exclusively discussed in academic circles as pertaining to fluorinated *arenes*, rather than olefins—this, despite the fact that there are currently no commercial products containing a fluoroarene (to the knowledge of this author as of the writing of this chapter) which actually employ an HDF step in their manufacture. Furthermore, medicinal chemists upstream of the factory floor have little need to fuss about fluorination (or defluorination) of fluoroarenes as these derivatives can easily be procured with nearly every imaginable substitution pattern at reasonable prices from specialty chemical retailers such as Synquest Labs. And yet, our literature is full of recently-disclosed methods and catalysts with which we can selectively strip C–F bonds from polyfluorinated aromatics such as C_6F_6 and C_5F_5N. I ask only, *for whom?*

In contrast to aromatics, the supplier catalogs are much less rich in choices for partially-reduced fluoro-, chlorofluoro-, or bromofluoro-olefins. Those which *are* available in great quantities and for little money have likely already been investigated, optimized, and put to market; thus, there is very little appetite for laboratory-scale syntheses therefor. However, there exist a great many partially-reduced olefins (such as **1122a** or

1132) which are exceedingly expensive to purchase and are only available in pack sizes of 25 grams or less.,[54] and for which researchers would appreciate a practical lab route.

This emphasizes the true real-world utility of the methods outlined in this thesis. I have read far too many patents and industry papers to give any pretence to my methods having a commercial future. However, the use of such transition metal-catalyzed routes as HDFD and HDF could provide industrial chemists with a means to obtain research quantities of these potentially important new models to test for favorable properties. In essence, this is the medicinal-chemistry argument, but applied to the fluororefrigerant industry, and it has borne itself out well in our fruitful relationship with Arkema Inc. It is my hope that in the future, academic practitioners interested in HDF will leave the fluoroarene space behind and instead focus their efforts on specialty fluoroölefins, if only they would overcome their resistance to working with gases or low-boiling liquids. For those brave enough to enter, it is a field ripe with opportunity and scarce in (academic) competition, both features which should appeal to the more ambitious younger faculty.

With regards to metallacycle research in particular, this author's 'holy grail' of inventions—a non-reductive fluoroölefin dimerization proceeding *via* a fluorometallacycle which undergoes spontaneous β-hydride elimination—has yet to be created. The functional superiority of such a process is fairly obvious, there being no need for extraneous reductant and therefore no limitation (save for the mean-time-to-failure of the catalyst

[54] Though this seems reasonable, I would remind the reader that when dealing with gases, 25 grams is in practice a very small sample. Realistic testing (in compressors for refrigeration, *e.g.*) requires ≥ 3–5 lbs.

itself) on the amount of feed dimerized in a single pot. One could easily imagine such a process being carried out on a semicontinuous basis. A sensible next step would be to perform a *de novo* DFT study on T-shaped metallacycles of varying substitution patterns to divine which among them show a promising energetic capacity for β-fluoride or β-hydride elimination. It may unfortunately be the case that VF2 is a unique olefin in this regard, and that β-fluoride elimination is a pathway made available by the [–CH_2–CF_2–CH_2–] fragment. It may likewise be that the ideal metallacycle(s) for β-elimination cannot be formed by cyclodimerization of the olefins at a Ni(0) center.[55]

6.4 Intervening Work

In the span of time between the thesis submission and defence, some additional work was done to apprehend the metallacycle from Chapter 3 using DMAP to capture the nascent 3-coördinate metallacycle. In the experiments discussed in Section 3.6, $Ni(cod)_2$, IAd, and DMAP were used in a stoichiometric (1:1:1) ratio using C_6D_6 as the solvent. A subsequent attempt was performed using a five-fold excess of DMAP, but in

[55] In collaboration with B. Ghaffari of our group, some preliminary work *has* been done in attempting to HDFD other olefins with Ni/IAd, but after shaking the tree, the scope of such a reaction appears smaller than we had hoped. First, HFP, rather than forming a metallacycle, undergoes spontaneous C–F bond activation, giving a Ni fluoride which then catalyzes HFP oligomerization. **1234ze** also undergoes C–F bond activation, while **1233zd** and CTFE undergo C–Cl bond activation, as would be expected for such an electron-rich Ni(0) center. Some time ago, K. Giffin attempted VF3, and obtained promising tetrafluorobutadiene products accompanied by precipitation of insoluble NiF_2—a failure mode which is not reversible by silane.

order to carry out this experiment, the solvent had to be switched from benzene to toluene, owing to DMAP's relatively low solubility in the former. This experiment resulted in observations which diverge completely from that discussed in Section 3.6. Adding VF2 to the aforementioned precursor mix, the solution turned bright yellow-orange, and remained that color, rather than undergoing the typical and rapid transition to the characteristic dark red-orange color of the trifluorobutenyl complexes. After 5 minutes at room temperature, ^{19}F NMR showed, as the major product, a pair of heteroleptic π-VF2 complexes (*cis*/*trans* isomers) containing both IAd and DMAP (Figure 6.4.1, compounds Ia and Ia', $^{3}J_{F\text{-}H}$ = 10 and 11 Hz, respectively), and four signals integrating 1:1:1:1 (compounds Ib and Ib'). The observation of F–F and F–H triplets ($^{3}J_{F\text{-}H}$ = 17 Hz, and $^{4}J_{F\text{-}F}$ = 4 Hz), as well as a complex multiplet that collapses to a matching F–F triplet on ^{1}H decoupling, together suggest the –CF_2–CH_2–CF_2–CH_2– grouping. That there are two pairs of such signals suggests that, like the parent π-complex, such a metallacycle is subject to *cis*/*trans* isomerism with respect to the IAd and DMAP. The simple *tt* likely corresponds to the C_α–F_2 groups while the complex multiplets (likely *ttt*) correspond to the C_β–F_2 groups. To confirm this rare sighting, future work will require repeating this experiment in toluene-d_8, obtaining a convincing ^{1}H NMR, and, if possible, obtaining an X-ray quality crystal.

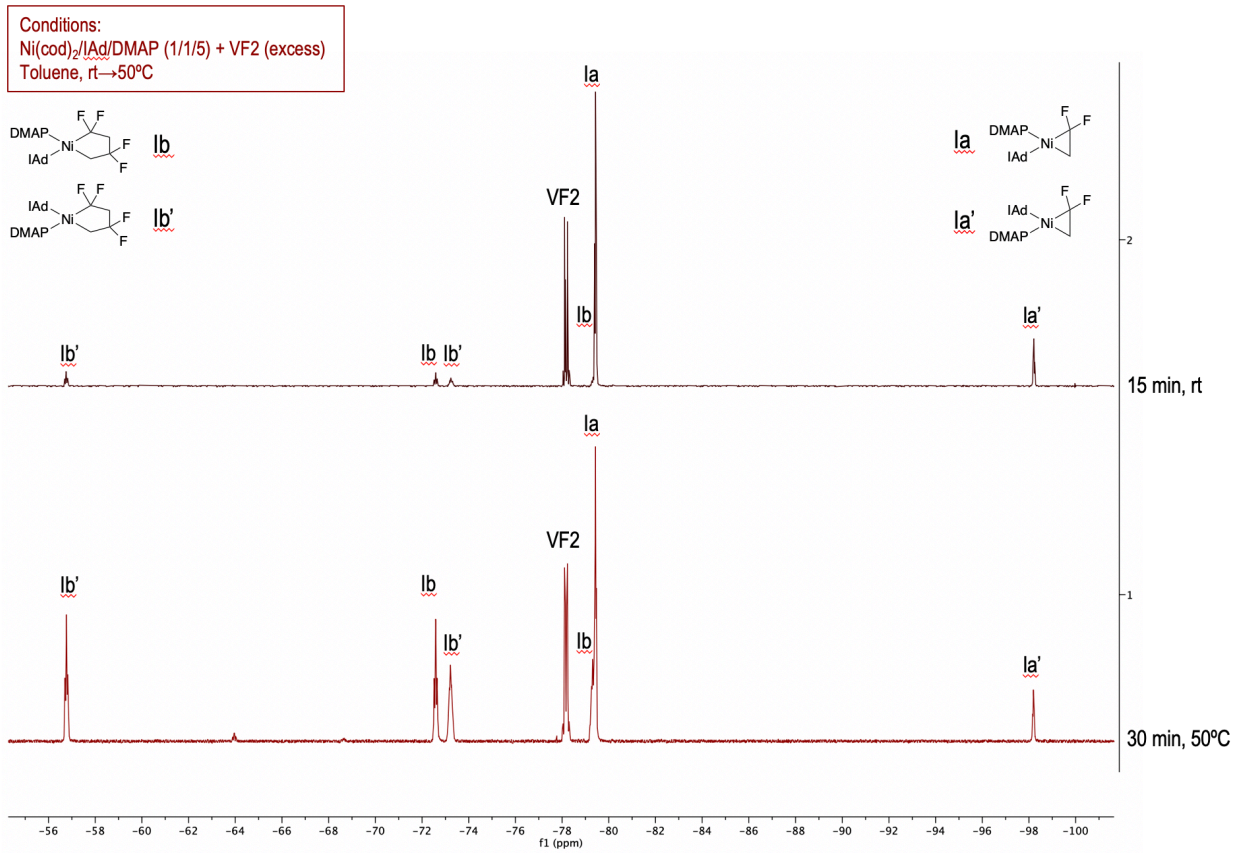


Figure 6.4.1: Potential observation by ^{19}F NMR (282 MHz) of head-tail metallacycles containing both IAd and DMAP

6.5 Final Thoughts

In my years of graduate study up to and including the pursuit of this doctoral degree, I have attempted to channel the inventive spirit of Midgley to solve problems for an industry that receives precious little attention from university researchers. Though Midge's prodigious resumé is one to which I may only ever aspire, never to quite reach, it has become a sort of guiding orientation that will no doubt follow me through my post-doctoral and industrial pursuits in future. Both the HDFD and HDF reactions outlined

here have given rise to countless possible other avenues to be taken by upcoming graduate students and researchers. It might be through either of these methods that a future researcher reveals the next great model of that elusive 'ideal fluorocarbon gas,' and in so doing stumbles upon the *éclat* of a grand discovery.

One final concluding lesson learned here is that a great wealth of inspiration and ideas may yet be found in old and forgotten texts. Much of the work that supports HDFD in ***Chapter 3*** is based on reports going as far back as 1961,[33] long forgotten until Baker et al. leveraged it in the 1990s for the synthesis of HFC-**338pcc**.[34] Much of what supports the phosphine-based C–F bond reductions of ***Chapter 4*** is derived from reports by Burton et al. in the 1970s.[35,36] Even the refrigerant **1234yf** itself was first reported as early as 1946,[37] and then promptly shelved until interest in HFOs was renewed in the early '00s. It is worth looking back (in some cases, *far* back) in search of inventions and innovations which may have come ahead of their time. The writing of *Fluorocarbon Refrigerants and their Syntheses* gave me the opportunity to do just that, through a deep investigation of the patent literature going as far back as the 1910s. Despite the slow and grinding nature of such a project, I would recommend such surveys to new students without reservation.

Beyond HDF and HDFD, a few practitioners are bravely attempting to apply other known homogeneously-catalyzed reactions to small fluorinated olefins. One example is in the realm of olefin metathesis, in which a couple of recent and highly impactful examples by Schrock[38] (based on Mo) and Takahira[39] (based on Ru) have cut a preliminary path forward. With the recent emergence of exceedingly fast-activating

metathesis catalysts functional at sub-mol% loading,[40,41] the notion of carrying out such transformations at a large scale on a semicontinuous basis is a practical impossibility no longer. Beyond small molecules, the wide availability of small vinylic chlorides might prove useful as a means to reductively affix fluorovinyl-groups to large, and more complex molecules using Ni- or Pd-catalyzed cross-coupling.[56] For practitioners more interested in such molecules, the ready availability of such vinylic feedstocks should prove an attractive entry point. The list of possible crossover applications goes on, but I will not. In summary, despite being nearly a century old, the fluororefrigerant industry is not short on potential, and, thanks to an inexhaustible group of courageous inventors, chemists, engineers, and business developers, manages to retain its youthful and hopeful glow from the previous century. I am proud to have registered herein my modest contribution to it, and eagerly look forward to whatever lies ahead, not only for my own research, but more widely for this boundlessly innovative industry.



[56] Though it is possible to purchase many R^F-bearing precursors, commercial med-chem feedstocks bearing fluorinated *vinyl* groups are uncommon, and must typically be synthesized in the lab for testing.

6.6 References

(1) Wu, R.; Wang, X.; Cheng, L.; Ren, C.; Wei, X.; Zhang, X. Experimental and Theoretical Studies on the Thermal Decomposition of: Trans -1-Chloro-3,3,3-Trifluoropropene and 2-Chloro-3,3,3-Trifluoropropene and Their Fire-Extinguishing Performance. *New J. Chem.* **2020**, *44*, 12932–12941.

(2) Taniguchi, T.; Okamoto, H.; Furuta, S.; Takeuchi, Y. Composition Containing Trifluoroethylene. US 10,081,749 B2, 2018.

(3) (AGC). Technical information of AMOLEA X, Y series. https://www.agc-chemicals.com/file.jsp?id=30035 (accessed Jul 20, 2021).

(4) Fukushima, M.; Mitsuoka, H.; Tasaka, M. Composition for Heat Cycle System, and Heat Cycle System. US 10,851, 2020.

(5) Fukushima, M. Working Fluid for Heat Cycle, Composition for Heat Cycle System, and Heat Cycle System. US 10,975,280 B2, 2021.

(6) Feiring, A. E.; Hulbert, J. D. Trifluoroethylene Deflagration. *Chem. Eng. News* **1997**, *75*, 6.

(7) Taniguchi, T.; Furuta, S. Method for Producing 1-Chloro-1,2-Difluoroethylene. JP Appl. 2015-120670 A, 2013.

(8) Usui, T. Method for Producing 1,2-Dichloro-1,2-Difluoroethane (HCFC-132), Method for Producing 1-Chloro-1,2-Difluoroethylene (HCFO-1122a), and Method for Separating HCFC-132. JP 6,610,625 B2.

(9) Yates, S. F.; Harnish, D. F.; Smith, A. M. Process for Removing 2-Chloro-1,1-Difluoroethylene from 1,1,1,2-Tetrafluoroethane and Co-Producing 2-Chloro-1,1,1,2-Tetrafluoroethane. 5,336,377, 1994.

(10) Mather, J. D.; Tapscott, R. E. *NIST SP - 984-4: Environmentally Acceptable Flame Extinguishants*; Gaithersburg, MD, 2005.

(11) Midgley, T. J.; Henne, A. L.; McNary, R. R. Improvements in or Relating to Refrigeration. GB 357,263, 1930.

(12) Minor, B. H.; Waterland, R. L. Compositions Comprising E-1,2-Difluoroethylene and Uses Thereof. US 8,961,811 B2, 2015.

(13) Minor, B. H.; Waterland, R. L. Compositions Comprising Z-1,2-Difluoroethylene and Uses Thereof. US 8,961,812 B2, 2015.

(14) Takagi, Y.; Otsuka, T. Method of Producing 1,2-Dichloro-1,2-Difluoroethylene and 1,2-Difluoroethylene. JP Appl. 2013-237624 A, 2013.

(15) Taniguchi, T.; Furuta, S. Method for Producing 1,2-Difluoroethylene. JP Appl. 2016-56132 A, 2016.

(16) Komatsu, Y. Method for Preparing 1,2-Difluoroethylene and/or 1,1,2-Trifluoroethane. US Appl. 2021/0163381 A1, 2021.

(17) Trane to conduct field trials on R466A https://www.coolingpost.com/world-news/trane-to-conduct-field-trials-on-r466a/ (accessed Jul 20, 2021).

(18) Devecioğlu, A. G.; Oruç, V. Energetic Performance Analysis of R466A as an Alternative to R410A in VRF Systems. *Eng. Sci. Technol. an Int. J.* **2020**, *23*, 1425–1433.

(19) Sekiya, A.; Misaki, S. The Potential of Hydrofluoroethers to Replace CFCs, HCFCs and

PFCs. *J. Fluor. Chem.* **2000**, *101*, 215–221.
(20) Tsai, W. T. Environmental Risk Assessment of Hydrofluoroethers (HFEs). *J. Hazard. Mater.* **2005**, *119*, 69–78.
(21) Klug, D. L.; Minor, B. H.; Patron, D. M.; Chisolm-Carter, T.; Sievert, A. C. Compositions of a Hydrofluoroether and a Hydrofluorocarbon. US 6,905,630 B2, 2005.
(22) Minor, B. H.; Chisolm, T. E. C.; Shealy, G. S. Azeotrope(like) Compositions with Fluoromethyl Trifluoromethyl Ether and Dimethyl Ether. US 5,607,616, 1997.
(23) Zakhidov, A. A.; Lee, J. K.; Fong, H. H.; DeFranco, J. A.; Chatzichristidi, M.; Taylor, P. G.; Ober, C. K.; Malliaras, G. G. Hydrofluoroethers as Orthogonal Solvents for the Chemical Processing of Organic Electronic Materials. *Adv. Mater.* **2008**, *20*, 3481–3484.
(24) Govaerts, F.; Keane, D. D. Using Hydrofluoroether Solvents to Replace HCFC-141b, Part I. *Med. Device Technol.* **2001**, *12*, 31–34.
(25) Govaerts, F.; Keane, D. D. Using Hydrofluoroether Solvents to Replace HCFC-141b, Part II. *Med. Device Technol.* **2001**, *12*, 28–30.
(26) Hošek, J.; Šimůnek, O.; Lipovská, P.; Kolaříková, V.; Kučnirová, K.; Edr, A.; Štěpánková, N.; Rybáčková, M.; Cvačka, J.; Kvíčala, J. Medium Fluorous Separation Using Hydrofluoroether and Weakly Polar Solvents for Environmentally Friendly Recycling of Catalysts. *ACS Sustain. Chem. Eng.* **2018**, *6*, 7026–7034.
(27) Cooper, D. L.; Cunningham, T. P.; Allan, N. L.; McCulloch, A. Tropospheric Lifetimes of Potential CFC Replacements: Rate Coefficients for Reaction with the Hydroxyl Radical. *Atmos. Environ. Part A, Gen. Top.* **1992**, *26*, 1331–1334.
(28) Owens, J. G. (3M S. M. Low GWP Alternatives to HFCs and PFCs John G. Owens. *Proc. 1999 Taipei Int. Conf. Atmos. Prot.* **1999**.
(29) Rached, W.; Devic, M. Refrigerant Fluid Containing Cyclic Diether. WO Appl. 2008/104648 A2, 2008.
(30) Hösl, A.; Pachin, J.; Chachereau, A.; Kornath, A.; Franck, C. M. Perfluoro-1,3-Dioxolane and Perfluoro-Oxetane: Promising Gases for Electrical Insulation. *J. Phys. D. Appl. Phys.* **2019**, *52*.
(31) Powell, R. L.; Morrison, J. D. Compositions Useful as Refrigerants. WO Appl. 93/14173, 1993.
(32) Schulz, M.; Kourkoulas, D. Regulation (EU) No 517/2014 of the European Parliament and of the Council of 16 April 2014 on Fluorinated Greenhouse Gases and Repealing Regulation (EC) No 842/2006. *Off. J. Eur. Union* **2014**, *2014*, L150/195-230.
(33) Coyle, T. D.; Kings, R. B.; Pitcher, E.; Stafford, S. L.; Teichel, P.; Stone, F. G. A. A Novel Heterocyclic Cobalt Compound. *J. Inorg. Nucl. Chem.* **1961**, *20*, 172–173.
(34) Baker, R. T.; Beatty, R. P.; Farnham, W. B.; Wallace, R. L. J. Process for the Manufacture of Selected Halogenated Hydrocarbons Containing Fluorine and Hydrogen and Compositions Provided Therein. US 5,545,769, 1994.
(35) Burton, D. J.; Greenlimb, P. E. Olefination via Metal Dehalogenation of Phosphonium Salt. *J. Fluor. Chem.* **1973**, *3*, 447–449.
(36) Burton, D. J.; Shinya, S.; Howells, R. D. The Role of α and β Fluorine in Product Determination of Fluoro Olefin Tertiary-Phosphine Reactions. Ylide vs. Vinylphosphorane Formation. *J. Am. Chem. Soc.* **1979**, *101*, 3689–3690.
(37) Henne, A. L.; Waalkes, T. P. Fluorinated Derivatives of Propane and Propylene. VI. *J. Am. Chem. Soc.* **1946**, *68*, 496–497.

(38) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. Molybdenum Chloride Catalysts for Z-Selective Olefin Metathesis Reactions. *Nature* **2017**, *542*, 80–85.
(39) Takahira, Y.; Morizawa, Y. Ruthenium-Catalyzed Olefin Cross-Metathesis with Tetrafluoroethylene and Analogous Fluoroolefins. *J. Am. Chem. Soc.* **2015**, *137*, 7031–7034.
(40) Peeck, L. H.; Savka, R. D.; Plenio, H. Fast Olefin Metathesis at Low Catalyst Loading. *Chem. - A Eur. J.* **2012**, *18*, 12845–12853.
(41) Kos, P.; Savka, R.; Plenio, H. Fast Olefin Metathesis: Synthesis of 2-Aryloxy-Substituted Hoveyda-Type Complexes and Application in Ring-Closing Metathesis. *Adv. Synth. Catal.* **2013**, *355*, 439–447.

A-I

Appendix I

This appendix contains the NMR, X-Ray, and DFT information associated with the experimental section of **Chapter 3**. *In order of appearance.*

Figure AI-1. ^{19}F NMR of product 3.1a (282 MHz, C_6D_6)

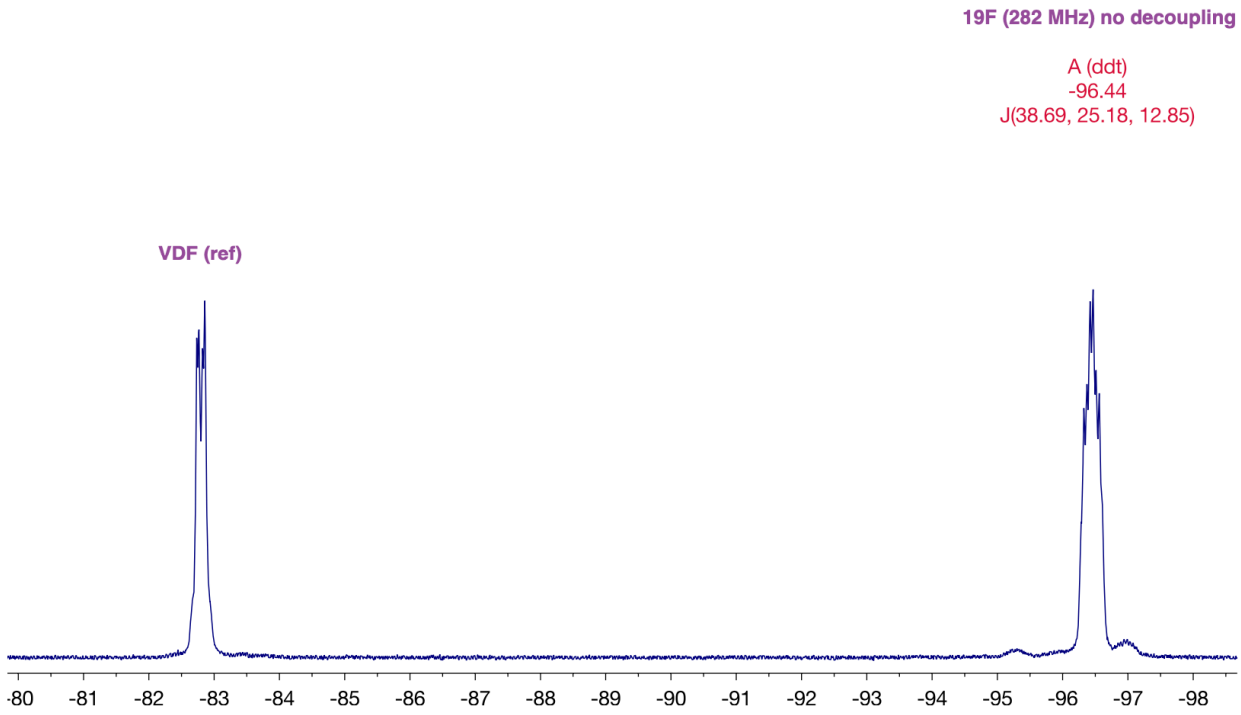


Figure AI-2. $^{31}P\{^1H\}$ NMR of product 3.1a (121 MHz, C_6D_6)

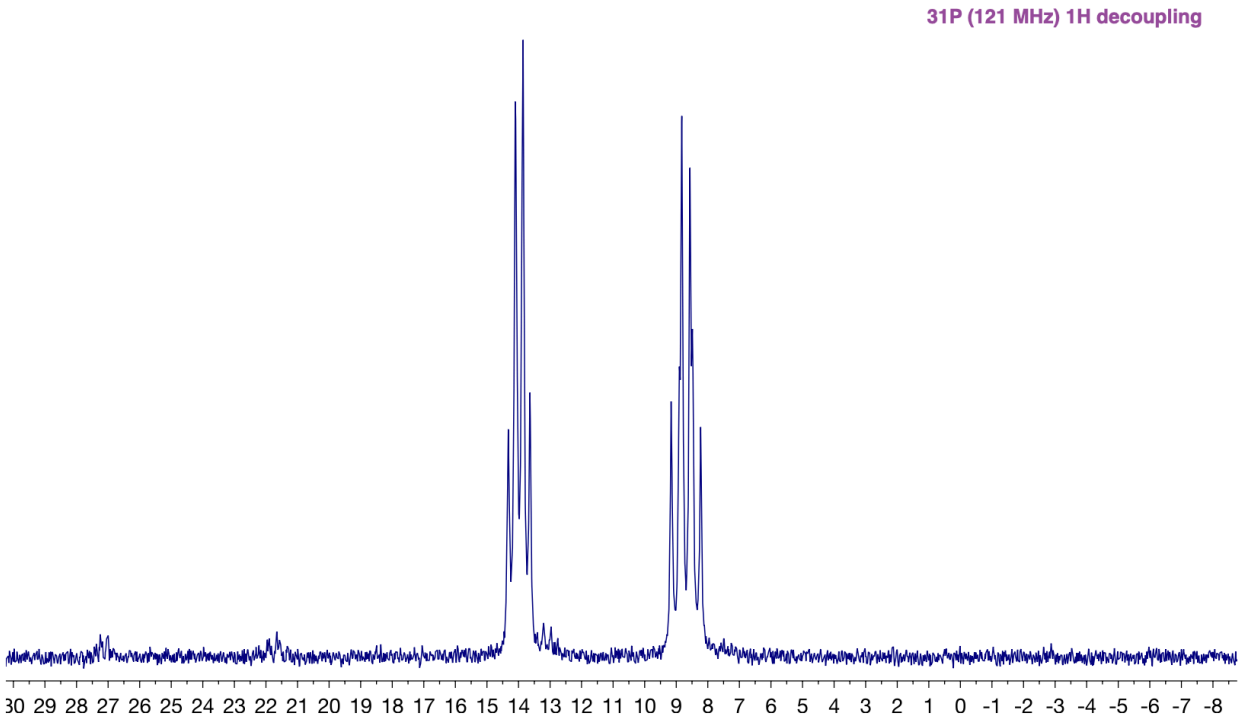


Figure AI-3. ^{19}F NMR of product 3.1b (282 MHz, C_6D_6)

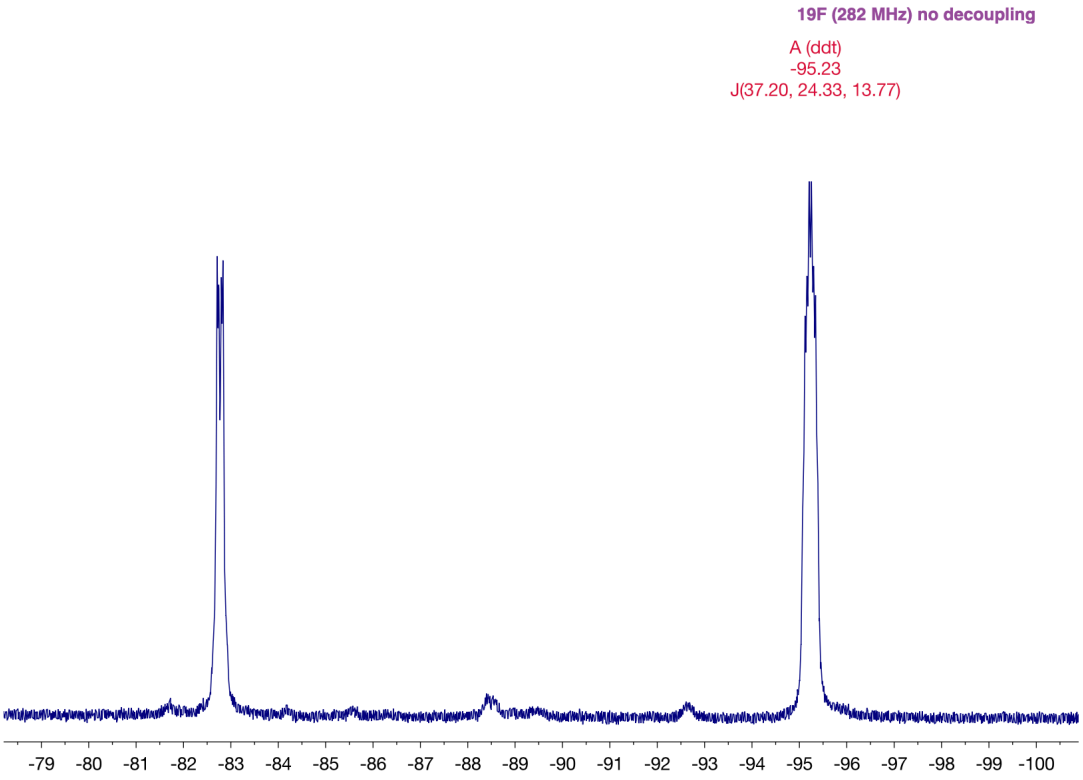


Figure AI-4. $^{31}P\{^{1}H\}$ NMR of product 3.1b (121 MHz, C_6D_6)

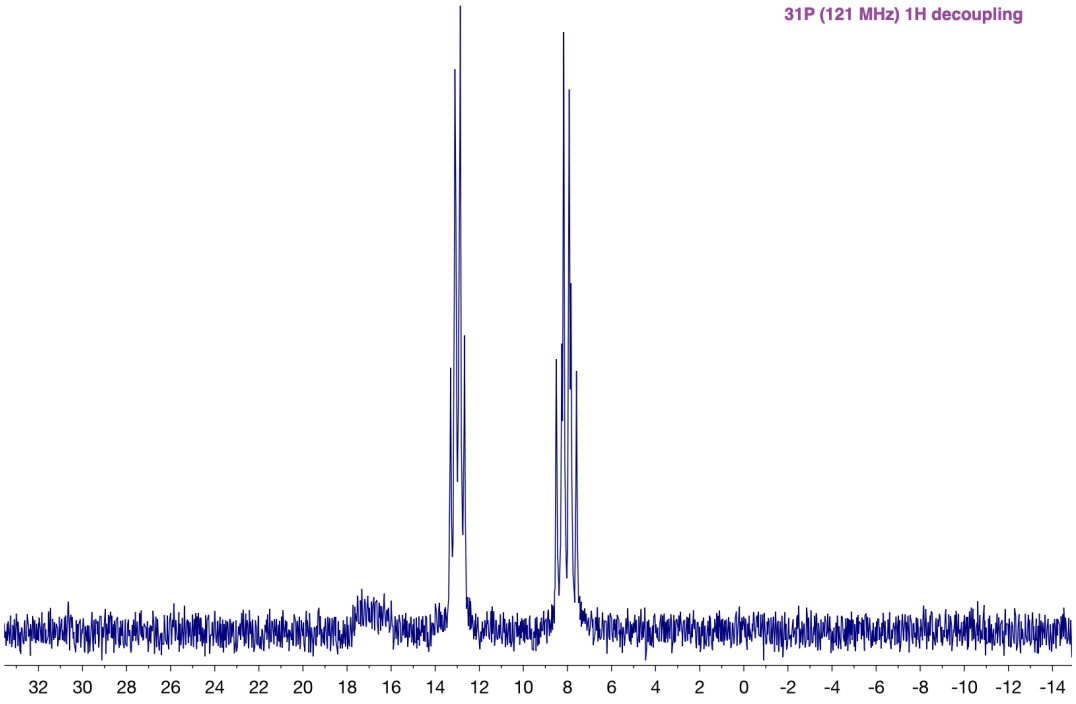


Figure AI-5. ^{19}F NMR of product 3.1c (282 MHz, C_6D_6)

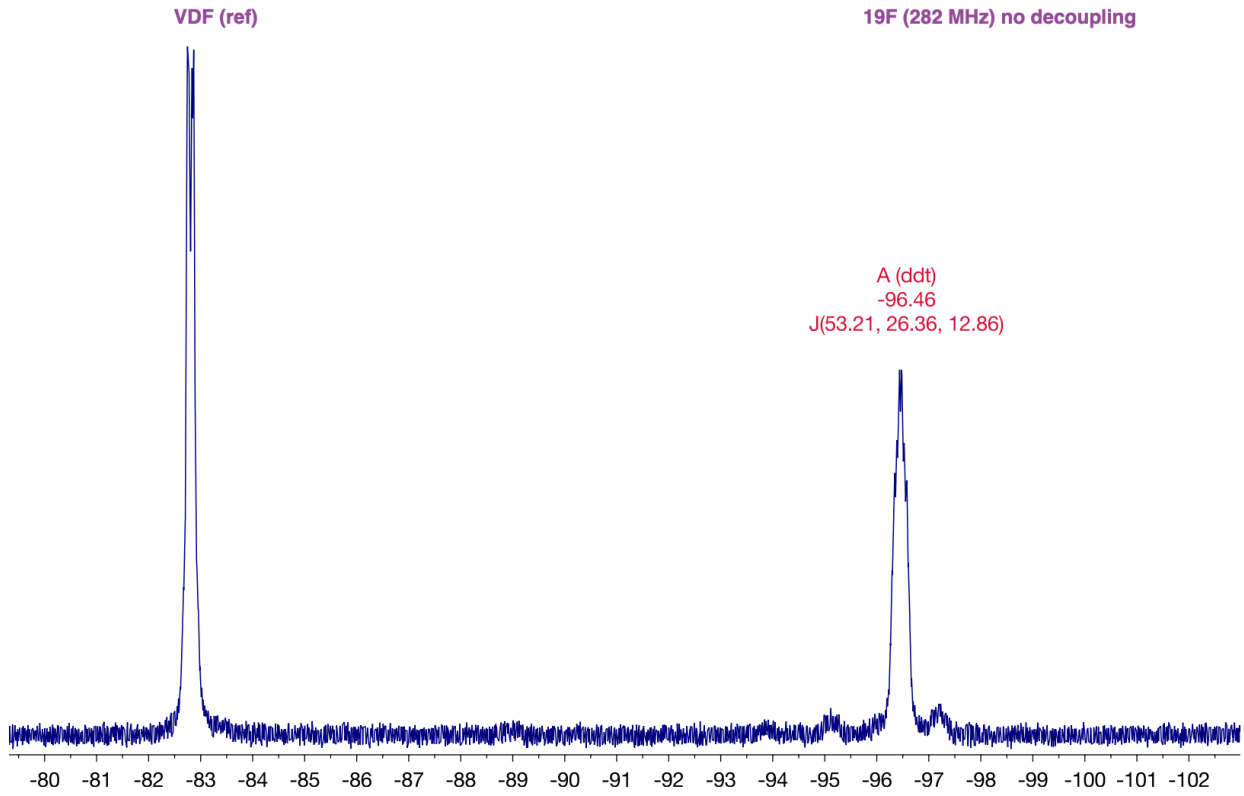


Figure AI-6. $^{31}P\{^{1}H\}$ NMR of product 3.1c (121 MHz, C_6D_6)

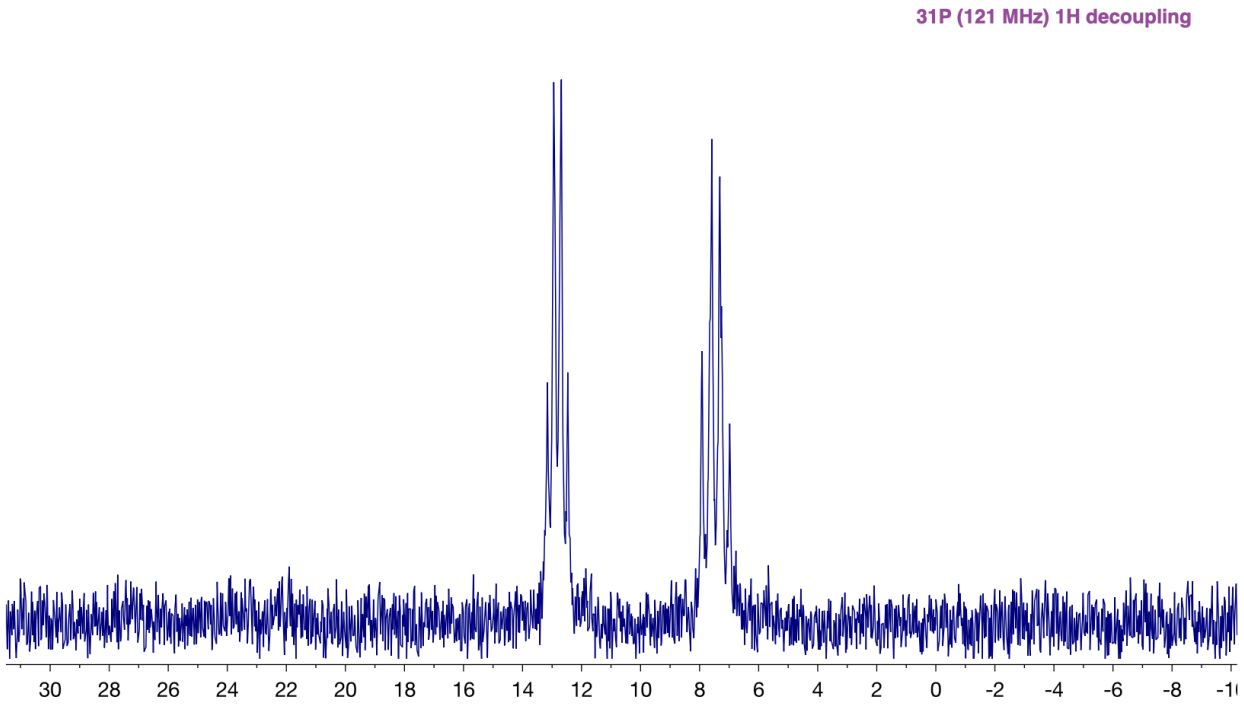


Figure AI-7. ^{19}F NMR of product **3.1d** (282 MHz, C_6D_6)

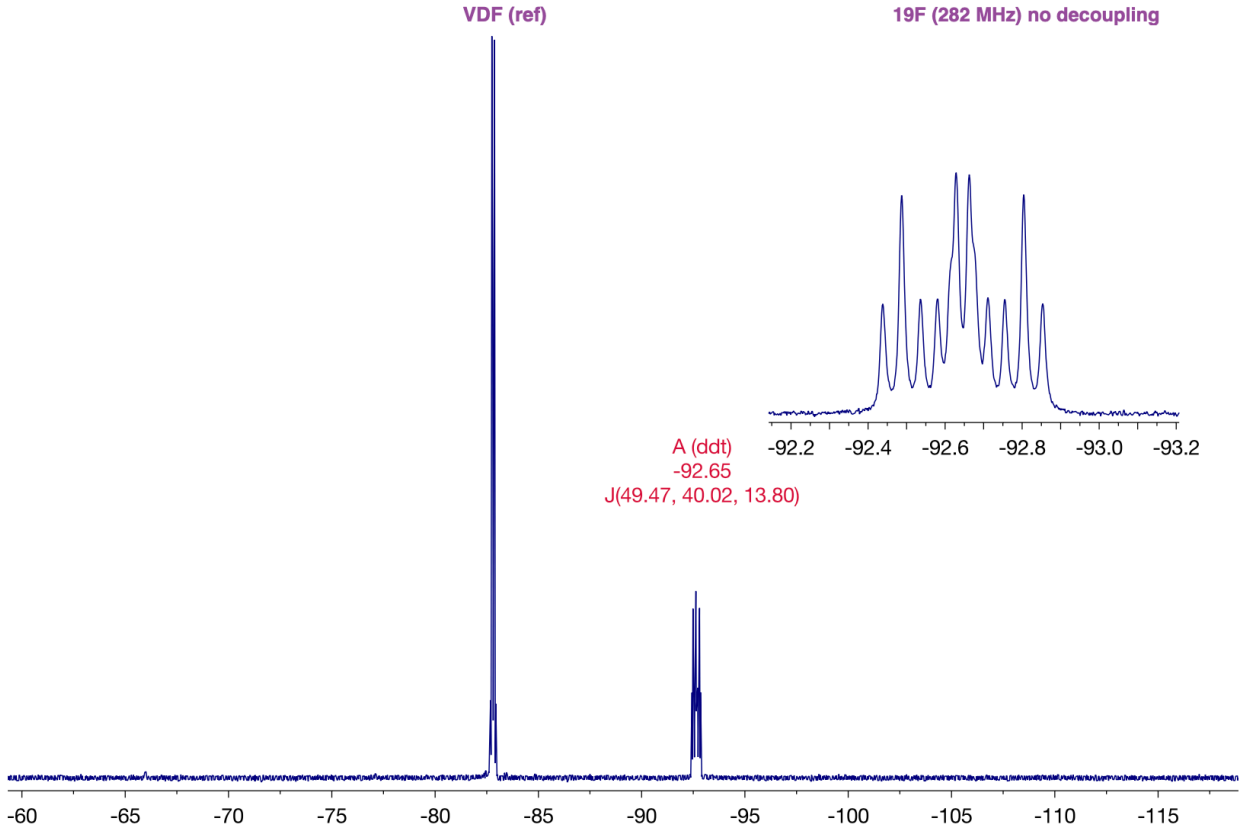


Figure AI-8. $^{31}P\{^1H\}$ NMR of product **3.1d** (121 MHz, C_6D_6)

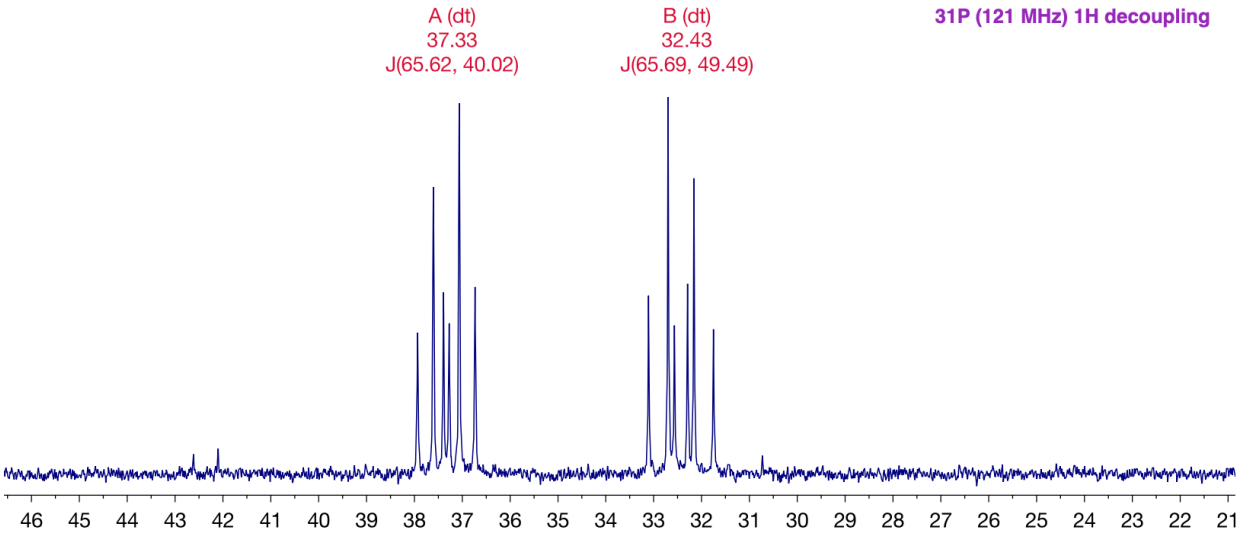


Figure AI-9. ^{19}F NMR of product **3.1e** (282 MHz, C_6D_6)

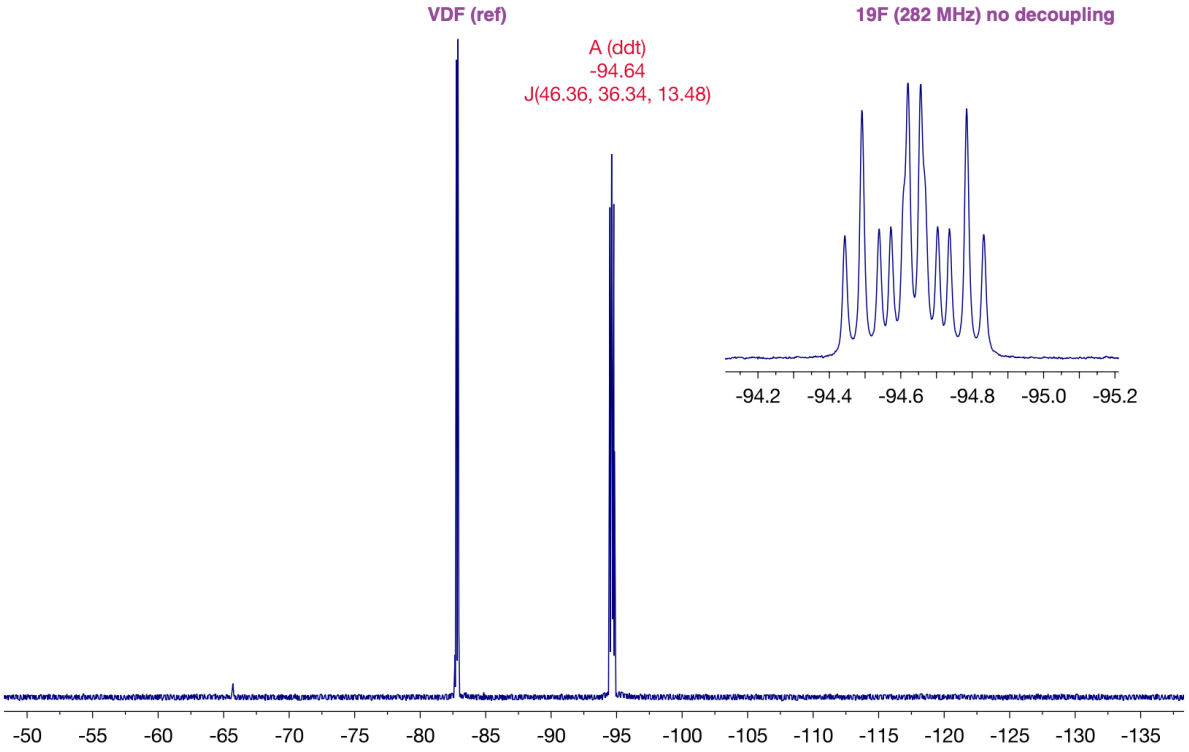


Figure AI-10. $^{31}P\{^{1}H\}$ NMR of product **3.1e** (121 MHz, C_6D_6)

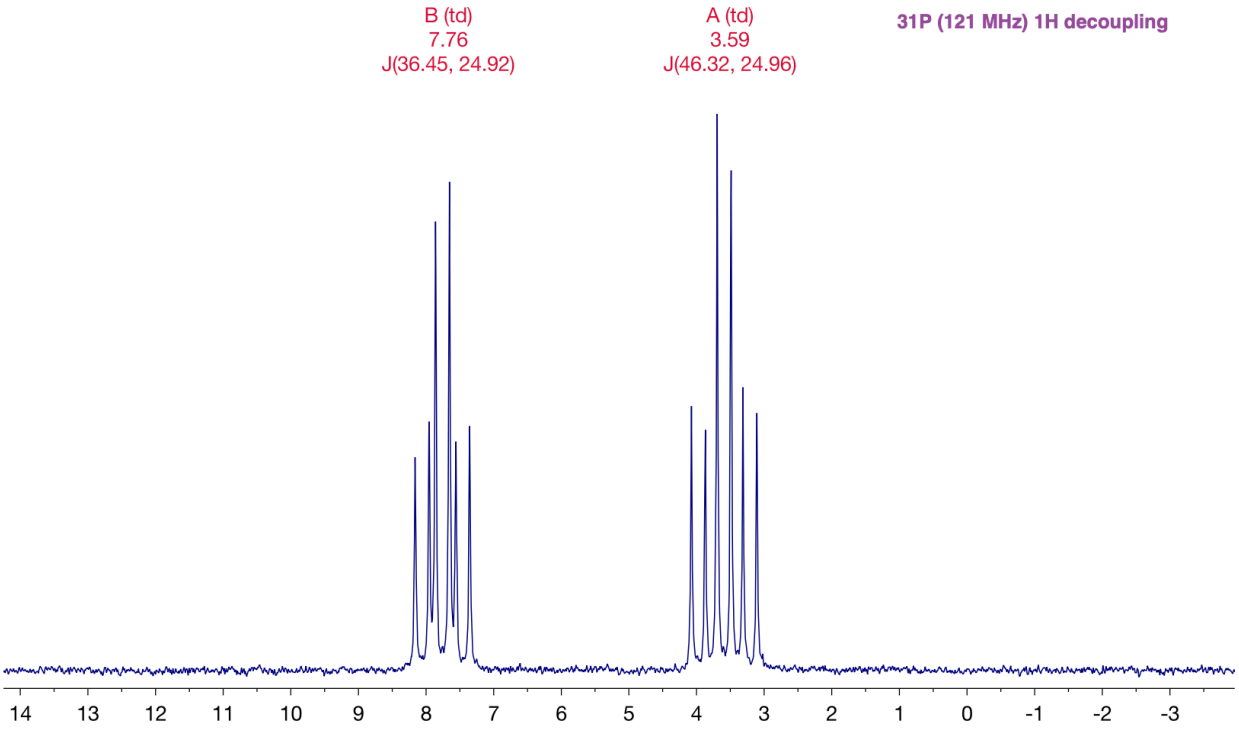


Figure AI-11. ^{19}F NMR of product 3.1f (282 MHz, C_6D_6)

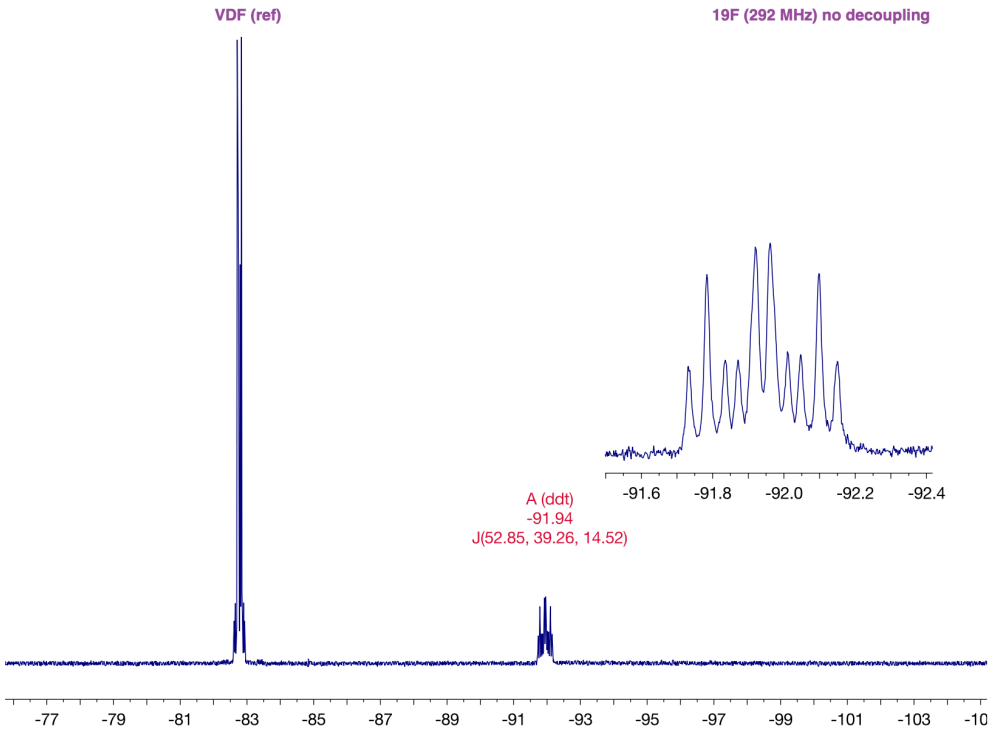


Figure AI-12. $^{31}P\{^{1}H\}$ NMR of product 3.1f (121 MHz, C_6D_6)

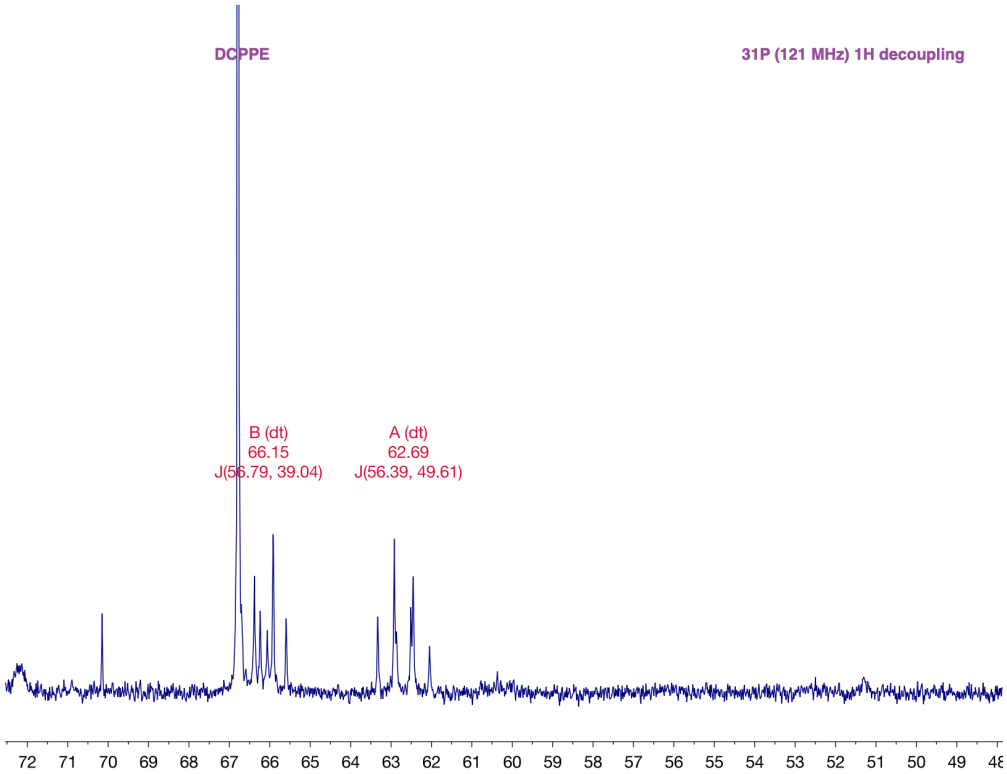


Figure AI-13. ^{19}F NMR of product 3.1g (282 MHz, C_6D_6)

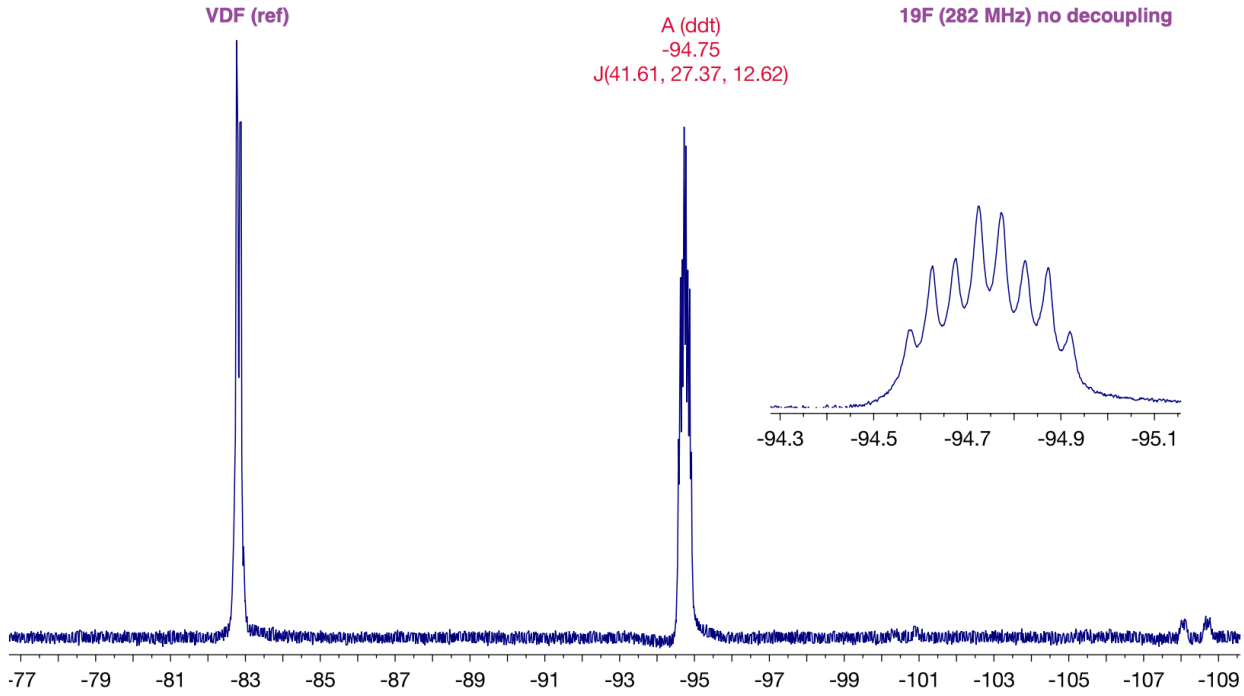


Figure AI-14. $^{31}P\{^{1}H\}$ NMR of product 3.1g (121 MHz, C_6D_6)

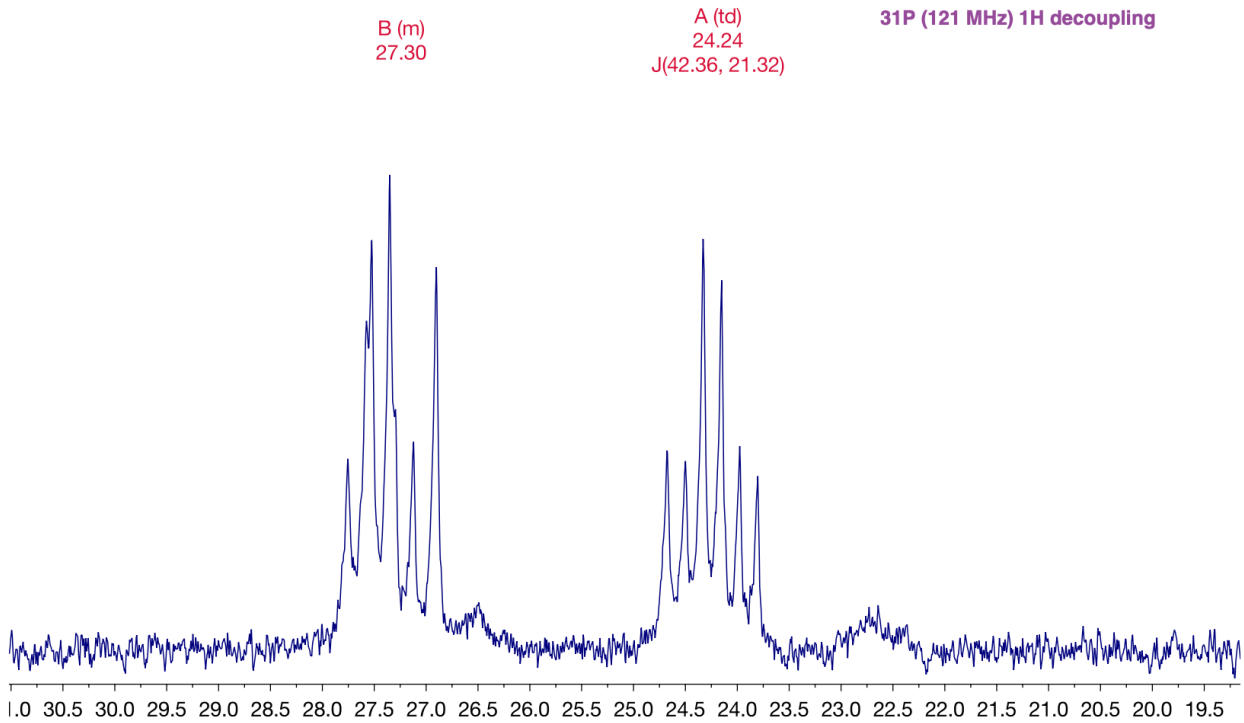


Figure AI-15. ^{19}F NMR of product 3.1h (282 MHz, C_6D_6)

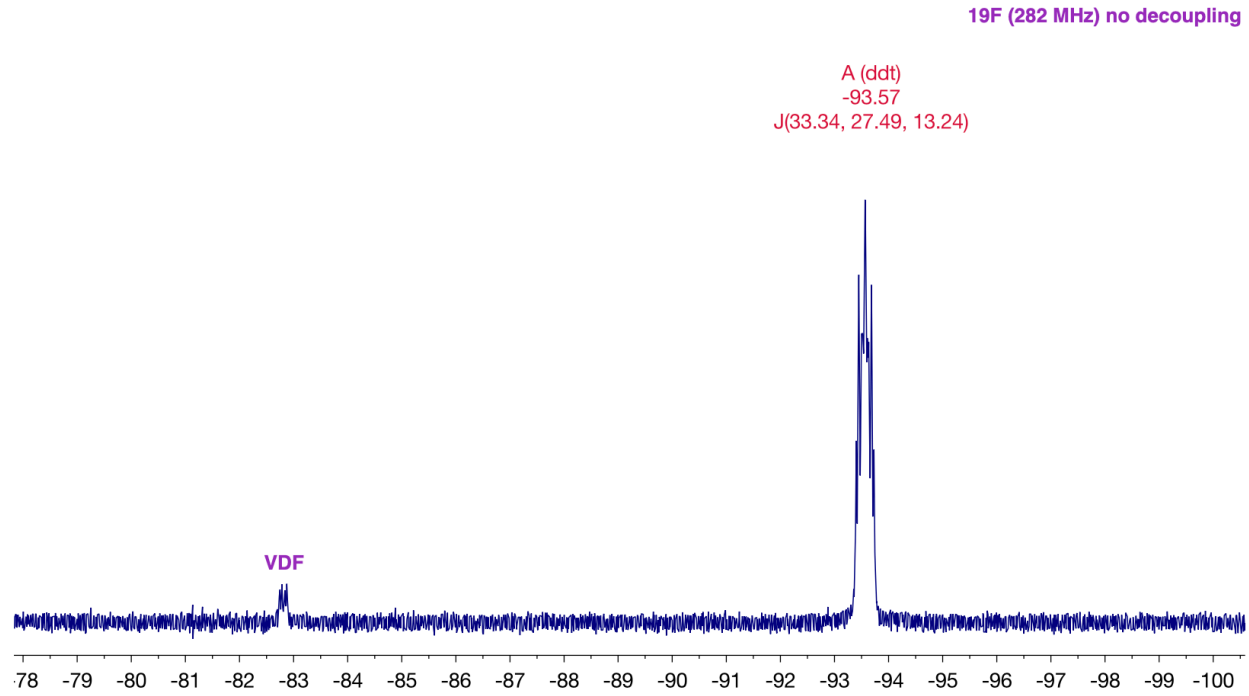


Figure AI-16. $^{31}P\{^{1}H\}$ NMR of product 3.1h (121 MHz, C_6D_6)

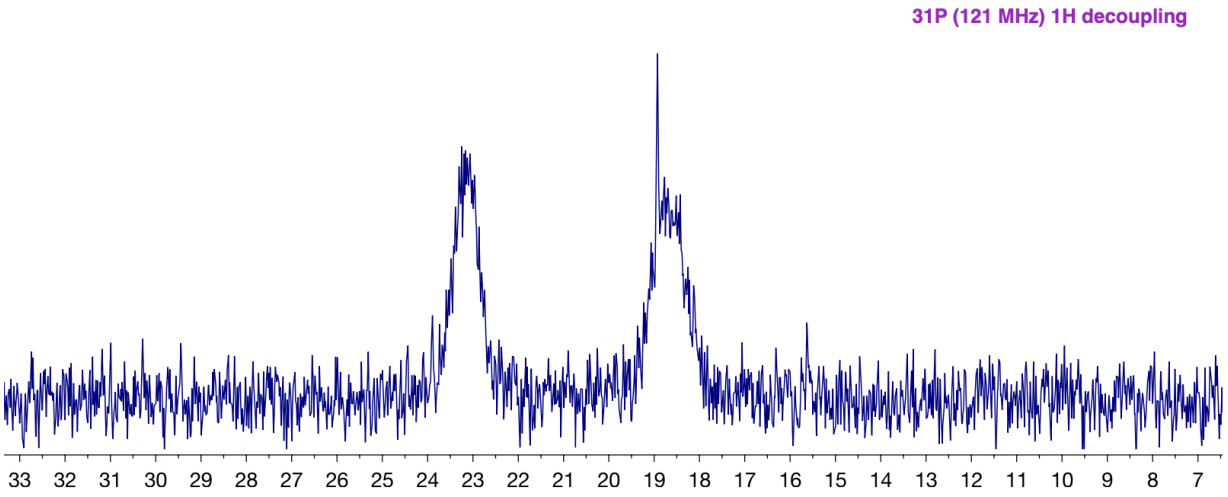


Figure AI-17. ^{19}F NMR of product 3.2a (376 MHz, C_6D_6)

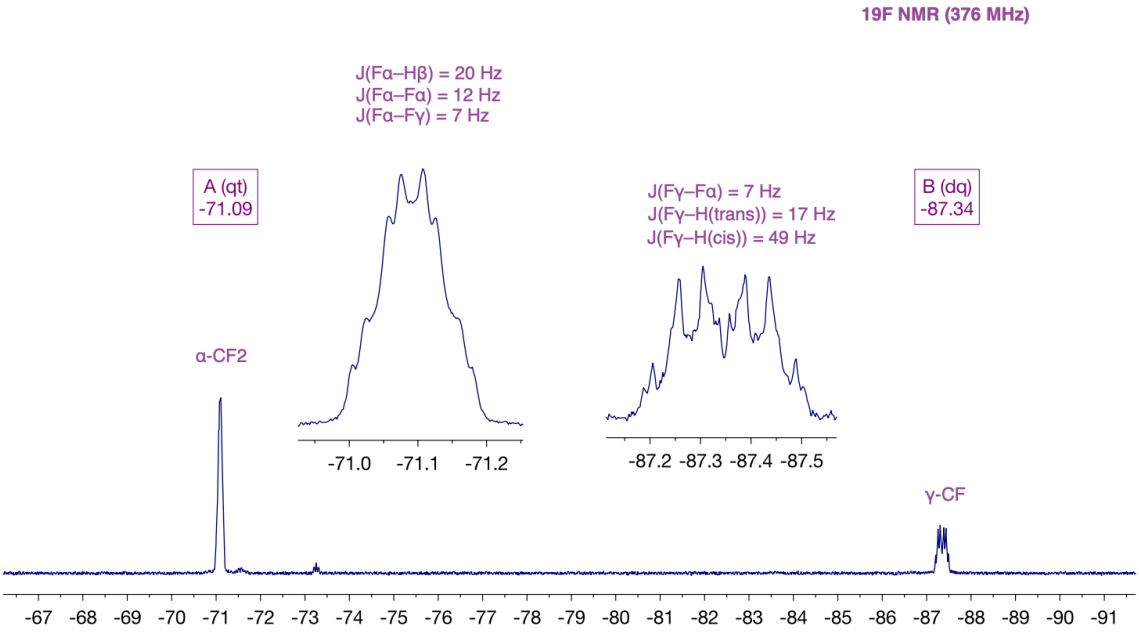


Figure AI-18. ^{1}H NMR of product 3.2a (400 MHz, C_6D_6)

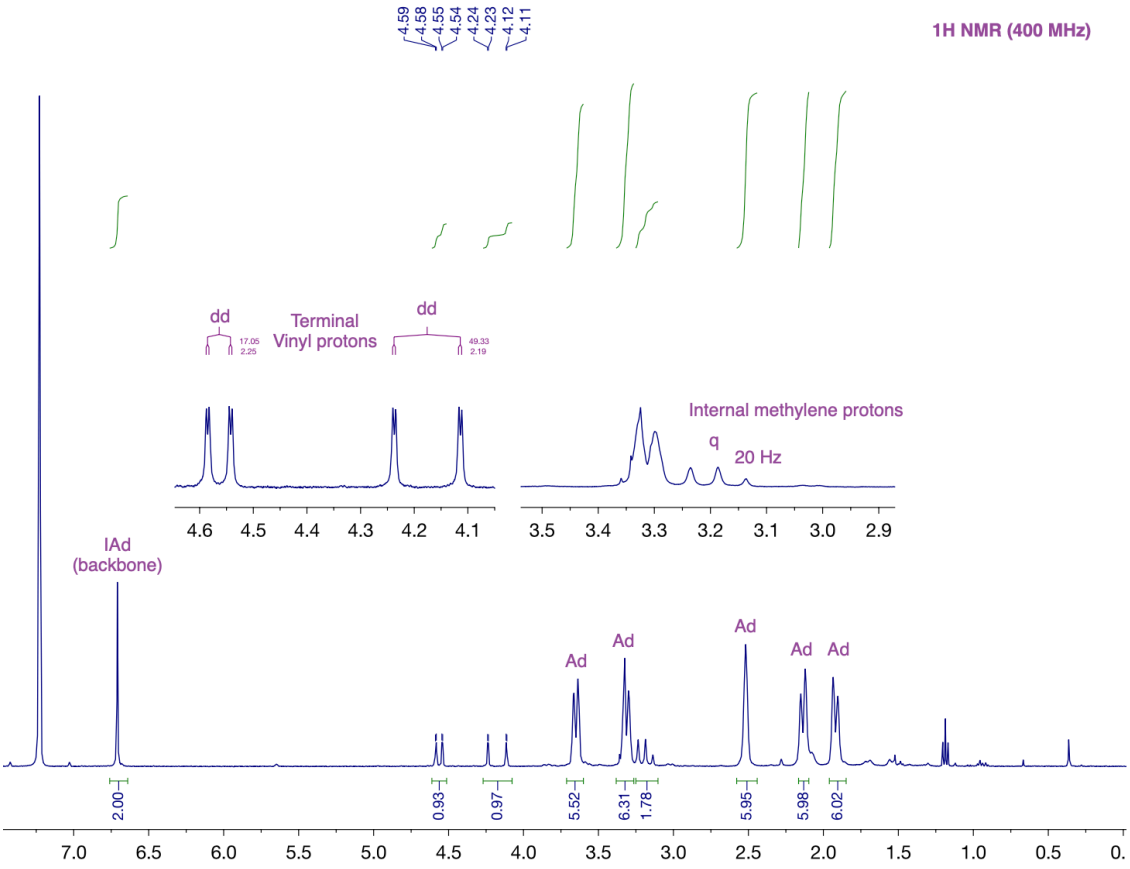


Figure AI-19. ^{19}F NMR of product 3.2b (282 MHz, C_6D_6)

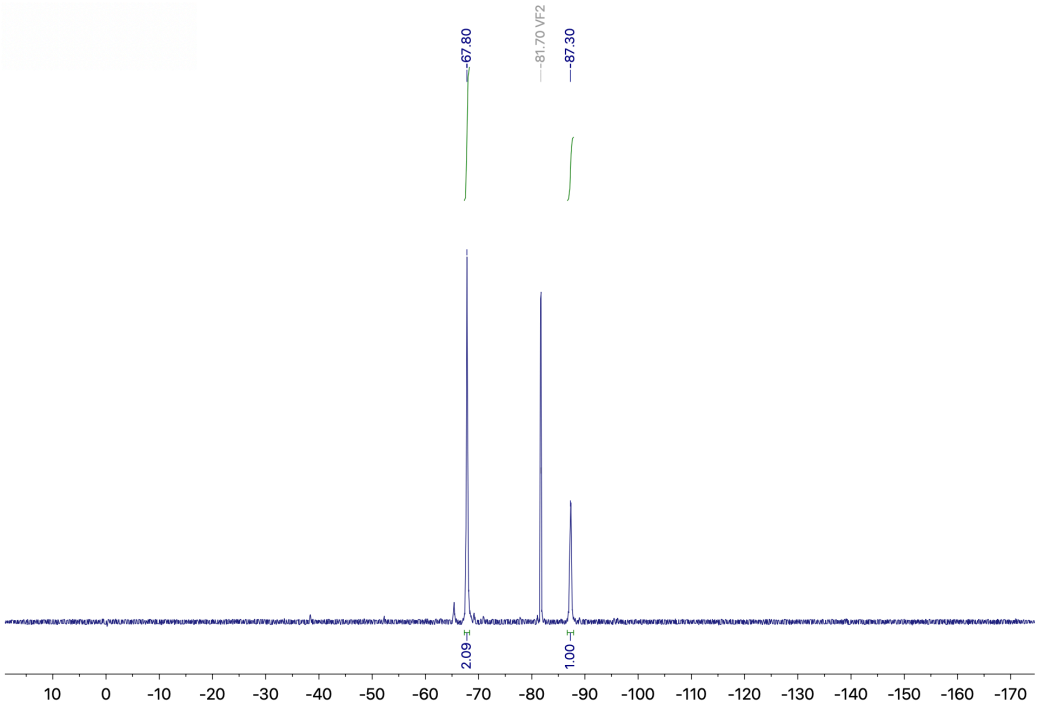


Figure AI-20. ^{19}F NMR of product 3.2b (Ni–F region) (282 MHz, C_6D_6)

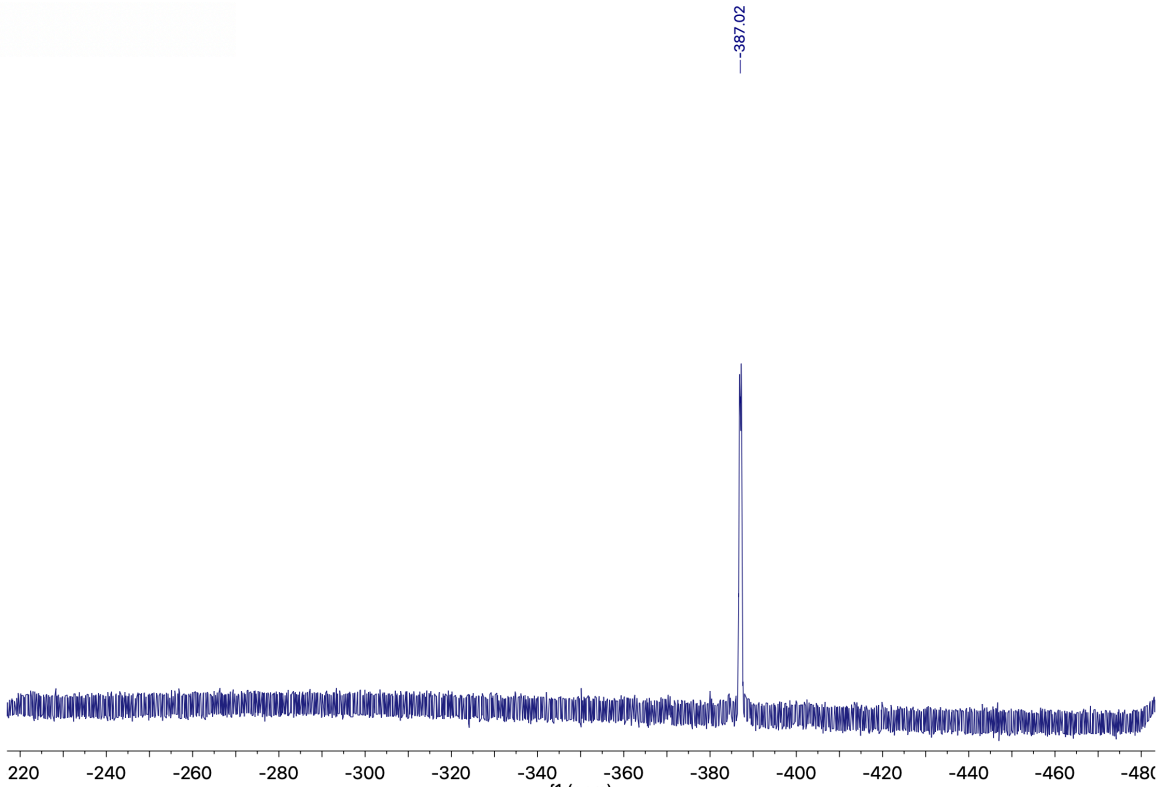


Figure AI-21. $^{31}P\{^{1}H\}$ NMR of product 3.2b (121 MHz, C_6D_6)

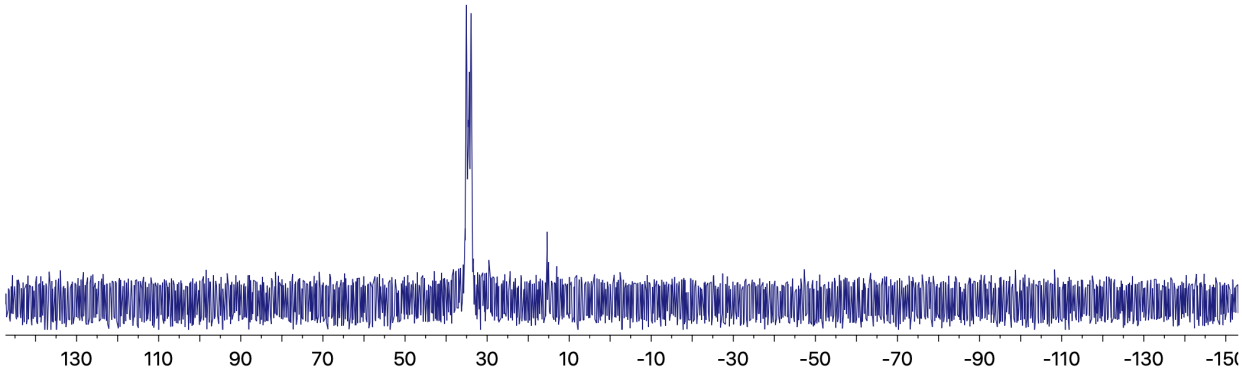


Figure AI-22. ^{19}F NMR of product 3.2c (282 MHz, C_6D_6)

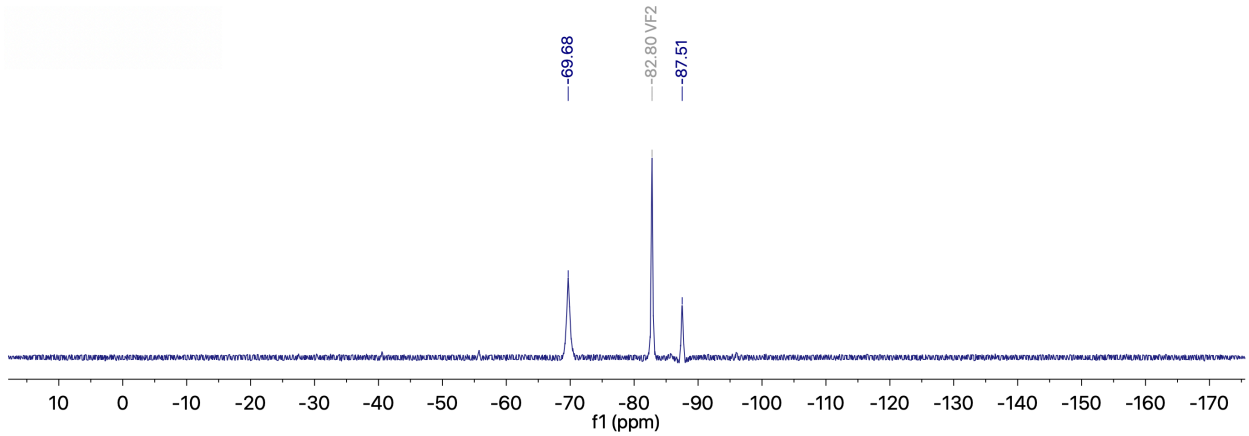


Figure AI-23. ^{19}F NMR of product 3.2c (Ni–F region) (282 MHz, C_6D_6)

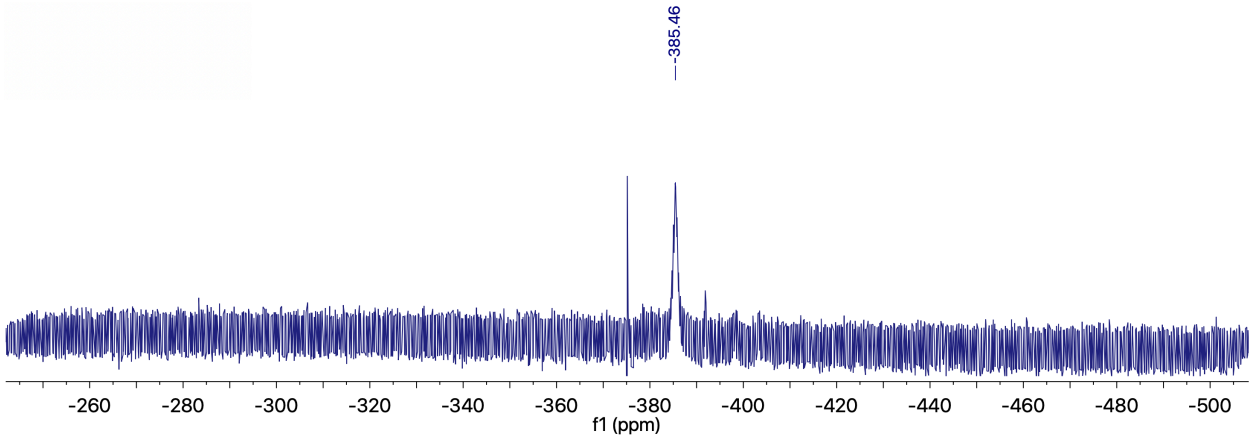


Figure AI-24. ^{19}F NMR of products 3.1i/3.1i' (282 MHz, C_6D_6)*

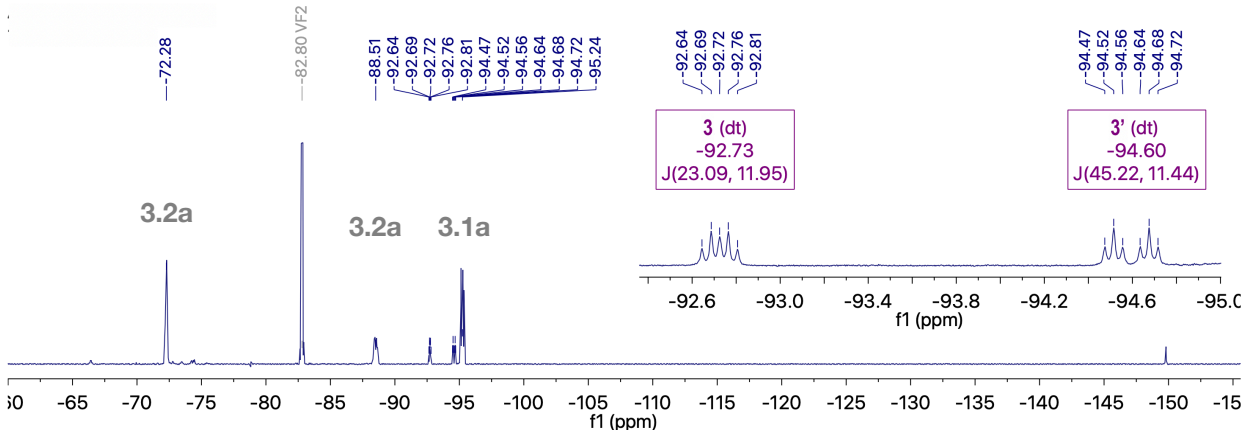
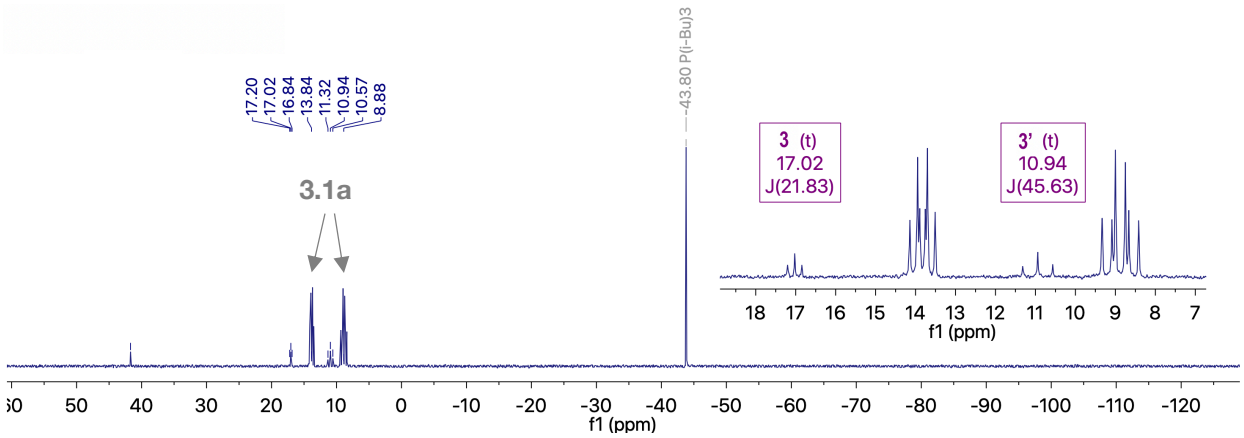
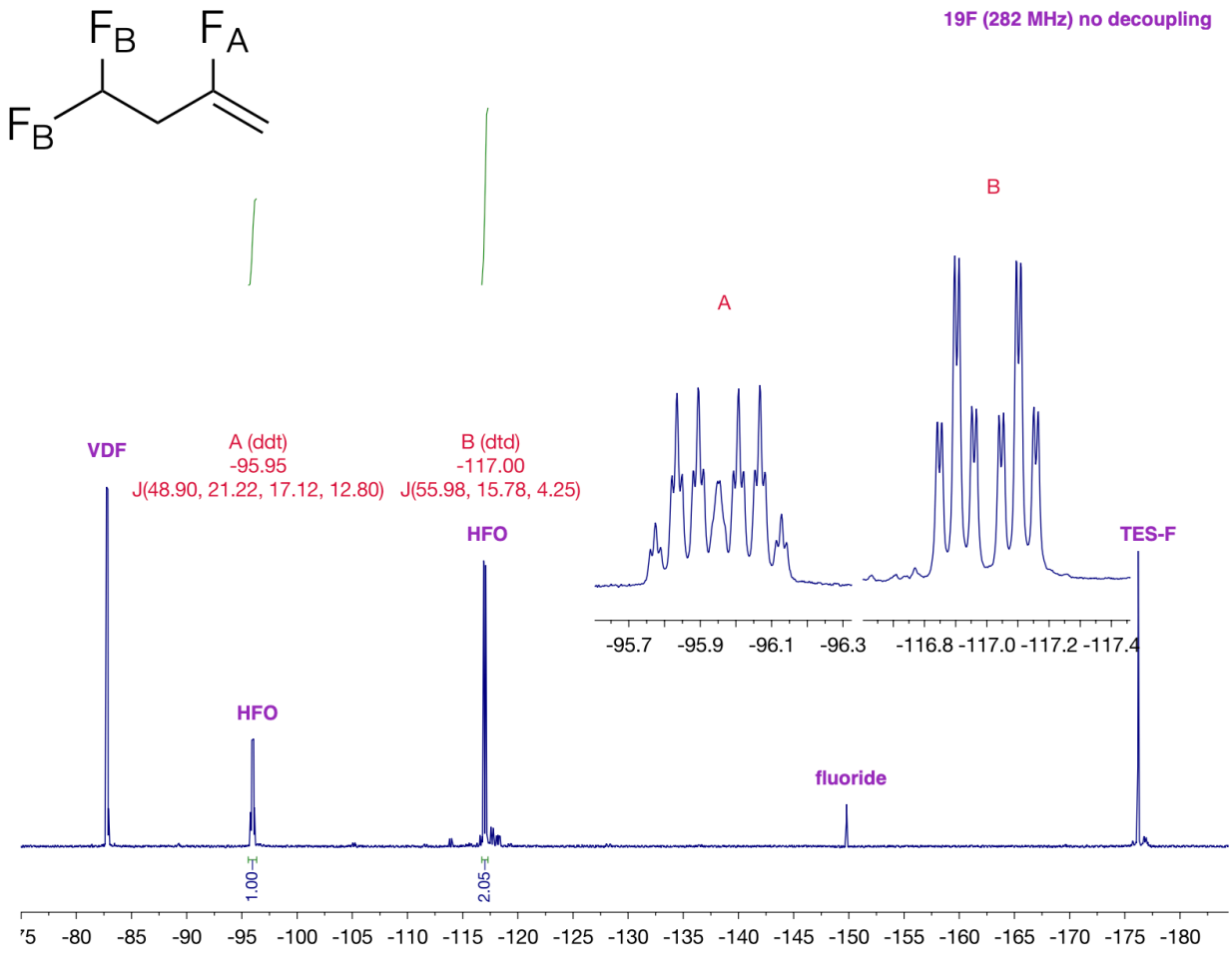


Figure AI-25. $^{31}P\{^1H\}$ NMR of products 3.1i/3.1i' (181 MHz, C_6D_6)*



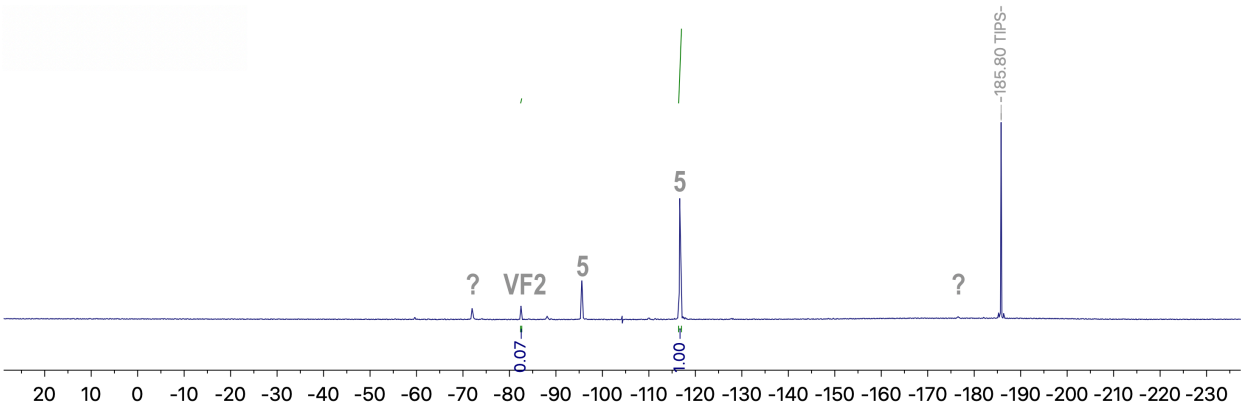
* NB: In these schemes (formatted for publication), the compound numbers 3 and 3' correspond to **3.1i** and **3.1i'**, respectively.

Figure AI-26. ^{19}F NMR of HFO-1363pfy (282 MHz, C_6D_6)*



* Taken after 45 minutes of Ni-catalyzed HDFD using TES-H. See experimental entry 17 in ***Section 3.10***.

Figure AI-27. ^{19}F NMR of Table 3.6.1, ex. 1 (282 MHz, C_6D_6)*



* Compound **1363pfy** labeled here as **5**

Figure AI-28. ^{19}F NMR of Table 3.6.1, ex. 2 (282 MHz, C_6D_6)*

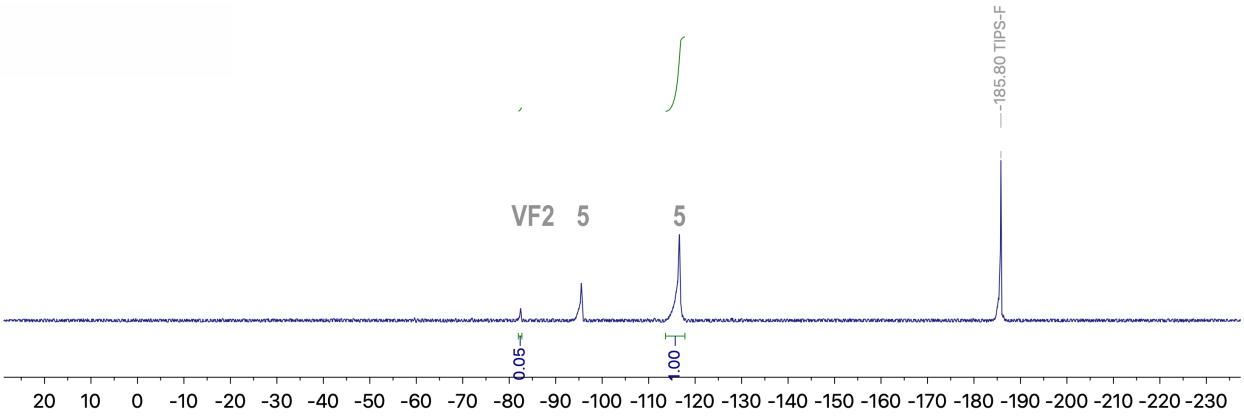


Figure AI-29. ^{19}F NMR of Table 3.6.1, ex. 3 (282 MHz, C_6D_6)*

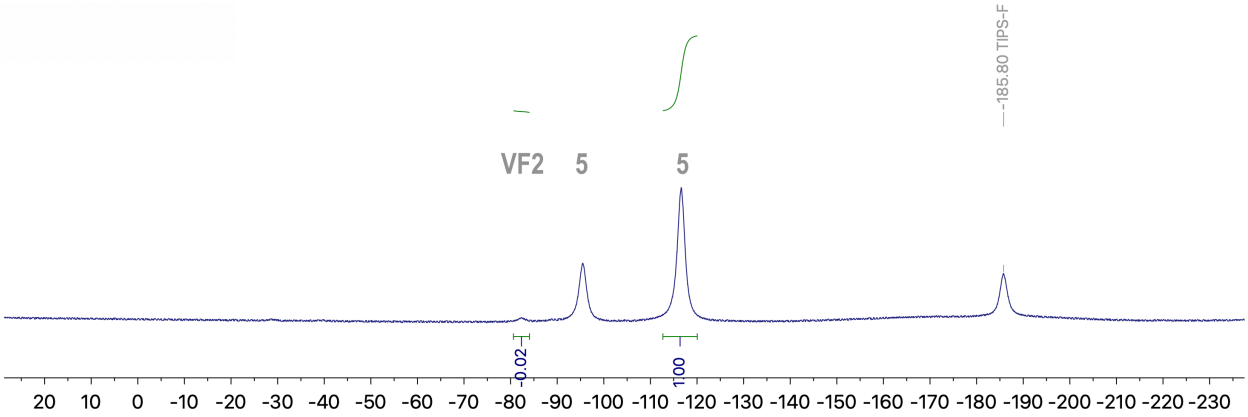


Figure AI-30. ^{19}F NMR of Table 3.6.1, ex. 4 (282 MHz, C_6D_6)*

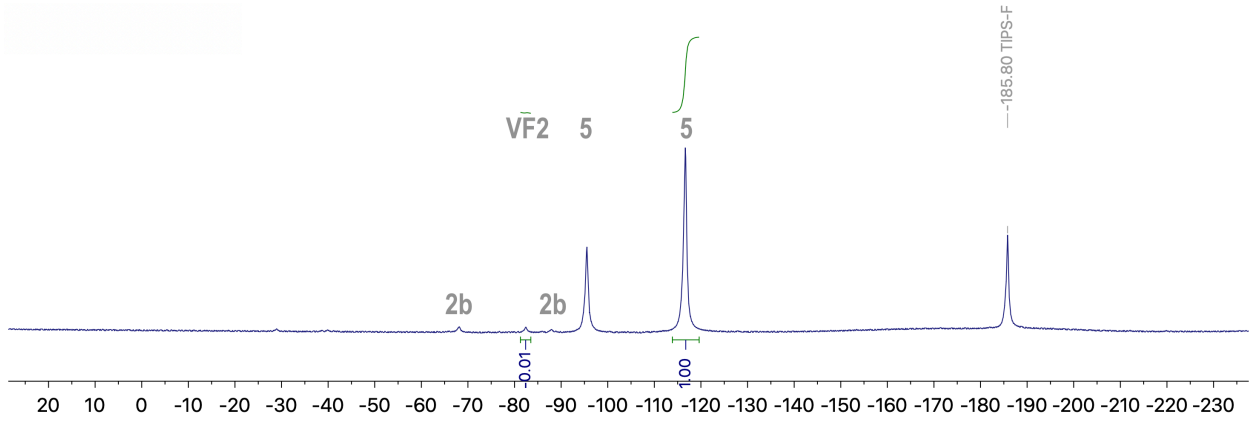


Figure AI-31. ^{19}F NMR of Table 3.6.1, ex. 5 (282 MHz, C_6D_6)*

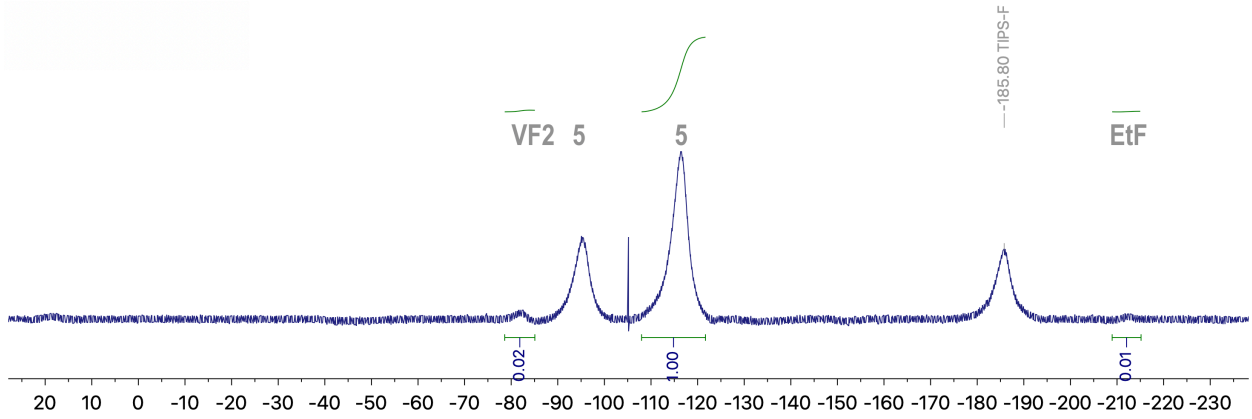


Figure AI-32. ^{19}F NMR of Table 3.6.1, ex. 6 (282 MHz, C_6D_6)*

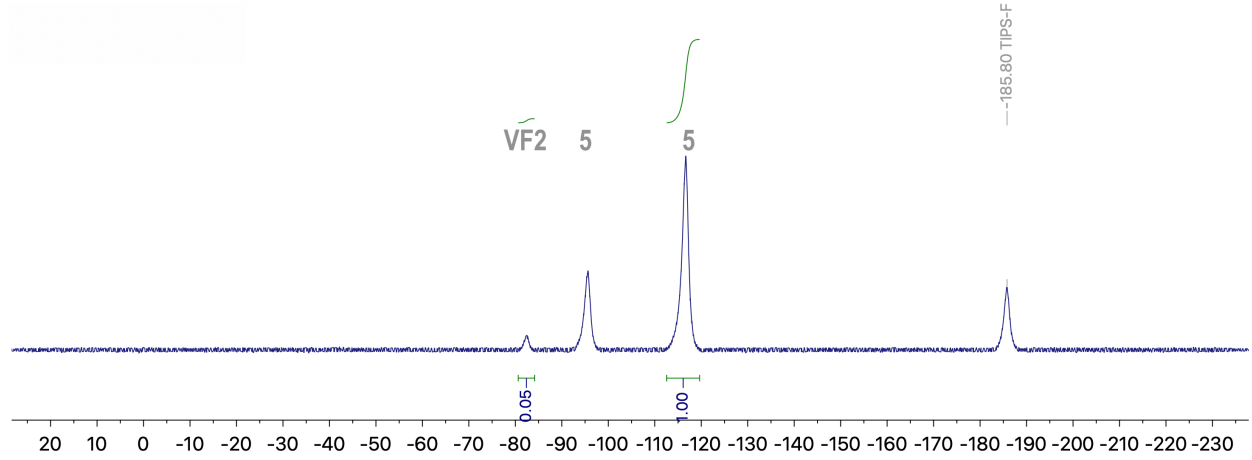


Figure AI-33. ^{19}F NMR of Table 3.6.1, ex. 7 (282 MHz, C_6D_6)*

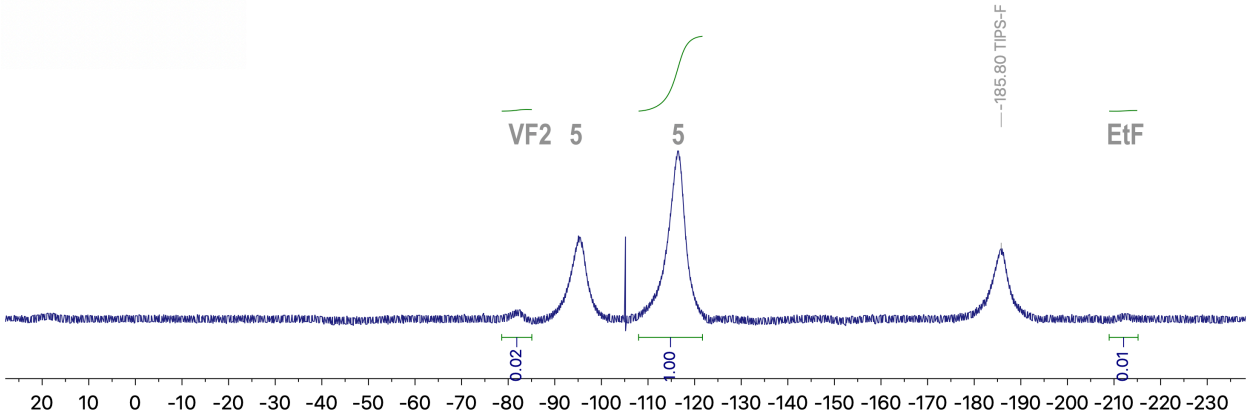


Figure AI-34. ^{19}F NMR of Table 3.6.1, ex. 8 (282 MHz, C_6D_6)*

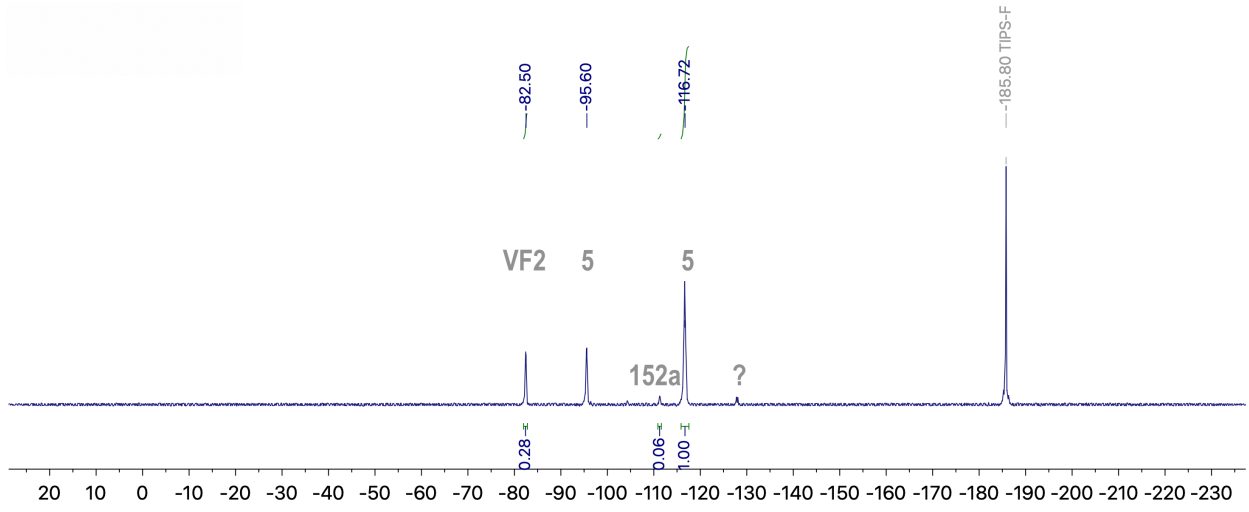
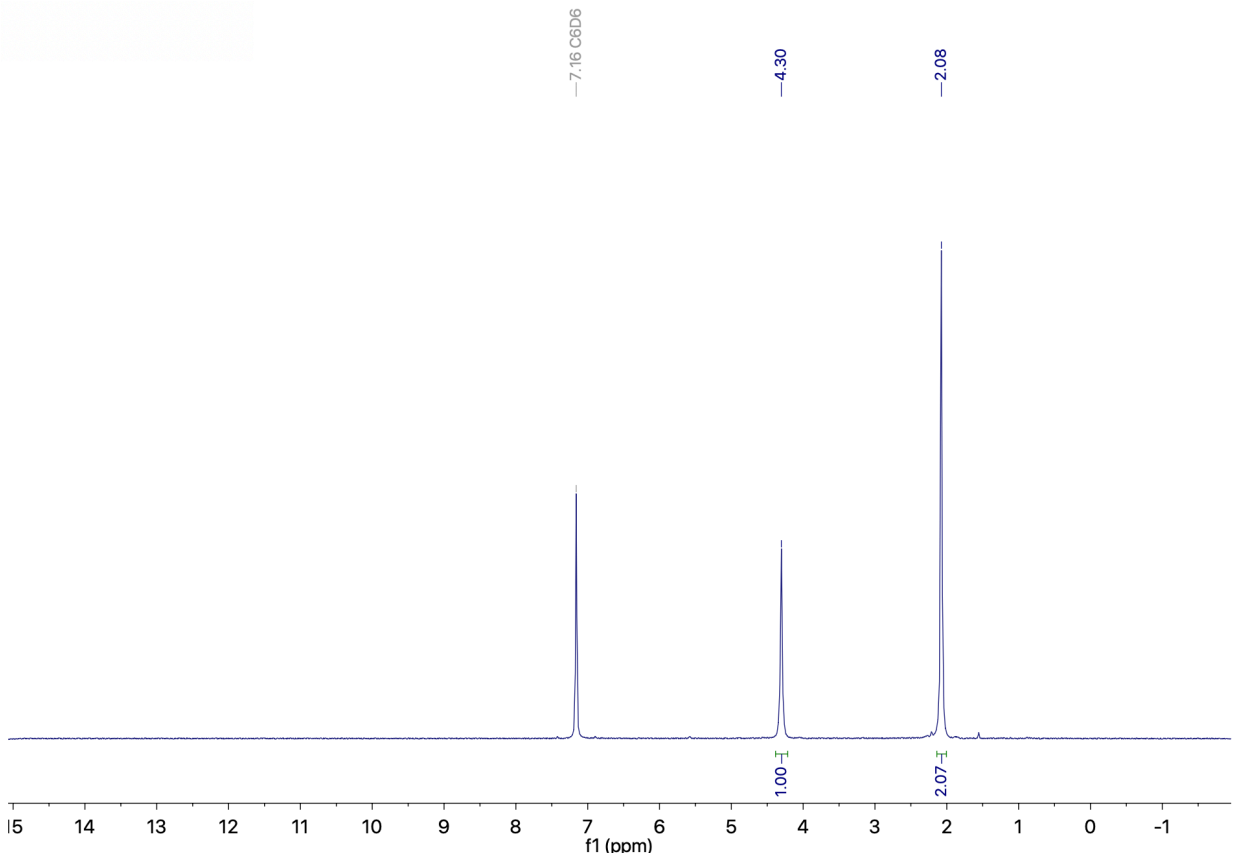


Figure AI-35. ^{1}H NMR of Ni(cod)$_2$ (Table 3.5.1, ex. 5, 282 MHz, C_6D_6)



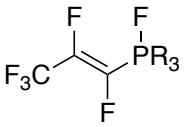
A-II

Appendix II

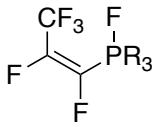
This appendix contains the NMR spectra associated with the experimental section of **Chapter 4**.

Note to the reader:

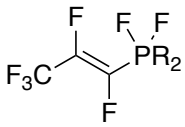
The spectra provided in this section are copied from the electronic supplementary information (ESI) of the paper in which this work was originally drafted. The spectra themselves are annotated using the compound numbering system from same, and thus do not match exactly the numbering system used in this thesis. For the reader's greater ease of interpretation, the thesis numbers in **boldface** (and their corresponding ASC paper equivalents *in italic*) are reiterated below:



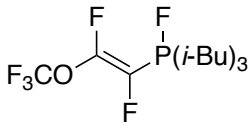
R = *n*-Pr (**4.1a**, *1a*)
R = *n*-Bu (**4.1b**, *1b*)
R = *i*-Bu (**4.1c**, *1c*)



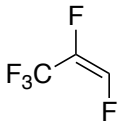
R = *n*-Pr (**4.1a'**, *(Z)-1a*)
R = *n*-Bu (**4.1b'**, *(Z)-1b*)



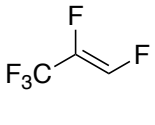
R = *n*-Pr (**4.2a**, *4a*)
R = *n*-Bu (**4.2b**, *4b*)



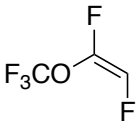
(**4.3**, *5*)



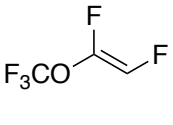
1225ye*(E)*, *(E)-2*



1225ye*(Z)*, *(Z)-2*



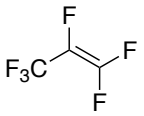
E1225ye*(E)*, *(E)-6*



E1225ye*(Z)*, *(Z)-6*

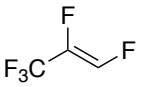
Furthermore, though many of the spectra contain insets to show additional multiplicity detail and labelling, a color-coding system was used to label individual peaks in the wider spectrum, and thus this section is best viewed in color. If this document is being read in B&W, then the precise chemical shift assignments can be made out using the chart on the following page, or by referring back to the experimental section in Chapter 4.

HFP derivatives



HFP

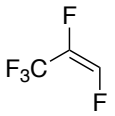
–70.9 ppm
–91.6 ppm
–106.1 ppm
–195.7 ppm



(Z)-**2**

1225ye*(Z)*

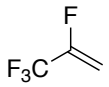
–72.6 ppm
–155.1 ppm
–159.0 ppm



(E)-**2**

1225ye*(E)*

–70.1 ppm
–165.9 ppm
–180.1 ppm

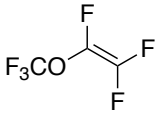


3

1234yf

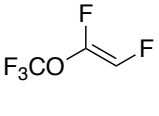
–73.8 ppm
–124.0 ppm

PMVE derivatives



PMVE

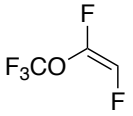
–61.9 ppm
–115.0 ppm
–122.7 ppm
–137.6 ppm



(Z)-**6**

E1225ye*(Z)*

–62.0 ppm
–105.1 ppm
–177.6 ppm

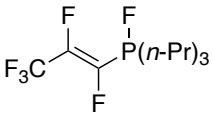


(E)-**6**

E1225ye*(E)*

–60.8 ppm
–130.1 ppm
–185.4 ppm

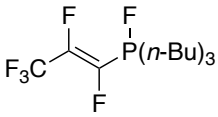
P–F Phosphoranes



(Z)-**1a**

δ(^{19}F)
–18.1 ppm
–67.3 ppm
–142.0 ppm
–169.1 ppm

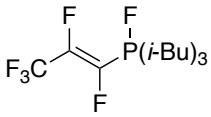
δ(^{31}P)
–64.8 ppm



(Z)-**1b**

δ(^{19}F)
–17.3 ppm
–67.4 ppm
–141.7 ppm
–169.0 ppm

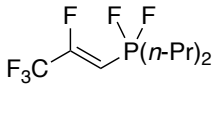
δ(^{31}P)
–63.6 ppm



(Z)-**1c**

δ(^{19}F)
–14.7 ppm
–67.2 ppm
–138.6 ppm
–165.6 ppm

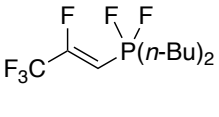
δ(^{31}P)
–64.3 ppm



4

δ(^{19}F)
–41.5 ppm
–67.4 ppm
–125.1 ppm

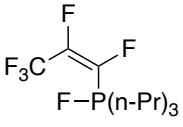
δ(^{31}P)
–16.4 ppm



4b

δ(^{19}F)
–40.7 ppm
–67.5 ppm
–125.5 ppm

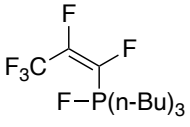
δ(^{31}P)
–15.5 ppm



(E)-**1a**

δ(^{19}F)
–12.7 ppm
–68.4 ppm
–143.3 ppm
–172.7 ppm

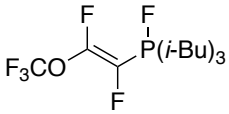
δ(^{31}P)
–77.7 ppm



(E)-**1b**

δ(^{19}F)
–11.9 ppm
–68.4 ppm
–124.8 ppm
–142.8 ppm

δ(^{31}P)
–76.3 ppm



5

δ(^{19}F)
–10.8 ppm
–60.4 ppm
–116.3 ppm
–152.7 ppm

δ(^{31}P)
–68.5 ppm

Figure AII-1. $^{19}F\{^{1}H\}$ NMR (471 MHz) of compound 4.1a

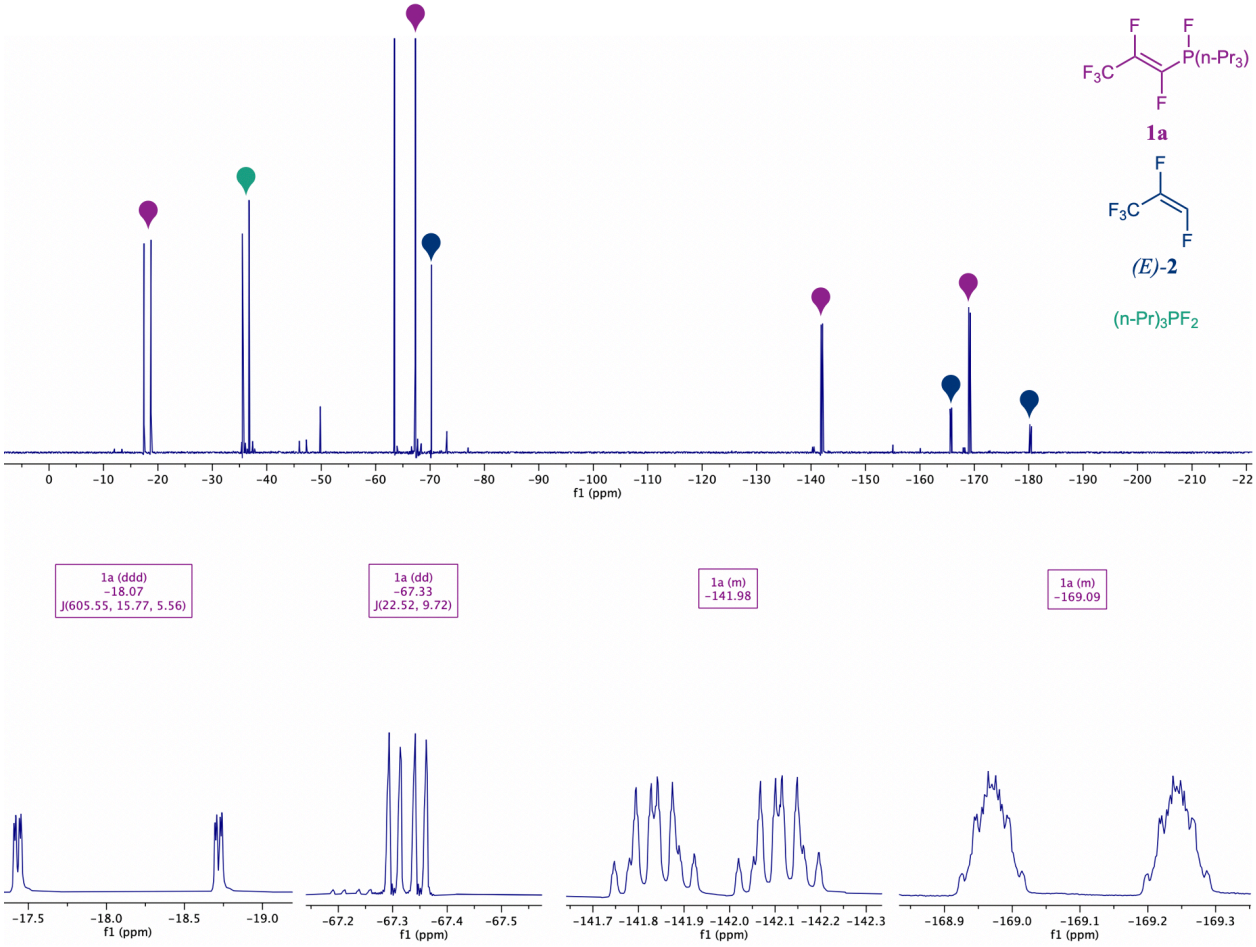


Figure AII-2. $^{31}P\{^{1}H\}$ NMR (202 MHz) of product 4.1a

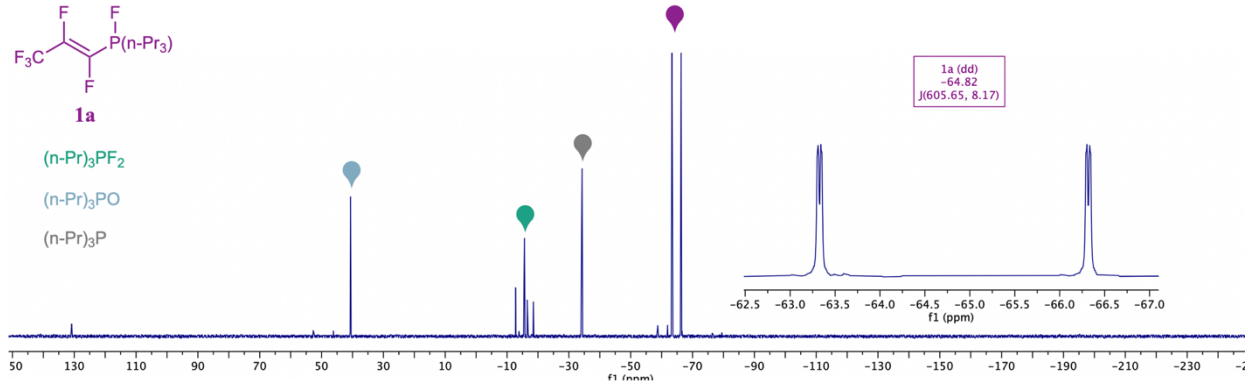


Figure AII-3. $^{19}F\{^{1}H\}$ NMR (471 MHz) of compound 4.1b

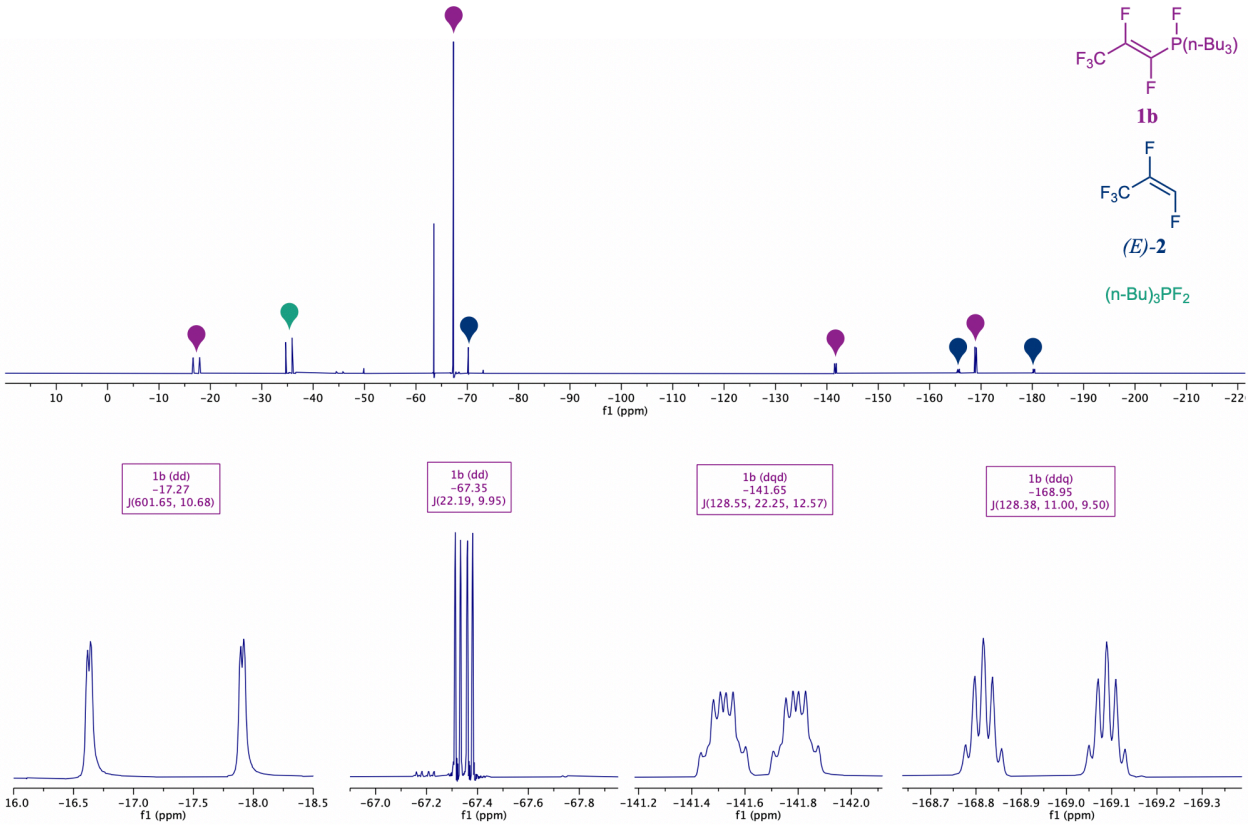


Figure AII-4. $^{31}P\{^{1}H\}$ NMR (202 MHz) of compound 4.1b

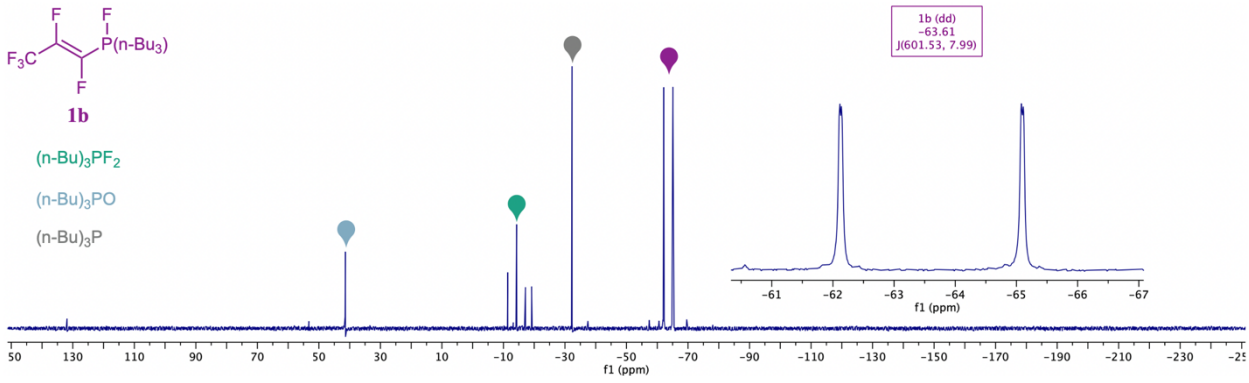


Figure AII-5. $^{19}F\{^{1}H\}$ NMR (471 MHz) of compound 4.1c

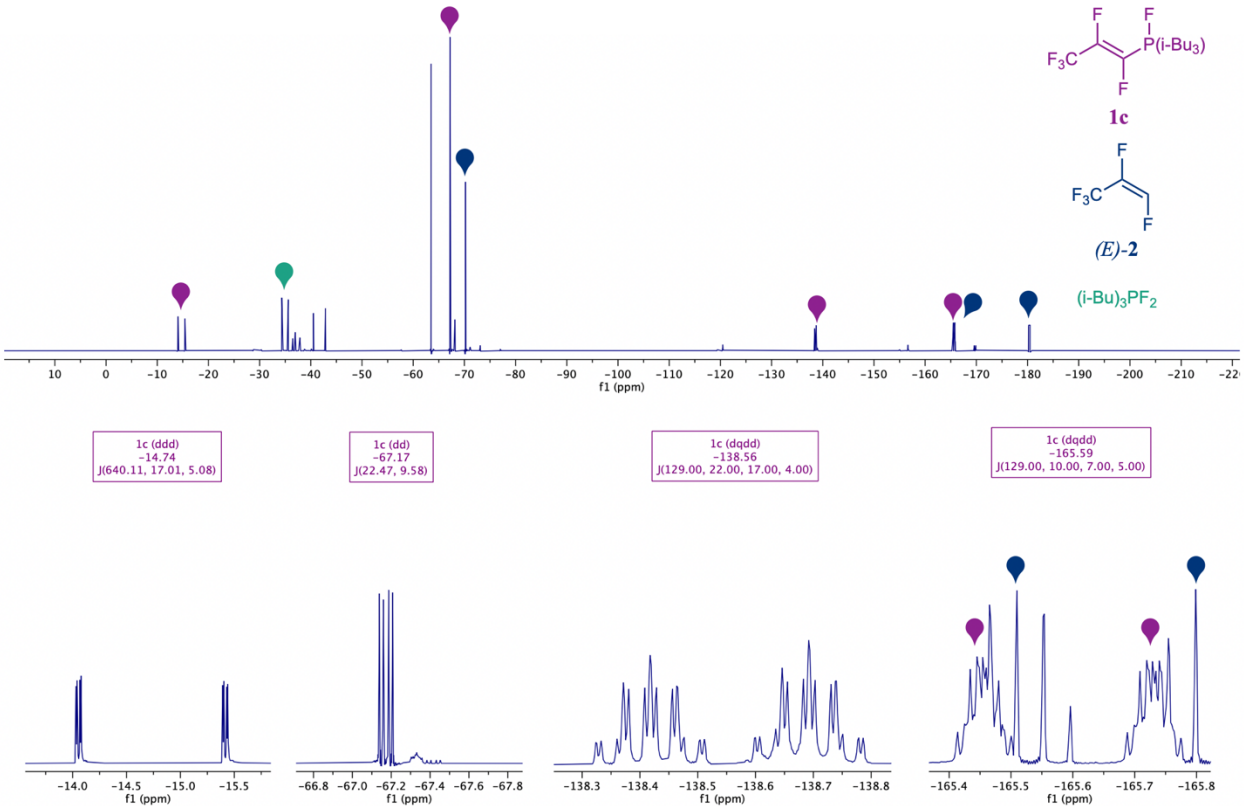


Figure AII-6. $^{31}P\{^{1}H\}$ NMR (202 MHz) of compound 4.1c

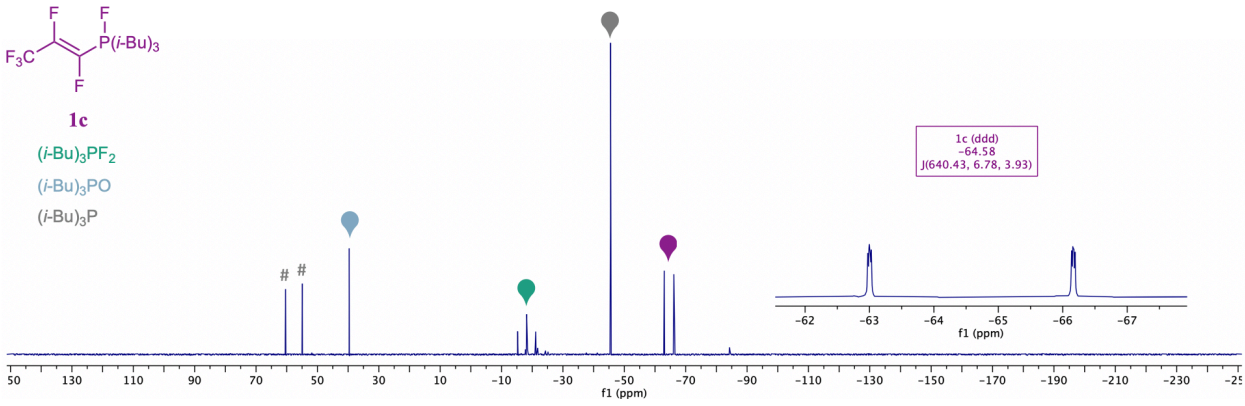


Figure AII-8. $^{19}F\{^{1}H\}$ NMR (471 MHz) of compound 4.2a and 4.1a'

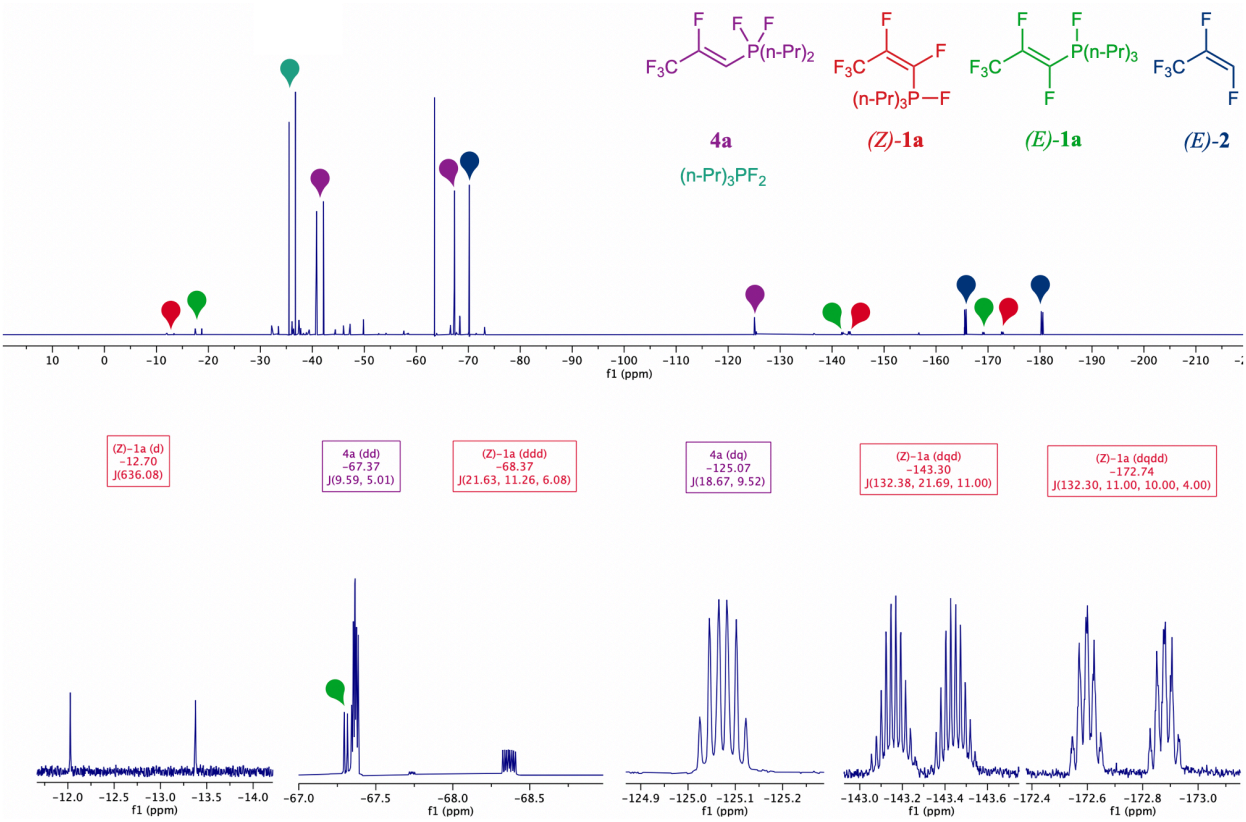


Figure AII-9. $^{31}P\{^{1}H\}$ NMR (202 MHz) of compound 4.2a and 4.1a'

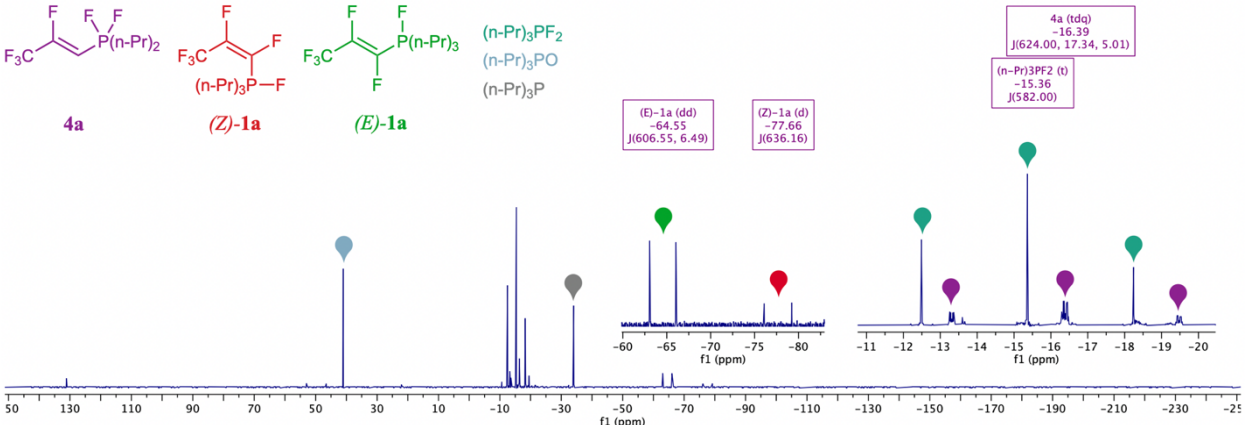


Figure AII-10. $^{19}F\{^{1}H\}$ NMR (471 MHz) of compound 4.2b and 4.1b'

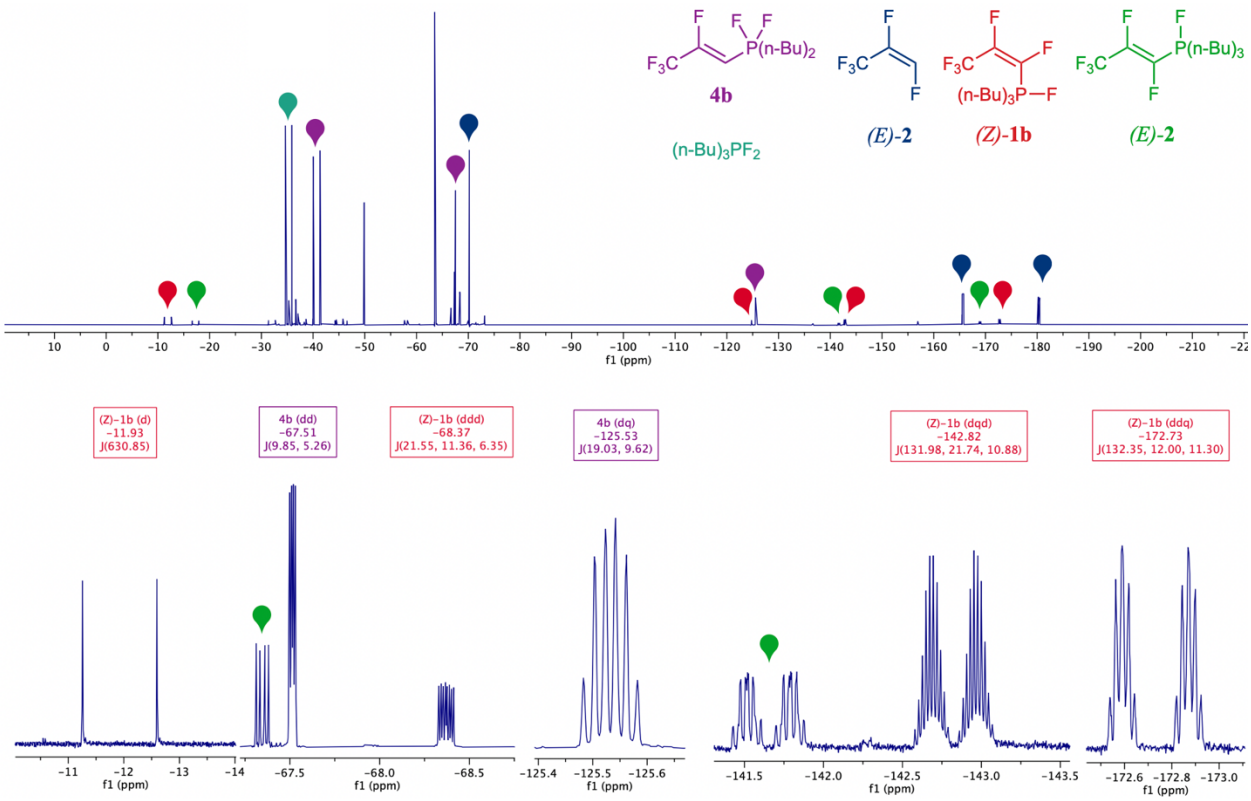


Figure AII-11. $^{31}P\{^{1}H\}$ NMR (202 MHz) of compound 4.2b and 4.1b'

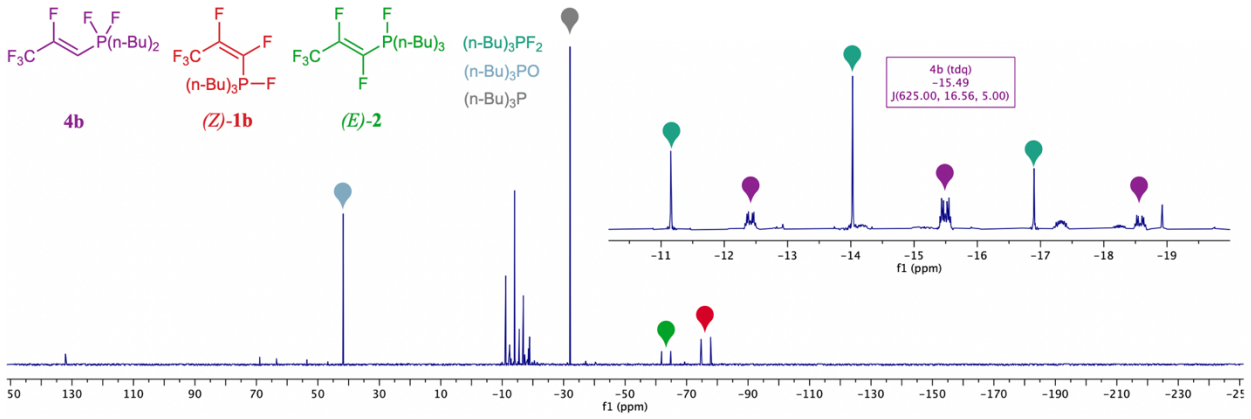


Figure AII-12. $^{19}F\{^{1}H\}$ NMR (471 MHz) of Table 4.3.1, Ex. 5

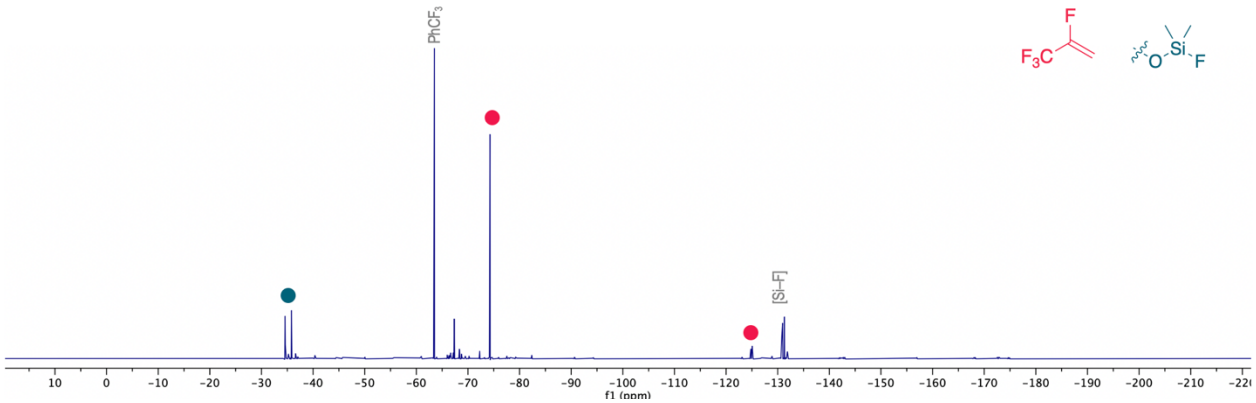


Figure AII-13. $^{31}P\{^{1}H\}$ NMR (202 MHz) of Table 4.3.1, Ex. 5

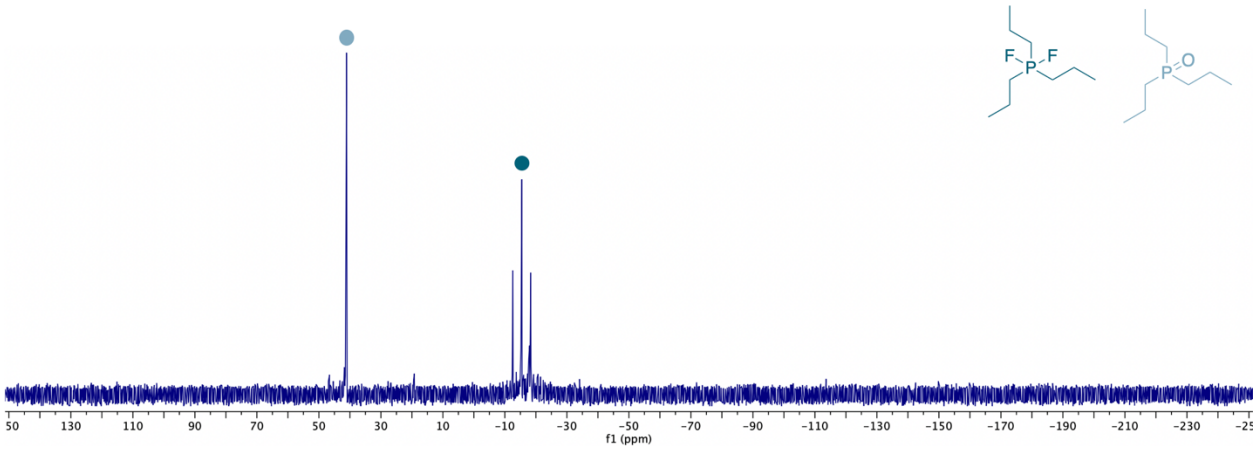


Figure AII-14. $^{19}F\{^{1}H\}$ NMR (471 MHz) of Table 4.3.1, Ex. 12

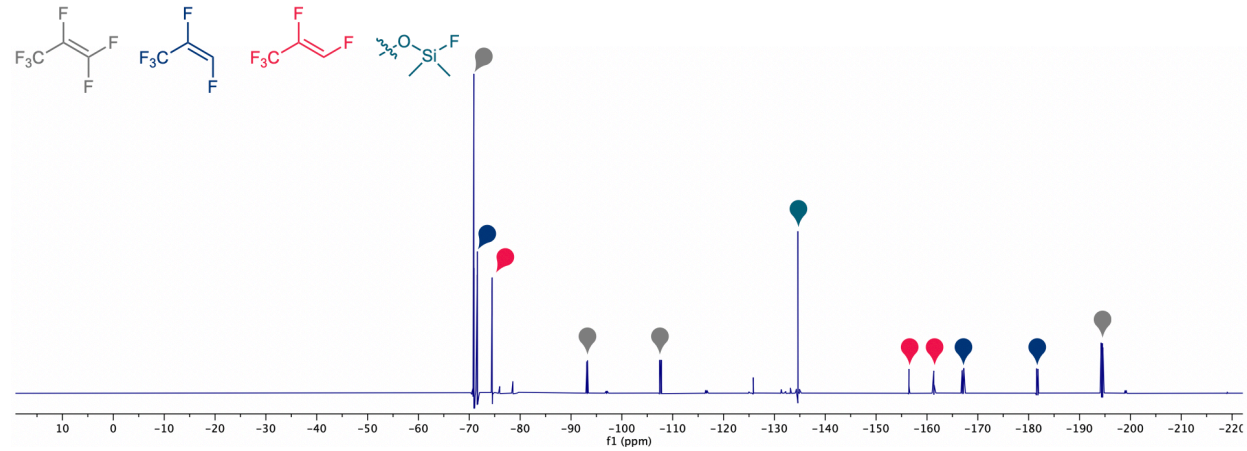


Figure AII-15. $^{19}F\{^{1}H\}$ NMR (471 MHz) of compounds 4.3 and E1225ye

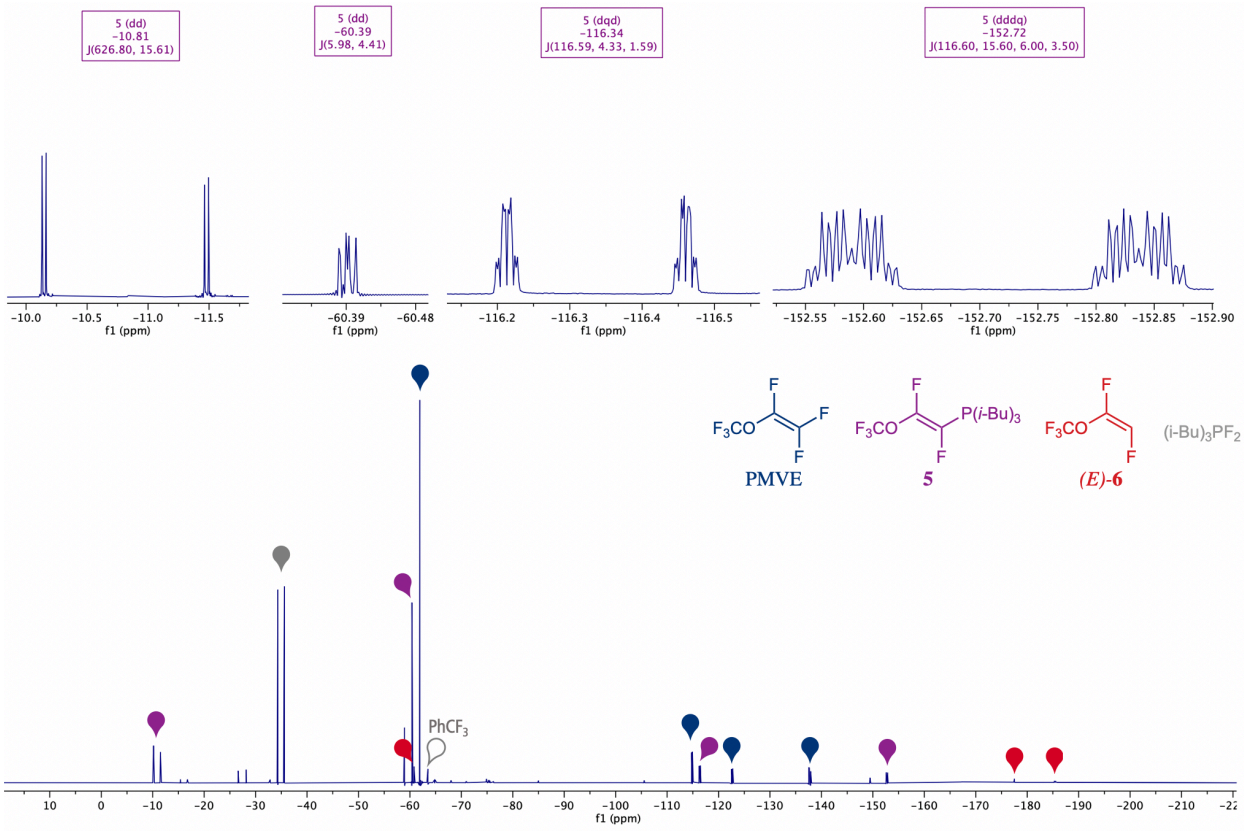


Figure AII-16. $^{31}P\{^{1}H\}$ NMR (202 MHz) of compound 4.3

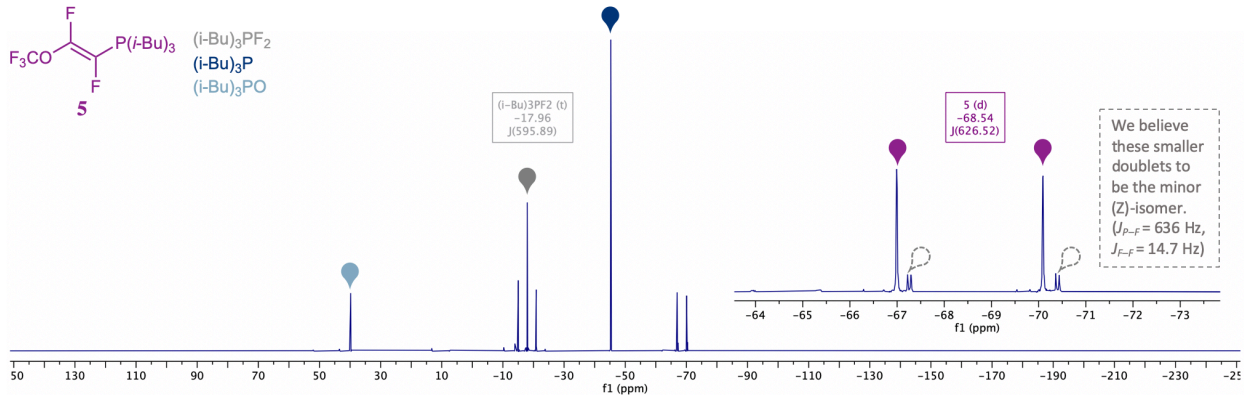
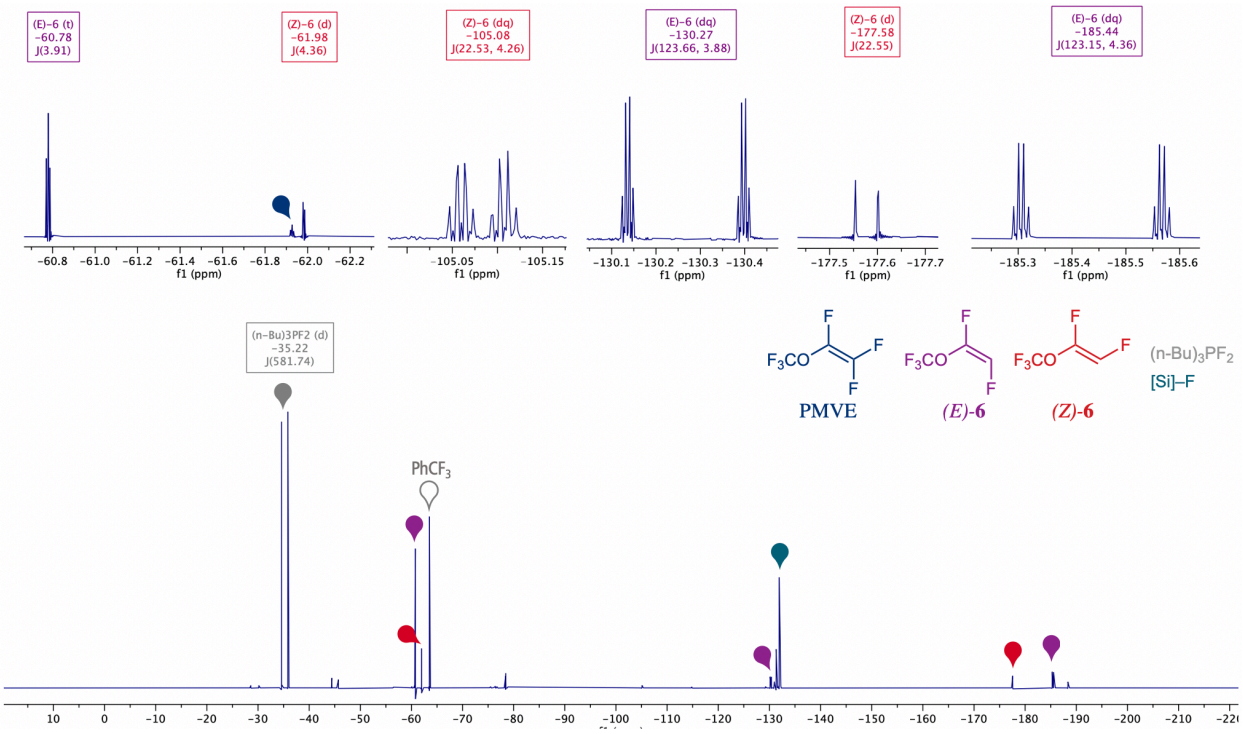


Figure AII-17. $^{19}F\{^{1}H\}$ NMR (471 MHz) of Table 4.4.1, Ex. 4



A-III

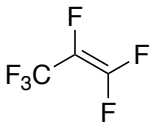
Appendix III

This appendix contains the NMR spectra associated with the experimental section of Chapter 5.

Note to the reader:

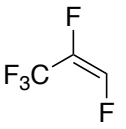
The spectra provided in this section containing organic compounds which are labelled as per the ASHRAE nomenclature. Understanding that this nomenclature may not come naturally to a reader of this thesis not well-versed in fluororefrigerants, a chart of relevant compounds, their ASHRAE numbers, and their ^{19}F chemical shifts is provided on the following page for easy reference. Alternatively, ***Appendix IV*** provides the reader with a complete list of ASHRAE numbers for fluorinated methanes, ethanes, and propanes, along with selected higher compounds of relevance to this thesis.

Figure AIII-1. Relevant fluorocarbons and their ^{19}F chemical shifts



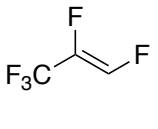
HFP

–70.9 ppm
–91.6 ppm
–106.1 ppm
–195.7 ppm



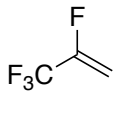
1225ye*(E)*

–70.1 ppm
–165.9 ppm
–180.1 ppm



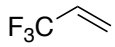
1225ye*(Z)*

–72.6 ppm
–155.1 ppm
–159.0 ppm



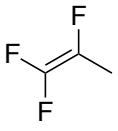
1234yf

–74.3 ppm
–124.7 ppm



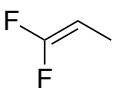
1243zf

–67.2 ppm



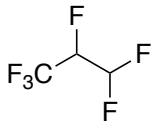
1243yc

–107.2 ppm
–127.1 ppm
–168.2 ppm



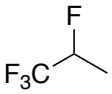
1252zc

–90.5 ppm
–94.2 ppm



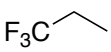
236ea

–77.1 ppm
–131.1 ppm
–131.5 ppm
–217.5 ppm



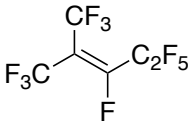
254eb

–81.4 ppm
–195.3 ppm



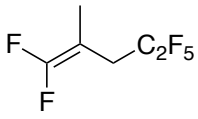
263fb

–69.5 ppm



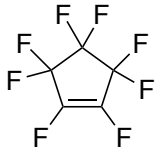
***F*-2M2P**

–58.8 ppm
–61.5 ppm
–84.7 ppm
–98.9 ppm
–117.8 ppm



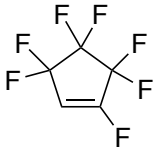
1567mcftc

–81.4 ppm
–195.3 ppm



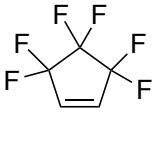
PFCP

–118.2 ppm
–130.3 ppm
–150.0 ppm



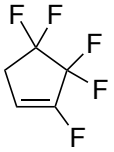
c1427yz

–107.4 ppm
–120.7 ppm
–126.6 ppm
–130.1 ppm



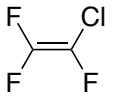
c1436zz

–110.4 ppm
–133.1 ppm



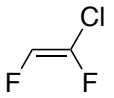
c1445yzf

–115.2 ppm
–122.2 ppm
–138.3 ppm



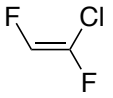
CTFE

–101.9 ppm
–119.5 ppm
–143.6 ppm



1122a*(E)*

–105.6 ppm
–155.7 ppm



1122a*(Z)*

–130.5 ppm
–173.2 ppm

Figure AIII-2. $^{19}F\{^{1}H\}$ NMR of Table 5.3.1 ex. 1 (18 h) (471 MHz, C_6D_6)

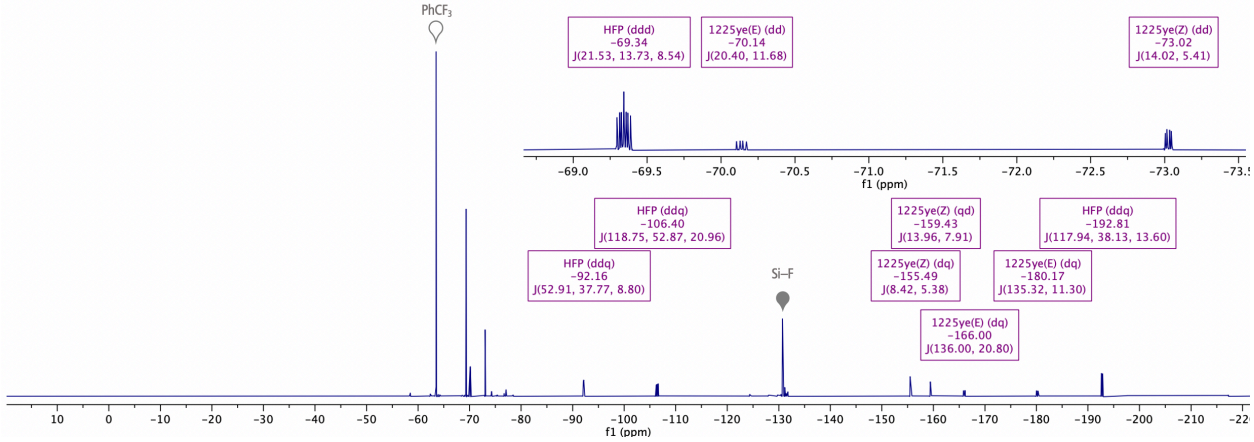


Figure AIII-3. $^{19}F\{^{1}H\}$ NMR of Table 5.3.1 ex. 2 (18 h) (471 MHz, C_6D_6)

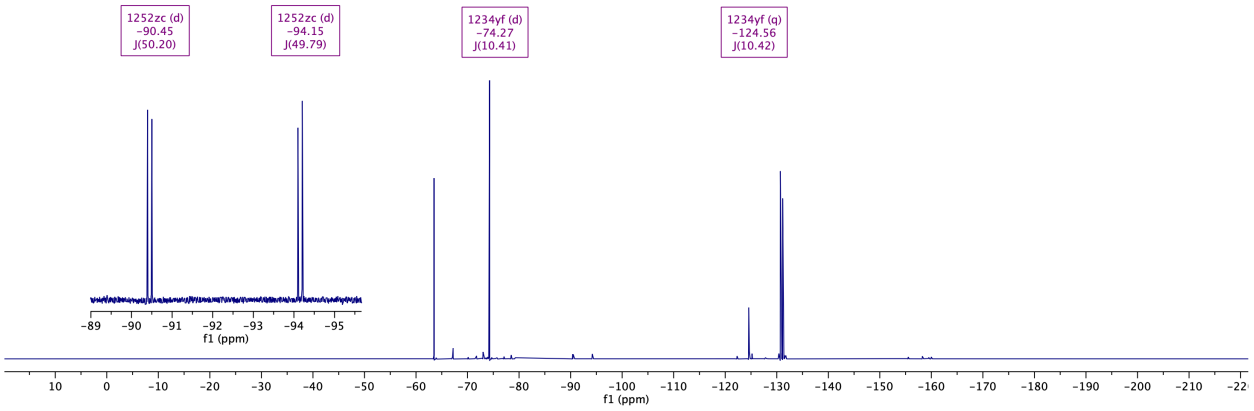


Figure AIII-4. $^{19}F\{^{1}H\}$ NMR of Table 5.3.1 ex. 3 (471 MHz, C_6D_6)

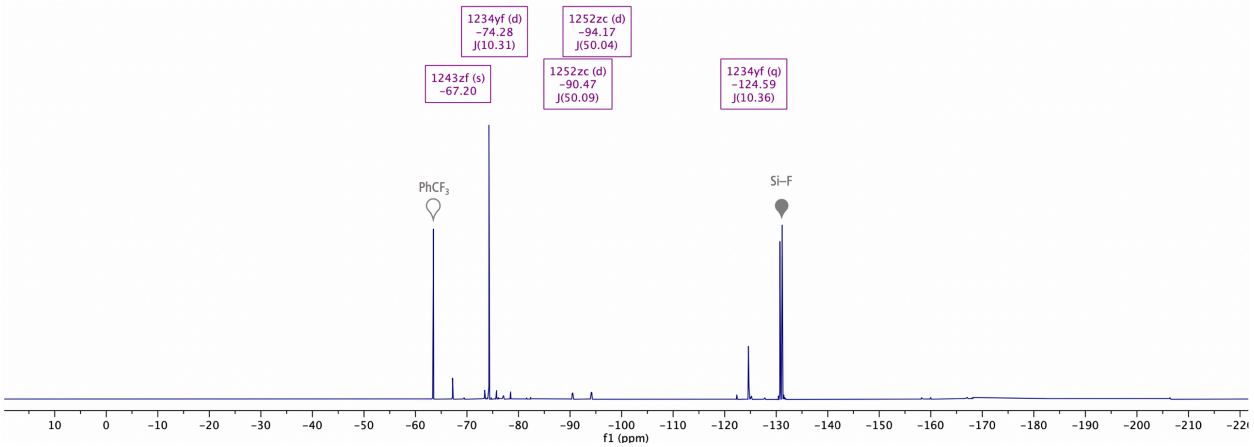


Figure AIII-5. $^{19}F\{^{1}H\}$ NMR of Table 5.3.1 ex. 4 (471 MHz, C_6D_6)

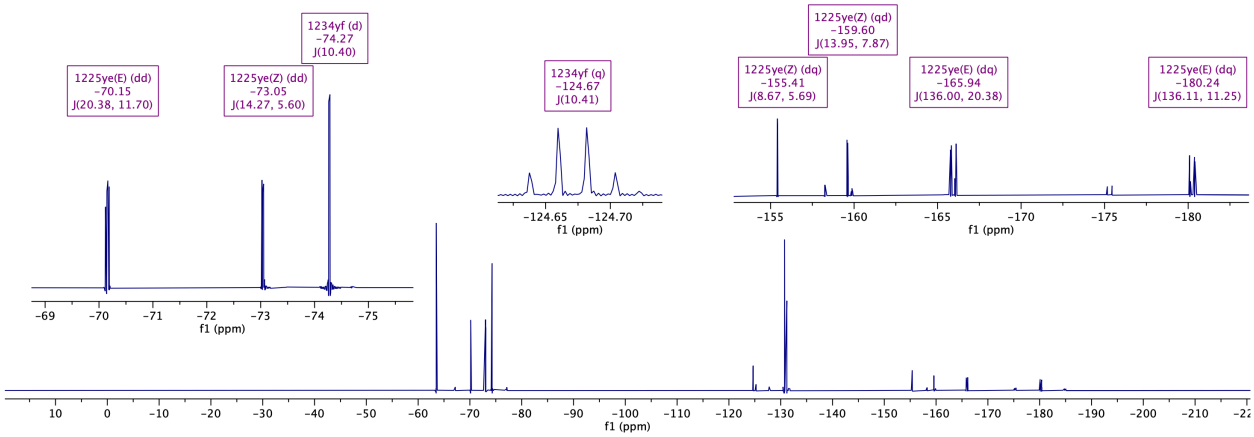


Figure AIII-6. $^{19}F\{^{1}H\}$ NMR of Table 5.3.1 ex. 5 (471 MHz, C_6D_6)

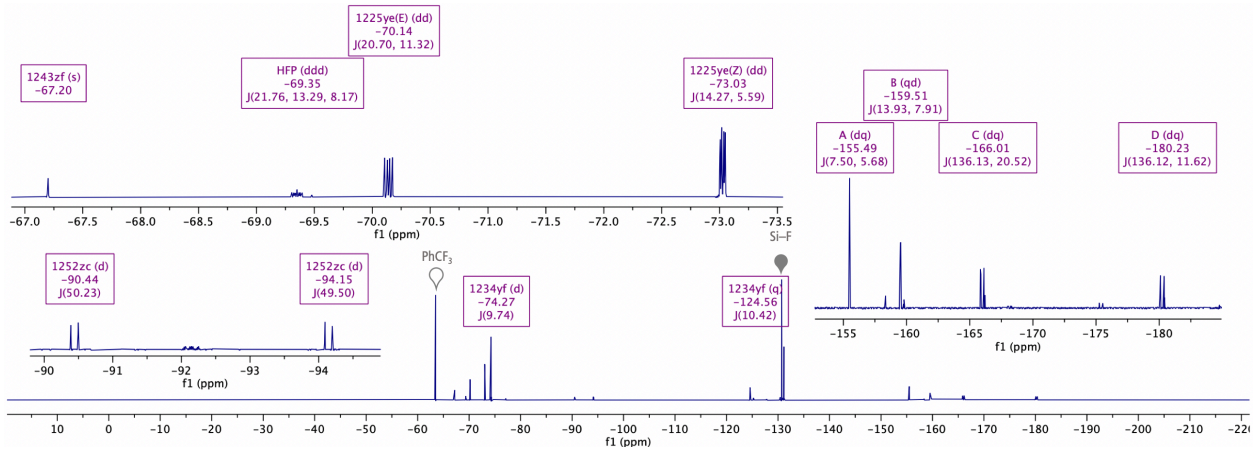


Figure AIII-7. $^{19}F\{^{1}H\}$ NMR of Table 5.3.1 ex. 6 (471 MHz, C_6D_6)

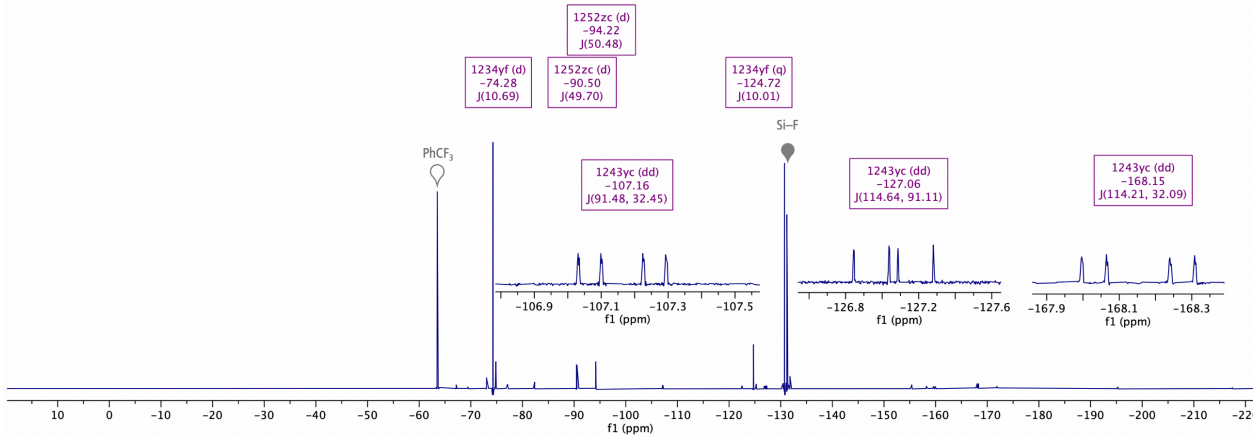


Figure AIII-8. $^{19}F\{^{1}H\}$ NMR of Table 5.3.1 ex. 7 (471 MHz, C_6D_6)

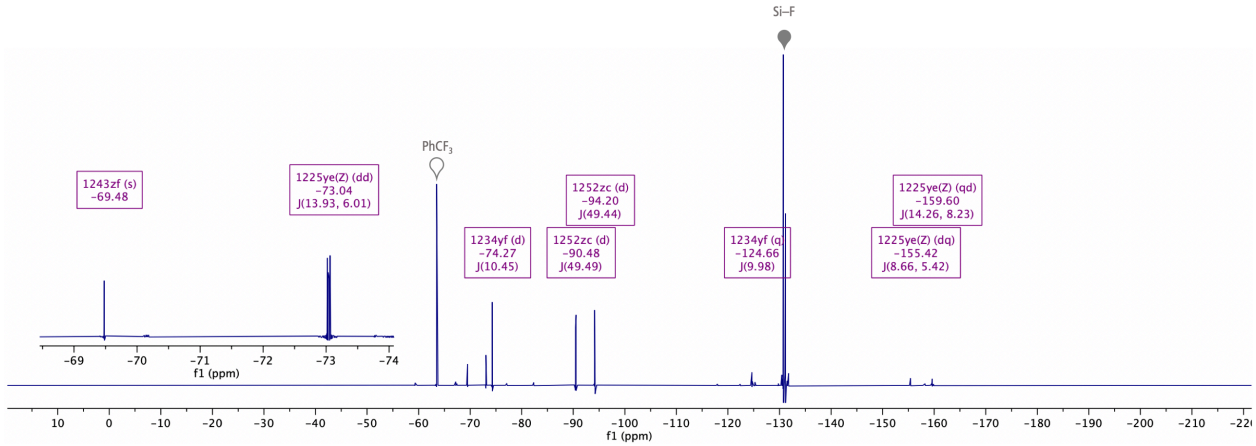


Figure AIII-9. $^{19}F\{^{1}H\}$ NMR of Table 5.3.1 ex. 8 (471 MHz, C_6D_6)

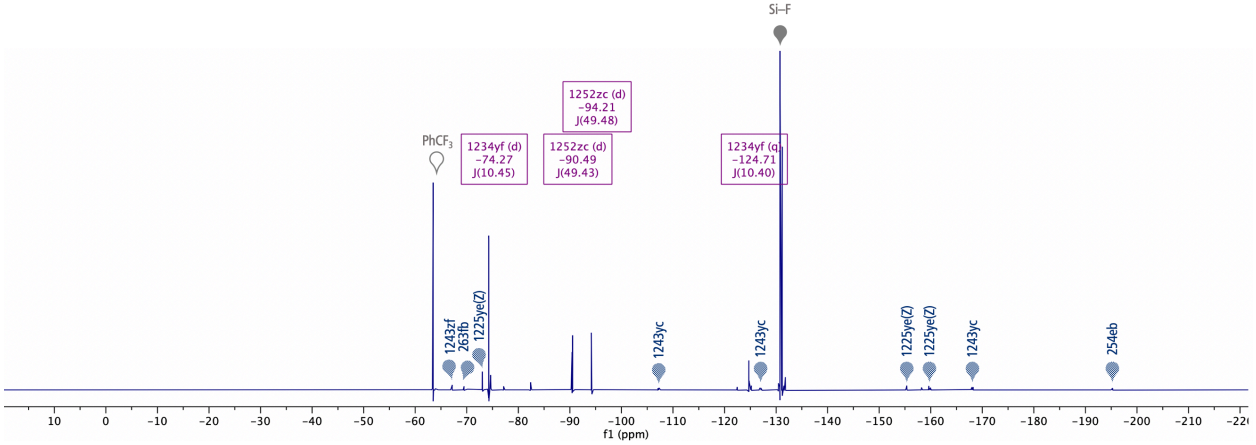


Figure AIII-10. $^{19}F\{^{1}H\}$ NMR of Table 5.3.1 ex. 9 (471 MHz, C_6D_6)

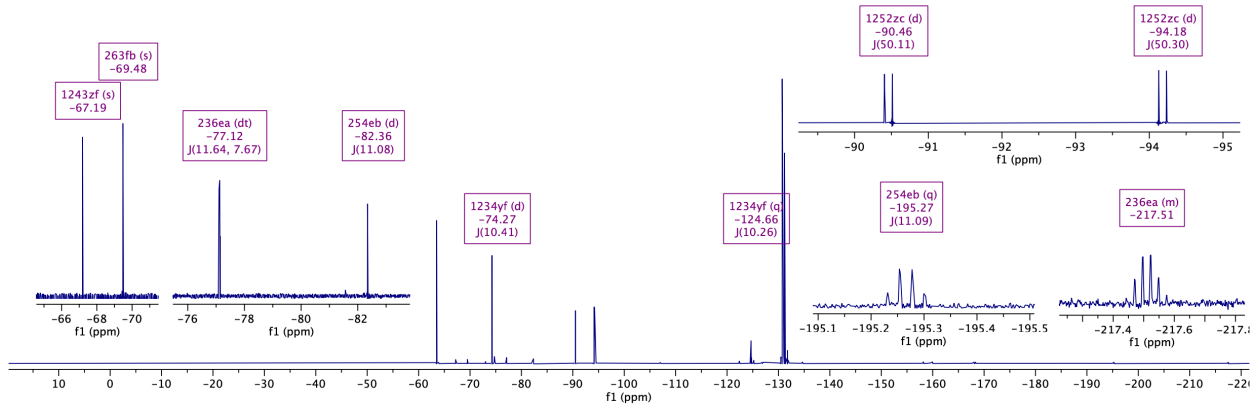


Figure AIII-11. $^{19}F\{^{1}H\}$ NMR of Table 5.3.2 ex. 1 (471 MHz, C_6D_6)

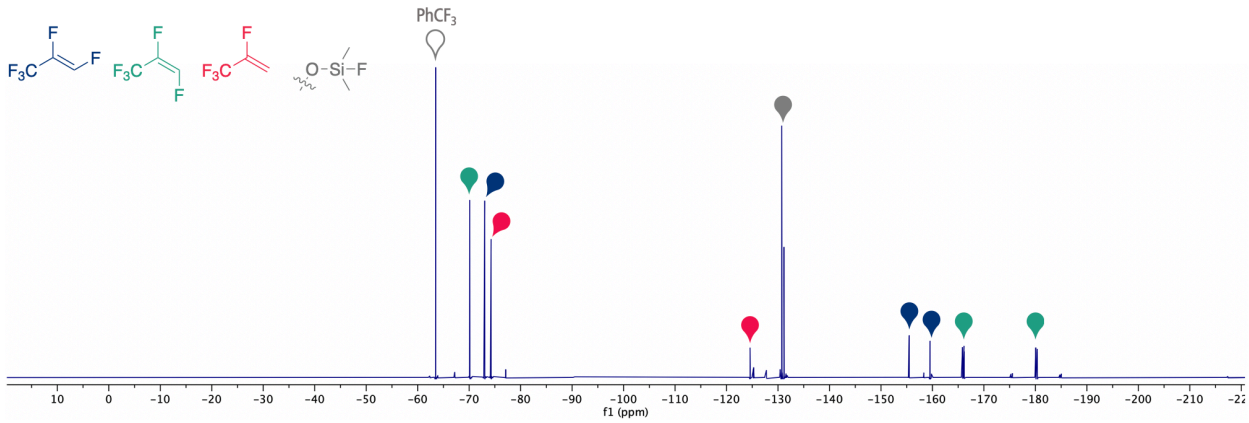


Figure AIII-12. $^{19}F\{^{1}H\}$ NMR of Table 5.3.2 ex. 6 (471 MHz, C_6D_6)

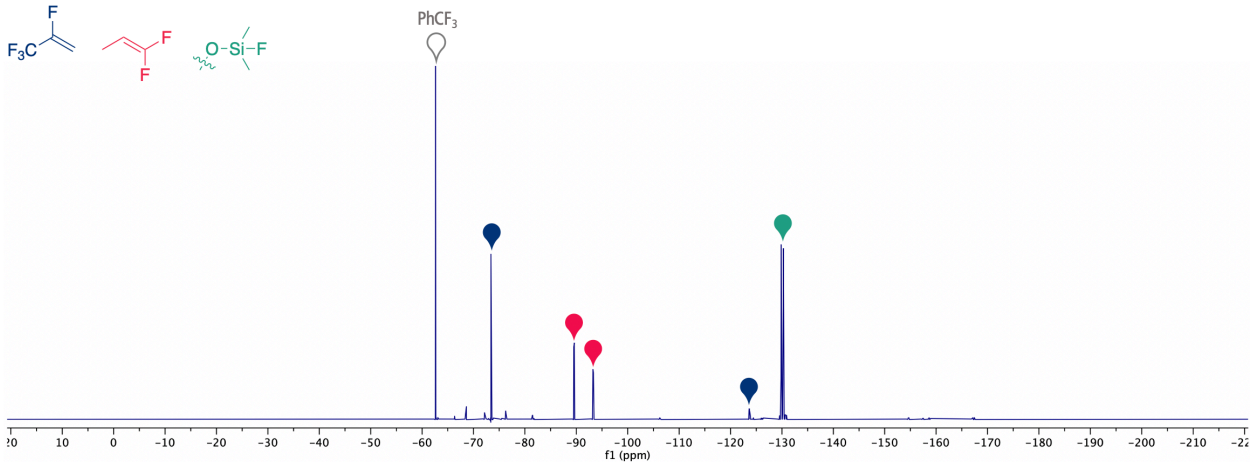


Figure AIII-13. $^{19}F\{^{1}H\}$ NMR of exp. 5.6.3 (471 MHz, neat)

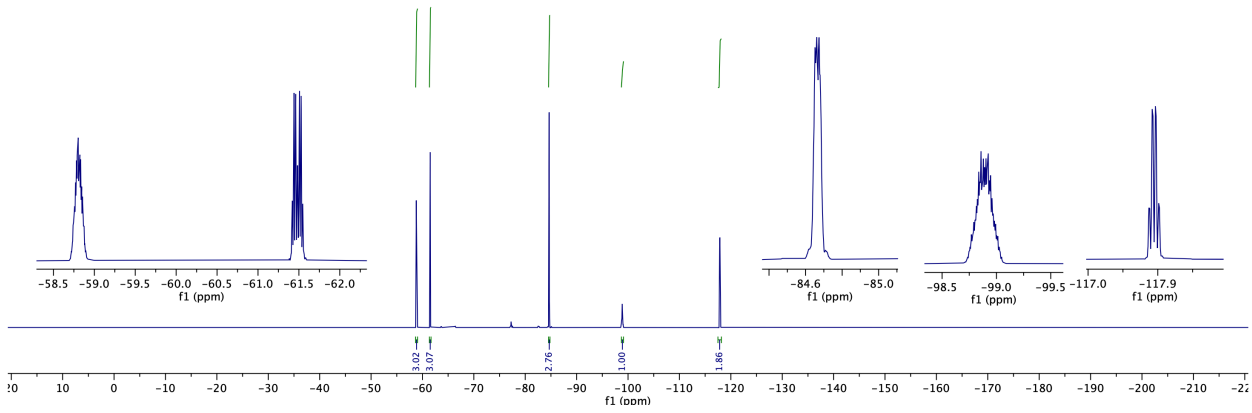


Figure AIII-14. $^{19}F\{^{1}H\}$ NMR of exp. 5.6.3 w/CsF recycle (471 MHz, neat)

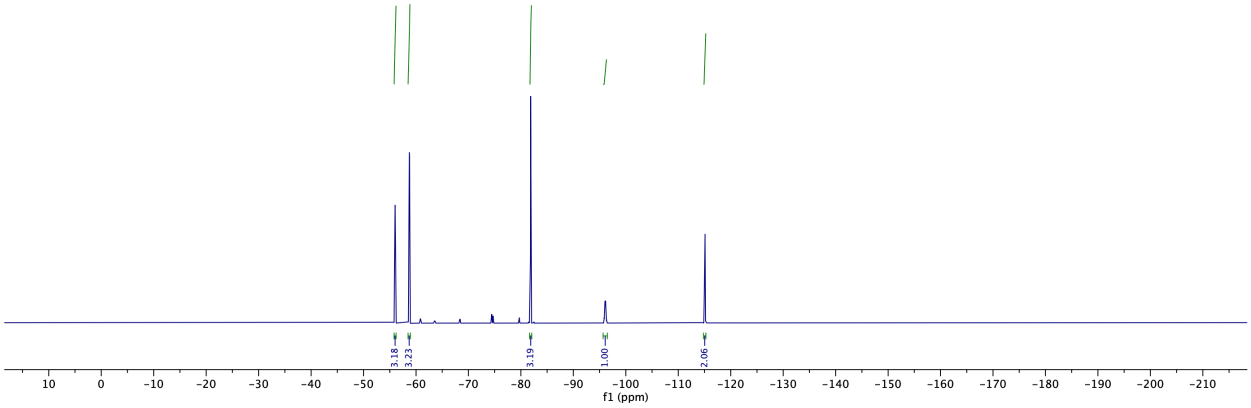


Figure AIII-15. $^{19}F\{^{1}H\}$ NMR of exp. 5.6.4 (471 MHz, C_6D_6)

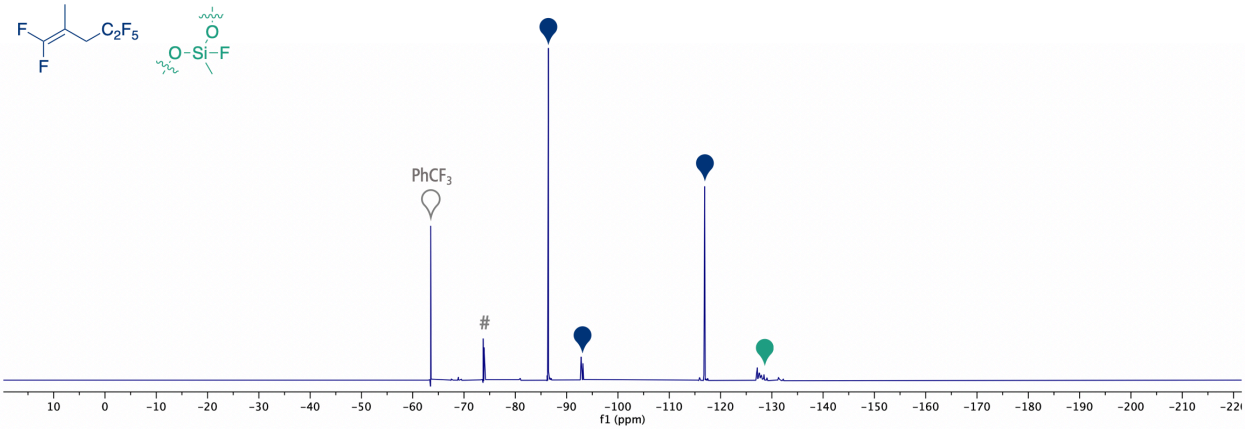


Figure AIII-16. $^{19}F\{^{1}H\}$ NMR of exp. 5.6.4 (471 MHz, C_6D_6, under air)

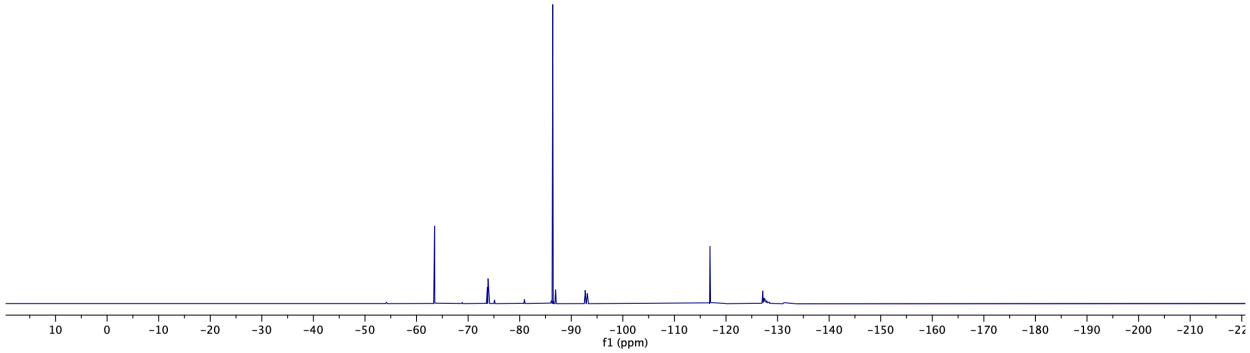


Figure AIII-17. **$^{19}F\{^{1}H\}$ NMR of exp. 5.6.4 (471 MHz, C_6D_6)**

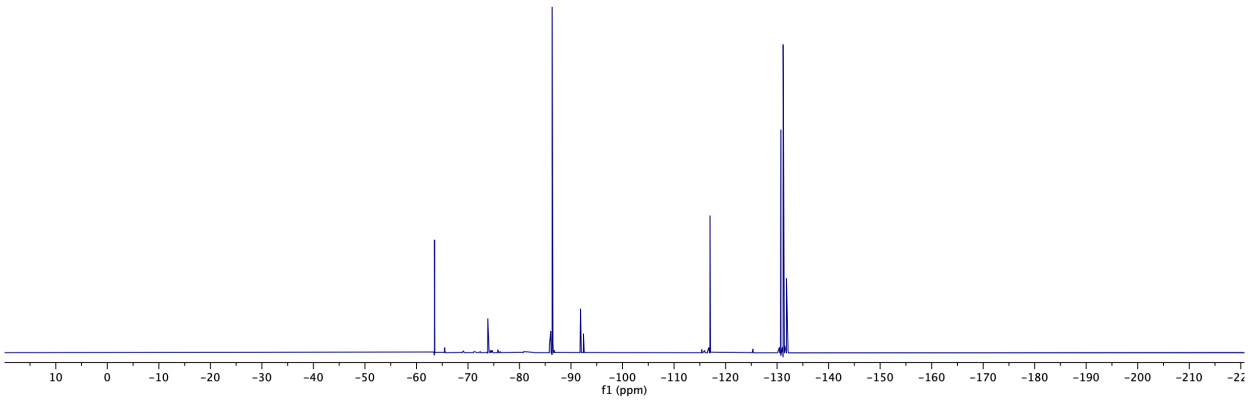


Figure AIII-18. **$^{19}F\{^{1}H\}$ NMR of exp. 5.6.5 (282 MHz, CPME)**

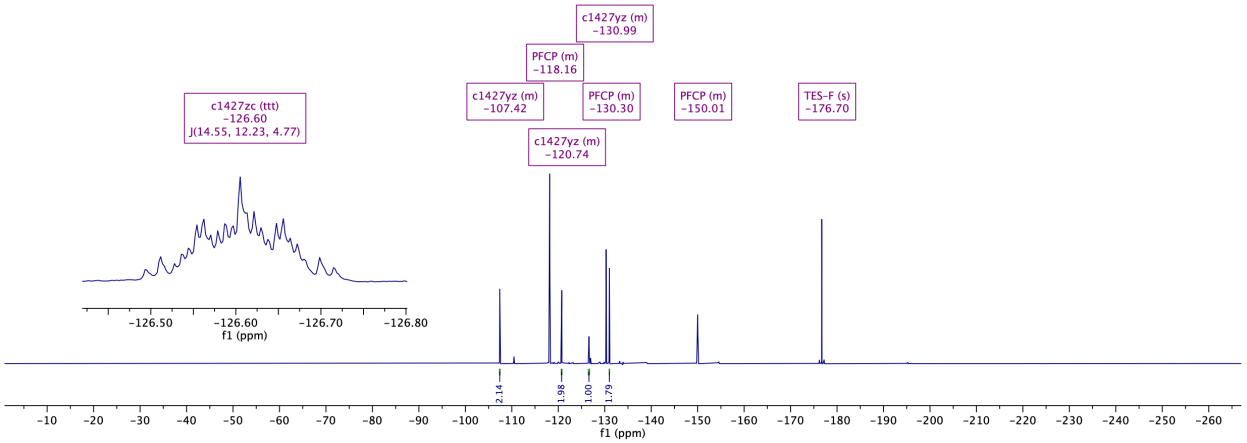


Figure AIII-19. **$^{19}F\{^{1}H\}$ NMR of exp. 5.6.6 (282 MHz, neat TMDS)**

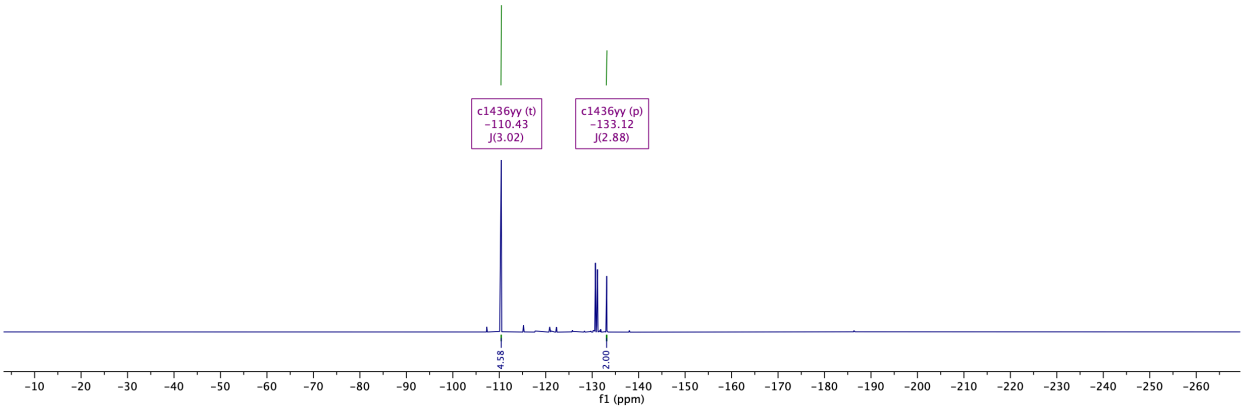


Figure AIII-20. $^{19}F\{^{1}H\}$ NMR of exp. 5.6.7 (282 MHz, neat TMDS)

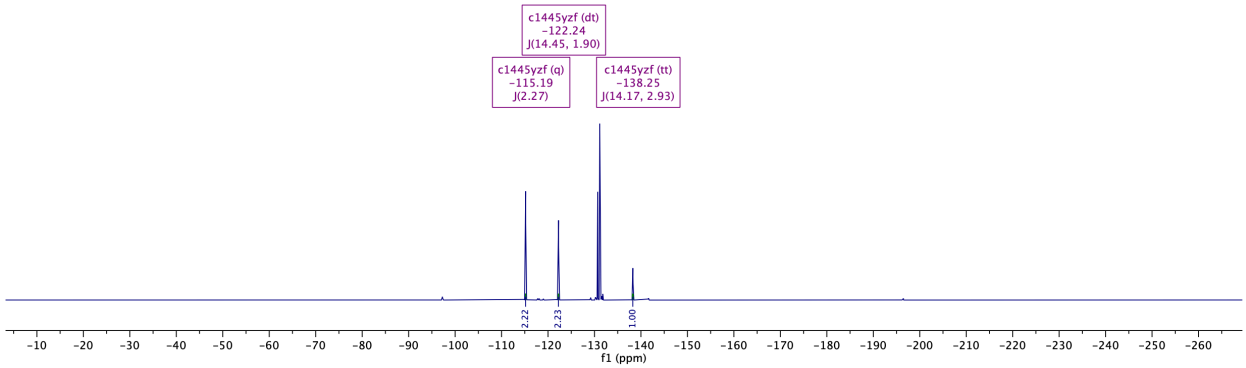


Figure AIII-21. $^{19}F\{^{1}H\}$ NMR of Table 5.3.3 exp. 1 (18 h) (282 MHz, C_6D_6)

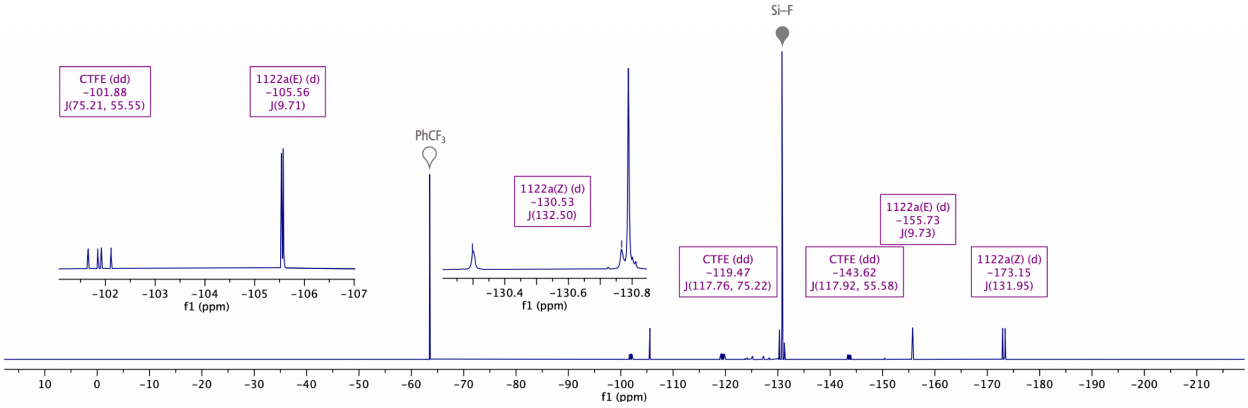


Figure AIII-22. ^{1}H NMR of Table 5.3.3 exp. 1 (18 h) (300 MHz, C_6D_6)

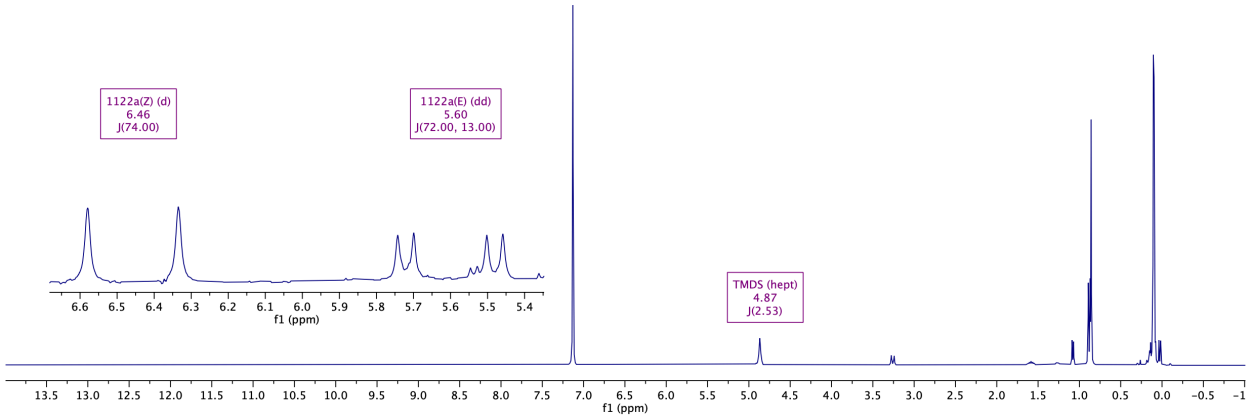


Figure AIII-23. $^{19}F\{^{1}H\}$ NMR of Table 5.3.3 exp. 2 (18 h) (282 MHz, C_6D_6)

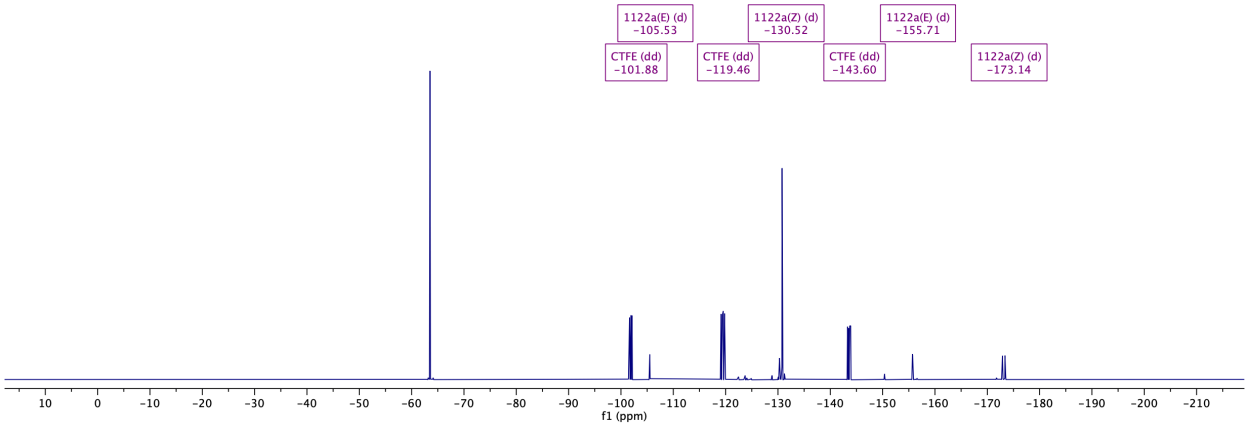


Figure AIII-24. $^{19}F\{^{1}H\}$ NMR of Table 5.3.3 exp. 3 (18 h) (282 MHz, C_6D_6)

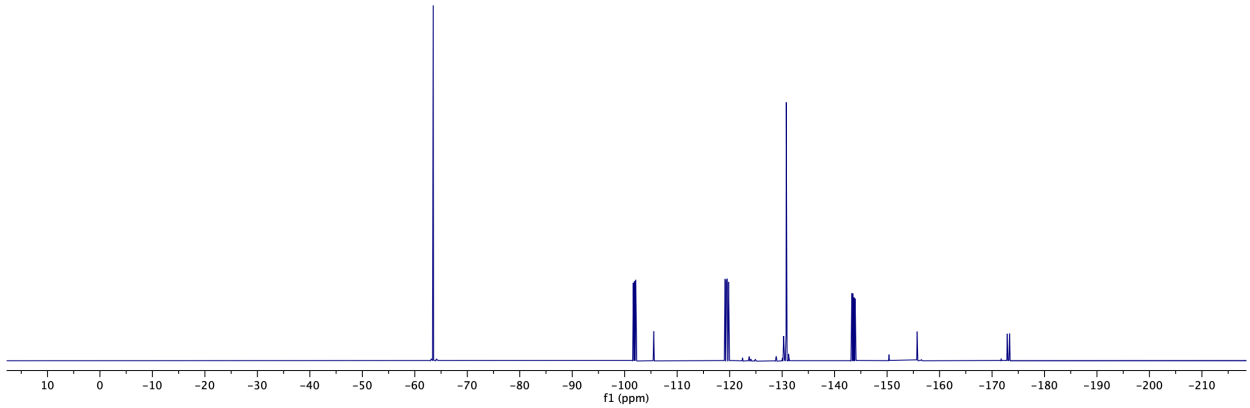


Figure AIII-25. $^{19}F\{^{1}H\}$ NMR of Table 5.3.3 exp. 4 (18 h) (282 MHz, C_6D_6)

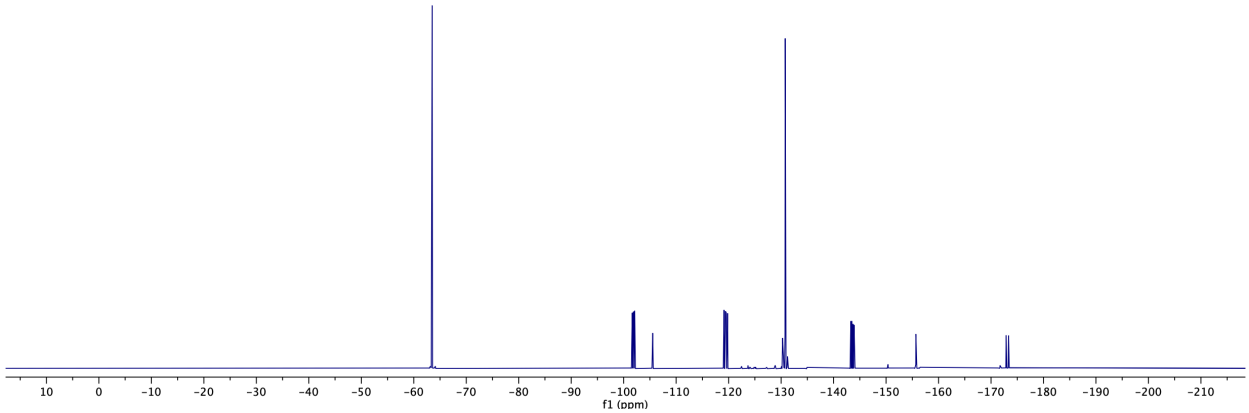


Figure AIII-26. $^{19}F\{^{1}H\}$ **NMR of Table 5.3.3 exp. 4 (18 h) (282 MHz, C_6D_6)**

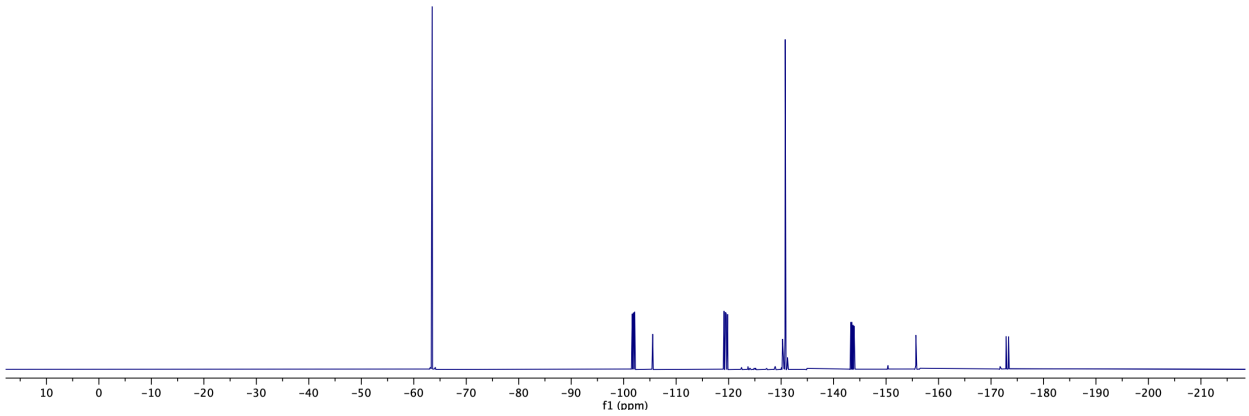


Figure AIII-27. $^{19}F\{^{1}H\}$ **NMR of Table 5.3.3 exp. 5 (18 h) (282 MHz, C_6D_6)**

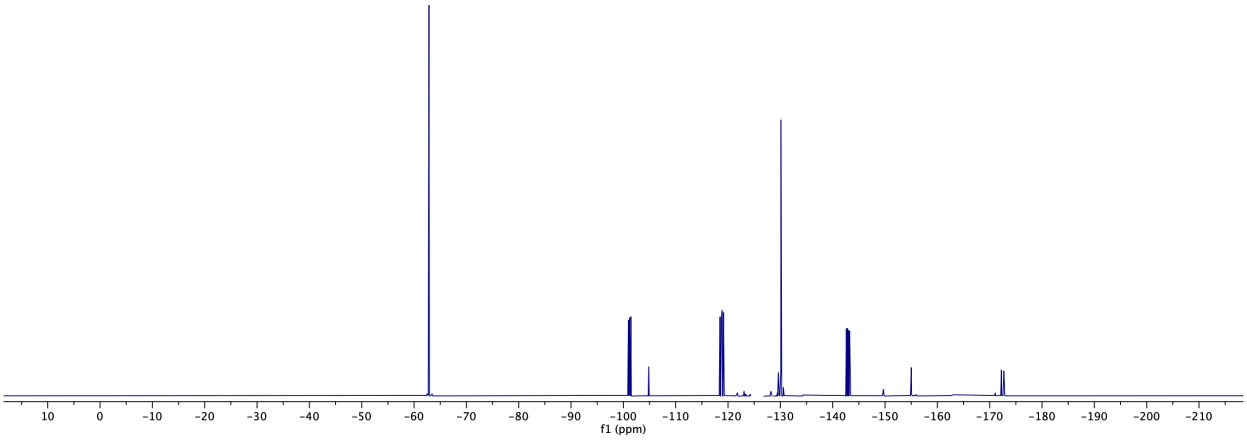


Figure AIII-28. $^{19}F\{^{1}H\}$ **NMR of Table 5.3.3 exp. 6 (18 h) (282 MHz, C_6D_6)**

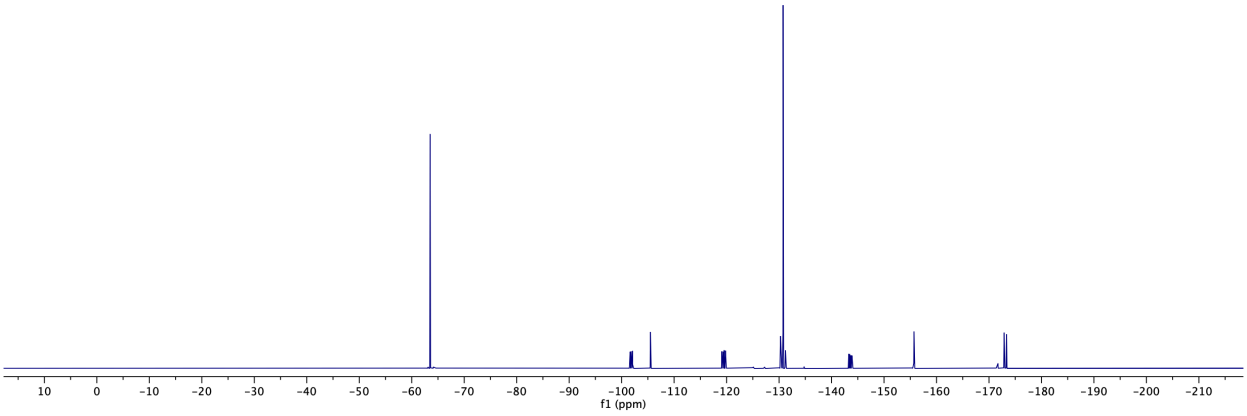


Figure AIII-29. $^{19}F\{^{1}H\}$ **NMR of Table 5.3.3 exp. 7 (18 h) (282 MHz, C_6D_6)**

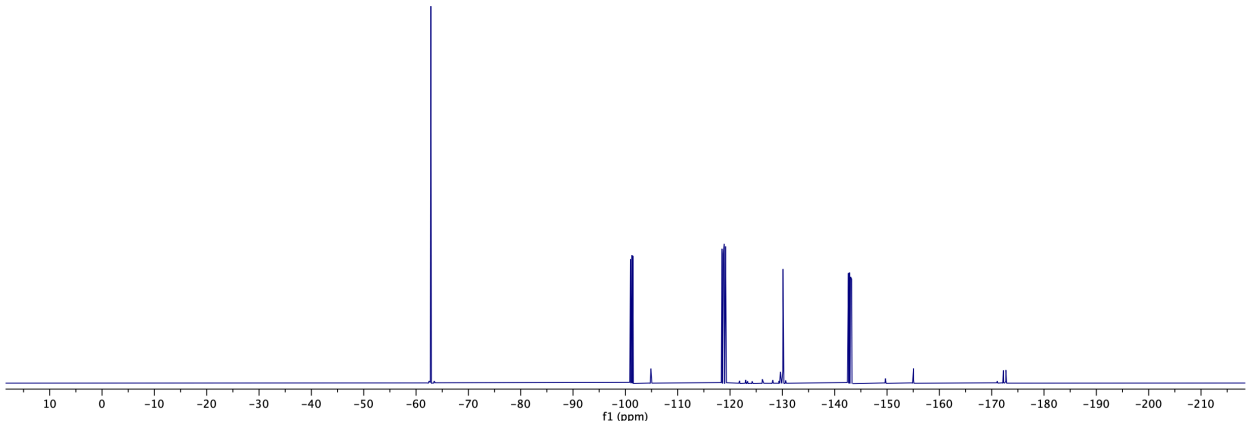
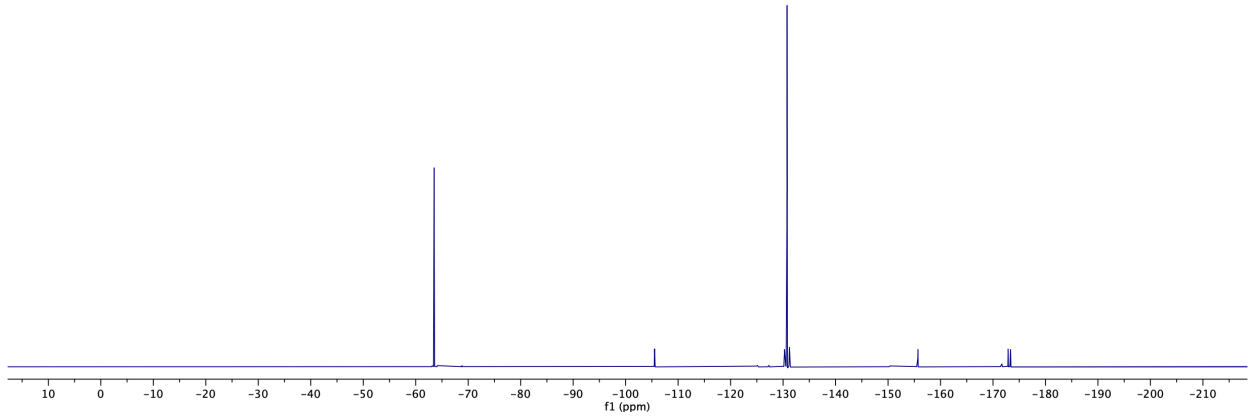


Figure AIII-30. $^{19}F\{^{1}H\}$ **NMR of Table 5.3.3 exp. 7 (72 h) (282 MHz, C_6D_6)**



A-IV

Appendix IV

This appendix contains an ASHRAE number/structure legend.

C_1 CFCs

11	$CFCl_3$
12	CF_2Cl_2
13	$CFCl_3$

C_1 HCFCs

21	$CHCl_2F$
22	$CHClF_2$
31	CH_2ClF

C_1 HFCs

41	CH_3F
32	CH_2F_2
23	CHF_3

C_2 CFCs

111	CCl_3—CCl_2F
112	$CFCl_2$—$CFCl_2$
112a	CCl_3—CF_2Cl
113	$CFCl_2$—CF_2Cl
113a	CCl_3—CF_3
114	CF_2Cl—CF_2Cl
114a	$CFCl_2$—CF_3
115	CF_3—CF_2Cl

C_2 HCFCs

121	$CFCl_2$—$CHCl_2$
121a	CCl_3—$CClFH$
122	CF_2Cl—$CHCl_2$
122a	$CFCl_2$—$CClFH$
122b	CCl_3—CF_2H
123	CF_3—$CHCl_2$
123a	CF_2Cl—$CClFH$
123b	$CFCl_2$—CF_2H
124	CF_3—$CClFH$
124a	CF_2Cl—CF_2H
131	$CHCl_2$—$CClFH$
131a	$CFCl_2$—CH_2Cl
131b	CCl_3—CH_2F
132	$CHClF$—$CHClF$
132a	$CHCl_2$—CHF_2
132b	CF_2Cl—CH_2Cl
132c	$CFCl_2$—CH_2F
133	CF_2H—$CClFH$
133a	CF_3—CH_2Cl
133b	CF_2Cl—CH_2F
141	$CHClF$—CH_2Cl
141a	$CHCl_2$—CH_2F
141b	$CFCl_2$—CH_3
142	CF_2H—CH_2Cl
142a	CH_2F—$CClFH$
142b	CF_2Cl—CH_3
151a	$CHClF$—CH_3

C_2 HFCs

125	CF_3—CF_2H
134	CF_2H—CF_2H
134a	CF_3—CH_2F
143	CF_2H—CH_2F
143a	CF_3—CH_3
152	CH_2F—CH_2F
152a	CF_2H—CH_3

C_2 CFOs

1111	CCl_2=$CFCl$
1112	$CFCl$=$CFCl$
1112a	CF_2=CCl_2
1113	CF_2=$CFCl$

C_2 HCFOs

1121	$CFCl$=$CHCl$
1121a	CFH=CCl_2
1122	$CHCl$=CF_2
1122a	$CFCl$=CFH
1131	$CHCl$=CHF

1131a	$CFCl{=}CH_2$

C_2 HFOs

1123	$CFH{=}CF_2$
1132	$CHF{=}CHF$
1132a	$CF_2{=}CH_2$
1141	$CFH{=}CH_2$

C_3 CFCs

211aa	CCl_3—CCl_2—CCl_2F
211ba	CCl_3—$CFCl$—CCl_3
212aa	$CFCl_2$—CCl_2—$CFCl_2$
212ba	$CFCl_2$—$CFCl$—CCl_3
212ca	CCl_3—CF_2—CCl_3
213aa	CF_2Cl—CCl_2—$CFCl_2$
213ba	CF_2Cl—$CFCl$—$CFCl_2$
213ca	CCl_3—CF_2—$CFCl_2$
214aa	CF_2Cl—CCl_2—CF_2Cl
214ba	$CFCl_2$—$CFCl$—CF_2Cl
214bb	CF_3—$CFCl$—CCl_3
214ab	CF_3—CCl_2—$CFCl_2$
214ca	$CFCl_2$—CF_2—$CFCl_2$
214cb	CF_2Cl—CF_2—CCl_3
215aa	CF_3—CCl_2—CF_2Cl
215ba	CF_2Cl—$CFCl$—CF_2Cl
215bb	CF_3—$CFCl$—$CFCl_2$
215ca	CF_2Cl—CF_2—$CFCl_2$
215cb	CF_3—CF_2—CCl_3
216aa	CF_3—CCl_2—CF_3
216ba	CF_3—$CFCl$—CF_2Cl
216ca	CF_2Cl—CF_2—CF_2Cl
216cb	CF_3—CF_2—$CFCl_2$

C_3 HCFCs

221aa	$CFCl_2$—CCl_2—$CHCl_2$
221ab	CCl_3—CCl_2—$CFHCl$
221ba	CCl_3—$CFCl$—$CHCl_2$
221da	CCl_3—$CHCl$—$CFCl_2$
221ea	CCl_3—CFH—CCl_3
222aa	CF_2Cl—CCl_2—$CHCl_2$
222ab	$CFCl_2$—CCl_2—$CFHCl$
222ac	CCl_3—CCl_2—CF_2H
222ba	$CFCl_2$—$CFCl$—$CHCl_2$
222bb	CCl_3—$CFCl$—$CFHCl$
222ca	CCl_3—CF_2—$CHCl_2$
222da	$CFCl_2$—$CHCl$—$CFCl_2$
222db	CCl_3—$CHCl$—CF_2Cl
222ea	CCl_3—CFH—$CFCl_2$
223aa	CF_3—CCl_2—$CHCl_2$
223ab	CF_2Cl—CCl_2—$CFHCl$
223ac	$CFCl_2$—CCl_2—CF_2H
223ba	CF_2Cl—$CFCl$—$CHCl_2$
223bb	$CFCl_2$—$CFCl$—$CFHCl$
223bc	CCl_3—$CFCl$—CF_2H
223ca	$CFCl_2$—CF_2—$CHCl_2$
223cb	CCl_3—CF_2—$CFClH$
223da	$CFCl_2$—$CHCl$—CF_2Cl
223ea	$CFCl_2$—CFH—$CFCl_2$
223eb	CCl_3—CFH—CF_2Cl
224aa	CF_3—CCl_2—$CFHCl$
224ab	CF_2Cl—CCl_2—CF_2H
224ba	CF_3—$CFCl$—$CHCl_2$
224bb	CF_2Cl—$CClF$—$CFHCl$
224ca	CF_2Cl—CF_2—$CHCl_2$
224cb	$CFCl_2$—CF_2—$CFHCl$
224da	CF_2Cl—$CHCl$—CF_2Cl
224db	CF_3—$CHCl$—$CFCl_2$
224ea	$CFCl_2$—CFH—CF_2Cl
224eb	CCl_3—CFH—CF_3
225aa	CF_3—CCl_2—CF_2H
225ba	CF_3—$CFCl$—$CFHCl$
225bb	CF_2Cl—$CFCl$—CF_2H
225ca	CF_3—CF_2—$CHCl_2$
225cb	CF_2Cl—CF_2—$CFHCl$
225cc	$CFCl_2$—CF_2—CF_2H
225da	CF_3—$CHCl$—CF_2Cl
225ea	CF_2Cl—CFH—CF_2Cl
225eb	CF_3—CFH—$CFCl_2$
226ba	CF_3—$CFCl$—CF_2H
226ca	CF_3—CF_2—$CFHCl$
226cb	CF_2H—CF_2—CF_2Cl
226da	CF_3—$CHCl$—CF_3
226ea	CF_3—CHF—CF_2Cl
231aa	$CHCl_2$—CCl_2—$CFHCl$
231ba	$CHCl_2$—$CFCl$—$CHCl_2$

231bb CCl_3—$CFCl$—CH_2Cl
231da $CFCl_2$—$CHCl$—$CHCl_2$
231db CCl_3—$CHCl$—$CFHCl$
231ea CCl_3—CHF—$CHCl_2$
231fa CCl_3—CH_2—$CFCl_2$
232aa $CFHCl$—CCl_2—$CFHCl$
232ab $CHCl_2$—CCl_2—CHF_2
232ac CF_2Cl—CCl_2—CH_2Cl
232ad $CFCl_2$—CCl_2—CHF_2
232ba $CHCl_2$—$CFCl$—$CFHCl$
232bb $CFCl_2$—$CFCl$—CH_2Cl
232bc CCl_3—$CFCl$—CH_2F
232ca $CHCl_2$—CF_2—$CHCl_2$
232cb CCl_3—CF_2—CH_2Cl
232da CF_2Cl—$CHCl$—$CHCl_2$
232db $CFCl_2$—$CHCl$—$CFHCl$
232dc CCl_3—$CHCl$—CHF_2
232ea $CFCl_2$—CFH—$CHCl_3$
232eb CCl_3—CFH—$CFHCl$
232fa $CFCl_2$—CH_2—$CFCl_2$
232fb CCl_3—CH_2—$CFCl_2$
233aa CF_2H—CCl_2—$CFHCl$
233ab CF_3—CCl_2—CH_2Cl
233ac CF_2Cl—CCl_2—CH_2F
233ba $CFHCl$—$CClF$—$CFHCl$
233bb $CHCl_2$—$CFCl$—CHF_2
233bc CF_2Cl—$CFCl$—CH_2Cl
233bd $CFCl_2$—$CFCl$—CH_2F
233ca $CHCl_2$—CF_2—$CFHCl$
233cb $CFCl_2$—CF_2—CH_2Cl
233cc CCl_3—CF_2—CH_2F
233da CF_3—$CHCl$—$CHCl_2$
233db CF_2Cl—$CHCl$—$CFHCl$
233dc $CFCl_2$—$CHCl$—CHF_2
233ea CF_2Cl—CHF—$CHCl_2$
233eb $CFCl_2$—CHF—$CFHCl$
233ec CCl_3—CHF—CHF_2
233fa $CFCl_2$—CH_2—CF_2Cl
233fb CCl_3—CH_2—CF_3
234aa CF_2H—CCl_2—CF_2H
234ab CF_3—CCl_2—CH_2F
234ba $CFHCl$—$CFCl$—CF_2H
234bb CF_3—$CFCl$—CH_2Cl
234bc CF_2Cl—$CFCl$—CH_2F
234ca $CFHCl$—CF_2—$CFHCl$
234cb $CHCl_2$—CF_2—CHF_2
234cc CF_2Cl—CF_2—CH_2Cl
234cd $CFCl_2$—CF_2—CH_2F
234da CF_3—$CHCl$—$CFHCl$
234db CF_2Cl—$CHCl$—CHF_2
234ea CF_3—CF_2—$CFHCl$
234ec $CFCl_2$—CHF—CHF_2
234fa CF_2Cl—CH_2—CF_2Cl
234fb CF_3—CH_2—$CFCl_2$
235ba CF_2H—$CClF$—CF_2H
235bb CF_3—$CFCl$—CH_2F
235ca $CFHCl$—CF_2—CHF_2
235cb CF_3—CF_2—CH_2Cl
235cc CF_2Cl—CF_2—CH_2F
235da CF_3—$CHCl$—CHF_2
235ea CF_3—CHF—$CFHCl$
235eb CF_2Cl—CHF—CHF_2
235fa CF_3—CH_2—CF_2Cl
241aa $CFHCl$—CCl_2—CH_2Cl
241ab $CHCl_2$—CCl_2—CH_2F
241ac $CFCl_2$—CCl_2—CH_3
241bb CCl_3—$CFCl$—CH_3
241da $CHCl_3$—$CHCl$—$CFHCl$
241db $CFCl_2$—$CHCl$—CH_2Cl
241dc CCl_3—$CHCl$—CH_2F
241ea $CHCl_2$—CHF—$CHCl_2$
241eb CCl_3—CHF—CH_2Cl
241fa $CFCl_2$—CH_2—$CHCl_2$
241fb CCl_3—CH_2—$CFHCl$
242aa CHF_2—CCl_2—CH_2Cl
242ab $CFHCl$—CCl_2—CH_2F
242ac CF_2Cl—CCl_2—CH_3
242ba $CFHCl$—$CFCl$—CH_2Cl
242bb $CHCl_2$—$CHCl$—CHF_2
242bc $CFCl_2$—$CFCl$—CH_3
242ca $CHCl_2$—CF_2—CH_2Cl
242cb CCl_3—CF_2—CH_3
242da CH_2Cl—CHF—$CFHCl$
242db $CHCl_2$—$CHCl$—CHF_2
242dc CF_2Cl—$CHCl$—CH_2Cl
242dd $CFCl_2$—$CHCl$—CH_2F
242ea $CHCl_2$—CHF—$CFHCl$
242eb CCl_3—CHF—CH_2F
242ec CCl_3—CHF—CH_2F
242fa CF_2Cl—CH_2—$CHCl_2$

242fb $CFCl_2$—CH_2—$CFHCl$
242fc CCl_3—CHF—CH_2F
243aa CF_2H—CCl_2-CH_2F
243ab CF_3—CH_2—$CHCl_2$
243ba CHF_2—$CFCl$—CH_2Cl
243bb $CFHCl$—$CFCl$—CH_2F
243bc CF_2Cl—$CFCl$—CH_3
243ca $CFHCl$—CF_2—CH_2Cl
243cb $CHCl_2$—CF_2—CH_2F
243cc $CFCl_2$—CF_2—CH_3
243da CHF_2—$CHCl$—$CFHCl$
243db CF_3—$CHCl$—CH_2Cl
243ea $CFHCl$—CHF—$CHFCl$
243eb CHF_2—CHF—$CHCl_2$
243ec CF_2Cl—CHF—CH_2Cl
243ed $CFCl_2$—CHF—CH_2F
243fa CF_3—CH_2—$CHCl_2$
243fb CF_2Cl—CH_2—$CFHCl$
243fc $CFCl_2$—CH_2—CHF_2
244ba CF_2H—$CFCl$—CH_2F
244bb CF_3—$CFCl$—CH_3
244ca CHF_2—CF_2—CH_2Cl
244cb $CFHCl$—CF_2—CH_2F
244cc CF_2Cl—CF_2—CH_3
244da CHF_2—$CHCl$—CHF_2
244db CF_3—$CHCl$—CH_2F
244ea CHF_2—CHF—$CFHCl$
244eb CF_3—CHF—CH_2Cl
244ec CF_2Cl—CHF—CH_2F
244fa CF_3—CH_2—$CFHCl$
244fb CF_2Cl—CH_2—CHF_2
251aa CH_2Cl—CCl_2—CH_2F
251ab $CFHCl$—CCl_2—CH_2Cl
251ba CH_2Cl—$CFCl$—CH_2Cl
251bb $CHCl_2$—$CFCl$—CH_3
251db $CHCl_2$—$CHCl$—CH_2F
251dc $CFCl_2$—CHF—CH_3
251ea $CHCl_2$—CHF—CH_2Cl
251eb CCl_3—CHF—CH_3
251fa $CHCl_2$—CH_2—$CFHCl$
251fb $CFCl_2$—CH_2—CH_2Cl
251fc CCl_3—CH_2—CH_2F
252aa CH_2F—CCl_2—CH_2F
252ab CHF_2—CCl_2—CH_3
252ba CH_2Cl—$CFCl$—CH_2F
252bb $CFHCl$—$CFCl$—CH_3
252ca CH_2Cl—CF_2—CH_2Cl
252cb $CHCl_2$—CF_2—CH_3
252da CF_3—$CHCl$—CH_2Cl
252db $CFHCl$—$CHCl$—CH_2F
252dc CF_2Cl—$CHCl$—CH_3
252ea $CFHCl$—CHF—CH_2Cl
252eb $CHCl_2$—CHF—CH_2F
252ec $CFCl_2$—CHF—CH_3
252fa $CFHCl$—CH_2—$CFHCl$
252fb $CHCl_2$—CH_2—CHF_2
252fc CF_2Cl—CH_2—CH_2Cl
252fd $CFCl_2$—CH_2—CH_2F
253ba CHF_2—$CFCl$—CH_2F
253bb CHF_2—$CFCl$—CH_3
253ca CH_2Cl—CF_2—CH_2F
253cb $CFHCl$—CF_2—CH_3
253da CHF_2—$CHCl$—CH_2F
253db CF_3—$CHCl$—CH_3
253ea CHF_2—CHF—CH_2Cl
253eb $CFHCl$—CHF—CH_2F
253ec CF_2Cl—CHF—CH_3
253fa CF_2H—CH_2—$CFHCl$
253fb CF_3—CH_2—CH_2Cl
253fc CF_2Cl—CH_2—CH_2F
261aa CH_2F—CCl_2—CH_3
261ba CH_2Cl—$CFCl$—CH_3
261da CH_2Cl—$CHCl$—CH_2F
261db $CFHCl$—$CHCl$—CH_3
261ea CH_2Cl—CHF—CH_2Cl
261eb $CHCl_2$—CHF—CH_3
261fa $CFHCl$—CH_2—CH_2F
261fb $CHCl_2$—CH_2—CH_2F
261fc $CFCl_2$—CH_2—CH_3
262ba CH_2F—$CFCl$—CH_3
262ca CH_2Cl—CF_2—CH_3
262da CH_2F—$CHCl$—CH_2F
262db CHF_2—$CHCl$—CH_3
262ea CH_2Cl—CHF—CH_2F
262eb $CFHCl$—CHF—CH_3
262fa CH_2F—CH_2—CH_2Cl
262fb $CFHCl$—CH_2—CH_2F
262fc CF_2Cl—CH_2—CH_3
271ba CH_3—$CFCl$—CH_3
271da CH_2F—$CHCl$—CH_3

271ea	$CH_2Cl—CH_2—CH_3$
271fa	$CH_2F—CH_2—CH_2Cl$
271fb	$CFHCl—CH_2—CH_3$

C_3 HFCs

227ca	$CF_3—CF_2—CHF_2$
227ea	$CF_3—CHF—CF_3$
236ca	$CHF_2—CF_2—CHF_2$
236cb	$CF_3—CF_2—CH_2F$
236ea	$CF_3—CHF—CHF_2$
236fa	$CF_3—CH_2—CF_3$
245ca	$CF_2H—CF_2—CH_2F$
245cb	$CF_3—CF_2—CH_3$
245ea	$CHF_2—CHF—CHF_2$
245eb	$CF_3—CHF—CH_2F$
245fa	$CF_3—CH_2—CHF_2$
254ca	$CH_2F—CF_2—CH_2F$
254cb	$CHF_2—CF_2—CH_3$
254ea	$CHF_2—CHF—CH_2F$
254eb	$CF_3—CHF—CH_3$
254fa	$CHF_2—CH_2—CHF_2$
254fb	$CF_3—CH_2—CH_2F$
263ca	$CH_2F—CF_2—CH_3$
263fa	$CHF_2—CH_2—CH_2F$
263fb	$CF_3—CH_2—CH_3$
272ca	$CH_3—CF_2—CH_3$
272ea	$CH_2F—CHF—CH_3$
272fa	$CH_2F—CH_2—CH_2F$
272fb	$CHF_2—CH_2—CH_3$
281ea	$CH_3—CHF—CH_3$
281fa	$CH_2F—CH_2—CH_3$

C_3 CFOs

1211xa	$CFCl_2—CCl=CCl_2$
1211xb	$CCl_3—CCl=CClF$
1211ya	$CCl_3—CF=CCl_2$
1212xa	$CClF_2—CCl=CCl_2$
1212xb	$CFCl_2—CCl=CClF$
1212xc	$CCl_3—CCl=CF_2$
1212ya	$CCl_2F—CF=CCl_2$
1212yc	$CCl_3—CF=CClF$
1213xa	$CF_3—CCl=CCl_2$
1213xb	$CF_2Cl—CCl=CClF$
1213xc	$CCl_2F—CCl=CF_2$
1213ya	$CClF_2—CF=CCl_2$
1213yb	$CCl_2F—CF=CClF$
1213yc	$CCl_3—CF=CF_2$
1214xb	$CF_3—CCl=CClF$
1214xc	$CF_2Cl—CCl=CF_2$
1214ya	$CF_3—CF=CCl_2$
1214yb	$CF_2Cl—CF=CClF$
1214yc	$CFCl_2—CF=CF_2$
1215xc	$CF_3—CCl=CF_2$
1215yb	$CF_3—CF=CFCl$
1215yc	$CF_2Cl—CF=CF_2$

C_3 HCFOs

1221xa	$CFHCl—CCl=CCl_2$
1221xb	$CHCl_2—CCl=CClF$
1221xd	$CFCl_2—CCl=CHCl$
1221xe	$CCl_3—CCl=CHF$
1221ya	$CHCl_2—CF=CCl_2$
1221yd	$CCl_3—CF=CHCl$
1221za	$CFCl_2—CH=CCl_2$
1221zb	$CCl_3—CH=CClF$
1222xa	$CF_2H—CCl=CCl_2$
1222xb	$CFHCl—CCl=CClF$
1222xc	$CHCl_2—CCl=CF_2$
1222ya	$CFHCl—CF=CCl_2$
1222yb	$CHCl_2—CF=CClF$
1222za	$CF_2Cl—CH=CCl_2$
1222zb	$CFCl_2—CH\text{-}CClF$
1222zc	$CCl_3—CH=CF_2$
1223xb	$CHF_2—CCl=CClF$
1223xc	$CFHCl—CCl=CF_2$
1223xd	$CF_3—CCl=CHCl$
1223ya	$CHF_2—CF=CCl_2$
1223yb	$CFHCl—CF=CClF$
1223yc	$CHCl_2—CF=CF_2$
1223yd	$CF_2Cl—CF=CHCl$
1223ye	$CFCl_2—CF=CHF$
1223za	$CF_3—CH=CCl_2$
1223zb	$CF_2Cl—CH=CClF$
1223zc	$CFCl_2—CH=CF_2$
1224xc	$CHF_2—CCl=CF_2$

1224xe	CF_3—CCl=CHF
1224yb	CHF_2—CF=$CClF$
1224yc	$CFHCl$—CF=CF_2
1224yd	CF_3—CF=$CHCl$
1224ye	CF_2Cl—CF=CHF
1224zb	CF_3—CH=$CClF$
1224zc	CF_2Cl—CH=CF_2
1231xa	CH_2F—CCl=CCl_2
1231xb	CH_2Cl—CCl=$CClF$
1231xd	$CFHCl$—CCl=$CHCl$
1231xe	$CHCl_2$—CCl=CHF
1231xf	$CFCl_2$—CCl=CH_2
1231ya	CH_2Cl—CF=CCl_2
1231yd	$CHCl_2$—CF=$CHCl$
1231yf	CCl_3—CF=CH_2
1231za	$CFHCl$—CH=CCl_2
1231zb	$CHCl_2$—CH=$CClF$
1231zd	$CFCl_2$—CH=$CHCl$
1231ze	CCl_3—CH=CHF
1232xb	CH_2F—CCl=$CClF$
1232xc	CH_2Cl—CCl=CF_2
1232xd	CHF_2—CCl=$CHCl$
1232xe	$CFHCl$—CCl=CHF
1232xf	CF_2Cl—CCl=CH_2
1232ya	CH_2F—CF=CCl_2
1232yb	CH_2Cl—CF=$CClF$
1232yd	$CFHCl$—CF=$CHCl$
1232ye	$CHCl_2$—CF=CHF
1232yf	$CFCl_2$—CF=CH_2
1232za	CHF_2—CH=CCl_2
1232zb	$CFHCl$—CH=$CClF$
1232zc	$CHCl_2$—CH=CF_2
1232zd	CF_2Cl—CH=$CHCl$
1232ze	$CFCl_2$—CH=CHF
1233xc	CH_2F—CCl=CF_2
1233xe	CHF_2—CCl=CHF
1233xf	CF_3—CCl=CH_2
1233yb	CH_2F—CF=$CClF$
1233yc	CH_2Cl—CF=CF_2
1233yd	CHF_2—CF=$CHCl$
1233ye	$CFHCl$—CF=CHF
1233yf	CF_2Cl—CF=CH_2
1233zb	CHF_2—CH=$CClF$
1233zc	$CFHCl$—CH=CF_2
1233zd	CF_3—CH=$CHCl$
1233ze	CF_2Cl—CH=CHF
1241xb	CH_3—CCl=$CClF$
1241xd	CH_2F—CCl=$CHCl$
1241xe	CH_2Cl—CCl=CHF
1241xf	$CFHCl$—CCl=CH_2
1241ya	CH_3—CF=CCl_2
1241yd	CH_2Cl—CF=$CHCl$
1241yf	$CHCl_2$—CF=CH_2
1241za	CH_2F—CH=CCl_2
1241zb	CH_2Cl—CH=$CClF$
1241zd	$CFHCl$—CH=$CHCl$
1241ze	$CHCl_2$—CH=CHF
1241zf	$CFCl_2$—CH=CH_2
1242xc	CH_3—CCl=CF_2
1242xe	CH_2F—CCl=CHF
1242xf	CHF_2—CCl=CH_2
1242yb	CH_3—CF=$CClF$
1242yd	CH_2F—CF=$CHCl$
1242ye	CH_2Cl—CF=CHF
1242yf	$CFHCl$—CF=CH_2
1242zb	CH_2F—CH=$CClF$
1242zc	CH_2Cl—CH=CF_2
1242zd	CHF_2—CH=$CHCl$
1242ze	$CFHCl$—CH=CHF
1242zf	CF_2Cl—CH=CH_2
1251xe	CH_3—CCl=CHF
1251xf	CH_2F—CCl=CH_2
1251yd	CH_3—CF=$CHCl$
1251yf	CH_2Cl—CF=CH_2
1251zb	CH_3—CH=$CClF$
1251zd	CH_2F—CH=$CHCl$
1251ze	CH_2Cl—CH=CHF
1251zf	$CFHCl$—CH=CH_2

C_3 HFOs

1225yc	CHF_2—CF=CF_2
1225ye	CF_3—CF=CHF
1225zc	CF_3—CH=CF_2
1234yc	CH_2F—CF=CF_2
1234ye	CHF_2—CF=CHF
1234yf	CF_3—CF=CH_2
1234zc	CHF_2—CH=CF_2
1234ze	CF_3—CH=CHF

1243yc	CH_3—CF=CF_2
1243ye	CH_2F—CF=CHF
1243yf	CHF_2—CF=CH_2
1243zc	CH_2F—CH=CF_2
1243ze	CHF_2—CH=CHF
1243zf	CF_3—CH=CH_2
1252ye	CH_3—CF=CHF
1252yf	CH_2F—CF=CH_2
1252zc	CH_3—CH=CF_2
1252ze	CH_2F—CH=CHF
1252zf	CHF_2—CH=CH_2
1261yf	CH_3—CF=CH_2
1261ze	CH_3—CH=CHF
1261zf	CH_2F—CH=CH_2

Other (Misc.)

338pcc	CHF_2–$(CF_2)_2$–CHF_2
347pcc	CHF_2–$(CF_2)_2$–CH_2F
356qcc	CH_2F–$(CF_2)_2$–CH_2F
374pc	CHF_2–CF_2–C_2H_5
c438ee	*cyclo*-[$CHFCHF(CF_2)_3$]
c447ze	*cyclo*-[$CHFCH_2(CF_2)_3$]
1336mzz	CF_3–CH=CH–CF_3
1363pfy	CHF_2–CH_2–CF=CH_2
E1225ye	CF_3O–CF=CHF
c1427yz	*cyclo*-[$CFCH(CF_2)_3$]
c1436zz	*cyclo*-[$CHCH(CF_2)_3$]
c1445yzf	*cyclo*-[$CFCHCH_2(CF_2)_2$]
1567mcftc	C_2F_5–CH_2–$C(CH_3)$=CF_2