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Phase-Transfer Deracemization, Development of Reagents for Electrophilic Trifluoromethylation, and Hydrogen-Mediated Deoxydehydration

Author
Samant, Andrew Vivek

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Phase-Transfer Deracemization, Development of Reagents for Electrophilic Trifluoromethylation, and Hydrogen-Mediated Deoxydehydration

By

Andrew Vivek Samant

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University of California, Berkeley

Committee in charge:

Professor F. Dean Toste, Chair
Professor Robert G. Bergman
Professor James K. Bishop

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Abstract

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As is often the case in the chemical sciences, the research presented here represents a path that followed naturally from one step to the next in the laboratory while ending up in seemingly disparate areas of focus at the end of each project.

Chapter 1 describes the development of a purely chemical deracemization system. Typical asymmetric reactions fall into two categories: those where the starting material must be transformed into a new compound, and those where enantioenriched starting materials can be recovered in a maximum of 50% yield. Deracemization is an alternate strategy which can generate enantioenriched starting material in 100% maximum yield. The major challenge to implementing a successful chemical deracemization is that, on its own, solution-phase deracemization is always thermodynamically unfavorable. In order to circumvent this, we developed a system where the deracemization process could be chemically pumped by coupling it to the quenching of a strong oxidant and a strong reductant. In particular, we used a phase-transfer strategy to promote selective reaction of the substrate with both a cationic, water-soluble oxidant and a highly insoluble reductant, rather than having the oxidant and reductant react directly with one another.

An interest in cationic reagents similar to the oxidant used to accomplish deracemization led (albeit quite indirectly) to the development of the reagents described in Chapter 2. Widely used iodine(III)-based electrophilic trifluoromethyling agents (e.g. Togni reagents) are typically neutral species, which require activation by a Lewis acid in order to trifluoromethylate nucleophiles such as alcohols and imidazoles. In contrast, we have developed a new class of trifluoromethyliodonium chlorides, which possess a high degree of cationic character and are capable of accomplishing these trifluoromethylations in the absence of an activator. Furthermore, we have demonstrated that these iodonium chlorides serve as good surrogates for reactive intermediates produced during acid-mediated trifluoromethylation. This equivalence has allowed us to gain a better understanding of these

systems and has led to observations that could aid in the development of even more effective classes of reagent in the future.

Chapter 3 describes a new and promising method for the conversion of biomass into commodity chemicals. Most modern commercial biomass conversion relates to the transformation of lipids (e.g. triglycerides) into chemically simple biofuels. Carbohydrate-based feedstocks, which include abundant natural resources such as glucose and cellulose, have the potential to be converted into more complex monomers and fine chemicals. In the course of our research, we developed a system capable of reducing sugar-derived compounds, such as glucaric acid and its derivates, directly to commercially relevant starting materials such as adipate esters using hydrogen gas as the reductant. This dual-catalytic system uses palladium on carbon to activate hydrogen gas and high-valent soluble rhenium catalysts to deoxygenate polyols. Additionally, we have investigated the unusual alpha,beta-selectivity that this deoxydhydration system provides, and used to selectively convert ribonolactone and gluconolactone into compounds which retain a high degree of chemical complexity but are less highly oxygenated than the starting materials.

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First, I'd like to thank Dean for fostering a group environment that rewards independent thought and the pursuit of interesting research. Dean has always managed to balance an incredible knowledge of and interest in the chemical sciences with a light touch that allows new researchers to develop their own projects and learn to think independently. This strategy as a PI is one that I consider to be leaps and bounds superior to what one might consider the "state of the art" in the field of organic chemistry, and it's thanks to Dean's approach that I've been able to develop into the chemist that I am now.

Several group members mentored me when I was a younger student, and I thank all of them for phrasing their criticism in a way that was at times perhaps more constructive than I deserved it to be. Aaron Lackner and Miles Johnson were the more experienced grad students who took me under their wing when I first joined the group, teaching me everything from how to run my first non-automated silica column to what to do when I wanted to make sure my solvent was actually dry. Andrew Neel and Willie Wolf were two very helpful grad students a year ahead of me, and always impressed me with their wisdom (at least when it came to chemistry). I'd also like to thank Matt Winston, who was as knowledgeable and approachable as it is possible to be, and was always down to clown.

Additionally, one of the most important skills to learn in research is the value in collaborating with other people. To that end, I want to thank Aaron Lackner (again), John Brantley, and Reed Larson for working with me in various capacities on various projects.

I'd also like to specifically thank the other graduate students in my cohort, Dave Kaphan, Mark Levin, and Rebecca Triano, as well as the students a year below me, Cindy Hong and Richard Thornbury. I couldn't have asked for a more intelligent, scientifically-minded, or collegial group of people to go through grad school with. More generally, I owe the entire Toste group a debt of gratitude for being an environment where illuminating hallway conversations (and coffee breaks, of course) abound, and where everyone has useful advice and input for each other.

Outside the sometimes-insular world of the Toste group, I'd like to thank Noelle Catarineu for her companionship and support throughout my time at Berkeley.

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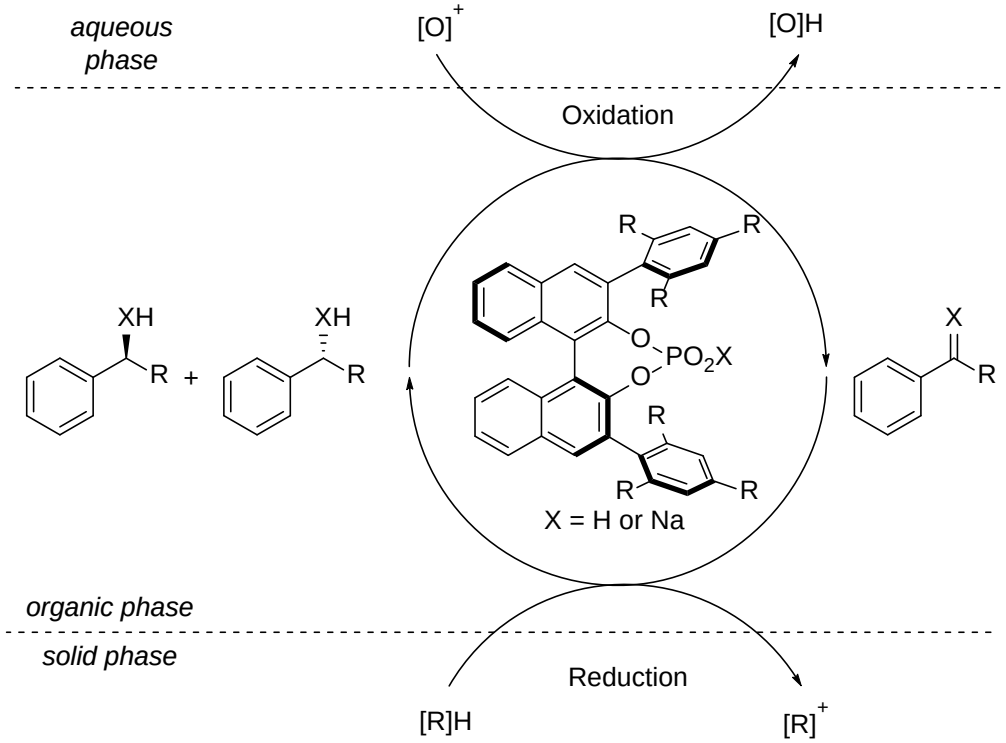
Chapter 1

A Purely Chemical Deracemization of Tetrahydroisoquinolines Enabled by Phase Separation of Otherwise Incompatible Reagents

1.1 Preface

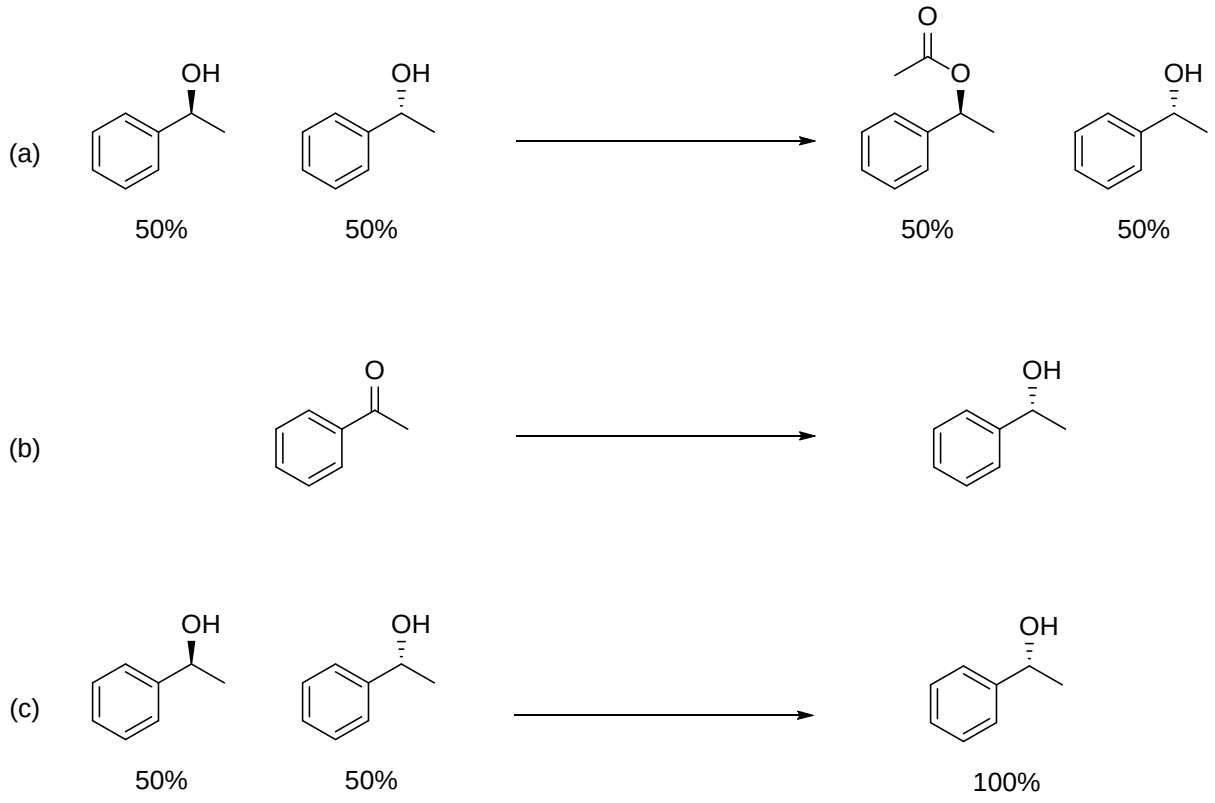
Broadly speaking, there are two major classes of enantioselective processes used to convert racemic starting materials into enantioenriched compounds. The first class, which includes classical and kinetic resolutions, proceeds without transforming any stereocenters, and therefore can be used to produce enantioenriched starting material, but only in a maximum of 50% yield (when starting from a racemic mixture). The second class, which can broadly be described as asymmetric transformations but also includes dynamic kinetic resolutions and dynamic asymmetric transformations, enantioselectively creates or transforms a stereocenter, and can therefore reach 100% theoretical yield while transforming the starting material into a new product. A third class can be envisioned which epimerizes a stereocenter to convert racemic starting material directly into enantioenriched starting material with 100% theoretical yield. This type of process, herein referred to as deracemization, is necessarily thermodynamically unfavorable in dilute solution, and has thus been difficult to demonstrate in a purely chemical system. Herein, we describe a new technique for chemical deracemization, which uses phase separation to effect the deracemization of 2-substituted tetrahydroisoquinolines by coupling this process to a thermodynamically favorable redox cycle.

Portions of this chapter are based on work done in collaboration with Dr. Aaron D. Lackner.



1.2 Introduction

There are currently several major approaches that are used to produce enantioenriched products from racemic or achiral starting materials. One of the oldest and simplest techniques is chiral resolution, wherein a racemic compound of interest is complexed with a cheaply available chiral reagent, such as tartaric acid or proline, to form a diastereomeric pair of adducts. This may take the form of a salt, a hydrogen-bonded species, or a true covalent linkage, but regardless of the specific method, the underlying principle is that, unlike the enantiomeric pair of starting materials, the two diastereomeric adducts are distinct compounds with different physical properties, and may be thusly separated.[1–3] A related approach is kinetic resolution, wherein a racemic mixture of starting materials is subjected to a catalytic process with a chiral catalyst, selectively transforming one enantiomer of starting material and leaving the other unchanged.[4]



Scheme 1. Examples of a) resolution, b) asymmetric transformation, and c) deracemization.

The above two approaches do not in any way alter the initial stereochemistry of the starting material, which means that the undesired enantiomer of starting material is simply discarded and the maximum yield of this process is only 50% (**Scheme 1a**). Two other approaches involve the direct chemical manipulation of the stereocenter of interest. Asymmetric transformations using a chiral catalyst or reagent can take an achiral starting material and selectively transform it into a chiral center with the desired geometry (**Scheme**

1b). Finally, dynamic kinetic asymmetric transformation is a related process wherein the starting material is able to rapidly interconvert between two enantiomers on the timescale of the reaction, followed by an irreversible asymmetric transformation (or kinetic resolution) in the same reaction mixture. This facile epimerization causes both enantiomers of starting material to ultimately be transformed into a single enantiomer of product by funneling the racemic starting material into whichever enantiomeric form reacts more favorably with the chiral catalyst.[5,6]

These approaches are all very useful in certain contexts, but each also presents its own limitations. As mentioned previously, simple and kinetic resolutions suffer from a maximum yield of 50%. More subtly, asymmetric transformations have a thermodynamic requirement that they transform starting material into a chemically distinct product. While many times this does not present a problem, in a scenario where the starting material is the substance that is desired, it becomes necessary to append a second synthetic step to the process in order to reverse the effects of the transformation.[7,8]

The major goal of this project was to create a set of reaction conditions which could accomplish a chemical deracemization: in other words, a system that transformed racemic starting material into enantioenriched starting material with 100% theoretical yield (**Scheme 1c**). Current examples in the literature of deracemization fall into two categories. The first is dynamic preferential crystallization, wherein a supersaturated solution of an easily-epimerized compound is treated with an enantiopure seed crystal of the same compound. In these circumstances, further crystal formation may sometimes be selective for the same enantiomer of compound as is present in the seed crystal. In essence, this can be thought of as a dynamic kinetic resolution where the “irreversible step” is a physical change of state rather than a chemical transformation.[9–11] Additionally, there are literature examples of chemoenzymatic deracemization, wherein an amino acid is oxidized enzymatically and reduced in the same reaction mixture by a borohydride reductant.[12–14] Both of these techniques are very useful in situations where they apply, but they are both inherently limited in the choices of substrates available (in the former case, the compound must possess the physical property that it prefers to crystallize as two separate chiral crystals; in the latter case, an enzyme capable of enantioselectively transforming the compound must exist). Based on these limitations, our interest turned to addressing the problem in a less substrate-selective way by using a purely chemical system.

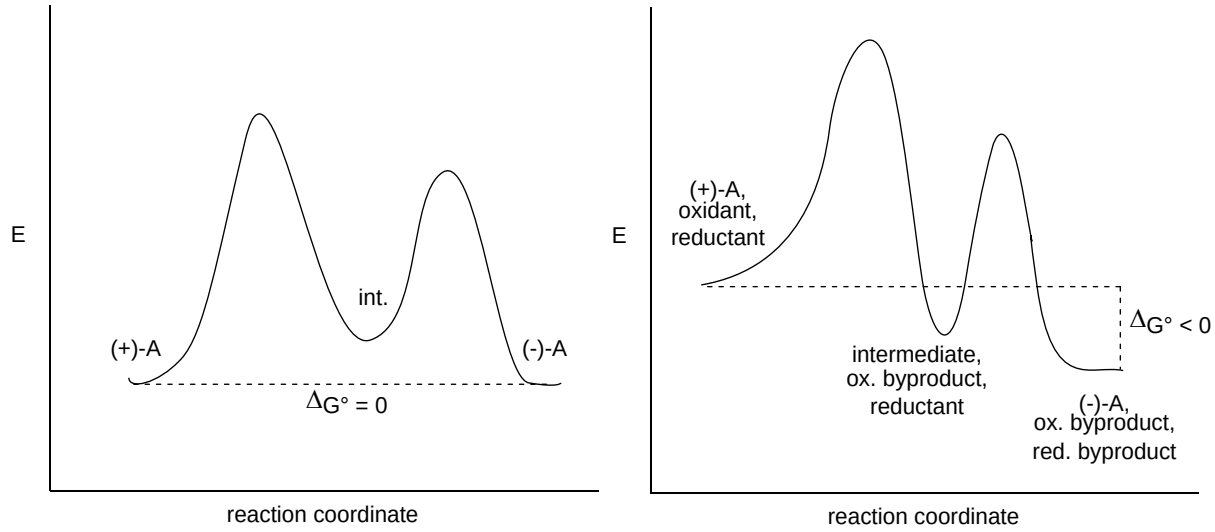


Figure 1. Thermodynamics of uncoupled and coupled (de)racemization

The primary challenge in developing such a reaction is the need for a thermodynamic driving force for the reaction. From a purely ground-state perspective, a dilute solution of racemic compound is identical enthalpically to an enantioenriched sample of the same, but the former is more favorable entropically due to the presence of a larger number of degenerate states (specifically, the mixture of S and R stereocenters). Because of this, the conversion from racemic to enantioenriched compound is always endergonic in dilute solution, and in order for the reaction to proceed as desired it must be coupled to some external energy "pump" (**Figure 1**).

1.3 Results and Discussion

1.3.1 Reaction Design

The observation that a solution-phase deracemization requires a thermodynamic driving force led us to consider what sources of chemical energy we might be able to use. The primary challenge, we reasoned, would be devising a system where one reagent would transform the starting material into an intermediate, and a second reagent would enantioselectively convert the intermediate back into starting material. In general, the challenge with a system of this type would be direct reaction of the two reagents: there is a high likelihood that any given oxidant strong enough to react with the substrate and any given reductant capable of reducing the resulting intermediate are also capable of reacting directly with one another in a competitive process.

Rather than attempting to find a specific combination of reagents that could be tuned to be selective for the organic substrate rather than each other, we opted to use a phase-transfer strategy to segregate the various components of the reaction from one another.[15,16] In order for

phase separation to be successful, we reasoned that we would need three phases: one phase with high concentration of substrate and low concentrations of both reagents, a second phase with high concentration of one reagent, and a third phase with high concentration of the other reagent (**Figure 2**).

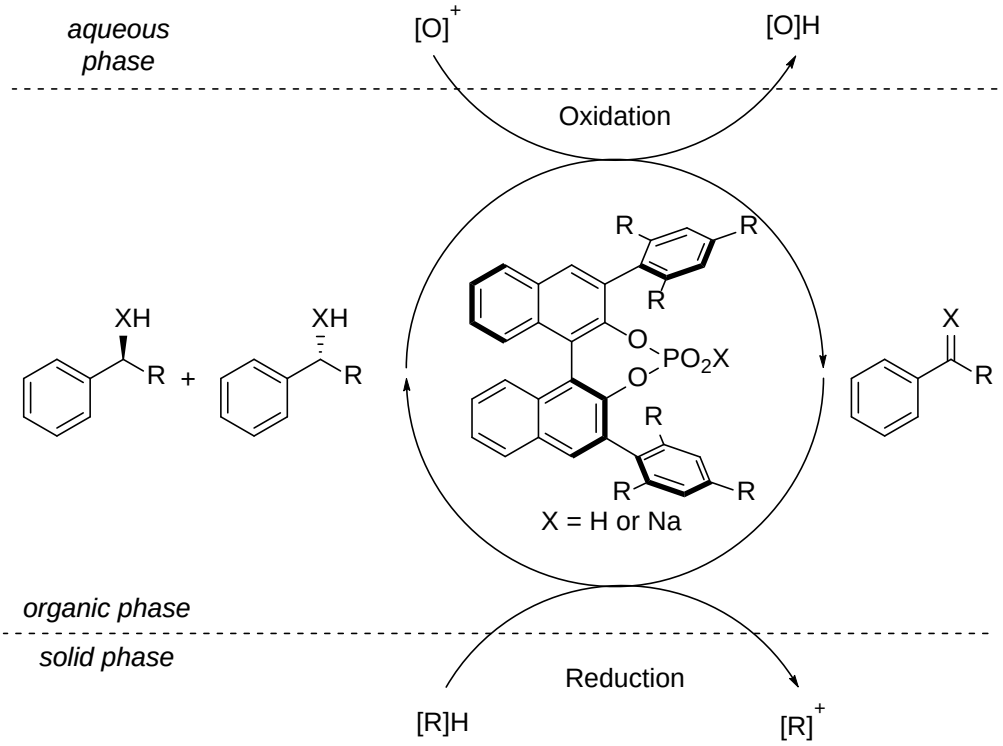
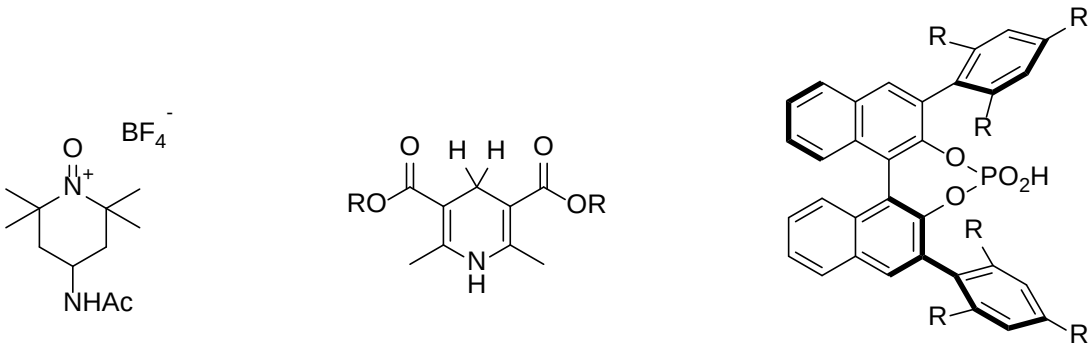


Figure 2. Triphasic deracemization system

The idea of using a straightforward redox couple as the chemical pump was attractive, due to the fact that there are a wide variety of reductive processes capable of setting stereocenters, as well as many oxidation reactions which are capable of removing them. For the sake of generality, we considered it advantageous to design a system where the both the oxidant and reductant had low solubility in the organic phase, allowing a variety of organic substrates to be subjected to the reaction conditions without the need to fine tune the solvent system for each substrate. In particular, we investigated a system where the oxidant was a water-soluble oxopiperidinium salt **1**, and the reductant was a Hanztsch-type dihydropyridine **2**.



1

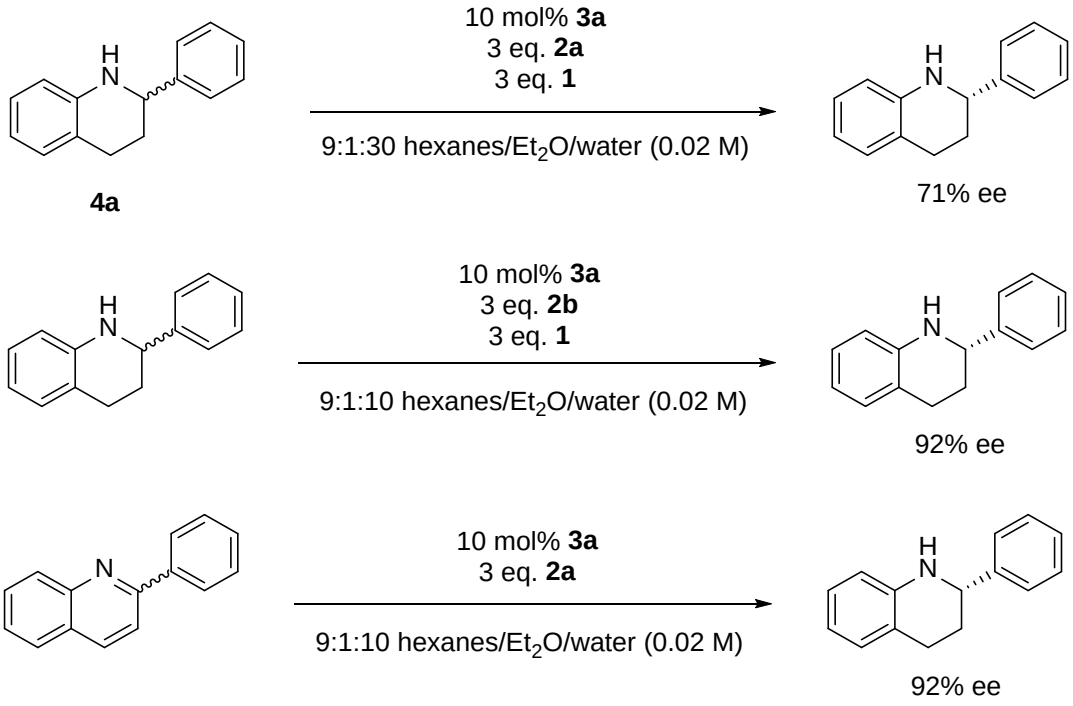
2a: R = Et
2b: R = 4-ClBn
2c: R = 2,6-Cl_2Bn

3a: (*S*)-TRIP, R = iPr
3b: (*S*)-TCYP, R = Cy

Figure 3. Reagents and catalysts employed for deracemization

The oxopiperidinium component of the system was chosen because it is quite water soluble, has negligible solubility in non-polar organic solvents, and is commercially available. Additionally, we were able to demonstrate that it is capable of cleanly and rapidly oxidizing saturated nitrogen heterocycles to their unsaturated counterparts in homogeneous organic solution, giving us reason to expect that it would be capable of doing so as a heterogeneous mixture on a reasonable timescale.

As reductants, Hantzsch ester hydrides presented us with several advantages. Their straightforward, modular synthesis allowed us to experiment with various ester side linkages, which have minimal influence on the reactivity of the reductant but can result in marked changes in solubility properties. Additionally there are a wide variety of enantioselective reductions which have been reported using these dihydropyridines in conjunction with lipophilic chiral phosphoric acid catalysts.[17–20] We envisioned that this system might allow the phosphoric acid to serve two separate roles: an asymmetric catalyst to effect the reduction and a phase-transfer catalyst to bring traces of the oxopiperidinium salt into solution.



Scheme 2. Initial results for tetrahydroisoquinoline deracemization

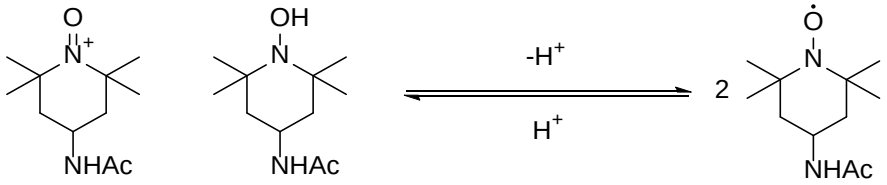
1.3.2 Initial Reaction Optimization

Our initial work used a 9:1:30 mixture of hexanes, diethyl ether, and water as the solvent system, and commercially available Hantzsch ester hydride **2a** as the reductant. Using 2-phenyl-1,2,3,4-tetrahydroquinoline (**4a**) as a substrate in the presence of **1**, **2a** and **3a** in a triphasic aqueous/organic/solid system gave 72% ee of the recovered starting material. This promising result was obtained despite the fact that **3a** is somewhat soluble in non-polar organic solvents.[a]

In light of these results, we began exploring modifications to the ester moieties of the Hantzsch ester reductant. We found that bis-4-chlorobenzyl ester (**3b**) had dramatically reduced organic solubility when compared to the initial reductant, and that it displayed concomitantly higher enantioselectivity when used to deracemize **4a**. The obtained value of 92% ee compares quite well with the asymmetric induction provided by directly reducing intermediate quinoline **5a** (92% ee).

[a] It should be noted at the outset that obtaining NMR yields of recovered starting material for these reactions is challenging: the presence of the paramagnetic byproduct **7** precluded comparing the crude reaction mixture to a T_0 containing an internal standard, and the small scale made the post-facto addition of standard after removal of **7** an unreliable method. As such, rather than obtaining isolated yields at each stage of the optimization process, we used the purity of the recovered starting material as a rough surrogate for product yield. This was ultimately borne out as a valid approximation once isolated yields were determined using optimized conditions.

An additional factor we later found important for maintaining the reproducibility of the deracemization reaction was the pH, requiring us to run it under slightly acidic conditions. In the absence of acid, the pyridine byproduct produced from the reductant will slowly raise the pH of the reaction mixture, which causes two complications. Because the reduction is acid-catalyzed, its rate may be decreased once the pyridine concentration builds up. Additionally, the oxidant and its byproduct **6** exist in an equilibrium with the free radical species **7**; at low pH this strongly favors formation of the oxidant, but as the solution becomes more alkaline this shifts to produce the nitroxyl radical, which we observed to be incapable of performing the desired oxidation (**Figure 4**).[21]

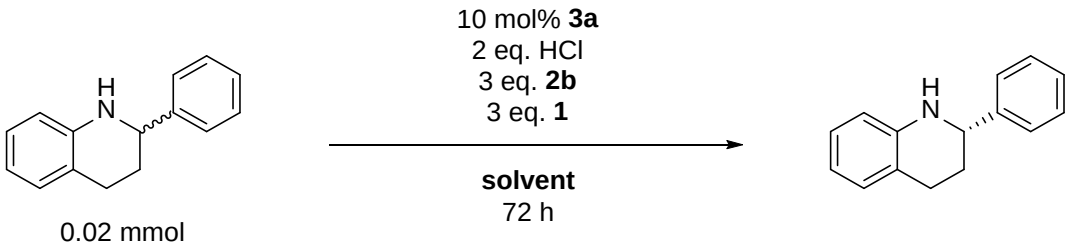


6 **7**

Figure 4. Conproportionation of oxidant and byproduct

We then began to optimize the polarity of the organic solvent, as we reasoned that the system must allow significant solubility of our substrates of interest while maintaining a low degree of solubility for the reductant.[b] As we expected, the solvent environment had a significant impact on the outcome of the reaction; while a solvent mixture of predominantly hexanes gave good results, switching to a mixture where the major component was toluene or diethyl ether drastically decreased the degree of asymmetric induction. Interestingly, using pure hexanes as the organic component gave somewhat decreased enantioselectivity. This may be the result of poor substrate solubility leading to competitive direct reaction of the oxidant and reductant in a manner similar to that seen at low stir rates (*vide infra*). Ultimately, we found that a 4:1 mixture of hexanes and toluene as the organic phase gave good enantioselectivity while still utilizing common solvents.

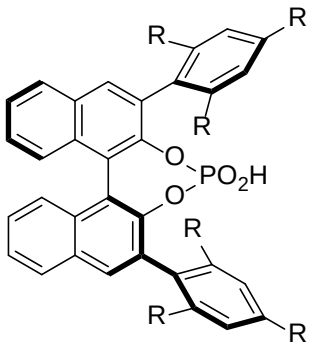
[b] The oxidant, as a salt, has very low solubility in any of the organic phases tested.



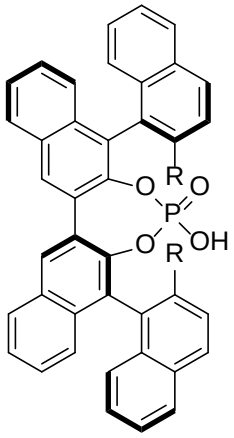
Solvent System	ee%
1:1 hexanes/water	84
4:1:5 hexanes/toluene/water	92
9:1:10 hexanes/toluene/water	89
1:4:5 hexanes/toluene/water	24
4:1:5 hexanes/diethyl ether/water	90
1:4:5 hexanes/diethyl ether/water	racemic
4:1:5 hexanes/mesitylene/water	93

Table 1. Solvent optimization

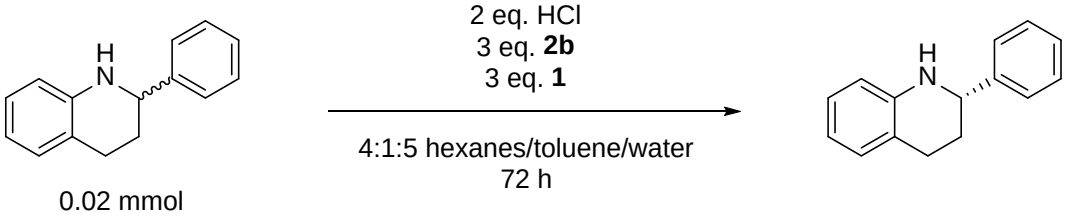
We also explored various phosphoric acid catalysts. In recent years, there have been a wide variety of chiral phosphoric acids and related derivatives that have been demonstrated to be excellent catalysts for a variety of enantioselective acid-catalyzed reactions.[17–20] However, due to the high level of synthetic effort and material expense required to synthesize most of these catalysts, we focused primarily on examining the behavior of known catalysts available in our laboratory. Interestingly, while doubly-axial phosphoric acids **8a-c** showed good enantioselectivity in organic solvents, in the presence of an aqueous phase their selectivity dropped dramatically. This can most easily be attributed to changes in the hydrogen-bonding network of the transition state. In contrast, initial catalyst **3a** gave high asymmetric induction in both monophasic and biphasic systems, and as a result subsequent development focused on systems with this catalyst (**Table 2**).



3a: (*S*)-TRIP, R = iPr
3b: (*S*)-TCYP, R = Cy



R = cyclohexyloxy; **8a**
R = phenyl; **8b**
R = 4-biphenyl; **8c**



0.02 mmol

Catalyst	ee% (organic solvent)	ee% (triphasic)
3a	93	92
3b	92	94
8a	86	75
8b	88	49
8c	72	N.D.

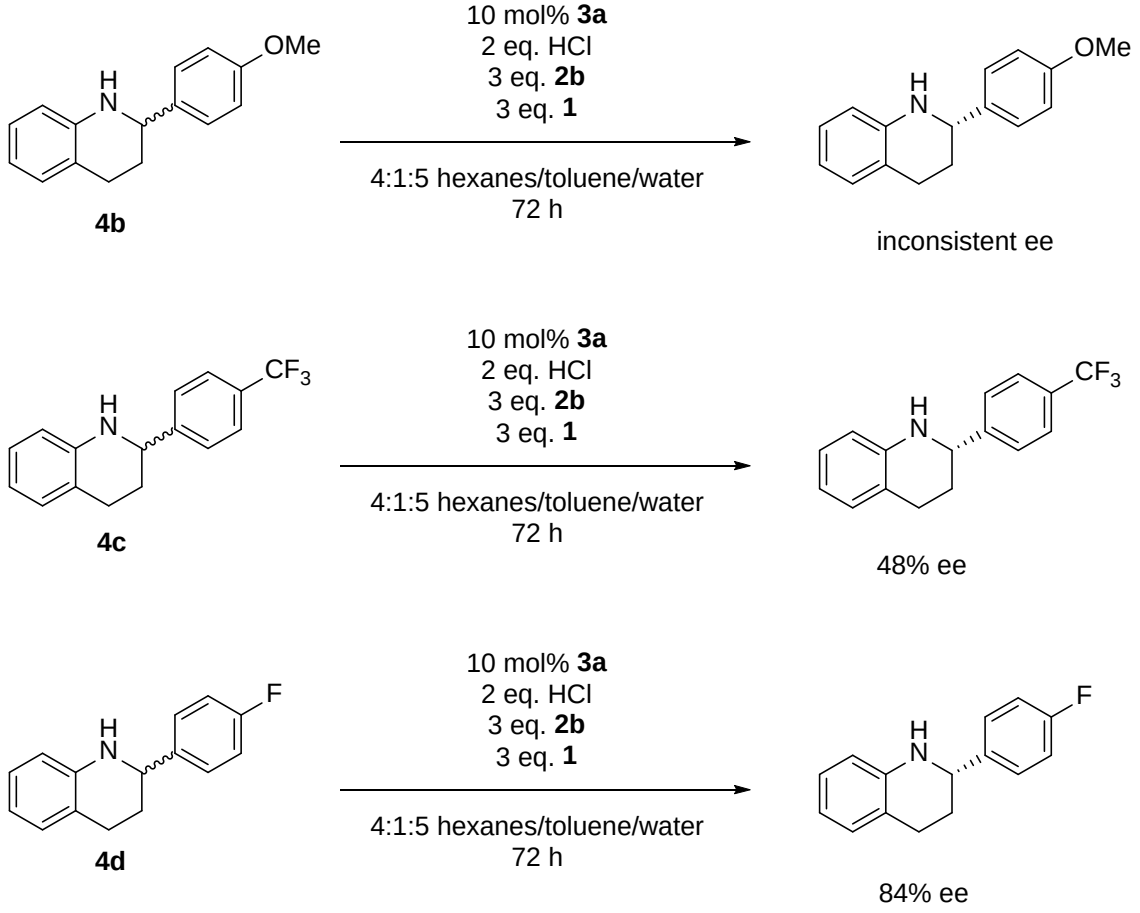
Table 2. Catalyst optimization

1.3.3 Scope and Limitations of 2-Aryl-1,2,3,4-Tetrahydroquinoline Substrates

With these results in hand, we began to explore the substrate scope of the deracemization. We found after several attempts with the electron-rich substrate **4b** that this

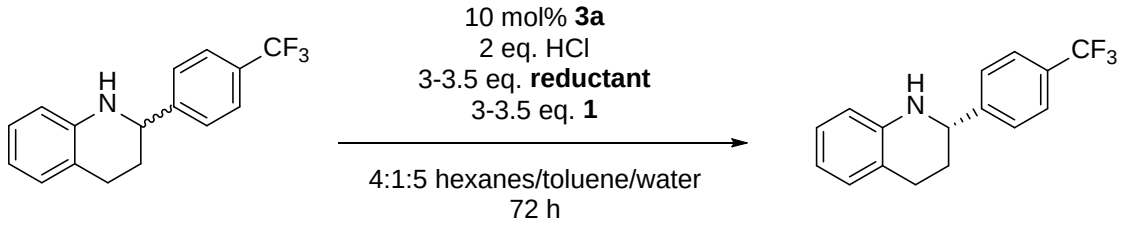
particular reaction gave irreproducible enantioselectivity as well as the formation of byproducts. When we directly treated the independently synthesized intermediate 2-(4-methoxyphenyl)quinoline with the oxopiperidinium salt, we found that the NMR spectrum of the reaction mixture was quite complex, indicating that this intermediate itself is capable of undergoing further reaction under these conditions. While we did not explore this pathway further, plausible candidates for this undesired reactivity are oxidation of the p-anisyl ring and formation of the quinoline N-oxide. As a result, we were led to the conclusion that this reaction system is unsuitable for the deracemization of electron-rich substrates.

Electron-poor substrates proved more tractable, although enantioselectivities of the initial deracemizations of tetrahydroisoquinoline **4c** and **4d** fell short of those observed for the direct reduction of the corresponding quinoline. As might be expected, these electron-poor substrates were more difficult to oxidize than the initial compound; while **4a** was completely oxidized within minutes by the oxopiperidinium salt, **4c** showed only 63% conversion over the course of an hour. This sluggish oxidation introduces two potential sources of unproductive reagent use.



Scheme 3. Reactivity of electronically modified substrates

One potential difficulty with a slow oxidation step is that the direct reaction of oxidant and reductant may become more competitive, thereby lowering the overall efficiency of the chemical pump. To overcome this, we synthesized the bis-2,6-dichlorobenzyl Hantzsch ester **2b**, which has dramatically lower solubility than even the 4-chlorobenzyl analog in organic solvents. We found that this new reagent improved the enantioselectivity of the deracemization to 74% ee, which was a significant improvement but still much lower than the value obtained for the direct enantioselective reduction.



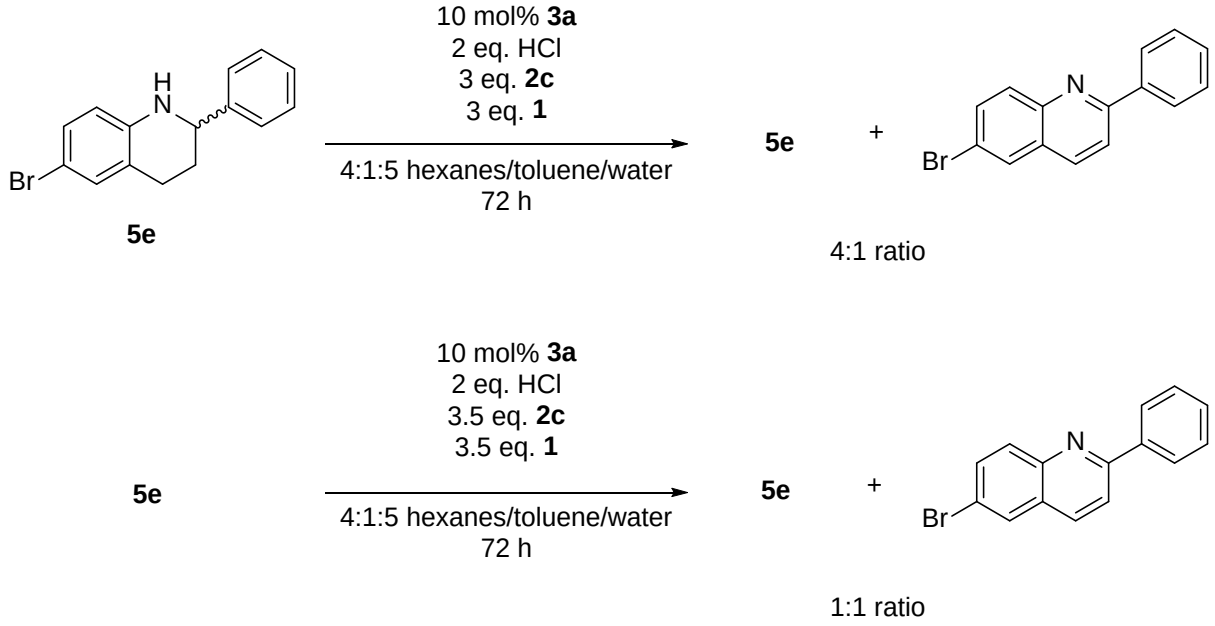
Reductant	Equivalents of reagents	ee%
2b	3.0	48%
2c	3.0	74%
2c	3.5	90%

Table 3. Effect of reductant choice on electron-poor substrate

The second challenge with a slow oxidation is that unproductive cycling of the reagent may occur *via* re-oxidation of substrate that has already been oxidized and reduced once. Because there is no significant degree of enantiodiscrimination in the oxidation step (*vide infra*), if oxidation occurs on the same timescale as reduction then the desired enantiomer of starting material will continue to react with the oxidant as the deracemization proceeds. Unlike direct reagent quenching, which we were able to avoid by modification of the reagents, this pathway is essentially identical to the desired deracemization. As such, we found that for electron-poor substrates it was necessary to increase the loading of both oxidant and reductant to 3.5 equivalents; doing so increased the enantioselectivity of the deracemization of **4c** to near that observed for the direct reduction of the quinoline.

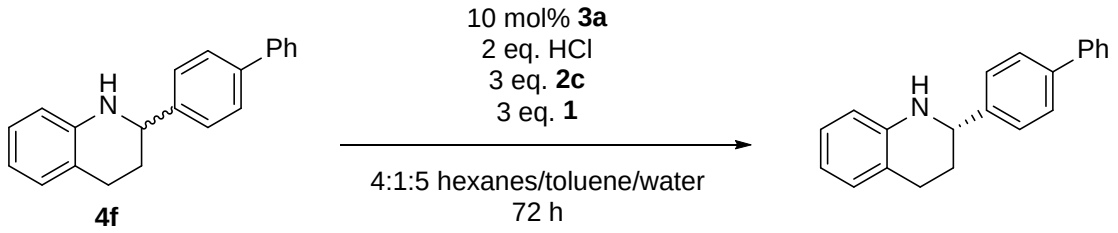
Once we had worked out the challenges associated with electron-poor substrates, we wanted to determine whether this system was applicable to a wider array of substrates. While we obtained moderate to good enantioselectivities for several substrates, we found that in several cases we observed a significant buildup of intermediate quinoline even after extended reaction times. Of particular note was the fact that in the case of substrate **5e**, we observed a higher degree of intermediate built up after extended reaction times when using 3.5 equivalents of both reagents than when using 3.0 equivalents (**Scheme 4**). We were unable to

find a purely chemical rationale for these results, which led to the possibility that this was an issue related to the physical properties of the reaction mixture.



Scheme 4. Increased oxidized intermediate observed at higher reagent loading

In particular, because of the highly insoluble nature of the reductant (as well as its pyridine byproduct), we observed that in some cases, the reaction mixture grew viscous and difficult to stir after significant reaction progress had occurred. In order to quantify the effects this might have on the reaction, we undertook a study on the effect of stir rate on its yield and enantioselectivity. We found that the deracemization of **5f** occurred with excellent enantioselectivity at 800 rpm and above, but at slower stir rates the selectivity began to degrade to a small but measurable extent, and in the extreme case where the reaction was not stirred, only the oxidized quinoline intermediate was observed (**Table 4**).

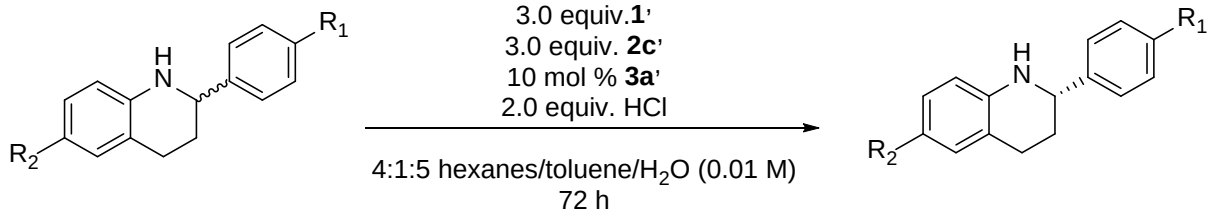


Stir rate (rpm)	Isolated Yield (%)	ee%
no stirring	None recovered	-
200	88	81 (79.7, 81.2)
400	89	87 (89.2, 84.6)
600	86	89 (88.3, 88.6)
800	94	93 (92.5, 93.4)
1000	88	92 (91.1, 93.1)

[a]Average of two trials [b]Data from individual trials in parentheses

Table 4. Effect of stir rate on reaction outcome

These results suggested that there is an ideal substrate concentration which would vary from compound to compound. At high concentrations, stir rate becomes an issue, whereas at lower concentrations, a more significant amount of reductant is solubilized and direct reaction of the reagents becomes more problematic. We found that for most substrates, 0.01M was a good balance between these two opposing issues, although for **4c** (which has the most significant issues with direct reagent reaction) a somewhat more concentrated mixture gave optimal results. Ultimately, we were able to successfully deracemize a variety of 2-aryl-1,2,3,4-tetrahydroquinolines, in many cases with enantioselectivities approaching those attained by direct reduction of the intermediate quinoline.



Substrate	R_1	R_2	Isolated Yield[a]	%ee[a,b]
4a	H	H	94 ± 3%	91.7 ± 0.8% (92%)
4c[c]	CF_3	H	75 ± 5%	90.7 ± 1.2% (97%)
4d[c]	F	H	87 ± 6%	93.1 ± 0.5% (94%)
4e	H	Br	95 ± 3%	80 ± 7% (94%)
4f	Ph	H	94 ± 6%	92.7 ± 1.8% (96%)
4g	Me	H	90 ± 5%	84.0 ± 1.6% (90%)
4h	2-naphthyl	H	86 ± 6%	86.3 ± 1.4% (95%)

[a] N = 3; [b] Enantioenrichment of stepwise reaction listed in parentheses; [c] 3.5 equivalents of **1** and **2c**; [d] Reaction run at 0.02 M

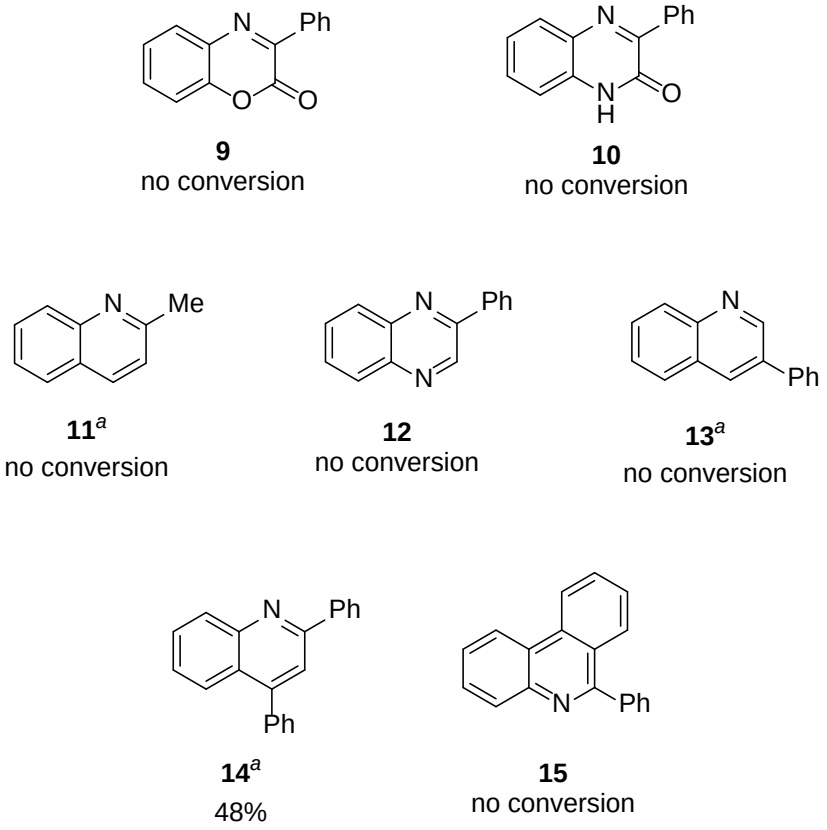
Table 5. Deracemization substrate scope.

1.3.4 Mechanistic Remarks

One of the questions we hoped to answer was what role the chiral phosphoric acid played in this reaction. While it was clear that the enantioinduction of the overall deracemization derived at least in part from the enantioselectivity of the reduction step, we were curious if it was also possible that this catalyst played a role in the oxidation step. Studies of other systems in our group have demonstrated that in certain cases enantioselectivity can be imparted from the formation of a chiral ion pair between a cationic reagent and a chiral phosphate anion.[15,21] However, when **4c** was treated with **1** and **3a**, the remaining starting material at various time points was always racemic, indicating that no significant degree of kinetic resolution occurred during the oxidation step of the reaction ($S < 1.1$).

A further question that followed from this observation was whether the phosphoric acid acts as a phase-transfer catalyst. This proved to be a challenging question to answer

conclusively; the oxidation step is quite rapid under standard conditions, and the biphasic nature of the system prevents both reliable kinetics and cooling of the reaction mixture below 0 ºC. Qualitatively though, the oxidation is still essentially complete within several minutes even in the absence of phosphoric acid. This, of course, doesn't exclude the possibility that oxidation is significantly faster in the presence of phosphoric acid. However, the fact that the uncatalyzed oxidation still proceeds on a much faster timescale than the phosphoric acid-catalyzed reduction suggests that, even if the phosphate conjugate base is responsible for phase-transfer catalysis, this catalysis is merely a byproduct of the other components of the system and does not impact the overall course of the reaction.



Reaction conditions: 1 equiv. substrate, 2 equiv. HCl, 10 mol% **3a**, 1.5 equiv. **2c**; [a] 3 equiv. **2c** used

Figure 5. Attempted reduction of other unsaturated nitrogen heterocycles

1.3.5 Other Heterocyclic Substrates

After successful deracemization of 2-aryltetrahydroisoquinolines, we examined a variety of unsaturated nitrogen heterocycles with reported Hantzsch ester-mediated enantioselective reductions to determine whether these reductions would also be feasible in

non-polar organic solvents. However, with the exception of the 2-arylquinolines detailed above as well as 2-aryl-3H-indoles[22], none of the classes we examined were capable of undergoing reduction on a reasonable timescale in the non-polar solvents necessary for the deracemization. In the cases of highly electron-deficient rings such as benzoxazines and quinoxalines, this is perhaps an unsurprising result, as the protonation of the nitrogen would be expected to be much less favorable. It is less clear why modified quinolines such as **13** and **14** fail to react, as their electronic properties should be similar to those of the successful substrates. Nonetheless, in most cases these potential intermediates showed no sign of reduction under the reaction conditions, meaning that their corresponding reduced forms would be poor candidates for deracemization in this system.

1.4 Conclusion

Our work is the first demonstrated example of a purely chemical, single-operation deracemization reaction. It demonstrates the power of phase separation to suppress undesired side reactivity that would otherwise occur on much faster timescale than that of the desired deracemization reaction. Since this work was first disclosed, more examples of chemical deracemization have appeared in the literature, and we hope that the ideas underpinning this methodology will be used to allow the realization of other challenging synthetic problems in the future.[23,24]

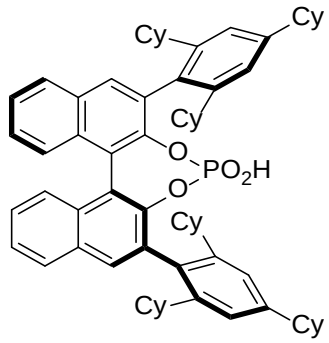
1.5 Supporting Information

General Considerations

Unless otherwise noted, reactions were performed without any special effort to exclude water or air. Solvents and reagents were used as-received from commercial suppliers except in the following cases: *N*-Bromosuccinimide was recrystallized from boiling water and dried *in vacuo* immediately prior to use. 2-Aminophenol was recrystallized from boiling water. 4-acetamido-2,2,6,6-tetramethyloxopiperidinium tetrafluoroborate was dissolved in acetonitrile (roughly 40 mL solvent per gram of salt) and precipitated with excess diethyl ether. The precipitate was filtered and then dried under vacuum overnight.

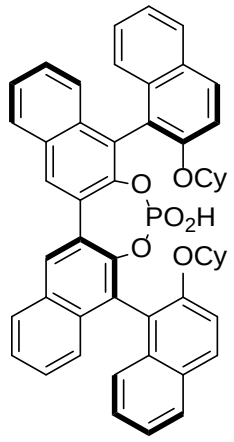
All column chromatography was performed using Sorbent Technology silica gel, (60 Å, 40-63 μm). All NMR spectra were recorded with a Bruker AVQ-400 spectrometer, and were referenced to residual nondeuterated solvent peaks. Chemical shifts are reported in ppm. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. Mass spectral data were obtained from the MicroMass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley using a Thermo LTQ-FT for ESI spectra and a Waters AutoSpec Premier for EI spectra. Enantiomeric excesses were determined on a Shimadzu VP Series Chiral HPLC with an IB column, using 19:1 hexanes/isopropanol as the mobile phase unless otherwise noted. Melting points were measured using an Electrothermal IA 9100 melting point apparatus.

Chiral phosphoric acid catalyst **3a** is commercially available. Other catalysts were prepared according to literature procedures or straightforward modifications thereof.[16,25,26]



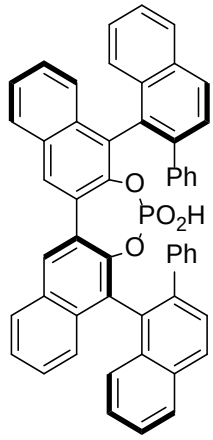
(*S*)-4-hydroxy-2,6-bis(2,4,6-tricyclohexylphenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (S-TCyp, 3b)

White powder. 1H NMR (400 MHz, CDCl3) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.73 (s, 2H), 7.49-7.44 (m, 2H), 7.18-7.28 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 4H), 2.45-0.54 (m, 66H).



(*R*,*R*)- 5,9-bis(2- (cyclohexyloxy)naphthalen- 1- yl)- 7- hydroxydinaphtho[2, 3-d:2',3'- f][1,3,2] dioxaphosphepine 7-oxide (4 a)

White powder. 1H NMR (400 MHz, CDCl3) δ 8.39 (s, 2H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.8, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.56-7.52 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.35-7.30 (m, 2H), 7.24-7.19 (m, 4H), 7.17- 7.13 (m, 4H), 7.10 (d, *J* = 8.4 Hz, 2H), 1.80-0.99 (m, 22H).



(*R*,*R*)- 7-hydroxy- 5,9- bis(2- phenylnaphthalen- 1- yl)dinaphtho[2,3- d:2',3'-f][1,3,2] dioxaphosphepine 7- oxide (4b)

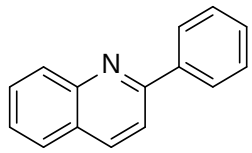
White powder. 1H NMR (400 MHz, CDCl3) δ 7.92 (s, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.77-7.74 (m, 4H), 7.45- 7.36 (m, 4H), 7.32-7.28 (m, 4H), 7.17- 7.14 (m, 6H), 7.05-7.03 (m, 6H), 6.91-6.89 (m, 4H).

General Procedure for Deracemization Reaction

To a shell-type 1- dram vial equipped with a 12 mm x 5 mm oblong magnetic stir bar was added substrate (0.02 mmol, 1 equiv), **2c** (0.06-0.07 mmol, 3.0- 3.5 equiv), and (*S*)-TRIP (1.5 mg, 0.002 mmol, 10 mol%). Organic solvent (1 mL) was added to the vial and the mixture was stirred briefly to dissolve substrate and catalyst (the reductant does not dissolve). To the resulting mixture was quickly added a solution of 2N HCl (20 μL, 0.04 mmol, 2 equiv) and **1** (0.06-0.07 mmol, 3.0- 3.5 equiv) in water (1 mL). The reaction mixture was subjected to stirring at a rate that allowed for thorough mixing but did not result in residue being ejected onto the upper wall of the vial (typically 800 rpm). The mixture was stirred in this manner for 72 h, at which time it was quenched with sat. aq. Na_2SO_3, extracted twice with DCM, concentrated, and purified by passing the resulting solid through a silica plug with 10% ethyl acetate/hexanes.

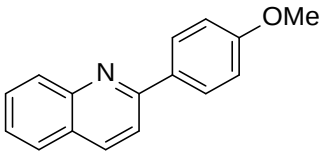
Procedure for Synthesis of 2-arylquinolines

A round bottom flask equipped with a magnetic stir bar was charged with 2-chloroquinoline (489 mg, 3.0 mmol, 1 equiv), arylboronic acid (3.9 mmol, 1.3 equiv) and anhydrous sodium carbonate (1.6 g, 15 mmol, 5 equiv). A 4:1 mixture of dioxane/water (30 mL) was added and the resulting suspension was sparged thoroughly with N_2 while stirred. To this suspension was added tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.03 mmol, 1 mol%). The flask was fitted with a reflux condenser and the reaction mixture was stirred at reflux overnight. The reaction mixture was then allowed to cool to room temperature and filtered through Celite. The filter cake was washed with ethyl acetate, and the organic layer of the filtrate was separated, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting residue was purified as indicated in each individual entry.



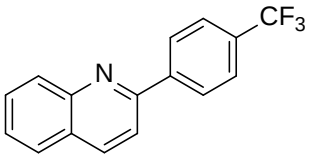
2-phenylquinoline

Purified by silica gel chromatography (10% Et_2O/hexanes) to afford a white powder (517 mg, 2.52 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (t, *J* = 8.8 Hz, 1H), 8.18 (d, *J* = 7.2 Hz, 3H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 3H), 7.48 (t, *J* = 7.2 Hz, 1H). Spectral data matched those reported in the literature.[27]



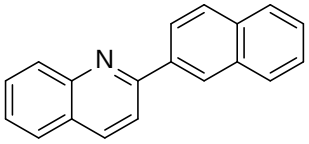
2-(4- methoxyphenyl)quinoline

Purified by recrystallization from layered DCM/hexanes to afford a colorless crystalline solid (619 mg, 2.63 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.15 (m, 4H), 7.81 (t, *J* = 9.2 Hz, 2H), 7.74-7.70 (m, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H). Spectral data matched those reported in the literature.[27]



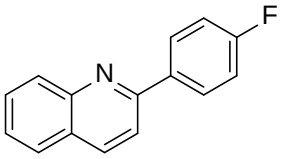
2-(4- trifluoromethylphenyl)quinoline

Purified by recrystallization from layered DCM/hexanes to afford a white powder (567 mg, 2.07 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31-8.29 (m, 3H), 8.20 (d, *J* = 7.6 Hz, 1H), 7.93-7.91 (m, 1H), 7.89- 7.87 (m, 1H), 7.81-7.79 (m, 3H), 7.59 (t, *J* = 7.6 Hz, 1H). Colorless crystalline solid. Spectral data matched those reported in the literature.[27]



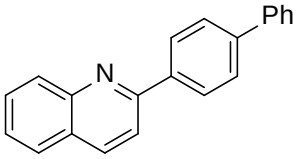
2-(naphthalen- 2- yl)quinoline

Purified by recrystallization from layered DCM/hexanes to afford pale orange flakes (598 mg, 2.34 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.39 (d, *J* = 8.8 Hz, 1H), 8.29-8.23 (m, 2H), 8.06- 8.01 (m, 3H), 7.92-7.90 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.56-7.54 (m, 3H). Spectral data matched those reported in the literature.[28]



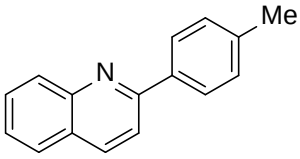
2-(4- fluorophenyl)quinoline

Purified by silica gel chromatography (10% Et2O/hexanes) to afford a white powder (565 mg, 2.53 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 1H), 8.19-8.15 (m, 3H), 7.86-7.84 (m, 2H), 7.76- 7.72 (m, 1H), 7.56-7.52 (m, 1H), 7.24- 7.20 (m, 2H). Spectral data matched those reported in the literature.[28]



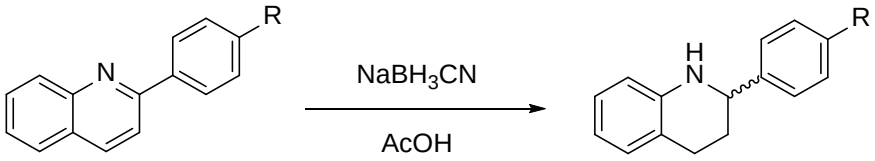
2-([1,1'- biphenyl]- 4- yl)quinoline

Purified by recrystallization from layered DCM/hexanes to afford colorless flakes (572 mg, 2.03 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.25 (m, 3H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.80-7.74 (m, 3H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H). Spectral data matched those reported in the literature.[28]

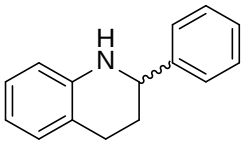


2-(4- methylphenyl)quinoline

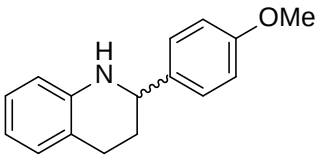
Purified by silica gel chromatography (10% Et_2O/hexanes) to afford a white powder (592 mg, 2.70 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H). Spectral data matched those reported in the literature.[28]



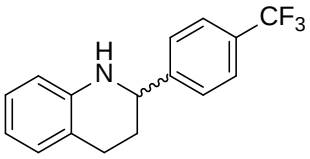
Procedure for the Synthesis of 2-aryl- 1,2,3,4- tetrahydroquinolines (4a-d, 4f-h)
To a 20-mL scintillation vial equipped with a stir bar was added 467 m g (2.28 mmol) 2-phenylquinoline (467 mg, 2.28 mmol, 1 equiv), followed by glacial acetic acid (15 mL). To the resulting solution was added sodium cyanoborohydride (286 mg, 4.55 mmol, 2.0 equiv) in one portion. The reaction mixture was stirred overnight at room temperature, poured into saturated aqueous sodium carbonate, stirred for 15 min and diluted with DCM. The organic layer was separated and the aqueous layer was extracted twice more with DCM. The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure, and purified by column chromatography on silica (20% DCM/hexanes followed by 5% Et_2O/hexanes).



2-pheny l-1,2,3,4- tetrahydroquinoline (4 a)
Performed on a 2.28 mmol scale. Pale yellow oil (350 mg, 1.67 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 7.06- 7.03 (m, 2H), 6.70- 6.67 (m, 1H), 6.57 (d, J = 8.0 Hz, 1H), 4.48-4.46 (m, 1H), 4.10 (br s, 1H), 3.00-2.92 (m, 1H), 2.78- 2.75 (m, 1H), 2.20-2.13 (m, 1H), 2.07-2.01 (m, 1H). Spectral data matched those reported in the literature.[17]

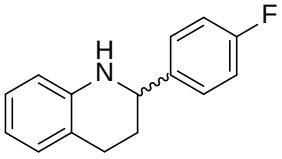


2-(4- methoxyphenyl)- 1,2,3,4- tetrahydroquinoline (4b)
Performed on a 2.10 mmol scale. Amorphous white solid (350 mg, 1.46 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 2H), 7.03-7.00 (m, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.66 (t, J = 7.6 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 4.41-4.38 (dd, J = 9.4, 3.0 Hz, 1H), 4.00 (br s, 1H), 3.83 (s, 3H), 2.99-2.90 (m, 1H), 2.79- 2.72 (m, 1H), 2.12-2.07 (m, 1H), 2.03-1.93 (m, 1H). Sp ectral data matched those reported in the literature.[17]



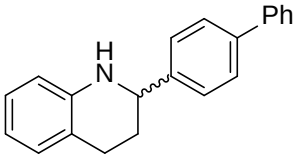
2-(4- trifluoromethylphenyl)-1,2,3,4- tetrahydroquinoline (4 c)

Performed on 1.50 mmol scale. Amorphous white solid (241 mg, 0.869 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.06-7.01 (m, 2H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 4.56-4.53 (m, 1H), 4.07 (br s, 1H), 2.96-2.88 (m, 1H), 2.75- 2 .69 (m, 1H), 2.17-2.12 (m, 1H), 2.04-1.98 (m, 1H). Spectral data matched those reported in the literature.[17]



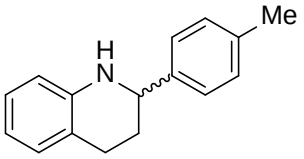
2-(4- fluorophenyl)-1,2,3,4- tetrahydroquinoline (4d)

Performed on 1.50 mmol scale. Amorphous white solid (241 mg, 1.06 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (m, 2H), 7.06- 7.01 (m, 4H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.43 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz), 2.97-2.89 (m, 1H), 2.77- 2.71 (m, 1H), 2.13-2.07 (m, 1 H), 2.02-1.99 (m, 1H). Spectral data matched those reported in the literature.[29]



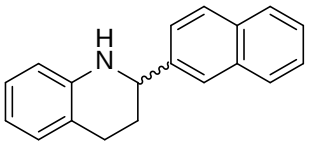
2-([1,1'- biphenyl]- 4- yl)-1,2,3,4- tetrahydroquinoline (4 f)

Performed on a 1.00 mmol scale. Amorphous white solid (190 mg, 0.665 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.58 (m, 4H), 7.49- 7.43 (m, 3H), 7.38- 7.34 (m, 1H), 7.03-7.02 (m, 2H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 4.50 (dd, *J* = 9.4 Hz, 3.4 Hz, 1H), 2.96-2.92 (m, 1H), 2 .80-2.76 (m, 1H), 2.21- 2.14 (m, 1H), 2.11-2.06 (m, 1H). Spectral data matched those reported in the literature.[17]



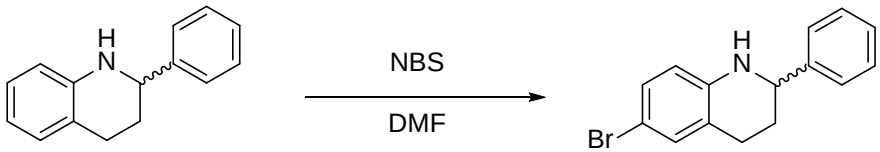
2-(4- methylphenyl)- 1,2,3,4- tetrahydroquinoline (5g)

Performed on 1.50 mmol scale. Amorphous white solid (228 mg, 1.02 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.03-7.00 (m, 2H), 6.66 (t, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 4.41 (dd, *J* = 9.6 Hz, 3.2 Hz, 1H), 2.98-2.90 (m, 1H), 2.79-2.72 (m, 1H), 2.35 (s, 3H), 2.15-2.08 (m, 1H), 2.04-1.97 (m, 1H). Spectral data matched those reported in the literature.[29]



2-(naphthalen- 2- yl)- 1,2,3,4- tetrahydroquinoline (5d)

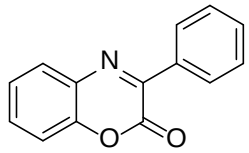
Performed on 1.50 mmol scale. Amorphous white solid (221 mg, 0.852 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.87 (m, 4H), 7.58- 7.51 (m, 3H), 7.13- 7.08 (m, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 4.64 (dd, *J* = 9.0 Hz, 3.4 Hz, 1H), 4.17 (br s, 1H), 3.05-2.97 (m, 1H), 2.85- 2.78 (m, 1H), 2.27- 2.21 (m, 1H), 2.18- 2.12 (m, 1H). Spectral data matched those reported in the literature.[29]



6-bromo- 2- phenyl -1,2,3,4- tetrahydroquinoline (5e)

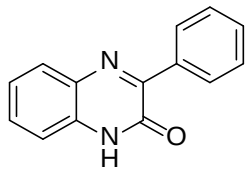
A stirred solution of 2-phenyl- 1,2,3,4- tetrahydroquinoline (350 mg, 1.67 mmol, 1 equiv) in DMF (10 mL) was cooled to 0 °C. To this solution was added dropwise a solution of *N*-bromosuccinimide (298 mg, 1.67 mmol, 1 equiv) in 5 mL DMF. The solution was stirred at 0 °C for 3 h, then at room temperature for 48 h. The reaction mixture was then diluted with ethyl acetate, washed thoroughly with 10% aqueous lithium chloride, dried ($MgSO_4$), concentrated under reduced pressure and purified by silica gel chromatography (10-20% DCM/hexanes) to yield an amorphous off-white solid (249 mg, 0.876 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.36 (m, 4H), 7.32- 7.29 (m, 1H), 7.12- 7.08 (m, 2H), 6.43 (d, *J* = 8.4 Hz, 1H), 4.43 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 2.92-2.84 (m, 1H), 2.74- 2.67 (m, 1H),

2.14-2.10 (m, 1H), 2.01-1.93 (m, 1H). Spectral data matched those reported in the literature.[29]



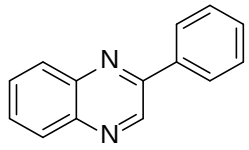
3-phenyl-2*H*-benzo[*b*][1,4]-oxazin-2-one (9)

A solution of ethyl phenylglyoxylate (800 μL, 5.0 mmol, 1 equiv) and 2-aminophenol (600 mg, 5.5 mmol, 1.1 equiv) in 50 mL ethanol was heated at reflux overnight with stirring. The reaction mixture was cooled, concentrated under reduced pressure, and purified by silica gel chromatography (10% ethyl acetate/hexanes). The fractions containing the desired product were concentrated and recrystallized from layered DCM/hexanes, yielding pale yellow needles (565 mg, 2.53 mmol, 51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35-8.33 (m, 2H), 7.87 (d, J = 8.0 Hz, 1H), 7.56-7.52 (m, 4H), 7.41 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H). Spectral data matched those reported in the literature.[30]



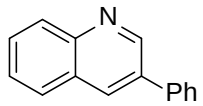
3-phenylquinoxalin-2(1H)-one (10)

To a stirred solution of *o*-phenylenediamine (1.14 g, 10.5 mmol, 3.5 equiv) in 9:1 water/acetic acid (15 mL) was added ethyl phenylglyoxylate (480 μL, 3.0 mmol, 1 equiv). The mixture was stirred overnight at room temperature, filtered, and the filter cake was washed with water followed by absolute ethanol to yield a sufficiently pure yellow powder (619 mg, 2.79 mmol, 93% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.33 (br s, 1H), 8.43-8.41 (m, 2H), 7.96 (d, J = 7.6 Hz, 1H), 7.54-7.53 (m, 4H), 7.41-7.37 (m, 1H), 7.32 (d, J = 8.0 Hz, 1H). Spectral data matched those reported in the literature.[30]



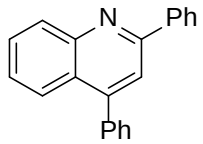
2-phenylquinoxaline (12)

A solution of *o*-phenylenediamine (220 mg, 2.03 mmol, 1.03 equiv) and phenylglyoxal monohydrate (300 mg, 1.97 mmol, 1 equiv) in ethanol (30 mL) was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified on silica (15- 25% ethyl acetate/hexanes) to afford a pale yellow solid (360 mg, 1.75 mmol, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.22-8.19 (m, 2H), 8.17-8.13 (m, 2H), 7.83- 7.75 (m, 2 H), 7.61-7.53 (m, 3H). Spectral data matched those reported in the literature.[31]



3-phenylquinoline (13)

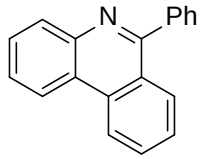
A round bottom flask was charged with 3-bromoquinoline (200 μL, 1.5 mmol, 1 equiv), phenylboronic acid (238 mg, 1.95 mmol, 1.3 equiv) and anhydrous sodium carbonate (800 mg, 7.5 mmol, 5 equiv). A 4:1 mixture of dioxane/water (10 mL) was added and the resulting suspension was sparged thoroughly with N_2 while stirred. To this suspension was added tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.03 mmol, 2 mol%). The flask was fitted with a reflux condenser and heated at reflux overnight. The reaction mixture was then cooled to room temperature and filtered through Celite. The filter cake was washed with ethyl acetate, and the organic layer of the filtrate was separated, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (20% ethyl acetate/hexanes) to afford an orange oil (214 mg, 1.04 mmol, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.32 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.91-7.89 (m, 1H), 7.76- 7 .73 (m, 3H), 7.62-7.60 (m, 1H), 7.58-7.53 (m, 2H), 7.44- 7.47 (m, 1H). Spectral data matched those reported in the literature.[32]



2,4-diphenylquinoline (14)

A round bottom flask was charged with 2,4-dichloroquinoline (500 mg, 2.52 mmol, 1 equiv), phenylboronic acid (760 mg, 6.25 mmol, 2.5 equiv) and anhydrous sodium carbonate (1.6 g,

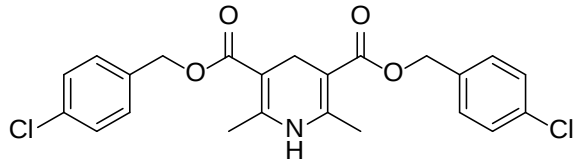
15 mmol, 6.0 equiv). A 4:1 mixture of dioxane/water (25 mL) was added and the resulting suspension was sparged thoroughly with N2 while stirred. To this suspension was added tetrakis(triphenylphosphine)palladium(0) (30 mg, 0.03 mmol, 1 mol%). The flask was fitted with a reflux condenser and heated at reflux overnight. The reaction mixture was then allowed to cool to room temperature and filtered through Celite. The filter cake was washed with ethyl acetate, and the organic layer of the filtrate was separated, washed with brine, dried ($MgSO_4$) and concentrated. The resulting solid was dissolved in a small amount of DCM, diluted with methanol, and recrystallized by slow evaporation of DCM to yield a colorless crystalline solid (510 mg, 1.81 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (m, 1H), 8.22-8.20 (m, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.77-7.74 (m, 1H), 7.58- 7.47 (m, 9H). Spectral dat a matched those reported in the literature.[33]



6-phenylphenanthridine (15)

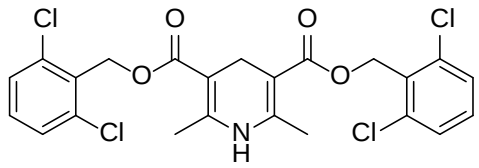
To an ice-cold solution of 2- biphenylamine (1.00 g, 5.91 mmol, 1 equiv) and pyridine (1 mL) in DCM (25 mL) was added slowly benzoyl chloride (720 µL, 6.2 mmol, 1.05 equiv). The reaction solution was allowed to warm to room temperature and stirred for 16 h, then washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was concentrated under reduced pressure and the crude product used directly in the next step. 1.30 g (80% yield).

Crude *N*-([1,1'- biphenyl]- 2- yl)benzamide (1.30 g, 4.76 mmol) and polyphosphoric acid (15 g) were heated to 120 °C and stirred overnight at this temperature. While still hot, the reaction mixture was poured onto ice chips. The resulting aqueous suspension was extracted three times with DCM and the combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and purified by silica gel chromatography (5% ethyl acetate/hexanes) to yield an off-white powder (430 mg, 1.68 mmol, 35% yield): 1H NMR (400 MHz, CDCl3) δ 8.73 (d, *J* = 8.4 Hz, 1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.90-7.86 (m, 1H), 7.80- 7.69 (m, 4H), 7.65- 7.54 (m, 4H). Spectral data matched those reported in the literature.[34]



bis(4-chlorobenzyl) 2,6- dimethyl- 1,4- dihyd ropyridine-3,5- dicarboxylate (2b)
A solution of ethyl acetoacetate (10 mL, 79 mmol, 1 equiv) and 4-chlorobenzyl alcohol (1 3.7 g, 96.1 mmol, 1.22 equiv) in toluene (120 mL) was stirred at reflux overnight. The mixture was concentrated under reduced pressure and then purified by silica gel chromatography (25% Et2O/hexanes). The oil thus obtained was stirred at 40 °C overnight under high vacuum to remove residual ethyl acetoacetate. Yellow oil (5.50 g, 24.3 mmol, 30% yield).

To a solution of 4-chlorobenzyl 3- oxobutanoate (5.50 g, 24.3 mmol, 2.1 equiv) and ammonium acetate (11.4 mmol, 879 mg, 1 equiv) in ethanol (100 mL) was added paraformaldehyde (342 mg, 11.4 mmol, 2.1 equiv). The resulting suspension was heated at reflux overnight, cooled to room temperature, and concentrated *in vacuo*. The resulting residue was dissolved DCM and recrystallized by layering hexanes. A second crop was obtained from the concentrate of the mother liquor by the same method. The compound typically contains detectable traces of the oxidized pyridine species; however, this does not appear to interfere with the deracemization reaction. Fibrous, off-white solid (3.93 g, 8.81 mmol, 77% yield): Melting point 151-153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.30 (m, 8H), 5.25 (br s, 1H), 5.12 (s, 4H), 3.36 (s, 2H), 2.20 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 145.6, 135.3, 133.6, 129.1, 128.6, 99.1, 64.7, 24.8, 19.2. IR (ATR) νmax/cm-1 3419, 2954, 2924, 2851, 1698, 1656, 1620, 1487, 1457, 1307, 1298, 1276, 1201, 1146, 1120, 1092, 1053, 1013, 952, 801, 754, 486, 478, 461, 423 cm^{-1}. HRMS(EI) [M-H $_2$] found 443.0688, $C_{23}H_{19}NO_4{}^{35}Cl_2$ requires 443.0690.



bis(2,6-dichlorobenzyl) 2,6- dimethyl- 1,4- dihyd ropyridine-3,5- dicarboxylate (2c)
A mixture of 2,6-dichlorobenzyl alcohol (3.50 g, 19.8 mmol, 1 equiv), ethyl acetoacetate (5.0 mL, 40 mmol, 2 equiv) and toluene (30 mL) was stirred at 120 °C overnight. Toluene was removed under reduced pressure, then the resulting oil was heated to 60 °C and stirred under high vacuum overnight to remove residual ethyl acetoacetate. Yellow oil. (3.58 g, 13.7 mmol, 69% yield). To a solution of 2,6-dichlorobenzyl 3- oxobutanoate (3.58, 13.7 mmol, 2.2 equiv) and ammonium acetate (478 mg, 6.20 mmol, 1 equiv) in ethanol (50 mL) was added paraformaldehyde (186 mg, 6.20 mmol, 1 equiv). The resulting suspension was heated

at reflux overnight, cooled to room temperature, and concentrated under reduced pressure. The residue thus obtained was dissolved in hot DCE (75 mL). Remaining insoluble solids were removed by hot filtration, and the filtrate was allowed to cool to room temperature and left standing overnight. The obtained solid was filtered and washed with diethyl ether. A second crop was obtained from the concentrate of the mother liquor via the same method. The compound typically contains detectable traces of the oxidized pyridine species; however, this does not appear to interfere with the deracemization reaction. Crystalline yellow solid (2.85 g, 5.53 mmol, 39% yield): Melting point 188-194 °C. ^{1}H NMR (400 MHz, DMF- d_7) δ 8.52 (s, 1H), 7.57-7.47 (m, 6H), 5.34 (s, 4H), 3.19 (s, 2H), 2.18 (s, 6H). ^{13}C NMR (101 MHz, DMF-d_7) δ 167.0, 147.8, 136.4, 132.2, 131.4, 129.0, 97.2, 60.4, 24.9, 17.7. IR (ATR) νmax/cm^{-1} 3357, 1702, 1650, 1580, 1562, 1487, 1434, 1377, 1316, 1258, 1196, 1149, 1101, 1083, 1045, 1007, 984, 959, 882, 835, 790, 756, 728, 709, 654, 623, 581, 535, 416. HRMS(EI) [M-H$_2$] found 510.9896, $C_{23}H_{17}NO_4{}^{35}Cl_4$ requires 510.9912.

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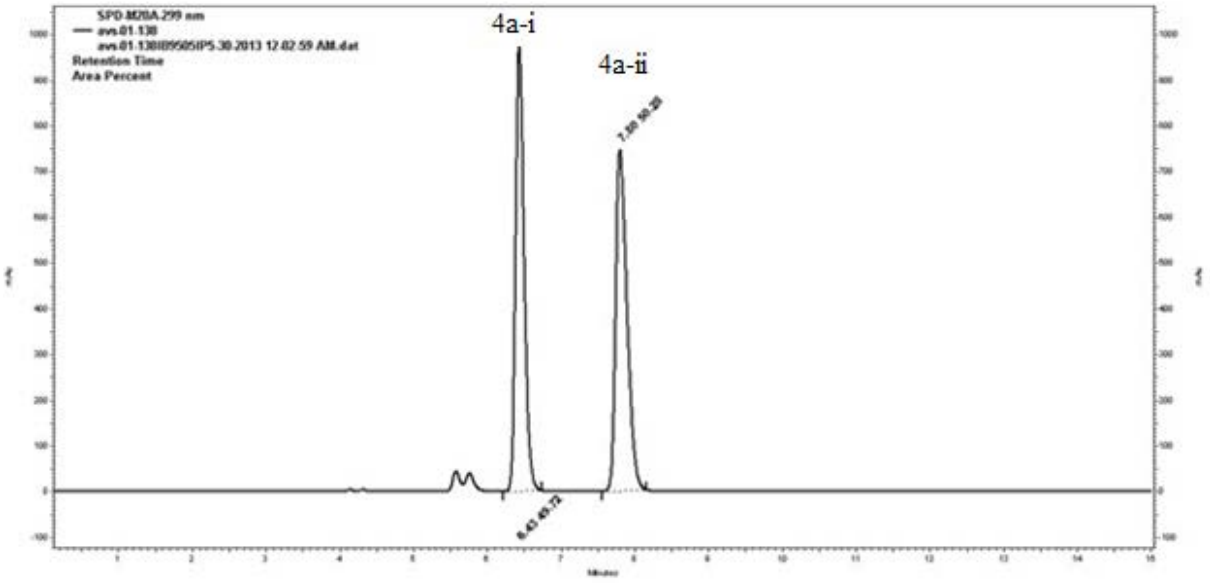
1.7 NMR and HPLC spectra

4a racemic trace



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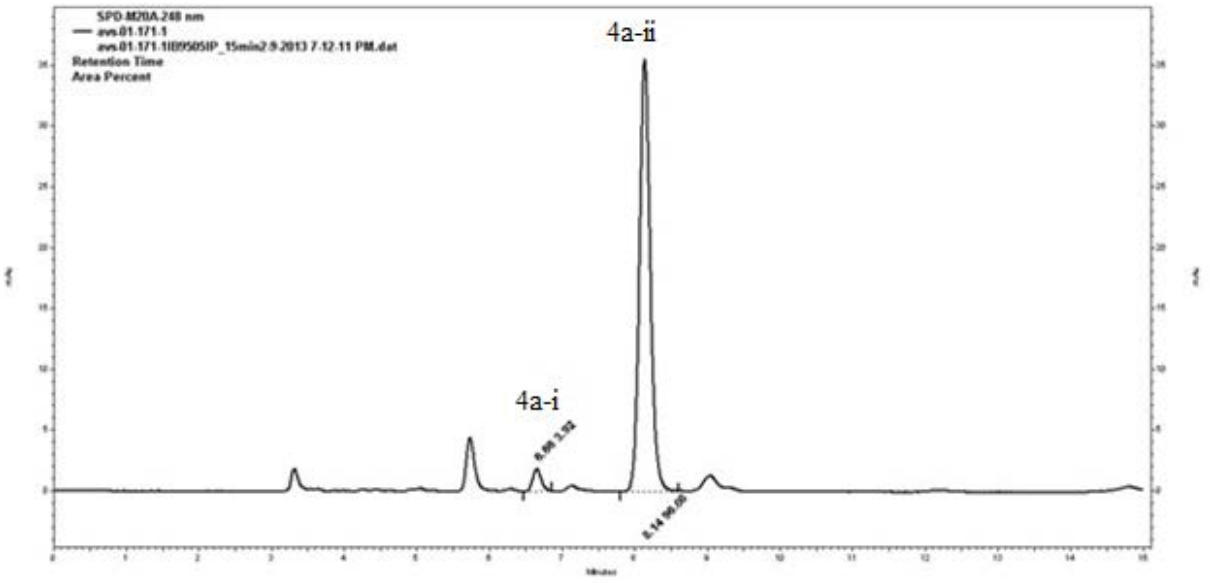

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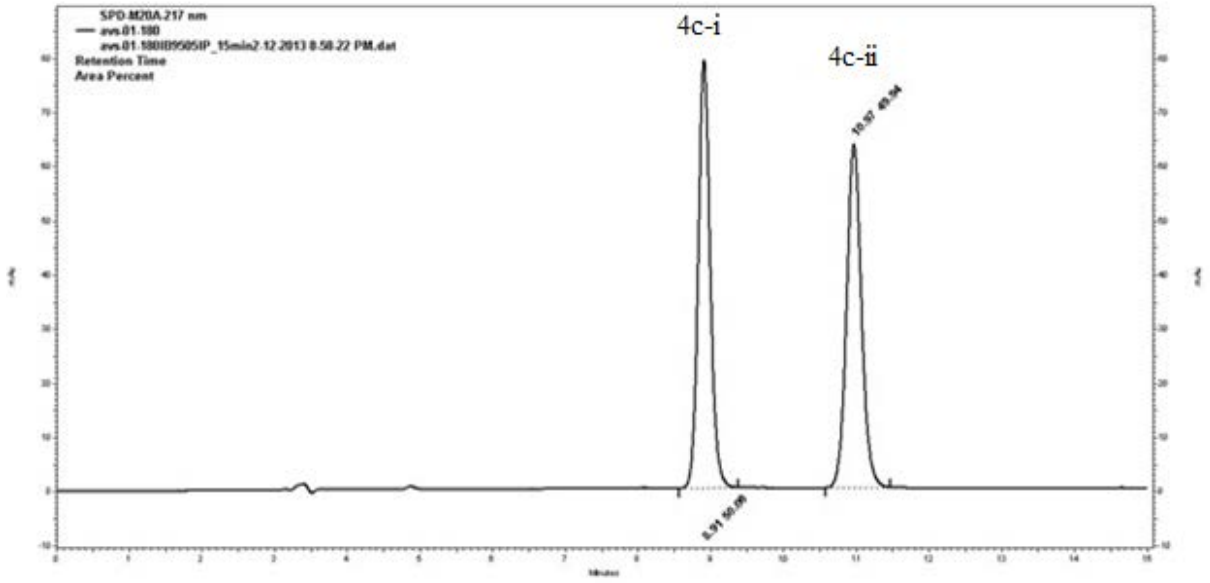

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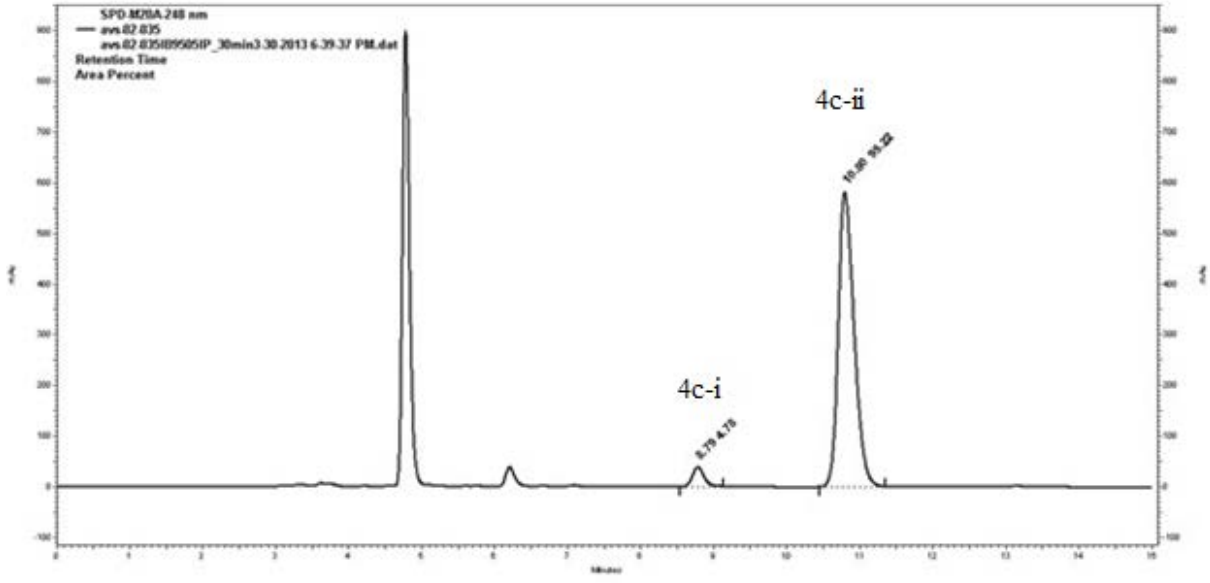

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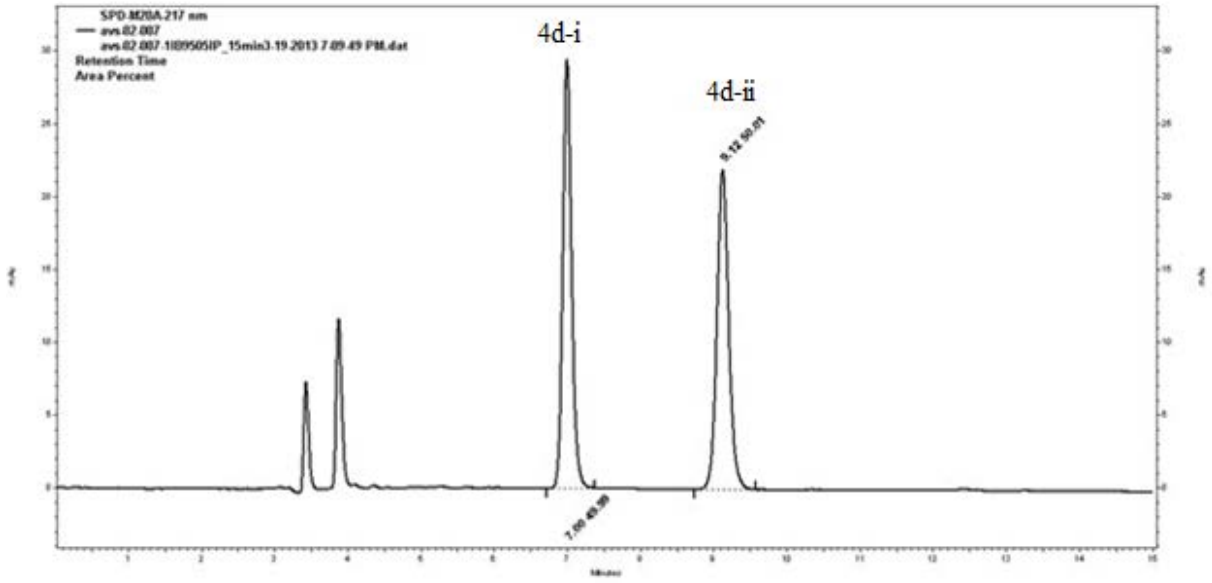

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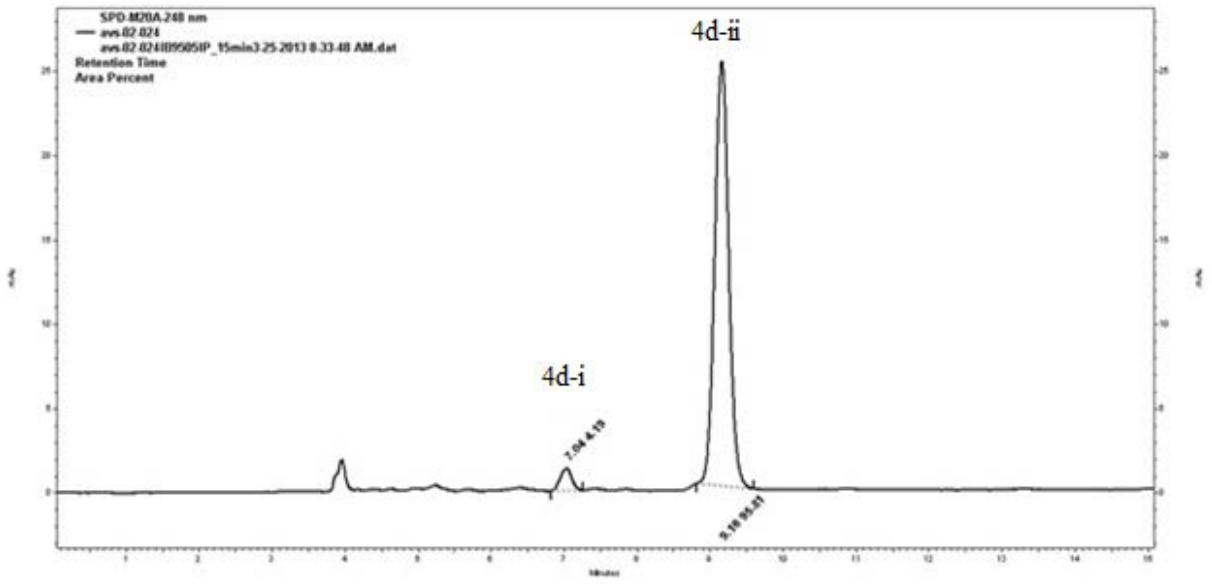

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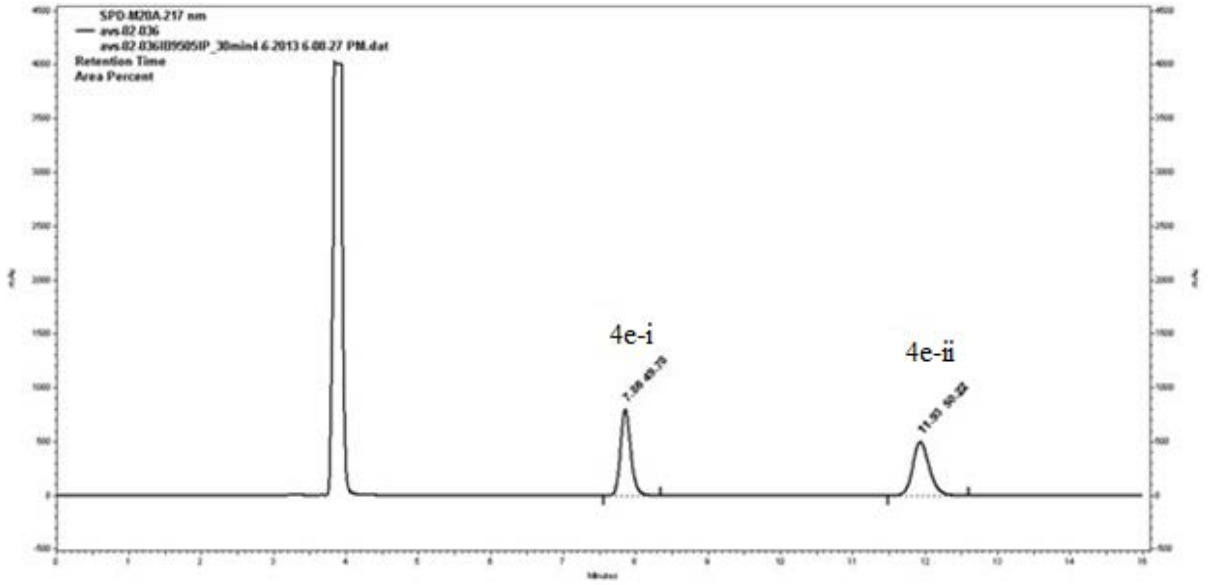

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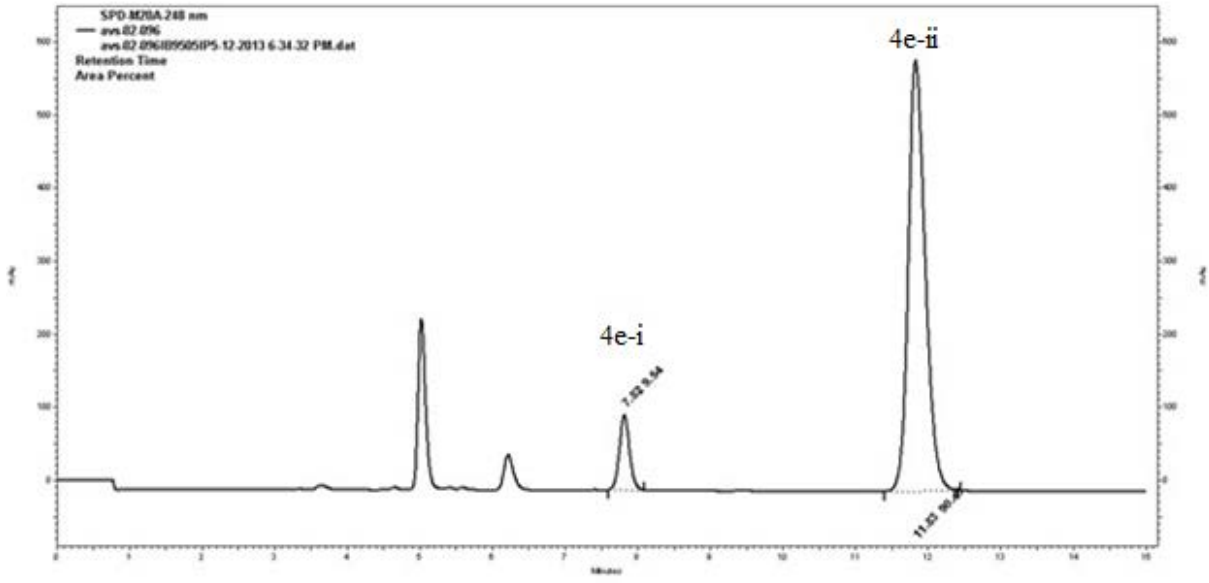

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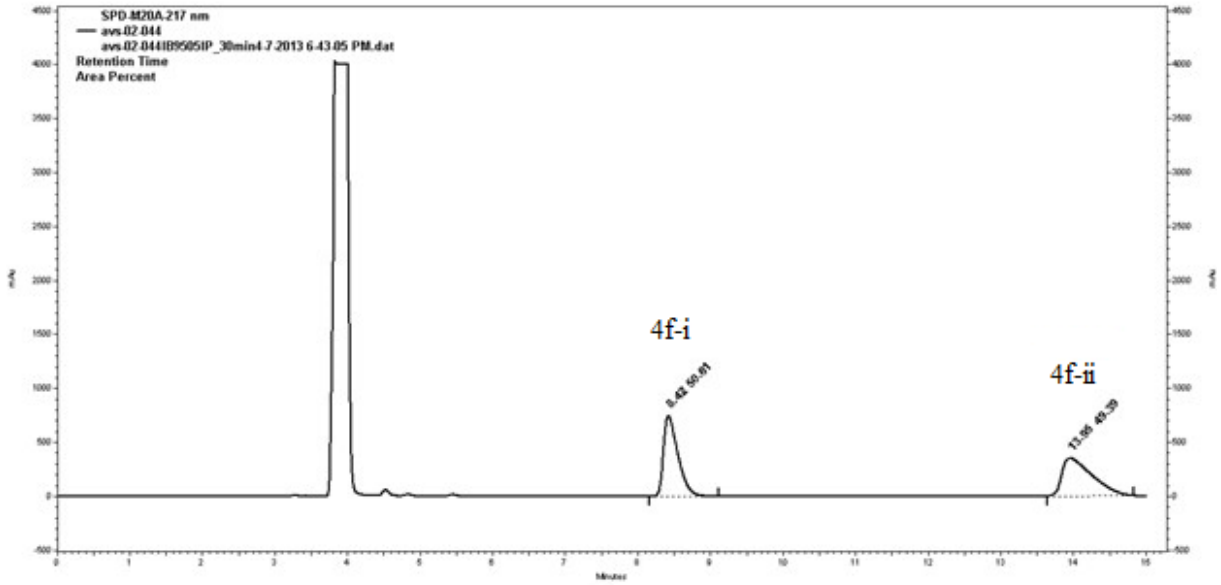

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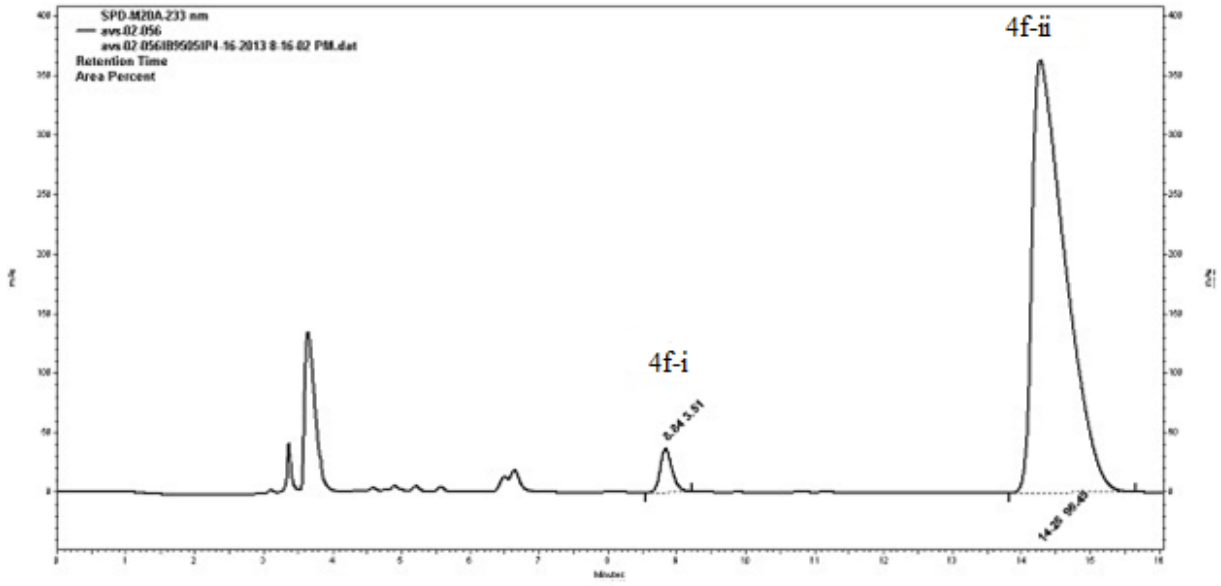

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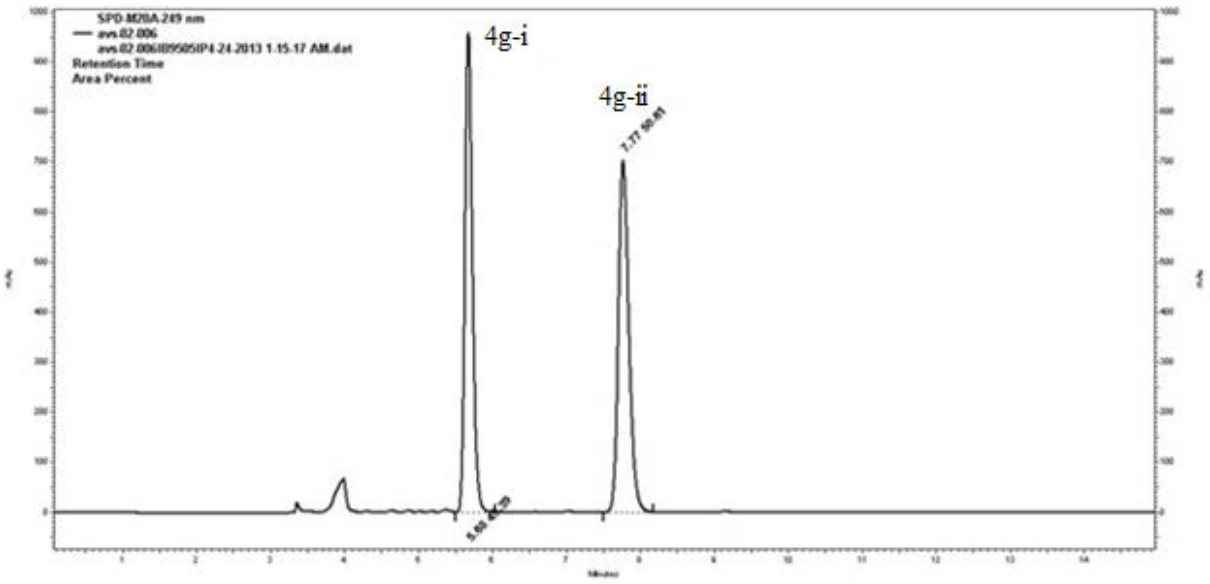

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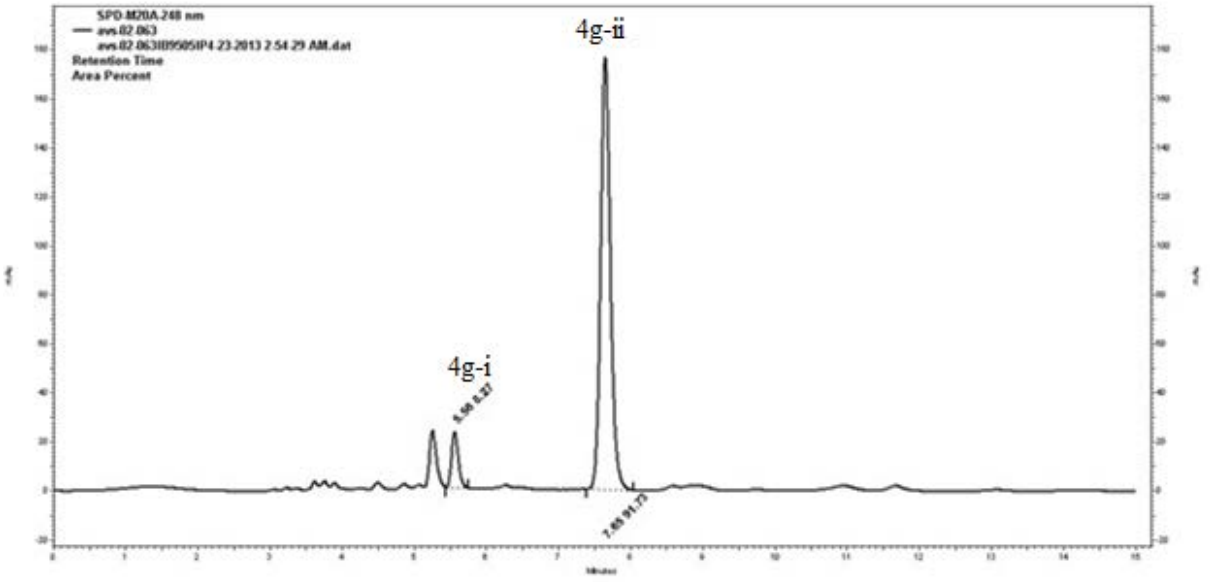

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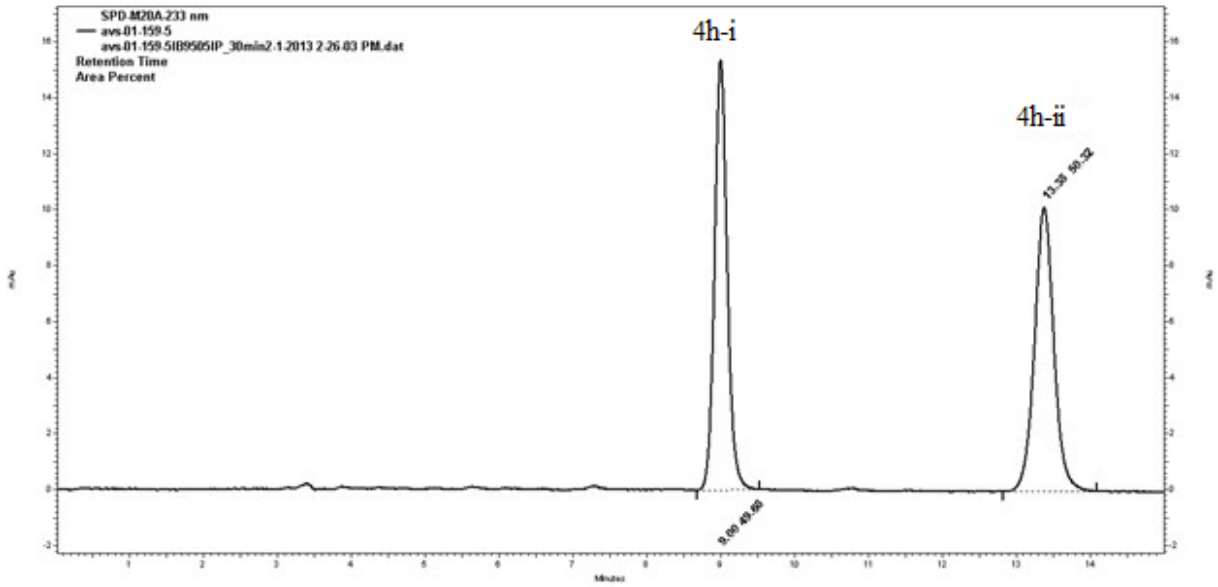

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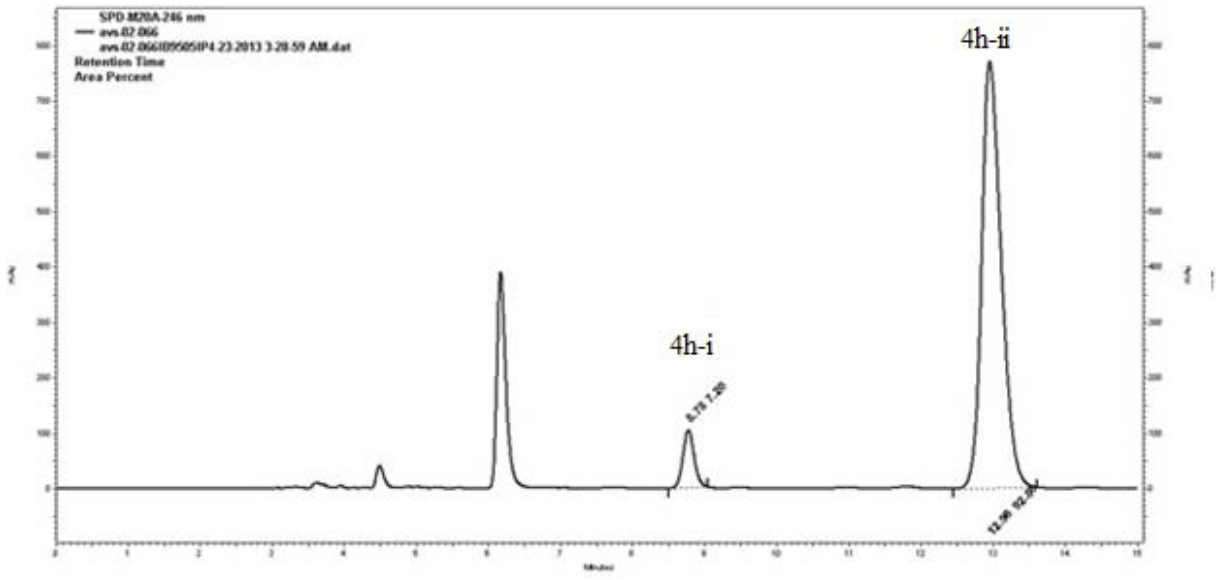

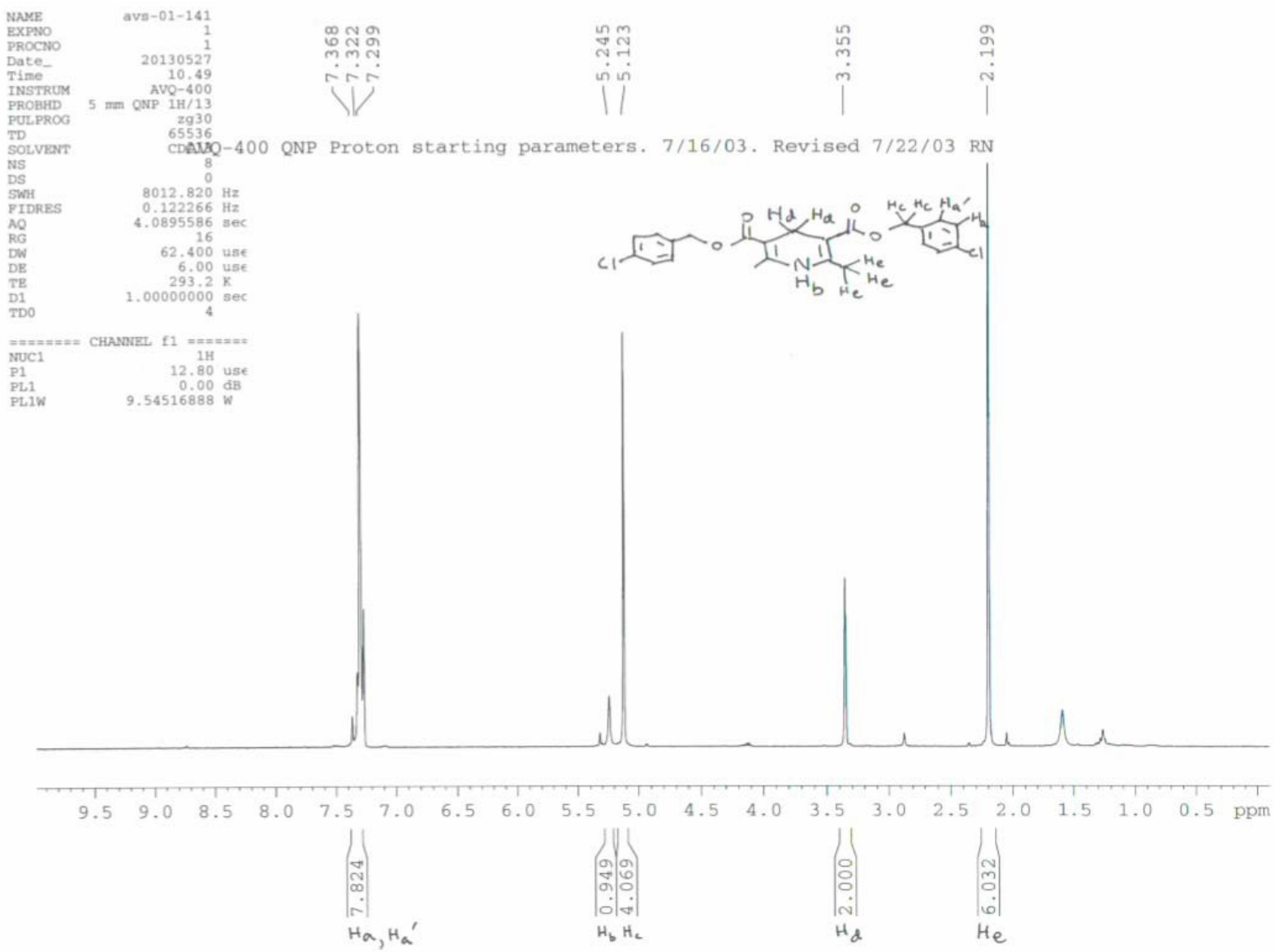
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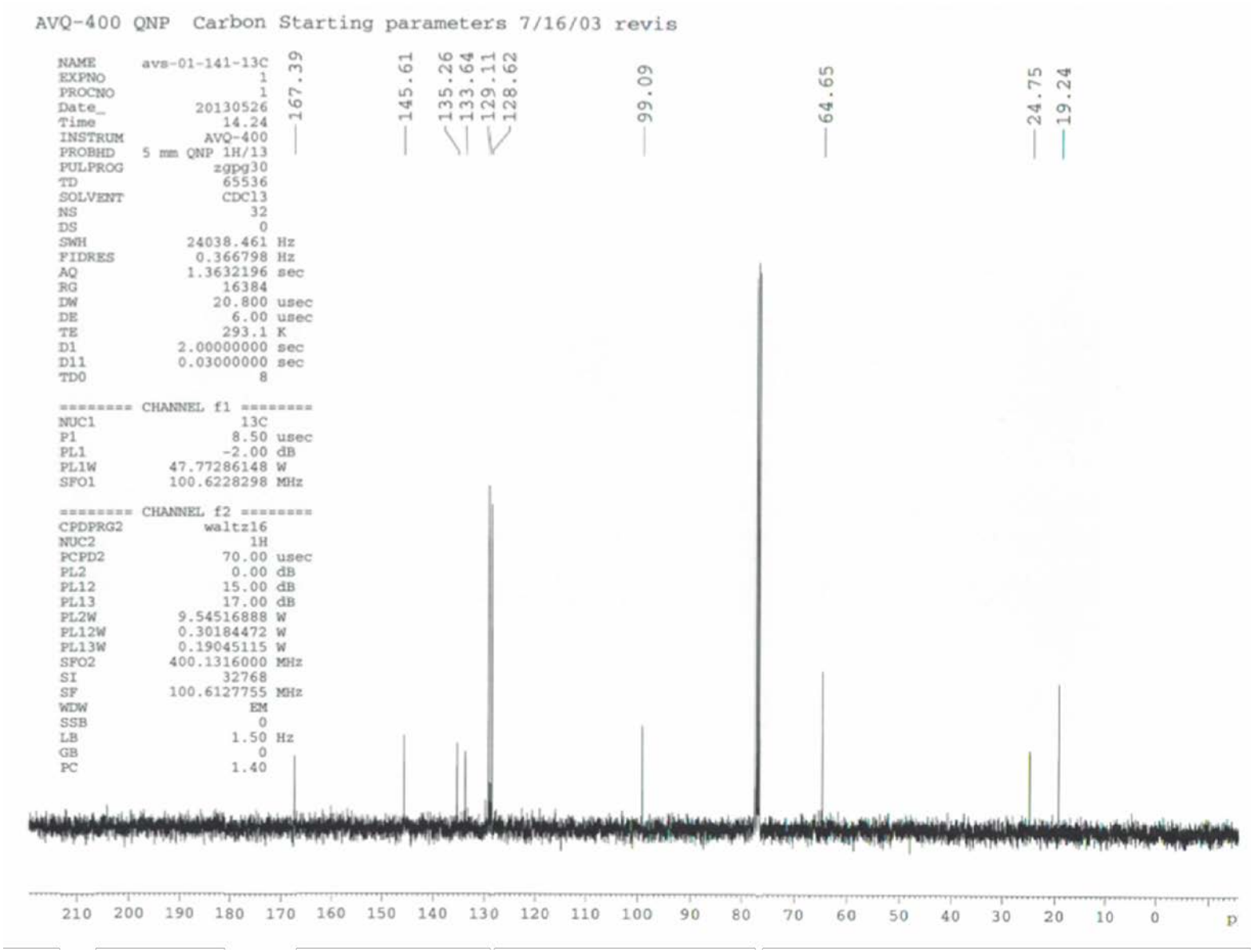
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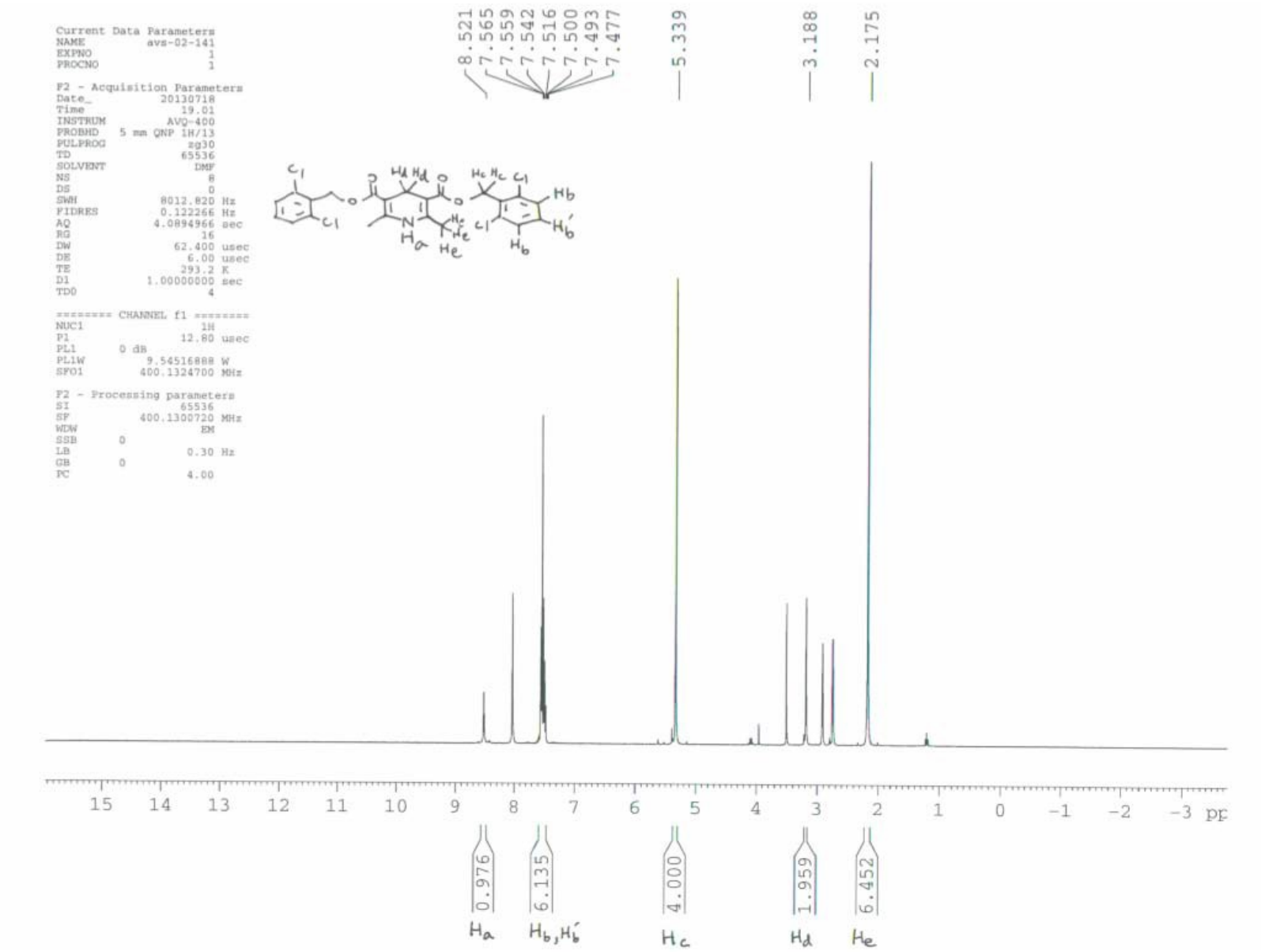
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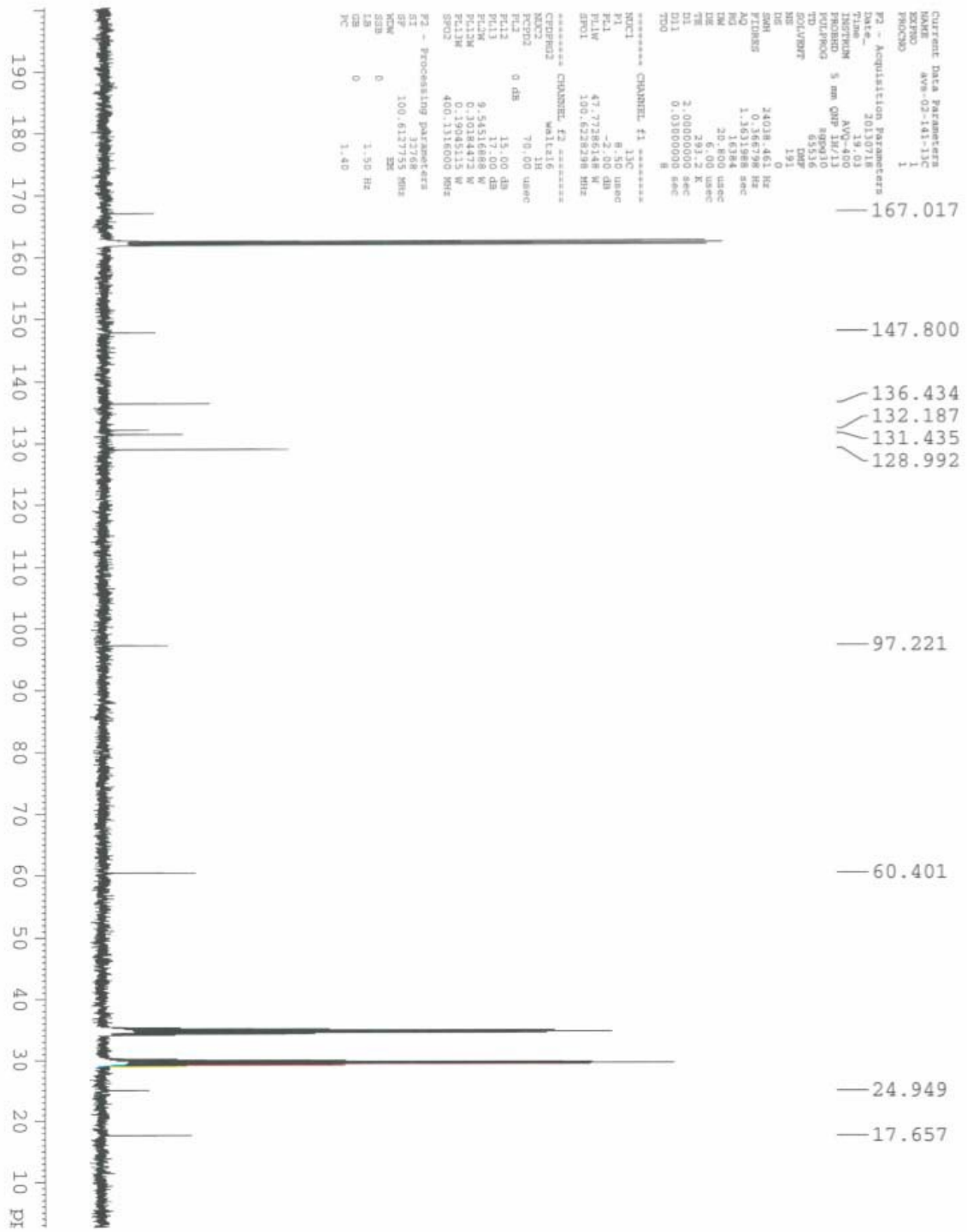
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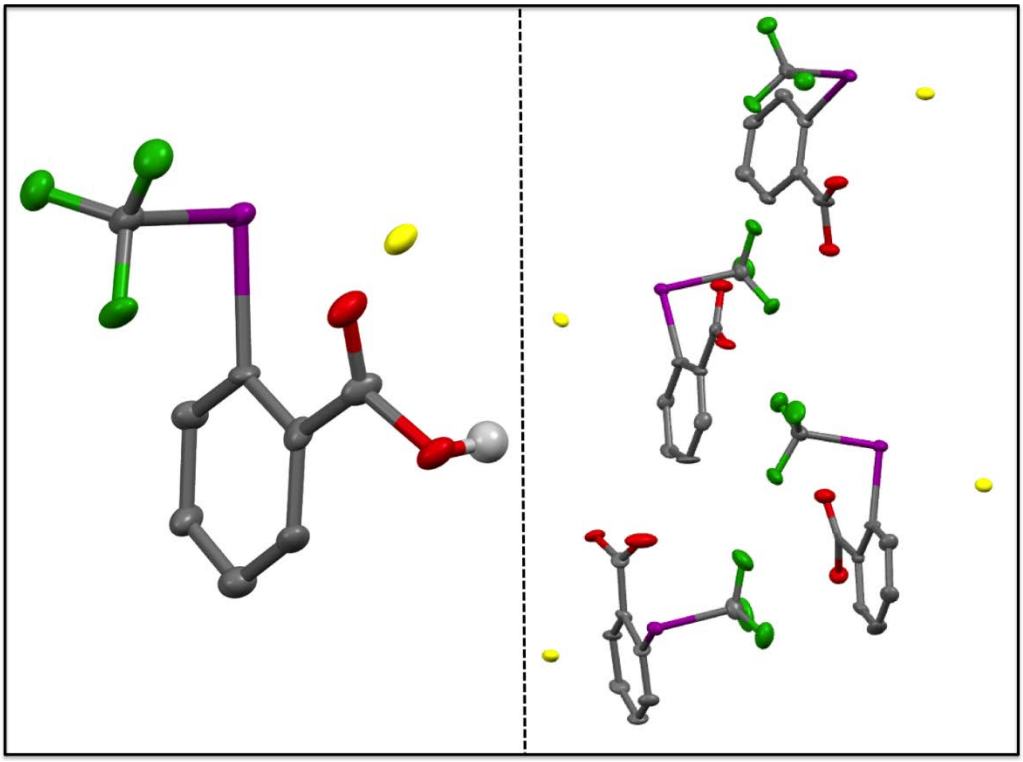
Chapter 2

Synthesis and Reactivity of Trifluoromethyliodonium Chlorides

2.1 Preface

The trifluoromethylation of organic substrates is of ongoing interest due to the unique way in which the introduction of fluorine atoms modifies the physicochemical and metabolic properties of small organic molecules. Here, we describe the isolation and properties of a new class of trifluoromethylating reagents, trifluoromethyliodonium salts. In addition to being fundamentally interesting (and unexpectedly stable) compounds in their own right, these iodonium species have allowed us to develop a better understanding of the underlying mechanism of the electrophilic trifluoromethylation of oxygen- and nitrogen-centered nucleophiles.

Portions of this chapter are based on work done in collaboration with Dr. Johnathan N. Brantley, as well as X-ray crystallographic data collected by Dr. William J. Wolf and Cynthia M. Hong.



2.2 Introduction

The introduction of the trifluoromethyl group into agrochemicals and pharmaceuticals is a powerful way to modify their physical and biological properties. In particular, the introduction of carbon-fluorine bonds in place of carbon-hydrogen bonds can dramatically increase a compound's resistance to oxidative metabolism as well as modify its distribution within an organism's tissues.[35–39]

1 "Togni I" **2** "Togni II"

Figure 1. Iodine(III)-based electrophilic trifluoromethylating reagents.

Because of these attributes, there has been a surge of interest in the trifluoromethylation of small organic molecules in recent years, and many new reagents have been developed to effect this type of transformation. In particular, the use of stoichiometric electrophilic reagents has proven to be a powerful strategy for the introduction of the CF_3 group onto bioactive compounds. One class of electrophilic trifluoromethylating reagents that has become prominent within the past decade is the hypervalent 10-I-3 scaffold.[40,41] The two most widely used reagents in this class, **1** and **2** (commonly known as Togni I and Togni II, respectively), are capable of effecting a wide variety of electrophilic trifluoromethylations, with nucleophiles from Groups 14-17 having been demonstrated to be competent substrates.[41–57]

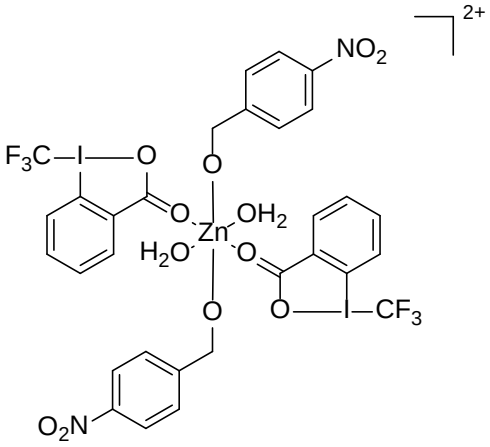


Figure 2. A reported Lewis acid adduct of Togni II (ref. 24)

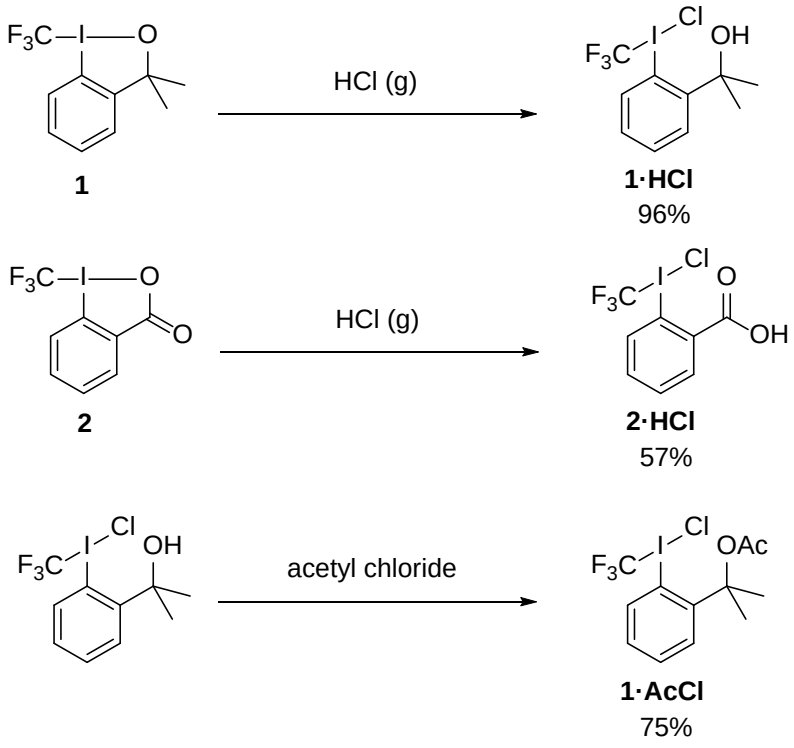
Despite these advances, many common oxygen- and nitrogen-centered nucleophile classes still lack effective means of trifluoromethylation: in some cases (e.g. alcohols, azoles), yields and functional group tolerance are poor[42,46,58,59], while in other cases (e.g. carboxylic acids, amides), there are no reported procedures for direct electrophilic trifluoromethylation. For substrates in these classes where reactivity has been demonstrated, the reaction conditions invariably require the presence of a Lewis or Brønsted acid, and while the isolation of a putative intermediate has been reported[58], the underlying mechanism involved in this reaction has not been elucidated. Based on the reported Lewis acid adduct of the Togni reagent (**Figure 2**), we became interested in the question of whether more easily-accessible adducts could also be prepared, and if so, whether their study would help us gain insight into the details of electrophilic trifluoromethylation reactions.

2.3 Results and Discussion

2.3.1 Synthesis of Trifluoromethyliodonium Chlorides

We found that treatment of **1** with excess dry hydrogen chloride gas formed the stable adduct **1·HCl**. In contrast to **1**, which is light-sensitive and is typically stored below 0 °C, we found that **1·HCl** is stable even when stored at room temperature in direct sunlight.[c] Treatment of **2** was also found to produce the adduct **2·HCl**. Unlike in the previous case, this compound decomposes slowly at room temperature, but is still stable enough to isolate and store for moderate periods of time at low temperatures (half-life ≈ 10 years at -30 °C).

[c] No decomposition was detected after being stored in direct sunlight in a clear container for one year.



Scheme 1. Synthesis and modification of Togni hydrochloride adducts

In order to determine whether a protic functional group was necessary to promote the stability of these chloride complexes, we also explored the synthesis of analogs that were not simple hydrochloride adducts. To this end, treatment of **1·HCl** with neat acetyl chloride resulted in the formation of **1·AcCl**. Additionally, we found that **2** could be activated by oxalyl chloride to produce acid chloride **3**. While this compound was too unstable to isolate, we were able to infer its identity by quenching the reaction mixture with excess methanol and isolating the methylated product **2·MeCl**. Further investigation indicated that this transformation is fairly specific to methanol (likely due to either its high molar density or high nucleophilicity): attempts to isolate the ethyl and menthyl analogues of **2·MeCl** produced complex reaction mixtures from which no iodine(III) compounds could be isolated, whereas attempts to prepare amides resulted in amine oxidation (*vide infra*).[d]

[d] While **1·AcCl** and **2·HCl** were broadly similar to **1·HCl** and **2·MeCl**, we found that **1·AcCl** tended to be much less persistent than the other compounds at elevated temperatures and that **2·HCl** has extremely poor solubility in most organic solvents. As such, the bulk of subsequent experimental work was performed with **1·HCl** and **2·MeCl**.

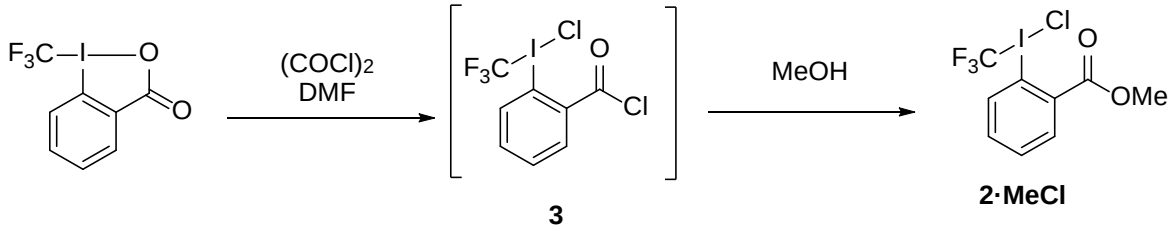
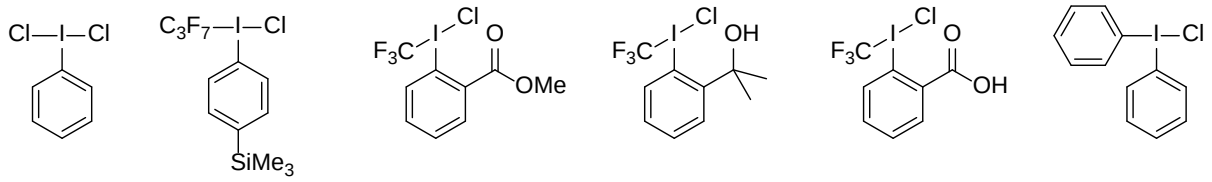


Figure 3. Preparation of 2·MeCl

The long-term persistence of these compounds was somewhat unexpected, as all previously reported attempts to synthesize acyclic aryl trifluoromethyl iodine(III) compounds had met with failure. Attempts to access these compounds using the Prakash reagent as a nucleophilic trifluoromethyl source, in analogy to the strategy used to prepare the Togni reagents, produces none of the desired product.[40] Additionally, in higher perfluoroalkyl iodides oxidation with trifluoroperacetic acid allows entry into aryl perfluoroalkyl iodine(III) compounds via the bistrifluoroacetates, but in the specific case of trifluoromethyl iodide, this initial oxidation instead causes cleavage of the C-I bond and produces iodine(III) trifluooracetate.[60–62] The failure of the former strategy had led to speculation that trifluoromethyliodine(III) species were inherently unstable in the absence of an anionic chelating group. However, our successful isolation of **1·AcCl** and **2·MeCl** demonstrates that the limitation is in fact a kinetic one (at least in the case where a chloride ligand is present), and that in principle other routes to compounds of this type might be feasible as well.

2.3.2 Structure and Bonding

Analysis of the solid state structures of these compounds demonstrates that they have iodine-chlorine bond lengths ranging from 2.81 to 3.00 Å. This is significantly longer than the bonds observed in covalent compounds such as $PhICl_2$ and CF_3ICl_2 (2.45 to 2.48 Å) and begin to approach those observed in the highly ionic Ph_2ICl (3.06 and 3.11 Å).[63–65] This suggested to us the possibility that compounds of this type might behave like iodonium salts, in contrast to the covalent iodanes **1** and **2**. Bulk solubility properties of these compounds are also consistent with the idea that they are much more polar than typical iodanes. **1·HCl**, **2·HCl**, and **2·MeCl** are all highly soluble in polar solvents such as acetonitrile and methanol but dissolve only sparingly in chlorinated solvents; the corresponding parent iodanes, on the other hand, are highly soluble in both chloroform and dichloromethane.



4

Figure 4. Crystallographic iodine-chlorine bond lengths in various chloroiodanes

However, solution-phase data indicate dissolution of the compounds keeps the long iodine-chlorine bond intact rather than producing any detectable amount of the free ion pair. By analogy to known trifluoromethyliodine(III) compounds, if ionization of **2·MeCl** were to occur, it would likely result in coordination of the pendent carbonyl to the newly open coordination site on the iodine center, causing the C=O bond to weaken measurably.[58] However, FT-IR studies of **2·MeCl** showed no significant change in the C=O absorption band when analyzing the solid compound compared to a solution in chloroform or acetonitrile. Additionally, adding excess chloride to a solution of **1·HCl** produces no change in the ^{19}F NMR chemical shift of the trifluoromethyl group; perturbations of the iodine center would be expected to produce a measurable change in the fluorine spectrum, further suggesting that any equilibrium towards an ion pair lies far to the left. Nonetheless, despite the fact that spontaneous ionization does not appear to be thermodynamically favorable, the heterolytic cleavage of the iodine-chlorine bond is quite facile, and the chloride can be readily exchanged with a variety of other ions through salt metathesis (*vide infra*).

The structure of these chloride adducts is significantly different from the parent iodanes in several other respects. While the latter compounds exhibit a covalent iodine-oyxgen bond, the iodine and oxygen in the former are far enough apart (2.95-3.08 Å) that there is no significant degree of covalency between them.[15,32] As a result, these compounds lack the planar structure found in the parent Togni reagents: they possess a dihedral angle $C(Ar_2)$-$C(Ar_1)$-I-Cl of more than 80º, placing the CF_3-I-Cl axis nearly perpendicular to where it would be in the presence of a chelating group.

A more directly comparable set of compounds that has been previously prepared are the longer-chain perfluoroalkyliodanes.[61,66] Although a variety of compounds in this class have been reported in the literature, no crystal structure of any such species had previously been described. As such, we prepared aryl perfluoropropyl iodonium chloride **4** in order to compare its metrical parameters to those of the trifluoromethyl compounds. Analysis of the crystal structure of **4** revealed an asymmetric unit containing two crystallographically non-equivalent molecules, having I-Cl bond lengths of 2.75 and 2.78 Å. While these bond lengths are only slightly shorter than those found in the trifluoromethyliodonium chlorides, we also observed markedly different solubility properties and reactivity patterns between the two compound classes (notably, higher perfluoroalkyl compounds are soluble in pentane and do not react with methanol or sulfonate anions; *vide infra*) which suggest that the higher perfluoroalkyl compounds have a much less polarized bond and a significantly lower propensity to undergo heterolytic cleavage.

In light of the unique structure of these new iodine(III) compounds, we became interested in determining their reactivity in a variety of contexts.

2.3.3 Oxidative Chemistry

We hypothesized that if the iodine center in the chloride adducts had an atypically high degree of cationic character, it should behave as a significantly stronger oxidant than typical trifluoromethyliodanes. Indeed, we found that both **1·HCl** and **2·HCl** are capable of

oxidizing ferrocene to ferrocenium at room temperature within minutes. Additionally, **2·MeCl** was found to rapidly oxidize triphenylphosphine gold(I) *p*-tolyl (**5**) to a mixture of isomers of trifluoromethylgold(III) **6a** and **6b**.[e] In contrast, even at elevated temperatures, neither **1** nor **2** demonstrates this reactivity, either on its own or in the presence of non-chloride-containing acid activators.

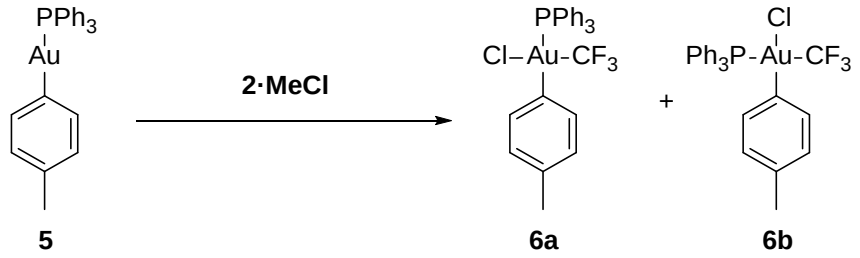


Figure 5. Oxidation of gold(I) to gold(III)

Additionally, treatment of **2·MeCl** with tertiary amines results in an extremely rapid and exothermic reaction at room temperature. The ^{19}F NMR spectrum of the reaction mixture of **2·MeCl** and triethylamine contains multiple quartets, while replacing trimethylamine with Hünig's base gives a complex spectrum with peaks of various multiplicities. While these reactions are low-yielding and complex, precluding isolation of the observed products, we were able to infer some mechanistic information from other experiments: when run in the presence of dihydroanthracene, we observed formation of anthracene in the final reaction mixture, and treatment of 2·MeCl with triphenylamine produces a bright green coloration consistent with the formation of triphenylamine radical cation upon mixing of the reagents. These observations are consistent with one-electron oxidation of the amines to form amine radical cations. This radical cation can then be deprotonated at the alpha position to form an alpha-amino radical, which can recombine with the trifluoromethyl radical generated from reduction of **2·MeCl**. This recombination ultimately results in C-CF_3 bond formation, which is consistent with the multiplets observed via fluorine NMR.

2.3.4 Reactivity with Organometallic Reagents

Due to the evidence that there may be a significant degree of cationic character in these chloro(trifluoromethyl)iodanes, we examined their reactivity with various organometallic compounds. With few exceptions, these reagents failed to give any significant yield of the desired C-CF_3 bond formation products. Broadly speaking, substrates with more ionic carbon-metal bonds (M = Li, Mg, Zn, Al) decomposed the reagent, while those bearing less electropositive metals (M = B, Sn, Si, Cu) simply failed to react to any significant extent.

[e] While **1·HCl** also produced traces of the same gold(III) complexes under these conditions, the OH group present in this reagent was sufficiently acidic that the primary product observed was PPh_3AuCl derived from protodemetallation.

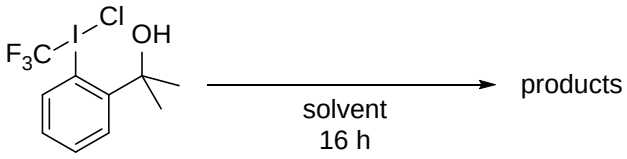
The poor reactivity of the reagents bearing electropositive metals may be understood in the context of the one-electron oxidation chemistry that these reagents have been demonstrated to be capable of: the organometallic compounds in question are likely sufficiently reducing that they are capable of destroying the reagent via a radical mechanism more easily than they are capable of undergoing a productive reductive elimination pathway. On the other hand, while these iodonium salts have demonstrated themselves to be capable of effecting electrophilic aromatic substitution, this has only been unambiguously observed in the presence of solvent concentrations of substrate. As such, while it is very likely that the iodonium compounds may be coaxed to react with aryl metalloids, it may require an impractically high excess of the substrate.

The only exception to these trends was the reaction of potassium 2-ethoxycarbonyl-1-cyclopentanone with **2·MeCl**, which provided the C-trifluoromethylation product in 22% NMR yield. However, given the strongly electron-withdrawing substituents on the nucleophilic carbon atom, this reaction may be more analogous to the salt metathesis chemistry of heteroatomic anions (*vide infra*) than it is with the reactions of more conventional organometallic reagents.

2.3.5 Reactivity with Neutral Organic Nucelophiles

Given that protonated trifluoromethyliodanes have been proposed as intermediates in electrophilic trifluoromethylation reactions previously, we wanted to investigate the possibility that these iodine(III) chlorides would be capable of reacting with nucleophiles in the absence of a Lewis acid activator. Initial studies indicated to us that these reagents will react solvolitically with a number of functional groups (**Table 1**). In general, we found most common solvents to be incompatible with the compounds at the temperatures necessary to effect transformations with neutral nucleophiles; chlorinated solvents were the most broadly applicable class of solvents, although in certain cases we found that acetonitrile reacted slowly enough to be useful as a solvent.

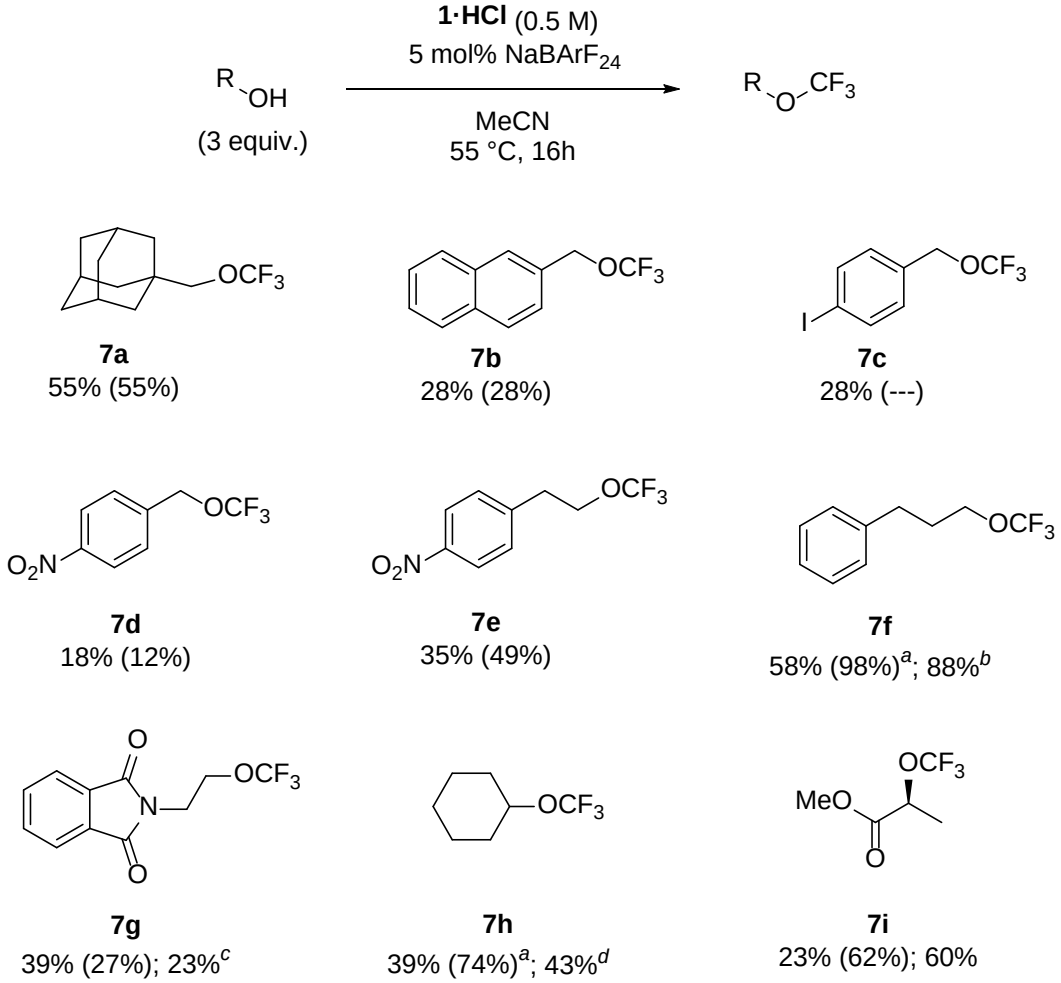
The solvolytic reactivity observed with methanol suggested to us that alcohols might be a good substrate class for the application of these compounds. Previous work has demonstrated the trifluoromethylation of alcohols using **2** in the presence of zinc bistriflimidate as a catalyst, but had poor functional group tolerance and required an excess of substrate relative to electrophilic trifluoromethylating reagent. Given that cationic intermediates have been proposed as being responsible for alcohol trifluoromethylation, we wanted to determine whether the trifluoromethyliodonium chlorides would allow us to gain some level of mechanistic understanding about why this reaction is so challenging.



Solvent	Temperature	Result
MeOH	r.t.	CF_3OMe
Et_2O	60 °C	CF_3OEt
THF	60 °C	poly-THF
C_6H_6	60 °C	$PhCF_3$
MeCN	60 °C	decomposition
DMF	r.t.	decomposition
CH_2Cl_2	60 °C	no reaction
$CHCl_3$	60 °C	no reaction

Table 1. Solvolytic reactivity of **1·HCl**

The solvolytic reaction with methanol could be generalized fairly readily: reaction of **1·HCl** in 3-phenyl-1-propanol provided the expected trifluoromethyl ether in 75% yield (albeit requiring an elevated temperature of 55 °C). However, when we attempted to use **1·HCl** directly to react with alcohol substrates in chlorinated solvents, we had difficulty obtaining reproducible results due to the high concentrations required by the reaction and the relatively low solubility of the reagent in non-polar solvents. Using acetonitrile as the solvent and adding catalytic sodium tetrakis(3,5-trifluoromethylphenyl)borate ($NaBArF_{24}$) as a phase transfer catalyst allowed reactivity to be reproducibly demonstrated. For a variety of aliphatic alcohols, we observed yields comparable to those described previously in the literature (**Figure 6**).

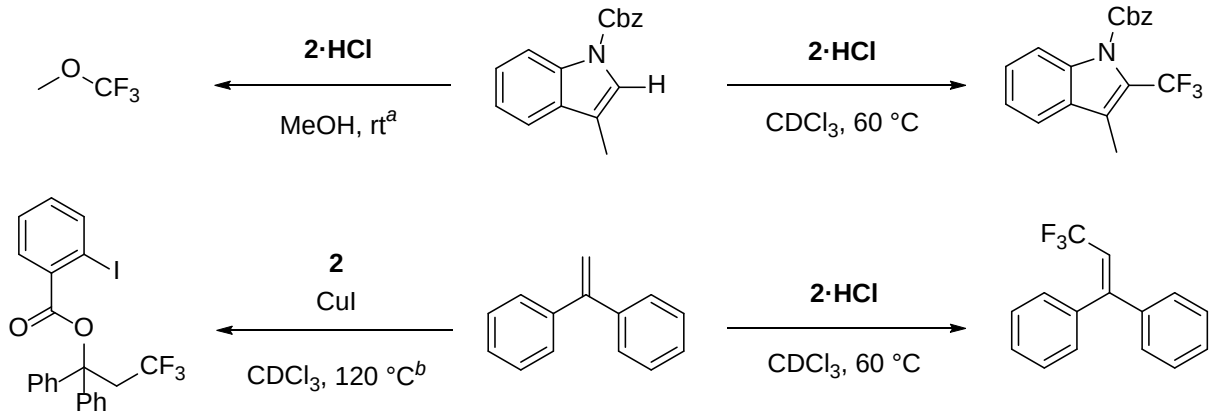


Yields determined by ^{19}F NMR by comparison to 4-fluorobiphenyl internal standard. All yields are the average of at least two independent trials. Parenthetical yields are from ref. 24 for comparison. [a]Yield from ref 24. using 75 equivalents of substrate. [b]Yield using 75 equivalents of substrate. [c]Isolated yield. [d]Yield using 10 equivalents of substrate.

Figure 6. Trifluoromethylation of alcohols

Iodonium chlorides were also found to react with other classes of neutral heteroatomic nucleophiles for which there is precedented reactivity using a Togni reagent and a non-redox-active Lewis acid.[46,59] Both benzotriazole and benzimidazole were successfully trifluoromethylated using iodonium reagents (see supporting information for details). On the other hand, in cases where there is literature precedent using copper catalysis, we found that these reagents gave significantly different reaction outcomes.[49,67] In particular, indole trifluoromethylation using **2·HCl** proceeded only at higher temperature and in a different solvent than a similar reported reaction using **2** and copper acetate, whereas treating 1,1-

diphenylethyelene with **2·HCl** proceeded at a lower temperature than the corresponding copper-catalyzed reaction, but yielded a trifluoromethyl alkene rather than the expected trifluoromethylcarboxylation product (**Scheme 2**).



[a]Compare to conditions in ref. 15 [b]See ref. 33

Scheme 2. Comparison of hydrochloride adducts to copper-catalyzed systems

Having demonstrated that these reagents were capable of recapitulating the yields observed using Togni reagent-Lewis acid systems, we decided to use them to investigate the causes behind the low yield and functional group tolerance observed in these reactions. We found that, while **1·HCl** showed no signs of decomposition in dichloromethane when heated overnight at 60 °C, addition of one equivalent of 1-adamantanemethanol caused decomposition of the reagent to occur within several hours. Notably, at one equivalent of alcohol, we observed rearrangement of the reagent into trifluoromethyl 2-iodobenzoate but no trifluoromethyl ether formation. Similar results were obtained by adding one equivalent of *N*,*N*-dimethylacetamide, suggesting that decomposition of the reagent is catalyzed by the presence of polar functional groups.

Performing the same experiment in the presence of hexamethyldisiloxanerevealed that a second decomposition pathway also occurred, generating inorganic fluoride (detected as Me_3SiF). Finally, when we attempted to treat 1-adamantanemethanol with excess **1·HCl**, we detected the presence of bis(1-adamantylmethyl)carbonate by NMR. It appears likely, therefore, that the constraint that substrate (rather than trifluoromethylating reagent) be provided in excess is mandated by the fact that the reagents decompose to some extent to generate carbonyl fluoride (in conjunction with inorganic fluoride), which goes on to form the observed carbonates rather than productive trifluoromethylation.

2.3.6 Salt Metathesis Reactivity

We also investigated whether the use of other counterions in place of chloride would result in isolable compounds. While in some instances compounds of this type could in

principle be formed directly from a Brønsted acid in a manner similar to that used to prepare the chloride, we elected instead to use a salt metathesis approach with **2·MeCl** and **1·HCl** to circumvent the differing acidity and oxidizing power of various acids.

	1·HCl	**2·MeCl**
NaOTf	CF_3OTf	CF_3OTf
NaI	CF_3I	CF_3I
NaBr	CF_3Br	CF_3Br
$NaBF_4$	$1{\cdot}BF_4$	decomposition
$NaBArF_{24}$	$1{\cdot}HBArF_{24}$	decomposition
NaF	deprotonation	no reaction
AgF	deprotonation	decomposition

Table 2. Salt metathesis reactions with various anions

Treatment of either **2·MeCl** or **1·HCl** with bromide, iodide, or sulfonate salts resulted in successful salt metathesis, but the resulting complexes were unstable with respect to reductive elimination, and attempts to isolate these compounds ultimately resulted in reduced iodoarene and trifluoromethyl halide or sulfonate. On the other hand, non-coordinating counterions such as sodium $BArF_{24}$ allowed isolation of protonated iodane **1·HBArF$_{24}$** in the case of **1·HCl**, whereas in the case of **2·MeCl** this salt metathesis resulted in decomposition. Other weakly-coordinating counterions (e.g. SbF_6^-, BF_4^-) showed similar behavior, forming protonated adducts of **1** but causing decomposition of **2·MeCl**. Finally, while sodium fluoride simply deprotonated **1·HCl** to generate **1**, it was incapable of undergoing salt metathesis with **2·MeCl**. Using silver fluoride to drive the equilibrium to the right resulted in decomposition of **2·MeCl** to methyl 2-iodobenzoate.

As such, it appears that the chloride ion is uniquely capable of stabilizing these acyclic trifluoromethyliodanes; it seems to strike a balance between being iodophilic enough to have an appreciable degree of interaction with the iodine center (in contrast to fluoride or weakly coordinating anions), while at the same time not being reactive enough to undergo reductive elimination on a practical timescale (unlike the heavier halides).

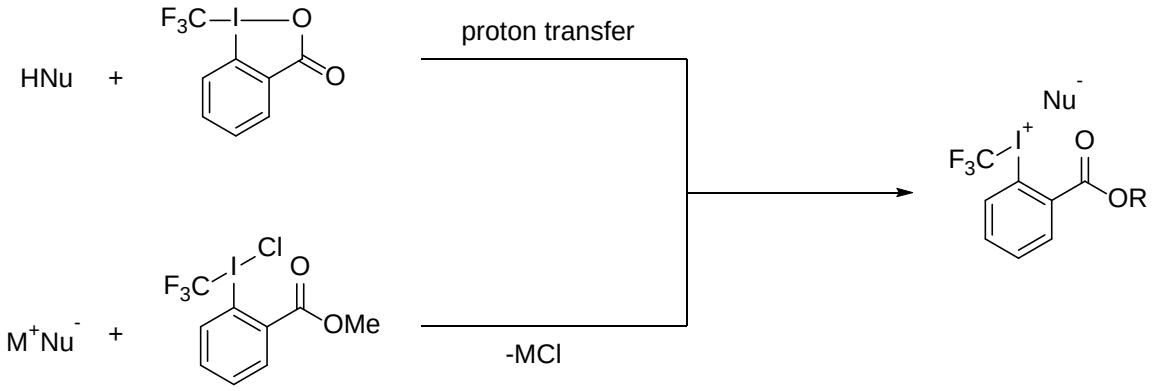
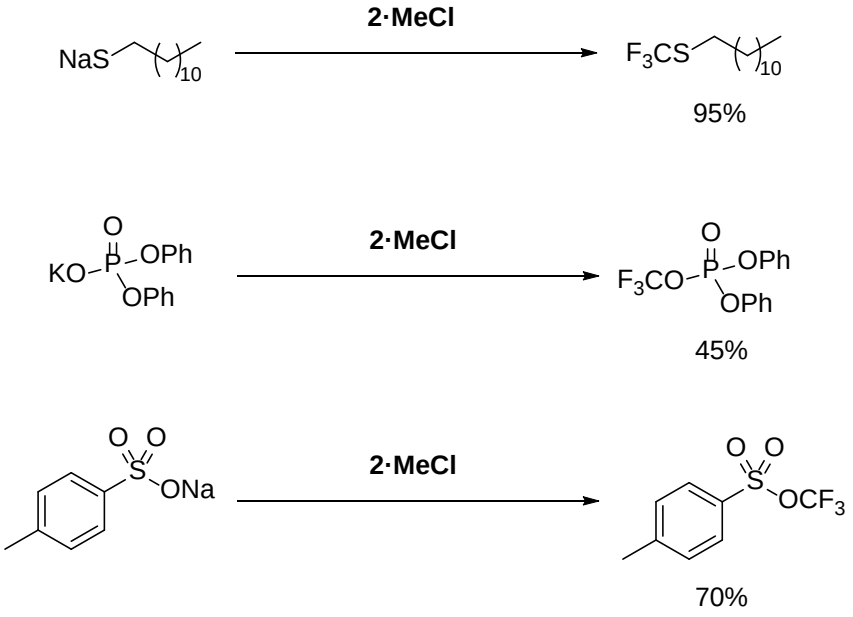


Figure 7. Proposed similar intermediates between neutral and salt metathesis mechanisms

Our observation that we were able to observe reductive elimination with halides and sulfonates led us to wonder whether this would be a viable pathway towards trifluoromethylation of nucleophilic substrates. Certain substrates are known to react directly with neutral Togni reagents and are proposed to do so via a protonation-reductive elimination mechanism.[45,68] As such, we reasoned that if this mechanistic hypothesis is correct, salt metathesis between an anionic nucleophile and **2·MeCl** should be produce a very similar intermediate, and should lead to formation of the same product (**Figure 7**).



Scheme 3. Reaction of **2·MeCl** with anionic nucleophiles

Phosphoric acids, thiols, and sulfonic acids are three classes of compound capable of reacting directly with the Togni reagents, and when we treated **2·MeCl** with the

corresponding conjugate bases, we observed formation of the expected trifluoromethylation products in moderate to good yields (**Scheme 3**).[44,45,68] Interestingly, reaction of either dodecanethiol or diphenylphosphoric acid failed to produce a significant yield of the expected trifluoromethylation products when treated with **2·MeCl**, providing support for the hypothesis that deprotonation is essential for the activation of these nucleophiles when reacting directly with the Togni reagent. On the other hand, the reaction of **2·MeCl** with p-toluenesulfonic acid produced trifluoromethyl p-toluenesulfonate in 78% yield; this may simply be due to the high acidity of the substrate allowing kinetically relevant concentrations of the anion to exist in neutral solution.[f]

As mentioned previously, many oxygen- and nitrogen-centered nucleophiles are known to react with Togni reagents only in the presence of Lewis acid activators. The typical explanation for this has been that the Lewis acid is necessary in order to activate the iodine-oxygen bond; unfortunately, their presence precludes the use of anionic nucleophiles and as a result the more weakly nucleophilic neutral compounds are used.[41] By analogy to our previous results with phosphates and sulfides, we envisioned the possibility that the use of **2·MeCl** would provide a "pre-activated" iodine(III) center that would be compatible with anionic substrates but still reactive enough to effect the desired trifluoromethylation reaction.

To this end, we examined the reactivity of potassium tert-butoxide, potassium benzotriazolate, sodium benzoate, and potassium phthalimide. In each case, we observed precipitation consistent with a successful salt metathesis reaction; however, in none of these cases did we observe formation of the desired product. Instead, the initial intermediates from the metathesis reactions decomposed over a period of minutes or hours to produce methyl 2-iodobenzoate without any observable fluorinated products. These results suggest that the reductive elimination process is somewhat more complex than initially anticipated. Given that relatively weak nucleophiles such as triflate successfully react with the reagent, one possibility is that the operative mechanism contains a step which favors dissociation of the nucleophile from the iodine center (e.g. a reductive elimination involving S_N2-like attack by a dissociated nucleophile, which has been proposed previously based on computational results).[69]

2.4 Conclusion

We have isolated, characterized, and investigated the reactivity of a novel class of iodine(III) compounds. These aryl(chloro)trifluoromethyliodanes have an unusual degree of cationic character at the iodine center which makes them distinct both from the more well-documented chelation-stabilized trifluoromethyliodanes as well as the higher aryl(chloro)perfluoroalkyliodane analogs. This new class of compounds has helped us

[f] Initially, we attempted to use salt metathesis chemistry to obtain kinetic information about the reductive eliminations involved in these reactions. Unfortunately, we found that these reactions appear to be precipitation-driven: when we attempted to perform the salt metathesis reactions in methanol (in which the resulting alkali chlorides have significant solubility), we observed no product formation.

develop a better understanding of electrophilic trifluoromethylation chemistry, and shows promise as a means to further improve this class of reaction.

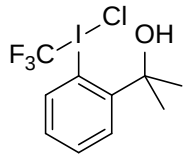
2.5 Supporting Information

General Considerations

Solvents and reagents were used as-received from commercial suppliers except in the following case: *p*-fluorobiphenyl was dissolved in pentane, passed through a plug of silica, and reisolated by concentration. 2-(2-hydroxyethyl)isoindoline-1,3-dione, $Ph_3PAu(4\text{-}CH_3\text{-}C_6H_4)$, and sodium tetrakis(3,5-trifluoromethyl)phenylborate ($NaBArF_{24}$) were prepared according to previously reported procedures. Potassium salts of diphenylphosphoric acid, ethyl 2-oxocyclopentane-1-carboxylate, and benzotriazole were prepared by treating a suspension of the corresponding conjugate acid in water with one equivalent of potassium hydroxide, followed by concentration under reduced pressure and drying under high vacuum. While both **1** and **2** are commercially available, we found it convenient and economical to prepare the latter compound from 2-iodobenzoic acid using the procedure of Togni and co-workers.[70]

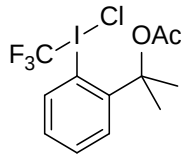
Small-scale reactions were run in conical Eppendorf tubes (1.0 mL). Unless otherwise noted, reactions were conducted without taking precautions to exclude air or moisture. Dichloromethane (CH_2Cl_2) and acetonitrile (MeCN) used in moisture-sensitive reactions were purified by passage through an activated alumina column under argon. Thin-layer chromatography analysis of reaction mixtures was performed using Merck silica gel 60 F254 TLC plates, and visualized under UV or by staining with $KMnO_4$. Flash column chromatography was carried out on Merck Silica Gel 60 Å, 230 X 400 mesh.

Nuclear magnetic resonance (NMR) spectra were recorded using Bruker DRX-500, AVQ-400 and AV-600 spectrometers. ^1H and ^{13}C NMR chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peaks. ^{19}F NMR chemical shifts are reported in ppm relative to $CFCl_3$ (external standard). ^{31}P NMR chemical shifts are reported in ppm relative to phosphoric acid (external standard). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. Mass spectral data were obtained from the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley using a Thermo LTQ-FT for ESI spectra and a Waters AutoSpec Premier for EI spectra. X-ray crystallographic data were collected at the University of California, Berkeley College of Chemistry X-ray Crystallography Facility.



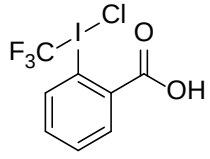
2-(2-(chloro(trifluoromethyl)-λ^3-iodanyl)phenyl)propan-2-ol (1·HCl)

*Caution: **1·HCl** was found to decompose violently when heated above 100 ºC; due care should be taken when handling or synthesizing this reagent.* A 50 mL flask was charged with 3,3-dimethyl-1-(trifluoromethyl)-1,2,-benziodoxole (1.0 g; 3.0 mmol) and $CHCl_3$ (15 mL). The resultant solution was sparged with HCl gas (generated *ex situ* using NaCl and H_2SO_4) for approximately 5 minutes, after which the reaction mixture was allowed to sit at room temperature for 30 minutes. The mixture was concentrated under reduced pressure and subsequently washed with pentane (3 x 15 mL) to afford **1·HCl** as a white solid (1.05 g; 96% yield). Single crystals of **1·HCl** spontaneously formed from a saturated $CDCl_3$ solution and were analyzed by X-ray crystallography. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.62-7.53 (m, 2H), 7.36 (t, *J* = 7.7 Hz, 1H), 1.74 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150.9 MHz) δ 147.6, 135.9, 132.2, 130.4, 128.9, 115.2, 75.1, 31.1 (C_{CF_3} signal not observed due to heteroatom coupling). ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -27.2 (s). HRMS (ESI) Calc'd for $C_{10}H_{11}F_3IO$ $[M\text{-}Cl]^+$: 330.9801; found 330.9791.



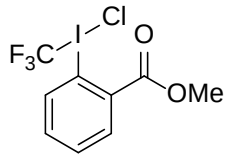
2-(2-(chloro(trifluoromethyl)-λ^3-iodanyl)phenyl)propan-2-yl acetate (**1·AcCl**)

*Caution: While no thermal decomposition data exists for **1·AcCl**, the related compound **1·HCl** was found to decompose violently when heated above 100 ºC; due care should be taken when handling or synthesizing this reagent.* A 40 mL scintillation vial was charged with **1·HCl** (20.0 mg; 0.05 mmol) and acetyl chloride (2.0 mL; 28.1 mmol). The resultant suspension was sonicated for 5 minutes, after which the reaction mixture was allowed to sit at room temperature for 8 hours. The mixture was concentrated under reduced pressure and subsequently washed with pentane (3 x 5 mL) to afford **1·AcCl** as a white solid (16.7 mg; 75% yield). Single crystals of **1·AcCl** spontaneously grew within the mother liquor during the acylation reaction and were analyzed by X-ray crystallography. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 8.39 (d, *J* = 7.9 Hz, 1H), 7.74-7.73 (m, 2H), 7.41-7.36 (m, 1H), 2.16 (s, 3H), 2.03 (s, 6H). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 150.9 MHz) δ 169.3, 145.5, 141.4, 133.2, 131.1, 129.3, 82.1, 28.3, 22.7 (C_{CF_3} signal not observed due to heteroatom coupling). ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -31.5 (s). HRMS (ESI) Calc'd for $C_{12}H_{13}F_3IO_2$ $[M\text{-}Cl]^+$: 372.9907; found 372.9900.



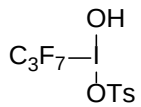
2-(chloro(trifluoromethyl)-λ^3-iodanyl)benzoic acid (**1·HCl**)

*Caution: **1·HCl** was found to decompose violently when heated above 100 ºC; due care should be taken when handling or synthesizing this reagent.* A 100 mL flask was charged with 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (1.58 g; 5.0 mmol), CH_2Cl_2 (50 mL), and a stir bar. The resultant solution was stirred vigorously and sparged with HCl gas (generated *ex situ* using NaCl and H_2SO_4) for approximately 30 minutes. The precipitated white solid was collected on a fritted funnel and washed with CH_2Cl_2 (3 x 15 mL) to afford **1·HCl** (1.0 g; 57% yield). Single crystals of **1·HCl** formed from a solution in MeCN at -30 ºC and were analyzed by X-ray crystallography (see Figure 5 in the main text). ^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.48 (d, J = 7.9 Hz, 1H), 8.21 (dd, J = 7.7, 1.7 Hz, 1H), 7.82 (t, J = 7.5 Hz, 1H), 7.73 (td, J = 7.7, 1.7 Hz, 1H). ^{13}C{^{1}H} NMR (DMSO-d_6, 150.9 MHz) δ 165.4, 138.5 (m), 135.2, 132.6, 131.7, 130.5, 120.0 (m), 109.2 (q, J = 389 Hz). Spectrum shows traces of 2-iodobenzoic acid from decomposition during collection. ^{19}F NMR (DMSO-d_6, 376.5 MHz) δ -34.3 (s). HRMS (ESI) Calc'd for $C_8H_5F_3IO_2$ $[M\text{-}Cl]^+$: 316.9281; found 316.9284.



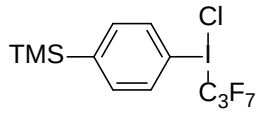
Methyl 2-(chloro(trifluoromethyl)-λ^3-iodanyl)benzoate (**2·MeCl**)

*Caution: While no thermal decomposition data exists for **2·MeCl**, the related compound **2·HCl** was found to decompose violently when heated above 100 ºC; due care should be taken when handling or synthesizing this reagent.* A 50 mL flask was charged with 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (0.63 g; 2.0 mmol), CH_2Cl_2 (20 mL), N,N-dimethylformamide (1 drop), and a stir bar. The vessel was placed under a N_2 atmosphere, and oxalyl chloride (1.7 mL; 20 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 30 minutes, after which time the vessel was cooled to 0 ºC. Methanol (10 mL) was added in a single portion, and the reaction mixture was immediately concentrated under reduced pressure. Subsequent washing with diethyl ether (3 x 15 mL) afforded **2·MeCl** as a white solid (0.32 g; 43% yield). Single crystals of **2·MeCl** were obtained by vapor diffusion of pentane into a CH_2Cl_2 solution and analyzed by X-ray crystallography (see Scheme 2 in the main text). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.47 (d, J = 8.0 Hz, 1H), 8.37-8.33 (m, 1H), 7.79 (t, J = 7.4 Hz, 1H), 7.71-7.65 (m, 1H), 4.05 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 163.7, 139.5, 135.9, 133.2, 132.6, 128.7, 120.6, 53.6 (C_{CF_3} signal not observed due to heteroatom coupling). ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -33.4 (s). HRMS (ESI) Calc'd for $C_9H_7F_3IO_2$ $[M\text{-}Cl]^+$: 330.9437; found 330.9476.



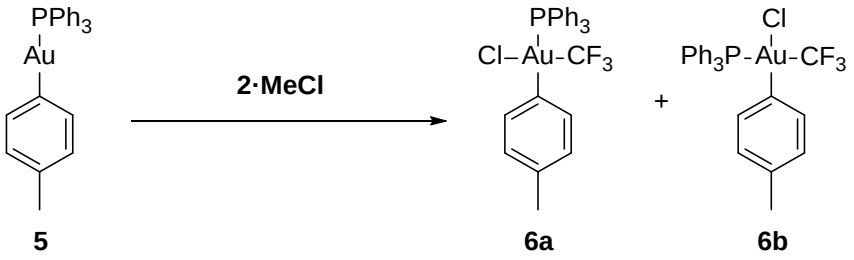
Hydroxy(perfluoropropyl)iodonium tosylate

A 50 mL flask was charged with trifluoroacetic anhydride (11 mL; 78 mmol), trifluoroacetic acid (10 mL; 131 mmol), and a stir bar. The reaction mixture was cooled to 0 ºC, and a 30% aqueous solution of hydrogen peroxide (1.2 mL, 12 mmol) was added dropwise. The mixture was then stirred at room temperature for 5 minutes, after which time perfluoropropyl iodide (1.4 mL, 10 mmol) was added slowly. The reaction mixture was stirred for 16 hours at room temperature and then concentrated under reduced pressure (Note: the temperature should be kept below 25°C). The resulting oil was taken up in 40 mL MeCN, and p-toluenesulfonic acid monohydrate (1.90 g; 10 mmol) was added in one portion. The mixture was stirred vigorously at room temperature for 1 hour, and the resulting precipitate was collected by filtration, washed with a small amount of MeCN, and dried in air to yield hydroxy(perfluoropropyl)iodonium tosylate as an off-white solid (1.83 g; 34% yield). Spectroscopic characterization was in agreement with literature reports.



Chloro(4-trimethylsilylphenyl)perfluoropropyliodane (4)

A 50 mL Schlenk flask was charged with hydroxy(perfluoropropyl)iodonium tosylate (484 mg; 1.0 mmol), 1,4-bis(trimethylsilyl)benzene (400 mg; 1.8 mmol), and a stir bar. The vessel was placed under a N_2 atmosphere, and anhydrous CH_2Cl_2 (15 mL) was added. The reaction mixture was cooled to 0 ºC, and BF_3 etherate (220 µL, 12 mmol) was added dropwise. The mixture was then stirred at room temperature for 3 hours, after which time brine (20 mL) was added at 0 ºC. The biphasic mixture was stirred several minutes, partitioned, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The resulting material was taken up in a mixture of diethyl ether/hexanes (1:1 v/v), and the resulting precipitate was collected by filtration, washed with a small amount of ice-cold hexanes, and air-dried to obtain the product as a white solid (94 mg; 20% yield). Single crystals were obtained from a saturated pentane solution at -30 ºC and analyzed using X-ray crystallography. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.07 (d, *J* = 7.9 Hz, 2H), 7.65 (d, *J* = 7.8 Hz, 2H), 0.32 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 147.7, 136.9, 134.5, 120.3, -1.4 (perfluorinated carbons appear as a set of complex multiplets between 120 and 106). ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -78.8 (t, *J* = 8.0; 3F), -86.4 (q, *J* = 8.0, 2F), -119.6 (s, 2F). HRMS (ESI) Calc'd for $C_{12}H_{13}F_7ISi$ $[M\text{-}Cl]^+$: 444.9714; found 444.9710.



Oxidation of $Ph_3PAu(4\text{-}CH_3\text{-}C_6H_4)$ to $Ph_3PAu(4\text{-}CH_3\text{-}C_6H_4)(CF_3)(Cl)$

A 1 dram vial wrapped in aluminum foil was charged with $Ph_3PAu(4\text{-}CH_3\text{-}C_6H_4)$ (**5**) (12.5 mg; 0.02 mmol), **2·MeCl** (8.3 mg; 0.02 mmol), 4-fluoro-biphenyl (11.7 mg; 0.06 mmol; internal standard), and CD_2Cl_2 (0.5 mL). The reaction mixture was shaken for 2 minutes, and transferred to a foiled NMR tube. ^{19}F and ^{31}P NMR analyses were both consistent[71] with the formation of the Au(III) complexes **6a** and **6b** as an approximately 1:1 mixture of isomers (42% yield, combined). ^{19}F NMR (CD_2Cl_2, 376.5 MHz) δ -29.9 (d, $^3J_{P\text{-}F}$ = 68 Hz, *trans*), -28.8 (d, $^3J_{P\text{-}F}$ = 45 Hz, *cis*). $^{31}P\{^1H\}$ NMR (CD_2Cl_2, 161.9 MHz) δ 23.0 (q, $^3J_{P\text{-}F}$ = 69 Hz, *trans*), 36.3 (q, $^3J_{P\text{-}F}$ = 44 Hz, *cis*).

In a separate experiment, A 1 dram vial wrapped in aluminum foil was charged with $Ph_3PAu(4\text{-}CH_3\text{-}C_6H_4)$ (12.5 mg; 0.02 mmol), **1·HCl** (8.3 mg; 0.02 mmol), 4-fluoro-biphenyl (11.7 mg; 0.06 mmol; internal standard), and CD_2Cl_2 (0.5 mL). The reaction mixture was shaken for 2 minutes, and transferred to a foiled NMR tube. ^{19}F and ^{31}P NMR analyses were both consistent with the formation of the above gold(III) complexes (10% yield). The primary byproducts were determined to be Ph_3PAuCl and 3,3-dimethyl-1-(trifluoromethyl)-1,2,-benziodoxole (**1**) by ^{31}P and ^{19}F NMR, respectively. This suggests that **1·HCl** is sufficiently acidic to preferentially induce protodeauration.

Oxidation of ferrocene to the ferrocenium cation

A 1 dram vial was charged with ferrocene (5.6 mg; 0.03 mmol) and CH_2Cl_2 (400 μL). Two aliquots of the resulting solution (100 μL each) were transferred to two separate 1 dram vials, one containing 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (4.8 mg; 0.02 mmol) and the other containing **2·HCl** (5.3 mg; 0.02 mmol). Both reaction mixtures were diluted with CH_2Cl_2 (final volume of 3.0 mL) and stirred at room temperature for 20 minutes. The resulting solutions were filtered through a 0.45 μm syringe filter and analyzed by ultraviolet-visible spectroscopy. The reaction between ferrocene and **2·HCl** showed a characteristic absorbance at approximately 620 nm that is consistent with the formation of ferrocenium.[72] In contrast, the reaction between ferrocene and 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one showed no absorbance at the aforementioned wavelength.

In a separate experiment, a 1 dram vial was charged with ferrocene (5.6 mg; 0.03 mmol) and CH_2Cl_2 (400 μL). Two aliquots of the resulting solution (100 μL each) were transferred to two separate 1 dram vials, one containing 3,3-dimethyl-1-(trifluoromethyl)-1,2,-benziodoxole (7.5 mg; 0.02 mmol) and the other containing **1·HCl** (8.5 mg; 0.02 mmol). Both reaction mixtures

were diluted with CH_2Cl_2 (final volume of 3.0 mL) and stirred at room temperature for 20 minutes. The resulting solutions were filtered through a 0.45 μm syringe filter and analyzed by ultraviolet-visible spectrophotometry (Figure S1B). The reaction between ferrocene and **1·HCl** showed a characteristic absorbance at approximately 620 nm that is consistent[72] with the formation of ferrocenium. In contrast, the reaction between ferrocene and 3,3-dimethyl-1-(trifluoromethyl)-1,2,-benziodoxole showed no absorbance at the aforementioned wavelength.

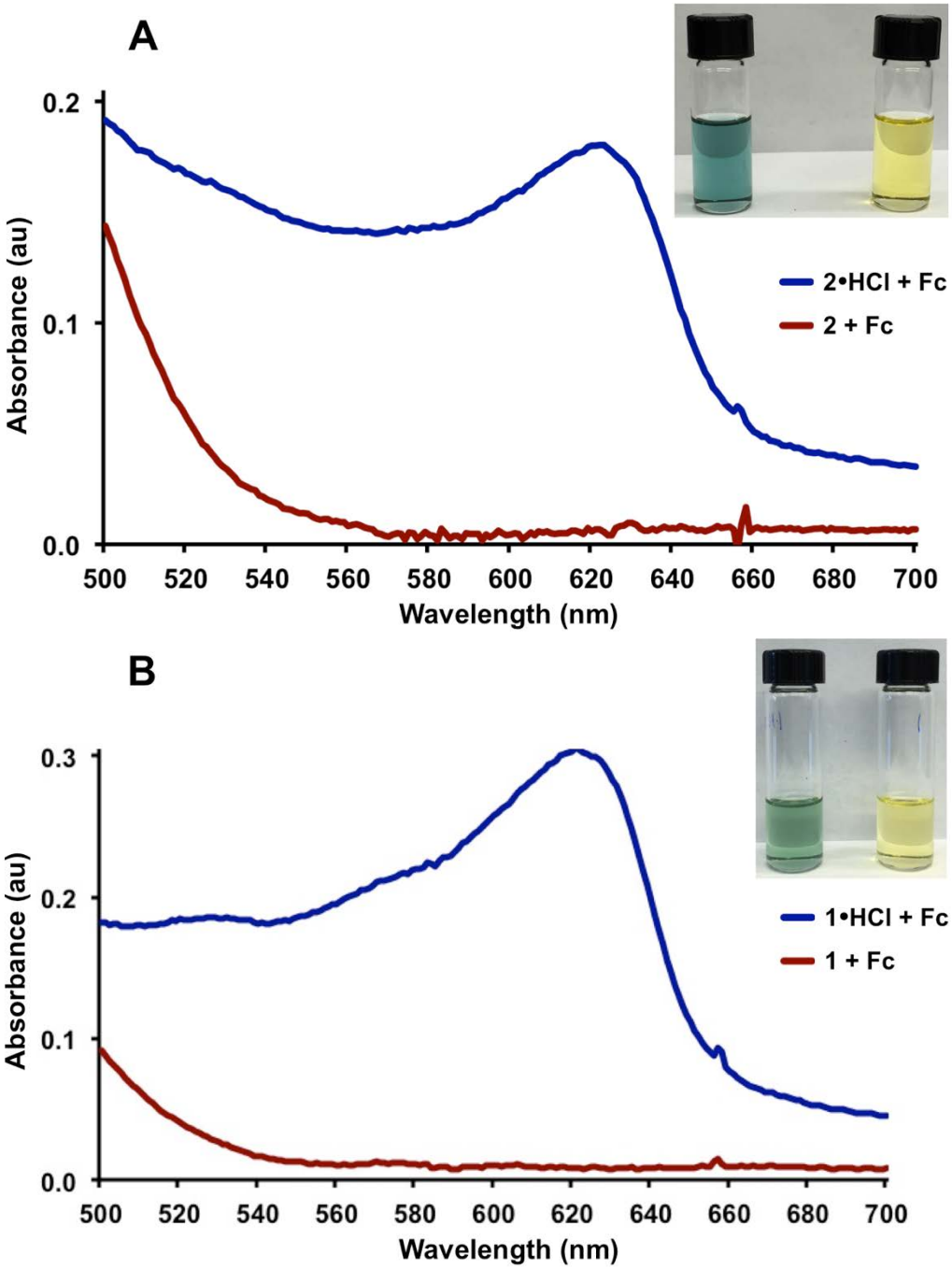
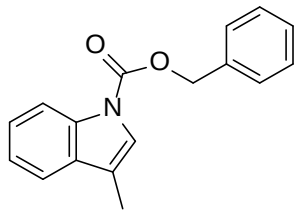


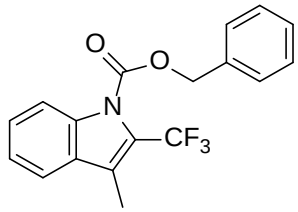
Figure S1. Ultraviolet-visible absorption profiles for ferrocene oxidation products. (A) Ferrocene (Fc) was oxidized to the ferrocenium (Fc^+) cation by **2·HCl** (Blue; [**2·HCl**] = 0.007 M; CH_2Cl_2). No reaction is observed when the parent iodane is reacted with Fc under identical conditions (Red; [**2**] = 0.007 M; CH_2Cl_2). The inset photograph shows the crude reaction mixtures using **2·HCl** (left) and **2** (right). (B) Fc was oxidized to Fc^+ by **1·HCl** (Blue; [**1·HCl**] = 0.007 M; CH_2Cl_2). No reaction is observed when the parent iodane is reacted with

Fc under identical conditions (Red; [**1**] = 0.007 M; CH_2Cl_2). The inset photograph shows the crude reaction mixtures using **1·HCl** (left) and **1** (right).



Benzyl 3-methylindole-1-carboxylate

A 50 mL flask was charged with 3-methylindole (656 mg; 5.0 mmol), sodium hydroxide (600 mg; 15 mmol), tetrabutylammonium bisulfate (85 mg; 0.35 mmol), CH_2Cl_2 (25 mL), and a stir bar. The suspension was stirred at room temperature for 1 hour, after which the mixture was cooled to 0 ºC and benzyl chloroformate (1.4 mL; 10 mmol) was added dropwise. The mixture was stirred for 16 hours at room temperature, then partitioned between CH_2Cl_2 and saturated aqueous ammonium chloride. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL), and the combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by silica chromatography (5-7% ethyl acetate/hexanes eluent) to afford the desired product as a pale orange oil (1.18 g; 89%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.20 (br, 1H), 7.54-7.49 (m, 3H), 7.45-7.38 (m, 4H), 7.37-7.33 (m, 1H), 7.31-7.27 (m, 1H), 5.46 (s, 2H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150.9 MHz) δ 150.8, 135.6, 135.3, 131.5, 128.7, 128.6, 128.4, 124.5, 122.7, 122.3, 119.0, 117.3, 115.2, 68.4, 9.6. HRMS (EI) Calc'd for $C_{17}H_{15}NO_2$ $[M]^+$: 265.1103; found 265.1106.



Trifluoromethylation of benzyl 3-methylindole-1-carboxylate

A conical plastic tube was charged with **2·HCl** (70 mg; 0.20 mmol), benzyl 3-methyl-1H-indole-1-carboxylate (80 mg; 0.30 mmol), $CHCl_3$ (400 μL), and a stir bar. The reaction mixture was stirred at 60 ºC for 3 hours, after which the reaction was diluted with CH_2Cl_2 (5 mL) and extracted with saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, concentrated, and purified by silica chromatography (10-30% CH_2Cl_2/hexanes eluent) to afford the desired product as a colorless oil (33 mg; 49% yield).

Benzyl 3-methyl-1H-indole-1-carboxylate (31 mg; 39% yield) could be recovered by further elution. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.53-7.36 (m, 6H), 7.31 (t, *J* = 7.5 Hz, 1H), 5.46 (s, 2H), 2.45 (q, *J* = 3.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ 150.4, 136.5, 134.5, 129.0, 128.89, 128.85, 128.7, 127.6, 124.1 (q, *J* = 2.8 Hz), 123.5, 122.7, 120.1, 115.8, 122.2 (q, *J* = 37.6 Hz), 69.6, 9.7 (q, *J* = 3.4 Hz). ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -53.9 (s). HRMS (EI) Calc'd for $C_{18}H_{14}F_3NO_2$ $[M]^+$: 330.0977; found 330.9800.

Representative procedure for alcohol trifluoromethylation

A conical plastic tube was charged with 2-(2-hydroxyethyl)isoindoline-1,3-dione (39.5 mg; 0.20 mmol), **1·HCl** (25.0 mg; 0.07 mmol), $NaBArF_{24}$ (6.0 mg; 0.007 mmol) and MeCN (140 μL). The suspension was heated at 55 ºC with stirring for 16 hours, after which the reaction mixture was filtered through a 0.45 μm syringe filter and loaded onto a silica column. Elution with 30% diethyl ether in pentane afforded the desired product as a colorless solid (4.0 mg; 23% yield). Spectroscopic characterization was in agreement with literature[58] reports. The remaining products shown in Table 1 were prepared using an analogous procedure; product yields (which are an average of at least two independent experiments) were determined using ^{19}F NMR with 4-fluorobiphenyl as an internal standard. ^{19}F NMR chemical shifts were consistent[58,73] with previous literature reports and are tabulated below [^{19}F NMR (CD_2Cl_2, 376.5 MHz, δ)]:

7a: -59.7 (s)

7b: -60.9 (s)

7c: -61.1 (s)

7d: -59.9 (s)

7e: -60.1 (s)

7f: -59.7 (s)

7g: -60.1 (s)

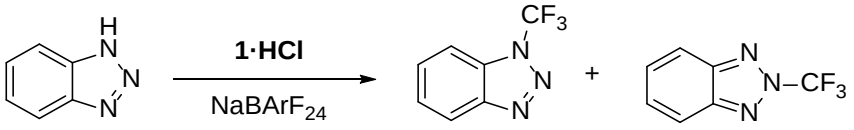
7h: -56.8 (s)

7i: -60.3 (s)

In a separate experiment, a conical plastic tube was charged with 1-adamantanemethanol (10.0 mg; 0.060 mmol), **1·HBArF$_{24}$** (3.3 mg; 0.003 mmol), 4-fluoro-biphenyl (1.5 mg; 0.009 mmol) and MeCN (55 μL). The suspension was heated at 55 ºC for 16 hours, after which the reaction mixture was analyzed by ^{19}F NMR. The product was observed in 35% yield.

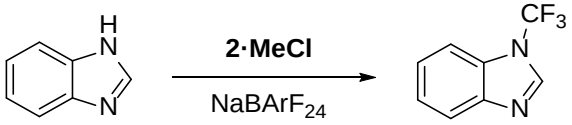
1·HCl and **2·HCl** could also be used directly for alcohol trifluoromethylations under solvolytic conditions. In one experiment, a plastic conical tube was charged with **1·HCl** (5.0

mg; 0.013 mmol), 4-fluoro-biphenyl (7.0 mg; 0.041 mmol), and 3-phenyl-1-propanol (0.5 mL). The mixture was heated at 55 ºC for 16 hours, after which the reaction was analyzed by ^{19}F NMR. The desired product was observed in 75% yield. In a separate experiment, a plastic conical tube was charged with **2·HCl** (5.0 mg; 0.014 mmol), 4-fluoro-biphenyl (7.3 mg; 0.042 mmol), and 3-phenyl-1-propanol (0.5 mL). The mixture was heated at 55 ºC for 16 hours, after which the reaction was analyzed by ^{19}F NMR. The desired product was observed in 70% yield.



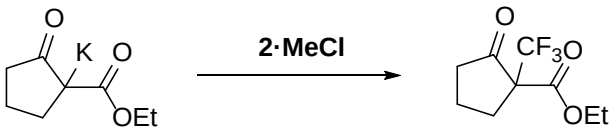
Trifluoromethylation of benzotriazole

A conical plastic tube was charged with benzotriazole (10.0 mg; 0.08 mmol), **1·HCl** (10.0 mg; 0.03 mmol), $NaBArF_{24}$ (2.4 mg; 0.003 mmol), 4-fluoro-biphenyl (4.7 mg; 0.03 mmol), and CH_2Cl_2 (55 μL). The suspension was heated at 55 ºC for 16 hours, after which time the reaction mixture was analyzed by ^{19}F NMR. The desired products were observed in 59% combined yield. ^{19}F NMR (CD_2Cl_2, 376.5 MHz) δ -57.0 (s; 1-CF_3), -60.0 (s; 2-CF_3). Spectroscopic data were in agreement with previous literature reports.[46]



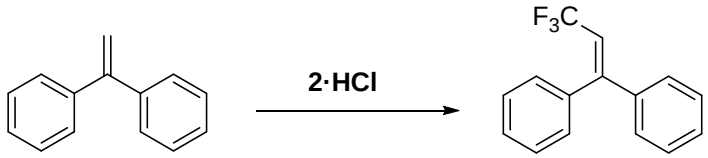
Trifluoromethylation of benzimidazole

A conical plastic tube was charged with benzimidazole (5.0 mg; 0.04 mmol), **2·MeCl** (5.0 mg; 0.01 mmol), $NaBArF_{24}$ (1.2 mg; 0.001 mmol), 4-fluoro-biphenyl (2.3 mg; 0.01 mmol), and MeCN (27 μL). The suspension was heated at 55 ºC for 16 hours, after which time the reaction mixture was analyzed by ^{19}F NMR. The desired product was obtained in 41% yield. ^{19}F NMR (CD_2Cl_2, 376.5 MHz) δ -56.9 (s) Spectroscopic data were in agreement with previous literature reports.[59]



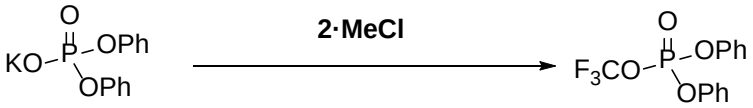
Trifluoromethylation of potassium 2-ethoxycarbonyl-1-cyclopentanone

A 1 dram vial was charged with potassium 2-ethoxycarbonyl-1-cyclopentanone (9.7 mg; 0.06 mmol), p-fluorobiphenyl (25.8 mg; 0.15 mmol), CD_2Cl_2 (1.0 mL), and a stir bar. To the suspension was added **2·MeCl** (18.3 mg; 0.05 mmol), and the mixture stirred at room temperature for 2 hours. The mixture was filtered through celite, and analysis by ^{19}F NMR indicated the formation of the desired product in 22% yield. ^{19}F NMR (CD_2Cl_2, 376.5 MHz) δ -68.4 (s). Spectral data are in agreement with literature reports.[74]



Trifluoromethylation of 1,1-diphenylethylene

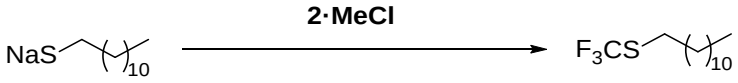
A conical plastic tube was charged with diphenylethylene (27 mg; 0.15 mmol), **2·HCl** (17.6 mg; 0.050 mmol), p-fluorobiphenyl (25.8 mg; 0.15 mmol), and $CDCl_3$ (200 μl). The reaction mixture was heated at 60 °C for 16 hours. Analysis by ^{19}F NMR indicated formation of the desired product in 37% yield. ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -55.2 (d, J = 8.4 Hz). Spectral data are in agreement with literature reports.[75]



Trifluoromethylation of potassium diphenylphosphate

A 1 dram vial was charged with potassium diphenylphosphate (14.4 mg, 0.050 mmol), **2·MeCl** (18.3 mg, 0.050 mmol), p-fluorobiphenyl (25.8 mg, 0.15 mmol), and a stir bar. The solids were suspended in CD_2Cl_2 (1.0 mL) and stirred at room temperature for 2 hours. The reaction mixture was filtered through a plug of celite and analyzed by ^{19}F NMR, which indicated the desired product was present in 45% yield. ^{19}F NMR (CD_2Cl_2, 376.5 MHz) δ -52.0 (d; $^3J_{P\text{-}F}$ = 4.6 Hz). Diphenyl fluorophosphate was also observed in 12% yield. ^{19}F NMR (CD_2Cl_2, 376.5 MHz) δ -77.3 (d; $J_{P\text{-}F}$ = 1001 Hz).

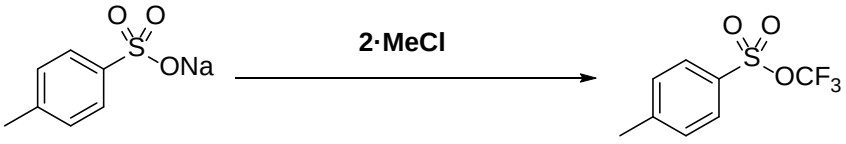
In a separate experiment, a 1 dram vial was charged with diphenylphosphoric acid (12.5 mg, 0.050 mmol), **2·MeCl** (18.3 mg, 0.050 mmol), p-fluorobiphenyl (25.8 mg, 0.15 mmol), and a stir bar. The solids were suspended in CD_2Cl_2 (1.0 mL) and stirred at room temperature for 16 hours. The reaction mixture was filtered through a plug of celite and analyzed by ^{19}F NMR, which indicated that the desired product was formed in 6% yield.



Trifluoromethylation of dodecanethiol

A 10 mL Schlenk flask was charged with sodium hydride (6.7 mg of a 60% suspension in mineral oil; ~0.2 mmol) and a stir bar. The flask was evacuated and backfilled with N_2 (3 x), and dry MeCN (2.0 mL) was added. The vessel was cooled to 0 ºC, and dodecanethiol (20 μL; 0.2 mmol) was added under a countercurrent of N_2. The resulting suspension was stirred at 0 ºC for 10 minutes, and then room temperature for an additional 30 minutes. **2·MeCl** (10.0 mg; 0.027 mmol) was added under a countercurrent of N_2, and the resulting mixture was stirred at room temperature for 16 hours. 4-fluoro-biphenyl (14.0 mg; 0.08 mmol) was added, an aliquot of the mixture (0.5 mL) was diluted with CD_2Cl_2 and analyzed by ^{19}F NMR. The desired product was observed in 95% yield. ^{19}F NMR (CD_2Cl_2, 376.5 MHz) δ -41.2 (s). Spectral data are in agreement with literature reports.[76]

In a separate experiment, a 1 dram vial was charged with dodecanethiol (10.1 mg, 0.050 mmol), **2·MeCl** (18.3 mg, 0.050 mmol), p-fluorobiphenyl (25.8 mg, 0.15 mmol), and a stir bar. The reactants were dissolved in CD_3CN (1.0 mL) and stirred at room temperature for 16 hours. No formation of the desired product was observed by ^{19}F NMR.



Trifluoromethylation of p-toluenesulfonate

A 1 dram vial was charged with sodium p-toluenesulfonate (9.7 mg, 0.050 mmol), **2·MeCl** (18.3 mg, 0.050 mmol), p-fluorobiphenyl (25.8 mg, 0.15 mmol), and a stir bar. The solids were suspended in CD_2Cl_2 (1.0 mL) and stirred at room temperature for 16 hours. The reaction mixture was filtered through a plug of celite and analyzed by ^{19}F NMR, which indicated that the desired product was formed in 70% yield. ^{19}F NMR (CD_2Cl_2, 376.5 MHz, δ): -53.6 (s). Spectral data were in agreement with previous reports.[45]

In a separate experiment, a 1 dram vial was charged with p-toluenesulfonic acid monohydrate (9.5 mg, 0.050 mmol), **2·MeCl** (18.3 mg, 0.050 mmol), p-fluorobiphenyl (25.8 mg, 0.15 mmol), and a stir bar. The solids were suspended in CD_2Cl_2 (1.0 mL) and stirred at room temperature for 16 hours. The reaction mixture was analyzed by ^{19}F NMR, which indicated that trifluoromethyl tosylate was formed in 78% yield.

2.6 References

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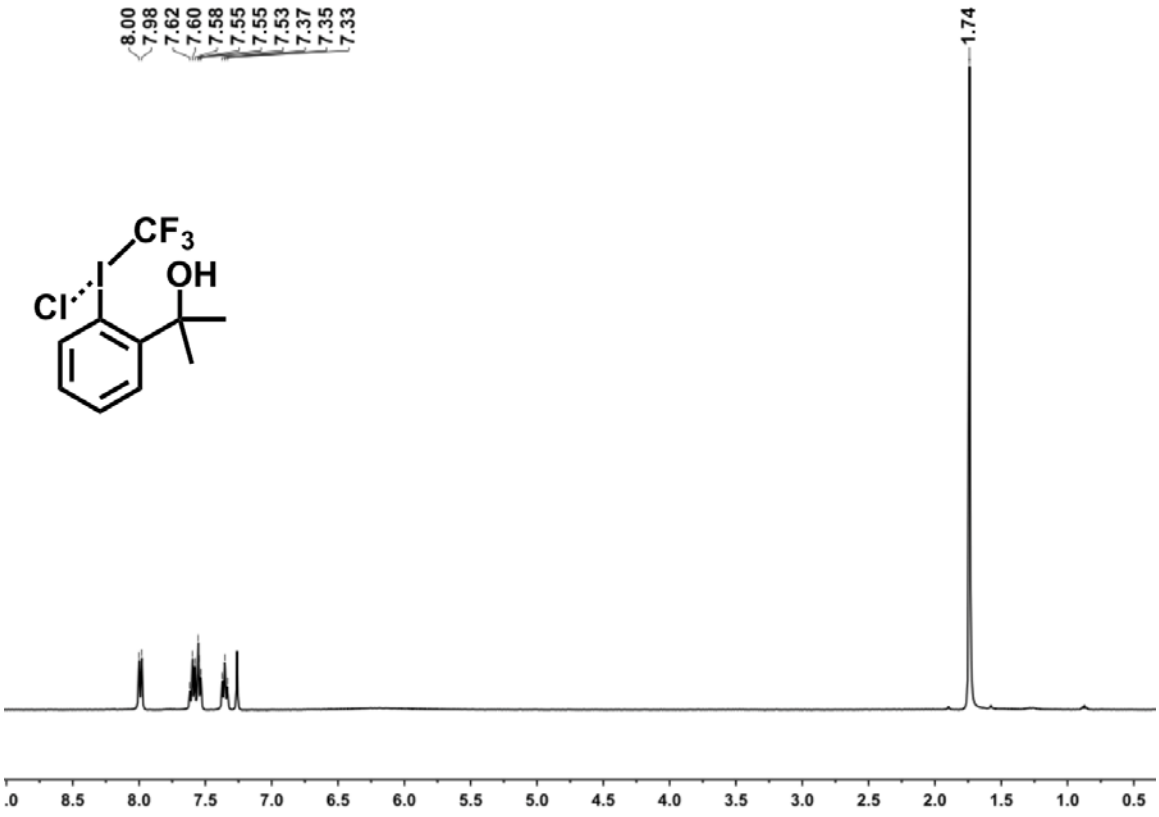
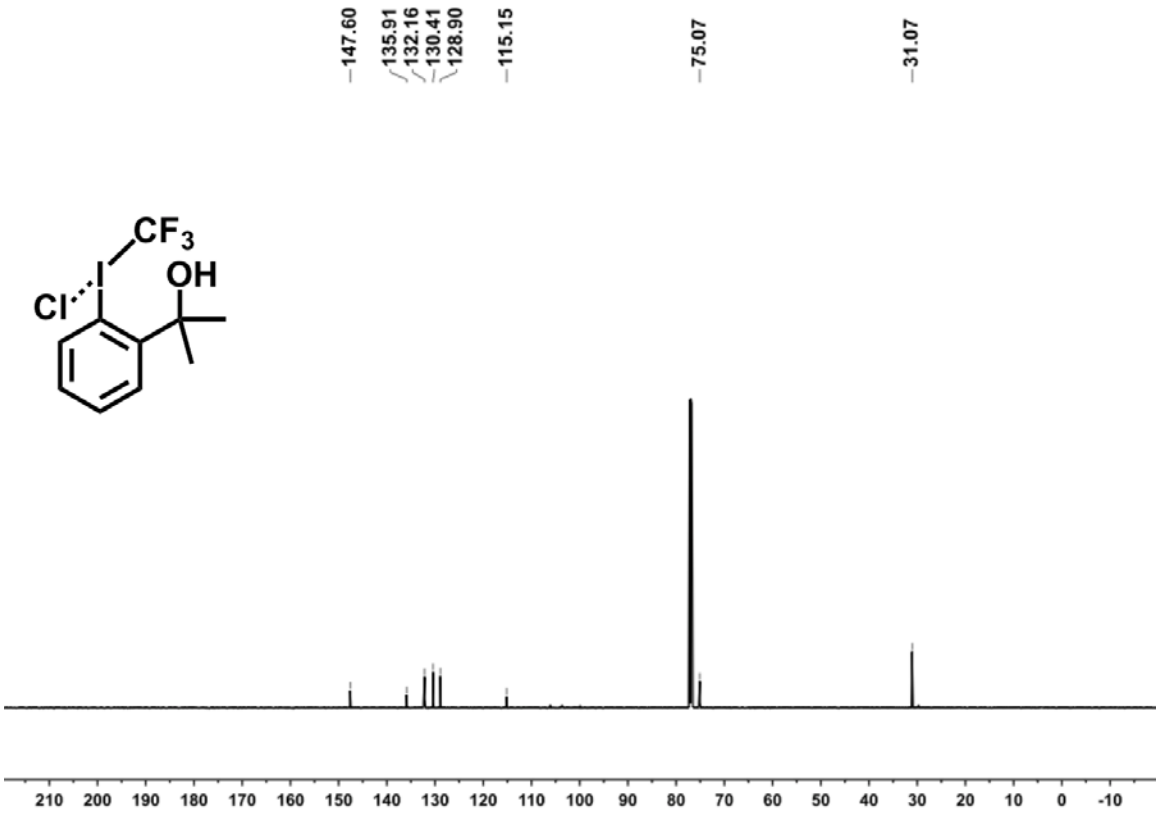
2.7 NMR Spectra of New Compounds

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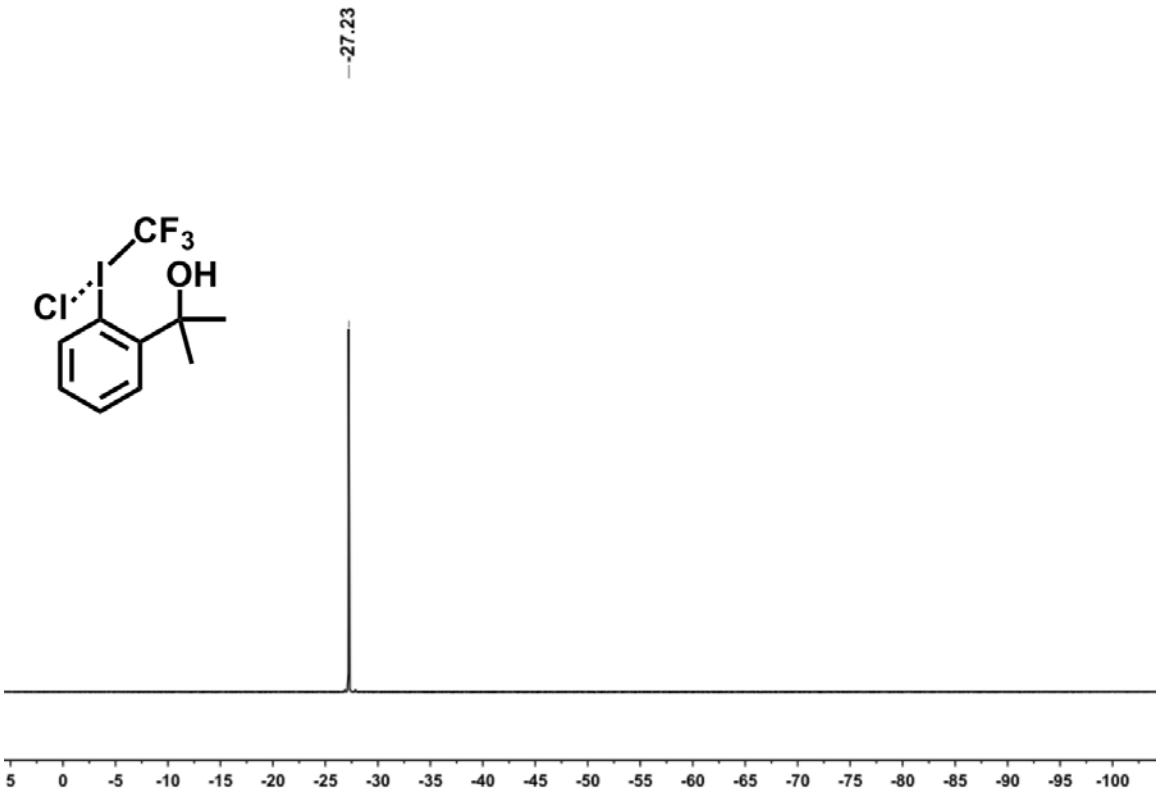
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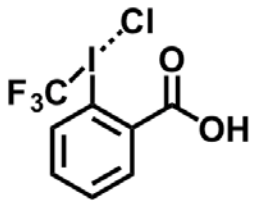
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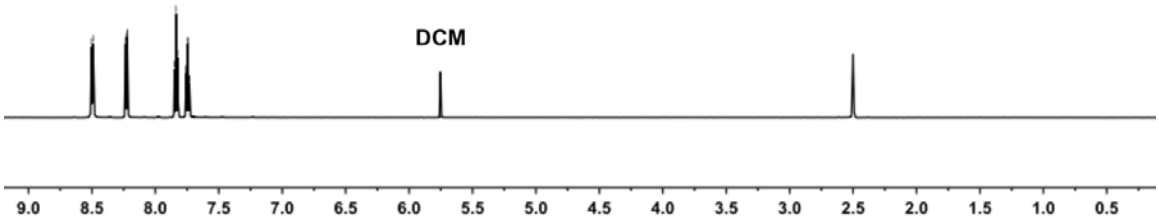
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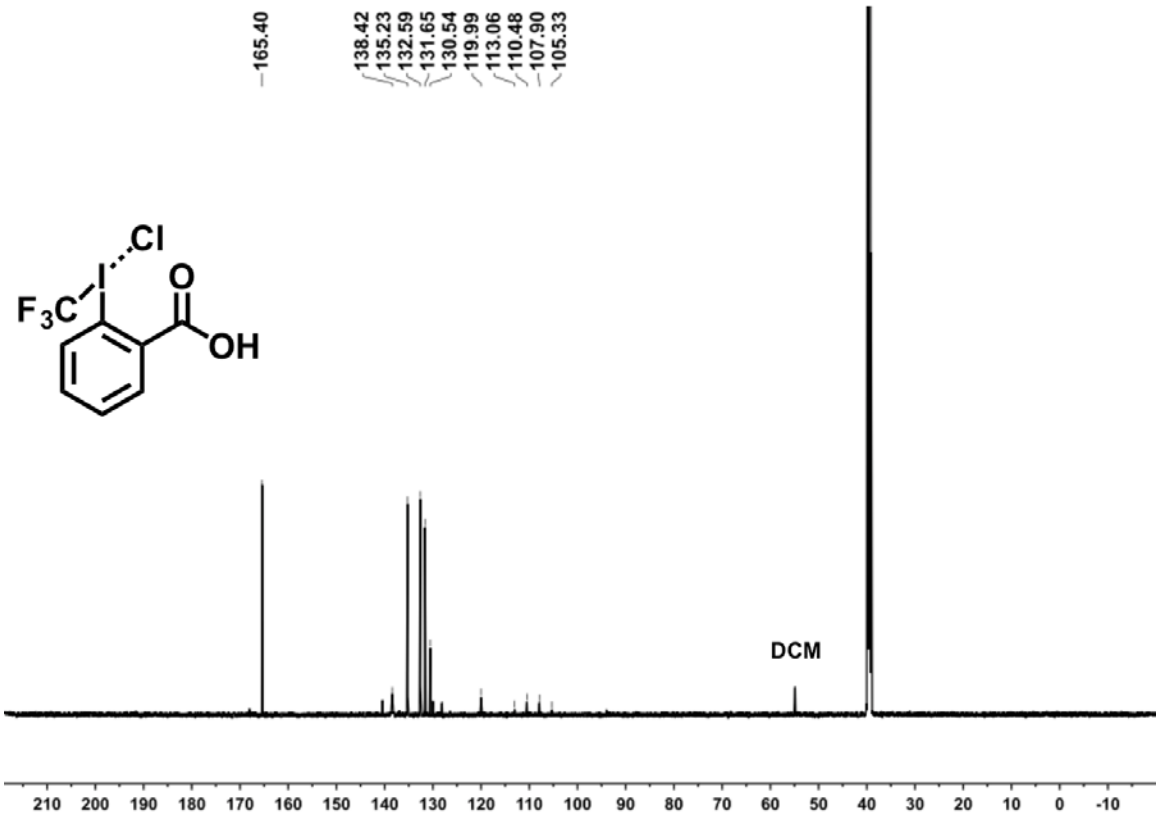
1.5
1.0
0.5


165.40
138.42
135.23
132.59
131.65
130.54
119.99
113.06
110.48
107.90
105.33
Cl
I
O
F3C
OH
DCM
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

2.8 Crystallographic Data

Table C1. Crystal data and structure refinement for **1·HBF$_4$**

Identification code	shelx	
Empirical formula	C10 H11 B F7 I O S0	
Formula weight	417.90	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 15.9890(9) Å	α= 90°.
	b = 8.7606(5) Å	β= 93.788(3)°.
	c = 19.0524(11) Å	γ = 90°.
Volume	2662.9(3) Å^3	
Z	8	
Density (calculated)	2.085 Mg/m^3	
Absorption coefficient	2.479 mm^{-1}	
F(000)	1600	
Crystal size	0.060 x 0.020 x 0.020 mm^3	
Theta range for data collection	1.276 to 25.396°.	
Index ranges	-19<=h<=19, -10<=k<=10, -22<=l<=22	
Reflections collected	75792	
Independent reflections	4884 [R(int) = 0.0489]	

Completeness to theta = 25.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.745 and 0.688
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4884 / 0 / 361
Goodness-of-fit on F^2	1.092
Final R indices [I>2sigma(I)]	R1 = 0.0480, wR2 = 0.1144
R indices (all data)	R1 = 0.0565, wR2 = 0.1200
Extinction coefficient	n/a
Largest diff. peak and hole	3.333 and -1.095 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **1·HBF$_4$**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8832(3)	1807(6)	4500(3)	21(1)
C(2)	9612(3)	3449(5)	5902(3)	15(1)
C(3)	10313(3)	3265(6)	5525(3)	19(1)
C(4)	11098(3)	3474(6)	5877(3)	23(1)
C(5)	11152(3)	3844(6)	6579(3)	21(1)
C(6)	10433(3)	4023(6)	6946(3)	19(1)
C(7)	9637(3)	3855(5)	6612(3)	15(1)
C(8)	8845(3)	4067(6)	7008(3)	17(1)
C(9)	8551(3)	2542(6)	7288(3)	21(1)
C(10)	8948(3)	5250(6)	7585(3)	26(1)
C(11)	6198(3)	6979(6)	5403(3)	24(1)
C(12)	5379(3)	8572(6)	4002(3)	15(1)
C(13)	4673(3)	8406(6)	4376(3)	18(1)
C(14)	3895(3)	8571(6)	4016(3)	22(1)
C(15)	3841(3)	8931(6)	3306(3)	20(1)
C(16)	4571(3)	9089(5)	2946(3)	17(1)
C(17)	5360(3)	8924(5)	3289(3)	14(1)

C(18)	6160(3)	9085(6)	2895(2)	16(1)
C(19)	6050(3)	10148(6)	2263(3)	22(1)
C(20)	6464(3)	7521(6)	2678(3)	19(1)
O(1)	8182(2)	4582(4)	6501(2)	21(1)
O(2)	6796(2)	9716(4)	3390(2)	19(1)
F(1)	9333(2)	708(4)	4725(2)	28(1)
F(2)	9210(2)	2666(4)	4049(2)	30(1)
F(3)	8148(2)	1217(4)	4175(2)	35(1)
F(4)	5819(2)	7761(4)	5879(2)	32(1)
F(5)	6897(2)	6397(4)	5696(2)	38(1)
F(6)	5703(2)	5876(4)	5165(2)	28(1)
F(7)	8724(2)	7222(4)	5918(2)	46(1)
F(8)	8055(2)	8598(5)	6700(2)	48(1)
F(9)	7956(2)	9266(4)	5561(2)	49(1)
F(10)	9180(2)	9591(4)	6209(2)	29(1)
F(11)	5787(2)	4277(5)	3838(2)	51(1)
F(12)	6569(3)	2538(5)	4488(2)	59(1)
F(13)	6780(2)	2865(4)	3340(2)	34(1)
F(14)	7136(2)	4689(5)	4134(2)	56(1)
I(1)	8407(1)	3185(1)	5377(1)	19(1)
I(2)	6581(1)	8451(1)	4543(1)	19(1)

B(1)	8469(4)	8679(7)	6099(3)	19(1)
B(2)	6553(4)	3591(7)	3950(3)	19(1)

Table 3. Crystal data and structure refinement for **5**.

Identification code	shelx	
Empirical formula	C_{12} H_{13} Cl F_7 I Si	
Formula weight	480.66	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 12.0089(4) Å	α= 90°.
	b = 25.0752(9) Å	β= 115.4650(10)°.
	c = 12.5156(4) Å	γ = 90°.
Volume	3402.6(2) $Å^3$	
Z	8	
Density (calculated)	1.877 Mg/m^3	
Absorption coefficient	2.169 mm^{-1}	

F(000)	1856
Crystal size	0.100 x 0.060 x 0.030 mm^3
Theta range for data collection	1.624 to 25.384°.
Index ranges	-13<=h<=14, -30<=k<=25, -15<=l<=14
Reflections collected	39280
Independent reflections	6244 [R(int) = 0.0385]
Completeness to theta = 25.000°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.745 and 0.642
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6244 / 0 / 403
Goodness-of-fit on F^2	1.095
Final R indices [I>2sigma(I)]	R1 = 0.0246, wR2 = 0.0561
R indices (all data)	R1 = 0.0263, wR2 = 0.0569
Extinction coefficient	n/a
Largest diff. peak and hole	1.055 and -0.603 e.$Å^{-3}$

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **5**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5766(3)	4566(1)	2339(3)	22(1)
C(2)	5770(3)	4317(1)	3453(2)	24(1)
C(3)	6833(3)	3926(1)	4144(3)	29(1)
C(4)	4840(2)	5750(1)	2147(2)	19(1)
C(5)	5528(3)	6034(1)	1703(2)	22(1)
C(6)	5982(2)	6526(1)	2198(2)	22(1)
C(7)	5767(2)	6740(1)	3128(2)	18(1)
C(8)	5072(3)	6427(1)	3549(2)	24(1)
C(9)	4601(3)	5934(1)	3067(2)	23(1)
C(10)	5074(3)	7738(1)	4059(3)	28(1)
C(11)	6564(3)	7818(1)	2609(2)	25(1)
C(12)	7744(3)	7376(1)	5154(2)	23(1)
C(13)	9032(3)	5047(1)	7518(2)	22(1)
C(14)	9263(3)	5332(1)	6547(3)	32(1)
C(15)	8285(3)	5745(1)	5811(3)	41(1)
C(16)	9959(2)	3850(1)	7736(2)	19(1)
C(17)	10542(3)	3639(1)	7092(2)	25(1)

C(18)	10160(3)	3143(1)	6570(3)	26(1)
C(19)	9208(2)	2859(1)	6673(2)	19(1)
C(20)	8633(3)	3103(1)	7311(2)	21(1)
C(21)	8998(2)	3595(1)	7858(2)	20(1)
C(22)	8392(3)	1774(1)	7116(3)	27(1)
C(23)	7375(3)	2208(1)	4582(3)	26(1)
C(24)	10078(3)	1856(1)	5872(3)	27(1)
F(1)	5833(2)	4186(1)	1622(1)	31(1)
F(2)	6743(2)	4891(1)	2629(2)	37(1)
F(3)	4712(2)	4050(1)	3156(2)	36(1)
F(4)	5801(2)	4710(1)	4191(2)	46(1)
F(5)	6684(2)	3483(1)	3541(2)	48(1)
F(6)	6816(2)	3805(1)	5160(2)	48(1)
F(7)	7898(2)	4134(1)	4339(2)	66(1)
F(8)	8028(2)	4738(1)	7014(2)	32(1)
F(9)	8834(2)	5408(1)	8202(2)	29(1)
F(10)	9326(3)	4963(1)	5806(2)	61(1)
F(11)	10345(2)	5585(1)	7043(2)	51(1)
F(12)	7194(3)	5539(1)	5370(3)	115(2)
F(13)	8289(3)	6150(1)	6458(2)	71(1)
F(14)	8517(3)	5933(1)	4956(2)	88(1)

Si(1)	6314(1)	7428(1)	3752(1)	18(1)
Si(2)	8755(1)	2163(1)	6044(1)	19(1)
Cl(1)	1907(1)	5619(1)	120(1)	23(1)
Cl(2)	12729(1)	3954(1)	10090(1)	23(1)
I(1)	4010(1)	5027(1)	1326(1)	18(1)
I(2)	10681(1)	4561(1)	8686(1)	18(1)

Table 5. Crystal data and structure refinement for **2·HCl**.

Identification code	shelx	
Empirical formula	$C_{8.50} H_{5.75} Cl F_3 I N_{0.25} O_2$	
Formula weight	362.73	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C c	
Unit cell dimensions	a = 18.8002(13) Å	α= 90°.
	b = 16.2335(11) Å	β= 108.8840(10)°.
	c = 15.7805(11) Å	γ = 90°.
Volume	4556.9(5) $Å^3$	

Z	16
Density (calculated)	2.115 Mg/m^3
Absorption coefficient	3.067 mm^{-1}
F(000)	2744
Crystal size	0.200 x 0.100 x 0.080 mm^3
Theta range for data collection	1.698 to 25.437°.
Index ranges	-22<=h<=22, -19<=k<=19, -19<=l<=19
Reflections collected	52041
Independent reflections	8303 [R(int) = 0.0373]
Completeness to theta = 25.000°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7452 and 0.5911
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8303 / 2 / 573
Goodness-of-fit on F^2	1.126
Final R indices [I>2sigma(I)]	R1 = 0.0280, wR2 = 0.0684
R indices (all data)	R1 = 0.0291, wR2 = 0.0692
Absolute structure parameter	-0.040(6)
Extinction coefficient	n/a
Largest diff. peak and hole	1.879 and -0.897 $e.Å^{-3}$

Table 6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2·HCl**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4580(5)	11347(5)	6673(6)	21(2)
C(2)	3799(4)	9978(5)	7410(5)	17(2)
C(3)	3893(5)	10038(5)	8311(5)	22(2)
C(4)	4145(5)	9356(5)	8858(5)	25(2)
C(5)	4297(5)	8623(5)	8493(6)	27(2)
C(6)	4183(4)	8575(5)	7585(5)	21(2)
C(7)	3924(4)	9247(5)	7017(5)	18(2)
C(8)	3791(5)	9169(5)	6032(6)	22(2)
C(9)	5510(5)	8627(6)	5081(6)	25(2)
C(10)	6592(5)	7459(5)	4471(5)	19(2)
C(11)	6630(5)	6641(5)	4737(6)	21(2)
C(12)	6661(5)	6033(5)	4143(6)	25(2)
C(13)	6645(6)	6254(5)	3297(6)	29(2)
C(14)	6603(5)	7061(5)	3023(6)	22(2)
C(15)	6559(4)	7690(4)	3609(5)	15(2)
C(16)	6519(5)	8567(5)	3323(6)	21(2)
C(17)	4448(5)	6101(5)	3846(6)	25(2)

C(18)	3387(4)	4870(5)	2503(6)	18(2)
C(19)	3401(5)	4956(5)	1639(6)	24(2)
C(20)	3427(5)	4251(6)	1155(6)	24(2)
C(21)	3411(5)	3486(6)	1511(6)	27(2)
C(22)	3393(5)	3419(5)	2385(6)	19(2)
C(23)	3391(4)	4108(5)	2900(5)	16(2)
C(24)	3398(4)	4001(4)	3869(5)	12(2)
C(25)	5615(5)	3692(6)	2650(6)	29(2)
C(26)	6593(5)	2467(5)	4083(5)	18(2)
C(27)	6451(5)	1672(5)	3766(6)	22(2)
C(28)	6353(5)	1064(5)	4342(6)	24(2)
C(29)	6426(5)	1253(5)	5210(6)	24(2)
C(30)	6585(5)	2066(5)	5517(6)	21(2)
C(31)	6666(4)	2687(5)	4957(5)	15(2)
C(32)	6766(5)	3555(5)	5281(6)	20(2)
C(33)	5035(5)	3603(6)	5440(6)	26(2)
C(34)	5079(6)	4222(7)	6114(8)	43(3)
O(1)	3819(4)	9718(3)	5544(4)	26(1)
O(2)	3648(3)	8382(3)	5771(4)	22(1)
O(3)	6360(4)	9122(3)	3761(4)	26(1)
O(4)	6619(3)	8679(3)	2548(4)	21(1)

O(5)	3565(4)	4560(3)	4392(4)	26(1)
O(6)	3227(4)	3249(3)	4020(4)	24(1)
O(7)	6651(5)	4124(4)	4768(5)	41(2)
O(8)	6944(3)	3629(4)	6149(4)	22(1)
F(1)	4864(3)	11969(3)	7219(4)	28(1)
F(2)	4574(3)	11536(3)	5860(3)	28(1)
F(3)	5010(3)	10696(3)	6956(4)	29(1)
F(4)	5419(3)	9434(3)	5018(3)	30(1)
F(5)	5205(3)	8352(4)	5671(4)	39(1)
F(6)	5155(3)	8300(3)	4292(4)	30(1)
F(7)	4742(3)	6685(3)	3496(4)	39(1)
F(8)	4561(3)	6286(4)	4695(4)	36(1)
F(9)	4787(3)	5395(3)	3809(4)	35(1)
F(10)	5557(3)	4498(3)	2766(4)	41(1)
F(11)	5339(3)	3548(4)	1793(4)	44(2)
F(12)	5226(3)	3318(4)	3071(5)	47(2)
Cl(1)	1951(1)	10453(1)	6742(1)	18(1)
Cl(2)	8301(1)	7848(1)	5948(1)	18(1)
Cl(3)	1666(1)	5515(1)	2015(1)	18(1)
Cl(4)	8344(1)	2751(1)	3879(1)	20(1)
I(1)	3433(1)	11070(1)	6674(1)	16(1)

I(2)	6712(1)	8313(1)	5527(1)	15(1)
I(3)	3238(1)	5990(1)	3110(1)	16(1)
I(4)	6804(1)	3305(1)	3157(1)	16(1)
N(1)	4993(5)	3120(5)	4904(6)	37(2)

Table 7. Crystal data and structure refinement for **1·HCl**.

Identification code	shelx	
Empirical formula	C_{10} H_{11} Cl F_3 I O	
Formula weight	366.54	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 8.1777(4) Å	α= 90°.
	b = 17.9834(8) Å	β= 115.8250(10)°.
	c = 8.8898(4) Å	γ = 90°.
Volume	1176.79(9) $Å^3$	
Z	4	
Density (calculated)	2.069 Mg/m^3	
Absorption coefficient	2.963 mm^{-1}	
F(000)	704	
Crystal size	0.100 x 0.080 x 0.040 mm^3	
Theta range for data collection	2.265 to 25.379°.	
Index ranges	-9<=h<=9, -21<=k<=21, -10<=l<=10	
Reflections collected	23541	
Independent reflections	2156 [R(int) = 0.0482]	

Completeness to theta = 25.000°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.745 and 0.590
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2156 / 0 / 148
Goodness-of-fit on F^2	1.319
Final R indices [I>2sigma(I)]	R1 = 0.0376, wR2 = 0.0784
R indices (all data)	R1 = 0.0401, wR2 = 0.0793
Extinction coefficient	n/a
Largest diff. peak and hole	0.993 and -0.655 e.$Å^{-3}$

Table 8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **1·HCl**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3452(7)	3390(3)	4385(7)	13(1)
C(2)	4181(8)	3899(3)	5731(7)	14(1)
C(3)	6049(8)	3950(3)	6508(7)	18(1)
C(4)	7160(8)	3553(3)	5979(7)	20(1)
C(5)	6411(8)	3074(4)	4616(7)	20(1)
C(6)	4544(8)	2996(3)	3824(7)	18(1)
C(7)	3016(8)	4374(3)	6307(7)	17(1)
C(8)	2262(8)	3912(3)	7322(7)	16(1)
C(9)	4062(10)	5045(4)	7369(8)	26(2)
O(1)	1531(6)	4653(2)	4827(5)	22(1)
I(1)	657(1)	3129(1)	3067(1)	13(1)
F(1)	-968(5)	4503(2)	1099(4)	27(1)
F(2)	1853(5)	4399(2)	1658(4)	28(1)
F(3)	-134(5)	3726(2)	-263(4)	25(1)
C(10)	308(8)	4022(3)	1232(7)	18(1)
Cl(1)	1541(2)	2018(1)	5558(2)	19(1)

Table 9. Crystal data and structure refinement for **1·AcCl**

Identification code	shelx
Empirical formula	C_{12} H_{13} Cl F_3 I O_2
Formula weight	408.57
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	P 21/c	
Unit cell dimensions	a = 11.2059(11) Å	α= 90°.
	b = 13.8263(13) Å	β= 94.868(2)°.
	c = 9.0501(9) Å	γ = 90°.
Volume	1397.1(2) $Å^3$	
Z	4	
Density (calculated)	1.942 Mg/m^3	
Absorption coefficient	2.512 mm^{-1}	
F(000)	792	
Crystal size	0.200 x 0.080 x 0.080 mm^3	
Theta range for data collection	1.824 to 25.388°.	
Index ranges	-13<=h<=13, -16<=k<=16, -10<=l<=10	
Reflections collected	53119	
Independent reflections	2574 [R(int) = 0.0503]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8620 and 0.7420	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2574 / 0 / 175	
Goodness-of-fit on F^2	1.138	
Final R indices [I>2sigma(I)]	R1 = 0.0262, wR2 = 0.0623	

R indices (all data)	R1 = 0.0300, wR2 = 0.0647
Extinction coefficient	n/a
Largest diff. peak and hole	1.774 and -0.361 e.Å^{-3}

Table 10. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **1·AcCl**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6728(3)	3710(2)	3150(3)	14(1)
C(2)	5648(3)	3222(2)	3008(3)	16(1)
C(3)	4921(3)	3271(2)	1692(4)	17(1)
C(4)	5311(3)	3808(2)	532(3)	16(1)
C(5)	6402(3)	4293(2)	705(3)	16(1)
C(6)	7150(3)	4281(2)	2025(3)	14(1)
C(7)	8328(3)	4849(2)	2108(3)	15(1)
C(8)	8477(3)	5480(2)	753(3)	20(1)
C(9)	9422(3)	4202(2)	2323(4)	18(1)
C(10)	6731(3)	4593(2)	6286(3)	18(1)
C(11)	7728(3)	6253(2)	3512(4)	23(1)
C(12)	8155(4)	6876(3)	4802(4)	33(1)
F(1)	6227(2)	5195(1)	5267(2)	21(1)
F(2)	7468(2)	5109(1)	7206(2)	23(1)
F(3)	5872(2)	4233(1)	7043(2)	26(1)
Cl(1)	8615(1)	1883(1)	3526(1)	19(1)

I(1)	7690(1)	3415(1)	5232(1)	14(1)
O(1)	6892(2)	6444(2)	2629(3)	26(1)
O(2)	8412(2)	5460(2)	3476(2)	19(1)

Table 11. Crystal data and structure refinement for **2·MeCl**.

Identification code	AVS7020
Empirical formula	$C_9 H_7 Cl F_3 I O_2$
Formula weight	366.50
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	P 21/c	
Unit cell dimensions	a = 6.4617(2) Å	α= 90°.
	b = 18.6546(7) Å	β= 94.8330(10)°.
	c = 9.1924(4) Å	γ = 90°.
Volume	1104.12(7) $Å^3$	
Z	4	
Density (calculated)	2.205 Mg/m^3	
Absorption coefficient	3.165 mm^{-1}	
F(000)	696	
Crystal size	0.160 x 0.160 x 0.040 mm^3	
Theta range for data collection	2.183 to 25.352°.	
Index ranges	-7<=h<=7, -22<=k<=20, -11<=l<=9	
Reflections collected	8551	
Independent reflections	2004 [R(int) = 0.0785]	
Completeness to theta = 25.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.490 and 0.388	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2004 / 0 / 146	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0376, wR2 = 0.0998	

R indices (all data)	R1 = 0.0390, wR2 = 0.1013
Extinction coefficient	n/a
Largest diff. peak and hole	2.712 and -2.056 e.Å^{-3}

Table 12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2MeCl**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5048(6)	6608(2)	3389(4)	17(1)
C(2)	3139(7)	6927(2)	3005(5)	19(1)
C(3)	2136(6)	6785(2)	1643(5)	21(1)
C(4)	3037(6)	6338(2)	687(4)	22(1)
C(5)	4932(6)	6008(2)	1088(4)	20(1)
C(6)	5970(6)	6132(2)	2463(4)	17(1)
C(7)	7978(6)	5755(2)	2900(4)	20(1)
C(8)	10369(6)	4889(2)	2258(5)	29(1)
C(9)	4472(6)	6101(2)	6442(4)	21(1)
O(1)	9018(5)	5846(2)	4016(3)	34(1)
O(2)	8480(4)	5286(2)	1886(3)	24(1)
F(1)	2751(4)	6408(2)	6823(4)	49(1)
F(2)	3925(4)	5590(1)	5513(3)	40(1)
F(3)	5419(4)	5799(2)	7608(3)	42(1)
Cl(1)	8384(1)	7885(1)	3671(1)	21(1)
I(1)	6458(1)	6912(1)	5460(1)	14(1)

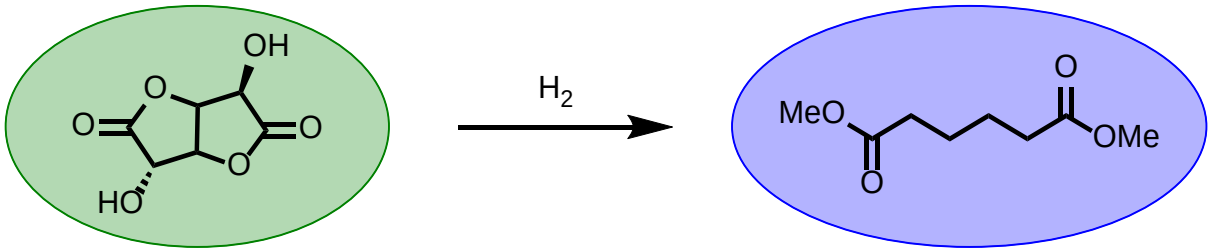
Chapter 3

Hydrogen-Mediated Deoxygenation of Polyhydroxylated Esters and Acids using the Rhenium-Catalyzed Deoxydehydration Reaction

3.1 Preface

The conversion of biomass into commercially relevant monomers and fine chemicals is an important challenge that must be addressed in order to reduce our reliance on petrochemical feedstocks. To this end, we have developed a system which partially deoxygenates carbohydrate-derived precursors, producing compounds that are less highly oxygenated than the starting materials but still contain enough functionality to be chemically interesting. In particular, we have developed a high-yielding synthesis of the high-volume monomer adipic acid from oxidized derivatives of glucose.

Portions of this chapter are based on work done in collaboration with Dr. Reed T. Larson; Dr. Jianbin Chen and Woojin Lee also assisted with some experimental work.



3.2 Introduction

The development of biomass-based feedstocks to replace petroleum is an important goal towards a truly sustainable economy. Currently, most commercial processes in this field are related to the conversion of lipids into biofuels.[77–80] The production of biofuel is attractive from an engineering perspective due to the relative simplicity of the chemical steps involved. In contrast, the transformation of biomass into chemically relevant monomers and feedstocks in a cost-effective manner is, in the general sense, an unsolved problem. For this purpose, carbohydrates possess a more attractive profile as starting materials: in contrast to the large, unfunctionalized molecules present in lipid sources, sugars and other saccharides possess a wealth of chemical complexity that can be leveraged to produce chemical feedstocks if suitably selective and economical defunctionalization reactions can be developed.[81,82]

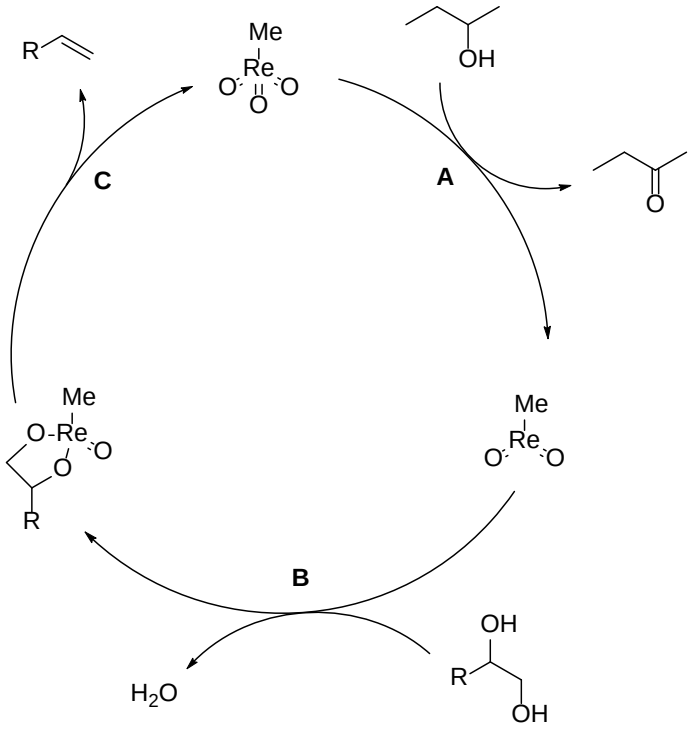


Figure 1. Mechanism of rhenium-catalyzed deoxydehydration: **A.** Reduction from Re(VII) to Re(V). **B.** Coordination of diol substrate. **C.** Extrusion of alkene product.

A particularly attractive target for the exploration of new biomass conversion methods is adipic acid. This simple aliphatic diacid is one of the primary components in Nylon-6,6 as well as a component of various other polymers. Adipic acid is produced in multi-megatonne quantities annually, and essentially all commercial production is currently based on petrochemical-derived benzene.[83–85] Furthermore, as a six-carbon compound, adipic acid presents the advantage that its synthesis from common C6 sugars requires only the manipulation of oxygenated functional groups rather than more challenging carbon-carbon bond formation and cleavage reactions. Furthermore, while there is a report in the patent

literature describing the conversion of glucaric acid to adipic acid using superstoichiometric hydrogen bromide, the harsh acidic conditions present in this system generate challenges in terms of product separation and safe reactor design, and a system that avoided the use of strong acid would be highly desirable.[86]

A promising platform for the partial deoxygenation of polyols which avoids strongly acidic conditions is the deoxydehydration (DODH) reaction, which converts vicinal diols into olefins. There are several catalytic systems that can effect this transformation, including examples using high-valent vanadium, high-valent molybdenum, and both low- and high-valent rhenium.[87–91] The latter catalyst system has been used to great effect in recent years, with the deoxygenation of complex substrates such as mucic acid and erythritol having been demonstrated.[92,93]

Mechanistically, deoxydehydration using high-valent metals is the microscopic reverse of the more widely-known olefin dihydroxylation, run under reducing rather than oxidizing conditions to effect the opposite transformation. For instance, with methyltrioxorhenium (MTO) as the catalyst, the catalytic cycle involves three primary steps: reduction of the initial complex to a Re(V) species by a stoichiometric terminal reductant, condensation with a 1,2-diol substrate to form a five-membered dioxarhenacycle, and extrusion of the alkene product to regenerate the Re(VII) complex (**Figure 1**).[94,95]

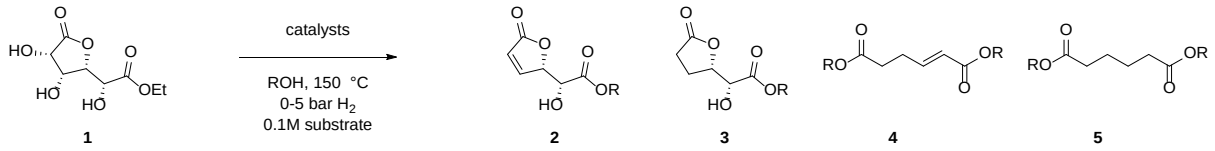
The major drawback to the DODH reaction from a practical perspective has been the available choices of terminal reductant. Typically, these systems utilize relatively expensive compounds, such as phosphines or secondary alcohols, to drive the reaction to completion. While there have been some efforts to utilize the much more economically appealing hydrogen gas as the reductant, thus far these catalytic systems have not demonstrated yields and selectivities that would make them amenable to the practical reduction of complex polyols.[87,96–99] As such, we became interested in exploring this area further to develop a more effective, practical catalytic system for the biomass-to-adipic acid process.

3.3 Results and Discussion

3.3.1 Development of the Catalytic System

One of the first questions we considered was the choice of substrate for reaction optimization. Glucaric acid seems to be the ideal intersection of cost and simplicity, being cheaply derived from an abundant hexose monosaccharide and possessing the correct oxidation state at both terminal carbons.[100] However, glucaric acid itself is not an article of commerce (presumably due to instability with respect to various lactonization reactions), and its various salts showed poor solubility in all organic solvents. We therefore settled on the use of ethyl glucarate 6,3-lactone (**1**) as our model substrate; this starting compound can be synthesized in pure, crystalline form and is soluble in polar organic solvents, allowing us to reproducibly measure yields while still serving as a good surrogate for more economically relevant glucarate-based substrates.

When selecting our initial catalyst system, we recognized that rhenium(VII) catalysts are generally slow to react with dihydrogen, and as such we considered the simple, direct reduction to be unfeasible at easily attained pressures. However, previous reports in the literature have indicated that combining high-valent rhenium with a hydrogenolytic co-catalyst such as palladium on carbon allows the rhenium center to promote the reduction of various substrates.[97–99,101] We therefore began by combining MTO with palladium on carbon in the hope that the palladium would serve to both transfer hydrogen to the rhenium catalyst and reduce the olefin product of the DODH reaction.



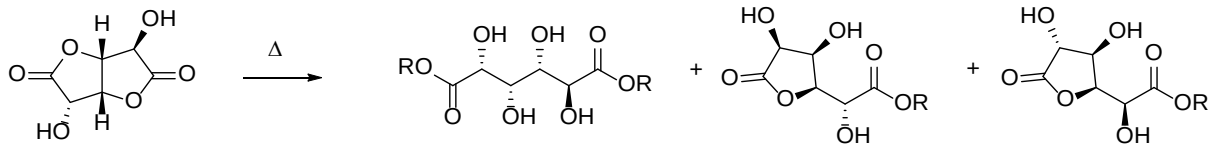
Entry	Catalyst and Additives	H_2 Pressure	Solvent	Reaction Time	**2**	**3**	**4**	**5**
1	10 mol% $MeReO_3$	-	3-octanol	2 h	55%[a]	-	-	-
2	10 mol% $MeReO_3$	-	EtOH	5 h	42%[b]	-	-	-
3	10 mol% $MeReO_3$, 2.5 mol% Pd/C	-	EtOH	5 h	40%[b]	-	-	-
4	10 mol% $MeReO_3$	1 bar	EtOH	5 h	39%[b]	-	-	-
5	10 mol% $MeReO_3$, 2.5 mol% Pd/C	1 bar	EtOH	5 h	65%[b]	trace	-	-
6	10 mol% $MeReO_3$, 2.5 mol% Pd/C	5 bar	EtOH	5 h	-	32%[b]	-	-
7	10 mol% $MeReO_3$, 2.5 mol% Pd/C	5 bar	EtOH	18 h	-	28%[b]	-	-
8	10 mol% $KReO_4$, 2.5 mol% Pd/C	5 bar	EtOH	18 h	-	30%[b]	-	22%[b]
9	10 mol% $KReO_4$, 2.5 mol% Pd/C	5 bar	MeOH	18 h	-	-	18%[c]	61%[c]
10	1 mol% $KReO_4$, 0.75 mol% Pd/C, 27 wt% activated C	5 bar	MeOH	18 h	-	-	-	71%[c,d]
11	1 mol% $KReO_4$, 0.75 mol% Pd/C, 3 mol% H_3PO_4, 27 wt% activated C	5 bar	MeOH	18 h	-	-	-	88%[c,d] (83%)[e]

Reactions run at 0.75 mmol scale. [a]3-octyl ester [b]ethyl ester [c]methyl ester [d]Reaction run at 7.5 mmol scale and 1M concentration. [e]Isolated yield of adipic acid from hydrolysis of crude product with 2N HCl in parentheses.

Table 1. Optimization of reaction conditions

Deoxydehydration under literature conditions with 3-octanol as the solvent and reductant gave a good yield of product, but with a significant amount of charring and precipitation of solid byproducts. Changing the solvent to ethanol eliminated the charring reaction; also, the yield was also somewhat decreased.[g] To our surprise, upon modification of the reaction conditions to include palladium on carbon and 1 atm H_2 gas, unsaturated lactone **2-Et** remained the major product, with no detectable traces of the expected saturated products **3-Et** or **5-Et**. On the other hand the yield of **2-Et** was noticeably higher in the presence of both palladium and hydrogen than in the absence of one of the two, suggesting that we were observing at least some degree of hydrogen-mediated deoxydehydration (**Table 1**, entries 1-5).

Upon increasing the hydrogen pressure to 5 atm, we began to observe formation of **3-Et**, but in significantly lower yield than the amount of **2-Et** produced at 1 atm. Furthermore, no increase in yield was obtained by extending the reaction time, suggesting that some type of catalyst decomposition or poisoning was occurring (**Table 1**, entries 6-7). Given that the palladium-catalyzed reduction seemed more effective at higher pressures, we posited that the MTO was unstable to higher pressures of hydrogen, possibly due to the presence of the carbon-rhenium bond. Accordingly, changing the rhenium source to the somewhat less active but more stable potassium perrhenate improved the overall yield dramatically while also providing the first evidence that we could successfully form the target diethyl adipate (**5-Et**) in detectable quantities.



7

in EtOH	2.5	2.9	2.9
in MeOH	5.3	4.0	4.0

Table 2. Degree of transesterification of glucarodilactone in ethanol and methanol.

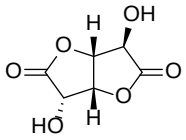
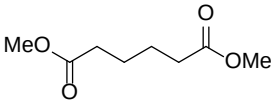
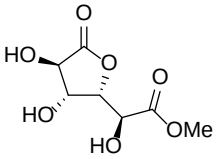
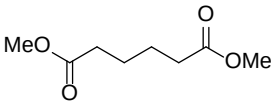
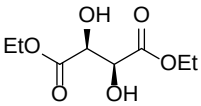
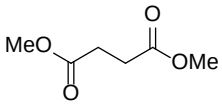
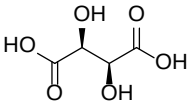
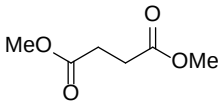
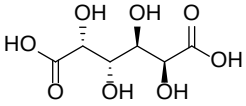
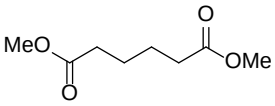
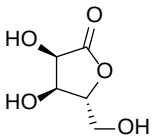
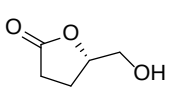
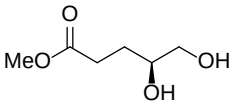
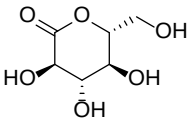
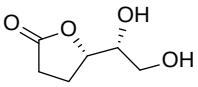
We realized that in order to promote full conversion to **5** on a reasonable timescale, we would need to favor the ring-opening reaction of **3**. One observation that aided in this task was that delactonization of glucarodilactone (**7**) was much more favorable in methanol than in ethanol. By analogy, we expected that the delactonization of **3** would be more favorable in

[g] We briefly explored non-alcoholic solvents such as dioxane and toluene, but found that in these cases the substrate converted rapidly into glucarodilactone (**7**), which possesses no free diols and is therefore unreactive.

methanol as well. Indeed, changing the reaction solvent to methanol produced a mixture of dimethyl adipate (**5-Me**) and the partially unsaturated **4-Me** (**Table 1**, entry 8).

We found that addition of activated charcoal helped promote full conversion of **4-Me** to **5-Me** and allowed us to increase the concentration of substrate from 0.1 M to 1.0 M. While we haven't conclusively established the role that the added carbon plays in promoting the reaction, one possibility is that it serves to adsorb trace compounds which would otherwise poison the surface of the palladium catalyst.[h] Finally, inclusion of catalytic phosphoric acid further improved the yield to 88%, presumably by further increasing the rate at which delactonization occurs (**Table 1**, entries 9-10).

[h] SEM-EDS analysis of the activated charcoal shows no detectable metal impurities prior to use in the reaction. Analysis of the surface once the reaction is complete under optimized reaction conditions indicates that significant deposition of rhenium occurs over the course of the reaction; however, using the more soluble complex nBu_4NReO_4 as the catalyst produces similar yields with no detectable deposition of rhenium. This suggests that the active rhenium catalyst is likely homogenous, and that the activated carbon does not promote the reaction by acting as a solid support.

Substrate	Product	Yield
 **7**		71% (78%)[a]
 **8**		86%
 **9**		88%
 **10**		88%
 **11**		86%[a]
 **12**	 +  **14a** **14b**	75%, 22%
 **13**	 **15**	60%

[a]Reaction conditions: 7.5 mmol substrate, 1 mol % $KReO_4$, 3 mol % H_3PO_4, 0.75 mol % Pd/C, 25 wt % activated carbon, 5 bar H_2, 7.5 mL MeOH, 150 °C, 18 h. [b]Substrate prestirred at 120 °C in MeOH for 3 h. [c]48 h reaction time.

Table 3. Substrate scope

3.3.2 Substrate Scope and Selectivity

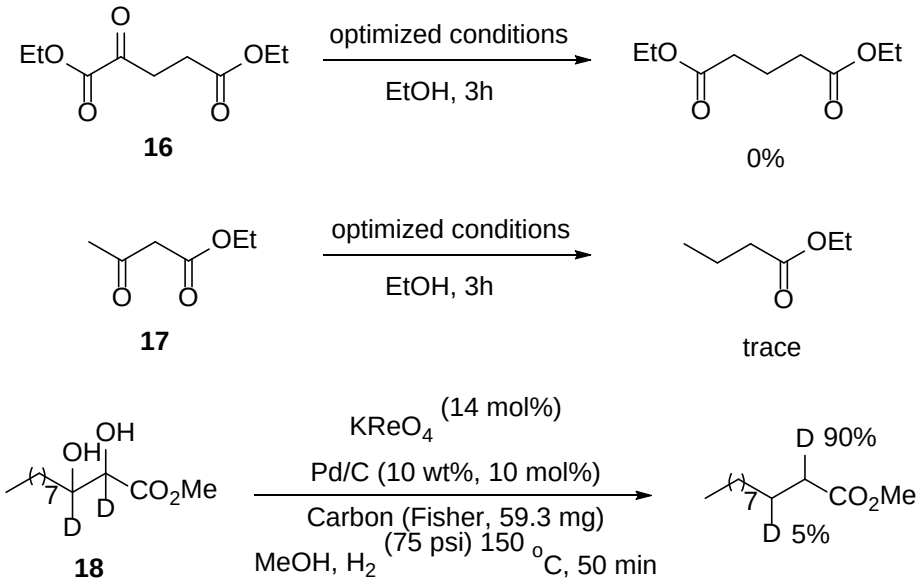
With our optimized reaction conditions in hand, we began to explore whether this chemistry could be used to convert other sugar acids. We found that other forms of glucarate starting material are tolerated well: while **7** required pre-treatment at lower temperature to promote the formation of unmasked diol functional groups, both it and methyl glucarate 1,4-lactone (**8**) produced the desired dimethyl adipate in good yield. The use of diethyl tartrate (**9**) as well as the free acids tartaric acid (**10**) and mucic acid (**11**) also produced the corresponding saturated ester products in good yield.

In contrast to sugar acids, sugar alcohols such as sorbitol and mannitol showed no propensity to react under these conditions. Additionally, using ribonolactone (**12**) and gluconolactone (**13**) generated unexpected products: the final products of ribonolactone and gluconolactone are **14** and **15** respectively, rather than the fully dehydroxylated methyl pentanoate and methyl monohydroxyhexanoate (**Table 3**).

Based on the unexpected products formed from these two compounds, we became interested in the extent of selectivity that this catalyst system has for diols at the α,β positions to esters and carboxylic acids. A competition experiment between 1,2-dodecanediol and diethyl tartrate demonstrated complete selectivity for reduction of the latter compound. This stands in stark contrast to most other DODH catalytic systems, where unsubstituted aliphatic diols are typically competent substrates, and suggested to us that the selectivity pattern was likely quite general.

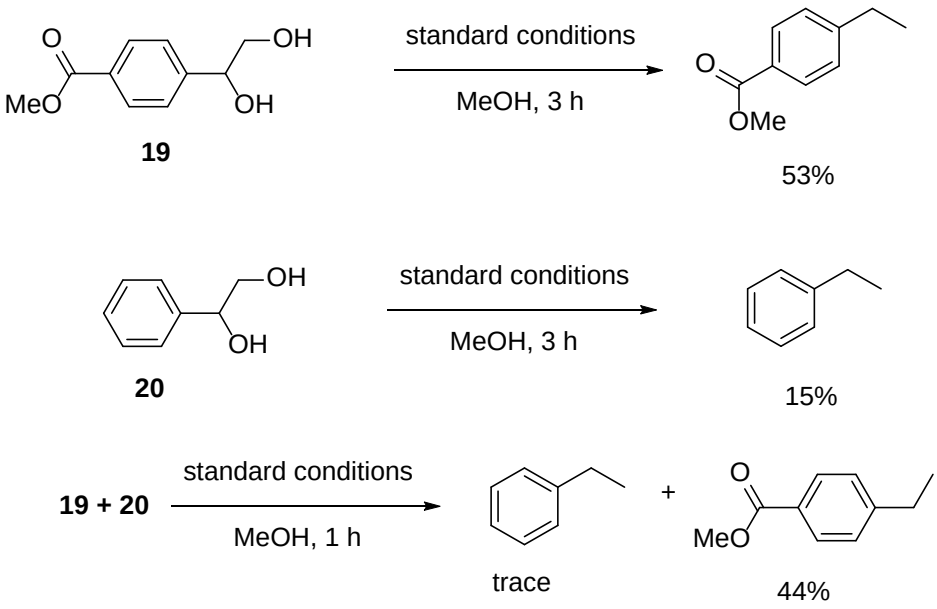
We developed several hypotheses that might explain the source of this unusual selectivity. One possibility that we initially considered was that, rather than the typically invoked retro-[3+2]-cycloaddition that is postulated to occur in most DODH reactions, this catalytic initially proceeded by dehydration/tautomerization to form either an α- or β-ketoester. The reduction of both of these compounds to fully saturated esters has been previous demonstrated.[102–104] However, neither α-ketoester **16** nor β-ketoester **17** yielded the expected saturated esters upon subjection to the reaction conditions. Additionally, the reaction of deuterated diol **18** in protio-methanol with H_2 as the terminal reductant showed 90% retention of deuterium at the α position.[i] This rules out formation of an α-ketoester and strongly suggests the absence of a β-ketoester intermediate as well, since in the latter case exchange of α-hydrogens with the solvent should be quite facile (**Scheme 1**).

[i] We did observe erosion of deuterium at the β-position, but this should likely be attributed to palladium-catalyzed hydrogen exchange at the alkene stage.



Scheme 1. Investigation of ketonic intermediates.

In light of these results, we proposed two other hypotheses for the involvement of the ester group in the reaction. We considered that the ester might either serve as a directing group for the rhenium catalyst or that the relevant transition state might involve a build-up of negative charge on the α-carbon, with the ester serving simply as an electron-withdrawing group. In order to distinguish between these two pathways we synthesized vinical diol **19**, which we expected might have similar electronic parameters to those of a typical α,β-diol, but should be unable to simultaneously bind the ester and diol moieties to the catalyst.



Scheme 2. Identification of electronically controlled selectivity.

Upon subjecting **19** to the reaction conditions we were able to obtain the fully reduced compound in 53% yield. Furthermore, under the same reaction conditions only 15% conversion was obtained for the parent styrene glycol **20**, and a competition experiment between the two substrates also indicated that the ester-bearing compound reacts much more rapidly than the unsubstituted one. Taken together, these data support the conclusion that the selectivity of this catalyst arises from a build-up of electron density on the α carbon in the rate-limiting transition state and that the ester promotes this by accepting electron density into its π* orbital. (While attempting to make more specific claims regarding the mechanism of alkene extrusion by analogy to other known catalytic system may be tempting, computational evidence suggests that the exact nature of the transition state can vary dramatically based on the ligand set of the rhenium complex).[105,106]

3.4 Conclusion

We have combined hydrogenation and deoxydehydration catalysts to provide a selective, hydrogen-mediated reduction of sugar acids. This work has allowed us to produce commercially relevant adipate esters in excellent yields, and also holds promise for the partial reduction of other biomass-derived starting materials. Furthermore, we have explored the atypical selectivity observed in this catalytic system and have determined that it is determined by the electronic properties of the substrate.

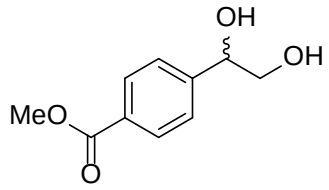
3.5 Supporting Information

General: Unless otherwise noted, all commercial reagents were used without further purification. Activated carbon was purchased from Fisher.[j] THF was deoxygenated with argon and passed through alumina to remove water. Thin-layer chromatography analysis of reaction mixtures was performed using Merck silica gel 60 F254 TLC plates, and visualized under UV or by staining with ceric ammonium molybdate or $KMnO_4$. Flash column chromatography was carried out on Merck Silica Gel 60 Å, 230 x 400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker AV-600, DRX-500, AVQ-400 and AV-300 spectrometers. ^1H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak ($CHCl_3$; $\delta_H = 7.26$ and $\delta_C = 77.0$) Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance. Mass spectral data were obtained from the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley using a Thermo LTQ-FT for ESI spectra and a Waters AutoSpec Premier for EI spectra. A Zieiss Gemini Ultra-55 Analytical Field Emission Scanning Electron Microscope operating at 20 keV accelerating voltage was used for both electron imaging and elemental analysis.

Synthesis of substrates:

Most substrates are either commercially available or may be prepared using literature procedures.[2] In instances where ethyl glucarate-6,3-lactone was insufficiently pure, it was recrystallized from hot ethanol, yielding a crystalline material which decomposed into an amorphous glass at 117-119 °C (lit. m.p. 121-123 °C).[107]

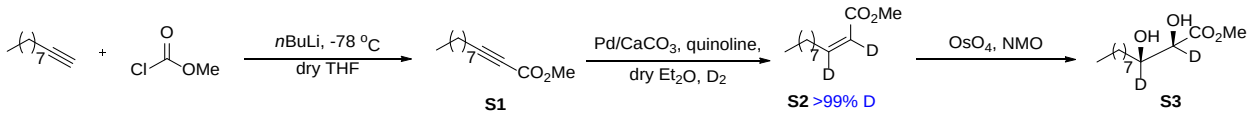
Procedures to synthesize substrates are listed below:

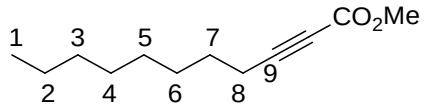


Methyl 4-(1,2-dihydroxyethyl)benzoate (19): To a solution of $K_2OsO_4 \cdot 2H_2O$ (22 mg mg, 0.06 mmol, 1 mol%) and $(DHQ)_2PHAL$ (47 mg, 0.06 mmol, 1 mol%) in 12 mL of 1:1 t-BuOH/H_2O was added 50% aq. *N*-methylmorpholine oxide (1.6 mL, 7.5 mmol, 1.25 eq.) The mixture was stirred for 15 minutes at room temperature, at which point ethyl 4-vinylbenzoate (973 mg, 6 mmol, 1 eq.) was added in one portion. The reaction mixture was stirred at room temperature for 16 h. The mixture was partitioned between DCM and aq. Na_2SO_3, the organic layer washed with 1N aq. HCl, dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by silica gel chromatography (70% EA/hexanes) to yield 795 mg (4.05 mmol,

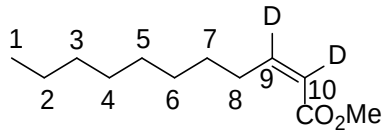
[j] Lot 080440 was used for the bulk of the experimental work, although other lots showed similar results.

67%) of a colorless oil which slowly solidified on standing. Spectral data were consistent with those described in the literature.[108]

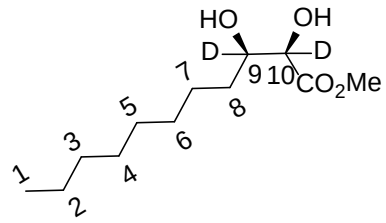




Methyl undec-2-ynoate (S2): *n*-Butyllithium (1.7M in hexane, 11.10 mL, 18.42 mmol) was added dropwise to a solution of 1-decyne (2.31 g, 16.74 mmol) in THF (30 mL) at -78 °C, followed after 2 h by addition of methyl chloroformate (1.94 mL, 25.11 mmol). After the mixture was stirred for 1 h at -78 °C and for 7 h at room temperature, water (50 mL) was added. The mixture was extracted with ether (3 x 60 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to give a residue, and flash chromatographed on silica gel (EA/hexanes 1:40) to give the desired intermediate as colorless liquid (1.55g, 47%).



Methyl (Z)-undec-2-enoate-2,3-*d*$_2$ (S3): A solution of methyl undec-2-ynoate **(S2)** (1.96 g, 10 mmol, 1.0 equiv.) in 10 mL of anhydrous diethyl ether was stirred with palladium on barium sulfate (20 mg, 0.09 mmol %), and quinoline (19.4 mg, 1.5 mmol %) under an atmosphere of D_2 gas (deuterium, balloon) at 0 °C for 36 h. After hydrogenation was complete, the catalyst was removed by filtration through a Celite pad. The solution was concentrated to give a residue, and flash chromatographed on silica gel (Et_2O: hexane = 1:40) to give the **(S2)** as colorless liquid oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.70 (s, 3H), 2.64 (C8, t, *J* = 7.4 Hz, 2H), 1.47-1.38 (C7, m, 2H), 1.35-1.20 (C6-C2, m, 10H), 0.90-0.85 (C1, m, 3H).



Methyl 2,3-dihydroxyundecanoate-2,3-d_2 (18): The compound **S3** (0.75 mmol, 149.8 mg) was dissolved in acetone. To the colorless solution was added a solution of 4% wt of OsO_4 in H_2O (5 mmol%), followed by *N*-methylmorpholine *N*-oxide (1.5 equiv.) at rt. Reactions were monitored by TLC with potassium permanganate stain. Upon completion, 10 mL DCM and 10 mL H_2O was added. The mixture was extracted with DCM (3 x 10 mL), and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated to give a residue which was purified by flash chromatography on silica gel (EA/hexane 1:3) to give the **S3** as colorless liquid (137.8 mg, 79%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.79 (s, 3H), 2.94 (br, 2H), 1.51 – 1.25 (m, 14H), 0.85 (t, *J* = 6.9 Hz, 3H). Spectral data were consistent with those reported in the literature for the non-deuterated isotopologue.[109]

Deoxydehydration conditions:

Reactions without hydrogen: Ethyl glucarate 6,3-lactone[2] (165 mg, 0.75 mmol), methyltrioxorhenium (19 mg, 0.075 mmol, 10 mol%), and (where applicable) 10% palladium on carbon (20 mg, 0.019 mmol, 2.5 mol%) were placed in a thick-walled glass tube with a stir bar. To this was added 7.5 mL of alcohol solvent; no special precautions were taken to exclude air or moisture. The reaction vessel was tightly sealed, placed in a pre-heated 150 ºC oil bath, and stirred for the listed reaction time. The reaction mixture was cooled to room temperature, filtered through celite to remove solids, concentrated, mesitylene was added as NMR standard, and the reaction yield was determined by ^{1}H NMR.

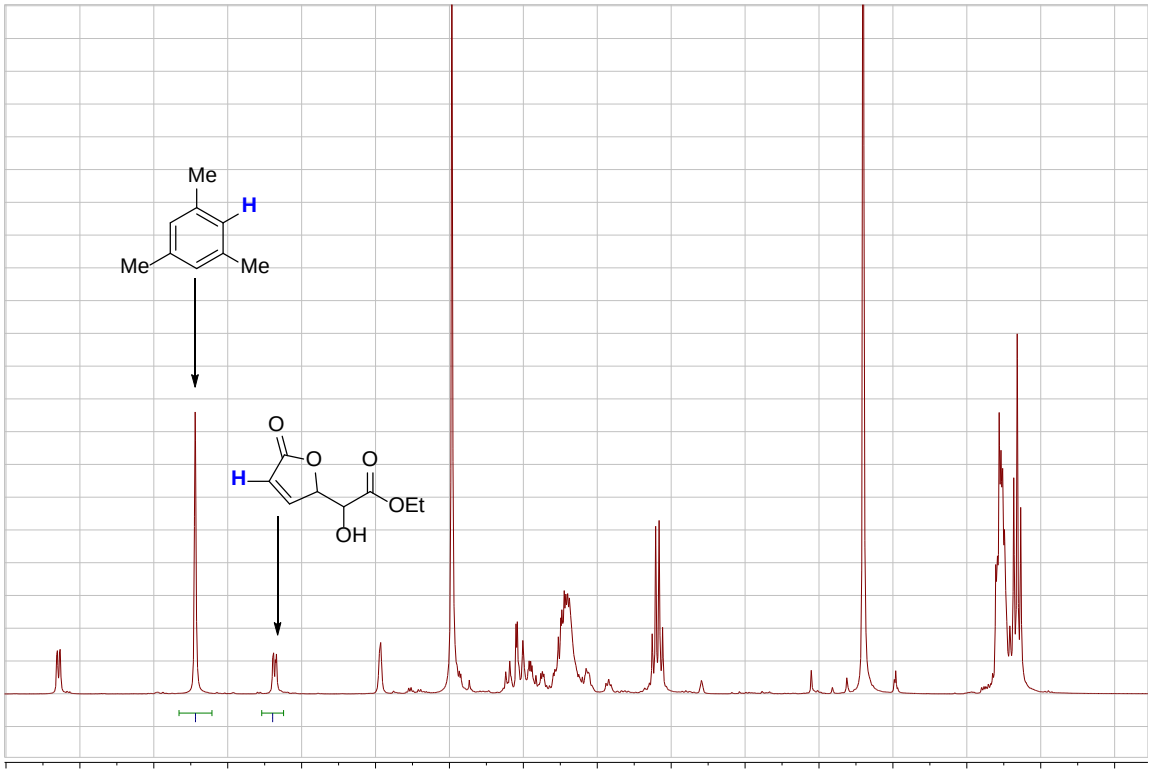
Reactions at 1-5 bar H_2: Ethyl glucarate 6,3-lactone (165 mg, 0.75 mmol), rhenium catalyst (10 mol%), 10% palladium on carbon (20 mg, 0.019 mmol, 2.5 mol%), and (where applicable) 85% phosphoric acid (6 mg, 0.023 mmol, 3 mol%) were placed in a Parr reactor with 200 mL internal volume, followed by 7.5 mL of solvent. The vessel was pressurized with H_2, purged, and re-pressurized for a total of three cycles, placed in a pre-heated 150 ºC oil bath, and stirred for the listed reaction time. The reaction mixture was cooled to room temperature, filtered through filter paper to remove solids, and concentrated. Mesitylene was added as an NMR standard, and the reaction yield was determined by ^{1}H NMR.

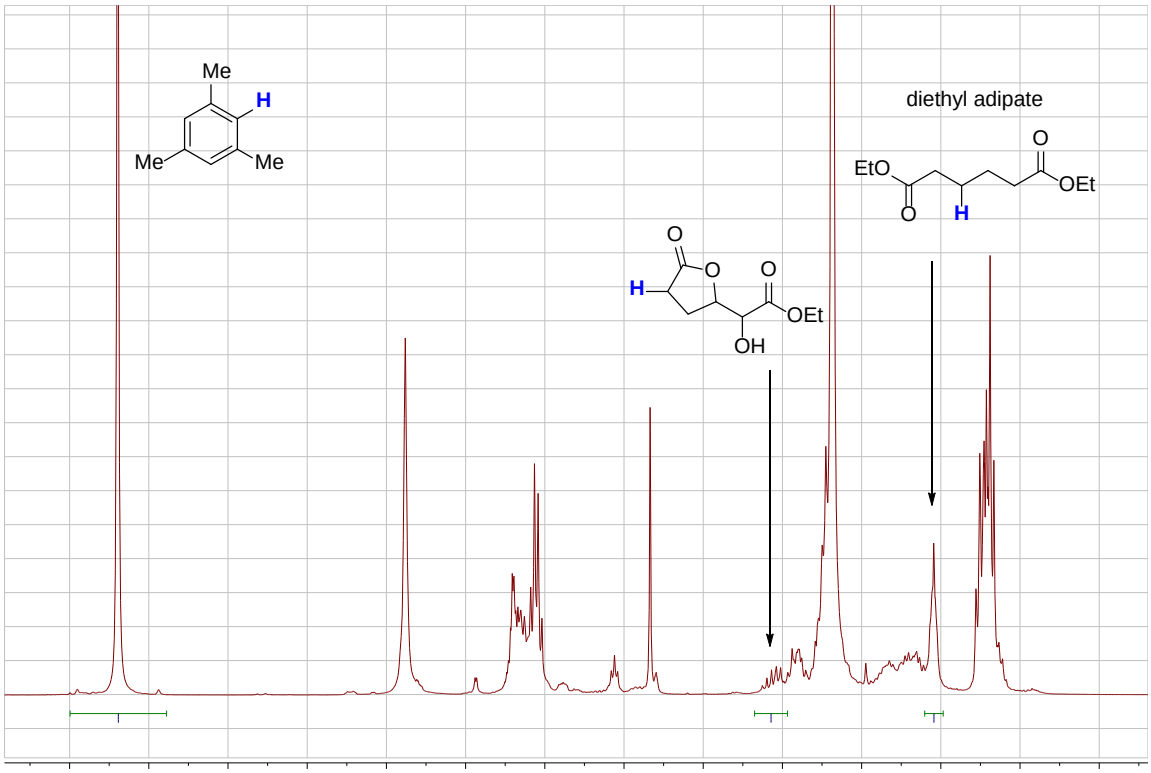
Optimized reaction conditions: Substrate (7.5 mmol), potassium perrhenate (22 mg, 0.075 mmol, 1 mol%), 10% palladium on carbon (60 mg, 0.056 mmol, 0.75 mol%), 85% phosphoric acid (26 mg, 0.23 mmol, 3 mol%), and 450 mg activated carbon were placed in a Parr reactor with 200 mL internal volume, followed by 7.5 mL of methanol. The vessel was pressurized with H_2, purged, and re-pressurized for a total of three cycles to a final pressure of 5 bar, placed in a pre-heated 150 ºC oil bath, and stirred for the listed reaction time. No repressurization or off-gassing was performed over the course of the reaction. The reaction mixture was cooled to room temperature, filtered through filter paper to remove solids, and concentrated. Mesitylene was added as an NMR standard, and the reaction yield was determined by ^{1}H NMR.

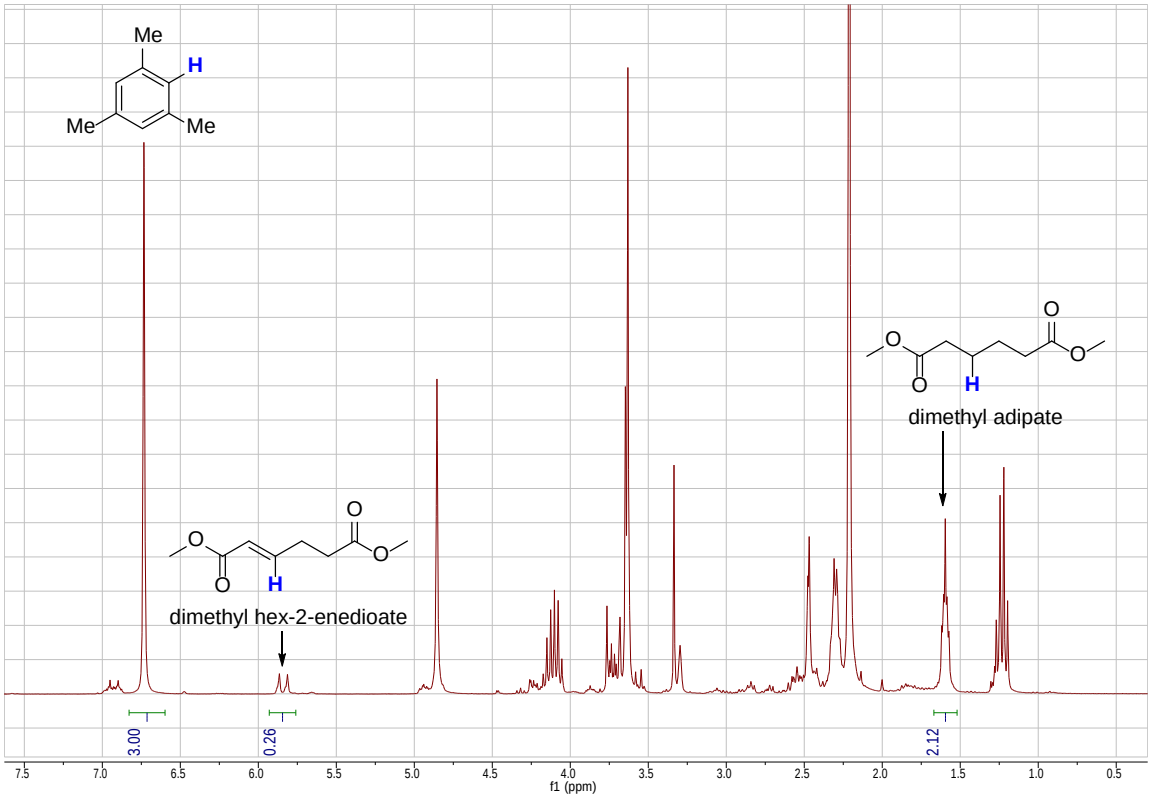
Isolation of adipic acid: The reaction was carried out as above, and the concentrated crude product was stirred vigorously overnight in 20 mL 2N aqueous HCl. Volatiles were removed under reduced pressure, and the resulting solid was washed with a small amount of ice-cold

water to remove rhenium and potassium salts. Adipic acid was obtained as a white powder (910 mg, 6.2 mmol, 83% yield). ^{1}H NMR spectrum was consistent with reported values: (400 MHz, DMSO-d_6) δ 12.0 (2H, br s), 2.21-2.13 (4H, m), 1.51-1.40 (4H, m).[110]

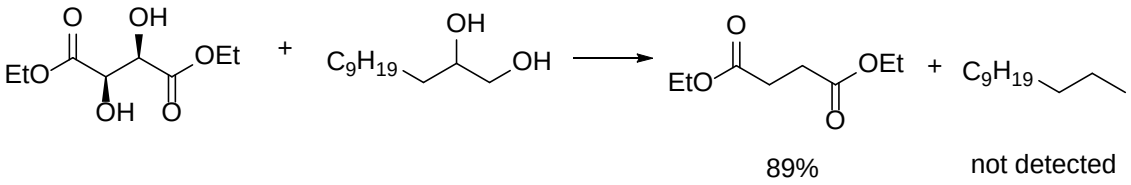
Representative NMR spectra of final reaction mixtures indicating the peaks used to estimate the yields of various products are displayed below:




Me
H
Me
Me
diethyl adipate
EtO
O
OEt
O
H
O
O
O
H
OEt
OH

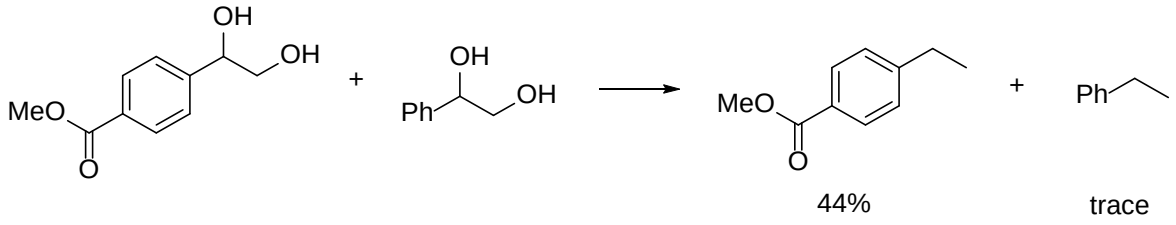

Me
H
Me
Me
O
O
H
O
dimethyl adipate
O
O
O
H
dimethyl hex-2-enedioate
3.00
0.26
2.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

Competition experiment between activated and un-activated diols:



To a 200 mL Parr reactor were added 1.03 g (5 mmol, 1 eq.) (*R*,*R*)-diethyl tartrate, 1.01 g (5 mmol, 1 eq.) (+/-)-1,2-dodecanediol, 15 mg (0.05 mmol, 1 mol%) potassium perrhenate, 40 mg (0.04 mmol, 0.75 mol%) 10% palladium on carbon, 17 mg (0.15 mmol, 3 mol%) 85% aq. H_3PO_4, 300 mg activated carbon, and 5 mL ethanol. The reaction vessel was pressurized to 5 bar H_2 (3 cycles), placed in a pre-heated oil bath at 150 ºC, stirred for 3 h, cooled to room temperature, and filtered through filter paper to remove solids. Yield of diethyl succinate (89%) was determined by comparison to a known amount of mesitylene by ^{1}H NMR; GC-MS analysis of the reaction mixture showed no trace of dodecane.

Competition between electron-neutral and electron-poor styrene glycols:

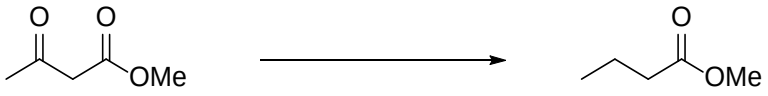


To a 200 mL Parr reactor were added 345 mg (2.5 mmol, 1 eq.) styrene glycol, 491 mg (2.5, 1 eq.) 4-methoxycarbonyl styrene glycol, 15 mg (0.05 mmol, 2 mol%) potassium perrhenate, 40 mg (0.04 mmol, 1.5 mol%) 10% palladium on carbon, 17 mg (0.15 mmol, 6 mol%) 85% aq. H_3PO_4, 300 mg activated carbon, and 5 mL methanol. The reaction vessel was pressurized to 5 bar H_2 (three cycles), placed in a pre-heated oil bath at 150 ºC, stirred for 1 h, cooled to room temperature, and filtered through filter paper to remove solids. To the reaction mixture was added methyl benzoate, and the yields of both products were analyzed by GC by comparison to measured relative response factors of authentic samples.

Kinetic competency of α-ketoester:

To a 200 mL Parr reactor were added 1.01 g (5 mmol, 1 eq.) diethyl 2-oxoglutarate, 15 mg (0.05 mmol, 1 mol%) potassium perrhenate, 40 mg (0.04 mmol, 0.75 mol%) 10% palladium on carbon, 17 mg (0.15 mmol, 3 mol%) 85% aq. H_3PO_4, 300 mg activated carbon, and 5 mL ethanol. The reaction vessel was pressurized to 5 bar H_2 (3 cycles), placed in a pre-heated oil bath at 150 ºC, stirred for 1 h, cooled to room temperature, and filtered through filter paper to remove solids. ^{1}H NMR analysis showed complete decomposition of starting material but no signals corresponding to diethyl glutarate.

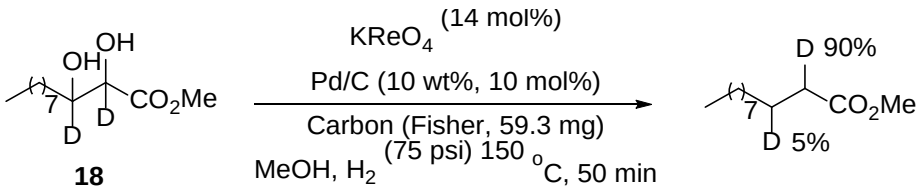
Kinetic competency of β-ketoester:



trace

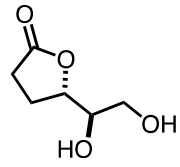
To a 200 mL Parr reactor were added methyl acetoacetate (233 mg, 2.0 mmol, 1 eq.), potassium perrhenate (22 mg, 0.075 mmol, 3.8 mol%), 10% palladium on carbon (60 mg, 0.056 mmol, 2.8 mol%), activated carbon (60 mg) and methanol-d_4. The reactor was pressurized to 5 bar H_2 (3 cycles) and heated at 150 ºC for 18 h. NMR analysis showed only trace formation of methyl pentanoate.

Deuterium labeling experiment:



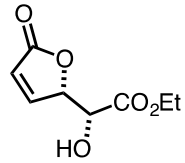
To a 200 mL Parr reactor were added **18** (16.9 mg, 0.072 mmol, 1 eq.), potassium perrhenate (2.9 mg, 0.010 mmol, 14 mol%), 10% palladium on carbon (7.9 mg, 0.0075 mmol, 10 mol%) and methanol (7.5 mL). Pressurized to 5 bar H_2 (three cycles), placed in a pre-heated oil bath at 150 ºC, and stirred at this temperature for 50 min. NMR analysis of the reaction mixture showed integrations of 1.10 and 1.95 for the α and β protons respectively, corresponding to 90% and 5% retention of deuterium at those positions.

Characterization of new products:

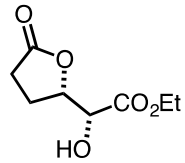


(S)-5-((R)-1,2-dihydroxyethyl)dihydrofuran-2(3H)-one (14): ^{1}H NMR (600 MHz, MeOD-d_4) δ 4.62 (1H, td, J = 7.1, 4.4 Hz), 3.81 (1H, td, J = 5.7, 4.4 Hz), 3.57 (2H, m), 2.54 (2H, m),

2.24 (2H, m); ^{13}C NMR (125 MHz, MeOD-d_4) δ 180.3, 82.2, 73.6, 63.7, 29.3, 23.0; HRMS (ESI): exact mass calcd for $C_6H_{10}NaO_4$ $[M+Na]^+$, 169.0477, found 169.0469; $[\alpha]_D$ = + 18.3 ° (c = 0.0126 g/3 mL, $CHCl_3$).



Ethyl (S)-2-hydroxy-2-((S)-5-oxo-2,5-dihydrofuran-2-yl)acetate (2-Et): ^{1}H NMR (600 MHz, MeOD-d_4) δ 7.67 (1H, dd, J = 5.8, 1.7 Hz), 6.22 (1H, dd, J = 5.8, 2.0 Hz), 5.50 (1H, dt, J = 2.6, 1.8 Hz), 4.55 (1H, d, J = 2.7 Hz), 4.27 (2H, m), 1.31 (3H, t, J = 7.1 Hz); ^{13}C NMR (125 MHz, MeOD-d_4) δ 175.1, 172.1, 155.7, 123.3, 85.6, 70.7, 62.8, 14.5; HRMS (ESI): exact mass calcd for $C_8H_{10}NaO_5$ $[M+Na]^+$, 209.0426, found 209.0402; $[\alpha]_D$ = – 14.7 ° (c = 0.0118 g/3 mL, MeOH).



Ethyl (S)-2-hydroxy-2-((S)-5-oxotetrahydrofuran-2-yl)acetate (3-Et): ^{1}H NMR (600 MHz, MeOD-d_4) δ 4.98 (1H, ddd, J = 7.9, 5.4, 2.2 Hz), 4.30–4.19 (3H, m), 2.62 (1H, ddd, J = 17.4, 10.3, 6.9 Hz), 2.52 (1H, ddd, J = 17.4, 10.1, 6.5 Hz), 2.4–2.27 (2H, m), 1.30 (3H, t, J = 7.1 Hz); ^{13}C NMR (125 MHz, MeOD-d_4) δ 179.9, 172.8, 82.22, 73.4, 62.6, 29.2, 24.3, 14.5; HRMS (ESI): exact mass calcd for $C_8H_{10}NaO_5$ $[M+Na]^+$, 211.0577, found 211.0572; $[\alpha]_D$ = + 82.4 ° (c = 0.0196 g/3 mL, MeOH).

Analysis of deposited rhenium: Ribonolactone (60 mg, 0.41 mmol, 1 equiv.), perrhenate salt (0.02 mmol, 5 mol%), and 10% palladium on carbon (16 mg, 0.015 mmol, 3.8 mol%) were suspended in ethanol in a Parr reactor. The reaction vessel was pressurized to 5 bar H_2 (3 cycles) and heated at 70 ºC for 8 hours. The reaction mixture was filtered at 70 ºC and the filtrate concentrated. Yields were determined by ^{1}H NMR using mesitylene as an internal standard: 25% yield with $KReO_4$ and 31% yield with nBu_4NReO_4.

The residual solids obtained from the previous filtration were analyzed by SEM-EDX, which indicated a 2.2 to 1 mole ratio of palladium to rhenium present on the solid support using $KReO_4$ as the catalyst, and a >99 to 1 mole ratio of palladium to rhenium present using nBu_4NReO_4.

Figure S1. SEM-EDX of solid support after nBu_4NReO_4 catalysis.

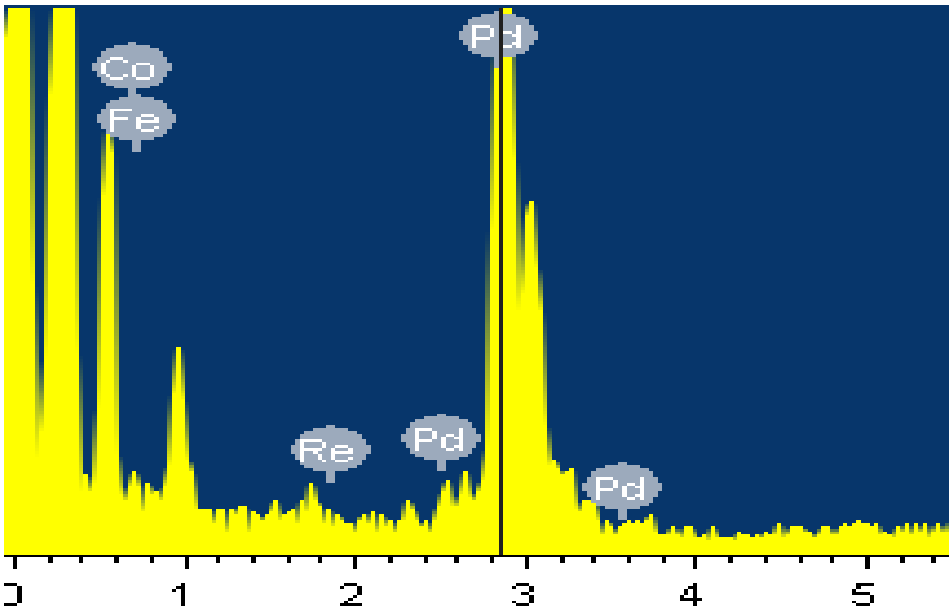


Figure S2. SEM-EDX of solid support after $KReO_4$ catalysis.

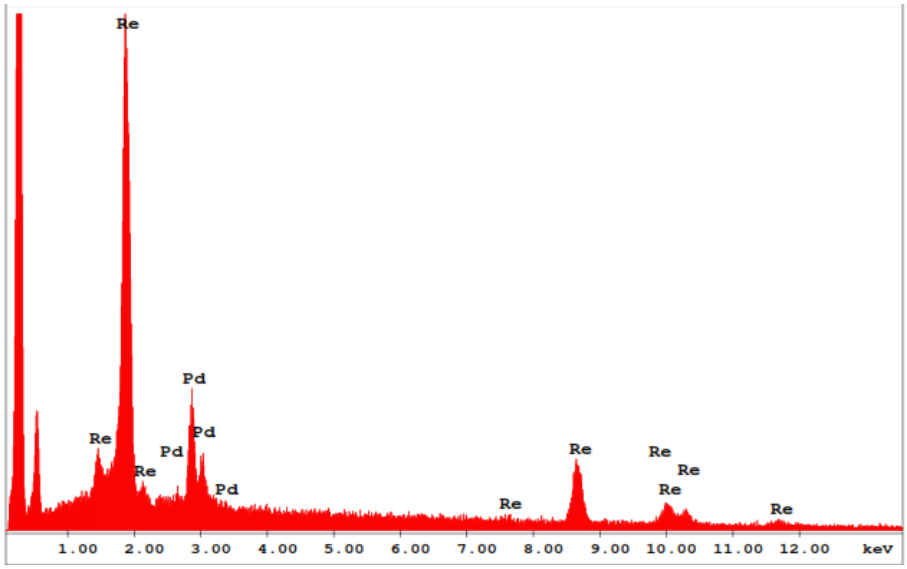
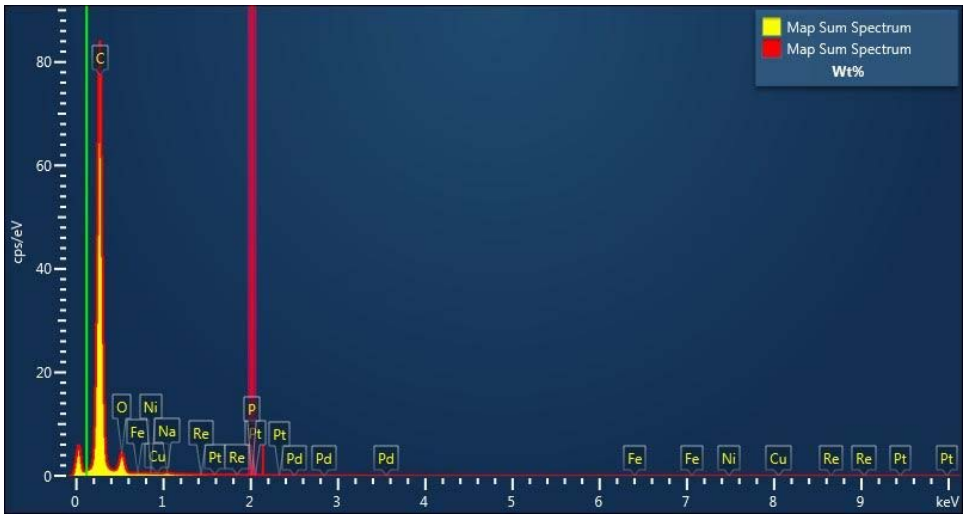


Figure S3. SEM-EDX of activated carbon before reaction



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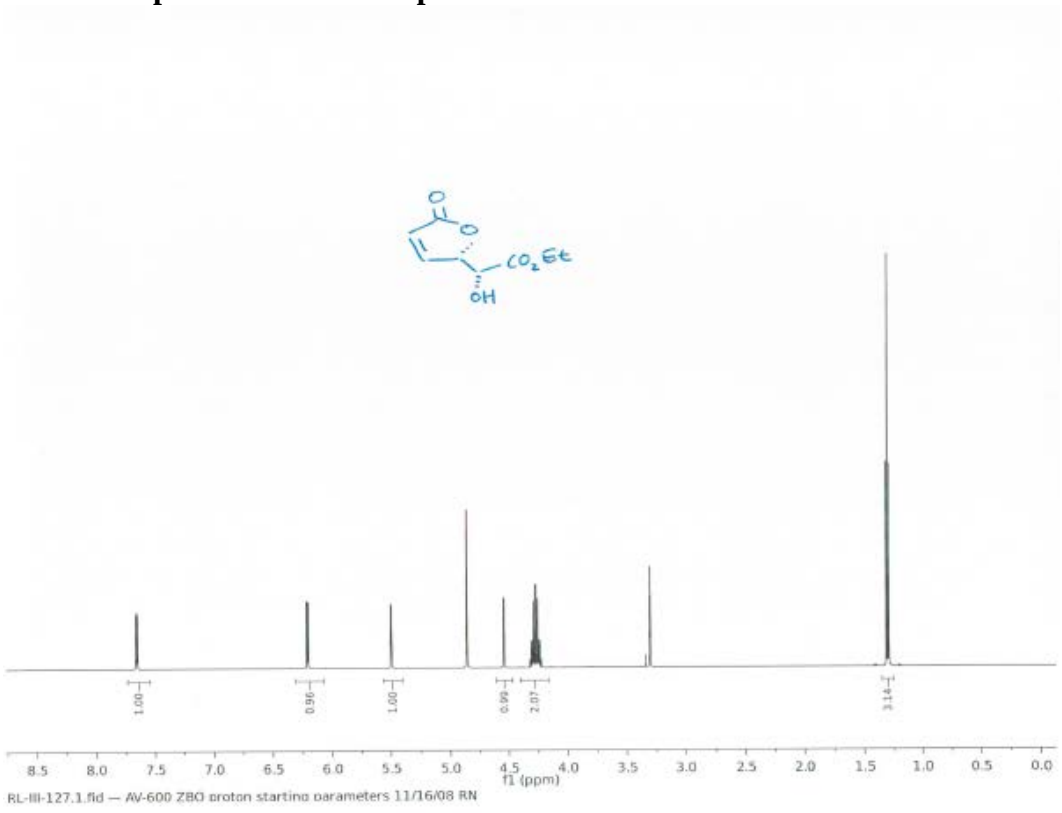
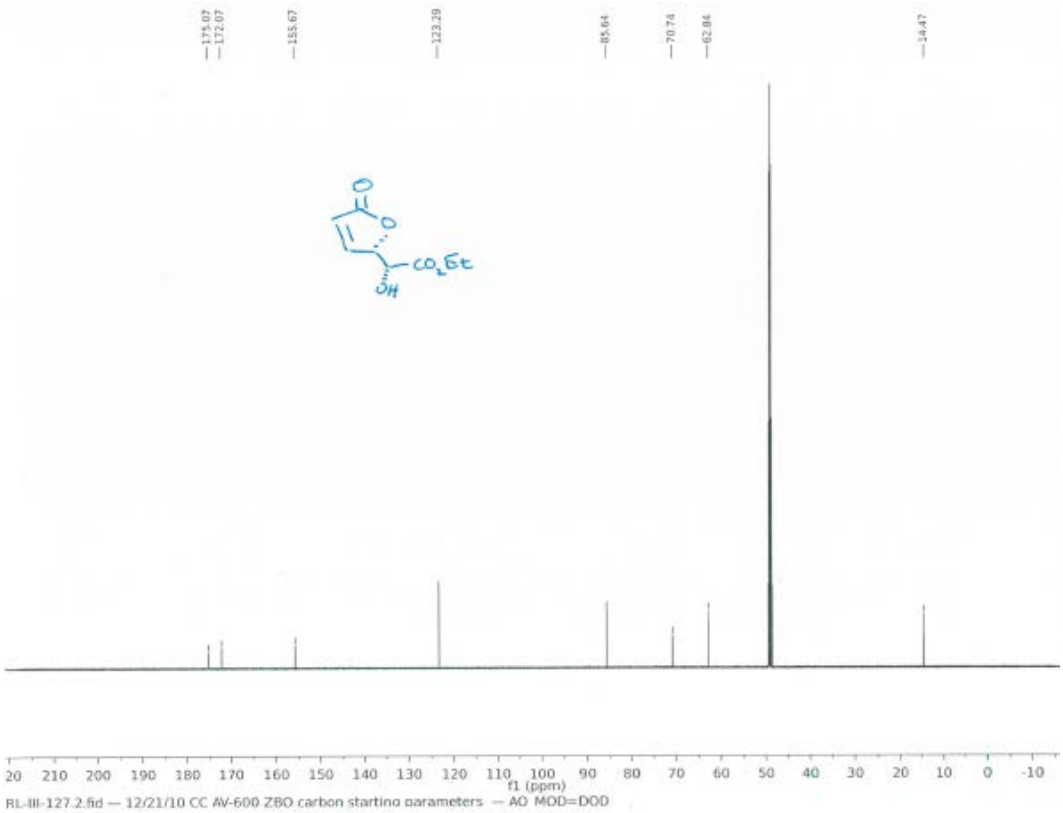
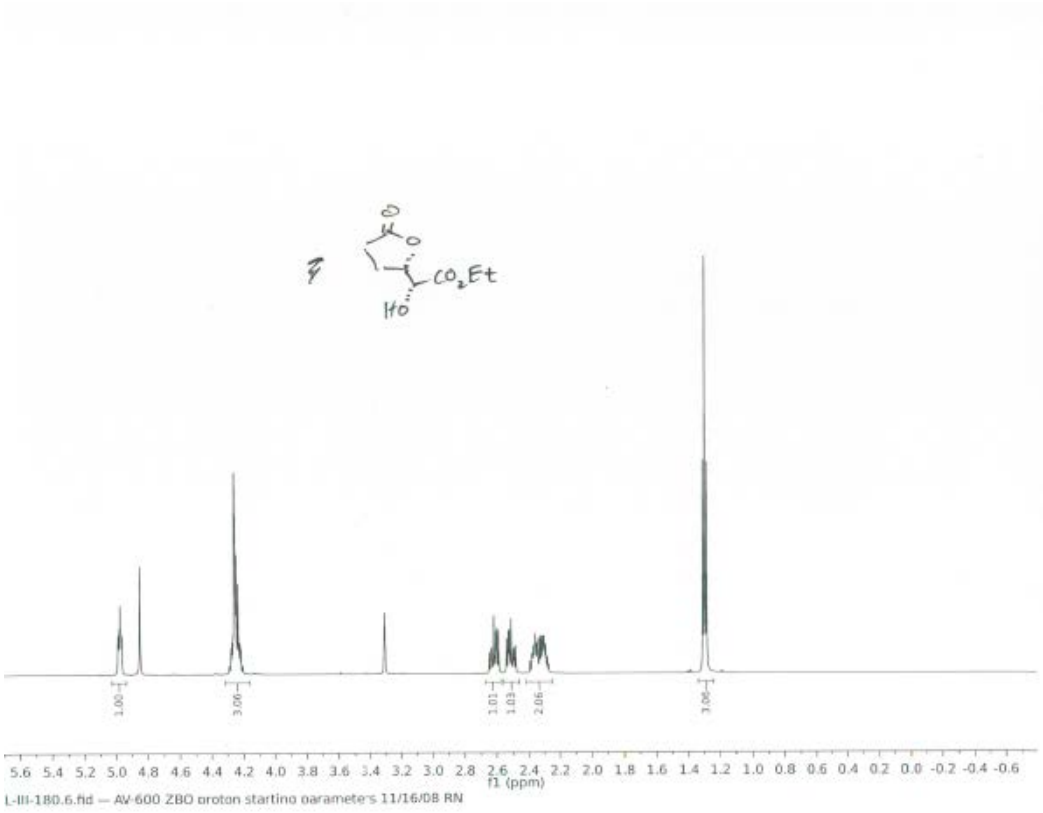
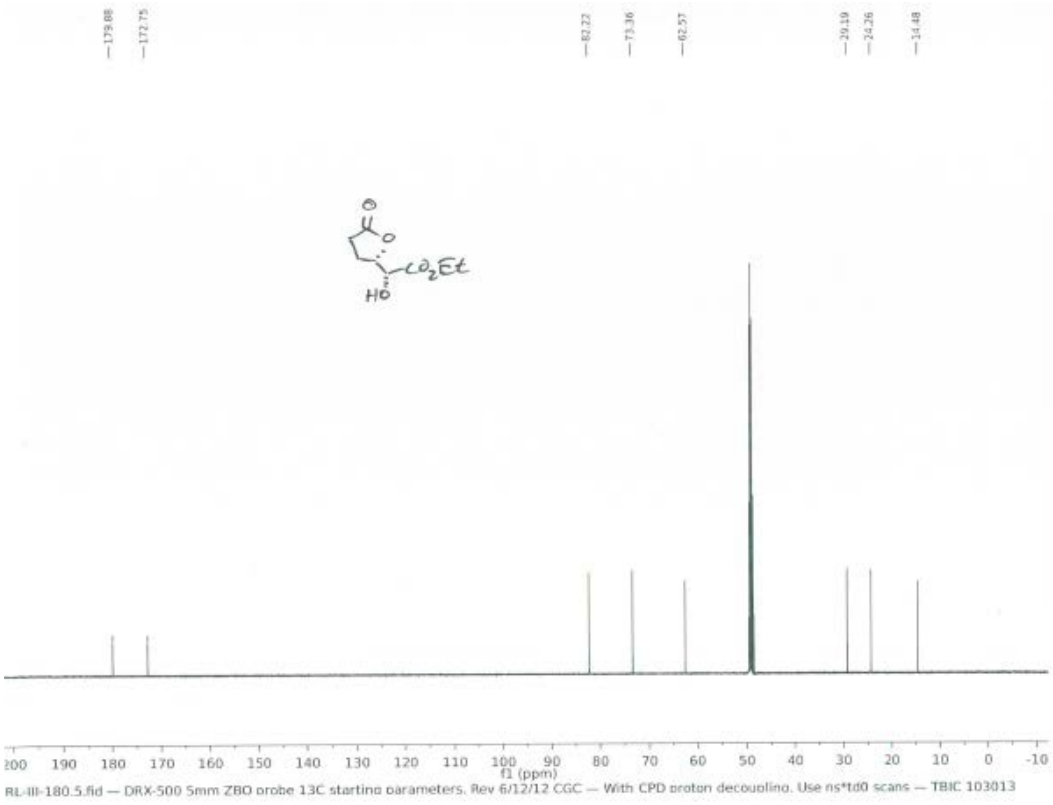
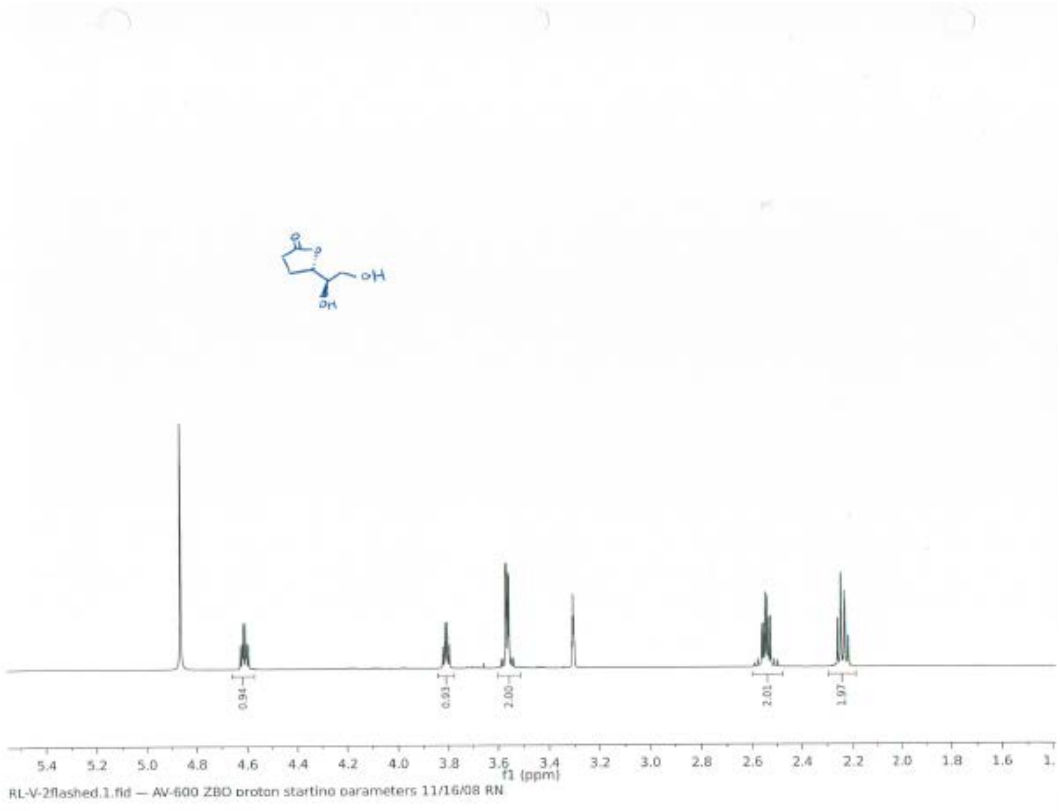
3.7 NMR Spectra of New Compounds

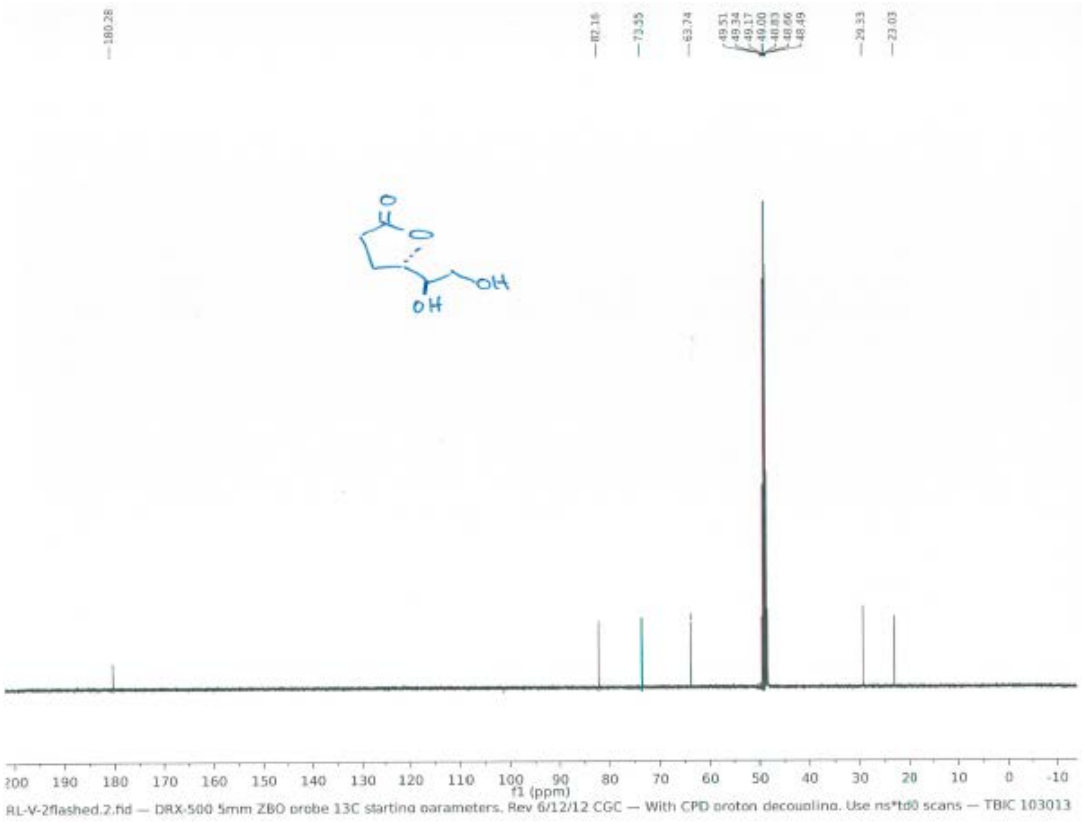


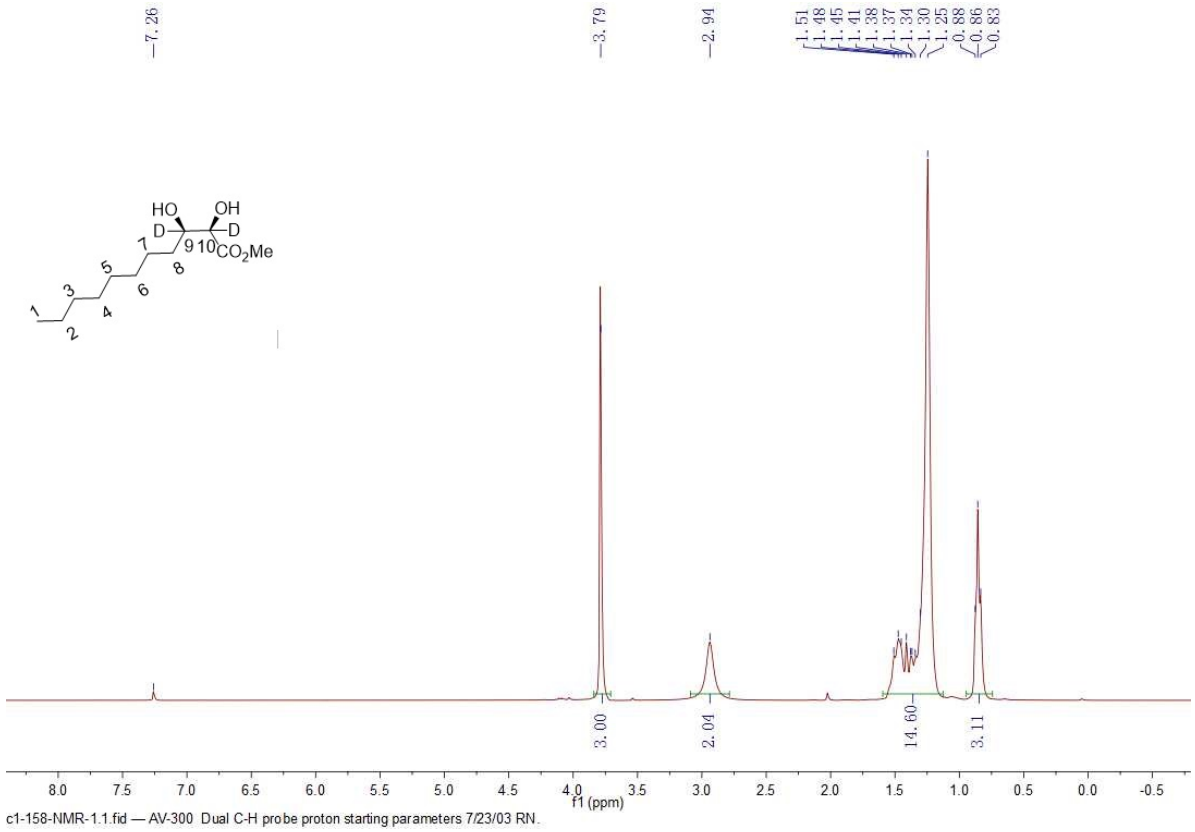

175.07
172.07
155.67
123.29
85.64
70.74
62.84
14.47
CO2Et
OH
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
RL-III-127.2.fid — 12/21/10 CC AV-600 ZBO carbon starting parameters — AQ_MOD=DQD

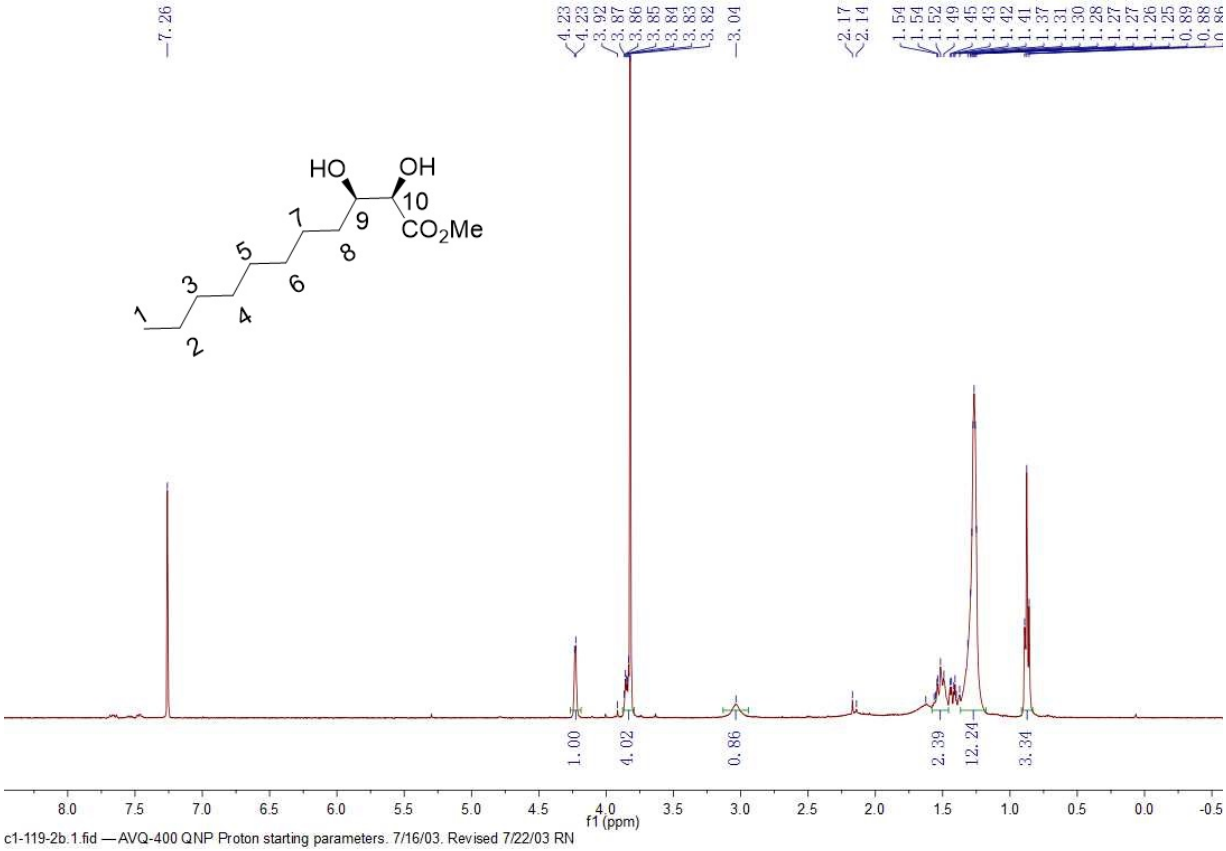

CO2Et
HO
1.00
3.06
1.01
1.03
2.06
3.06
5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0 -0.2 -0.4 -0.6
f1 (ppm)
L-III-180.6.fid — AV-600 ZBO proton startino parameters 11/16/08 RN

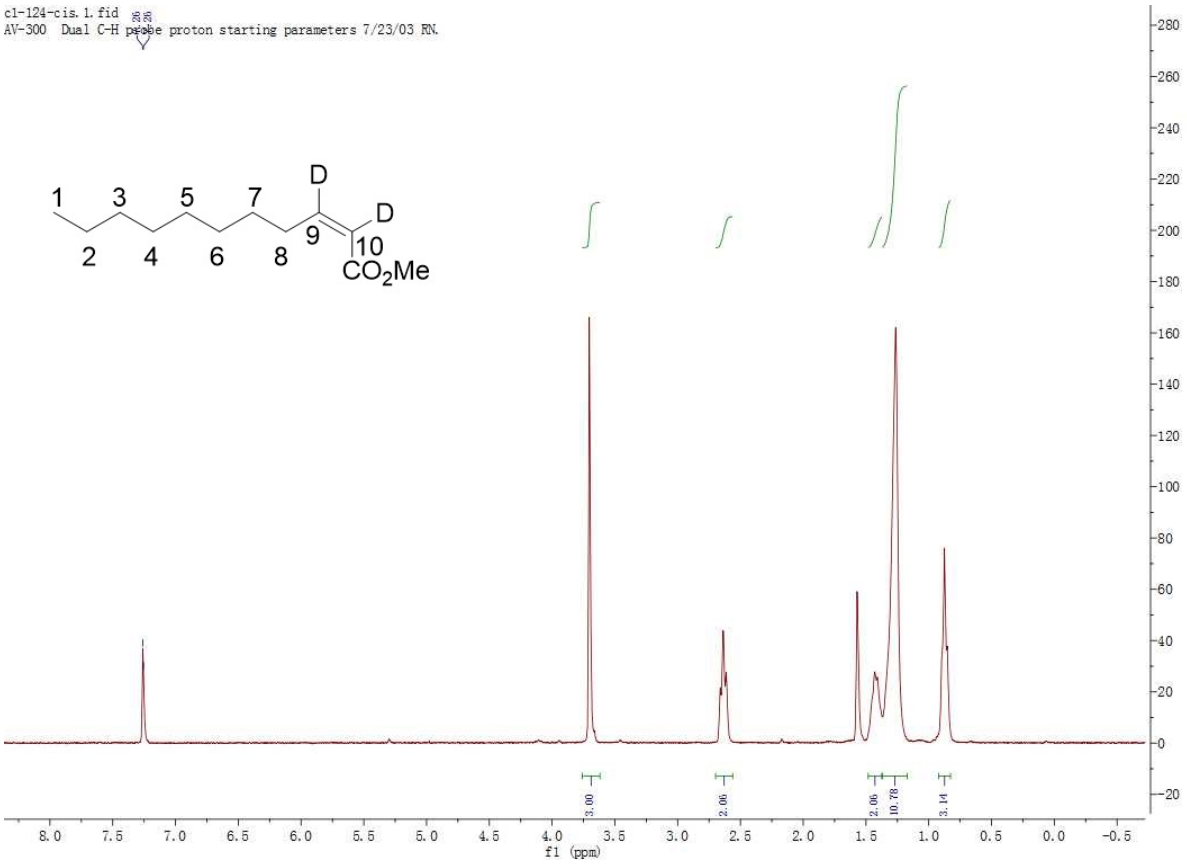

179.88
172.75
82.22
73.36
62.57
29.19
24.26
14.48
HO
CO2Et
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
RL-III-180.5.fid — DRX-500 5mm ZBO probe 13C starting parameters. Rev 6/12/12 CGC — With CPD proton decoupling. Use ns*td0 scans — TBIC 103013

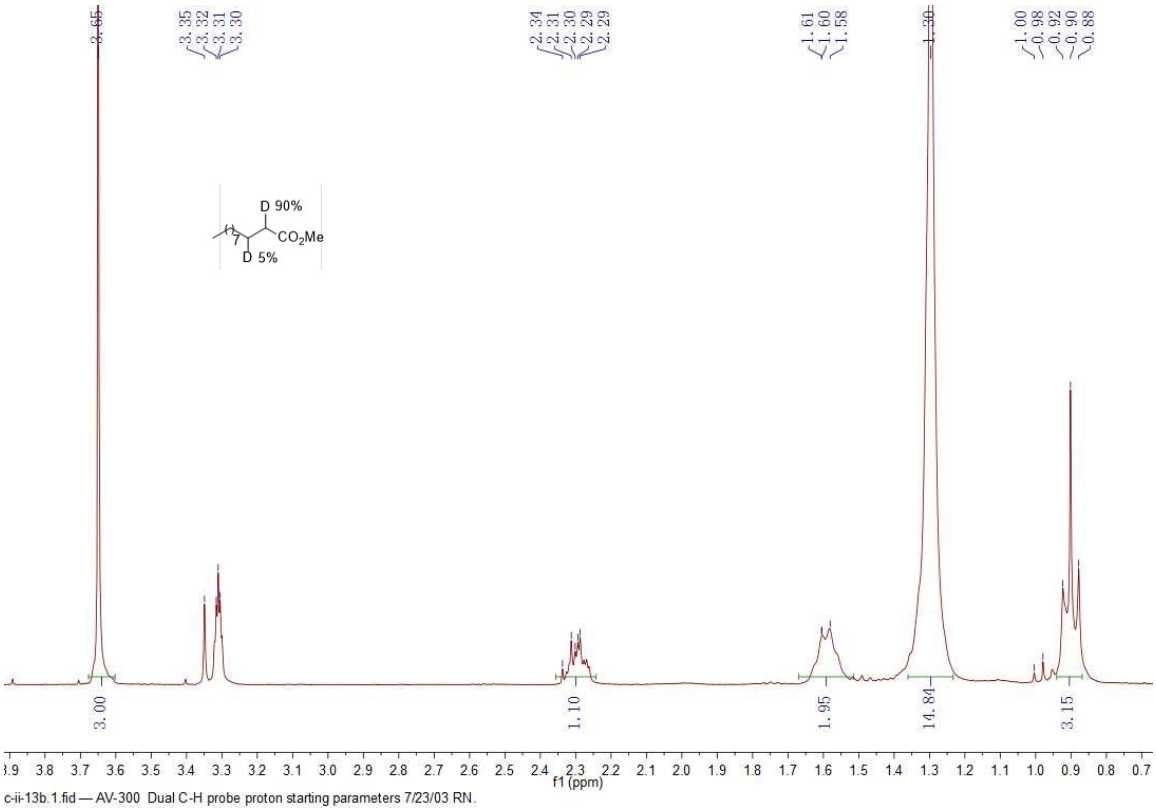

OH
OH
0.94
0.93
2.00
2.01
1.97
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)
RL-V-2flashed.1.fid — AV-600 ZBO proton startino parameters 11/16/08 RN


180.28
82.16
73.55
63.74
49.51
49.34
49.17
49.00
48.83
48.66
48.49
29.33
23.03
O
O
OH
OH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
RL-V-2flashed.2.fid — DRX-500 5mm ZBO probe 13C starting parameters, Rev 6/12/12 CGC — With CPD proton decoupling, Use ns*td0 scans — TBIC 103013


7.26
3.79
2.94
1.51
1.48
1.45
1.41
1.38
1.37
1.34
1.30
1.25
0.88
0.86
0.83
HO
OH
D
D
CO2Me
3.00
2.04
14.60
3.11
f1 (ppm)
c1-158-NMR-1.1.fid — AV-300 Dual C-H probe proton starting parameters 7/23/03 RN.


7.26
4.23
4.23
3.92
3.87
3.86
3.85
3.84
3.83
3.82
3.04
2.17
2.14
1.54
1.54
1.52
1.49
1.45
1.43
1.42
1.41
1.37
1.31
1.30
1.28
1.27
1.27
1.26
1.25
0.89
0.88
HO
OH
10
CO2Me
1
2
3
4
5
6
7
8
9
1.00
4.02
0.86
2.39
12.24
3.34
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
c1-119-2b.1.fid — AVQ-400 QNP Proton starting parameters. 7/16/03. Revised 7/22/03 RN


c1-124-cis.1.fid
AV-300 Dual C-H probe proton starting parameters 7/23/03 RM
1 3 5 7 D
2 4 6 8 9 10 D
CO2Me
3.00
2.06
2.06
10.78
3.14
f1 (ppm)


3.65
3.35
3.32
3.31
3.30
2.34
2.31
2.30
2.29
2.29
1.61
1.60
1.58
1.30
1.00
0.98
0.92
0.90
0.88
D 90%
CO2Me
D 5%
3.00
1.10
1.95
14.84
3.15
f1 (ppm)
c-ii-13b.1.fid — AV-300 Dual C-H probe proton starting parameters 7/23/03 RN.

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