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The Development of Palladium-Catalyzed C-H Oxidation Reactions and Cooperative Chemoenzymatic Reactions

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The Development of Palladium-Catalyzed C-H Oxidation Reactions and Cooperative Chemoenzymatic Reactions

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Abstract

The Development of Palladium-Catalyzed C-H Oxidation Reactions and Cooperative Chemoenzymatic Reactions

By

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Doctor of Philosophy in Chemistry

University of California, Berkeley

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The following dissertation discusses the development and study of palladium-catalyzed C-H oxidation reactions and cooperative chemoenzymatic reactions.

Chapter 1 provides a summary of methods for the synthesis of anilines and related compounds. An overview of C-N and C-O bond formation from the reductive elimination of palladium (IV) complexes is discussed, and the history of allylic C-H acetoxylation is reviewed. A brief discussion of the types of chemoenzymatic transformations is also included in this chapter.

Chapter 2 describes a palladium-catalyzed amination of arenes to form N-aryl phthalimides with regioselectivity controlled predominantly by steric effects. The scope and challenges associated with the development of this reaction are discussed.

Chapter 3 summarizes mechanistic information about the C-H amination of arenes and describes the synthesis of model complexes to evaluate the possibility of C-N bond formation from the reductive elimination of a palladium (IV) intermediate.

Chapter 4 describes the development of a palladium-catalyzed oxidation of hindered alkenes to form linear allylic esters. The scope and the functional group tolerance of this reaction are discussed in detail.

Chapter 5 describes the development of a new type of cooperative chemoenzymatic system that combines the photocatalytic isomerization of alkenes with enzymatic reduction to generate enantioenriched products in high yields and ee’s.

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Acknowledgements

"A man who has been through bitter experiences and travelled far enjoys even his sufferings after a time."

-Homer

Graduate school was a challenging experience. The main thing I've learned is how little I know. One thing that I'm certain of is that I wouldn't be here without the dedicated effort of many people.

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Chapter 1

Introduction

1.1 General Introduction

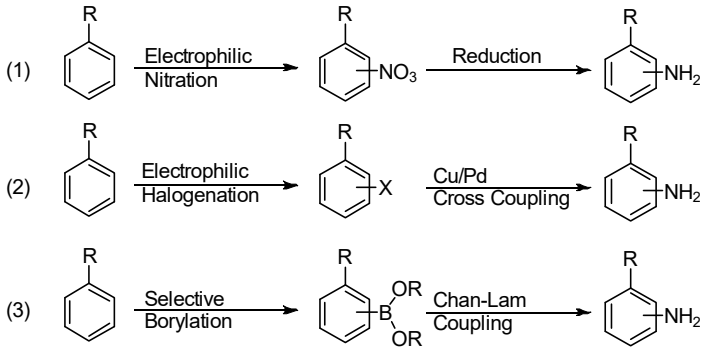
Catalytic reactions generate compounds that are crucial for modern industry. Pharmaceutical manufacturers have traditionally relied upon reactions catalyzed by homogeneous small-molecule catalysts or enzymes to synthesize biologically active compounds. Because of the high value of biologically active compounds and their intermediates, fundamental research on catalytic reactions has focused on the development of chemoselective transformations. Over the past 20 years, C-H activation has also dominated academic research on homogeneous catalysis because it enables direct routes to valuable compounds.

This dissertation includes studies of chemoselective palladium-catalyzed C-H oxidation reactions and systems that combine enzymes and photocatalysts. This introduction briefly summarizes information relevant to, and the context of, these reactions.

1.2 Methods for the Synthesis of Anilines

The abundance of amines and esters in biologically active compounds has motivated the development of reactions that form C-O and C-N bonds. Specifically, methods for the synthesis of anilines generate valuable pharmaceuticals, polymers, dyes, herbicides, and agrochemicals.[1-4] The traditional syntheses of anilines rely upon two-step synthetic sequences. For example, the industrial synthesis of aniline is accomplished via the electrophilic nitration of benzene followed by the hydrogenation of nitrobenzene with a transition-metal catalyst and hydrogen gas.[5] In an alternate approach, benzene is converted to phenol, which is subsequently converted to aniline with ammonia. Both routes require harsh conditions, require multiple steps, and exhibit poor overall atom economies. The limitations of these methods inspired the development of milder cross-coupling methods to form C-N bonds (Figure 1).

Figure 1. Traditional Methods for Aniline Synthesis



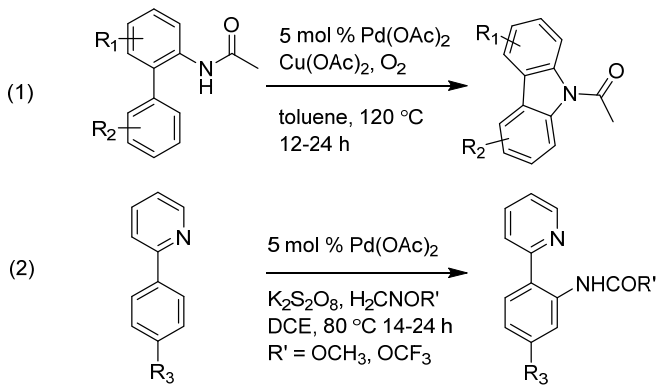
In 1903, Ullman reported the first coupling of aryl halides with amines in the presence of stoichiometric quantities of copper.[6] A related reaction was published by Goldberg in 1906.[7] The harsh conditions, limited scope, and the requirement for stoichiometric quantities of copper reduced the synthetic applications of this coupling. In 1983, Migita and Kosugi developed the first palladium-catalyzed cross coupling of N,N-diethylamino-tributyltin with aryl halides.[8] Although an important discovery, the use of aminostannanes as the nitrogen source for this reaction prevented the widespread adoption of this coupling. In 1995, Buchwald and Hartwig

reported the palladium-catalyzed coupling of aryl halides with amines.[9-10] Over the next 10 years, this method was improved and modified to couple a range of nitrogen sources with aryl iodides, bromides, chlorides, and triflates.[11-12] The mechanisms of these transformations were investigated, and the method is now widely applied in medicinal chemistry.[13]

In 1998, the copper mediated cross coupling of arylboronic acids with amines was reported.[14-16] The scope of the nitrogen source was expanded to include amines, anilines, amides, ureas, carbamates, and sulfonamides.[14-18] In 2000, a catalytic variant of this reaction was developed.[19] Although this reaction compliments existing palladium-catalyzed cross-couplings, a two-step procedure is still required to generate the desired aniline product. The limitations of both palladium-catalyzed and copper-catalyzed coupling reactions have inspired the development of C-H amination reactions that do not require pre-functionalization of the arene substrate.

A variety of methods have been developed for the direct C-H amination of aromatic compounds. Many reports describe intramolecular or directed approaches to the C-H amination of arenes, and extensive reviews have described these methods.[20] Examples of intermolecular and directed C-H amination are depicted in Figure 2.[21-22]

Figure 2. Directed Intermolecular C-H Amination and Intramolecular C-H Amination



The two most common strategies for C-H bond cleavage are 1) the insertion of a nitrene generated by a metal-catalyst into a C-H bond, or 2) cyclometallation deprotonation (CMD) of a C-H bond. Although methods for the directed and intermolecular amination of arenes are now high-yielding and synthetically useful, they require the use of specialized directing groups or pre-functionalized substrates.[23] In directed or intramolecular systems, the regioselectivity of the amination reaction is controlled by the substrate. The C-H amination of aromatic compounds lacking directing groups is challenging because 1) the C-H bonds of simple aromatic compounds are unreactive, and 2) weak interactions between the catalyst and arene substrate dictate the regioselectivity of the reaction. Because these challenges, only a few systems for the direct intermolecular C-H amination of simple arenes have been developed.

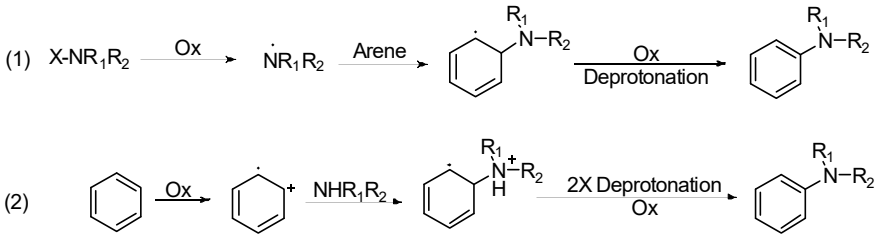
One of the early approaches for direct C-H amination relied upon the insertion of nitrenes into the C-H bonds of aromatic compounds. An article published in 2003 describes the amination of benzene with a nitrene.[24] This approach has not yet been widely adopted for the

functionalization of simple arenes because of side-reactions with the nitrene source and difficulties in controlling the regioselectivity of the amination.[25]

A series of metal-free C-H amination reactions that employ hypervalent iodine oxidants were published between 2011-2012.[26-28] These reports describe reactions that are conducted at high-temperatures and exhibit low regioselectivities. This work, along with a recent publication from the Hartwig group on an intramolecular amination of arenes,[29] motivated the development of a sterically controlled, palladium-catalyzed intermolecular amination of arenes (Ch 2).[30] This reaction generated aryl amines with regioselectivity dictated by steric factors. This reaction proceeded via a mechanism distinct from that of the metal-free process. There are two major limitations to this system 1) the formation of byproducts 2) the requirement that the reaction must be conducted with large excesses of arenes.

Subsequent reports on direct C-H amination of simple arenes described electrophilic[31] or radical[32-41] based mechanisms (not CMD). In some cases, N-centered radicals are generated by photocatalytic methods or other approaches and then are allowed to react with arenes to form aryl radicals.[32-35, 39-40] The aryl radicals are subsequently oxidized and deprotonated to form the final products (Figure 3, 1). In other systems,[36, 38, 41] an aromatic radical cation is directly generated, and a nitrogen source attacks the radical cation. Subsequent oxidation and deprotonation produces N-aryl amines (Figure 3, 2).

Figure 3. Synthesis of Anilines via Radical Pathways



In some of the reported methods, stoichiometric quantities of arene are used.[38-41] The use of limiting quantities of arenes overcomes a major limitation of previous methods for the direct C-H amination of simple arenes. However, the regioselectivity of the C-H amination reactions involving radical mechanisms is often poor, and complex product mixtures are obtained. Future work will undoubtedly focus on controlling the regioselectivity of C-H amination reactions while maintaining limiting quantities of arene substrate.

1.3 C-N and C-O Bond Formation from High-Valent Palladium Complexes

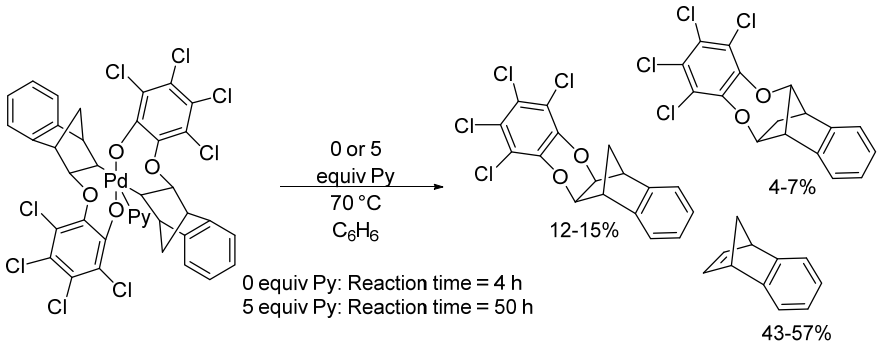
To develop a direct C-H amination reaction that is both limiting in arene and regio-selective, mechanistic investigations were initiated on the Hartwig group's system for the direct C-H amination of arenes (Ch 3).[30] Specifically, an understanding of the factors that control C-N vs. C-O bond formation could enable the development of conditions that could favor one or the other. The Hartwig group's investigations suggested that the reaction was analogous to the C-H acetoxylation of arenes,[42] and existing work suggests that arylpalladium (II) imidate[43] complexes

do not undergo reductive elimination the absence of an oxidant.[44] Based on this information, the possibility that C-N bond formation might occur from a high-valent palladium intermediate was considered.

The first Pd (IV) complexes were synthesized in the 1970's.[45] In contrast to Pt(IV) complexes, Pd (IV) complexes were unstable and prone to decomposition. In 1986, the first X-ray structure of the Pd (IV) complex [$PdIMe_3(bpy)$] was reported.[46] This unambiguous evidence for the existence of an isolable pallidum (IV) complex spurred efforts to characterize and synthesize related complexes. Investigators found that strong donor ligands were necessary to stabilize electron deficient Pd (IV) complexes, and that oxidants such as Cl_2, Br_2, I_2, $(PhCOO)_2$, PhSeSePh, PhSSPh, could convert Pd (II) complexes to Pd (IV) complexes.[45] The oxidative addition of alkyl halides to Pd (II) complexes was also used extensively to form Pd(IV) complexes. Hypervalent iodine(III) reagents were used to form new complexes. Among the most commonly used oxidants were $PhI(OAc)_2$, $PhICl_2$, and ArI=O.[45]

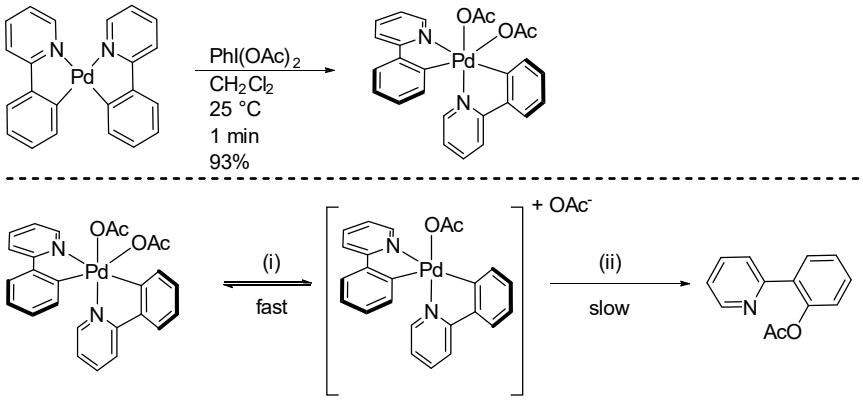
The first example of C-O reductive elimination from an isolated Pd(IV) complex was reported by Yamamoto in 2002 (Figure 4).[43] In this case, an sp^3 C-O bond was formed upon reductive elimination.

Figure 4. Sp^3 C-O Bond Formation from a Pd (IV) Intermediate



The Sanford group reported the first sp^2 C-O reductive elimination in 2005 from a cyclometalated phenylpyridine Pd (IV) complex (Figure 5).[47] A mechanistic investigation suggested that the reductive elimination occurred from a 5-coordinate intermediate that formed after the dissociation of an acetate ligand. This result informed a later study on the mechanism the intermolecular (non-directed) C-H acetoxylation of arenes.[42]

Figure 5. Sp^2 C-O Bond Formation from a Pd (IV) Intermediate

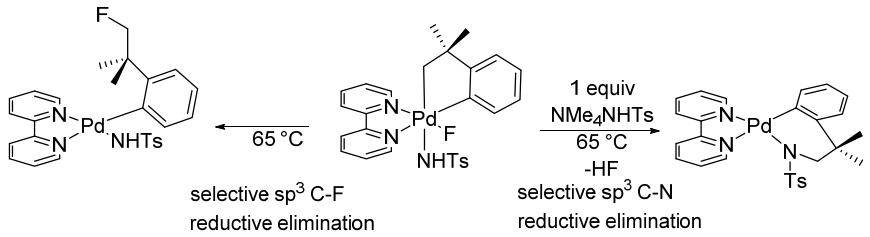


During a study of a similar palladium-catalyzed C-H acetoxylation reaction with phenylpyridine, the Ritter group found that the resting state of the catalytic reaction was a cyclometalated palladium dimer. When the Pd (II) complex was allowed to react with $PhI(OAc)_2$ a Pd (III) complex was isolated. This complex underwent C-O reductive elimination at a lower temperature than the corresponding Pd (IV) complex did (Figure 6).[48]

Figure 6. Sp^2 C-O Bond Formation from a Pd (III) Intermediate

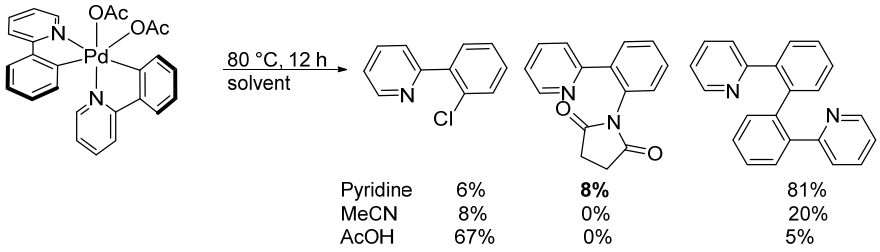
C-N bond formation from the reductive elimination of Pd (IV) and Pd (III) complexes has been less extensively investigated than the corresponding reductive eliminations to form C-O bonds. However, Sanford has reported the first examples of both sp^3 and sp^2 C-N bond formation from isolated Pd (IV) complexes (Figure 7, Figure 8).[49-50] To study the reductive elimination from a Pd (IV) complex to form a sp^3 C-N bond, a bypridine ligated Pd (IV) complex was prepared. Since the complex contains both a sulfonamide and fluoride ligand, competitive C-F vs. C-N bond formation was anticipated. When the complex was heated in acetonitrile in the absence of an additive, the products of C-F bond formation were generated preferentially. However, if 1.0 equiv of NMe_4NHTs was added to the reaction mixture, C-N bond formation was favored. Based on this observation and the rate-law of the reaction, the authors proposed that the C-N bond formation occurred via a nucleophilic attack of free sulfonamide on the sp^3 carbon.

Figure 7. Sp^3 C-N Bond Formation from a Pd (IV) Intermediate



Up to 2017,[51] the only example of sp^2 C-N bond formation via the reductive elimination of an isolated Pd (IV) complex was reported in a study on sp^2 C-Cl reductive elimination from a Pd (IV) complex (Figure 8).[49] The Pd (IV) complex was generated upon oxidative addition of N-chloro succinimide to a cyclometalated phenylpyridine complex. When this complex was heated in pyridine 8% of N-aryl imide product was observed.

Figure 8. Sp^2 C-N Bond Formation (Byproduct) from a Pd (IV) Intermediate



Based on Sanford's studies and other precedents, I was hypothesized that arylpalladium (II) imidate complexes could be oxidized to Pd (IV) and undergo reductive elimination in the presence of oxidants to form sp^2 C-N bonds. If acetate ligands were bound to the intermediate arylpalladium (IV) imidate complex, both C-N and C-O reductive elimination could occur. A systematic study of the factors that control the C-N vs. C-O reductive elimination could be used to devise reaction conditions that would favor the formation of N-aryl amines over N-aryl esters.

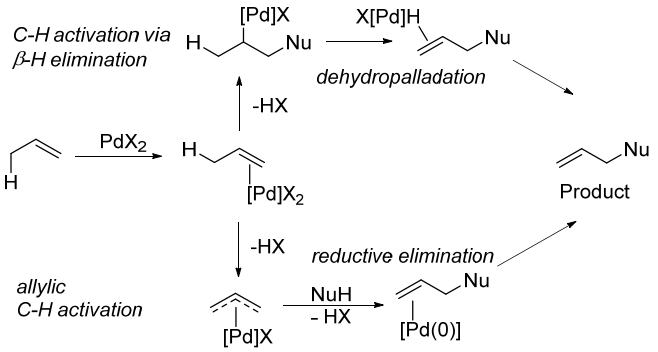
1.4 Allylic Oxidation Reactions

The fourth chapter describes a reaction discovered by Dr. Sharma and developed by me, due to my experience with palladium catalyzed reactions and oxidative conditions: the palladium-catalyzed oxidation of alkenes to form allylic esters.

The first catalytic allylic oxidation of olefins was reported in the 1970's.[52-53] Since that time, many groups have developed palladium-catalyzed acetoxylation of allylic C-H bonds with different ligands, terminal oxidants, and solvents.[54] The two mechanisms that are typically proposed for these transformations are depicted in Figure 9. In the first pathway, a pallidum (II) species coordinates to an alkene and then cleaves the allylic C-H bond to form a palladium allyl intermediate. Reductive elimination via nucleophilic attack on the palladium allyl intermediate generates the substituted product bound to palladium (0). The product is released, and the

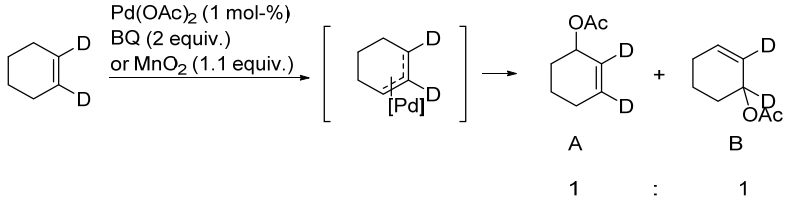
palladium (0) species is re-oxidized to a palladium (II) species. In the second mechanism, a palladium (II) species inserts into an alkene. The product is formed upon β-hydride elimination and dissociation of the palladium (0) species. This palladium (0) species must be re-oxidized to a palladium (II) species to complete the catalytic cycle.

Figure 9. Mechanisms for Palladium-Catalyzed Allylic Acetoxylation



In 1994 Bäckvall described the allylic acetoxylation of cyclic olefins with palladium catalysts.[55] When deuterated cyclic olefins were allowed to react with an oxidant and a palladium catalyst, products were observed that would only be generated by a nucleophilic attack on a n^3-allyl palladium intermediate (Figure 10). This finding was consistent with previous data in studies that had included n^3-allyl palladium intermediates in their mechanisms. In later studies Gusevskaya reported the oxidation of terpenes containing multiple alkenes.[56] In some cases, one of the alkenes directed the regioselectivity of the reaction. This relationship was confirmed by the observation that limonene (which contains a pendant olefin that can act as a directing group) was oxidized but caromenthene (which lacks a pendant olefin) was not. The n^3 allyl intermediates that Gusevskaya observed by ^{1}H NMR supported the intermediacy of a palladium-allyl species in the catalytic cycle for C-H acetoxylation of olefins.

Figure 10. Evidence for Intermediacy of Palladium-allyl species in Palladium-Catalyzed Allylic Acetoxylation



Since these early studies, the field of allylic oxidation has advanced significantly. Reactions with a variety of ligands, terminal oxidants, and solvents have been investigated.[54-55, 57-64] High selectivity for both the linear and branched allylic acetates has been achieved, and acid base sensitive substrates can be functionalized under certain conditions.[65-68,69-70] The acetoxylation of substrates containing amides, esters, and acetals has been accomplished in

moderate to good yields.[71] The Sthal group pioneered the use of oxygen as a terminal oxidant in allylic oxidations.[64] These reactions require a palladium catalyst, diazafluorenone, and benzoquinone. Mechanistic studies of this transformation have been conducted, and crystal structures of Pd (II) complexes ligated by diazafluorenone have been published.[64, 72] Monomeric and dimeric Pd (II) complexes were isolated with mondentate, bidentante, and bridging diazafluorenone ligands.[72]

Inspired by this work, the Hartwig group developed a one-pot Pd (II) allylic oxidation and allylic substitution reaction.[73] The conditions for the allylic oxidation reaction were tailored to not deactivate the catalyst used for the subsequent allylic substitution reaction. A reaction in which alkenes were oxidized in the presence of a palladium catalyst, diazafluorenone, and tert-butyl perbenzoate reacted was developed. These mild (neutral) conditions enabled the desired one-pot allylic oxidation and substitution procedure. The extent of the alkene scope was not exhaustively explored, and it was hypothesized that the mild conditions for allylic oxidation might enable the functionalization of hindered alkenes with sensitive functional groups.

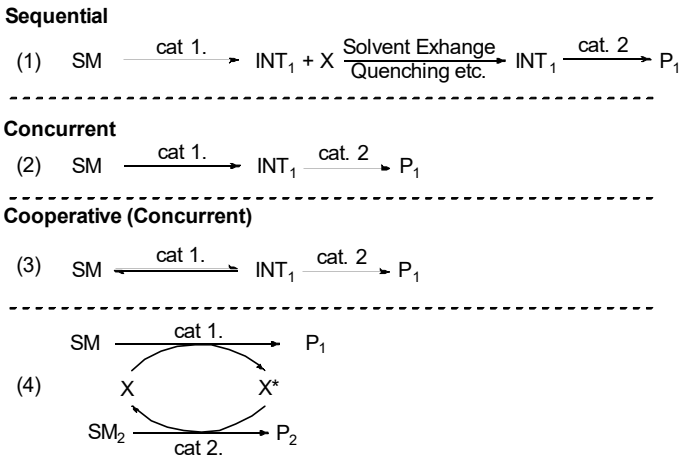
1.5 Chemoenzymatic Reactions

The final part of my thesis focuses on combining enzymes and photocatalyst to enable transformations that cannot be accomplished by the individual catalysts. This work was performed in collaboration with Yajie Wang of the Huimin Zhao group.

Living organisms rely upon concurrent reactions catalyzed by mutually compatible and selective enzymes to synthesize complex natural products and other metabolites. Many of these catalytic processes have been refined by evolution to exhibit high total turnover numbers (TTNs) and be highly enantioselective. In contrast, traditional artificial synthetic strategies consist of many sequential reactions with intermediate purification steps. Individual steps are typically conducted under different conditions, and the catalysts that enable these transformations are often mutually incompatible. In addition, artificial catalysts often generate unwanted side-products. However, artificial synthetic strategies are still widely employed because they enable transformations that have no biological counterpart. The limitations of both enzymes and artificial catalysts have inspired the development of systems that combine the reactivity of chemical catalysis with the selectivity of enzymatic catalysis.

Over the last 50 years, many groups have developed systems that combine enzymes and chemical catalysts.[74] These systems are 1) sequential, 2) concurrent, or 3) cooperative (also concurrent) (Figure 11). In sequential chemoenzymatic reactions, a catalyst or enzyme is allowed to react with a substrate. The intermediate product is then reacted with a second catalyst or enzyme. In some cases, a solvent exchange is required, or a catalyst, reagent, or enzyme must be added to the reaction mixture. Sequential transformations are both the least challenging and least valuable type of chemoenzymatic system. In most cases, conducing the individual reactions in different vessels is as (or more) convenient than allowing them to react them in a single vessel.

Figure 11. Systems that Combine Enzymes with Artificial Catalysts



In concurrent chemoenzymatic systems, a catalyst and an enzyme simultaneously catalyze two reactions in the same medium. Concurrent chemoenzymatic systems are more valuable than sequential systems because they require no solvent exchange or catalyst addition. If an unstable intermediate is generated in such a process by one catalyst, a second catalyst can rapidly convert the intermediate into a stable product, and thereby prevent the decomposition of the intermediate. However, despite these possible benefits, in practice sequential reactions are often simpler and provide higher yields than concurrent reactions. The most challenging and useful class of chemoenzymatic reactions are cooperative.

Cooperative chemoenzymatic systems combine chemical catalysts and enzymatic catalysts to generate products in yields and ee's that cannot be obtained from the sequential reactions of the individual catalysts on their respective substrates. The catalysts in these systems must operate concurrently and be mutually compatible. In some cases, a metal complex catalyses a reversible reaction, and a selective enzyme catalyses an irreversible second reaction Chemoenzymatic dynamic kinetic resolutions are accomplished in this fashion (Figure 11, 3).[75] Products can be obtained in high yields and ee's from these processes. In contrast, sequential systems can only accomplish kinetic resolutions in which 50 % of a racemic substrate is converted to an enantioenriched product.

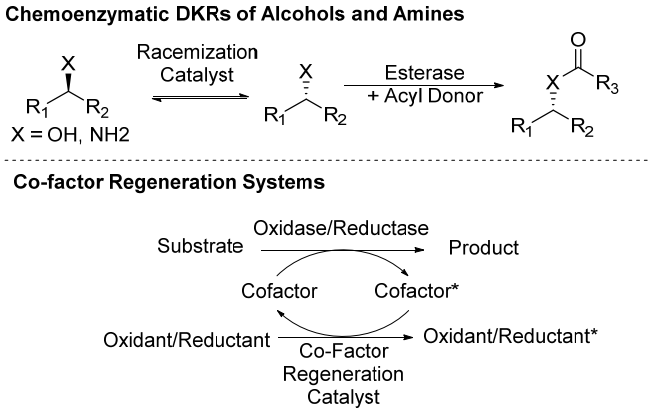
Another type of cooperative reaction recycles a key intermediate (Figure 11, 4).[74, 76] If such a reaction were conducted in a sequential manner, the number of turnovers would be restricted by the quantity of the key intermediate in the reaction mixture. However, in a cooperative system, there is no such restriction because intermediates can be recycled.

There are many challenges associated with the development of cooperative enzymatic systems.[75] Traditional synthetic organic methods are unusually conducted in organic solvent at high temperature. However, most enzymes only operate in aqueous media at ambient temperature. In addition, all catalysts within a concurrent cooperative system must be mutually compatible. In systems combining organometallic catalysts and enzymes, extensive catalyst and enzyme deactivation is often observed.[77-78] As a result, high catalyst loadings, high enzyme loadings, and extended reaction times are often required.

Many groups have reported cooperative reactions that combine enzymatic and chemical catalysis.[75-76, 79] The reported chemoenzymatic cooperative reactions can be mainly divided into two categories: 1) the chemoenzymatic dynamic kinetic resolutions of alcohols and amines[75] and

2) systems in which an enzymatic co-factor regeneration system is modified or replaced (Figure 12).[76]

Figure 12. Common Systems that Combine Enzymes with Artificial Catalysts



In the first system, the combination of an esterase with a catalyst that can racemize an alcohol or an amine enables the dynamic kinetic resolution of these substrates (Figure 12).[75] Unlike most enzymes, the esterases used in these systems maintain high catalytic activities in organic solvent and can operate at elevated temperatures. These properties permit esterases to catalyze reactions in the same medium as an organometallic catalyst that can racemize alcohols or amines.

In the second type of cooperative system, an enzyme that mediates the regeneration of cofactors for an oxidoreductase is replaced by a chemical catalyst (Figure 12).[76] Many oxidoreductases require nicotinamide and (or) flavin cofactors, which are too expensive and unstable to be used as terminal oxidants or reductants in synthetic applications. These limitations have motivated the development of organometallic, photochemical, and electrochemical methods for the in-situ regeneration of cofactors. However, enzymatic systems for the regeneration of cofactors are more frequently employed than chemical systems because of their superior compatibility with other enzymes.[76]

The development of new cooperative chemoenzymatic reactions is extremely difficult because chemical and enzymatic catalysts generally operate in different media at different temperatures and can deactivate each other. Because of these compatibility issues, few novel cooperative chemoenzymatic systems have been reported in recent years.[80-82]

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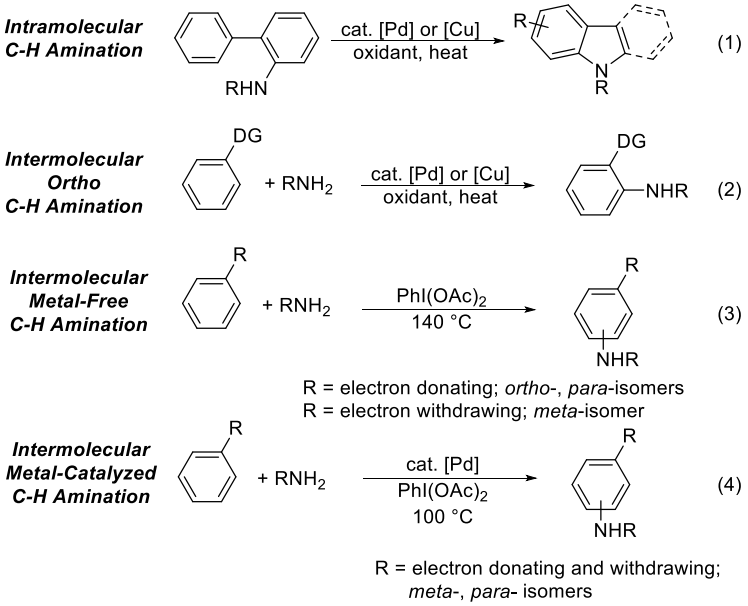
Chapter 2

Sterically Controlled, Palladium-Catalyzed Intermolecular Amination of Arenes

2.1 Introduction

The abundance of amines in medicine, agroscience, and material science makes them valuable synthetic targets.[1-4] Conventional methods for the synthesis of aromatic amines involve the nitration of arenes, followed by reduction.[5] To mitigate the harsh reaction conditions associated with these early methods, alternative approaches such as Cu-catalyzed[6-11] and Pd-catalyzed coupling reactions[11-12] of amines with aromatic halides or pseudohalides were developed. These approaches have been used widely in academia[13-14] and industry,[15-16] but these reactions require pre-functionalization of arenes to aromatic halides. Thus, the regioselectivity of the reaction reflects the regioselectivity for halogenation of the arene.

Therefore, a sterically controlled direct amination of aromatic C−H bonds would complement cross-coupling.[17-21] The direct amination of arenes with Cu[6, 22-26] and Pd[27-31] catalysts, as well as under metal-free[24, 32-34] conditions, has been reported. However, the metal-catalyzed reactions are limited to intramolecular processes (eq 1)[27-29, 35-38] or intermolecular processes with reactivity and regioselectivity governed by a directing group (eq 2).[30-31, 35, 39-40] A few uncatalyzed intermolecular reactions with substrates lacking a directing group have been reported.[24, 32-34] These reactions provide high yields of amination products but require high reaction temperatures and, most relevant to the work reported here, occur with regioselectivity dictated by the electronic effects that control electrophilic aromatic substitution (eq 3).

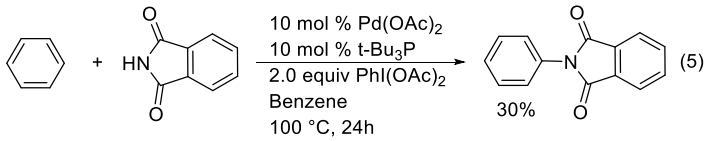


One method to conduct sterically controlled aminations of arenes is the combination of arene borylation[41] and Chan−Lam amination of the resulting arylboronate ester.[42] A direct, intermolecular amination of arenes with this steric control of regioselectivity would avoid the arylboronate intermediate, but such a process has not been reported (eq 4).

This chapter presents a Pd-catalyzed intermolecular oxidative amination of mono-, di-, and trisubstituted arenes with regioselectivities guided by steric effects.[43] The selectivity contrasts that for related Pd-catalyzed acetoxylation of arenes,[44-46] suggesting that a different species cleaves the C−H bond in the two classes of reactions.

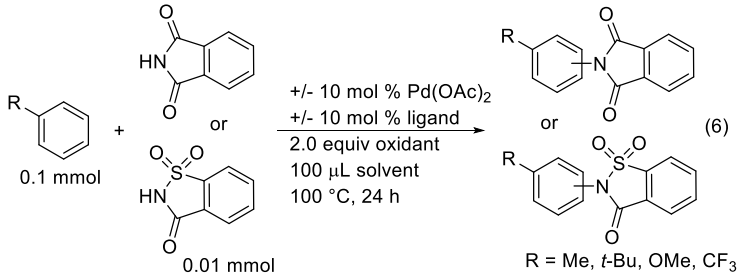
2.2 Results and Discussion

Previously, the Hartwig group reported Pd-catalyzed intramolecular aminations of aromatic C−H bonds with oxime esters to form substituted indoles;[29] however, an intermolecular version of this reaction has not been reported. During preliminary studies to develop an intermolecular variant, the formation of N-phenyl phthalimide was observed in 30−40% yield in the presence of a Pd catalyst, phthalimide, and $PhI(OAc)_2$ as an oxidant in benzene at 100 °C (eq 5).



Encouraged by this result, a series of ligands, oxidants, and solvents were investigated by high-throughput experimentation (HTE) methods to identify variable(s) that affect the yield of amination product (See Supporting Information). The reactions of electron-rich and -poor arenes with phthalimide and saccharin as the nitrogen source were conducted in the presence of catalytic amounts of $Pd(OAc)_2$ and mono- and bidentate N-based ligands, catalytic amounts of $Pd(OAc)_2$ alone, or no catalyst in polar and nonpolar solvents at 100 °C (eq 6).

The data from HTE revealed six general features of the reaction: (1) electron-rich arenes reacted in higher yields than electron-poor arenes; $PhCF_3$ reacted in low yield (10−20%), while PhMe, PhOMe and *t*-BuPh reacted in modest yield (30−50%); (2) reactions of arenes with phthalimide provided the desired amination product, but the reactions with saccharin gave several byproducts having the same mass as that of the desired amination product;[47-49] (3) $PhI(OAc)_2$ provided the highest yield of amination product among the oxidants tested; (4) reactions run in neat arene occurred in higher yields and with higher selectivities than those run in a solvent; (5) the observed selectivities were similar in the presence or absence of a ligand; and (6) the selectivities of reactions run in a solvent (1,2-DCE and MeCN providing high yields) were the same when run in the presence of Pd catalysts as in the absence of catalyst.



With the knowledge gained from HTE, the factors that control reaction yield were determined. The reactions were run using phthalimide as the N-source in neat benzene at 100 °C with catalytic amounts of $Pd(OAc)_2$ and *t*-Bu_3P, with catalytic amounts of $Pd(OAc)_2$ alone, and without a Pd catalyst. Figure 1 shows the kinetic profiles of these reactions. The reaction with $Pd(OAc)_2$ alone occurred more slowly than that conducted with $Pd(OAc)_2$ and *t*-Bu_3P. However, both reactions with and without ligand were complete within 3 h and formed a 35−45% yield of the amination product. Upon further heating, no additional amination product formed. Instead, Pd-black formed. Reactions run under metal-free conditions were slow at 100 °C and provided only 10% of the N-aryl imide after 6 h.[34]

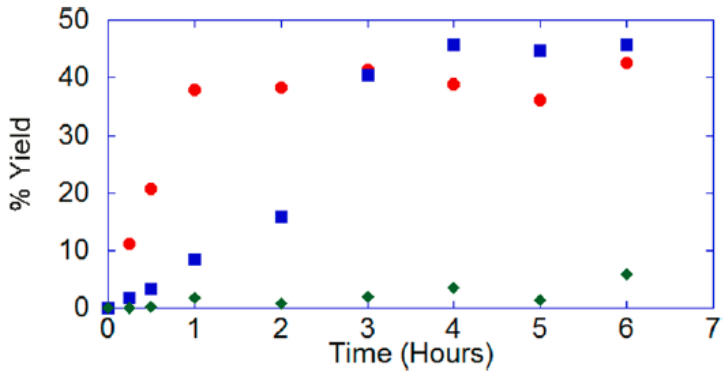


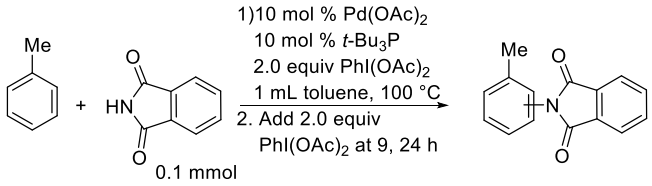
Figure 1. Comparison of amination of benzene with phthalimide in the presence of catalytic amounts of $Pd(OAc)_2$ /*t*-Bu_3P (●), catalytic amounts of $Pd(OAc)_2$ alone (■), and without a Pd catalyst (◆).

Due to their shorter reaction times, reactions catalyzed by the combination of $Pd(OAc)_2$ and *t*-Bu_3P were studied to determine if catalyst deactivation or consumption of phthalimide or $PhI(OAc)_2$ in an undesired pathway were responsible for the lack of full conversion. Reactions conducted with activated 3-, 4-, and 5-Å molecular sieves, acetic acid, and bases (such as Cs_2CO_3, NaOAc, and CsOH) gave the amination product in yields that were comparable to or lower than those for reactions run without these additives, implying that the catalyst was not affected by adventitious water or the acetic acid product (See Supporting Information). The addition of 10 mol % $Pd(OAc)_2$, 10 mol % *t*-Bu_3P, or 10 mol % of $Pd(OAc)_2$ and *t*-Bu_3P together after Pd-black had formed (5 h reaction time) also did not increase the yield of the amination product.

These results suggested that catalyst deactivation is not responsible for the modest yields. Likewise, addition of an extra equivalent of phthalimide at 5 h did not increase the amination product yield (See Supporting Information). In contrast, addition of an additional 2 equiv of $PhI(OAc)_2$ after 5 h of reaction time reverted the Pd-black to a soluble Pd species and increased the amination product yield from 35% to 55% based on phthalimide. Additions of two further portions of 2 equiv of oxidant at 5 h intervals gave an 83% yield of N-phenyl phthalimide product (See Supporting Information).

With conditions to form the amination product in high yield, the plausibility of a direct amination reaction that could be conducted with sterically controlled regioselectivity was examined. Conditions developed for the amination of benzene were applied to the reaction of toluene (Table 1). With two sequential additions of 2 equiv of $PhI(OAc)_2$ at 9 and 24 h reaction times, a 70% yield of the amination product was observed with a sterically controlled regioselectivity of 1:9:8 (o:m:p, entry 1).[50] Reactions run under similar conditions with $Pd(OAc)_2$ as the catalyst in the absence of ligand occurred in a similar yield and selectivity as reactions run with ligand (entries 2 and 1 respectively). This result is consistent with those observed in HTE.

Table 1. Regioselective Amination of Toluene[a]



Entry		Yield[b]	Selectivity[c] (o:m:p)
1	as above, no change	70%	1:9:8
2	no *t*-Bu_3P added	65%	1:6:6
3	no $Pd(OAc)_2$ or *t*-Bu_3P added	42%	2:1:1
4	with 8 equiv of $PhI(OAc)_2$ added initially	56%	1:13:13
5	without sequential addition on benchtop	68%	1:7:6
6	with 10 equiv of PhMe in 1 mL of 1,2-DCE	34%	1:3:4
7	with 10 equiv of PhMe in 1 mL of MeCN	38%	1:3:3
8	with 10 equiv of PhMe in 1 mL of mesitylene	10%	1:1:1

[a]Reactions were assembled in a nitrogen-filled glovebox on 0.1 mmol scale with 1 mL of toluene and run for 33 h total. [b]Corrected GC yield vs dodecane internal standard. [c]Crude GC selectivity.[50]

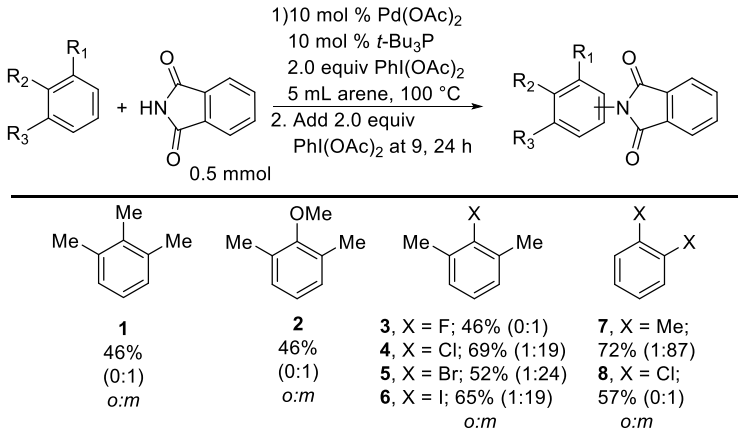
In contrast, the uncatalyzed reaction with sequential addition of the oxidant occurred in low yield with the selectivity derived from electronic effects (o:m:p = 2:1:1, entry 3).[33] The reaction catalyzed by $Pd(OAc)_2$ and *t*-Bu_3P with 8 equiv of the oxidant at the beginning of the reaction occurred in lower yield (entry 4). Finally, the presence of oxygen or moisture introduced from reactions assembled on the benchtop did not affect the yield of the product, but led to a slightly lower regioselectivity (entry 1 vs 5) (See Supporting Information). Likewise, reactions conducted with 10:1 toluene/ phthalimide in 1,2-DCE, MeCN, or mesitylene as a solvent at 100 °C occurred in lower yield and with a lower selectivity for m-, p-isomers vs an o-isomer (entries 6−8) than reactions run in neat arene. In summary, the reaction conditions described in Table 1 entry 1 lead to the sterically controlled direct oxidative amination of a substituted arene in high yield with high regioselectivity.[43]

Having identified conditions for the amination of a substituted arene with steric control, the selectivity for the amination of a variety of mono-, di-, and trisubstituted arenes with phthalimide using catalytic amounts of $Pd(OAc)_2$ and *t*-Bu_3P, catalytic amounts of $Pd(OAc)_2$, and without a Pd catalyst was examined (See Supporting Information). In all cases, the yield and regioselectivity of the metal-catalyzed reactions were higher than those observed for the uncatalyzed reactions. Slightly higher yields and selectivities were observed with added *t*-Bu_3P in some cases.

The scope of the reactions of tri-, di-, and monosubstituted arenes under conditions with the catalyst derived from $Pd(OAc)_2$ and *t*-Bu_3P is shown in Schemes 1 and 2. Reactions of 1,2,3-trisubstituted arenes and symmetric 1,2-disubstituted arenes (**1**− **8**) gave the less hindered products as the major constitutional isomer. A single isomer was isolated upon purification by silica gel column chromatography. In these cases, the regioselectivity observed with the catalyst

derived from $Pd(OAc)_2$ and *t*-Bu_3P is the opposite of the selectivity from the electronically controlled amination of arenes under uncatalyzed thermal conditions.[24, 32-34]

Scheme 1. Scope of the Sterically Controlled Amination of Symmetric Arenes[a]



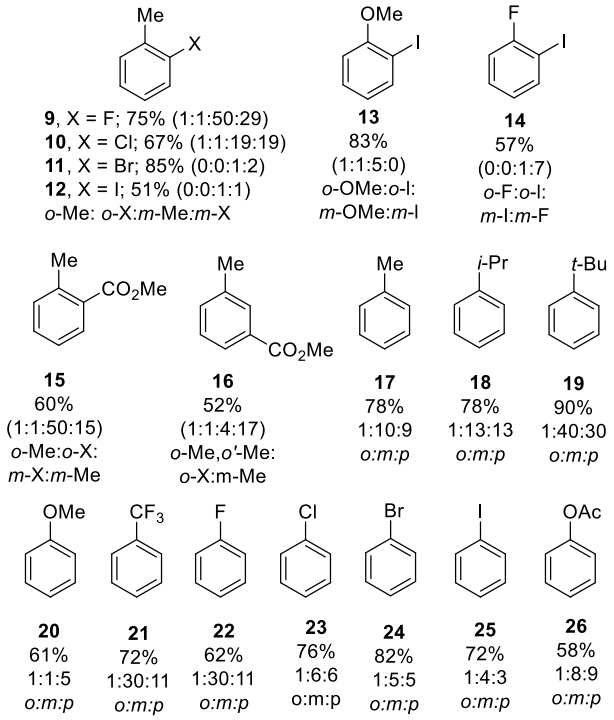
[a]Reactions were assembled in a nitrogen-filled glovebox in 20 mL scintillation vials on 0.5 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 5 mL of arene and 2.0 equiv of $PhI(OAc)_2$ at the beginning of the reaction. Another 2.0 equiv of $PhI(OAc)_2$ were added at 9 and 24 h of the reaction. The reactions were run for 33 h total. Yield represents isolated yield after silica gel column chromatography. Selectivities are reported based on GC analysis after isolation.[50]

The reaction also occurred with unsymmetrical 1,2- disubstituted arenes (**9**−**15**) to provide good yields of the two amination products containing the phthalimide group meta to both substituents (Scheme 2). Under the developed conditions, 1,2-disubstituted arenes were more reactive than the corresponding 1,3-disubstituted arenes (**15** vs **16**) (See Supporting Information).

In addition, the catalytic amination reaction occurred with electron-rich and -poor monosubstituted arenes (**17**−**26**) to provide monoamination products exclusively (Scheme 2). Substrates with larger substituents on the arene reacted with higher selectivity for amination of the less hindered C−H bonds (**17** vs **18** vs **19**). Arenes containing carbon−halogen bonds in mono-, di-, and trisubstituted arenes (**3**−**6**, **8**−**14**, **22**−**25**) underwent the C−H amination reaction without any observed proto dehalogenation or C−X amination. In all cases, the reactions were selective for the less hindered meta- and para- isomers. In some cases (**12, 13, 15, 16, 18, 20, 21, 24**), recrystallization of a mixture of meta- and para- isomers from MeOH/hexanes allowed for isolation of a single isomer. It is noteworthy that the transformations can be conducted on the benchtop, at the expense of a slight decrease in selectivity (Table 1, entry 1 vs 5).

Expansion of the scope of the N-source has been challenging. Studies of the reactions with imides possessing different electronic properties showed that the reactions of phthalimide and 4-methylphthalimide occurred in similar yields and selectivity, but reactions of the electron-poor imides 4- chlorophthalimide or 3,4,5,6-tetrachlorophthalimide and reactions of maleimide, succinimide, or saccharin occurred to low conversion. The reactions of amides or amines in place of imides occurred to low conversion (See Supporting Information). Nevertheless, the current results demonstrate that commercially available phthalimide can be used to generate a wide range of protected anilines[51] from readily available aromatic compounds.

Scheme 2. Scope of the Sterically Controlled Amination of Unsymmetrical Disubstituted Arenes and Monosubstituted Arenes[a]



[a]Reactions conducted with the conditions of Scheme 1. Yields are of isolated material.

The selectivity of this amination of arenes is clearly distinct from that of the related acetoxylations of arenes.[44-46] Crabtree showed that the acetoxylation of toluene, phenyl acetate, anisole, chlorobenzene, and iodobenzene occurs to form predominantly the ortho- and para-substituted products.[44] Many studies since then have suggested that the C−H bond is cleaved by a concerted metalation−deprotonation (CMD) sequence.[52-56] For the amination to occur with regioselectivity distinct from that of the acetoxylation process, the species that cleaves the C−H bond in the two reactions must be distinct, or the C−H bond cleavage step must be reversible and the amination step is faster for the less hindered arylpalladium intermediate than for the more hindered arylpalladium intermediate. To distinguish between these possibilities, the kinetic isotope effect (KIE) from the reaction of a mixture of C_6H_6 and C_6D_6 was measured. The KIE from these experiments was 4.1 ± 0.1, implying that the C−H bond is cleaved irreversibly (See Supporting Information). Thus, the species that cleaves the C−H bond in the acetoxylation and amination is different. Studies to compare CMD pathways for reactions of phthalimidate and acetate complexes will be the subject of future work.

2.3 Conclusion

In conclusion, a regioselective, intermolecular Pd-catalyzed oxidative amination of arenes with phthalimide has been developed. Sequential addition of the oxidant allows the reactions to occur in good yield in neat arene. This process points to an avenue to develop alternatives to Pd-catalyzed amination of aryl halides and the potential to conduct sterically controlled amination without initial borylation of the arene. Further studies to expand the scope of nitrogen sources based on mechanistic data are ongoing.

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2.5 Experimental

Table of Contents

I. Chemicals.

Palladium and Ligands:
$Pd(OAc)_2$, and ligands; 2,2'-bipyridine, 1,10-phenanthroline, 1,8-Diazafluoren-9-one, 8-hydroxyquinoline,2,2'-bipyrimidine, 1,2-diaminobenzene, 1,1'-binaphthyl-2,2'-diamine, 1-(2,6-diisopropylphenyl)-3-(2,4,6-trimethylphenyl)-imidazolium chloride, sparteine, 2,6-lutidine, pyridine, 2-phenylpyridine, acridine, quinuclidine, 3,5-dichloropyridine, benzoquinoline and tri-*tert*-butylphosphine were purchased from commercial sources (Strem, Aldrich, Acros, TCI America as available), stored in an InnovativeTechnologies nitrogen filled glove box, and used as received.

Oxidants:
Tert-butylperbenzoate, benzoquinone, potassium persulfate, copper (II) acetate, silver oxide, cerium sulfate, cerium ammonium nitrate, *p*-methoxy-iodosobenzene(diacetate), *o*-methoxyiodosobenzene(diacetate), *o*-isopropyl-iodosobenzene(diacetate), iodosobenzene(trifluoroacetate), iodosobenzene(diacetate), *N*-fluoropyridiniumtriflate, selectfluor hexafluorophosphate, *N*-fluoro-2,4,6- trimethylpyridinium triflate, and *N*-fluorobenzenesulfonimide (NFSI) were purchased from commercialsources and used as received.

Arenes:
Benzene, toluene, isopropylbenzene, *tert*-butylbenzene, methoxybenzene, trifluoromethylbenzene, fluorobenzene, chlorobenzene, bromobenzene, iodobenzene, acetoxybenzene, 1,2,3-trimethylbenzne, 2,6-dimethylanisole, 2,6-dimethylfluorobenzene, 2,6-dimethylchlorobenzene, 2,6-dimethylbromobenzene, 2,6-dimethyliodobenzene, 1,2 dimethylbenzene, 1,2-dichlorobenzene, 2-fluorotoluene, 2-chlorotoluene, 2-bromotoluene, 2-iodotoluene, 2-iodoanisole, 2-fluoroiodobenzene, methyl-2-methylbenzoate, and methyl-3-methylbenzoate were purchased from commercial sources and used as received without further purification.

Nitrogen Sources:
Phthalimide, 4-methylphthalimide, 4-chlorophthalimide, 3,4,5,6-tetrachlorochlorophthalimide, saccharin, maleimide, succinimide, benzamide, thioacetamide, acetamide, *N* methyltrifluoroacetamide, and trifluoromethanesulfonamide were purchased from commercial sources and used as received without further purification.

Solvents:
Anhydrous *N*,*N*-dimethylformamide (Acros), 1,2-dichloroethane (Aldrich), 1,4-dioxane (Aldrich), 1,3- Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (Aldrich), acetonitrile (Acros), and cyclopentyl methyl ether (Aldrich) were purchased from commercial sources and used as received.

Other Reagents:
Dodecane (Aldrich), and glacial acetic acid (Mallinckrodt) were purchased commercially and used without further purification.

II. Methods.

NMR Spectroscopy: 1H, 13C and 19F NMR spectra were recorded on a Bruker model AM-400 (101 MHz, 13C) spectrometer operating at 400.13 proton NMR frequency, and data analysis was performed using the iNMR software package (version 4.2.0, Nucleomatica, September 2011). NMR chemical shifts are reported in ppm and referenced to the residual solvent peak CDCl3 (δ = 7.26 ppm, 1H; δ = 77.16 ppm, 13C) as an internal standard or 1% CFCl3 in CDCl3 as an external standard (δ = 0 ppm, 19F) unless otherwise noted. Chemical shifts are reported in parts per million (ppm), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz.

Infrared Spectroscopy (IR): Infrared (IR) spectra were recorded on a Thermo Fisher Scientific Nicolet iS5 Fourier Transform Infrared (FT-IR) spectrophotometer and are reported in wavenumbers (cm-1).

Gas Chromatography: GC analyses were performed on Hewlett Packard HP 6890 series GC system equipped with Agilent Technologies F693 autosampler, HP-5 columns (25 m x 200 μm x 0.33 μm), dual FID detectors, and helium as the carrier gas. The analysis method for high-throughput experimentation (Procedure A, vide infra) was 1 μL injection of sample, injector temperature of 300 ºC, and 50:1 split ratio. The initial inlet pressure was 57.7 psi but varied as the column flow was held constant at 1.9 mL/min for the duration of the run. The initial oven temperature of 175 ºC was ramped to 300 ºC at 40 ºC/min, and the final temperature was held at 300 ºC for 1.88 min. The total run time was 5 min. The FID temperature was 325 ºC. The analysis method used in all other cases (Procedures B-D, vide infra) was 1 μL injection of sample, injector temperature of 300 ºC, and 50:1 split ratio. The initial inlet pressure was 41.1 psi but varied as the column flow was held constant at 1.9 mL/min for the duration of the run. The initial oven temperature of 100 ºC was held for 3.0 min, followed by a temperature ramp to 300 ºC at 40 ºC/min. The final temperature was held at 300 ºC for 2.5 min. The total run time was 10.5 min. The FID temperature was 325 ºC.

Gas Chromatography/Mass Spectrometry: GC/MS analyses were performed on Agilent Technologies 5975C VLMSD equipped with an HP-5MS (5% Phenyl Methyl Siloxane) column Model 19091S-433 from Agilent (30 m x 0.25 mm x 0.25 μm) with a Triple Axis Detector and helium as the carrier gas. The analysis method used in all cases was 1 μL injection of sample, injector temp of 300 ºC, and 10:1 split ratio. The initial inlet pressure was 10.0 psi, but varied as the column flow was held constant at 100 mL/min for the duration of the run. The interface temperature was held at 300 ºC, and the electron impact (EI, 30 eV) ion source was held at 300 ºC. The initial oven temperature was held at 45 ºC for 2.25 min with the detector off, followed by a temperature ramp to 300 ºC at 40 ºC/min with the detector turned on at 3.75 min. The final temperature was held at 300 ºC for 3 min. The total run time was 12.00 min. Data are reported in the form of m/z (intensity relative to the base peak = 100, ion).

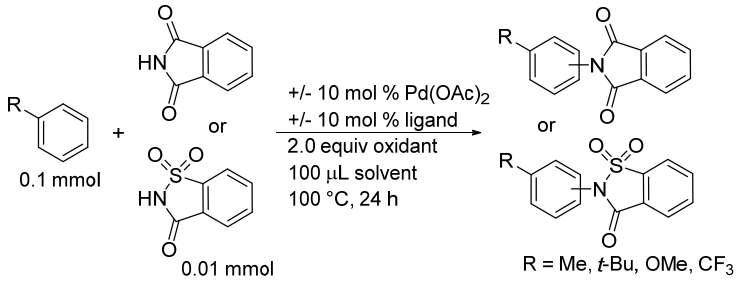
High Resolution Mass Spectrometry: High-resolution mass spectra (HRMS) under electron impact ionization (+ mode) were obtained on a LTQ-FT instrument at the University of California, Berkeley Mass Spectrometry Facility.

Thin Layer / Column Chromatography: Thin layer chromatography was performed on EMD Chemicals TLC Silica Gel 60 F254 plates. Visualization was accomplished with ultraviolet light and *p*-anisaldehyde or potassium permanganate stain. Flash chromatography was performed with Fisher Scientific silica gel (230-400 mesh, grade 60) following standard methods.
High-Throughput Experiments: High-throughput experiments were performed on V&P Scientific Inc. 96-well plate heating block equipped with a Watlow SD temperature controller and a V & P Scientific Inc. Magnetic Tumble Stirrer

III. Procedures.

(A) Procedure for reactions assembled in a glove box and run under nitrogen for high-throughput experimentation:

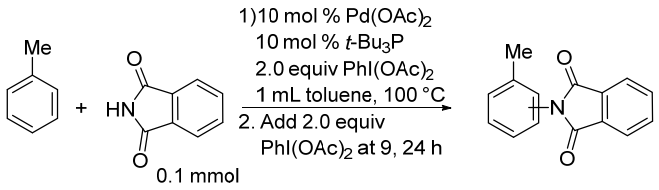
*This procedure was used for high-throughput experimentation (**Equation 6**)*



Reactions were assembled in a nitrogen-filled glove box in a 96-well anodized aluminum parallel synthesis reactor hardware kit. The aluminum plate was filled with 1 mL glass tubes (6 x 50 mm, d x l), and taken into the glove box. These ligands (1.0 mmol) were dosed into the 96-well reactor 1-mL vial as solutions (50 mL of a 0.02 M solution in THF). Plates of these ligands may be generated in advance of the experiment; the solvent is removed on a JKem-blow-down block, and the plates are stored in the glovebox. The reagent for amination (10 μmol, 50 mL of a 0.20 M solution in THF) was then added to the reaction vials, and the resulting mixture was evacuated under reduced pressure to dryness on a JKemblow-down block. The oxidant (20 μmol, 50 mL of a 0.40 M solution in MeCN) was then added, and the mixture was again evacuated to dryness on a JKem-blow-down block. A parylene coated VP 711D, 1.98 mm x 4.80 mm stir bar was added to each reaction vial. $Pd(OAc)_2$ (1 μmol) and dodecane (1.00 μmol) were then dosed together in the reaction solvent (100 μL of a 0.0100 M solution each). The reaction vials were sealed with PFA sheet and bottom rubber mat. The top plate was fixed into place with screws tightened with a screwdriver. This sealed well plate was then removed from the glove box and heated in a V&P Scientific Inc. 96-well plate heating block on the benchtop at 300 rpm while the temperature was maintained at 100 °C. After 24 h, the reaction assembly was removed from the heating plate, cooled to room temperature and diluted with 1 mL ethyl acetate. The resulting solution was analyzed by gas chromatography, and the reported percent yield was calculated versus the dodecane internal standard.

(B) Procedure for reactions assembled in a glove box and run under nitrogen for optimization experiments and control reactions:

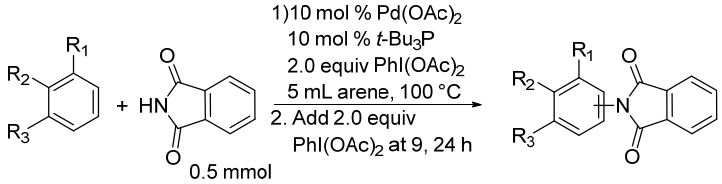
*This procedure was used for **Equation 5, Figure 1, and Table 1***



Reactions were conducted in a nitrogen-filled glovebox in an oven-dried 1-dram vial. $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv), *t*-Bu_3P (2.0 mg, 0.010 mmol, 0.10 equiv), phthalimide (14.7 mg, 0.100 mmol, 1.00 equiv) and $PhI(OAc)_2$ (64 mg, 0.20 mmol, 2.0 equiv) were weighed directly into a 1-dram vial equipped with a Teflon-coated stir bar (10 mm × 3 mm). Arene (1 mL), and dodecane (10.0 μL internal standard) were added using an automatic pipet. The vial was then capped with a PTFE-faced silicone septum, removed from the glove box and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C. For reactions in **Equation 5** and **Figure 1**, at desired time points, the reactions were cooled to room temperature, taken back into a nitrogen-filled glovebox, and an aliquot (10 μL) of the reaction mixture was removed using an automatic pipet, and diluted with ethyl acetate (1 mL). The resulting solution was analyzed by gas chromatography. For reactions involving sequential addition of $PhI(OAc)_2$ (**Table 1**), at 9 and 24 h, the reaction was cooled to room temperature, taken back into a nitrogen-filled glovebox, an aliquot (10 μL) of the reaction mixture was removed using an automatic pipet, diluted with ethyl acetate (1 mL) for GC analysis, and two portions of additional 2.00 equiv of $PhI(OAc)_2$ were added. After 33 h total reaction time, the yield of amination product formed was determined by GC analysis vs dodecane internal standard. The ratios of constitutional isomers were determined by comparison to the authentic products synthesized from condensation of commercially available aniline isomers with phthalic anhydride in acetic acid at 120 °C. (See Procedure D below).

(C) Procedure for reactions assembled in a glovebox and run under nitrogen to isolate amination
products.

*This procedure was used **Schemes 1** and **2***

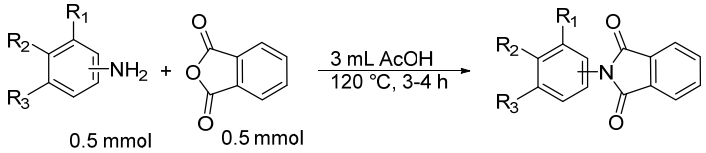


Reactions were conducted in a nitrogen-filled glovebox in oven-dried 20 mL scintillation vials. $Pd(OAc)_2$ (11.0 mg, 0.0500 mmol, 0.100 equiv), *t*-Bu_3P (10.0 mg, 0.0500 mmol, 0.100 equiv), phthalimide (73.6 mg, 0.500 mmol, 1.00 equiv) and $PhI(OAc)_2$ (322 mg, 1.00 mmol, 2.00 equiv) were weighed directly into a 20 mL scintillation vial equipped with a Teflon-coated stir bar (10 mm × 3 mm). Arene (5 mL), and dodecane (50.0 μL internal standard) were added using an automatic pipet. The vial was then capped with a PTFE-faced silicone septum, removed from the glove box, and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C. At 9 and 24 h, the reaction was cooled to room temperature, taken back into a nitrogen-filled glovebox and two portions of additional 2.00 equiv of $PhI(OAc)_2$

were added. After 33 h total reaction time, the amount of amination product formed was determined by GC analysis. An aliquot (50 μL) of reaction mixture was removed using an automatic pipet and diluted with ethyl acetate (1 mL). The resulting solution was analyzed by gas chromatography. The reaction mixture was purified by silica gel column chromatography (5.5" l × 1.5" d column) and the selectivity of constitutional isomers of the *N*-aryl imide product was determined.

(D) Procedure for reactions assembled on the bench and run under air to synthesize authentic amination products[1]

This procedure was used for synthesis of authentic products to determine regioisomeric ratios of products
*formed in **Schemes 1** and **2**.*

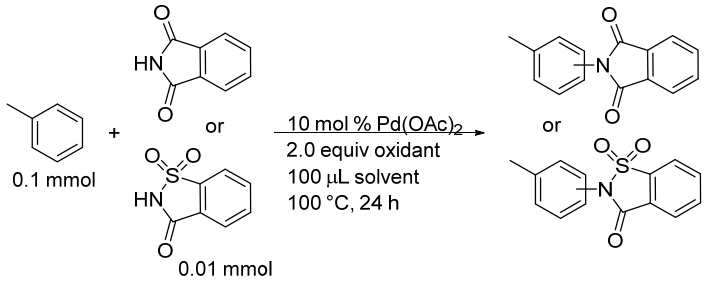


No precautions were taken to exclude air or moisture. On the benchtop, the arylamine (0.500 mmol, 1.00 equiv) and phthalic anhydride (74.0 mg, 0.500 mmol, 1.00 equiv) were weighed directly into a 1-dram vial equipped with a Teflon-coated stir bar (10 mm × 3 mm). Glacial acetic acid (3 mL) was added using an automatic pipet. The vial was then capped with a PTFE-faced silicone septum and stirred at 120 °C at 1200 rpm for 3-4 h. The reaction was then cooled to room temperature and added to cold water (10 mL), causing precipitation of the phthalimide protected aniline product. The resulting precipitate was filtered and washed with cold water (10 mL) and hexanes (10 mL), and then dried under high vacuum. The GC retention time of the resulting product was determined and compared to the crude reaction mixtures from Procedures A-C to determine the isomeric ratios of products formed from direct C-H amination reactions. 1H and 13C NMR were acquired.
1.

IV. Supplementary Results

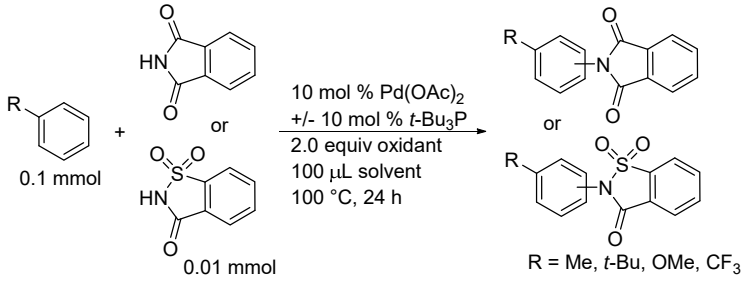
(A) High-Throughput Experiments (Selected data from reactions that provided the highest yield of
products are shown in Table S1)

(i) High-throughput experiment (HTE) #1 consisted of two 96-well plates for amination of toluene with
phthalimide or saccharin as the amination reagent and $Pd(OAc)_2$ as pre-catalyst under ligandless conditions. Sixteen oxidants in six different solvents were investigated



Oxidants:
Tert-butylperbenzoate, benzoquinone, potassium persulfate, copper (II) acetate, silver oxide, cerium sulfate, cerium ammonium nitrate, *p*-methoxy-iodosobenzene(diacetate), *o*-methoxyiodosobenzene(diacetate), *o*-isopropyl-iodosobenzene(diacetate), iodosobenzene(trifluoroacetate),iodosobenzene(diacetate), *N*-fluoropyridiniumtriflate, selectfluor hexafluorophosphate, *N*-fluoro-2,4,6-trimethylpyridinium triflate, *N*-fluorobenzenesulfonimide (NFSI).

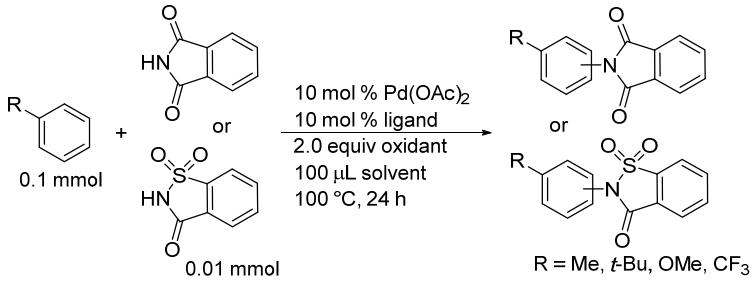
Solvents:
N,*N*-dimethylformamide, 1,2-dichloroethane, 1,4-dioxane, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone (DMPU), acetonitrile, cyclopentyl methyl ether.
(***ii) High-throughput experiment (HTE) #2*** consisted of three 96-well plates for amination of anisole, *tert*-butylbenzene and trifluoromethylbenzene with phthalimide or saccharin as the amination reagent and $Pd(OAc)_2$ as pre-catalyst in the presence and absence of *t*-Bu_3P ligand. Four oxidants and six different solvents were investigated



Oxidants:
selectfluor hexafluorophosphate, iodosobenzene(diacetate), copper (II) acetate, benzoquinone

Solvents:
N,*N*-dimethylformamide, 1,2-dichloroethane, 1,4-dioxane, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)- pyrimidinone (DMPU), acetonitrile, cyclopentyl methyl ether.

(***iii) High-throughput experiment (HTE) #3*** consisted of six 96-well plates for amination of anisole, *tert*butylbenzene and trifluoromethylbenzene with phthalimide or saccharin as the amination reagent and $Pd(OAc)_2$ as pre-catalyst. Seven bidentate nitrogen ligands and one carbene ligand were investigated with three oxidants in four solvents.



Oxidants:
selectfluor hexafluorophosphate, iodosobenzene(diacetate), copper (II) acetate, benzoquinone

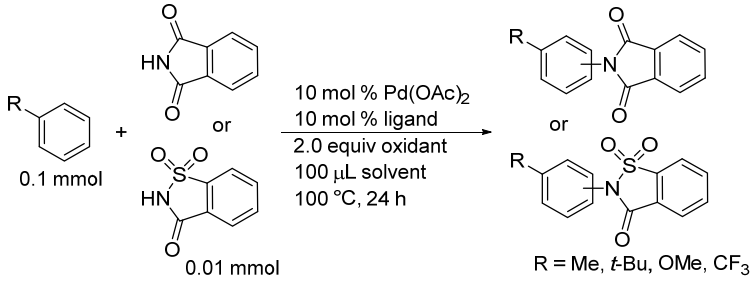
Solvents:
N,*N*-dimethylformamide, 1,2-dichloroethane, 1,4-dioxane, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(*1H*)- pyrimidinone (DMPU), acetonitrile, cyclopentyl methyl ether.

(***iii) High-throughput experiment (HTE) #3*** consisted of six 96-well plates for amination of anisole, *tert*butylbenzene and trifluoromethylbenzene with phthalimide or saccharin as the amination reagent and $Pd(OAc)_2$ as pre-catalyst. Seven bidentate nitrogen ligands and one carbene ligand were investigated with three oxidants in four solvents.

Ligands:
2,2'-bipyridine, 1,10-phenanthroline, 1,8-Diazafluoren-9-one, 8-hydroxyquinoline, 2,2'-bipyrimidine, 1,2- diaminobenzene, 1,1'-binaphthyl-2,2'-diamine, 1-(2,6-diisopropylphenyl)-3-(2,4,6-trimethylphenyl)-imidazolium chloride

Oxidants:
N-fluorobenzenesulfonimide (NFSI), iodosobenzene(diacetate), copper (II) acetate

Solvents:
1,2-dichloroethane, 1,4-dioxane, acetonitrile, neat arene.
(***iv) High-throughput experiment (HTE) #4*** consisted of three 96-well plates for amination of anisole, *tert*-butylbenzene and trifluoromethylbenzene with phthalimide or saccharin as the amination reagent and $Pd(OAc)_2$ as the pre-catalyst. Eight nitrogen ligands were investigated with three oxidants in two solvents.



Ligands:
Sparteine, 2,6-lutidine, pyridine, 2-phenylpyridine, acridine, quinuclidine, 3,5-dichloropyridine, benzoquinoline

Oxidants:
N-fluorobenzenesulfonimide (NFSI), iodosobenzene(diacetate), copper (II) acetate
Solvents:
1,2-dichloroethane, acetonitrile
Table S1. Selected data from reactions that gave product

Entry	Arene	Amine	Ligand	Oxidant	Solvent	Yield[a]	Selectivity[b] (*o*:*m*:*p*)
1	*t*-BuPh	Phthalimide	1,10-phenanthroline	$PhI(OAc)_2$	1,2-DCE	28%	1:4:3
2	*t*-BuPh	Phthalimide	1,10-phenanthroline	$PhI(OAc)_2$	MeCN	9%	1:4:3
3	*t*-BuPh	Phthalimide	1,10-phenanthroline	$PhI(OAc)_2$	Neat Arene	2%	1:5:3
4	*t*-BuPh	Phthalimide	Acridine	$PhI(OAc)_2$	1,2-DCE	29%	1:6:4
5	*t*-BuPh	Phthalimide	None	$PhI(OAc)_2$	1,2-DCE	10%	1:6:5
4	*t*-BuPh	Phthalimide	2,2'-bipyridine	$PhI(OAc)_2$	1,2-DCE	6%	1:6:5
7	*t*-BuPh	Phthalimide	2,2'-bipyridine	$PhI(OAc)_2$	MeCN	7%	1:4:3
8	*t*-BuPh	Phthalimide	1,8-diaza-fluoren-9-one	$PhI(OAc)_2$	1,2-DCE	28%	1:3:2
9	*t*-BuPh	Phthalimide	1,2-phenylene diamine	$PhI(OAc)_2$	1,2-DCE	30%	1:5:4
10	*t*-BuPh	Phthalimide	2,6-lutidine	$PhI(OAc)_2$	1,2-DCE	25%	1:3:2
11	*t*-BuPh	Phthalimide	Acridine	$PhI(OAc)_2$	1,2-DCE	32%	1:4:3
12	*t*-BuPh	Phthalimide	3,5-dichloropyridine	$PhI(OAc)_2$	1,2-DCE	26%	1:4:3
13	*t*-BuPh	Saccharin	1,10-phenanthroline	$PhI(OAc)_2$	1,2-DCE	28%	1:23:22
14	*t*-BuPh	Saccharin	2,2'-bipyridine	$PhI(OAc)_2$	1,2-DCE	28%	1:3:2
15	*t*-BuPh	Saccharin	pyridine	$PhI(OAc)_2$	MeCN	26%	1:26:24
16	*t*-BuPh	Saccharin	2,6-lutidine	$PhI(OAc)_2$	1,2-DCE	26%	1:12:13
17	*t*-BuPh	Saccharin	Acridine	$PhI(OAc)_2$	1,2-DCE	25%	0:12:13

18	*t*-BuPh	Saccharin	3,5-dichloropyridine	$PhI(OAc)_2$	1,2-DCE	48%	0:21:27
19	*t*-BuPh	Saccharin	8-hydroxyquinoline	$PhI(OAc)_2$	1,2-DCE	48%	1:13:14
20	*t*-BuPh	Saccharin	Pyridine	$PhI(OAc)_2$	MeCN	26%	1:26:24
21	*t*-BuPh	Saccharin	None	$PhI(OAc)_2$	1,2-DCE	29%	0:16:23
22	CF_3Ph	Phthalimide	*t*-Bu_3P	Any oxidant	Any Solvent	<3%	Not determined

*a*Reactions were run in a nitrogen filled glove box using high-throughput experimentation assembled on 0.01 mmol scale. Yields reported are uncorrected GC yield vs dodecane internal standard. *b*Selectivity for amination with phthalimide determined based on GC analysis by comparison to authentic products. Selectivity for amination with saccharin determined analogously.

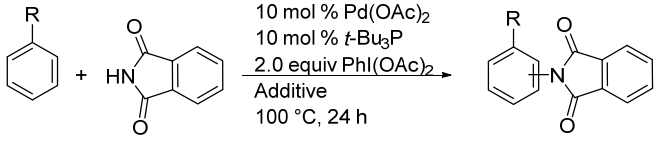


Table S2. Effect of Additives and Oxidants on Yield of Amination Product

Entry	Arene	Additive	% Yield[a]
1	MePh	None	30% (1:13:10)
2	MePh	None, $PhI(OC(O)^iPr)_2$ in place of $PhI(OAc)_2$	19% (1:11:8)
3	MePh	None, $PhI(OC(O)^tBu)_2$ in place of $PhI(OAc)_2$	14% (1:8:6)
4	MePh	None, $PhI(OC(O)CF_3)_2$ in place of $PhI(OAc)_2$	6% (1:2:2)
5	MePh	None, *t*-BuOOH in place of $PhI(OAc)_2$	0% (N.D.)
6	MePh	None, *t*-BuO_3CPh in place of $PhI(OAc)_2$	8% (1:4:4)
7	MePh	None, BzOOBz in place of $PhI(OAc)_2$	0% (N.D.)
8	MePh	None, Oxone in place of $PhI(OAc)_2$	0% (N.D.)
9	MePh	4.0 equiv 3-Å molecular sieves	30%
10	MePh	4.0 equiv 4-Å molecular sieves	33%
11	MePh	4.0 equiv 5-Å molecular sieves	21%
12	*t*-BuPh	None	43%
13	*t*-BuPh	0.25, 0.50 or 1.0 equiv Cs_2CO_3	<5%
14	*t*-BuPh	0.25, 0.50 or 1.0 equiv NaOAc	5-10%
15	PhH	None	35%
16	PhH	CsOH	NP
17	MePh	1eq AcOH	25% (1:17:14)
18	MePh	10eq AcOH	21% (1:16:14)
19	MePh	100eq AcOH	6% (1:4:5)
20	MePh	10 mol% $Pd(OAc)_2$ added at 2 or 5 h reaction time	37%
21	MePh	10 mol% *t*-Bu_3P added at 2 or 5 h reaction time	20%

22	PhH	10 mol% $Pd(OAc)_2$/*t*-Bu_3P added at 5 h reaction time	34%
23	PhH	1.0 equiv phthalimide added at 5 h reaction time	18%
24	PhH	2.0 equiv $PhI(OAc)_2$ added at 2 h reaction time	35%
25	PhH	2.0 equiv of $PhI(OAc)_2$ added at 5 h reaction time	53%
26	PhH	Three portions of 2.0 equiv of $PhI(OAc)_2$ added at 5 h intervals	83% (Figure S1)

a Reactions were assembled in a nitrogen-filled glove box in 1-dram vial on 0.1 mmol scale. Yields reported are uncorrected GC yield vs dodecane internal standard

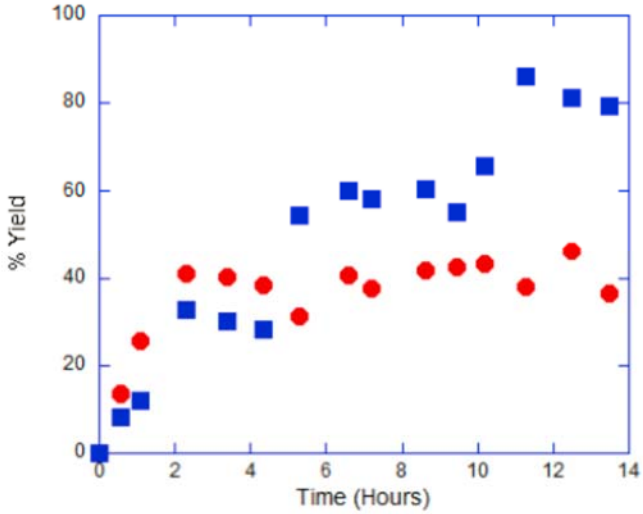
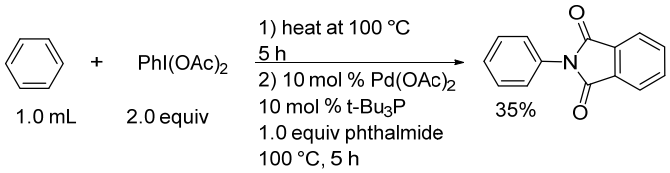


Figure S1. %Yield of benzene amination product with sequential addition of $PhI(OAc)_2$ at 5 h intervals (■) vs with only 2 equiv of $PhI(OAc)_2$ added at the beginning of the reaction (●).

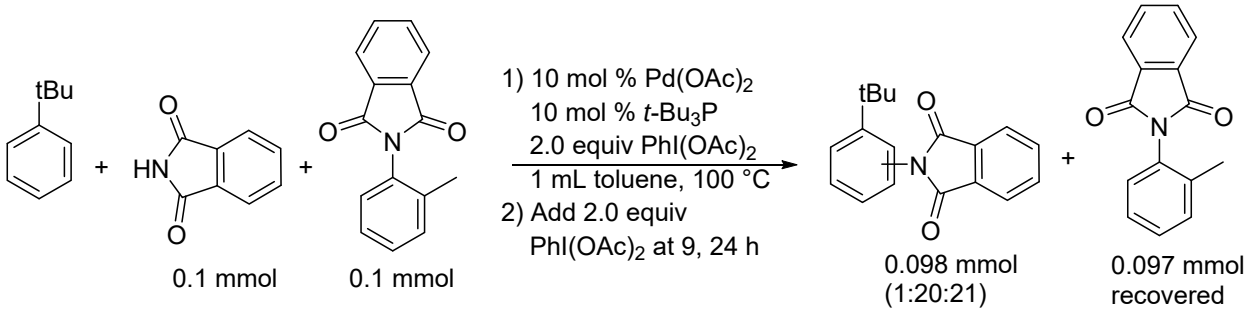
(B) Probing the consumption of $PhI(OAc)_2$



In a nitrogen-filled glove box, $PhI(OAc)_2$ (64.4 mg, 0.200 mmol, 2.00 equiv), benzene (950 µL) and a Teflon-coated stir bar (10 mm x 3 mm) were added to an oven-dried 1-dram vial. The vial was then capped with a PTFE-faced silicone septum cap 0.75", removed from the glove box and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C for 5 h. After 5 h, the reaction was cooled to room temperature and taken back into the glove box. The vial was uncapped, and a 50 µL solution of $Pd(OAc)_2$ (11.0 mg, 0.0500 mmol, 0.100 equiv), *t*-Bu_3P (10.0 mg, 0.0500 mmol, 0.100 equiv) in 250 µL of benzene and phthalimide (14.7mg, 0.100 mmol, 1.00 equiv) and 10.0 µL of dodecane were added to the

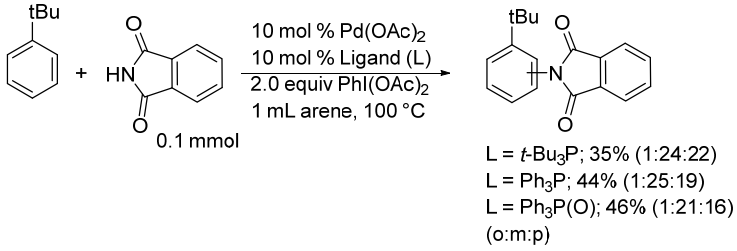
vial. The vial was recapped, removed from the glove box, and heated at 100 °C. After an additional 2 h of reaction time, the reaction was complete. The reaction vial was removed from heat, 50 μL of the reaction was removed from the vial (keeping the septum intact) and injected onto a 1 cm long plug of silica in a Pasteur pipet. The plug was then washed with 1 mL of ethyl acetate, and the filtrate was collected for GC analysis. The yield of the amination product was determined by GC analysis vs dodecane internal standard. The same procedure was repeated with *t*-butylbenzene in place of benzene. The yield of product from the amination of benzene was 35%. The 35% yield for this experiment is comparable to that observed for the same reaction without heating the oxidant prior to addition of the catalyst. Thus, thermal decomposition of the oxidant $PhI(OAc)_2$ is not responsible for its consumption. Instead, competitive acetoxylation of the arene is observed.[2-4] The product from acetoxylation is observed when the reaction is run with *t*-butylbenzene in place of benzene. Under the standard reaction conditions with 2 equiv of $PhI(OAc)_2$, the ratio of amination: acetoxylation product was observed to be 1:2 based on yield of amination product with respect to phthalimide versus acetoxylation product with respect to the oxidant. The regioselectivity of the acetoxylation product was 2.4:1:2.4 *o*:*m*:*p*. The selectivity was determined by comparison to the authentic products synthesized according to literature protocol. However, the relative amounts of product from amination vs acetoxylation vary with substrate and reaction time.

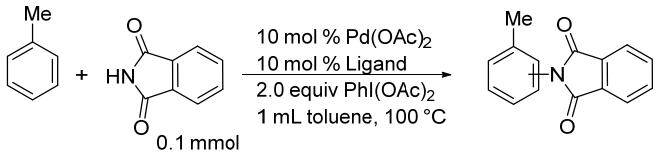
(D) Evaluation of the Stability of the *ortho*-Amination Product



The reaction was conducted in a nitrogen-filled glovebox in an oven-dried 1-dram vial. $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv), *t*-Bu_3P (2.0 mg, 0.010 mmol, 0.10 equiv), phthalimide (14.7 mg, 0.100 mmol, 1.00 equiv), $PhI(OAc)_2$ (64.4 mg, 0.200 mmol, 2.00 equiv) and *ortho*-phthalimido(toluene) (23.7 mg, 0.100 mmol, 1.00 equiv) were weighed directly into a 1-dram vial equipped with a Teflon-coated stir bar (10 mm × 3 mm). *t*-Butylbenzene (1 mL), and dodecane (10.0 μL internal standard) were added using an automatic pipet. The vial was then capped with a PTFE-faced silicone septum, removed from the glove box, and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C. At 9 and 24 h, the reaction was cooled to room temperature, taken back into a nitrogen-filled glovebox. An aliquot (10 μL) of the reaction mixture was removed using an automatic pipet, diluted with ethyl acetate (1 mL) for GC analysis, and two additional portions of 2.00 equiv of $PhI(OAc)_2$ were added. After 33 h total reaction time, the yield of the amination product, as well as the percentage of *ortho*-phthalimido(toluene) remaining after 33 h reaction time, was determined by GC analysis vs dodecane internal standard.

(E) Selectivity of Amination With a Phosphine vs a Phosphine Oxide Ligand

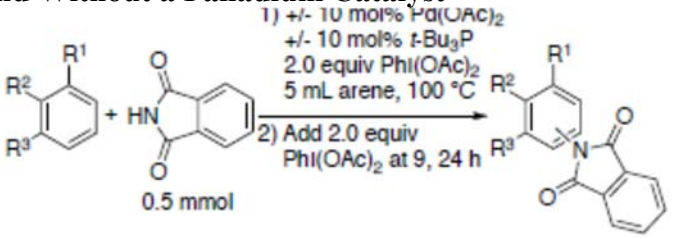




Entry	Ligand	% Yield[a]	Selectivity (*o:m:p*)[b]
1	None	23%	1:12:9
2	P(t-Bu)$_3$	30%	1:13:10
3	P(i-Pr)$_3$	29%	1:12:11
4	P(Cy)$_3$	29%	1:13:11

Reactions were conducted in a nitrogen-filled glovebox in oven-dried 1-dram vial. $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv), ligand (0.010 mmol 0.10 equiv) phthalimide (14.7 mg, 0.100 mmol, 1.00 equiv) and $PhI(OAc)_2$ (64.4 mg 0.200 mmol, 2.00 equiv) were weighed directly into a 1-dram vial, and a Teflon-coated stir bar (10 mm x 3 mm) was added. *t*-Butylbenzene (1 mL) and dodecane (10.0 μL) were added using an automatic pipet. The vial was then capped with open PTFE-faced silicone septum caps 0.75", removed from the glove box, and heated in a reaction block on the benchtop at 1200 rpm while the temperature was maintained at 100 °C. At various reaction times, 50 μL of the reaction was removed from the vial (keeping the septa intact) and injected onto a 0.5 cm long plug of silica in a Pasteur pipet. The plug was then washed with 1 mL of ethyl acetate, and the filtrate was collected for GC analysis. After approximately 9 h, the reaction was removed from the heat and considered complete. The yields of the amination product were determined by GC analysis vs dodecane internal standard. The ratios of constitutional isomers were determined by comparison to the authentic products synthesized from condensation of commercially available aniline isomers with phthalic anhydride in acetic acid at 120 °C. (See Procedure D above) Similar selectivities were observed for reactions conducted with Ph_3P or $Ph_3P(O)$ as ligand, suggesting that the decrease in selectivity for reactions conducted on the benchtop cannot be attributed to ligand oxidation. Consistent with this conclusion, the selectivity of the reaction conducted without added ligand also decreases when air is introduced into the reaction vial.

(F) Comparison of Yield and Selectivity For Amination of Arenes Using $Pd(OAc)_2$/*t*-Bu_3P-Catalyst,
$Pd(OAc)_2$-Catalyst and Without a Palladium Catalyst



	1	2	3	4	5
$Pd(OAc)_2$/*t*-Bu_3P	57% (1:14)	46% (1:10)	45% (1:15)	57% (1:18)	52% (1:24)
$Pd(OAc)_2$	55% (1:14)	55% (1:10)	47% (1:7)	52% (1:6)	39% (1:10)
Uncatalyzed	21% (4:1)	12% (1:1)	7% (2:1)	71% (3:1)	8% (2:1)
	o:*m*	*o*:*m*	*o*:*m*	*o*:*m*	*o*:*m*

	6	7	8	9	10
	53% (1:9)	77% (1:28)	50% (1:7)	60 (2:1:26:15)	66% (0:0:1:1)
	49% (1:7)	73% (1:22)	56% (1:4)	54% (2:1:25:14)	62% (0:0:1:1)
	28% (3:1)	22% (1:1)	29% (1:2)	22% (2:1:3:2)	23% (2:1:4:4)
	o:*m*	*o*:*m*	*o*:*m*	*o*-Me:*o*-X:*m*-Me:*m*-X	*o*-Me:*o*-X:*m*-Me:*m*-X

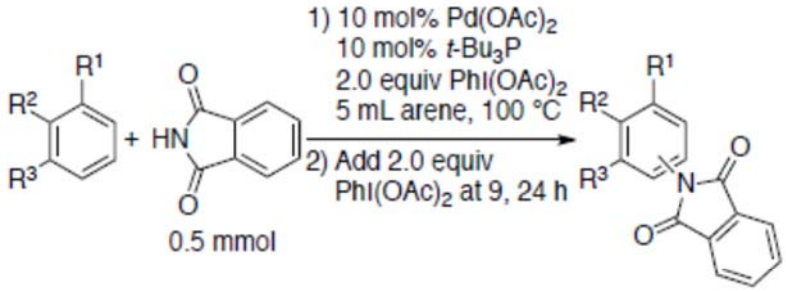
	11	12	13	14
	72% (0:1:7:9)	53% (0:0:1:14)	72% (0:0:1:5)	48% (1:7:3:1)
	60% (0:0:1:1)	52% (0:0:1:14)	59% (1:3:15:1)	46% (2:13:6:1)
	20% (1:1:1:1)	16% (0:0:1:2)	36% (5:1:2:10)	10% (1:2:2:0)
	o-Me:*o*-X:*m*-Me:*m*-X	*o*-Me:*o*-X:*m*-Me:*m*-X	*o*-OMe:*o*-I:*m*-OMe:*m*-I	*o*-F:*o*-I:*m*-I:*m*-F

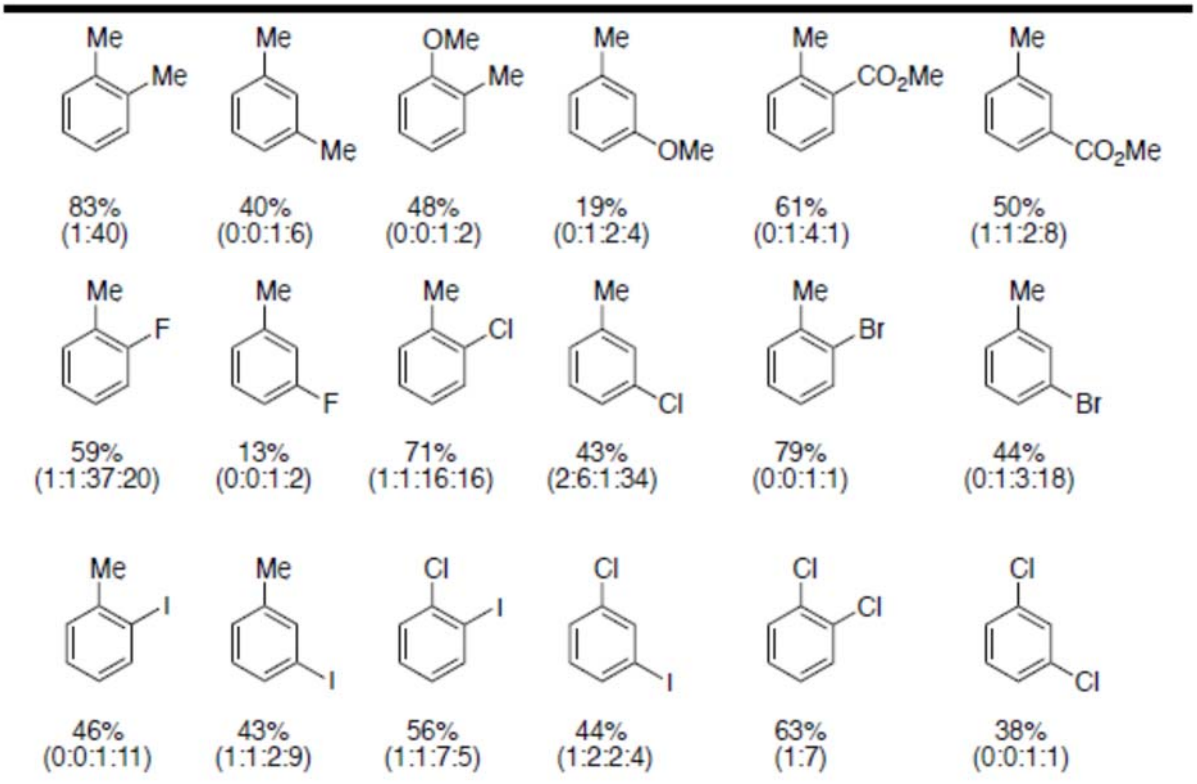
	15	16	17	18	19
	61% (0:1:4:1)	50% (1:1:2:8)	70% (1:9:8)	77% (1:10:8)	101% (1:18:14)
	59% (0:1:4:1)	45% (1:1:2:9)	65% (1:6:6)	71% (1:12:10)	127% (1:16:14)
	20% (0:2:2:1)	25% (1:1:2:2)	42% (1:1:1)	17% (1:2:2)	98% (1:3:2)
	o-Me:*o*-X:*m*-X:*m*-Me	*o*-Me:*o*-Me:*o*-X:*m*-Me	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*

	20	21	22	23	24	25	26
	46% (1:1:4)	66% (1:16:5)	45% (15:3)	65% (2:18:1)	82% (1:5:5)	80% (1:4:3)	62% (1:8:9)
	50% (1:1:3)	75% (1:10:4)	42% (1:5:2)	68% (2:20:1)	72% (1:4:4)	88% (1:3:2)	63% (1:6:7)
	60% (1:0:1)	110% (1:4:1)	18% (1:2:1)	17% (1:3:1)	18% (1:1:2)	16% (1:1:1)	21% (1:1:2)
	o:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*	*o*:*m*:*p*

[a]Reactions were assembled in a nitrogen-filled glove box in 20 mL scintillation vials on 0.5 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 5 mL arene as a solvent and 2.0 equiv of $PhI(OAc)_2$ at the beginning of the reaction. Another 2.0 equiv of $PhI(OAc)_2$ were added at 9, and 24 h of the reaction. The reactions were run for 33 h total. Yield represents uncorrected GC yield vs dodecane internal standard observed for a crude reaction mixture after 33 h reaction time. Selectivities are reported based on GC analysis.

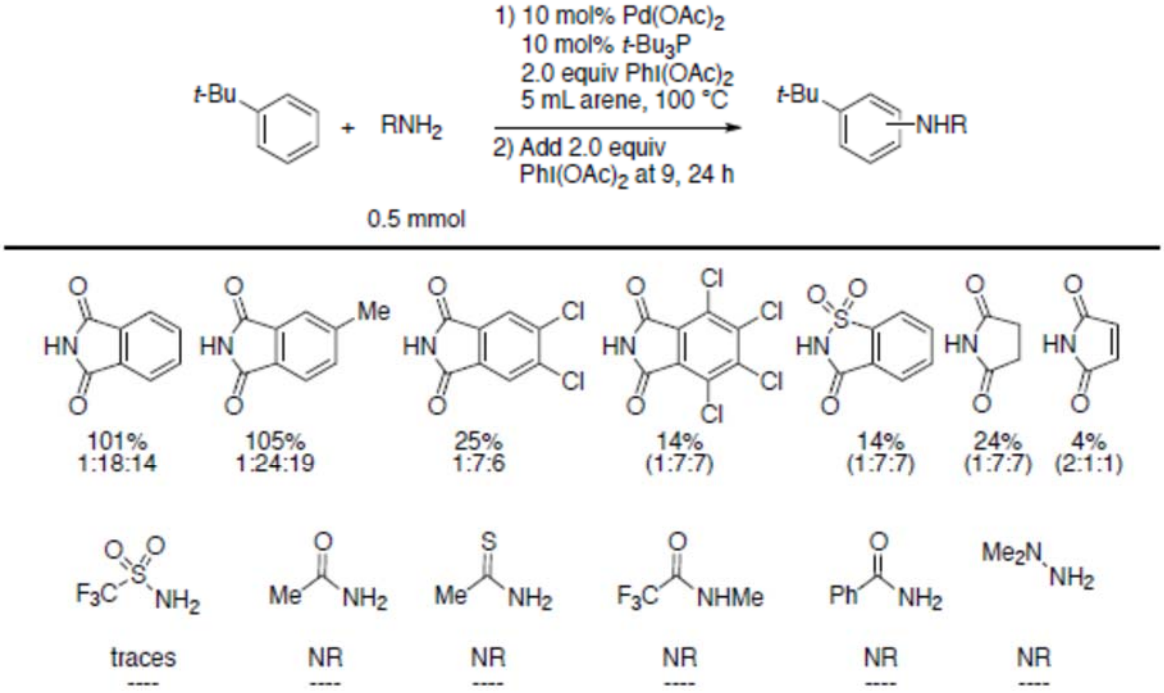
(G) Comparison of Yield and Selectivity For 1,2- vs 1,3-Disubstituted Arenes*a*





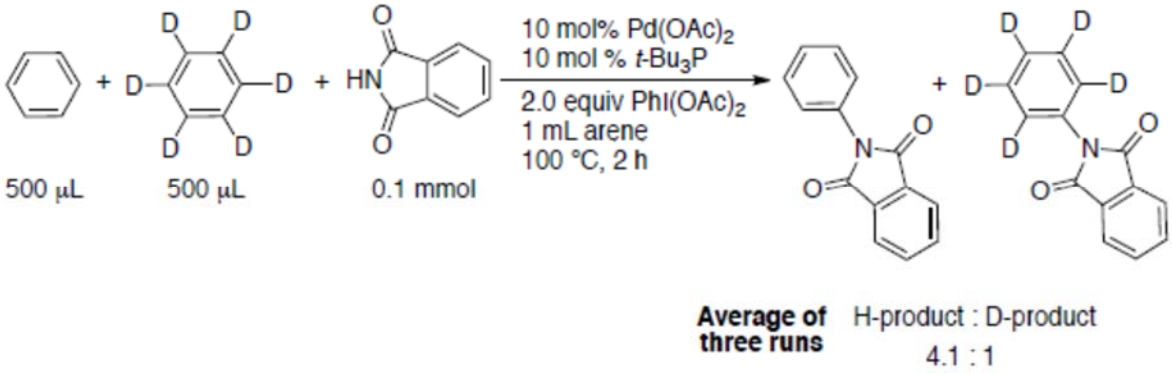
[a]Reactions were assembled in a nitrogen-filled glove box in 20 mL scintillation vials on 0.5 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 5 mL arene as a solvent and 2.0 equiv of $PhI(OAc)_2$ at the beginning of the reaction. Another 2.0 equiv of $PhI(OAc)_2$ were added at 9, and 24 h of the reaction. The reactions were run for 33 h total. Yield represents GC yield vs dodecane internal standard observed for a crude reaction mixture after 33 h reaction time. Selectivities are reported based on GC analysis.

(H) Scope of Nitrogen Sources



[a]Reactions were assembled in a nitrogen-filled glove box in 20 mL scintillation vials on 0.5 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 5 mL arene as a solvent and 2.0 equiv of $PhI(OAc)_2$ at the beginning of the reaction. Another 2.0 equiv of $PhI(OAc)_2$ were added at 9, and 24 h of the reaction. The reactions were run for 33 h total. Yield represents GC yield vs dodecane internal standard observed for a crude reaction mixture after 33 h reaction time. Selectivities are reported based on GC analysis

(I) Kinetic Isotope Effect



Reactions were conducted in a nitrogen-filled glovebox in oven-dried 1-dram vials in triplicates. $Pd(OAc)_2$ (2.2 mg, 0.010 mmol, 0.10 equiv), *t*-Bu_3P (2.0 mg, 0.010 mmol 0.10 equiv) phthalimide (14.7 mg, 0.100 mmol, 1.00 equiv) and $PhI(OAc)_2$ (64.4 mg 0.200 mmol, 2.00 equiv) were weighed directly into a 1-dram vial, and a Teflon-coated stir bar (10 mm x 3 mm) was added. Benzene (500 µL), deuterated benzene (500 µL) and dodecane (10.0 µL) were added using an automatic pipet. The vial was then capped with PTFE-faced silicone septum cap, removed from the glove box and heated in a reaction block on the benchtop at 1200 rpm, while

the temperature was maintained at 100 °C. After 2 h reaction time, the vial was cooled to room temperature, and 50 μL of the reaction mixture was removed using an automatic pipet and diluted with ethyl acetate (1 mL) for GC/MS analysis. The ratio of protonated product versus deuterated product was determined, based on the relative abundance of isotopomers observed
(**Table S3**).

Entry	Trial #	Ratio of H-product : D- product based on C-12 isotope	Ratio of H-product : D- product based on C-13 isotope
1	1	3.57	3.76
2	2	4.29	4.28
3	3	4.30	4.30
Average		4.05	4.11
Average of averages		4.10	
Standard deviation		0.06	

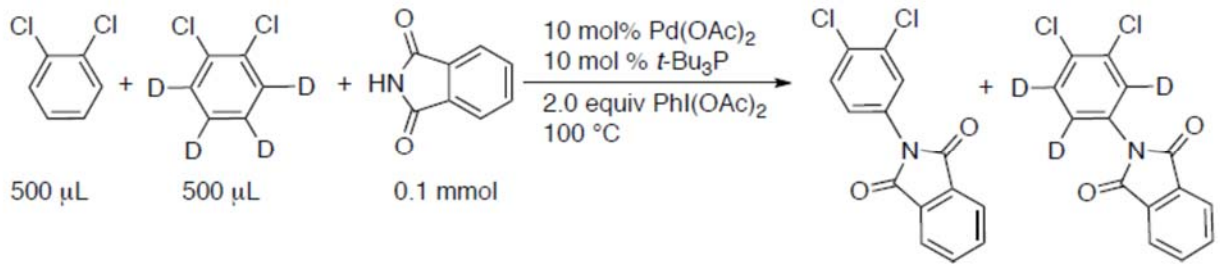
a Reactions were assembled in a nitrogen-filled glove box in 1-dram vials on 0.1 mmol scale with 10 mol % $Pd(OAc)_2$/*t*-Bu_3P in 1 mL arene and 2.0 equiv of $PhI(OAc)_2$ and run for 2 h. H/D ratios are reported based on relative abundance of isotopomers observed by GC-MS.

Isotope Effect for Acetoxylation Under Oxidative Amination Conditions

Table S4. Study on isotope effect for acetoxylation under oxidative amination conditions.*a*

Entry	Trial #	Ratio of H-product : D- product based on C-12 isotope	Ratio of H-product : D- product based on C-13 isotope
1	1	5.91	5.42
2	2	5.73	5.64
3	3	5.82	5.50
Average		5.82	5.52
Average of averages		5.67	
Standard deviation		0.21	

Isotope Effect of Disubstituted Arene

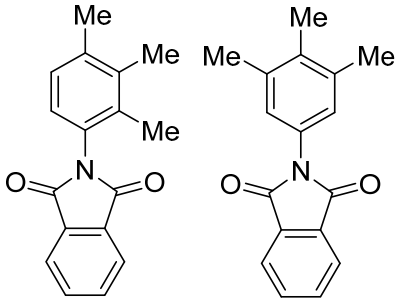


Average of two runs

H-product : D-product
2.9 : 1

V. Compound Characterization.

Amination of 1,2,3-trimethylbenzene (1)



1a **1b**

General procedure **(III)(C)** was followed with 5 mL of 1,2,3-trimethylbenzene (**1**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **1b** was confirmed by the synthesis of authentic product.

Data for **1a**, **1b**

GC Yield (Selectivity; **1a**:**1b**): 50% (1:15)

Isolated Yield (Selectivity; **1a**:**1b**): 122 mg white solid, 46% (0:1)

TLC: Rf 0.41 (20% EtOAc in hexanes)

1H NMR (400 MHz, CDCl3)

1b: δ 7.94 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.04 (s, 2H), 2.34 (s, 6H), 2.21 (s, 3H).

13C NMR (101 MHz; CDCl3)

1b: δ 167.7, 137.6, 135.9, 134.3, 132.0, 128.4, 125.9, 123.7, 20.8, 15.4

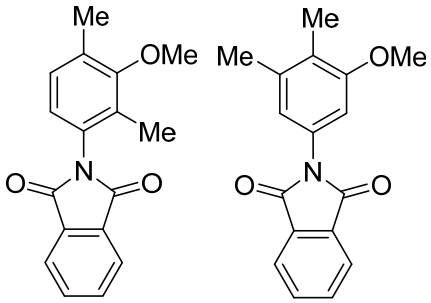
IR (υ, cm-1):

2922, 2865, 1763, 1715, 1589, 1487, 1465, 1378, 1272, 1237, 1194, 1109, 1084, 1008, 959, 912, 886, 856, 817, 792 779, 764, 749, 714, 699, 662, 646.

HRMS (EI+):

Calc. for C1H15NO2 [M]+: 265.1103; Found: 265.1105

Amination of 2,6-dimethylanisole (2)



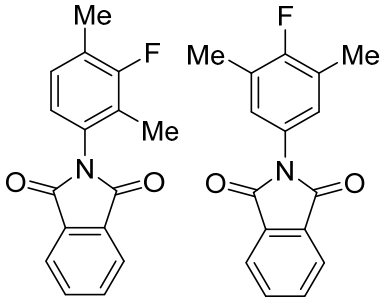
2a **2b**

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethylanisole (**2**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **2b** was confirmed by the synthesis of authentic product.

Data for **2a**, **2b**

GC Yield (Selectivity; **2a**:**2b**): 56% (1:10)
Isolated Yield (Selectivity; **2a**:**2b**): 129 mg off-white solid, 46% (0:1)
TLC: Rf 0.35 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
2b: δ 7.94 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.04 (s, 2H), 3.75 (s, 3H), 2.33 (s, 6H).
13C NMR (101 MHz; CDCl3)
2b: δ 167.7, 156.9, 134.4, 132.09, 131.91, 127.3, 126.8, 123.8, 59.8, 16.4
IR (υ, cm-1):
2948, 1720, 1604, 1486 1420, 1387, 1280, 1225, 1192, 1163, 1111, 1086, 1010, 953, 889, 866, 853, 791, 749, 716, 648, 605.
HRMS (EI+):
Calc. for C17H15NO3 [M]+: 281.1052; Found: 281.1059

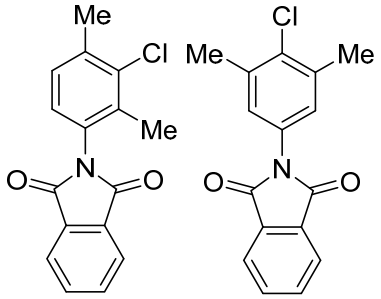
Amination of 2,6-dimethylfluorobenzene (3)



3a **3b**

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethylfluorobenzene (**3**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer determined by analogy to compounds **1b** and **2b**.
Data for **3a**, **3b**
GC Yield (Selectivity; **3a**:**3b**): 50% (1:15)
Isolated Yield (Selectivity; **3a**:**3b**): 124 mg white solid, 46% (0:1)
TLC: Rf 0.42 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
3b: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.05 (d, *J* = 6.4 Hz, 2H), 2.31 (d, *J* = 2.2 Hz, 6H).
13C NMR (101 MHz; CDCl3)
3b: δ 167.6, 134.5, 131.9, 128.3, 127.44 (d, *J* = 5.6 Hz), 125.7 (d, *J* = 19.4 Hz), 123.9, 14.9 (d, *J* = 4.2 Hz).
19F NMR (376 MHz; CDCl3)
3b: δ -120.2
IR (υ, cm-1):
2956, 1769, 1730, 1593, 1470, 1437, 1416, 1376, 1279, 1197, 1110, 1086, 1035, 956, 892, 856, 788, 749, 711, 669
HRMS (EI+):
Calc. for C16H12FNO2 [M]+: 269.0852 ; Found: 269.0850

Amination of 2,6-dimethylchlorobenzene (4)



4a **4b**

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethylchlorobenzene (**4**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer determined by analogy to compounds **1b** and **2b**.

Data for **4a**, **4b**

GC Yield (Selectivity; **4a**:**4b**): 66% (1:16)

Isolated Yield (Selectivity; **4a**:**4b**): 197 mg off-white solid, 69% (1:19)

TLC: Rf 0.49 (20% EtOAc in hexanes)

1H NMR (400 MHz, CDCl3)

4a: Not detected

4b: δ 7.94-7.92 (m, 2H), 7.79-7.77 (m, 2H), 7.15 (s, 2H), 2.42 (s, 6H).

13C NMR (101 MHz; CDCl3)

4a: Not detected

4b: δ 167.3, 137.4, 134.7, 134.5, 131.8, 129.3, 126.6, 123.8, 21.0

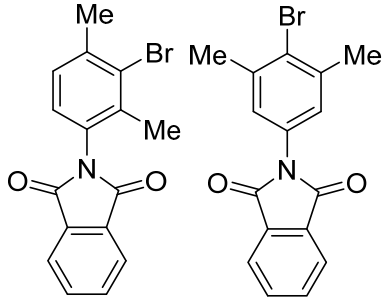
IR (υ, cm-1):

2957, 1768, 1721, 1647, 1596, 1472, 1438, 1420, 1379, 1323, 1279, 1197, 1110, 1085, 1065, 1041, 956, 890, 856, 789, 764, 749, 711, 670, 648.

HRMS (EI+):

Calc. for C16H12ClNO2 [M]+: 285.0557; Found: 285.0559

Amination of 2,6-dimethylbromobenzene (5)



5a **5b**

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethylbromobenzene (**5**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer determined by analogy to compounds **1b** and **2b**.

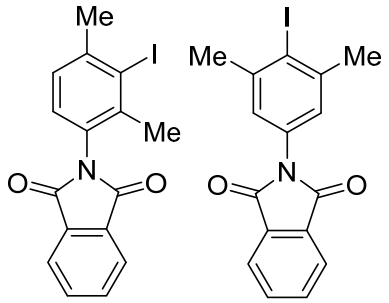
Data for **5a**, **5b**

GC Yield (Selectivity; **5a**:**5b**): 46% (1:12)

Isolated Yield (Selectivity; **5a**:**5b**): 172 mg pale yellow solid, 52% (1:24)

TLC: Rf 0.44 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
5a: Not detected
5b: δ 7.94 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.15 (s, 2H), 2.46 (s, 6H).
13C NMR (101 MHz; CDCl3)
5a: Not detected
5b: δ 167.3, 139.5, 134.6, 131.8, 130.0, 127.6, 126.3, 123.9, 24.2
IR (υ, cm-1):
2955, 2361, 1770, 1751, 1717, 1590, 1468, 1436, 1414, 1374, 1278, 1197, 1169, 1110, 1099, 1086,1030, 955, 893, 857, 787, 750, 711, 668.
HRMS (EI+):
Calc. for C16H12BrNO2 [M]+: 329.0051; Found: 329.0053

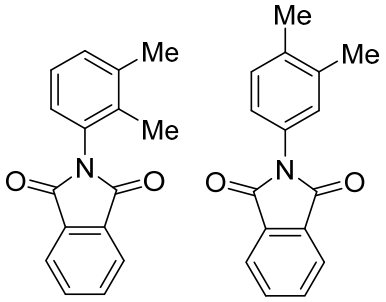
Amination of 2,6-dimethyliodobenzene (6)



6a **6b**

General procedure **(III)(C)** was followed with 5 mL of 2,6-dimethyliodobenzene (**6**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer determined by analogy to compounds **1b** and **2b**.
Data for **6a**, **6b**
GC Yield (Selectivity; **6a**:**6b**): 51% (1:12)
Isolated Yield (Selectivity; **6a**:**6b**): 245 mg pale yellow solid, 65% (1:19)
TLC: Rf 0.44 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
6a: Not detected
6b: δ 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.14 (s, 2H), 2.53 (s, 6H).
13C NMR (101 MHz; CDCl3)
6a: Not detected
6b: δ 167.2, 143.2, 134.5, 131.7, 131.1, 124.9, 123.8, 108.1, 29.9
IR (υ, cm-1):
3059, 2948, 1769, 1719, 1581, 1485, 1465, 1409, 1375, 1277, 1193, 1110, 1085, 1007, 950, 887, 857, 791, 735, 718, 663, 648.
HRMS (EI+):
Calc. for C16H12INO2 [M]+: 376.9913; Found: 376.9911

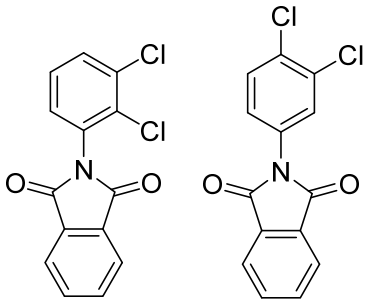
Amination of 1,2-dimethylbenzene (7)



7a **7b**

General procedure **(III)(C)** was followed with 5 mL of 1,2,dimethylbenzene (**7**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **7b** was confirmed by the synthesis of authentic product.
Data for **7a**, **7b**
GC Yield (Selectivity; **7a**:**7b**): 83% (1:40)
Isolated Yield (Selectivity; **7a**:**7b**): 181 mg white solid, 72% (1:87)
TLC: Rf 0.40 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
7a: Not detected
7b: δ 7.94 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.28 (s,), 7.19-7.13 (m, 2H), 2.32 (s, 3H), 2.31 (s, 3H).
13C NMR (101 MHz; CDCl3)
7a: Not detected
7b: δ 167.6, 137.7, 137.1, 134.4, 131.9, 130.4, 129.2, 127.8, 124.2, 123.7, 20.0, 19.7
IR (υ, cm-1):
3464, 3065, 2977, 1770, 1719, 1607, 1583, 1505, 1467, 1414, 1379, 1274, 1261, 1239, 1209, 1180, 1131, 1109, 1085, 1028, 1007, 940, 890, 873, 814, 791, 749, 715, 691.
HRMS (EI+):
Calc. for C16H13NO2 [M]+: 251.0946; Found: 251.0947

Amination of 1,2-dichlorobenzene (8)

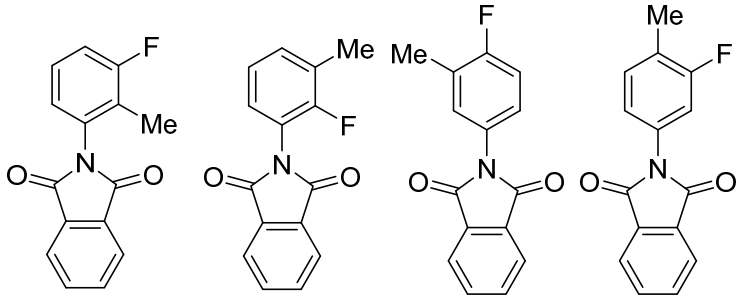


8a **8b**

General procedure **(III)(C)** was followed with 5 mL of 1,2,dichlorobenzene (**8**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **8b** was confirmed by the synthesis of authentic product.
Data for **8a**, **8b**
GC Yield (Selectivity; **8a**:**8b**): 46% (1:7)

Isolated Yield (Selectivity; **8a**:**8b**): 166 mg white solid, 57% (0:1)
TLC: Rf 0.34 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
8a: Not detected
8b: δ 7.97 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.64 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.37 (dd, *J* = 8.6, 2.4 Hz, 1H).
13C NMR (101 MHz; CDCl3)
8a: Not detected
8b: δ 166.8, 134.9, 133.2, 132.3, 131.6, 131.2, 130.8, 128.3, 125.7, 124.1
IR (υ, cm-1):
1766, 1715, 1478, 1465, 1382, 1257, 1221, 1202, 1150, 1134, 1115, 1096, 1083, 1031, 886, 860, 821, 785, 710, 688, 680.
HRMS (EI+):
Calc. for C14H7Cl2NO2 [M]+: 290.9854; Found: 290.9857

Amination of 2-fluorotoluene (9)

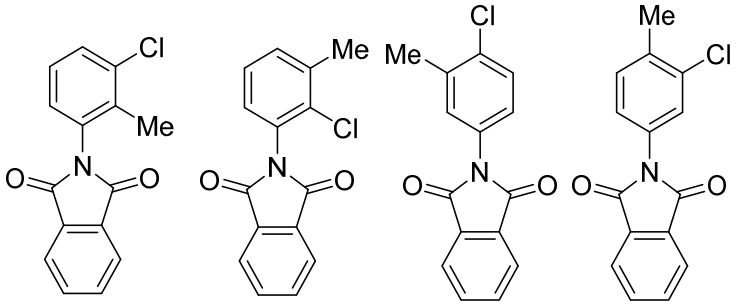


9a **9b** **9c** **9d**

General procedure **(III)(C)** was followed with 5 mL of 2-fluorotoluene (**9**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **9c** and **9d** were confirmed by the synthesis of authentic products.
Data for **9a-d**
GC Yield (Selectivity; **9a**:**9b**:**9c**:**9d**): 59% (1:1:37:20)
Isolated Yield (Selectivity; **9a**:**9b**:**9c**:**9d**): 191 mg white solid, 75% (1:1:50:29)
TLC: Rf 0.33 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
9c: δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.29-7.22 (m, 2H), 7.15 (t, *J* = 8.9 Hz, 1H), 2.35 (d, *J* = 1.9 Hz, 3H).
9d: δ 7.95 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.26-7.20 (m, 2H), 7.17-7.11 (m, 1H), 2.33 (s, 3H) 13C NMR (101 MHz; CDCl3)
9c: δ 167.4, 160.7 (d, *J* = 242 Hz), 134.5, 131.7, 129.84 (d, *J* = 6 Hz), 127.21, 127.18, 126.07 (d, *J* = 19 Hz), 125.88 (d, *J* = 8 Hz), 123.8, 115.8 (d, *J* = 30 Hz), 14.72 (d, *J* = 4 Hz).
9d: δ 167.1, 161.0 (d, *J* = 242 Hz), 134.6, 131.63 (d, *J* = 6 Hz), 130.45 (d, *J* = 10 Hz), 125.08 (d, *J*= 17 Hz), 123.9, 121.97, 121.94, 113.6 (d, *J* = 30 Hz) 14.45 (d, *J* = 3 Hz).
19F NMR (376 MHz; CDCl3)
9c: δ -116.3
9d: δ -114.15, -114.17, -114.20
IR (υ, cm-1):

1772, 1719, 1588, 1503, 1466, 1419, 1380, 1287, 1247, 1180, 1106, 1085, 943, 889, 872, 822, 792, 759, 714, 604, 579.
HRMS (EI+):
Calc. for C15H10FNO2 [M]+: 255.0696; Found: 255.0697

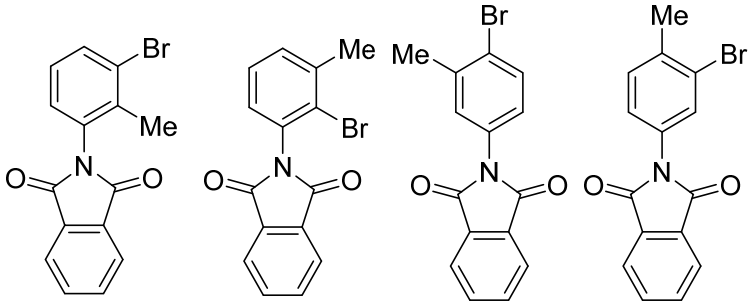
Amination of 2-chlorotoluene (10)



10a **10b** **10c** **10d**

General procedure **(III)(C)** was followed with 5 mL of 2-chlorotoluene (**10**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **10c** and **10d** were confirmed by the synthesis of authentic products.
Data for **10a-d**
GC Yield (Selectivity; **10a**:**10b**:**10c**:**10d**): 71% (1:1:16:16)
Isolated Yield (Selectivity; **10a**:**10b**:**10c**:**10d**): 182 mg white solid, 67% (1:1:19:19)
TLC: Rf 0.34 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
10c: δ 7.93 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* =
2.4 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.5 Hz, 1H), 2.42 (s, 3H).
10d: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.26 (dt, *J* = 5.6, 2.6 Hz, 1H), 2.42 (s, 3H).
13C NMR (101 MHz; CDCl3)
10c: δ 167.1, 137.2, 134.64, 134.58, 134.2, 131.69, 131.2, 130.3, 129.7, 128.9, 125.3, 123.86, 20.3
10d: δ 167.1, 136.3, 134.64, 134.58, 134.2, 131.7, 131.2, 130.3, 127.1, 124.8, 123.9, 123.86,19.9
IR (υ, cm-1):
3026, 1715, 1499, 1483, 1465, 1391, 1274, 1261, 1232, 1205, 1098, 1083, 1050, 887, 862, 806, 764, 750, 709, 703, 682.
HRMS (EI+):
Calc. for C15H10ClNO2 [M]+: 271.0407 ; Found: 271.0405

Amination of 2-bromotoluene (11)



11a **11b** **11c** **11d**

General procedure **(III)(C)** was followed with 5 mL of 2-bromotoluene (**11**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **11c** and **11d** were confirmed by the synthesis of authentic products.

Data for **11a-d**

GC Yield (Selectivity; **11a**:**11b**:**11c**:**11d**):79% (0:0:1:1)

Isolated Yield (Selectivity; **11a**:**11b**:**11c**:**11d**): 269 mg off-white solid, 85% (0:0:1:2)

TLC: Rf 0.32 (20% EtOAc in hexanes)

1H NMR (400 MHz, CDCl3)

11c: δ 7.92 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* =

2.2 Hz, 1H), 7.13 (dd, *J* = 8.5, 2.1 Hz, 1H), 2.43 (s, 3H).

11d: δ 7.94 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.63 (d, *J* = 2.1 Hz, 1H), 7.36-7.34

(m, 1H), 7.29 (dd, *J* = 8.2, 2.0 Hz, 1H), 2.43 (s, 3H).

13C NMR (101 MHz; CDCl3)

11c: δ 167.1, 139.0, 134.6, 133.0, 131.6, 130.8, 128.7, 125.4, 124.7, 123.8, 23.2

11d: δ 167.0, 138.0, 134.6, 131.64, 131.0, 130.3, 125.4, 124.7, 124.0 22.8, 20.9

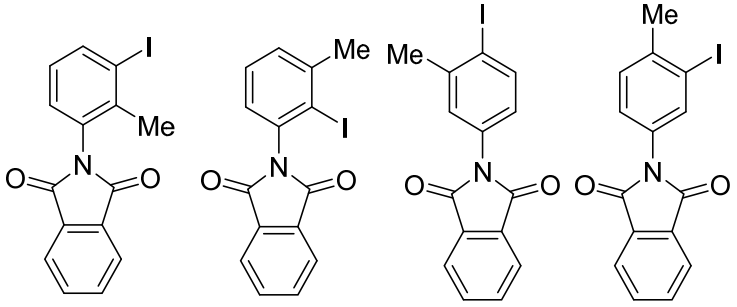
IR (υ, cm-1):

2922, 1768, 1716, 1603, 1488, 1466, 1407, 1381, 1272, 1205, 1099, 1084, 1028, 888, 817, 749, 711.

HRMS (EI+):

Calc. for C15H10BrNO2 [M]+: 314.9895; Found: 314.9894, 316.9868

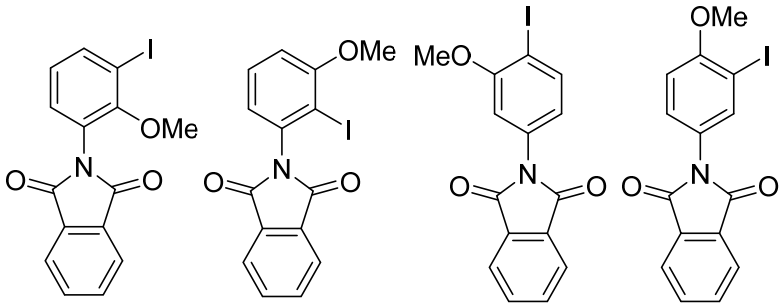
Amination of 2-iodotoluene (12)



12a **12b** **12c** **12d**

General procedure **(III)(C)** was followed with 5 mL of 2-iodotoluene (**12**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **12c** and **12d** were confirmed by the synthesis of authentic products.
Data for **12a-d**
GC Yield (Selectivity; **12a**:**12b**:**12c**:**12d**): 46% (0:0:1:1)
Isolated Yield (Selectivity; **12a**:**12b**:**12c**:**12d**): 185 mg pale yellow solid, 51% (0:0:1:1)
Single isomer could be recrystallized from MeOH/hexanes
TLC: Rf 0.34 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
12c: δ 7.91-7.88 (m, 3H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.32 (d, *J* = 2.3 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.4 Hz,
1H), 2.45 (s, 3H)
12d: δ 7.94 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.89 (d, *J* = 1.6 Hz, 1H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.35 (t, *J* =
1.4 Hz, 2H), 2.48 (s, 3H)
13C NMR (101 MHz; CDCl3)
12c: δ 166.9, 142.5, 139.5, 134.5, 131.6, 127.5, 125.4, 123.77, 123.74, 100.4, 28.3
12d: δ 167.1, 141.7, 136.7, 134.6, 131.7, 130.1, 129.8, 126.4, 123.9, 100.5, 27.9
IR (υ, cm-1):
1770, 1724, 1595, 1564, 1491, 1474, 1465, 1404, 1382, 1275, 1261, 1217, 1102, 1083, 889, 867, 818, 787, 764, 749, 716, 665, 645.
HRMS (EI+):
Calc. for C15H10INO2 [M]+: 362.9756; Found: 362.9763

Amination of 2-iodoanisole (13)

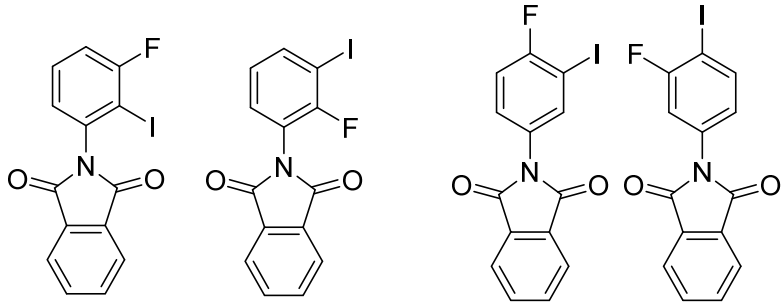


13a **13b** **13c** **13d**

General procedure **(III)(C)** was followed with 5 mL of 2-iodoanisole (**13**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **13d** was confirmed by the synthesis of authentic product.
Data for **13a-d**
GC Yield (Selectivity; **13a**:**13b**:**13d**:**13c**): 72% (1:1:5:0)
Isolated Yield (Selectivity; **13a**:**13b**:**13d**:**13c**): 315 mg off-white solid, 83% (1:1:5:0)
Single isomer could be recrystallized from MeOH/hexanes
TLC: Rf 0.30 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)

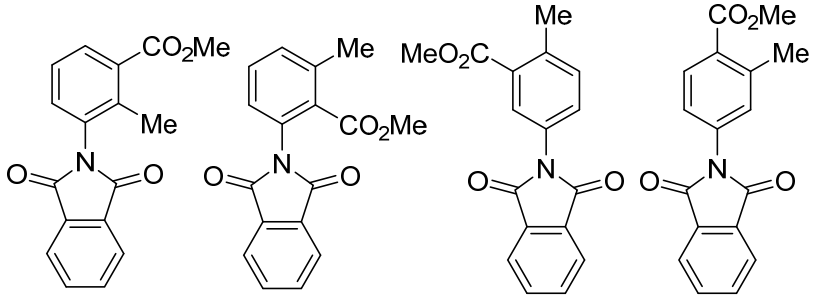
13d: δ 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.81-7.78 (m, 2H), 7.40 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 3.93 (s, 3H).
13C NMR (101 MHz; CDCl3)
13d: δ 167.4, 158.1, 137.6, 134.6, 131.8, 128.0, 125.5, 123.9, 110.7, 85.8,56.8
IR (υ, cm-1):
2956, 1770, 1600, 1491, 1460, 1407, 1275, 1261, 1219, 1111, 1083, 889, 867, 787, 749, 716, 645
HRMS (EI+):
Calc. for C15H10INO3 [M]+: 378.9705; Found: 378.9711

Amination of 2-fluoroiodobenzene (14)



General procedure **(III)(C)** was followed with 5 mL of 2-fluoroiodobenzene (**14**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structure of the major isomer **14d** was determined by analogy to compound **13d**.
Data for **14a-d**
GC Yield (Selectivity; **14a**:**14b**:**14c**:**14d**): 45% (0:0:1:7)
Isolated Yield (Selectivity; **14a**:**14b**:**14c**:**14d**): 209 mg pale yellow solid, 57% (0:0:1:7)
TLC: Rf 0.35 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
14d: δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.86 (dd, *J* = 5.4, 2.5 Hz, 1H), 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.43 (ddd, *J* = 8.8, 4.4, 2.5 Hz, 1H), 7.19 (dd, *J* = 8.8, 7.4 Hz, 1H)
13C NMR (101 MHz; CDCl3)
14d: δ 167.0, 137.39, 137.37, 134.8, 131.6, 128.41 (d, *J* = 8 Hz), 124.1, 115.9 (d, *J* = 20.2 Hz).
19F NMR (376 MHz; CDCl3)
IR (υ, cm-1):
2925, 1771, 1717, 1590, 1489, 1466, 1423, 1408, 1377, 1276, 1260, 1236, 1192, 1099, 1085, 1007, 951, 886, 869, 906, 784, 764, 749, 713, 662, 647.
HRMS (EI+):
Calc. for C14H7FINO2[M]+: 366.9505; Found: 366.9511

Amination of methyl-2-methylbenzoate (15)



15a **15b** **15c** **15d**

General procedure **(III)(C)** was followed with 5 mL of methyl-2-methylbenzoate (**15**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **15c** and **15d** were confirmed by the synthesis of authentic products.

Data for **15a-d**

GC Yield (Selectivity; **15a**:**15b**:**15c**:**15d**): 61% (0:1:4:1)

Isolated Yield (Selectivity; **15a**:**15b**:**15c**:**15d**): 177 mg white solid, 60% (1:1:50:15)

Single isomer could be recrystallized from MeOH/hexanes

TLC: Rf 0.34 (20% EtOAc in hexanes)

1H NMR (400 MHz, CDCl3)

15c: δ 8.03 (d, *J* = 2.3 Hz, 1H), 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.49 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 3.89 (s, 3H), 2.66 (s, 3H).

15d: δ 8.06 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.97 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.39-7.37 (m, 2H), 3.92 (s, 3H), 2.67 (s, 3H)

13C NMR (101 MHz; CDCl3)

15c: δ 167.24, 167.04, 140.7, 134.6, 132.6, 131.8, 130.2, 130.0, 129.5, 128.9, 123.9, 52.1, 21.7

15d: δ 167.4, 167.0, 141.8, 134.88, 134.75, 131.77, 131.69, 129.5, 129.2, 129.0, 124.0, 123.6, 52.1, 22.1

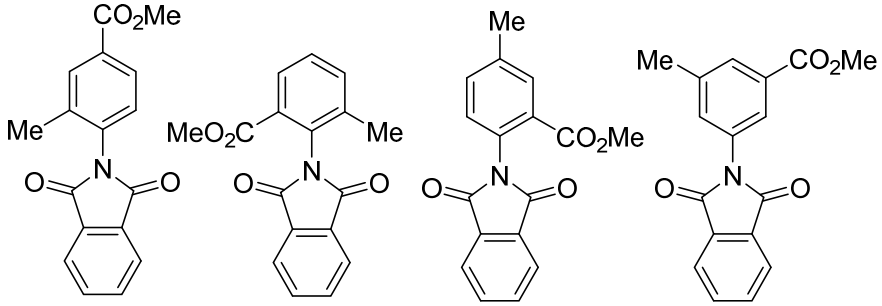
IR (υ, cm-1):

2948, 1774, 1724, 1607, 1575, 1506, 1466, 1431, 1387, 1303, 1289, 1258, 1216, 1186, 1160, 1122, 1105, 1081, 980, 912, 880, 827, 778, 713, 677, 605.

HRMS (EI+):

Calc. for C17H13NO4 [M]+: 298.0845; Found: 298.0844

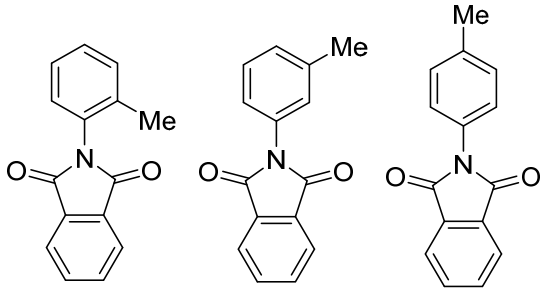
Amination of methyl-3-methylbenzoate (16)



16a **16b** **16c** **16d**

General procedure **(III)(C)** was followed with 5 mL of methyl-3-methylbenzoate (**16**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The identity of the major isomer **16d** was determined by splitting pattern on 1H NMR.
Data for **16a-d**
GC Yield (Selectivity; **16a**:**16b**:**16c**:**16d**): 50% (1:1:2:8)
Isolated Yield (Selectivity; **16a**:**16b**:**16c**:**16d**): 153 mg white solid, 52% (1:1:4:17)
Single isomer could be recrystallized from MeOH/hexanes
TLC: Rf 0.28 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
16d: δ 7.97 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.92 (s, 2H), 7.81 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.45 (s, 1H), 3.92 (s, 3H), 2.47 (d, *J* = 0.5 Hz, 3H).
13C NMR (101 MHz; CDCl3)
16d: δ 167.2, 166.5, 139.6, 134.7, 131.88, 131.79, 131.77, 131.3, 130.1, 125.2, 124.0, 52.4, 21.5
IR (υ, cm-1):
3206, 2952, 1773, 1719, 1604, 1466, 1435, 1377, 1294, 1224, 1107, 1084, 1053, 888, 867, 792, 769, 715, 676, 647
HRMS (EI+):
Calc. for C17H13NO4 [M]+: 298.0845; Found: 298.0851

Amination of toluene (17)

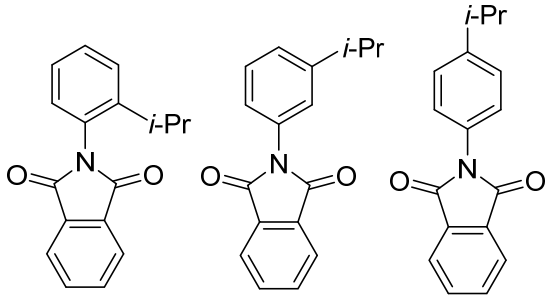


17a **17b** **17c**

General procedure **(III)(C)** was followed with 5 mL of toluene (**17**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **17b** and **17c** were confirmed by the synthesis of authentic products.
Data for **17a-c**
GC Yield (Selectivity; **17a**:**17b**:**17c**): 80% (1:9:9)
Isolated Yield (Selectivity; **17a**:**17b**:**17c**): 185 mg white solid, 78% (1:10:9)
TLC: Rf 0.41 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
17b: δ 7.94 (dd, *J* = 3, 5.2 Hz, 2 H), 7.78 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.26 (s, 1 H), 7.24 (t, *J* = 6.8 Hz, 2 H), 2.43 (s, 3 H).
17c: δ 7.94 (dd, *J* = 3, 5.2 Hz, 2 H), 7.78 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.26 (s, 4 H), 2.36 (s, 3 H).
13C NMR (101 MHz; CDCl3)
17b: δ 167.2, 138.9, 134.2, 131.8, 131.5, 128.9, 128.8, 127.1, 123.7, 123.6, 21.4.
17c: δ 167.3, 138.0, 134.2, 131.8, 129.6, 128.9, 126.3, 123.7, 21.2.
IR (υ, cm-1):
2923, 1770, 1715, 1606, 1587, 1517, 1492, 1465, 1376, 1284, 1211, 1110, 1080, 904, 883, 817, 784, 750, 713, 697, 687, 630

HRMS (EI+):
Calc. for C15H11NO2 [M]+: 237.0790; Found: 237.0795

Amination of isopropylbenzene (18)



18a **18b** **18c**

General procedure **(III)(C)** was followed with 5 mL of isopropylbenzene (**18**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **18b** and **18c** were confirmed by the synthesis of authentic products.

Data for **18a-c**

GC Yield (Selectivity; **18a**:**18b**:**18c**): 77% (1:6:5)

Isolated Yield (Selectivity; **18a**:**18b**:**18c**): 207 mg white solid, 78% (1:13:13)

Single isomer could be recrystallized from MeOH/hexanes

TLC: Rf 0.44 (20% EtOAc in hexanes)

1H NMR (400 MHz, CDCl3)

18b: δ 7.96 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.29-7.27 (m, 2H), 7.24 (ddd, *J* = 7.8, 2.0, 1.2 Hz, 1H), 2.98 (dt, *J* = 13.9, 6.9 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H).

18c: δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.36 (d, *J* = 3.2 Hz, 4H), 2.98 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H).

13C NMR (101 MHz; CDCl3)

18b: δ 167.4, 150.0, 134.3, 131.8, 131.5, 129.0, 126.4, 124.9, 124.0, 123.7, 71.8, 34.0, 23.9

18c: δ 167.6, 149.0, 134.5, 132.0, 129.3, 127.4, 126.6, 123.8, 34.1, 24.1

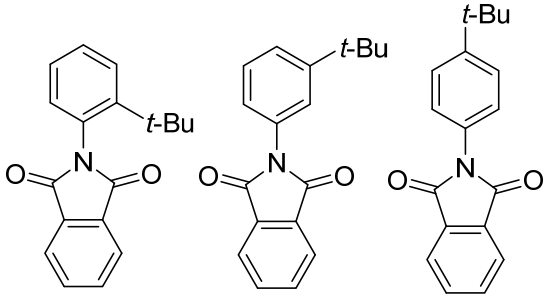
IR (υ, cm-1):

3055, 2964, 2929, 2870, 1766, 1740, 1705, 1606, 1589, 1516, 1490, 1466, 1448, 1379, 1265, 1231, 1196, 1114, 1082, 884, 831, 790, 737, 716, 631.

HRMS (EI+):

Calc. for C17H15NO2 [M]+: 265.1103; Found: 265.1108

Amination of *tert*-butylbenzene (19)



19a **19b** **19c**

General procedure **(III)(C)** was followed with 5 mL of *tert*-butylbenzene (**19**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **19b** and **19c** were confirmed by the synthesis of authentic products.

Data for **19a-c**

GC Yield (Selectivity; **19a**:**19b**:**19c**): 118% (1:28:22)

Isolated Yield (Selectivity; **19a**:**19b**:**19c**): 251 mg white solid, 90% (1:40:30)

TLC: Rf 0.45 (20% EtOAc in hexanes)

1H NMR (400 MHz, CDCl3)

19b:

δ 7.94 (dd, *J* = 3, 5.2 Hz, 2 H), 7.78 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.26 (s, 1 H), 7.24 (t, *J* = 6.8 Hz, 2 H), 2.43 (s, 3 H).

19c:

δ 7.94 (dd, *J* = 3, 5.2 Hz, 2 H), 7.78 (dd, *J* = 3.2, 5.6 Hz, 2 H), 7.26 (s, 4 H), 2.36 (s, 3 H).

13C NMR (101 MHz; CDCl3)

19b:

δ 167.2, 138.9, 134.2, 131.8, 131.5, 128.9, 128.8, 127.1, 123.7, 123.6, 21.4.

19c:

δ 167.3, 138.0, 134.2, 131.8, 129.6, 128.9, 126.3, 123.7, 21.2.

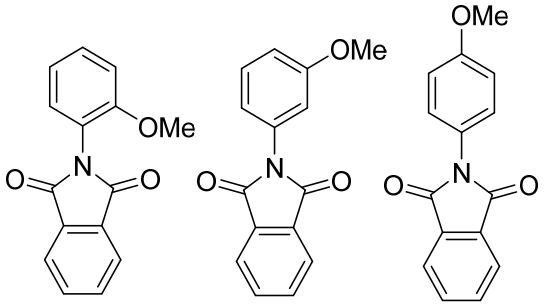
IR (υ, cm-1):

3479, 3061, 2963, 2869, 1782, 1724, 1605, 1517, 1492, 1467, 1431, 1379, 1287, 1269, 1216, 1114, 1099, 1082, 1021, 885, 874, 830, 788, 716, 699, 631, 557, 530.

HRMS (EI+):

Calc. for C18H17NO2 [M]+: 279.1259; Found: 279.1260

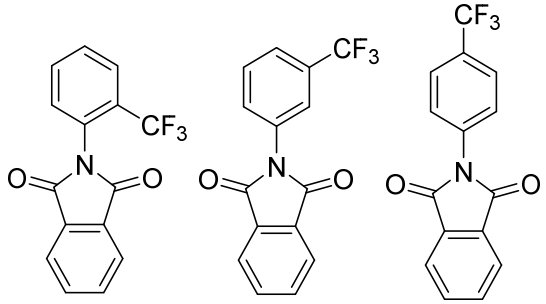
Amination of methoxybenzene (20)



20a **20b** **20c**

General procedure **(III)(C)** was followed with 5 mL of methoxybenzene (**20**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **20b** and **20c** were confirmed by the synthesis of authentic products.
Data for **20a-c**
GC Yield (Selectivity; **20a**:**20b**:**20c**): 53% (1:1:5)
Isolated Yield (Selectivity; **20a**:**20b**:**20c**): 154 mg off-white solid, 61% (1:1:5)
Single isomer could be recrystallized from MeOH/hexanes
TLC: Rf 0.25 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
20b: δ 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.04-6.94 (m,
3H), 3.84 (s, 3H)
20c: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.36-7.32 (m, 2H), 7.04-7.00 (m, 2H), 3.85 (s, 3H).
13C NMR (101 MHz; CDCl3)
20b: δ 167.3, 160.2, 134.5, 132.8, 131.9, 129.9, 123.9, 119.0, 114.2, 112.5
20c: δ 167.7, 159.4, 134.4, 132.0, 128.1, 124.4, 123.8, 114.6, 55.7
IR (υ, cm-1):
3204, 3060, 2838, 1773, 1745, 1703, 1606, 1513, 1466, 1384, 1304, 1276, 1257, 1214, 1113, 1082, 1054, 1028, 883, 886, 827, 750, 715, 782, 715.
HRMS (EI+):
Calc. for C15H11NO3 [M]+: 253.0739; Found: 253.0745

Amination of trifluoromethylbenzene (21)

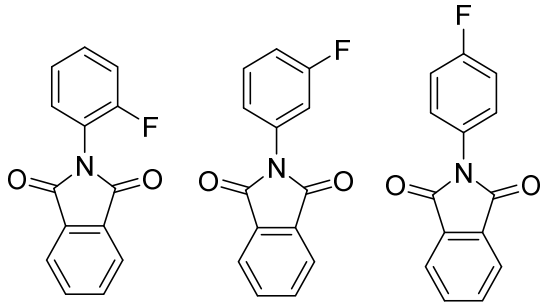


21a **21b** **21c**

General procedure **(III)(C)** was followed with 5 mL of trifluoromethylbenzene (**21**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **21b** and **21c** were confirmed by the synthesis of authentic products.
Data for **21a-c**
GC Yield (Selectivity; **21a**:**21b**:**201c**): 66% (1:16:5)
Isolated Yield (Selectivity; **21a**:**21b**:**21c**): 210 mg off-white solid, 72% (1:30:11)
Single isomer could be recrystallized from MeOH/hexanes
TLC: Rf 0.36 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
21b: δ 7.97 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.83-7.78 (m, 3H), 7.70-7.61 (m, 3H).

21c: δ 7.99 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.84-7.82 (m, 2H), 7.79-7.77 (m, 2H), 7.65 (d, *J* = 8.7 Hz, 2H).
13C NMR (101 MHz; CDCl3)
21b: δ 166.7, 134.7, 132.3, 131.4 (q, *J* = 24.2 Hz), 129.62, 129.57, 124.9 (q, *J* = 272.2 Hz), 124.6 (q, *J* = 4 Hz), 123.9, 122.3 (q, *J* = 4 Hz).
21c: δ 176.9, 134.9, 131.6, 126.6, 126.2 (q, *J* = 3 Hz), 124.2, 77.5, 77.2, 76.8, 20.8 (quartets for the CF2
carbon could not be located).
19F NMR (376 MHz; CDCl3)
21b: δ -61.8
21c: δ -61.8
IR (υ, cm-1):
3479, 3107, 1774, 1752, 1715, 1610, 1494, 1467, 1467, 1455, 1375, 1323, 1314, 1265, 1217, 1178, 1166, 1112, 1069, 1021, 954, 920, 891, 876, 836, 805, 785, 736, 710, 694, 658, 628.
HRMS (EI+):
Calc. for C15H8F3NO2 [M]+: 291.0507; Found: 291.0508

Amination of fluorobenzene (22)

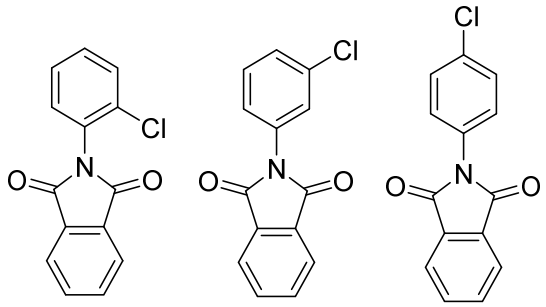


22a **22b** **22c**

General procedure **(III)(C)** was followed with 5 mL of fluorobenzene (**22**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **22b** and **22c** were confirmed by the synthesis of authentic products.
Data for **22a-c**
GC Yield (Selectivity; **22a**:**22b**:**22c**): 48% (1:7:4)
Isolated Yield (Selectivity; **22a**:**22b**:**22c**): 149 mg white solid, 62% (1:10:6)
TLC: Rf 0.40 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
22b: δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.47 (td, *J* = 8.2, 6.2 Hz, 1H), 7.30-7.23 (m, 2H), 7.11 (td, *J* = 8.4, 2.5 Hz, 1H)
22c: δ 7.95 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.80 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.44-7.41 (m, 2H), 7.21-7.17 (m, 2H).
13C NMR (101 MHz; CDCl3)
22b: δ 167.0, 162.7 (d, *J* = 252.5 Hz), 134.4 (d, *J* = 11 Hz), 133.14, 131.7, 130.33 (d, *J* = 9 Hz), 124.0, 122.14, 122.11, 115.1 (d, *J* = 20.2 Hz), 114.1 (d, *J* = 30.3 Hz).
22c: δ 167.3, 162.05 (d, *J* = 252.5 Hz), 134.6, 131.8, 128.50 (d, *J* = 9 Hz), 127.7, 123.9, 116.2 (d, *J* = 30.3 Hz).
19F NMR (376 MHz; CDCl3)

22b: δ -110.33, -110.36, -110.38, -110.40
22c: δ -112.21, -112.22, -112.23, -112.24, -112.26, -112.26, -112.28, -112.24
IR (υ, cm-1):
3065, 2361, 1752, 1714, 1604, 1591, 1516, 1466, 1397, 1381, 1286, 1184, 1111, 1084, 885, 832, 785, 714, 680.
HRMS (EI+):
Calc. for C14H8FNO2 [M]+: 241.0539; Found: 241.0540

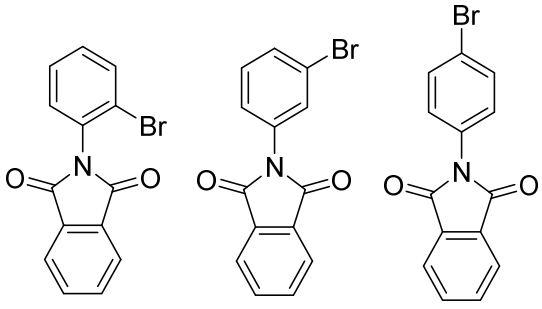
Amination of chlorobenzene (23)



23a **23b** **23c**

General procedure **(III)(C)** was followed with 5 mL of chlorobenzene (**23**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **23b** and **23c** were confirmed by the synthesis of authentic products.
Data for **23a-c**
GC Yield (Selectivity; **23a**:**23b**:**23c**): 65% (1:6:6)
Isolated Yield (Selectivity; **23a**:**23b**:**23c**): 196 mg white solid, 76% (1:6:6)
TLC: Rf 0.41 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
23b: δ 7.95 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.49 (t, *J* = 1.9 Hz, 1H), 7.46-7.42 (m,
1H), 7.38 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.36 (t, *J* = 2.1 Hz, 1H).
23c: δ 7.96-7.94 (m, 2H), 7.81-7.79 (m, 2H), 7.48-7.46 (m, 2H), 7.43-7.40 (m, 2H).
13C NMR (101 MHz; CDCl3)
23b: δ 166.9, 134.72, 134.70, 132.9, 131.6, 130.1, 128.3, 126.8, 124.7, 124.0
23c: δ 167.1, 134.7, 133.9, 131.7, 130.3, 129.4, 127.8, 124.0
IR (υ, cm-1): 3063, 2962, 1743, 1707, 1592, 1497, 1483, 1465, 1432, 1395, 1374, 1274, 1265, 1202, 1171, 1120, 1109, 1083, 1015, 942, 885, 869, 852, 823, 784, 763, 749, 714, 683, 627.
HRMS (EI+):
Calc. for C14H8ClNO2 [M]+: 257.0244; Found: 257.0249

Amination of bromobenzene (24)



24a **24b** **24c**

General procedure **(III)(C)** was followed with 5 mL of bromobenzene (**24**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **24b** and **24c** were confirmed by the synthesis of authentic products.

Data for **24a-c**

GC Yield (Selectivity; **24a**:**24b**:**24c**): 84% (1:5:4)

Isolated Yield (Selectivity; **24a**:**24b**:**24c**): 247 mg off-white solid, 82% (1:5:5)

Single isomer could be recrystallized from MeOH/hexanes

TLC: Rf 0.38 (20% EtOAc in hexanes)

1H NMR (400 MHz, CDCl3)

24b: δ 7.96 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.65-7.61 (m, 2H), 7.37-7.34 (m, 2H).

24c: δ 7.96 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.65-7.61 (m, 2H), 7.37-7.34 (m, 2H).

13C NMR (101 MHz; CDCl3)

24b: δ 166.9, 134.7, 133.1, 131.6, 131.2, 130.4, 129.6, 125.2, 124.0, 122.5

24c: δ 167.0, 134.7, 132.4, 131.7, 130.9, 128.0, 124.0, 121.9

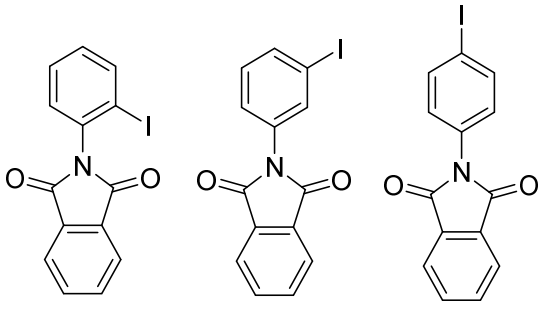
IR (υ, cm-1):

3489, 3064, 2925, 1716, 1587, 1577, 1494, 1478, 1427, 1377, 1286, 1270, 1214, 1172, 1120, 1108, 1080, 1011, 942, 886, 868, 851, 819, 782, 715, 669, 677, 625.

HRMS (EI+):

Calc. for C14H8BrNO2 [M]+: 300.9738; Found: 300.9739, 302.9179

Amination of iodobenzene (25)

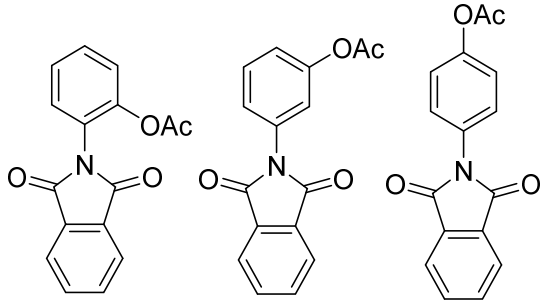


25a **25b** **25c**

General procedure **(III)(C)** was followed with 5 mL of iodobenzene (**25**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The

structures of the major isomers **25b** and **25c** were confirmed by the synthesis of authentic products.
Data for **25a-c**
GC Yield (Selectivity; **25a**:**25b**:**25c**): 64% (1:4:3)
Isolated Yield (Selectivity; **25a**:**25b**:**25c**): 251 mg pale yellow solid, 72% (1:4:3)
TLC: Rf 0.35 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
25b: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.81 (td, *J* = 4.9, 2.8 Hz, 3H), 7.73 (ddd, *J* = 8.0, 1.6, 1.0 Hz, 1H),
7.44 (ddd, *J* = 8.1, 2.0, 1.0 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H).
25c: δ 7.95 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.82 (tt, *J* = 8.8, 2.5 Hz, 4H), 7.24-7.21 (m, 2H).
13C NMR (101 MHz; CDCl3)
25b: δ 166.9, 137.2, 135.3, 134.7, 132.9, 131.6, 130.6, 125.9, 124.0, 93.8
25c: δ 167.0, 138.4, 134.7, 131.7, 128.2, 124.0, 93.4
IR (υ, cm-1):
3061, 1742, 1712, 1585, 1475, 1423, 1395, 1371, 1262, 1204, 1120, 1081, 1061, 1007, 885, 849, 818, 783, 750, 713, 678, 657, 626.
HRMS (EI+):
Calc. for C14H8INO2 [M]+: 348.9600; Found: 348.9601

Amination of acetoxybenzene (26)



26a **26b** **26c**

General procedure **(III)(C)** was followed with 5 mL of acetoxybenzene (**26**). After 33 h, the reaction mixture was purified by silica gel column chromatography to afford yellow solid. The structures of the major isomers **26b** and **26c** were confirmed by the synthesis of authentic products.
Data for **26a-c**
GC Yield (Selectivity; **26a**:**26b**:**26c**): 62% (1:8:9)
Isolated Yield (Selectivity; **26a**:**26b**:**26c**): 163 mg white solid, 58% (1:8:9)
TLC: Rf 0.30 (20% EtOAc in hexanes)
1H NMR (400 MHz, CDCl3)
26b: δ 7.96 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (td, *J* = 5.8, 2.6 Hz, 2H), 7.48 (t, *J* = 8.1 Hz, 2H), 7.24 (t, *J* = 2.1
Hz, 1H), 7.15 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 2.33 (s, 3H)
26c: δ 7.96 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 2.31 (s, 3H).
13C NMR (101 MHz; CDCl3)

26b: δ 169.1, 167.0, 150.9, 148.7, 137.1, 134.7, 132.7, 131.6, 129.7, 124.2, 124.0, 123.6, 121.2, 119.7, 21.3
26c: δ 169.3, 167.2, 150.1, 134.6, 131.8, 129.3, 127.6, 124.0, 122.4, 21.3
IR (υ, cm-1):
2973, 1767, 1724, 1605, 1466, 1387, 1292, 1237, 1101, 1089, 1061, 888, 867, 796, 766, 725, 686, 647
HRMS (EI+):
Calc. for C16H11NO4 [M]+: 281.0688; Found: 281.0694

References for Experimental Section

1. Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Biorg. Med. Chem.* **2004**, *12*, 327.
2. Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A: Chem.* **1996**, *108*, 35.
3. Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.
4. Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9409.

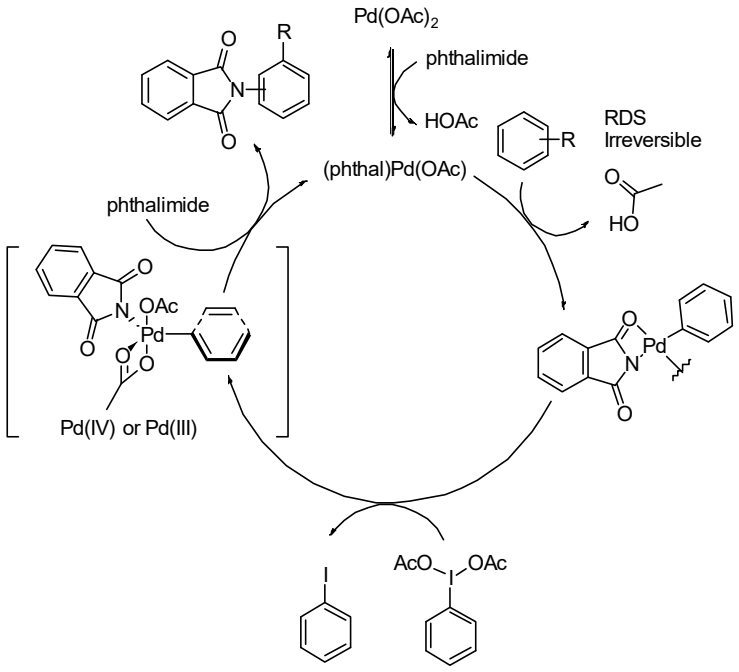
Chapter 3

Studies on the Reductive Elimination of Arylpalladium Imidate Complexes to form C-N Bonds

3.1 Introduction

I previously contributed to the development of an intermolecular imidation of simple arenes that occurs with sterically-controlled regioselectivity catalyzed by palladium acetate.[1] Although the reported reaction is conceptually valuable, the synthetic utility of this arene imidation is limited by competitive acetoxylation of the arene. A mechanistic investigation could reveal the factors that promote this side reaction, but little mechanistic information was collected during the original study due to two factors: 1) the absence of stable organometallic intermediates that could be isolated, 2) the prevalence of competing side reactions, including the acetoxylation[2-3] and homocoupling[4] of arenes. The first factor hindered the examination of elementary steps of the reaction, and the second factor prevented the determination of a rate law for the reaction. However, some valuable information about the reaction was obtained. Based on the large values obtained for independent rate and competitive KIE measurements (3.8 and 4.1 respectively), we concluded that the C-H bond cleavage was irreversible. Based on the analogous acetoxylation reaction, we proposed a mechanism by which the C-N bond is formed by reductive elimination from a high-valent arylpalladium imidate complex (Figure 1).[5-6]

Figure 1. Plausible Mechanism for the C-H Amination of Arenes

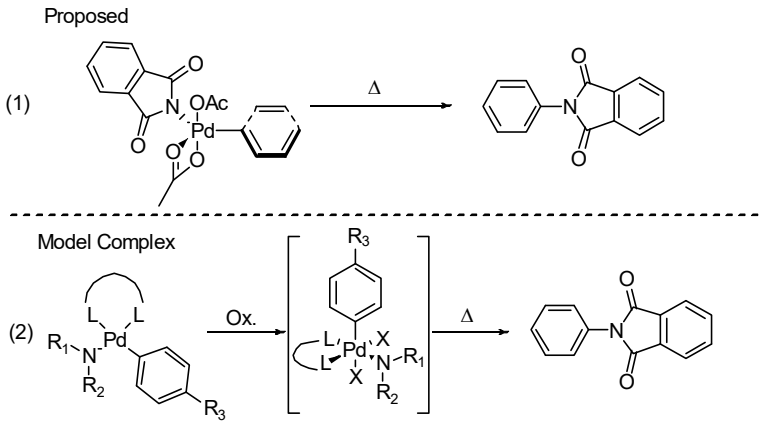


Thermal reductive elimination of arylpalladium(II) imidate complexes to form N-aryl imides is unlikely to occur with the ligandless catalyst system we developed. Although studies have shown that phosphine-ligated arylpalladium amido complexes undergo reductive elimination at elevated temperatures,[7] experiments by Beletskaya et al. demonstrated that arylpalladium (II) imidate complexes do not undergo reductive elimination, even at elevated temperatures.[8] This observation was rationalized by comparing the rates of reductive elimination to the basicity of the

N-bound ligand on the metal center: the more basic the N-bound ligand, the faster the rate of reductive elimination.[8] I hypothesized that if an arylpalladium intermediate were formed in the previously described catalytic system,[1] reductive elimination would occur from either a palladium (III) or (IV) intermediate (Figure 2, 1).[9-11] A competitive C-O reductive elimination from such an intermediate could account for the observed acetoxylation byproducts,[5] although the distinct selectivity for C-N vs C-O bond formation led us to conclude from our initial studies that the arylpalladium species in the process that forms an *N*-aryl imide is distinct from that in the process that forms the acetoxyarene.

In this chapter I report the synthesis of novel arylpalladium imidate complexes and their ability to undergo reductive elimination in the presence of various oxidants (Figure 2, 2).

Figure 2. Proposed Reductive Elimination



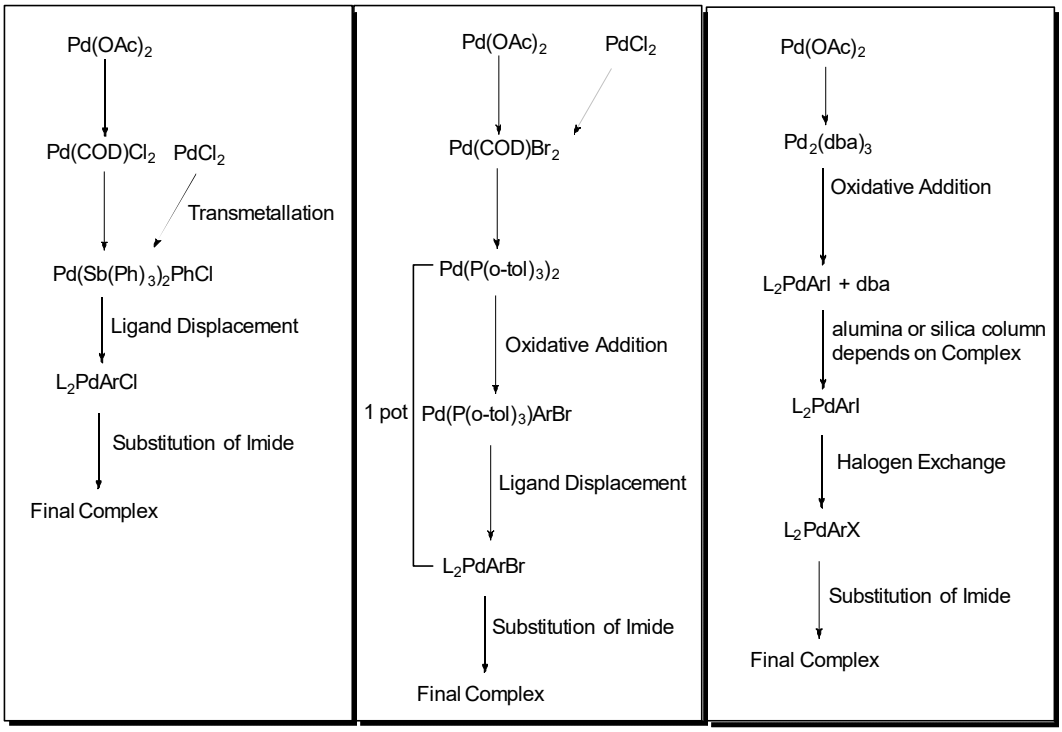
3.2 Results and Discussion

At the time of this work, only a single example of reductive elimination to form an sp^2 C-N bond from an arylpalladium imidate complex had been reported.[12] The model complex described in this system was designed to investigate reductive elimination from a phenylpyridine palladacycle to form a C-Cl bond.[12] In one experiment, an N-aryl imide was formed as byproduct in 8% yield by reductive elimination from a palladium (IV) model complex. Although this result demonstrates that a high-valent arylpalladium imidate complex can undergo reductive elimination to form N-aryl imides, the palladium (IV) complex described is not a close analogy for the intermediate depicted in Figure 2: the denticity and electronic properties of phenylpyridine aryl ligands differ from those of simple aryl ligands. The only two reported arylpalladium imidate complexes that contain simple aryl groups are ligated with phosphines.[8, 13] These complexes are unsuitable precursors for the proposed intermediate complex because phosphine ligands are oxidized in the presence of strong oxidants. It was therefore necessary to identify ligands that could both promote the reductive elimination of an arylpalladium imidate complex and resist oxidation under the conditions required to form a high-valent palladium intermediate. Sanford reported the synthesis and isolation of arylpalladium(II) CF_3 complexes ligated by bipyridine and diamines.[14] The oxidation of these complexes and subsequent reductive

elimination generated trifluoromethyl arenes. Based on this precedent, I hypothesized that an analogous arylpalladium imidate complex ligated with bipyridine or diamines could be oxidized and undergo reductive elimination to form N-aryl imides.

A synthesis of arylpalladium imidate complexes with diamine or bipyridine ligands was unknown, so multiple synthetic strategies were devised to access these complexes (Figure 3). All of these strategies rely upon substitution of the halide in an arylpalladium halide complex with an imide as the final step (Figure 3).

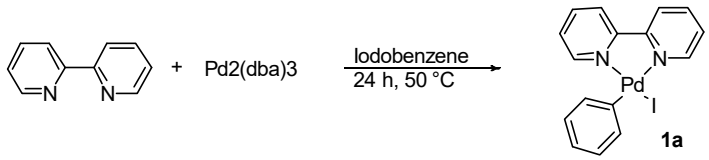
Figure 3. Synthesis of New Palladium Complexes



The oxidative addition of aryl iodides to palladium(0) dibenzylideneacetone ($Pd_2(dba)_3$) in the presence of an L-type ligand is one of the most common ways to generate arylpalladium iodide complexes. An arylpalladium iodide complex ligated by a bipyridine was previously synthesized in this manner.[15-17] However, this procedure generated low yields of the arylpalladium iodide complexes in my hands (37% vs. reported 46%). The low yield was in part due to the variable quality of both commercially available $Pd_2(dba)_3$ and $Pd_2(dba)_3$ synthesized from $Pd(OAc)_2$.[18] Although arylpalladium complexes ligated with diamines can also be generated via the oxidative addition of an aryl iodide to $Pd_2(dba)_3$, the removal of dibenzylideneacetone from the crude reaction mixture is difficult. Arylpalladium halide complexes ligated by diamines are often soluble in ether and co-precipitate with dba upon addition of pentane. If diamine- and bipyridine- ligated arylpalladium iodide complexes could be obtained in high yields, a method to substitute the iodide ligand with imide would still need to be developed. I found that in the presence of triethylamine and phthalimide, arylpalladium iodide complex **1a** did not undergo substitution to form an arylpalladium imidate complex. Similarly,

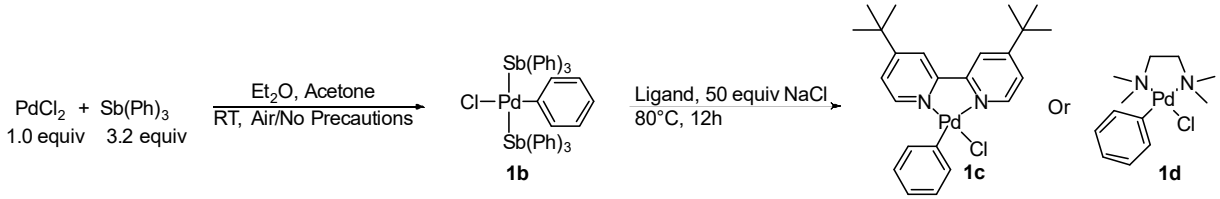
when complex **1a** was heated in THF in the presence of potassium phthalimide, no substitution of the iodide ligand was observed. Although initial efforts to convert arylpalladium iodide complexes into arylpalladium imidate complexes were unsuccessful, a solution to this problem was later developed (Figure 7).

Figure 4. Oxidative Addition of Aryl Iodides to $Pd_2(dba)_3$



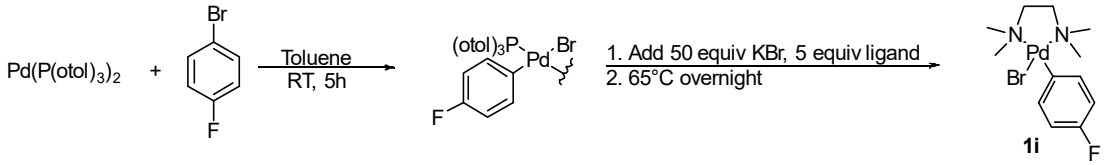
An alternative strategy for the synthesis of the arylpalladium halide complexes involves the transmetalation of an aryl group from triphenyl antimony to palladium (II) dichloride.[19] By following the reported conditions, I obtained the arylpalladium chloride complex **1b** bis-ligated with $Sb(Ph)_3$ in modest yields. By increasing the equivalents of triphenyl antimony in the reaction, I was able to achieve excellent yields of complex **1b**. This modified procedure could be conducted on a gram-scale without rigorous exclusion of air and moisture from the reaction mixture. Substitution of the two triphenyl antimony ligands on complex **1b** with diamines or bipyridine ligands was accomplished. The triphenyl antimony byproducts were easily removed with hexane washes from the concentrated reaction mixtures obtained after ligand exchange reactions. Substitution of the chloride ligands of arylpalladium halide complexes such as **1c** and **1d** with phthalimide and triethylamine was facile. The only drawbacks of this procedure were 1) the scarcity of commercially available triaryl antimony compounds with different aryl groups and 2) the mild toxicity of triphenyl antimony.

Figure 5. Transmetalation Strategy with $Sb(Ph)_3$



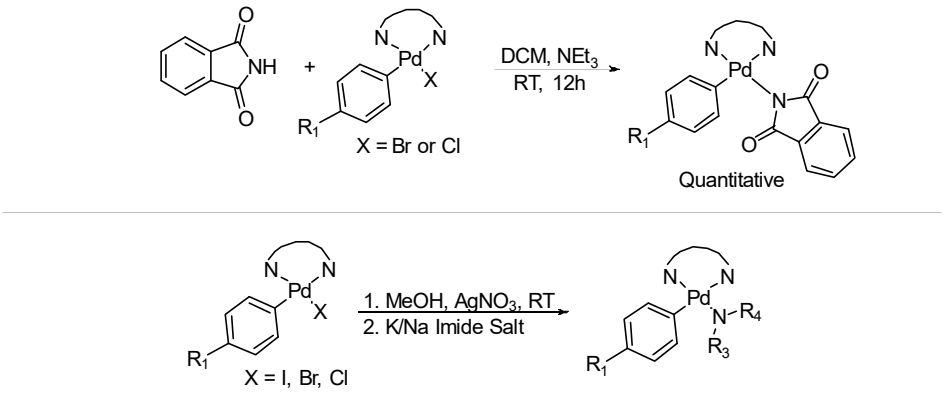
The most versatile and synthetically useful method I devised for the synthesis of arylpalladium halide complexes relied upon the oxidative addition of aryl bromides to Pd(P(*o*-tol)$_3$)$_2$,[20] followed by a ligand exchange reaction with diamine or bipyridine ligands. Pd(P(*o*-tol)$_3$)$_2$ is a stable Pd(0) complex that can be synthesized from simple palladium precursors like $Pd(COD)Br_2$ in high yields. Under the conditions that I developed, the oxidative addition of a range of aryl bromides to Pd(P(*o*-tol)$_3$)$_2$ and the subsequent ligand substitution can be carried out in one pot without solvent exchange or intermediate purification steps. At the end of this reaction, P(*o*-tol)$_3$ is removed with pentane or hexane washes, and the arylpalladium bromide complex is typically obtained in high yields (Figure 6).

Figure 6. Synthetic Strategy with Pd(P(*o*-tol)$_3$)$_2$ as the Palladium (0) Precursor



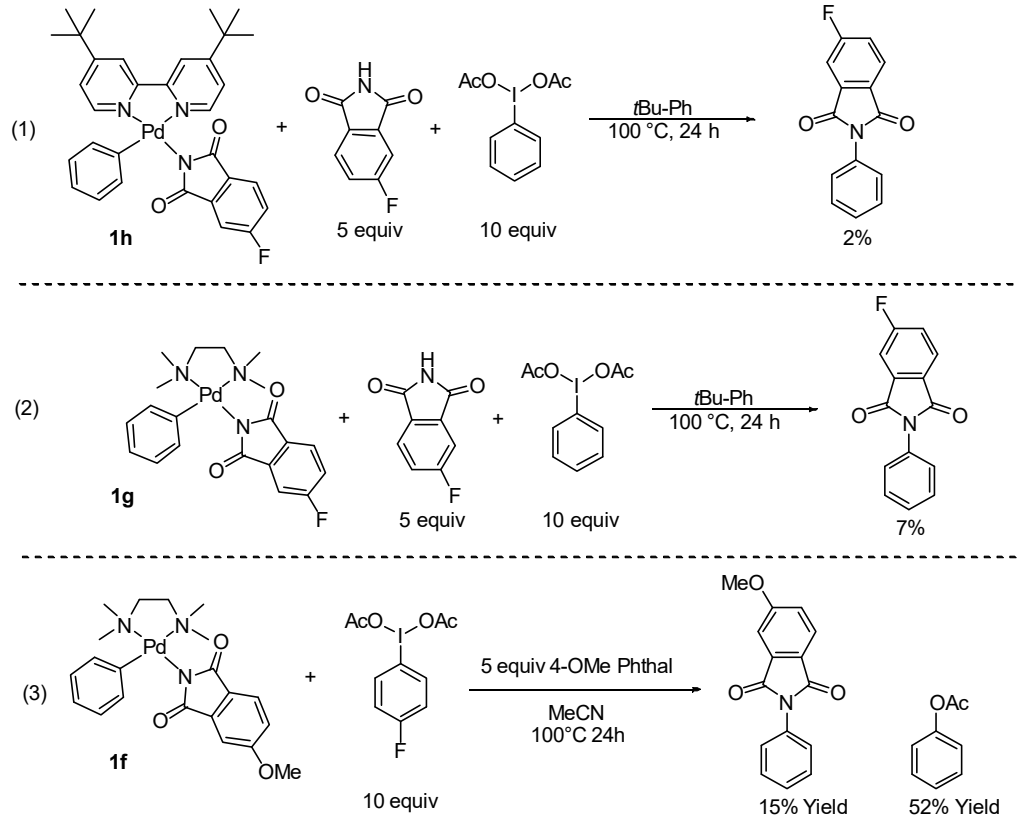
A series of arylpalladium halide complexes were synthesized by the methods described in Figures 4, 5, and 6. I found that the addition of triethylamine and phthalimide to arylpalladium bromide or chloride complexes consistently produced the corresponding arylpalladium imidate complexes in high yields. However, this exchange did not occur when related amides such as saccharin were used in place of phthalimide. This problem was solved by converting arylpalladium halide complexes into arylpalladium nitrate complexes in methanol with silver nitrate. Both the reactants and products of this salt-metathesis reaction were insensitive to moisture and air, and the reaction was conducted with arylpalladium iodides, chlorides, or bromides. The arylpalladium nitrate complexes were converted to arylpalladium imidates upon addition of a sodium or potassium imidate salt. The resulting arylpalladium imidate complexes were purified on basic alumina.

Figure 7. Halide Displacement with Imides and Imide Salts



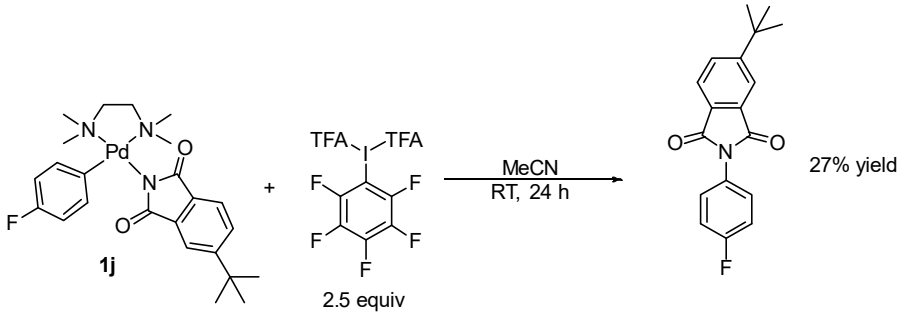
A series of arylpalladium imidate complexes containing chelating ligands, imides, and aryl groups were synthesized. When complex **1h** ligated by 4,4'-Di-tert-butyl-2,2'-bipyridine (Figure 8, 1) was heated in the absence of an oxidant, no N-aryl imide product was observed. However, when the same complex was heated in the presence of an oxidant, trace quantities of *N*-aryl imide were observed (Figure 8, 1).

Figure 8. Oxidation of Arylpalladium Imidate Complexes with $PhI(OAc)_2$



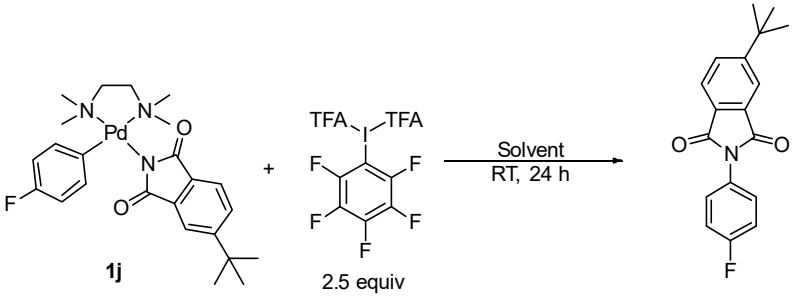
When an arylpalladium imidate complex ligated with tetramethylenediamine (TMEDA) **1g** was subjected to similar oxidative conditions, a 7% yield of *N*-aryl imide was obtained (Figure 8, 2). Higher yields were obtained when the reaction was conducted in acetonitrile with a slightly different arylpalladium imidate complex **1f** (Figure 8, 3). Under the conditions depicted in Figure 8-3, large quantities of phenyl acetate formed. When a complex ligated by p-fluorobenzene and *tert*-butyl phthalimide (**1j**) was treated with the oxidant [bis(trifluoroacetoxy)iodo]pentafluorobenzene (PerFPIFA), higher yields of N-aryl imides were obtained than were obtained under previous conditions (Figure 9). Aryl acetate products were not observed in this reaction (Figure 9). Strikingly, this reaction was extremely rapid even at room temperature.

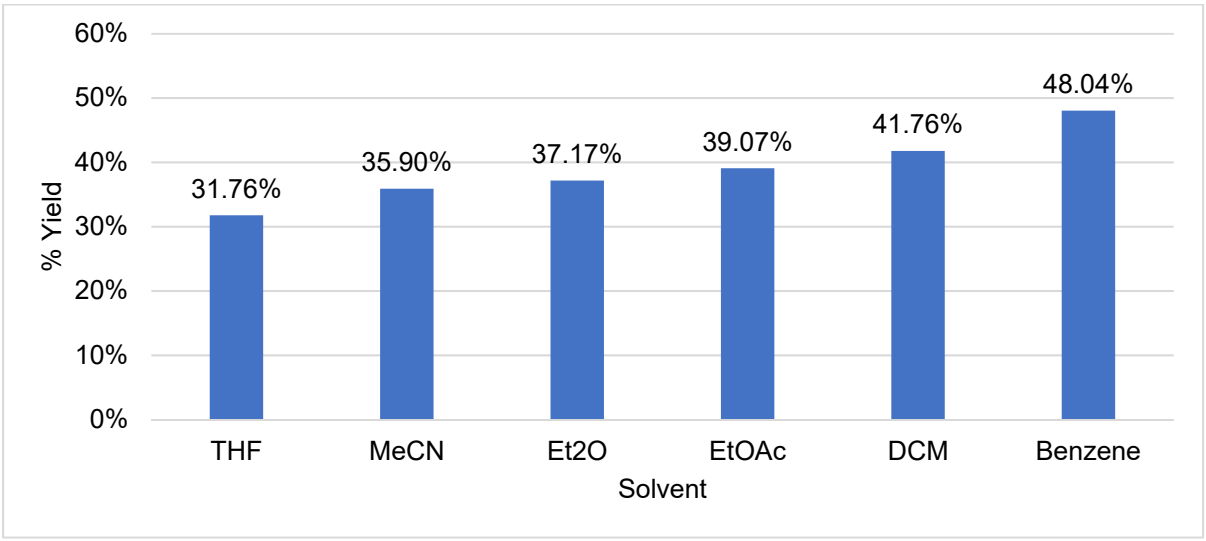
Figure 9. Oxidation of Arylpalladium Imidate Complex with PerFPIFA



A series of reactions were conducted with complex **1j** depicted in Figure 9 with PerFPIFA in different solvents. The highest yields of N-aryl imide products were obtained when the reaction was conducted in benzene (Figure 10).

Figure 10. Effect of Solvent on the Yield of Product of C-N Reductive Elimination

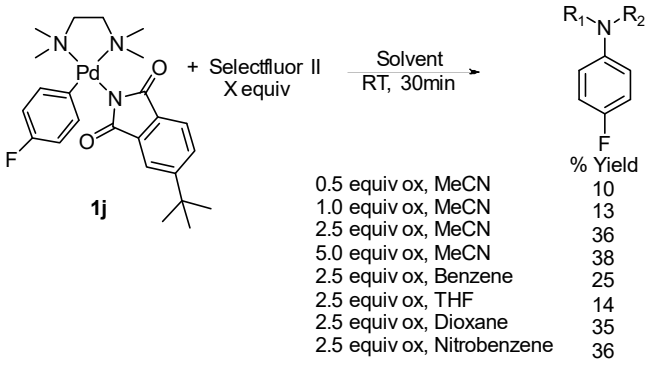




When arylpalladium imidate complexes ligated with TMEDA were allowed to react with F+ type oxidants at room temperature, N-aryl imides were obtained in modest yields. The yield of N-aryl imide product was highest when the reaction was conducted in acetonitrile (Figure 11).

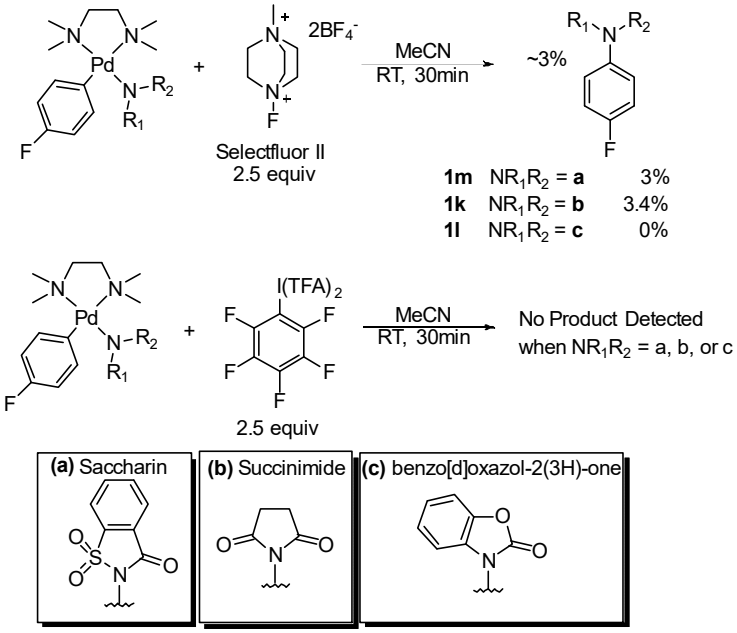
Increasing the oxidant loading beyond 2.5 equivalents only slightly improved the yield of the N-aryl imide product.

Figure 11. Yields of C-N Product with Different Solvents and Equivalents of Oxidant



A range of complexes with varying nitrogen containing ligands were evaluated for C-N reductive elimination in the presence of Selectfluor II and PerFPIFA (Figure 12). Arylpalladium saccharin **1m**, succinimide **1k**, and benzo[d]oxazol-2(3H)-one **1l** complexes were allowed to react with both oxidants. Only trace yields of N-aryl imide product were obtained when Selectfluor II was used as an oxidant, and no N-aryl imide products were detected when PerFPIFA was used.

Figure 12. Reductive Elimination of Palladium Complexes with Different Nitrogen Containing Ligands



Arylpalladium imidate complexes such as **1o** bearing a 3-fluoroarene also gave low yields when they were allowed to react with PerFPIFA and Selectfluor II (Figure 13). Complexes ligated with different diamines were also synthesized (**1p)** and were allowed to react with Selectfluor II and PerFPIFA. In the presence of these oxidants, arylpalladium imidate complexes

ligated with N,N,N′,N′-tetraethylethylenediamine (TEEDA) underwent reductive elimination in lower yields than analogous complexes ligated with TMEDA did (Figure 14).

Figure 13. Evaluating 3-Fluorophenyl Substituted Complexes for Reductive Elimination

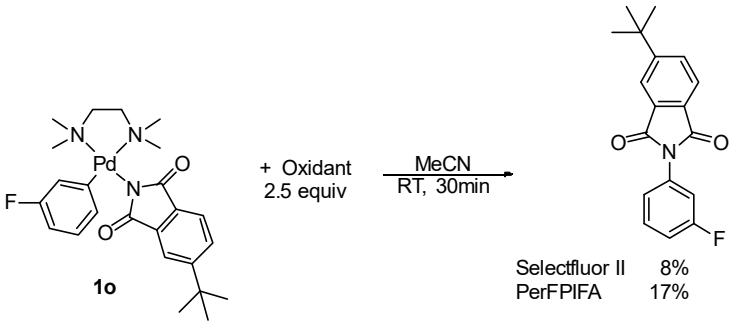
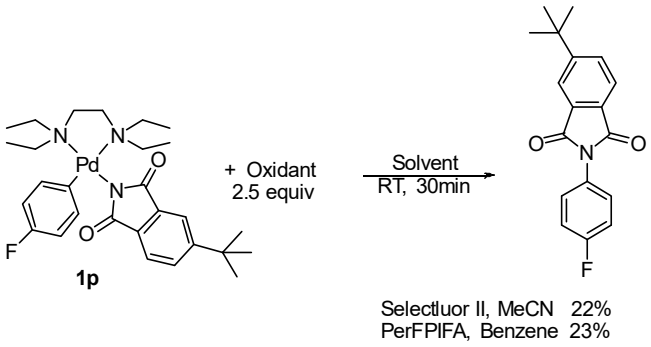
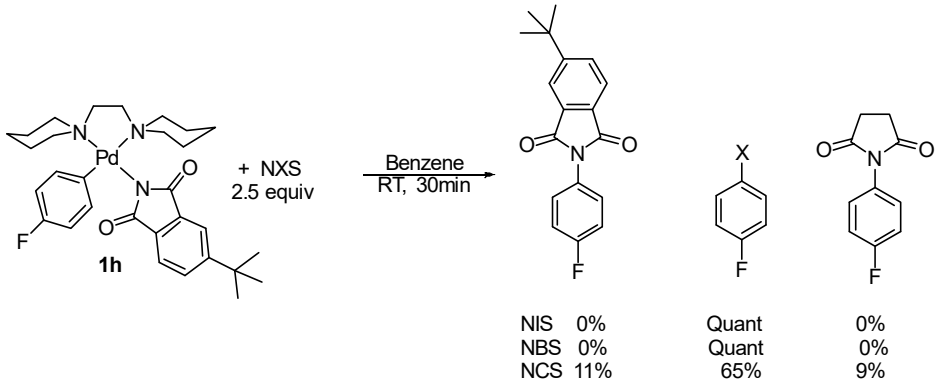


Figure 14. Evaluating TEEDA Complex for Reductive Elimination



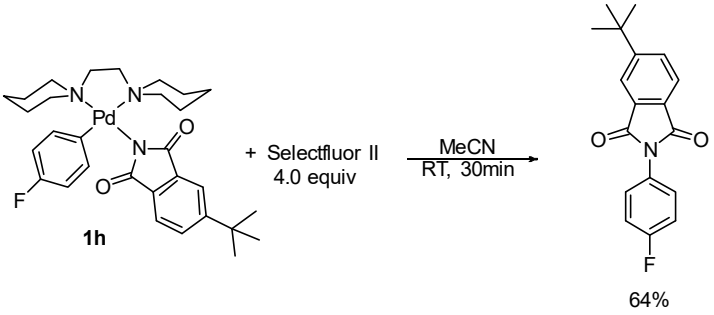
Arylpalladium imidate complexes ligated with 1,1'-(1,2-ethanediyl)bis-piperidine (TPIPDA) were also synthesized (**1h**), and their ability to undergo reductive elimination in the presence of various oxidants was evaluated. When the TPIPDA arylpalladium imidate complex **1h** was allowed to react with N-chlorosuccinimide, N-bromosuccinimide, and N-iodosuccinimide, aryl halide products were observed (Figure 15). In all cases, the formation of halogenated arenes was favored over the formation of N-aryl imides. Small quantities of N-aryl imide products were observed when the complex **1h** was allowed to react with N-chlorosuccinimide.

Figure 15. Oxidation of Arylpalladium Complexes with NXS Oxidants



When the complex was allowed to react with 4 equivalents of Selectfluor II, 64% of the desired N-aryl imide was obtained (Figure 16). This is the highest yield of aryl imide that was obtained from the reductive elimination of any of the complexes I have synthesized. Attempts to isolate the high-valent intermediate complex failed due to the rapidity with which the complex underwent reductive elimination at both room temperature and -40 ºC.

Figure 16. Evaluating TPIPDA Complex for Reductive Elmination



3.3 Conclusion

To assess the feasibility of reductive elimination to form the C-N bond in an *N*-aryl imide from a high-valent arylpalladium imidate intermediate, a series of complexes were synthesized and allowed to react in the presence of an oxidant. By developing new procedures, I was able to synthesize complexes containing a series of imide groups, chelating ligands, and aryl groups. Bipyridine-ligated complexes typically gave very low yields of N-aryl imides when they were allowed to react with various oxidants, and these complexes did not undergo thermal C-N reductive elimination. However, I found that diamine-ligated arylpalladium imidate complexes generated moderate quantities of N-aryl imides when they were allowed to react with both hypervalent iodine and F+ type oxidants. When these complexes were allowed to react with diacetoxyiodobenzene, the aryl acetates were formed preferentially. However, when PerFPIFA was used, these byproducts were not observed. Efforts to isolate the putative high-valent arylpalladium imidate intermediates were thwarted by the rapidity with which these complexes underwent reductive elimination. At the time of this work, the sp^2 C-N reductive elimination from a high-valent palladium complex was largely unknown, and few analogous model complexes existed. The factors that control C-N vs. C-O reductive elimination in the undirected intermolecular amination of remain unclear, but recent work on this topic has provided new insights for intramolecular amination systems.[21]

3.4 References

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3.5 Experimental

Table of Contents

I. General Procedures

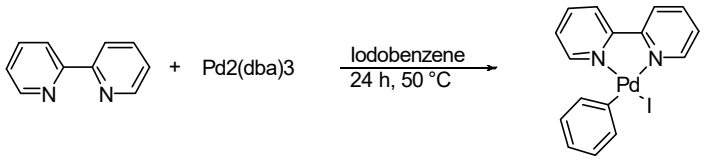
Procedure 1: Synthesis of $Pd(COD)Br_2$ from $PdCl_2$ from Inorganic Syntheses[1]:

To a flask with a stirbar, $PdCl_2$ (2.00 g, 11.3 mmol, 1.00 equiv) and 5 mL of concentrated HCl were added. The reaction was gently warmed until the $PdCl_2$ dissolved completely. Then a solution containing 7 mL of water and sodium bromide (4.65 g, 45.2 mmol, 4.00 equiv) was added. The combined solution was warmed to 50 °C for 10 minutes. The mixture was diluted with 50 mL of absolute ethanol and cooled for 15 minutes. The solution was filtered, and the flask and filter paper were washed with three 10 mL portions of 75% aqueous ethanol to remove residual palladium salts. To the vessel containing the filtrate, 1,5-cyclooctadiene (2.77 mL, 22.6 mmol, 2.00 equiv) was added, and the solution in the flask was swirled. An orange precipitate formed after 10 minutes and was collected on a Büchner funnel. The product remaining in the flask was transferred to the funnel with 50 mL of H_2O. The product was washed with an additional 50 mL of water and 200 mL of Et_2O. A bright orange solid was obtained (3.96 g, 10.6 mmol, 94% yield.)

Procedure 2: Preparation of $Pd(COD)Br_2$ from $Pd(OAc)_2$

To a flask with a stir bar, $Pd(OAc)_2$ (3.51 g, 15.6 mmol, 1.00 equiv) and 8.75 mL of 37% HCl were added. The flask was heated until the $Pd(OAc)_2$ dissolved. Then a solution with NaBr $(H_2O)_2$ (6.44 g, 46.2 mmol, 2.95 equiv) of and 12.25 mL of H_2O was added, and the solution was heated to 50 °C for five minutes. The reaction mixture was allowed to cool, 84 mL of absolute ethanol was added, and the reaction was stirred at 0 °C for 15 minutes and filtered through a disposable frit. The flask was washed with 3 portions of a 75% aqueous ethanol solution (40 mL in total). To the filtrate, 1,5-cyclooctadiene (4.20 mL, 34.2 mmol, 2.19 equiv) was added, and the filtrate was swirled. A bright orange precipitate formed, and was transferred onto disposable frit with 20 mL of water. The orange solid was washed with 70 mL of water and 275 mL of Et_2O. The product was collected and subjected to high vacuum. A bright orange solid was obtained (5.30 g, 14.2 mmol, 91% yield).

Procedure 3: Oxidative Addition of Aryl Iodides to $Pd_2(dba)_3$•$CHCl_3$



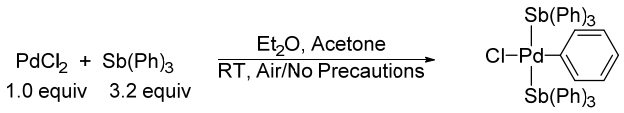
In a nitrogen-filled glovebox, $Pd_2(dba)_3$•$CHCl_3$ (0.503 g, 1.94 mmol (Pd), 1.00 equiv), iodobenzene (162 uL, 1.45 mmol, 1.49 equiv), and 12 mL of anhydrous benzene were added to a 20 mL vial equipped with a stir bar. The solution was sonicated for 5 minutes, and bipyridine (0.197 g, 2.52 mmol, 2.59 equiv) was added. The reaction mixture was heated to 50 ºC for 30 minutes. The reaction was allowed to cool to room temperature, and the product was filtered

over Celite. The crude solid that remained on the filter was washed with 50 mL of benzene. The solid product was dissolved in DCM, filtered through Celite, and the solvent was evaporated in vacuo. The product was isolated as an off-white solid (0.170 g, 0.363 mmol, 37% yield) and required no further purification.

Procedure 4: Synthesis of $Pd(P(otol)_3)_2$ see page

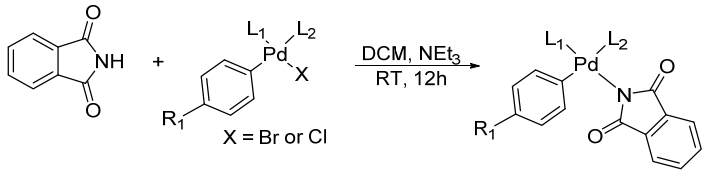
In a nitrogen-filled glovebox, (COD)$PdBr_2$ (1.01 g, 2.69 mmol, 1.00 equiv) and 6 mL of toluene were added to a dry 100 mL flask equipped with a stirbar. To a separate 20 mL vial, anhydrous powdered KOH (0.318 g, 5.66 mmol, 2.11 equiv) and 6 mL of degassed anhydrous methanol were added. To a third vial, $P(o\text{-}tol)_3$ (1.83 g, 6.01 mmol, 2.24 equiv) and 8.4 mL of degassed toluene were added. All three vessels were sealed with rubber septa and removed from the box. The solution containing (COD)$PdBr_2$ was chilled to 0 ºC, and the solution containing KOH was added. The reaction mixture in the 100 mL flask was stirred for 35 minutes at 0 ºC with frequent swirling. Over the course of the 35 minutes, the solution became light yellow. The solution containing $P(o\text{-}tol)_3$ was added to the yellow solution, the reaction mixture was warmed to room temperature, and the solution was stirred for 7.5 h. At the end of this time, 3 mL of anhydrous degassed methanol was added to the solution, and the solution was cooled to -25 ºC and allowed to remain at this temperature for 2 h. The reaction vessel was then unsealed, and the crude reaction mixture was immediately filtered on a Büchner funnel with fine filter paper. The crude solid as washed with 10 mL of methanol and 10 mL of pentane (both at 0 ºC) in air. The bright yellow solid was immediately collected and transferred to a vial. The vial was flushed with nitrogen and then subjected to high-vacuum for 12 h. A crude yellow solid was obtained (1.98 g). The product was used in subsequent reactions without further purification. The product was stored under nitrogen at -25 ºC.

Procedure 5: $PdPh(Sb(Ph)_3)_2Cl$



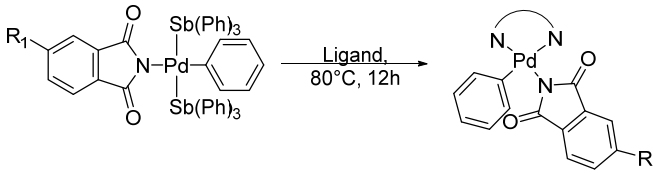
To a 200 mL flask equipped with a stir bar, $PdCl_2$ (0.727 g, 4.10 mmol, 1.00 equiv) and 65 mL of acetone were added. To a second 50 mL flask, $Sb(Ph)_3$ (4.46 g, 12.6 mmol, 3.08 equiv) and 15 mL of Et_2O were added. The solution containing $Sb(Ph)_3$ was added slowly to the 200 mL flask containing the solution of $PdCl_2$. The 200 mL flask was then sealed with a rubber septum, and the solution was stirred at room temperature for 24 h. The reaction mixture was concentrated, and the crude solid was filtered over Celite with 200 mL of Et_2O. The solid product was dissolved in DCM, filtered through Celite, and the solvent was evaporated in vacuo. The product was isolated as an off-white solid (3.34 g, 3.61 mmol, 88% yield).

Procedure 6: General Procedure for the Substitution of Arylpalladium halide Complexes with NEt_3 and Phthalimide Derivatives Page



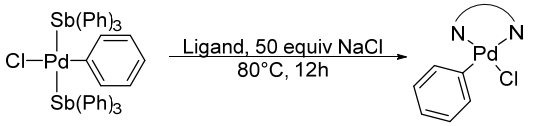
To a 20 mL vial equipped with a stir bar, an arylpalladium chloride or bromide complex (0.250 mmol, 1 equiv), imide (0.275 mmol, 1.1 equiv), NEt_3 (8.02 mL, 5.75 mmol, 23 equiv), and 6 mL of DCM were added. The reaction mixture was stirred at room temperature for 12 h and then transferred to a separatory funnel with H_2O. The reaction mixture was extracted with DCM, dried with Na_2SO_4, and concentrated under vacuum.

Procedure 7: General Procedure for Ligand Substitution of $PdAr(Sb(Ph)_3)$imidate Complexes with Diamines



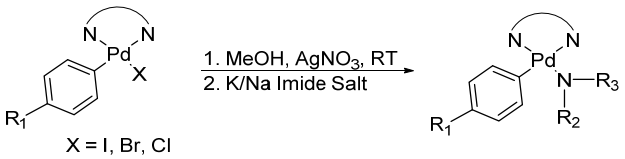
To a 20 mL vial equipped with a stir bar, an arylpalladium bis-$Sb(Ph)_3$ imidate complex (0.600 mmols, 1.00 equiv), diamine (3.00 mmol, 5.00 equiv), and 15 mL of toluene were added. The reaction mixture was heated to 80 ºC for 15 h. The reaction mixture was filtered through a plug of Celite with DCM. The filtrate was concentrated, and the solid was washed over Celite again with pentane. The remaining solid was dissolved in DCM and passed through the Celite pad. The filtrate was concentrated under vacuum.

Procedure 8: General Procedure for Ligand Substitution of $PdAr(Sb(Ph)_3)Cl$ Complexes with Diamines



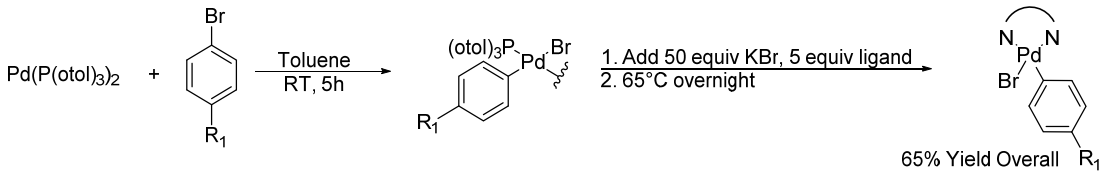
To a 4 mL vial equipped with a stir bar, complex **1b** (0.100 mmols, 1.00 equiv), NaCl (0.584 g, 10.0 mmol, 100 equiv), diamine (3.00 mmol, 30.0 equiv), and 2 mL of toluene were added. The reaction mixture was heated to 80 ºC for 18 h. The reaction mixture was filtered through a plug of Celite with DCM. The filtrate was concentrated, and the solid was washed over Celite again with pentane. The remaining solid was dissolved in DCM and passed through the Celite pad. The filtrate was concentrated under vacuum.

Procedure 9: Salt Metathesis and Imide Substitution of Arylpalladium halide Complexes with $AgNO_3$ prep



To a 20 mL vial equipped with a stir bar, an arylpalladium halide complex (0.0600 mmol, 1.00 equiv), $AgNO_3$ (0.120 mmol, 2.00 equiv), and 3 mL of MeOH were added. The reaction mixture was sonicated for 30 minutes. A solution consisting of 2 mL of MeOH and a sodium or potassium imide salt (0.180 mmol, 3.00 equiv) was added to the solution containing the arylpalladium nitrate complex. The combined solution was stirred at room temperature for 1 h. The reaction mixture was then passed through a plug of Celite with DCM. The filtrate was concentrated, and the crude solid was then filtered through a plug of basic alumina with acetone. The product was obtained after this filtrate was concentrated under vacuum.

Procedure 10: Oxidative Addition and Ligand Substitution



In a nitrogen-filled glovebox, $Pd(P(o\text{-tol})_3)_2$ (0.500 g, 0.700 mmol, 1.00 equiv), aryl bromide (3.50 mmol, 5.00 equiv), and 10 mL of toluene were added to a 20 mL vial equipped with a stir bar. The reaction mixture was stirred under nitrogen at room temperature for 7 h. The vial was uncapped under nitrogen, and TMEDA (0.524 mL, 3.50 mmol, 5.00 equiv) and KBr (3.60 g, 35.0 mmol, 50.0 equiv) were added. The reaction vial was sealed and heated to 65 ºC for 14 h. The crude reaction mixture was filtered through Celite with DCM to remove KBr, and the filtrate was concentrated under vacuum. The crude solid was sonicated in pentane and filtered over Celite. The solid collected on the Celite was washed with pentane. The solid was dissolved in DCM and filtered through the Celite pad. The filtrate was concentrated under vacuum.

Procedure 11: General Procedure for Oxidation of Arylpallaidum Imidate Complexes:

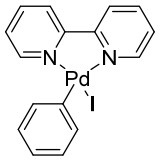
In a nitrogen-filled glovebox, an arylpalladium imidate complex (0.0250 mmol, 1.00 equiv), octafluoronapthalene (internal standard), and solvent (0.5 mL) were added to a 4 mL vial with a stirbar. The oxidant (2.50-4.00 equiv) was then added to the reaction mixture, and the vial was sealed with a Teflon cap. The products were stirred for 24 h at room temperature, the vial

was opened to air, and the solvent was removed in vaccuo. The solids were re-dissoved in $CDCl_3$, and the products were analyzed by ^{19}F NMR.

II. Synthesis and Characterization of Organometallic Complexes

purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes)

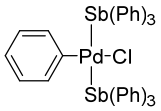
Complex **1a**



Complex **1a** was prepared according to Procedure 3. The product was obtained as an off-white solid (0.170 g, 0.363 mmol, 37% yield).

^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, *J* = 5.2 Hz, 1H), 8.13 – 7.91 (m, 4H), 7.70 (d, *J* = 5.5 Hz, 1H), 7.60 – 7.49 (m, 1H), 7.44 – 7.32 (m, 3H), 7.07 (t, *J* = 7.4 Hz, 2H), 6.99 – 6.89 (m, 1H).

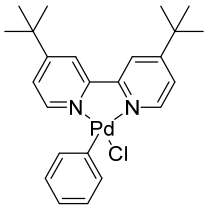
Complex **1b**



Complex **1b** was prepared according to Procedure 5. The product was obtained as an off-white solid (3.34 g, 3.61 mmol, 88% yield).

^1H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 30H), 6.97 (d, *J* = 7.1 Hz, 2H), 6.63 – 6.50 (m, 3H).

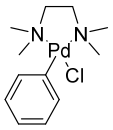
Complex **1c**



Complex **1c** was prepared according to Procedure 7 with **1b** (0.501 g, 0.542 mmol, 1.00 equiv) and 4,4'-Di-tert-butyl-2,2'-bipyridine (1.08 mmol, 2.00 equiv). After workup, the product was obtained as an off-white solid (0.242 g, 0.496 mmol, 92% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (dd, *J* = 5.7, 0.6 Hz, 1H), 8.03 – 7.83 (m, 3H), 7.53 (dd, *J* = 5.7, 1.8 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.29 (dd, *J* = 6.0, 2.1 Hz, 1H), 7.11 – 7.03 (m, 2H), 7.01 – 6.94 (m, 1H), 1.43 (s, 9H), 1.39 (s, 9H).

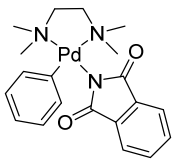
Complex **1d**



Complex **1d** was prepared according to Procedure 8 with **1b** (0.367 g, 0.396 mmol, 1.00 equiv). After workup product was obtained as a light-yellow solid (0.110 g, 0.328 mmol, 83% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 6.99 – 6.92 (m, 2H), 6.89 – 6.82 (m, 1H), 2.80 – 2.72 (m, 2H), 2.63 (s, 6H), 2.61 – 2.55 (m, 2H), 2.46 (s, 6H).

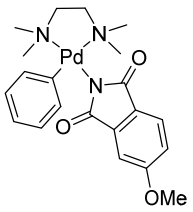
Complex **1e**



Complex **1e** was prepared as follows: Complex **1b** (0.130 g, 0.141 mmol, 1.00 equiv) was ligated with phthalimide according to Procedure 6. The resulting complex was substituted with TMEDA according to Procedure 7. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes). The product was obtained as an off-white solid (0.0605 g, 0.136 mmol, 96% overall yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.49 – 7.44 (m, 2H), 7.41 – 7.35 (m, 2H), 6.90 – 6.83 (m, 2H), 6.80 – 6.73 (m, 1H), 2.79 (dd, *J* = 6.9, 4.3 Hz, 2H), 2.63 – 2.58 (m, 2H), 2.55 (s, 6H), 2.50 (s, 6H).

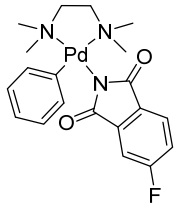
Complex **1f**



Complex **1f** was prepared as follows: Complex **1b** (0.206 g, 0.223 mmol, 1.00 equiv) was ligated with 4-methoxyphthalimide according to Procedure 6. The resulting complex was substituted with TMEDA according to Procedure 7. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes). The product was obtained as an off-white solid (0.107 g, 0.223 mmol, 100% overall yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.38 (m, 3H), 7.06 (d, *J* = 2.2 Hz, 1H), 6.90 – 6.82 (m, 3H), 6.76 (t, *J* = 7.1 Hz, 1H), 3.80 (d, *J* = 1.6 Hz, 3H), 2.78 (t, *J* = 5.5 Hz, 3H), 2.60 (t, *J* = 5.5 Hz, 1H), 2.55 (d, *J* = 1.6 Hz, 6H), 2.50 (d, *J* = 1.6 Hz, 6H).

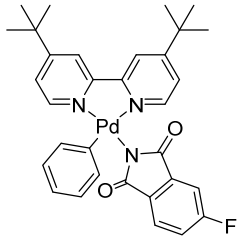
Complex **1g**



Complex **1g** was prepared as follows: Complex **1b** (0.512 g, 0.553 mmol, 1.00 equiv) was ligated with 4-fluorophthalimide according to Procedure 6. The resulting complex was substituted with TMEDA according to Procedure 7. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes). The product was obtained as an off-white solid (0.186 g, 0.400 mmol, 72% overall yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 4H), 7.19 (dd, *J* = 7.5, 2.2 Hz, 1H), 7.03 (ddd, *J* = 9.3, 8.1, 2.3 Hz, 1H), 6.87 (dd, *J* = 8.1, 6.6 Hz, 2H), 6.81 – 6.74 (m, 1H), 2.79 (dd, *J* = 6.9, 4.0 Hz, 2H), 2.66 – 2.57 (m, 2H), 2.55 (s, 6H), 2.50 (s, 7H).

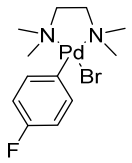
Complex **1h**



Complex **1c** (0.125 g, 0.256 mmol, 1.00 equiv) was ligated with 4-fluorophthalmide according to procedure 6. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes). The product was obtained as an off-white solid (0.144 g, 0.233 mmol, 91% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 5.6 Hz, 1H), 7.95 (d, *J* = 1.9 Hz, 2H), 7.88 (d, *J* = 6.0 Hz, 1H), 7.63 – 7.54 (m, 3H), 7.41 (dd, *J* = 5.7, 1.9 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.15 – 7.07 (m, 1H), 7.00 (t, *J* = 7.3 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 1.38 (s, 18H).

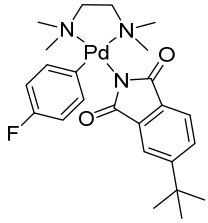
Complex **1i**



Complex **1i** was synthesized according to Procedure 10 with $Pd(P(o\text{-}tol)_3)_2$ (0.509 g, 0.712 mmol, 1.00 equiv) and 1-bromo-4-fluorobenzene. After workup, the product was obtained as an orange solid (0.208 g, 0.522 mmol, 73% overall yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (m, 2H), 6.76 (m, 2H), 2.75 (dd, *J* = 7.0, 4.1 Hz, 2H), 2.65 (s, 6H), 2.59 (dd, *J* = 6.8, 4.1 Hz, 2H), 2.41 (s, 6H).

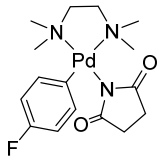
Complex **1j**



Complex **1j** was synthesized from complex **1i** (0.358 g, 0.899 mmol, 1.00 equiv) (according to Procedure 6 with 4-*tert*-butylphthalimide. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes). The product was obtained as an off-white solid (0.436 g, 0.838 mmol, 93% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.48 – 7.34 (m, 4H), 6.75 – 6.59 (m, 2H), 2.83 – 2.74 (m, 2H), 2.61 (dd, *J* = 6.6, 4.4 Hz, 2H), 2.55 (d, *J* = 1.7 Hz, 6H), 2.49 (s, 6H), 1.29 (s, 9H).

Complex **1k**

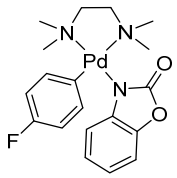


Complex **1k** was synthesized from complex **1i** (0.100 g, 0.252 mmol, 1.00 equiv) according to Procedure 9 with sodium succinimide. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0

EtOAc:Hexanes). The product was obtained as an off-white solid (0.0928 g, 0.223 mmol, 89% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 2H), 6.73 – 6.64 (m, 2H), 2.74 (dd, *J* = 6.9, 4.1 Hz, 2H), 2.58 (dd, *J* = 6.9, 4.1 Hz, 2H), 2.54 (s, 6H), 2.44-2.46 (m, 2 H), 2.45 (s, 6H), 2.40 – 2.29 (m, 2H).

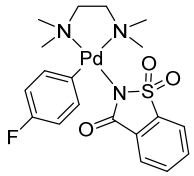
Complex **1l**



Complex **1l** was synthesized from complex **1i** (0.105 g, 0.265 mmol, 1.00 equiv) according to Procedure 9 with sodium benzo[d]oxazol-2(3H)-one. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes). The product was obtained as an off-white solid (0.0830 g, 0.184 mmol, 69% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 4H), 6.98 – 6.86 (m, 2H), 6.76 (td, *J* = 7.7, 1.3 Hz, 1H), 6.70 – 6.60 (m, 2H), 2.90-2.59 (m, 10H), 2.44 (d, *J* = 4.8 Hz, 6H).

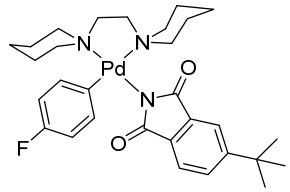
Complex **1m**



Complex **1m** was synthesized from complex **1i** (0.103 g, 0.259 mmol, 1.00 equiv) according to Procedure 9 with sodium saccharin. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 100:0 to 100:0 EtOAc:Hexanes to Acetone:EtOAc). product was obtained as an off-white solid (0.0807 g, 0.161 mmol, 62% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.71 (m, 1H), 7.70 – 7.61 (m, 1H), 7.56 – 7.49 (m, 2H), 7.40 (dd, *J* = 8.3, 6.0 Hz, 2H), 6.69 (t, *J* = 9.0 Hz, 2H), 3.00-2.55 (bm, 10H), 2.49 (s, 6H).

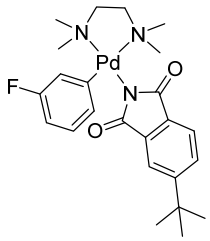
Complex **1n**



Complex **1n** was synthesized in two steps. The TPIPA ligated arylpalladium bromide complex was synthesized according to Procedure 10 with (0.5295 g, 0.740 mmol, 1.00 equiv) of $Pd(P(o\text{-}tol)_3)_2$ and TPIPA in place of TMEDA. The product was allowed to react with 4-*tert*-butylphthalimide according to the conditions in Procedure 6. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes). The product was obtained as an off-white solid (0.1471 g, 0.245 mmol, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.39 – 7.33 (m, 2H), 6.70 – 6.59 (m, 2H), 3.36 – 2.84 (m, 12H), 1.63 (m, 6H), 1.70-1.29 (bm, 15H).

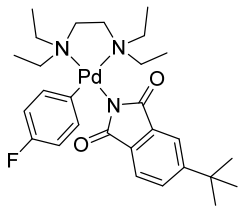
Complex **1o**



Complex **1o** was synthesized in two steps. The TMEDA ligated arylpalladium bromide complex was synthesized according to Procedure 10 with (0.288 g, 0.403 mmol, 1.00 equiv) of $Pd(P(o\text{-}tol)_3)_2$ and 1-bromo-3-fluorobenzene. The product was allowed to react with 4-*tert*-butylphthalimide according to the conditions in Procedure 6. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes). The product was obtained as an off-white solid (0.1235 g, 0.238 mmol, 59% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.6 Hz, 1H), 7.48 – 7.38 (m, 2H), 7.29 (s, 1H), 7.19 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.81 (q, *J* = 7.3 Hz, 1H), 6.54 – 6.37 (m, 1H), 2.85 – 2.74 (m, 2H), 2.66 – 2.58 (m, 2H), 2.55 (d, *J* = 1.9 Hz, 6H), 2.51 (d, *J* = 2.6 Hz, 6H).

Complex **1p**



Complex **1p** was synthesized in two steps. The TEEDA ligated arylpalladium bromide complex was synthesized according to Procedure 10 with (0.258 g, 0.360 mmol, 1.00 equiv) of $Pd(P(o\text{-}tol)_3)_2$ and TEEDA in place of TMEDA. The product was allowed to react with 4-*tert*-butylphthalimide according to the conditions in Procedure 6. After workup, the crude solid was purified on a basic alumina column using a mixture of ethyl acetate and hexanes (gradient 50:50 to 100:0 EtOAc:Hexanes). The product was obtained as an off-white solid (0.112 g, 0.195 mmol, 54% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (t, *J* = 1.2 Hz, 1H), 7.45 (s, 2H), 7.41 (td, *J* = 6.5, 2.6 Hz, 2H), 6.66 (dd, *J* = 9.7, 8.6 Hz, 2H), 2.95 (h, *J* = 6.8 Hz, 4H), 2.89 – 2.72 (m, 6H), 2.61 (dt, *J* = 12.5, 6.2 Hz, 2H), 1.67 (q, *J* = 6.9 Hz, 6H), 1.40 – 1.34 (m, 6H), 1.33 (s, 9H).

III. References for Experimental Section

1. Cotton, F. A.; Wiley, I. **1972**.

Chapter 4

The Oxidation of Hindered Allylic C–H Bonds with Applications to the Functionalization of Complex Molecules

4.1 Introduction

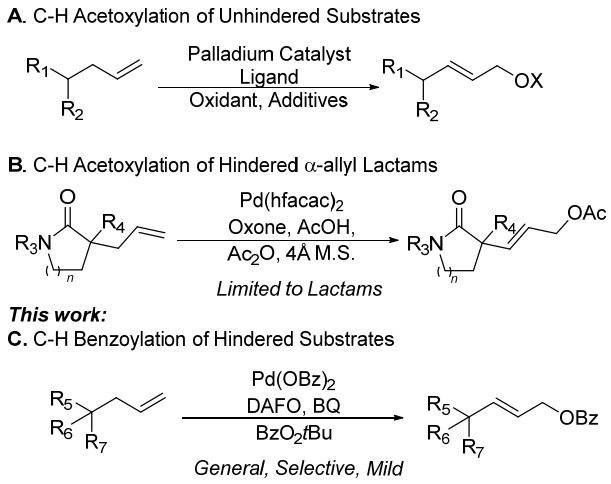
C-H bond functionalization reactions could enable concise routes to complex molecules in diverse synthetic contexts, but many C-H bond functionalization reactions conducted on simple substrates do not translate to more complex analogs.[1-5] Among C-H bond functionalization reactions, the oxidation of allylic C-H bonds has been investigated by many groups because of the prevalence of olefins and alcohols in natural products and the application of allylic alcohols as synthetic intermediates.[6] Although many methods for allylic oxidation have been reported, current systems do not generally address the challenge of conducting this class of reaction on hindered alkenes, such as those with fully substituted carbon atoms adjacent to the allylic unit.[7] Such allyl units flanked by quaternary carbons are common substructures in natural products. Thus, synthetic methods for the functionalization of such allyl groups would be valuable for both the synthesis and direct functionalization of natural products.[8]

Since the initial reports on the catalytic allylic oxidation of olefins in the 1970's, selective palladium-catalyzed acetoxylations of allylic C-H bonds have been reported (Scheme 1A).[9-11] Reactions with a variety of ligands, terminal oxidants, and solvents have been investigated.[7, 12-20] High selectivity for both the linear and branched allylic acetates has been achieved, and acid sensitive substrates can be functionalized under certain conditions.[21-24,25-26] The acetoxylation of substrates containing amides, esters, and acetals has been accomplished in moderate to good yields.[27] Recently, the Hartwig group reported a system for the palladium-catalyzed oxidation of α-olefins to linear allylic benzoates with high selectivity for the linear ester.[28] This reaction was combined with iridium-catalyzed allylic substitution to prepare synthetically valuable enantioenriched products containing new C-O, C-N, and C-C bonds in one pot.

Despite this progress, current methods for the oxidation of allylic C-H bonds have significant limitations. Most relevant to the present investigation, the oxidation of hindered alkenes tend to resist oxidation at the allylic position. Stoltz et al. recently highlighted these constraints (Scheme 1B).[29] The oxidation of substrates containing α-allyl lactams with quaternary centers next to the allyl group occurred to low conversions under both classical and modern catalytic conditions. Although the authors subsequently devised conditions for the selective oxidation of α-allyl lactams, only trace yields were obtained when other classes of hindered substrates were evaluated.

This chapter describes how conditions that had been developed for the oxidation of alkenes to terminal allylic esters were adapted to achieve the allylic oxidation of a range of sterically hindered alkenes and would tolerate diverse functional groups, while maintaining its selectivity to form linear products (Scheme 1C).

Scheme 1. C-H Oxidation of α-Olefins

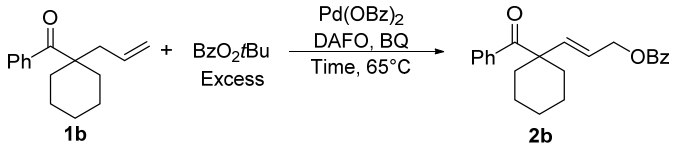


4.2 Results and Discussion

Herein the development of conditions for the palladium-catalyzed oxidation of hindered alkenes to form linear allylic benzoates is reported. The ability to oxidize these substrates and the high tolerance of the system for functional groups makes this process particularly valuable for the functionalization of complex natural products containing quaternary carbons at the position α to the allyl unit.

To develop a system capable of functionalizing compounds containing α-quaternary centers, the oxidation of model substrate **1b** was evaluated in conditions that were modified from those previously reported (Table 1). The combination of $Pd(OBz)_2$ and 4,5-diazafluoren-9-one (DAFO),[20] catalyzes the reaction of **1b** with *tert*-butyl benzoyl peroxide (BzO_2tBu) to form **2b** in 59% yield (Table 1, entry 3). No product was formed when either $Pd(OBz)_2$ or DAFO was omitted from the reaction (Table 1, entries 1,2). The high conversion of **1b** in the absence of DAFO suggest that unligated $Pd(OBz)_2$ catalyzes the decomposition of **1b** in the presence of *tert*-butyl benzoyl peroxide (Table 1, entry 2). The yield of the reaction conducted with four equivalents of oxidant was similar to that obtained when the reaction was conducted with two equivalents of oxidant (Table 1, entries 3,4). Neither increasing the loading of palladium and ligand to 20 mol % (Table 1, entry 5), nor increasing the loading of ligand to 20 mol % (while maintaining the loading of palladium at 10 mol %), increased the yield of **2b** (Table 1, entry 6). However, the yields of reactions conducted with benzoquinone (BQ) as an additive were higher than those without benzoquinone (Table 1, entries 7-9).

Table 1. Evaluation of Conditions for the Oxidation of Model Ketone **1b**



1b **2b**

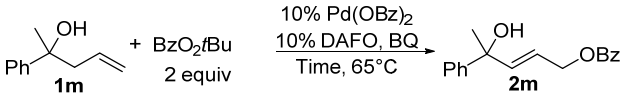
Entry	%Pd(OBz)$_2$	%DAFO	%BQ	Yield	Unreacted **1b**
1	0	10	0	0%	Quant
2	10	0	0	0%	22%
3	10	10	0	59%	0%
4[a]	10	10	0	58%	0%
5	20	20	0	55%	0%
6	10	20	0	51%	21%
7	10	10	10	74%	0%
8	10	10	50	78%	0%
9[b]	10	10	10	79%	0%

Conditions: Reactions were conducted with 0.1 mmol (1 equiv) of **1b** and 2.0 equiv of BzO_2*t*Bu. The ligand, 4,5-diazafluoren-9-one, is abbreviated as DAFO. The reaction duration was 20 h. Yields were determined by ^{1}H NMR. [a]Reaction was conducted with 4.0 equiv of BzO_2*t*Bu. [b]Average yield of two reactions; reaction duration was 10 h.

The presence of benzoquinone in the reaction mixture also increased the yields for the oxidation of unprotected homoallylic alcohols. The Sakurai-Hosomi reaction and other reactions of allyl nucleophiles with ketones have been developed for the synthesis of enantioenriched homoallylic alcohols, but the functionalization of tertiary, homoallylic alcohols is challenging because of the electron-withdrawing property of the alcohol and the steric hindrance at the allylic C-H bond.[30-33,34,35-39,40] In addition, terpenoids containing homoallylic alcohols, such as linalool, have been observed to undergo unproductive side reactions under oxidative conditions resulting in multiple products.[41]

Reactions of model substrate **1m** were conducted in the presence and absence of benzoquinone (Table 2). In the absence of benzoquinone, only low to moderate conversions of **1m** and yields of **2m** were obtained at 1 and 3 h (Table 2, entries 1,2). Reactions conducted for 48 h occurred to high conversion of **1m**, but gave a low yield of **2m** (Table 2, entry 3). In contrast, reactions conducted with added benzoquinone fully converted **1m** within an hour (Table 2, entries 4-6). The yield of **2m** from the reaction with 5 mol % of benzoquinone was the same as that with 10 mol % benzoquinone (Table 2, entries 4,5). Reactions containing 10 mol % of other quinones or metal salts gave lower conversions of **1m** at 1 h than did the reaction conducted with 10 mol % benzoquinone (See Supporting Information).

Table 2. Evaluation of Conditions for the Oxidation of Homoallylic Alcohol **1m**



Entry	%BQ	Time	Yield	Unreacted **1m**
1	0	1 h	28%	46%
2	0	3 h	28%	47%
3	0	48 h	25%	0%
4	5	1 h	70%	0%
5	10	1 h	70%	0%
6	50	1 h	69%	0%
7	10	3 h	69%	0%

Conditions: Reactions were conducted with 0.1 mmol (1 equiv) of **1m** and 2.0 equiv of BzO_2tBu. Yields were determined by ^1H NMR.

The origin of the higher rate and yield that are observed when the benzoylation reaction is conducted in the presence of benzoquinone than in the absence of benzoquinone is unclear. However, based on numerous precedents, we suggest that benzoquinone could serve as a ligand that promotes the reductive elimination of an allyl palladium intermediate (see Supporting Information).[22, 42-47] Alternatively, benzoquinone could prevent catalyst decomposition.

Having achieved high yields for the oxidation of two different classes of model substrates, conditions for the oxidation of allylic C-H bonds in a range of compounds were evaluated (Scheme 2). Many of the products derived from these alkenes could serve as valuable synthetic intermediates (Scheme 2, entries **2a-2f**, **2i-2m**). In addition, derivatives of natural products (Scheme 2, entries **2g**, **2h**, **2k**, **2l**, **2n-2p**) were oxidized to provide complex precursors for further diversification. In general, ^1H NMR yields were higher than isolated yields by 10-20% due to the need to separate the major product from minor byproducts having similar polarity to the major species. A representative ^1H NMR spectrum of the crude product derived from the oxidation of **1m** is included in the Supporting Information.

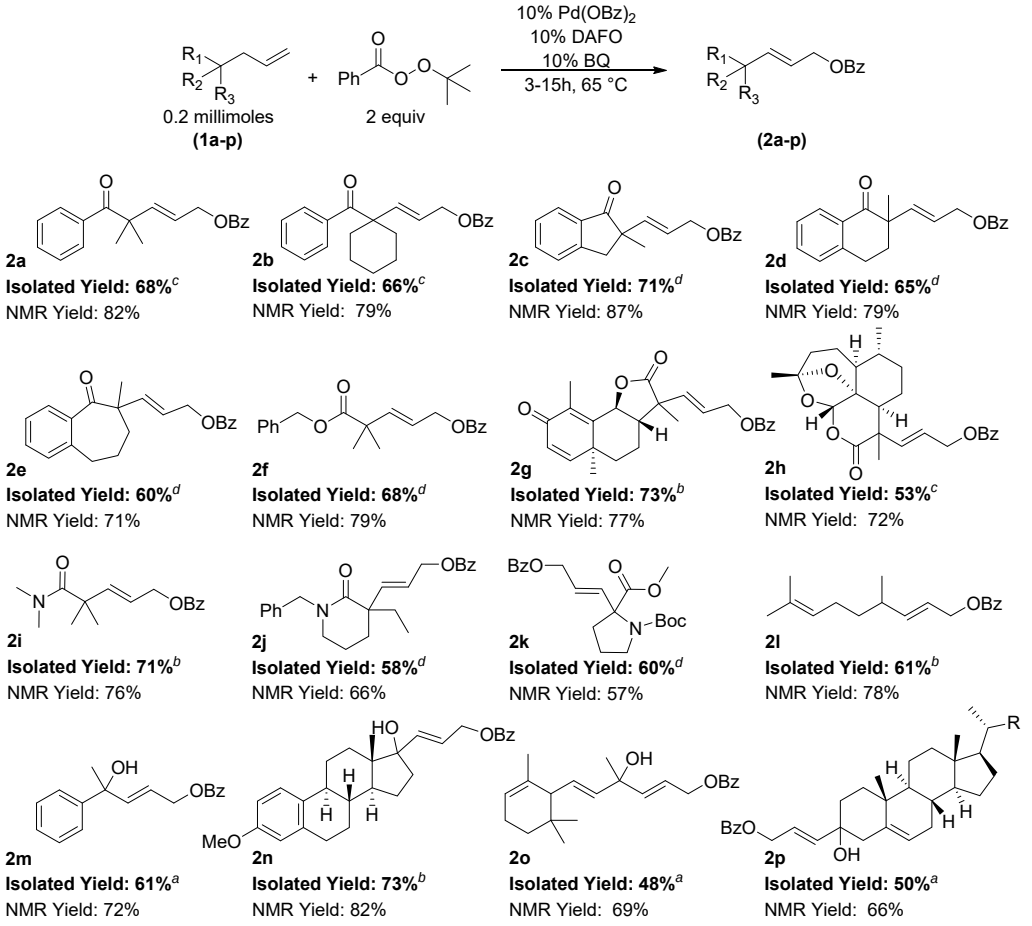
Published attempts to conduct the acetoxylation of C-H bonds of α-allyl ketones resulted in low conversion.[29] Reactions of acyclic ketones **1a** and **1b** occurred to full conversion in 10 h, despite the difference in the steric properties of the quaternary centers in these two ketones. Cyclic ketones containing 5-, 6-, and 7-membered rings underwent oxidation in high yields in 15 h (**1c**, **1d**, **1e**). The synthesis of enantioenriched variants of these substrates by asymmetric Tsuji allylic alkylation has been extensively developed because of their value as synthetic intermediates; the new functionalization methodology provides products which could be further elaborated.[20, 29, 48-53]

In addition to hindered ketones, hindered α-allyl esters and lactones underwent full conversion in less than 24 h. The model ester, **1f**, was oxidized to **2f** in good yield. Product **2f** is valuable because of its similarity to methyl (*E*)-5-hydroxy-2,2-dimethylpent-3-enoate, an intermediate in the synthesis of bryostatin.[54] Furthermore, the selective oxidation of **2f** demonstrates that benzyl esters are compatible with the standard oxidative reaction conditions.

With these results in hand, the allylic oxidation of more complex substrates was evaluated. A derivative of santonin, the five membered α-allyl lactone **1g**, underwent benzoylation under the

standard reaction conditions in high yield. The cyclohexadiene moiety of **1g**, which is responsible for the biological activity of santonin, did not undergo further oxidation.[55] The six membered lactone derived from deoxy-artemisnin, **1h** also underwent oxidation to furnish **2h** in moderate yield.

Scheme 2. Scope of C-H Benzoylation of Hindered and Complex Substrates



Conditions: Reactions were conducted with 0.2 mmol (1 equiv) of substrate and 2.0 equiv of BzO_2tBu. Yields were determined by ^1H NMR prior to isolation. [a]Reaction duration was 3 h. [b]Reaction duration was 5 h. [c]Reaction duration was 10 h. [d]Reaction Duration was 15 h. R = $(CH_2)_3i$-Pr

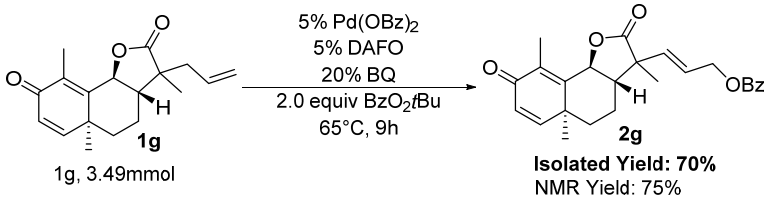
High product yields were also obtained when linear amide **1i** and lactam **1j** were oxidized under the newly developed conditions. Previous attempts to functionalize hindered, linear amides like **1i** resulted in low conversions; lactams were the only class of hindered carbonyl compound that underwent oxidation in synthetically relevant yields.[29] The oxidation of substrate **1k** to **2k** indicates that homoallylic carbamates are also tolerated in the standard reaction conditions.

The benzoylation of homoallylic alcohol **1m** led us to evaluate the oxidation of more complex homoallylic alcohols. Homoallylic alcohols derived from estrone and cholesterone

underwent selective allylic oxidation (**1n**, **1p**). These results confirm that alcohols derived from 5- and 6-membered cyclic ketones can be oxidized in moderate to good yields. Products derived from the oxidation of the trisubstituted olefin **1p** did not form in significant quantities, suggesting that this system for allylic oxidation is highly selective for reaction with terminal olefins. This observation is corroborated by the selective oxidation of citronellal derivative **1l** and α-ionone derivative **1o**. The selective oxidation of the terminal olefin of **1o** occurs in the presence of trisubstituted and disubstituted alkenes. This selectivity is valuable for the functionalization of terpenoid natural products which often contain multiple olefins.

The benzoylation of compounds derived from natural products, such as santonin, deoxy-artmesinin, proline, citronellal, estrone, cholesterone, and α-ionone, establishes the utility of this new method for the functionalization of complex molecules. To further demonstrate the synthetic value of the new benzoylation procedure, **2g** was prepared on a one gram scale. The selective benzoylation of **1g** is challenging because it contains multiple alkenes. This substrate underwent selective oxidation catalyzed by 5 mol % $Pd(OBz)_2$, 5 mol % DAFO, and 20 mol % benzoquinone. After 9 h at 65 °C, a 75% yield of **2g** was determined by ^1H NMR spectroscopy, and an isolated yield of 70% of **2g** was obtained. These results closely match those obtained when **1g** was benzoylated on a 0.2 mmol scale with a 10 mol % loading of palladium (Scheme 3). The gram scale synthesis of **2g** shows the practical applications of this new method for the late stage synthesis complex molecules.

Scheme 3. Gram Scale Oxidation of Allyl-Santonin



4.3 Conclusion

In conclusion, this chapter describes the benzoylation of hindered, terminal olefins in the presence of palladium (II) benzoate, 4,5-diazafluoren-9-one, and benzoquinone. In many cases, the inclusion of benzoquinone in the reaction conditions led to higher reaction rates and product yields than were obtained in its absence. Under these new conditions, hindered substrates undergo rapid and selective functionalization. The application of this method to natural products provides intermediates for further diversification. Finally, the synthetic relevance of this method has been validated by the gram scale oxidation of a santonin derivative.

4.4 References

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4.5 Experimental

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I. General Experimental Details

All air-sensitive manipulations were conducted in a nitrogen-filled glovebox or by standard Schlenk technique under nitrogen. All glassware was heated in an oven and cooled under an inert atmosphere prior to use. Vials (4 mL) were used as reaction vessels and were sealed with Teflon-lined caps. Products were visualized on TLC plates with an anisaldehyde stain and a heat gun. NMR spectra were acquired on 300 MHz, 400 MHz, 500 MHz, or 600 MHz Bruker instruments at the University of California. Flash chromatography was performed with a Teledyne ISCO CombiFlash RF 200 with Gold-Top silica. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^1H and 77.16 ppm for ^{13}C). Coupling constants are reported in hertz. NMR yields were determined by ^1H NMR spectroscopy with 1,3,5-Tribromo-2-methoxybenzene as an internal standard. High-resolution mass spectra were obtained via the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley.

Solvents and Reagents for Catalytic Oxidation Reaction

Tert-butyl benzoyl peroxide (98%) was purchased as a solution from Sigma-Aldrich and filtered through a plug of basic alumina before use. Palladium benzoate was purchased from Strem Chemicals Inc or prepared from commercial palladium acetate as previously described.[1] Benzoquinone was purchased from Sigma-Aldrich, dissolved in DCM, and filtered through a plug of basic alumina. The solvent was removed under high vacuum. 4,5-Diazafluoren-9-one (98%) was purchased from Alfa Aesar.

II. General Procedures

General allylation procedure I: Substrate Synthesis

To a dry 20 mL vial under N_2 containing a magnetic stir bar, substrate (5.00 mmol, 1.00 equiv) and THF (5 mL) were added, and the vial was sealed with a rubber septum. To a dry 100 mL flask containing a stir bar under N_2, LiHMDS (6.25 mmol, 1.25 equiv) and THF (15 mL) were added. The solution in the 100 mL flask was cooled to -78 °C in a bath of dry ice and acetone, and the solution from the vial was added slowly under N_2. The resulting mixture was allowed to stir for 1 h at -78 °C, and then allyl bromide (10.0 mmol, 2.00 equiv) was added dropwise. The flask was allowed to warm slowly to room temperature and stirred for 12 h. The reaction mixture was poured into a separatory funnel containing 200 mL of a saturated NH_4Cl solution and extracted with ether (3 x 40 mL). Anhydrous Na_2SO_4 was added to the combined organic layers. The resulting slurry was filtered through a frit containing additional anhydrous Na_2SO_4, and the remaining slurry was washed with ether (3 x 20 mL) and repeatedly filtered. The dried organic layer was concentrated in vacuo and purified via combiflash using a mixture of ethyl acetate and hexanes.

The relative quantitates of reagents were maintained when this procedure was conducted at varying scales.

General alkylation procedure II: Substrate Synthesis

To a dry 20 mL vial under N_2 containing a magnetic stir bar, were added substrate (10.0

mmol, 1.00 equiv) and THF (10 mL), and the vial was sealed with a rubber septum. To a dry 100 mL flask containing a stir bar under N_2, LiHMDS (12.5 mmol, 1.25 equiv) and THF (30 mL) were added. The solution in the 100 mL flask was cooled to -78 °C in a bath of dry ice and acetone, and the solution from the vial was added slowly under N_2. The resulting solution was allowed to stir for 1 h at -78 °C, and then the appropriate alkyl iodide (12.0-14.0 mmol, 1.20-1.40 equiv) was added dropwise. The flask was allowed to warm slowly to room temperature and stirred for 12 h. The reaction mixture was poured into a separatory funnel containing 200 mL of a saturated NH_4Cl solution and extracted with ether (3 x 40 mL). Anhydrous Na_2SO_4 was added to the combined organic layers. The resulting solution was filtered through a frit containing additional anhydrous Na_2SO_4, and the remaining slurry was washed with ether (3 x 20 mL) and repeatedly filtered. The dried organic layer was concentrated in vacuo and purified via combiflash using a mixture of ethyl acetate and hexanes.

The relative quantitates of reagents were maintained when this procedure was conducted at varying scales.

Benzoylation Procedure III on a 0.2 mmol scale:

To a dry 4 mL vial under N_2 containing a magnetic stir bar, $Pd(OBz)_2$ (0.020 mmol, 0.10 equiv), 4,5-diazafluoren-9-one (0.020 mmol, 0.10 equiv), and benzoquinone (0.020 mmol, 0.10 equiv) were added. Substrate was layered on the bottom of the vial (0.20 mmol, 1.0 equiv), and then (0.40 mmol, 2.0 equiv) of *tert*-butyl benzoyl peroxide was added. The reaction vial was sealed with a Teflon-lined cap and heated at 65 °C for 3-15 hours. Solid substrates rapidly dissolved in the reaction mixture upon heating. Upon completion, DCM was added, and the resulting brown oil was filtered through a silica plug. The filtrate was concentrated under vacuum, loaded onto silica, and purified via combiflash using a mixture of ethyl acetate and hexanes.

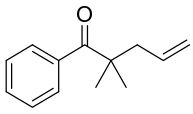
The relative quantitates of reagents were maintained when this procedure was conducted at a 0.10 mmol scale.

Large Scale Benzoylation Procedure IV:

To a dry 4 mL vial under N_2 containing a magnetic stir bar, $Pd(OBz)_2$ (0.17 mmol, 0.050 equiv), 4,5-diazafluoren-9-one (0.17 mmol, 0.050 equiv), and benzoquinone (0.70 mmol, 0.20 equiv) were added. Substrate **1g** was deposited on the bottom of the vial (3.49 mmol, 1.00 equiv), and then (6.98 mmol, 2.00 equiv) *tert*-butyl benzoyl peroxide was added. The reaction vial was sealed with a Teflon-lined cap and heated at 65 °C for 9 hours. Solid substrates rapidly dissolved in the reaction mixture upon heating. Upon completion, DCM was added, and the resulting brown oil was filtered through a silica plug. The filtrate was concentrated under vacuum, loaded onto silica, and purified via combiflash using a mixture of ethyl acetate and hexanes.

III. Synthesis of Starting Materials

Substrate (1a) 2,2-dimethyl-1-phenylpent-4-en-1-one

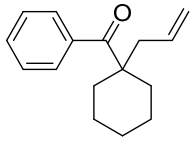


Substrate **1a** was prepared on a 3.37 mmol scale according to General Allylation Procedure I from commercially available 2-methyl-1-phenylpropan-1-one. After workup, the crude product

was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 0:100 to 5:95 EtOAc:Hexanes) to afford 2,2-dimethyl-1-phenylpent-4-en-1-one as a colorless oil (0.531 g, 2.82 mmol, 84% yield). The ^{1}H NMR spectrum matches that previously reported.[2]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.46 (m, 1H), 7.41 (m, 2H), 5.72 (m, 1H), 5.03 (m, 2H), 2.49 (dt, *J* = 7.3, 1.0 Hz, 2H), 1.32 (s, 6H).

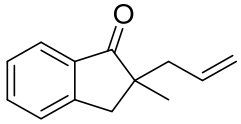
Substrate (1b) (1-allylcyclohexyl)(phenyl)methanone



Substrate **1b** was prepared on a 5.00 mmol scale according to General Allylation Procedure I from commercially available cyclohexyl(phenyl)methanone. After workup, the crude product was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 0:100 to 5:95 EtOAc:Hexanes) to afford (1-allylcyclohexyl)(phenyl)methanone as a colorless oil (0.939 g, 4.11 mmol, 82% yield). The ^{1}H NMR spectrum matches that previously reported.[2]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.45 (m, 1H), 7.38 (m, 2H), 5.71 (m, 1H), 5.04 (m, 2H), 2.55 (dt, *J* = 7.3, 1.0 Hz, 2H), 2.20 (m, 2H), 1.64-1.22 (m, 8H).

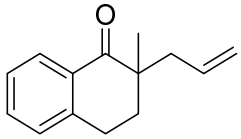
Substrate (1c) 2-allyl-2-methyl-2,3-dihydro-1H-inden-1-one



Substrate **1c** was prepared on a 5.00 mmol scale according to General Allylation Procedure I from commercially available 2-methyl-2,3-dihydro-1H-inden-1-one. After workup, the crude product was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 0:100 to 5:95 EtOAc:Hexanes) to afford 2-allyl-2-methyl-2,3-dihydro-1H-inden-1-one as a colorless oil (0.786 g, 4.22 mmol, 84% yield). The ^{1}H NMR spectrum matches that previously reported.[3]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.59 (m, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 5.66 (m, 1H), 5.10-4.98 (m, 2H), 3.16 (d, *J* = 17.2 Hz, 1H), 2.84 (d, *J* = 17.2 Hz, 1H), 2.38 (m, 1H), 2.29 (m, 1H), 1.23 (s, 3H).

Substrate (1d) 2-allyl-2-methyl-3,4-dihydronaphthalen-1(2H)-one

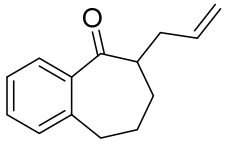


Substrate **1d** was prepared on a 5.80 mmol scale according to General Allylation Procedure I from commercially available 2-methyl-3,4-dihydronaphthalen-1(2H)-one. After workup, the crude product was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 0:100 to 5:95 EtOAc:Hexanes) to afford 2-allyl-2-methyl-3,4-dihydronaphthalen-1(2H)-one as a colorless oil (1.003 g, 5.010 mmol, 86% yield). The ^{1}H NMR spectrum matches that previously reported.[3]

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.45 (td, *J* = 7.4, 1.4 Hz, 1H), 7.30

(t, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 7.6, 1H), 5.79 (m, 1H), 5.09 (m, 2H), 2.98 (m, 2H), 2.46 (m, 1H), 2.28 (m, 1H), 2.08 (m, 1H), 1.90 (m, 1H), 1.19 (s, 3H).

6-allyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one

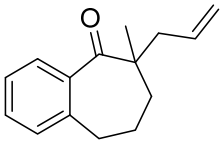


6-allyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one was synthesized from commercially available 6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one on a 10 mmol scale according to a modified version of General Allylation Procedure I:

To a dry 20 mL vial under N_2 containing a magnetic stir bar, substrate (10.0 mmol, 1.00 equiv) and THF (10 mL) were added, and the vial was sealed with a rubber septum. To a dry 100 mL flask containing a stir bar under N_2, LiHMDS (10.0 mmol, 1.00 equiv) and THF (30 mL) were added. The solution in the 100 mL flask was cooled to -78 °C in a bath of dry ice and acetone, and the solution from the vial was added slowly under N_2. The resulting mixture was allowed to stir for 1 h, and then allyl bromide (10.0 mmol, 1.00 equiv) was added dropwise. The flask was allowed to warm slowly to room temperature and stirred for 12 h. The reaction mixture was poured into a separatory funnel containing 200 mL of a saturated NH_4Cl solution and extracted with ether (3 x 40 mL). Anhydrous Na_2SO_4 was added to the combined organic layers. The resulting solution was filtered through a frit containing additional anhydrous Na_2SO_4, and the remaining slurry was washed with ether (3 x 20 mL) and repeatedly filtered. The dried organic layer was concentrated in vacuo and purified via combiflash using a mixture of ethyl acetate and hexanes (gradient 0:100 to 5:95 EtOAc:Hexanes). After the removal of di-allylated product 6-allyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one was obtained as a colorless oil (0.675 g, 3.37 mmol, 34% yield). The ^{1}H NMR spectrum matches that previously reported.[4]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.37 (td, *J* = 7.6, 1.0 Hz, 1H), 7.27 (m, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 5.77 (m, 1H), 5.03 (m, 2H), 2.94 (m, 3H), 2.68 (m, 1H), 2.23 (m, 1H), 2.06 (m, 1H), 1.96 (m, 1H), 1.69 (m, 1H), 1.59 (m, 1H).

Substrate (1e) 6-allyl-6-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one

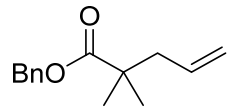


Substrate **1e** was prepared from 6-allyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one on a 3.37 mmol scale according to General Alkylation Procedure I with 4.00 equiv (13.5 mmol) of methyl iodide. After workup, the crude product was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 0:100 to 5:95 EtOAc:Hexanes) to afford 6-allyl-6-methyl-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one as a colorless oil (0.540 g, 2.52 mmol, 75% yield). The ^{1}H NMR spectrum matches that previously reported.[5]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.27 (dd, *J* = 4.9, 0.9 Hz, 2H), 7.13 (d, *J* = 7.4 Hz,

1H), 5.75 (m, 1H), 5.07 (m, 2H), 2.80 (m, 2H), 2.34 (m, 2H), 1.93 (m, 2H), 1.78 (m, 1H), 1.62 (m, 1H), 1.20 (s, 3H).

Substrate (1f) benzyl 2,2-dimethylpent-4-enoate



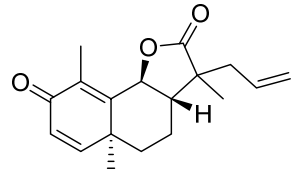
Substrate **1f** was prepared on a 5.00 mmol scale according to General Allylation Procedure I from commercially available benzyl isobutyrate. After workup, the crude product was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 0:100 to 5:95 EtOAc:Hexanes) to afford benzyl 2,2-dimethylpent-4-enoate as a colorless oil (0.670 g, 3.07 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.70 (m, 1H), 5.11 (s, 2H), 5.02 (m, 2H), 2.30 (d, *J* = 7.2 Hz, 2H), 1.20 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.3, 136.3, 134.1, 128.5, 128.0, 127.9, 118.0, 66.1, 44.7, 42.4, 24.8.

HRMS (EI+): *m/z* for $C_{14}H_{18}O_2$ $[M]^+$ calculated: 218.1307, found: 218.1312.

Substrate (1g) Allyl-santonin - (3aR,5aR,9bR)-3-allyl-3,5a,9-trimethyl-3a,5,5a,9b-tetrahydronaphtho[1,2-b]furan-2,8(3H,4H)-dione



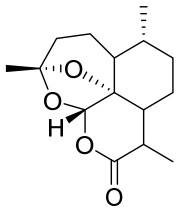
Substrate **1g** was prepared on a 5.00 mmol scale according to General Allylation Procedure I from commercially available (-)-α-Santonin. After workup, the crude product was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 5:95 to 50:50 EtOAc:Hexanes) to afford allyl-santonin as a tan solid (1.263 g, 4.410 mmol, 88% yield). The ^{1}H NMR spectrum has been previously reported, and the absolute configuration was assigned.[6]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (d, *J* = 9.8 Hz, 1H), 6.25 (d, *J* = 9.8, 1H), 5.86 (m, 1H), 5.21 (m, 2H), 5.05 (dd, *J* = 11.5, 1.3 Hz, 1H), 2.42 (m, 1H), 2.27 (m, 1H), 2.14 (d, *J* =1.3 Hz, 3H), 1.99 (m, 1H), 1.91 (m, 1H), 1.81 (m, 2H), 1.48 (m, 1H), 1.29 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 186.4, 179.2, 154.8, 151.8, 132.8, 128.9, 126.2, 119.5, 79.3, 56.7, 45.1, 41.5, 38.1, 36.9, 25.2, 22.1, 19.1, 11.1.

HRMS (EI+): *m/z* for $C_{18}H_{22}O_3$ $[M]^+$ calculated: 286.1569, found: 286.1572.

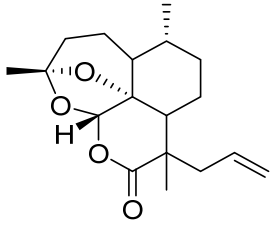
Deoxy-artemisinin



Deoxy-artemisinin was prepared commercially available artemisinin. To a dry 250 mL flask, 1.010 g (3.580 mmol, 1.000 equiv) of artemisinin and 55 mL of MeOH were added. The solution was degassed with N_2, and a slurry with 0.0270 g of 10% Pd/C in 4 mL of MeOH was added under N_2. The solution was purged twice with a balloon filled with hydrogen. Two hydrogen balloons were attached, and the reaction was allowed to stir at room temp for 24 h. At this time, the balloons were removed, and 0.0231 g of *p*-toluene sulfonic acid in 20 mL of toluene was added. The reaction was stirred until no diol remained as indicated by TLC (bottom spot disappears in approx. 2 h). The reaction mixture was filtered and concentrated under vacuum. The crude product was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 0:100 to 10:90 EtOAc:Hexanes) to afford deoxy-artemisinin as a white solid (0.854 g, 3.21 mmol, 90% yield). The ^{1}H NMR spectrum matches that previously reported.[7]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (s, 1H), 3.19 (m, 1H), 2.00 (ddd, *J* = 12.1, 4.4, 4.4 Hz, 1H), 1.90 (m, 2H), 1.78 (m, 2H), 1.60 (m, 1H), 1.53 (s, 3H), 1.25 (m, 3H), 1.20 (d, *J* = 7.3, 3H), 1.09 (m, 2H), 0.94 (d, 5.3 Hz, 3H).

Substrate (1h) (3a1R,6R,9S,10aR)-3-allyl-3,6,9-trimethyloctahydro-10aH-3a1,9-epoxyoxepino[4,3,2-ij]isochromen-2(3H)-one



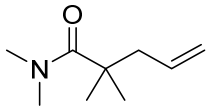
Substrate **1h** was prepared on a 3.00 mmol scale according to General Allylation Procedure I from deoxy-artemisinin. After workup, the crude product was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 0:100 to 10:90 EtOAc:Hexanes) to afford allyl-deoxy-artemisinin as a white solid (0.572 g, 1.87 mmol, 62% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 17.5, 10.2, 7.5 Hz, 1H), 5.74 (s, 1H), 5.15 (m, 2H), 3.01 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.48 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.04 (dd, *J* = 12.5, 4.2 Hz, 1H), 1.89 (m, 2H), 1.75 (m, 2H), 1.60 (m, 1H), 1.53 (s, 3H), 1.29 (m, 3H), 1.19 (s, 3H), 1.10 (m, 2H), 0.92 (d, *J* = 6.2, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.4, 133.5, 119.5, 109.8, 99.9, 83.4, 45.5, 44.6, 43.3, 41.5, 35.7, 34.3, 33.9, 26.8, 24.3, 23.4, 22.4, 18.9.

HRMS (EI+): *m/z* for $C_{18}H_{26}O_4$ $[M]^+$ calculated 306.1831, found: 306.1836.

Substrate (1i) N,N,2,2-tetramethylpent-4-enamide



Substrate **(1i)** was prepared according to the following procedure on a 7.74 mmol scale from commercially available N,N-dimethylisobutyramide.

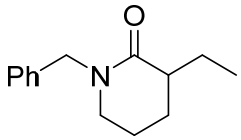
To a dry 100 mL flask under N_2 containing a magnetic stir bar, 1.6 mL of diisopropylamine (11.4 mmol 1.50 equiv) and anhydrous THF (6 mL) were added, and the flask was sealed with a rubber septum. The solution in the flask was cooled to 0 °C, and 4.6 mL of a 2.5 M *n*-butyllithium (11.5 mmol, 1.50 equiv) solution in hexanes was added. This solution was stirred for 20 min at 0 °C. To a second dry 100 mL flask under N_2 containing a magnetic stir bar, 1 mL of *N*,*N*-dimethylisobutyramide and 24 mL of anhydrous THF were added. This solution was cooled to 0 °C, and the solution from the first flask was added. The mixture was allowed to stir for 45 min at 0 °C, and then it was cooled to -78 °C. At this temperature, 4 mL (46.2 mmol, 6.00 equiv) of allyl bromide was added dropwise. The flask was allowed to warm slowly to room temperature and stirred for 12 h. The solution was poured into a separatory funnel containing 200 mL of a saturated NH_4Cl solution and extracted with ether (3 x 40 mL). Anhydrous Na_2SO_4 was added to the combined organic layers. The resulting solution was filtered through a frit containing additional anhydrous Na_2SO_4, and the remaining slurry was washed with ether (3 x 20 mL) and repeatedly filtered. The dried organic layer was concentrated in vacuo and purified via combiflash using a mixture of ethyl acetate and hexanes (gradient 5:95 to 20:80 EtOAc:Hexanes) to afford N,N,2,2-tetramethylpent-4-enamide as a clear oil (0.314 g, 2.02 mmol, 26% yield).[8]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.03 (m, 2H), 3.04 (s, 6H), 2.39 (dt, J = 7.2, 1.0 Hz, 2H), 1.27 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.6, 135.0, 117.5, 45.23, 42.4, 38.4, 26.4.

HRMS (EI+): *m/z* for $C_9H_{17}NO$ $[M]^+$ calculated 155.1310, found 155.1310.

1-benzyl-3-ethylpiperidin-2-one

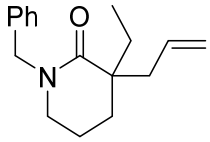


To a dry 20 mL vial under N_2 containing a magnetic stir bar, substrate (6.14 mmol, 1.00 equiv) and THF (6 mL) were added, and the vial was sealed with a rubber septum. To a dry 100 mL flask containing a stir bar under N_2, KHMDS (7.68 mmol, 1.25 equiv) and THF (18 mL) were added. The solution in the 100 mL flask was cooled to -78 °C in a bath of dry ice and acetone, and the solution from the vial was added slowly under N_2. The resulting solution was allowed to stir for 1 h, and then ethyl iodide (7.38 mmol, 1.20 equiv) was added dropwise. The flask was allowed to warm slowly to room temperature and was stirred for 12 h. The solution was poured into a separatory funnel containing 200 mL of a saturated NH_4Cl solution and extracted with ether (3 x 40 mL). Anhydrous Na_2SO_4 was added to the combined organic layers. The resulting solution was filtered through a frit containing additional anhydrous Na_2SO_4, and the remaining slurry was washed with ether (3 x 20 mL) and repeatedly filtered. The dried organic layer was concentrated

in vacuo and purified via combiflash using a mixture of ethyl acetate and hexanes (gradient 5:95 to 20:80 EtOAc:Hexanes) to afford 1-benzyl-3-ethylpiperidin-2-one as a clear oil (0.447 g, 2.06 mmol, 34% yield). The ^{1}H NMR spectrum matches that previously reported.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 2H), 7.24 (m, 3H), 4.59 (s, 2H), 3.19 (m, 2H) 2.30 (m, 1H), 1.95 (m, 2H), 1.84 (m, 1H), 1.70 (m, 1H), 1.59 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H)

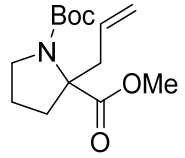
Substrate (1j) 3-allyl-1-benzyl-3-ethylpiperidin-2-one 1-Benzyl-2-piperidone



Substrate **1j** was prepared on a 2.05 mmol scale according to General Allylation Procedure I from benzyl-3-ethylpiperidin-2-one. After workup, the crude product was purified via combiflash with ethyl acetate and hexanes as eluents (gradient 5:95 to 20:80 EtOAc:Hexanes) to afford 3-allyl-1-benzyl-3-ethylpiperidin-2-one as a colorless oil (0.263 g, 1.02 mmol, 50% yield). The ^{1}H NMR spectrum matches that previously reported.[10]

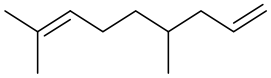
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.25 (m, 3H), 5.79 (m, 1H), 5.06 (m, 2H), 4.60 (m, 2H), 3.17 (m, 2H), 2.55 (ddt, *J* = 13.4, 6.7, 1.3 Hz, 1H), 2.21 (ddt, *J* = 13.5, 8.0, 1.1 Hz, 1H), 1.83 (m, 1H), 1.74 (m, 4H), 1.52 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H).

Substrate (1k) 1-(tert-butyl) 2-methyl 2-allylpyrrolidine-1,2-dicarboxylate



Substrate **(1k)** was prepared as previously described as a mixture of two rotomers in a 1:2 ratio.[11] ^{1}H NMR matches that previously reported. See Ref. 11 for extensive characterization.

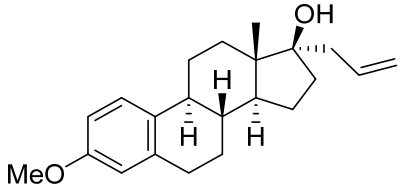
Substrate (1l) 4,8-dimethylnona-1,7-diene



Substrate **(1l)** was prepared as previously described.[12] The ^{1}H NMR spectrum matches that previously reported.[12]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.10 (m, 1H), 4.99 (m, 2H), 1.98 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H), 1.54 (m, 1H), 1.34 (m, 1H), 1.15 (m, 1H), 0.87 (br, 3H).

Substrate (1n) (8R,9S,13S,14S,17R)-17-allyl-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-ol

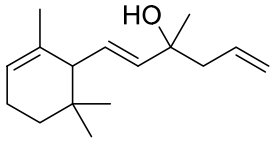


To a dry 100 mL flask under N_2 containing a magnetic stir bar, 3 mL of 1 M solution of

allyl magnesium bromide in diethyl ether (3.00 mmol, 3.00 equiv) was added. To a dry 20 mL vial under N_2 containing a magnetic stir bar, methoxy estrone (1.00 mmol, 1.00 equiv) was added, along with 6 mL of benzene. The allyl magnesium bromide solution was cooled to 0 °C , and the solution from the vial containing methoxy estrone was added dropwise to the flask containing the allyl magnesium bromide solution. An additional 3 mL of benzene was added to the 20 mL vial, and this solution was also transferred to the flask containing Grignard solution. The resulting solution was warmed to rt and stirred for 4 h. The solution was poured into a separatory funnel containing 100 mL of a saturated NH_4Cl solution and extracted with DCM (3 x 20 mL). Anhydrous Na_2SO_4 was added to the combined organic layers was added. The resulting solution was filtered through a frit containing additional anhydrous Na_2SO_4, and the remaining slurry was washed with ether (3 x 20 mL) and repeatedly filtered. The dried organic layer was concentrated in vacuo and purified via combiflash using a mixture of ethyl acetate and hexanes (gradient 0:100 to 10:90 EtOAc:Hexanes) to afford **1n** (0.281 g, 0.861 mmol, 86% yield). The ^{1}H NMR spectrum matches that previously reported.[13]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.7 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.63 (d, *J* = 2.9 Hz, 1H), 6.01 (m, 1H), 5.20 (m, 2H), 3.78 (s, 3H), 2.86 (m, 2H), 2.35 (m, 2H), 2.27 (m, 1H), 2.17 (m, 1H), 2.00 (m, 1H), 1.89 (m, 1H), 1.70-1.26 (10 H), 0.93 (s, 3H).

Substrate (1o) (E)-3-methyl-1-(2,6,6-trimethylcyclohex-2-en-1-yl)hexa-1,5-dien-3-ol



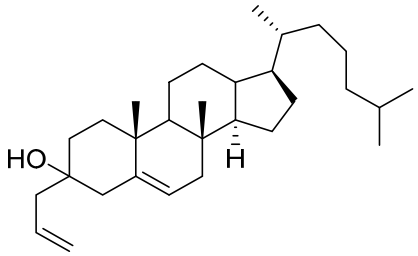
To a dry 100 mL flask under N_2 containing a magnetic stir bar, 22 mL of 1M solution of allyl magnesium bromide in diethyl ether (22.0 mmol, 1.51 equiv) was added. To a second dry 100 mL flask under N_2 containing a magnetic stir bar, α-ionone (14.6 mmol, 1.00 equiv) was added along with 40 mL of anhydrous toluene. The allyl magnesium bromide solution was cooled to 0 °C, and the solution containing α-ionone was added dropwise under N_2. The resulting solution was warmed to rt and stirred for 12 h. The solution was poured into a separatory funnel containing 200 mL of a saturated NH_4Cl solution and extracted with ether (3 x 20 mL). Anhydrous Na_2SO_4 was added to the combined organic layers. The resulting solution was filtered through a frit containing additional anhydrous Na_2SO_4, and the remaining slurry was washed with ether (3 x 20 mL) and repeatedly filtered. The dried organic layer was concentrated in vacuo and purified via combiflash using a mixture of ethyl acetate and hexanes (gradient 0:100 to 5:95 EtOAc:Hexanes) to afford **1o** (2.710 g, 11.60 mmol, 79% yield) as a mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.45 (m, 1H), 5.40 (m, 2H), 5.11 (m, 2H), 2.34 (m, 1H), 2.27 (m, 1H), 2.09 (d, *J* = 8.9 Hz, 1H), 1.99 (bs, 2H), 1.57 (m, 4H), 1.43 (m, 1H), 1.29 (s, 3H), 1.17 (m, 1H), 0.88 (s, 3H), 0.81 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ [138.44, 138.40], [134.30, 134.24], [134.18, 134.14], [128.98, 128.94], 121.11, [118.99, 118.91], [72.35, 72.33], [54.20, 54.18], [47.63, 47.60], [32.19, 32.12], [31.77, 31.75], [28.33, 28.32], [27.83, 27.71], [27.15, 27.14], 23.23, [23.08, 23.01].

HRMS (EI+): *m/z* for $C_{16}H_{26}O$ $[M]^+$ calculated: 234.1984, found: 234.1981.

Substrate (1p) (8S,9S,10R,13R,14S,17R)-3-allyl-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol.



To a dry 100 mL flask under N_2 containing a magnetic stir bar, 3 mL of 1M solution of allyl magnesium bromide in diethyl ether (1.15 mmol, 1.50 equiv) was added. To a dry 20 mL vial under N_2 containing a magnetic stir bar, 5-cholesten-3-one (0.764 mmol, 1.00 equiv) was added along with 6 mL of toluene. The allyl magnesium bromide solution was cooled to 0 °C, and the solution containing 5-cholesten-3-one was added dropwise. An additional 3 mL of toluene was added to the 20 mL vial, and this solution was transferred to the flask containing the Grignard reagent. The resulting solution was warmed to rt and stirred for 4 h. The solution was poured into a separatory funnel containing 100 mL of a saturated NH_4Cl solution and extracted with DCM (3 x 20 mL). Anhydrous Na_2SO_4 was added to the combined organic layers. The resulting solution was filtered through a frit containing additional anhydrous Na_2SO_4, and the remaining slurry was washed with ether (3 x 20 mL) and repeatedly filtered. The dried organic layer was concentrated in vacuo and purified via combiflash using a mixture of ethyl acetate and hexanes (gradient 0:100 to 10:90 EtOAc:Hexanes) to afford **1p** (0.165 g, 0.387 mmol, 51% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.6, 10.2, 7.5 Hz, 1H), 5.31 (dt, *J* = 4.9, 2.1 Hz, 1H), 5.17 (m, 1H), 5.12 (ddt, *J* = 17.1, 2.3, 1.3 Hz, 1H), 2.40 (dq, *J* = 13.4, 2.8 Hz, 1H), 2.18 (m, 2H), 2.00 (m, 3H), 1.84 (m, 1H), 1.74 (m, 1H), 1.71-1.05 (m, 20H), 1.03 (m, 3H), 1.01-0.94 (m, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (dd, *J* = 6.6, 2.7 Hz, 6H), 0.68 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.90, 133.82, 122.40, 119.12, 73.04, 56.97, 56.39, 50.73, 45.53, 42.52, 41.13, 39.98, 39.69, 36.76, 36.54, 36.38, 35.97, 34.26, 32.16, 32.15, 28.40, 28.18, 24.47, 24.03, 22.97, 22.72, 21.24, 19.67, 18.89, 12.02.

HRMS (EI+): *m/z* for $C_{30}H_{50}O$ $[M]^+$ calculated: 426.3862, found: 426.3864.

IV. Procedures and Spectral Data for Isolated Products

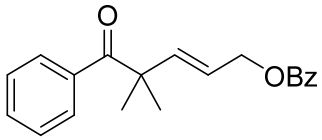
Benzoylation Procedure III on a 0.2 mmol scale:

To a dry 4 mL vial under N_2 containing a small magnetic stir bar, $Pd(OBz)_2$ (0.020 mmol, 0.10 equiv), 4,5-diazafluoren-9-one (0.020 mmol, 0.10 equiv), and benzoquinone (0.020 mmol, 0.10 equiv) were added. Substrate was layered on the bottom of the vial (0.20 mmol, 1.0 equiv), and then (0.40 mmol, 2.0 equiv) of *tert*-butyl benzoyl peroxide was added. The reaction vial was sealed with a Teflon-lined cap and heated at 65 °C for 3-15 hours. Solid substrates rapidly dissolved in the reaction mixture upon heating. Upon completion, the resulting brown oil was cooled to room temperature, and a solution consisting of 2,4,6-tribromoanisole dissolved in EtOAc was added (as an internal standard). DCM was added to the crude reaction mixture, and the resulting solution was filtered through a silica plug. The filtrate was concentrated under vacuum, and a proton NMR spectrum was acquired. Then the crude product was loaded onto silica and purified via combiflash using a mixture of ethyl acetate and hexanes.

Table S1 - Summary of 0.2 mmol Benzoylation and Isolation

Code	Shorthand	Page	Mass SM	Mass Prod	MW React	MW Prod	Mol Int Standard	React/Stand	Prod/Stand	NMR % Yield	Isolated % Yield	Time
2a	DM Ketone	5_280 A	0.0365	0.0407	188.27	308.38	2.13E-05	9.08	7.41	82	68	10h
2b	Cy Ketone	5_280 C	0.046	0.0464	228.333	348.44	2.13E-05	9.44	7.50	79	66	10h
2c	5 Ketone	5_210 D	0.0376	0.0437	186.253	306.36	2.26E-05	8.92	7.77	87	71	15h
2d	6 Ketone	5_210 E	0.0416	0.0435	200.283	320.39	2.26E-05	9.18	7.22	79	65	15h
2e	7 Ketone	5_210 F	0.0437	0.041	214.313	334.42	2.26E-05	9.01	6.44	71	60	15h
2f	Ester	5_210 C	0.0436	0.0458	218.293	338.4	2.26E-05	8.82	6.97	79	68	15h
2g	Allyl Sant	5_215 A	0.0579	0.0597	286.373	406.48	2.13E-05	9.51	7.30	77	73	5h
2h	Artemis	5_285 B	0.0633	0.0467	306.403	426.51	2.16E-05	9.58	6.87	72	53	10h
2i	Amide	6_19 A	0.0322	0.0404	155.243	275.35	2.13E-05	9.72	7.35	76	71	5h
2j	Lactam	5_210 I	0.0505	0.0426	257.373	377.48	2.26E-05	8.67	5.71	66	58	15h
2k	Proline	5_210 H	0.0555	0.0478	269.343	389.45	2.26E-05	9.10	5.18	57	60	15h
2l	Cit	5_223 A	0.0316	0.0344	152.283	272.39	2.40E-05	8.64	6.72	78	61	5h
2m	OHPH	5_266 A	0.0323	0.0343	162.233	282.34	1.23E-05	16.19	11.65	72	61	3h
2n	Estrone	5_293 A	0.0649	0.065	326.483	446.59	2.19E-05	9.07	7.45	82	73	5h
2o	ionone	5_299 A	0.0469	0.0337	234.383	354.49	2.16E-05	9.27	6.38	69	48	3h
2p	cholestrone	5_258 A	0.0836	0.0535	426.733	546.84	3.25E-05	6.03	3.99	66	50	3h

Product (2a) (E)-4,4-dimethyl-5-oxo-5-phenylpent-2-en-1-yl benzoate



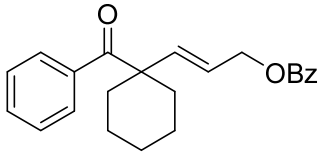
Product **2a** was synthesized according to General Benzoylation Procedure III with 0.0365 g of **1a** (0.194 mmol). The reaction duration was 10 h. A ^{1}H NMR yield of 82% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 2.5:97.5 EtOAc:Hexanes), and **2a** was obtained in a yield of 68% (0.0407 g).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.84 (m, 2H), 7.57 (m , 1H), 7.45 (t, *J* = 7.63 Hz, 3H), 7.34 (m, 2H), 6.22 (d, *J* = 15.9 Hz, 1H), 5.86 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.85 (dd, *J* = 6.2, 3.1 Hz, 2H), 1.42 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 204.14, 166.22, 140.74, 136.87, 132.96, 131.64, 130.11, 129.59, 129.15, 128.32, 127.94, 123.56, 65.07, 49.38, 26.20.

HRMS (ESI+): *m/z* for $C_{20}H_{20}O_3Na$ $[M+Na]^+$ calculated: 331.1305, found: 331.1299.

Product (2b) (E)-3-(1-benzoylcyclohexyl)allyl benzoate



Product **2b** was synthesized according to General Benzoylation Procedure III with 0.0460 g of **1b** (0.201 mmol). The reaction duration was 10 h. A ^{1}H NMR yield of 79% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 2.5:97.5 EtOAc:Hexanes), and **2b** was obtained in a yield of 66% (0.0464 g).

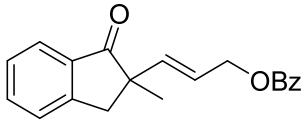
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.72 (d, *J* = 7.3 Hz, 2H) 7.56 (t, *J* = 7.5 Hz, 1H), 7.44 (m, 3H), 7.33 (t, *J* = 7.6 Hz, 2H), 6.16 (d, *J* = 16.0 Hz, 1H), 5.81 (dt, *J* = 16.0, 6.2

Hz, 1H), 4.85 (dd, *J* = 5.9, 1.4 Hz, 2H), 2.17 (m, 2H), 1.66 (m, 2H), 1.58-1.44 (m, 3H), 1.35 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 205.21, 166.41, 139.79, 138.19, 133.14, 131.34, 130.31, 129.76, 128.76, 128.51, 128.03, 125.59, 65.33, 53.69, 35.32, 25.81, 22.86.

HRMS (ESI+): *m/z* for $C_{23}H_{24}O_3Na$ $[M+Na]^+$ calculated: 371.1618, found: 371.1613.

Product (2c) (E)-3-(2-methyl-1-oxo-2,3-dihydro-1H-inden-2-yl)allyl benzoate



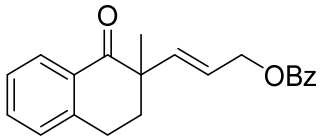
Product **2c** was synthesized according to General Benzoylation Procedure III with 0.0376 g of **1c** (0.202 mmol). The reaction duration was 15 h. A ^{1}H NMR yield of 87% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 10:90 EtOAc:Hexanes), and **2c** was obtained in a yield of 71% (0.0437 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (m, 1H), 7.42 (m, 4H), 5.98 (dt, *J* = 15.7, 1.3 Hz, 1H), 5.85 (dt, *J* = 15.7, 6.0 Hz, 1H), 4.80 (m, 2H), 3.34 (d, *J* = 17.2 Hz, 1H), 3.05 (d, *J* = 17.2 Hz, 1H), 1.40 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 207.71, 166.34, 152.02, 137.55, 135.21, 135.18, 133.02, 130.25, 129.72, 128.40, 127.76, 126.66, 124.83, 123.88, 65.31, 51.52, 41.28, 23.94.

HRMS (ESI+): *m/z* for $C_{20}H_{18}O_3Na$ $[M+Na]^+$ calculated: 329.1148, found: 329.1143.

Product (2d) (E)-3-(2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)allyl benzoate



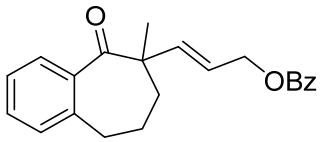
Product **2d** was synthesized according to General Benzoylation Procedure III with 0.0416 g of **1d** (0.208 mmol). The reaction duration was 15 h. A ^{1}H NMR yield of 79% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 10:90 EtOAc:Hexanes), and **2d** was obtained in a yield of 65% (0.0435 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 3H), 7.54 (m, 1H), 7.43 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 6.06 (dt, *J* = 15.9, 1.3 Hz, 1H), 5.65 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.77 (m, 2H), 3.04 (m, 1H), 2.95 (m, 1H), 2.13 (m, 2H), 1.36 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 200.06, 166.38, 143.56, 137.59, 133.42, 133.05, 131.85, 130.33, 129.76, 128.81, 128.45, 128.17, 126.85, 124.37, 65.41, 47.88, 35.45, 25.98, 23.69.

HRMS (ESI+): *m/z* for $C_{21}H_{21}O_3$ $[M+H]^+$ calculated: 321.1485, found: 321.1480.

Product (2e) (E)-3-(6-methyl-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl)allyl benzoate



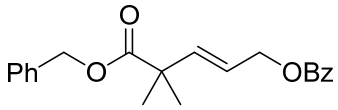
Product **2e** was synthesized according to General Benzoylation Procedure III with 0.0437 g of **1e** (0.204 mmol). The reaction duration was 15 h. A ^{1}H NMR yield of 71% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 5:95 EtOAc:Hexanes), and **2e** was obtained in a yield of 60% (0.0410 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (m, 2H), 7.59 (m, 1H), 7.47 (m, 2H), 7.38 (m, 1H), 7.33 (m, 1H), 7.29 (m, 1H), 7.15 (m, 1H), 6.11 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.82 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.84 (dd, *J* = 6.1, 1.4 Hz, 2H), 2.81 (m, 2H), 2.00 (m, 1H), 1.92 (m, 2H), 1.81 (m, 1H), 1.38 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 211.73, 166.39, 140.81, 138.24, 137.57, 133.05, 131.23, 130.37, 129.75, 128.65, 128.47, 127.60, 126.72, 123.93, 65.55, 51.69, 35.34, 32.40, 25.12, 22.99.

HRMS (ESI+): *m/z* for $C_{22}H_{22}O_3Na$ $[M+Na]^+$ calculated: 357.1461, found: 357.1457.

Product (2f) (E)-5-(benzyloxy)-4,4-dimethyl-5-oxopent-2-en-1-yl benzoate



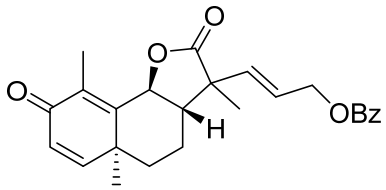
Product **2f** was synthesized according to General Benzoylation Procedure III with 0.0436 g of **1f** (0.200 mmol). The reaction duration was 15 h. A ^{1}H NMR yield of 79% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 5:95 EtOAc:Hexanes), and **2f** was obtained in a yield of 68% (0.0458 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.57 (m, 1H), 7.44 (m, 2H), 7.33 (m, 5H), 6.09 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.76 (dt, *J* = 15.8, 6.2 Hz, 1H), 5.14 (s, 2H), 4.81 (dd, *J* = 6.2, 1.4 Hz, 2H), 1.37 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.84, 166.40, 139.19, 136.20, 133.07, 130.32, 129.76, 128.62, 128.47, 128.18, 127.84, 122.90, 66.60, 65.35, 44.42, 25.00.

HRMS (ESI+): *m/z* for $C_{21}H_{22}O_4Na$ $[M+Na]^+$ calculated: 361.1410, found: 361.1406.

Product (2g) (E)-3-((3aR,5aR,9bR)-3,5a,9-trimethyl-2,8-dioxo-2,3,3a,4,5,5a,8,9b-octahydronaphtho[1,2-b]furan-3-yl)allyl benzoate



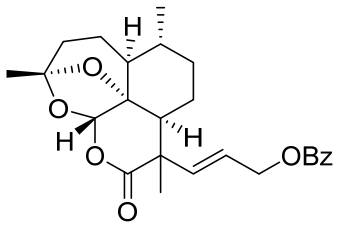
Product **2g** was synthesized according to General Benzoylation Procedure III with 0.0579 g of **1g**. (0.202 mmol). The reaction duration was 5 h. A ^{1}H NMR yield of 77% was measured. The product was purified with flash column silica chromatography (gradient 15:85 to 40:60 EtOAc:Hexanes), and **2g** was obtained in a yield of 73% (0.0597 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.56 (m, 1H), 7.43 (m, 2H), 6.64 (d, *J* = 9.9 Hz, 1H), 6.21 (d, *J* = 9.8 Hz, 1H), 5.77 (s, 2H), 4.84 (m, 3H), 2.12 (s, 3H), 1.97 (td, *J* = 12.0, 3.8 Hz, 1H), 1.84 (m, 1H), 1.78 (m, 1H), 1.73 (m, 1H), 1.45 (td, *J* = 13.1, 5.1 Hz, 1H), 1.37 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 186.28, 177.53, 166.33, 154.82, 151.24, 133.39, 130.14, 130.05, 129.75, 129.30, 128.62, 127.59, 126.12, 79.36, 64.61, 56.89, 49.24, 41.40, 37.75, 24.94, 21.34, 19.11, 11.16.

HRMS (ESI+): *m/z* for $C_{25}H_{27}O_5$ $[M+H]^+$ calculated: 407.1853, found: 407.1851.

Product (2h) (E)-3-((3aS,3a1R,6R,6aS,9S,10aR)-3,6,9-trimethyl-2-oxodecahydro-10aH-3a1,9-epoxyoxepino[4,3,2-ij]isochromen-3-yl)allyl benzoate



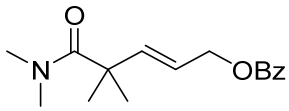
Product **2h** was synthesized according to General Benzoylation Procedure III with 0.0633 g of **1h** (0.207 mmol). The reaction duration was 10 h. A ^{1}H NMR yield of 72% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 20:80 EtOAc:Hexanes), and **2h** was obtained in a yield of 53% (0.0467 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2H), 7.53 (m, 1H), 7.40 (m, 2H), 6.04 (dd, *J* = 15.9, 1.7 Hz, 1H), 5.70 (s, 1H), 5.63 (dtd, *J* = 15.9, 6.4, 1.7 Hz, 1H), 4.77 (m, 2H), 2.05 (m, 1H), 2.00 (m, 1H), 1.87 (m, 1H), 1.78 (m, 1H), 1.66 (m, 1H), 1.53 (m, 1H), 1.39 (s, 3H), 1.31 (s, 3H), 1.23 (m, 3H), 1.08 (m, 2H), 0.90 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.68, 166.36, 141.51, 132.96, 130.30, 129.69, 128.36, 119.40, 110.15, 99.99, 82.60, 65.49, 46.50, 45.89, 45.23, 35.40, 33.99, 33.94, 25.79, 25.19, 23.51, 22.25, 18.66.

HRMS (ESI+): *m/z* for $C_{25}H_{30}O_6Na$ $[M+Na]^+$ calculated: 449.1935, found: 449.1926.

Product (2i) (E)-5-(dimethylamino)-4,4-dimethyl-5-oxopent-2-en-1-yl benzoate



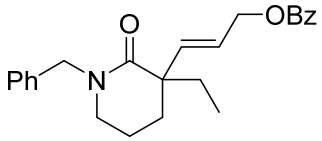
Product **2i** was synthesized according to General Benzoylation Procedure III with 0.0322 g of **1i** (0.207 mmol). The reaction duration was 5 h. A ^{1}H NMR yield of 76% was measured. The product was purified with flash column silica chromatography (gradient 5:95 to 50:50 EtOAc:Hexanes), and **2i** was obtained in a yield of 71% (0.0404 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 6.06 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.70 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.83 (dd, *J* = 6.2, 1.4 Hz, 2H), 2.96, (s, 6H), 1.34 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.17, 166.45, 141.26, 133.18, 130.33, 129.72, 128.56, 121.97, 65.37, 44.47, 26.80. (1 peak overlap)

HRMS (ESI+): *m/z* for $C_{16}H_{21}NO_3$ $[M+Na]^+$ calculated: 298.1414, found: 298.1408.

Product (2j) (E)-3-(1-benzyl-3-ethyl-2-oxopiperidin-3-yl)allyl benzoate



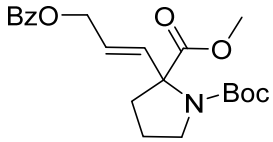
Product **2j** was synthesized according to General Benzoylation Procedure III with 0.0505 g of **1j** (0.196 mmol). The reaction duration was 15 h. A ^{1}H NMR yield of 66% was measured. The product was purified with flash column silica chromatography (gradient 5:95 to 40:60 EtOAc:Hexanes), and **2j** was obtained in a yield of 58% (0.0426 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.60 (m, 1H), 7.48 (m, 2H), 7.37-7.24 (m, 5H), 6.03 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.80 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.88 (d, *J* = 6.2 Hz, 2H), 4.62 (m, 2H), 3.23 (m, 2H), 1.91 (m, 1H), 1.83 (m, 3H), 1.71 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.73, 166.46, 139.79, 137.67, 133.00, 130.51, 129.78, 128.68, 128.45, 128.12, 127.38, 123.87, 65.69, 50.71, 48.61, 47.84, 31.99, 29.34, 19.43, 8.66.

HRMS (ESI+): *m/z* for $C_{24}H_{28}O_3$ $[M+H]^+$ calculated: 378.2064, found: 378.2063.

Product (2k) 1-(tert-butyl) 2-methyl (E)-2-(3-(benzoyloxy)prop-1-en-1-yl)pyrrolidine-1,2-dicarboxylate



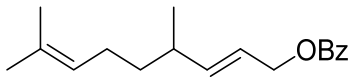
Product **2k** was synthesized according to General Benzoylation Procedure III with 0.0555 g of **1k** (0.206 mmol). The reaction duration was 15 h. A ^{1}H NMR yield of 57% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 20:80 EtOAc:Hexanes), and **2k** was obtained in a yield of 60% (0.0478 g) as a mixture of rotomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (m, 2H), 7.55 (m, 1H), 7.42 (m, 2H), 6.37 (d, *J* = 15.7 Hz, 1H), 5.69 (dt, *J* = 15.7, 6.3 Hz, 1H), 4.85 (m, 2H), 3.73 (m, 3H), 3.70-3.49 (m, 2H), 2.20 (m, 1H), 2.03 (m, 1H), 1.88 (m, 2H), 1.43 (s, 3H), 1.32 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.64, 173.46, 166.42, 166.32, 153.70, 153.42, 134.38, 133.48, 133.10, 133.02, 130.25, 129.76, 129.72, 128.45, 122.99, 122.93, 80.24, 80.09, 68.94, 68.71, 65.01, 64.87, 52.62, 52.47, 48.13, 47.98, 39.60, 38.29, 28.47, 28.28, 23.06, 22.18.

HRMS (ESI+): *m/z* for $C_{21}H_{28}NO_6$ $[M+H]^+$ calculated: 390.1911, found: 390.1905.

Product (2l) (E)-4,8-dimethylnona-2,7-dien-1-yl benzoate



Product **2l** was synthesized according to General Benzoylation Procedure III with 0.0316 g of **1l** (0.208 mmol). The reaction duration was 5 h. A ^{1}H NMR yield of 78% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 5:95 EtOAc:Hexanes), and **2l** was obtained in a yield of 61% (0.0344 g).

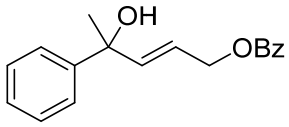
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.54 (m, 1H), 7.43 (m, 2H), 5.69 (m, 2H), 5.09 (tdt,

J = 7.4, 3.1, 1.6 Hz, 1H), 4.77 (d, *J* = 6.1 Hz, 2H), 2.19 (m, 1H), 1.97 (q, *J* = 7.5 Hz, 2H), 1.68 (s, 3H), 1.58 (s, 3H), 1.32 (m, 2H), 1.02 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.58, 142.25, 132.96, 131.58, 130.58, 129.74, 128.44, 124.59, 122.42, 65.97, 36.86, 36.15, 25.86, 20.30, 17.84. (1 peak overlap)

HRMS (EI+): *m/z* for $C_{18}H_{24}O_2$ $[M]^+$ calculated: 272.1776, found: 272.1746.

Product (2m) (E)-4-hydroxy-4-phenylpent-2-en-1-yl benzoate



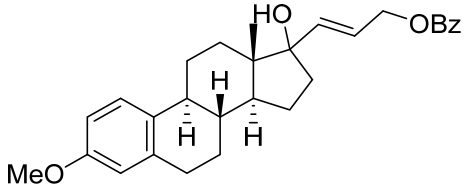
Product **2m** was synthesized according to General Benzoylation Procedure III with 0.0323 g of **1m** (0.199 mmol). The reaction duration was 3 h. A ^{1}H NMR yield of 72% was measured. The product was purified with flash column silica chromatography (5:95 EtOAc:Hexanes), and **2m** was obtained in a yield of 61% (0.0343 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.57 (m, 1H), 7.51 (m, 2H), 7.46 (m, 2H), 7.36 (m, 2H), 7.27 (m, 1H), 6.18 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.97 (dt, *J* = 15.6, 6.0 Hz, 1H), 4.86 (dd, *J* = 6.0, 1.4 Hz, 2H), 2.11 (br s, 1H), 1.70 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, CDCl3) δ 166.45, 146.31, 141.03, 133.14, 130.28, 129.79, 128.51, 128.49, 127.31, 125.28, 122.50, 74.34, 64.96, 29.80.

HRMS (ESI+): *m/z* for $C_{18}H_{18}O_3Na$ $[M+Na]^+$ calculated: 305.1148, found: 305.1145.

Product (2n) (E)-3-((8R,9S,13S,14S)-17-hydroxy-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yl)allyl benzoate



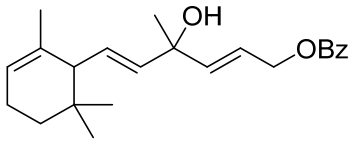
Product **2n** was synthesized according to General Benzoylation Procedure III with 0.0649 g of **1n** (0.199 mmol). The reaction duration was 5 h. A ^{1}H NMR yield of 82% was measured. The product was purified with flash column neutral alumina chromatography (gradient 0:100 to 15:85 EtOAc:Hexanes), and **2n** was obtained in a yield of 73% (0.0650 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 7.18 (d, *J* = 8.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 6.13 (d, *J* = 15.6 Hz, 1H), 5.89 (dt, *J* = 15.6, 6.2 Hz, 1H), 4.89 (m, 2H), 3.78 (s, 3H), 2.86 (m, 2H), 2.28 (m, 1H), 2.13 (m, 1H), 2.04 (m, 1H), 1.90 (m, 2H), 1.75 (m, 1H), 1.60 (m, 3H), 1.46 (m, 3H), 1.40 (m, 1H), 1.34 (m, 1H), 0.95 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.53, 157.62, 140.19, 138.09, 133.10, 132.73, 130.47, 129.77, 128.52, 126.45, 122.15, 113.97, 111.63, 83.79, 65.43, 55.36, 49.43, 47.16, 43.87, 39.65, 36.99, 32.48, 29.98, 27.61, 26.45, 23.44, 14.21.

HRMS (EI+): *m/z* for $C_{29}H_{34}O_4$ $[M]^+$ calculated: 446.2457, found: 446.2460.

Product (2o) (2E,5E)-4-hydroxy-4-methyl-6-(2,6,6-trimethylcyclohex-2-en-1-yl)hexa-2,5-dien-1-yl benzoate



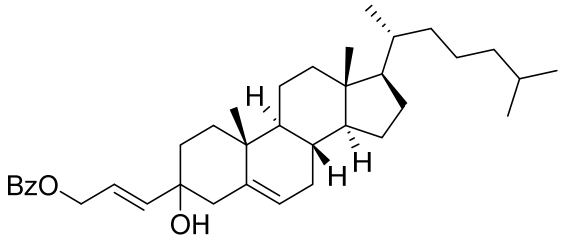
Product **2o** was synthesized according to General Benzoylation Procedure III with 0.0469 g of **1o** (0.200 mmol). The reaction duration was 3 h. A ^{1}H NMR yield of 69% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 20:80 EtOAc:Hexanes), and **2o** was obtained in a yield of 48% (0.0337 g) as a mixture of diastereomers.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.9 Hz, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 5.97 (dd, *J* = 15.7, 2.3 Hz, 1H), 5.90 (dt, *J* = 15.7, 5.4 Hz, 1H), 5.58 (d, *J* = 15.5 Hz, 1H), 5.46 (m, 1H), 5.39 (br s, 1H), 4.83, (d, *J* = 5.4 Hz, 2H), 2.10 (d, *J* = 9.2 Hz, 1H), 1.99 (br s, 2H), 1.64 (s, 1H), 1.56 (s, 3H), 1.41 (s, 3H), 1.25 (m, 1H), 1.16 (m, 1H), 0.88 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.23, [140.72, 140.63], 136.90, [133.80, 133.76], 132.88, 130.20, [129.93, 129.85], 129.57, 128.27, [121.95, 121.91], [121.10, 121.09], 72.63, 64.79, 53.91, [32.01, 31.99], 31.49, [28.33, 28.27], [27.54, 27.51], 26.89, 22.99, [22.83, 22.81].

HRMS (EI+): *m/z* for $C_{23}H_{30}O_3$ $[M]^+$ calculated: 354.2195, found: 354.2186.

Product (2p) (R)-3-((8S,9S,10R,13R,14S,17R)-3-hydroxy-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)allyl benzoate



Product **2p** was synthesized according to General Benzoylation Procedure III with 0.0836 g of **1p** (0.196 mmol). The reaction duration was 3 h. A ^{1}H NMR yield of 66% was measured. The product was purified with flash column silica chromatography (gradient 0:100 to 10:90 EtOAc:Hexanes), and **2p** was obtained in a yield of 50% (0.0535 g).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (m, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 6.05 (d, *J* = 15.9 Hz, 1H), 5.97 (dt, *J* = 15.9, 4.8 Hz, 1H), 5.33 (d, *J* = 4.8 Hz, 1H), 4.82 (d, *J* = 4.8 Hz, 2H), 2.54 (m, 1H), 2.17 (dd, *J* = 13.4, 2.7 Hz, 1H), 2.05-0.96 (m, 30H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.87 (dd, *J* = 6.6, 1.4 Hz, 6H), 0.67 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.41, 140.23, 139.13, 133.09, 130.48, 129.79, 128.51, 123.24, 122.95, 100.15, 73.05, 65.33, 56.88, 56.38, 50.44, 45.97, 42.48, 39.92, 39.68, 36.65, 36.38, 36.33, 36.06, 35.97, 32.04, 28.40, 28.18, 24.42, 24.04, 22.98, 22.72, 21.20, 19.67, 18.88, 12.01.

HRMS (ESI+): *m/z* for $C_{37}H_{54}O_3Na$ $[M+Na]^+$ calculated: 569.3965, found: 569.3970.

V. Raw Data For Tables 1 and 2

Table S2 – Masses of Substrate and Internal Standard for Table 1. Oxidation of Model Ketone 1b.

Exp	Sub	Mass	MW	Mol Sub	R/S Mol	P/S (NMR)	R/S (NMR)
A-1	1b	0.0236	228.34	0.000103	5.210	0	5.431
B-2	1b	0.0232	228.34	0.000102	5.122	0	1.140
C-3	1b	0.0233	228.34	0.000102	5.144	3.031	0
D-4	1b	0.0235	228.34	0.000103	5.188	2.998	0
E-5	1b	0.0229	228.34	0.0001	5.056	2.781	0
F-6	1b	0.0232	228.34	0.000102	5.122	2.643	1.081
G-7	1b	0.0232	228.34	0.000102	5.122	3.766	0
H-8	1b	0.0231	228.34	0.000101	5.100	3.987	0
I-9	1b	0.0233	228.34	0.000102	5.144	4.149	0
J-10	1b	0.0233	228.34	0.000102	5.144	3.943	0

Table S3 – Yields and Conversions for Table 1. Oxidation of Model Ketone 1b.

Exp	Sub	Yield	Remaining Reactant	Pd(Obz)2	DAFO	BQ	Time	Temp °C
A-1	1b	0	104%	X	10%	X	20h	65
B-2	1b	0	22%	10%	X	X	20h	65
C-3	1b	59%	0	10%	10%	X	20h	65
D-4	1b	58%	0	10%	10%	X	20h	65
E-5	1b	55%	0	20%	20%	X	20h	65
F-6	1b	52%	21%	10%	10%	X	20h	65
G-7	1b	74%	0	10%	10%	10%	20h	65
H-8	1b	78%	0	10%	10%	50%	20h	65
I-9	1b	81%	0	10%	10%	10%	10h	65
J-10	1b	77%	0	10%	10%	10%	10h	65
IJAVG	1b	79%	0	10%	10%	10%	10h	66

S = Internal Standard Tribromoanisole
R = Substrate **(1b)**
P = product **(2b)**
Cy = **1b**

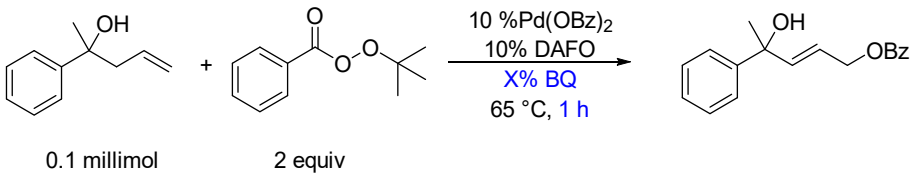
Table S4 – Masses of Substrate and Internal Standard for Table 2. Oxidation of Homoallylic Alcohol 1m

Exp	Exp #	Sub	Mass	MW	Mol Sub	R/S Mol	P/S (NMR)	R/S (NMR)
6_51 E	1	1m	0.0162	162.23	0.000100	4.8059	1.3222	2.2160
6_52B	2	1m	0.0165	162.23	0.000102	4.8949	1.3842	2.2768
6_51C	3	1m	0.0166	162.23	0.000102	4.9245	1.2271	0.0000
6_51F	4	1m	0.0170	162.23	0.000105	5.0432	3.5158	0.0000
6_51G	5	1m	0.0162	162.23	0.000100	4.8059	3.3408	0.0000
6_51H	6	1m	0.0165	162.23	0.000102	4.8949	3.3525	0.0000
6_52A	7	1m	0.0172	162.23	0.000106	5.1025	3.4990	0.0000

Table S5 – Yields and Conversions for Table 2. Oxidation of Homoallylic Alcohol 1m

Exp	Sub		Yield	Remaining Reactant	Pd(Obz)2	DAFO	BQ	Time	Temp °C
1	1m		28%	46%	10%	10%	X	1 h	65
2	1m		28%	47%	10%	10%	X	3 h	65
3	1m		25%	0%	10%	10%	X	48 h	65
4	1m		70%	0%	10%	10%	5%	1 h	65
5	1m		70%	0%	10%	10%	10%	1 h	65
6	1m		69%	0%	10%	10%	50%	1 h	65
7	1m		69%	0%	10%	10%	10%	3 h	65

VI. Investigation of the Effects of Additives on the Rate and Yield of C-H Oxidation



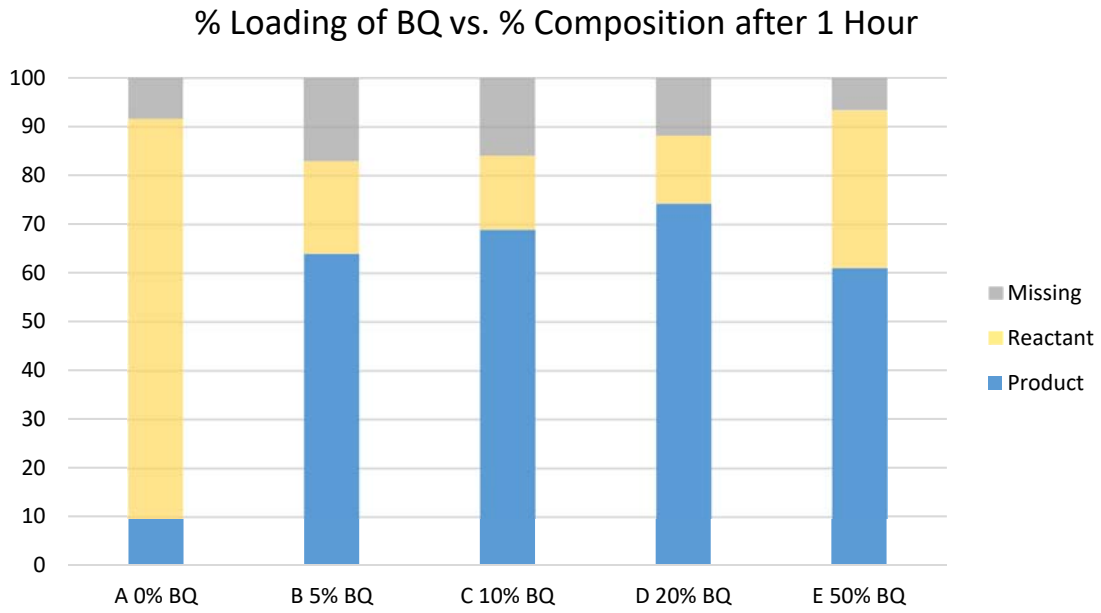
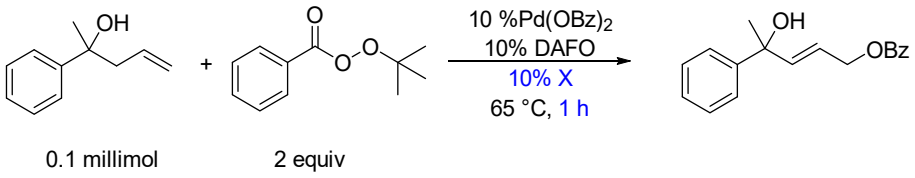


Figure S1 – The Effect of Varying the Loading of BQ on the Yield of 2m and Conversion of 1m



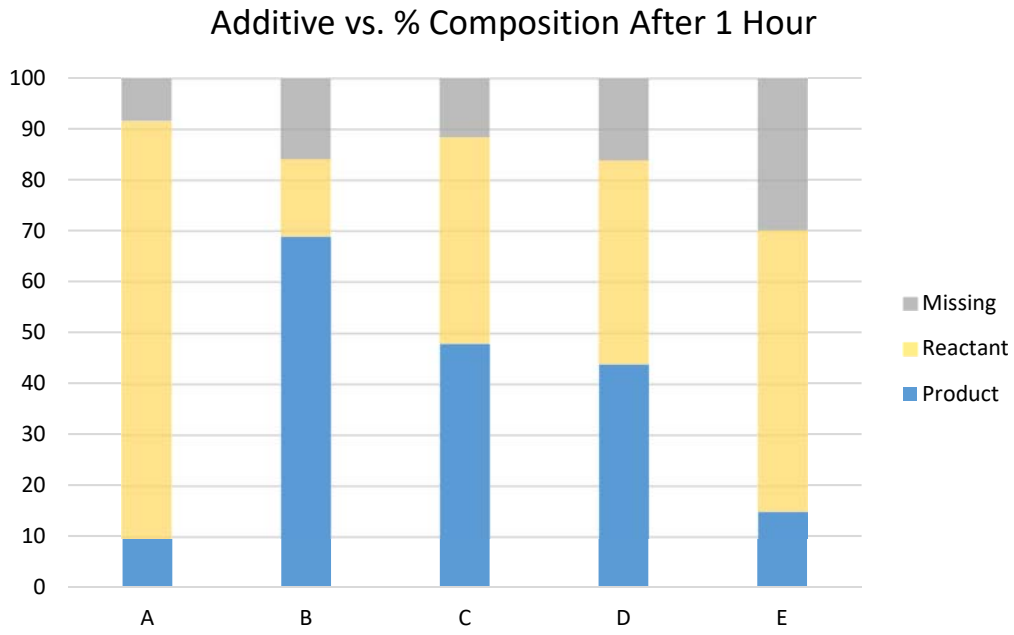


Figure S2 – The Effect of Varying the Structure of the Quinones on the Yield of 2m and Conversion of 1m

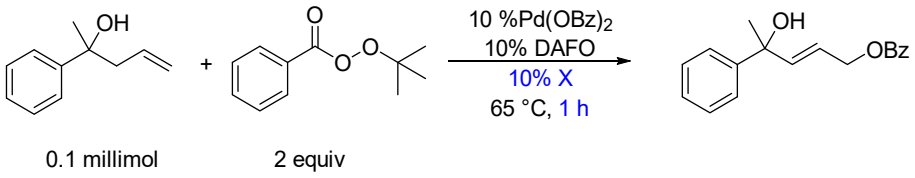
A = Control - no Additive

B = 10% Benzoquinone

C = 10% 2,6-dimethylcyclohexa-2,5-diene-1,4-dione

D = 10% 2,5-dimethylcyclohexa-2,5-diene-1,4-dione

E = 10% 2,3,5,6-tetrafluorocyclohexa-2,5-diene-1,4-dione



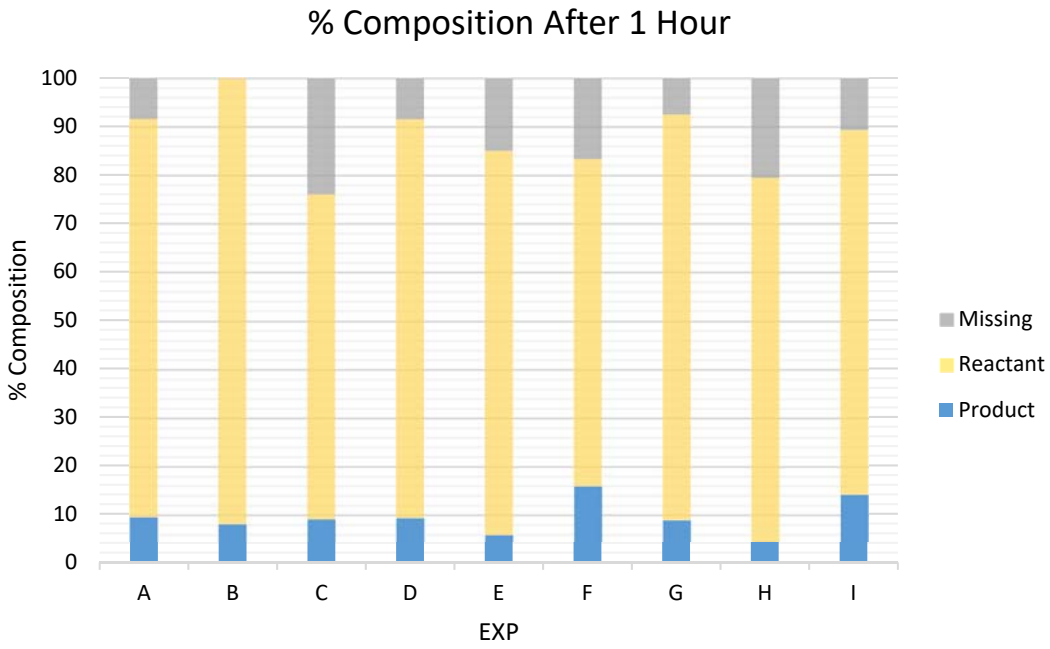


Figure S3 – The Effect of Metal Salts on the Yield of 2m and Conversion of 1m

A = CTRL no additive

B = 10% $NaVO_3$

C = 10% $VO(acac)_2$

D = 10% Fe_2O_3

E = 10% $Fe(acac)_3$

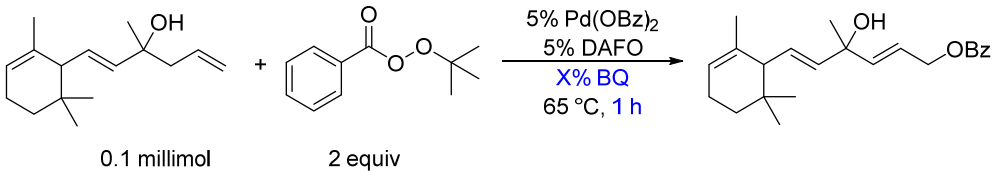
F = 10% Cu(O)

G = 10% (Co)Salophen (CAS 14167-18-1)

H = 10% $Fe(acac)_2$

I = Ferrocenium tetrafluoroborate (CAS: 1282-37-7)

VII. Optimization of Conditions for Large Scale Reaction



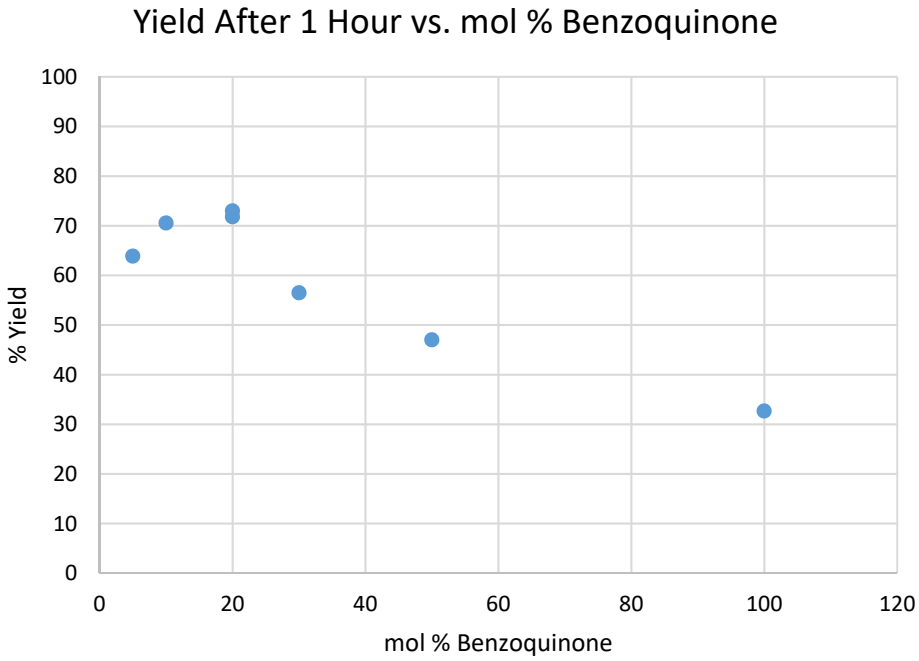


Figure S4 – The Effect of Varying the BQ Loading on the Yield of 2o and Conversion of 1o with 5 mol % $Pd(OBz)_2$ and DAFO

VIII. Crude NMR from the Oxidation of 1m

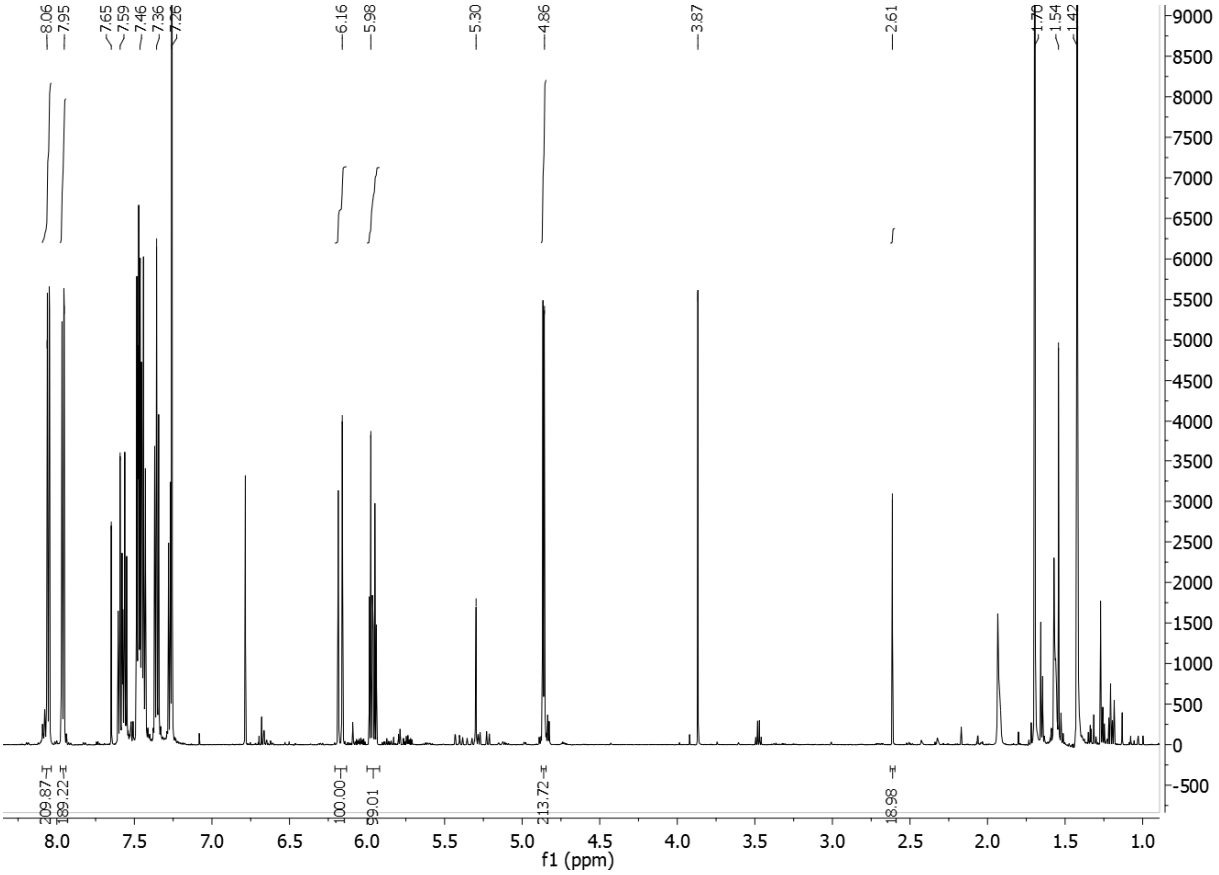


Figure S5 - Representative Crude ^{1}H NMR Spectrum for the Oxidation of 1m

IX. Possible Catalytic Cycle for Allylic Oxidation

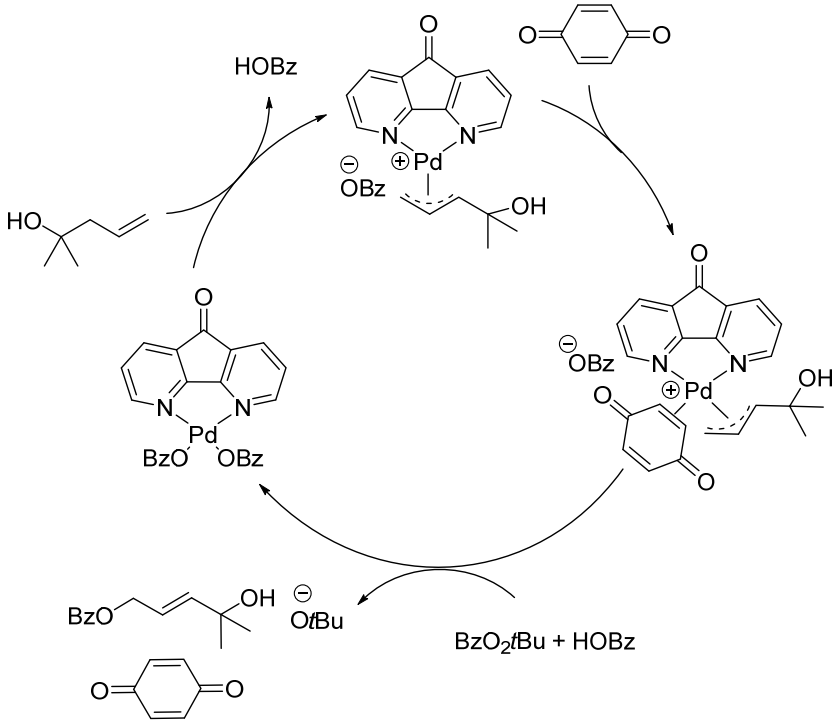


Figure S6 – Possible Catalytic Cycle for Allylic Oxidation

X. References for Experimental Section

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Chapter 5

Cooperative Reactions Combining Photocatalyzed Isomerization and Enzymatic Reduction

5.1 Introduction

Living organisms rely upon concurrent reactions that are catalyzed by mutually compatible and selective enzymes to synthesize complex natural products and other metabolites. Enzymes such as isomerases cooperate with other enzymes to generate products in yields and ee's that cannot be obtained from the sequential reactions of the individual catalysts on their respective substrates.[1] Many enzymes have been refined by evolution to be chemoselective, exhibit high total turnover numbers (TTNs), and be highly enantioselective. However, there are many synthetically desirable transformations that are unknown in biological systems. Traditionally, chemists have overcome these limitations by employing artificial chemical catalysts. However, unlike enzymes, small-molecule chemical catalysts are often mutually incompatible with other catalysts and enzymes and promote undesirable side reactions. The limitations of chemical and enzymatic catalysts have inspired the development of cooperative chemoenzymatic systems.

Of the cooperative chemoenzymatic reactions that have been reported over the last 30 years, the vast majority can be divided into two categories: 1) the chemoenzymatic dynamic kinetic resolutions of alcohols and amines and 2) enzymatic reactions requiring the simultaneous regeneration of a co-factor.[2-4] The first category of reactions has been extensively explored because of the synthetic utility of the products and because the esterases employed in these reactions are unusually stable in organic solvent at elevated temperatures. The second category of reactions has been studied because of the need to recycle or replace expensive or unstable biological cofactors with inexpensive terminal oxidants or reductants. In practice, enzymatic systems for the regeneration of cofactors are more frequently employed than chemical systems because of their superior compatibility with other enzymes.[4] New cooperative chemoenzymatic reactions are difficult to develop because chemical and enzymatic catalysts generally operate in different media at different temperatures and can deactivate each other. As a result of these compatibility issues, few novel cooperative chemoenzymatic systems have been reported in recent years.[5-7]

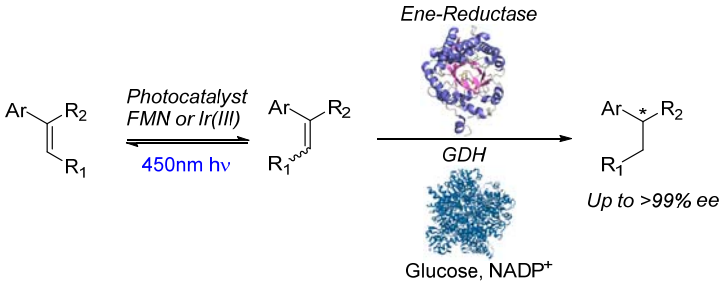
To combine the advantages of chemical and enzymatic catalysts, the Hartwig and Zhao groups in collaboration previously developed a process in which olefin metathesis and enzymatic epoxidation of one olefin component occurs cooperatively.[5] Another report described a sequential, non-cooperative combination of rhodium-catalyzed diazocoupling to form alkenes with an enzyme-catalyzed reduction of alkenes to provide enantioenriched 2-substituted acid diesters (Figure 1). The lack of cooperativity of this system inspired efforts to develop a conceptually new approach to cooperative chemoenzymatic catalysis. Diazo coupling reactions in which the diastereoselectivity was low gave low yields of the saturated product because the ene-reductase selectively reduced only one of the alkene isomers. Many of the most widely employed synthetic methods for the synthesis of olefins yield *E/Z* mixtures. In some cases, the *E* and the *Z* isomers cannot be separated by chromatography. A stereoconvergent catalytic system is required to achieve high yields and high ee's from the reduction of such inseparable mixtures. A highly selective enzyme would reduce a single isomer of the alkene mixture, resulting in a low yield but a high % ee. A less selective enzyme would reduce both isomers to generate the reduced products in a high combined yield but with a low % ee. A stereoconvergent catalytic system would also be advantageous in cases in which a synthetic method selectively generates an isomer that cannot be reduced by a known ene-reductase.

The combination of a catalyst that isomerizes alkenes and an ene-reductase that converts one isomer of a mixture of *E* and *Z* alkenes (or pure *Z* alkenes) into enantioenriched products

(Figure 1) could lead to high yields of highly enantioenriched products directly from an *E/Z* mixture of alkenes.

This chapter describes the development of a new type of cooperative chemoenzymatic system that combines the photocatalytic isomerization of alkenes with enzymatic reduction to generate enantioenriched products in high yields. Both *E* and *Z* isomers of a model substrate, 2-phenylbut-2-enedioic acid dimethyl ester (**1a**), were synthesized, and an enzyme that preferentially reduced a single isomer was identified. This substrate (**1a**) was evaluated for its ability to undergo photoisomerization in the presence of a series of catalysts. The cooperative reduction of the non-preferred isomer was accomplished, and similar reactions were conducted with a range of substrates.

Figure 1. A Combination of Enzymatic Reduction of Alkenes and Photocatalytic Isomerization



5.2 Results and Discussion

To develop a stereoconvergent enzymatic reduction, 2-phenylbut-2-enedioic acid dimethyl ester (**1a**) was selected as a model substrate. YersER, an ene-reductase isolated from *Yersinia bercovieri*, exclusively reduces the *E* isomer of 2-phenylbut-2-enedioic acid dimethyl ester to dimethyl 2-phenylsuccinate in high yields with excellent ee's in the presence of a glucose dehydrogenase (GDH) enzyme for co-factor regeneration.[8] Under ambient conditions in Tris buffer, neither *E* nor *Z* 2-phenylbut-2-enedioic acid dimethyl ester undergoes thermal isomerization (Supporting Information). To develop a stereoconvergent reduction reaction, a catalyst for the *E/Z* isomerization of olefins that is compatible with ene-reductases needed to be identified. An appropriate catalyst would 1) operate in aqueous solution at ambient temperature, 2) isomerize alkenes at rates that significantly exceed the rates of enzymatic reduction, 3) remain activate in the presence of ene-reductases, substrates, and products in the reaction mixture, 4) isomerize olefins at the low substrate concentrations required for enzymatic reduction, and 5) generate an *E/Z* mixture of isomers that includes the fast-reacting isomer of substrate. The isomerization catalyst must also 6) be mutually compatible with the ene-reductases, 7) be mutually compatible with a glucose dehydrogenase NADPH regeneration system, 8) not racemize the product, 9) and not promote side reactions.

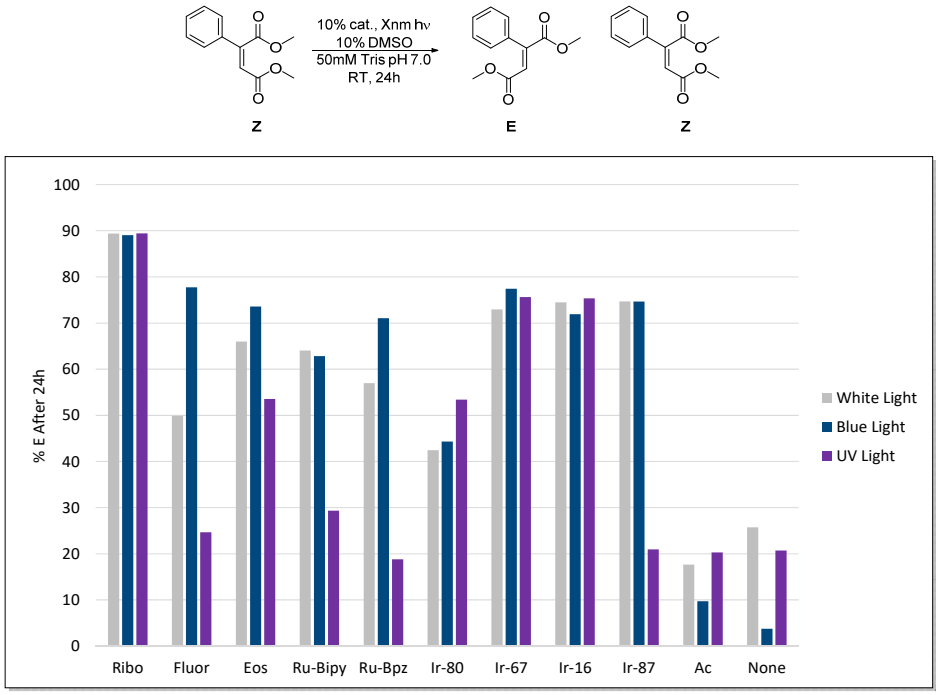
Development of Conditions for the Isomerization of Alkenes

Two strategies were considered to induce the isomerization of alkenes. In the first strategy, the thermal *E/Z* isomerization of alkenes would occur in the presence of a catalyst and appropriate

conditions. Initial experiments to induce the thermal isomerization *E* and *Z* 2-phenylbut-2-enedioic acid dimethyl ester in the presence of various metal salts and organic catalysts in Tris buffer (Supporting Information) were conducted. Negligible isomerization was observed.

The second strategy involved a photocatalytic approach to the isomerization of alkenes.[9-10] In 2015, Gilmour et al. reported the photoisomerization of α,β-unsaturated monoesters with riboflavin in the presence of UV (402 nm) light in acetonitrile.[9] This reaction is proposed to proceed via preferential singlet or triplet energy transfer from a photocatalyst to one alkene isomer.[11-12] Initial experiments assessed the photoisomerization of (*Z*)-2-phenylbut-2-enedioic acid dimethyl ester (**Z-1a**) in solvent mixtures appropriate for the reduction of alkenes by ene-reductases. *E* and *Z* 2-phenylbut-2-enedioic acid dimethyl ester (**1a**) isomerized in semi-aqueous media (1:9 DMSO:Tris Buffer) in the presence of riboflavin and UV (395 nm) or blue (450 nm) light (Figure 2). The *E:Z* ratios of **1a** were higher when the photoisomerization was conducted in semi-aqueous media than when it was conducted in pure DMSO. Negligible isomerization was observed in the presence riboflavin when light was omitted. Under UV or blue light in the absence of a photocatalyst, limited isomerization was observed.

Figure 2. Isomerization of 2-phenylbut-2-enedioic acid dimethyl ester in the Presence of a Series of Photocatalysts and Light Sources

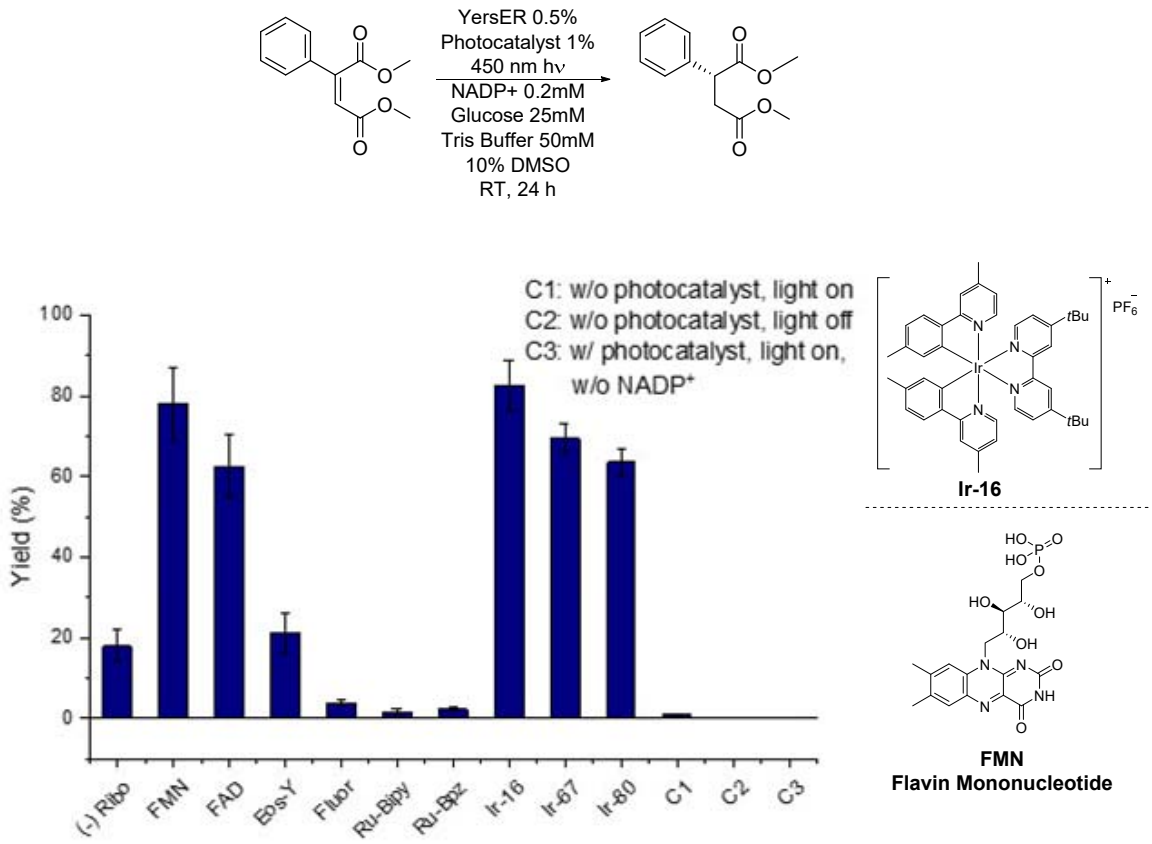


Ribo: Riboflavin, Fluor: Fluorescein Y, Ru-Bipy: $Ru(Bipy)_3Cl_2$, Ru-Bpz: $Ru(Bpz)_3(PF_6)_2$, Ir-80: CAS 808142-80-5, Ir-67: CAS 676525-77-2, **Ir-16**: CAS 1607469-49-7 , Ac: Acridinium Salt CAS - 674783-97-2

To identify other catalysts that would enable the *E/Z* isomerization of alkenes, the isomerization of 2-phenylbut-2-enedioic acid dimethyl ester was evaluated in the presence of a series of photocatalysts in 1:9 DMSO:50mM Tris buffer (Figure 2). The solutions were irradiated

with 450 nm light for 20 h, and the final *E*:*Z* ratios were determined. Greater than 50% conversion of (*Z*)-dimethyl 2-phenylmaleate to (*E*)-2-phenylbut-2-enedioic acid dimethyl ester was observed when the substrate was irradiated in the presence of many organometallic and organic photocatalysts, and the highest *E*:*Z* ratios exceeded 9:1. Increasing catalyst loading, increasing light intensity, and exclusion of oxygen increased the rate of photoisomerization of 2-phenylbut-2-enedioic acid dimethyl ester (Supporting Information). Because 2-phenylbut-2-enedioic acid dimethyl ester isomerized rapidly in the presence of blue light and various photocatalysts in air, all subsequent experiments were conducted in air.

Figure 3. Cooperative Photoisomerization and Reduction of 2-phenylbut-2-enedioic acid dimethyl ester with a Series of Catalysts



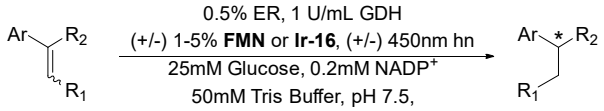
Ribo: Riboflavin, FMN: Flavin mononucleotide, FAD: Flavin adenine dinucleotide, Fluor: Fluorescein Y, Ru-Bipy: $Ru(Bipy)_3Cl_2$, Ru-Bpz: $Ru(Bpz)_3(PF_6)_2$, **Ir-80**: CAS 808142-80-5, **Ir-67**: CAS 676525-77-2, **Ir-16**: CAS 1607469-49-7 , Ac: Acridinium Salt CAS - 674783-97-2

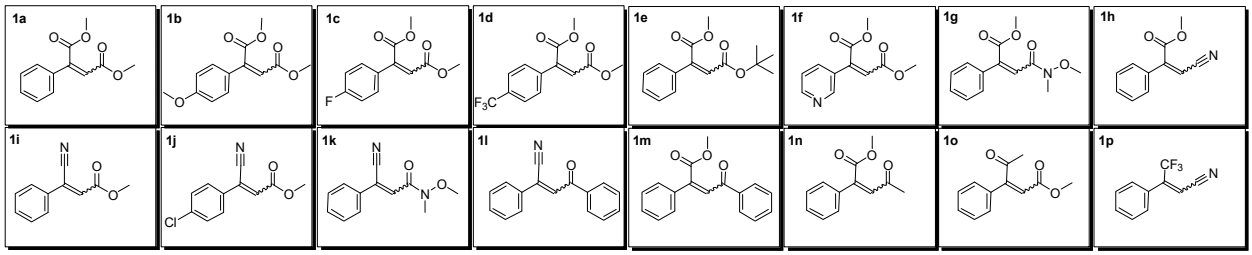
Having demonstrated that various photocatalysts isomerize (*Z*)-2-phenylbut-2-enedioic acid dimethyl ester to (*E*)-2-phenylbut-2-enedioic acid dimethyl ester in a semi-aqueous medium, the concurrent cooperative photoisomerization and enzymatic reduction of (*Z*)-2-phenylbut-2-enedioic acid dimethyl ester with a series of photocatalysts was evaluated (Figure 3). Moderate to

high yields of dimethyl 2-phenylsuccinate were obtained when a range of catalysts were used in the cooperative process. The highest conversions and yields were obtained when the cooperative reaction was conducted with 5% of the flavin photocatalyst flavin mononucleotide (FMN) or 1% of the cationic iridium (III) photocatalysts [4,4'-bis(tert-butyl)-2,2'-bipyridine]bis[5-methyl-2-(4-methyl-2-pyridinyl)phenyl]iridium(III) hexafluorophosphate (**Ir-16**), [4,4'-bis(tert-butyl)-2,2'-bipyridine]bis[2-(2-pyridinyl)phenyl]iridium(III) hexafluorophosphate (**Ir-67**), and [4,4'-bis(tert-butyl)-2,2'-bipyridine]bis[5-(tert-butyl)-2-[4-(tert-butyl)-2-pyridinyl]phenyl]iridium(III) hexafluorophosphate (**Ir-80**). Although $Ru(Bipy)_3Cl_2$ and riboflavin catalyze the isomerization of (*Z*)-2-phenylbut-2-enedioic acid dimethyl ester in the presence of blue light, low yields of reduced product were obtained when they were used as photocatalyst in the cooperative reaction. One possible explanation for the low yields obtained when riboflavin was used as photocatalyst could be related its structural similarity to FMN, which is the native co-factor of the YersER. Competitive binding of riboflavin to the FMN binding site of YersER could inhibit enzymatic activity and result in the low yields obtained when it is employed as a photocatalyst.[13]

The newly developed conditions were applied to cooperative reactions with a range of aryl diesters with the photocatalysts FMN and **Ir-16**. For each substrate, a panel of ene-reductases was evaluated (Supplementary Information), and the combination of photocatalyst and ene-reductase that provided the highest yield and ee is included in Table 1.

Table 1. Substrate Scope and Control Experiments for the Cooperative Reduction of Alkenes





Ex	Substrate	Enzyme	Photocat.	% E at PS[f]	% Conv.	% Yield	% ee
1	**1a-*Z***	YersER	-		0%	-	-
2	**1a-*Z***	YersER	Ir-16 (FMN)	66 (93)	88% (>99%)	87% (70%)	>99% (>99%)
3	**1a-*50%E***	YersER	Ir-16 (FMN)		96% (>99%)	89% (86%)	>99% (>99%)
4	**1b-*Z***	YersER	-		0%	-	-
5	**1b-*Z***	YersER	Ir-16 (FMN)	59 (62)	89% (72%)	89% (63%)	>99% (>99%)
6	**1c-*Z***	xenB	-		15%	15%	-
7	**1c-*Z***	xenB	Ir-16 (FMN)	53 (91)	89% (58%)	89% (39%)	>99% (>99%)
8	**1d-*Z***	xenB	-		12%	8%	-
9	**1d-*Z***	xenB	Ir-16 (FMN)	71 (90)	96% (80%)	87% (63%)	>99% (>99%)
10	**1e-*70%E***	OPR1	-		63%	52%	>99%
11	**1e-*70%E***	OPR1	Ir-16		98%	74%	>99%

12	**1f-68%*E***	xenB	-		63%	59%	-
13	**1f-68%*E***	xenB	Ir-16 (FMN)	54 (87)	98% (80%)	91% (60%)	91% (87%)
14	**1g-*Z***	OPR1	-		9%	9%	-
15	**1g-*Z***	OPR1	Ir-16 (FMN)	19 (91)	98% (28%)	82% (21%)	>99% (>99%)
16	**1h-*Z***	TOYE	-		5%	3%	-
17	**1h-*Z***	TOYE	Ir-16 (FMN[d])	61 (53)	88% (99%)	85% (90%)	>99% (>99%)
18	**1i-*Z***	OYE3	-		10%	5%	-
19	**1i-*Z***	OYE3	Ir-16 (FMN[d])	52 (55)	98% (>99%)	92% (98%)	98% (95%)
20	**1j-*Z***	OYE2	-		10%	3%	-
21	**1j-*Z***	OYE2	Ir-16[e] (FMN)	21 (4)	95% (88%)	79% (75%)	92% (90%)
22	**1k-*Z***	YersER	w/o light		0%	0%	-
23	**1k-*Z***	YersER	w/ light		100%	90%	99%
24	**1l-*Z***	OYE2	w/o light		0%	0%	-
25	**1l-*Z***	OYE2	w/ light	82	100%	95%	>99%
26	**1m-*Z***	OPR1	-		7%	7%	-
27	**1m-*Z***	OPR1	Ir-16 (FMN)	77 (87)	100% (100%)	91% (76%)	>99% (>99%)
28	**1n-*Z***	SYE1	-		10%	7%	-
29	**1n-*Z***	SYE1	Ir – 16 (FMN)		96% (90%)	80% (72%)	88% (76%)
30	**1o-*Z***	YersER	-		6%	5%	-
31	**1o-*Z***	YersER	Ir-16 (FMN)	51 (41)	95% (95%)	87% (89%)	96% (86%)
32	**1p-*E***	OYE3	-		17%	11%	-
33	**1p-*E***	OYE3	Ir-16 (FMN)		98% (85%)	74% (34%)	>99% (>99%)

The reaction was performed 24 hurs in 50 mM Tris buffer at pH 7.5 with 0.5 mol% ERs, 1 mol% Ir-16 or 5 mol% FMN, 1 U/mL GDH, 0.2 mM $NADP^+$, 25 mM glucose, 5 *v/v%* DMSO, with or without blue light. [a] [b]Determined by GC-MS using synthesized authentic standards. [c]Determined by Chiral HPLC. [d]1 mol% FMN. [e]5 mol% Ir-16. % E at PS is the E/Z ratio of substrate obtained after 24 hours of irradiation with 450 nm light with a photocatalyst. In the case of 1l, no photocatalyst was used.[f]Photostationary *E/Z* ratio obtained after substrate was irradiated in the presence of a catalyst for 24 h.

High yields were obtained for the cooperative isomerization and reduction of diesters containing electron-rich and electron-poor aryl groups with either FMN or **Ir-16** as photocatalysts. In addition, the ee's of the products obtained from the cooperative reaction of the *Z* alkenes matched those obtained when pure *E* alkenes were reduced in the absence of a photocatalyst. Unsymmetrical diesters and heteroaryl diesters also were evaluated. Both of these compounds (**1e** and **1f**) were obtained as inseparable mixtures of *E* and *Z* alkenes. As previously discussed, a stereoconvergent catalytic system is required to achieve high yields and high ee's from the reduction of such inseparable mixtures. The products from the cooperative chemoenzymatic reduction of the *E*:*Z* mixtures of **1e** and **1f** were obtained in high yields and with high ee's, indicating that the reactions were stereoconvergent.

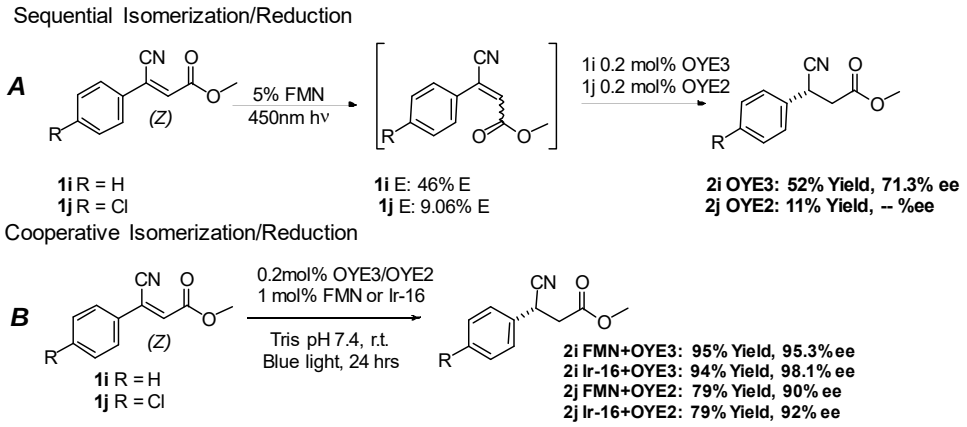
To determine if the cooperative reaction would give high yields and high enantioselectivities with mixtures of alkenes other than diesters, the cooperative reduction of unsaturated compounds containing diverse combinations of functional groups was evaluated. The *E* and *Z* isomers of **1g**-**1o** were allowed to react with a series of ene-reductases. In the absence of

light and a photocatalyst, the enzymatic reduction of the *Z* isomers of **1g**-**1o** typically resulted in low conversions. However, ene-reductases that reduced the *E* isomers of **1g**-**1o** to produce **2g**-**2o** in high yields and ee's were identified. Other experiments revealed that both **Ir-16** and FMN isomerize the *Z* isomers of substrates **1g**-**1o** in the presence of blue light. The combinations of photocatalyst and enzyme that generated the products in the highest yields and ee's from the *Z* isomers of **1g**-**1o** are listed in Table 1. High yields and ee's were obtained for the cooperative reduction of β-cyano-α,β-unsaturated esters and (*Z*)-**1h** α-cyano-α,β-unsaturated esters (*Z*)-**1i** and (*Z*)-**1j**. High yields and ee's were also obtained for cyanoketone (*Z*)-**1l**, β-keto-α,β-unsaturated esters (*Z*)-**1m** and (*Z*)-**1n**, and α-keto-α,β-unsaturated ester (*Z*)-**1o**. The cooperative reductions of amidoacrylate (*Z*)-**1g** and amidocyanate (*Z*)-**1k** are noteworthy because the products **2g** and **2k** were obtained in high yields and ee's, and also because similar enzymatic reductions of alkenes containing weinbreb amides have not been reported.

Control experiments revealed that YersER reduced (*Z*)-**1k** (Entry 22) and (*Z*)-**1l** (Entry 24) in the presence blue light in the absence of an added photocatalyst. In the absence of light, these substrates reacted to low conversion (Entries 23, 25). A series of experiments were conducted in the absence of ene-reductases to determine the origin of this observation. Upon irradiation with blue light, (*Z*)-**1l** underwent isomerization to form an 82:18 *E*/*Z* mixture of **1l**, but (*Z*)-**1k** did not. However, (*Z*)-**1k** underwent rapid isomerization in the presence of 0.1% FMN and blue light (Supporting Information). Thus, trace quantities of free or enzyme-bound FMN (the natural cofactor of YersER) in the reaction mixture likely catalyze the isomerization (*Z*)-**1k** upon irradiation with blue light.

An enzyme that reduced the *E* isomer of trifluoromethylcyanate **1p** in high yield and ee could not be identified, but OYE3 reduced the *Z* isomer of **1p** in high yield and ee. To determine if a cooperative reaction could convert (*E*)-**1p** to **2p**, the ability of (*E*)-**1p** to undergo photoisomerization in the presence of a **Ir-16** and blue light was evaluated. Isomerization of (*E*)-**1p** was observed, so the cooperative reaction was attempted. The product **2p** was obtained in a high yield and ee from the cooperative reduction of *E*-**1p**. This example illustrates an important benefit of the cooperative chemoenzymatic reaction: the system enables either isomerization of a *Z* alkene with concurrent enzymatic reduction of the *E* isomer of substrate, or isomerization of an *E* alkene with concurrent enzymatic reduction of the *Z* isomer of substrate. The conversion of (*E*)-**1p** to **2p** is also noteworthy because the enzymatic reduction of similar compounds to generate products that contain stereogenic centers substituted with trifluoromethyl groups has not been reported.

Figure 5. Sequential vs. Cooperative Reduction of Cyanoacrylates 1i and 1j

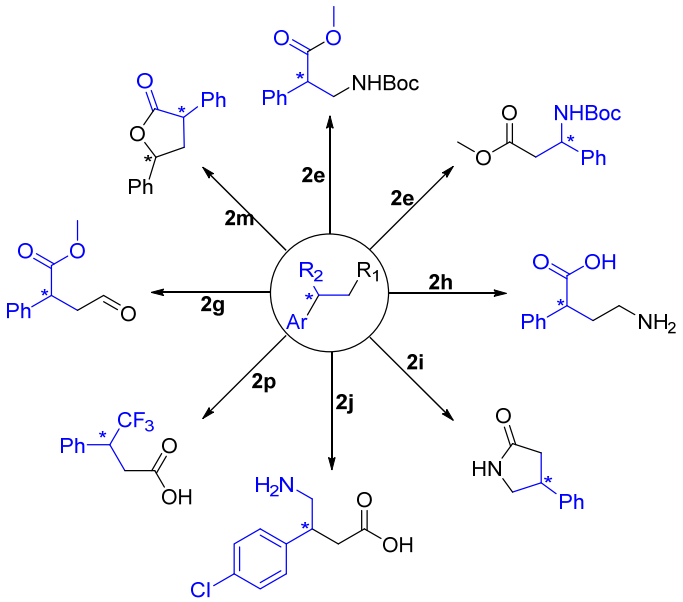


The cooperative enzymatic reduction of substrates **1i** and **1j** illustrates the benefits of a cooperative system over a sequential one (Figure 5). The photoisomerization of these substrates with **Ir-16** or FMN results in *E/Z* mixtures in which the less reactive *Z* isomer is the major component. As a result, low yields are obtained from the sequential isomerization and reduction of **1i** and **1j**. The low ee's obtained in the sequential isomerization and reduction of **1i** and **1j** can be explained by slow reduction of the *Z* isomers of **1i** and **1j** after rapid consumption of the *E* isomers. In contrast, the cooperative reduction of **1i** and **1j** generates products in high yields and ee's.

To demonstrate the synthetic value of this new method, preparative scale cooperative reactions of (***Z***)-**1a**, (**63:27** ***E*****/*****Z*****)-1e**, **(*Z*)-1g**, and (***Z***)-**1h** were conducted on a 50 mg scale. Product **2a** was isolated in 87% yield and >99% ee, product **2e** was isolated in 79% yield and >99% ee, product **2g** was isolated in 71% yield and >99% ee, and product **2h** was isolated in 96% yield and 92% ee (Supporting Information). The enantioenriched compounds that have been obtained from the cooperative isomerization and enzymatic reduction system can be transformed into a variety of bioactive molecules and valuable synthetic intermediates (Figure 6).

We devised reactions to convert the enantioenriched products into a series of valuable derivatives. For example, the selective hydrolysis of the *tert*-butyl ester in compound **2e** followed by a Curtius rearrangement yielded a β-amino ester. The hydrolysis of **2e** occurred in the presence of trifluoroacetic acid and DCM to form 4-methoxy-4-oxo-3-phenylbutanoic acid. Heating of this carboxylate in the presence of diphenylphosphoryl azide and NEt_3 generated an isocyanate, which was converted to a β-amino ester upon heating with *tert*-butanol and $Mo(O)_2Cl_2$. Upon completion of the reaction, a β-amino ester was isolated in 90% yield without significant erosion of enantiomeric excess (98% ee).

Figure 6. Derivatization of Enantioenriched Products



The selective reduction of the Weinreb amide present in compound **2g** with Schwartz's reagent yielded methyl 4-oxo-2-phenylbutanoate in 76% isolated yield and >99% ee. This compound is an intermediate in the synthesis of protein kinase inhibitors and microsomal triglyceride transfer protein inhibitors.[14-15] The acid-catalyzed hydrolysis of the nitrile in **2p** yielded 4,4,4-trifluoro-3-phenylbutanoic acid, a synthetically versatile intermediate.[16]

The conversion of a series of the reduction products to biologically active compounds and synthetically valuable precursors has been reported previously. For example, **2i** and **2j** have been converted to γ-amino acids (including balcofen and phenibut) and γ-lactams.[17] The conversion of **2h** into a γ^2 amino acid and a γ^2 lactam also has been reported.[18] The conversion of **2m** into a lactone and a cyclic ether natural product ent-calyxolane has been reported.[19] Finally, the conversion of **2l** into a 4-oxobutanamide, a core structure of many natural products has been reported.[20] Thus, the products of the cooperative chemoenzymatic reduction can be converted into valuable synthetic intermediates by newly disclosed and previously reported transformations.

5.3 Conclusion

In conclusion, a novel cooperative system that combines photocatalyzed isomerization with enzymatic reduction has been developed. This system catalyzes the stereoconvergent reduction of a wide range of substrates in high yields and ee's. The cooperative reduction of substrates **1i** and **1j** affords reduced products in dramatically higher yields and ee's than those obtained in the sequential isomerization and reduction of the same substrates. The high synthetic utility of this new system was shown by the diverse derivatization of the products generated by the cooperative reaction. By combining photocatalyzed isomerization and enzymatic reduction, the limitations the individual processes have been overcome. This report provides a framework to develop additional cooperative transformations that combine selective enzymatic transformations with photocatalyzed reactions.

5.4 References

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5.5 Experimental

Table of Contents

I. General Experimental Details

All air-sensitive manipulations were conducted in a nitrogen-filled glovebox or by standard Schlenk technique under nitrogen. All glassware was heated in an oven and cooled under an inert atmosphere prior to use. Vials (4 mL) were used as reaction vessels and were sealed with Teflon-lined-lined caps. Products were visualized on TLC plates with an anisaldehyde stain and a heat gun. NMR spectra were acquired on 300 MHz, 400 MHz, 500 MHz, or 600 MHz Bruker instruments at the University of California. Flash chromatography was performed with a Teledyne ISCO CombiFlash RF 200 with Gold-Top silica. NMR spectra were processed with MestReNova 5.0 (Mestrelab Research SL). Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). Coupling constants are reported in hertz. NMR yields were determined by ^{1}H NMR spectroscopy. High-resolution mass spectra were obtained via the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley.

Cloning, Expression and Purification of Enzymes

YersER

The Yers-ER investigated in this research is from *Yersinia bercovieri*. The codon-optimized gene was synthesized by IDT and cloned in pET28a with N-terminal His-tag. For expression of Yers-ER, a BL21 colony harboring pET28a-Yers-ER was inoculated in 5 mL LB containing 100 μg/mL ampicillin and grown overnight at 37 ºC. This overnight culture was used to inoculate 500 mL of TB medium containing 100 μg/mL ampicillin, which was grown at 37 ºC until an OD of ~0.6 was reached, and subsequently induced with the addition of 0.3 mM IPTG. The induced culture was placed at 25 ºC, 250 rpm, for 16 h for protein production.

OYE1/OYE2/OYE3

The OYE1/2/3 investigated in this research is from baker's yeast. The plasmid pET30a-OYE1/2/3 with N-terminal His tag was a gift from Dr. Francesco G. Gatti's lab. The plasmid was transformed into *E. coli* BL21. For expression of OYE1/2/3, a BL21 colony harboring pET30a-OYE1/2/3 respectively was inoculated in 5 mL LB containing 50 μg/mL kanamycin and grown overnight at 37 ºC. This overnight culture was used to inoculate 500 mL of LB medium containing 50 μg/mL kanamycin, which was grown at 37 ºC until an OD of ~0.6 was reached, and subsequently induced with the addition of 0.1 mM IPTG. The induced culture was placed at 25 ºC, 250rpm, for 16 h for protein production.

OPR1

The OPR1 investigated in this research is from *Lycopersicon esculentum* (tomato). The plasmid pET21b-OPR1 with C-terminal His tag was a gift from Dr. Kurt Faber's group. The plasmid was transformed into *E. coli* BL21. For expression of OPR1, a BL21 colony harboring pET21b-OPR1 was inoculated in 5 mL LB containing 100 μg/mL ampicillin and grown overnight at 37 ºC. This overnight culture was used to inoculate 500 mL of TB medium containing 100 μg/mL ampicillin, which was grown at 37 ºC until an OD of ~0.6 was reached, and subsequently induced with the addition of 1 mM IPTG. The induced culture was placed at 25 ºC, 250rpm, for 16 h for protein production.

OPR3

The OPR3 investigated in this research is from *Lycopersicon esculentum* (tomato). The plasmid pET21b-OPR3 with C-terminal His-tag was a gift from Dr. Kurt Faber's group. The plasmid was transformed into *E. coli* BL21. For expression of OPR3, a BL21 colony harboring pET21b-OPR3 was inoculated in 5 mL LB containing 100 μg/mL ampicillin and grown overnight at 37 ºC. This overnight culture was used to inoculate 500 mL of TB medium containing 100 μg/mL ampicillin, which was grown at 37 ºC until an OD of ~0.6 was reached, and subsequently induced with the addition of 1 mM IPTG. The induced culture was placed at 25 ºC, 250rpm, for 16 h for protein production.

XenA/XenB

The XenA/XenB investigated in this research are from *Pseudomonas putida* ATCC 17453. The plasmid pGaston-xenA and pGaston-xenB with C-terminal His-tag was a gift from Dr. Uwe T. Bornscheuer's group. The plasmid was transformed into *E. coli* BL21. For expression of *xenA* and *xenB*, a BL21 colony harboring pGaston-xenA/xenB was inoculated in 5 mL LB containing 100 μg/mL ampicillin and grown overnight at 37 ºC. This overnight culture was used to inoculate 500 mL of LB medium containing 100 μg/mL ampicillin, which was grown at 37 ºC at 180 rpm until an OD of ~0.6-0.8 was reached, and subsequently induced with the addition of 0.2% (w/v) r-rhamnose. The induced culture was placed at 25 ºC (XenB) or 30 ºC (XenA) for 8 h.

TOYE

The TOYE investigated in this research is from *Thermoanaerobacter pseudetahnolicus* E39. The plasmid pET21b-TOYE with C-terminal His tag was a gift from Dr. Uwe T. Bornscheuer's group. The plasmid was transformed into *E. coli* BL21. For expression of TOYE, a BL21 colony harboring pET21b-TOYE was inoculated in 5 mL LB containing 100 μg/mL ampicillin and grown overnight at 37 ºC. This overnight culture was used to inoculate 500 mL of LB medium containing 100 μg/mL ampicillin, which was grown at 25 ºC at 250 rpm until an OD of ~0.5 was reached, and subsequently induced with the addition of 0.4 mM IPTG. The induced culture was placed at 25 ºC for 12h.

Yqjm

The Yqjm investigated in this research is from *bacillus subtilis* strain *168K*. The codon-optimized gene was synthesized by IDT and cloned in pET28a with N-terminal His-tag. For expression of yqjm, a BL21 colony harboring pET28a-yqjm was inoculated in 5 mL LB containing 100 μg/mL ampicillin and grown overnight at 37 ºC. This overnight culture was used to inoculate 500 mL of TB medium containing 100 μg/mL ampicillin, which was grown at 37 ºC until an OD of ~0.6 was reached, and subsequently induced with the addition of 0.3 mM IPTG. The induced culture was placed at 25 ºC, 250rpm, for 16 h for protein production.

GDH from *Bacillus megaterium*

Bacillus megaterium B14308 was inoculated in 5 mL TGY medium and grown at 30 ºC for 18 h. Genomic DNA was isolated using the Wizard® Genomic DNA purification kit from Promega according to the manufacturer's protocol. The gene encoding the *gdh* was amplified from the genome of *B. megaterium* using primers *gdh*-NdeI-for and *gdh*-HindIII-rev. Restriction sites are

underlined. The gene was ligated into pET28a^{+} and transformed in *E. coli* DH5α.

The plasmid pET28a-*gdh* was transformed into *E. coli* BL21. For expression of GDH, a BL21 colony harboring pET28a-*gdh* was inoculated in 5 mL LB containing 50 µg/mL kanamycin and grown overnight at 37 ºC. This overnight culture was used to inoculate 500 mL of TB medium containing 50 µg/ml kanamycin, which was grown at 37 ºC until an OD of ~0.7 was reached, and subsequently induced with the addition of 0.3 mM IPTG. The induced culture was placed at 25 ºC for 16 h for protein production.

Following expression, BL21 cells were recovered by centrifugation (6000 x *g* for 15 min), lysed by sonication and clarified by centrifugation (18 000 x *g* for 30 min). The protein was subsequently purified by affinity chromatography using a HisTrap column fitted to an AKTA FPLC system (GE Health Life Sciences, Pittsburgh, PA). The purified protein was buffer exchanged against 100 mM KPi buffer, pH 8.1 using an Amicon Ultra concentration tube (10 kDa cut-off) before being stored in 15% glycerol as 100 µL aliquots at -80 ºC

Light Sources

Blue Lamp Light Source: 34 W Kessil KSH150B Blue LED Grow Light with cooling fan.
LED Light sources:

1. 450 nm Chanzon 5mm Blue LED Diode Lights (Clear Round Transparent DC 3V 20mA) Luminous Intensity: 7000-8000mcd Viewing Angle: 30 Degree.
2. 395 nm Chanzon 5mm UV LED Diode Lights (Clear Round Transparent DC 3V 20mA) 300-400mcd Viewing Angle: 30 Degree.

Leds were connected directly to Arduino Uno R3 Compatible Electronic ATmega328P Microcontroller via jumper wires. Arduinos were powered by AC / DC Adapter Charger Cord Plug - 9V 650mA. Code was written on the open-source Arduino Software (IDE) which is freely available https://www.arduino.cc/en/Main/Software.
The following is an example of the code used in an experiment in which 10 - 0.5 mL reactions with substrates at 5 mM concentrations were illuminated with a 450 nm light for 24 h:

```
int Blue1 = 2;
int Blue2 = 3;
int Blue3 = 4;
int Blue4 = 5;
int Blue5 = 6;
int Blue6 = 7;
int Blue7 = 8;
int Blue8 = 9;
int Blue9 = 10;
int Blue10 = 11;

void setup() {

  pinMode(2, OUTPUT);
```

```
  digitalWrite(Blue1, HIGH);

  pinMode(3, OUTPUT);
  digitalWrite(Blue2, HIGH);

  pinMode(4, OUTPUT);
  digitalWrite(Blue3, HIGH);

  pinMode(5, OUTPUT);
  digitalWrite(Blue4, HIGH);

  pinMode(6, OUTPUT);
  digitalWrite(Blue5, HIGH);

  pinMode(7, OUTPUT);
  digitalWrite(Blue6, HIGH);

  pinMode(8, OUTPUT);
  digitalWrite(Blue7, HIGH);

  pinMode(9, OUTPUT);
  digitalWrite(Blue8, HIGH);

  pinMode(10, OUTPUT);
  digitalWrite(Blue9, HIGH);

  pinMode(11, OUTPUT);
  digitalWrite(Blue10, HIGH);

  // Consecutive Delays

  delay(86400000);
  digitalWrite(Blue1, LOW);
  digitalWrite(Blue2, LOW);
  digitalWrite(Blue3, LOW);
  digitalWrite(Blue4, LOW);
  digitalWrite(Blue5, LOW);
  digitalWrite(Blue6, LOW);
  digitalWrite(Blue7, LOW);
  digitalWrite(Blue8, LOW);
  digitalWrite(Blue9, LOW);
  digitalWrite(Blue10, LOW);


}
```

```
// the loop function runs over and over again forever
void loop() {
}
```

Catalysts

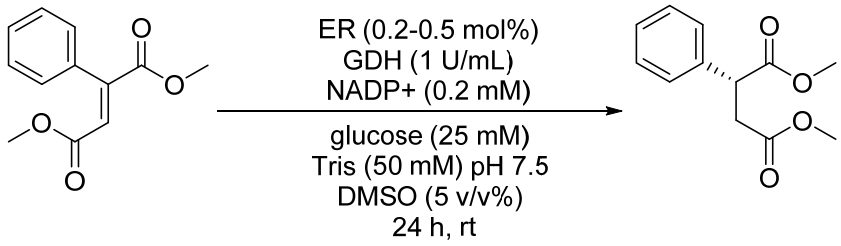
Organometallic photocatalysts were purchased from Aspira Scientific.
Ir-16 CAS: 1607469-49-7, **Ir-67** CAS: 676525-77-2, **Ir-80** CAS: 808142-80-5, **Ir-38** CAS: 387859-70-3, **Ir-87** CAS: 870987-63-6, $Ru(Bipy)_3Cl_2$, $Ru(Bpz)_3(PF_6)_2$
Organic photocatalysts were purchased from Sigma Aldrich:
$NaFMN(H_2O)_2$, Riboflavin, Eosin Y, Eosin B, Fluorescein, flavin adenine dinucleotide.

Precursors for Substrate Synthesis

Diethyl (2-(methoxy(methyl)amino)-2-oxoethyl)phosphonate CAS: 124931-12-0 can be purchased from Spectrum Chemicals & Laboratories Products or prepared by a previously reported method.[1] (*Z*)-3-cyano-3-phenylacrylic acid was prepared by a previously reported method.[2] All other chemicals were purchased from Sigma Aldrich.

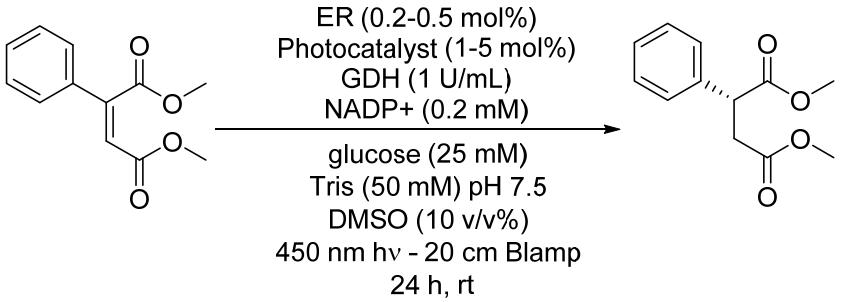
II. General Synthetic Procedures

Non-Cooperative Enzymatic Reduction



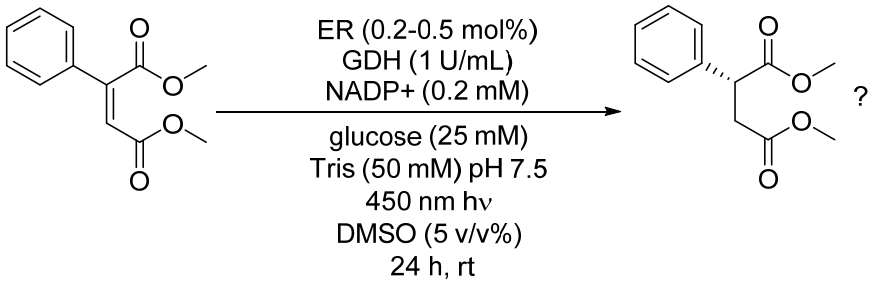
To a 20 mL vial, a solution of $NADP^+$ (50.0 μL of 20.0 mM stock, 0.0400 equiv), glucose (125 μL of a 1.00 M stock, 5.00 equiv), GDH (1.00 U/mL) and enoate reductase (0.200 or 0.500 mol %) in 50 mM pH 7.5 Tris buffer (~4.5 mL) was added a solution of alkene (0.0250 mmol, 1.00 equiv) in DMSO (250 μL) at room temperature. The final concentrations were as follows: 0.200 mM $NADP^+$, 25.0 mM glucose, 1 U/mL GDH, 10.0 μM enoate reductase, 5.00 mM substrate, 0.250 mM FMN or 0.05 mM Ir-16, 5.00 *v/v*% DMSO. The reaction was incubated overnight at 24 ºC on a magnetic stirrer. At the end of this period, EtOAc (10 mL) and dodecane (100 μL of 20 mg/mL stock in EtOAc) were added. An aliquot was removed from the organic layer for GC analysis. The reaction mixture was extracted twice with EtOAc and the combined organic layers were concentrated *in vacuo* and purified by preparative TLC. The ee of the product was analyzed by Chiral HPLC.

Cooperative Reactions with Photocatalysts and Light



To a 20 mL vial, a solution of $NADP^+$ (50.0 µL of 20.0 mM stock, 0.0400 equiv), glucose (125 µL of a 1.00 M stock, 5.00 equiv), GDH (1.00 U/mL) and enoate reductase (0.200 or 0.500 mol %) in 50 mM pH 7.5 Tris buffer (~4.25 mL) was added a solution of alkene (0.0250 mmol, 1.00 equiv) in DMSO (250 µL) and FMN (0.00125 mmol, 0.05 equiv) or Ir-16 (0.00025 mmol, 0.01 equiv) in DMSO (250 uL) at room temperature. The final concentrations were as follows: 0.200 mM $NADP^+$, 25.0 mM glucose, 1 U/mL GDH, 10.0 µM enoate reductase, 5.00 mM substrate, 0.250 mM FMN or 0.05 mM Ir-16, 10.0 *v/v*% DMSO. The reaction was incubated overnight at 24 ºC on a magnetic stirrer with a 450 nm LED lamp positioned 20 cm above the reaction vial. At the end of this period, EtOAc (10 mL) and dodecane (100 µL of 20 mg/mL stock in EtOAc) were added. An aliquot was removed from the organic layer for GC analysis. The reaction mixture was extracted twice with EtOAc and the combined organic layers were concentrated *in vacuo* and purified by preparative TLC. The ee of the product was analyzed by Chiral HPLC.

Reactions Conducted in the Absence of Photocatalysts but in the Presence of Light



To a 20 mL vial, a solution of $NADP^+$ (50.0 µL of 20.0 mM stock, 0.0400 equiv), glucose (125 µL of a 1.00 M stock, 5.00 equiv), GDH (1.00 U/mL) and enoate reductase (0.200 or 0.500 mol %) in 50 mM pH 7.5 Tris buffer (~4.5 mL) was added a solution of alkene (0.0250 mmol, 1.00 equiv) in DMSO (250 µL) at room temperature. The final concentrations were as follows: 0.200 mM $NADP^+$, 25.0 mM glucose, 1 U/mL GDH, 10.0 µM enoate reductase, 5.00 mM substrate, 0.250 mM FMN or 0.05 mM Ir-16, 5.00 *v/v*% DMSO. The reaction was incubated overnight at 24 ºC on a magnetic stirrer with a 450 nm LED lamp positioned 20 cm above the reaction vial. At the end of this period, EtOAc (10 mL) and dodecane (100 µL of 20 mg/mL stock in EtOAc) were added. An aliquot was removed from the organic layer for GC analysis. The reaction mixture was extracted twice with EtOAc, and the combined organic layers were concentrated *in vacuo* and purified by preparative TLC. The ee of the product was analyzed by Chiral HPLC.

General Knöevenagel Condensation Procedure: Substrate Synthesis[3]

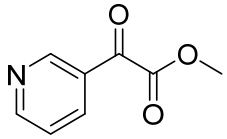
To 100 mL flask in air containing a magnetic stir bar, K_2CO_3 (37.5 mmol, 2.50 equiv), arylacetonitrile (15.0 mmol, 1.00 equiv), glyoxylic acid (22.5 mmol, 1.50 equiv), and 30 mL of MeOH were added. The reaction flask was attached to a reflux condenser and heated at 100 °C for 2-24 h. The solution was cooled to room temperature, and 100 mL of water was added. The resulting solution was cooled to 0 °C and filtered on a fritted funnel with filter paper. The crude product was washed with hexanes and used in the next step without further purification.

Combined Knöevenagel Condensation and Pinner Esterification Procedure

To 100 mL flask in air containing a magnetic stir bar, K_2CO_3 (37.5 mmol, 2.50 equiv), arylacetonitrile (15.0 mmol, 1.00 equiv), glyoxylic acid (22.5 mmol, 1.50 equiv), and 30 mL of MeOH were added. The reaction flask was attached to a reflux condenser and heated at 100 °C for 2-24 h. The solution was cooled to room temperature, and a solution with 10 mL of methanol and 4 mL of concentrated sulfuric acid was slowly added. The reaction flask was attached to the reflux condenser and heated at 100 °C for an additional 24 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum. The concentrated filtrate was dissolved in DCM, transferred to a separatory funnel with brine, and extracted three times with DCM. The organic layers were combined and concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes

Synthesis of Precursors

methyl 2-oxo-2-(pyridin-3-yl)acetate



To a dry 20 mL vial under nitrogen containing a magnetic stir bar, 3-iodopyridine (4.88 mmol, 1.00 equiv) and 15 mL of anhydrous THF were added. To a separate 300 mL flask under nitrogen containing a stir bar, dimethyl oxalate (14.6 mmol, 3.00 equiv) and 70 mL of anhydrous THF were added. To the vial containing 3-iodopyridine (5.85 mmol, 1.20 equiv), 3.0 M ethylmagnesium bromide in Et_2O was added at room temperature. The combined solution was allowed to stir for 30 minutes at room temperature. The aryl-Grignard solution was transferred to the 300 mL flask containing dimethyl oxalate with a syringe. The resulting solution was allowed to stir for 2 h at room temperature. At this time, the solution was quenched with water and brine, and the product was extracted with ethyl acetate. The organic layers were combined and concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 60:40 EtOAc:Hexanes). The product was dried over anhydrous Na_2SO_4, and a yellow oil was obtained (0.0965 g, 0.584 mmol, 12% yield).

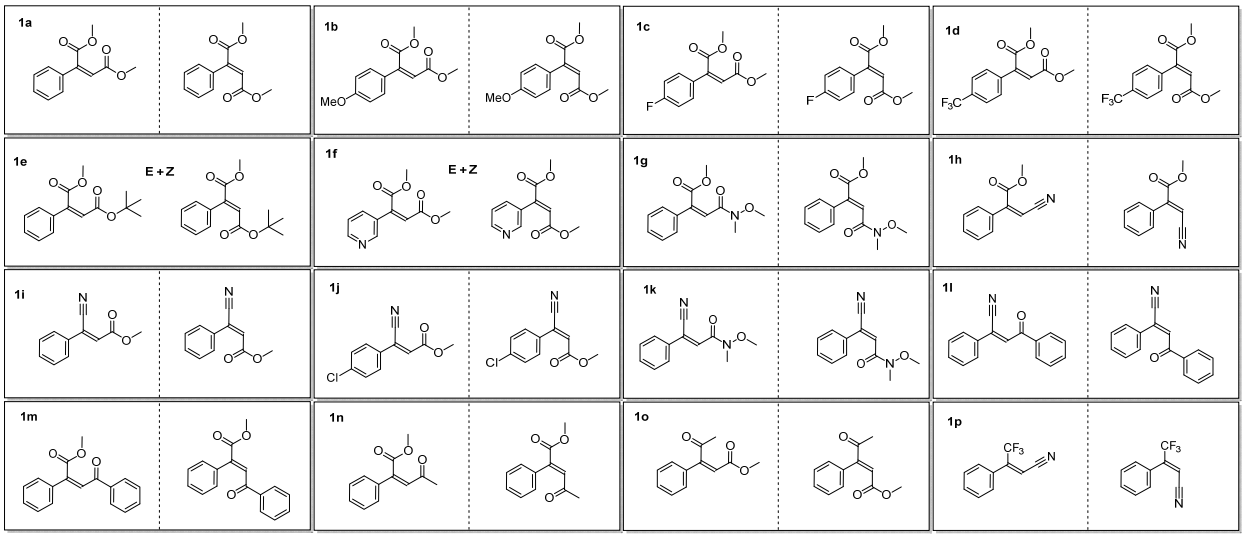
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (dd, J = 2.3, 0.9 Hz, 1H), 8.87 (dd, J = 4.9, 1.7 Hz, 1H), 8.37 (dt, J = 8.0, 2.0 Hz, 1H), 7.48 (ddd, J = 8.1, 4.9, 0.9 Hz, 1H), 4.01 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 184.35, 162.69, 155.02, 151.74, 137.40, 128.61, 123.86, 53.32.

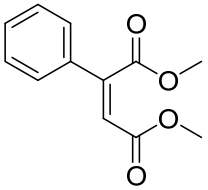
HRMS (EI+): *m/z* for $C_8H_7NO_3$ [M]+ calculated: 165.0426, found: 165.0429.

III. Synthesis of Substrates

Summary of Substrates



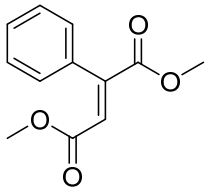
(*Z*)-1a dimethyl 2-phenylmaleate



To a 100 mL flask in air containing a magnetic stir bar, methyl 2-oxo-2-phenylacetate (6.00 mmol, 1.00 equiv), methyl (triphenylphosphoranylidene)acetate (9.00 mmol, 1.50 equiv), and 10 mL of toluene were added. The flask was attached to a reflux condenser, and the solution was heated at reflux for 4 h in air. The flask was cooled to room temperature, and the contents of the flask were filtered through a fritted funnel containing silica. The solid that remained on the silica was washed with ether. The filtrate was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). Both *E* and *Z* isomers of **1a** were obtained (*E* : *Z* - 82 : 18). The product (*Z*)**-1a** was obtained as a clear oil (0.205 g, 0.930 mmol, 16% yield). The ^{1}H NMR spectrum of (*Z*)**-1a** matches the one previously reported.[4]

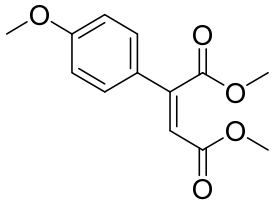
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 2H), 7.44 – 7.38 (m, 3H), 6.32 (s, 1H), 3.95 (s, 3H), 3.79 (s, 3H).

(*E*)-1a dimethyl 2-phenylfumarate



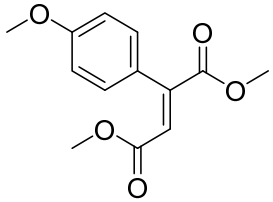
Compound (*E*)**-1a** was obtained from the procedure described above as a clear oil (0.937 g, 4.25 mmol, 71% yield). The ^{1}H NMR spectrum of (*E*)**-1j** matches the one previously reported.[4]
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 3H), 7.25 – 7.21 (m, 2H), 7.02 (s, 1H), 3.81 (s, 3H), 3.61 (s, 3H).

(*Z*)-1b dimethyl 2-(4-methoxyphenyl)maleate



To 100 mL flask in air containing a magnetic stir bar, K_2CO_3 (37.5 mmol, 2.50 equiv), 2-(4-methoxyphenyl)acetonitrile (15.0 mmol, 1.00 equiv), glyoxylic acid (22.5 mmol, 1.50 equiv), and 30 mL of MeOH were added. The reaction flask was attached to a reflux condenser and heated at 100 °C for 14 h. The solution was cooled to room temperature, and a solution with 10 mL of methanol and 4 mL of concentrated sulfuric acid was slowly added. The reaction flask was attached to the reflux condenser and heated at 100 °C for an additional 17 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum. The concentrated filtrate was dissolved in DCM, transferred to a separatory funnel with brine, and extracted three times with DCM. The organic layers were combined and concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 10:90 EtOAc:Hexanes). The product (*Z*)**-1b** was obtained as a clear oil (0.802 g, 3.21 mmol, 21% yield). The ^{1}H NMR spectrum of (*Z*)**-1b** matches the one previously reported.[4]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 2H), 6.96 – 6.83 (m, 2H), 6.23 (s, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H).

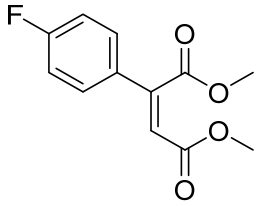
(*E*)-1b dimethyl 2-(4-methoxyphenyl)fumarate



To a 4 mL vial containing a stirbar (0.127 g, 0.500 mmol, 1.00 equiv), **(*Z*)-1b**, $NaFMN(H_2O)_2$ (0.00500 mmol, 0.0100 equiv), 0.6 mL DMSO, and 2.4 mL of H_2O were added. The vial was sealed with a cap containing a PFTE septum, and the reaction mixture was purged with nitrogen. The vial was irradiated with a 450 nm blue lamp at a distance of 5 cm for 20 h. The *E:Z* ratio of product obtained was 47:53. The reaction mixture was transferred to a

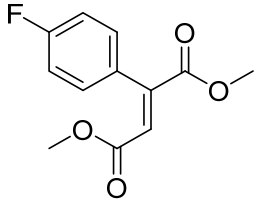
separatory funnel with brine and extracted with Et_2O. The organic layers were combined and concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product (*E*)**-1b** was obtained as a clear oil (0.0568 g, 0.230 mmol, 45% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.95 (s, 1H), 6.92 – 6.86 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.63 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.23, 165.99, 160.09, 144.00, 130.60, 127.82, 125.91, 113.44, 55.34, 53.02, 51.95.
HRMS (EI+): *m/z* for $C_{13}H_{14}O_5$ [M]+ calculated: 250.0841, found: 250.0844.

(*Z*)-1c dimethyl 2-(4-fluorophenyl)maleate



To 100 mL flask in air containing a magnetic stir bar, K_2CO_3 (37.5 mmol, 2.50 equiv), 2 2-(4-fluorophenyl)acetonitrile (15.0 mmol, 1.00 equiv), glyoxylic acid (22.5 mmol, 1.50 equiv), and 30 mL of MeOH were added. The reaction flask was attached to a reflux condenser and heated at 100 °C for 7 h. The solution was cooled to room temperature, and a solution with 10 mL of methanol and 4 mL of concentrated sulfuric acid was slowly added. The reaction flask was attached to the reflux condenser and heated at 100 °C for an additional 23 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum. The concentrated filtrate was dissolved in DCM and transferred to a separatory funnel. The product was extracted three times with DCM. The organic layers were combined and concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 10:90 EtOAc:Hexanes). The product (*Z*)**-1c** was obtained as a clear oil (2.61 g, 11.0 mmol, 73% yield). The ^{1}H NMR spectrum of (*Z*)**-1c** matches the one previously reported.[4]
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.13 – 7.06 (m, 2H), 6.26 (d, *J* = 0.5 Hz, 1H), 3.95 (s, 3H), 3.79 (s, 3H).

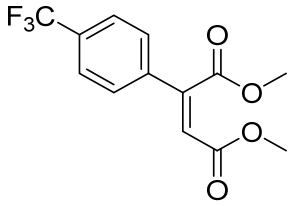
(*E*)-1c dimethyl 2-(4-fluorophenyl)fumarate



To a 4 mL vial containing a stirbar (0.242 g, 1.01 mmol, 1.00 equiv), (*Z*)-**1c**, $NaFMN(H_2O)_2$ (0.101 mmol, 0.100 equiv), 0.3 mL DMSO, and 2.7 mL of H_2O were added. The vial was sealed with a cap containing a PFTE septum, and the reaction mixture was purged with nitrogen. The vial was irradiated with a 450 nm blue lamp at a distance of 5 cm for 48 h. The *E:Z* ratio of product obtained was 50:50. The reaction mixture was transferred to a separatory funnel with brine and extracted with Et_2O. The organic layers were combined and concentrated under vacuum, and the crude product was purified by silica gel chromatography (combiflash), eluting

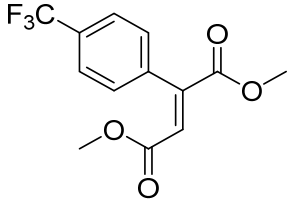
with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The product (*E*)-**1c** was obtained as a clear oil (0.0892 g, 0.370 mmol, 37% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 7.09 – 7.04 (m, 2H), 7.03 (s, 1H), 3.81 (s, 3H), 3.63 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.69, 165.61, 164.02, 162.04, 143.42, 130.99, 130.93, 129.71, 129.09, 115.21, 115.04, 53.17, 52.08.
HRMS (EI+): *m/z* for $C_{12}H_{11}FO_4$ [M]+ calculated: 238.0641, found: 238.0647.

(*Z*)-1d dimethyl 2-(4-(trifluoromethyl)phenyl)maleate



To 100 mL flask in air containing a magnetic stir bar, K_2CO_3 (37.5 mmol, 2.50 equiv), 2 2 2-(4-(trifluoromethyl)phenyl)acetonitrile (15.0 mmol, 1.00 equiv), glyoxylic acid (22.5 mmol, 1.50 equiv), and 30 mL of MeOH were added. The flask was stirred at room temperature for 12 h. To the reaction mixture, 150 mL of H_2O was added and the solution was cooled to 0 ºC. The solution was then filtered over a Büchner funnel, and the crude solid was collected. The crude solid was transferred to a 100 mL flask. A solution with 30 mL of methanol and 4 mL of concentrated H_2SO_4 was added. The flask was attached to a reflux condenser and the mixture was heated at 100 ºC for 17 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum. The concentrated filtrate was dissolved in DCM and transferred to a separatory funnel containing brine. The product was extracted three times with DCM. The product mixture was concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 10:90 EtOAc:Hexanes). The product (*Z*)-**1d** was obtained as a clear oil (1.86 g, 6.45 mmol, 43% yield). The ^{1}H NMR spectrum of (*Z*)-**1d** matches the one previously reported.[4]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 2H), 6.36 (s, 1H), 3.95 (s, 3H), 3.81 (s, 3H).

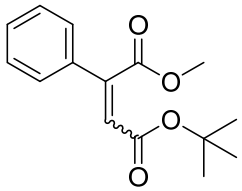
(*E*)-1d dimethyl 2-(4-(trifluoromethyl)phenyl)fumarate



To a 4 mL vial containing a stirbar, (0.288 g, 1.00 mmol, 1.00 equiv) of (*Z*)-**1d**, $NaFMN(H_2O)_2$ (0.100 mmol, 0.100 equiv), 0.3 mL DMSO, and 2.7 mL of H_2O were added. The vial was sealed with a cap containing a PFTE septum, and the reaction mixture was purged with nitrogen. The vial was irradiated with a 450 nm blue lamp at a distance of 5 cm for 48 h. The *E:Z* ratio of product obtained was 50:50. The reaction mixture was transferred to a separatory funnel with brine and extracted with Et_2O. The organic layers were combined and concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The

product (*E*)-**1d** was obtained as a clear oil (0.101 g, 0.350, 35%). The ^{1}H NMR spectrum of (*E*)-**1d** matches the one previously reported.[4]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.11 (s, 1H), 3.83 (s, 3H), 3.64 (s, 3H).

(*E/Z*)-1e 4-(tert-butyl) 1-methyl 2-phenylbut-2-enedioate



To a 4 mL vial in air containing a magnetic stir bar, methyl 2-oxo-2-phenylacetate (0.350 mmol, 1.00 equiv), (tert-Butoxycarbonylmethylene)triphenylphosphorane (0.420 mmol, 1.20 equiv), and 1 mL of toluene was added. The vial was sealed and heated at 120 ºC for 4 h. The vial was cooled to room temperature, and the contents of the vial were filtered through a plug of silica. The solid that remained on the silica was washed with ether. The filtrate was concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). After purification, the product **1e** was obtained as a 63:27 mixture of *E:Z* isomers (0.0733 g, 0.280 mmol, 80% yield).
(*Z*)-**1e** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.42 – 7.38 (m, 3H), 6.23 (s, 1H), 3.93 (s, 3H), 1.51 (s, 9H). (minor – *Z*)

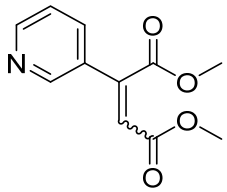
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.58, 164.25, 147.16, 133.80, 130.36, 129.08, 126.82, 120.32, 81.72, 52.70, 28.24.

The ^{1}H NMR and ^{13}C NMR spectra of (*E*)-**1e** match the ones previously reported.[5]
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 3H), 7.23 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.97 (s, 1H), 3.79 (s, 3H), 1.23 (s, 9H). (major – *E*)

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.15, 164.83, 141.87, 134.54, 131.71, 129.08, 128.46, 127.92, 82.03, 52.92, 27.79.

(*E/Z*)-**1e** HRMS (EI+): *m/z* for $C_{15}H_{18}O_4$ [M]+ calculated: 262.1205, found: 262.1206.

(*E/Z*)-1f dimethyl 2-(pyridin-3-yl)but-2-enedioate



To a 20 mL vial in air containing a magnetic stir bar, methyl 2-oxo-2-(pyridin-3-yl)acetate (2.58 mmol, 1.00 equiv), methyl (triphenylphosphoranylidene)acetate (3.87 mmol, 1.50 equiv), and 5 mL of toluene were added. The vial was sealed and heated at 120 ºC for 4 h. The vial was

cooled to room temperature, and the contents of the vial were filtered through a plug of silica. The solid that remained on the silica was washed with ether. The filtrate was concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The product was obtained as a 66:34 mixture of *E:Z* isomers after purification (0.376 g, 1.70 mmol, 66% yield).

(*Z*)-**1f** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 2.5, 0.9 Hz, 1H), 8.66 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.78 (ddd, *J* = 8.1, 2.4, 1.6 Hz, 1H), 7.37 – 7.33 (m, 1H), 6.36 (s, 1H), 3.95 (s, 3H), 3.81 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.52, 165.04, 151.41, 147.98, 145.77, 134.14, 129.60, 123.74, 119.42, 53.09, 52.41.

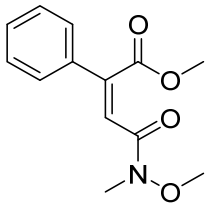
(*E*)-**1f** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.46 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.60 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.13 (s, 1H), 3.82 (s, 3H), 3.63 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.11, 165.17, 149.68, 149.46, 141.35, 136.65, 130.38, 130.01, 122.71, 53.28, 52.20.

Peak assignments based on characterization data reported for (Z)-diethyl 2-(pyridin-3-yl)maleate.[6]

HRMS (ESI+): *m/z* for $C_{11}H_{11}NO_4$ [M+H]+ calculated: 222.0761, found 222.0761

(*Z*)-1g methyl (*Z*)-4-(methoxy(methyl)amino)-4-oxo-2-phenylbut-2-enoate



In a nitrogen-filled glovebox, (12.0 mmol, 1.20 equiv) of LiHMDS and 30 mL of anhydrous THF were added to a dry 250 mL flask (Solution 1). To a 20 mL vial under nitrogen, diethyl (N-methoxy-N-methylcarbamoylmethyl)phosphonate[1] (12.0 mmol, 1.20 equiv) and 10 mL of anhydrous THF was added (Solution 2). To another 20 mL vial under nitrogen, methyl 2-oxo-2-phenylacetate (10.0 mmol, 1.00 equiv) and 10 mL of anhydrous THF were added (Solution 3). All solutions were sealed with rubber septa and removed from the nitrogen-filled glovebox. Solution 1 was cooled to -78 °C in a dry-ice acetone bath, and Solution 2 was added dropwise under nitrogen. The combined solution was warmed to room temperature and allowed to stir for

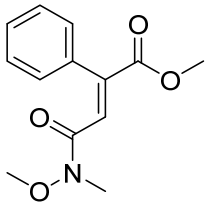
10 minutes. The combined solution was then cooled to -78 °C. Solution 3 was added to the combined solution dropwise. The reaction mixture was warmed to room temperature and allowed to stir at this temperature for 3 h. At the end of this time, the reaction mixture was filtered through a silica plug with Et_2O. The filtrate was concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 15:85 to 50:50 EtOAc:Hexanes). Three purifications were required to ensure the complete separation of the *E* and *Z* isomers of **1g**. The product (*E*)**-1g** was obtained as a clear oil (0.197 g, 0.790 mmol, 8% yield), and (*Z*)**-1g** was obtained as a white solid (1.98 g, 7.93 mmol, 79%).

(*Z*)-**1g** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.41 (dd, *J* = 5.1, 2.0 Hz, 3H), 6.85 (s, 1H), 3.94 (s, 3H), 3.76 (s, 3H), 3.28 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.25, 165.05, 147.28, 134.32, 130.28, 129.06, 126.97, 116.40, 62.22, 52.74, 32.43.

HRMS (ESI+): *m/z* for $C_{13}H_{15}NO_4$ [M+Na]+ calculated: 272.0893 , found 272.0899:

(*E*)-1g methyl (E)-4-(methoxy(methyl)amino)-4-oxo-2-phenylbut-2-enoate



The *E* isomer of **1g** can be obtained from the procedure described above or can be prepared as follows:

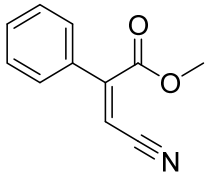
To a 4 mL vial containing a stir bar, (*Z*)**-1g** (0.516 mmol, 1.00 equiv), $NaFMN(H_2O)_2$ (0.00516 mmol, 0.01 equiv), 0.6 mL DMSO, and 2.4 mL of H_2O were added. The vial was sealed with a cap containing a PFTE septum and purged with nitrogen. The vial was irradiated with a 450 nm blue lamp at a distance of 5 cm for 20 h. The product was obtained in an *E:Z* ratio of 96:4. The reaction mixture was transferred to a separatory funnel with brine and extracted with Et_2O. The organic layers were combined and concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 50:50 EtOAc:Hexanes). The product (*E*)**-1g** was obtained as a clear oil (0.119 g 0.480 mmol, 92% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 6H), 3.81 (s, 3H), 3.65-3.47 (bs, 3H), 3.12-2.89 (bs, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.18, 166.59, 140.22, 134.28, 131.21, 129.17, 128.54, 127.99, 62.04, 52.87, 32.23.

HRMS (EI+): *m/z* for $C_{13}H_{15}O_4$ [M]+ calculated: 249.1001, found: 249.1004.

(*Z*)-1h methyl (*Z*)-3-cyano-2-phenylacrylate

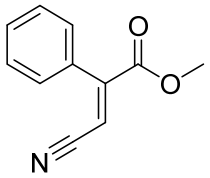


To a 20 mL vial in air containing a magnetic stir bar, methyl 2-oxo-2-phenylacetate (3.52 mmol, 1.00 equiv), (triphenylphosphoranylidene)acetonitrile (4.22 mmol, 1.20 equiv), and 10 mL

of toluene were added. The vial was sealed and heated at 120 ºC for 4 h. The vial was cooled to room temperature, and the contents of the vial were filtered through a plug of silica. The solid that remained on the silica was washed with ether. A 65:35 *E:Z* mixture of crude **1h** was obtained. The filtrate was concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 10:90 EtOAc:Hexanes). Two rounds of purification were required to separate the *E* and *Z* isomers of **1h**. The product (*Z*)**-1h** was obtained as a clear oil (0.161 g, 0.858 mmol, 24% yield). The ^{1}H NMR spectrum of (*Z*)**-1h** matches the one previously reported.[7-8]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.40 (m, 5H), 5.94 (s, 1H), 3.98 (s, 3H).

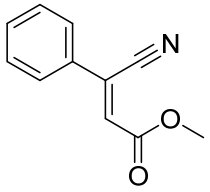
(*E*)-1h methyl (*E*)-3-cyano-2-phenylacrylate



Compound (*E*)-**1h** was obtained from the procedure described above as a clear oil (0.351 g, 1.87 mmol, 53% yield). The ^{1}H NMR spectrum of (*E*)**-1h** matches the one previously reported.[7-8]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 5H), 6.53 (s, 1H), 3.87 (s, 3H).

(*Z*)-1i methyl (*Z*)-3-cyano-3-phenylacrylate

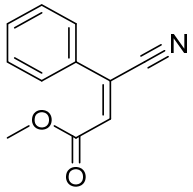


To 100 mL flask in air containing a magnetic stir bar, K_2CO_3 (37.5 mmol, 2.50 equiv), 2-phenylacetonitrile (15.0 mmol, 1.00 equiv), glyoxylic acid (22.5 mmol, 1.50 equiv), and 30 mL of MeOH were added. The reaction flask was attached to a reflux condenser and heated at 100 °C for 29 h. The solution was cooled to room temperature, 150 mL of water was added to the reaction mixture, and the combined solution was cooled to 0 °C. The solution was filtered through a Büchner funnel, and the solid was washed with another 100 mL of water. The crude solid was re-crystallized in water at 100 °C, and the crystals were filtered with a Büchner funnel. The crystals were air dried and used without further purification. (0.959 g, 4.54 mmol, 30% yield) of potassium (*Z*)-3-cyano-3-phenylacrylate was obtained and used without further purification.

To 20 mL vial in air containing a magnetic stir bar, (0.959 g, 4.54 mmol, 1.00 equiv) of potassium (*Z*)-3-cyano-3-phenylacrylate, 5 mL of DMF, and 1.5 mL of MeI (22.7 mmol, 5.00 equiv) were added. The vial was sealed with a Teflon-lined cap and heated at 50 °C for 19 h. The crude mixture was transferred to a separatory funnel containing a saturated solution of NH_4Cl. The product was extracted with DCM and concentrated under vacuum. The crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 10:90 EtOAc:Hexanes). The product (*Z*)**-1i** was obtained as a white solid (0.806 g, 4.30, 95% yield). The ^{1}H NMR spectrum of (*Z*)**-1i** matches the one previously reported.[9]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 – 7.67 (m, 2H), 7.54 – 7.43 (m, 3H), 6.88 (s, 1H), 3.90 (s, 3H).

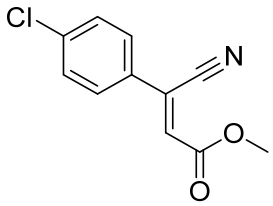
(*E*)-1i methyl (*E*)-3-cyano-3-phenylacrylate



To a 4 mL vial containing a stirbar, (0.510 mmol, 1.00 equiv) of **(*Z*)-1i** (mmol, equiv), 3 mL DMSO, and $Ru(Bpz)_3(PF_6)_2$ (0.00510 mmol, 0.0100 equiv) were added. The vial was sealed with a cap containing a PFTE septum, and the reaction mixture was purged with nitrogen. The vial was irradiated with a 450 nm blue lamp at a distance of 5 cm for 24 h. The *E:Z* ratio of product obtained was 89:11. The reaction mixture was transferred to a separatory funnel with brine and extracted with Et_2O. The organic layers were combined and concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The product (*E*)-**1i** was obtained as a clear oil (0.0682 g, 0.360 mmol, 71% yield). The ^{1}H NMR spectrum of (*E*)-**1i** matches the one previously reported.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 5H), 6.65 (s, 1H), 3.72 (s, 3H).

(*Z*)-1j methyl (*Z*)-3-(4-chlorophenyl)-3-cyanoacrylate

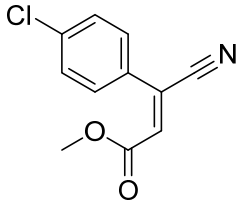


To 100 mL flask in air containing a magnetic stir bar, K_2CO_3 (37.5 mmol, 2.50 equiv), 2-(4-chlorophenyl)acetonitrile (15.0 mmol, 1.00 equiv), glyoxylic acid (22.5 mmol, 1.50 equiv), and 30 mL of MeOH were added. The reaction flask was attached to a reflux condenser and heated at 100 °C for 3 h. The solution was cooled to room temperature, 100 mL of water was added to the reaction mixture, and the combined solution was cooled to 0 °C. The solution was filtered through a Büchner funnel, and the solid was washed with hexanes. The crude solid was air-dried and used in the next step without further purification.

The crude solid was divided between two 20 mL vials containing magnetic stir bars. To each vial, 7.5 mL of DMF and 2.5 mL of MeI (40.0 mmol * 2, 2.68 equiv * 2) were added. The vials were sealed with a Teflon-lined caps and heated at 50 °C for 12 h. The crude mixtures were combined and transferred to a separatory funnel containing a saturated solution of NH_4Cl. The product was extracted with DCM and concentrated under vacuum. The crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The product (*Z*)-**1j** was obtained as a white solid (1.81 g, 8.15 mmol, 54% yield). The ^{1}H NMR spectrum of (*Z*)-**1j** matches the one previously reported.[9]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 2H), 7.48 – 7.44 (m, 2H), 6.86 (s, 1H), 3.90 (s, 3H).

(*E*)-1j methyl (*E*)-3-(4-chlorophenyl)-3-cyanoacrylate



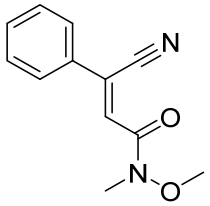
To a 4 mL vial containing a stirbar, (0.501 mmol, 1.00 equiv) of **(*Z*)-1j**, 3 mL DMSO, and $Ru(Bpz)_3(PF_6)_2$ (0.00501 mmol, 0.00100 equiv) were added. The vial was sealed with a cap containing a PFTE septum, and the reaction mixture was purged with nitrogen. The vial was irradiated with a 450 nm blue lamp at a distance of 5 cm for 24 h. The *E:Z* ratio of product obtained was 85:15. The reaction mixture was transferred to a separatory funnel with brine and extracted with Et_2O. The organic layers were combined and concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The product (*E*)**-1j** was obtained as a white solid (0.0872 g, 0.390 mmol, 79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.43 – 7.39 (m, 2H), 6.65 (s, 1H), 3.74 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.81, 137.19, 132.17, 130.27, 129.37, 129.06, 126.00, 117.65, 52.60.

HRMS (EI+): *m/z* for $C_{11}H_8ClNO_2$ [M]+ calculated: 221.0244, found: 221.0243.

(*Z*)-1k 3-cyano-N-methoxy-N-methyl-3-phenylacrylamide



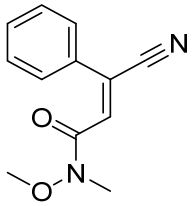
To a 20 mL vial containing a stirbar, (*Z*)-3-cyano-3-phenylacrylic acid[2] (5.78 mmol, 1.00 equiv) and 15 mL of anhydrous DCM were added. To the stirring reaction mixture, carbonyldiimidazole (CDI) (6.94 mmol, 1.20 equiv) was added portion-wise over 5 minutes. Evolution of CO_2 accompanied the addition of CDI. The reaction mixture was capped (but not sealed) and stirred at room temperature for 1 h. N,O-Dimethylhydroxylamine hydrochloride (9.25 mmol, 1.60 equiv) was added to the reaction mixture, and the vial was sealed with a Teflon-lined cap (*Note: ensure evolution of CO_2 has ceased). The reaction mixture was heated at 65 °C for 1 h. The crude reaction mixture was then filtered through a plug of silica with Et_2O. The organic layers were combined and concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The product (*Z*)**-1k** was obtained as a yellow solid (0.841 g, 3.89 mmol, 67% yield) of **(*Z*)-1k** was obtained.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.69 (m, 2H), 7.50 – 7.45 (m, 3H), 7.42 (s, 1H), 3.77 (s, 3H), 3.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.26, 132.86, 131.25, 129.39, 128.60, 127.12, 124.89, 115.90, 62.43, 32.51.

HRMS (EI+): *m/z* for $C_{12}H_{12}N_2O_2$ [M]+ calculated: 216.0899, found: 216.0901.

(*E*)-1k 3-cyano-N-methoxy-N-methyl-3-phenylacrylamide



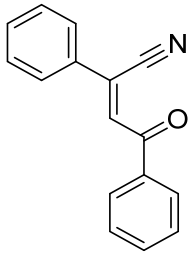
To a 4 mL vial containing a stirbar, (0.110 g, 0.508 mmol, 1.00 equiv) **(*Z*)-1k**, $NaFMN(H_2O)_2$ (0.00508 mmol, 0.00100 equiv), 1.5 mL diglyme, and 1.5 mL of H_2O were added. The vial was sealed with a cap containing a PFTE septum. The vial was irradiated with a 450 nm blue lamp at a distance of 5 cm for 20 h. The *E:Z* ratio of product obtained was 62:38. The reaction mixture was transferred to a separatory funnel with brine and extracted with Et_2O. The organic layers were combined and concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 40:60 EtOAc:Hexanes). The product (*E*)**-1g** was obtained as a clear oil (0.0590 g, 0.270 mmol, 54% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.41 (m, 3H), 6.98 (s, 1H), 3.65 (s, 3H), 3.23 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.67, 134.19, 131.39, 130.42, 128.90, 128.39, 122.31, 118.39, 62.29, 32.41.

HRMS (ESI+): *m/z* for $C_{12}H_{12}N_2O_2$ [M+Na]+ calculated: 239.0791, found: 239.0791.

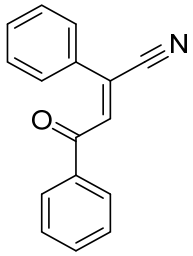
(*Z*)-1l 4-oxo-2,4-diphenylbut-2-enenitrile



To a 20 mL vial in air containing a magnetic stir bar, benzoyl cyanide (6.33 mmol, 1.00 equiv), (phenacylidene)triphenylphosphorane (6.96 mmol, 1.10 equiv), and 10 mL DCE were added. The vial was sealed with a Teflon-lined cap and heated at 80 °C for 24 h. The vial was cooled to room temperature, and the contents of the vial were filtered through a plug of silica. The solid that remained on the silica was washed with ether. The filtrate was concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). Both *E* and *Z* isomers of **1l** were obtained (*E*:*Z* - 26:74). The product (*Z*)**-1l** was obtained as a yellow solid (0.764 g, 3.28 mmol, 52% yield). The ^{1}H NMR spectrum of (*Z*)**-1l** matches the one previously reported.[10]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.01 (m, 2H), 7.92 (s, 1H), 7.87 – 7.79 (m, 2H), 7.69 – 7.62 (m, 1H), 7.58 – 7.48 (m, 5H).

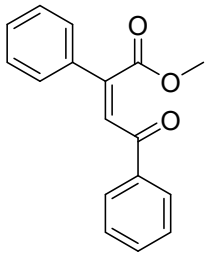
(*E*)-1l 4-oxo-2,4-diphenylbut-2-enenitrile



Compound (*E*)-**1l** was obtained from the procedure described above as a yellow solid (0.265 g, 1.14 mmol, 18% yield). The ^{1}H NMR spectrum of (*E*)-**1l** matches the one previously reported.[10]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.58 (m, 1H), 7.47 – 7.39 (m, 4H), 7.36 – 7.26 (m, 4H).

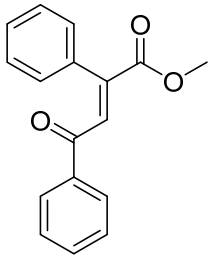
(*Z*)-1m methyl (*Z*)-4-oxo-2,4-diphenylbut-2-enoate



To a 20 mL vial in air containing a magnetic stir bar, **(*Z*)-1l** (1.02 mmol, 1.00 equiv), 15 mL of MeOH, and 2.5 mL of concentrated H_2SO_4 were added. The vial was sealed with a Teflon-lined cap and heated at 100 °C for 4 h. The reaction vial was cooled to room temperature, and the crude reaction mixture was transferred to a separatory funnel containing brine. The product was extracted with ether and concentrated under vacuum. The crude solid was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The product (*Z*)-**1m** was obtained as a yellow oil (0.0743 g, 0.280 mmol, 27% yield). The ^{1}H NMR spectrum of (*Z*)-**1m** matches the one previously reported.[11]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.98 (m, 2H), 7.64 – 7.57 (m, 3H), 7.51 (dd, J = 8.4, 7.0 Hz, 2H), 7.48 – 7.42 (m, 3H), 7.37 (s, 1H), 3.94 (s, 3H).

(*E*)-1m methyl (*E*)-4-oxo-2,4-diphenylbut-2-enoate

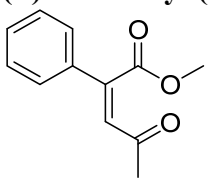


To a 20 mL vial in air containing a magnetic stir bar, methyl 2-oxo-2-phenylacetate (6.00 mmol, 1.00 equiv), (phenacylidene)triphenylphosphorane (7.20 mmol, 1.20 equiv), and 10 mL DCE were added. The vial was sealed with a Teflon-lined cap and heated at 80 °C for 24 h. The

vial was cooled to room temperature, and the contents of the vial were filtered through a plug of silica. The solid that remained on the silica was washed with ether. The filtrate was concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). *Note: Although *E* and *Z* isomers of **1m** formed in a ratio of ~85:15 *E*:*Z*, (*Z*)-**1m** could not be isolated because it co-eluted with an impurity. The product (*E*)-**1m** was obtained as a yellow oil (0.924 g, 3.47 mmol, 58% yield). The ^{1}H NMR spectrum of (*E*)-**1m** matches the one previously reported.[5]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.71 (s, 1H), 7.50 (s, 1H), 7.37 (s, 2H), 7.24 – 7.18 (m, 5H), 3.87 (s, 3H).

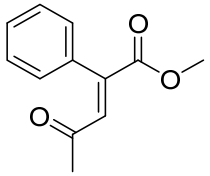
(*Z*)-1n methyl (*Z*)-4-oxo-2-phenylpent-2-enoate



To a 20 mL vial in air containing a magnetic stir bar, methyl 2-oxo-2-phenylacetate (6.00 mmol, 1.00 equiv), 1-(triphenyl-l5-phosphaneylidene)propan-2-one (9.00 mmol, 1.00 equiv), and 10 mL DCE were added. The vial was sealed with a Teflon-lined cap and heated at 80 °C for 12 h. The vial was cooled to room temperature, and the contents of the vial were filtered through a plug of silica. The solid that remained on the silica was washed with ether. The filtrate was concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). Product **1n** was obtained as a mixture of isomers in a ratio of 72:28 *E*:*Z*, The product (*Z*)-**1n** was obtained as a clear oil (0.281 g, 1.38 mmol, 23% yield). The ^{1}H NMR spectrum of (*Z*)-**1n** matches the one previously reported.[12]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.46 – 7.38 (m, 3H), 6.65 (s, 1H), 3.94 (s, 3H), 2.34 (s, 3H).

(*E*)-1n methyl (*E*)-4-oxo-2-phenylpent-2-enoate



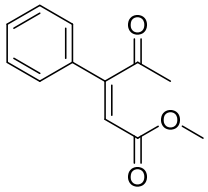
Compound (*E*)-**1a** was obtained from the procedure described above as a clear oil (0.706 g, 3.46 mmol, 58% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 3H), 7.25 (s, 2H), 7.14 (s, 1H), 3.81 (d, J = 1.7 Hz, 3H), 1.88 (d, J = 1.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 201.10, 167.28, 140.51, 137.88, 134.02, 129.42, 129.23, 128.46, 53.04, 30.50.

HRMS (EI+): *m/z* for $C_{12}H_{12}O_3$ [M]+ calculated: 204.0786, found: 204.0778.

(*Z*)-1o methyl (*Z*)-4-oxo-3-phenylpent-2-enoate



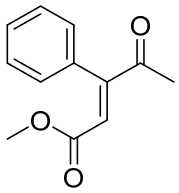
The following reagents were divided between two 20 mL vials containing magnetic stir bars: 1-phenylpropane-1,2-dione (13.6 mmol, 1.00 equiv), methyl (triphenylphosphoranylidene)acetate (27.2 mmol, 2.00 equiv), and EtOAc (20 mL). The vials were sealed with Teflon-lined caps and heated at 100 °C for 3 h. The vials were cooled to room temperature, and the contents of the vials were filtered through a fritted funnel containing silica. The solid that remained on the silica was washed with ether. A complex mixture of isomers was obtained. The crude products were concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). After two rounds of chromatography, the product (*Z*)-**1o** was obtained as a yellow oil (0.675 g, 3.31 mmol, 24% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 – 7.32 (m, 5H), 6.16 (s, 1H), 3.78 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 204.44, 166.05, 158.66, 132.89, 130.73, 129.32, 126.95, 115.06, 52.12, 30.47.

HRMS (EI+): *m/z* for $C_{12}H_{12}O_3$ [M]+ calculated: 204.0786, found: 204.0789.

(*E*)-1o methyl (*E*)-4-oxo-3-phenylpent-2-enoate



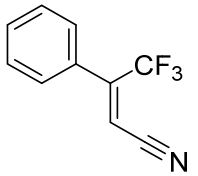
A stock solution consisting of (1.49 mmol, 1.00 equiv) of (*Z*)-**1o** and 1.8 mL of DMSO was prepared. Another stock solution consisting of (0.0149 mmol, 0.01 equiv) $NaFMN(H_2O)_2$ and 7.2 mL of H_2O was prepared. Both solutions were divided evenly between three 4 mL vials that were sealed with caps containing PFTE septa. The vials were purged with nitrogen and irradiated with the 450 nm Lamp at 5 cm for 24 h. Substrate 1o was obtained in a 52:48 *E*:*Z* ratio. The contents of the vials were combined and transferred to a separatory funnel containing brine. The product was extracted with Et_2O, concentrated under vacuum. The product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The product (*E*)-**1o** was obtained as a clear oil (0.141 g, 0.690 mmol, 46% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 3H), 7.22 – 7.15 (m, 2H), 6.75 (s, 1H), 3.60 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.09, 165.97, 151.59, 134.65, 128.70, 128.55, 128.32, 126.16, 52.00, 28.29.

HRMS (EI+): *m/z* for $C_{12}H_{12}O_3$ [M]+ calculated: 204.0786, found: 204.0785.

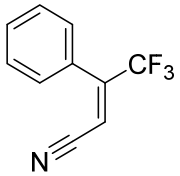
(*Z*)-1p 4,4,4-trifluoro-3-phenylbut-2-enenitrile



To a 20 mL vial in air containing a magnetic stir bar, 2,2,2-trifluoro-1-phenylethan-1-one (1.21 mmol, 1.00 equiv), (triphenylphosphoranylidene)acetonitrile (1.45 mmol, 1.20 equiv), and 10 mL toluene were added. The vial was sealed with a Teflon-lined cap and heated at 120 °C for 9 h. The vial was cooled to room temperature, and the contents of the vial were filtered through a plug of silica. The solid that remained on the silica was washed with ether. The filtrate was concentrated under vacuum and the crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). Isomers of **1p** were obtained in a ratio of 85:15 *E*:*Z*. The product (*Z*)**-1p** was obtained as a clear oil (0.0278 g, 0.140 mmol, 12% yield). The ^{1}H NMR spectrum of (*Z*)**-1p** matches the one previously reported.[13]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (m, 1H), 7.44 (m, 4H), 5.94 (s, 1H).

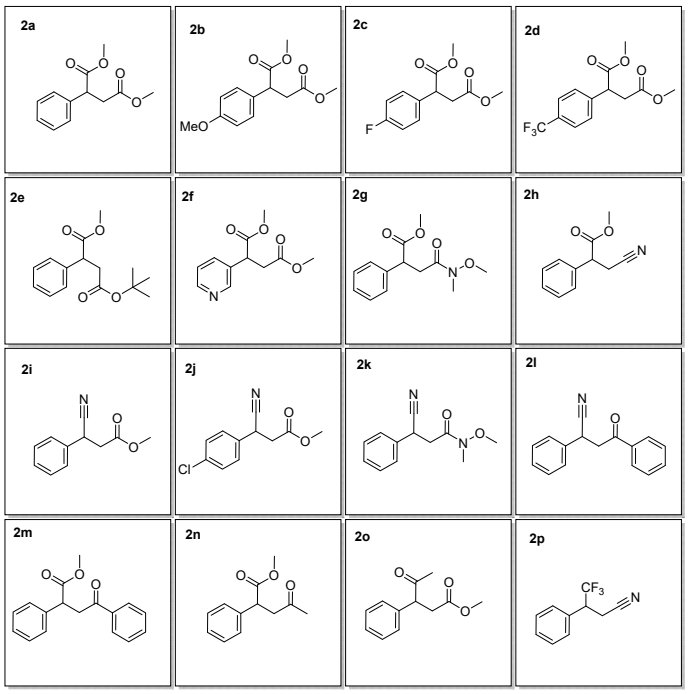
(*E*)-1p 4,4,4-trifluoro-3-phenylbut-2-enenitrile



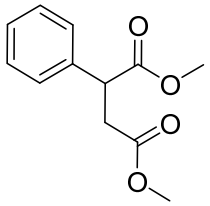
Compound (*E*)**-1p** was obtained from the procedure described above as a clear oil (0.154 g, 0.780 mmol, 65% yield). The ^{1}H NMR spectrum of (*E*)**-1p** matches the one previously reported.[13]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (m, 5H), 6.17 (q, J = 1.5 Hz, 1H).

IV. Synthesis and Characterization of Racemic Products



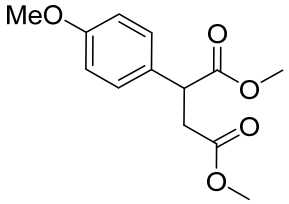
rac-2a dimethyl 2-phenylsuccinate



To a 20 mL vial in air containing a magnetic stir bar, (*E*)-**1a** (0.916 mmol, 1.00 equiv), EtOAc (4 mL), and g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The filtrate was concentrated under vacuum. The product rac-**2a** was obtained as a white solid (0.203 g, 0.914 mmol, 99% yield). The ^{1}H NMR spectrum of rac-**2** matches the one previously reported.[14]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (ddt, *J* = 9.1, 5.9, 1.4 Hz, 2H), 7.28 (tt, *J* = 5.9, 1.3 Hz, 3H), 4.09 (dd, *J* = 10.2, 5.2 Hz, 1H), 3.68 (d, *J* = 2.1 Hz, 6H), 3.21 (dd, *J* = 17.0, 10.2 Hz, 1H), 2.67 (dd, *J* = 17.0, 5.2 Hz, 1H).

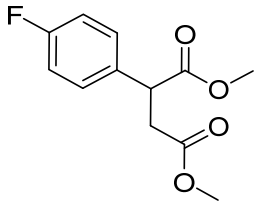
rac-2b dimethyl 2-(4-methoxyphenyl)succinate



To a 20 mL vial in air containing a magnetic stir bar, (*Z*)-**1b** (0.494 mmol, 1.00 equiv), MeOH (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 10:90 EtOAc:Hexanes). The product rac-**2b** was obtained as a clear oil (0.113 g, 0.448 mmol, 91% yield). The ^{1}H NMR spectrum of rac-**2b** matches the one previously reported.[15]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 2H), 6.89 – 6.82 (m, 2H), 4.04 (dd, *J* = 10.0, 5.4 Hz, 1H), 3.79 (s, 3H), 3.67 (d, *J* = 1.4 Hz, 6H), 3.17 (dd, *J* = 16.9, 10.0 Hz, 1H), 2.65 (dd, *J* = 16.9, 5.4 Hz, 1H).

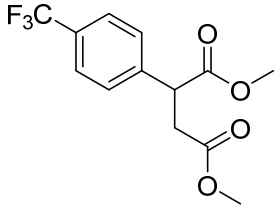
rac-2c dimethyl 2-(4-fluorophenyl)succinate



To a 20 mL vial in air containing a magnetic stir bar, (*Z*)-**1c** (0.504 mmol, 1.00 equiv), MeOH (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2c** was obtained as a clear oil (0.0997 g, 0.415 mmol, 82% yield). The ^{1}H NMR spectrum of rac-**2c** matches the one previously reported.[16]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 3H), 7.07 – 6.97 (m, 2H), 4.08 (dd, *J* = 9.7, 5.6 Hz, 1H), 3.68 (d, *J* = 3.2 Hz, 6H), 3.18 (dd, *J* = 16.8, 9.7 Hz, 1H), 2.66 (dd, *J* = 16.9, 5.6 Hz, 1H).

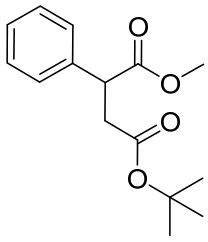
rac-2d dimethyl 2-(4-(trifluoromethyl)phenyl)succinate



To a 20 mL vial in air containing a magnetic stir bar, (*Z*)-**1d** (0.376 mmol, 1.00 equiv), MeOH (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2d** was obtained as a clear oil (0.0888 g, 0.306 mmol, 81% yield). The ^{1}H NMR spectrum of rac-**2d** matches the one previously reported.[4]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 4.15 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.68 (d, *J* = 4.0 Hz, 6H), 3.21 (dd, *J* = 17.0, 9.6 Hz, 1H), 2.68 (dd, *J* = 17.0, 5.7 Hz, 1H).

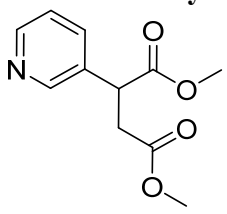
rac-2e 4-(tert-butyl) 1-methyl 2-phenylsuccinate



To a 20 mL vial in air containing a magnetic stir bar, 56:44 -*E*:*Z* **1e** (1.25 mmol, 1.00 equiv), MeOH (10 mL), and 0.0250 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 10:90 EtOAc:Hexanes). The product rac-**2e** was obtained as a clear oil (0.315 g, 1.19 mmol, 95% yield). The ^{1}H NMR spectrum of rac-**2e** matches the one previously reported.[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H), 4.02 (dd, *J* = 10.1, 5.5 Hz, 1H), 3.67 (s, 3H), 3.11 (dd, *J* = 16.6, 10.1 Hz, 1H), 2.60 (dd, *J* = 16.6, 5.5 Hz, 1H), 1.40 (s, 9H).

rac-2f dimethyl 2-(pyridin-3-yl)succinate



To a 20 mL vial in air containing a magnetic stir bar, 66:34 *E*:*Z*-1f (0.523 mmol, 1.00

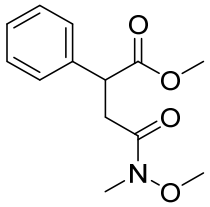
equiv), MeOH (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 50:50 EtOAc:Hexanes). The product rac-**2f** was obtained as a brown oil (0.103 g, 0.462 mmol, 88% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 – 8.51 (m, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 6.7 Hz, 1H), 4.12 (dd, *J* = 9.6, 5.8 Hz, 1H), 3.68 (dd, *J* = 10.8, 1.7 Hz, 6H), 3.21 (dd, *J* = 17.0, 9.5 Hz, 1H), 2.70 (dd, *J* = 17.1, 5.8 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.76, 171.56, 149.63, 149.30, 135.19, 133.52, 123.82, 52.74, 52.17, 44.83, 37.33.

HRMS (ESI+): *m/z* for $C_{11}H_{13}NO_4$ [M+H]+ calculated: 224.0917, found: 224.0917

rac-2g methyl 4-(methoxy(methyl)amino)-4-oxo-2-phenylbutanoate



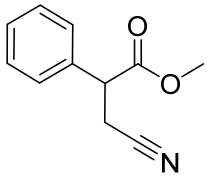
To a 20 mL vial in air containing a magnetic stir bar, (*Z*)-**1g** (0.125 g, 0.500 mmol, 1.00 equiv), MeOH (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 40:60 EtOAc:Hexanes). to provide **2g**-rac 0.1203 g, 0.479 mmol, 96% yield.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (s, 5H), 4.17 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.68 (d, *J* = 5.8 Hz, 6H), 3.37 (dd, *J* = 16.7, 10.8 Hz, 1H), 3.17 (s, 3H), 2.73 (d, *J* = 17.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.19, 138.58, 128.99, 128.01, 127.64, 61.35, 52.40, 46.82, 36.37, 32.29.

HRMS (ESI+): *m/z* for $C_{13}H_{17}NO_4$ [M+H]+ calculated: 252.1230, found: 252.1235

rac-2h methyl 3-cyano-2-phenylpropanoate

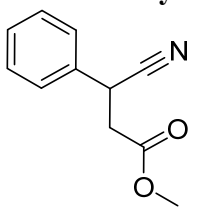


To a 20 mL vial in air containing a magnetic stir bar, (*E*)-**1h** (0.517 mmol, 1.00 equiv), MeOH (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting

with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2h** was obtained as a clear oil (0.0712 g, 0.376 mmol, 73% yield). The ^{1}H NMR spectrum of rac-**2h** matches the one previously reported.[18]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 5H), 3.95 (t, *J* = 7.6 Hz, 1H), 3.73 (s, 3H), 3.04 (ddd, *J* = 16.9, 7.6, 1.4 Hz, 1H), 2.81 (ddd, *J* = 16.8, 7.7, 1.4 Hz, 1H).

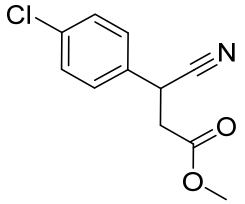
rac-2i methyl 3-cyano-3-phenylpropanoate



To a 4 mL vial in air containing a magnetic stir bar, (*Z*)-**1i** (0.500 mmol, 1.00 equiv), 1 mL of DCM and 1 mL of MeOH. $NaBH_4$ (0.800 mmol, 1.60 equiv) was added portion-wise and bubbling was observed. The solution was stirred for 1 h at room temperature. The solution was concentrated under vacuum and filtered through a plug of silica with ethyl acetate. The crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2i** was obtained as a clear oil (0.0351 g, 0.186 mmol, 37% yield). The ^{1}H NMR spectrum of rac-**2i** matches the one previously reported.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H), 4.30 (dd, *J* = 8.3, 6.7 Hz, 1H), 3.72 (s, 3H), 3.03 (dd, *J* = 16.6, 8.3 Hz, 1H), 2.85 (dd, *J* = 16.6, 6.7 Hz, 1H).

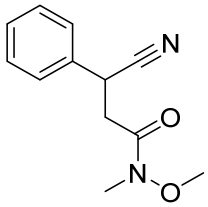
rac-2j methyl 3-(4-chlorophenyl)-3-cyanopropanoate



To a 4 mL vial in air containing a magnetic stir bar, (*Z*)-**1j** (0.517 mmol, 1.00 equiv), 1 mL of DCM and 1 mL of MeOH. $NaBH_4$ (0.879 mmol, 1.70 equiv) was added portion-wise and bubbling was observed. The solution was stirred for 1 h at room temperature. The solution was concentrated under vacuum and filtered through a plug of silica with ethyl acetate. The crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2j** was obtained as a white solid (0.0331 g, 0.148 mmol, 29% yield). The ^{1}H NMR spectrum of rac-**2j** matches the one previously reported.[9]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 2H), 7.35 – 7.29 (m, 2H), 4.28 (t, *J* = 7.4 Hz, 1H), 3.72 (s, 3H), 3.02 (dd, *J* = 16.7, 7.7 Hz, 1H), 2.83 (dd, *J* = 16.7, 7.0 Hz, 1H).

rac-2k 3-cyano-N-methoxy-N-methyl-3-phenylpropanamide



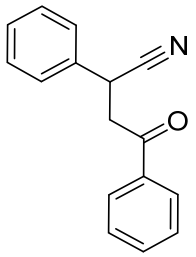
To a 20 mL vial in air containing a magnetic stir bar, (*Z*)-**1k** (0.528 mmol, 1.00 equiv), MeOH (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 45:55 EtOAc:Hexanes). The product rac-**2k** was obtained as a clear oil (0.0701 g, 0.231 mmol, 61% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H), 4.42 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.61 (s, 3H), 3.19 (s, 3H), 3.18 – 3.13 (m, 1H), 2.96 (dd, *J* = 16.6, 6.5 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.55, 135.41, 129.35, 128.50, 127.62, 120.78, 61.54, 38.51, 32.91, 32.40.

HRMS (EI+): *m/z* for $C_{12}H_{14}N_2O_2$ $[M]^+$ calculated: 218.1051, found: 218.1051.

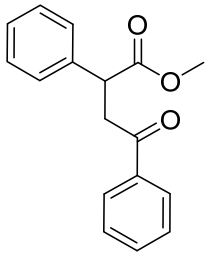
rac-2l 4-oxo-2,4-diphenylbutanenitrile



To a 20 mL vial in air containing a magnetic stir bar, (*E*)-**1m** (0.578 mmol, 1.00 equiv), EtOAc (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 6 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2m** was obtained as a yellow oil (0.0903 g, 0.384 mmol, 66% yield). The ^{1}H NMR spectrum of rac-**2m** matches the one previously reported.[19] *Note increasing the duration of this reaction resulted in the formation of byproducts.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.87 (m, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.52 – 7.30 (m, 7H), 4.66 – 4.52 (m, 1H), 3.74 (dd, *J* = 17.9, 7.9 Hz, 1H), 3.51 (dd, *J* = 17.9, 6.1 Hz, 1H).

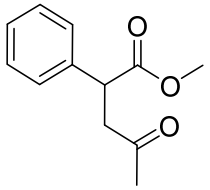
rac-2m methyl 4-oxo-2,4-diphenylbutanoate



To a 20 mL vial in air containing a magnetic stir bar, (*Z*)-**1l** (0.437 mmol, 1.00 equiv), EtOAc (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 6 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2l** was obtained as a clear oil (0.0839 g, 0.312 mmol, 71% yield). The ^{1}H NMR spectrum of rac-**2l** matches the one previously reported.[20] *Note increasing the duration of this reaction resulted in the formation of byproducts.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.59 – 7.54 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 4.3 Hz, 4H), 7.30 (h, *J* = 4.3 Hz, 1H), 4.30 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.96 (dd, *J* = 18.0, 10.4 Hz, 1H), 3.71 (s, 3H), 3.28 (dd, *J* = 18.0, 4.0 Hz, 1H).

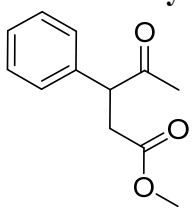
rac-2n methyl 4-oxo-2-phenylpentanoate



To a 20 mL vial in air containing a magnetic stir bar, (*E*)-**1n** (0.502 mmol, 1.00 equiv), MeOH (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 24 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2n** was obtained as a clear oil (0.0893 g, 0.432 mmol, 86% yield). The ^{1}H NMR spectrum of rac-**2n** matches the one previously reported.[21]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H), 4.11 (dd, *J* = 10.3, 4.3 Hz, 1H), 3.66 (s, 3H), 3.40 (dd, *J* = 18.0, 10.4 Hz, 1H), 2.72 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.18 (s, 3H).

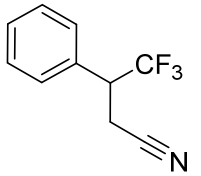
rac-2o methyl 4-oxo-3-phenylpentanoate



To a 20 mL vial in air containing a magnetic stir bar, (*Z*)-**1o** (0.502 mmol, 1.00 equiv), MeOH (10 mL), and 0.0100 g of 10% Pd/C was added. The vial was capped with a rubber septum, and the reaction mixture was purged with nitrogen then H_2. A balloon containing H_2 was affixed to the vial, and the mixture was stirred for 27 h at room temperature. The reaction was unsealed, and the crude solution was filtered through a plug of silica with EtOAc. The mixture was concentrated under vacuum and purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2o** was obtained as a clear oil (0.0889 g, 0.431 mmol, 86% yield). The ^{1}H NMR spectrum of rac-**2o** matches the one previously reported.[21]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 7.24 – 7.19 (m, 2H), 4.19 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.65 (s, 3H), 3.22 (dd, *J* = 17.0, 9.8 Hz, 1H), 2.53 (dd, *J* = 17.1, 4.9 Hz, 1H), 2.12 (s, 3H).

rac-2p 4,4,4-trifluoro-3-phenylbutanenitrile



To a 4 mL vial in air containing a magnetic stir bar, (*E*)-**1i** (1.04 mmol, 1.00 equiv), 1 mL of DCM and 1 mL of MeOH were added. The reaction mixture was cooled to 0° C, and $NaBH_4$ (1.46 mmol, 1.40 equiv) was added portion-wise and bubbling was observed. The solution warmed to room temperature and stirred for 2.5 h. The reaction was quenched with water, and the contents of the vial were transferred to a separatory funnel with Et_2O. The product was extracted with Et_2O, and the combined organic layers were concentrated under vacuum. The crude product was dissolved in Et_2O and filtered through a plug of silica. The crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 20:80 EtOAc:Hexanes). The product rac-**2p** was obtained as a clear oil (0.153 g, 0.769 mmol, 74% yield).

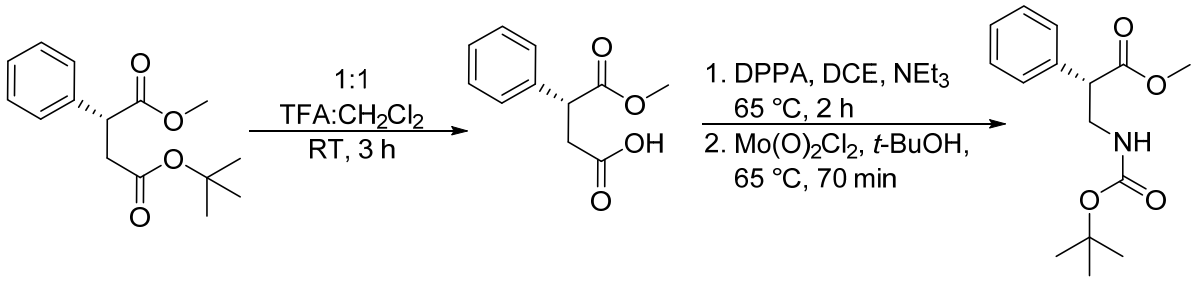
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 3H), 7.34 (dd, *J* = 6.7, 2.9 Hz, 2H), 3.74 – 3.64 (m, 1H), 3.05 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.95 (dd, *J* = 17.0, 9.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 131.59, 129.67, 129.42, 128.67, [128.23, 126.38, 124.52, 122.66] 125.45 (q, *J* = 280.3 Hz), 116.21, [47.17, 46.98, 46.79, 46.60] 46.88 (q, *J* = 28.6 Hz), [19.06, 19.04, 19.01, 18.99] 19.02 (q, *J* = 3.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -70.15.

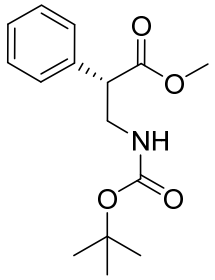
HRMS (EI+): *m/z* for $C_{10}H_8F_3N$ [M]+ calculated: 199.0609, found: 199.0607.

Synthesis of Derivatives

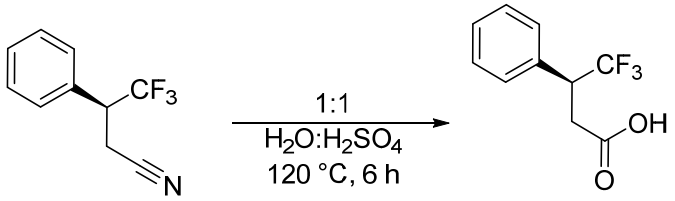


To a 4 mL vial in air containing a magnetic stir bar, (R)-**2e** (0.0766 mmol, 1.00 equiv), 0.6 mL of DCM and 0.6 mL of trifluoroacetic acid were added. The solution was stirred for 3 h at room temperature. The solution was concentrated under vacuum, and toluene was added to the crude solid. The solution was again concentrated under vacuum. The vial was moved to a nitrogen-filled glove box, and 0.6 mL of DCE, NEt_3 (0.130 mmol, 1.70 equiv) and (0.115 mmol, 1.50 equiv) of diphenyl phosphoryl azide were added. The vial was sealed with a cap containing a PFTE septum, moved out of the nitrogen-filled glove box, and heated at 65 °C for 2 h. The vial was allowed to cool and was unsealed in a nitrogen-filled glove box. To the reaction mixture, (0.00766 mmol, 0.100 equiv) of $Mo(O)_2Cl_2$ and 200 uL of anhydrous *t*-BuOH were added. The reaction vial was resealed, and heated at 65 °C for 70 minutes. The vial was allowed to cool and then unsealed. The mixture was concentrated under vacuum, and the crude solid was filtered through a plug of silica with Et_2O and $CHCl_3$. The crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of ethyl acetate and hexanes (gradient 0:100 to 15:85 EtOAc:Hexanes). The product (S)-**3e** was obtained as a white solid (0.0192 g, 0.0687 mmol, 90% yield, 98% ee).

(*S*)-3e methyl (*S*)-3-((tert-butoxycarbonyl)amino)-2-phenylpropanoate



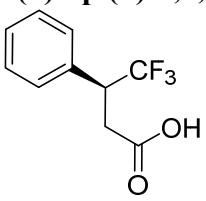
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.21 (m, 5H), 4.88 (m, 1H), 3.95 – 3.85 (m, 1H), 3.69 (s, 3H), 3.64 – 3.44 (m, 2H), 1.42 (s, 9H).[22]



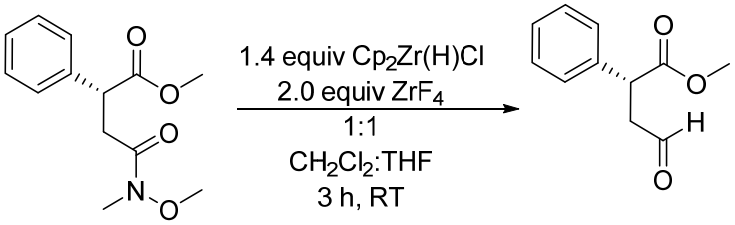
To a 4 mL vial in air containing a magnetic stir bar, (S)-**2p** (0.103 mmol, 1.00 equiv) and 1 mL of a 1:1 H_2O:H_2SO_4 solution was added. The vial was sealed with a cap containing a PFTE

septum, and the reaction mixture was heated at 120 °C for 6 h. The vial was unsealed and the reaction mixture was transferred to a separatory funnel with 4 mL of H_2O. The product was extracted with Et_2O. The organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum. The product was dissolved in Et_2O and filtered through a plug of silica. The product (S)-**3p** was obtained as a white solid (0.0217 g, 0.0994 mmol, 96% yield, >99% ee).

(S)-3p (S)-4,4,4-trifluoro-3-phenylbutanoic acid



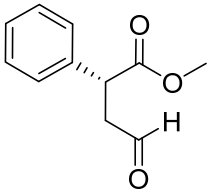
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 3H), 7.34 (dd, *J* = 6.7, 2.9 Hz, 2H), 3.75 – 3.63 (m, 1H), 3.05 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.95 (dd, *J* = 17.0, 9.7 Hz, 1H).[23]



In a nitrogen-filled glovebox, (R)-**2g** (0.0800 mmol, 1.00 equiv) and 1 mL of anhydrous THF were added to a 4 mL vial containing a magnetic stir bar. To a second 4 mL vial containing a magnetic stir bar, freshly prepared or newly purchased $Cp_2Zr(H)Cl$ (0.112 mmol, 1.40 equiv), anhydrous ZrF_4 (0.0800, 1.00 equiv) and 1 mL of anhydrous DCM were added. The solution containing **2g** was slowly added dropwise to the vial containing $Cp_2Zr(H)Cl$. The vial that contained **2g** was washed with 1 mL of a 1:1 DCM:THF solution, and this solution was also transferred to the vial containing $Cp_2Zr(H)Cl$ (for a total volume of 3 mL 1:1 THF:DCM). The reaction vial was sealed with a cap containing a PFTE septum and stirred at 300 rpm for 3 h at room temperature. At the end of this time, the reaction mixture was quenched with a few drops of 1M HCl. After bubbling ceased, the reaction solution was transferred to a separatory funnel with 1M HCl, and the product was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by silica gel chromatography (combiflash), eluting with a mixture of isopropanol and hexanes (gradient 0:100 to 5:95 IPrOH:Hexanes – visualize at 210 nm, 220 nm). The product 4-oxo-2-phenylbutanoate (R)-**3g** was obtained as a clear oil (0.0114 g, 0.0593 mmol, 74% yield, >99% ee).

*Notes: 1. It is difficult to visualize methyl 4-oxo-2-phenylbutanoate **3g** on TLC plates with $KMnO_4$, CAM, DNP, and p-anisaldehyde stains. Only concentrated samples of **3g** could be visualized on TLC plates with these stains. 2. The product should be stored under nitrogen at -25 ^oC or used immediately.

(R)-3g methyl (R)-4-oxo-2-phenylbutanoate

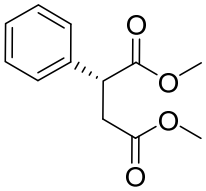


^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.37 – 7.27 (m, 5H), 4.14 (dd, *J* = 9.9, 4.6 Hz, 1H), 3.68 (s, 3H), 3.41 (ddd, *J* = 18.6, 9.9, 0.6 Hz, 1H), 2.81 (ddd, *J* = 18.6, 4.6, 0.6 Hz, 1H).[24]

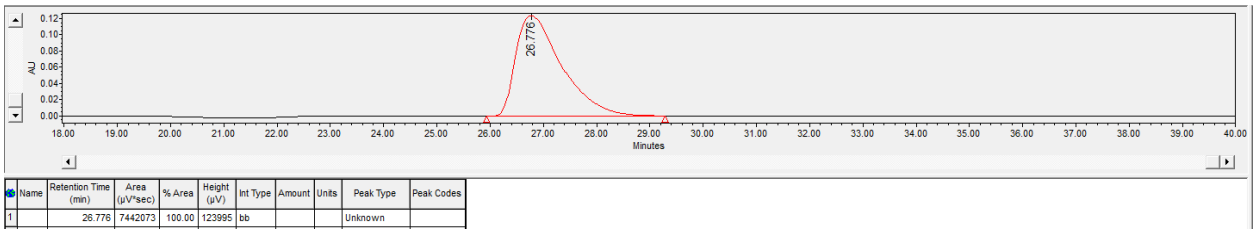
The ee (R)-**3g** was determined after converting the (R)-**3g** into 2-phenylbutane-1,4-diol. To a 4 mL vial with a stir bar, 0.0057 g of 4-oxo-2-phenylbutanoate and 0.4 mL of anhydrous ether were added. To this vial, 0.0050 g of $LiAlH_4$ was added portionwise. The reaction mixture was stirred for 5 h at room temperature. At the end of this time, the reaction mixture was quenched with a drop of H_2O, and transferred to a separatory funnel with 1 M HCl. The product was extracted with EtOAc and dried over Na_2SO_4. The crude 2-phenylbutane-1,4-diol was analyzed by chiral HPLC.[24]

V. Characterization of Enantioenriched Products

(R)-2a (R)-dimethyl 2-phenylsuccinate

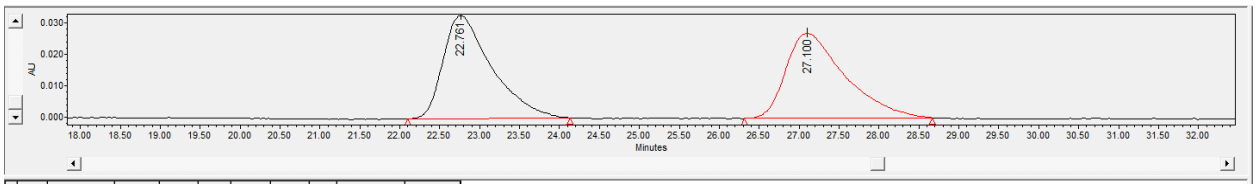


Enzyme: YersER
Column/Eluent: HPLC OJ-H, 5% iPrOH, 95% hexanes 1.0 mL/min, 220 nm; t_R (minor): 22.761 min, t_R(major): 27.100
Enantiomeric Excess: >99 % ee
Optical Rotation: $[\alpha]_D^{23}$ = -103.2 (c 0.50, $CHCl_3$)
Absolute Configuration: (R) Lit[4]
Authentic (R) Diester HPLC Trace



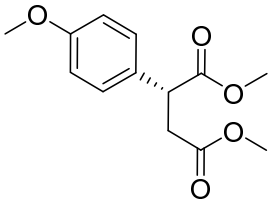
	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		26.776	7442073	100.00	123995	bb			Unknown	

Diester Racemate HPLC Trace



	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		22.761	1372280	49.97	32611	bb			Unknown	
2		27.100	1374164	50.03	26983	bb			Unknown	

(R)-2b (R)-dimethyl 2-(4-methoxyphenyl)succinate



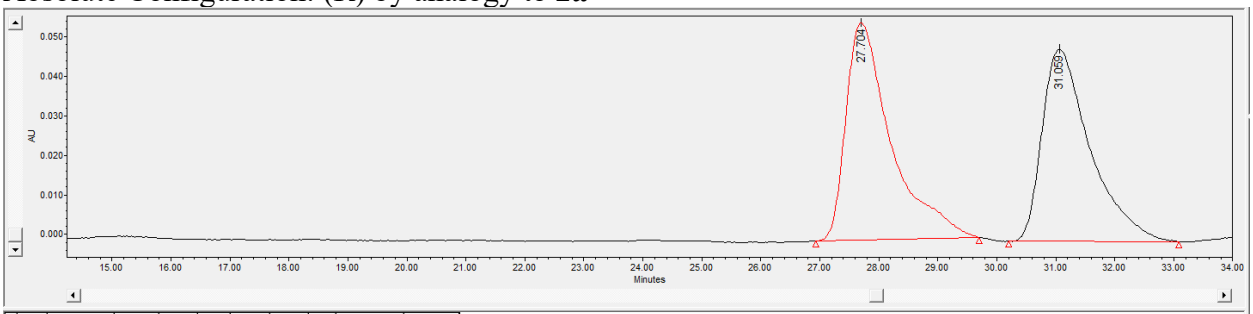
Enzyme: YersER

Column/Eluent: HPLC OJ-H, 10% iPrOH, 90% hexanes 1.0 mL/min, 220 nm; t_R (major): 27.704 min, t_R(minor): 31.059 min

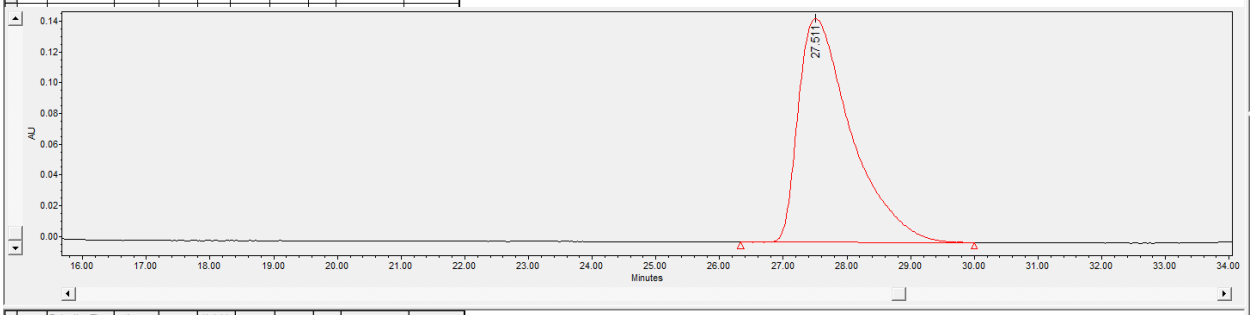
Enantiomeric Excess = >99% ee

Optical Rotation: $[\alpha]_D^{23}$ = -131.4 (c 1.00, $CHCl_3$)

Absolute Configuration: (R) by analogy to **2a**

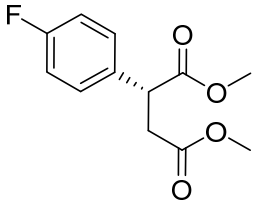


	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		27.704	2916306	51.41	54988	bb			Unknown	
2		31.059	2756399	48.59	48662	bb			Unknown	

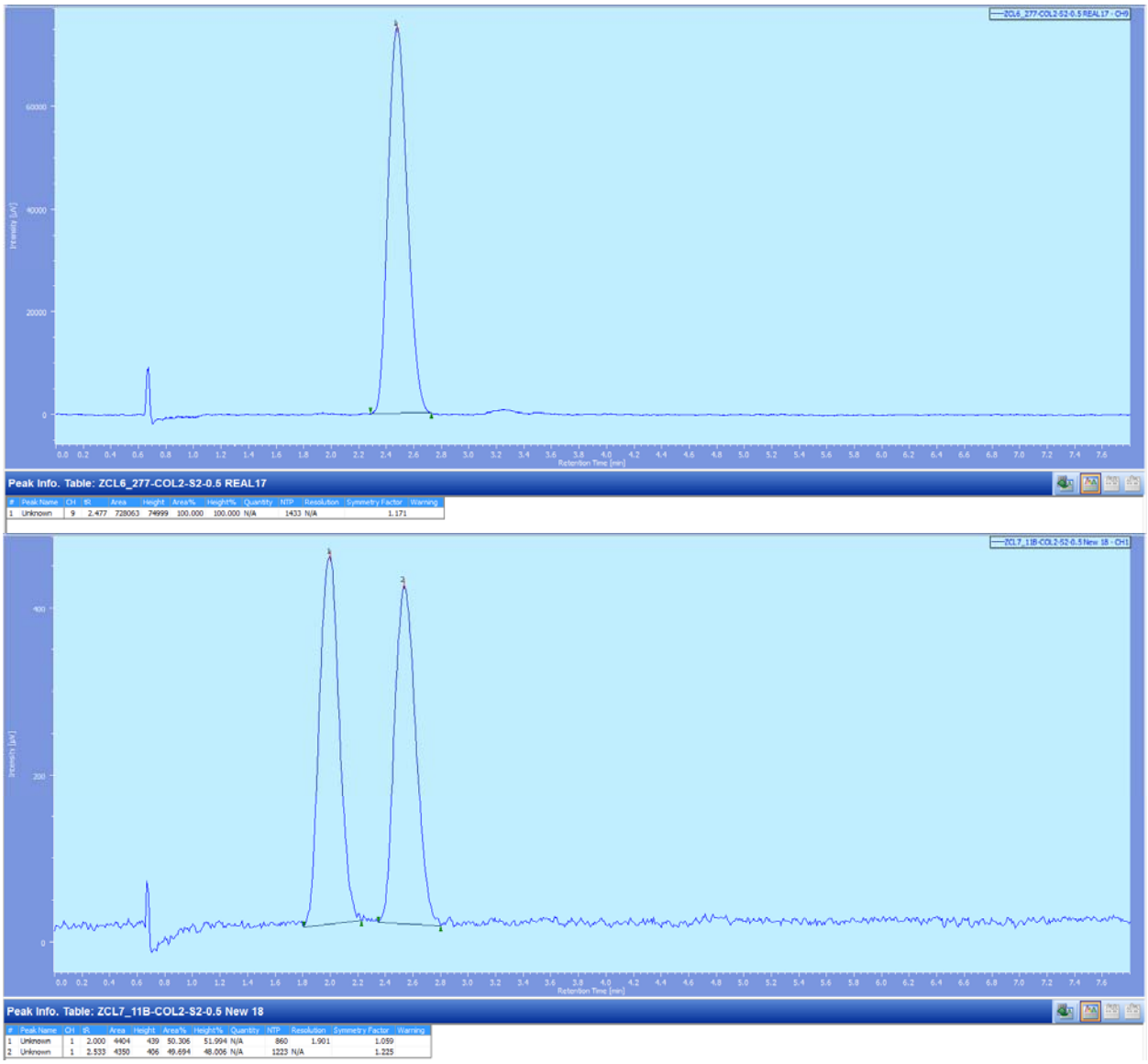


	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		27.511	8399362	100.00	145522	bb			Unknown	

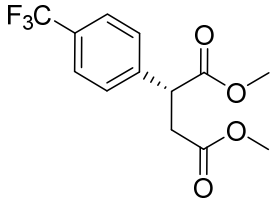
(R)-2c (R)-dimethyl 2-(4-fluorophenyl)succinate



Enzyme: xenB
Column/Eluent: SFC Column2 0.5% iPrOH 2.5mL/min
Enantiomeric Excess: >99 % ee
Optical Rotation: $[\alpha]_D^{23}$ = -116.5 (c 1.00, $CHCl_3$)
Absolute Configuration: (R) by analogy to **2a**



(R)-2d (R)-dimethyl 2-(4-(trifluoromethyl)phenyl)succinate



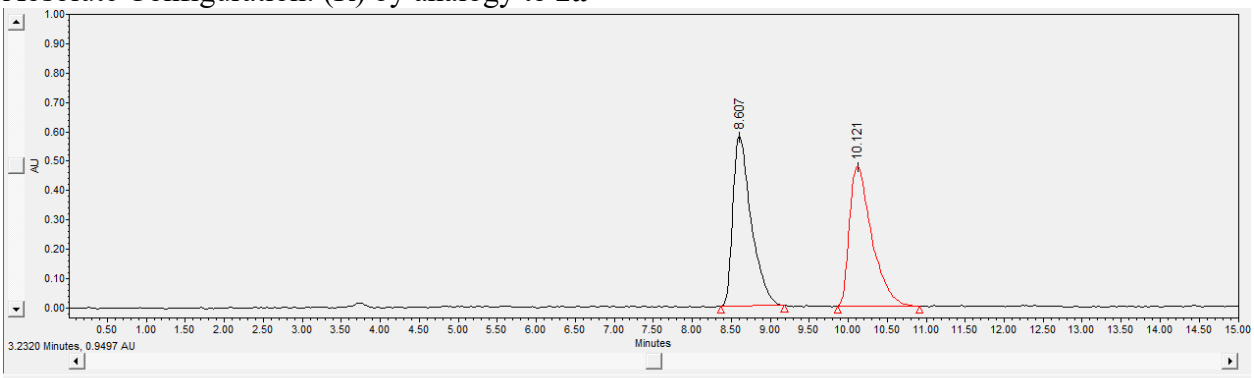
Enzyme: xenB

Column/Eluent: HPLC OJ-H, 5% iPrOH, 95% hexanes 1.0 mL/min, 220 nm; t_R (major): 8.607 min, t_R(minor): 10.121

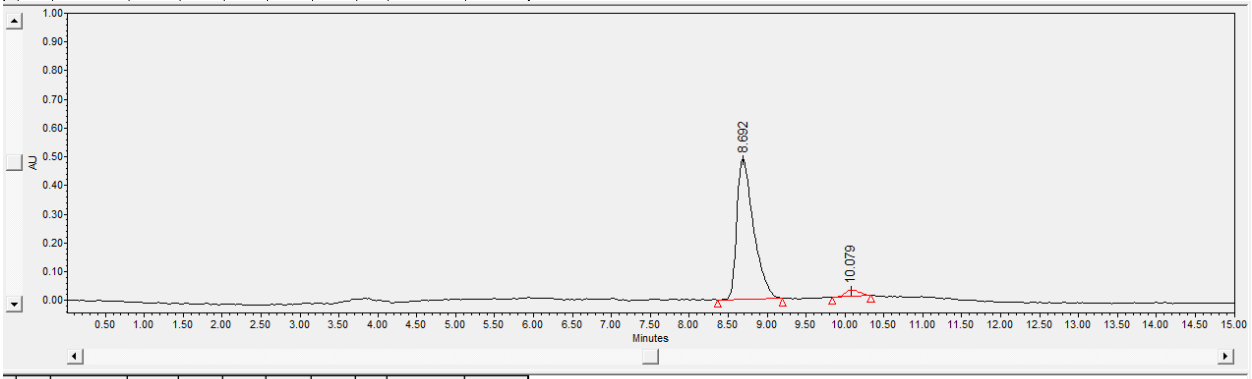
Enantiomeric Excess = 93 % ee

Optical Rotation: $[\alpha]_D^{23}$ = -87.1 (c 1.00, $CHCl_3$)

Absolute Configuration: (R) by analogy to **2a**

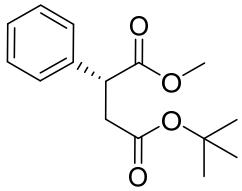


	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		8.607	9399066	50.07	579365	bb			Unknown	
2		10.121	9374656	49.93	473943	bb			Unknown	



	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		8.692	7323082	96.53	488909	bb			Unknown	
2		10.079	263456	3.47	19864	bb			Unknown	

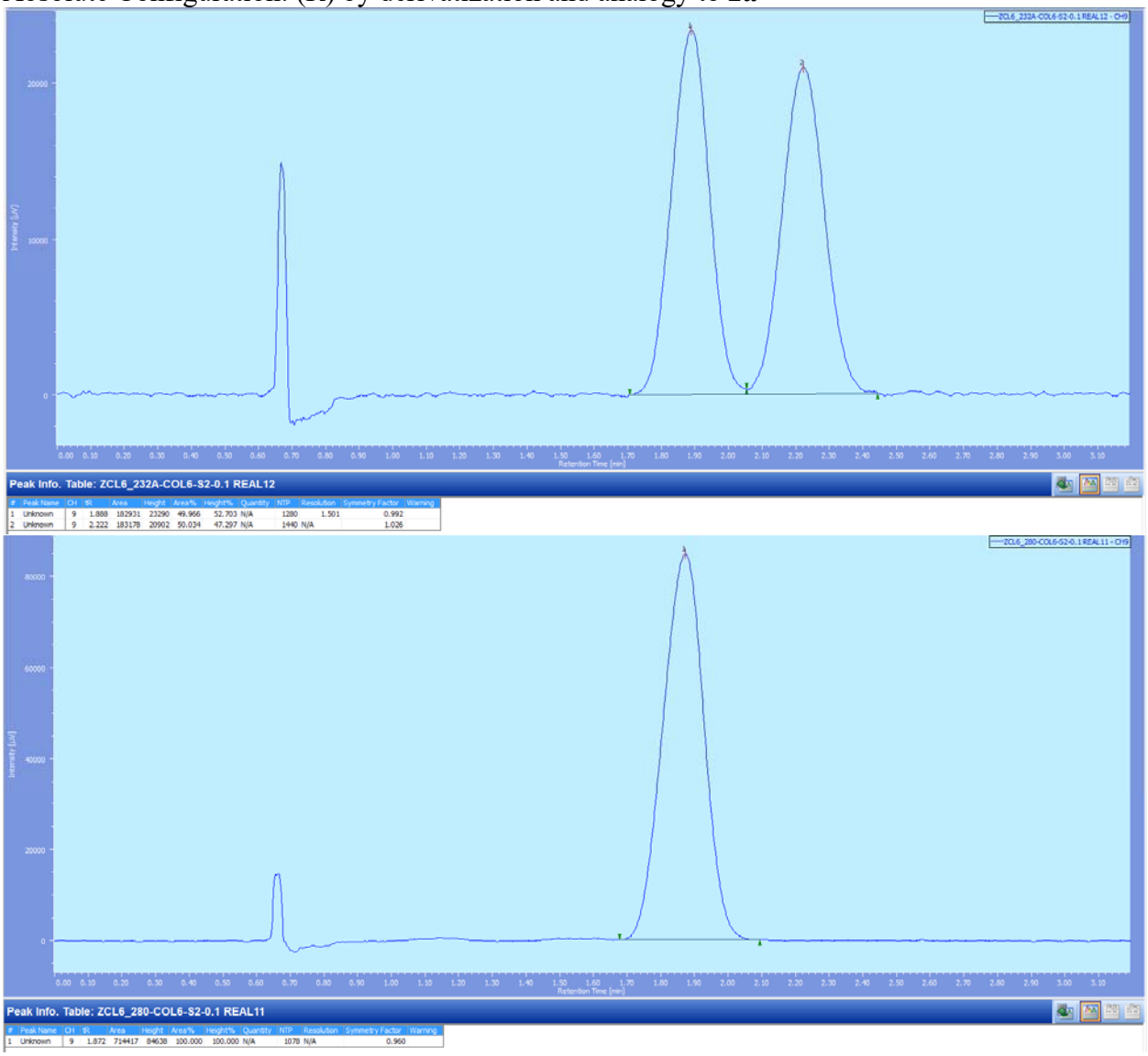
(R)-2e (R)-4-(tert-butyl) 1-methyl-2-phenylsuccinate



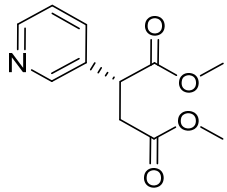
Enzyme: OPR1

Column/Eluent: OJ-H column, 0.1% iPrOH, 2.5 mL/min, 220 nm; t_R (major): 1.888 min,

t_R(minor): 2.222
Enantiomeric Excess = >99% ee
Optical Rotation: $[\alpha]_D^{23}$ = -100.2 (c 1.00, $CHCl_3$)
Absolute Configuration: (R) by derivatization and analogy to **2a**

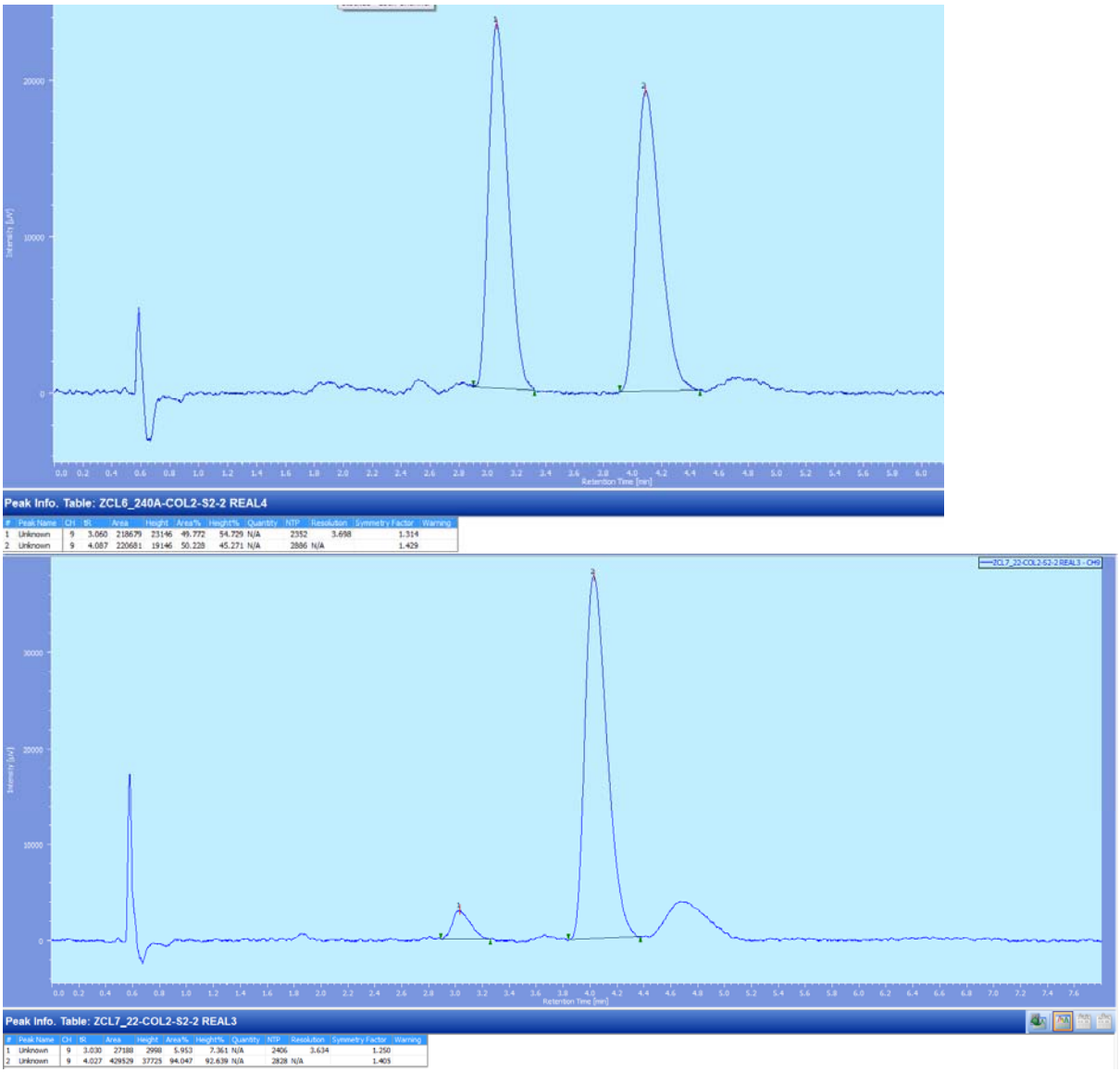


(R)-2f (R)-dimethyl 2-(pyridin-3-yl)succinate

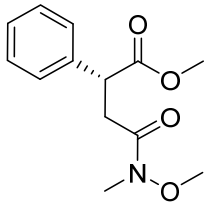


Enzyme: xenB
Column/Eluent: Chiral SFC: OD-H column, 2% iPrOH, 2.5 mL/min, 220 nm; t_R (minor): 3.060 min, t_R(major): 4.087
Enantiomeric Excess = 89% ee

Optical Rotation: $[\alpha]_D^{23}$ = -93.3 (c 1.00, $CHCl_3$)
Absolute Configuration: (R) by analogy to **2a**

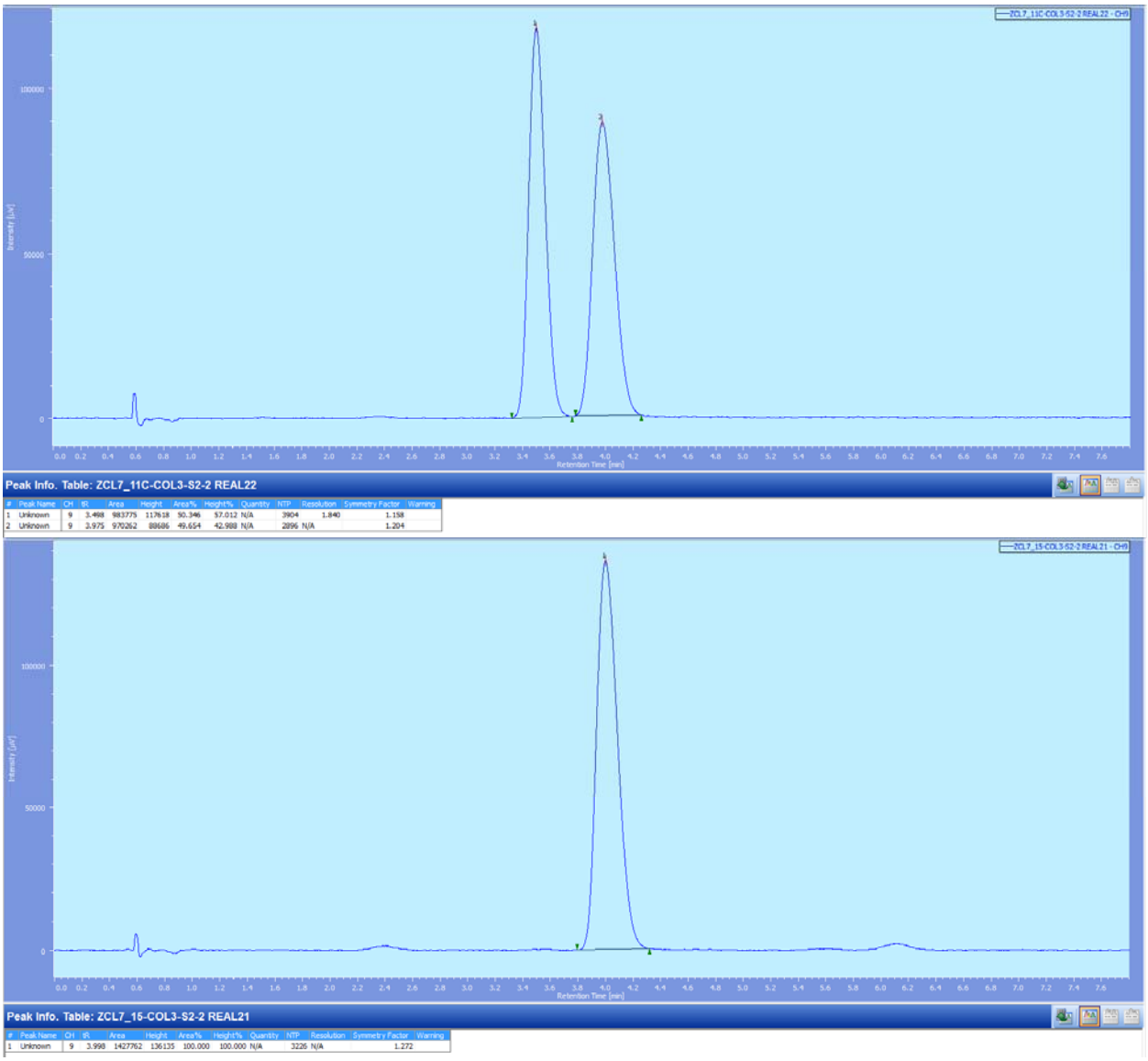


(R)-2g (R)-methyl 4-(methoxy(methyl)amino)-4-oxo-2-phenylbutanoate

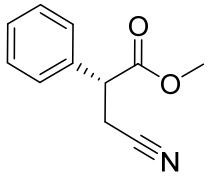


Enzyme: YersER/(OPR1)
Column/Eluent: Chiral SFC: Column AD-H 2% iPrOH, 2.5 mL/min, 220 nm; t_R (minor): 3.498 min, t_R(major): 3.975 min
Enantiomeric Excess = >99%ee (c 1.00 $CHCl_3$)

Optical Rotation: $[\alpha]_D^{23}$ = -124.6
Absolute Configuration: (R) by conversion to **2a**

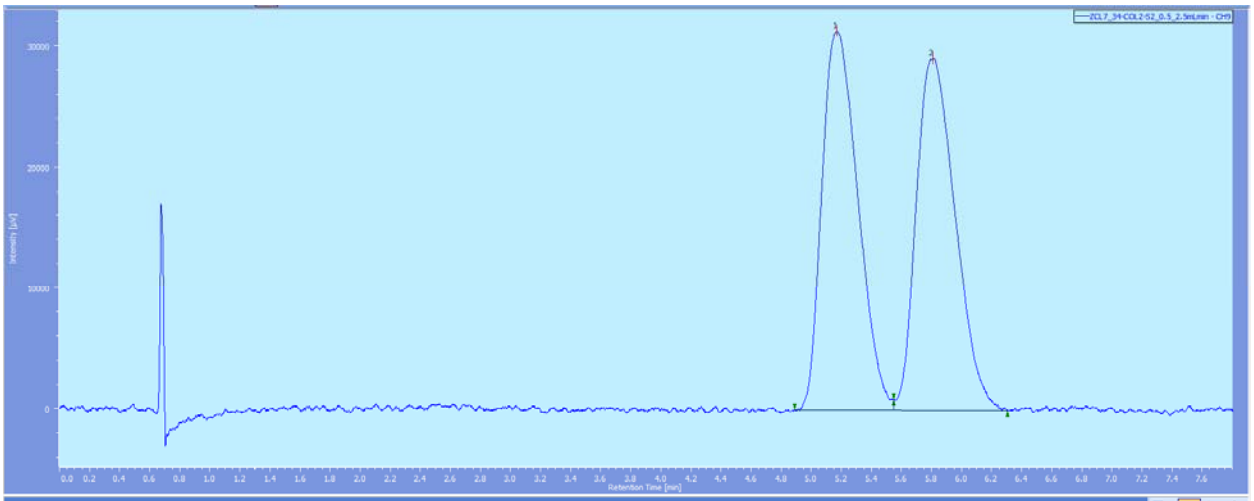


(R)-2h (R)-methyl 3-cyano-2-phenylpropanoate

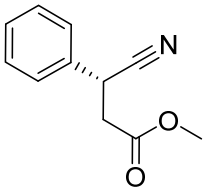


Enzyme: TOYE
Column/Eluent: SFC Column OD-H 0.5% iPrOH, 2.5 mL/min, 220 nm; t_R (minor): 5.167 min, t_R(major): 5.807 min
Enantiomeric Excess = >99% ee

Optical Rotation: $[\alpha]_D^{23}$ = -144.8 (c 1.00, $CHCl_3$)
Absolute Configuration: (R) Lit[8]

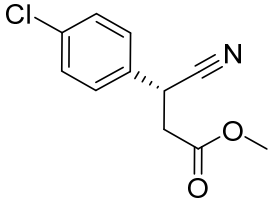


(R)-2i (R)-methyl 3-cyano-3-phenylpropanoate



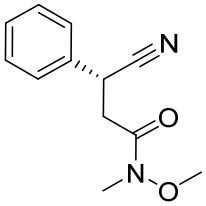
Enzyme: OYE3
Column/Eluent:
Enantiomeric Excess = >99%
Optical Rotation: $[\alpha]_D^{23}$ = + 10.0 (c 0.50, $CHCl_3$)
Absolute Configuration: (R) Lit[9]

(R)-2j (R)-methyl 3-(4-chlorophenyl)-3-cyanopropanoate

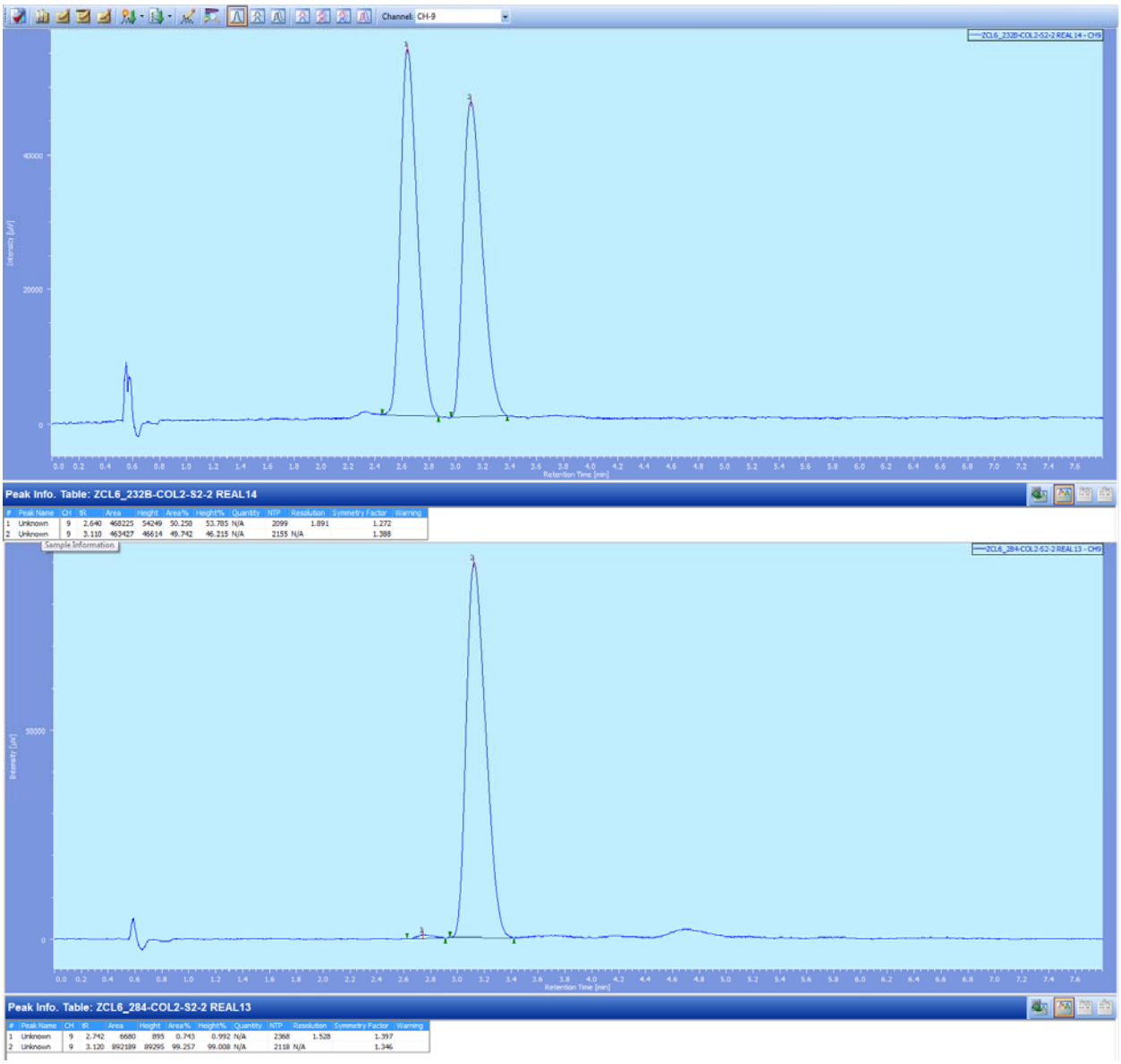


Enzyme: OYE2
Column/Eluent:
Enantiomeric Excess = 76% ee
Optical Rotation: $[\alpha]_D^{23}$ = +8.7 (c 1.00, MeOH)
Absolute Configuration: (R) Lit[9]

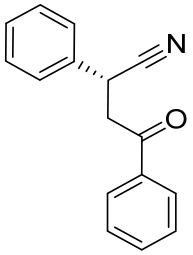
(R)-2k (R)-3-cyano-N-methoxy-N-methyl-3-phenylpropanamide



Enzyme: YersER
Column/Eluent: Chiral SFC: Column OD-H 2% iPrOH, 2.5 mL/min, 220 nm; t_R (minor): 2.640 min, t_R(major): 3.110 min
Enantiomeric Excess = 99% ee
Optical Rotation: $[\alpha]_D^{23}$ = +10.6 (c 1.00, $CHCl_3$)
Absolute Configuration: (R) by conversion to **2a**

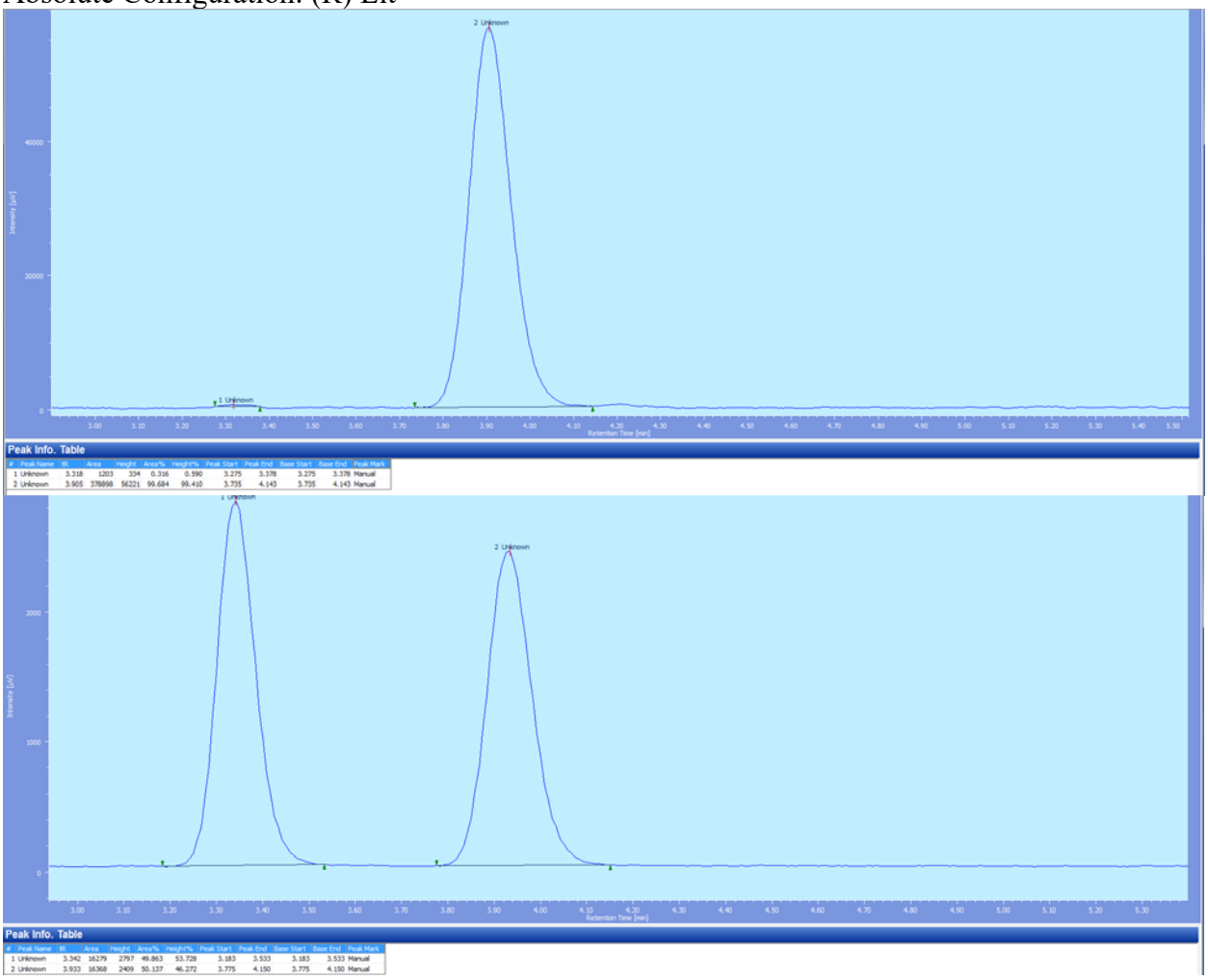


(R)-2l (R)-4-oxo-2,4-diphenylbutanenitrile

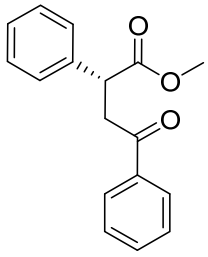


Enzyme: OYE2
Column/Eluent: SFC: OD-H column, 10% MeOH, 2.5 mL/min, 220 nm; t_R (minor): 3.342 min, t_R(major): 3.933 min
Enantiomeric Excess = 99%
Optical Rotation: $[\alpha]_D^{23}$ = +17.2 (c 0.80, $CHCl_3$)

Absolute Configuration: (R) Lit[25]



(R)-2m (R)-methyl 4-oxo-2,4-diphenylbutanoate



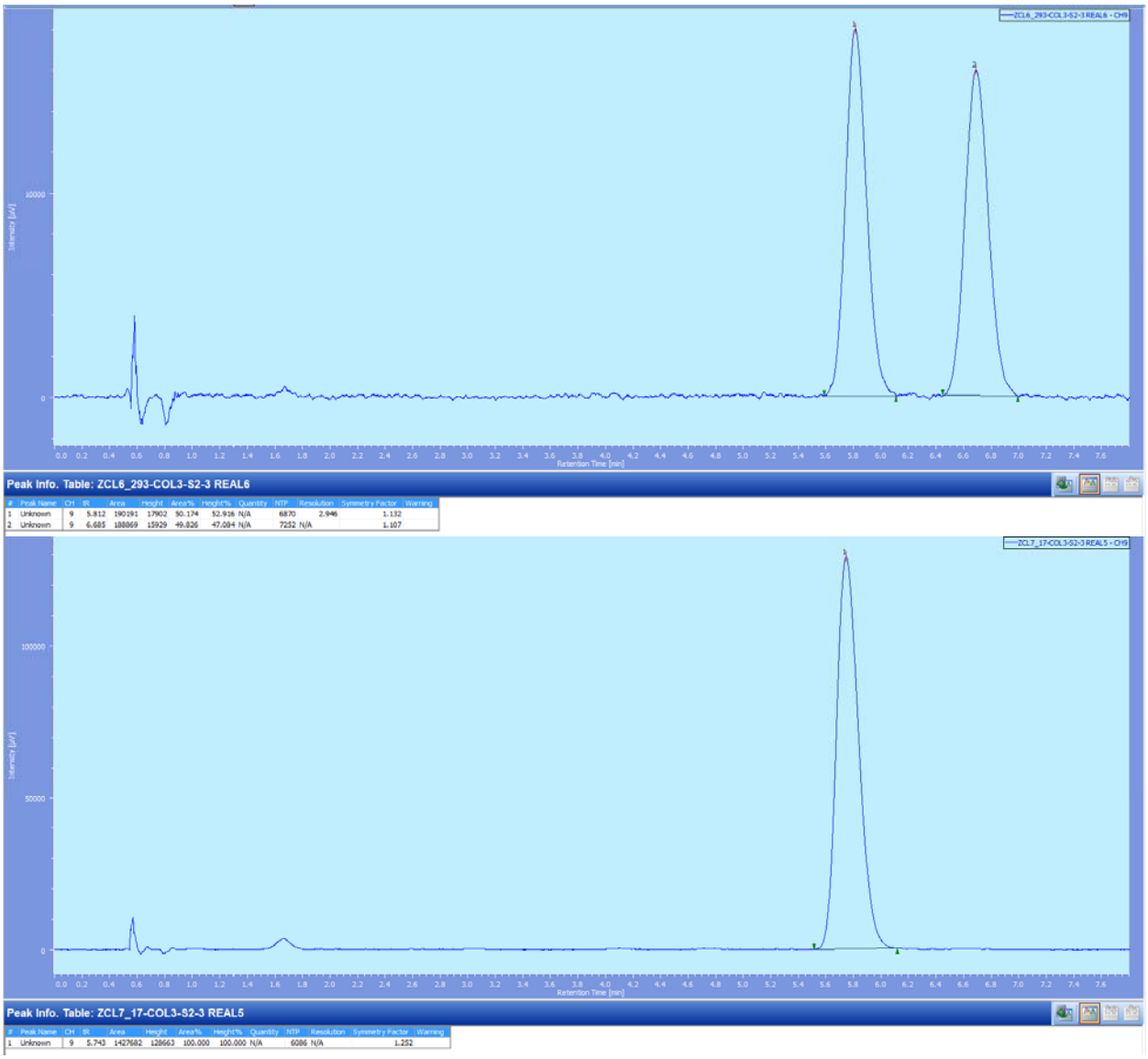
Enzyme: OPR1

Column/Eluent: SFC: AD-H column, 3% iPrOH, 2.5 mL/min, 220 nm; t_R (minor): 5.812 min, t_R(major): 6.685 min

Enantiomeric Excess = >99% ee

Optical Rotation: $[\alpha]_D^{23}$ = -130.5 (c 1.00, $CHCl_3$)

Absolute Configuration: (R) Lit[26]



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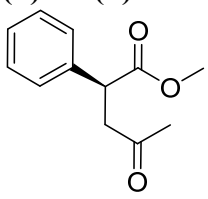
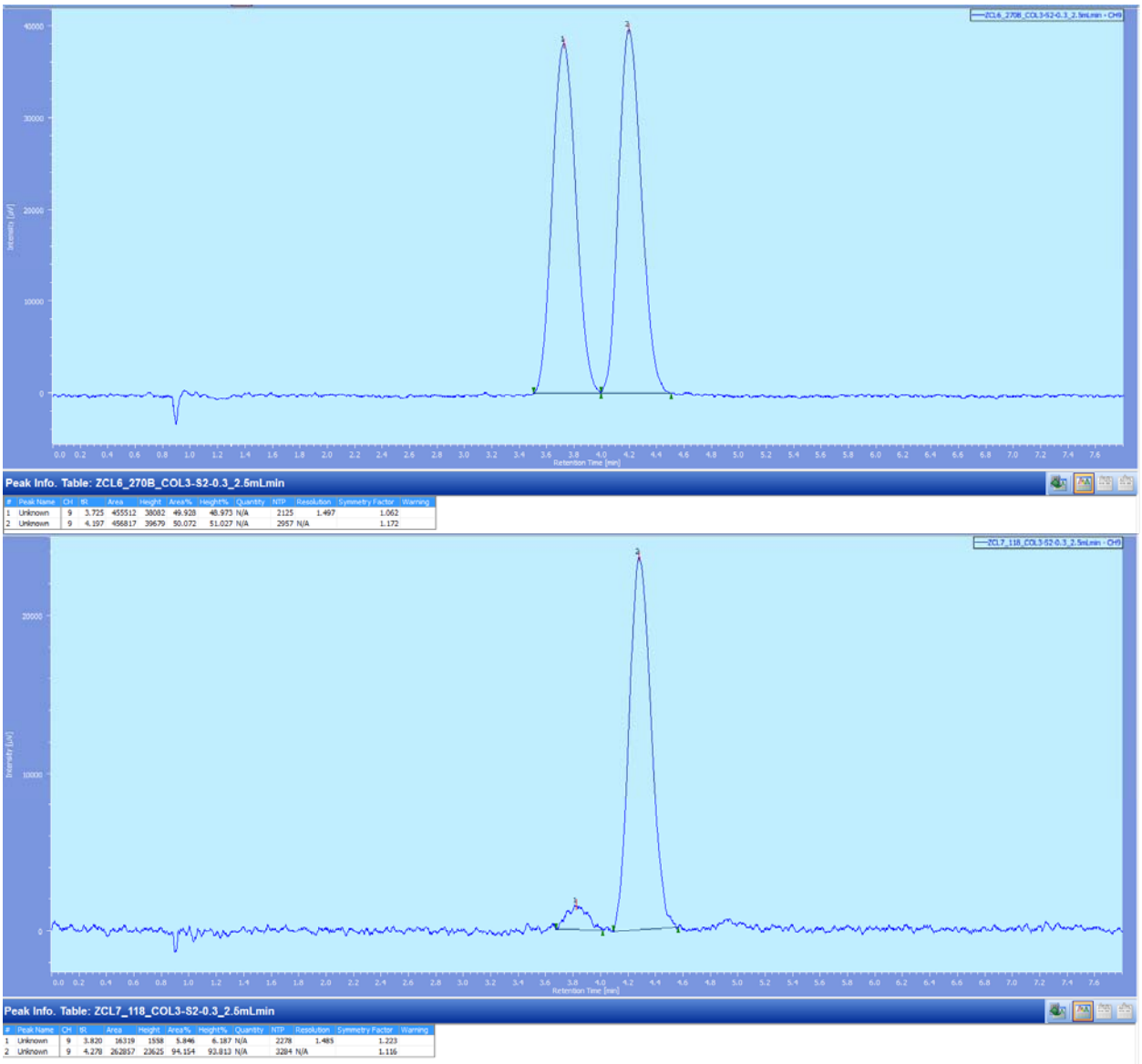
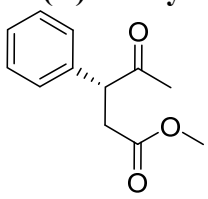
(S)-2n (S)-methyl 4-oxo-2-phenylpentanoate



Enzyme: SYE1
Column/Eluent: SFC AD-H, 0.3% iPrOH
Enantiomeric Excess = 88% ee
Optical Rotation: $[\alpha]_D^{23}$ = +140.0 (c 0.40, $CHCl_3$)
Absolute Configuration: (S) Lit[21]



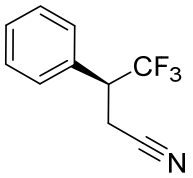
2o (R)-methyl 4-oxo-3-phenylpentanoate



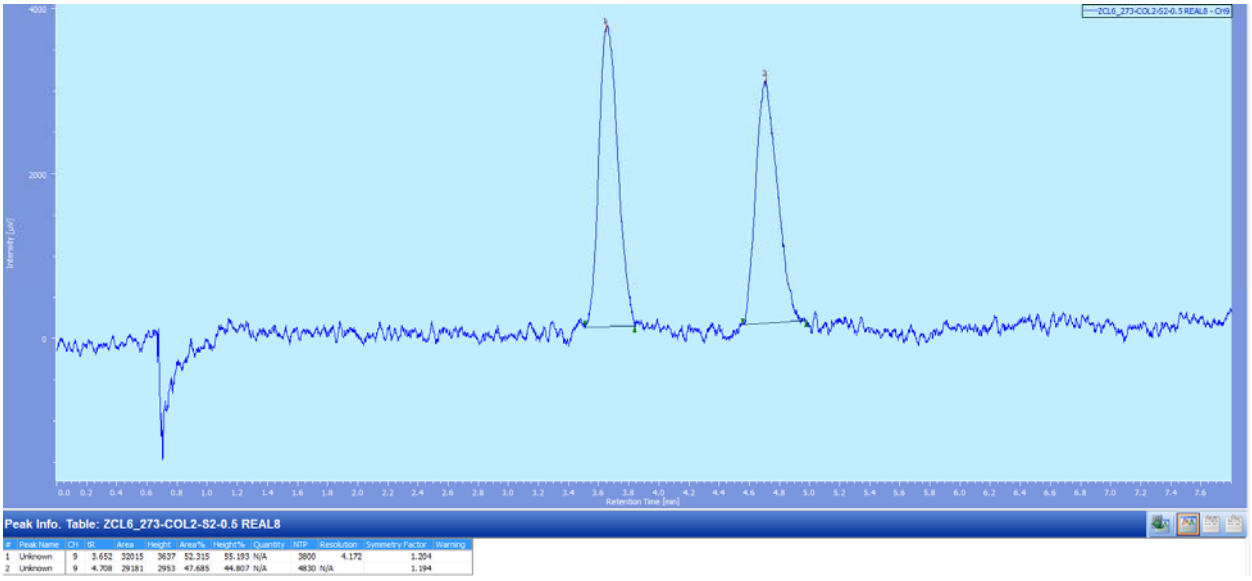
Enzyme: YersER
Column/Eluent:
Enantiomeric Excess =

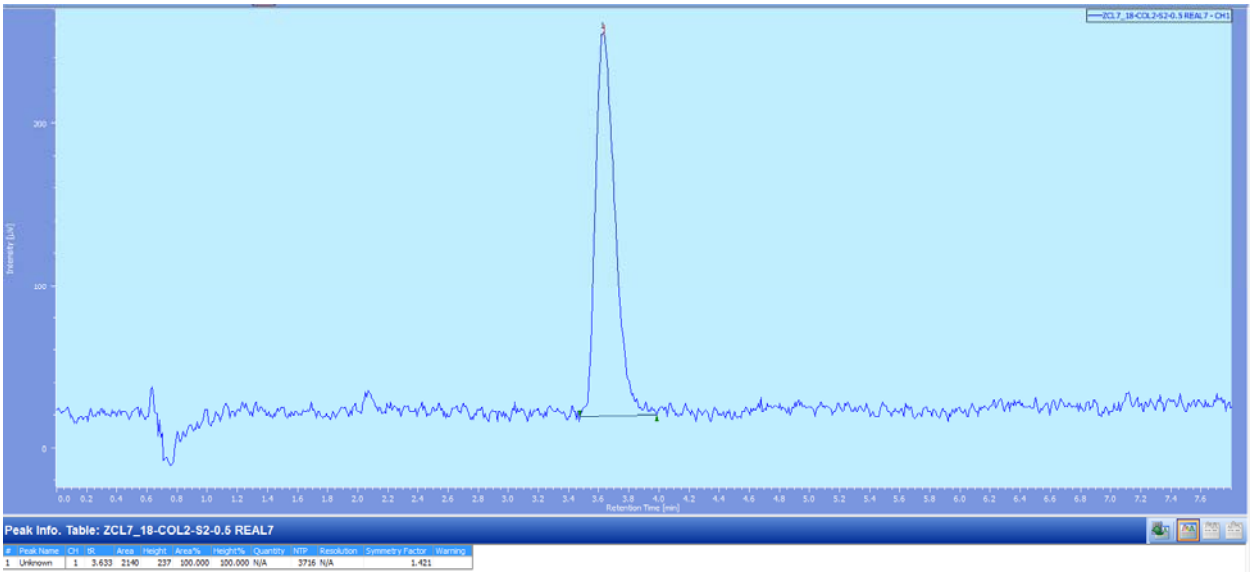
Optical Rotation: $[\alpha]_D^{23}$ =
Absolute Configuration: Lit[21]

(S)-2p (S)- 4,4,4-trifluoro-3-phenylbutanenitrile

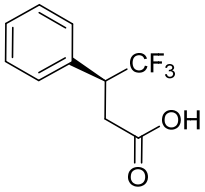


Enzyme: OYE3
Column/Eluent: Chiral SFC: OD-H column, 0.5% iPrOH, 2.5 mL/min, 260 nm; t_R (major): 3.652 min, t_R(minor): 4.708 (not observed)
Enantiomeric Excess = >99% ee
Optical Rotation: $[\alpha]_D^{23}$ = +64.3 (c 1.00, $CHCl_3$)
Absolute Configuration: (S) see hydrolysis product

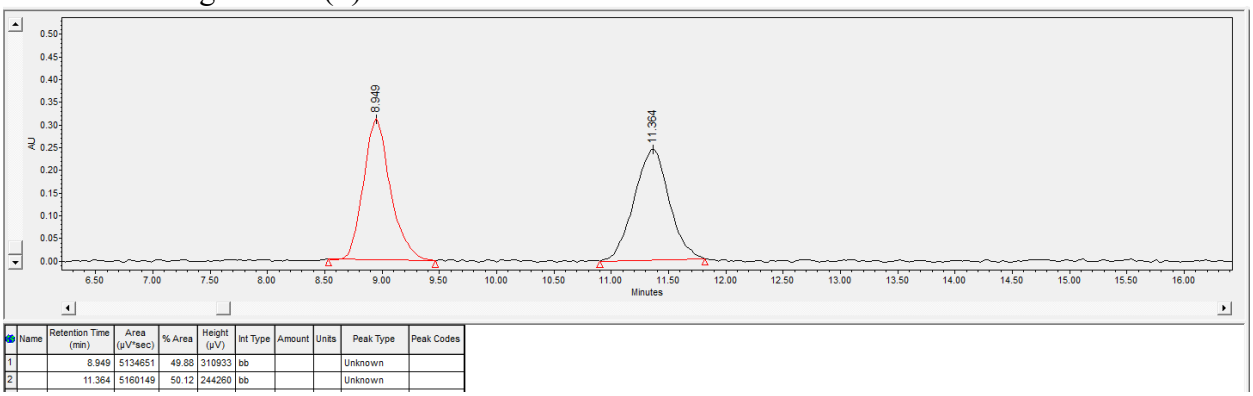




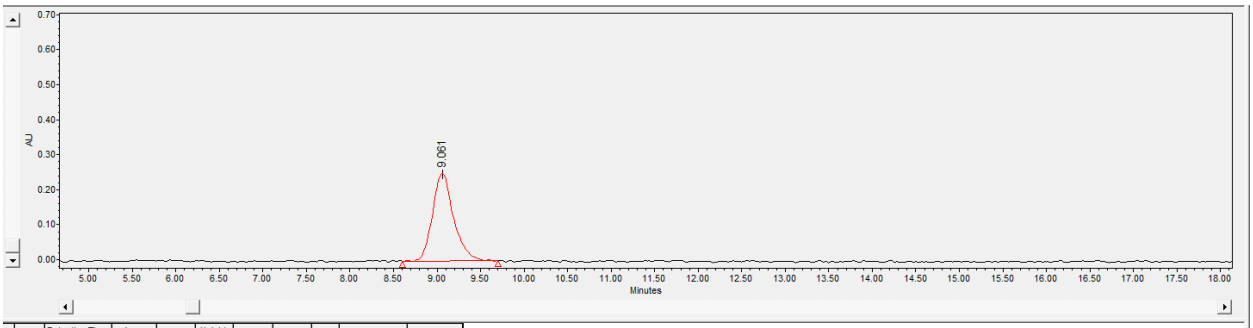
F. Characterization of Enantioenriched Derivatives
(S)-4,4,4-trifluoro-3-phenylbutanoic acid



Column/Eluent: HPLC OJ-H 10% iPrOH, 90% hexanes 1.0 mL/min, 220 nm; t_R (major): 8.949 min, t_R(minor): 11.364 (not observed)
Enantiomeric Excess = >99% ee
Optical Rotation: $[\alpha]_D^{23}$ = +52.2 (c 1.00, $CHCl_3$)
Absolute Configuration: (S) Lit[23]

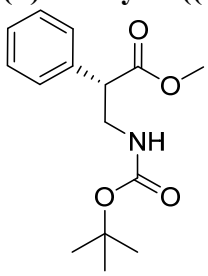


	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		8.949	5134651	49.88	310933	bb			Unknown	
2		11.364	5160149	50.12	244260	bb			Unknown	



Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1	9.061	4236851	100.00	250231	bb			Unknown	

(S)-methyl 3-((tert-butoxycarbonyl)amino)-2-phenylpropanoate

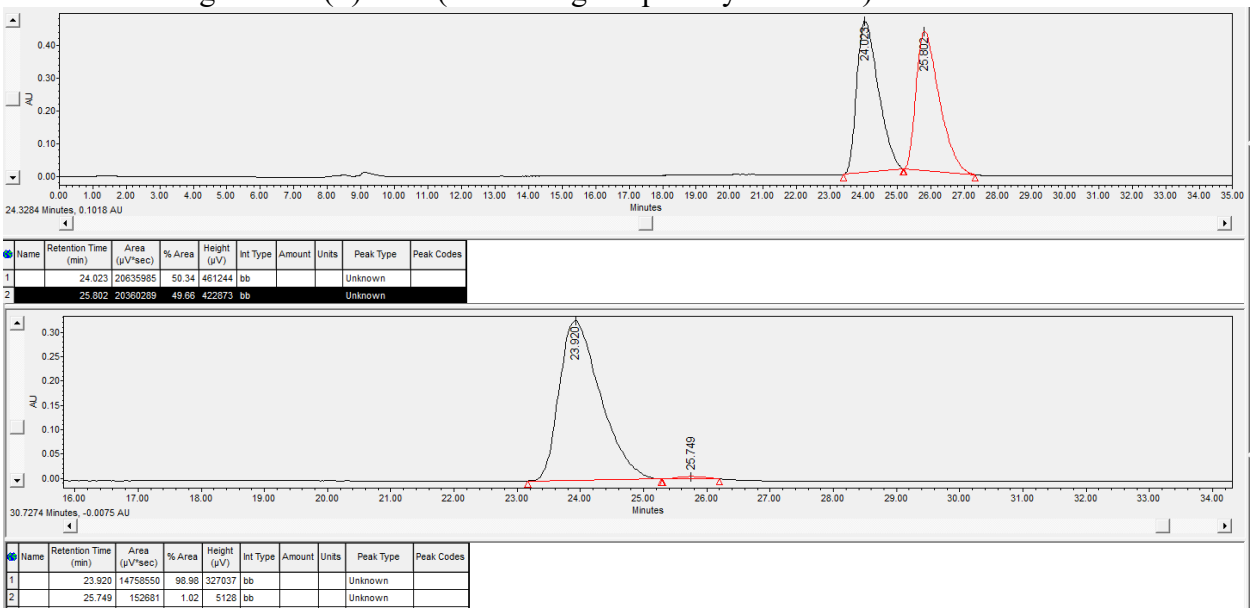


Column/Eluent: HPLC OJ-H 1% iPrOH, 99% hexanes 1.0 mL/min, 220 nm; t_R (major): 24.023 min, t_R(minor): 25.802

Enantiomeric Excess = 98% ee

Optical Rotation: $[\alpha]_D^{23}$ = -76.8 (c 1.00, $CHCl_3$)

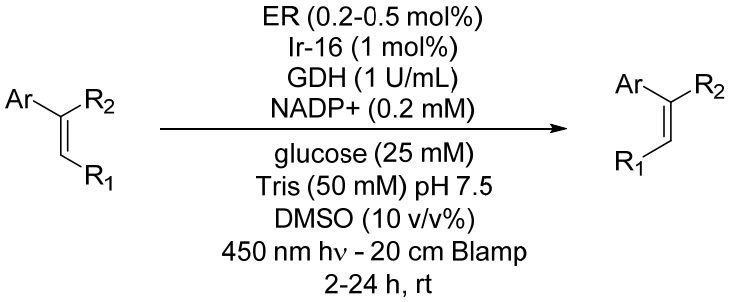
Absolute Configuration: (S) Lit[22] (note change in priority from SM)



Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1	24.023	20635985	50.34	461244	bb			Unknown	
2	25.802	20360289	49.66	422873	bb			Unknown	

Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1	23.920	14758550	98.98	327037	bb			Unknown	
2	25.749	152681	1.02	5128	bb			Unknown	

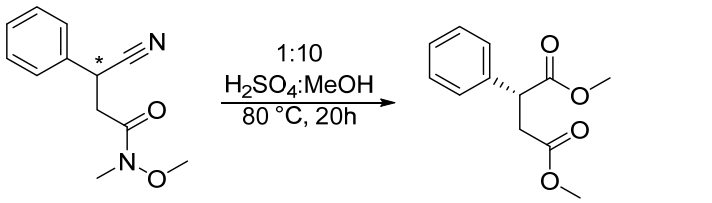
VI. Preparative Scale Cooperative Reactions



Preparative scale cooperative reactions were conducted according to the general procedure.

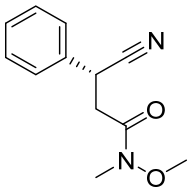
Sub	Abbrev	Enzyme	Catalyst	Mass R	Mass P	% Yield	%ee
1e	tBu	OPR1	1% Ir-16	0.0655	0.052	78.785603	>99%
1a	Diester	YERS-ER	1% Ir-16	0.055	0.0481	86.659647	>99%
1h	Est CN	TOYE	1% Ir-16	0.045	0.0438	96.227331	92%
1g	Wein Est	OPR1	1% Ir-16	0.0498	0.0356	70.914125	>99%

VII. Determination of Absolute Configuration of Products



$[\alpha]^{23}_D$ = + 10.6
(c = 1.00 $CHCl_3$)
99% ee

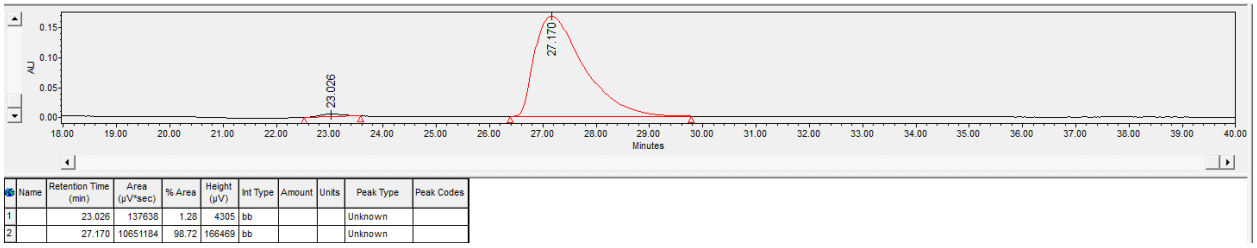
(R)-dimethyl 2-phenylsuccinate
HPLC matches Authentic
98% ee



(*R*)-3-cyano-*N*-methoxy-*N*-methyl-3-phenylpropanamide

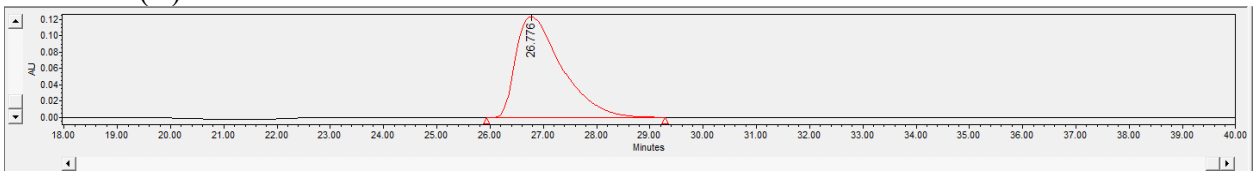
$[\alpha]^{23}_D$ = + 10.6
(c = 1.00 $CHCl_3$)
99% ee

Reaction Product HPLC Trace



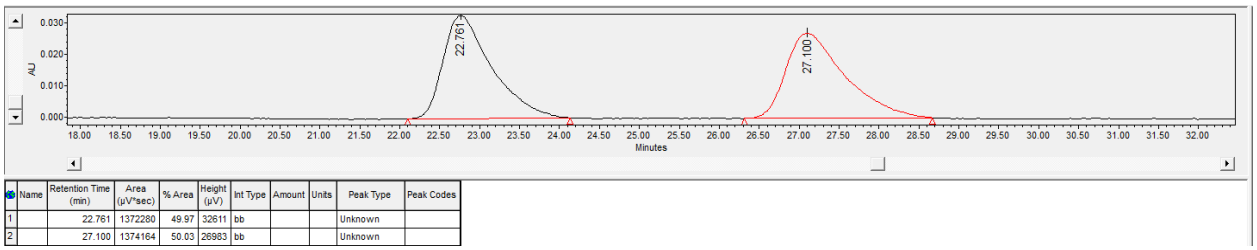
Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type	Amount	Units	Peak Type	Peak Codes
1	23.026	137638	1.28	4305	bb			Unknown	
2	27.170	10651184	98.72	166469	bb			Unknown	

Authentic (R) Diester HPLC Trace



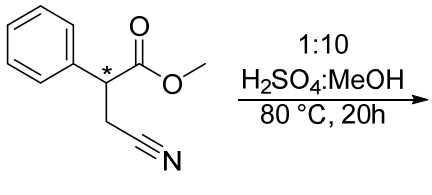
Name	Retention Time (min)	Area (μV*sec)	% Area	Height (μV)	Int Type	Amount	Units	Peak Type	Peak Codes
1	26.776	7442073	100.00	123995	bb			Unknown	

Diester Racemate HPLC Trace

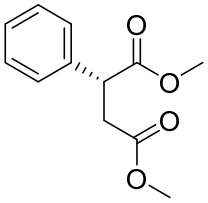


	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		22.761	1372280	49.97	32611	bb			Unknown	
2		27.100	1374164	50.03	26983	bb			Unknown	

HPLC OJ-H, 5% iPrOH, 95% hexanes 1.0 mL/min, 220 nm; t_R (minor): 22.761 min, t_R(major): 27.100

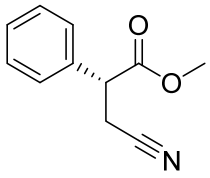


1:10
H_2SO_4:MeOH
80 °C, 20h



$[\alpha]^{23}_D$ = - 144.8
(c = 1.00 $CHCl_3$)
>99% ee

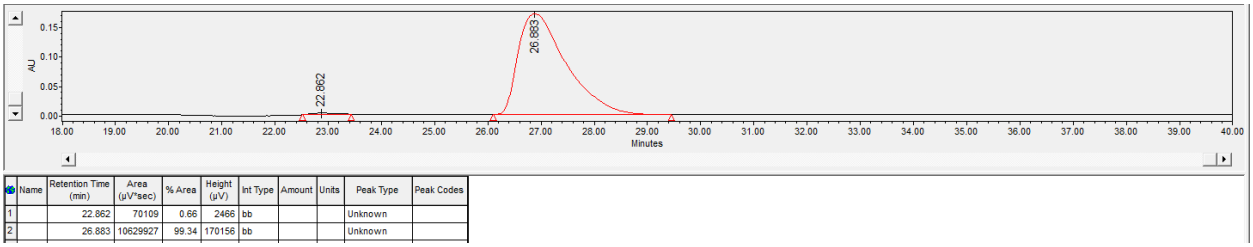
(R)-dimethyl 2-phenylsuccinate
HPLC matches Authentic
99% ee



(R)-methyl 3-cyano-2-phenylpropanoate

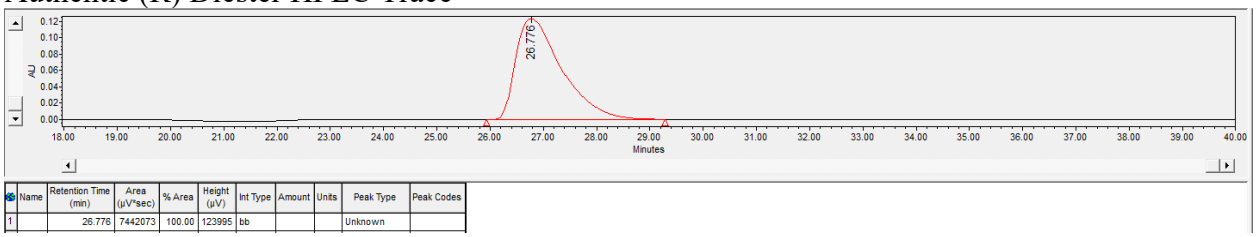
$[\alpha]^{23}_D$ = - 144.8
(c = 1.00 $CHCl_3$)
>99% ee

Reaction Product HPLC Trace



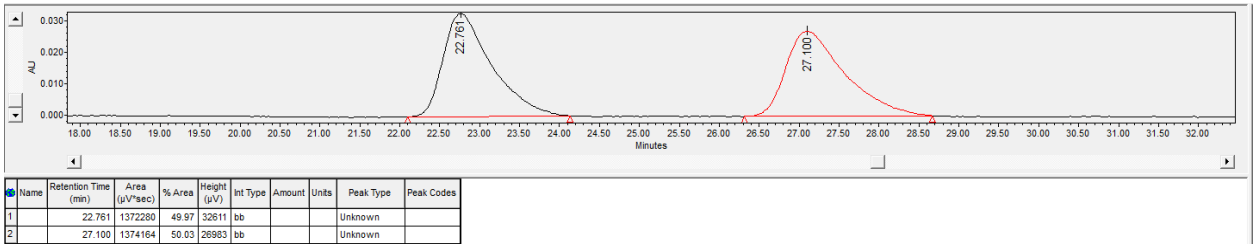
	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		22.862	70109	0.66	2466	bb			Unknown	
2		26.883	10629927	99.34	170156	bb			Unknown	

Authentic (R) Diester HPLC Trace



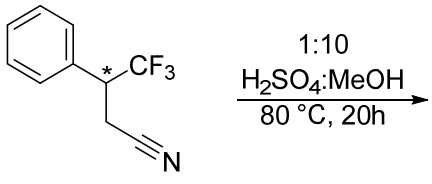
	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		26.776	7442073	100.00	123995	bb			Unknown	

Diester Racemate HPLC Trace

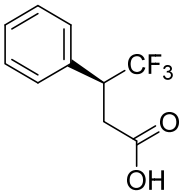


	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		22.761	1372280	49.97	32611	bb			Unknown	
2		27.100	1374164	50.03	26983	bb			Unknown	

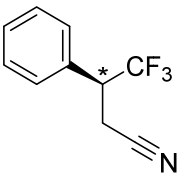
HPLC OJ-H, 5% iPrOH, 95% hexanes 1.0 mL/min, 220 nm; t_R (minor): 22.761 min, t_R(major): 27.100



$[\alpha]^{23}_D$ = + 64.3
(c = 1.00 $CHCl_3$)
>99% ee



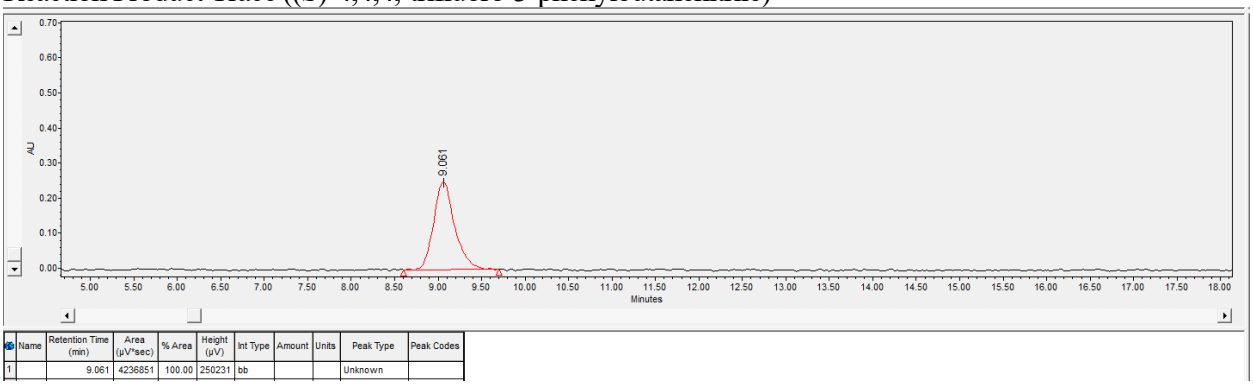
(*S*)-4,4,4-trifluoro-3-phenylbutanoic acid
$[\alpha]^{23}_D$ = + 52.2
(c = 1.00 $CHCl_3$)
>99% ee



(*S*)-4,4,4-trifluoro-3-phenylbutanenitrile

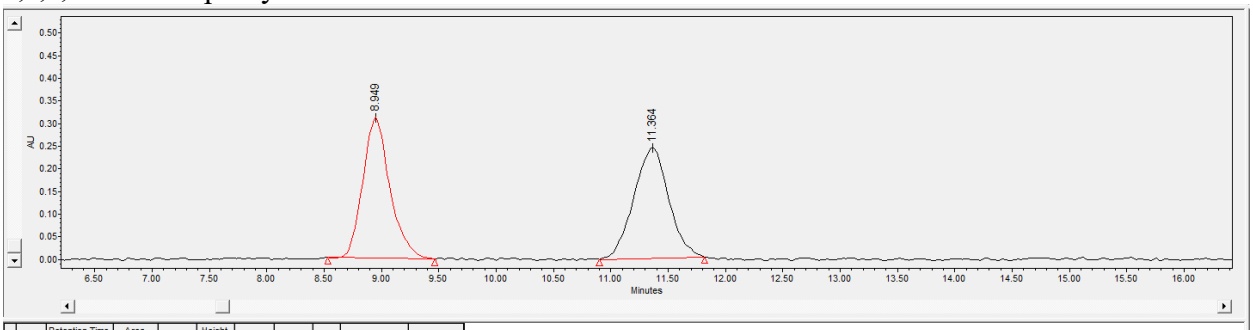
$[\alpha]^{23}_D$ = + 64.3
(c = 1.00 $CHCl_3$)
>99% ee

Reaction Product Trace ((S)-4,4,4,-trifluoro-3-phenylbutanenitrile)



Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1	9.061	4236851	100.00	250231	bb			Unknown	

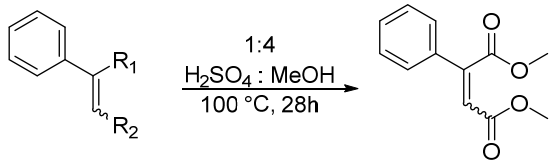
4,4,4,-trifluoro-3-phenylbutanenitrile Racemate Trace

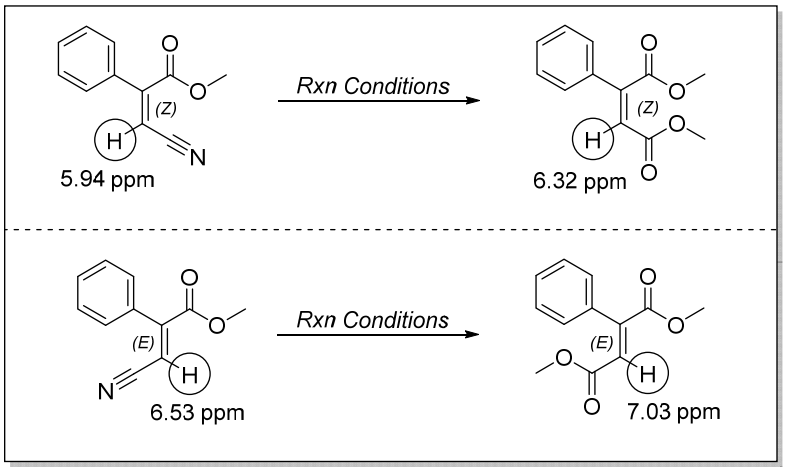


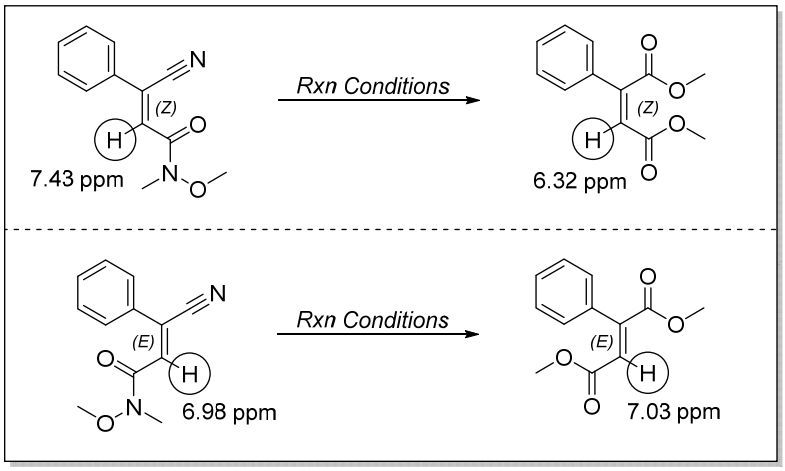
Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1	8.949	5134651	49.88	310933	bb			Unknown	
2	11.364	5160149	50.12	244260	bb			Unknown	

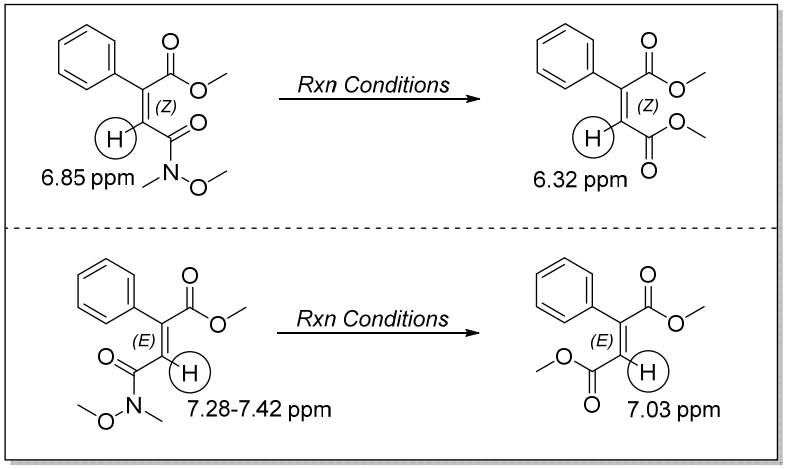
HPLC OJ-H, 10% iPrOH, 95% hexanes 1.0 mL/min, 220 nm; t_R (minor): 22.761 min, t_R(major): 27.100

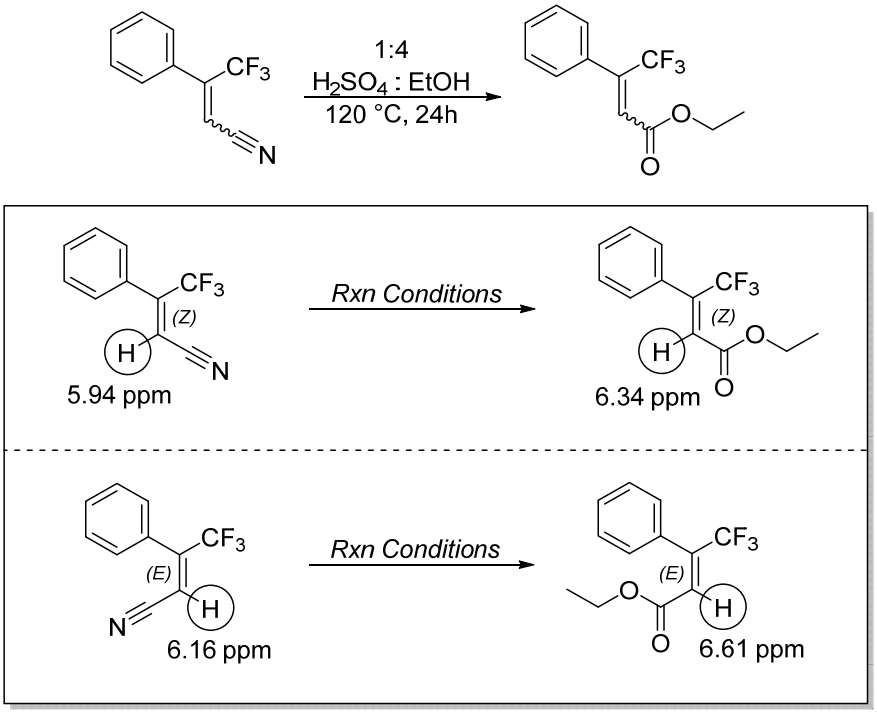
Determination/Confirmation of E/Z Configuration





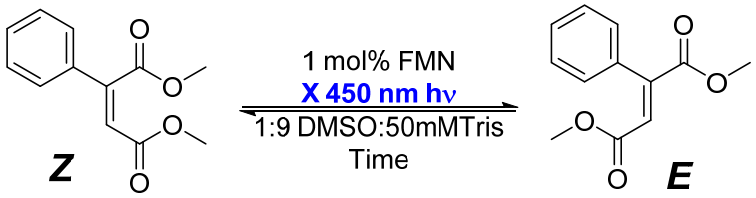


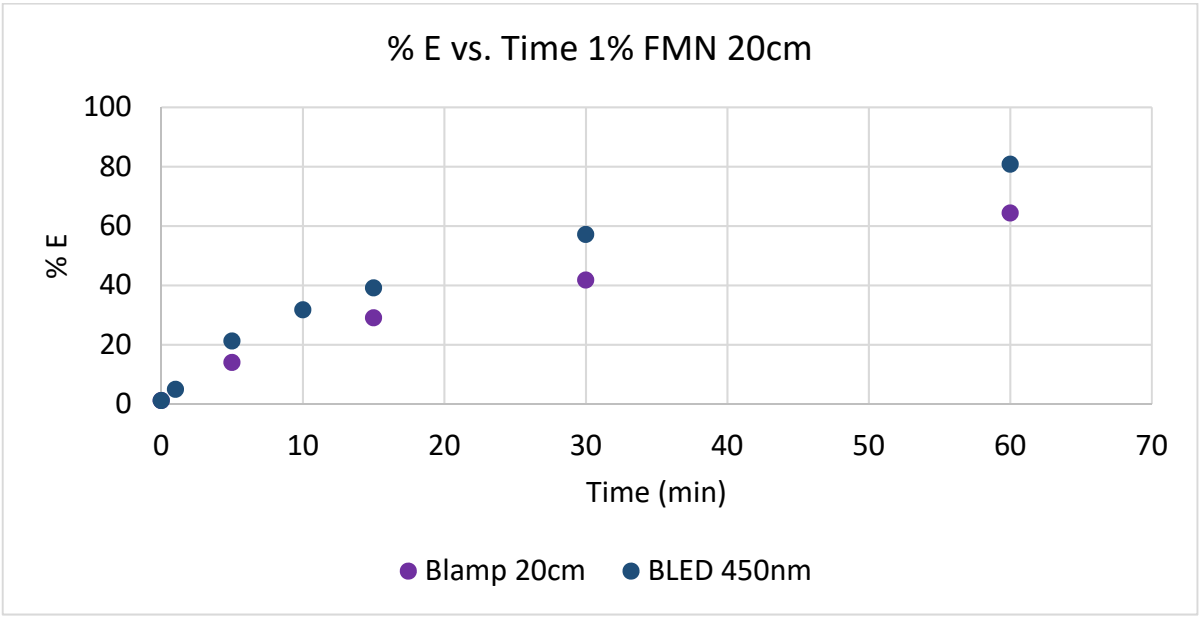



1:4
H2SO4 : EtOH
120 °C, 24h
CF3
N
O
(Z)
H
5.94 ppm
Rxn Conditions
6.34 ppm
(E)
6.16 ppm
6.61 ppm

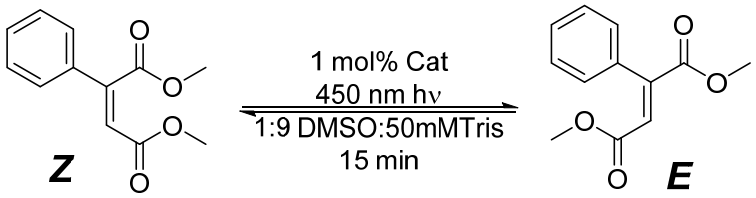
VIII. Photocatalyzed Isomerization Experiments

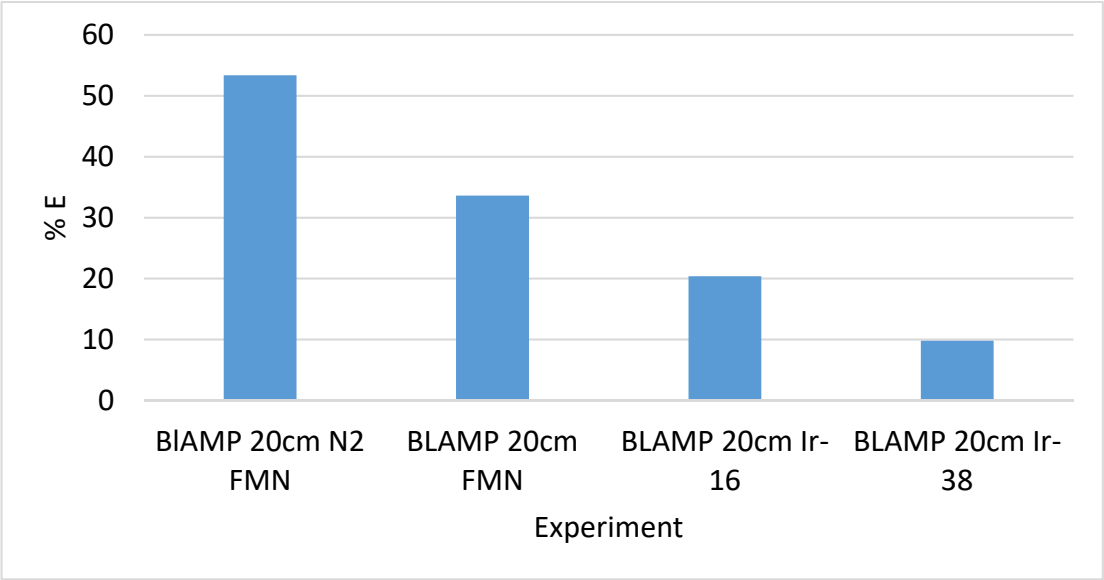
Rate of Isomerization of (Z)-1a to (E)-1a with Different 450 nm Light Sources



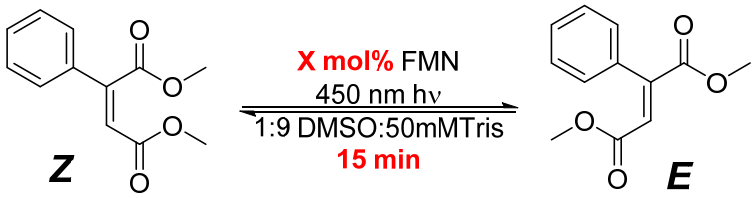


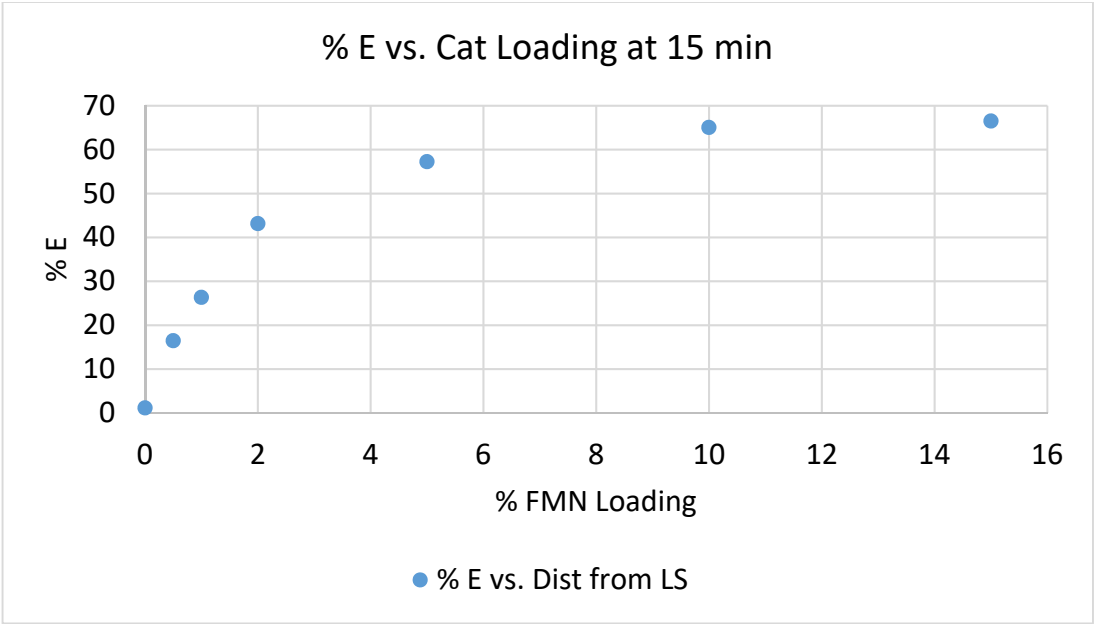
Effect of Oxygen on the Rate of Isomerization



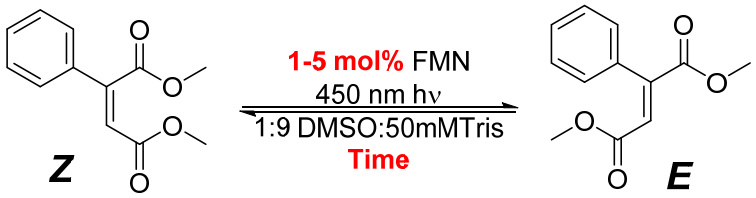


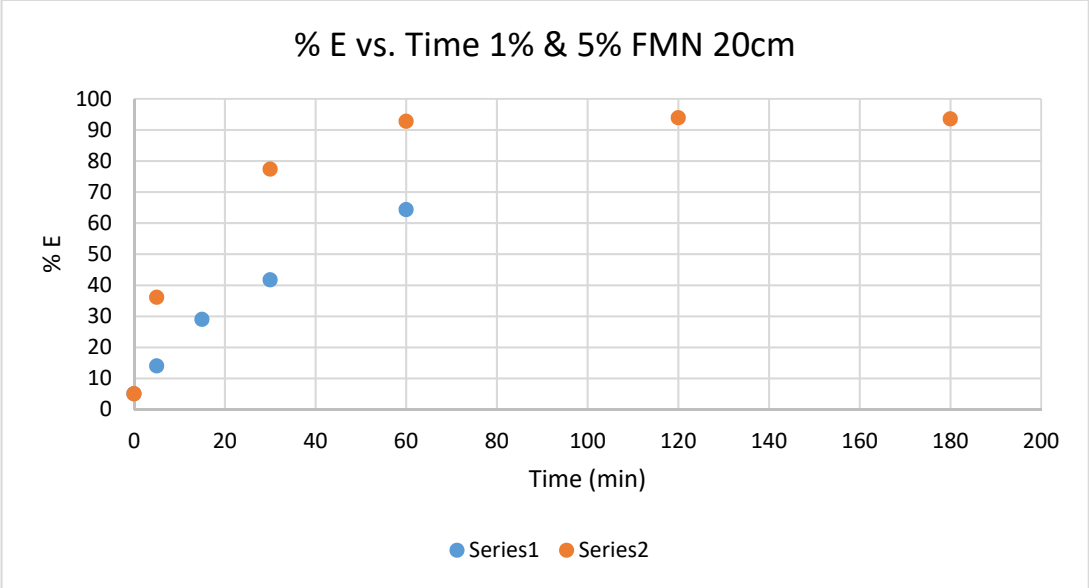
Catalyst Loading vs. Conv of (Z)-1a to (E)-1a at 15 min



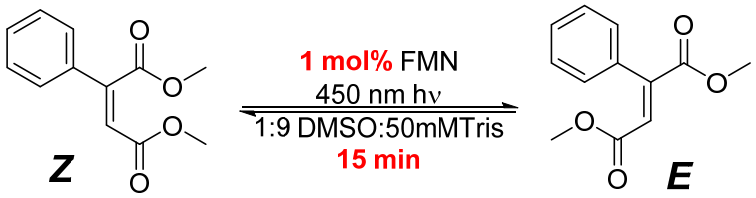


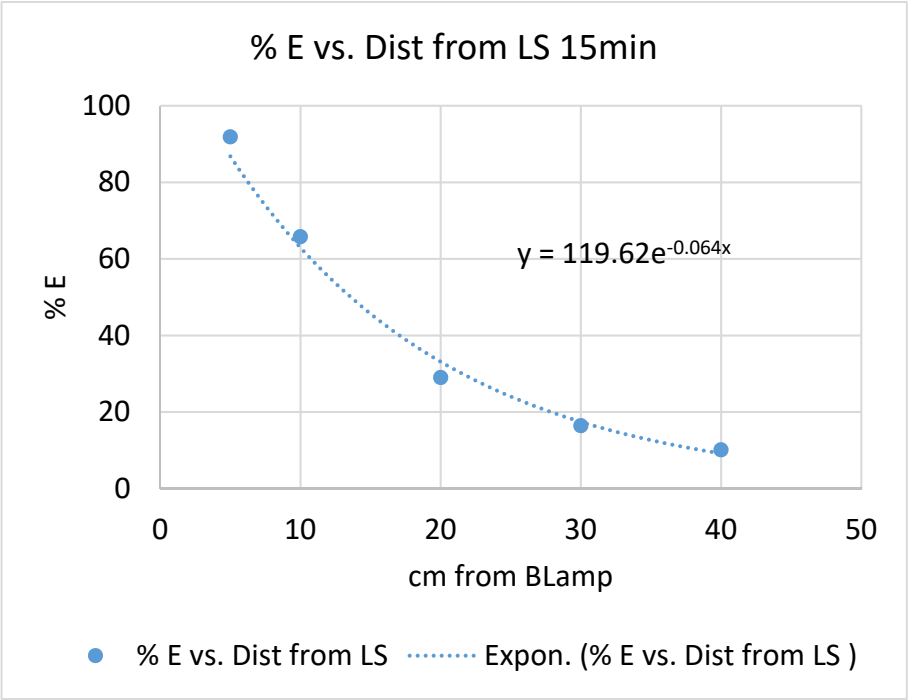
Rate of Isomerization of (Z)-1a with 1% and 5% FMN



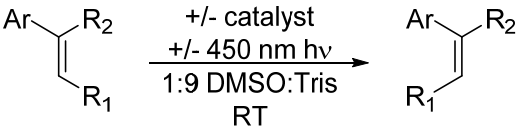


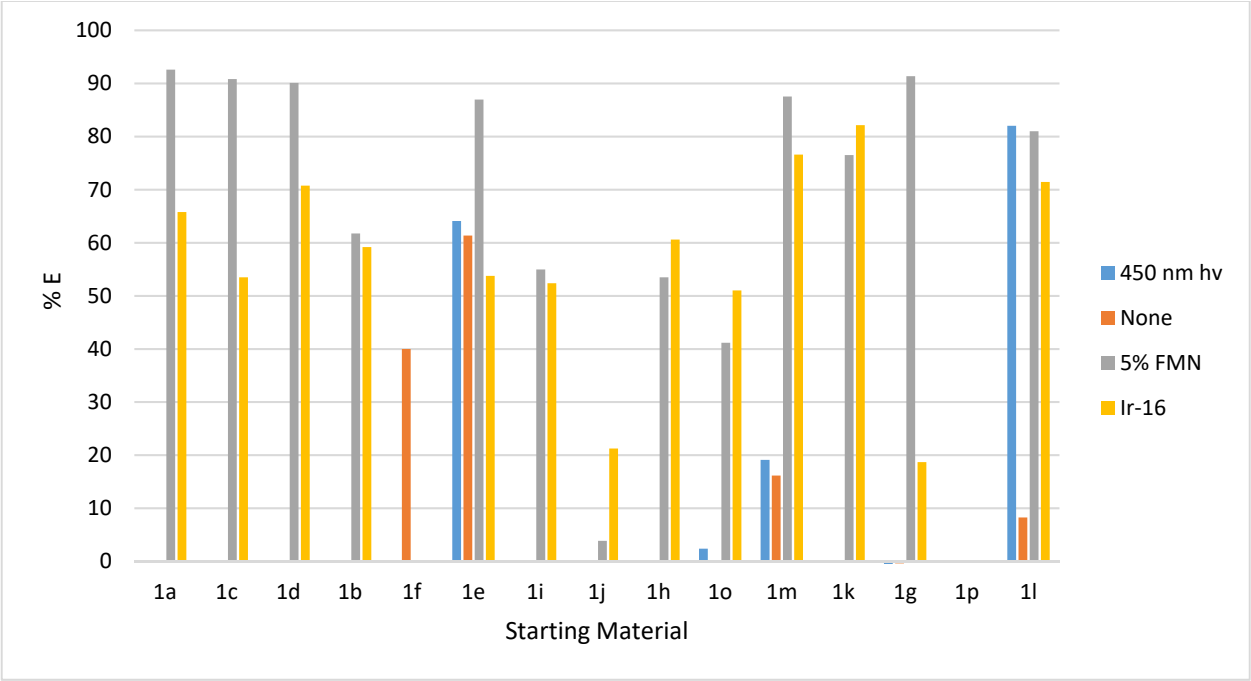
Light Source Intensity (Distance) vs. Conv of (Z)-1a to (E)-1a in 15 min





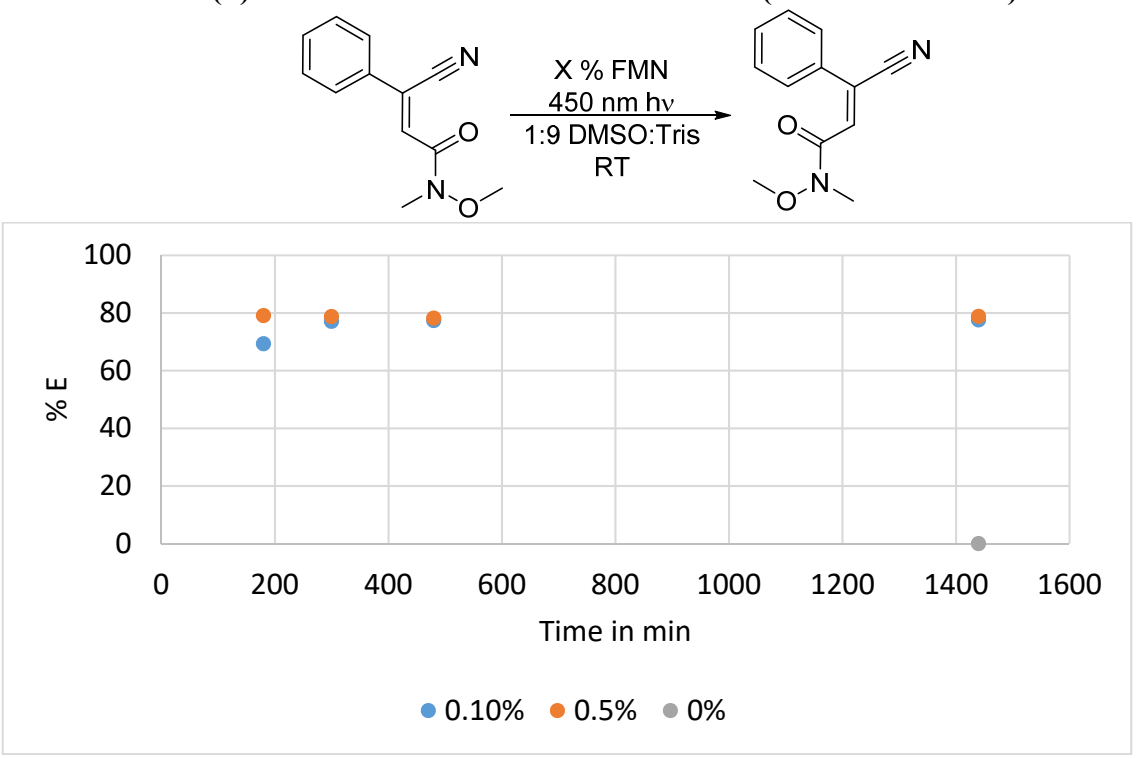
Isomerization of All Substrates in the Presence and Absence of Catalyst and In the Presence and Absence of Light





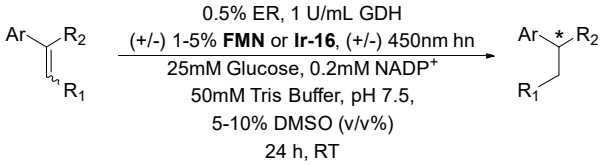
Please note this data is undergoing verification.

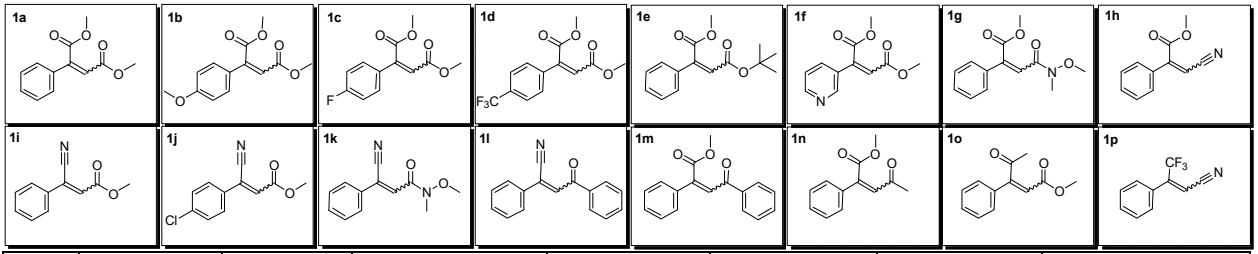
Isomerization of (Z)-1k in the Presence and Absence of FMN (450 nm Irradiation)



IX. Cooperative Reactions and Control Experiments

The following reactions were conducted according to the general procedures described in section B.





Ex	Substrate	Enzyme	Photocat.	% E at PS[f]	% Conv.	% Yield	% ee
1	**1a-*Z***	YersER	-		0%	-	-
2	**1a-*Z***	YersER	Ir-16 (FMN)	66 (93)	88% (>99%)	87% (70%)	>99% (>99%)
3	**1a-*50%E***	YersER	Ir-16 (FMN)		96% (>99%)	89% (86%)	>99% (>99%)
4	**1b-*Z***	YersER	-		0%	-	-

5	**1b-*Z***	YersER	Ir-16 (FMN)	59 (62)	89% (72%)	89% (63%)	>99% (>99%)
6	**1c-*Z***	xenB	-		15%	15%	-
7	**1c-*Z***	xenB	Ir-16 (FMN)	53 (91)	89% (58%)	89% (39%)	>99% (>99%)
8	**1d-*Z***	xenB	-		12%	8%	-
9	**1d-*Z***	xenB	Ir-16 (FMN)	71 (90)	96% (80%)	87% (63%)	>99% (>99%)
10	**1e-*70%E***	OPR1	-		63%	52%	>99%
11	**1e-*70%E***	OPR1	Ir-16		98%	74%	>99%
12	**1f- 68%*E***	xenB	-		63%	59%	-
13	**1f- 68%*E***	xenB	Ir-16 (FMN)	54 (87)	98% (80%)	91% (60%)	91% (87%)
14	**1g-*Z***	OPR1	-		9%	9%	-
15	**1g-*Z***	OPR1	Ir-16 (FMN)	19 (91)	98% (28%)	82% (21%)	>99% (>99%)
16	**1h-*Z***	TOYE	-		5%	3%	-
17	**1h-*Z***	TOYE	Ir-16 (FMN[d])	61 (53)	88% (99%)	85% (90%)	>99% (>99%)
18	**1i-*Z***	OYE3	-		10%	5%	-
19	**1i-*Z***	OYE3	Ir-16 (FMN[d])	52 (55)	98% (>99%)	92% (98%)	98% (95%)
20	**1j-*Z***	OYE2	-		10%	3%	-
21	**1j-*Z***	OYE2	Ir-16[e] (FMN)	21 (4)	95% (88%)	79% (75%)	92% (90%)
22	**1k-*Z***	YersER	w/o light		0%	0%	-
23	**1k-*Z***	YersER	w/ light		100%	90%	99%
24	**1l-*Z***	OYE2	w/o light		0%	0%	-
25	**1l-*Z***	OYE2	w/ light	82	100%	95%	>99%
26	**1m-*Z***	OPR1	-		7%	7%	-
27	**1m-*Z***	OPR1	Ir-16 (FMN)	77 (87)	100% (100%)	91% (76%)	>99% (>99%)
28	**1n-*Z***	SYE1	-		10%	7%	-
29	**1n-*Z***	SYE1	Ir – 16 (FMN)		96% (90%)	80% (72%)	88% (76%)
30	**1o-*Z***	YersER	-		6%	5%	-
31	**1o-*Z***	YersER	Ir-16 (FMN)	51 (41)	95% (95%)	87% (89%)	96% (86%)
32	**1p-*E***	OYE3	-		17%	11%	-

33	**1p-*E***	OYE3	Ir-16 (FMN)		98% (85%)	74% (34%)	>99% (>99%)

The reaction was performed 24 hurs in 50 mM Tris buffer at pH 7.5 with 0.5 mol% ERs, 1 mol% Ir-16 or 5 mol% FMN, 1 U/mL GDH, 0.2 mM $NADP^+$, 25 mM glucose, 5 *v/v%* DMSO, with or without blue light. [a] [b]Determined by GC-MS using synthesized authentic standards. [c]Determined by Chiral HPLC. [d]1 mol% FMN. [e]5 mol% Ir-16. % E at PS is the E/Z ratio of substrate obtained after 24 hours of irradiation with a 450 nm light with a photocatalyst. In the case of 1l, no photocatalyst was used.[f]Photostationary *E/Z* ratio obtained after substrate was irradiated in the presence of a catalyst for 24 h.

X. References

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