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DEVELOPMENT OF NEW USEFUL METHODS FOR ALDEHYDE SYNTHESIS AND ITS APPLICATION IN SYNTHESIS

He Huang
Doctoral Student, Chemistry

He Huang
Candidate

Department of Chemistry and Chemical Biology
Department

This dissertation is approved, and it is acceptable in quality and form for publication:

Approved by the Dissertation Committee:

Prof. Wei Wang, Chairperson

Prof. Patrick S. Mariano

Prof. Abhaya K. Datye

Prof. Fu-Sen Liang

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By

He Huang

B.S., Chemistry, Wuhan University, P.R. China, 2012

Ph.D. Chemistry, University of New Mexico, USA, 2018

DISSERTATION

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DEDICATION

To

My wife, Dr. Weixiao Ji

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ABSTRACT

Development of sustainable synthetic technologies for molecular construction is an important but formidably challenging task in modern organic synthesis. Aldehyde synthesis represents a long-standing interest in synthesis because of the synthetic utility. Classic methods for aldehyde synthesis have the drawbacks of the use of harsh reaction conditions, poor atom-economy and multi-step operation, and production of stoichiometric amount of chemical wastes. The state-of-the-art strategies employ transition metal complexes as catalysts to promote formylation reactions. The concerns of catalyst cost, operation complexity and poor functional group tolerance demands more efficient synthetic technologies. My Ph.D. study focuses on design of conceptually novel catalytic systems, invention of reagents and exploration of new reactivities to create unprecedented processes the synthesis of fundamentally important class of chemicals - aldehydes with the emphasis on sustainability, selectivity, practicality and utility.

A conceptually novel organocatalytic strategy for formylation of boronic acids is

developed. In the process, a new reactivity is engineered into the α-amino acid forming Petasis reaction occurring between aryl boron acids, amines and glyoxylic acid. The feasibility and preparative power of the protocol has been demonstrated by its use to prepare aldehydes from broadly accessible aryl and alkenyl boronic acids, glyoxylic acid, and the cheap N-alkylaniline derivatives, tetrahydroquinoline and indoline, as catalysts. Furthermore, the operational simplicity of the process, which is performed by simply mixing these reagents under ambient conditions, and its ability to generate structurally diverse and valued aryl, heteroaryl and α,β-unsaturated aldehydes containing a wide array of functional groups, demonstrates the practical utility of the newly unveiled synthetic strategy.

A simple formylation reaction of aryl halides, aryl triflates and vinyl bromides using synergistic nickel and organic dye mediated photoredox catalysis has been realized. Distinct from widely used palladium catalyzed formylation processes, this reaction proceeds by way of a two step mechanistic sequence involving initial in situ generation of the diethoxymethyl radical from diethoxyacetic acid by 1,2,3,5-tetrakis-(carbazol-yl)-4,6-dicyanobenzene (4CzIPN) mediated photoredox reaction. The formyl radical equivalent then undergoes nickel catalyzed substitution reactions with aryl halides and triflate and vinyl bromides to form the corresponding aldehyde products. Significantly, in addition to aryl bromides, less reactive aryl chlorides and triflates and vinyl halides serve as effective substrates for this process. The fact that the mild conditions involved in this reaction tolerate a plethora of functional groups enables the process to be applied to the efficient preparation of diverse aromatic aldehydes.

An unprecedented, chemo- and regio-selective, organo-photoredox catalyzed hydroformylation reaction of aryl olefins with diethoxyacetic acid as the formylation reagent is developed. In contrast to traditional transition metal promoted ionic hydroformylation reactions,

the new process follows a unique photoredox promoted, free radical pathway. In this process, a formyl radical equivalent, produced from diethoxacetic acid through the same dye 4CzIPN photocatalyzed, sequential oxidation-decarboxylation route, regio- and chemo-selectively adds to a styrene substrate. Importantly, under the optimized reaction conditions the benzylic radical formed in this manner is reduced by SET from the anion radical of 4CzIPN to generate a benzylic anion. Finally, protonation produces the hydroformylation product. By using the new protocol, aldehydes can be generated regioselectively in up to 90% yield. A broad array of functional groups is tolerated in the process, which takes place under mild, metal free conditions.

The broad synthetic utility of labile enol esters demands efficient methods for the stereo- and regio-selective synthesis of both *Z* and *E* isomers. The available synthetic methods dominated by metal catalysis cannot meet the challenge. Towards this end, we have developed a metal free organocatalytic divergent approach to both *E* and *Z* isomers of enol esters from the same reactant pools with the same catalytic system. A process involves an amine catalyzed conjugate addition of carboxylic acids to ynals, which triggers a rearrangement leading to enol esters. The reaction proceeds highly regio- and stereoselectivley. Simple manipulation of reaction temperatures enables to produce *Z*-isomers at 0 °C (*Z:E* 15:1 - >20:1), whereas at higher 30 °C to give *E*-isomers (*E:Z* 15:1 - >20:1). Furthermore, the mild reaction conditions accommodate a broad array of densely functionalized carboxylic acids including complex biologically relevant structures and ynals for the process. Therefore, synthetically valued, structurally diverse enol esters are efficiently synthesized. Preliminary mechanistic studies suggest an amine promoted conjugate addition-rearrangement pathway responsible for the formation of the enol esters.

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List of Abbreviations

Ac	acetyl, acetate
aq.	aqueous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
δ	chemical shift
dr	diastereomeric excess
DCE	1,2-Dichloroethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
equiv.	equivalent
EWG	electron-withdrawing group
EDG	electron-donating group
EtOAc	ethyl acetate
G	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz

i-PrOH	*iso*-propanol
J	coupling constant
LA	Lewis acid
LB	Lewis base
m	meta
MeOH	methanol
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliter
mmol	millimole
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
o	ortho
p	para
PTC	phase-transfer catalysis
Rt	room temperature
cat.	catalyst
TBS	*tert*-Butyldimethylsilyl
TEA	trimethylamine
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TLC	thin layer chromatography
TMS	trimethylsilyl
μM	microliter

Chapter 1

Introduction

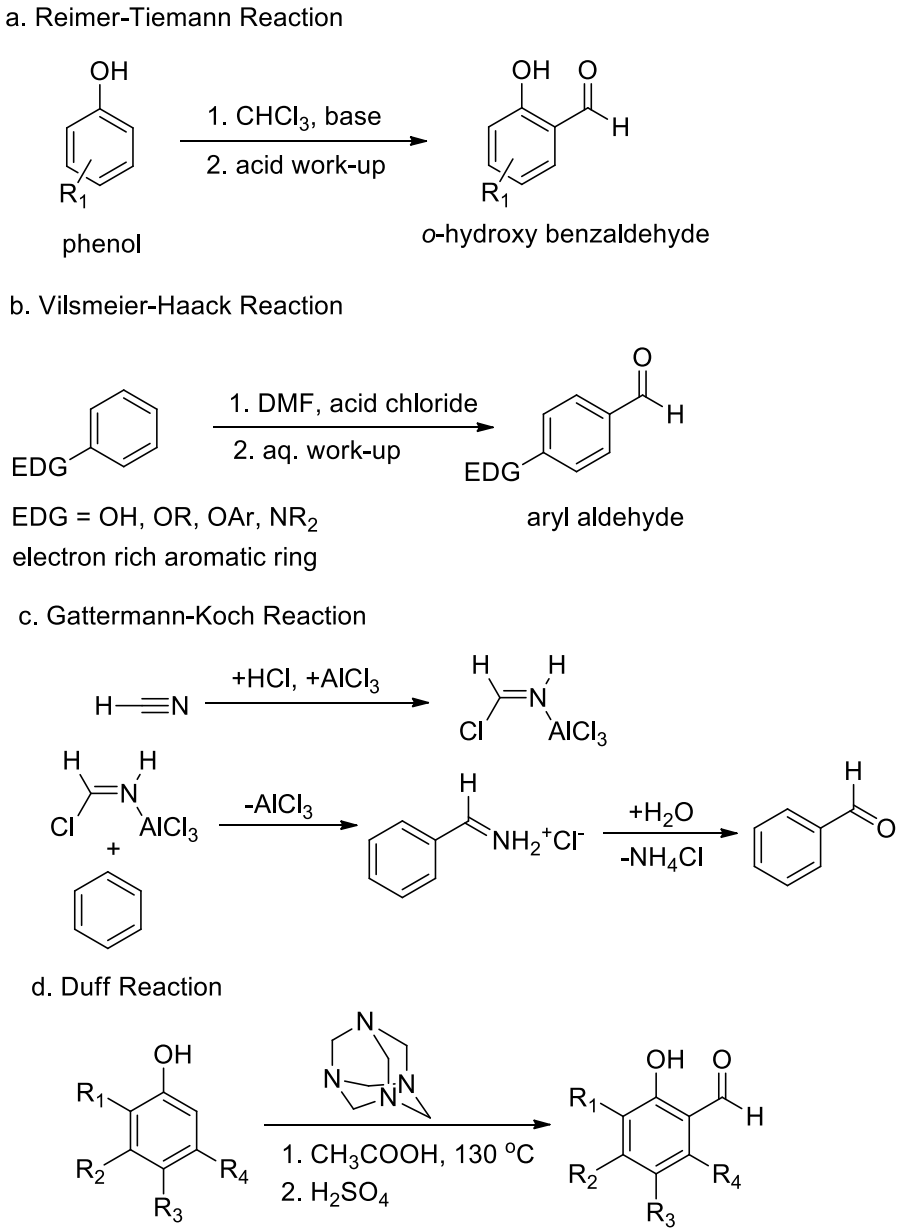
1.1 The Status of Formylation Reaction

We live in the world that many new chemicals, materials and therapeutics come from synthsis. Among them aldehydes have found a prominent place in synthesis due to the high reactivity and synthetic versatility of the functional group. It can be readily transformed into various functional groups and serves as a handle in complex biologically active molecule synthesis. For example, formaldehyde, an essential starting material for synthesis polyurethane,is produced about 6,000,000 tons per year.[1] The demand of about 2,500,000 tons annually butyraldehyde as reactant arises from the synthesis of plasticizer.[2] Nowadays, hydroformylation is the largest application of homogenous catalysis on an industrial scale with a capacity of more than 10 million tons of oxo product.[3] In addition to bulky chemicals, functionalized aldehydes are wildly used in the synthesis of fine chemicals, materials and therapeutics. Therefore, synthetic strategies capable of tolerance of various functional groups are particularly useful in aldehyde synthesis.

Aldehydes synthesis has a rich history. Classical methods for aldehyde synthesis, such as the Reimer–Tiemann (Scheme 1.1a), Vielsmeier–Haack (Scheme 1.1b), Gattermann–Koch (Scheme 1.1c) and Duff reactions (Scheme 1.1c),[4] generally require the use of large amounts of reagents and multi-step sequences. In addition, they frequently generate at least stoichiometric amounts of by-products. These features create significant environmental concerns, which may limit practical applications of these processes in an industrial setting. Furthermore, control of the regiochemical course of these reactions makes it difficult to introduce aldehyde functionality at desired positions in substrates.

To address these issues, state-of-the-art formylation technologies using transition metal catalysis have been developed recently. Here I briefly summarize the development in two categories: transition metal catalyzed formylation and hydroformylation reactions.

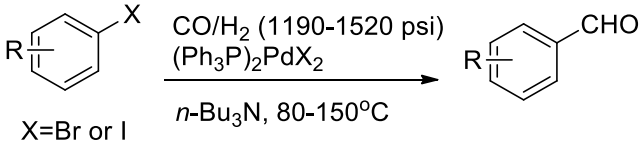
Scheme 1.1. Classical Methods for Aldehyde Synthesis



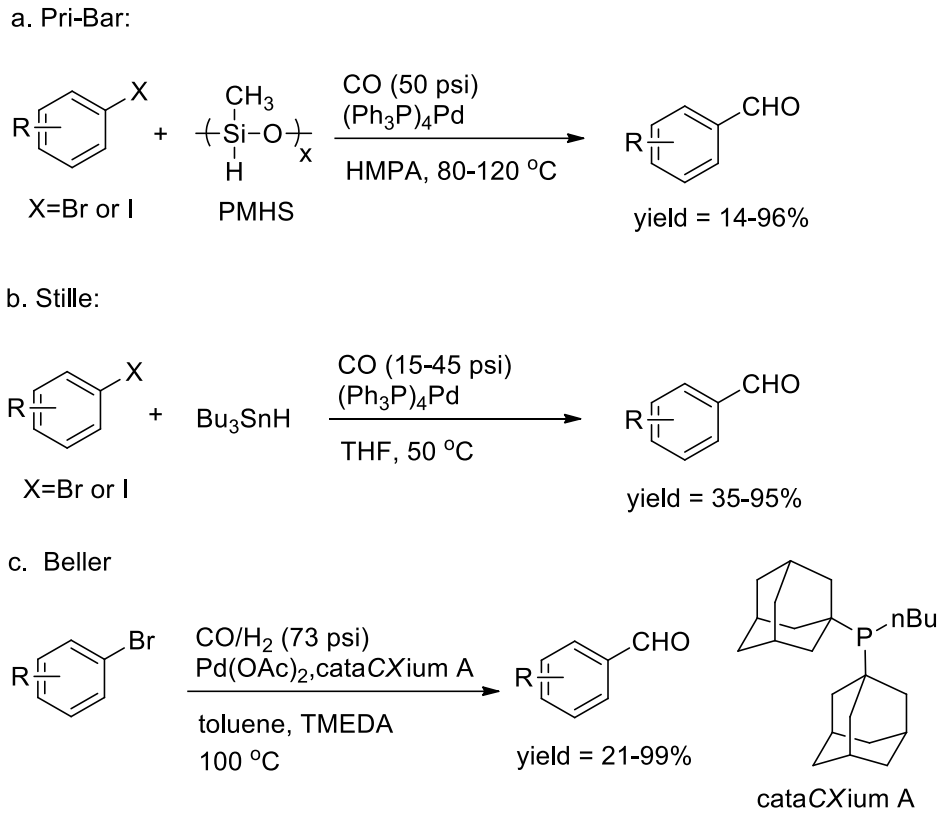
1.2 Transition Metal Catalyzed Formylation Reaction

Aromatic aldehydes are wildly present and used in the synthesis of nature products and fine chemicals. The catalytic synthetic methods were developed since the pioneering work of Heck and Schoenberg in 1974. Palladium catalyzed formylations using CO has been developed as a viable approach to a variety of aromatic aldehydes.[5] However, flammable and toxic CO/H_2 syngas used under high pressure makes this method difficult to be operated (Scheme 1.2). Several newly improved protocols were developed by designing different ligands and utilizing different reduing reagents and/or lower pressure of CO. Impressive results from studies of this topic have come from the laboratories of Pri-Bar, Stille, Beller and their co-wokers (Scheme 1.3).[6]

Scheme 1.2 First Example of Palladium Catalyzed Formylations

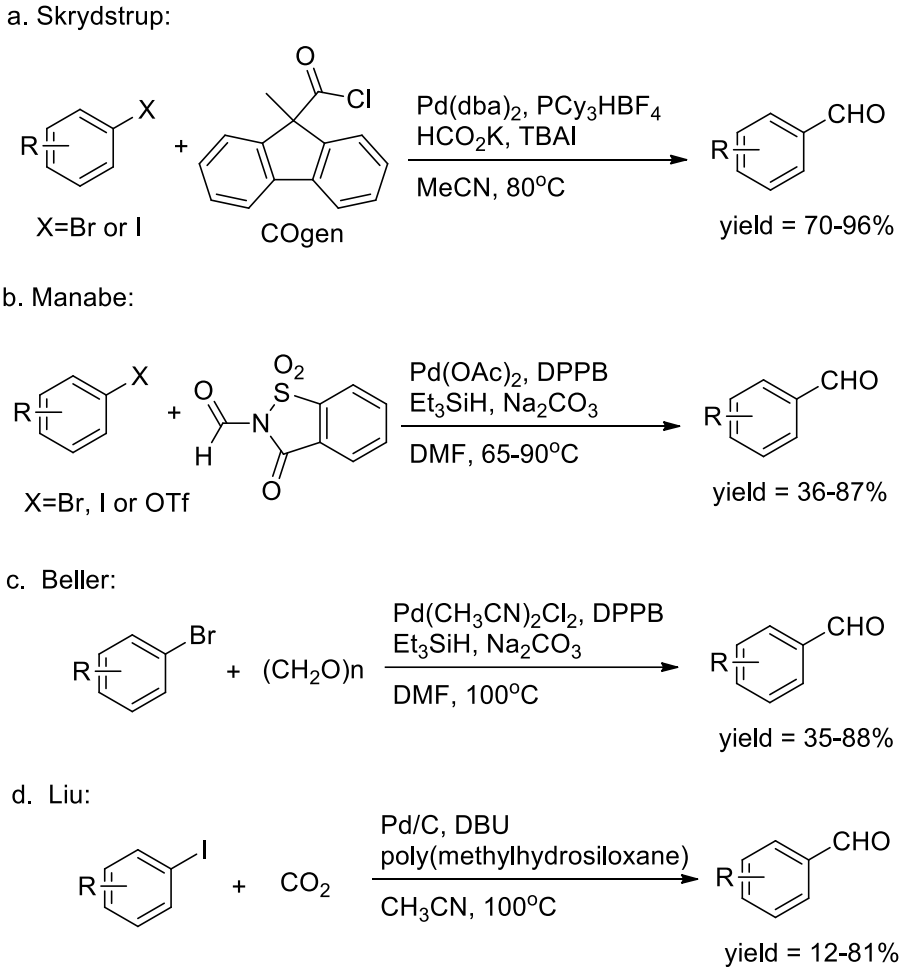


Scheme 1.3 Palladium Catalyzed Formylations by Using CO



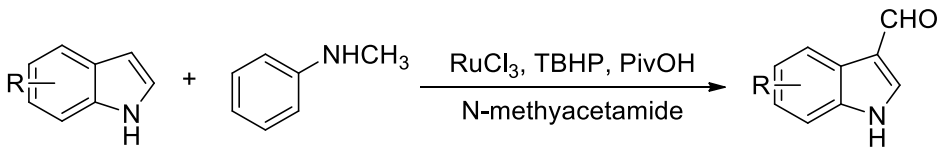
The CO-free carbonylations have also been developed from the groups of Skrydstrup, Manabe, Beller, and Liu (Scheme 1.4).[7]

Scheme 1.4 Palladium Catalyzed Formylations in CO-free Way



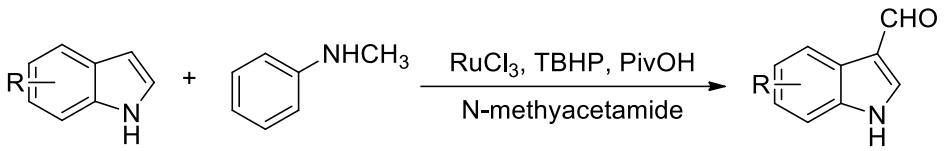
Beside palladium catalyzed formylation reaction, other transition metals are also explored for the process. For example, Su and co-workers described an efficient $RuCl_3$ catalyzed oxidative coupling reaction between indoles and *N*-methylanilines that results in the formation of 3-formylindoles (Scheme 1.5).[8]

Scheme 1.5 Ru Catalyzed Formylation Reaction



Although significant efforts have been made on improving the formylation reaction, there are still several drawbacks of the transition metal catalyzed process. First, in reported palladium catalyzed formylations, more active aryl bromides and iodides are typically required for efficient transformations. In contrast, very few studies of this process have focussed on arylchlorides,[6,7,9] which are more broadly available and cheaper while it is more difficult to activate the inerter C-Cl bond. Second, those process generally rely on precious transition metals like Pd or Ru, but inexpensive metal like nickel catalyzed formylation reaction has not been reported. This deficiency results from the low reactivity and difficulty of reductive elimination towards CO, demonstrated by Heck.[10] Third, the presence of heavy transition metal impurities in the final products presents a major problem regarding purification. Therefore, overcoming these challenging issues requires conceptually distinctive strategy.

Scheme 1.5 Ru Catalyzed Formylation Reaction

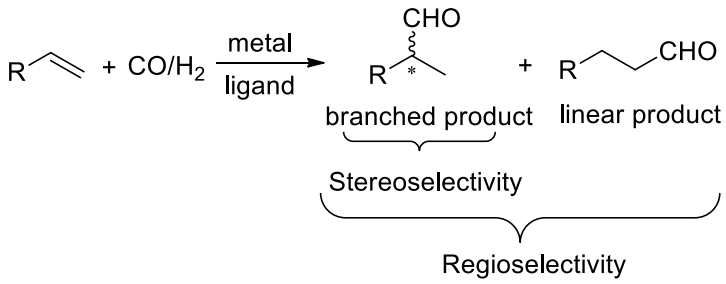


1.3 Hydroformylation Reaction

Hydroformylation of alkenes is a well documented process and serve as one of the most cost- and atom-efficient methods for the synthesis of aldehydes.[11] The reaction was first developed by Otto Roelen in the 1930s[12]. Nowadays the hydroformylation is the largest application of homogenous catalysis on an industrial scale with a capacity of more than 10 million tons of oxo product.[13] While significant advances have been made ondeveloping more

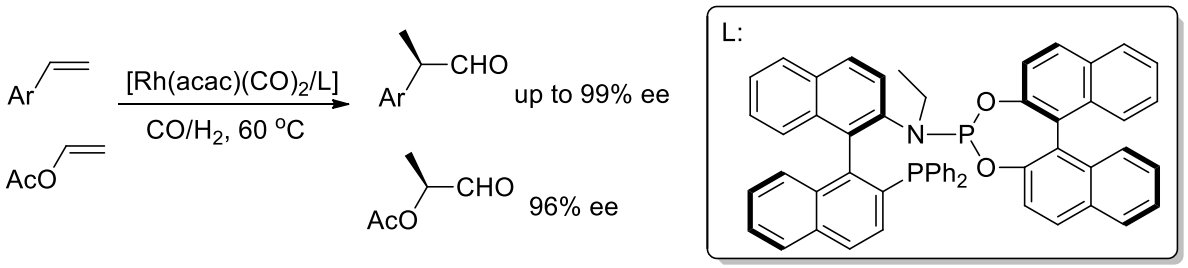
effective protocols, those approaches generally require the use of transition metals (such as Rh[14], Co[11e], Ir[15], Ru[16] and Pd[17]) as well as different kinds of complex ligands.[14-17] (Scheme 1.6)

Scheme 1.6 Metal Catalyzed Hydroformylation

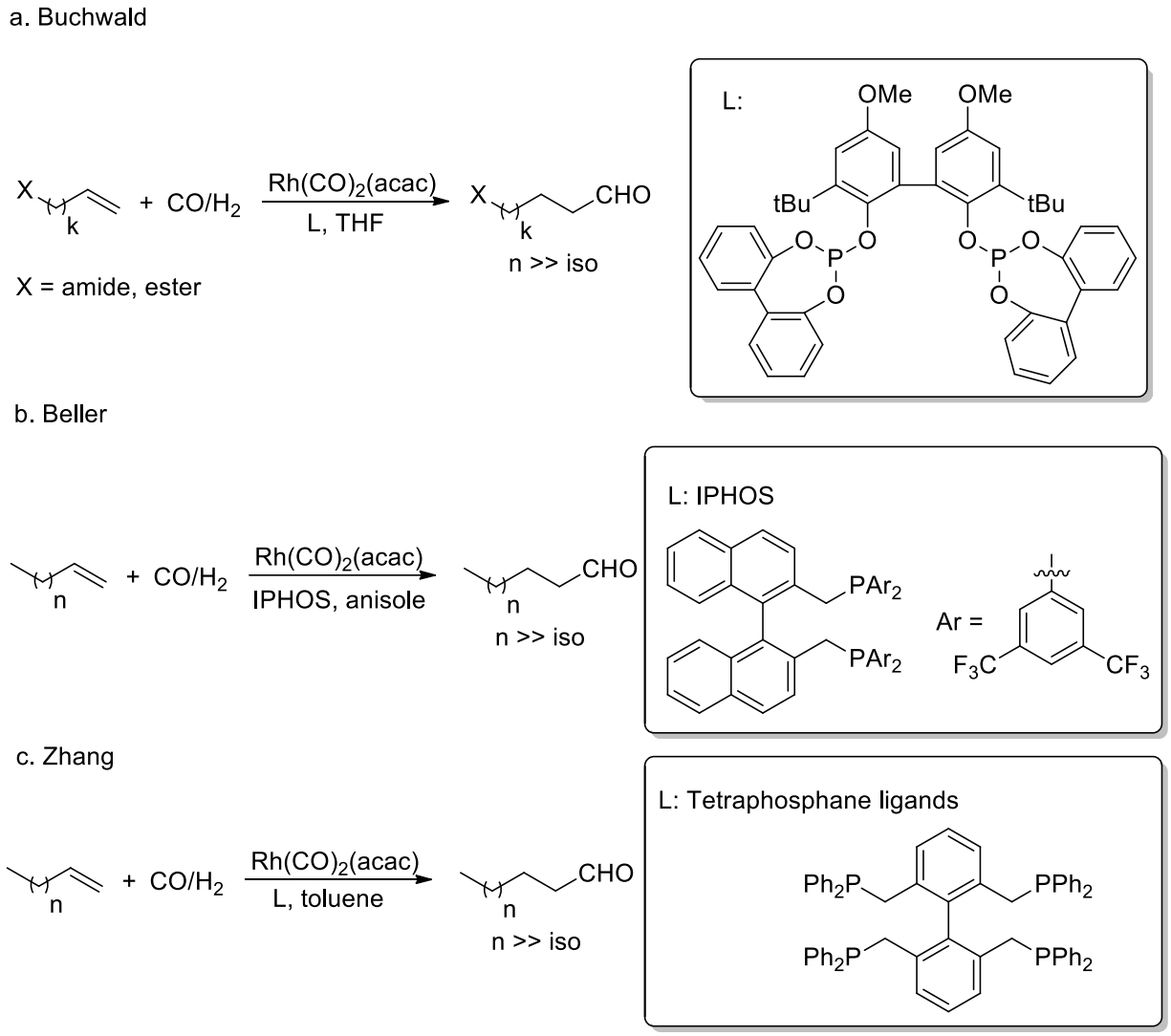


The challenges in the hydroformylation lie in to the efficient control of stereoselectivity and regioselectivity. A stereogenic center of branched products can be formed . Because of broad syntehitc utility of chiral aldehydes, asymmetric hydroformylation is highly vualued for the preparation of chiral building blocks. However, few studies have been conducted. Zhang's group developed a chiral hybrid phosphorus ligand by achieving high enantioselectivity(Scheme 1.7).

Scheme 1.7 Highly Enantioselective Asymmetric Hydroformylation



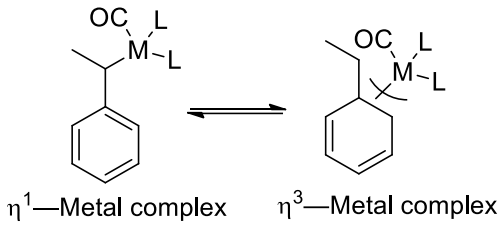
Scheme 1.8 Highly Regioselective Hydroformylation of Alkyl Olefins



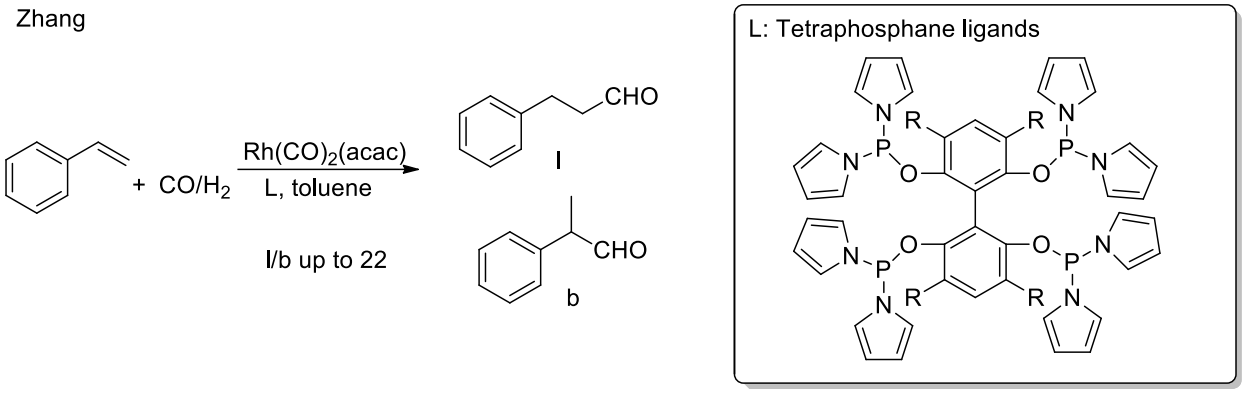
The high regioselectivity for linear aldehydes with alkyl olefins has been addressed.[14a, 14b, 14d, 14f, 14g, 14j] For example, Buchwald group developed a bis-organophosphite ligand to catalyze the hydroformylation reaction with high linear selectivity (Scheme 1.8a). Beller et al also discovered highly selective catalyst systems for the hydroformylation of internal olefins to deliver linear aldehydes (Scheme 1.8b). Zhang and coworkers applied tetraphosphane ligands into Rhodium-catalyzed hydroformylation of terminal olefins with high regioselectivity (Scheme

1.8c).

Scheme 1.9 Difficulty in Regioselective Hydroformylation of Styrene



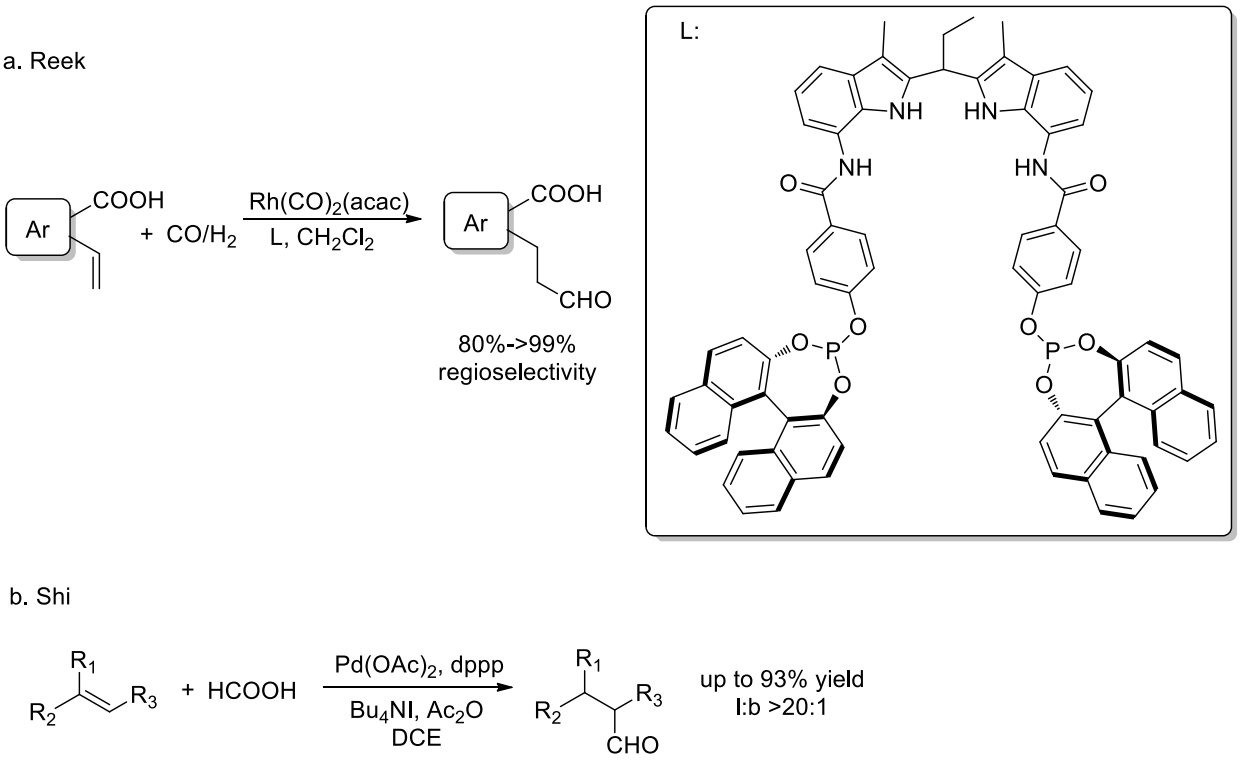
Scheme 1.10 Zhang's Regioselective Hydroformylation Of Styrene



However very limited processes, in which linear formylation of aryl olefins occurs, have been developed. The formation of a stable benzylic Rh-species induced by the η^2 electron donation from the benzene ring might contribute to the favorable formation of thebranched products (Scheme 1.9). For example, Zhang has designed a new tetraphosphorus ligands to highly regioselective hydroformylation of styrene and its derivatives with up to l/b up to 22 (Scheme 1.10).[14h, 14l] Reek[14m, 14o, 14r-t] group developed a supramolecular control method to regioselective hydroformylation of vinyl arenes (Scheme 1.11a). Linear selectivity was between 80%->99%. Recently, Shi's group reported an effective pd-catalyzed regioselective

hydroformylation of olefins with formic acid with can reach a result of l:b > 20:1 (Scheme 1.11b).[17b]

Scheme 1.11 Regioselective Hydroformylation of Styrene



In these reports, complex ligands or special substrates are required to improve the regioselectivity. Nevertheless, the approaches developed by these groups failed to achieve chemoselective hydroformylation between different kinds of C=C double bonds, which are often present in complex molecules.

1.4 Summary

In summary, classic formylation methods require the use of large amounts of reagents, harsh reactoin conditions, multi-step sequences and production of at least stoichiometric

amounts of byproducts. The state-of-the-art synthetic technologies rely on precious transition metals like Pd, Ir or Ru with CO and H_2 as carbonyl resources. However these approaches generally require high reaction temperatures and use precious metal complexes as promoters. Besides that, highly regioselective hydroformylation of styrene and its derivatives is still difficulty to achieve. These drawbacks request more cost-effective, environmentally friendly and mild protocols for aldehyde synthesis. To overcome these issues, I will detail my research efforts on the development of novel organocatalytic and photoredox catalytic reactions for aldehydes synthesis. Specifically, Chapter 2 describes the synthesis of aldehydes by organocatalytic formylation reactions of boronic acids with glyoxylic acid. Chapter 3 focuses on a visible light promoted nickel and organic co-catalyzed formylation reaction of aryl halides and triflates and vinyl bromides using diethoxyacetic acid as a formyl equivalent. Chapter 4 presents a new chemo- and regioselective organo-photoredox catalyzed hydroformylation of styrenes via a radical pathway. In the end, a reaction of using aldehyde compounds to produce *Z* and *E* enol esters in highly regio- and stereoselective manner is reported in Chapter 5

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Chapter 2

Synthesis of Aldehydes by Organocatalytic Formylation Reactions of Boronic Acids with Glyoxylic Acid

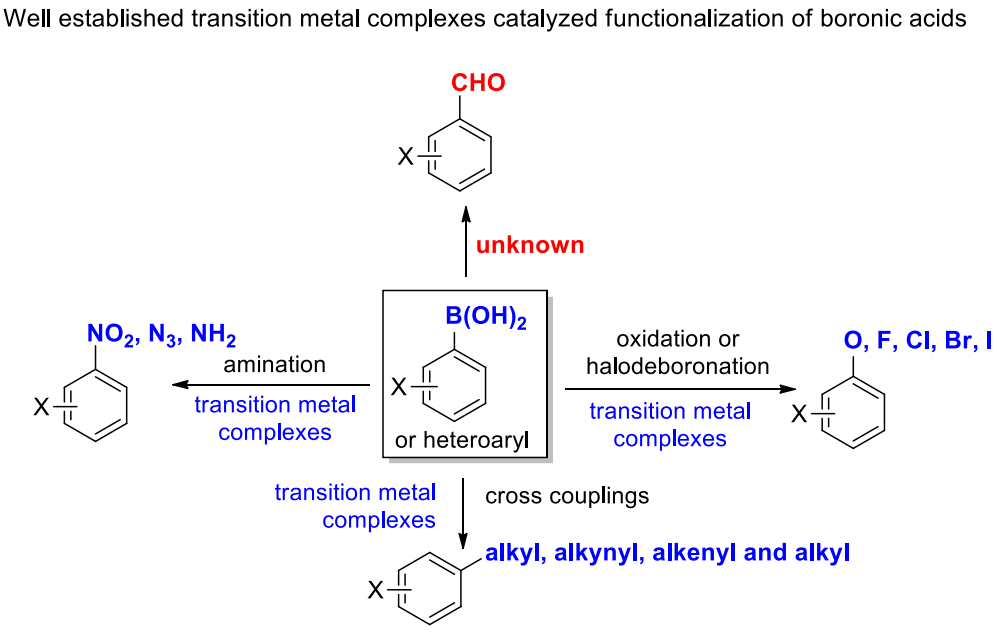
2.1 Introduction

With more than four thousand being commercially available, aryl boronic acids are one of the most versatile building blocks in organic synthesis.[1] Notably, recent significant advance in borylation methods has made aryl boronic acids, particularly those that are heavily functionalized, more readily accessible.[2] The unique reactivity of substances in this family has led to a myriad of carbon-carbon and carbon-heteroatom bond forming processes, which are difficult to carry out or show poor functional group tolerance and/or low efficiency when their halide counterparts are employed as substrates. These reactions, which include the introduction of oxygen,[3] nitrogen,[4] halogen,[5] and alkyl, alkynyl, alkenyl and alkyl moieties,[6] are generally accomplished using transition metal complexes. However, to the best of our knowledge, no examples of catalytic formylation reactions of arylboronic acids exist (Scheme 2.1).

Aldehydes occupy a unique position in organic chemistry owing to the versatility of the aldehyde group, which is capable of undergoing various transformations.[7] Classical methods[8] for aldehyde synthesis generally require large amounts of reagents and multi-step sequences, and they often result in the production of at least stoichiometric amounts of byproducts. Furthermore, the harsh reaction conditions needed for these processes are often not compatible with substances possessing acid and base sensitive functional groups. Finally, control of the regiochemical courses of these reactions makes it difficult to introduce aldehyde functionality at desired positions. Because of these limitations, the development of protocols for introduction of the

aldehyde functional group in a selective and predictable manner, and with a high functional group tolerance remains a key challenge in preparative organic chemistry.[9-10]

Scheme 2.1. Functionalization of Boronic Acids



2.2 Research Plan

In considering ways to address the challenges associated with devising a new, truly environmentally friendly strategy for the synthesis of aldehydes, our attention was drawn to the mild, three-component amino acid **6** forming Petasis reaction (Scheme 2.2).[11] This process is carried out using aryl boronic acids **1**, glyoxylic acid **2** and amines **3** and does not require the use of transition metals for activation. We believed that this process would serve as the foundation of an organocatalytic aldehyde forming protocol if the *in situ* formed α-amino acid **6** were properly designed to undergo O_2 promoted oxidative decarboxylation to form an iminium ion **7**. *In situ* hydrolysis of the iminium ion formed in this way would produce an aldehyde product **4** and

liberate the amine as part of a catalytic cycle. The critical challenge in developing a new formylation procedure based on this strategy is devising a system and conditions under which oxidative decarboxylation of amino acid **6** would occur. Knowledge gained from our earlier studies of oxidative enamine catalysis,[12] aniline catalyzed direct functionalization of aldehydes[13] and single electron transfer (SET) promoted formylation[14] and decarboxylation[15] reactions inspired us to propose that SET induced decarboxylation of amino acids derived by the Petasis reaction of *N*-alkylaniline derivatives, such as tetrahydroquinoline and indoline, might undergo O_2 promoted oxidative decarboxylation. This reasoning is based on a consideration of the respective oxidation potentials of +0.66 and +0.63 V (vs AgCl/Ag in CH_3CN, Figure 2.1) for 1-methyl-1,2,3,4-tetrahydroquinoline and *N*-methylindoline, and the reduction potential for O_2 (g) which is +0.682 V (AgCl/Ag in water).[16] These data suggest that SET to O_2 from the tetrahydroquinoline and indoline moieties of the corresponding amino acids would be exergonic and, thus rapid. In contrast, $E^{red}_{1/2}$ (vs AgCl/Ag) in CH_3CN of aliphatic amines such as *N*-methylpyrrolidine and its Petasis adduct 2-phenyl-2-(pyrrolidin-1-yl)acetic acid are 0.82 V and 1.16 V (Figure 2.1), respectively, which suggest that the latter substance would not be rapidly oxidized by O_2. When coupled to the fact that aminium radicals formed by SET oxidation of α-amino acids undergo rapid decarboxylation and that the resulting α-amino radicals are rapidly oxidatively converted to iminium ions,[15] the data suggest that O_2 will promote oxidative decarboxylation of secondary aniline derived Petasis adducts **6** to generate iminium ions **7**, which upon hydrolysis will form the target aldehydes **4** and regenerate the amine organocatalyst **3**.

Scheme 2.2 The First Organocatalytic Formylation of Boronic Acids

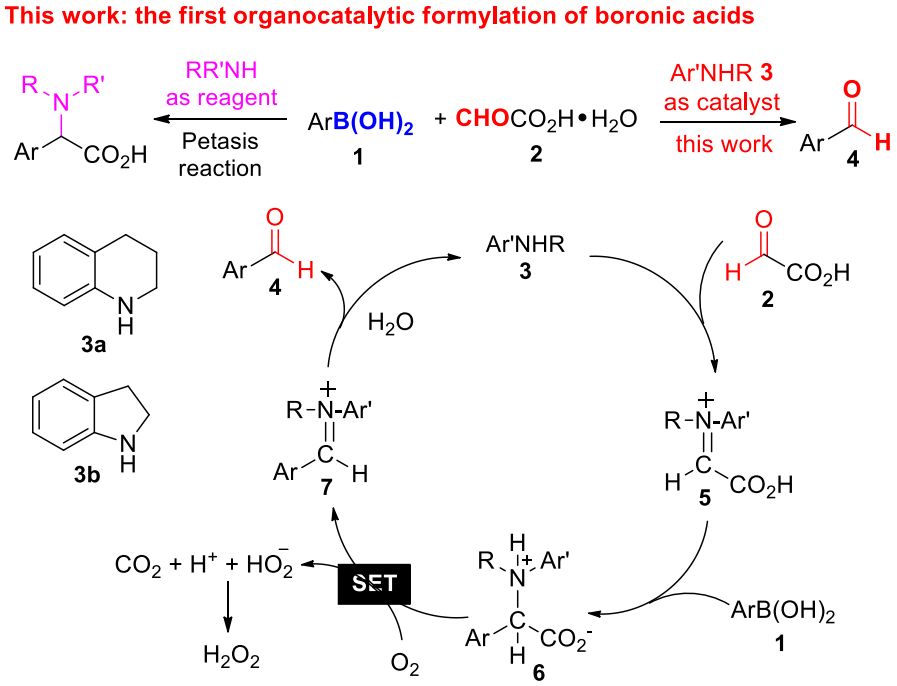
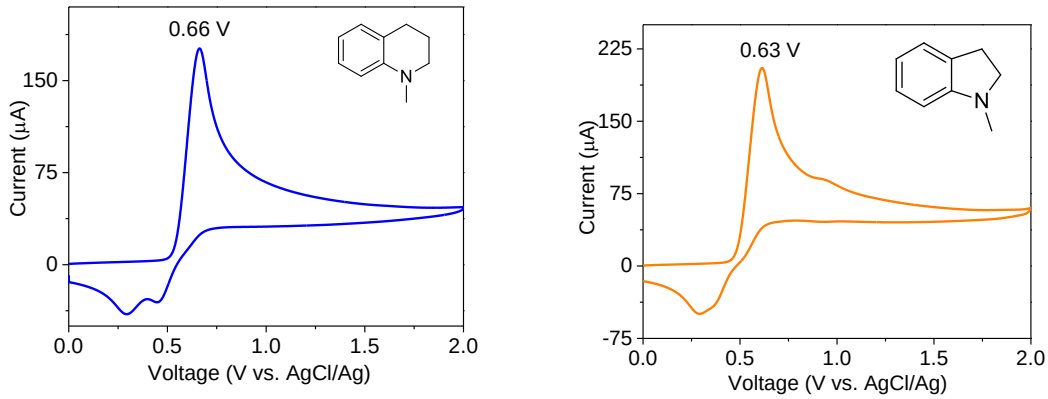
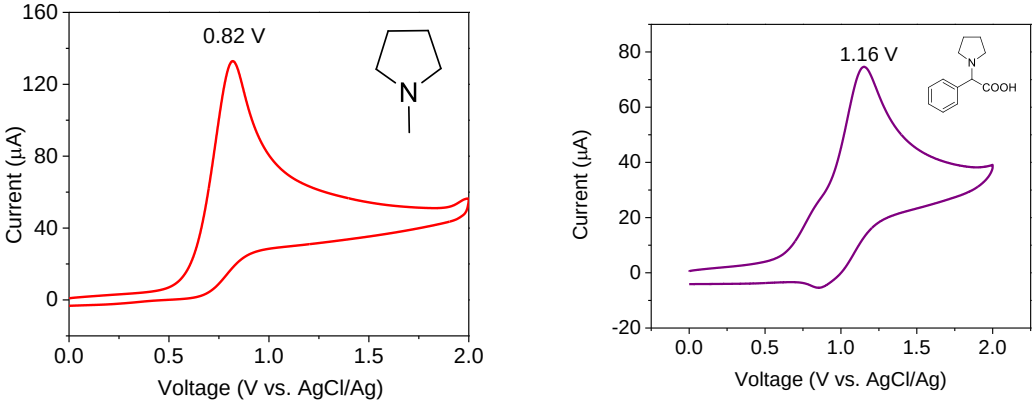


Figure 2.1 Cyclic voltammogram of amine





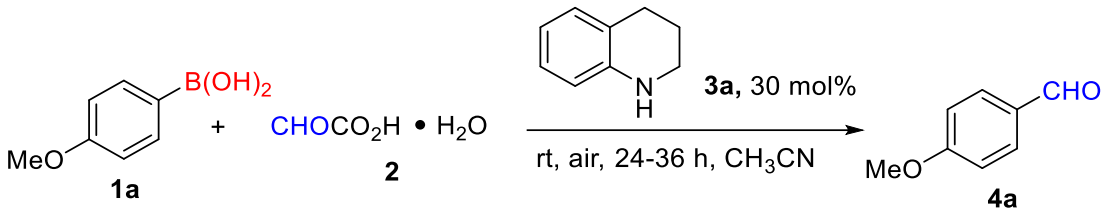
Bu_4NPF_6 as supporting electrolyte (0.1 M) and referenced against ferrocene/ferrocenium redox couple (scan rate: 100 mV/s) in CH_3CN.

2.3 Results and discussion

2.3.1 Optimization of Reaction Conditions

Proof-of-concept of the newly proposed formylation strategy began with a study of the reaction of 4-methoxyphenylboronic acid (**1a**) with glyoxylic acid monohydrate (**2**) in the presence of tetrahydroquinoline **3a** in CH_3CN under ambient conditions and an air atmosphere (Table 2.1). In full accord with our proposal, the process proceeds efficiently to form the desired aldehyde **4a** in 75% yield. (entry 1). In the absence of an air atmosphere, **4a** is not generated (entry 2) but instead the Petasis product is formed. In addition to O_2, **3a** is essential for the process (entry 3). Furthermore, only the Petasis reaction derived amino acid is formed when pyrrolidine is used as the promoter and conditions are employed that are identical to those used for **3a** catalyzed conversion of boronic acid **1a** to aldehyde **4a** (entry 4). Finally, we showed that the protocol can be adapted to a large-scale synthesis of aldehydes. Specifically, 3.04 g of **1a** produces 2.10 g (77% yield) of aldehyde **4a** under the conditions described above even when the low catalyst loading of 20 mol% (entry 5) is utilized. Other amines are also tested and **3a** gives the highest yield (Scheme 2.3).

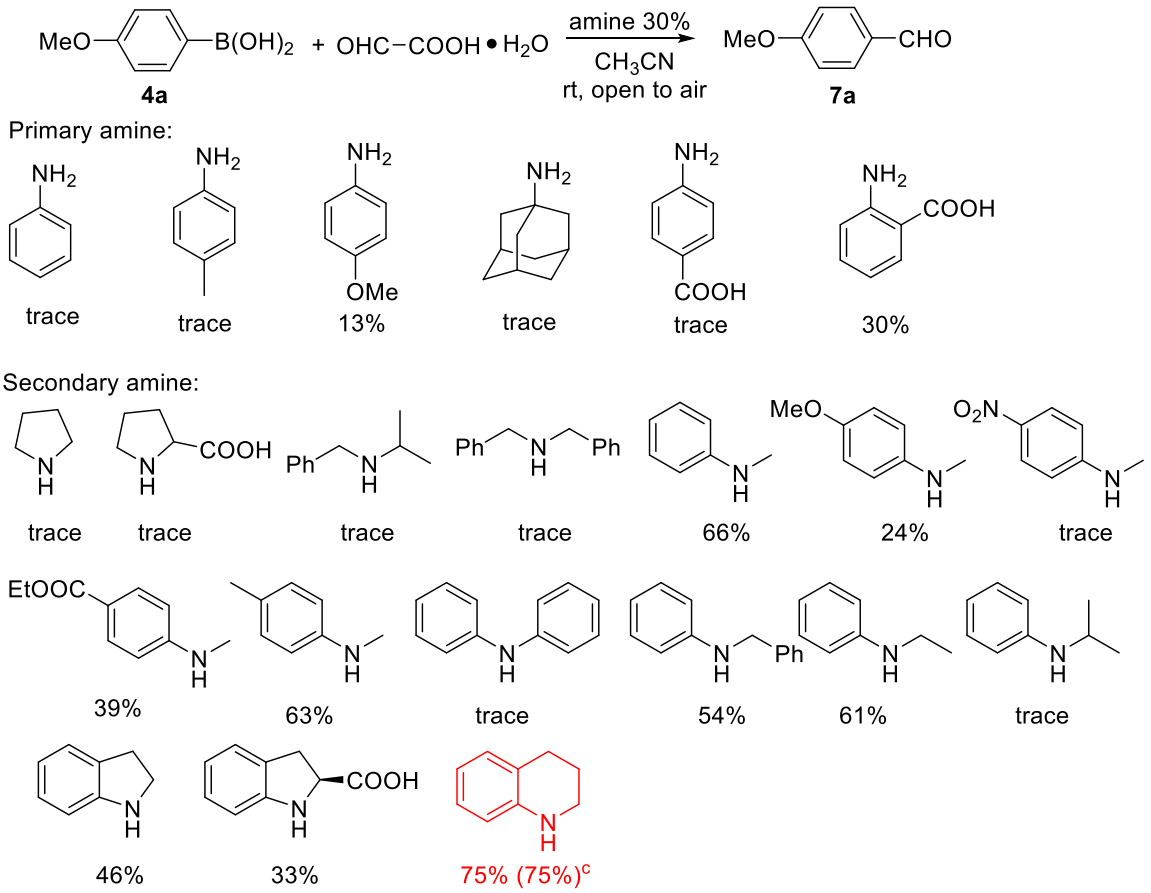
Table 2.1. Optimization of Reaction Conditions[a]



entry	deviation from "standard conditions"[a]	% yield[b]
1	-	75 (75)[c]
2	under N_2 (without O_2)	0
3	without **3a**	0
4	Pyrrolidine[d]	0
5	20 mol% **3a** and 3.04 g of **1a** used	77[c]

[a] Standard reaction conditions: unless specified, a mixture of **1a** (0.2 mmol, 1.0 equiv), **2** (0.21 mmol, 1.05 equiv.) and **3a** (30 mol %) in CH_3CN (5.0 mL) was stirred at rt under ambient conditions for 24-36 h and see SI for detail. [b] Yields were determined by using ^1H NMR with dimethyl maleate as an internal standard. [c] Isolated yields. [d] Petasis product observed.

Scheme 2.3 Optimization of Organocatalyzed Formylation of Arylboronic Acids.[abc]



[a] Reaction conditions: **4a** (0.2 mmol, 1 equiv.), glyoxylic acid monohydrate (0.21 mmol, 1.05 equiv.), amine (0.06 mmol, 0.3 equiv.) in acetonitrile (5 mL) exposed to air for 36 h at RT. [b] NMR yield, dimethyl maleate as internal standard substance. [c] Isolated yields.

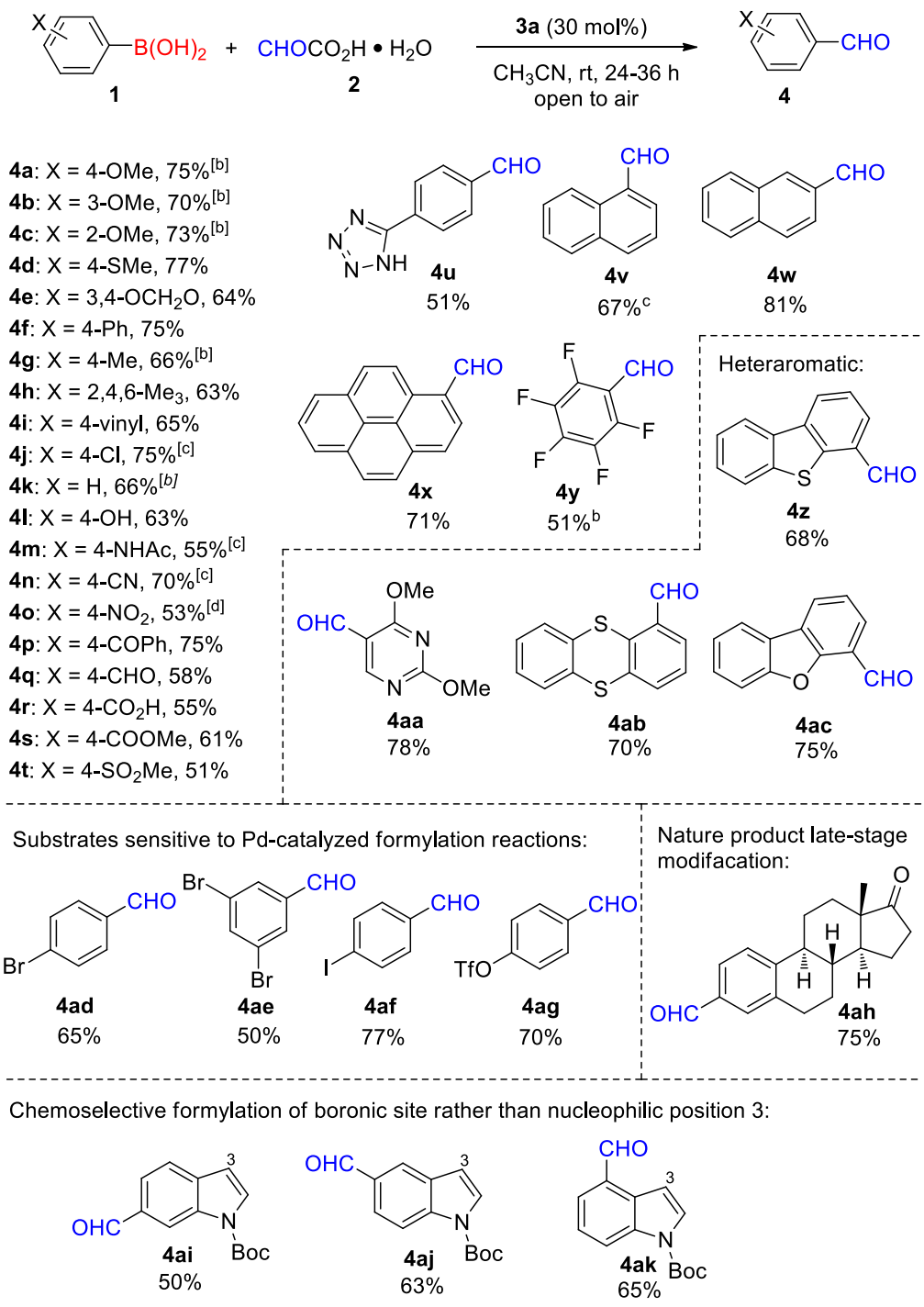
2.3.2 Investigation of Substrate Scope

The new methodology described above is applicable to the synthesis of a variety of aromatic aldehydes (Scheme 2.4). Notably, the efficiency of the reaction is not significantly affected by variations in the aryl boronic acids, as is demonstrated by the observation that the electronic nature and position of substituents on the aromatic ring of the substrates do not impact the yields of these reactions. Notably, the mild nature of the formylation reaction enables

survival of a variety of functional groups. Particularly noteworthy is the fact that the process is orthogonal to Pd-catalyzed formylation reactions, which use aryl bromides and iodides as substrates. In the new process, formylation of aromatic boronic acids bearing chloride, bromide, iodide and OTf groups occurs without affecting aryl-halide and -OTf functionalities (eg., formation of **4j**, and **4ad-4ag**). Furthermore, the formylation protocol is applicable to the production of *p*-nitrobenzaldehyde (**4o**) and pentafluorobenzaldehyde (**4y**), difficult tasks when transition metal catalytic methods are employed.[10] In addition, a variety of structurally diverse aromatic ring containing boronic acids effectively participate in the process as demonstrated by the formation of aldehydes **4v-4x** in high yields. Moreover, pharmaceutically relevant heteroaromatic aldehyde building blocks (eg., **4z-4ac**) are efficiently prepared starting with the corresponding boronic acids. Finally, the new formylation procedure was found to be applicable to a late-stage synthetic elaboration of a steroidal boronic acid to generate the biologically relevant aldehyde **4ah**.

A major effort has been given to the development of formylation reactions of indoles, all of which take advantage of the high nucleophilic reactivity of the C-3 position.[17] Devising methods for formylation at other positions of this heterocycle ring system are plagued by difficulties associated with regiocontrol and poor functional group compatibility. Given the fact that other regioisomeric formyl-indoles are highly valuable building blocks for the synthesis of a broad range of indole ring containing substances, we explored formylation reactions of several *N*-Boc protected indole boronic acid. As can be seen by viewing the results outlined in Scheme 2, *N*-Boc protected 6-, 5- and 4-boronic acid derivatives of indole are efficiently converted to the corresponding formylindoles **4ai-4ak** utilizing the newly developed protocol.

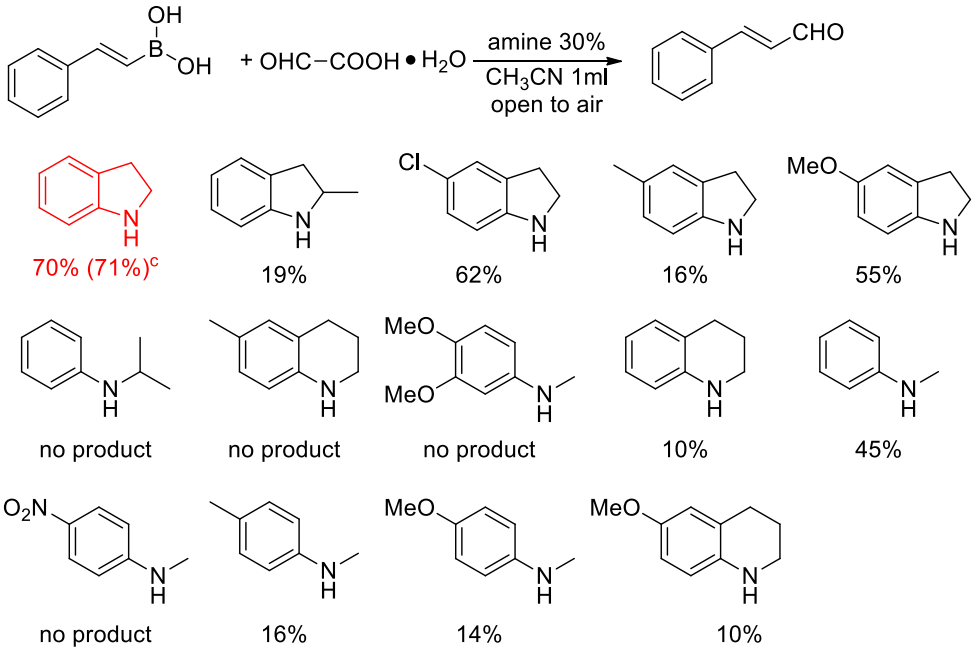
Scheme 2.4 Scope of the Formylation Reaction with Aryl Boronic Acids



[a] Standard reaction conditions: unless specified, see reaction conditions in Table 1 and yields refer to isolated ones. [b] NMR yield with dimethyl maleate as an internal standard. [c] Reaction carried out at 70 ºC for 24 h. [d] Reaction carried out at 40 ºC for 36 h.

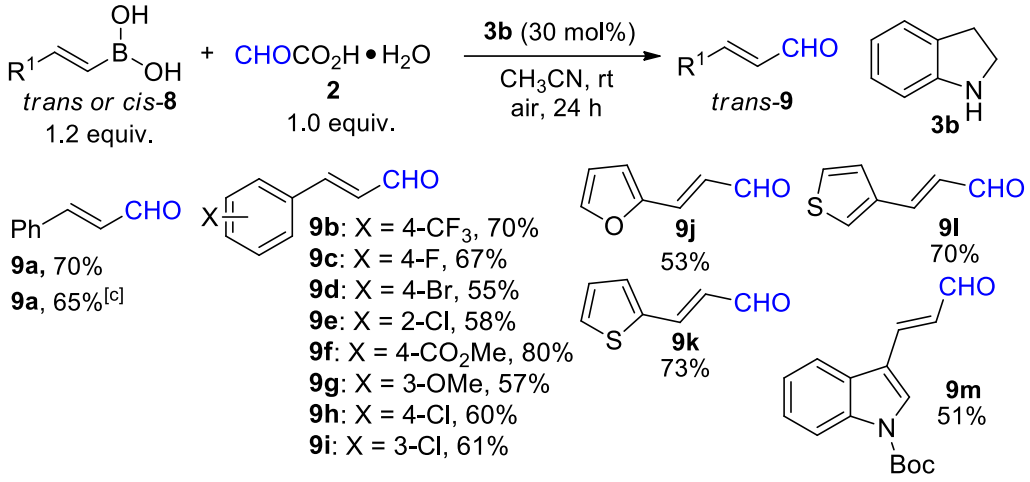
It is should be noted that reaction of 4-cyanophenylboronic acid under the optimized conditions produced the target aldehyde **4n** along with a significant amount (33%) of 4-cyanophenol. This observation indicates that a reactive oxygen species (eg., hydrogen peroxide, superoxide ion), formed under the oxygen rich conditions oxidizes 4-cyanophenylboronic acid to form the corresponding phenol.[3b] We observed that side-product phenols of this type in reactions that form **4j**, **4m-4n** and **4v** can be reduced by carrying out the processes at 70 ºC (Scheme 2.4).

Scheme 2.5 Optimization of Organocatalyzed Formylations of Alkenylboronic Acids.[abc]



[a] Reaction conditions: phenylvinylboronic acid (0.12 mmol, 1.2 equiv.), glyoxylic acid monohydrate (0.1 mmol, 1.0 equiv.), amine (0.03 mmol, 0.3 equiv.) in acetonitrile (1 mL) exposed to air for 24 h at RT. [b] NMR yield, dimethyl maleate as internal standard substance. [c] Isolated yields.

Scheme 2.6 Formylation Reactions of Alkenyl Boronic Acids.



[a] Standard reaction conditions: unless specified, see Scheme 2 and SI for details. [b] Isolated yields. [c] *cis*-Styrylboronic acid used.

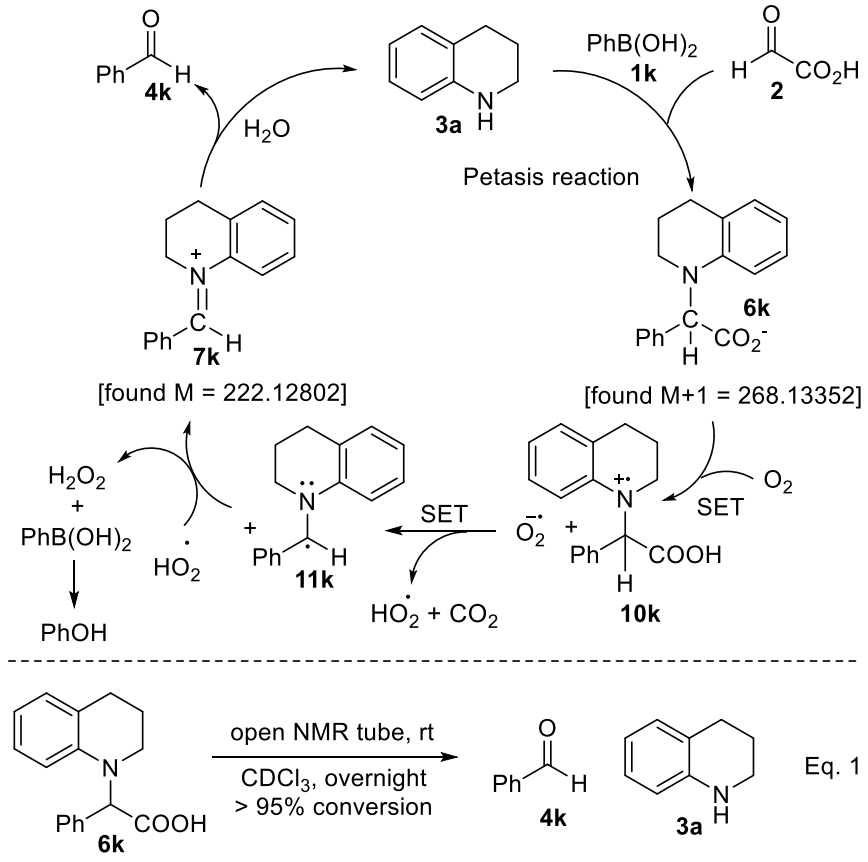
To determine if the scope of the new procedure could be expanded to include the preparation of enals **9** (optimization of reaction conditions in Scheme 2.5 and scoup in Scheme 2.6), which are versatile substances used in iminium catalysis,[18] we explored formylation reactions of several alkenylboronic acids **8**. Using the optimized conditions developed for formylation of aryl boronic acids (see above), which utilize tetrahydroquinoline **3a** as the organocatalyst, β-styryl boronic acid is transformed to cinnamaldehyde (**9a**) but in only 10% yield (see Scheme 2.5). A brief screen of amines demonstrated that indoline (**3b**) is a superior catalyst for preparation of **9a** from the corresponding boronic acid, which takes place in 70% yield. Moreover, we observed that formylation reactions employing **3b** as the organocatalyst occur efficiently to produce the corresponding enals **9** (Scheme 2.6) with moderate to high

efficiency. However, we found that *cis* styrylboronic acid **8a** also generates *trans* enal **9a** under the formylation reaction conditions. Interestingly, **8a** produces a Petasis product that contains a *cis* styryl moiety.[19] This observation suggests that the initially formed *cis* radical intermediate in the SET-promoted decarboxylation process equilibrates to form the thermodynamically more stable *trans* counterpart prior to oxidation to form the iminium ion (see Scheme 2.6, **9a**).[20]

2.3.3 Mechanism Study

The results presented above suggest that the initially formed amino acid **6**, produced by the Petasis reaction between boronic acids, glyoxylic acid **2**, and aromatic amines like **3a**, undergo the oxidative decarboxylation to produce the iminium ion precursor of aldehyde **7** (Schemes 2.2 and 2.7). Several experiments were carried out to gain information about subtle features of the process and the validity of our mechanistic proposals. First, the *in situ* formed Petasis product **6k** and iminium ion **7k** intermediate in the **3a** promoted reaction of phenylboronic acid with **2** were detected by using *in situ* mass spectrometric analysis (Scheme 2.8). Moreover, we found that the **3a** promoted reaction of glyoxylic acid with phenylboronic acid, carried out under O_2 free conditions, does not generate the corresponding aldehyde **4k** (Table 2.1, entry 2). Furthermore, amino acid **6k**, the proposed Petasis intermediate in this formylation process, was independently synthesized (see Experimental Section) and found to be quantitatively transformed under an air atmosphere ($CDCl_3$, rt, overnight, ^1H NMR analysis) to benzaldehyde **4k** and amine **3a** (Scheme 2.8). Aliphatic amine like pyrrolidine participate in the formation of the Petasis product, but the derived amino acids do not undergo subsequent oxidative decarboxylation in air (Table 2.1, entry 4). Thus, the selection of a proper amine catalysts is critical requirement for the success of the new formylation protocol.

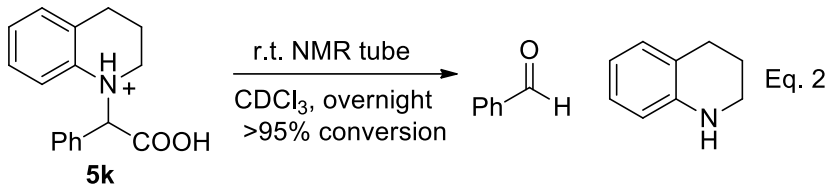
Scheme 2.7 Experiments to Elucidate Subtle Features and Proposed Catalytic Cycle Involving Oxidative SET Decarboxylation for the Formylation Reaction.

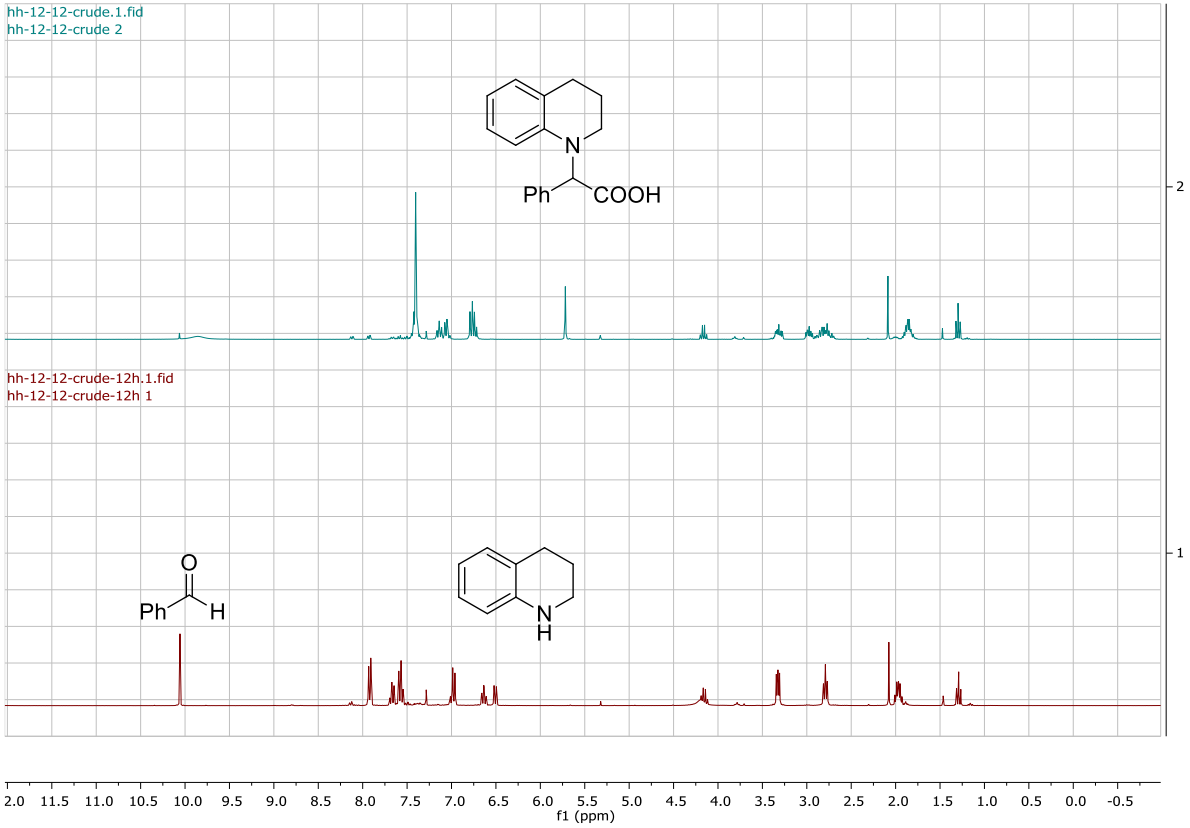


As discussed above, the *N*-alkylaniline derivatives have lower redox potentials than that of O_2 and, therefore, they undergo rapid SET oxidation in air (O_2). In contrast, aliphatic amines can be oxidized by O_2 but only with the assistance of light in the presence of photosensitizer.[15,17,21] In a similar manner to the photochemical processes,[15,22] the O_2 mediated SET process initially generates an aminium radical **10k** and superoxide ion (Scheme 2.7). The aminium radical **10k** then undergoes decarboxylation to form a-amino radical **11k**, which is oxidized to produce the iminium ion **7k** with concurrent production of H_2O_2.[15] We observed

phenol side products in the formylation reaction, particularly **4j**, **4m-4n** and **4v**. It is believed that their formation comes from the oxidation of boronic acids by H_2O_2 (see above).[3b]

Scheme 2.8 *In situ* NMR Analysis





2.4 Conclusion

In conclusion, in the study described above we uncovered an unprecedented organocatalytic method for facile installation of the highly valued aldehyde functional group

from aryl and alkenyl boronic acids. The reaction is truly environmentally friendly and atom economical. The simple aniline derivatives, tetrahydroquinoline and indoline, serve as catalysts for the process and the feedstock chemical glyoxylic acid is used as the formylation reagent. The reaction is performed under metal-free, mild and operationally simple conditions and produces non-toxic CO_2 and boric acid as by-products. The new formylation reaction displays a broad substrate range that includes aryl, heteroaryl and alkenyl boronic acids, and it tolerates a wide array of functional groups. Notably, the process is capable of selectively installing the aldehyde group in halogen-contained aryl boronic acids, which stands in contrast with the difficulty of executing these transformations using transition metal promoted formylation processes. Furthermore, selective formylation of *N*-Boc indole derived boronic acids can be utilized to generate indole aldehydes that have the formyl group at positions other than C3. It is expected that the simplicity and efficiency of the new formylation reaction will make it useful in approaches for the practical production of highly valued aromatic and α, β-unsaturated aldehydes.

2.5 Experimental Section

2.5.1 General Information

Commercially available reagents were purchased from Sigma Aldrich, Matrix Chemical, AK Sci, Alfa Aesar, Combi-blocks or TCI. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with a fluorescence F_{254} indicator were used for thin-layer chromatography (TLC) analysis. ^{1}H, ^{13}C, ^{11}B and ^{19}F NMR spectra were recorded on Bruker Avance 300 and 500 MHz. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) relative to residual chloroform (7.26 ppm) or dimethyl sulfoxide (2.50 ppm) as internal standards. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d =

doublet, m = multiplet), coupling constant in Hertz (Hz) and hydrogen numbers based on integration intensities. ^{13}C NMR chemical shifts are reported in ppm relative to the central peak of $CDCl_3$ (77.16 ppm) or $(CD_3)_2SO$ (39.52 ppm) as internal standards. ^{11}B NMR chemical shifts are reported in ppm relative to the central peak of BF_3 Et_2O (0.0 ppm) as internal standards. ^{19}F NMR chemical shifts are reported in ppm relative to the central peak of $C_6H_5CF_3$ (-63.72 ppm) as internal standards.

2.5.2 Measurement of Cyclic Voltammetry

Cyclic voltammetry was performed at 25 °C on a CH Instrument CHI604xD electrochemical analyzer using a glassy carbon working electrode, a platinum wire counter electrode, and a Ag/AgCl reference electrode calibrated using ferrocene redox couple (4.8 eV below vacuum).

2.5.3 General Procedures

Procedure A: (Formylations of Arylboronic Acids) (Scheme 2.4)

Arylboronic acid (0.2 mmol, 1.0 equiv.) and glyoxylic acid monohydrate (0.21 mmol, 1.05 equiv., 19.4 mg) were placed in a clear borosilicate glass test tube with a stir bar. Acetonitrile (5 mL) was injected into the vial and then 30 mol% catalyst (0.06 mmol, 7.5 µL) was added. The mixture was stirred at room temperature for 24-36 h exposed to air. Reaction was monitored by TLC plates. After 24-36 h later, the solvent was reduced in *vacuo*, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to provide the title compounds.

Procedure B: (Gram scale)

4-Methoxyphenylboronic acid (20.0 mmol, 3.04 g) and glyoxylic acid monohydrate (21.0

mmol, 1.93 g) were placed in a 250 mL flask with a stir bar. Acetonitrile (100 mL) was injected into the flask and then 20 mol% catalyst (4.0 mmol, 0.5 mL) was added. The mixture was stirred at room temperature for 48 h exposed to air. After stirred for 48 h, the solvent was reduced in *vacuo*, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to provide the title compounds.

Procedure C: (Formylation of Alkenylboronic Acids) (Scheme 2.5)

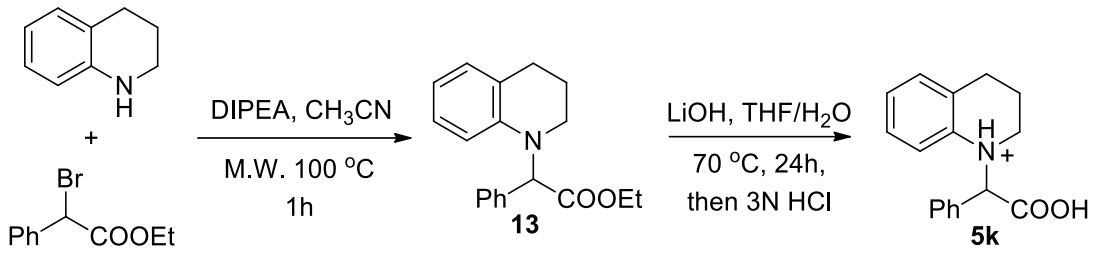
Alkenylboronic acids (0.12 mmol, 1.2 equiv.) and glyoxylic acid monohydrate (0.1 mmol, 1.0 equiv., 9.2 mg) were placed in a 4 mL brown-colored glass vial with a stir bar. Acetonitrile (1.0 mL) was injected into the vial and then 30 mol% catalyst (0.03 mmol, 3.4 µL) was added. The mixture was stirred at room temperature for 24 h exposed to air. After stirred for 24 h, the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to provide the title compounds.

Procedure D: (Formylation of Arylboronic Acids for Compounds 7j, 7m, 7n, 7o and 7v)

Arylboronic acid (0.2 mmol, 1.0 equiv.) and glyoxylic acid monohydrate (0.21 mmol, 1.05 equiv., 19.4 mg) were placed in a clear borosilicate glass test tube with a stir bar. Acetonitrile (5 mL) was injected into the vial and then 30 mol% catalyst (0.06 mmol, 7.5 µL) was added. The mixture (**7j**, **7m**, **7n** and **7v**) was stirred at 70 ^oC for 24 h exposed to air. Or the mixture (**7o**) was stirred at 40 ^oC for 36 h exposed to air. Reaction was monitored by TLC plates. After 24-36 h later, the solvent was reduced in *vacuo*, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to provide the title compounds.

2.5.4 Mechanism Studies

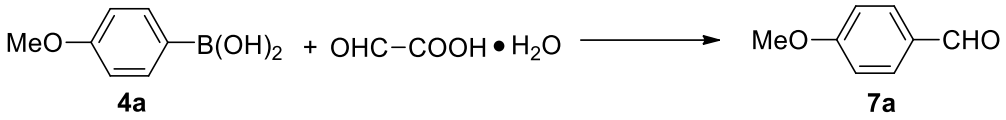
Synthesis of compound 5k:



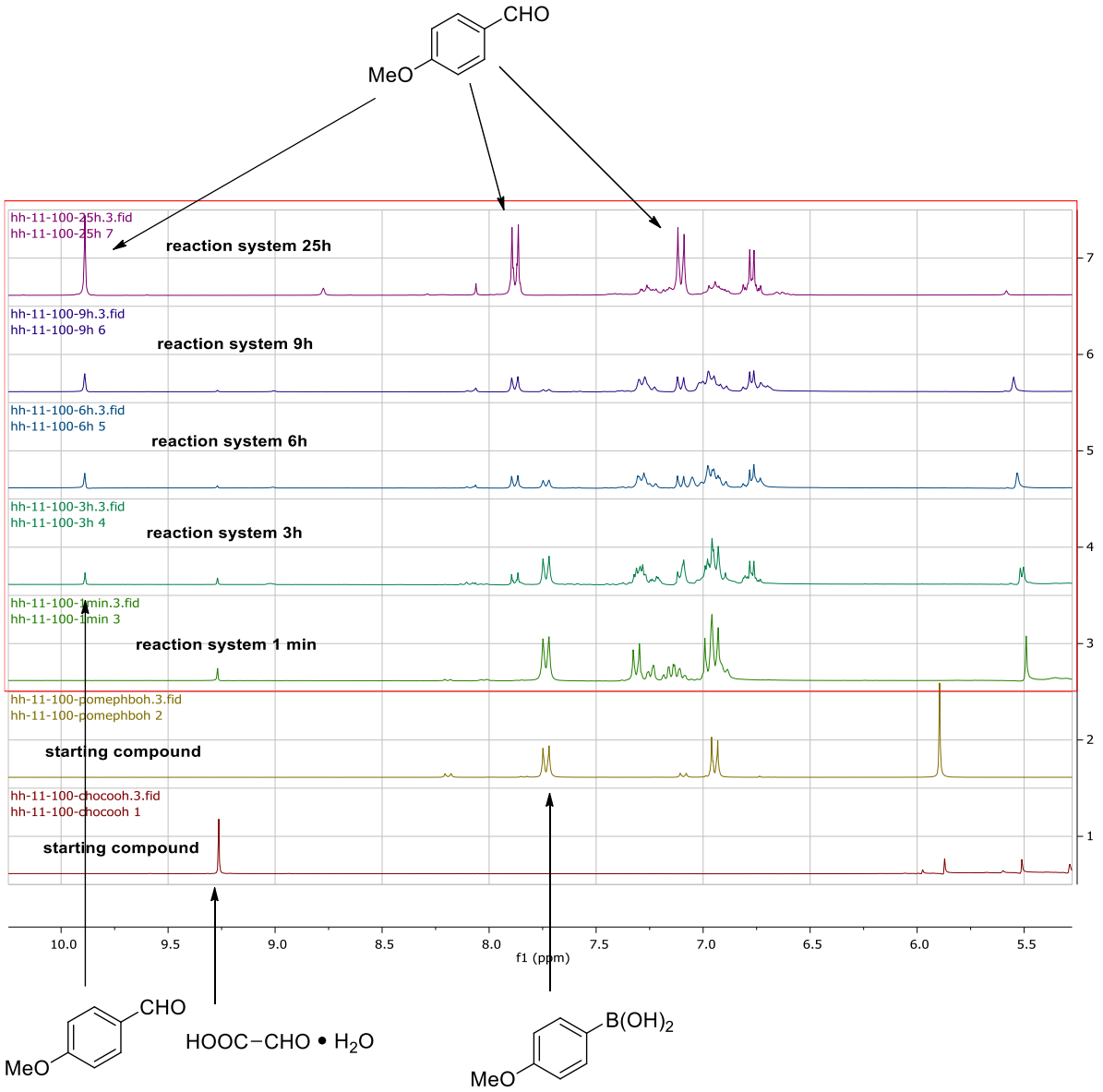
A vial containing a mixture of 1,2,3,4-tetrahydroquinoline (350 μL, 2.6 mmol), ethyl α-bromophenylacetate (350 μL, 2.0 mmol) and *N, N*-diisopropylethylamine (453 μL, 2.6 mmol) in acetonitrile (2 mL) was sealed and subjected to microwave irradiation, programmed at 100 °C and 120 W. After a period of 3-5 min, the temperature reached a plateau, 100 °C, and remained constant. After completion of the reaction (1 h), the vial was cooled to room temperature. Then the solvent was reduced in *vacuo,* and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to provide the title compounds **13** in 78% yield.

Compound **13** (295 mg, 1.0 mmol) and LiOH•H_2O (126 mg, 3.0 mmol) were placed in a 10 mL flask with a stir bar. THF (0.5 mL) and water (1.5 ml) was injected into the flask. The mixture was stirred at 70 ºC for 24 h. After 24 h, 3N HCl was added slowly till pH was about 1 and the mixture was evaporated. Water (3ml) was added, and the residue was triturated obtaining a brown suspension that was filtered on a buckner funnel washing with water and then with acetonitrile. The solid was dried under *vacuo* for 2 min to obtain compound **5k** in 52% yield.

***In situ* ^{1}H NMR analysis of the decarboxylation reaction of 5k.**



4a **7a**



[a] The *in situ* ^{1}H NMR analysis was carried out with 0.1 mmol of **4a** and 0.11 mmol of glyoxylic acid monohydrate in 2.5 mL of $CDCl_3$ with 30 mol% 1,2,3,4-tetrahydroquinoline.

The *in situ* mass spectra:

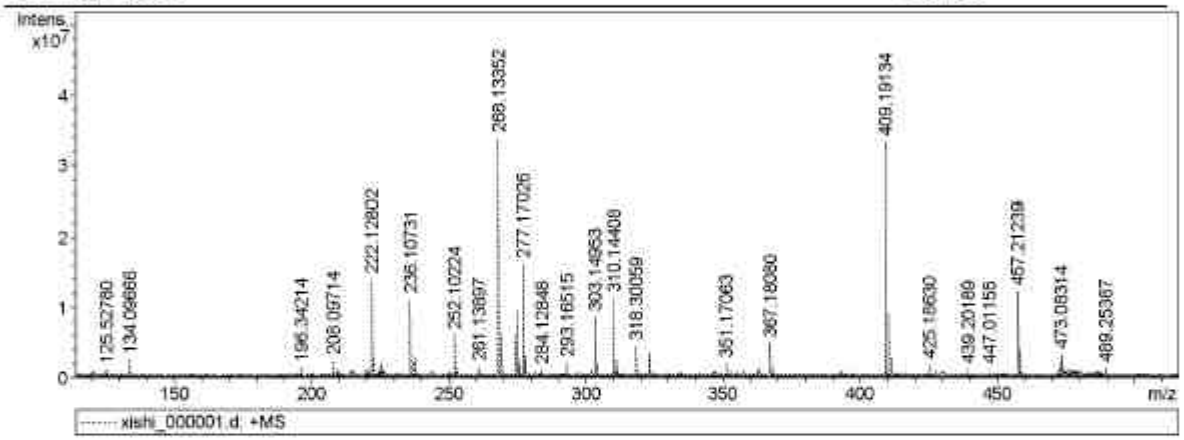
Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name	D:\Data\teachers\liu hai long\160123_zhou\xishi_000001.d		
Method	20151029_4M@Pos_lhl	Operator	Administrator
Sample Name		Instrument	solariX
Comment			

Acquisition Parameter

Polarity	Positive
n/a	n/a
Broadband Low Mass	101.1 m/z
Broadband High Mass	1500.0 m/z
Acquisition Mode	Single MS
Pulse Program	basic
Source Accumulation	0.001 sec
Ion Accumulation Time	0.050 sec
Flight Time to Acq. Cell	0.001 sec

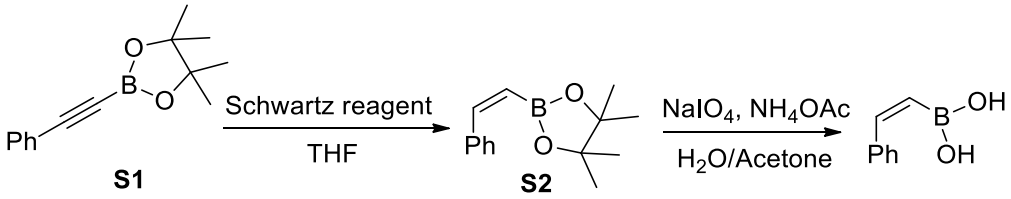


Meas. m/z	#	Formula	Score	m/z	err [ppm]	Mean err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
208.09714	1	C 11 H 14 N O 3	100.00	208.09682	-1.53	-1.53	71.2	5.5	even	ok
222.12802	1	C 16 H 16 N	100.00	222.12773	-1.35	-1.39	12.2	9.5	even	ok
236.10731	1	C 16 H 14 N O	100.00	236.10699	-1.34	-1.37	21.1	10.5	even	ok
244.06104	1	C 13 H 10 N O 4	100.00	244.06043	-2.50	-2.50	83.9	9.5	even	ok
	2	C 14 H 6 N 5	49.62	244.06177	2.98	2.98	98.4	14.5	even	ok
252.10224	1	C 16 H 14 N O 2	100.00	252.10191	-1.32	-1.33	19.6	10.5	even	ok
268.13352	1	C 17 H 18 N O 2	100.00	268.13321	-1.19	-1.20	12.7	9.5	even	ok
275.15461	1	C 19 H 19 N 2	100.00	275.15428	-1.23	-1.26	14.7	11.5	even	ok
277.17026	1	C 19 H 21 N 2	100.00	277.16993	-1.20	-1.23	15.5	10.5	even	ok
284.12848	1	C 17 H 18 N O 3	100.00	284.12812	-1.25	-1.25	109.1	9.5	even	ok
293.16515	1	C 19 H 21 N 2 O	100.00	293.16484	-1.07	-1.07	123.5	10.5	even	ok
303.14953	1	C 20 H 19 N 2 O	100.00	303.14919	-1.13	-1.11	17.6	12.5	even	ok
310.14408	1	C 19 H 20 N O 3	100.00	310.14377	-1.00	-1.01	17.0	10.5	even	ok
318.30059	1	C 18 H 40 N O 3	100.00	318.30027	-1.02	-1.00	15.0	-0.5	even	ok
323.17575	1	C 20 H 23 N 2 O 2	100.00	323.17540	-1.08	-1.08	130.2	10.5	even	ok
351.17063	1	C 7 H 15 N 18	100.00	351.17216	4.34	4.34	82.1	9.5	even	ok
	2	C 21 H 23 N 2 O 3	12.23	351.17032	-0.90	-0.90	136.7	11.5	even	ok
362.32682	1	C 20 H 44 N O 4	100.00	362.32649	-0.94	-0.94	131.3	-0.5	even	ok
	2	C 21 H 40 N 5	29.67	362.32782	2.75	2.75	145.5	4.5	even	ok
367.18080	1	C 25 H 23 N 2 O	100.00	367.18049	-0.84	-0.88	33.3	15.5	even	ok
425.18630	1	C 11 H 25 N 10 O 8	100.00	425.18513	-2.73	-2.73	91.4	4.5	even	ok
	2	C 12 H 21 N 14 O 4	85.01	425.18647	0.41	0.41	105.6	9.5	even	ok
	3	C 15 H 29 N 4 O 10	39.14	425.18782	3.58	3.58	106.4	3.5	even	ok
	4	C 13 H 17 N 18	19.38	425.18781	3.56	3.56	120.0	14.5	even	ok
	5	C 27 H 25 N 2 O 3	5.51	425.18597	-0.77	-0.77	151.8	16.5	even	ok

Mass Spectrum SmartFormula Report

Meas. m/z	#	Formula	Score	m/z	err [ppm]	Mean err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
439.20189	1	C 12 H 27 N 10 O 8	100.00	439.20078	-2.51	-2.51	97.7	4.5	even	ok
	2	C 16 H 31 N 4 O 10	67.59	439.20347	3.61	3.61	99.5	3.5	even	ok
	3	C 13 H 23 N 14 O 4	77.27	439.20212	0.54	0.54	111.9	9.5	even	ok
	4	C 14 H 19 N 18	16.79	439.20346	3.58	3.58	126.4	14.5	even	ok
	5	C 28 H 27 N 2 O 3	4.99	439.20162	-0.61	-0.61	157.4	16.5	even	ok
447.01155	1	C 8 H 15 O 21	97.60	447.01003	-3.39	-3.39	52.1	1.5	even	ok
	2	C 6 H 3 N 14 O 11	50.02	447.01002	-3.41	-3.41	71.4	12.5	even	ok
	3	C 9 H 11 N 4 O 17	100.00	447.01137	-0.39	-0.39	72.5	6.5	even	ok
	4	C 10 H 7 N 8 O 13	36.74	447.01271	2.60	2.60	84.9	11.5	even	ok
	5	C 26 H 7 O 8	0.97	447.01354	4.46	4.46	143.2	23.5	even	ok
	6	C 22 H 3 N 6 O 6	1.23	447.01086	-1.54	-1.54	152.4	24.5	even	ok
457.21239	1	C 29 H 25 N 6	63.68	457.21352	2.47	2.42	27.8	20.5	even	ok
	2	C 28 H 29 N 2 O 4	100.00	457.21218	-0.46	-0.47	28.6	15.5	even	ok
473.08314	1	C 34 H 9 N 4	100.00	473.08217	-2.05	-2.05	194.6	32.5	even	ok
489.25387	1	C 20 H 41 O 13	100.00	489.25417	0.60	0.60	115.9	0.5	even	ok
	2	C 21 H 37 N 4 O 9	27.89	489.25551	3.34	3.34	125.4	5.5	even	ok
	3	C 17 H 33 N 10 O 7	28.27	489.25282	-2.15	-2.15	131.5	6.5	even	ok
	4	C 18 H 29 N 14 O 3	20.00	489.25416	0.58	0.58	143.6	11.5	even	ok
	5	C 33 H 33 N 2 O 2	0.90	489.25365	-0.45	-0.45	187.4	18.5	even	ok

Synthesis of (*Z*)-phenylvinylboronic acid:

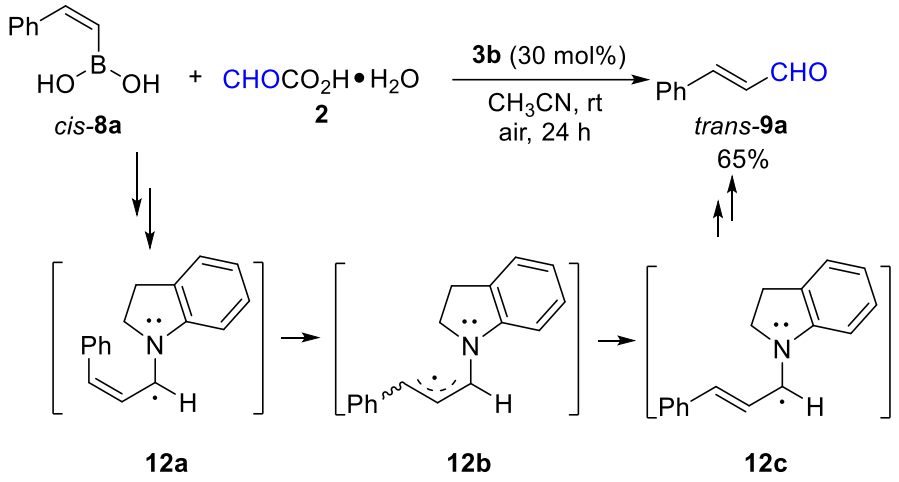


(*Z*)-2-Phenylvinylboronic acid pinacol ester S2, is synthesized according to a modified literature procedure.[23-24] To a stirred suspension of Schwartz reagent $Cp_2ZrCl(H)$ (1.23 mmol, 1.23 equiv., 317.2 mg) in 4.0 ml dry THF at 25 ºC under an atmosphere of argon was added 2.0 mL of a 0.5 M solution of pinacol boronate **S1** (1.0 mmol, 1.0 equiv., 228.1 mg) in THF. The reaction was stirred for an additional 30 min until it turned clear and became orange in color. Addition of excess H_2O led to the disappearance of the color and the appearance of a precipitate. After stirring for an additional 30 min, the THF was evaporated and the reaction mixture was extracted with hexanes (3 x 10 mL). Evaporation of the solvent and the pure (*Z*)-boronate **S2** was isolated by column chromatography as light yellow oil in 43.5% yield (100 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H), 7.39-7.24 (m, 4H), 5.65 (d, 1H, *J* = 14.7 Hz), 1.34 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 138.5, 128.7, 128.0, 128.0, 118.7 (broad peak for the carbon attached to boron), 83.5, 24.8. ^{11}B NMR (96 MHz, $CDCl_3$): δ 30.28. The data agrees with the reported literature values.[1]

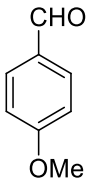
(*Z*)-phenylvinylboronic acid, is synthesized according to a modified literature procedure.[24] To a solution of (Z)-boronate **S2** (69 mg, 0.3 mmol, 1 equiv) in acetone and water (3 mL, 2:1) was added sodium metaperiodate (192.5 mg, 0.9 mmol, 3.0 equiv) and ammonium acetate (69.3 mg, 0.9 mmol, 3.0 equiv). The resulting cloudy solution was stirred at room temperature. After 36 h, the reaction mixture was placed under reduced pressure to remove acetone, was diluted with ethyl acetate (5 mL) and the phases separated. The aqueous layer was extracted with ethyl

acetate (2 x 5 mL) and the combined organic layers were washed with brine (15 mL), were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure to provide boronic acid (*Z*)-phenylvinyl boronic acid as a colorless oil (33 mg, 75%). ^{1}H NMR (500 MHz, $(CD_3)_2CO$): δ 7.49-7.50 (m, 2H), 7.33-7.30 (m, 2H), 7.26-7.23 (m, 1H), 7.00 (s, 1H), 6.95 (d, 1H, *J* = 15.0 Hz), 5.70 (d, 1H, *J* = 15.0 Hz); ^{13}C NMR (125 MHz, $(CD_3)_2CO$): δ 142.8, 140.2, 129.1, 128.7, 128.3. No signal was observed for the carbon attached to boron. ^{11}B NMR (160 MHz, $(CD_3)_2CO$): δ 30.20. The data agrees with the reported literature values.[25]

Rationalization of production of trans enal 9a from *cis*-phenylvinyl boronic acid 8a.

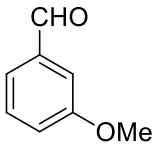


2.6 Characterization

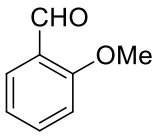


4-Methoxybenzaldehyde (4a): The title compound was prepared according to the general procedure A using (4-methoxyphenyl)boronic acid (1 equiv, 0.2 mmol, 30.4 mg) and glyoxylic

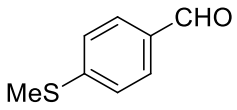
acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography. NMR yield with dimethyl maleate as an internal standard (75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.81-7.77 (m, 2H), 6.98-6.94 (m, 2H), 3.84 (d, 3H, *J* = 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 164.6, 131.9, 129.9, 114.3, 55.6.



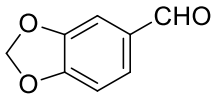
3-Methoxybenzaldehyde (4b): The title compound was prepared according to the general procedure A using (3-methoxyphenyl)boronic acid (1 equiv, 0.2 mmol, 30.4 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography. NMR yield with dimethyl maleate as an internal standard (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.45-7.43 (m, 2H), 7.41-7.39 (m, 1H), 7.19-7.15 (m, 1H), 3.85 (d, 3H, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.1, 160.1, 137.8, 130.0, 123.5, 121.5, 112.1, 55.4.



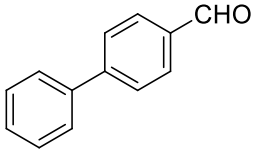
2-Methoxybenzaldehyde (4c): The title compound was prepared according to the general procedure A using (2-methoxyphenyl)boronic acid (1 equiv, 0.2 mmol, 30.4 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography. NMR yield with dimethyl maleate as an internal standard (73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (s, 1H), 7.84-7.81 (m, 1H), 7.58-7.52 (m, 1H), 7.04-6.97 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.8, 161.8, 136.0, 128.5, 124.8, 120.6, 111.6, 55.6.



4-(Methylthio)benzaldehyde (4d): The title compound was prepared according to the general procedure A using (4-(methylthio)phenyl)boronic acid (1 equiv, 0.2 mmol, 33.6 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography (23.4 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.76 (dd, 2H, J_1= 6.6 Hz, J_2= 1.8 Hz), 7.32 (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.8 Hz), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2, 147.9, 133.0, 130.0, 125.2, 14.7.

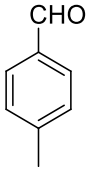


Benzo[d][1,3]dioxole-5-carbaldehyde (4e): The title compound was prepared according to the general procedure A using benzo[d][1,3]dioxol-5-ylboronic acid (1 equiv, 0.2 mmol, 33.2 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography (19.2 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.39 (dd, 2H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.31 (d, 1H, J = 1.5 Hz), 6.9 (d, 1H, J = 7.1 Hz), 6.06 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 153.1, 148.7, 131.9, 128.7, 108.3, 106.9, 102.1.

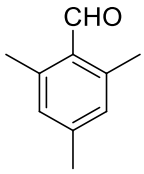


[1,1'-Biphenyl]-4-carbaldehyde (4f): The title compound was prepared according to the general procedure A using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.2 mmol, 39.6 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (27.3 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.06 (s, 1H),

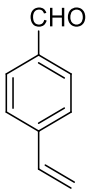
7.97 (m, 2H), 7.94 (m, 2H), 7.77-7.75 (m, 2H), 7.66-7.63 (m, 2H), 7.52-7.42 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.9, 147.2, 139.7, 135.2, 130.3, 129.0, 128.5, 127.7, 127.4.



4-Methylbenzaldehyde (4g): The title compound was prepared according to the general procedure A using *p*-tolylboronic acid (1 equiv, 0.2 mmol, 27.2 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography. NMR yield with dimethyl maleate as an internal standard (66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.94 (d, 1H, *J* = 1.8 Hz), 7.78-7.75 (m, 2H), 7.33-7.30 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 145.6, 134.2, 129.9, 129.7, 21.9.

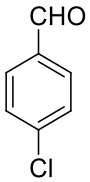


2,4,6-Trimethylbenzaldehyde (4h): The title compound was prepared according to the general procedure A using mesitylboronic acid (1 equiv, 0.2 mmol, 32.8 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography (18.7 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.56 (s, 1H), 6.90 (s, 2H), 2.58 (s, 6H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.1, 143.9, 141.5, 130.5, 130.0, 21.5, 20.5.

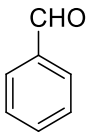


4-Vinylbenzaldehyde (4i): The title compound was prepared according to the general procedure

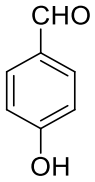
A using (4-vinylphenyl)boronic acid (1 equiv, 0.2 mmol, 29.6 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography (17.2 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.0 (s, 1H), 7.83 (d, 2H, J_1 = 8.4 Hz), 7.54 (d, 2H, J_1 = 8.4 Hz), 6.77 (dd, 1H, J_1 = 17.4 Hz, J_2 = 10.8 Hz), 5.90 (dd, 1H, J_1 = 17.7 Hz, J_2 = 0.6 Hz), 5.42 (d, 1H, J_1 = 11.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.7, 143.5, 135.9, 135.7, 130.1, 126.7, 117.5.



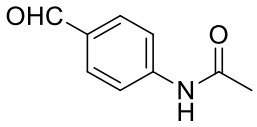
4-Chlorobenzaldehyde (4j): The title compound was prepared according to the general procedure D using (4-chlorophenyl)boronic acid (1 equiv, 0.2 mmol, 31.3 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography (21.1 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.84 (d, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 141.0,134.7, 130.9, 129.5.



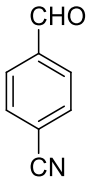
Benzaldehyde (4k): The title compound was prepared according to the general procedure A using phenylboronic acid (1 equiv, 0.2 mmol, 24.4 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography. NMR yield with dimethyl maleate as an internal standard (66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.91-7.87 (m, 2H), 7.67-7.61 (m, 1H), 7.57-7.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 141.0,134.7, 130.9, 129.5.



4-Hydroxybenzaldehyde (4l): The title compound was prepared according to the general procedure A using (4-hydroxyphenyl)boronic acid (1 equiv, 0.2 mmol, 27.6 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (15.4 mg, 63%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.59 (s, 1H), 9.78 (s, 1H), 7.77-7.74 (m, 2H), 6.94-6.91 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 191.4, 163.8, 132.6, 128.9, 116.3.

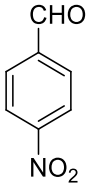


N-(4-Formylphenyl)acetamide (4m): The title compound was prepared according to the general procedure D using (4-acetamidophenyl)boronic acid (1 equiv, 0.2 mmol, 35.8 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (18.0 mg, 55%).^{1}H NMR (300 MHz, DMSO-d_6): δ 10.4 (b, 1H), 9.86 (s, 1H), 7.84 (m, 2H), 7.12 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 192.0, 169.6, 145.3, 131.6, 131.3, 119.0.

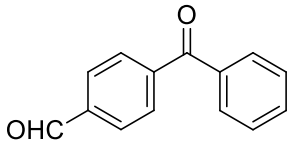


4-Formylbenzonitrile (4n): The title compound was prepared according to the general procedure D using (4-cyanophenyl)boronic acid (1 equiv, 0.2 mmol, 29.4 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after

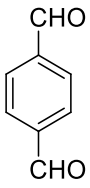
silica gel chromatography (18.4 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.99 (m, 2H), 7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.6, 138.8, 132.9, 129.9, 117.7, 117.6.



4-Nitrobenzaldehyde (4o): The title compound was prepared according to the general procedure D using (4-nitrophenyl)boronic acid (1 equiv, 0.2 mmol, 33.4 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (16.0 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.37 (d, 2H, *J* = 8.4 Hz), 8.06 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4, 151.1, 140.1, 130.5, 124.3.

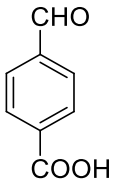


4-Benzoylbenzaldehyde (4p): The title compound was prepared according to the general procedure A using (4-benzoylphenyl)boronic acid (1 equiv, 0.2 mmol, 45.2 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (31.5 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.01 (m, 2H), 7.92 (m, 2H), 7.82-7.79 (m, 2H), 7.63-7.61 (m, 1H), 7.55-7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.8, 191.6, 142.6, 138.5, 136.8, 133.1, 130.3, 130.1, 129.5, 128.5.

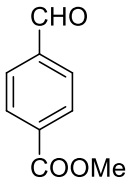


Terephthalaldehyde (4q): The title compound was prepared according to the general procedure

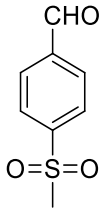
A using (4-formylphenyl)boronic acid (1 equiv, 0.2 mmol, 30.0 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (15.6 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.13 (s, 2H), 8.05 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.5, 140.0, 130.1.



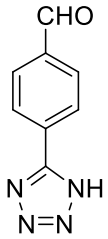
4-Formylbenzoic acid (4r): The title compound was prepared according to the general procedure A using 4-boronobenzoic acid (1 equiv, 0.2 mmol, 33.2 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (16.5 mg, 55%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.10 (s, 1H), 8.12 (m, 2H), 8.01 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 193.4, 167.0, 139.3, 136.1, 130.4, 130.0.



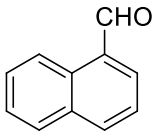
Methyl 4-formylbenzoate (4s): The title compound was prepared according to the general procedure A using (4-(methoxycarbonyl)phenyl)boronic acid (1 equiv, 0.2 mmol, 36 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (20.0 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.17 (d, 2H, J = 8.4 Hz), 7.93 (d, 2H, J = 8.4 Hz), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.6, 166.0, 139.2, 135.1, 130.2, 129.5, 52.6.



4-(Methylsulfonyl)benzaldehyde (4t): The title compound was prepared according to the general procedure A using (4-(methylsulfonyl)phenyl)boronic acid (1 equiv, 0.2 mmol, 40.0 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (18.8 mg, 51%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.15 (s, 1H), 8.16 (s, 4H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 193.1, 130.7, 129.8, 128.2, 116.2, 43.6.

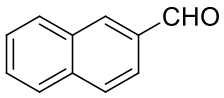


4-(1H-tetrazol-5-yl)benzaldehyde (4u): The title compound was prepared according to the general procedure A using (4-(1H-tetrazol-5-yl)phenyl)boronic acid (1 equiv, 0.2 mmol, 38.0 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (17.8 mg, 51%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.11 (s, 1H), 8.27 (m, 2H), 8.13 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 193.2, 138.1, 130.8, 130.1, 129.9, 128.1.

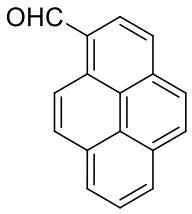


1-Naphthaldehyde (4v): The title compound was prepared according to the general procedure A using naphthalen-1-ylboronic acid (1 equiv, 0.2 mmol, 34.4 mg) and glyoxylic acid monohydrate

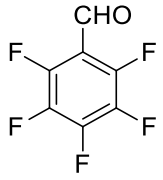
(1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a light yellow solid after silica gel chromatography (20.9 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.385 (s, 1H), 9.26 (d, 1H, *J* = 8.7 Hz), 8.07 (t, 1H, *J* = 8.1 Hz), 7.97-7.89 (m, 2H), 7.71-7.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.6, 136.7, 135.3, 133.7, 131.4, 130.5, 129.1, 128.5, 127.0, 124.9.



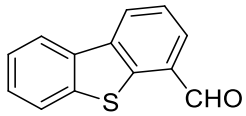
2-Naphthaldehyde (4w): The title compound was prepared according to the general procedure A using naphthalen-2-ylboronic acid (1 equiv, 0.2 mmol, 34.4 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a light yellow solid after silica gel chromatography (25.3 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.32 (s, 1H), 8.01-7.88 (m, 4H), 7.67-7.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3, 136.5, 134.5, 134.1, 132.7, 129.5, 129.1, 128.1, 127.1, 122.8.



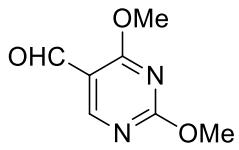
Pyrene-1-carbaldehyde (4x): The title compound was prepared according to the general procedure A using pyren-1-ylboronic acid (1 equiv, 0.2 mmol, 49.2 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a light yellow solid after silica gel chromatography (32.7 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.67 (s, 1H), 9.25 (d, 1H, *J* = 9.3 Hz), 8.28 (d, 1H, *J* = 8.1 Hz), 8.21-7.92 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 135.3, 131.2, 130.9, 130.8, 130.6, 130.6, 130.3, 127.2, 127.1, 127.0, 126.7, 126.5, 124.4, 123.9, 122.8.



2,3,4,5,6-Pentafluorobenzaldehyde (4y): The title compound was prepared according to the general procedure A using (perfluorophenyl)boronic acid (1 equiv, 0.2 mmol, 42.4 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography. NMR yield with dimethyl maleate as an internal standard (51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.6, 149.2, 149.1, 147.1, 146.9, 145.7, 145.6, 143.6, 143.5, 139.6, 139.4, 139.3, 139.2, 139.1, 136.2, 136.1, 136.0, 135.9, 111.0.^{19}F NMR (282 MHz, $CDCl_3$): δ -141.77--141.91 (m, 1F), -142.76--142.83 (m, 2F),-158.78--158.92 (m, 2F);

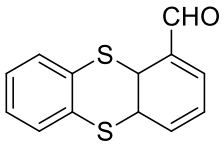


Dibenzo[b,d]thiophene-4-carbaldehyde (4z): The title compound was prepared according to the general procedure A using dibenzo[b,d]thiophen-4-ylboronic acid (1 equiv, 0.2 mmol, 45.6 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a colorless oil after silica gel chromatography (28.9 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.29 (s, 1H), 8.42 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 8.23-8.2 (m, 1H), 8.00-7.95 (m, 2H), 7.67 (t, 1H, J_1 = 7.5 Hz), 7.54-7.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3, 141.7, 137.4, 133.6, 132.9, 130.7, 127.4, 127.0, 124.8, 124.4, 123.1, 121.5.

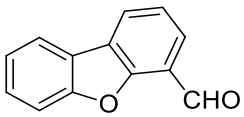


2,4-Dimethoxypyrimidine-5-carbaldehyde (4aa): The title compound was prepared according

to the general procedure A using (2,4-dimethoxypyrimidin-5-yl)boronic acid (1 equiv, 0.2 mmol, 36.8 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a light brown solid after silica gel chromatography (26.2 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.77 (s, 1H), 4.11 (s, 3H), 4.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.4, 171.1, 167.6, 161.4, 112.3, 55.7, 54.6.

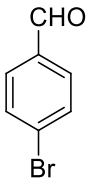


4a,10a-Dihydrothianthrene-1-carbaldehyde (4ab): The title compound was prepared according to the general procedure A using (4a,10a-dihydrothianthren-1-yl)boronic acid (1 equiv, 0.2 mmol, 52.4 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a light brown solid after silica gel chromatography (34.5 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.59 (d, 1H, J_1 = 0.3 Hz), 7.84 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 7.72 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.5 Hz), 7.58-7.50 (m, 2H), 7.42-7.28 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0, 140.0, 137.8, 135.7, 134.8, 134.0, 133.7, 129.2, 128.9, 128.8, 128.5, 128.1, 127.4.

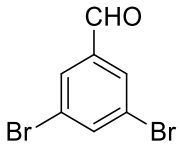


Dibenzo[b,d]furan-4-carbaldehyde (4ac): The title compound was prepared according to the general procedure A using dibenzo[b,d]furan-4-ylboronic acid (1 equiv, 0.2 mmol, 42.4 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a light yellow solid after silica gel chromatography (29.4 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.59 (s, 1H), 8.18 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.2 Hz), 7.99-7.93 (m, 2H), 7.69 (d, 1H, J = 8.4 Hz), 7.56-7.38 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.4, 156.6, 155.9, 128.1, 127.5, 126.7,

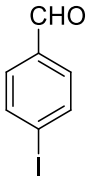
126.0, 123.5, 122.9, 122.8, 121.3, 120.8, 112.2.



4-Bromobenzaldehyde (4ad): The title compound was prepared according to the general procedure A using (4-bromophenyl)boronic acid (1 equiv, 0.2 mmol, 40.2 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (24.1 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.77-7.67 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.9, 134.9, 132.3, 130.8, 129.6.

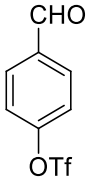


3,5-Dibromobenzaldehyde (4ae): The title compound was prepared according to the general procedure A using (3,5-dibromophenyl)boronic acid (1 equiv, 0.2 mmol, 55.9 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (26.4 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.94-7.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.1, 139.6, 138.9, 131.2, 123.9.

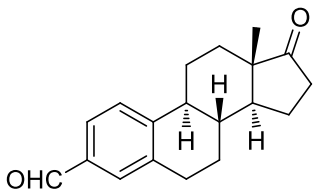


4-Iodobenzaldehyde (4af): The title compound was prepared according to the general procedure A using (4-iodophenyl)boronic acid (1 equiv, 0.2 mmol, 49.6 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (35.7 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.95 (s, 1H), 7.91 (d,

2H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 138.4, 135.6, 130.8, 102.8.

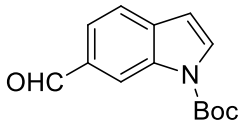


4-Formylphenyl trifluoromethanesulfonate (4ag): The title compound was prepared according to the general procedure A using (4-(((trifluoromethyl)sulfonyl)oxy)phenyl)boronic acid (1 equiv, 0.2 mmol, 57.0 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (35.6 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.99 (d, 2H, *J* = 8.7 Hz), 7.58 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.2, 153.2, 135.9, 131.7, 121.5, 118.6 (q, *J* = 319 Hz).

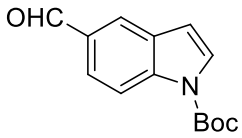


(*8R,9S,13S,14S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3-carbaldehyde (4ah): The title compound was prepared according to the general procedure A using ((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)boronic acid (1 equiv, 0.2 mmol, 59.6 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a white solid after silica gel chromatography (42.4 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.65-7.60 (m, 2H), 7.46-7.43 (m, 1H), 3.0-2.98 (m, 2H), 2.49-2.34 (m, 3H), 2.18-1.97 (m, 4H), 1.65-1.44 (m, 6H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.2, 192.0, 146.9, 137.4, 134.1, 130.0, 127.1, 125.9, 50.4, 47.7, 44.7, 37.6, 35.6, 31.4, 29.0,

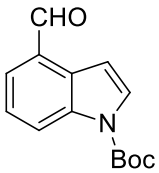
26.0, 25.4, 21.4, 13.6.



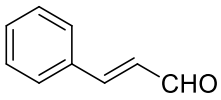
Indole-6-carboxaldehyde (4ai): The title compound was prepared according to the general procedure A using (1-(tert-butoxycarbonyl)-1H-indol-6-yl)boronic acid (1 equiv, 0.2 mmol, 52.2 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a light yellow solid after silica gel chromatography (24.5 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.67 (s, 1H), 7.78 (m, 2H), 7.66 (d, 1H, J_1 = 8.1 Hz), 6.64 (d, 1H, J_1 = 3.6 Hz), 1.70 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3, 149.2, 135.5, 134.9, 133.0, 129.6, 122.9, 121.4, 118.7, 107.3, 84.7, 28.1.



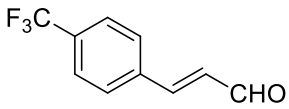
Indole-5-carboxaldehyde (4aj): The title compound was prepared according to the general procedure A using (1-(tert-butoxycarbonyl)-1H-indol-5-yl)boronic acid (1 equiv, 0.2 mmol, 52.2 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a light yellow solid after silica gel chromatography (30.9 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.06 (s, 1H), 8.47 (d, 1H, J_1 = 8.4 Hz), 8.09 (s, 1H), 7.85 (d, 1H, J_1 = 8.7 Hz), 7.68 (d, 1H, J_1 = 3.9 Hz), 1.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.1, 149.2, 138.7, 131.7, 130.7, 127.7, 125.1, 124.2, 115.6, 107.8, 84.6, 28.1.



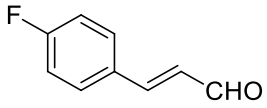
Indole-5-carboxaldehyde (4ak): The title compound was prepared according to the general procedure A using (1-(tert-butoxycarbonyl)-1H-indol-4-yl)boronic acid (1 equiv, 0.2 mmol, 52.2 mg) and glyoxylic acid monohydrate (1.05 equiv, 0.21 mmol, 19.4 mg) to afford the title compounds a light yellow solid after silica gel chromatography (31.9 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.24 (s, 1H), 8.47 (d, 1H, J_1 = 8.1 Hz), 7.78-7.71 (m, 2H), 7.49-7.39 (m, 2H), 1.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.6, 149.4, 136.0, 129.0, 128.9, 128.9, 128.4, 123.8, 121.0, 106.7, 84.5, 28.2.



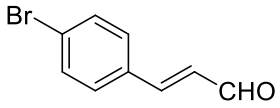
***trans*-Cinnamaldehyde (9a):** The title compound was prepared according to the general procedure C using (*E*)-styrylboronic acid (1.2 equiv, 0.12 mmol, 17.8 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a colorless oil after silica gel chromatography (9.3 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (d, 1H, J = 7.8 Hz), 7.57-7.50 (m, 2H), 7.44-7.42 (m, 4H), 6.70 (dd, 1H, J_1 = 16.2 Hz, J_2 = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.8, 152.8, 134.0, 131.3, 129.1, 128.6, 128.5.



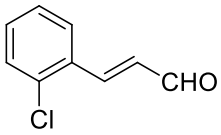
(*E*)-3-(4-(Trifluoromethyl)phenyl)acrylaldehyde (9b): The title compound was prepared according to the general procedure C using (*E*)-(4-(trifluoromethyl)styryl)boronic acid (1.2 equiv, 0.12 mmol, 25.9 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a colorless oil after silica gel chromatography (14.0 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (d, 1H, J = 7.5 Hz), 7.71 (s, 4H),7.53 (d, 1H, J = 16.2 Hz), 6.80 (dd, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.2, 150.3, 137.3, 132.6 (q, J = 32.9Hz), 130.5,128.6, 126.0 (d, J = 3.6 Hz), 123.7 (q, J= 270.8 Hz).



***(E)*-3-(4-Fluorophenyl)acrylaldehyde (9c):** The title compound was prepared according to the general procedure C using (*E*)-(4-fluorostyryl)boronic acid (1.2 equiv, 0.12 mmol, 19.9 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a colorless oil after silica gel chromatography (10.1 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.69 (d, 1H, *J* = 7.5 Hz), 7.59-7.56 (m, 2H),7.44 (d, 1H, *J* = 16.0 Hz), 7.59-7.56 (m, 2H), 6.65 (dd, 1H, J_1 = 15.5 Hz, J_2 = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3, 151.2, 130.4, 130.3, 128.3, 128.2, 116.2 (q, *J* = 21.2 Hz).

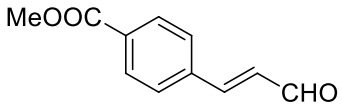


***(E)*-3-(4-Bromophenyl)acrylaldehyde (9d):** The title compound was prepared according to the general procedure C using (*E*)-(4-bromostyryl)boronic acid (1.2 equiv, 0.12 mmol, 27.2 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a white solid after silica gel chromatography (11.6 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (d, 1H, *J* = 7.5 Hz), 7.59-7.56 (m, 2H), 7.45-7.39 (m, 3H), 6.70 (dd, 1H, J_1 = 15.9 Hz, J_2 = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.3, 151.1, 132.9, 132.4, 129.8, 129.1, 125.7.

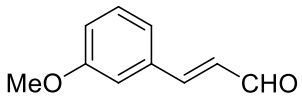


***(E)*-3-(2-Chlorophenyl)acrylaldehyde (9e):** The title compound was prepared according to the general procedure C using (*E*)-(2-chlorostyryl)boronic acid (1.2 equiv, 0.12 mmol, 21.9 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a colorless oil after silica gel chromatography (9.7 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76

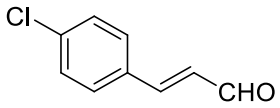
(d, 1H, J = 7.8 Hz), 7.95 (d, 1H, J = 16.2 Hz), 7.69-7.65 (m, 1H), 7.48-7.26 (m, 3H), 6.70 (dd, 1H, J_1 = 15.9 Hz, J_2 = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.6, 148.0, 135.2, 132.0, 130.6, 130.4, 129.1, 127.9, 127.3.



***(E)*-Methyl 4-(3-oxoprop-1-en-1-yl)benzoate (9f):):** The title compound was prepared according to the general procedure C using (*E*)-(4-(methoxycarbonyl)styryl)boronic acid (1.2 equiv, 0.12 mmol, 24.7 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a white solid after silica gel chromatography (15.2 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.74 (d, 1H, J = 7.5 Hz), 8.09 (d, 2H, J = 8.1 Hz), 7.63 (d, 2H, J = 8.4 Hz), 7.50 (d, 1H, J = 15.9 Hz), 6.79 (dd, 1H, J_1 = 16.2 Hz, J_2 = 7.5 Hz), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.3, 166.2, 150.8, 138.1, 132.2, 130.4, 130.3, 128.3, 52.4.

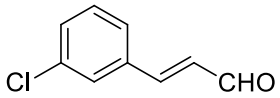


***(E)*-3-(3-Methoxyphenyl)acrylaldehyde (9g):** The title compound was prepared according to the general procedure C using (*E*)-(3-methoxystyryl)boronic acid (1.2 equiv, 0.12 mmol, 21.4 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a colorless oil after silica gel chromatography (9.2 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (d, 1H, J = 7.5 Hz), 7.45 (d, 1H, J = 16.0 Hz), 7.37-7.34 (m, 1H),7.16 (d, 1H, J = 8.0 Hz), 7.09-7.08 (m, 1H), 7.01-6.99 (m, 1H), 6.71 (dd, 1H, J_1 = 16.0 Hz, J_2 = 7.5 Hz), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 159.9, 152.6, 135.2, 130.0, 128.8, 121.1, 117.0, 113.2, 55.3.

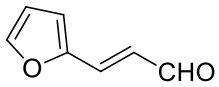


***(E)*-3-(4-Chlorophenyl)acrylaldehyde (9h):** The title compound was prepared according to the

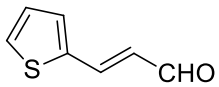
general procedure C using (*E*)-(4-chlorostyryl)boronic acid (1.2 equiv, 0.12 mmol, 21.9 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a colorless oil after silica gel chromatography (10.0 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (d, 1H, J = 7.5 Hz), 7.50-7.38 (m, 5H), 6.67 (dd, 1H, J_1 = 16.2 Hz, J_2 = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.4, 151.1, 137.3, 132.5, 129.6, 129.4, 129.0.



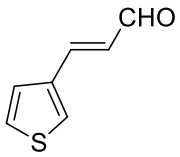
***(E)*-3-(3-chlorophenyl)acrylaldehyde (9i):** The title compound was prepared according to the general procedure C using (*E*)-(3-chlorostyryl)boronic acid (1.2 equiv, 0.12 mmol, 21.9 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a colorless oil after silica gel chromatography (10.2 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (d, 1H, J = 7.5 Hz), 7.55 (s, 1H),7.46-7.36 (m, 4H), 6.71 (dd, 1H, J_1 = 16.0 Hz, J_2 = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.2, 150.6, 135.7, 135.1, 131.0, 130.2, 129.6, 128.1, 126.4.



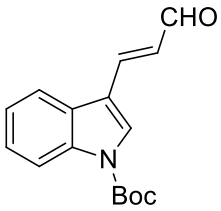
(*E*)-3-(furan-2-yl)acrylaldehyde (9j): The title compound was prepared according to the general procedure C using (E)-(2-(furan-2-yl)vinyl)boronic acid (1.2 equiv, 0.12 mmol, 16.5 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a white solid after silica gel chromatography (6.5 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.61 (d, 1H, J = 8.0 Hz), 7.56-7.56 (m, 1H), 7.20 (d, 1H, J = 15.5 Hz), 6.77-6.76 (m, 1H), 6.57 (dd, 1H, J_1 = 15.5 Hz, J_2 = 8 Hz), 6.52-6.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.8, 150.5, 145.8, 137.7, 125.9, 116.6, 112.8.



(E)-3-(thiophen-2-yl)acrylaldehyde (9k): The title compound was prepared according to the general procedure C using (E)-(2-(thiophen-2-yl)vinyl)boronic acid (1.2 equiv, 0.12 mmol, 18.5 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a yellow oil after silica gel chromatography (10.1 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 (d, 1H, J = 7.8 Hz), 7.61-7.49 (m, 2H), 7.36-7.35 (m, 1H), 7.12-7.09 (m, 1H), 6.50 (dd, 1H, J_1 = 15.6 Hz, J_2 = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.9, 144.4, 139.3, 132.1, 130.4, 128.5, 127.4.



(E)-3-(thiophen-3-yl)acrylaldehyde (9l): The title compound was prepared according to the general procedure C using (E)-(2-(thiophen-3-yl)vinyl)boronic acid (1.2 equiv, 0.12 mmol, 18.5 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a yellow oil after silica gel chromatography (9.7 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (d, 1H, J = 7.8 Hz), 7.65-7.64 (m, 1H), 7.53-7.34 (m, 3H), 6.55 (dd, 1H, J_1 = 15.9 Hz, J_2 = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.8, 145.8, 137.4, 129.6, 128.4, 127.5, 125.3.



(E)-tert-butyl 3-(3-oxoprop-1-en-1-yl)-1H-indole-1-carboxylate (9m): The title compound was prepared according to the general procedure C using (E)-(2-(1-(tert-butoxycarbonyl)-1H-indol-3-yl)vinyl)boronic acid (1.2 equiv, 0.12 mmol, 34.5 mg) and glyoxylic acid monohydrate (1.0 equiv, 0.1 mmol, 9.2 mg) to afford the title compounds a colorless oil after silica gel chromatography (13.8 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.68 (d, 1H, J = 7.5 Hz), 8.22-

8.20 (m, 1H), 7.96 (s, 1H), 7.85-7.83 (m, 1H), 7.62 (d, 1H, J = 16.0 Hz), 7.43-7.35 (m, 2H), 6.84 (dd, 1H, J_1 = 16.0 Hz, J_2 = 7.5 Hz), 1.70 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 148.9, 144.4, 136.2, 129.7, 127.9, 127.3, 125.5, 123.8, 120.1, 116.6, 115.6, 85.0, 28.0.

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Chapter 3

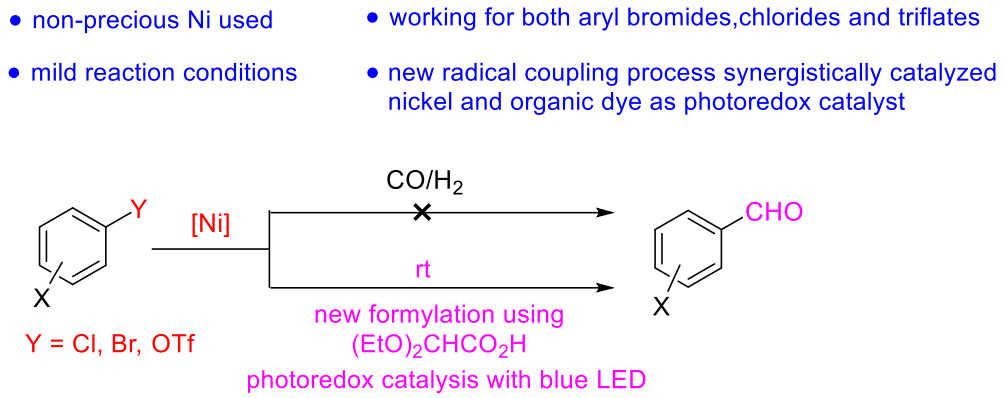
Visible Light Promoted Nickel and Organic Co-Catalyzed Formylation Reaction of Aryl Halides and Triflates and Vinyl Bromides Using Diethoxyacetic Acid as a Formyl Equivalent

3.1 Introduction

Arguably, aromatic aldehydes are the most fundamentally important substances used in organic synthesis.[1] Therefore, the availability of predictable and chemoselective methods for formylation of aromatic compounds will continue to have a profound impact on chemical synthesis. Classical methods for the preparation of aromatic aldehydes, such as the Reimer–Tiemann, Vielsmeier–Haack, Gattermann–Koch and Duff reactions,[2] require the use of large amounts of reagents and multi-step sequences. In addition, these processes frequently produce at least stoichiometric amounts of by-products. Furthermore, the lack of control of the regiochemical course of these reactions makes it difficult to employ them to introduce aldehyde functionality at desired positions. As a result of these limitations, state-of-the-art formylation technologies employing transition metal catalysts have been developed. The pioneering work on palladium catalyzed formylation of aryl halides, using CO and H_2, by Heck[3] triggered significant interests in developing more efficient protocols. Impressive results from studies of this topic have come from the laboratories of Pri-Bar, Stille, Beller, Manabe, Skrydstrup, Kotsuki and Liu (see introduction part).[4] However, the approaches developed by these groups generally require high reaction temperatures, aryl-bromides or -iodides as substrates, and precious palladium complexes as promoters.[5] Moreover, in some cases, toxic CO gas[4a-c, 4h-4i] and tin compounds[4b] are used. These issues highlight the demand more cost-effective, environmentally

friendly and mild protocols for aryl-aldehyde synthesis.

Scheme 3.1. New Nickel-Photoredox Catalyzed Methods for Formylation of Aryl Halides and Triflates



Although significant advances have been made recently in the development of inexpensive nickel-catalyzed cross-coupling reactions,[6] no reports exist describing nickel catalyzed formylation reactions. This deficiency results from the low reactivity and difficulty of reductive elimination towards CO, demonstrated by Heck (Scheme 3.1).[1c,3] Furthermore, in reported palladium catalyzed formylations, more active aryl bromides and iodides are typically required for efficient transformations. In contrast, very few studies of this process have focused on arylchlorides,[4,7] which are more broadly available and cheaper. Clearly, a new nickel promoted formylation strategy, which would enable aryl chlorides to serve as coupling partners, would have substantial synthetic utility within both academic and industrial settings. Toward this end, we have carried out a recent investigation that uncovered a new synergistic nickel and organic photoredox catalyzed formylation process. In this reaction, 2,2-diethoxyacetic acid serves as the formylation reagent, thus avoiding the need for CO. The process combines a organic dye mediated photoredox catalyzed formyl radical forming reaction with a nickel

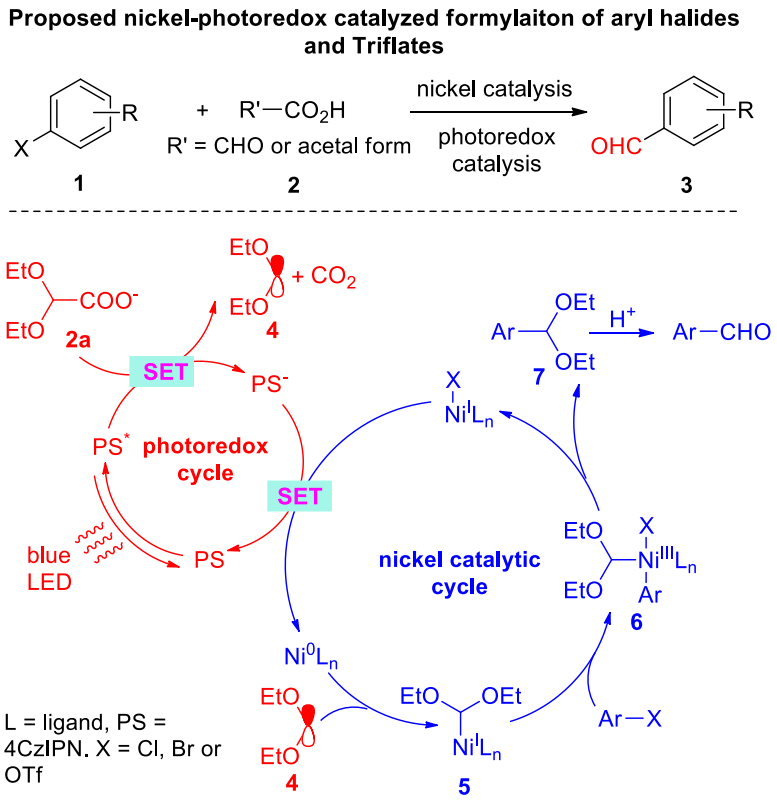
promoted radical coupling process. Moreover, readily available aryl chlorides can serve as substrates (Scheme 3.1) and the transformation employs simple and mild conditions that tolerate a plethora of functional groups and it does not produce abundant amounts of chemical wastes.

3.2 Research Plan

Although nickel catalyzed reactions of aryl halides with CO/H_2 fail to generate formylation products,[3] the capacity of Ni catalysts to activate C-Cl bonds of aryl chlorides[6] to produce highly reactive organic radicals in cross-coupling reactions is highly attractive.[8] We reasoned that generation of a formyl radical equivalent in the presence of an aryl chloride and a Ni catalyst might lead to a cross coupling process that corresponds to the long sought after Ni promoted formylation reaction. Accordingly, the key to the successful development of this process is the identification of a new reagent that would efficiently produce a formyl radical equivalent under conditions that are compatible with nickel catalysis. The results of studies of photochemical decarboxylation reactions of glyoxylic acid and its acetals by us,[9] and related recent efforts by MacMillan, Doyle and Overman,[10] indicated that these inexpensive and abundant substances might be ideal precursors of formyl radical equivalents. This consideration suggested that merging visible light photoredox catalysis with nickel catalysis, in a manner earlier demonstrated by MacMillan, Doyle and Molander,[11,12] would serve as the foundation for the new transformation. Specifically, we hypothesize that photoredox-mediated single electron transfer (SET) oxidation of glyoxylic acid or its acetals followed by loss of CO_2 would form a formyl radical equivalent **4** (Scheme 3.2). Reaction of the Ni(0) complex with radical **4** would form the diacetal-Ni(I) intermediate **5**.[12d] Oxidative activation of aryl halide **1** by **5** then would generate the putative Ni(III) complex **6**, which should undergo reductive elimination to produce

the desired aryl diacetal **7**, a substance that can be easily converted to aryl aldehyde **3** under aqueous acid work up conditions.

Scheme 3.2 Proposed Nickel-Photoredox Catalyzed Formylation of Aryl Halides and Triflates



Thus far, ruthenium and iridium complexes have been typically used as photocatalysts in photoredox-nickel catalyzed reactions. It is somewhat surprising that far fewer reports exist describing reactions of this type in which organic dyes serve as photocatalysts, despite the relatively lower costs, wider availability, higher stabilities and superior properties of these substances as compared to those of their inorganic and organometallic counterparts in many cases.[13] Because of this comparison, we decided to exploit organic dyes as photoredox catalysts for the new formylation reaction. Among the family of carbazoyl-dicyanobenzenes reported by

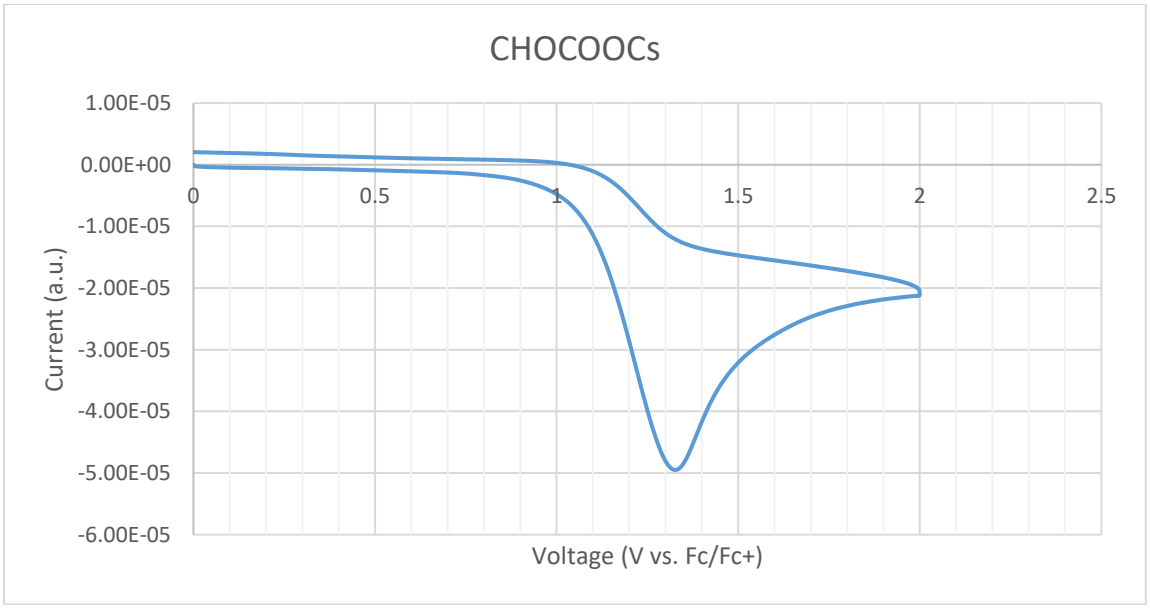
Adachi *et al*. as light-harvesters in organic light emitting diodes, we were attracted to the readily available 1,2,3,5-tetrakis-(carbazol-yl)-4,6-dicyanobenzene (4CzIPN).[14,15] The high reduction potential of the photoexcited state of 4CzIPN (E^{*red}= +1.35 V vs. SCE) augurs well for the use of this substance to promote photooxidative decarboxylation reactions.

3.3 Results and Discussion

3.3.1 Optimization of Reaction Conditions

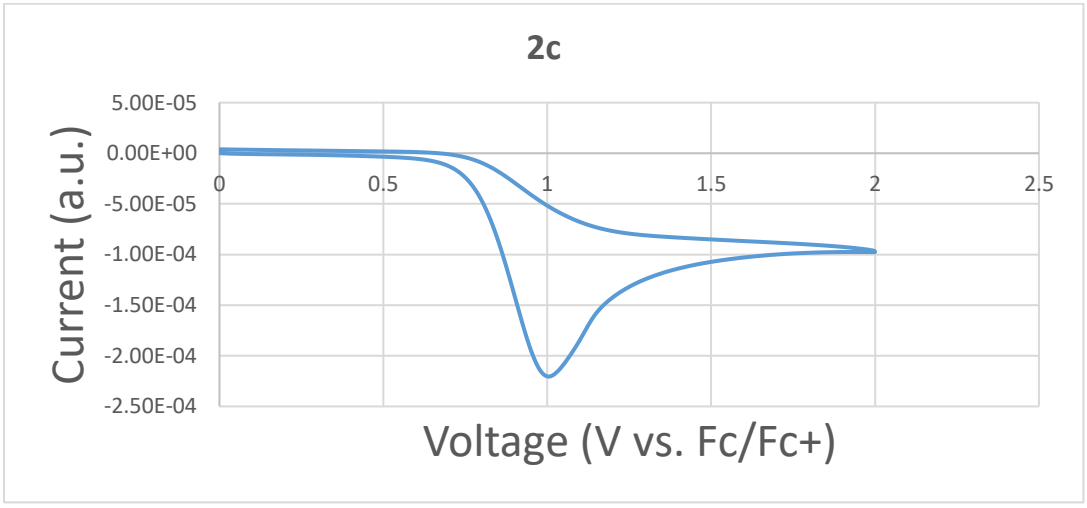
In initial studies probing the feasibility of the new formylation reaction, we used glyoxylic acid as the formyl radical source. Unfortunately none of the desired aldehyde product **3a** was produced when a mixture of 4-bromobenzonitrile (**1a**), glyoxylic acid monohydrate, $NiCl_2$•glyme (glyme = ethylene glycol dimethyl ether), 4CzIPN, 4,4′-di-tert-butyl-2,2′-bipyridine (dtbbpy) and Cs_2CO_3 in DMF at rt is irradiated using blue-light-emitting diodes (LEDs) for 24 h (Table 1, entry 1). We reasoned that the failure of this reaction might be associated with the difficulty of promoting SET oxidation of glyoxylic acid because of its high oxidation potential (E^{ox} = +1.33 V vs SCE, CH_3CN, Figure 3.1) and lability.[16] A careful search uncovered the fact that the readily available and inexpensive diethylacetal derivative of glyoxylic acid **2a**, generated by hydrolysis of ethyl diethoxyacetate ($0.56/g),[17] has a much lower oxidation potential [E^{ox} (**2a** Cs salt) = +0.95 V vs SCE, CH_3CN (Figure 3.2). Thus, this acetal should be more readily oxidized by SET to the excited state of 4CzIPN. Significantly, irradiation of a mixture containing **1a**, **2a**, $NiCl_2$•glyme, 4CzIPN, dtbbpy and Cs_2CO_3 in DMF at rt using blue-light-emitting diodes (LEDs) leads to smooth formation of the formylation product **3a** in 72% yield (Table 3.1, entry 2).

Figure 3.1. Cyclicvoltammogram of $CHOCO_2Cs$.



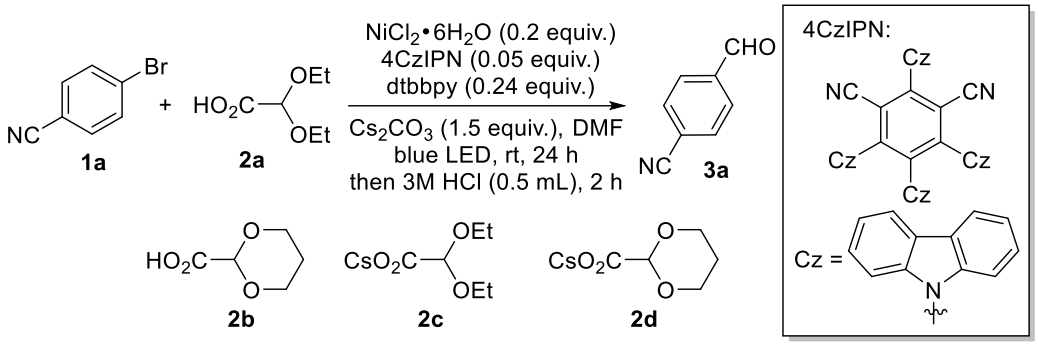
Bu_4NPF_6 as supporting electrolyte (0.1 M) and referenced against ferrocene/ferrocenium redox couple (scan rate: 100 mV/s) in CH_3CN. E^{ox} ($CHOCO_2Cs$) = +1.33 V vs SCE.

Figure 3.2. Cyclic Voltammogram of $(EtO)_2CHCO_2Cs$ **2c**.



Bu_4NPF_6 as supporting electrolyte (0.1 M) and referenced against ferrocene/ferrocenium redox couple (scan rate: 100 mV/s) in CH_3CN.E^{ox} ($CHOCO_2Cs$) = +0.95 V vs SCE.

Table 3.1. Exploration and Optimization [a]

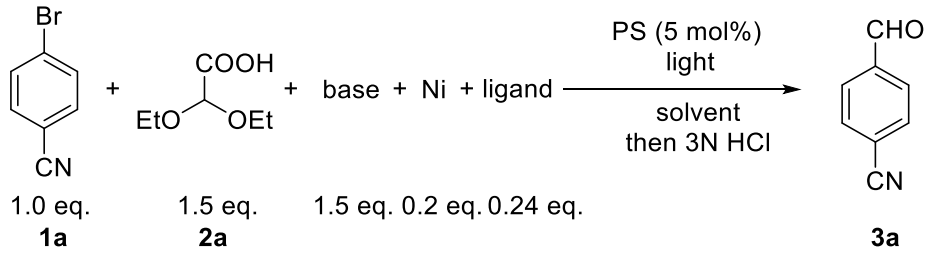


entry	deviation from "standard conditions"[a]	% yield[b]
1	$CHOCO_2H•H_2O$ instead of **2a**	0
2	$NiCl_2$•glyme instead of $NiCl_2•6H_2O$	72
3	none	75 (75)[c]
4	9-mesityl-10-methylacridinium instead of 4CzIPN	0
5	Eosin Y instead of 4CzIPN	0
6	Na_2CO_3instead of Cs_2CO_3	0
7	[**1a**] of reaction is 0.2 M instead of 0.02 M	19
8	[**1a**] of reaction is 0.04 M instead of 0.02 M	45
9	**2b** instead of **2a**	25
10	**2c** instead of **2a**	0
11	**2d** instead of **2a**	0
12	no light	trace
13	without $NiCl_2•6H_2O$	0
14	without 4CzIPN	trace
15	without N_2 protection	30

[a] Standard reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $NiCl_2•6H_2O$ (0.04 mmol), dtbbpy (0.048 mmol), 4CzIPN (0.01mmol), Cs_2CO_3 (0.3 mmol), DMF (10 mL), irradiated with the blue LEDs at rt for 24 h then 0.5 mL of 3N HCl was added and see SI for detail. [b] Yields were determined by using ^1H NMR with dimethyl maleate as an internal standard. [c] Isolated yields.

Encouraged by this preliminary result, we evaluated the effects of several parameters, including Ni salts, photosensitizers, bases, solvents, ligands and light sources on this transformation (Table 3.2). The results show that use of a combination of $NiCl_2$•glyme, 4CzIPN, dtbbpy and Cs_2CO_3 in DMF along with irradiation using a blue LED leads to formation of **3a** in a high yield (72%, entry 2 and Table 3.2). A slightly higher efficiency is achieved when $NiCl_2$•glyme is replaced by the less expensive $NiCl_2$•$6H_2O$ (entry 3, 75% yield). The findings also show that the photocatalyst 4CzIPN plays a crucial role in the process. Other photocatalysts, including commonly used dyes such as 9-mesityl-10-methylacridinium and eosin Y (entries 4-5) (for more dyes screened, see Table 3.2), fail to promote aldehyde formation. Other observations show that Cs_2CO_3 is the best base for the process (entry 6 and Table 3.2) and that the concentration of aryl bromide **1a** strongly influences the efficiency of the reaction. Specifically, irradiation of solutions containing 0.02, 0.04 and 0.2 M **1a** (entries 3 and 7-8) generated **3a** in respective 75%, 45% and 19% yields. Interestingly, cyclic acetal acid **2b** participates in this reaction but the yields are appreciably lower (entry 9). Furthermore, when the Cs salts of **2c** and **2d** are utilized, the formylation reaction does not take place (entries 10-11). As expected, light irradiation, and the nickel and 4CzIPN catalysts are essential for success of the process (entries 12-14). Finally, the presence of molecular oxygen leads to a decreased reaction efficiency (entry 15).

Table 3.2 Exploration and Optimization [a]



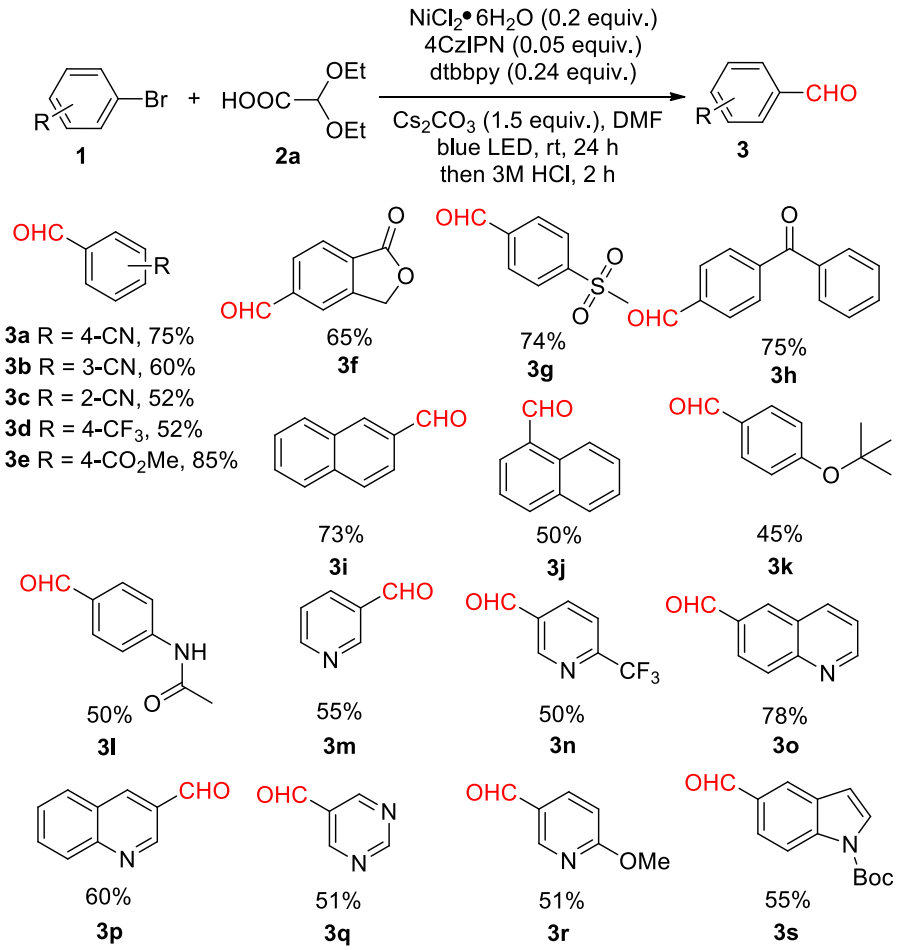
entry	photosensitizers	base	solvent	light	[c]M	Ligand	Ni	yield[a,b]
1	eosin Y	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$•glyme	No product
2	eosin B	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$•glyme	No product
3	rose Bengal	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$•glyme	No product
4	rhodamine B	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$•glyme	No product
5	rhodamine 6G	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$•glyme	No product
6	9,10-dicyanoanthracene	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$•glyme	No product
7	2,4,6-triphenylpyrylium tetrafluoroborate	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$•glyme	No product
8	quinizarin	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	No product
9	9-mesityl-10-methylacridinium	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	No product
10	4CzIPN	Cs_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	14%
11	4CzIPN	$(nBu)_4NOH$ (40% aq.)	DMF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	No product
12	4CzIPN	K_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	8%
13	4CzIPN	KOH	DMF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	1%
14	4CzIPN	$CsOHH_2O$	DMF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	4.1%
15	4CzIPN	Na_2CO_3	DMF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	No product
16	4CzIPN	K_2HPO_4	DMF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	No product

17	4CzIPN	Cs_2CO_3	CH_3CN	CFL	0.2	dtbbpy	$NiCl_2$*glyme	7%
18	4CzIPN	Cs_2CO_3	THF	CFL	0.2	dtbbpy	$NiCl_2$*glyme	Trace
19	4CzIPN	Cs_2CO_3	DMSO	CFL	0.2	dtbbpy	$NiCl_2$*glyme	8%
20	4CzIPN	Cs_2CO_3	Toluene	CFL	0.2	dtbbpy	$NiCl_2$*glyme	Trace
21	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.2	dtbbpy	$NiCl_2$*glyme	30%
22	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.2	bpy	$NiCl_2$*glyme	12%
23	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.2	1,10-Phenanthroline	$NiCl_2$•glyme	6%
24	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.2	bathophenanthroline	$NiCl_2$•glyme	9%
25	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.4	dtbbpy	$NiCl_2$•glyme	21%
26	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.04	dtbbpy	$NiCl_2$•glyme	44%
27	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.02	dtbbpy	$NiCl_2$•glyme	72%
28	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.02	dtbbpy	$Ni(acac)_2$	No product
29	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.02	dtbbpy	$Ni(dppf)Cl_2$	No product
30	4CzIPN	Cs_2CO_3	DMF	Blue LED	0.02	dtbbpy	$NiCl_2$•$6H_2O$	75%
31	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ [c]	Cs_2CO_3	DMF	Blue LED	0.02	dtbbpy	$NiCl_2$•$6H_2O$	47%

[a] Standard reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Ni (0.04 mmol), ligand (0.048 mmol), photosensitizer (0.01 mmol), base (0.3 mmol), DMF, irradiated with the light at rt for 24 h then 3N HCl aq solution (0.5 mL) was added. See method for detail. [b] Yields were determined by NMR using dimethyl maleate as an internal standard. [c] 2% was used.

3.3.2 Investigation of Substrate Scope

Scheme 3.3 Scope of the Formylation Reaction with Aryl Bromides



[a] Standard reaction conditions: unless specified, **1** (0.2 mmol), **2a** (0.3 mmol), $NiCl_2$•$6H_2O$ (0.04 mmol), dtbbpy (0.048 mmol), 4CzIPN (0.01 mmol), Cs_2CO_3 (0.3 mmol), DMF (10 mL), irradiated with the blue LEDs at rt for 24 h then 3N HCl (0.5 mL) was added and stirred for 2 h and see SI for detail. [b] Isolated yields.

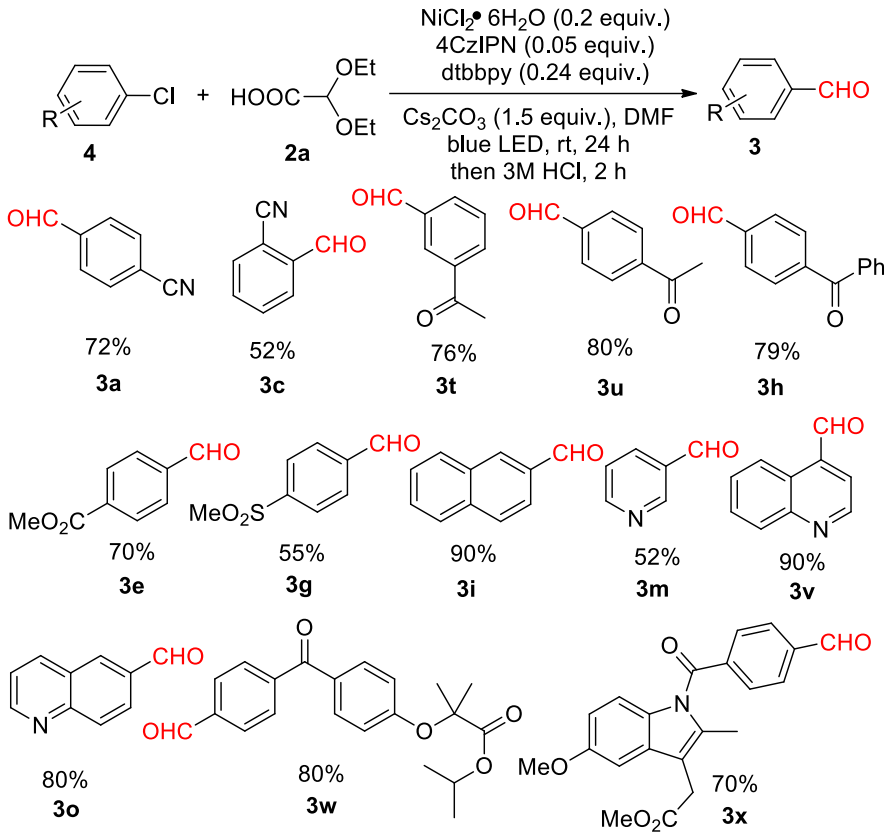
The aryl bromide scope of the transformation (Scheme 3.3) was explored using the optimized reaction conditions (Table 3.1, entry 3). Members of a series of structurally diverse aryl bromides were found to undergo highly efficient formylation reactions using diethoxyacetic

acid as the formyl equivalent. Although substituents at the *meta* and *para* positions of the aryl ring in these substrates have little effect on the efficiency of the process (eg. **3a** and **3b**), *ortho* substitution results in diminished yields (**3c**). Furthermore, the process tolerates a variety of functionality including a trifluoromethyl (**3d**), ester (**3e** and **3f**), methanesulfonyl (**3g**), ketone (**3h**), ether (**3k**), and amide (**3l**) groups. Polyaromatic bromides also serve as effective substrates in this reaction producing the corresponding aldehydes (**3i** and **3j**) in moderate to good yields. Moreover, electron rich aryl bromides react under the optimized conditions, but in only moderate yields (**3k** and **3l**). Of high significance is the fact that the formylation method can be employed to transform a broad range of pharmaceutically relevant heteroaromatic bromides, including those containing the pyridine, quinoline, pyrimidine and indole ring systems, to the corresponding aldehydes (**3m-3s**) in moderate to high yields.

Having developed the new protocol for the synthesis of aldehydes from aryl bromides, our attention turned to expanding the scope of the process to include more readily available and less expensive aryl chlorides (Scheme 3.4). As mentioned above, the development of methods to promote formylation of the chloride containing substrates using previously developed catalysts have been unsuccessful.[1c,3] Significantly, we observed that under the optimal conditions for reactions of their bromide counterparts, a broad range of aryl chlorides undergo formylation to form the corresponding aldehyde products in similarly high yields. Again, the reaction can be applied to generate aldehydes from aryl chlorides containing pharmaceutically relevant functionality, such as nitrile (**3a** and **3c**), ketone (**3h**, **3t** and **3u**), ester (**3e**), and methanesulfonyl (**3g**), fused aromatic (**3i**) and hetereocycle (**3m**, **3v** and **3o**) groups. Finally, we demonstrated that the mild reaction conditions enable the process to be employed for late-stage synthetic elaboration of biologically relevant substances, including fenofibrate (**3w**) and methyl

indomethacin (**3x**).

Scheme 3.4 Formylation Reactions of Aryl Chloride

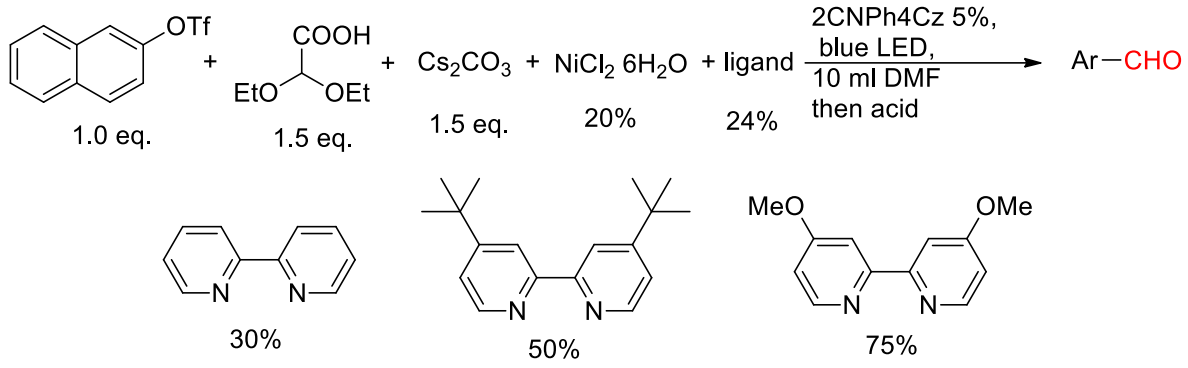


[a] Standard reaction conditions: unless specified, see Scheme 3 and SI for details. [b] Isolated yields.

Having established an efficient protocol for the synthesis of aldehyde from aryl halides, we next investigated the use of aryl triflates as coupling partners. Substrates of this type have not been used previously for formylation reactions. Significantly, when the more electron-rich ligand 4,4′-$(MeO)_2$-bpy (4,4′-dimethoxy-2,2′- bipyridine) is used along with the optimized conditions described above, a variety of aryl triflates are converted to the corresponding aromatic aldehydes (**3a**, **3d, 3e, 3i, 3t** and **3u**) in Scheme 3.6 (Scheme 3.5 for the results of optimization studies). Moreover, the new formylation procedure is applicable to late-stage synthetic elaboration of the

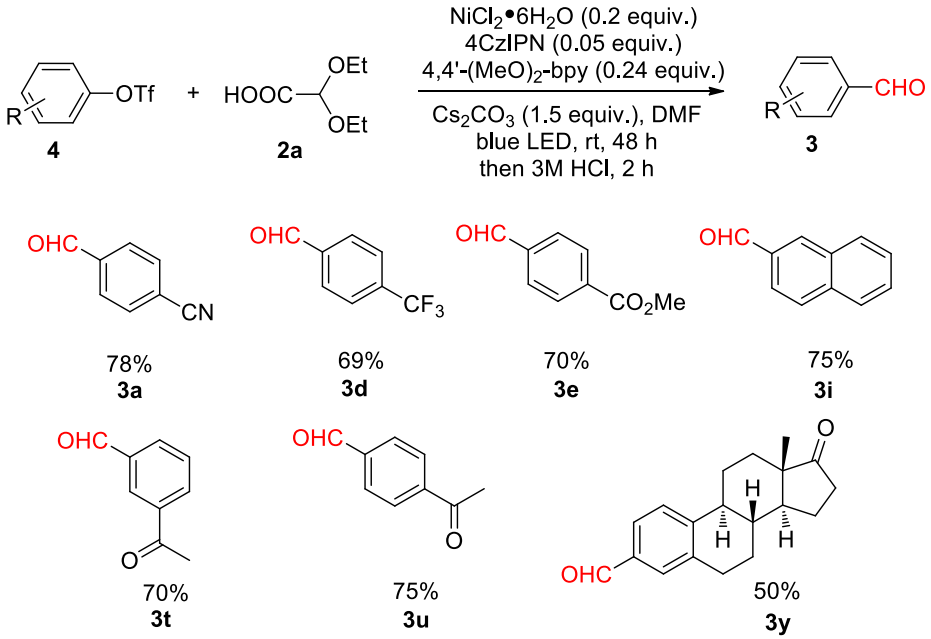
biologically relevant substances such as estrone (**3y**).

Scheme 3.5 Optimization of Reaction Conditions in Formylation Reactions of Aryl Triflates



[a] Standard reaction conditions: unless specified, **1** (0.2 mmol), **2a** (0.3 mmol), $NiCl_2$•$6H_2O$ (0.04 mmol), 4,4′-dOMe-bpy (0.048 mmol), 4CzIPN (0.01 mmol), Cs_2CO_3 (0.3 mmol), DMF (10 mL), irradiated with the blue LEDs at rt for 48 h then 3N HCl (0.5 mL) was added and stirred for 2 h and see procedure C for detail. [b] Isolated yields.

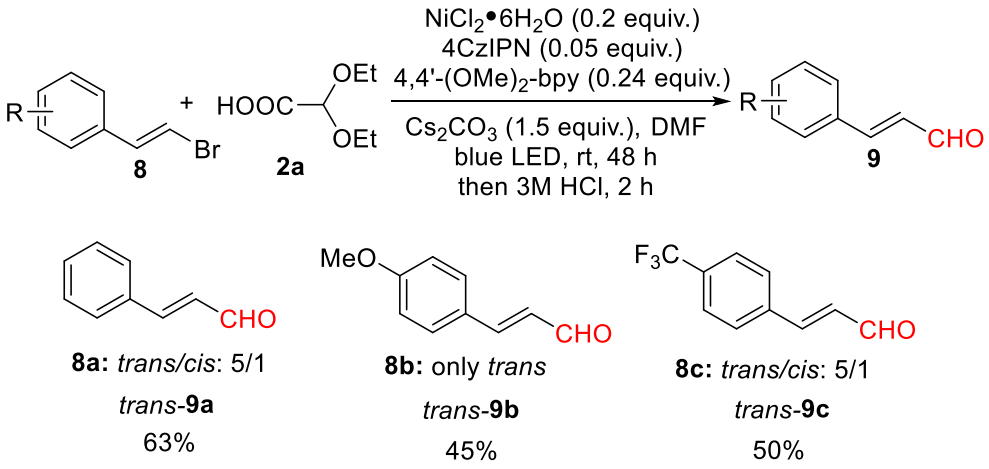
Scheme 3.6 Formylation Reactions of Aryl Triflates.



[a] Standard reaction conditions: unless specified, **1** (0.2 mmol), **2a** (0.3 mmol), $NiCl_2$•$6H_2O$ (0.04 mmol), 4,4′-dOMe-bpy (0.048 mmol), 4CzIPN (0.01 mmol), Cs_2CO_3 (0.3 mmol), DMF (10 mL), irradiated with the blue LEDs at rt for 48 h then 3N HCl (0.5 mL) was added and stirred for 2 h and see SI for detail. [b] Isolated yields.

Finally, we demonstrated that the protocol can be used to transform vinyl bromides to *α*, *β*-unsaturated aldehydes **9a-c** in moderate to good yields (Scheme 3.7). Notably, it is observed that only *trans* products (**9a** and **9c**) are formed even a mixture of *trans* and *cis* bromides are used. To the best of our knowledge, these are the first examples of formylation reactions of vinyl bromides that employ non-precious metal catalysts.[18]

Scheme 3.7 Formylation Reactions of Vinyl Bromides



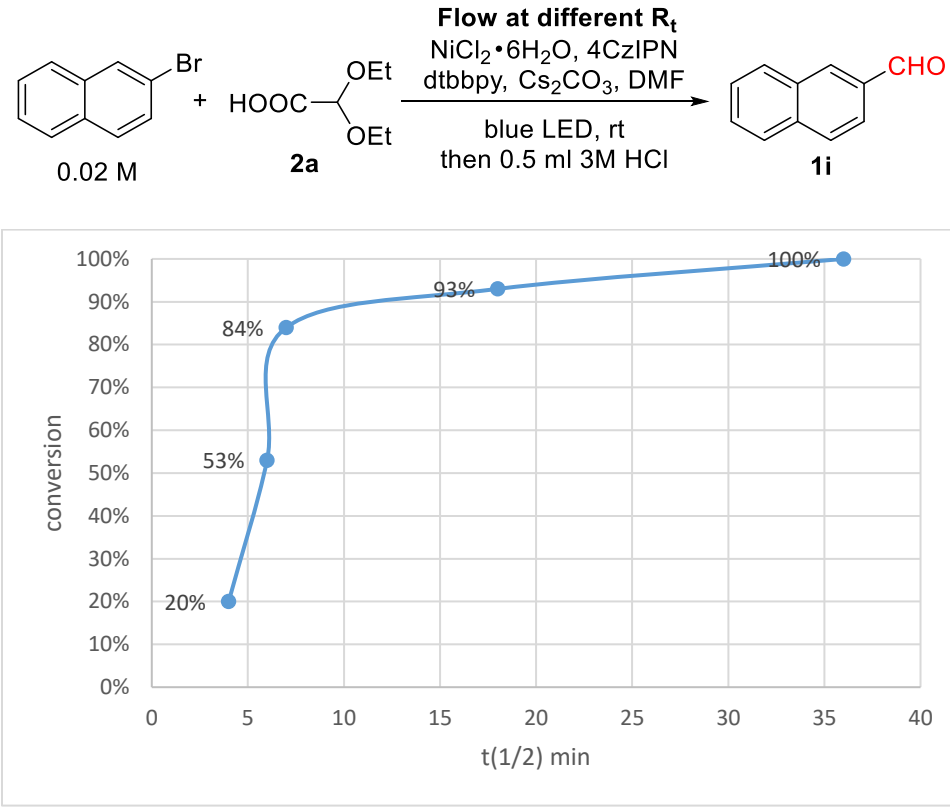
[a] Standard reaction conditions: unless specified, see Scheme 5 and SI for details. [b] Isolated yields.

3.3.3 Gram Scale Reactions Performed in Flow System

In the final phase of this investigation, we assessed the practical utility of the new

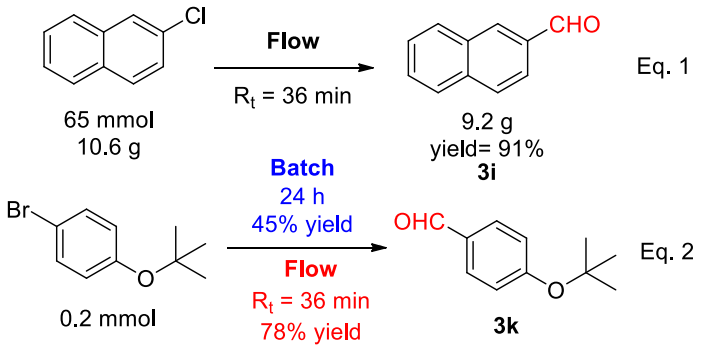
formylation protocol in a potential industrial process scale setting. An attractive approach to large scale synthesis involves the use of a continuous flow procedure.[19] We found that the new formylation methodology is compatible with the continuous flow technology (Scheme 3.8-3.10). In this way, reaction of 10.6 g of 2-chloronaphthalene performed in flow system utilizing the short residence time 36 min produces 9.2 g (91%) of the corresponding aldehyde **3i** (Scheme 3.9, eq. 1). Furthermore, reactant concentration, whose variation has a pronounced effect on the efficiency of the batch process (see above), does not limit reaction in the continuous flow system. Specifically, even reaction of a 0.5 M solution (1 mmol scale) of 2-chloronaphthalene gives rise to a 93% yield of **3i**. The improved efficiency associated with the continuous flow technique is also demonstrated by its use in efficiently formylating 4-*t*-butoxy-bromobenzene (**3k**, 45% in batch vs 78% in flow, Scheme 3.9. Eq. 2).

Scheme 3.8 Optimization of Residence Time (R_t)



[a] Standard reaction conditions: unless specified, see Scheme 5 and SI for details

Scheme 3.9 Reactions Performed in Flow System.



[a] Standard reaction conditions: unless specified, see Scheme 5 and SI for details. [b] Isolated yields.

Scheme 3.10 Continuous flow technology

3.4 Conclusion

In summary, a novel, cost-effective formylation strategy has been developed in this effort. Distinct from extensively studied palladium catalyzed methods, the new process takes place through nickel promoted coupling between an aryl halide, aryl triflates or vinyl bromides and a formyl radical equivalent, generated by organic dye mediated photoredox catalysis. In the process, readily available diethoxyacetic acid serves as the precursor of the formyl radical equivalent. The reaction, which relies on synergistic metal-organic catalysis, occurs at room temperature, tolerates a wide range of functional groups and utilizes challenging aryl chlorides as substrates. The results of this study have expanded the scope of nickel and photodox catalysis by providing a practical approach to the preparation of members of the fundamentally important family of aromatic aldehydes.

3.5 Experimental Section

3.5.1 General Information:

Commercially available reagents were purchased from Sigma Aldrich, Matrix Chemical, AKSci, Alfa Aesar, or TCI, and used as received unless otherwise noted. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with a fluorescence F_{254} indicator were used for thin-layer chromatography (TLC) analysis.^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) relative to residual chloroform (7.26 ppm) or dimethyl sulfoxide (2.50 ppm) as internal standards. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet), coupling constant in Hertz (Hz) and hydrogen numbers based on integration intensities. ^{13}C NMR chemical shifts are reported in ppm relative to the central peak of $CDCl_3$ (77.16 ppm) or $(CD_3)_2SO$ (39.52 ppm) as internal standards. Cyclic voltammetry was performed at 25 °C on a CH Instrument CHI604xD electrochemical analyzer using a glassy carbon working electrode, a platinum wire counter electrode, and a Ag/AgCl reference electrode calibrated using ferrocene redox couple (4.8 eV below vacuum).

3.5.2 General Procedures

Procedure A for compounds 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3l, 3t, 3u, 3w and 3x in scheme 3.3 and 3.4

To an oven-dried 20 mL-Schlenk tube equipped with a stir bar, was added $NiCl_2$•$6H_2O$ (9.6 mg, 0.02 mmol), Cs_2CO_3 (97.7 mg, 0.3mmol), 4CzIPN (7.9 mg, 0.01mmol), dtbbpy (12.8 mg, 0.024mmol), aryl halide (0.2 mmol if it is solid). Then, DMF (10 mL) was added followed by aryl halide (0.2 mmol if it is liquid) and 2,2-diethoxyacetic acid (45 μL, 0.3mmol), were

injected into the tube by syringe under a N_2 atmosphere. The mixture was degassed for 30 min by bubbling N_2 stream, then sealed with parafilm. The solution was then stirred at room temperature under the irradiation of a blue LED strip for 24 h. After completion of the reaction, the mixture was quenched by addition of0.5 mL of 3.0 M HCl, stirred for 2 h and extracted with ether(three times). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.

Procedure B for compounds 3m, 3n, 3o, 3p, 3q, 3r, 3s and 3v in scheme 3.3 and 3.4

To an oven-dried 20 mL-Schlenk tube equipped with a stir bar, was added $NiCl_2•6H_2O$ (9.6 mg, 0.02 mmol), Cs_2CO_3 (97.7 mg, 0.3mmol), 4CzIPN (7.9 mg, 0.01mmol), dtbbpy (12.8 mg, 0.024mmol), aryl halide (0.2 mmol). Then DMF (10 mL) was added to the tube through a syringe, followed by injection of aryl halide (0.2 mmol if it is liquid) and 2,2-diethoxyacetic acid (45 μL, 0.3mmol), into the tube by syringe under N_2 atmosphere. The mixture was degassed for 30 min by bubbling N_2 stream, then sealed with parafilm. The solution was then stirred at room temperature under the irradiation of a blue LED strip for 24 h. After completion of the reaction, the reaction was quenched by 0.5 mL of 3.0 M HCl, stirred for 2 h, then saturated $NaHCO_3$ solution was added to adjust pH to basic. Then the solution was extracted with ether (three times). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.

Procedure C for compounds in scheme 3.6 and 3.7

To an oven-dried 20 mL-Schlenk tube equipped with a stir bar, was added $NiCl_2•6H_2O$

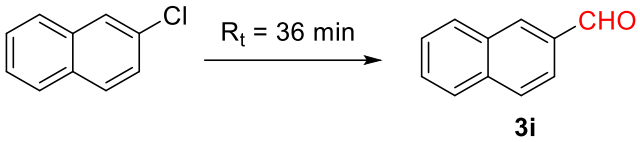
(9.6 mg, 0.02 mmol), Cs_2CO_3(97.7 mg, 0.3mmol), 4CzIPN (7.9 mg, 0.01 mmol), 4,4′-dOMe-bpy (10.4 mg, 0.024 mmol), aryl triflates or vinyl bromides (0.2 mmol). Then DMF (10 mL) was added to the tube through a syringe, followed by injection of aryl triflates or vinyl bromides (0.2 mmol if it is liquid) and 2,2-diethoxyacetic acid (45 μL, 0.3mmol), into the tube by syringe under N_2 atmosphere. The mixture was degassed for 30 min by bubbling N_2 stream, then sealed with parafilm. The solution was then stirred at room temperature under the irradiation of a blue LED strip for 48 h. After completion of the reaction, the reaction was quenched by 0.5 mL of 3.0 M HCl, stirred for 2 h. Then the solution was extracted with ether (three times). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.

Procedure for optimization of residence time (R_t)

To an oven-dried 20 mL-Schlenk tube equipped with a stir bar was added $NiCl_2$•$6H_2O$ (9.6 mg, 0.02 mmol), Cs_2CO_3 (97.7 mg, 0.3 mmol), 4CzIPN (7.9 mg, 0.01 mmol), dtbbpy (12.8 mg, 0.024 mmol), 2-chloronaphthalene (32.5 mg, 0.2 mmol). Then, degassed DMF (10 mL) was added to the tube through a syringe, followed by 2,2-diethoxyacetic acid (45 μL, 0.3 mmol) by syringe under N_2 atmosphere. The reaction mixture was degassed and stirred for 30 min by bubbling N_2 stream, then sealed with parafilm. The reaction mixture is then pumped through the photoreactor at a flow rate to achieve a setting residence time and collected in the flask. After completion, the reaction was quenched by addition of 0.5 mL of 3.0 M HCl, stirred for 2 h and extracted by ether three times. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. Dimethyl maleate was used as an internal standard to calculate the yield by ^{1}H NMR.

After testing different residence time: 4 min, 6 min, 7 min, 18 min and 36 min, residence time of 36 min can reach 100 % conversion.

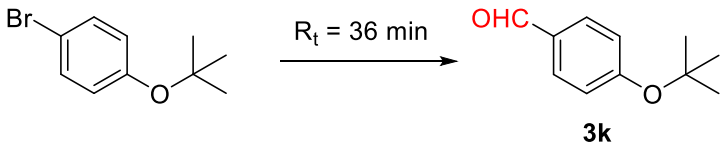
Procedure for Continuous flow reaction for synthesis of 3i in large scale (Scheme 3.9, Eq. 1)



3i

To an oven-dried 20 mL-Schlenk tube equipped with a stir bar was added $NiCl_2$•$6H_2O$ (3 g, 13mmol), Cs_2CO_3 (31.7g, 97.5mmol), 4CzIPN (2.5g, 3.25mmol), dtbbpy (4.2g, 15.6mmol), 2-chloronaphthalene (10.6g, 65mmol). Then, degassed DMF (130 mL) was added to the tube through a syringe, followed by injection of 2,2-diethoxyacetic acid (14.4 g, 97.5mmol), into the tube by syringe under N_2 atmosphere. The reaction mixture was degassed and stirred for 60 min by bubbling N_2 stream, then sealed with parafilm. The mixture was then pumped through the photoreactor at a flow rate to achieve a residence time of 36 min and collected in the flask. After completion of the reaction, the mixture was cooled to -10ºCthen quenched by 163 mL of 3.0 M HCl slowly, stirred for 3 h and extracted with ether (three times). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained of 9.4 g after purification by flash chromatography on silica gel with hexanes and ethyl acetate.

Procedure for Continuous flow reaction for synthesis of 3k (Scheme 3.9, Eq.2)



3k

Into an oven-dried 20 mL-Schlenk tube equipped with a stir bar was added $NiCl_2$•$6H_2O$ (9.6 mg, 0.02 mmol), Cs_2CO_3(97.7 mg, 0.3 mmol), 4CzIPN (7.9 mg, 0.01 mmol), dtbbpy (12.8 mg, 0.024 mmol), 1-bromo-4-*tert*-butoxybenzene (45.8 mg, 0.2 mmol). Then, degassed DMF (10 mL) was added to the tube through a syringe, followed by injection of 2,2-diethoxyacetic acid (45 μL, 0.3 mmol), into the tube by syringe under N_2 atmosphere. The mixture was degassed and stirred for 30 min by bubbling N_2 stream, then sealed with parafilm. The mixture was then pumped through the photoreactor at a flow rate to achieve a residence time of 36 min and collected in the flask. After completion of the reaction, the mixture was quenched by 0.5 mL of 3.0 M HCl, stirred for 2 h and extracted with ether (three times). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.

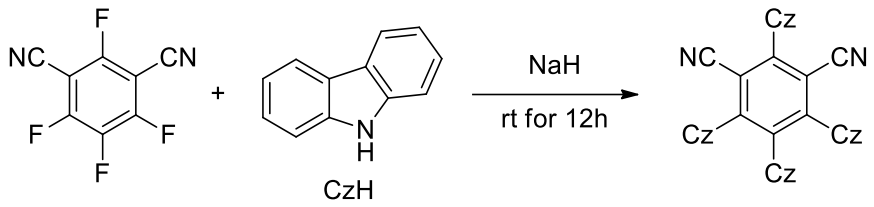
3.5.3 Preparation of Substrates and Catalysts

Preparation of 2,2-diethoxyacetic acid (2a)[20]

To a solution of ethyl 2,2-diethoxyacetate (3.8 g, 21.6 mmol) in EtOH (10 mL) was added 1 N NaOH (21.6 mL). The mixture was stirred for 3h at rt. The organic solvent was evaporated under vacuum and the aqueous phase was extracted with Et_2O (1×20 mL). The

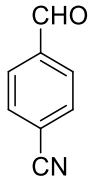
aqueous layer was made acidic with 2.0 N HCl at -10ºC and extracted with EtOAc (4×20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum to give 2.7 g (85% yield) of compound **2a** as a light yellow oil.

2,4,5,6-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN)[15a]

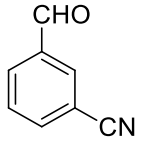


NaH (60% in oil, 0.60g, 15.0mmol) was added slowly to a stirred solution of carbazole (1.67g, 10.0mmol) or diphenylamine (1.69g, 10.0mmol) in dry THF (40 mL) under a nitrogen atmosphere at room temperature. After 30 min, tetrafluoroisophthalonitrile (0.40g, 2.00mmol)was added. After stirring at room temperature for 12 h, 2 mL of water was added to the mixture to quench the excess NaH. The resulting mixture was then concentrated under reduced pressure and washed with water and EtOH to yield the crude product, which was purified by recrystallization from hexane/CH_2Cl_2, column chromatography on silica gel (CH_2Cl_2:hexane, 4:1v/v) were used for further purification) to give 1.51g (96%, 4CzIPN).^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ6.71 (t, J = 8.0 Hz, 2H), 6.82 (t, J = 8.0 Hz, 2H),7.04~7.19 (m, 8H), 7.42~7.57 (m, 6H), 7.69~7.80 (m, 6H), 7.87 (d, J = 4.0Hz, 4H), 8.21 (d, J =8.0Hz, 2H), 8.37 (d, J = 8.0Hz, 2H).

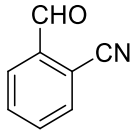
3.6 Characterization



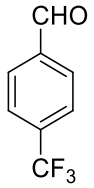
4-Formylbenzonitrile **(3a):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.99 (d, 1H, *J* = 8.4 Hz), 7.84 (d, 1H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.6, 138.8, 132.9, 129.9, 117.7, 117.6.



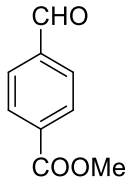
3-Formylbenzonitrile **(3b):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.05 (s, 1H), 8.17 (s, 1H), 8.11-8.14 (m, 1H), 7.93-7.92 (m, 1H), 7.70 (dd, 1H, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.9, 137.2, 136.9, 133.3, 133.2, 130.1.



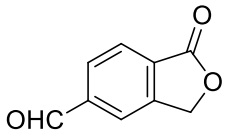
2-Formylbenzonitrile **(3c):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.36 (s, 1H), 8.07-8.04 (m, 1H), 7.86-7.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.5, 136.8, 134.2, 134.1, 133.2, 129.6, 116.0, 114.0.



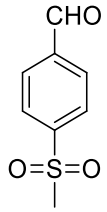
4-(Trifluoromethyl)benzaldehyde **(3d):** The title compound was prepared according to the general procedure A as a colorless oil after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.08 (s, 1H), 7.98 (d, 2H, *J* = 8.1 Hz), 7.77 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.0, 138.7, 135.4 (q, *J*= 37.5Hz), 128.9, 126.0 (q, *J*= 7.5Hz), 123.4 (q, *J*= 270Hz).



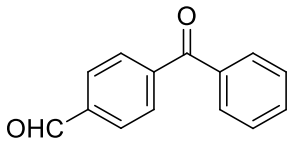
Methyl 4-formylbenzoate **(3e):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.17 (d, 2H, *J* = 8.4 Hz), 7.93 (d, 2H, *J* = 8.4 Hz), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.6, 166.0, 139.2, 135.1, 130.2, 129.5, 52.6.



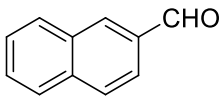
1-Oxo-1,3-dihydroisobenzofuran-5-carbaldehyde **(3f):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.17 (s, 1H), 8.11-8.03 (m, 3H), 5.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.9, 169.7, 146.9, 140.4, 130.8, 130.6, 126.7, 123.0.



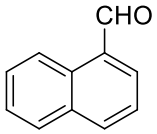
4-(Methylsulfonyl)benzaldehyde **(3g):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.17 (s, 1H), 8.18-8.09 (m, 4H), 3.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.7, 145.4, 139.7, 130.4, 128.2, 44.3.



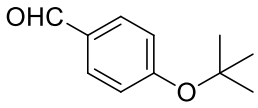
4-Benzoylbenzaldehyde **(3h):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.01 (d, 2H, *J* = 8.1 Hz), 7.92 (d, 2H, *J* = 8.1 Hz), 7.82-7.79 (m, 2H), 7.63-7.61 (m, 1H), 7.55-7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.8, 191.6, 142.6, 138.5, 136.8, 133.1, 130.3, 130.1, 129.5, 128.5.



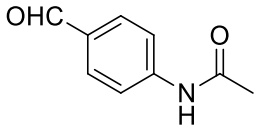
2-Naphthaldehyde **(3i):** The title compound was prepared according to the general procedure A as a light yellow solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.32 (s, 1H), 8.01-7.88 (m, 4H), 7.67-7.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3, 136.5, 134.5, 134.1, 132.7, 129.5, 129.1, 128.1, 127.1, 122.8.



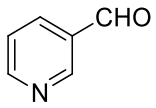
1-Naphthaldehyde **(3j):** The title compound was prepared according to the general procedure A as a light yellow solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.385 (s, 1H), 9.26 (d, 1H, *J* = 8.7 Hz), 8.07 (t, 1H, *J* = 8.1 Hz), 7.97-7.89 (m, 2H), 7.71-7.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.6, 136.7, 135.3, 133.7, 131.4, 130.5, 129.1, 128.5, 127.0, 124.9.



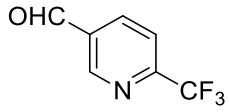
4-(Tert-butoxy)benzaldehyde **(3k):** The title compound was prepared according to the general procedure A as a colorless oil after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.94 (s, 1H), 7.82 (d, 2H, *J* = 8.4 Hz), 7.12 (d, 2H, *J* = 8.4 Hz), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.1, 161.7, 131.2, 131.1, 122.4, 28.9.



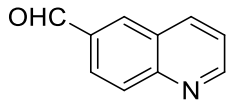
N-(4-formylphenyl)acetamide **(3l):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.4 (b, 1H), 9.86 (s, 1H), 7.84 (d, 2H, *J* = 8.7 Hz), 7.12 (d, 2H, *J* = 8.7 Hz), 2.10 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 192.0, 169.6, 145.3, 131.6, 131.3, 119.0.



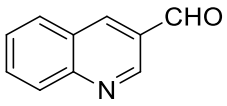
***Nicotinaldehyde*(3m):** The title compound was prepared according to the general procedure B as a yellow oil after silica gel chromatography.[1]H NMR (300 MHz, $CDCl_3$): δ 10.08 (d, 1H, *J* = 0.9 Hz), 9.04 (s, 1H), 8.82-8.79 (m, 1H), 8.15-8.12 (m, 1H), 7.47-7.43 (m, 1H); [13]C NMR (75 MHz, $CDCl_3$): δ 190.8, 154.8, 152.1, 135.8, 131.4, 124.1.



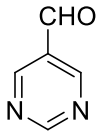
***6-(Trifluoromethyl)nicotinaldehyde*(3n):** The title compound was prepared according to the general procedure B as a brown solid after silica gel chromatography. [1]H NMR (300 MHz, $CDCl_3$): δ 10.18 (s, 1H), 9.15 (s, 1H), 8.34 (d, 1H, *J* = 8.1 Hz), 7.85 (d, 1H, *J* = 8.1 Hz); [13]C NMR (75 MHz, $CDCl_3$): δ 189.4, 152.0 (q, J^2= 34.9Hz), 151.6, 137.7, 133.0, 121.0, 120.9 (q, J^1= 272.9Hz).



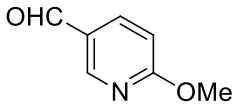
***Quinoline-6-carbaldehyde* (3o):** The title compound was prepared according to the general procedure B as a light yellow solid after silica gel chromatography. [1]H NMR (300 MHz, $CDCl_3$): δ 10.15 (s, 1H), 9.01-8.99 (m, 1H), 8.29-8.26 (m, 2H), 8.15 (s, 2H), 7.49-7.45 (m, 1H); [13]C NMR (75 MHz, $CDCl_3$): δ191.5, 153.1, 150.9, 137.4, 134.3, 133.7, 130.8, 127.7, 126.7, 122.2.



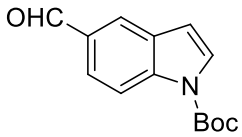
Quinoline-3-carbaldehyde **(3p):** The title compound was prepared according to the general procedure B as a light yellow solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.26 (s, 1H), 9.37 (d, 1H, *J* = 1.8 Hz), 8.63 (d, 1H, *J* = 1.5 Hz), 8.19 (d, 1H, *J* = 8.4 Hz), 8.01-7.91 (m, 1H), 7.89-7.86 (m, 1H), 7.70-7.64 (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 190.7, 150.6, 149.2, 140.1, 132.7, 129.8, 129.4, 128.6, 127.9, 127.1.



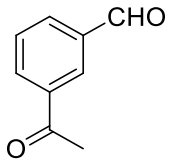
Pyrimidine-5-carbaldehyde **(3q):** The title compound was prepared according to the general procedure B as a dark brown solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.13 (s, 1H), 9.38 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.0, 162.3, 157.9, 128.6.



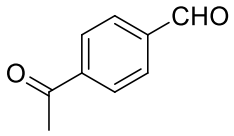
6-Methoxynicotinaldehyde **(3r):** The title compound was prepared according to the general procedure B as a light brown solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.96 (s, 1H), 8.63 (d, 1H, J_1 = 2.1 Hz), 8.06 (dd, 1H, J_1 = 8.7 Hz, J_2 = 2.4 Hz), 6.83 (d, 1H, J_1 = 8.7 Hz), 4.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.5, 167.8, 152.9, 137.4, 126.6, 112.1, 54.3.



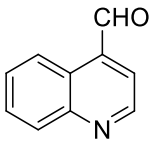
Indole-5-carboxaldehyde **(3s):** The title compound was prepared according to the general procedure B as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.06 (s, 1H), 8.47 (d, 1H, J_1 = 8.4 Hz), 8.09 (s, 1H), 7.85 (d, 1H, J_1 = 8.7 Hz), 7.68 (d, 1H, J_1 = 3.9 Hz), 1.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.1, 149.2, 138.7, 131.7, 130.7, 127.7, 125.1, 124.2, 115.6, 107.8, 84.6, 28.1.



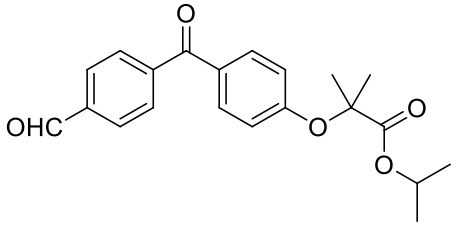
3-Acetylbenzaldehyde **(3t):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.45-8.43 (m, 1H), 8.24-8.21 (m, 1H), 8.10-8.07 (m, 1H), 7.69-7.63 (m, 1H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 191.4, 137.8, 136.7, 133.7, 133.6, 129.5, 26.7.



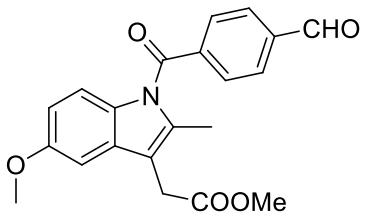
4-Acetylbenzaldehyde **(3u):** The title compound was prepared according to the general procedure A as a colorless oil after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.11 (s, 1H), 8.10 (d, 2H, J = 8.4 Hz), 7.98 (d, 2H, J = 8.4 Hz), 2.663 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 191.6, 141.2, 139.1, 129.8, 128.3, 27.0.



Quinoline-4-carbaldehyde **(3v):** The title compound was prepared according to the general procedure B as a light yellow solid after silica gel chromatography.[1]H NMR (300 MHz, $CDCl_3$): δ 10.45 (d, 1H, *J* = 2.7 Hz), 9.14 (d, 1H, *J* = 4.2 Hz), 8.96 (d, 1H, *J* = 8.4 Hz), 8.17 (d, 1H, *J* = 8.4 Hz), 7.80-7.66 (m, 3H); [13]C NMR (75 MHz, $CDCl_3$): δ 192.9, 150.4, 149.2, 136.7, 130.2, 130.0, 129.4, 125.8, 124.4, 123.8.

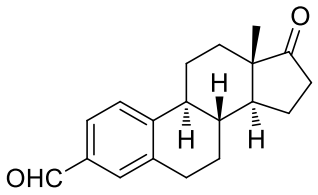


Isopropyl 2-(4-(4-formylbenzoyl)phenoxy)-2-methylpropanoate **(3w):** The title compound was prepared according to the general procedure A as a white solid after silica gel chromatography. [1]H NMR (300 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.98 (d, 2H, *J* = 8.1 Hz), 7.86 (d, 2H, *J* = 8.1 Hz), 7.76 (d, 2H, *J* = 9.0 Hz), 6.86 (d, 2H, *J* = 8.7 Hz), 5.08 (tt, 1H, *J* = 6.0 Hz), 1.66 (s, 6H), 1.20 (d, 6H, *J* = 6.3 Hz); [13]C NMR (75 MHz, $CDCl_3$): δ 194.5, 191.6, 173.0, 160.2, 143.3, 138.2, 132.1, 130.0, 129.7, 129.5, 117.3, 79.5, 69.4, 25.4, 21.5.

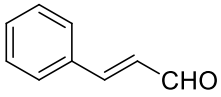


Methyl 2-(1-(4-formylbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate **(3x):** The title

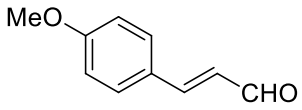
compound was prepared according to the general procedure A as a colorless oil after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.00 (d, 2H, *J* = 7.8 Hz), 7.85 (d, 2H, *J* = 7.8 Hz), 6.96 (s, 1H), 6.84 (d, 1H, *J* = 9.0 Hz), 6.64 (d, 1H, *J* = 9.0 Hz), 3.83 (s, 3H), 3.71 (s, 3H), 3.67 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3, 171.2, 168.2, 156.3, 140.8, 138.7, 135.8, 130.9, 130.6, 130.0, 129.9, 115.1, 113.1, 111.7, 101.5, 55.7, 52.2, 30.1, 13.6.



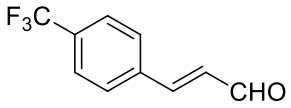
(8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3-carbaldehyde **(3y):** The title compound was prepared according to the general procedure C as a white solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.93 (s, 1H), 7.65-7.60 (m, 2H), 7.46-7.43 (m, 1H),3.0-2.98 (m, 2H),2.49-2.34 (m, 3H),2.18-1.97 (m, 4H),1.65-1.44 (m, 6H),0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.2, 192.0, 146.9, 137.4, 134.1, 130.0, 127.1, 125.9, 50.4, 47.7, 44.7, 37.6, 35.6, 31.4, 29.0, 26.0, 25.4, 21.4, 13.6.



trans-Cinnamaldehyde **(9a):** The title compound was prepared according to the general procedure A as a colorless oil after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (d, 2H, *J* = 7.8 Hz), 7.57-7.50 (m, 2H), 7.44-7.42 (m, 4H), 6.70 (dd, 1H, J_1= 16.2 Hz, J_2= 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.8, 152.8, 134.0, 131.3, 129.1, 128.6, 128.5.



***(E)-3-(4-Methoxyphenyl)acrylaldehyde* (9b):** The title compound was prepared according to the general procedure A as a yellow solid after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.62 (d, 1H, *J* = 7.8 Hz), 7.49 (d, 2H, *J* = 8.1 Hz), 7.40 (d, 1H, *J* = 15.9 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 6.58 (dd, 1H, J_1= 15.9 Hz, J_2= 7.8 Hz),3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.7, 162.2, 152.7, 130.4, 126.8, 126.5, 114.6, 55.5.



***(E)-3-(4-(Trifluoromethyl)phenyl)acrylaldehyde* (9c):** The title compound was prepared according to the general procedure B as a light yellow solid after silica gel chromatography.^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (d, 1H, *J* = 7.5 Hz), 7.71 (s, 4H), 7.53 (d, 1H, *J* = 16.2 Hz), 6.80 (dd, 1H, J_1= 15.9 Hz, J_2= 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.2, 150.3, 137.3, 132.6 (q, *J*= 32.9Hz), 130.5,128.6, 126.0 (d, *J*= 3.6Hz), 123.7 (q, *J*= 270.8Hz).

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Chapter 4

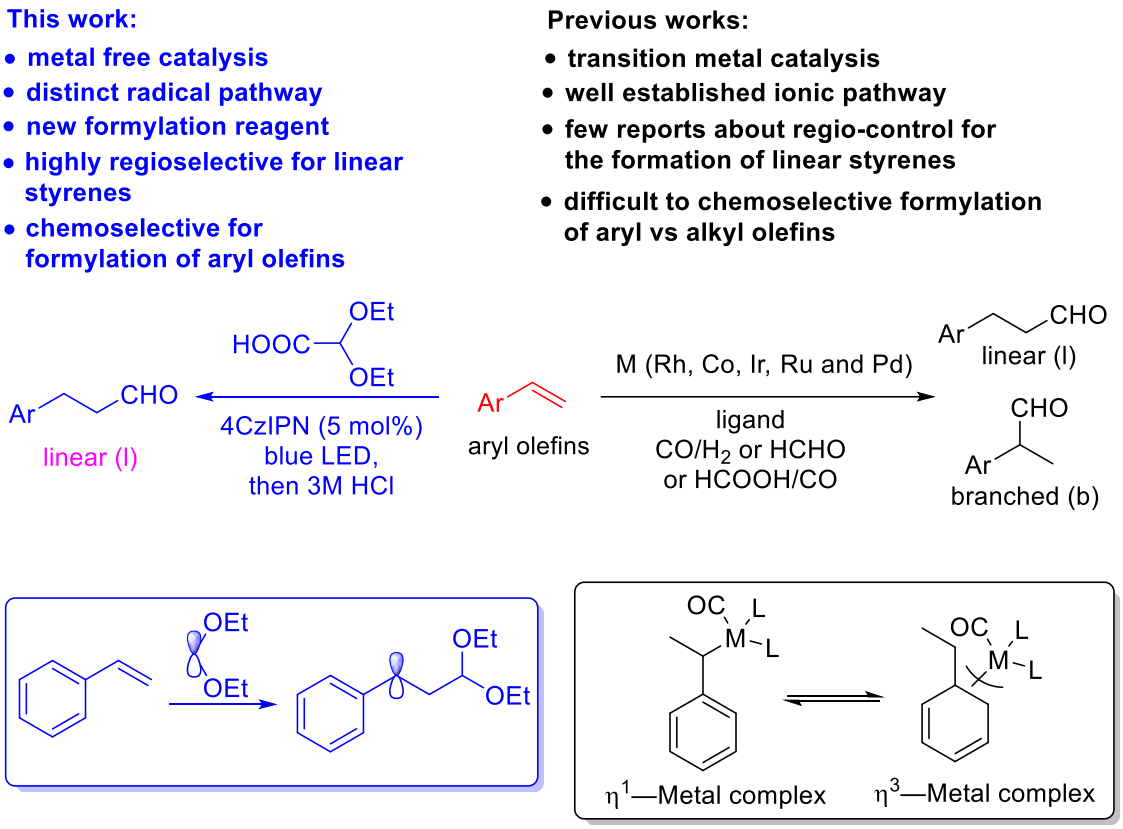
Chemo- and Regio-Selective Organo-Photoredox Catalyzed Hydroformylation of Styrenes via a Radical Pathway

4.1 Introduction

Aldehydes are perhaps the most important class of compounds used in organic synthesis. Hydroformylation reactions of alkenes, which are feedstock chemicals, are among the most cost-effective methods for synthesis of aldehydes.[1] Hydroformylation, developed by Roelen in the 1930s,[2] is currently the most highly productive homogenous catalyzed process used on an industrial scale to generate more than 10 million tons of oxo products annually.[3] This success is attributable to significant efforts made to develop efficient protocols for aldehyde synthesis. Among these protocols are those that chiefly employ transition metal complexes (e.g., Rh,[4] Co,[1e] Ir,[5] Ru[6] and Pd[7]) as catalysts (see Chapter 1). Unfortunately, these approaches rely on the use of high pressures of toxic syngas (CO/H_2). In addition, other important issues associated with these approaches include the control of chemoselectivity and regiochemistry when unsymmetric olefins are substrates. In particular, while the regioselectivity of reactions producing linear aldehydes from alkyl substituted olefins has been addressed,[4a, 4b, 4d, 4f, 4g, 4j] methods for regioselective formylation of aryl olefins remain elusive. In these cases, branched rather than linear formylation products are formed predominantly because CO transfer produces more stable benzylic metal-species as a result of η^2 electron donation from the aromatic ring (Scheme 4.1). Although limited in number, a few processes, in which linear formylation of aryl olefins occurs, have been developed by Zhang,[4h, 4l] Reek[4m, 4o, 4r-t] and Shi[7b]. These approaches require the use of transition metal complexes containing highly functionalized ligands,[4h, 4l, 4m, 4o,

[4r-t, 7b] and/or that special substrates.[4o] Furthermore, an intrinsic limitation of transition metal catalyzed processes is associated with the difficulty in controlling chemoselectivity when both alkyl and aryl substituted C=C bonds are present in the substrate.

Scheme 4.1. Organo-Photoredox Catalyzed and Transition-Metal Catalyzed Hydroformylation Reactions



4.2 Research Plan

It is clear that a new synthetic paradigm is needed to address the development of an viable olefin hydroformyation process that overcomes shortcomings of the current transition metal catalyzed reactions. We envisioned that a free radical based approach involving addition of a formyl radical equivalent to an olefin might be an effective strategy (Scheme 4.1). However,

the most significant challenge of using a free radical approach is the need to avoid occurrence of competitive and undesired polymerization reactions. This may well be the reason why, to the best of our knowledge, a radical based hydoformylation strategy has not been devised thus far.

In a recently completed study[8] that led to a novel method for formylation of haloarenes, we have developed a free radical based protocol for regio- and chemo-selective hydroformylation of aryl olefins. Specifically, in the current effort we demonstrated that a formyl radical equivalent, produced from 2,2-diethoxyacetic acid via a 1,2,3,5-tetrakis-(carbazolyl)-4,6-dicyanobenzene (4CzIPN) visible light photocatalyzed oxidation-decarboxylation sequence[9, 10] adds in an anti-Markovnikov fashion to the C=C bond[11] of styrene derivatives (Scheme 4.1). In addition, the benzylic radicals generated are reduced by SET from the anion radical of 4CzIPN which upon protonation form hydroformylation products. Significantly, this process occurs with minimal contribution from competitive polymerization.

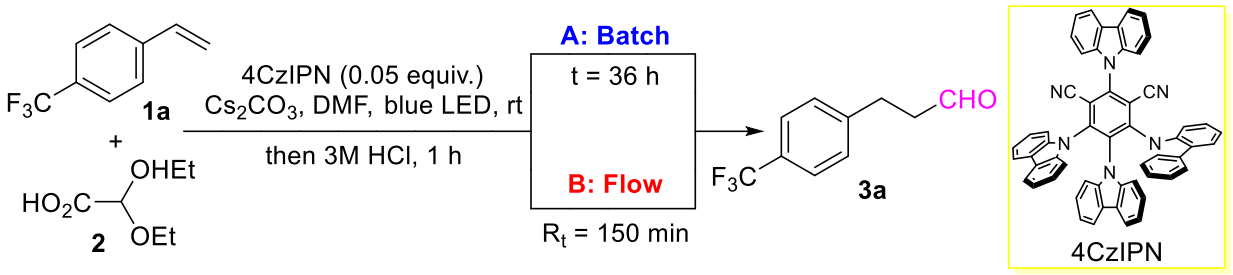
4.3 Results and Discussion

4.3.1 Optimization of Reaction Condition

To gain information about the feasibility of the new free radical hydroformylation strategy, we explored the effects of several parameters, including the reactant ratio, photosensitizer, base and solvent, on this transformation (Table 4.1 and 4.2). The results show that the use of **1a** (0.4 mmol), **2** (0.2 mmol), 4CzIPN (0.01 mmol), Cs_2CO_3 (0.2 mmol), DMF (10 mL) and blue LED irradiation leads to formation of **3a** in a 70% yield with only linear product (Table 4.1 and 4.2). More importantly, the presence of molecular oxygen leads to a dramatic decrease in the reaction efficiency (entry 2 in Table 4.1). This finding suggests that O_2 captures radical intermediates in the reaction pathway. Moreover, attempts to eliminate competitive

polymerization of styrene by adding the radical polymerization inhibitors *p*-dihydroxybenzene and $FeCl_3$[12] were not successful (Table 4.2).

Table 4.1. Metal-catalyzed Cyclization of 3-Pentynoic Acid[a]



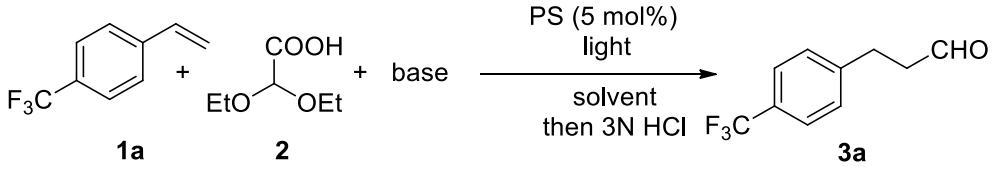
entry	method used	deviation from "standard conditions"[a]	% conversion[b]	% yield[c]
1	Batch	none	100	70
2	Batch	without N_2 protection	90	trace
4	Flow	[**1a**] of reaction is 0.02 M, R_t = 18 min	25	12
5	Flow	none	100	93 (85)[d]
6	Flow	without adding 3M HCl	100	82[e]
7	Flow	3.44g of **1a**	100	87[d]

[a] Standard conditions: see SI for detail. [b] % conversions were determined by using ^{1}H NMR. [c] Yields were determined by using ^{1}H NMR. [d] Isolated yields. [e] Isolated yield of 1-(3,3-diethoxypropyl)-4-(trifluoromethyl)benzene.

A common technique to enhance the efficiencies of photochemical reactions involves the utilization of a continuous flow system.[8,13] To minimize competitive polymerization, visible light induced photoreaction of a mixture of **1a** and **2** (2.0 equiv.) in DMF containing Cs_2CO_3 (2.0 equiv.) and 4CzIPN (5 mol%) was performed using a continuous flow system with various residence times (R_t) and styrene concentrations (Table 4.1 and 4.2). Extending the residence time and elevating the concentration of **1a** improve both conversion and yield (Table 4.1 entry 4-5 and

Table 4.2). Furthermore, no polymerization occurs (by NMR) when the continuous flow system is employed. What's more, 82% yield of 1-(3,3-diethoxypropyl)-4-(trifluoromethyl)benzene (**3a-ace**) can be reached without treatment with acid. This gives an additional advantage of this method. Finally, a gram scale reaction was carried out under flow conditions, occurring on a 3.44 g scale using only 3 mol% of 4CzIPN, forms 3.52 g **3a** (Table 4.1, entry 7).

Table 4.2. Optimization of Reaction Conditions.[ab]



entry	photosensitizers	base	solvent	[c]M of **1a**	Method	**1a**/**2**	conversion	yield[a,b]
1	eosin Y	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
2	eosin B	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
3	rose Bengal	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
4	rhodamine B	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
5	rhodamine 6G	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
6	9,10-dicyanoanthracene	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
7	2,4,6-triphenylpyrylium tetrafluoroborate	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
8	quinizarin	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
9	9-mesityl-10-methylacridinium	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
10	4CzIPN	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	100	70%
11	4CzIPN	$(nBu)_4NOH$ (40% aq.)	DMF	0.02	Batch	0.4/0.2 mmol	85	No product
12	4CzIPN	K_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	100	10%
13	4CzIPN	KOH	DMF	0.02	Batch	0.4/0.2 mmol	100	<5%
14	4CzIPN	$CsOHH_2O$	DMF	0.02	Batch	0.4/0.2 mmol	100	<5%
15	4CzIPN	Na_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	60	12%
16	4CzIPN	K_2HPO_4	DMF	0.02	Batch	0.4/0.2 mmol	100	15%
17	4CzIPN	Cs_2CO_3	CH_3CN	0.02	Batch	0.4/0.2 mmol	80	13%
18	4CzIPN	Cs_2CO_3	THF	0.02	Batch	0.4/0.2 mmol	32	No product
19	4CzIPN	Cs_2CO_3	DMSO	0.02	Batch	0.4/0.2 mmol	100	20%
20	4CzIPN	Cs_2CO_3	Toluene	0.02	Batch	0.4/0.2 mmol	<5	No product
21	4CzIPN	Cs_2CO_3	DMF	0.08	Batch	0.4/0.2 mmol	68	39%
22	4CzIPN	No base	DMF	0.02	Batch	0.4/0.2 mmol	<5	No product
23	No PS	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	trace
24[c]	4CzIPN	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	<5	trace
25[d]	4CzIPN	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	90	15%

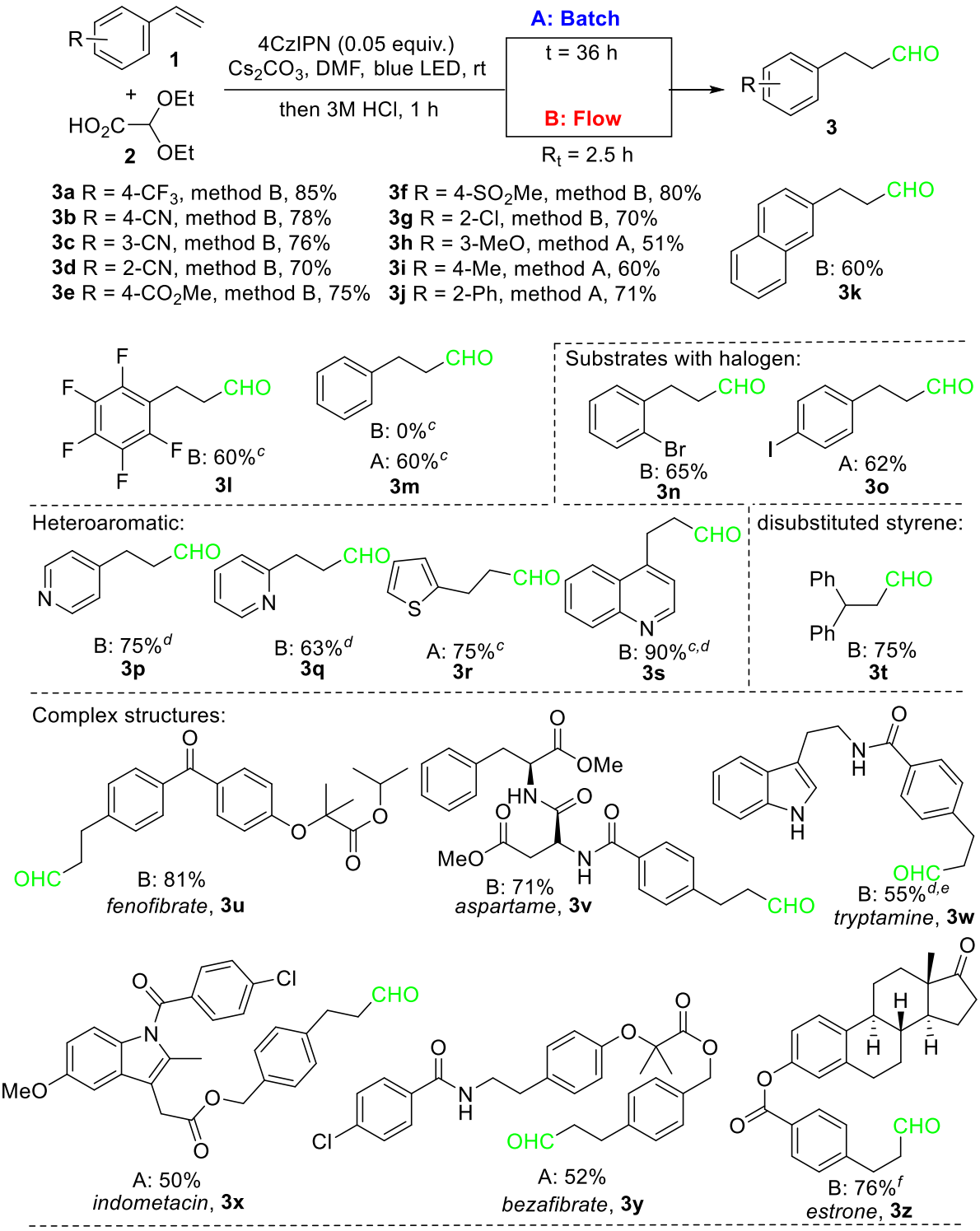
26[e]	4CzIPN	Cs_2CO_3	DMF	0.02	Batch	0.4/0.2 mmol	100	<5%
27	4CzIPN	Cs_2CO_3	DMF	0.02	Flow [f]	0.2/0.4 mmol	25	12%
28	4CzIPN	Cs_2CO_3	DMF	0.02	Flow [g]	0.2/0.4 mmol	43	28%
29	4CzIPN	Cs_2CO_3	DMF	0.02	Flow [h]	0.2/0.4 mmol	90	42%
30	4CzIPN	Cs_2CO_3	DMF	0.1	Flow [h]	0.2/0.4 mmol	100	90%
31	4CzIPN	Cs_2CO_3	DMF	0.2	Flow [h]	0.2/0.4 mmol	100	93%
32[i]	4CzIPN	Cs_2CO_3	DMF	0.2	Flow [h]	0.2/0.4 mmol	80	No product

[a] Standard reaction conditions: Batch, **1a** (0.4 mmol), **2** (0.2 mmol), 4CzIPN (0.01mmol), Cs_2CO_3 (0.2 mmol), DMF (10 mL), irradiated with the blue LED at rt in tube under N_2 then 0.8 mL of 3N HCl was added and see method for detail; Flow, **1** (0.2 mmol), **2** (0.4 mmol), 4CzIPN (0.01mmol), Cs_2CO_3 (0.4 mmol), DMF (1 mL), irradiated with the blue LEDs at rt in flowing then 0.8 mL of 3N HCl was added and see method for detail. [b] Yields were determined by NMR using dimethyl maleate as an internal standard. [c] No light [d] 0.2 mmol *p*-dihydroxybenzene was added [e] 0.2 mmol $FeCl_3$ was added. [f] R_t = 18 min. [g] R_t = 36 min. [h] R_t = 150 min. [i] 0.4 mmol TEMPO was added.

4.3.2 Investigation of Substrate Scope

The generality of the new hydroformylation reaction was explored next (Scheme 4.2). The process carried out using the flow system serves as a general approach to the preparation of structurally diverse 3-arylpropanals in 50-90% yields and with high levels of regioselectivity independent of the nature of the substituent on the styrene phenyl ring. A variety of functional groups are tolerated under the mild conditions used. In addition, aldehydes bearing pharmaceutically relevant groups, such as trifluoromethyl (**3a**), nitrile (**3b**-**3d**), ester (**3e**), methanesulfonyl (**3f**), chloride (**3g**), fused aromatic (**3k**), pentafluoro-aromatic ring (**3l**) and heterocycle (**3p**-**3s**) can be efficiently prepared using this method. This procedure can also be applied to 1,1-disubstituted styrene to give 75% yield (**3t**).

Scheme 4.2 Scope of the Hydroformylation Reaction[a]



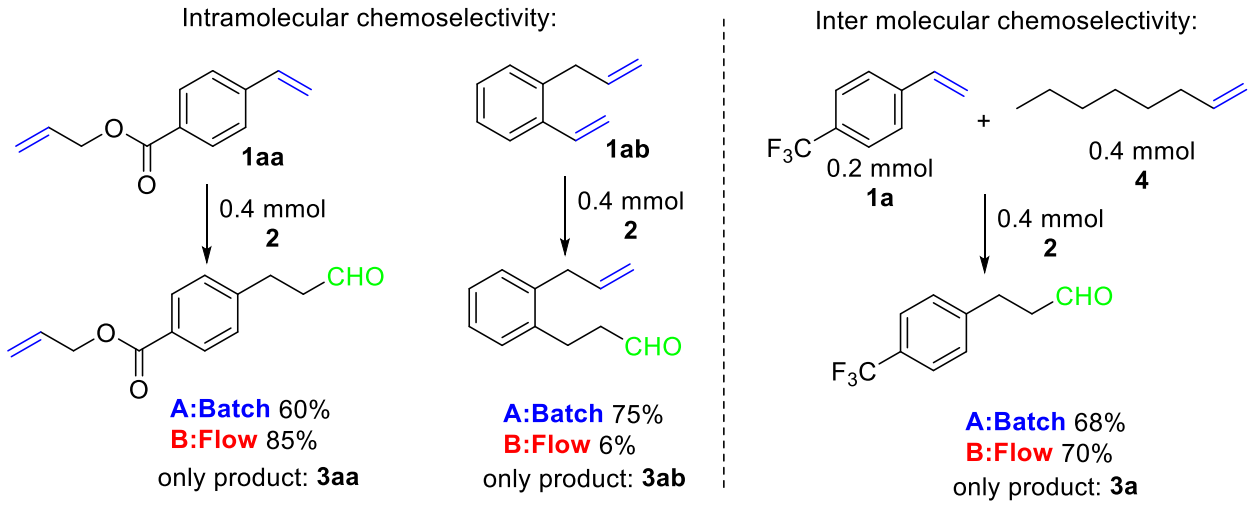
[a] See SI for detailed procedures. [b] Isolated yields. [c] Yields were determined by using ^{1}H NMR [d] 1.2 mL of 3N HCl for 12 h. [e] 0.8 mmol of **2** and Cs_2CO_3 was used. [f] 1N HCl was used.

In contrast to the results presented above, we observed that styrenes possessing electron-neutral and donating (EDG) arene ring substituents failed to generates aldehyde products in acceptable yields when subjected to the continuous flow conditions. For example, aldehyde **3m** is not formed when unsubstituted styrene is subjected to these conditions, which involve a high styrene concentration. Instead, a large amount of polymers/oligomers are produced (see below). To minimize polymerization, the batch method, was employed because it uses a much lower concentration of styrene (0.04 M, 2.0 equiv). Indeed, under these conditions **3m** is generated in 60% yield. However, a notable amount of polymers/oligomers are also produced in this reaction. Utilizing the batch method, styrenes that contain electron neutral or rich arene ring substituents like methoxy (**3h**), methyl (**3i**) and phenyl (**3j**) undergo formylation smoothly to form the corresponding aldehydes in moderate to high yields. Notably, the new process is compatible with formylations of bromo- and iodo-substituted arene ring styrenes, which are problematic substrates in metal catalyzed hydroformylations.[7b] Moreover, the mild conditions enable the process to be applied to late-stage synthetic elaboration of biologically relevant complex substances (eg., **3u**-**3z**).

One limitation of transition metal promoted hydroformylation reactions arises from the difficulties associated with differentiation between aliphatic and aryl olefins. To determine whether the approach developed in this effort displays acceptable levels of olefin selectivity, hydroformylation reactions of substrates **1aa** and **1ab**, which contain both alkyl and aryl substituted alkene moieties, were explored (Scheme 4.3). The exclusive formation (by ^{1}H NMR) of the respective aldehydes **3aa** and **3ab** shows that hydroformylation reactions of these substances take place in a highly selective manner on the aryl substituted C=C bond. A similar outcome is seen when a mixture of styrene **1a** and the alkyl substituted olefin, 1-octene (**4**), are

subjected to the hydroformylation conditions. In this case, the aldehyde derived from the aryl substituted alkene **1a** is generated exclusively.

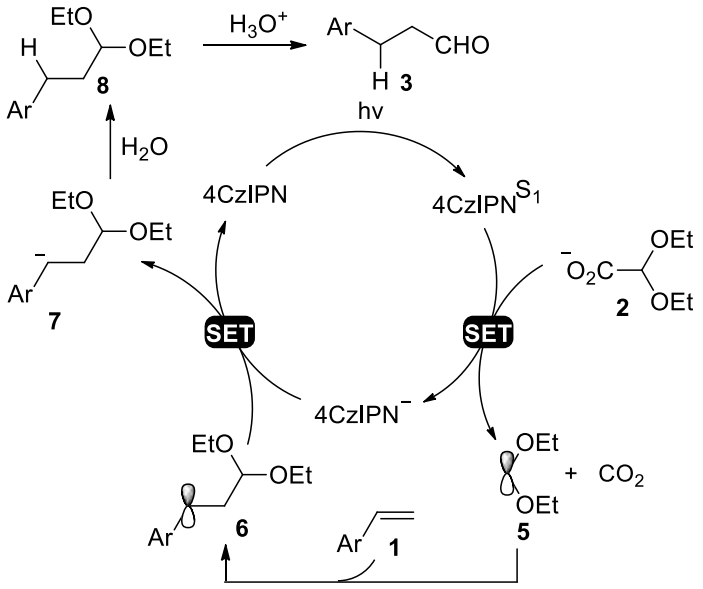
Scheme 4.3 Intra- and Intermolecular Chemoselectivity



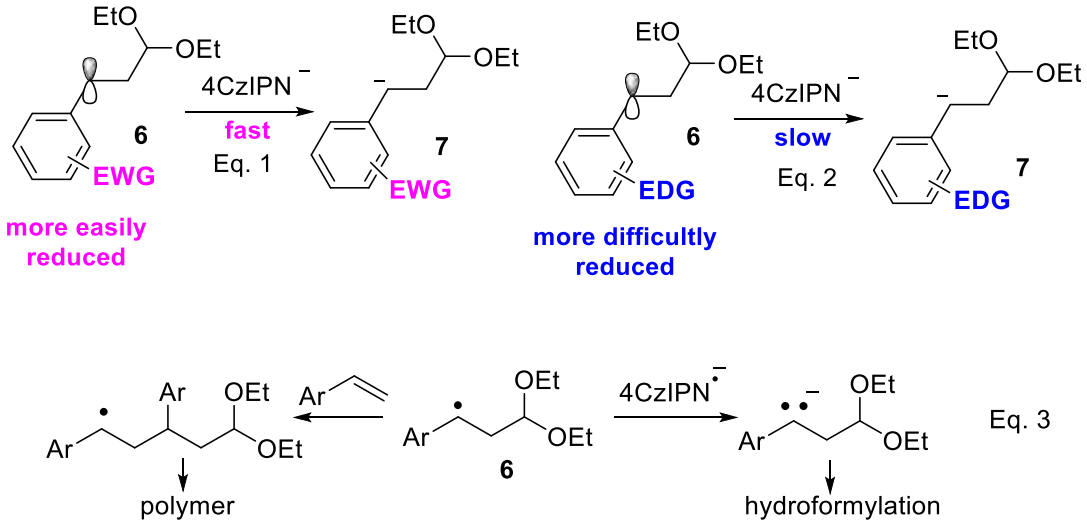
4.3.3 Mechanism Study

A plausible mechanism for the organo-photocatalyzed, free radical hydroformylation process (Scheme 4.4) is initiated by single electron transfer (SET) from 2,2-diethoxyacetate to the singlet excited state of 4CzlPN formed by blue LED irradiation. Rapid decarboxylation of the formed carboxy radical generates the formyl radical equivalent **5** which undergoes anti-Markovnikov addition to the C=C bond of styrene to produce the stable benzylic radical **6**. The process is then terminated by SET from the radical anion of 4CzIPN to **6** to form anion **7** and concurrent generation of the photocatalyst 4CzIPN. Protonation of **7** followed by acid catalyzed hydrolysis of the acetal then yields the target aldehyde.

Scheme 4.4 Proposed Catalytic Cycle



Scheme 4.5 Benzyl Radical Quenching Process



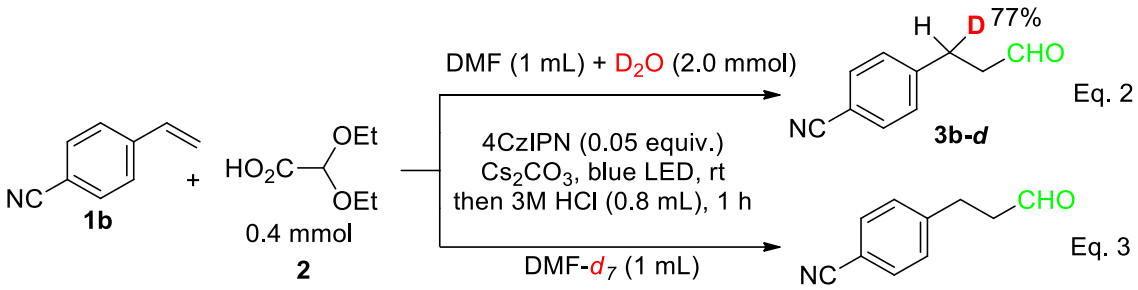
The effects of styrene arene ring substituents on the relative efficiencies of hydroformylation and polymerization, noted above, are fully consistent with the mechanistic pathway outlined in Scheme 4.4. Specifically, the aldehyde to polymer ratio formed in this

process should be governed by the relative rates of reduction of benzyl radical **6** by SET from the radical anion of 4CzlPN and addition of radical **6** to the styrene (Scheme 4.5). It is known[14] that the rates of benzyl radical additions to *p*-substituted styrenes are retarded when the substituents are electron withdrawing. Consequently, the observation made in this study that electron withdrawing *p*-substituents on the styrenes lead to increased aldehyde formation efficiencies must be a consequence of substituent effects on the rates of reduction of benzyl radical **6**. The rates of this reduction process should parallel the thermodynamic driving force for SET, governed by the oxidation potential of the radical anion of 4CzlPN (-1.21 V, vs SCE)[15] and the reduction potentials of the substituted benzyl radicals. It is known[16] that benzyl radicals bearing electron withdrawing arene ring substituents, have lower reduction potentials (eg., -0.71 V vs SCE for *p*-C(O)Me and -0.77 V vs SCE for *p*-CN). In contrast, neutral and electron donating arene ring substituted benzyl radicals have higher reduction potentials (eg., -1.43 vs SCE for H and -1.62 V vs SCE for *p*-methyl).[16] Because the redox potentials of the 4CzlPN anion radical and the benzyl radicals were determined using completely different methods, they cannot be employed to calculate free energy changes in an accurate manner. However, the redox potentials suggest that SET from the radical anion of 4CzlPN to benzylic radicals bearing electron withdrawing groups will be exergonic while SET to benzylic radicals bearing electron donating arene groups will be endergonic. Thus, it is reasonable to conclude that the observed substituents effects on the relative efficiencies of hydroformylation and polymerization are a result of variations in the rates of conversion of benzyl free radical **6** to the corresponding anion **7**.

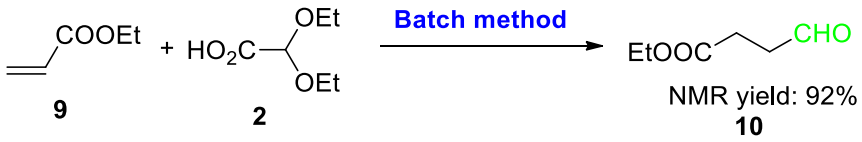
When 2.0 mmol (10 equiv) of D_2O is present in the mixture employed to hydroformylate **1b**, the deuterated aldehyde **3b-*d***, (77% d-content, ca. 83% of theoretical) is formed (Scheme 4.6, Eq. 1). A control experiment using DMF-d_7 as solvent was conducted to verify that the benzylic

hydrogen in the product does not arise in part from DMF (Scheme 4.6, Eq. 2). The results show that the aldehyde produced under these conditions does not contain deuterium. Reaction can be also applied into electron-poor olefins (Scheme 4.7).

Scheme 4.6 Experiments for Preliminary Mechanism Study



Scheme 4.7 Reaction with electron-poor olefins



4.4 Conclusion

In summary, the investigation described above led to the development of an unprecedented, chemo- and regio-selective, organo-photoredox catalyzed hydroformylation reaction of aryl olefins that utilizes diethoxyacetic acid as the formylation reagent. This process takes place via a photoredox promoted free radical pathway, which differs significantly from those followed in traditional transition metal promoted formylation protocols. The process produces linear aldehydes in up to 90% yield. A broad array of functional groups are tolerated because of the mild conditions employed for the reactions. Further efforts are underway to gain a

more detailed understanding the mechanism of this process and to develop unique, preparatively useful photoredox catalyzed reactions.

4.5 Experimantal Section

4.5.1 General Information

Commercially available reagents were purchased from Sigma Aldrich, Matrix Chemical, AKSci, Alfa Aesar, or TCI, and used as received unless otherwise noted. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with a fluorescence F_{254} indicator were used for thin-layer chromatography (TLC) analysis.^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 and 500 MHz. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) relative to residual chloroform (7.26 ppm) or dimethyl sulfoxide (2.50 ppm) as internal standards. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet), coupling constant in Hertz (Hz) and hydrogen numbers based on integration intensities. ^{13}C NMR chemical shifts are reported in ppm relative to the central peak of $CDCl_3$ (77.16 ppm) or $(CD_3)_2SO$ (39.52 ppm) as internal standards. ^{19}F NMR chemical shifts are reported in ppm relative to the central peak of $C_6H_5CF_3$ (-63.72 ppm) as internal standards. Cyclic voltammetry was performed at 25 °C on a CH Instrument CHI604xD electrochemical analyzer using a glassy carbon working electrode, a platinum wire counter electrode, and a Ag/AgCl reference electrode calibrated using ferrocene redox couple (4.8 eV below vacuum). DMF was degassed by the freeze-pump-thaw method and used within 2 days.

4.5.2 General Procedures

Procedure A for compounds 3h, 3i, 3j, 3m, 3o, 3r, 3x, 3y, 3aa and 3ab in scheme 4.2 and 4.3

To an oven-dried 20 mL-Schlenk tube equipped with a stir bar, was added Cs_2CO_3 (65.2 mg, 0.2 mmol), 4CzIPN (7.9 mg, 0.01 mmol), aryl olefins (0.4 mmol if it is solid). Then, DMF (10 mL) was added followed by aryl olefins (0.4 mmol if it is liquid) and 2,2-diethoxyacetic acid (30 μL, 0.2 mmol), were injected into the tube by syringe under a N_2 atmosphere. The mixture was degassed for 30 min by bubbling N_2 stream, then sealed with parafilm. The solution was then stirred at room temperature under the irradiation of a blue LED strip for 36 h. After completion of the reaction, the mixture was quenched by addition of 0.8 mL of 3.0 M HCl, stirred for 1.0 h and 40 mL of water was added. The combined solution was extracted with ethyl acetate (three times). The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.

Procedure B for compounds 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3k, 3l, 3n, 3t, 3u, 3v, 3w, 3z, 3aa and 3ab in scheme 4.2 and 4.3

To an oven-dried 10 mL-Schlenk tube equipped with a stir bar was added Cs_2CO_3 (130.4 mg, 0.4 mmol), 4CzIPN (7.9 mg, 0.01mmol), aryl olefins (0.2 mmol if it is solid). Then, DMF (1.0 mL) was added followed by aryl olefins (0.2 mmol if it is liquid) and 2,2-diethoxyacetic acid (60 μL, 0.4 mmol), were injected into the tube by syringe under a N_2 atmosphere. The mixture was degassed for 30 min by bubbling N_2 stream, then sealed with parafilm. The reaction mixture is then pumped through the photoreactor at a flow rate to achieve a setting residence time and collected in the flask. After completion, the reaction was quenched by addition of 0.8 mL of 3.0 M HCl, stirred for 1.0 h and 5 mL of water was added. The combined solution extracted by ethyl acetate three times. The combined organic layer was washed with brine and

then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.

Procedure C for compounds 3p, 3q, 3s and 3w in scheme 4.2

To an oven-dried 10 mL-Schlenk tube equipped with a stir bar was added Cs_2CO_3 (130.4 mg, 0.4 mmol), 4CzIPN (7.9 mg, 0.01mmol), aryl olefins (0.2 mmol if it is solid). Then, DMF (1.0 mL) was added followed by aryl olefins (0.2 mmol if it is liquid) and 2,2-diethoxyacetic acid (60 μL, 0.4 mmol), were injected into the tube by syringe under a N_2 atmosphere. The mixture was degassed for 30 min by bubbling N_2 stream, then sealed with parafilm. The reaction mixture is then pumped through the photoreactor at a flow rate to achieve a setting residence time and collected in the flask. After completion, the reaction was quenched by addition of 1.2 mL of 3.0 M HCl, stirred for 12 h and then saturated $NaHCO_3$ solution was added to adjust pH to basic. Then 5 mL of water was added. The combined solution extracted by ethyl acetate three times. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.

Procedure D for compounds 3a in gram scale

To an oven-dried 250 mL-Schlenk tube equipped with a stir bar was added Cs_2CO_3 (13 g, 40 mmol), 4CzIPN (474 mg, 0.6 mmol). Then, DMF (100 mL) was added followed by 1-(trifluoromethyl)-4-vinylbenzene (3.44 g, 3.0 ml, 20 mmol) and 2,2-diethoxyacetic acid (6.0 mL, 40 mmol), were injected into the tube by syringe under a N_2 atmosphere. The mixture was degassed for 60 min by bubbling N_2 stream, then sealed with parafilm. The reaction mixture is

then pumped through the photoreactor at a flow rate to achieve a setting residence time of 150 min and collected in the flask. After completion of the reaction, the mixture was cooled to -10 ºC then quenched by 80 mL of 3.0 M HCl slowly, stirred for 2 h at rt and 500 ml water was added. The combined solution extracted by ethyl acetate three times. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired product was obtained of 3.52 g product in 87% yields after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.

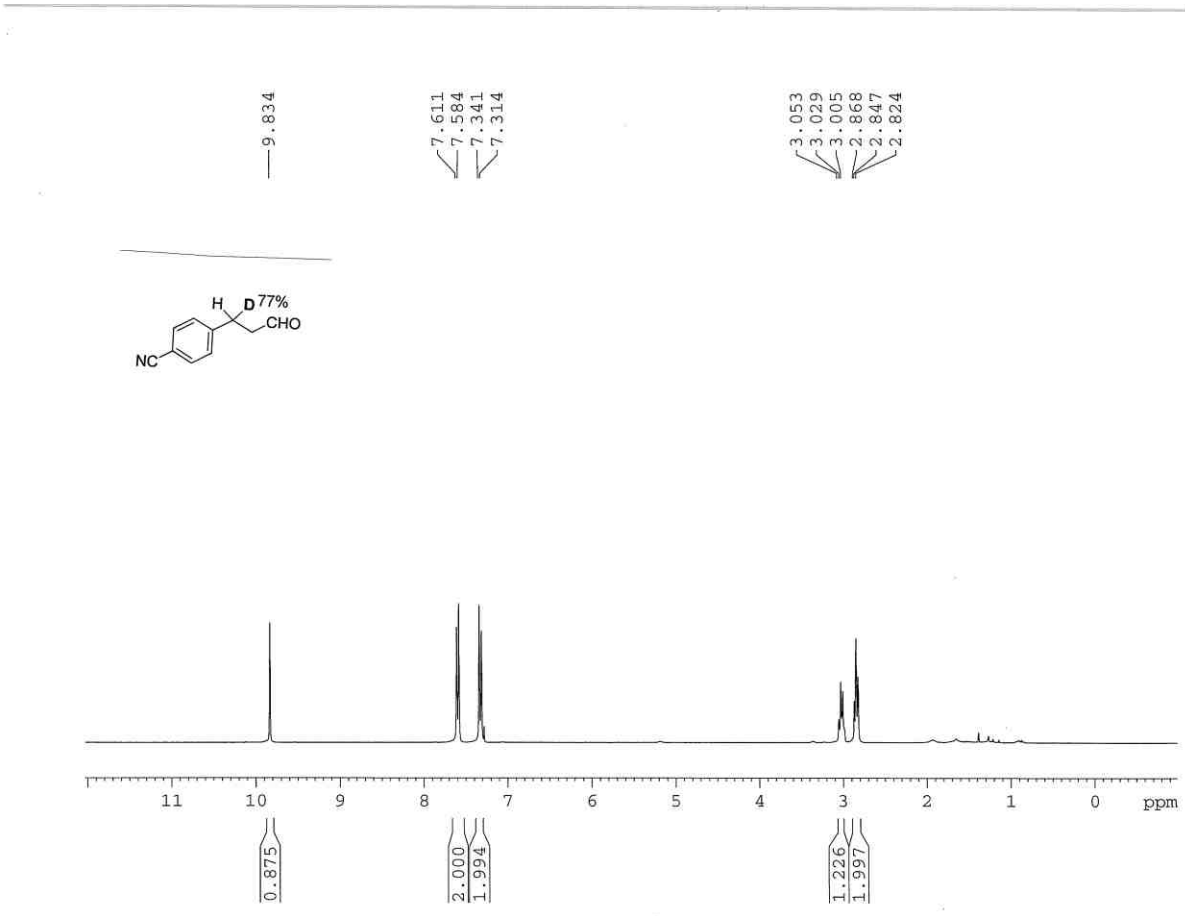
Procedure E for compounds 3a-ace in table 4.1

To an oven-dried 10 mL-Schlenk tube equipped with a stir bar was added Cs_2CO_3 (130.4 mg, 0.4 mmol), 4CzIPN (7.9 mg, 0.01mmol). Then, DMF (1.0 mL), 1-(trifluoromethyl)-4-vinylbenzene (34.4 mg, 0.2 mmol) and 2,2-diethoxyacetic acid (60 µL, 0.4 mmol), were injected into the tube by syringe under a N_2 atmosphere. The mixture was degassed for 30 min by bubbling N_2 stream, then sealed with parafilm. The reaction mixture is then pumped through the photoreactor at a flow rate to achieve a setting residence time and collected in the flask. After completion, 5 mL of water was added. The combined solution extracted by ethyl acetate three times. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products were obtained in the corresponding yield after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.

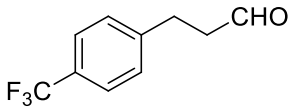
Procedure for machnism study

To an oven-dried 10 mL-Schlenk tube equipped with a stir bar was added Cs_2CO_3 (130.4 mg, 0.4 mmol), 4CzIPN (7.9 mg, 0.01mmol). Then, DMF (1.0 mL) was added followed by 4-vinylbenzonitrile (25.8 mg, 0.2 mmol), D_2O (40 µl, 2 mmol) and 2,2-diethoxyacetic acid (60 µL,

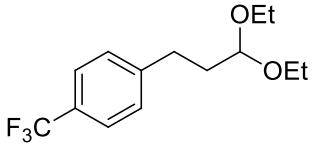
0.4 mmol), were injected into the tube by syringe under a N_2 atmosphere. The mixture was degassed for 30 min by bubbling N_2 stream, then sealed with parafilm. The reaction mixture is then pumped through the photoreactor at a flow rate to achieve a setting residence time and collected in the flask. After completion, the reaction was quenched by addition of 0.8 mL of 3.0 M HCl, stirred for 1.0 h and 5 mL of water was added. The combined solution extracted by ethyl acetate three times. The combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4 and evaporated in vacuum. The desired products **3b-*d*** were obtained in the corresponding yields after purification by flash chromatography on silica gel eluting with hexanes and ethyl acetate.



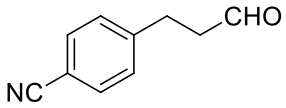
4.6 Characterization



3-(4-(trifluoromethyl)phenyl)propanal **(3a):** The title compound was prepared according to the general procedure B as a colorless oil (34.4 mg, yield = 85%) after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.56 (d, 2H, *J* = 8.1 Hz), 7.33 (d, 2H, *J* = 8.1 Hz), 3.04 (t, 2H, *J* = 7.2 Hz), 2.87-2.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 144.4, 128.6, 128.5 (q, *J* = 32.5 Hz), 125.4 (q, *J* = 3.75 Hz), 124.1 (q, *J* = 271.3 Hz), 44.7, 27.7.

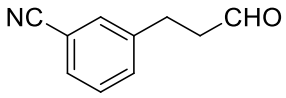


allyl 4-(3-oxopropyl)benzoate **(3a-ace):** The title compound was prepared according to the general procedure E as a colorless oil (45.3 mg, yield = 82%) after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, 1H, *J* = 8.1 Hz), 7.30 (d, 1H, *J* = 7.8 Hz), 4.48 (t, 1H, *J* = 5.4 Hz), 3.71-3.61 (m, 2H), 3.55-3.44 (m, 2H), 2.78-2.72 (m, 2H), 1.98-1.91 (m, 2H), 1.24-1.19 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.0, 128.7, 128.2 (q, *J* = 32.3 Hz), 125.2 (d, *J* = 3.6 Hz), 124.4 (q, *J* = 270 Hz), 101.9, 61.2, 34.8, 30.8, 15.3.

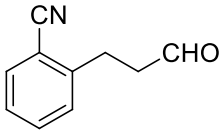


4-(3-oxopropyl)benzonitrile **(3b):** The title compound was prepared according to the general procedure B as a colorless oil (24.8 mg, yield = 78%) after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.83 (s, 1H), 7.59 (d, 2H, *J* = 8.1 Hz), 7.33 (d, 2H, *J* = 8.1 Hz), 3.03 (t, 2H, *J* = 7.5 Hz), 2.87-2.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 146.1, 132.4, 129.2,

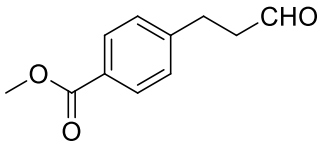
118.9, 110.3, 44.5, 28.0.



3-(3-oxopropyl)benzonitrile **(3c):** The title compound was prepared according to the general procedure B as a colorless oil (24.2 mg, yield = 76%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.53-7.52 (m, 2H), 7.48-7.46 (m, 1H), 7.43-7.41 (m, 1H), 3.01 (t, 2H, *J* = 7.5 Hz), 2.86-2.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.3, 141.8, 132.9, 131.8, 130.0, 129.3, 118.7, 112.5, 44.6, 27.4.

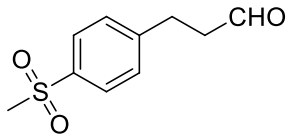


2-(3-oxopropyl)benzonitrile **(3d):** The title compound was prepared according to the general procedure B as a colorless oil (22.3 mg, yield = 70%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.66-7.65 (m, 1H), 7.56-7.53 (m, 1H), 7.40-7.33 (m, 2H), 3.20 (t, 2H, *J* = 7.5 Hz), 2.93-2.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.0, 144.2, 132.9, 132.9, 129.1, 126.9, 117.7, 112.2, 44.0, 26.7.

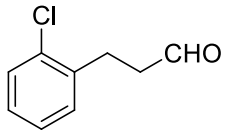


methyl 4-(3-oxopropyl)benzoate **(3e):** The title compound was prepared according to the general procedure B as a white solid (28.8 mg, yield = 75%) after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.97 (d, 2H, *J* = 8.1 Hz), 7.27 (d, 2H, *J* = 8.4 Hz), 3.90

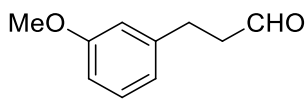
(s, 3H), 3.01 (t, 2H, *J* = 7.5 Hz), 2.84-2.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.7, 166.8, 145.7, 129.8, 128.2, 51.9, 44.7, 27.9.



3-(4-(methylsulfonyl)phenyl)propanal **(3f):** The title compound was prepared according to the general procedure B as a white solid (34.0 mg, yield = 80%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (t, 1H, *J* = 1.0 Hz), 7.81 (d, 2H, *J* = 8.0 Hz), 7.38 (d, 2H, *J* = 8.0 Hz), 3.02-3.00 (m, 5H), 2.84-2.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.4, 147.0, 138.4, 129.3, 127.5, 44.4, 27.7.

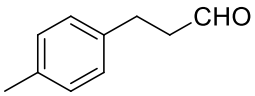


3-(2-chlorophenyl)propanal **(3g):** The title compound was prepared according to the general procedure B as a colorless oil (23.6 mg, yield = 70%) after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.86 (t, 1H, *J* = 1.2 Hz), 7.39-7.36 (m, 1H), 7.28-7.18 (m, 3H), 3.09 (t, 2H, *J* = 7.2 Hz), 2.85-2.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.1, 138.0, 133.9, 130.5, 129.6, 127.9, 127.0, 43.5, 26.2.

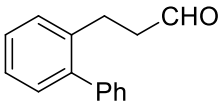


3-(3-methoxyphenyl)propanal **(3h):** The title compound was prepared according to the general procedure A as a colorless oil (16.7 mg, yield = 51%) after silica gel chromatography. ^{1}H

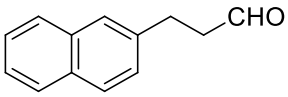
NMR (300 MHz, $CDCl_3$): δ 9.85 (t, 1H, *J* = 0.9 Hz), 7.29-7.21 (m, 1H), 6.82-6.77 (m, 3H), 3.82 (s, 3H), 2.96 (t, 2H, *J* = 7.5 Hz), 2.83-2.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.5, 159.7, 141.8, 129.5, 120.5, 114.0, 111.4, 55.1, 45.1, 28.0.



3-(p-tolyl)propanal **(3i):** The title compound was prepared according to the general procedure A as a colorless oil (17.8 mg, yield = 60%) after silica gel chromatography. ^1H NMR (500 MHz, $CDCl_3$): δ 9.82 (t, 1H, *J* = 1.5 Hz), 7.10-7.08 (m, 4H), 2.93 (t, 2H, *J* = 7.5 Hz), 2.78-2.75 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 137.1, 135.7, 129.2, 128.1, 45.3, 27.6, 20.9.

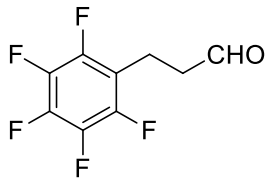


3-([1,1'-biphenyl]-2-yl)propanal **(3j):** The title compound was prepared according to the general procedure A as a light yellow oil (29.9 mg, yield = 71%) after silica gel chromatography. ^1H NMR (300 MHz, $CDCl_3$): δ 9.66 (t, 1H, *J* = 1.5 Hz), 7.45-7.25 (m, 9H), 2.98 (t, 2H, *J* = 7.2 Hz), 2.60-2.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 141.9, 141.3, 137.6, 130.2, 129.0, 128.9, 128.2, 127.6, 127.0, 44.8, 25.6.

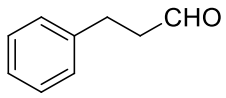


3-(naphthalen-2-yl)propanal **(3k):** The title compound was prepared according to the general procedure B as a colorless oil (22.1 mg, yield = 60%) after silica gel chromatography. ^1H

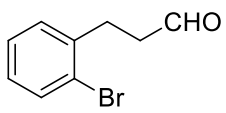
NMR (500 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.84-7.80 (m, 3H), 7.66 (s, 1H), 7.51-7.45 (m, 2H), 7.37-7.35 (m, 1H), 3.16 (t, 2H, *J* = 7.5 Hz), 2.92-2.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 137.7, 133.5, 132.0, 128.2, 127.5, 127.3, 126.8, 126.3, 126.0, 125.4, 45.1, 28.2.



3-(perfluorophenyl)propanal **(3l):** The title compound was prepared according to the general procedure B as a colorless oil (NMR yield = 60%, with dimethyl maleate as an internal standard) after silica gel chromatography. ^1H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H), 3.02 (t, 2H, *J* = 7.2 Hz), 2.81-2.76 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ -142.12--142.20 (m, 2F), -155.38 (s, 1F), -160.91--161.01 (m, 2F).

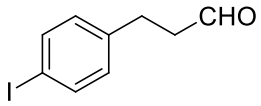


3-phenylpropanal **(3m):** The title compound was prepared according to the general procedure A as a colorless oil (NMR yield = 60%, with dimethyl maleate as an internal standard) after silica gel chromatography. ^1H NMR (500 MHz, $CDCl_3$): δ 9.85 (t, 1H, *J* = 1.5 Hz), 7.35-7.23 (m, 5H), 3.00 (t, 2H, *J* = 7.5 Hz), 2.83-2.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.5, 140.2, 128.5, 128.2, 126.2, 45.2, 28.0.

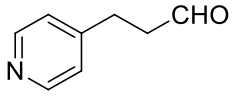


3-(2-bromophenyl)propanal **(3n):** The title compound was prepared according to the

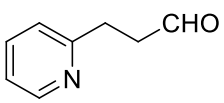
general procedure B as a colorless oil (27.7 mg, yield = 65%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.57-7.55 (m, 1H), 7.29-7.27 (m, 2H), 7.12-7.09 (m, 1H), 3.09 (t, 2H, *J* = 7.5 Hz), 2.85-2.82 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9, 139.6, 132.9, 130.4, 128.0, 127.6, 124.2, 43.6, 28.6.



***3-(4-iodophenyl)propanal* (3o):** The title compound was prepared according to the general procedure A as a white solid (32.3 mg, yield = 62%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.83 (t, 1H, *J* = 1.0 Hz), 7.63 (d, 2H, *J* = 8.0 Hz), 6.97 (d, 2H, *J* = 8.0 Hz), 2.93 (t, 2H, *J* = 7.5 Hz), 2.81-2.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9, 139.9, 137.5, 130.3, 91.3, 44.9, 27.4.

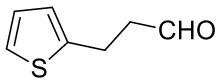


***3-(pyridin-4-yl)propanal* (3p):** The title compound was prepared according to the general procedure C as a white solid (20.3 mg, yield = 75%) after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (s, 1H), 8.45 (d, 2H, *J* = 6.0 Hz), 7.07 (d, 2H, *J* = 6.0 Hz), 2.90 (t, 2H, *J* = 7.5 Hz), 2.80-2.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 149.9, 149.3, 123.7, 43.9, 27.2.

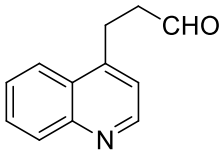


***3-(pyridin-2-yl)propanal* (3q):** The title compound was prepared according to the general

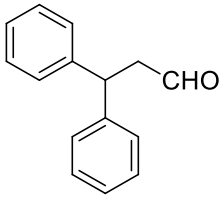
procedure C as a white solid (17.0 mg, yield = 63%) after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.88 (s, 1H), 8.51-8.50 (m, 1H), 7.62-7.57 (m, 1H), 7.21-7.10 (m, 2H), 3.14 (t, 2H, *J* = 7.2 Hz), 2.97-2.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.5, 159.6, 149.1, 136.3, 122.9, 121.2, 42.5, 30.2.



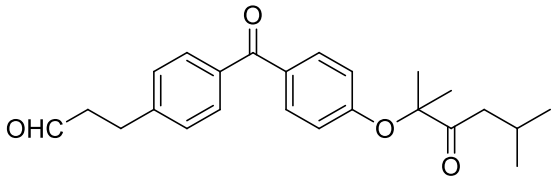
3-(thiophen-2-yl)propanal **(3r):** The title compound was prepared according to the general procedure A as a colorless oil (NMR yield = 75%, with dimethyl maleate as an internal standard) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.83 (s, 1H), 7.14-7.13 (m, 1H), 6.93-6.91 (m, 1H), 6.82-6.82 (m, 1H), 3.18 (t, 2H, *J* = 8.0 Hz), 2.86-2.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9, 142.9, 126.9, 124.7, 123.6, 45.3, 22.4.



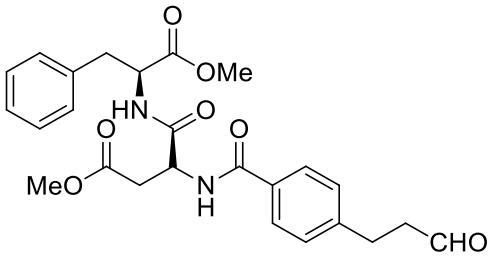
3-(quinolin-4-yl)propanal **(3s):** The title compound was prepared according to the general procedure C as a white solid (NMR yield = 90%, with dimethyl maleate as an internal standard) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.92 (t, 1H, *J* = 1.0 Hz), 8.85-8.85 (m, 1H), 8.17-8.15 (m, 1H), 8.04-8.02 (m, 1H), 7.77-7.74 (m, 1H), 7.63-7.60 (m, 1H), 7.28-7.28 (m, 1H), 3.45 (t, 2H, *J* = 7.5 Hz), 3.01-2.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.1, 150.1, 148.3, 146.1, 130.4, 129.2, 127.0, 126.6, 122.9, 120.6, 43.4, 24.0.



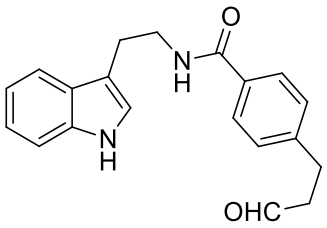
3,3-diphenylpropanal **(3t):** The title compound was prepared according to the general procedure B as a white solid (31.5 mg, yield = 75%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (t, 1H, *J* = 2.0 Hz), 7.32-7.19 (m, 10H), 4.63 (t, 1H, *J* = 8.0 Hz), 3.19-3.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9, 143.1, 128.6, 127.6, 126.6, 49.3, 44.9.



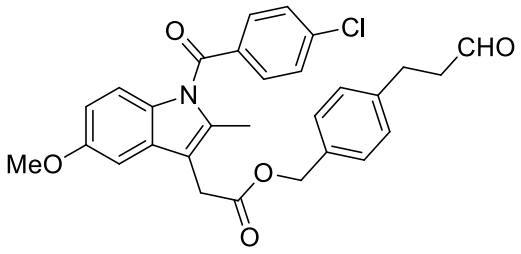
3-(4-(4-((2,5-dimethyl-3-oxohexan-2-yl)oxy)benzoyl)phenyl)propanal **(3u):** The title compound was prepared according to the general procedure B as a white solid (61.6 mg, yield = 81%) after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.83 (t, 1H, *J* = 1.2 Hz), 7.75-7.67 (m, 4H), 7.30-7.26 (m, 2H), 6.87-6.84 (m, 2H), 5.12-5.03 (m, 1H), 3.03 (t, 2H, *J* = 7.5 Hz), 2.85-2.81 (m, 2H), 1.65 (s, 6H), 1.19 (d, 6H, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.9, 195.1, 173.2, 159.5, 144.9, 136.3, 131.9, 130.7, 130.2, 128.2, 117.2, 79.4, 69.3, 44.9, 28.0, 25.4, 21.5.



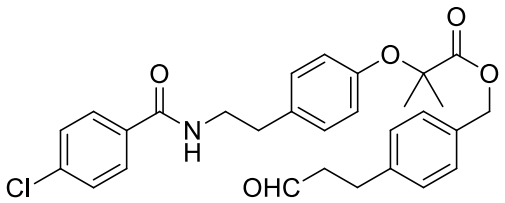
(R)-methyl-4-(((S)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-4-oxo-3-(4-(3 oxopropyl)benzamido)butanoate **(3v):** The title compound was prepared according to the general procedure B as a white solid (66.5 mg, yield = 71%) after silica gel chromatography. ^{1}H NMR (500 MHz, DMSO-*d6*): δ 9.72 (s, 1H), 9.13-9.11 (m, 1H), 7.79-7.77 (m, 2H), 7.36-7.22 (m, 7H), 5.02-4.95 (m, 1H), 4.68-4.45 (m, 1H), 3.70 (s, 3H), 3.43-3.39 (m, 1H), 3.11-2.89 (m, 6H), 2.83-2.74 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.0, 175.0, 173.4, 168.6, 167.2, 162.6, 144.9, 136.4, 130.6, 128.9, 128.5, 127.5, 127.054.0, 52.9, 49.2, 44.6, 36.5, 35.5, 34.0, 27.7.



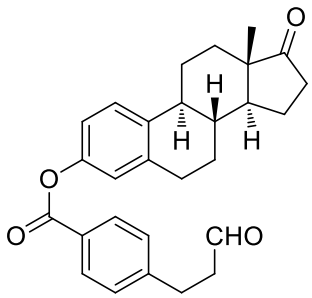
N-(2-(1H-indol-3-yl)ethyl)-4-(3-oxopropyl)benzamide **(3w):** The title compound was prepared according to the general procedure C as a light yellow solid (35.2 mg, yield = 55%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.18 (br, 1H), 7.66-7.64 (m, 1H), 7.60-7.59 (m, 2H), 7.40-7.38 (m, 1H), 7.24-7.06 (m, 5H), 6.21 (br, 1H), 3.79 (q, 2H, *J* = 6.5 Hz), 3.09 (t, 2H, *J* = 6.5 Hz), 2.96 (t, 2H, *J* = 7.5 Hz), 2.80-2.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.0, 167.1, 143.9, 136.3, 132.6, 128.4, 127.2, 127.1, 122.2, 122.0, 119.5, 118.7, 112.9, 111.2, 44.8, 40.1, 27.7, 25.2.



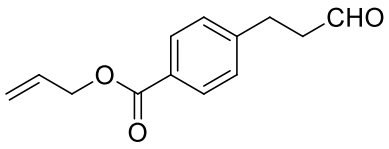
4-(3-oxopropyl)benzyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate **(3x):** The title compound was prepared according to the general procedure A as a white solid (50.4 mg, yield = 50%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (t, 1H, *J* = 1.5 Hz), 7.65 (d, 2H, *J* = 8.5 Hz), 7.45 (d, 2H, *J* = 8.5 Hz), 7.27-7.25 (m, 2H), 7.19-7.17 (m, 2H), 6.97-6.92 (m, 2H), 6.70-6.68 (m, 1H), 5.13 (s, 2H), 3.78 (s, 3H), 3.73 (s, 2H), 2.96 (t, 2H, *J* = 7.5 Hz), 2.79-2.76 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.3, 170.6, 168.1, 155.9, 140.6, 139.1, 135.8, 133.8, 133.7, 131.1, 130.7, 130.5, 129.0, 128.5, 128.4, 114.9, 112.4, 111.7, 101.1, 66.5, 55.5, 45.0, 30.3, 27.6, 13.3.



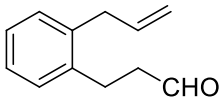
4-(3-oxopropyl)benzyl 2-(4-(2-(4-chlorobenzamido)ethyl)phenoxy)-2-methylpropanoate **(3y):** The title compound was prepared according to the general procedure A as a white solid (52.8 mg, yield = 52%) after silica gel chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (t, 1H, *J* = 1.5 Hz), 7.64-7.61 (m, 2H), 7.33-7.30 (m, 2H), 7.22-7.12 (m, 4H), 7.01-6.98 (m, 2H), 6.74-6.71 (m, 3H), 5.15 (s, 2H), 3.60-3.58 (m, 2H), 2.95-2.73 (m, 6H), 1.58 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.6, 174.1, 166.5, 154.0, 140.6, 137.5, 133.4, 133.0, 132.6, 129.4, 128.7, 128.6, 128.5, 128.4, 119.5, 79.2, 66.8, 45.0, 41.4, 37.7, 27.7, 25.4.



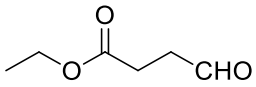
(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-(3-oxopropyl)benzoate **(3z):** The title compound was prepared according to the general procedure B as a colorless oil (65.4 mg, yield = 76%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.85 (s, 1H), 8.11 (d, 2H, *J* = 8.0 Hz), 7.33 (d, 3H, *J* = 8.0 Hz), 6.98-6.94 (m, 2H), 3.05 (t, 1H, *J* = 7.5 Hz), 2.94-2.93 (m, 2H), 2.86-2.83 (m, 2H), 2.54-1.96 (m, 8H), 1.64-1.56 (m, 3H), 1.55-1.48 (m, 2H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 220.7 200.6, 165.2, 148.7, 146.5, 138.0, 137.3, 130.4, 128.4, 127.7, 126.4, 121.6, 118.8, 50.3, 47.9, 44.7, 44.1, 17.9, 35.8, 31.4, 29.3, 28.0, 26.3, 25.7, 21.5, 13.7.



allyl 4-(3-oxopropyl)benzoate **(3aa):** The title compound was prepared according to the general procedure B as a colorless oil (37.1 mg, yield = 85%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.85 (t, 1H, *J* = 1.0 Hz), 8.02-8.01 (m, 2H), 7.29 (d, 2H, *J* = 8.0 Hz), 6.09-6.02 (m, 1H), 5.45-5.40 (m, 1H), 5.32-5.29 (m, 1H), 4.84-4.83 (m, 2H), 3.03 (t, 2H, *J* = 7.5 Hz), 2.85-2.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.7, 166.0, 145.8, 132.1, 129.9, 128.3, 128.2, 118.1, 65.4, 44.7, 27.9.



3-(2-allylphenyl)propanal **(3ab):** The title compound was prepared according to the general procedure A as a colorless oil (36.1 mg, yield = 75%) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.83 (t, 1H, *J* = 1.0 Hz), 7.18-7.15 (m, 4H), 6.01-5.93 (m, 1H), 5.10-5.06 (m, 1H), 5.00-4.96 (m, 1H), 3.42-3.40 (m, 2H), 2.96 (t, 2H, *J* = 7.5 Hz), 2.77-2.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 138.3, 137.5, 136.9, 129.9, 128.8, 126.6, 126.5, 115.8, 44.7, 37.0, 24.7.



ethyl 4-oxobutanoate **(10):** The title compound was prepared according to the general procedure A as a colorless oil (NMR yield = 92%, with dimethyl maleate as an internal standard) after silica gel chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (t, 1H, *J* = 0.5 Hz), 4.17-4.13 (m, 2H), 2.80 (t, 2H, *J* = 6.5 Hz), 2.64-2.61 (m, 2H), 1.28-1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.9, 172.1, 60.7, 38.4, 26.5, 14.0.

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Chapter 5

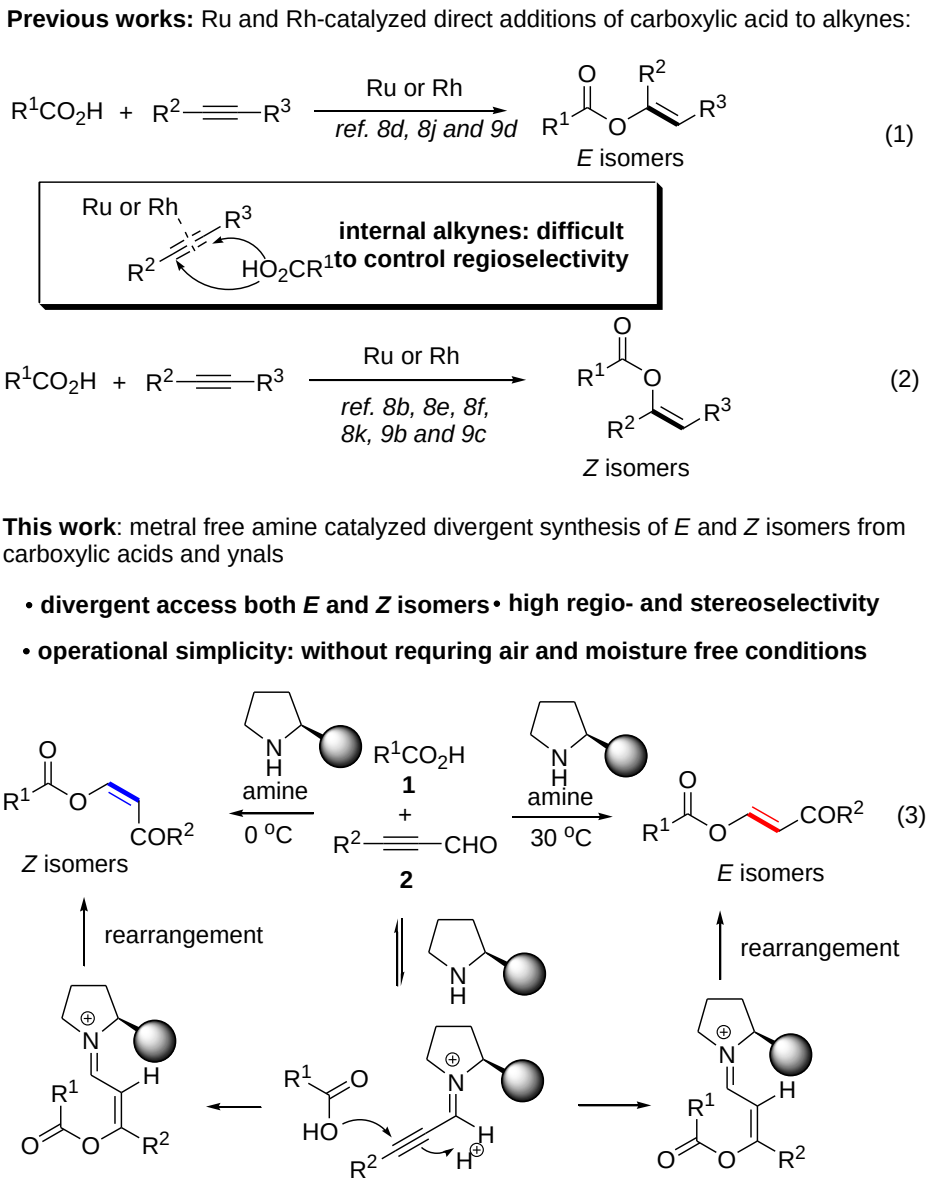
Highly Regio- and Stereoselective Synthesis of *Z* and *E* Enol Esters by an Amine Catalyzed Unexpected Conjugate Addition-rearrangement Reaction of Ynals with Carboxylic Acids

5.1 Introduction

Enol esters are a unique class of compounds. They are more labile than those of enol ethers and aryl esters. However, the functionality is featured in a number of natural products with intriguing biological properties such as anti-cancer, inhibitory BACE1, and anti-viral activities.[1] Moreover, their lability endows high activity as versatile building blocks in organic synthesis. They have been widely used for a variety of transformations such as aldol and Mannich,[2] asymmetric hydrogenation,[3] cyclization,[4] and cross-coupling[5] reactions. The stereo-configuration of products produced highly depend on the geometry of *E* and *Z* isomers of the enol esters employed. Therefore the stereoselective synthesis of *E* and *Z* isomers is critically important for their synthetic applications. The state-of-the-art technologies for their syntheses are dominated by transition metal catalysis.[6-11] One of the attractive approaches involves the direct addition of simple carboxylic acids to alkynes in the presence of transition metal promoters. The pioneering study of Ru promoted addition of carboxylic acids to alkynes by Rotem and Shvo[8a] has triggered significant interests on the development of effective Ru,[8] or Rh[9] complexes as catalysts aimed at improving *E* and *Z* selectivity and/or regioselectivity (Scheme 5.1, Eq. 1 and 2). However, only a handful of approaches are disclosed for the preparation of *E* by Dixneuf,[8d] Itoh[8j] Cramer[9d] or *Z* by Dixneuf,[8b] Gooßen,[8e] Leong,[8f] Inoue,[8k] and Breit[9b,9c] isomers. In principle, *E* and *Z* isomers can be accessed from the same pool of reactants. Nonetheless, to the

best of our knowledge, a strategy capable of producing *E* and *Z* isomers in an efficient divergent fashion remains elusive. Furthermore, it is difficult for the Ru and Rh activation mode to achieve good regioselectivity for internal alkynes (Scheme 5.1). Finally, in addition to toxicity and cost concerns and the lability of ligand-metal complexes, these transition metals catalyzed reactions are generally performed under restricted air and moisture free conditions.

Scheme 5.1. Methods for Synthesis of Enol Esters.



Herein we wish to report a new alternative catalytic approach to enol esters using metal-free amine as a facilitator for the first time under operationally simple ambient conditions.[11] We found that an amine catalyzed conjugate addition of carboxylic acids to ynals triggered an unexpected subsequent rearrangement leading to highly regio- and stereo-controlled *Z* and *E* enol ester products in a divergent manner (Scheme 5.1, Eq. 3). At lower temperature (0 °C), *Z*-isomers are formed highly stereoselectively (> 15:1 *Z:E*), while at higher temperature (30 °C), thermodynamic control *E* products are produced dominantly (> 15:1 *E:Z*). The strategy reported in this study is distinct from that of widely studied transition metal Ru and Rh catalysis. An unprecedented amine catalyzed the conjugate addition of carboxylic acid to C≡C triple bonds leads to an unexpected rearrangement process for the enol ester formation.

5.2 Research Plan

Iminium catalysis has enjoyed great success.[12] A diverse array of nucleophiles can participate in conjugate addition processes to form new C-C and C-X bonds. Nonetheless, to the best of our knowledge, carboxylic acids as nucleophiles for the amine promoted conjugate addition reactions with enals have not been developed. We believe that weak nucleophilicity and high leaving tendency of carboxylic acids are difficult to be added into an iminium ion in the reversible process. Inspired by our and other groups' studies with ynals in organocatalysis,[13-15] we proposed the use of ynals instead of enals because of the formation of irreversible adduct due to p-π conjugation of the lone pair electrons with the C=C double bond and higher reactivity of ynals than that of enals (Scheme 5.2, Eq. 1).

Scheme 5.2 Amine Catalyzed Conjugate Addition of Carboxylic Acids to Ynals

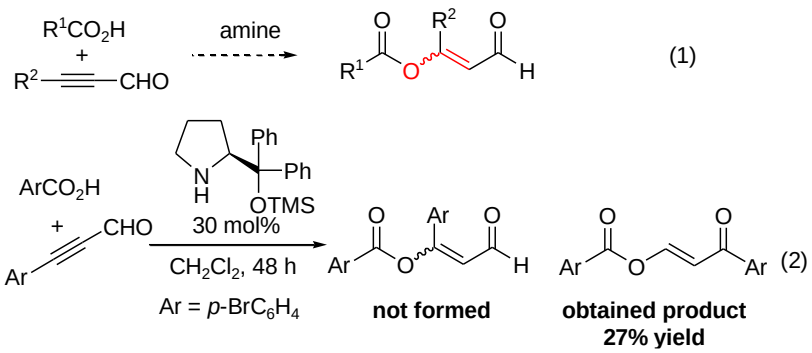
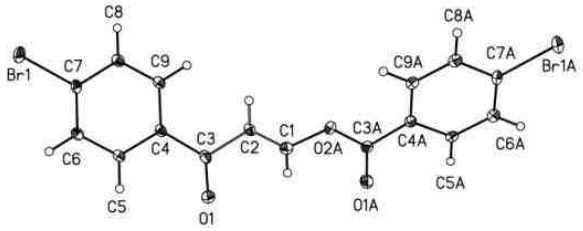
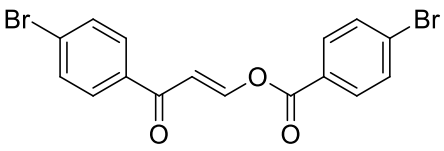


Figure 5.1 X-ray single crystal structure





To validate the feasibility, we performed an exploratory investigation of reacting of 4-bromobenzolic acid with (4-bromophenyl)propynal in the presence of diphenyl prolinol TMS ether (30 mol%) in CH_2Cl_2 (Eq. 2). To our delight but unexpectedly, an *E*-enol ester rather than a conjugate addition adduct was obtained, verified by X-ray single crystal structure (Figure.

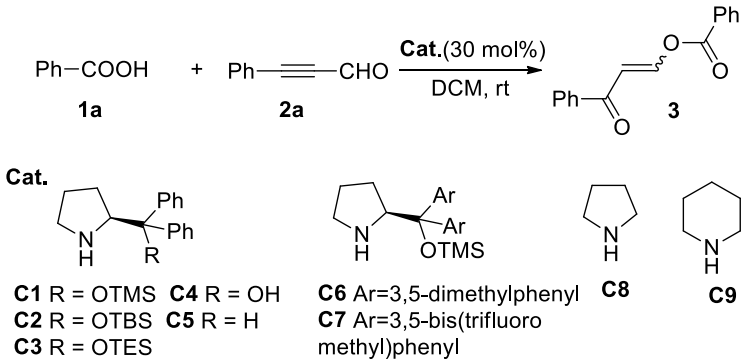
5.1).[16]

5.3 Results and Discussion

5.3.1 Optimization of Reaction Conditions

The unexpected outcomes prompted us to investigate the interesting process in details. In the initial effort, we attempted to optimize the reaction conditions to improve the reaction yields using benzoic acid **1a** and phenylpropiolaldehyde **2a** as substrates in the present of an amine catalyst (Table 5.1). Screening of catalysts (entries 1-9) revealed **C7** giving the best results (76% yield, entry 7). Decreasing the catalyst loading to 20 mol % furnished lower yield (60%, entry 10). We found that the addition of the catalyst in three portions led to improved yield (72%, entry 11). We also noticed that after 24 h at rt the *Z/E* ratio of the product **3a** was 5/1 based on ^{1}H NMR analysis of the reaction mixture. This suggests that the process could involve a kinetic/thermodynamic control. Indeed, at lower temperature (0 °C, entry 12), a kinetic control product *Z* isomer (> 20:1 *Z/E*) was obtained in 80% yield. Higher temperature was favored for the thermodynamic control *E* isomer. Only *E* isomer was produced at 30 °C after 96 h in 72% yield (entry 13). To the best of our knowledge, this study represents the first example, enabling synthesis of both *E* and *Z* enol esters using the same catalytic system and the same reactants.

Table 5.1 Optimization of Amine Catalyzed Synthesis of Enol Esters[a]



Entry	Cat.	t (h)	Yield (%)[b]
1	**C1**	24	29
2	**C2**	24	16
3	**C3**	24	24
4	**C4**	24	36
5	**C5**	48	-
6	**C6**	24	32
7	**C7**	24	76
8	**C8**	48	-
9	**C9**	48	-
10[c]	**C7**	24	60
11[d]	**C7**	24	72
12[d,e]	**C7**	24	80
13[d,f]	**C7**	96	72

[a] Reaction conditions: unless specified, the reaction was carried out with 0.24 mmol of **1a** and 0.2 mmol of **2a** in 0.8 mL of CH_2Cl_2 with 30 mol% catalyst was stirred at rt for a specified time.

Unless specified, see the Experimental Section for reaction conditions. [b] Isolated yields with both isomers. [c] 20% catalyst was used. [d] 20% catalyst was added in three times, each time 1/3 of the total amount catalyst was used, see Methods for details. [e] 0 ºC, Z/E > 20/1. [f] 30 ºC, *E*/*Z* > 20/1.

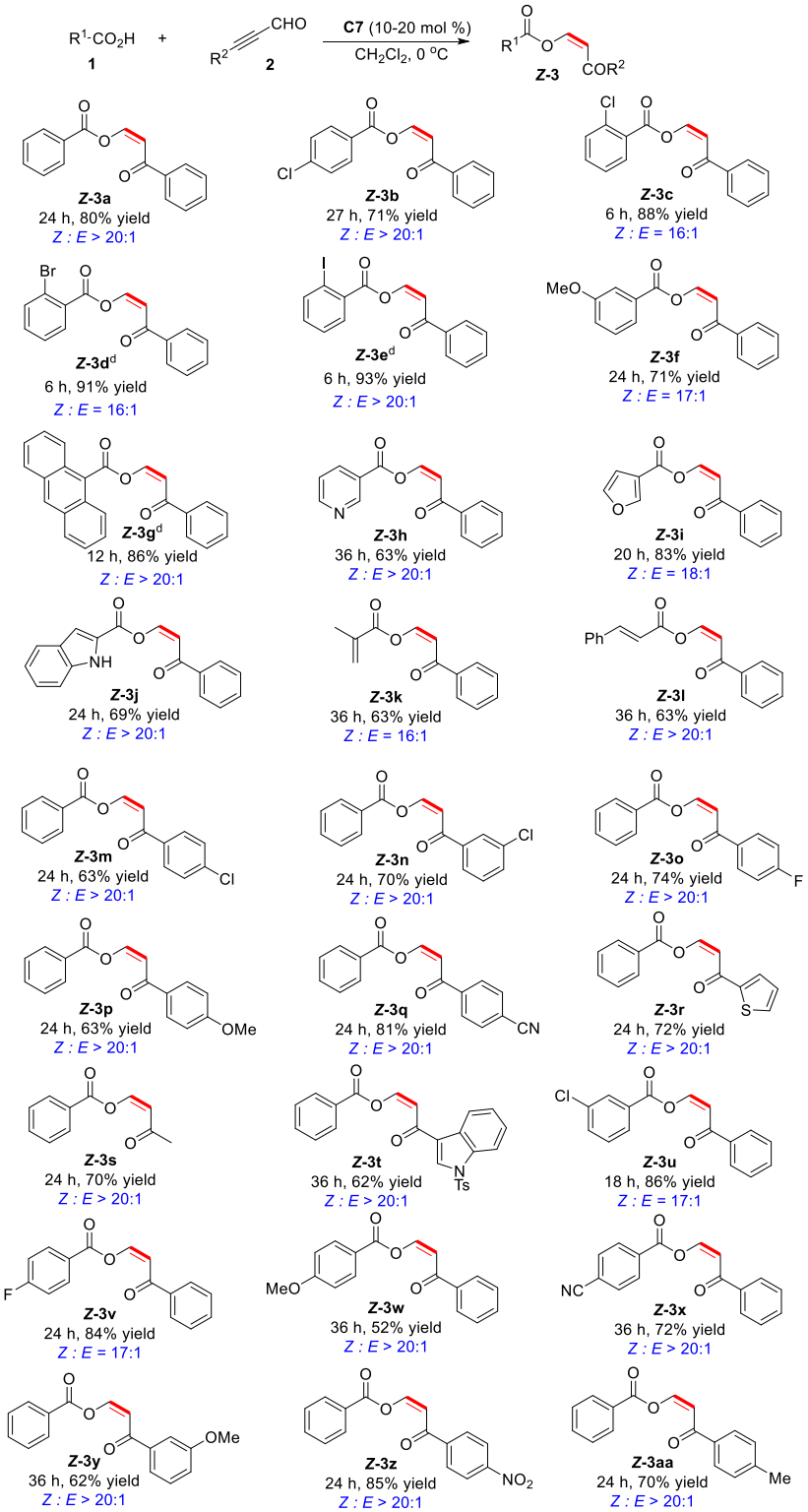
5.3.2 Investigation of Substrate Scope

Synthesis of *Z* isomers

We first probe the scope of the process for the formation of *Z* isomer products. As shown in Scheme 5.3, clean *Z*-enol esters are produced (*Z*/*E* > 15/1). It appears that the reactions have significant tolerance toward structural variations of both reactants, carboxylic acids **1** and ynals **2**. Therefore, structurally diverse *Z*-enol esters are obtained under the mild reaction conditions. First, the electronic and steric effects of different functional groups on the phenyl ring in acids **1** were examined (***Z*-3a** - ***Z*-3f**). It was found that regardless of the electron-neutral, -donating or -withdrawing groups installed on the substrates, all afford the desired products in good to high yields. In addition to substituted phenyl systems, fused aromatic (e.g., 9-anthracenyl, ***Z*-3g**) and heteroaromatic structures including 3-pyridinyl, 3-furanyl and 2-indolyl (***Z*-3h** - ***Z*-3j**) can effectively engage in the processes. It is interestingly observed that for 2-indolyl carboxylic acid, the CO_2H rather than C_3 position, which is considered more nucleophilic, participated in the reaction (***Z*-3j**). We also found that α, β-unsaturated acids such as methacrylic acid (***Z*-3k**) and *trans*-cinnamic acid (***Z*-3l**) could be tolerated by the process in good yields. Examination of the structural alternation of ynals reveals a similar trend (***Z*-3m** - ***Z*-3q**). Furthermore, heteroaromatic and aliphatic systems could be applied (***Z*-3r** - ***Z*-3t**). It is also realized the limitation of the process. Aliphatic acids can participate in the process, but the reactivity is lower than that of aromatics ones. It takes longer reaction time and it produces a mixture of *Z* and *E*

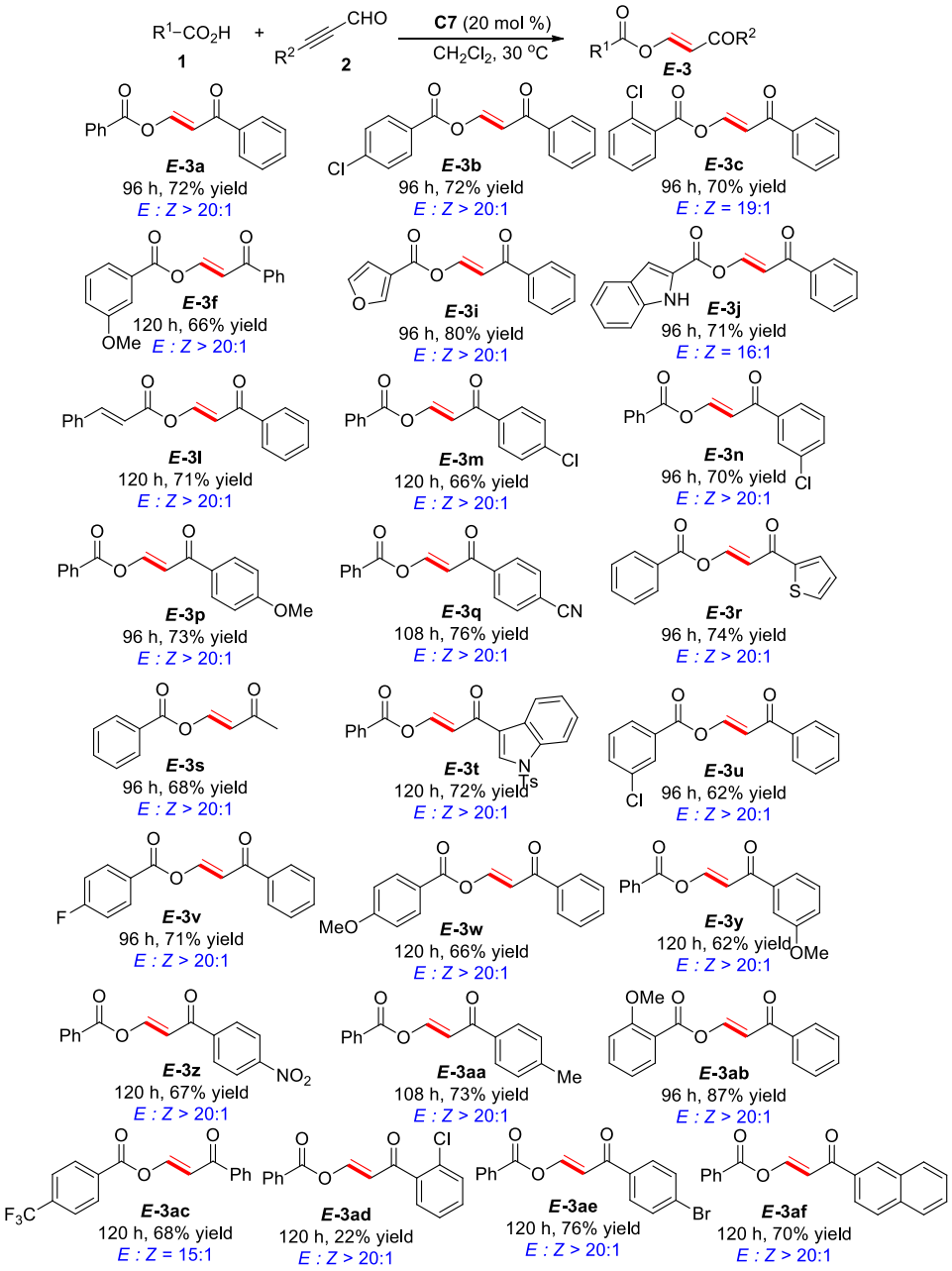
isomers.

Scheme 5.3 Substrate Scope of C7-catalyzed Synthesis of *Z*-enol Esters



[a] Unless stated otherwise, see SI Methods for detail of the reaction conditions. [b] isolated yields. [c] Determined by ^{1}H NMR. [d] 10 mol % **C7** used.

Scheme 5.4 Scope of C7-catalyzed Synthesis of *E*-enol Esters



[a] Unless stated otherwise, see SI Methods for detail of the reaction conditions. [b] Isolated yield.

Synthesis of *E* isomers

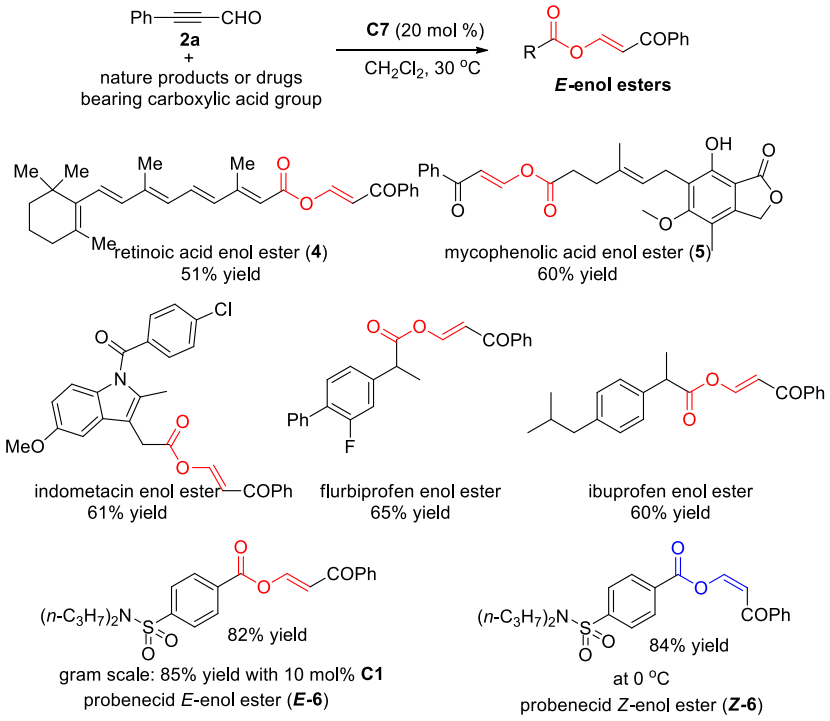
Having established an efficient protocol for the synthesis of *Z*-enol esters, we then turned our attention on the construction of *E*-enol esters. Since the more stable *E*-enol esters are thermodynamically controlled products, we conducted studies by raising the reaction temperature and/or extending the reaction time. To our delight, the desired *E*-enol esters were obtained when the reaction was performed at 30 °C and longer reaction time (96-120 h) (Scheme 5.4). Notably under the reaction conditions, again clean *E*-isomers (15:1 - > 20:1 *E : Z* ratio) were attended in good to high yields (62-92%). Again, a variety of acids and ynals as reactants can be applied for this process with a broad substrate scope and therefore this offers a viable approach to *E*-enol esters with various structure features.

Derivatization of complex carboxylic acids

In addition to the relative simple acids, we also demonstrated that the mild reaction conditions enable biologically relevant, more complex carboxylic acids to selectively react with ynals using phenyl propynal as example (Scheme 5.5). It was found that under the thermodynamically controlled reaction conditions, heavily functionalized acids can effectively participate in the reactions chem-, regio- and stereo-selectively to deliver interesting *E*-enol ester derivatives **4-6** in high yields. They include retinoic acid,[17] mycophenolic acid,[18] an immunosuppressant drug and others (Scheme 5.5). It is noteworthy that the reaction conditions can tolerate highly acid sensitive polyene and nucleophilic phenol moieties in retinoic acid and mycophenolic acid. Finally, we chose therapeutic probenecid[19] to show divergent synthesis of its *Z* and *E* enol esters. Both cases offered good yields and excellent *Z* and *E* selectivity. Furthermore, this protocol can be conveniently scaled up, as shown in the use of probenecid (5.0

mmol) and phenylpropiolaldehyde (3.6 mmol) with 10 mol% catalyst **C7**, delivering ***E*-6** in 85% yield (Scheme 5.5).

Scheme 5.5 Synthesis of Enol Esters Derived from Natural Products and Therapeutics



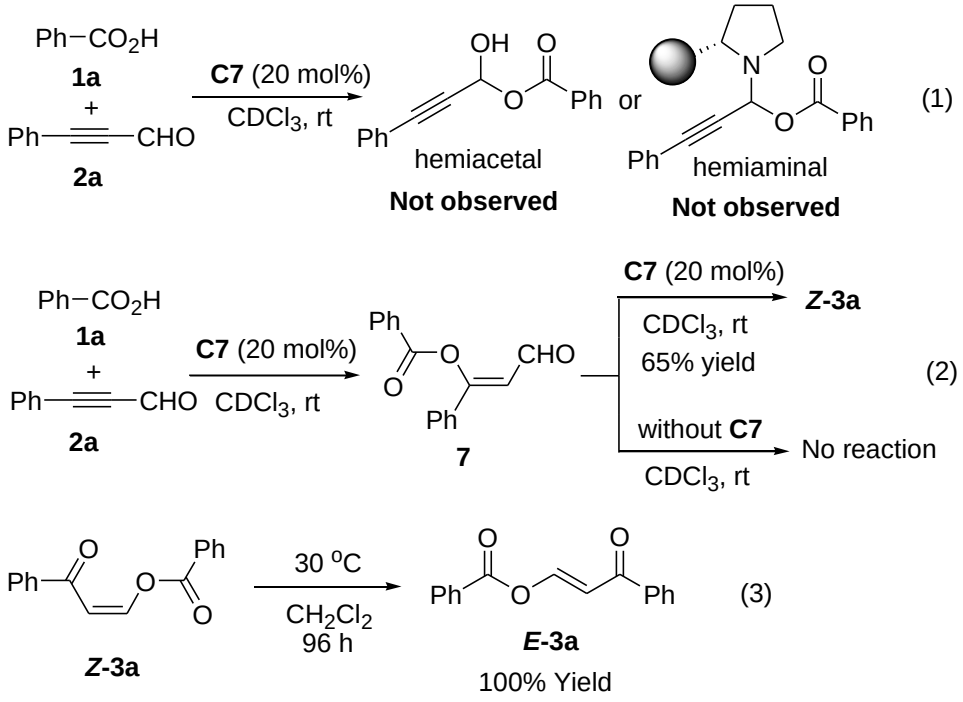
[a] Unless stated otherwise, see SI Methods for detail of the reaction conditions. [b] Isolated yield.

5.3.3 Mechanism Study

The unexpected enol ester formation from carboxylic acids and ynals prompted us to conduct preliminary studies of the interesting reaction mechanism. We found that the process involving the Meyer−Schuster type rearrangement[20] was ruled out because the formation of the hemiacetal or hemiaminal was not observed (Scheme 5.6, Eq. 1), which is an essential precursor for the rearrangement. Instead, a Michael adduct **7** was formed initially, observed by *in situ* ^{1}H NMR (Fig 5.2). Furthermore, we isolated and characterized the product by reaction of benzoic

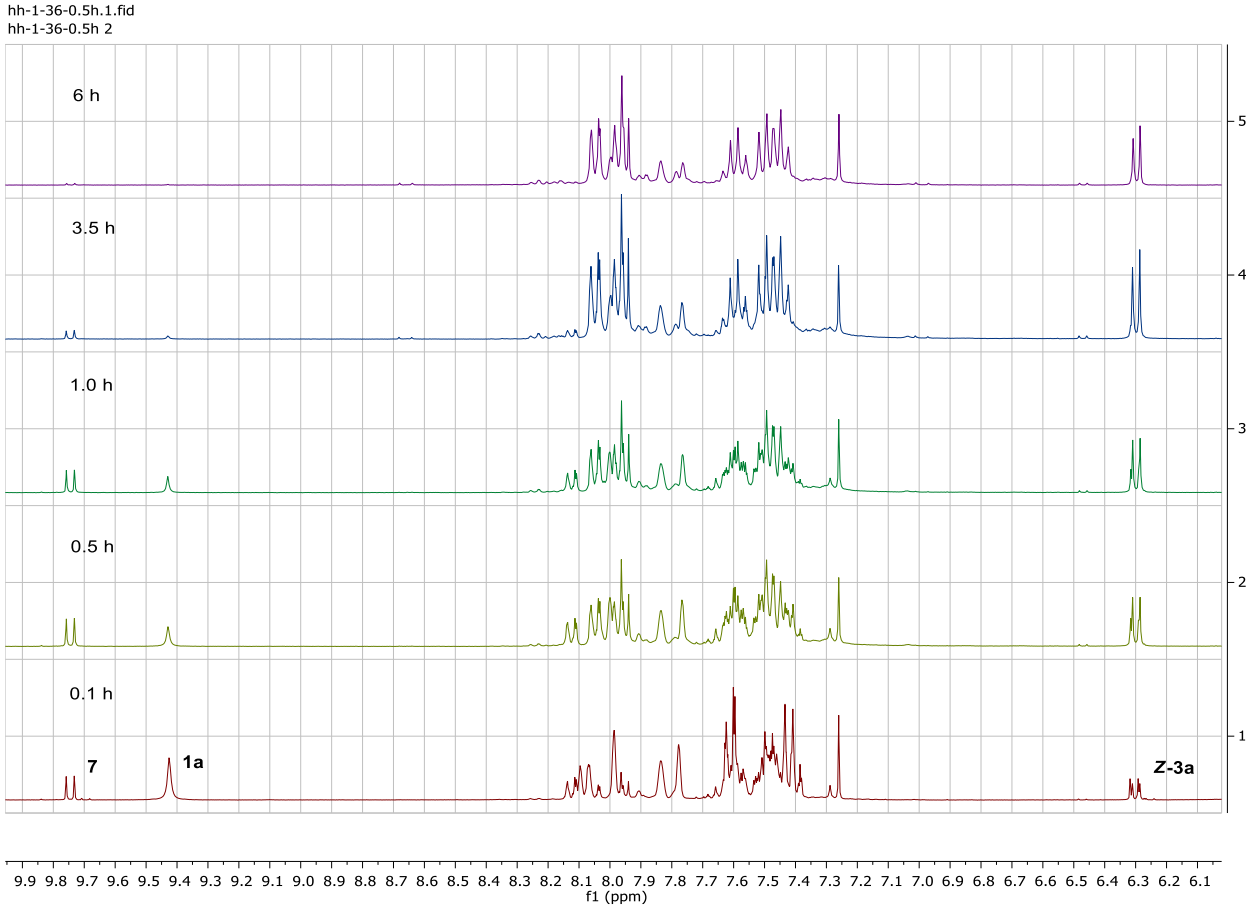
acid **1a** with ynal **2a**. It was found that only in the presence of **C7**, the adduct was able to converted into enol ester ***Z*-3a** (Eq. 2). Without the catalyst, no reaction occurred. These results suggest that the catalyst is necessary for the initial Michael and subsequent rearrangement reactions.

Scheme 5.6 Reactions Designed for Study of Reaction Mechanism



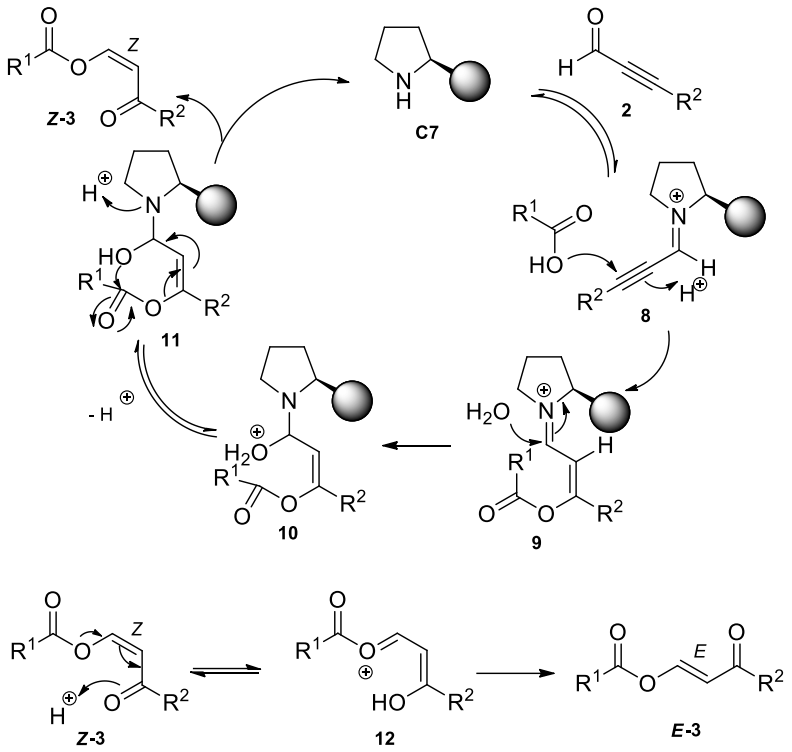
Based on the above studies, we proposed a catalytic cycle for the formation of enol esters **3** (Scheme 5.7). Nucleophilic attack of benzoic acid from less hindered side of the iminium ion **8** is followed by protonation of α-carbon gives *cis*-iminium ion **9**. Nucleophilic addtion H_2O to the iminium ion leads to hemiaminal **11** after proton transfer with **10**. Hydroxyl group triggers an interesting rearrangement *via* intramolecular transesterification to gives rise to a *Z*-enol ester ***Z*-3** with concomitant release of the catalyst.

Figure 5.2 Reaction Progress of C7 Catalyzed Reaction of 1a with 3a**.**



[a] The *in situ* ^{1}H NMR analysis was carried out with 0.12 mmol of **1a** and 0.1 mmol of **2a** in 2 mL of $CDCl_3$ with 30 mol% catalyst **C7**.

Scheme 5.7 Proposed Catalytic Cycle



5.4 Conclusion

In conclusion, we have established a new divergent organocalytic protocol for the preparation of both *E*- and *Z*-enol esters from a diverse array of simple carboxylic acids and ynals. Under kinetic control conditions, *Z*-enol esters are produced highly stereoselectively while *E*-isomers are selectively formed by thermodynamic control. Preliminary mechanistic studies suggest an amine catalyzed unprecedented Michael-rearrangement pathway for the formation of enol esters. Different from transition metal catalysis of carboxylic acids with alkynes, a novel organocatalytic catalysis strategy is implemented for the conjugate addition of carboxylic acid to polarized C≡C triple bonds. Further investigation of the reaction mechanism in detail and the exploration of the chemistry for new transformations are currently pursued in our laboratories.

5.5 Experimental Section

5.5.1 General Information:

Commercially available reagents were used without purification. Commercially available reagents were purchased from Sigma Aldrich, Matrix Chemical, Alfa Aesar, or TCI, and used as received unless otherwise noted. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with a fluorescence F_{254} indicator were used for thin-layer chromatography (TLC) analysis. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance 300. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) relative to residual chloroform (7.26 ppm) or dimethyl sulfoxide (2.50 ppm) as internal standards. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, m = multiplet), coupling constant in Hertz (Hz) and hydrogen numbers based on integration intensities. ^{13}C NMR chemical shifts are reported in ppm relative to the central peak of $CDCl_3$ (77.16 ppm) or $(CD_3)_2SO$ (39.52 ppm) as internal standards.

5.5.2 General Procedures

Procedure A: (20 mol% catalyst)

Ynals (0.2 mmol, 1.0 equiv.) and carboxlic acids (0.24 mmol, 1.2 equiv.) were placed in a 4 mL brown-colored glass vial with a stir bar. DCM (0.8 mL) was injected into the vial and then 7 mol% catalyst was added. The mixture was stirred at specified temperature for 6h and then 7 mol% catalyst was added. After 6h later, the rest of the catalyst was added. After stirred at the same temperature for a specified time, the solvent was reduced in *vacuo*, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to provide the title compounds.

Procedure B: (10 mol% catalyst)

Ynals (0.2 mmol, 1.0 equiv.) and carboxlic acids (0.24 mmol, 1.2 equiv.) were placed in a 4 mL brown-colored glass vial with a stir bar. DCM (0.8 mL) was injected into the vial and then 5 mol% catalyst was added. The mixture was stirred at specified temperature for 2h and then 5 mol% catalyst was added. After stirred at the same temperature for a specified time, the solvent was reduced in *vacuo*, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to provide the title compounds.

Procedure C: (gram scal)

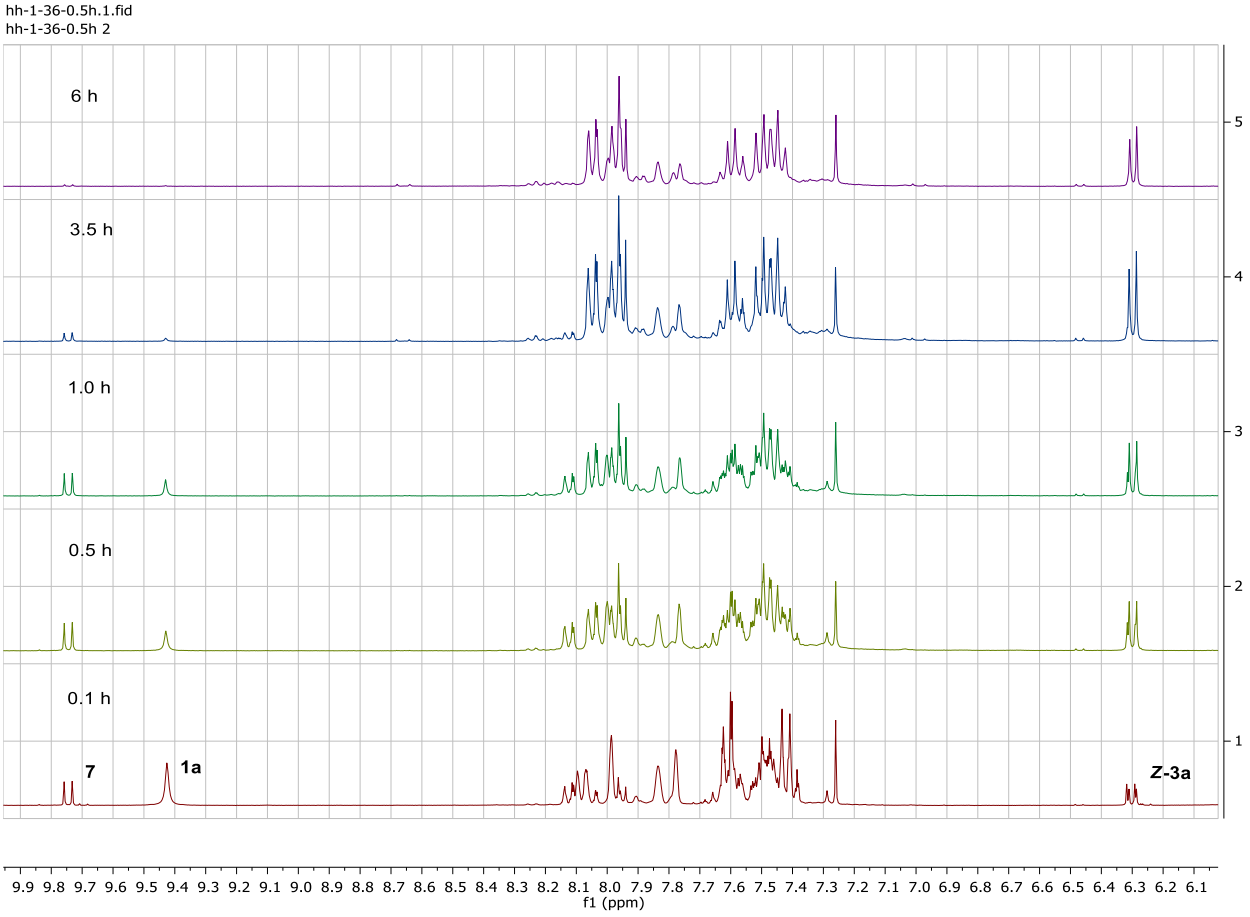
Probenecid (5.0 mmol) and phenylpropiolaldehyde (3.6 mmol) were placed in a 50 mL flask with a stir bar. DCM (20 mL) was injected into the flask and then 3 mol% catalyst was added. The mixture was stirred at 30 ^oC for 24h and then 3 mol% catalyst was added. After 24h later, the rest of the catalyst was added. After stirred at the same temperature for another 72h, the solvent was reduced in vacuo, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc) to provide the title compounds.

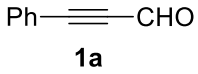
Procedure D: (Compound 7)

2a (0.2 mmol, 1.0 equiv.) and **1a** (0.24 mmol, 1.2 equiv.) were placed in a 4 mL brown-colored glass vial with a stir bar. $CDCl_3$ (1 ml, deuterated solvent was used for directly monitor the reaction by NMR) was injected into the vial and then 20 mol% catalyst was added. After stirred at the room temperature for 30 min, the solvent was reduced in *vacuo*, and the residue was purified by column chromatography (SiO_2, hexanes/EtOAc = 20/1) carefully to provide the product **7** in 35% yield.

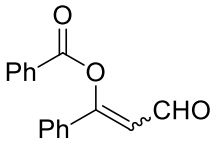
5.5.3 Mechanism study

Figure 5.3 *In situ* ^{1}H NMR Analysis of the Reaction Process.

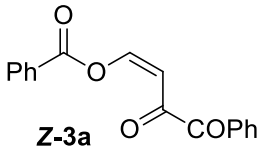




1a



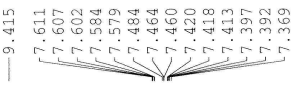
7

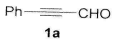


***Z*-3a**

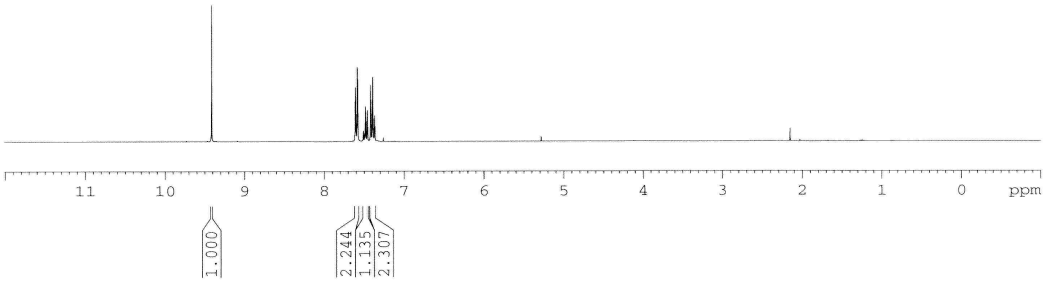
[a] The *in situ* ^{1}H NMR analysis was carried out with 0.12 mmol of 1a and 0.1 mmol of 2a in 2 mL of $CDCl_3$ with 30 mol% catalyst.

hh-1-43





1a



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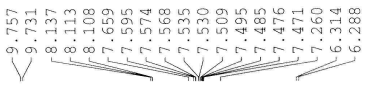
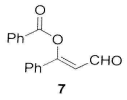
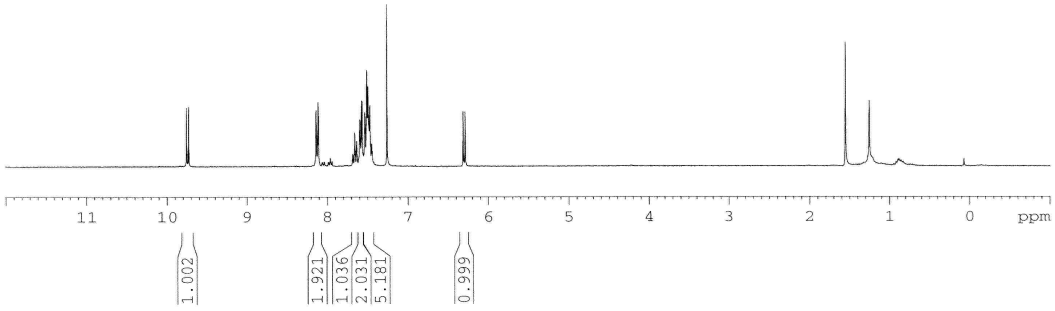
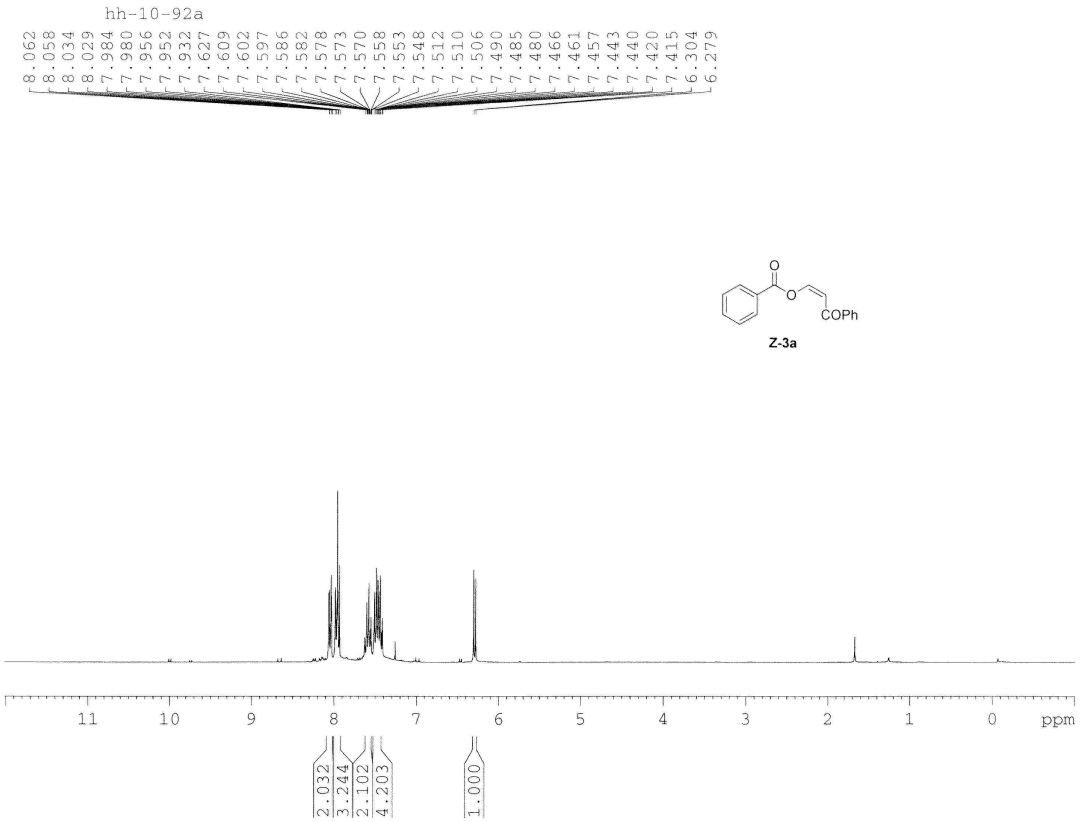


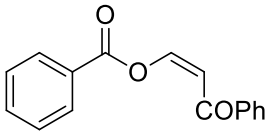


7





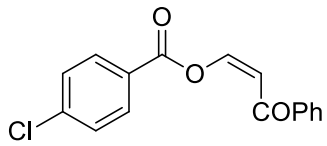
5.6 Characterization



***Z*-3a**

(*Z*)-3-Oxo-3-phenylprop-1-enyl benzoate:

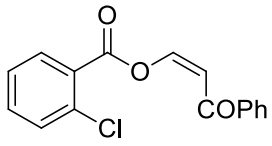
Yield (80%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.04 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.98-7.93(m, 3H), 7.63-7.56 (m, 3H), 7.51-7.42 (m, 4H), 6.29 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.70, 162.54, 143.11, 138.32, 134.12, 132.71, 130.49, 128.54, 128.49, 128.26, 127.60, 107.91.



***Z*-3b**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 4-chlorobenzoate:

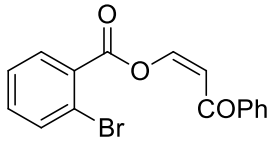
Yield (71%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 7.99-7.94 (m, 3H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.59-7.56 (m, 1H), 7.51-7.47 (m, 2H), 7.43-7.40 (m, 2H), 6.30 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.8, 161.9, 143.0, 141.0, 138.4, 133.0, 132.0, 129.1, 128.7, 128.4, 126.3, 108.3.



***Z*-3c**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 2-chlorobenzoate:

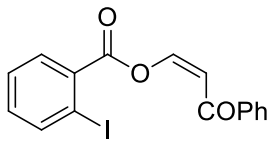
Yield (88%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.03-8.01 (m, 1H), 7.96-7.94 (m, 2H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.57-7.45 (m, 5H), 7.34-7.30 (m, 1H), 6.32 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.6, 160.5, 142.9, 138.3, 135.9, 134.2, 133.1, 133.0, 131.7, 128.7, 128.4, 127.0, 126.3, 108.4.



***Z*-3d**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 2-bromobenzoate:

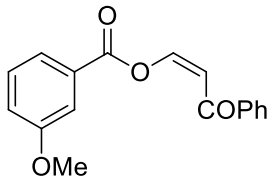
Yield (91%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.03-7.93 (m, 3H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.71-7.68 (m, 1H), 7.56-7.54 (m, 1H), 7.50-7.44 (m, 2H), 7.38-7.35 (m, 2H), 6.32 (d, *J* = 6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.6, 161.0, 143.0, 138.3, 135.1, 134.2, 133.3, 133.0, 128.7, 128.4, 128.0, 127.6, 123.8, 108.5.



***Z*-3e**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 2-iodobenzoate:

Yield (91%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.07-8.04 (m, 2H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.57-7.54 (m, 1H), 7.50-7.38 (m, 3H), 7.20-7.17 (m, 1H), 6.33 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.6, 161.4, 143.1, 142.3, 138.3, 134.2, 133.04, 133.0, 130.6, 128.7, 128.4, 128.4, 108.5, 96.0.

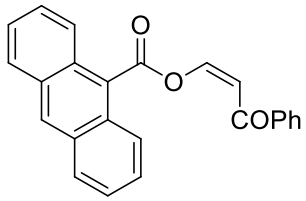


***Z*-3f**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 3-methoxybenzoate:

Yield (71%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 7.98-7.91 (m, 3H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.57-7.54 (m, 2H), 7.50-7.45 (m, 2H), 7.20-7.17 (m, 1H), 7.33 (dd, J_1 = J_2 = 8.1 Hz, 2H), 7.15-7.12 (m, 1H), 6.26 (d, *J* = 7.2 Hz, 1H), 3.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.8, 162.6, 159.7, 143.1, 138.4, 132.9, 129.7, 129.0, 128.6, 128.5, 123.2, 121.2, 114.5, 108.2,

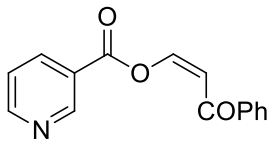
55.5.



***Z*-3g**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl anthracene-9-carboxylate:

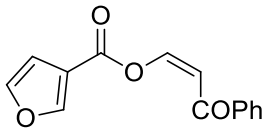
Yield (86%); Yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.55 (s, 1H), 8.19-8.13 (m, 3H), 7.99 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 6.9 Hz, 1H), 7.58-7.48 (m, 5H), 7.40-7.36 (m, 2H), 6.41 (d, J = 7.5 Hz, 1H), 3.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.2, 165.9, 142.6, 137.7, 133.0, 131.3, 130.9, 129.4, 128.7, 128.5, 127.6, 125.6, 125.0, 124.3, 109.5.



***Z*-3h**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl nicotinate:

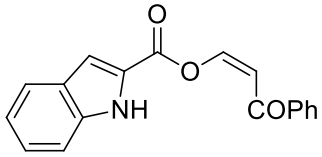
Yield (63%); Dark yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 9.16 (d, J = 1.5 Hz, 1H), 8.81 (dd, J_1 = 4.8 Hz, J_2 = 1.5 Hz, 1H), 8.81 (ddd, J_1 = 8.1 Hz, J_2 = J_3 = 1.8 Hz, 1H), 7.96-7.90 (m, 3H), 7.59-7.56 (m, 1H), 7.51-7.46 (m, 2H), 7.41-7.37 (m, 1H), 6.32 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.6, 161.6, 154.5, 151.8, 142.4, 138.3, 137.9, 133.1, 128.7, 128.4, 124.0, 123.5, 109.0.



***Z*-3i**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl furan-3-carboxylate:

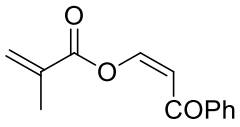
Yield (83%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 7.93-7.91 (m, 3H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.59-7.54 (m, 1H), 7.53-7.42 (m, 3H), 6.96 (d, *J* = 1.5 Hz, 1H), 6.18 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0, 158.8, 150.0, 144.3, 142.5, 138.5, 132.9, 128.6, 128.4, 117.3, 109.7, 108.0.



***Z*-3j**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 1H-indole-2-carboxylate:

Yield (69%); White solid; ^{1}H NMR (DMSO-d6, 300 MHz) d 12.12 (s, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 7.70-7.64 (m, 2H), 7.59-7.78 (m, 3H), 7.34-7.29 (m, 1H), 7.14-7.06 (m, 2H), 6.53 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (DMSO-d6, 75 MHz) δ 189.6, 158.0, 143.8, 139.0, 138.5, 133.5, 129.3, 128.7, 127.0, 126.2, 125.2, 123.0, 121.1, 113.2, 111.1, 108.8.

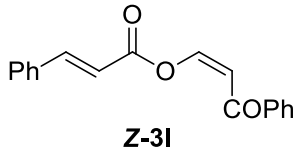


***Z*-3k**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl methacrylate:

Yield (63%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 7.94-7.92 (m, 2H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.57-7.55 (m, 1H), 7.51-7.46 (m, 2H), 6.24 (s, 1H), 6.20 (d, *J* = 7.2 Hz, 1H), 5.75

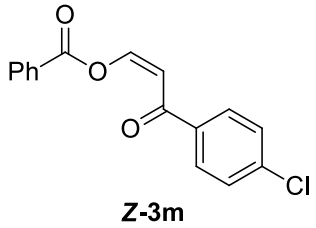
(s, 1H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.9, 163.3, 143.1, 138.4, 134.2, 132.8, 129.6, 128.6, 128.4, 108.0, 17.8.



***Z*-3l**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl cinnamate:

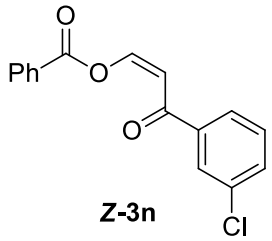
Yield (63%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 7.97-7.95 (m, 2H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 15.9 Hz, 1H), 7.58-7.39 (m, 8H), 6.46 (d, *J* = 16.2 Hz, 1H), 6.21 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.9, 162.8, 148.6, 143.2, 138.4, 133.8, 132.9, 131.1, 129.0, 128.6, 128.5, 115.6, 107.7.



***Z*-3m**

(*Z*)-3-(4-Chlorophenyl)-3-oxoprop-1-en-1-yl benzoate:

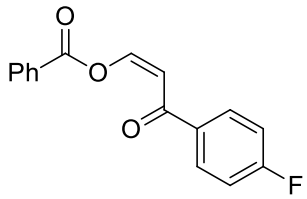
Yield (63%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.05 (d, *J* = 7.2 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.65-7.60 (m, 1H), 7.50-7.45 (m, 4H), 6.24 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.5, 162.6, 143.7, 139.3, 136.8, 134.4, 130.6, 129.8, 129.0, 128.8, 127.6, 107.6.



***Z*-3n**

(*Z*)-3-(3-Chlorophenyl)-3-oxoprop-1-en-1-yl benzoate:

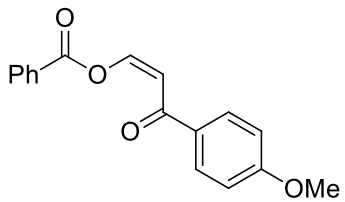
Yield (70%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.08 (d, *J* = 7.2 Hz, 2H), 7.98-7.95 (m, 2H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.65-7.60 (m, 1H), 7.56-7.53 (m, 1H), 7.53-7.40 (m, 3H), 6.26 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.2, 162.6, 144.1, 140.0, 135.0, 134.4, 132.7, 130.7, 130.0, 128.8, 128.5, 127.6, 126.4, 107.4.



***Z*-3o**

(*Z*)-3-(4-Fluorophenyl)-3-oxoprop-1-en-1-yl benzoate:

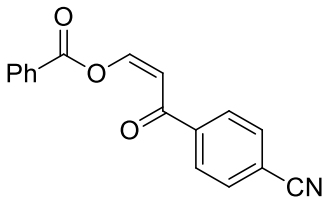
Yield (74%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.06 (d, *J* = 7.2 Hz, 2H), 8.02-7.97 (m, 2H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.64-7.59 (m, 1H), 7.48-7.43 (m, 2H), 7.18-7.12 (m, 2H), 6.25 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.1, 165.1 ($J_{C\text{-}F}$ = 253.1 Hz), 162.6, 143.4, 134.8, 134.4, 131.0 ($J_{C\text{-}F}$ = 9.2 Hz), 130.6, 128.7, 127.7, 115.7 ($J_{C\text{-}F}$ = 21.8 Hz), 107.7.



***Z*-3p**

(*Z*)-3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl benzoate:

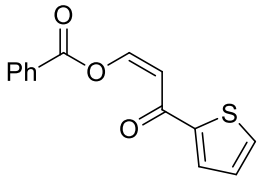
Yield (63%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.09 (d, *J* = 7.8 Hz, 2H), 7.97 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.60-7.58 (m, 1H), 7.47-7.42 (m, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.27 (d, *J* = 7.5 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.2, 163.5, 162.8, 142.6, 134.2, 131.3, 130.8, 130.6, 128.7, 127.9, 113.9, 108.2, 55.5.



***Z*-3q**

(*Z*)-3-(4-Cyanophenyl)-3-oxoprop-1-en-1-yl benzoate:

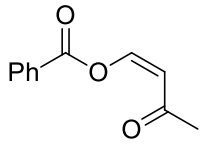
Yield (81%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.03-7.99 (m, 5H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.65-7.60 (m, 1H), 7.49-7.44 (m, 2H), 6.26 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.2, 162.4, 144.9, 141.7, 134.6, 132.5, 130.6, 128.8, 128.7, 127.4, 117.9, 16.0, 107.0.



***Z*-3r**

(*Z*)-3-Oxo-3-(thiophen-2-yl)prop-1-en-1-yl benzoate:

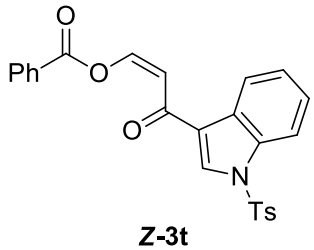
Yield (72%); Light yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.28-8.25 (m, 2H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.75 (dd, J_1 = 3.6 Hz, J_2 = 0.9 Hz, 1H), 7.69-7.62 (m, 2H), 7.53-7.48 (m, 2H), 7.16 (dd, J_1 = 4.8 Hz, J_2 = 3.9 Hz, 1H), 6.30 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.8, 162.8, 145.8, 413.7, 134.4, 134.0, 131.7, 130.9, 128.8, 128.3, 127.8, 107.0.



***Z*-3s**

(*Z*)-3-Oxobut-1-en-1-yl benzoate:

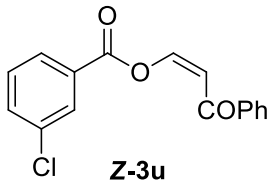
Yield (70%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.18 (d, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 7.68-7.65 (m, 1H), 7.56-7.51 (m, 2H), 5.59 (d, *J* = 7.2 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.5, 162.5, 142.9, 134.5, 130.4, 128.9, 128.5, 112.5, 31.8.



***Z*-3t**

(*Z*)-3-Oxo-3-(1-tosyl-1H-indol-3-yl)prop-1-en-1-yl benzoate:

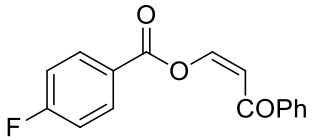
Yield (62%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.47-8.44 (m, 1H), 8.26 (s, 1H), 8.23-8.20 (m, 2H), 7.97-7.94 (m, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.50-7.45 (m, 2H), 7.40-7.36 (m, 2H), 7.26-7.22 (m, 2H), 6.24 (d, *J* = 7.2 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.8, 162.9, 145.9, 142.8, 135.0, 134.5, 134.3, 131.7, 130.8, 130.2, 128.8, 127.8, 127.8, 127.2, 125.9, 124.8, 123.2, 122.5, 113.1, 108.5, 21.6.



***Z*-3u**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 3-chlorobenzoate:

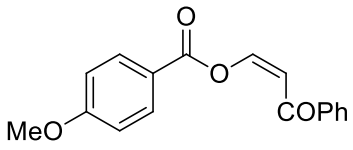
Yield (86%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 7.97-7.88 (m, 5H), 7.59-7.57 (m, 2H), 7.50 (dd, $J_1 = J_2$ = 7.5 Hz, 2H), 7.39 (dd, $J_1 = J_2$ = 8.1 Hz, 1H), 6.28 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0, 161.6, 142.7, 138.4, 134.9, 134.3, 133.1, 130.4, 130.0, 129.6, 128.7, 128.7, 128.4, 108.9.



***Z*-3v**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 4-fluorobenzoate:

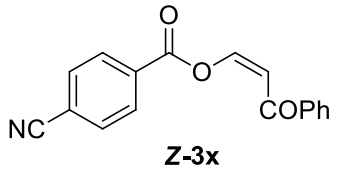
Yield (84%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.10-8.05 (m, 2H), 7.97-7.90 (m, 3H), 7.60-7.55 (m, 1H), 7.51-7.46 (m, 2H), 7.11 (dd, $J_1 = J_2$ = 8.4 Hz, 2H), 6.30 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.7, 166.1 ($J_{C\text{-}F}$ = 255.0 Hz), 161.7, 143.2, 138.4, 133.4 ($J_{C\text{-}F}$ = 9.6 Hz), 132.9, 128.7, 128.4, 124.0, 115.9 ($J_{C\text{-}F}$ = 22.0 Hz), 108.1.



***Z*-3w**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 4-methoxybenzoate:

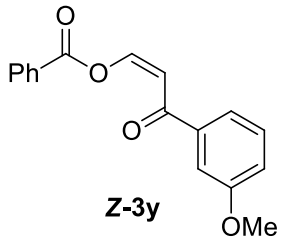
Yield (53%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.01-7.92 (m, 5H), 7.57-7.55 (m, 1H), 7.51-7.46 (m, 2H), 6.90 (d, J = 9 Hz, 2H), 6.25 (d, J = 7 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0, 164.5, 162.3, 143.6, 138.6, 132.9, 132.8, 128.6, 128.4, 119.9, 114.0, 107.5, 55.5.



***Z*-3x**

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 4-cyanobenzoate:

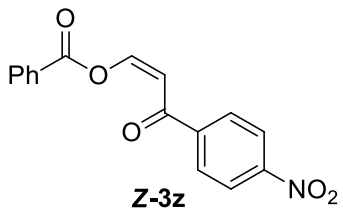
Yield (72%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.16 (d, *J* = 8.1 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.62-7.57 (m, 1H), 7.52-7.47 (m, 2H), 6.37 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.4, 161.2, 142.6, 138.2, 133.1, 132.5, 131.7, 131.0, 128.8, 128.4, 117.7, 117.6, 109.0.



***Z*-3y**

(*Z*)-3-(3-Methoxyphenyl)-3-oxoprop-1-en-1-yl benzoate:

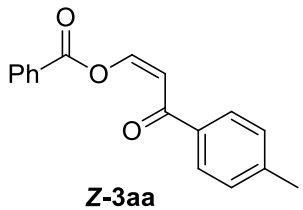
Yield (62%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.10 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.61-7.36 (m, 6H), 7.12 (dd, J_1 = 8.1 Hz, J_2 = 1.8 Hz, 1H), 6.29 (d, *J* = 7.2 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.3, 162.8, 160.0, 143.4, 139.8, 134.3, 130.7, 129.6, 128.7, 127.8, 121.0, 119.6, 112.5, 108.0, 55.5.



***Z*-3z**

(*Z*)-3-(4-Nitrophenyl)-3-oxoprop-1-en-1-yl benzoate:

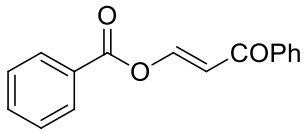
Yield (85%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.32 (d, *J* = 8.7 Hz, 2H), 8.11-8.02 (m, 5H), 7.63-7.61 (m, 1H), 7.49-7.44 (m, 2H), 6.30 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.9, 162.4, 150.1, 145.1, 143.2, 134.7, 130.6, 129.3, 128.8, 127.3, 123.9, 107.0.



***Z*-3aa**

(*Z*)-3-Oxo-3-(p-tolyl)prop-1-en-1-yl benzoate:

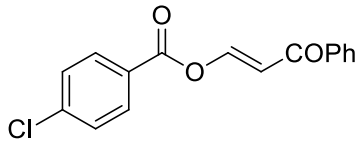
Yield (70%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.08-8.06 (m, 2H), 7.93-7.86 (m, 3H), 7.63-7.58 (m, 1H), 7.47-7.42 (m, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.28 (d, *J* = 7.2 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.4, 162.8, 143.7, 142.9, 135.9, 134.2, 130.7, 129.3, 128.7, 128.6, 127.9, 108.2, 21.6.



***E*-3a**

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl benzoate:

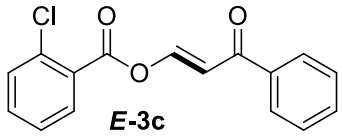
Yield (72%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.66 (d, *J* = 12.0 Hz, 1H), 8.18-8.15 (m, 2H), 7.97-7.95 (m, 2H), 7.67-7.50 (m, 6H), 6.99 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.3, 162.8, 150.7, 137.9, 134.4, 133.0, 130.4, 128.8, 128.7, 128.4, 127.8, 110.5.



***E*-3b**

(*E*)-3-(4-Chlorophenyl)-3-oxoprop-1-enyl benzoate:

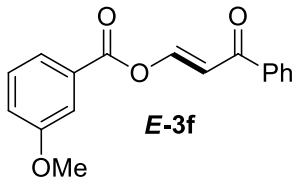
Yield (72%); Light yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.61 (d, *J* = 12.0 Hz, 1H), 8.11-8.07 (m, 2H), 7.97-7.94 (m, 2H), 7.60-7.57 (m, 1H), 7.52-7.47 (m, 4H), 6.98 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.1, 161.9, 150.4, 141.1, 137.8, 133.1, 131.7, 129.2, 128.7, 128.3, 126.2, 110.7.



***E*-3c**

(*E*)-3-(2-Chlorophenyl)-3-oxoprop-1-enyl benzoate:

Yield (60%); Brown oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.61 (d, *J* = 12.3 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.96-7.93 (m, 2H), 7.61-7.47 (m, 5H), 7.43-7.37 (m, 1H), 6.60 (d, *J* = 12 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.2, 161.3, 150.2, 137.7, 135.1, 134.0, 133.0, 132.2, 131.6, 128.7, 128.3, 127.2, 126.8, 110.9.

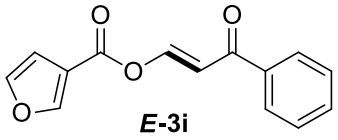


***E*-3f**

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl 3-methoxybenzoate:

Yield (66%); Light Yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.64 (d, *J* = 12.3 Hz, 1H), 7.97-7.94 (m, 2H), 7.76-7.74 (m, 1H), 7.64-7.39 (m, 5H), 7.21-7.18 (m, 1H), 7.09 (d, *J* = 12.3

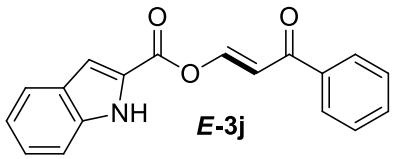
Hz, 1H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.3, 162.7, 159.8, 150.7, 137.9, 133.0, 129.8, 129.0, 128.7, 128.4, 122.8, 120.9, 114.7, 110.5, 55.6.



***E*-3i**

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl furan-3-carboxylate:

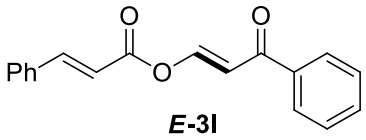
Yield (80%); Light yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.56 (dd, J_1 = 12 Hz, J_2 = 1.2 Hz, 1H), 8.19 (s, 1H), 7.94-7.92 (m, 2H), 7.59-7.45 (m, 4H), 6.90 (dd, J_1 = 12.3 Hz, J_2 = 1.5 Hz, 1H), 6.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.2, 158.9, 150.2, 149.5, 144.5, 137.8, 133.0, 128.7, 128.3, 117.4, 110.1, 109.8.



***E*-3j**

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl 1H-indole-2-carboxylate:

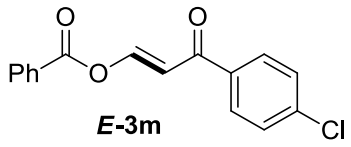
Yield (71%); Light yellow solid; ^{1}H NMR (DMSO-d6, 300 MHz) d 8.46 (d, J = 12.3 Hz, 1H), 8.06-8.03 (m, 2H), 7.74 (d, J = 8.1 Hz, 1H), 7.69-7.66 (m, 1H), 7.60-7.50 (m, 3H), 7.45-7.44 (m, 1H), 7.37-7.28 (m, 2H), 7.17-7.11 (m, 1H); ^{13}C NMR (DMSO-d6, 75 MHz) δ 189.9, 158.1, 150.4, 138.9, 137.7, 133.9, 129.4, 128.7, 127.1, 126.4, 125.0, 123.1, 121.2, 113.2, 111.3, 110.3.



***E*-3l**

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl cinnamate:

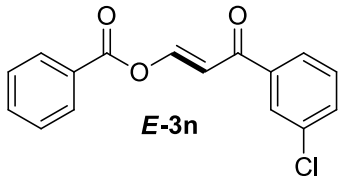
Yield (71%); Light yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.57 (d, *J* = 12.3 Hz, 1H), 7.95-7.87 (m, 3H), 7.60-7.56 (m, 3H), 7.51-7.42 (m, 5H), 6.89 (d, *J* = 12.3 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.4, 162.9, 150.7, 148.6, 137.9, 133.7, 133.0, 131.3, 129.1, 128.7, 128.6, 128.3, 115.4, 110.0.



***E*-3m**

(*E*)-3-(4-Chlorophenyl)-3-oxoprop-1-enyl benzoate:

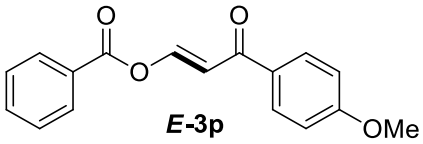
Yield (72%); Light yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.66 (d, *J* = 12.0 Hz, 1H), 8.16-8. 61(m, 2H), 8.03-7.88 (m, 2H), 7.69-7.64 (m, 1H), 7.54-7.44 (m, 4H), 6.95 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.9, 162.6, 150.9, 139.4, 136.1, 134.5, 130.4, 129.7, 128.9, 128.8, 127.6, 109.6.



***E*-3n**

(*E*)-3-(3-Chlorophenyl)-3-oxoprop-1-enyl benzoate:

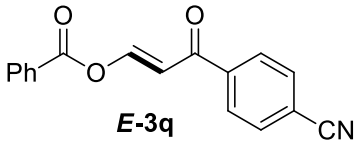
Yield (70%); Yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.67 (d, *J* = 12.3 Hz, 1H), 8.17-8.14 (m, 2H), 7.93-7.92 (m, 1H), 7.84-7.80 (m, 1H), 7.70-7.64 (m, 1H), 7.57-7.41 (m, 4H), 6.94 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.9, 162.6, 151.2, 139.4, 135.0, 134.50, 132.9, 130.4, 123.0, 128.8, 128.4, 127.6, 126.4, 109.9.



***E*-3p**

(*E*)-3-(4-Methoxyphenyl)-3-oxoprop-1-enyl benzoate:

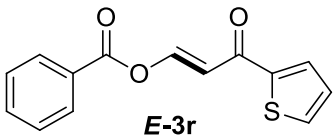
Yield (73%); Light yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.63 (dd, J_1 = 12.3 Hz, J_2 = 0.6 Hz, 1H), 8.16-8.13(m, 2H), 7.97-7.93 (m, 2H), 7.65-7.62 (m, 1H), 7.53-7.48 (m, 2H), 7.01-6.95 (m, 3H), 3.87 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 188.4, 163.5, 162.7, 149.9, 134.3, 130.7, 130.6, 130.3, 128.7, 127.81, 113.8, 110.1, 55.4.



***E*-3q**

(*E*)-3-(4-Cyanophenyl)-3-oxoprop-1-enyl benzoate:

Yield (76%); Light yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.68 (d, *J* = 12.3 Hz, 1H), 8.16-8.13 (m, 2H), 8.04-8.01 (m, 2H), 7.81-7.78 (m, 2H), 7.70-7.65 (m, 1H), 7.55-7.50 (m, 2H), 6.94 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.9, 162.6, 151.23, 139.4, 135.0, 134.5, 132.9, 130.4, 129.9, 128.8, 128.4, 127.6, 126.4, 109.9.

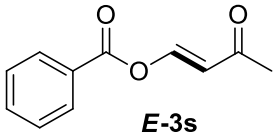


***E*-3r**

(*E*)-3-Oxo-3-(thiophen-2-yl)prop-1-en-1-yl benzoate:

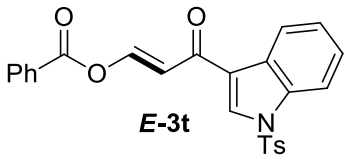
Yield (74%); Deep Yellow Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.70 (d, *J* = 12.0 Hz, 1H), 8.16 (d, *J* = 8.1 Hz, 2H), 7.78-7.50 (m, 5H), 7.19-7.16 (m, 1H), 6.89 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.0, 162.6, 150.0, 145.1, 134.4, 134.1, 131.9, 130.4, 128.8, 128.2,

127.7, 110.2.



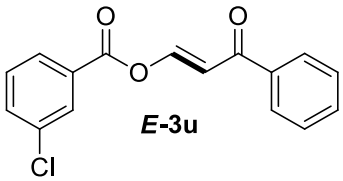
(*E*)-3-Oxobut-1-en-1-yl benzoate:

Yield (68%); White Solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.49 (d, *J* = 12.9 Hz, 1H), 8.14-8.11 (m, 2H), 7.66-7.64 (m, 1H), 7.53-7.48 (m, 2H), 6.18 (d, *J* = 12.9 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.3, 162.7, 149.7, 134.5, 130.4, 128.8, 127.6, 115.7, 27.5.



(*E*)-3-Oxo-3-(1-tosyl-1H-indol-2-yl)prop-1-en-1-yl benzoate:

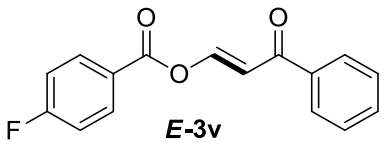
Yield (72%); Light yellow Solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.69 (d, *J* = 12.3 Hz, 1H), 8.41-8.16 (m, 4H), 7.97-7.84 (m, 4H), 7.67-7.50 (m, 3H), 7.40-7.26 (m, 3H), 6.89 (d, *J* = 12.3 Hz, 1H), 2.354 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.7, 162.7, 149.3, 145.9, 135.0, 134.4, 131.7, 130.3, 130.2, 128.8, 127.8, 127.1, 125.9, 124.9, 123.2, 122.1, 113.1, 111.3, 21.6.



(*E*)-3-Oxo-3-phenylprop-1-en-1-yl 3-chlorobenzoate:

Yield (51%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.62 (d, *J* = 12.0 Hz, 1H),

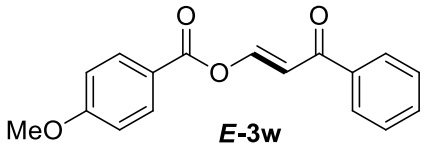
8.14-8.13 (m, 1H), 8.06-8.03 (m, 1H), 7.97-7.94 (m, 2H), 7.65-7.44 (m, 5H), 7.02 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0, 161.6, 150.2, 137.7, 135.0, 134.4, 133.1, 130.3, 130.1, 129.5, 128.7, 128.5, 128.3, 110.8;



***E*-3v**

(E)-3-(4-Fluorophenyl)-3-oxoprop-1-enyl benzoate:

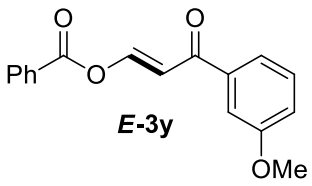
Yield (69%); Yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.66 (d, *J* = 12.0 Hz, 1H), 8.17-8.14(m, 2H), 8.00-7.97 (m, 2H), 7.70-7.65 (m, 1H), 7.55-7.50 (m, 2H), 7.26-7.14 (m, 2H), 6.96 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.2, 166.2 (J_{C-F} = 255.2 Hz), 161.8, 150.5, 137.8, 133.1, 133.0, 128.7, 128.3, 124.0, 116.0 (J_{C-F} = 22.1 Hz), 110.5.



***E*-3w**

(*E*)-3-(4-Methoxyphenyl)-3-oxoprop-1-enyl benzoate:

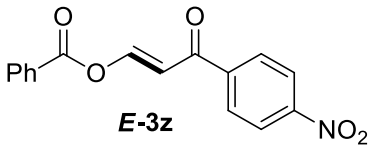
Yield (73%); Light yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.63 (d, 1H, *J* = 12.3 Hz), 8.10 (d, *J* = 9 Hz, 2H), 7.97-7.93 (m, 2H), 7.65-7.62 (m, 1H), 7.53-7.48 (m, 2H), 7.00 (s, 1H), 6.94 (d, *J* = 12.6 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.5, 164.5, 162.3, 150.9, 137.9, 132.9, 132.6, 128.6, 128.3, 119.8, 114.1, 110.0, 55.5.



***E*-3y**

(*E*)-3-(3-Methoxyphenyl)-3-oxoprop-1-enyl benzoate:

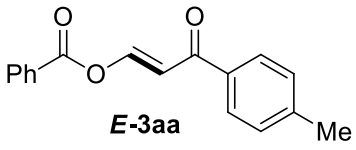
Yield (62%); Light yellow Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.65 (d, *J* = 12.0 Hz, 1H), 8.17-8.14 (m, 2H), 7.66-7.37 (m, 6H), 7.15-7.11 (m, 1H), 6.97 (m, *J* = 1.23 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0, 162.7, 159.9, 150.6, 139.2, 134.4, 130.3, 129.6, 128.75, 127.7, 120.9, 119.6, 112.5, 110.4, 55.4.



***E*-3z**

(*E*)-3-(4-Nitrophenyl)-3-oxoprop-1-enyl benzoate:

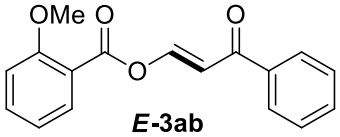
Yield (67%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.66 (d, *J* = 12.3 Hz, 1H), 8.36-8.32 (m, 2H), 8.18-8.07 (m, 4H), 7.71-7.66 (m, 1H), 7.56-7.51 (m, 2H), 6.96 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.8, 162.5, 152.1, 150.2, 142.3, 134.7, 130.5, 129.3, 128.9, 127.4, 123.9, 109.9.



***E*-3aa**

(*E*)-3-Oxo-3-p-tolylprop-1-enyl benzoate:

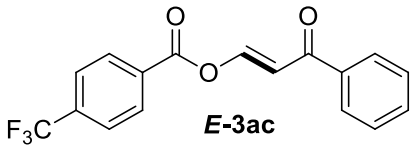
Yield (72%); Light yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.64 (d, *J* = 12.3 Hz, 1H), 8.17-8.13 (m, 2H), 7.88-7.86 (m, 2H), 7.65-7.26 (m, 5H), 6.98 (d, *J* = 12.0 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.7, 162.7, 150.3, 143.9, 135.3, 134.3, 130.3, 129.3, 128.7, 128.4, 127.8, 110.3, 21.6.



***E*-3ab**

(*E*)-3-(2-Methoxyphenyl)-3-oxoprop-1-enyl benzoate:

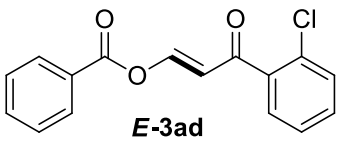
Yield (62%); Light yellow Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.64 (d, *J* = 12.3 Hz, 1H), 7.98-7.93 (m, 3H), 7.60-7.55 (m, 2H), 7.51-7.46 (m, 2H), 7.07-7.02 (m, 2H), 6.89 (d, 1H, *J* = 12.3 Hz), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.7, 161.4, 160.5, 151.0, 138.0, 135.4, 132.9, 132.4, 128.6, 128.3, 120.3, 117.0, 112.3, 110.2, 56.1.



***E*-3ac**

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl 4-(trifluoromethyl)benzoate:

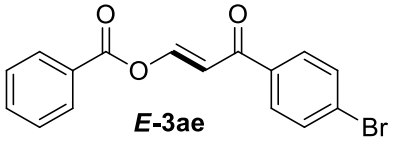
Yield (68%); Light yellow solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.63 (d, 1H, *J* = 12.3 Hz), 8.10 (d, *J* = 8.1 Hz, 2H), 7.98-7.95 (m, 2H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.60-7.58 (m, 1H), 7.53-7.48 (m, 2H), 7.03 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0, 161.7, 150.1, 137.7, 135.7 (J_{C-F} = 32.8 Hz), 133.2, 130.8, 128.7, 128.4, 127.0 (J_{C-F} = 271.1 Hz), 128.8 (J_{C-F} = 3.45 Hz), 111.1, 108.8.



***E*-3ad**

(*E*)-3-(2-Chlorophenyl)-3-oxoprop-1-enyl benzoate:

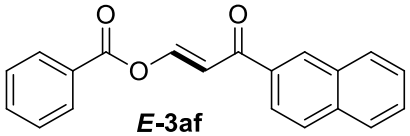
Yield (60%); Brown oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.33 (d, *J* = 12.6 Hz, 1H), 8.14-8.11 (m, 2H), 7.67-7.54 (m, 1H), 7.54-7.38 (m, 6H), 6.60 (d, *J* = 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.2, 162.5, 152.3, 138.6, 134.6, 131.6, 131.2, 130.4, 130.2, 129.1, 128.8, 128.5, 127.5, 126.9, 115.0.



***E*-3ae**

(*E*)-3-(4-Bromophenyl)-3-oxoprop-1-enyl benzoate:

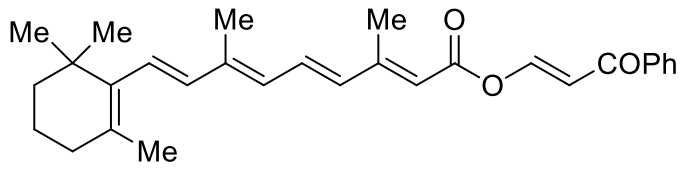
Yield (76%); White solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.66 (d, *J* = 12.0 Hz, 1H), 8.16-8.14(m, 2H), 7.83-7.81 (m, 2H), 7.69-7.46 (m, 5H), 6.94 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.1, 162.6, 151.0, 136.5, 134.5, 131.9, 130.6, 130.3, 129.8, 128.1, 127.6, 109.8.



***E*-3af**

(*E*)-3-(Naphthalen-2-yl)-3-oxoprop-1-en-1-yl benzoate:

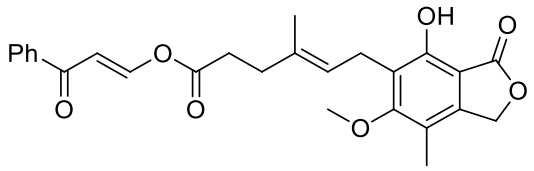
Yield (70%); Light yellow Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.73 (d, 1H, *J* = 12.0 Hz), 8.47(s, 1H), 8.18-8.05(m, 2H), 8.00-7.89 (m, 3H), 7.68-7.51 (m, 5H), 6.17 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.0, 162.7, 150.6, 135.6, 135.2, 134.4, 132.5, 130.4, 129.9, 129.5, 128.8, 128.6, 128.5, 127.8, 126.8, 124.1, 110.4;



retinoic acid enol ester (**4**)

(*2E,4E,6E,8E*)-(E)-3-Oxo-3-phenylprop-1-en-1-yl 3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoate:

Yield (51%); Light yellow Solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.53 (d, *J* = 12.0 Hz, 1H), 7.92-7.90 (m, 2H), 7.56-7.54 (m, 1H), 7.50-7.45 (m, 2H), 7.18-7.09 (m, 1H), 6.77 (d, *J* = 12.3 Hz, 1H), 6.35 (d, *J* = 15.0 Hz, 2H), 6.19-6.14 (m, 2H), 5.84 (s, 1H), 2.43 (s, 3H), 2.03 (s, 5H), 1.72 (s, 3H), 1.64-1.60 (m, 2H), 1.49-1.45 (m, 2H), 1.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.8, 162.5, 158.4, 151.2, 141.5, 138.1, 137.6, 137.1, 134.2, 133.3, 132.7, 130.5, 129.7, 129.2, 128.6, 128.3, 115.0, 109.2, 39.6, 34.2, 33.2, 29.0, 21.8, 19.2, 14.4, 13.0.

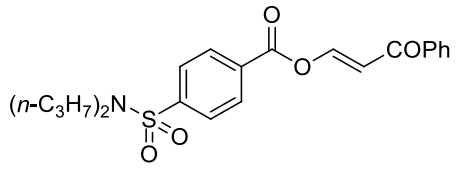


mycophenolic acid enol ester (**5**)

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate:

Yield (60%); Yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.31 (d, *J* = 12.3 Hz, 1H), 7.89-7.86 (m, 2H), 7.67 (s, 1H), 7.57-7.55 (m, 1H), 7.49-7.44 (m, 2H), 6.71 (d, *J* = 12.3 Hz, 1H), 5.27-5.25 (m, 1H), 5.13 (s, 2H), 3.75 (s, 3H), 3.38 (d, *J* = 6.9 Hz, 2H), 2.62-2.57 (m, 2H), 2.41-2.36 (m, 2H), 2.11 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.2, 172.9, 169.3, 163.6, 153.5, 150.2, 144.1, 137.8, 133.2, 133.0, 128.7, 128.2, 123.6, 121.8, 116.8, 109.6, 106.4, 70.1, 61.0,

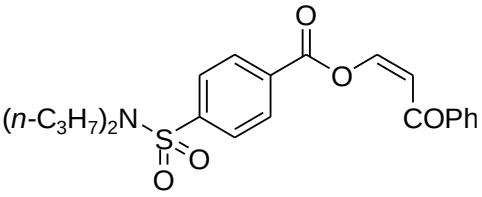
34.1, 32.7, 22.6, 16.1, 11.5.



probenecid *E*-enol ester (***E*-6**)

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl 4-(N,N-dipropylsulfamoyl)benzoate:

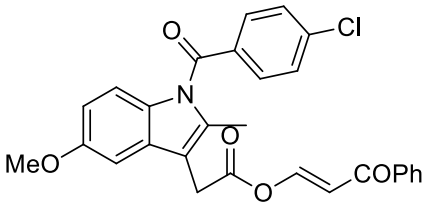
Yield (82%); Light yellow Solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.61 (d, *J* = 12.3 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 2H), 7.96-7.93 (m, 4H), 7.60-7.57 (m, 1H), 7.52-7.47 (m, 2H), 7.03 (d, *J* = 12.3 Hz, 1H), 3.14-3.09 (m, 4H), 1.59-1.51 (m, 4H), 0.89-0.84 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.8, 161.4, 149.9, 145.5, 137.5, 133.1, 131.1, 130.8, 128.6, 128.2, 127.1, 110.9, 49.7, 21.7, 11.0.



probenecid *Z*-enol ester (***Z*-6**)

(*Z*)-3-Oxo-3-phenylprop-1-en-1-yl 4-(N,N-dipropylsulfamoyl)benzoate:

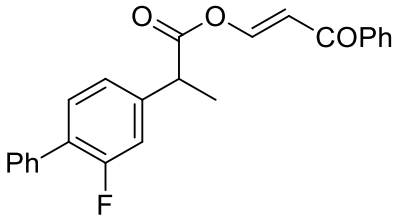
Yield (84%); Yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.18 (dd, J_1 = 7.2 Hz, J_2 = 1.8 Hz, 1H), 7.97-7.92 (m, 2H), 7.90-7.86 (m, 2H), 7.61-7.56 (m, 1H), 7.51-7.46 (m, 2H), 6.36 (d, *J* = 7.2 Hz, 1H), 3.11-3.06 (m, 4H), 1.56-1.49 (m, 4H), 0.88-0.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.4, 161.3, 145.3, 142.7, 138.0, 132.9, 131.1, 130.9, 128.6, 128.2, 127.0, 108.6, 49.7, 21.7, 11.0.



indometacin enol ester

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate:

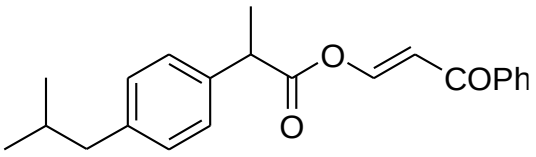
Yield (61%); White Solid; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.39 (d, J = 12.3 Hz, 1H), 7.91-7.88 (m, 2H), 7.70-7.67 (m, 2H), 7.58-7.55 (m, 1H), 7.49-7.45 (m, 4H), 6.95 (d, J = 2.4 Hz, 1H), 6.83 (dd, J_1 = 13.8 Hz, J_2 = 9.3 Hz, 1H), 6.69 (dd, J_1 = 9 Hz, J_2 = 2.4 Hz, 1H), 3.86 (s, 2H), 3.85 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.2, 168.3, 166.9, 156.2, 150.3, 139.5, 137.7, 136.5, 133.1, 131.2, 130.8, 133.2, 129.2, 128.7, 128.3, 155.1, 111.9, 110.7, 110.4, 101.1, 55.8, 30.0, 13.3.



flurbiprofen enol ester

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoate:

Yield (65%); Yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.41 (d, J = 12.3 Hz, 1H), 7.91-7.89 (m, 2H), 7.57-7.55 (m, 3H), 7.53-7.38 (m, 6H), 7.20-7.14 (m, 2H), 6.80 (d, J = 12.3 Hz, 1H), 3.91 (q, J_1 = 7.2 Hz, 1H), 1.63 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.2, 170.2, 160.0 ($J_{C\text{-}F}$ = 247.5 Hz), 150.3, 140.0 ($J_{C\text{-}F}$ = 7.7 Hz), 137.7, 135.2, 133.1, 131.2, 129.0, 128.7, 128.5, 128.3, 127.8, 123.5 ($J_{C\text{-}F}$ = 3.2 Hz), 115.6, 115.3, 110.4, 44.8, 18.2.



ibuprofen enol ester

(*E*)-3-Oxo-3-phenylprop-1-en-1-yl 2-(4-isobutylphenyl)propanoate:

Yield (60%); Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) d 8.40 (d, *J* = 12.3 Hz, 1H), 7.90-7.87 (m, 2H), 7.56-7.53 (m, 1H), 7.48-7.43 (m, 2H), 7.26-7.21 (m, 2H), 7.15-7.12 (m, 2H), 6.76 (d, *J* = 12.3 Hz, 1H), 3.85 (q, J_1 = 6.9 Hz, 1H), 2.46 (d, *J* = 7.2 Hz, 1H), 1.91-1.79 (m, 1H), 1.58 (d, *J* = 7.2 Hz, 1H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.2, 170.7, 150.5, 141.1, 137.6, 135.9, 132.8, 129.5, 128.5, 128.1, 127.1, 109.9, 44.87, 44.81, 30.02, 22.2, 18.2.

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