Applications of α-Keto Carbocations in Carbon-Carbon and Carbon-Nitrogen Bond Formation

by

Ping-Shan (Sunny) Lai

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy of Science
Graduate Department of Chemistry
University of Toronto

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Degree of Doctor of Philosophy of Science

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2012

Abstract

This thesis describes synthetic applications of α-keto carbocations, which represent potentially useful, but poorly studied, reversed polarity equivalents of enolates.

In the first chapter, a Ag(I) – mediated method for the nucleophilic displacement of α-halocarbonyl compounds to construct carbon-carbon bonds is described. The highly electrophilic nature of the putative α-keto carbocation intermediates enables the use of relatively unreactive nucleophiles in both intra- and intermolecular contexts. Such intermediates also present interesting opportunities for stereocontrol: our efforts to carry out diastereoselective additions to chiral α-keto carbocations are described.

Oxazoles are an important class of heterocycles, and several syntheses are addressed in Chapter 2. Our approach to this class of compounds employs a TMSOTf mediated Ritter reaction to construct the carbon-nitrogen bond. Cycloaddition of 2-alkoxyoxazoles with alkynes presents a facile route for furan synthesis.

The final chapter describes our attempts to apply anion–π interaction in organocatalysis. These interactions between anions and electron-deficient arenes have been characterized in some detail and have recently been applied in ion transport. Applications of prolinol-based secondary amines incorporating electron-deficient aromatic groups are described.
Acknowledgments

I am honoured to work with Professor Mark S. Taylor during my Ph. D. studies. His insight and expertise provided a great mentorship and guidance to me. I am also grateful for his helpful advice to solve scientific problems. I learned a lot from his dedication to helping students and his devotion to science and his family. He has been a great figure for me as he is extremely passionate and meticulous about the subject of chemistry. My chemistry career is greatly advanced by his care and assistance. Thank you so much, Mark.

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One of the reasons that I would pursue a chemistry career was because of my enjoyable learning experience in my fourth year organic chemistry course which was taught by Professor Victor Snieckus. His experience and passion in chemistry immensely inspired me. From then on, I was given the first opportunity to conduct research in organic chemistry in the summer of 2004 with Professor Snieckus and with both Professors Snieckus and Robert P. Lemieux for my master degree in chemistry. I personally thank them for their encouragement and supports during my master degree at Queen's University.

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I would like to thank my parents, Winston Lai and Charlene Lui to indulge me for letting me make the choice of my life – pursue a career in organic chemistry. I definitely would not have gone this far without their support throughout the years after I decided to return to school in Ontario from another discipline quite different from organic chemistry.
My final thanks are dedicated for my very beautiful girl friend Dan Wang whom I've known since the time I was in Kingston. There is a 480 km of distance between the two cities that we've lived in for the past four years. Our care for each other was and is, nevertheless, not interrupted, and I never felt lonely because of her love. She is a really talented person and scientist. Her attitude toward her works is a source of my inspiration, and her patience and care made our relationship amazing. It does not go without saying that I am really grateful for what she has done for me, and I am also grateful for her supports during my time in graduate school at University of Toronto. Together we have overcome many obstacles and accomplished what it was already impossible. I thank you and I love you, Dan.
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<tr>
<td>$\alpha_{11}$</td>
<td>molecular polarizability</td>
</tr>
<tr>
<td>AgBF$_4$</td>
<td>silver tetrafluoroborate</td>
</tr>
<tr>
<td>Ag$_2$CO$_3$</td>
<td>silver carbonate</td>
</tr>
<tr>
<td>AgOMs</td>
<td>silver methanesulfonate</td>
</tr>
<tr>
<td>AgOAc</td>
<td>silver acetate</td>
</tr>
<tr>
<td>AgOTf</td>
<td>silver trifluoromethanesulfonate</td>
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<tr>
<td>AgOTs</td>
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<td>DCM</td>
<td>dichloromethane</td>
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<tr>
<td>DIC</td>
<td>$N,N'$-diisopropylcarbodiimide</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
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</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N)-(dimethylamino)pyridine</td>
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<tr>
<td>DMAD</td>
<td>dimethylacetylenedicarboxylate</td>
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<td>(N,N)-dimethylformamide</td>
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<td>dimethyl sulfide</td>
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<td>dimethyl sulfoxide</td>
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<td>d.r.</td>
<td>diastereomeric ratio</td>
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<td>enantiomeric excess</td>
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<td>electron impact</td>
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<td>HOAc</td>
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<td>HPLC</td>
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<td>1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene</td>
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<td>IR</td>
<td>infrared</td>
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<td>J</td>
<td>coupling constant</td>
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<td>δ</td>
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<td>m/z</td>
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<td>NaS₂O₃</td>
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<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
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<td>PTSA</td>
<td>p-toluenesulfonic acid monohydrate</td>
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<td>Q zz</td>
<td>permanent quadrupole moment</td>
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<td>r.t.</td>
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<td>SAMP</td>
<td>(S)-1-amino-2-methoxymethyl pyrrolidine</td>
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<tr>
<td>SmI₂</td>
<td>samarium iodide</td>
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<td>TBAF</td>
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<td>TDS</td>
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<td>trifluoroacetic acid</td>
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<td>TFAA</td>
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<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TMSOTf</td>
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<td>TOF</td>
<td>time of flight</td>
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<td>Tp</td>
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Chapter 1
Umpolung or Polarity Reversal

The introduction of this chapter will address syntheses that employ reversed polarity equivalents of the carbonyl group. The main goal of our research, which will be described in the Research Objectives section was to investigate the utilities of chiral $\alpha$-carbonyl cation in synthesis. In the ensuing section, the results of our efforts in carbon – carbon bond forming reactions, synthesis of different heterocycles and attempts in making different sialyl donors will be discussed.

Introduction

1.1 Concept of Umpolung

Devising methods to prepare structurally complex organic molecules can be a formidable task since not a single methodology can serve as a tool to comprehensively cover all chemical syntheses. Hence, developing formal ‘rules’ for planning the synthesis of a given structure has been a long standing aim of organic chemistry. For this purpose, synthetic strategies are devised through recognition of key synthons in the retrosynthetic analysis, guided by the reactivity pattern of functionalized organic compounds. In general, the reactivity of functionalized organic compounds follows a pattern of alternating donor and acceptor properties in which $X$ denotes a heteroatom, “d” denotes an electron donor-like atom and “a” denotes an electron acceptor like atom (Scheme 1.01). If polar reactivity is used to construct C – C bonds, nucleophilic reactivity may be exploited at C$_2$, C$_4$, C$_6$… and electrophilic reactivity at C$_1$, C$_3$, C$_5$… The Claisen condensation, for example, exploits such reactivity to generate 1,3-diketone products. However, methods employing the inherent reactivity of the carbons can only lead to 1,3-, 1,5-…1, (2n+1)-disubstituted products and are not suitable for the synthesis of 1,2-, 1,4-…1, (2n)- disubstituted products (Scheme 1.01).
In order to overcome these limitations, operations—“umpolung”—that accomplish polarity inversion of the functional group are required. The concept of polarity inversion was first introduced by Corey\(^3\), but it was not until late 1970’s that Seebach\(^1\) used the term “umpolung” to describe any process by which donor and acceptor reactivity of an atom are interchanged. Many such processes have been developed to meet the aforementioned challenges. Three important synthons that represent umpolung reactivity of the carbonyl group—acyl anions, homoenolates and α-carbonyl electrophiles—are depicted in Scheme 1.02.

Scheme 1.02. Umpolung synthons of carbonyl group.
1.2 Acyl Anions

Because of the acceptor reactivity of $C_1$ of carbonyl compounds (Scheme 1.01), attempts to generate acyl anions using strong bases such as $n$-BuLi generally result in 1,2-addition to the carbonyl functionality. The problem associated with the acceptor ability of $C_1$ can be resolved by temporary replacement of the heteroatom oxygen by a dithianyl group, which enhances the acidity of $C_1$ position and provides protection against nucleophilic addition by strong bases. According to Streitweiser scale, the $pK_a$'s of 1,3-dithanes range from 26 to 37 depending on the $R$ group of the aldehyde from which they are derived. Consequently, alkyllithiums ($pK_a > 35$) can be used to deprotonate at $C_1$, generating acyl anion equivalents ($d^1$ synths) capable of reacting with electrophiles such as alkyl halides, epoxides, ketones, aldehydes, and acyl halides. The utility of this chemistry is exemplified in the synthesis of 1-phenylpropan-2-one and 1-(1-hydroxycyclohexyl)ethanone, which are not easily accessible using enolate chemistry. Subsequent quench of dithianyl lithium with benzyl bromide and cyclohexanone would lead to 1-phenylpropan-2-one and 1-(1-hydroxycyclohexyl)ethanone precursors respectively. The dithane moiety can be converted to the carbonyl group by Hg-assisted hydrolysis (Scheme 1.03).

Scheme 1.03. Carbonyl addition and alkylation of dithianyl lithiums.

In addition, dithianes may be reduced to methylene groups using Raney nickel. Although $C_1$ reactivity umpolung by dithiane is a convenient method to generate acyl anions in the synthesis of some interesting compounds, removal of the dithianyl group can be difficult and often requires stoichiometric amounts of toxic metals. With these limitations of dithiane
chemistry in mind, umpolung of C\textsubscript{1} reactivity using hydrazones and nitronates has been exploited.

Hydrazones play important roles in organic chemistry,\textsuperscript{6} participating in such transformations as Shapiro, hydrazone iodination and Bamford-Stevens reactions to afford unsymmetrical alkenes. Lithiated chiral N, N-dialkyl hydrazones such as SAMP developed by Enders react in many useful asymmetric transformations with electrophiles.

Understanding that hydrazones can activate the carbonyl after deprotonation to form ambident anions, not only the azomethine nitrogen atom but also the azomethine carbon atom can serve as a nucleophile under suitable conditions. It was demonstrated by Baldwin\textsuperscript{7,8} that, with sterically demanding groups such as tert-butyl or trityl groups, aldehyde hydrazone carbanions react regioselectively with electrophilic alkyl halides, aldehydes or ketones (Scheme 1.05).
Scheme 1.05. Ambident hydrazone carbanions as acyl anions.

It was envisaged by Lassaletta and coworkers\(^9\) that SAMP could be introduced as the chiral element to induce stereoselectivity for umpolung of C\(_1\) of hydrazones. Hence, chiral acyl anion equivalents derived from proline can react with Michael acceptors at −78 °C to afford 1,4-dicarbonyl products with very high diastereoselectivity. Acyclic and cyclic α,β-unsaturated ketones were found to be suitable acceptors in this process in which the diastereoselectivity can be interpreted in terms of the minimization of steric repulsion between the CH\(_2\)OMe and TDS group on the oxygen atom in a proposed geometry of the transition state. In contrast to the harsh conditions employed in the deprotection of dithianes, mild ozonolysis and HCl-mediated cleavage of chiral auxiliaries were used to convert hydrazones to 1,4-dicarbonyl products with no degradation of stereoselectivity (Scheme 1.06).
Scheme 1.06. Employment of SAMP-derived hydrazones in stereoselective conjugate addition.

A common strategy employed in the construction of C-C bonds is the Henry reaction\textsuperscript{10,11} in which nitroalkanes react with aldehydes and ketones to give β-nitro alcohols in the presence of a base (Scheme 1.07). Treatment of the β-nitro alcohols with weak aqueous acid, HOAc or with oxidizing reagents such as DMDO, KMnO\textsubscript{4} or H\textsubscript{2}O\textsubscript{2} results in the formation of 1,2-diketones.\textsuperscript{12} Through this indirect approach, nitroalkanes may act as surrogates of acyl anions, not only providing 1,2 dicarbonyl products but also enabling the synthesis of a variety of useful building blocks, some of which are listed in Scheme 1.07.\textsuperscript{13}
Nitroalkane as acyl anion in reactions with ketones, imines and α,β-unsaturated ketones.

Although nitroalkanes have proved to be very versatile acyl anion equivalents, they are usually prepared from the nucleophilic substitution of alkyl halides with toxic sodium azide followed by oxidative cleavage or from the corresponding oximes using strong oxidizing reagents such as peroxytrifluoroacetic acid. Another approach to generate acyl anions is the use of cyanide ion which was discovered by A. Lapworth in 1903. The incentive of this pioneering study was to improve the synthesis of cyanohydrins by examining the effects of acids and bases on these reactions. Yellow color appeared when potassium cyanide was added to a solution of benzaldehyde, indicating the decomposition of the cyanohydrin which is colorless. After careful scrutiny, Lapworth determined that benzoin had been formed by dimerization of benzaldehyde and decomposition of the resulting cyanohydrin.

Lapworth (1903)

Scheme 1.07. Nitroalkane as acyl anion in reactions with ketones, imines and α,β-unsaturated ketones.

Scheme 1.08. Lapworth’s study of cyanohydrins in the benzoin condensation.
Based on mechanistic investigations by Schowen, all of the steps in the cyanide-catalyzed benzoin condensation are reversible (Scheme 1.08), and the major limitation arises in the coupling of two different aldehydes; four products are possible, and the distribution of the products in the cross benzoin condensation is generally determined by the relative thermodynamic stabilities of the products. Therefore, using an excess of one aldehyde or using premade and protected cyanohydrin derivatives can prevent promiscuous production of isomers in cross benzoin reactions. Alternatively, Johnson's research team developed a practical cyanide-catalyzed cross silyl-benzoin reaction to afford diverse α-hydroxycarbonyl compounds with either KCN catalyst and 18-crown-6 cocatalyst or La(CN)$_3$ alone. The latter was found to be a more competent catalyst for condensation of aliphatic aldehydes. Further experimental data suggested that aldehyde cyanation occurs but is reversible under the reaction conditions. However, addition of cyanide to the acyl silane is kinetically favored and irreversible, and is followed by [1,2]-Brook rearrangement to yield the (silyloxy)nitrile anion. The cross benzoin reaction is highly regioselective due to irreversible carbon-carbon bond formation. The silyl group is shuttled between two adjacent oxygen atoms, and the cyanide catalyst is regenerated due to the instability of labile M-O bonds (Scheme 1.09).

\[
\text{Scheme 1.09. Cyanide-catalyzed cross silyl benzoin condensation.}
\]
The cyanide – catalyzed benzoin condensation represents an appealing method to prepare 1,2-dicarbonyl compounds by umpolung of C1. In nature, nucleophilic acylation reactions are catalyzed by transketolase enzymes together with vitamin B1, a natural thiazolium derivative that operates by a mechanism similar to that proposed for catalysis by cyanide. The conventional mechanism of the thiazolium-catalyzed condensation was elucidated by R. Breslow who proposed that an α-hydroxy-enamidine-type intermediate, now known as the Breslow intermediate, functions as the nucleophilic acylating agent. The Breslow intermediate subsequently reacts with a second equivalent of the aldehyde to yield the α-hydroxy ketone product and the original carbene catalyst (Scheme 1.10).

Scheme 1.10. Thiazolium-catalyzed benzoin condensation.

The asymmetric benzoin condensation was first examined by Sheehan and coworkers employing a chiral thiazolium salt as the catalyst precursor. This initial attempt resulted in low enantiomeric excess and modest yield. Several research teams have developed chiral catalysts that display improved efficiency and selectivity since Sheehan's seminal report. Enders and colleagues designed a triazolium-based carbene precursor that showed promising ee's, and since then the design of the catalysts for asymmetric benzoin condensation has been focused on triazolium derivatives. Using only 5 mol% of t-butyl bearing triazolium salt and 10 mol% KOrBu, Enders' team was able to obtain various α-hydroxy ketones in good yield and high ee's (up to 95% ee) (Scheme 1.11).
**Scheme 1.11.** Enders’ triazolium salt in the synthesis of α-hydroxy ketones.

### 1.3 Homoenolate Equivalents

Homoenolates are homologs of enolates in which the negative charge is β to the carbonyl group. Unlike α-enolization which is generally facile, homo-enolization generally requires harsh and strongly basic conditions. In addition, the challenges associated with the formation of homoenolates are exacerbated if the α-position is not fully substituted, resulting in mixtures of products from conventional homo-enolization. These problems have been largely overcome through two general approaches: (1) masking the carbonyl group and simultaneous activation with anion stabilizing group(s) at β-position, or (2) control of ambident nuclophilicity of heteroatom- substituted allylic anions. Kondo and Tunemoto prepared phenylsulfone acetals and ketals to study alkylation of their conjugate bases. Acid hydrolysis followed by elimination of benzenesulfinic acid yielded the corresponding alkylated α,β-unsaturated ketones or aldehydes (Scheme 1.12).

**Scheme 1.12.** Generation of homoenolates from phenylsulfone acetals.

Ketone homoenolate equivalents generated by bis-lithiation from 1-alken-3-ols have been used in nucleophilic substitution reactions. The substitution occurred at the γ-position of the allyl group via the dilithiated species (Scheme 1.13).
Scheme 1.13. Alkylation of a dilithiated homoenolate equivalent.

Kuwajima’s studies$^{30-32}$ also revealed that putative homoenolates can be generated from acyltrimethylsilanes which, after treatment with vinlylmagnesium, undergo Brook rearrangement to the O-silyl enol ethers. Introduction of various electrophiles afforded products of alkylation, Michael addition, epoxide opening and carbonyl addition reactions (Scheme 1.14).


$N,N$-Diisopropylcarbamate has shown to be a potent anion stabilizing group,$^{33,34}$ and was employed by Hoppe’s research group in the development of a useful synthetic homoenolate equivalent.$^{35}$ Deprotonation using alkyllithium/TMEDA resulted in good $\gamma$-regioselectivity in the carbonyl addition reaction. Further improvements in regioselectivity and anti/syn diastereoselectivity were achieved after exchange of lithium with tetra-(isopropoxy)titanium, which favors an ordered transition state by chelation (Scheme 1.15).
The studies outlined above employing metallated homoenolate equivalents represent useful methods for making $C - C$ bonds in a way that is complementary to that of enolate chemistry. However, the preparation of such homoenolate equivalents is still quite difficult because of their instability, and their reactivity is dependent on the nature of metal counterion. If the homoenolate is too reactive ($M = Li, Na, ..$), cyclization to the corresponding cyclopropanol derivative predominates (Scheme 1.16). On the other hand, several isolable metallic species (Sn (IV) and Hg (II)) do not react with various electrophiles.

The equilibration between the open homoenolate and metallated cyclopropanoxide has prompted the development of a new type of homoenolate equivalent. 1-Alkoxy-1-siloxycyclopropanes can be obtained by reductive silylation of $\beta$-halo esters with metallic sodium or potassium-sodium alloy in the presence of chlorosilanes or by the Simmons-Smith cyclopropanation of ketone silyl enol ethers (Scheme 1.17).
Scheme 1.17. Preparation of 1-alkoxy-1-siloxycyclopropanes.

After screening several Lewis acids, Kuwajima and Nakamura found that TiCl$_4$ combined with 0.5 equivalents of Ti(O-$t$-Bu)$_4$ is the ideal reagent for opening cyclopropane rings to generate titanium homoenolate species.$^{39}$ These optimal conditions are particularly useful since use of only TiCl$_4$ could result in chlorination for some cases as well as lower reactivity towards electrophiles.$^{40}$ As a result, a variety of aldehydes, ketones and acetals are suitable electrophiles in the reaction to give the corresponding alcohols or butyrolactones. Furthermore, good levels of diastereoselectivity were observed in the preparation of $\gamma$-lactones (Scheme 1.18).

![Scheme 1.18](image)

Scheme 1.18. 1-Alkoxy-1-siloxycyclopropanes as homoenolate equivalents in synthesis.

On the contrary to the high reactivity displayed by titanium homoenolates towards carbonyl compounds, zinc homoenolates$^{41}$ do not add to aldehydes or ketones, and they can be isolated as dimeric structures after treatment of 1-alkoxy-1-siloxycyclopropanes with ZnCl$_2$. Alternatively, the intermediates can be used without isolation in copper-catalyzed reactions with acylating reagents or $\alpha,\beta$-unsaturated ketones (Scheme 1.19).
Scheme 1.19. Zinc homoenolates in conjugate additions and acylations.

N-Heterocyclic carbene (NHC)-catalyzed redox transformations of functionalized aldehydes allow the generation of reactive intermediates that behave as homoenolate equivalents. Initial studies were carried out independently by the groups of Bode and Glorius, both of whom used IMes·HCl as the catalyst in the coupling of α, β-unsaturated enals with electrophilic aldehydes or ketones to form cis-γ-butyrolactones (Scheme 1.20).

Scheme 1.20. NHC-catalyzed formation of cis-γ-butyrolactones.

Recently, Scheidt's research group applied Lewis acids along with an NHC organocatalyst for the synthesis of highly substituted cyclopentanes. It was not obvious at first that Lewis basic N-heterocyclic carbenes could be compatible with Lewis acids for the dual activation of electrophile and nucleophile. However, if the Lewis acid is carefully chosen to bind preferentially to unsaturated ketoesters without impairing the ability of NHC to form the Breslow intermediate, homoenolates derived from the NHC can add to the Michael acceptor which is activated by Lewis acid. Indeed, no products were observed in the absence of titanium alkoxide.
In addition, the enantioselectivity of this process arises from selective attack of the homo-enolate to generate the C – C bond as depicted in the catalytic cycle in Scheme 1.21.

Scheme 1.21. Proposed catalytic cycle for asymmetric synthesis of cyclopentanes.

1.4 α-Carbonyl Electrophiles

Ketone α-alkylation is a fundamental transformation in organic chemistry. Addition of alkyl halides to preformed enolates or aza-enolates is the most frequently employed method to achieve such C-C bond formation. However, ketone α-arylation has been challenging using traditional enolate chemistry. Umpolung of the α-carbon reactivity by installation of heteroatoms such as halides provides an attractive alternative to enolate-based methods. It can be envisaged
that the reactivity of the α-keto carbon might be reversed to generate a carbocation assisted by a Lewis acid. However, the existence of a carbocation α to carbonyl group can be counterintuitive since the electron withdrawing carbonyl group could inductively destabilize the carbocation to a large extent, suppressing the carbocation formation. Despite the aforementioned idea, α-carbonyl carbocations have been generated and studied by Creary and coworkers. In their investigation, the norbornyl system was chosen for study because of its semi-predictable rearrangement patterns. In the acetolysis study of a methyl substituted tresylate, four products I-IV were formed. Because the stereochemistry of the tresylate leaving group precluded concerted Wagner-Meerwein rearrangement, these four products were suggested to arise from carbocation intermediates, a hypothesis which was also supported by the positive, secondary α-methyl-d3 isotope effect (Scheme 1.22). Moreover, rate studies of V-IX indicated that the rate retardation of solvolysis by the carbonyl group could be ameliorated by the presence of methyl or aryl groups with electron donating functionality at the para-position. Hyperconjugation or conjugation provided by the methyl or aryl groups was able to counteract the carbocation – destabilizing effect of the carbonyl group in the norbornyl system.

**Scheme 1.22.** Creary’s study of carbocations in the norbornyl system.
In further studies of the solvolysis of secondary benzylic or tertiary α-keto carbocations, racemization occurred in the reaction of (+)-ethyl α-mesityl phenylacetate, supporting the formation of a carbocation in this process (not shown in Scheme 1.23). Creary and coworkers\textsuperscript{48} surprisingly did not find a rate retarding effect due to the presence of the carbonyl group. In fact, \textit{t}-butyl α-mesityl norbornylacetate underwent solvolysis slightly faster than its α–H analogue in acetic acid. In difluoromethanol, the solvolysis rate ratio of benzyl mesylate and ethyl α-mesityl phenyl acetate was found to be 200:1. The lack of rate retardation due to the carbonyl group was proposed to be the result of π-conjugation which was also suggested for α-cyano carbocations\textsuperscript{49} (Scheme 1.23).

![Scheme 1.23: Rate studies of α-carbonyl carbocations.](image)

The use of ferric oxide as a Lewis acid to activate α-chloroacids (C\textsubscript{2}) was exercised by Kitamura in 1951\textsuperscript{50} for the preparation of α-naphthalene fatty acids. Condensations of naphthalene with α-chloropropionic acid or α-bromobutyric acid were carried out in the presence of ferric oxide. In the case of α-chloropropionic acid, potassium bromide was added in order to obtain α-naphthalenepropionic acid. Yields of both reactions were nevertheless poor (Scheme 1.24).
Scheme 1.24. Kitamura’s synthesis of α-naphthalene fatty acid.

Interesting silver-assisted reactions of α-halo ketones or esters were illustrated by the Charpentier-Morize group. For example, AgSbF$_6$-assisted reactions of a saturated α-bromo ester afforded a mixture of five and six-membered lactones, presumably through hydrolysis of oxonium ions (Scheme 1.25). The oxonium intermediates likely arose from the common α-carbonyl carbocation followed by successive hydride migrations. This result implied that n-participation of carbonyl group might be important to stabilize the carbocation.

Scheme 1.25. Ag (I)-assisted lactone formation from an α-halo ester.

Based on their previous studies, the substitution reaction of desyl bromide with AgSbF$_6$ has also been investigated by Charpentier-Morize. An α-carbonyl carbocation, which was identified by spectroscopic techniques at low temperature, participated in a $S_N$1 reaction with methanol or a Friedel-Crafts reaction with benzene as solvents to give the methyl ether or α-diphenyl acetophenone, respectively, albeit with low yields (Scheme 1.26).
Scheme 1.26. Ag (I) assisted SN1 and Friedel-Crafts reactions of desyl bromide.

Although α-carbonyl carbocations can be generated using conventional Lewis acids, nucleophiles may react with the carbonyl carbon (C1) since it functions naturally as an acceptor. To circumvent this competing pathway, an earlier study\(^ {54}\) used imino derivatives as surrogates for the carbonyl functionality (Scheme 1.27). Sterically hindered ketones\(^ {55}\) have also been employed in BF\(_3\)•Et\(_2\)O-promoted reactions (Scheme 1.28).

Because α-halogenated aldehydes were known to undergo addition with aryl groups at the carbonyl site (C1), Charpentier-Morize and coworkers\(^ {54}\) investigated the imino functionality as a surrogate for the aldehyde in the arylation reaction. It was shown that aluminum chloride was the ideal promoter to accomplish arylation of α-chloro aldimines, but a high yield was obtained only when R\(^ 2\) = Me and R\(^ 3\) = Ph. Apart from benzene, other arene nucleophiles resulted in poor yields. α,β-Unsaturated aldimine byproducts were generated if either R\(^ 2\) or R\(^ 3\) contained a β-hydrogen, thus lowering the product yields (Scheme 1.27).

![Scheme 1.27. Arylation of aldimines using AlCl\(_3\).](image)

Smith and Johnson\(^ {55}\) reported Lewis acid promoted Friedel-Crafts alkylation or arylation of α-ketophosphates, which can be prepared from readily available α-hydroxy acetophenone. When an enantioenriched α-ketophosphate was treated with furan and BF\(_3\)•Et\(_2\)O in methylene
chloride at 23 °C, the enantiomeric ratio of the resulting product was 50:50, thus suggesting an $S_N1$ mechanistic pathway via an $\alpha$-carbonyl cation (Scheme 1.28). Not only arenes were suitable but also other less reactive nucleophiles such as trimethylsilyl azide and vinyl trifluoroborate salts, provided the desired products with reasonable yields.

![Scheme 1.28](image)

Johnson (2010)

**Scheme 1.28.** $\alpha$-Keto phosphates in BF$_3$·Et$_2$O-mediated Friedel-Crafts reactions.

Another strategy for arylation or alkylation of $\alpha$-carbonyl electrophiles involves nucleophilic additions of cuprate reagents ($S_N2$) without generation of carbocations. $\alpha$-Halo tosylhydrazones were utilized by Fuchs and Sacks$^{56}$ to reverse the reactivity of the $\alpha$-keto carbon. Organocopper reagents were added in excess because one equivalent is needed to deprotonate the hydrazone, eliminating the halide and generating the $p$-toluenesulfonylazo olefin intermediate, which reacts with another equivalent of nucleophile to give the arylated products. Conversion of hydrazones to the corresponding ketones was smoothly carried out using BF$_3$·Et$_2$O (Scheme 1.29).
Scheme 1.29. Cuprate addition to α-halocarbonyl electrophiles.

TBS-protected oximes were found by Weinreb and coworkers\textsuperscript{57} to be robust surrogates for carbonyl groups, surviving the bases needed for the \textit{in-situ} deprotonation of diethyl malonate. The putative nitrosoalkene intermediate was presumably formed upon treatment with TBAF. Interestingly, these reactions are highly stereoselective when a chirality center is present in the β-position. The relative configurations of these products were established as anti by X-ray crystallography. The stereochemical outcome can be explained by a modified Felkin-Ahn model which favors the attack of nucleophile from the least hindered face of the electrophile in its reactive conformation (Scheme 1.30).

Scheme 1.30. \textit{In-situ} nitrosoalkene formation in diastereoselective alkylations.

Arylation and vinylation of α-diazocarbonyl compounds were accomplished by Wang and coworkers.\textsuperscript{58} In their extensive study, boroxines activated by diisopropylamine were found to be competent nucleophiles to furnish α-arylated and α-vinylated carbonyl compounds. Ketones, amides, esters and oxindole were tolerated under these mild conditions.
Durst and coworkers\textsuperscript{59} obtained optically active $\alpha$-amino esters via highly diastereoselective, dynamic kinetic resolutions. X-ray crystallography of relevant $\alpha$-bromo esters revealed that the plane in which the carbonyl sits is perpendicular to that of the chiral auxiliaries under the influence of the geminal dimethyl groups. Transition state $A$ is more favorable than $B$ due to fewer eclipsing interactions, and the preference for nucleophilic attack from this side was explained by the favorable H-bonding with the carbonyl group of the ester and blockage by the geminal dimethyl groups.

**Scheme 1.31.** Base promoted reaction of $\alpha$-diazocarbonyl compounds with boroxines.
Scheme 1.32. Synthesis of optically active α-amino esters via dynamic kinetic resolution.

Over the years, metal-catalyzed reactions not only have evolved to become mainstream methods in organic chemistry, but also have been applied in the synthesis of α-substituted carbonyl compounds. Two complementary and yet mechanistically divergent types of metal-catalyzed reactions have been developed to generate C-C bonds α to carbonyl groups. The enolates, that were generated by the deprotonation of the α-carbons, can substitute the X group of the LnPd(II)ArX complex in the catalytic cycle in which the final intermediates were converted to α-substituted carbonyl compounds after a reductive elimination process (Scheme 1.33). This approach benefits from the inherent polarity of C₂ and rate enhancement by the Pd catalyst to form α-arylated ketones that cannot be prepared by traditional enolate chemistry. However, the drawbacks of this approach may include functional group incompatibility due to the strong bases employed. The formation of overalkylated or overarylated side products also likely occur since
α-carbons of the desired products are more acidic and more prone to be deprotonated than the starting materials, leading to another round of alkylation or arylation.

![Catalytic cycle for Pd-catalyzed arylation of ketone using aryl halide as coupling partners.](image)

**Scheme 1.33.** Catalytic cycle for Pd-catalyzed arylation of ketone using aryl halide as coupling partners.

On the contrary, the second approach accomplishes an umpolung of C$_2$ by using α-haloketones which undergo cross coupling reaction with organometallic reagents. The latter approach was initially examined by Ready and coworkers$^{61}$ in the copper catalyzed cross coupling of alkyl zinc halides with α-chloroketones. As a result, a large array of sterically encumbered α-alkylated ketones were obtained (**Scheme 1.34**).

![Copper-catalyzed cross coupling reaction of alkylzinc halides with α-chloroketones.](image)

**Scheme 1.34.** Copper-catalyzed cross coupling reaction of alkylzinc halides with α-chloroketones.
Asymmetric cross coupling reactions of α-halo ketones with a variety of organometallic reagents have been achieved. Fu and coworkers have discovered asymmetric Suzuki,\textsuperscript{62} Hiyama,\textsuperscript{63} Negishi\textsuperscript{64} and Kumada\textsuperscript{65} cross coupling reactions of α-halo ketones.

Scheme 1.35. Asymmetric cross-coupling reactions of α-halo ketones, esters and amides.

1.5 Research Objectives

Thus, α-carbonyl electrophiles have been implicated in mechanistic studies and in some instances are useful for forming carbon-carbon bonds next to the keto group. In theory,
carbocations with chiral substituents or chiral auxiliaries, could be used to form C-C bonds stereoselectively. However, $S_N1$ reactions via chiral $\alpha$-keto carbocations are largely unexplored, and only one study published by Heaney and coworkers, briefly looked into diastereoselective additions of indole and pyrrole nucleophiles to 2-indolyl acetate-derived carbocations bearing the 9-phenylmenthyl chiral auxiliary (Scheme 1.36). It was not clear to us whether this process could be extended to more reactive carbocations that do not benefit from vinylogous iminium-type stabilization. Moreover, benzylic carbocations have been shown to be generated from $\alpha$-keto phosphates by Lewis acids or from $\alpha$-keto benzyl alcohol by Brønsted acids. At present, only a few synthetically useful protocols carbon-carbon bond forming reactions of $\alpha$-carbonyl carbocations exist, and diastereoselective versions have not been demonstrated. In principle, diastereoselectivity may be induced by the use of a chiral auxiliary in a Lewis acid promoted $S_N1$ reaction of $\alpha$-carbonyl cation. Based on this assumption, the primary goals of this project were:

1. to formulate protocols for $S_N1$ reactions of benzylic carbocations bearing esters and amides,
2. to examine the effects of several amido and ester chiral auxiliaries in controlling facial selectivities of $S_N1$ reactions of this type, (3) to develop an intramolecular variant for both preparation of useful classes of heterocycles, and to investigate stereocontrol in these cyclizations (Scheme 1.37).

![Scheme 1.36. Heaney’s synthesis of diarylacetic esters.](image-url)
Results and Discussion

1.6 Optimization of Conditions for Intermolecular Nucleophilic Displacements

Initially, α-keto tosylates were employed as substrates for screening optimal conditions, including a range of nucleophiles, Brønsted and Lewis acids; this work was carried out by Josh Dubland and Golam Sarwar who were graduate students in the group. However, the yields of these reactions were low. Unexpected formation of an oxazole was observed in the reaction of α-oxo-tosylate and allyltrimethylsilane using substoichiometric scandium (III) triflate (OTf) in acetonitrile solvent. Presumably, this occurred through a Ritter type-reaction followed by cyclization of the nitrilium intermediate (Scheme 1.38). The further optimization and expansion of the scope of this reaction will be described in Chapter 2. Later, it was concluded that the product of the allylation could be obtained using stoichiometric aluminum (III) chloride in methylene chloride. Experiments with enantioenriched 2.2a that resulted in the formation of racemic 1.3a are consistent with a reaction mechanism involving an α-carbonyl cation. Due to the difficulty in improving the lead result, efforts were instead devoted to C-C bond formation using α-bromo esters or amides as starting materials.
Scheme 1.38. Lewis acid-promoted substitution reactions of tosylate 2.2a.

The focus was then switched to methyl 2-bromo-2-phenylacetate 1.1a as the substrate, keeping in mind that halides can be abstracted by silver salts.\textsuperscript{69} N-Methylindole was employed as an active nucleophile in the $S_N1$ reaction of benzylic carbocations. It is noteworthy that, in previous studies,\textsuperscript{68} Ag(I) salts with non-coordinating cations generally found to be more useful for promoting reactions of $\alpha$-halocarbonyl compounds. In this study, Ag(I) trifluoroacetate and triflate, whose counterions are considered to possess intermediate coordinating ability, were found to be the most competent promoters for this reaction (Table 1). The reaction can be optimally carried out from $-78 \, ^{\circ}C$ to room temperature in dichloromethane using three equivalents of 1-methylindole.
Table 1. Optimization of reaction conditions for the Ag(I)-promoted Friedel-Crafts reaction of \textbf{1.1a}.

Under the optimized reaction conditions, a range of arenes engaged in Friedel-Crafts reactions with \(\alpha\)-bromo ester \textbf{1.1a} (Table 2). Efficient reaction with unsubstituted benzene was observed, and did not require the use of the latter as reaction solvent (entry 6). The method is tolerant of replacement of the ester group with an amide (entry 7), and of substitution of the aromatic ring in \textbf{1.1a} (entry 8); however, substrates \textbf{1.1} lacking the carbocation-stabilizing aryl group \(\text{Ar}\) did not participate in Friedel-Crafts reactions under these conditions. In addition to arenes, allyl- and methallytrimethylsilane also underwent the Ag-promoted reaction with \textbf{1.1a}. Surprisingly, the reaction of \textbf{1.1a} with methallytrimethylsilane resulted in the formation of lactone \textbf{1.3e}. Cyclization mediated by in-situ generated triflic acid was likely the cause for the unexpected formation of the lactone. Indeed, when 2,6-lutidine was added as a base to the reaction mixture, methallylated product \textbf{1.3d} was obtained (Scheme 1.39). However, when 1, 2-methyl-1-trimethylsiloxypropene, one of the more activated enol equivalents according to Mayr’s scale,\textsuperscript{70} was employed, the reaction afforded only an inseparable mixture of products.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ar$^+$-H</th>
<th>Product</th>
<th>Yield ($%$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td><img src="image" alt="NMe" /></td>
<td><img src="image" alt="Ph" /></td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td><img src="image" alt="OMe" /></td>
<td><img src="image" alt="Ph" /></td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td><img src="image" alt="OMe" /></td>
<td><img src="image" alt="Ph" /></td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td><img src="image" alt="OMe" /></td>
<td><img src="image" alt="Ph" /></td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td><img src="image" alt="Br" /></td>
<td><img src="image" alt="Ph" /></td>
<td>84$^b$</td>
</tr>
</tbody>
</table>
Table 2. Ag(I)-promoted Friedel-Crafts reactions of α-bromocarbonyl compounds.

- Isolated yield of pure product after column chromatography on silica gel. AgOTf was employed in all entries except 3 and 8, for which AgO₂CCF₃ was employed.
- Isolated as a 7:1 para/ortho isomer mixture
- C₆H₆ (10 equiv) was employed
Reactions of α-bromocarbonyl compounds with allylsilane reagents.

Synthesis of Heterocycles by Intramolecular Friedel-Crafts Reactions of α-Bromoesters and –Amides

Lactones and lactams are abundant motifs in natural products which often possess useful biological activities. In this study, we explored intramolecular variants of the Friedel-Crafts reactions of α-bromoesters and –amides by tethering the potential nucleophile and halo leaving groups in the same molecule. The closest precedent for such transformations is work of the group of Levacher, who reported five examples of δ-lactam formation from α-acetoxy amides promoted by sulfuric acid (20-86% yield). In their study, the stereochemistry of enantio-enriched substrates underwent inversion, the extent of which depended on the substitution pattern of the nucleophilic aryl group (Scheme 1.40).
Scheme 1.40. Access to enantiopure 1,4-dihydro-4-phenyl isoquinolinones via Friedel-Crafts type cyclization.

Under the current Ag(I)-mediated conditions, a range of γ-lactams including 1,2-dihydroisoquinolinones and oxindoles can be smoothly generated. A γ-lactone was also formed using a substrate bearing an electron rich aryl group. Electron poor aromatics were found to be inactive nucleophiles under these conditions. In entry 6 of Table 3, the aryl group with an electron rich methoxy functional group cyclized to in preference to a nitroaryl group. Nevertheless, amide 1.04e with an ortho-chloro group was able to undergo Friedel-Crafts reaction to furnish the desired γ-lactam, using the non-coordinating counterion BF₄⁻. Therefore, γ-lactams and γ-lactones, which are core structures of biologically active 3-aryl-oxindoles and 4-aryltetrahydroisoquinolines, can be assembled using the current method.
\[
\text{Ph-CH}_2\text{Y(Ph)}(\text{R})\text{Br} \quad 1.4a-h \xrightarrow{1.5 \text{ equiv. AgX}} \quad \text{Ph-CH}_2\text{Y(Ph)}(\text{R})\text{O} \quad 1.5a-h
\]

\[
\begin{array}{cccc}
\text{Entry} & \text{Substrate} & \text{Product} & \text{Yield (\%)} \\
1 & \text{Ph-CH}_2\text{ON}^-\text{Ph} & \text{Ph-CO} & >99 \\
2 & \text{Ph-CH}_2\text{ON}^-\text{Bn} & \text{Ph-CO} & >99 \\
3 & \text{Ph-CH}_2\text{ON}^-\text{Me} & \text{Ph-CO} & 82 \\
4 & \text{Ph-CH}_2\text{ON}^-\text{Ph} & \text{Ph-CO} & 86 \\
5 & \text{Ph-CH}_2\text{ON}^-\text{Me} & \text{Ph-CO} & 66 \\
\end{array}
\]
Table 3. Ag(I)-promoted Friedel-Crafts cyclizations of α-bromoamides and esters.

1.8 Studies of Diastereoselective Substitution Reactions of Chiral α-Carbonyl Carbocations

The stereochemical outcomes of many organic reactions can be profoundly affected by the chiral catalysts and chiral auxiliaries. Recently, Bach and coworkers have demonstrated the stereoselective additions of arene nucleophiles to benzylic carbocations. In their study, it was suggested that the conformation of the benzylic carbocation was fixed due to minimization of A1,3 allylic strain, and selectivity was imposed by the bulky tert-butyl blocking the entry of the nucleophile from the top face (Scheme 1.41). As a result, the nucleophilic addition to the benzyl carbocation can occur in high diastereoselectivity.
Scheme 1.41. Highly diastereoselective intermolecular reaction of chiral benzylic cation.

The possibility of using chiral auxiliaries that exhibit significant cation-π or cation-n interactions to control the stereochemical information of α-carbonyl carbocations is intriguing. A series of preliminary computations were carried out by Mike Chudzinski, a graduate student in the Taylor group, to examine this postulate. The calculated optimum geometries (gas phase, B3LYP/6-31+G (d)), depicted in Figure 1, illustrate an interesting range of potential interactions. The 2-aryl groups of the calculated structures 1.6a and 1.6b, bearing Whitesell-type 2-arylcyclohexanol auxiliaries, do not appear to be in proximity of carbocation for cation-π contacts. In contrast, a cation-π interaction is present in the calculated geometry of phenylmenthol- based cation 1.6c, and the Evans’ auxiliary of 1.6d and Boon’s auxiliary of 1.6e also appear to engage in cation-n interactions.
Figure 1. Calculated (B3LYP/6-31+G(d)) gas-phase structures of chiral carbocations 1.06a-e.

In terms of substrate preparation, the syntheses of 1.7a-c and 1.7e were achieved by straightforward carbodiimide-mediated couplings of corresponding alcohols with α-bromophenylacetic acid. The synthesis of 1.7d was carried out by Joshua Dubland and 1.7d was obtained from the bromination of an imide-derived enolate in modest yield (Scheme 1.42).
Scheme 1.42. Preparation of chiral α-bromocarbonyl compounds 1.7a-e.

Silver (I) promoted reactions of 1.7a-e with N-methylindole were then undertaken. While the reactions provided the desired products of Friedel-Crafts alkylation, the diastereomeric ratios of these reactions were uniformly low. Representative results are shown in Table 4. Variation of the silver salts did not improve the diastereoselectivity of the reactions; Evans’ chiral auxiliary which was calculated to be a good cation stabilizing group, did not exert significant influence on the stereoselectivity and only led to the lower d.r. All diastereomeric ratios of the products were determined by $^1$H NMR spectra. The diastereomeric ratio displayed from the reaction of 1.7e was not determined due to the complication of the $^1$H NMR signals in the presence of other byproducts.
Diastereoselective, intramolecular Friedel-Crafts reactions were continued to investigate in the context of α-methylbenzylamine-derived amides 1.9a and 1.9b. Disappointing levels of diastereoselectivity were also observed, as in the intermolecular cases. Product 1.10b was isolated in diastereomerically pure form and resubjected to the reaction conditions. The diastereomeric ratio did not change, suggesting that the mixtures obtained do not result from a thermodynamically controlled process in this case. Interestingly, different batches of 1.9a and 1.9b with varying diastereomeric ratio yielded the γ-lactams with different stereochemical outcomes. Cyclization of 1.9a furnished 1.10a with almost no diastereoselectivity regardless of the dr of the substrate or the choice of solvent employed. In contrast, the d.r. of 1.10b was the same as that of 1.9b. These results may imply mechanistic differences between the reactions of 1.9a and 1.9b. The behaviour of 1.9a was consistent with a mechanism involving the generation of an α-carbonyl carbocation. Meanwhile, an S_N2 mechanism may be proposed for the reaction of 1.9b as seen in the Levacher’s study of the six membered ring lactam formation.\textsuperscript{66}

Table 4. Ag(I)-promoted Friedel-Crafts reactions of 1.7a-e with N-methylindole.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>AgX</th>
<th>Solvent</th>
<th>Yield (%)\textsuperscript{a}</th>
<th>d.r.\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.7a</td>
<td>AgOTf</td>
<td>CH_2Cl_2</td>
<td>70</td>
<td>2.3:1</td>
</tr>
<tr>
<td>2</td>
<td>1.7a</td>
<td>AgOTf</td>
<td>THF</td>
<td>95</td>
<td>1.8:1</td>
</tr>
<tr>
<td>3</td>
<td>1.7a</td>
<td>AgOTf</td>
<td>CH_3CN</td>
<td>80</td>
<td>1.7:1</td>
</tr>
<tr>
<td>4</td>
<td>1.7a</td>
<td>AgPF\textsubscript{6}</td>
<td>CH_2Cl_2</td>
<td>90</td>
<td>1.8:1</td>
</tr>
<tr>
<td>5</td>
<td>1.7a</td>
<td>AgOTf</td>
<td>DCE</td>
<td>95</td>
<td>2.1:1</td>
</tr>
<tr>
<td>6</td>
<td>1.7b</td>
<td>AgOTf</td>
<td>CH_2Cl_2</td>
<td>85</td>
<td>1.4:1</td>
</tr>
<tr>
<td>7</td>
<td>1.7c</td>
<td>AgOTf</td>
<td>CH_2Cl_2</td>
<td>75</td>
<td>1.4:1</td>
</tr>
<tr>
<td>8</td>
<td>1.7d</td>
<td>AgOTf</td>
<td>CH_2Cl_2</td>
<td>30</td>
<td>1.3:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yield determined by \textsuperscript{1}H NMR with 1,3,5-trimethoxybenzene as a quantitative internal standard
\textsuperscript{b} Diastereomeric ratio (dr) determined by \textsuperscript{1}H NMR. The relative configuration of the major diastereomer was not determined
\textsuperscript{c} Reaction was carried out at 23–70 °C
1.9 Synthesis of Chiral Sialic Esters

In another attempt to employ chiral carbocations for stereoselective C-C bond formation, we aimed to apply this concept to sialylation – glycosylation of sialic acid. Sialic acids, namely N-acetylneuraminic acids (αNeu5Ac, βNeu5Ac, αNeu5Gc) and 3-deoxy-D-galacto-non-2-ulopyranosonic acid (KDN), are a family of naturally occurring 2-keto-3-deoxy-nononic acids...
(Figure 2), and they play important roles in many of biological processes.\(^{74,75}\) For example, polysialic acids in glycoproteins of embryonic neural membranes function as neural cell adhesion molecules.\(^{74,76-78}\) At the same time, a tetra-saccharide, which consists of an αNeu5Ac, was found to be the key component on the surface of eggs to signal sperm for entrance so that fertilization can occur.\(^{79}\) Sialic acid-rich antibodies on the surface of a regulatory macrophage population can suppress inflammation, thus inhibiting adverse autoimmune responses.\(^{75}\) Furthermore, studies have suggested that incorporation of sialic acids to tumor cells leads to a higher immunoreactivity of the tumor cells, rendering them prone to be targeted for destruction.\(^{80}\)

![Diagram of sialic acids](image)

**Figure 2.** Naturally occurring sialic acids.

Hence, chemical syntheses may be useful for understanding biological processes that involve sialic acids, and stereoselective sialylation to make α-anomers has been of great interest.\(^{81}\) Glycosides of N-acetyl neuraminic acid can be introduced by approaches similar to those used for conventional glycosylation. However, the employment of Neu5Ac derivatives as glycosyl donors can be complicated by the fact that no C\(^3\) functionality is present to direct the stereochemical outcome. Introduction of auxiliaries at C\(^1\) to direct the selectivity of sialylation has been explored but with limited success.\(^{82-84}\) Our goal was to develop a system employing sterically encumbered chiral auxiliaries to improve the stereochemical outcomes of sialylation. Furthermore, based on the high affinity displayed by the chiral thioether derivative towards a carbocation,\(^{85,86}\) we envisaged that glycosylation of sialic acid could also benefit from having
such group at C₁ position to afford the α anomer preferentially. Sialyl donors bearing chiral auxiliaries such as **1.14**, **1.15** and **1.20** (Figure 3) were targeted in this study.

**Figure 3.** Chiral sialic esters targeted in this study.

The synthesis of **1.14** and **1.15** began by the global acetylation of the hydroxyl groups of sialic acid to give **1.11**, which was then employed in an esterification using DIC as coupling reagent. Attempts to purify **1.12** and **1.13** by recrystallization or by column chromatography were unsuccessful as judged by the ¹H NMR spectra. Both mixtures were then subjected to the next set of conditions in the hope of generating products that could be more easily separated. However, treatment with HCl/AcOH or BF₃•Et₂O-promoted reaction with thiophenol resulted in no reaction or multiple products that were not separable by chromatography (Scheme 1.43).

**Scheme 1.43.** Attempts to prepare α-substituted sialic chiral esters **1.14** and **1.15**.

Consequently, attention was switched to the synthesis of **1.20** bearing a chiral thioether motif. LiAlH₄ reduction of mandelic acid yielded (S)-1-phenylethane-1,2-diol, **1.16**, whose
primary hydroxyl group was selectively sulfonylated using a borinic acid-catalyzed method developed in our lab.\textsuperscript{87,88} Nucleophilic substitution of 1.17 afforded the desired chiral auxiliary, 1.18 bearing a phenylthio group. Peracetylated sialic acid, 1.11 was first treated with thiophenol in the presence of BF\textsubscript{3}•Et\textsubscript{2}O to yield two isomers of 2-phenylthianyl peracetylated sialic acid, 1.19 with a 62:38 β/α ratio. Coupling of 1.18 and 1.19, mediated by DCC, yielded inseparable mixtures.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{1.23}
\caption{Scheme 1.44. Attempts to prepare α-substituted sialic chiral ester 1.23.}
\end{figure}

As illustrated in Schemes 1.43 and 1.44, esterification via the carbodiimide approach seems to be complicated by issues that are particularly associated with the structure of the sialic acid. The work of Liu and coworkers\textsuperscript{89} suggests that the treatment of peracetylated sialic acid, 1.11 with a variety of carbodiimides generates an O-acyl isourea intermediate that may undergo O→N acyl migration to give an N-acyl urea in the absence of nucleophile (Scheme 1.45). If this postulate is confirmed, the esterification via the carbodiimide approach might be undesirable since the attack of nucleophile onto the O-acyl isourea would be required to compete with intramolecular O→N acyl migration, resulting in promiscuous generation of products.
It may be concluded at this stage that other synthetic routes, which do not involve the carbodiimide approach, are required for the preparation of 1.14, 1.15 and 1.20. Based on the work of Gin and coworkers, the syntheses of chiral sialic esters may be devised as shown in Scheme 1.46. Peracetylated sialic acid 1.11 may be esterified through carbonate base promoted nucleophilic replacement of chiral auxiliary derivatives. Subsequently, a sequence of functional group interconversions (FGI) could furnish chiral sialic esters bearing (+)-menthol, (R)-methylmandelate or (S)-1-phenyl-2-(phenylthio)ethanol auxiliaries, respectively.

Scheme 1.45. Liu’s synthesis of sialyl spirohydantoins by domino reactions.

Scheme 1.46. Proposed route to α-substituted chiral sialic esters.
1.10 Conclusions and Outlook

The silver promoted Friedel-Crafts type reaction described above represents a reversed polarity equivalent of enolate chemistry for carbon-carbon bond formation next to carbonyl groups. Starting from readily available α-bromophenyl esters or amides, a range of electron rich π carbon based nucleophiles may be employed. Nevertheless, expansion of the substrate scope would be valuable if other nucleophiles such as potassium organotrifluoroborates and β-dicarbonyl compounds can be incorporated. Intramolecular variants of this transformation proved to be useful for constructing various dihydroisoquinolinone or 3-phenyl-oxindole moieties which are valuable building blocks for natural products or pharmaceutical targets. Further elaboration of the tethering nucleophiles may be an interesting notion for the synthesis of unusual heterocycles which may not be easily obtained by other routes. Meanwhile, integration of cation stabilizing alkyne or allylic groups into the α-carbon of the α-bromo-esters or amides could provide a broader scope for this method (Scheme 1.47).

Scheme 1.47. Proposed future work for Ag (I) promoted C-C bond formation.

Gas phase calculations suggest that cation-π interactions may be utilized to shield one face of the chiral carbocations. Exploration of this interaction to induce high diastereoselectivity with the use of chiral auxiliaries was challenging. Whitesell and Evans’ auxiliaries were employed to aim for high diastereoselectivity in the substitution reaction of chiral α-halo ester or imido substrates, but only low diastereomeric ratio of the desired products could be achieved.
Nevertheless, the collection of chiral auxiliaries tested here is relatively small, and the approach of utilizing chiral auxiliaries to enforce stereocontrol for this process could still be an attractive avenue. Other chiral auxiliaries such as Oppolzer’s and Helmchen’s camphor derived sulfonamide and Myers’ pseudoephedrine may be useful for the improvement in diastereoselectivities (Scheme 1.48).

Scheme 1.48. Common used chiral auxiliaries.

Alternatively, screening of different chiral catalysts could afford a desired enantioselective bond formation of α-carbonyl carbon. In fact, this concept was proved to be feasible by Dubland using Ag salts of chiral phosphate counteranion to afford poor but significant enantiomeric excess in the production of 1.2a (Scheme 1.49). During the development of diastereoselective versions of the intramolecular reaction, distinct mechanisms appeared to operate for the construction of dihydro isoquinolinone and 3-phenyl-oxindole. Further mechanistic studies may be helpful for understanding and improving the stereoselectivities of the heterocyclization.
Scheme 1.49. Chiral Ag (I) salt of chiral counterion in the synthesis of 1.2a.
Experimental Section

General Procedure

All reactions were carried out in oven-dried round bottom flasks or Schlenk tubes. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of nitrogen, unless otherwise noted. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using neutral silica gel from Silicycle company or using basic, activated alumina gel from Sigma Aldrich company.

Materials

HPLC grade 1,2-dichloroethane was purchased from Sigma-Aldrich Chemical and further dried by oven activated molecular sieves. All other solvents were dried using a solvent purification system equipped with columns of activated alumina, under argon (Innovative Technology, Inc.). Commercial reagents were purchased from Sigma Aldrich, Fluka, Alfa Aesar or Lancaster, and used as received.

Instrumentation

$^1$H and $^{13}$C NMR were recorded in CDCl$_3$ solutions using a Varian Mercury 300 MHz and 400 MHz spectrometer. Chemical shifts for protons are reported in parts per million (ppm) relative to tetramethylsilane and referenced to residual protium in the solvent (CHCl$_3$: $\delta$ 7.25). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl$_3$: $\delta$ 77.0). Spectral features are tabulated in the following order: chemical shift ($\delta$, ppm); multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublets, dt-doublet of triplets, m-complex multiplet); number of protons; coupling constants (J, Hz). Infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum 100 instrument equipped with a single-reflectance diamond / ZnSe ATR accessory, either in the solid state or neat liquids. Spectral feature are tabulated as follows: wavenumber (cm$^{-1}$); intensity (s-strong, m- medium, w- weak); High-resolution mass spectra (HRMS) were obtained on a VS 70-250S (double focusing) mass spectrometer at 70 eV. Chiral HPLC analysis was performed on a Hewlett-Packard 1050.
1.11 Experimental Details for Ag(I) − Mediated Nucleophilic Displacement of α-Halocarbonyl Compounds

Preparation of benzylamine derivatives

\[
\begin{align*}
\text{Acetyl R}^1 \text{R}^2 & \quad \text{NH}_2 \quad \text{R}^3 & \quad \text{Step 1} & \quad \text{Step 2} \\
1.2 \text{ equiv.} & \quad \text{N} & \quad \text{R}^1 \text{R}^2 & \quad \text{HN} & \quad \text{R}^1 \text{R}^2 \\
\end{align*}
\]

Step 1. Preparation of ketimine or aldimine

Step 2. Preparation of benzylamine derivatives from ketimine or aldimine

**General procedure A. Preparation of ketimine or aldimine**

A solution of ketone or aldehyde (1 equiv.) and amine (1.2 equiv.) in toluene (1.7 M) was stirred in a flask equipped with 4 Å molecular sieves at reflux temperature for 24 hours. After stirring for 24 hours, the reaction mixture was filtered, concentrated, and the crude product was directly used in the reaction without further purification.

\((E)-\text{N-(1-Phenylethylidene)aniline}\)

General procedure A described was carried out on 25 mmol scale, using acetophenone (2.916 mL, 25 mmol, 1 equiv.) and aniline (2.73 mL, 30 mmol, 1.2 equiv.) in 15 mL of toluene. After stirring for 24 hours, the reaction mixture was worked up as described above. The product was
obtained as a yellow solid (4.8 g, 98%). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.99-7.97 (m, 2H), 7.48-7.43 (m, 3H), 7.37-7.33 (m, 2H), 7.11-7.07 (m, 1H), 6.80 (dd, J = 8.4, 8 Hz, 2H), 2.24 (s, 3H). Characterization data were in agreement with literature values.$^{94}$

(E)-N-(3,5-Dimethoxybenzylidene)-1-phenylethanamine

![Chemical Structure](image)

General procedure A described was carried out on 2.0 mmol scale, using 3,5-dimethoxybenzaldehyde (333 mg, 2.0 mmol, 1 equiv.) and α-methylbenzylamine (309 µL, 2.4 mmol, 1.2 equiv.) in 2 mL of toluene. After stirring for 24 hours, the product was obtained as a colorless oil (440 mg, 82%). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 8.28 (s, 1H), 7.44-7.41 (m, 2H), 7.36-7.34 (m, 2H), 7.25-7.21 (m, 1H), 6.94 (d, J = 3.2 Hz, 2H), 6.52 (d, J = 3.2 Hz, 1H), 4.55 (q, J = 9.2 Hz, 1H), 3.83 (s, 6H), 1.59 (d, J = 9.2 Hz, 3H).

(E)-1-(4-Methoxyphenyl)-N-(4-nitrobenzylidene)methanamine

![Chemical Structure](image)

General procedure A described was carried out on 2.0 mmol scale, using 4-nitro-benzaldehyde (302 mg, 2.0 mmol, 1 equiv.) and 4-methoxybenzylamine (288 mg, 2.1 mmol, 1.2 equiv.) in 4 mL of toluene. After stirring for 24 hours, the reaction mixture was worked up as described above. The product was obtained as a yellow solid (482 mg, 90%). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.58 (s, 1H), 8.33 (d, J = 8.7 Hz, 2H), 8.07 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.75 (s, 2H).
**General procedure B. NaBH₄ reduction of Imine**

To a stirred solution of imine (1 equiv.) in methanol (0.5M), sodium borohydride (NaBH₄, 1.67 equiv.) was added under a positive pressure of argon at room temperature. The reaction mixture was stirred at room temperature for 15 hours and was quenched by the addition of aqueous saturated NaHCO₃ solution. The resulting solution was extracted with diethyl ether (Et₂O ×2), and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica.

**N-(4-Methoxybenzyl)-1-(4-nitrophenyl)methanamine**

General procedure B described was carried out on 1.5 mmol scale, using (E)-1-(4-methoxyphenyl)-N-(4-nitrobenzylidene)methanamine (405 mg, 1.5 mmol, 1 equiv.) and NaBH₄ (95 mg, 2.51 mmol, 1.67 equiv.) in 3 mL of MeOH. After stirring for 15 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane, then 30% EtOAc in n-pentane) yielding the title compound as a yellow oil (372 mg, 91%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.18, (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 7.5 Hz, 2H), 6.88 (d, J = 7.5 Hz, 2H), 3.90 (s, 2H), 3.81 (s, 3H), 3.75 (s, 2H). Characterization data were in agreement with literature values.

**N-(3,5-Dimethoxybenzyl)-1-phenylethanamine**
General procedure B described was carried out on 1.1 mmol scale, using \((E)-N-(3,5\text{-dimethoxybenzylidene})-1\text{-phenylethylamine}\) (296 mg, 1.5 mmol, 1 equiv.) and NaBH\(_4\) (69 mg, 1.83 mmol, 1.67 equiv.) in 2.5 mL of MeOH. After stirring for 15 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in \(n\)-pentane, then 30% EtOAc in \(n\)-pentane) yielding the title compound as a colorless oil (298 mg, >99%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.35 (d, \(J = 4.8\) Hz, 4H), 7.26-7.21 (m, 1H), 6.45 (d, \(J = 3.2\) Hz, 2H), 6.35 (t, \(J = 3.2\) Hz, 1H), 3.81 (q, \(J = 8.8\) Hz, 1H), 3.78 (s, 6H), 3.64 (d, \(J = 17.6\) Hz, 1H), 3.56 (d, \(J = 17.6\) Hz, 1H), 1.37 (d, \(J = 8.8\) Hz, 3H).

\(N\)-(1-Phenylethyl)aniline

A modified version of the procedure\(^96\) was employed to prepare the title compound. To a stirred solution of \((E)-N-(1\text{-phenylethylidene})\text{-aniline}\) (1.99 g, 10.2 mmol, 1.0 equiv.) and benzoic acid (1.25 g, 10.2 mmol, 1.0 equiv.) in THF (12 mL, 0.9M), NaBH\(_4\) (388 mg, 10.2 mmol, 1.0 equiv.) was added under a positive pressure of argon at room temperature. The reaction mixture was stirred at room temperature overnight and was quenched by the addition of aqueous saturated NaHCO\(_3\) solution. The resulting solution was extracted with diethyl ether (12 mL×2), and the combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica (2% EtOAc in \(n\)-pentane) yielding the title compound as a yellow oil (1.81 g, 89%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.39-7.29 (m, 5H), 7.10 (t, \(J = 7.5\) Hz, 2H), 6.64 (t, \(J = 7.5\) Hz, 1H), 6.51 (d, \(J = 7.5\) Hz, 2H), 4.50 (q, \(J = 6.6\) Hz, 1H), 4.02 (s, br, 1H), 1.52 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 147.5, 145.4, 129.3, 128.9, 127.1, 126.1, 117.4, 113.5, 53.7, 25.3; IR (cm\(^{-1}\), neat) 3408 (m), 2964 (m), 1599 (s), 1504 (s); HRMS (EI, M+) calcd for C\(_{14}\)H\(_{15}\)N: 197.1204, found 197.1209.

Preparation of methyl 2-bromo-2-phenylacetate (1.1a)
To a stirred solution of α-bromophenylacetic acid (1.2 g, 5.6 mmol, 1 equiv.) in 17 mL of MeOH (0.33 M) was added 2 drops of sulfuric acid at room temperature. The reaction mixture was then heated to reflux at 80 °C. After stirring at refluxing temperature for 15 hours (or judged completion by TLC), the reaction mixture was diluted with dichloromethane and quenched with water. The resulting solution was extracted with CH₂Cl₂ (15 mL × 2), and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (10% EtOAc in n-pentane) yielding the title compound as a colorless oil (1.04 g, 81%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.56-7.53 (m, 2H), 7.39-7.26 (m, 3H), 5.36 (s, 1 H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 169.01, 136.0, 129.5, 129.1, 128.9, 53.6, 46.7. Characterization data were in agreement with literature values.⁹⁷

**General procedure C. Esterification of α-bromophenylacetic acid**

To a stirred solution of α-bromophenylacetic acid (1 equiv.), the appropriate alcohol (1 equiv.) and 4-N, N'-dimethylaminopyridine, DMAP (10 mol %) in CH₂Cl₂ (0.2 M) was added N, N'-Diisopropylcarbodiimide, DIC (1.1 equiv.) at 0 °C. The reaction mixture was then allowed to warm to room temperature. After stirring at room temperature for 24 hours (or judged completion by TLC), the reaction mixture was diluted with CH₂Cl₂ and quenched with water. The resulting solution was extracted with CH₂Cl₂ (×2), and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica.

**3,5-Dimethoxybenzyl 2-bromo-2-phenylacetate (1.4h)**
General procedure C described was carried out on 1.0 mmol scale, using α-bromophenylacetic acid (215 mg, 1 equiv.), (3,5-dimethoxyphenyl)methanol, DMAP (12 mg, 0.10 mmol, 10 mol %) and DIC (171 µL, 1.1 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as an amorphous, colorless solid (287 mg, 79%).

**1H NMR** (300 MHz, CDCl$_3$) δ (ppm) 7.57-7.54 (m, 2H), 7.37-7.34 (m, 3H), 6.43-6.41 (m, 3 H), 5.41 (s, 1 H), 5.17 (d, J = 15.6 Hz, 1H), 5.13 (d, J = 15.6 Hz, 1H), 3.75 (s, 6H); **13C NMR** (100 MHz, CDCl$_3$) δ (ppm) 168.2, 161.2, 137.5, 135.9, 129.6, 129.1, 129.0, 105.8, 100.7, 68.0, 55.6, 46.9; IR (cm$^{-1}$, powder) 2944 (m), 1715 (s), 1432 (m). HRMS (EI, M+) calcd for C$_{17}$H$_{17}$O$_4$ (M-Br)$^+$: 285.1127, found 285.1169.

(S)-1-phenyl-2-(phenylthio)ethyl 2-bromo-2-phenylacetate (1.7e)

General procedure C described was carried out on 0.25 mmol scale, using α-bromophenylacetic acid (54 mg, 1 equiv.), the (S)-1-phenyl-2-(phenylthio)ethanol 1.18 (63 mg, 0.28 mmol, 1.1 equiv.), DMAP (3 mg, 0.03 mmol, 10 mol %) and DIC (42 µL, 0.28 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless oil (93 mg, 87%, d.r. = 1:1). **1H NMR** (300 MHz, CDCl$_3$) δ (ppm) 7.55-7.52 (m, 1H), 7.47-7.44 (m, 1H), 7.40-7.15 (m, 13H), 5.90-5.86 (m, 1H), 5.33 (s, 0.5H), 5.31 (s, 0.5H), 3.45-3.38 (m, 1H), 3.28-3.21 (m, 1H); **13C NMR** (100 MHz, CDCl$_3$) δ (ppm) 167.5, 167.2, 138.3, 138.2, 135.9, 135.8, 135.5, 135.5, 130.7, 130.5, 129.5, 129.5, 129.4, 129.3, 129.1, 129.0, 129.0, 128.9, 128.9, 128.8, 128.8, 127.1, 127.0, 126.8, 126.6, 47.5, 46.7, 40.3, 40.2. IR (cm$^{-1}$,
neat) 2954 (m), 1737 (s), 1455 (m). HRMS (DART, M+NH₄⁺) calcd for C₂₂H₂₃BrNO₂S: 444.0615, found 444.0633.

**General procedure D. Bromination of methyl arylacetate**

![Reaction scheme](image)

A modified version of the procedure was employed to prepare the title compound. To a stirred solution of methyl 4-methoxy-phenylacetate (1 equiv.) and N-bromosuccinimide, NBS (1.1 equiv.) in carbon tetrachloride, CCl₄ (0.5 M), 2,2'-azobis-2-methylbutyronitrile, AMBN (5 mol%) was added under a positive pressure of argon. The reaction mixture was heated to reflux for 5 hours and was cooled to room temperature. Diethyl ether was added to the reaction mixture, filtered through a plug of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica.

**Methyl 2-bromo-2-(4-(trifluoromethyl)phenyl)acetate (1.1c)**

![Methyl 2-bromo-2-(4-(trifluoromethyl)phenyl)acetate](image)

General procedure C described was carried out on 1.0 mmol scale, using methyl (4-trifluoromethyl)phenylacetate (150 µL, 1 equiv.), NBS (196 mg, 1.1 mmol, 1.1 equiv.), AMBN (10 mg, 0.05 mmol, 5 mol%). After stirring for 5 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (2% ethylacetate in n-pentane) yielding the title compound as a colorless solid (193 mg, 65%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.67 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 5.37 (s, 1H), 3.81 (s, 3H). Characterization data were in agreement with literature values.⁹⁸

**Methyl 2-bromo-2-(4-methoxyphenyl)acetate (1.1d)**
General procedure C described was carried out on 1.0 mmol scale, using methyl(4-methoxy)phenylacetate (159 µL, 1 equiv.), NBS (196 mg, 1.1 mmol, 1.1 equiv.), AMBN (10 mg, 0.05 mmol, 5 mol %). After stirring for 5 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% ethylacetate in n-pentane) yielding the title compound as a yellow oil (193 mg, 75%). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.48 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 9.2 Hz, 2H), 5.35 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H). Characterization data were in agreement with literature values.

**General procedure E. Amide coupling of α-bromophenylacetic acid.**

![Diagram of amide coupling reaction]

To a stirred solution of α-bromophenylacetic acid (1 equiv.), the appropriate amine (1 equiv.) and 4-N, N'-dimethylaminopyridine, DMAP (10 mol %) in CH$_2$Cl$_2$ (0.2 M) was added N, N'-Diisopropylcarbodiimide, DIC (1.1 equiv.) at 0 °C. The reaction mixture was then allowed to warm to room temperature. After stirring at room temperature for 24 hours (or judged completion by TLC), the reaction mixture was diluted with dichloromethane and quenched with water. The resulting solution was extracted with CH$_2$Cl$_2$ (× 2), and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude products were purified by flash chromatography.

**2-Bromo-N,N-diethyl-2-phenylacetamide (1.1b)**

![Diagram of 2-bromo-N,N-diethyl-2-phenylacetamide]
General procedure E described was carried out on 3.0 mmol scale, using α-bromophenylacetic acid (645 mg, 1 equiv.), diethylamine (310 µL, 3.0 mmol, 1 equiv.), DMAP (37 mg, 0.30 mmol, 10 mol%) and DIC (511 µL, 3.3 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as a colorless oil (405 mg, 50%). \( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.57-7.55 (m, 2H), 7.38-7.32 (m, 3H), 5.67 (s, 1H), 3.44-3.29 (m, 4H), 1.16 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H); \( ^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 166.6, 137.0, 129.1, 129.0, 128.9, 47.0, 42.8, 41.6, 14.7, 12.8; IR (cm\(^{-1}\), neat) 2973 (m), 1651 (s), 1431 (m). HRMS (ESI, M+H) calcd for C\(_{12}\)H\(_{17}\)BrNO: 270.0488, found 270.0480.

**2-Bromo-N-methyl-N,2-diphenylacetamide (1.4a)**

![Structure](image)

General procedure E described was carried out on 0.5 mmol scale, using α-bromophenylacetic acid (108 mg, 1 equiv.), N-methylaniline (54 µL, 0.50 mmol, 1 equiv.), DMAP (6 mg, 0.05 mmol, 10 mol%) and DIC (85 µL, 0.55 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as a colorless oil (127 mg, 84%). \( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.46-7.37 (m, 4 H), 7.29-7.26 (m, 4H), 7.14 (s, 2H), 5.33 (s, 1H), 3.30 (s, 3H). \( ^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 167.6, 143.1, 136.9, 130.3, 129.1, 129.0, 128.9, 128.8, 127.6, 46.0, 38.6; IR (cm\(^{-1}\), neat) 3028 (m), 1664 (s), 1494 (m); HRMS (EI, M+) calcd for C\(_{15}\)H\(_{14}\)NO (M-Br): 303.0259, found 303.0262.

**N-Benzyl-2-bromo-N,2-diphenylacetamide (1.4b)**

![Structure](image)
General procedure E described was carried out on 0.27 mmol scale, using \( \alpha \)-bromophenylacetic acid (59 mg, 1 equiv.), the \( N \)-phenyl-\( N \)-benzylamine (49 mg, 0.27 mmol, 1 equiv.), DMAP (3 mg, 0.03 mmol, 10 mol%) and DIC (47 μL, 0.30 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in \( n \)-pentane) yielding the title compound as a colorless oil (78 mg, 76%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.40-7.15 (m, 13 H), 6.91 (s, 2H), 5.28 (s, 1H), 4.99 (d, \( J = 17.6 \) Hz, 1H), 4.81 (d, \( J = 17.6 \) Hz, 1H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 167.6, 141.3, 136.8, 130.0, 129.2, 129.1, 129.1, 129.0, 129.0, 128.9, 128.8, 128.7, 127.8, 54.1, 46.5; IR (cm\(^{-1}\), neat) 3058 (m), 1666 (s), 1493 (m); HRMS (DART, M+H) calcd for \( C_{21}H_{19}BrNO \): 380.0650, found 380.0636.

\( N \)-benzyl-2-bromo-\( N \)-methyl-2-phenylacetamide (1.4c)

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{N} \\
\text{Ar}
\end{array}
\]

General procedure E described was carried out on 0.27 mmol scale, using \( \alpha \)-bromophenylacetic acid (59 mg, 1 equiv.), the \( N \)-phenyl-\( N \)-benzylamine (49 mg, 0.27 mmol, 1 equiv.), DMAP (3 mg, 0.03 mmol, 10 mol%) and DIC (47 μL, 0.30 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in \( n \)-pentane) yielding the title compound as a colorless oil (78 mg, 76%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.40-7.15 (m, 13 H), 6.91 (s, 2H), 5.28 (s, 1H), 4.99 (d, \( J = 17.6 \) Hz, 1H), 4.81 (d, \( J = 17.6 \) Hz, 1H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 167.6, 141.3, 136.8, 130.0, 129.2, 129.1, 129.1, 129.0, 129.0, 128.9, 128.8, 128.7, 127.8, 54.1, 46.5; IR (cm\(^{-1}\), neat) 3058 (m), 1666 (s), 1493 (m); HRMS (DART, M+H) calcd for \( C_{21}H_{19}BrNO \): 380.0650, found 380.0636.

\( N \),\( N \)-Dibenzyl-2-bromo-2-phenylacetamide (1.4d)

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{N} \\
\text{Ar}
\end{array}
\]
General procedure E described was carried out on 0.50 mmol scale, using α-bromophenylacetic acid (108 mg, 1 equiv.), dibenzylamine (96 µL, 0.50 mmol, 1 equiv.), DMAP (6 mg, 0.05 mmol, 10 mol %) and DIC (85 µL, 0.55 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in \(n\)-pentane) yielding the title compound as a colorless oil (174 mg, 88%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.46-7.44 (m, 2H), 7.38-7.22 (m, 11H), 7.13 (d, \(J = 6.8\) Hz, 2H), 5.60 (s, 1H), 4.85 (d, \(J = 17.6\) Hz, 1H), 4.61 (d, \(J = 17.6\) Hz, 1H), 4.51 (d, \(J = 17.2\) Hz, 1H), 4.44 (d, \(J = 17.2\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 168.5, 136.9, 136.5, 136.2, 129.4, 129.3, 129.3, 128.9, 128.9, 128.4, 128.2, 127.8, 126.3, 50.7, 49.9, 46.2; IR (cm\(^{-1}\), neat) 3028 (m), 1654 (s), 1452 (m). HRMS (EI, M+) calcd for \(C_{22}H_{20}NO\) (M-Br): 313.1467, found 313.1453.

2-Bromo-N-(2-chlorobenzyl)-N-methyl-2-phenylacetamide (1.4e)

General procedure E described was carried out on 0.8 mmol scale, using α-bromophenylacetic acid (172 mg, 0.8 mmol, 1 equiv.), \(N\)-methyl-\(N\)-benzylamine (112 µL, 0.80 mmol, 1 equiv.), DMAP (10 mg, 0.05 mmol, 10 mol %) and DIC (139 µL, 0.88 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in \(n\)-pentane, then 10% EtOAc in \(n\)-pentane) yielding the title compound as a colorless solid (201 mg, 72%) which appears as a mixture of two rotamers in NMR time scale (ratio of 1.5:1). M.p. = 94 – 97 °C (EtOAc/\(n\)-pentane). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.54-7.0 (m, 9H), 5.76 (s, 0.6H), 5.54 (s, 0.4H), 4.77 (s, 1.2H), 4.64 (s, 0.8H), 3.04 (s, 1.2H), 2.97 (s, 1.8H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 168.8, 167.9,
136.2, 136.1, 134.2, 133.5, 133.0, 132.5, 132.5, 130.3, 130.2, 129.8, 129.3, 129.1, 129.0, 129.0, 128.4, 128.3, 127.6, 127.4, 127.1, 58.5, 57.8, 51.6, 49.5, 35.7, 35.6; IR (cm\(^{-1}\), powder) 2924 (m), 1653 (s), 1403 (m). HRMS (DART, M+H) calcd for C\(_{16}\)H\(_{16}\)BrClNO: 352.0104, found 352.0097.

2-Bromo-N-(4-methoxybenzyl)-N-(4-nitrobenzyl)-2-phenylacetamide (1.4f)

![Structure of the compound](image)

General procedure E described was carried out on 0.80 mmol scale, using \(\alpha\)-bromophenylacetic acid (172 mg, 1 equiv.), \(N\)-(4-methoxybenzyl)-1-(4-nitrophenyl)methanamine (218 mg, 0.80 mmol, 1 equiv.), DMAP (10 mg, 0.08 mmol, 10 mol %) and DIC (136 \(\mu\)L, 0.88 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (20% EtOAc in \(n\)-pentane) yielding the title compound as a colorless solid (239 mg, 64%) which appears as a mixture of two rotamers in NMR time scale (ratio of 2.4:1). M.p. = 72 – 76 °C (EtOAc/\(n\)-pentane). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.21-8.13 (m, 2H), 7.50-6.83 (m, 11H), 5.70 (s, 0.71H), 5.50 (s, 0.29H), 4.89-4.43 (m, 4H), 3.83-3.79 (s, 2H), 3.79 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 168.6, 159.8, 147.6, 145.3, 144.6, 143.8, 138.5, 137.5, 136.1, 130.0, 129.6, 129.5, 129.2, 129.1, 129.0, 128.9, 128.8, 128.4, 128.0, 127.8, 127.3, 127.2, 124.5, 124.1, 114.9, 114.5, 55.6, 55.5, 51.1, 50.7, 49.4, 49.1, 46.4, 46.0; IR (cm\(^{-1}\), powder) 2837 (m), 1652 (s), 1511 (s), 1454 (m). HRMS (DART, M+H) calcd for C\(_{23}\)H\(_{23}\)BrN\(_2\)O\(_4\): 469.0763, found 469.0751.

2-Bromo-N-(3-methoxy-2-propoxybenzyl)-N-methyl-2-phenylacetamide (1.4g)
General procedure E described was carried out on 2.0 mmol scale, using α-bromophenylacetic acid (430 mg, 1 equiv.), 1-(3-methoxy-2-propoxyphenyl)-N-methylmethanamine (418 mg, 1.80 mmol, 1 equiv.), DMAP (24 mg, 0.2 mmol, 10 mol %) and DIC (341 µL, 2.2 mmol, 1.1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as a colorless oil (583 mg, 72%) which appears as a mixture of two rotamers in NMR time scale (ratio of 1:1). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.57 (dd, \(J = 8.1, 1.8\) Hz, 1H), 7.49-7.46 (m, 1H), 7.38-7.30 (m, 3H), 6.90 (d, \(J = 7.2\) Hz, 0.5H), 6.81 (t, \(J = 6.6\) Hz, 1H), 6.61 (d, \(J = 7.5\) Hz, 0.5H), 5.75 (s, 0.5H), 5.64 (s, 0.5 H), 4.79-4.56 (m, 2H), 3.99-3.95 (m, 1H), 3.91-3.84 (m, 4H), 3.04 (s, 1.5 H), 2.97 (s, 1.5H), 1.83-1.73 (m, 2H), 1.03 (t, \(J = 7.2\) Hz, 1.5H), 1.01 (t, 7.2Hz, 1.5H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 168.2, 167.6, 153.0, 152.9, 150.7, 146.0, 141.2, 136.8, 136.7, 130.6, 130.0, 129.4, 129.2, 128.9, 128.8, 128.4, 124.4, 124.3, 120.9, 118.5, 112.4, 111.7, 75.3, 75.1, 56.1, 55.9, 49.3, 47.2, 46.5, 46.3, 35.8, 35.6, 23.8, 23.7, 10.8, 10.6; IR (cm\(^{-1}\), neat) 2932 (m), 2929 (m), 1653 (s), 1477 (m). HRMS (DART, M+H) calcd for C\(_{20}\)H\(_{25}\)BrNO\(_3\): 406.1018, found 406.1023.

**General procedure F. Acylation with α-chlorophenylacetyl chloride**

To a stirred solution of the appropriate amine (1 equiv.) in CH\(_2\)Cl\(_2\) (0.2 M), diisopropylethylamine, DIPEA (1 equiv.) and α-chlorophenylacetyl chloride (1 equiv.) were added sequentially at −78 °C under a positive pressure of argon. The reaction mixture was then
allowed to warm to room temperature. After stirring at room temperature for 24 hours (or judged completion by TLC), the reaction mixture was diluted with dichloromethane and quenched with water. The resulting solution was extracted with CH$_2$Cl$_2$ ($\times 2$), and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica.

2-Chloro-N,2-diphenyl-N-(1-phenylethyl)acetamide (1.9a)

[Chemical Structure Image]

General procedure F described was carried out on 1.75 mmol scale, using $\alpha$-chlorophenylacetyl chloride (308 µL, 1.75 mmol, 1 equiv.), N-(1-phenylethyl)aniline (500 µL, 1.75 mmol, 1 equiv.) and DIPEA (305 µL, 1.75 mmol, 1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless oil (453 mg, 74%, d.r = 1.6:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.50-7.48 (m, 0.8H), 7.37-7.15 (m, 11.6H), 7.09-7.06 (m, 1.2H), 6.99-6.90 (m, 0.6H), 6.76 (d, J = 7.2 Hz, 0.4H), 6.44 (d, J = 7.8 Hz, 0.4H), 6.29 (q, J = 7.2 Hz, 1H), 5.14 (s, 0.6H), 5.06 (s, 0.4H), 1.50 (d, J = 7.2 Hz, 1.8H), 1.38 (d, J = 7.2 Hz, 1.2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 167.4, 167.3, 149.9, 140.6, 140.3, 137.1, 136.8, 136.7, 131.1, 130.6, 129.5, 129.4, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.4, 128.3, 128.2, 128.0, 127.8, 58.5, 58.0, 53.5, 53.5, 17.3, 17.0; IR (cm$^{-1}$, neat) 3028 (m); HRMS (DART, M+H) calcd for C$_{22}$H$_{21}$ClNO: 350.1312, found 350.1312.

2-Chloro-N-(3,5-dimethoxybenzyl)-2-phenyl-N-(1-phenylethyl)acetamide (1.9b)

[Chemical Structure Image]
General procedure F described was carried out on 0.50 mmol scale, using α-chlorophenylacetyl chloride (88 µL, 0.50 mmol, 1 equiv.), N-(3,5-dimethoxybenzyl)-1-phenylethanamine (136 mg, 0.50 mmol, 1 equiv.) and DIPEA (87 µL, 0.50 mmol, 1 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless oil (178 mg, 84%, d.r. = 2.4:1). 1H NMR (300 MHz, CDCl3) δ (ppm) 7.47-7.27 (m, 8.9H), 7.22-7.21 (m, 0.8H), 7.05-7.02 (m, 0.3H), 6.36-6.18 (m, 3H), 5.45 (s, 0.29H), 5.34 (s, 0.71H), 4.82 (d, J = 15.6 Hz, 0.2H), 4.51 (d, J = 18.3 Hz, 0.6H), 4.20-4.11 (m, 1H), 3.99 (d, J = 15.6 Hz, 0.2H), 3.73 (s, 1.76H), 3.70 (s, 4.24H) 3.69-3.68 (m, 1H), 1.54-1.48 (m, 3H); 13C NMR (100 MHz, CDCl3) δ (ppm) 162.9, 161.6, 140.8, 140.7, 140.4, 136.1, 129.5, 129.5, 129.4, 129.3, 129.1, 129.1, 129.0, 128.9, 128.9, 128.7, 128.6, 128.5, 127.9, 127.8, 127.7, 126.8, 103.9, 103.8, 103.7, 99.8, 57.0, 56.8, 55.6, 55.5, 52.6, 47.2, 16.8, 16.8; IR (cm⁻¹, neat) 2939 (m), 1656 (s), 1455 (m); HRMS (DART, M+H) calcd for C25H27ClNO3: 424.1680, found 424.1688.

**General procedure G. Ag-Promoted Substitution of α-Bromo esters and amides**

![Chemical Structure]

A stirred solution of silver salt (0.15 mmol) in CH2Cl2 (0.2 mL) was first cooled to −78 °C under a positive pressure of argon and the nucleophile (0.30 mmol) was added dropwise. A solution of the α-bromo ester or amide (0.10 mmol) in CH2Cl2 (0.2 mL) was added dropwise and the reaction tube was washed with an additional portion of CH2Cl2 (0.1 mL). Total reaction concentration was 0.2 M. The reaction mixture was allowed to warm to room temperature over 20 hours, diluted with CH2Cl2 and filtered through a plug of Celite to remove the precipitated silver bromide and any other traces of silver salts. The crude product was purified by flash chromatography on silica.

**Methyl 2-(1-methyl-1H-indol-3-yl)-2-phenylacetate (1.2a)**
General procedure G described was carried out on 0.20 mmol scale, using methyl 2-bromo-2-phenylacetate 1.1a (32 µL, 0.20 mmol), silver trifluoromethanesulfonate (77 mg, 0.30 mmol, 1.5 equiv.) and 1-methylindole (74 µL, 0.60 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (3% EtOAc in n-pentane) yielding the title compound as a colorless oil (52 mg, 92%). 

\[ \text{H NMR (300 MHz, CDCl}_3) \delta (ppm) 7.48-7.43 (m, 3 H), 7.36-7.29 (m, 4H), 7.27-7.20 (m, 1H), 7.11-7.06 (m, 2H), 5.28 (s, 1H), 3.76 (s, 6H); \]
\[ \text{C NMR (100 MHz, CDCl}_3) \delta (ppm) 173.8, 139.0, 137.3, 128.8, 128.6, 128.1, 127.5, 127.3, 122.1, 119.5, 119.3, 112.3, 109.6, 52.5, 49.0, 33.0; \]
\[ \text{IR (cm}^{-1}, \text{neat) 2949 (m, br), 1732 (s); HRMS (EI, M+) calcd for C}_{18}H_{17}NO_{2}: 279.1259, \]
\[ \text{found 279.1261. Characterization data were in agreement with literature values.} \]

Methyl 2-phenyl-2-(2,4,6-trimethoxyphenyl)acetate (1.2b)

General procedure G described was carried out on 0.15 mmol scale, using methyl 2-bromo-2-phenylacetate 1.1a (24 µL, 0.15 mmol), silver trifluoromethanesulfonate (59 mg, 0.23 mmol, 1.5 equiv.) and 1,3,5-trimethoxybenzene (77 mg, 0.45 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as a colorless solid (26 mg, 82%). 

\[ \text{H NMR (300 MHz, CDCl}_3) \delta (ppm) 7.35-7.19 (m, 5 H), 6.16 (s, 2H), 5.33 (s, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 3.69 (s, 3H); \]
\[ \text{C NMR (100 MHz, CDCl}_3) \delta (ppm) 174.4, \]
Methyl 2-(2,4-dimethoxyphenyl)-2-phenylacetate (1.2c)

General procedure G described was carried out on 0.15 mmol scale, using methyl 2-bromo-2-phenylacetate 1.1a (24 µL, 0.15 mmol), silver trifluoromethanesulfonate (59 mg, 0.23 mmol, 1.5 equiv.) and 1,3-dimethoxybenzene (59 µL, 0.45 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless oil (35 mg, 80%). \( ^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.36-7.27 (m, 5 H), 6.94 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 6.41 (dd, J = 8.4, 2.4 Hz, 1H), 5.25 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.72 (s, 3H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 173.9, 158.0, 138.3, 129.9, 129.2, 128.9, 128.7, 127.3, 104.3, 98.8, 55.8, 55.6, 52.4, 50.5; IR (cm\(^{-1}\), neat) 2950 (m, br), 1734 (s); HRMS (EI, M+) calcd for C\(_{17}\)H\(_{18}\)O: 286.1205, found 286.1205.

Methyl 2-phenyl-2-(2,3,4-trimethoxyphenyl)acetate (1.2d)

General procedure G described was carried out on 0.15 mmol scale, using methyl 2-bromo-2-phenylacetate 1.1a (24 µL, 0.15 mmol), silver trifluoroacetate (50 mg, 0.23 mmol, 1.5 equiv.) and 1,2,3-trimethoxybenzene (77 mg, 0.45 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash
chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as a colorless oil (23 mg, 73%). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.36-7.27 (m, 5 H), 6.77 (d, J = 8.7 Hz, 1H), 6.59 (d, J = 8.7 Hz, 1H), 5.26 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 173.7, 153.3, 151.7, 142.2, 138.4, 129.2, 128.9, 128.8, 128.7, 127.4, 125.5, 123.6, 107.1, 60.9, 56.1, 53.3, 50.9; IR (cm$^{-1}$, neat) 2938 (m, br), 1736 (s); HRMS (EI, M+) calcd for C$_{18}$H$_{20}$O$_5$: 316.1311, found 316.1305.

**Methyl 2-(4-bromophenyl)-2-phenylacetate (1.2e)**

![Methyl 2-(4-bromophenyl)-2-phenylacetate](image)

General procedure G described was carried out on 0.15 mmol scale, using methyl 2-bromo-2-phenylacetate 1.1a (24 µL, 0.15 mmol), silver trifluoromethanesulfonate (58 mg, 0.225 mmol, 1.5 equiv.) and bromobenzene (95 µL, 0.90 mmol, 6 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as a colorless oil (38 mg, 84%). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.46 (d, J = 8.8 Hz, 2H), 7.36-7.28 (m, 5H), 7.19 (d, J = 8.4 Hz, 2H), 4.99 (s, 1H), 3.75 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 172.8, 138.3, 137.9, 131.9, 130.6, 128.7, 128.6, 127.8, 121.7, 56.6, 52.7; IR (cm$^{-1}$, neat) 2951 (m, br), 1734 (s), 1488 (s), 1152 (s); HRMS (EI, M+) calcd for C$_{15}$H$_{13}$BrO$_2$: 304.0099, found 304.0099. Characterization data were in agreement with literature values.$^{58}$

**Methyl 2,2-diphenylacetate (1.2f)**

![Methyl 2,2-diphenylacetate](image)
General procedure G described was carried out on 0.15 mmol scale, using methyl 2-bromo-2-phenylacetate \textbf{1.1a} (24 µL, 0.15 mmol), silver trifluoromethanesulfonate (58 mg, 0.225 mmol, 1.5 equiv.) and benzene (134 µL, 1.5 mmol, 10 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in \textit{n}-pentane) yielding the title compound as a colorless solid (27 mg, 80%). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) 7.36-7.27 (m, 10 H), 5.05 (s, 1H), 3.76 (s, 3H). Characterization data were in agreement with literature values.\textsuperscript{58}

\textit{N,N-diethyl-2-phenyl-2-(2,4,6-trimethoxyphenyl)acetamide (1.2g)}

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

General procedure G described was carried out on 0.12 mmol scale, using 2-bromo-\textit{N,N-diethyl-2-phenylacetamide} \textbf{1.1b} (33 mg, 0.12 mmol), silver trifluoromethanesulfonate (47 mg, 0.18 mmol, 1.5 equiv.) and 1,3,5-trimethoxybenzene (61 mg, 0.36 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in \textit{n}-pentane, then 50% EtOAc in \textit{n}-pentane) yielding the title compound as a colorless solid (34 mg, 78%). M.p. = 140 – 143 °C (EtOAc/\textit{n}-pentane). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) 7.32-7.21 (m, 5H), 6.13 (s, 2H), 5.36 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.55-3.51 (m, 1H), 3.24-3.05 (m, 3H), 1.12 (t, \(J = 7.2\) Hz, 3H), 0.83 (t, \(J = 7.2\) Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) 171.9, 160.6, 158.9, 140.9, 129.7, 127.9, 126.2, 110.3, 91.3, 55.9, 55.5, 45.6, 42.2, 40.7, 13.7, 13.2; IR (cm\textsuperscript{-1}, powder) 2970 (m), 1648 (s), 1453 (s); HRMS (EI, M+H) calcd for C\textsubscript{21}H\textsubscript{28}NO\textsubscript{4}: 358.2012, found 358.2010.

\textbf{Methyl 2-(1-methyl-1H-indol-3-yl)-2-(4-(trifluoromethyl)phenyl)acetate (1.2h)}
General procedure G described was carried out on 0.15 mmol scale, using methyl 2-bromo-2-(4-(trifluoromethyl)phenyl)acetate **1.1c** (45 mg, 0.15 mmol), silver trifluoroacetate (50 mg, 0.225 mmol, 1.5 equiv.) and 1-methylindole (58 µL, 0.45 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in *n*-pentane) yielding the title compound as a colorless oil (43 mg, 83%). $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 7.58 (dd, J = 6.4, 4 Hz, 4 H), 7.41 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.27-7.26 (m, 1H), 7.10 (t, J = 8.0 Hz, 2H), 5.34 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 173.1, 143.0, 137.3, 129.7 (q, J$_{C-F}$ = 32.1 Hz), 129.4, 129.0, 128.1, 127.0, 125.8 (q, J$_{C-F}$ = 3.6 Hz), 121.0 (q, J$_{C-F}$ = 251.5 Hz), 119.7, 119.1, 111.3, 109.7, 52.7, 48.8, 33.1; IR (cm$^{-1}$, neat) 2954 (m), 1736 (s), 1324 (s); HRMS (ESI, M+H) calcd for C$_{19}$H$_{17}$F$_3$NO$_2$: 348.1205, found 348.1215.

**Methyl 2-phenylpent-4-enoate (1.3a)**

General procedure G described was carried out on 0.30 mmol scale, using methyl 2-bromo-2-phenylacetate **1.1a** (47 µL, 0.30 mmol), silver trifluoromethanesulfonate (116 mg, 0.45 mmol, 1.5 equiv.) and allyltrimethylsilane (143 µL, 0.90 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (2% Et$_2$O in *n*-pentane) yielding the title compound as a colorless oil (25 mg, 45%). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.33-7.26 (m, 5H), 5.79-5.65 (m, 1H), 5.10-5.0 (m, 2H), 3.66-3.64 (m, 4H), 2.85-2.81 (m, 1H), 2.56-2.49 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 174.1, 138.9, 135.5, 128.9, 128.1, 127.6, 117.2, 52.2, 51.6, 37.8; IR (cm$^{-1}$, neat)
2951 (m, br), 1735 (s), 1435 (m), 1163 (s); HRMS (EI, M+) calcd for C_{12}H_{14}O_2: 190.0994, found 190.0998.

**Methyl 2-phenylpent-4-enoate (1.3b)**

![Methyl 2-phenylpent-4-enoate](image)

General procedure G described was carried out on 0.13 mmol scale, using 2-bromo-\(N,N\)-diethyl-2-phenylacetamide \(1.1b\) (35 mg, 0.13 mmol), silver trifluoromethanesulfonate (50 mg, 0.195 mmol, 1.5 equiv.) and allyltrimethylsilane (46 µL, 0.39 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in \(n\)-pentane) yielding the title compound as an amorphous, colorless solid (17 mg, 57%). \(^1\)H NMR (400 MHz, CDCl_3) \(\delta\) (ppm) 7.25-7.13 (m, 5H), 5.73-5.63 (m, 1H), 4.99-4.88 (m, 2H), 3.63 (dd, \(J = 8.4, 8.0\) Hz, 1H), 3.39 (dq, \(J = 14.0, 7.2\) Hz, 1H), 3.31-3.15 (m, 2H), 3.06 (dq, \(J = 14.0, 7.2\) Hz, 1H), 2.82-2.75 (m, 1H), 2.38-2.30 (m, 1H), 1.00 (t, \(J = 7.2\) Hz, 3H), 0.93 (t, \(J = 7.2\) Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl_3) \(\delta\) (ppm) 171.7, 140.4, 136.8, 128.9, 128.1, 127.1, 116.5, 49.3, 41.9, 40.6, 39.9, 14.6, 13.1; IR (cm\(^{-1}\), neat) 2972 (m), 1637 (s), 1435 (m), 1163 (s); HRMS (EI, M+H) calcd for C_{15}H_{22}NO: 232.1701, found 232.1712.

**Methyl 2-(4-methoxyphenyl)pent-4-enoate (1.3c)**

![Methyl 2-(4-methoxyphenyl)pent-4-enoate](image)

General procedure G described was carried out on 0.15 mmol scale, using methyl 2-bromo-2-(4-methoxyphenyl)acetate \(1.1d\) (39 mg, 0.15 mmol), silver trifluoromethanesulfonate (58 mg, 0.225 mmol, 1.5 equiv.) and allyltrimethylsilane (72 µL, 0.45 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash
chromatography on silica (3% Et₂O in n-pentane) yielding the title compound as a colorless oil (25 mg, 76%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.22 (dd, J = 6.8, 2.0 Hz, 2H), 6.85 (dd, J = 6.8, 2.0 Hz, 2H), 5.81-5.76 (m, 1H), 5.09-5.02 (m, 2H), 3.79 (s, 3H), 3.66 (s, 3H), 3.60 (dd, J = 8.0, 7.2 Hz, 1H), 2.78-2.75 (m, 1H), 2.52-2.46 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 174.4, 159.1, 135.6, 130.8, 129.2, 117.1, 114.2, 55.5, 52.1, 50.8, 37.9; IR (cm⁻¹, neat) 2953 (m), 1733 (s), 1511 (s); HRMS (EI, M+) calcd for C₁₃H₁₆O₃: 220.1099, found 220.1094.

Methyl 4-methyl-2-phenylpent-4-enoate (1.3d)

A stirred solution of silver trifluoromethanesulfonate (116 mg, 0.3 mmol) in CH₂Cl₂ (0.9 mL) was first cooled to –78 °C under a positive pressure of argon and then methallytrimethylsilane (158 µL, 0.90 mmol, 3.0 equiv.) and 2,6-lutidine (52 µL, 0.45 mmol, 1.5 equiv.) was added dropwise. Next, a solution of the methyl 2-bromo-2-phenylacetate 1.1a (47 µL, 0.30 mmol, 1.0 equiv.) dissolved in CH₂Cl₂ (0.2 mL) was added drop wise and the syringe was washed with an additional portion of CH₂Cl₂ (0.1 mL). Total reaction concentration was 0.2 M. After stirring at room temperature for 20 hours, the reaction mixture was worked up as the general procedure G. The residue was purified by flash chromatography on silica (2% Et₂O in n-pentane) yielding the title compound as a colorless oil (32 mg, 52%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.33-7.26 (m, 5H), 4.75 (s, 1H), 4.69 (s, 1H), 3.81 (dd, J = 12.4, 8.8 Hz, 1H), 3.65 (s, 3H), 2.85 (dd, J = 19.6, 12.4 Hz, 1H), 2.43 (dd, J = 19.6, 8.8 Hz, 1H) 1.72 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 174.3, 142.9, 139.0, 128.8, 128.1, 127.5, 112.4, 52.2, 50.2, 41.6, 22.8; IR (cm⁻¹, neat) 2951 (m, br), 1736 (s), 1259 (m), 1157 (s); HRMS (ESI, M+H) calcd for C₁₃H₁₇O₂: 205.1223, found 205.1230.

5,5-Dimethyl-3-phenyldihydrofuran-2(3H)-one (1.3e)
General procedure G described was carried out on 0.30 mmol scale, using methyl 2-bromo-2-phenylacetate 1.1a (47 μL, 0.10 mmol), silver trifluoromethanesulfonate (116 mg, 0.225 mmol, 1.5 equiv.) and methallyltrimethylsilane (158 μL, 0.90 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (50% CH<sub>2</sub>Cl<sub>2</sub> in n-pentane) yielding the title compound as a colorless oil (30 mg, 53%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 7.32-7.19 (m, 5H), 3.96 (dd, J = 15.6, 12 Hz, 1H), 2.51 (dd, J = 16.4, 12 Hz, 1H), 2.17 (t, J = 16.4 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) 176.7, 137.2, 128.3, 127.8, 127.7, 82.3, 47.2, 44.4, 29.1, 27.2; IR (cm<sup>−1</sup>, neat) 2976 (m, br), 1763 (s), 1259 (s), 1138 (s); HRMS (EI, M+) calcd for C<sub>12</sub>H<sub>14</sub>O<sub>2</sub>: 190.0994, found 190.0989. Characterization data were in agreement with literature values.<sup>100</sup>

<sup><i>N</i>,<i>N</i>-diethyl-4-methyl-2-phenylpent-4-enamide (1.3f)</i>

General procedure G described was carried out on 0.15 mmol scale, using 2-bromo-<i>N</i>,<i>N</i>-diethyl-2-phenylacetamide 1.1b (40 mg, 0.15 mmol), silver trifluoromethanesulfonate (58 mg, 0.23 mmol, 1.5 equiv.) and methallyltrimethylsilane (79 μL, 0.45 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as an amorphous, colorless solid (19 mg, 52%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.30-7.21 (m, 5H), 4.72 (s, 1H), 4.62 (s, 1H), 3.89 (dd, J = 8.4, 6.0 Hz, 1H), 3.49-3.31 (m, 3H), 3.19 (dq, J = 14.7, 7.2 Hz, 1H), 2.92 (dd, J = 14.4, 8.4 Hz, 1H), 2.37 (dd, J = 14.4, 6.0 Hz, 1H), 1.70 (s, 3H), 1.07 (t, J = 7.2 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm) 171.8, 144.1, 140.8, 128.9, 128.0, 127.0, 111.6, 47.7, 43.2, 41.9, 40.7, 23.4, 14.5, 13.0; IR (cm<sup>−1</sup>,
powder) 2932 (m), 1637 (s), 1429 (m); HRMS (EI, M+H) calcd for C_{16}H_{24}NO: 246.1858, found 246.1858.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(1-methyl-1H-indol-3-yl)-2-phenylacetate (1.8c)

![Chemical structure image]

General procedure G described was carried out on 0.15 mmol scale, using (1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-bromo-2-phenylacetate 1.7c (54 mg, 0.15 mmol), silver trifluoromethanesulfonate (59 mg, 0.23 mmol, 1.5 equiv.) and 1-methylindole (56 µL, 0.45 mmol, 3 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless oil (44 mg, 61%, d.r. = 1.4:1). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.44-7.42 (m, 1.6H), 7.33-7.05 (m, 12.8H), 6.93 (s, 0.6H), 4.81-4.78 (m, 1H), 4.75 (s, 0.58H), 4.48 (s, 0.42H), 3.80 (s, 1.25H), 3.73 (s, 1.75H), 2.00-1.93 (m, 1.4H), 1.81-1.75 (m, 0.6H), 1.63-1.42 (m, 3.9H), 1.29-1.25 (m, 2.1H), 1.19 (s, 1.2H), 1.15 (d, J = 3.9 Hz, 2.9H), 1.02-0.9 (m, 2.3H), 0.83-0.76 (m, 2.6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 172.4, 151.3, 138.8, 137.2, 129.0, 128.5, 128.3, 128.2, 127.6, 127.2, 127.0, 125.8, 125.7, 125.5, 125.2, 121.9, 121.8, 119.4, 119.3, 119.1, 113.1, 109.4, 109.3, 50.7, 50.6, 48.9, 48.7, 41.5, 41.1, 40.2, 34.8, 33.0, 33.0, 31.5, 27.7, 27.6, 27.2, 26.9, 26.1, 22.0; IR (cm$^{-1}$, neat) 2953 (m), 1725 (s), 1455 (m); HRMS (DART, M+H) calcd for C$_{33}$H$_{38}$NO$_2$: 480.2903, found 480.2889.

General procedure H. Ag Promoted Synthesis of dihydroisoquinolinone
A stirred solution of silver salt (0.23 mmol) in CH$_2$Cl$_2$ (0.3 mL) was first cooled to $-78 \, ^\circ$C under a positive pressure of argon and then 2-bromo-2-phenylacetamide (0.15 mmol) in CH$_2$Cl$_2$ (0.3 mL) was added drop wise. Next, the reaction tube was washed with an additional portion of CH$_2$Cl$_2$ (2.4 mL). Total reaction concentration was 0.05 M. The reaction mixture was allowed to warm to room temperature and stirred for 20 hours, diluted with CH$_2$Cl$_2$ and filtered through a plug of Celite to remove the precipitated silver bromide and any other traces of silver salts. The crude product was purified by flash chromatography on silica.

1-Methyl-3-phenyldolin-2-one (1.5a)

General procedure H described was carried out on 0.15 mmol scale, using N-methyl-2-bromo-N$_2$2-diphenylacetamide 1.4a (45 mg, 0.15 mmol), silver trifluoroacetate (50 mg, 0.23 mmol, 1.5 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (20% EtOAc in n-pentane) yielding the title compound as a colorless solid (33 mg, 99%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.38-7.06 (m, 8H), 6.93 (d, J = 7.8 Hz, 1H), 4.65 (s, 1H), 3.29 (s, 3H). Characterization data were in agreement with literature values.$^{101}$

1-Benzyl-3-phenyldolin-2-one (1.5b)
General procedure H described was carried out on 0.15 mmol scale, using \( N\)-benzyl-2-bromo-N,2-diphenylacetamide 1.4b (57 mg, 0.15 mmol), silver trifluoroacetate (50 mg, 0.23 mmol, 1.5 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (20% EtOAc in \( n \)-pentane) yielding the title compound as a colorless solid (45 mg, >99%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.38-7.15 (m, 12H), 7.03 (t, \( J = 7.7 \) Hz, 1H), 6.79 (d, \( J = 7.7 \) Hz, 1H), 5.0 (d, \( J = 15.6 \) Hz, 1H), 4.90 (d, \( J = 15.6 \) Hz, 1H), 4.71 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 176.3, 143.8, 137.0, 136.1, 129.2, 129.0, 128.7, 128.5, 127.9, 127.8, 127.6, 125.3, 123.0, 109.4, 52.3, 44.2. Characterization data were in agreement with literature values.\(^{101}\)

**2-Methyl-4-phenyl-1,2-dihydroisoquinolin-3(4H)-one (1.5c)**

![Structure](image)

General procedure H described was carried out on 0.15 mmol scale, using \( N\)-benzyl-2-bromo-\( N\)-methyl-2-phenylacetamide 1.4c (48 mg, 0.15 mmol), silver trifluoroacetate (50 mg, 0.23 mmol, 1.5 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (30% EtOAc in \( n \)-pentane) yielding the title compound as an amorphous, yellow solid (29 mg, 82%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.32-7.21 (m, 6H), 7.14-7.12 (m, 3H), 4.88 (s, 1H), 4.65 (d, \( J = 15.9 \) Hz, 1H), 4.32 (d, \( J = 15.9 \) Hz, 1H), 3.10 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 170.3, 139.1, 135.8, 131.7, 128.9, 128.2, 128.1, 127.9, 127.3, 127.3, 125.5, 52.8, 52.7, 35.2; IR (cm\(^{-1}\), powder) 2927 (m), 1625 (s), 1495 (m); HRMS (EI, M+) calcd for C\(_{16}\)H\(_{15}\)NO: 237.1154, found 237.1154.

**2-Benzyl-4-phenyl-1,2-dihydroisoquinolin-3(4H)-one (1.5d)**

![Structure](image)
General procedure H described was carried out on 0.15 mmol scale, using $N,N$-dibenzyl-2-bromo-2-phenylacetamide 1.4d (59 mg, 0.15 mmol), silver trifluoroacetate (50 mg, 0.23 mmol, 1.5 equiv.). After stirring for 20 hours at room temperature, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in $n$-pentane) yielding the title compound as a yellow oil (41 mg, 86%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.31-7.13 (m, 14H), 4.99 (s, 1H), 4.74 (s, 2H), 4.46 (d, $J = 15.9$ Hz, 1H), 4.23 (d, $J = 15.9$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 170.4, 138.8, 136.8, 135.6, 132.0, 128.9, 128.7, 128.2, 128.1, 127.7, 127.4, 127.3, 125.6, 53.3, 50.5, 50.1; IR (cm$^{-1}$, neat) 3027 (m), 1647 (s), 1447 (m); HRMS (DART, M+H) calcd for C$_{22}$H$_{20}$NO: 314.1545, found 314.1536.

8-Chloro-2-methyl-4-phenyl-1,2-dihydroisoquinolin-3(4H)-one (1.5e)

![Image of structure]

General procedure H described was carried out on 0.20 mmol scale, using 2-bromo-$N$-(2-chlorobenzyl)-$N$-methyl-2-phenylacetamide 1.4e (70 mg, 0.20 mmol), silver tetrafluoroborate (58 mg, 0.30 mmol, 1.5 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in $n$-pentane) yielding the title compound as an amorphous, colorless solid (35 mg, 65%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.35-7.22 (m, 5H), 7.11 (d, $J = 7.5$ Hz, 2H), 7.04 (d, $J = 7.5$ Hz, 1H), 4.86 (s, 1H), 4.60 (d, $J = 17.1$ Hz, 1H), 4.54 (d, $J = 17.1$ Hz, 1H), 3.13 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 169.3, 139.3, 138.0, 131.3, 129.4, 129.3, 129.0, 128.1, 127.9, 127.5, 127.4, 52.4, 50.7, 35.2; IR (cm$^{-1}$, powder) 2925 (m), 1633 (s), 1445 (m); HRMS (ESI, M+H) calcd for C$_{16}$H$_{15}$ClNO: 272.0837, found 272.0839.

6-Methoxy-2-(4-nitrobenzyl)-4-phenyl-1,2-dihydroisoquinolin-3(4H)-one (1.5f)
General procedure H described was carried out on 0.15 mmol scale, using 2-bromo-N-(4-methoxybenzyl)-N-(4-nitrobenzyl)-2-phenylacetamide 1.4f (71 mg, 0.15 mmol), silver trifluoroacetate (50 mg, 0.23 mmol, 1.5 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (20% EtOAc in n-pentane) yielding the title compound as a colorless oil (33 mg, 57%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.10 (d, J = 6.8 Hz, 2H), 7.30-7.22 (m, 5H), 7.17 (dd, J = 7.6, 2.0 Hz, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.86 (dd, J = 8.4, 2.4 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 4.95 (s, 1H), 4.79 (d, J = 15.6 Hz, 1H), 4.75 (d, J = 15.6 Hz, 1H), 4.46 (d, J = 15.2 Hz, 1H), 4.15 (d, J = 15.2 Hz, 1H), 3.78 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 159.8, 144.5, 138.1, 136.6, 136.6, 129.0, 128.4, 128.4, 128.0, 127.7, 126.7, 124.1, 123.8, 113.8, 113.4, 55.6, 53.4, 50.2, 50.1; IR (cm$^{-1}$, neat) 2922 (m), 1651 (s), 1447 (m); HRMS (EI, M+) calcd for C$_{23}$H$_{20}$N$_2$O$_4$: 388.1423, found 388.1421.

7-Methoxy-2-methyl-4-phenyl-8-propoxy-1,2-dihydroisoquinolin-3(4H)-one (1.5g)

General procedure H described was carried out on 0.20 mmol scale, using 2-chloro-N-(3-methoxy-2-propoxybenzyl)-N-methyl-2-phenylacetamide 1.4g (81 mg, 0.20 mmol), silver trifluoromethanesulfonate (77 mg, 0.30 mmol, 1.5 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (20% EtOAc in n-pentane) yielding the title compound as a colorless oil (35 mg, 54%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.28-7.20 (m, 3H), 7.14-7.11 (m, 2H),
6.87 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.79 (s, 1H), 4.55 (d, J = 16.8 Hz, 1H), 4.44 (d, J = 16.8 Hz, 1H), 4.06-3.98 (m, 2H), 3.85 (s, 3H), 3.09 (s, 3H), 1.85 (t, J = 7.2 Hz, 1H), 1.77 (t, J = 7.2 Hz, 1H), 1.06 (t, J = 7.5 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ (ppm) 170.2, 151.2, 143.8, 139.8, 128.9, 128.8, 128.0, 127.2, 125.9, 123.6, 112.7, 75.0, 56.1, 52.2, 48.2, 35.3, 23.9, 10.75; IR (cm⁻¹, neat) 2933 (m), 1653 (s), 1494 (m); HRMS (EI, M⁺) calcd for C20H23NO3: 325.1678, found 325.1670.

### Preparation of 5,7-dimethoxy-4-phenylisochroman-3-one (1.5h)

![Chemical structure](image)

General procedure H described was carried out on 0.15 mmol scale, using 3,5-dimethoxybenzyl 2-bromo-2-phenylacetate **1.4h** (55 mg, 0.15 mmol) and silver trifluoromethanesulfonate (58 mg, 0.23 mmol, 1.5 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as an amorphous, pink solid (28 mg, 66%). 1H NMR (400 MHz, CDCl3) δ (ppm) 7.31-7.10 (m, 5H), 6.54 (d, J = 2 Hz, 1H), 6.42 (d, J = 2 Hz, 1H), 5.42 (s, 1H), 5.19 (d, J = 14.0 Hz, 1H), 5.04 (d, J = 14.0 Hz, 1H), 3.98 (s, 3H), 3.82 (s, 3H); 13C NMR (100 MHz, CDCl3) δ (ppm) 168.9, 158.3, 155.4, 132.2, 131.6, 126.5, 125.2, 124.8, 112.0, 98.7, 96.1, 67.3, 53.3, 53.2, 42.5; IR (cm⁻¹, neat) 2925 (m), 1726 (s), 1494 (m); HRMS (EI, M⁺) calcd for C17H16NaO (M+Na): 307.0940, found 307.0933.

### 3-Phenyl-1-(1-phenylethyl)indolin-2-one (1.10a)

![Chemical structure](image)
General procedure H described was carried out on 0.15 mmol scale, using 2-chloro-N,2-diphenyl-N-(1-phenylethyl)acetamide 1.9a (52 mg, 0.15 mmol, 1 equiv.), silver trifluoroacetate (58 mg, 0.23 mmol, 1.5 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless solid (47 mg, >99%, d.r. = 1.1:1). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.41-7.18 (m, 10H), 7.14 (d, J = 7.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 5.90 (q, J = 7.2 Hz, 1H), 4.75 (s, 0.48H), 4.72 (s, 0.52H), 1.88 (dd, J = 7.2, 1.8 Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 175.3, 137.3, 129.2, 129.2, 128.9, 128.7, 128.6, 128.1, 127.8, 127.6, 126.9, 125.3, 122.5, 111.1, 52.3, 52.2, 16.3; IR (cm\(^{-1}\), neat) 2980 (m), 1705 (s), 1465 (m); HRMS (DART, M+H) calcd for C\(_{22}\)H\(_{20}\)N\(_2\)O: 314.1545, found 314.1541.

**5,7-Dimethoxy-4-phenyl-2-(1-phenylethyl)-1,2-dihydroisoquinolin-3(4H)-one (1.10b)**

![Chemical Structure](image)

General procedure H described was carried out on 0.10 mmol scale, using 2-chloro-N-(3,5-dimethoxybenzyl)-2-phenyl-N-(1-phenylethyl)acetamide 1.9b (42 mg, 0.10 mmol), silver hexafluorophosphate (38 mg, 0.15 mmol, 1.5 equiv.). After stirring for 20 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as a colorless solid (34 mg, 88%, d.r. = 1.7:1, 55% for the major diastereomer). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.32-7.20 (m, 10H), 6.41 (d, J = 2.8 Hz, 1H), 6.14-6.10 (m, 2H), 5.28 (s, 1H), 4.24 (d, J = 15.3 Hz, 1H), 3.82 (d, J = 15.3 Hz, 1H), 3.75 (s, 6H), 1.48 (d, J = 7.2 Hz, 3H); representative \(^1\)H NMR of the minor diastereomer (300 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.20 (m, 10H), 6.41 (d, J = 2.1Hz, 1H), 6.28 (d, J = 2.1 Hz, 1H), 6.10 (q, J = 6.9 Hz, 1H), 5.24 (s, 1H), 3.86-3.82 (m, 1H), 3.79 (s, 3H), 3.76-3.75 (m, 1H), 3.74 (s, 3H) 1.55 (d, J = 6.9 Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 170.5, 159.9, 157.5, 140.2, 138.3, 134.5, 128.5, 128.5, 127.3, 127.2, 127.1, 126.8, 116.7, 101.4, 97.5,
55.6, 55.4, 50.3, 47.0, 44.5, 16.0; IR (cm\(^{-1}\), powder) 2932 (m), 1643 (s), 1421 (m); HRMS (DART, M+H) calcd for C\(_{25}\)H\(_{26}\)NO\(_3\): 388.1913, found 388.1915.

\textbf{2,4,7,8,9-Penta-\(O\)-acetyl-\(N\)-acetylneuraminic acid (1.11)}\(^{102}\)

To a stirred, ice-cooled suspension of D-NeuAc (77mg, 0.25 mmol) in pyridine (0.96 mL, 11.9 mmol, 48 equiv.) was added acetic anhydride (1.15 mL, 49 equiv.). The mixture was stirred overnight at room temperature. The whole solution was concentrated to crude. The pyridine residual was removed through dilution with ethyl acetate and concentration (\(\times 3\)), yielding the title compound as a colorless solid (124 mg, 95%). \(^1\)H NMR (300 MHz, D\(_2\)O) \(\delta\) ppm 5.33 (dd, \(J = 7.8, 1.5\) Hz, 1H), 5.16 (ddd, \(J = 11.1, 10.8, 5.1\) Hz, 1H), 5.04 (1H, m), 4.33 (dd, \(J = 12.6, 2.5\) Hz, 1H), 4.11-3.99 (m, 2H), 3.83 (t, \(J = 10.2\) Hz, 1H), 2.42 (dd, \(J = 13.5, 4.8\) Hz, 1H), 2.01 (dd, \(J = 13.6, 5.1\) Hz, 1H), 2.06, 2.04, 1.96, 1.95, 1.92, 1.81 (s, each 3H). Characterization data were in agreement with literature values.\(^{103}\)

\textbf{2,4,7,8,9-Penta-\(O\)-acetyl-\(N\)-acetylneuraminic acid (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol ester (1.12)}

To a stirred solution of 1.11 (208 mg, 0.4 mmol), (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol (78 mg, 0.5 mmol, 1.25 equiv.) and DMAP (5 mg, 0.04 mmol, 0.1 equiv.) in CH\(_2\)Cl\(_2\) (0.2 M) was added DIC (68 \(\mu\)L, 0.44 mmol, 1.1 equiv.) at 0 °C. The reaction mixture was then allowed to warm to room temperature. After stirring at room temperature for 24 hours (or judged completion by TLC), the reaction mixture was diluted with CH\(_2\)Cl\(_2\) and quenched with water. The resulting solution was extracted with CH\(_2\)Cl\(_2\) (\(\times 2\)), and the combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by
flash chromatography on silica (1.6% MeOH in chloroform), yielding the title compound as a colorless solid (107 mg, 41%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 5.38 (m, 1H), 5.27 (m, 2H), 5.09 (ddd, J = 6.3, 3.6, 2.7 Hz, 1H), 4.75 (ddd, J = 15.3, 10.8, 4.5 Hz, 1H), 4.38 (dd, J = 12.6, 2.7 Hz, 1H), 4.21 (dd, J = 12.6, 6.6 Hz, 1H), 4.15-4.08 (m, 2H), 4.05-3.82 (m, 1H), 2.54 (dd, J = 13.5, 4.8 Hz, 1H), 2.14 (s, 3H), 2.13-2.12 (m, 2H), 2.11-2.09 (m, 1H), 2.07 (m, 10H), 1.90 (s, 3H), 1.68 (d, J = 11.7 Hz, 2H), 1.47 (m, 2H), 1.34-1.23 (m, 3H), 1.14 (d, J = 6.3 Hz, 1H), 1.08-1.0 (m, 1H), 0.92-0.88 (m, 5H), 0.75 (d, J = 6.9 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 171.2, 170.7, 170.5, 170.5, 170.3, 168.2, 165.3, 98.1, 73.0, 71.4, 68.6, 61.9, 49.7, 47.1, 40.2, 36.0, 34.3, 31.6, 26.3, 23.4, 22.2, 21.1, 21.0, 20.9, 16.2.

2,4,7,8,9-Penta-O-acetyl-N-acetylneuraminic acid methylmandelic ester (1.13)

To a stirred solution of 1.11 (208 mg, 0.4 mmol), (S) methylmandelate (83 mg, 0.5 mmol, 1.25 equiv.) and DMAP (5 mg, 0.04 mmol, 0.1 equiv.) in CH$_2$Cl$_2$ (0.2 M) was added DIC (68 µL, 0.44 mmol, 1.1 equiv.) at 0 °C. The reaction mixture was then allowed to warm to room temperature. After stirring at room temperature for 24 hours, the reaction mixture was diluted with CH$_2$Cl$_2$ and quenched with water. The resulting solution was extracted with CH$_2$Cl$_2$ (×2), and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica (1.6% MeOH in chloroform), yielding the title compound as a colorless solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.42-7.39 (m, 5H), 5.95 (s, 1H), 5.39-5.24 (m, 3H), 5.10-5.05 (m, 1H), 4.46 (dd, J = 12.3, 2.7 Hz, 1H), 4.23-4.07 (m, 2H), 3.93-3.82 (m, 1H), 3.73 (s, 3H), 2.68 (dd, J = 13.5, 5.1 Hz, 1H), 2.19-2.10 (m, 1H), 2.15 (s, 3H), 2.07-2.04 (m, 12H), 2.02 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 171.2, 170.7, 170.6, 170.4, 168.7, 168.3, 165.0, 133.2, 129.6, 129.0, 127.7, 97.0, 72.9, 71.6, 68.3, 68.2, 62.1, 53.0, 49.7, 36.6, 23.7, 23.4.

Synthesis of 1.18 from mandelic acid
To a solution of (S)-mandelic acid (1.07 g, 7 mmol) in diethyl ether (5.3 mL) was added slowly LiAlH₄ (2.55 g, 14 mmol). After the reaction mixture was refluxed for 2h, ethyl acetate was added slowly and then poured into ice water. The organic phase was separated and dried (MgSO₄), filtered and the filtrate was concentrated in vacuo. The residue was purified by recrystallization (hexane/ethyl acetate) to afford the title compound as a colorless solid (656 mg, 69%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.37-7.26 (m, 5H), 4.82 (dd, J = 8.1, 3.6 Hz, 1H), 3.76 (dd, J = 11.4, 3.6 Hz, 1H), 3.66 (dd, J = 11.4, 8.1 Hz, 1H), 2.42 (brs, 2H). Characterization data were in agreement with literature values.⁸⁵

To a solution of 1.16 (277 mg, 2 mmol) in CH₃CN were sequentially added catalyst (45 mg, 0.2 mmol, 0.1 equiv.), Ts₂O (980 mg, 3 mmol, 1.5 equiv.) and Et(𝑖-Pr)₂N (0.52 ml, 3 mmol, 1.5 equiv.) at room temperature for 16 h, the reaction mixture was diluted with ethylacetate and washed with brine. The organic phase was dried (MgSO₄), filtered and the filtrate was
concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethyl acetate in n-pentane) to afford the title compound as a colorless oil (458 mg, 78%). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.70 (d, J = 8.4 Hz, 2H), 7.37-7.26 (m, 7 H), 5.01-4.96 (m, 1H), 4.16 (dd, J = 10.5, 3.3 Hz, 1H), 4.05 (dd, J = 8.4, 10.5 Hz, 1H), 2.53 (d, J = 3.3 Hz, 1H), 2.45 (s, 3H). Characterization data were in agreement with literature values.$^{104}$

(S)-1-phenyl-2-(phenylthio)ethanol (1.18)

To a solution of 1.17 (204 mg, 0.7 mmol) in THF (10 mL) was added benzenethiol, sodium salt (122 mg, 0.92 mmol, 1.3 equiv.). The reaction mixture was stirred at room temperature for 12 hours; it was then concentrated in vacuo. The residue was dissolved with CH$_2$Cl$_2$ and washed with brine. The organic phase was dried (MgSO$_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (25% ethylacetate in n-pentane) to afford the title compound as a colorless oil (126 mg, 78%). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.34 (m, 10H), 4.73 (dd, J = 5.7, 2.1 Hz, 1H), 3.33 (dd, J = 8.4, 2.1 Hz, 1H), 3.10 (dd, J = 8.4, 5.7 Hz, 1H), 2.81 (s, 1H). Characterization data were in agreement with literature values.$^{105}$

4,7,8,9-Tetra-O-acetyl-N-acetyl-2-phenthianlyneuraminic acid (1.19)

To a solution of peracetylated sialic acid, 1.11 (390 mg, 0.75 mmol) and thiophenol (0.33 mL, 3.21 mmol, 4.3 equiv.) in CH$_2$Cl$_2$ (8 mL) at 0°C was added BF$_3$•Et$_2$O (0.396 mL, 3.21 mmol, 4.3 equiv.) and the reaction mixture was allowed to slowly warm to room temperature and stirred for 16 h. The reaction mixture was poured into a saturated aqueous solution of NaHCO$_3$, dried (MgSO$_4$), filtered and concentrated under reduced pressure to peracetylated thioside which was
further purified by column chromatography, yielding the title compound as a colorless oil (141 mg, β/α = 62:38, 33%). $^1$H NMR (400 MHz, D$_2$O) δ (ppm) 7.55 (d, J = 6.6 Hz, 2H), 7.34-7.31 (m, 3H), 5.63 (d, J = 10.2 Hz, 0.77 H), 5.49-5.41 (m, 1.64H), 5.00 (br, s, 0.86H), 4.61-4.49 (m, 1.69 H), 4.20-4.06 (m, 2.04H), 3.89 (dd, J = 12, 8.1 Hz, 0.90 H), 2.92 (d, J = 23.1 Hz, 0.41H), 2.57 (dd, J = 12, 8.1 Hz, 0.69 H), 2.11 (s, 3.7H), 2.10 (s, 2.3H), 2.04 (s, 1.71H), 2.02 (s, 2.51H), 1.96 (s, 2.53H), 1.90 (s, 2.25H). Characterization data were in agreement with literature values.
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Chapter 2
Preparation of Substituted Oxazoles by Ritter Reactions of $\alpha$-Oxo Tosylates

Approaches to oxazole containing compounds will be addressed in the introduction. The main goal of our research, which will be described in research objectives, was to develop a reliable route to trisubstituted oxazoles from readily available materials. In the ensuing section, the results of our efforts in oxazole synthesis and applications of the products in furan synthesis will be discussed.

Introduction

2.1 Oxazoles in Natural Products

Many oxazole-containing natural products found in marine organisms exhibit significant biological activities. For example, calyculin A was isolated from the marine sponge Discodermia calyx and exhibits potent cytotoxicity against L1210 leukemia cells. Hennoxazole A, which was isolated from the marine sponge Polyfibrospnia sp., displays potent activity against the herpes simplex virus type 1 (IC$_{50}$ = 0.6 µg/mL). Phorboxazoles are marine macrolides isolated from the marine sponge Phorbas sp, and they showed exceptional antifungal activities against Candidas albicans. Diazonamide A is the secondary metabolite isolated from the marine colonial ascidian Diazona chinensis and it exhibits potent in vitro activity against B-16 murine melanoma cancer cell lines (IC$_{50}$ < 15 ng/mL). Leucascandrolide A displays potent cytotoxicity against KB and P388 tumor cell lines and strong antifungal activity against Candida albicans. Muscoride A, isolated from the freshwater cyanobacterium Nostoc muscorum exhibits antibiotic activity to some extent. Bengazole A was isolated from marine sponges of the genus Jaspis, and displays potent in vitro antifungal activity against Candida albicans and fluconazole-resistant Candida strains.
Scheme 2.01. Oxazole-containing natural products.
Due to their potent bioactivities and their fascinating structures, it is important to address the syntheses of these five membered ring heterocycles. One of the major challenges associated with oxazole syntheses is the need for mild and selective methods for oxazole formation in the presence of other sensitive functional groups. Many of the syntheses highlighted later in this chapter made use of biomimetic approaches to construct the oxazole heterocycle from amino acid-derived precursors. In addition, recent developments are now focused on direct manipulations of the parent heterocycle to generate substituted derivatives.

2.2 Synthesis of Oxazoles

2.2.1 Biosynthesis of Oxazoles

In nature, enzymatic post-translational modification of peptide precursors\textsuperscript{119} bestow oxazole rings on these natural products. Cyclic hemiaminals are formed after nucleophilic attack of a hydroxyl moiety on the carbonyl group. Subsequent dehydration and two-electron oxidation furnishes oxazoles (Scheme 2.02).

![Scheme 2.02. Biomimetic synthesis of oxazole-containing products.](image)

2.2.2 Modular Chemical Synthesis of Oxazoles

Due to the presence of oxazole rings in numerous natural products, many synthetic methodologies to afford oxazoles have been developed, the first of which appeared more than a century ago. One of the classical methods, which is still in use today, is Hantzsch’s oxazole synthesis (1887).\textsuperscript{120} Condensation of an α-bromo ketone and primary amide result in the formation of the oxazole core of (-)-calyculin A (Scheme 2.03).\textsuperscript{121,122}
Scheme 2.03. Hantzsch’s oxazole synthesis in Masamune’s total synthesis of (-)-calyculin A.

A similar approach by Bredereck and coworkers\textsuperscript{123} employed α-halo ketones in the synthesis of 4,5-substituted oxazoles by condensation of ammonium formate with α-halo ketones upon heating (Scheme 2.04).

Scheme 2.04. Bredereck’s oxazole synthesis.

In 1896, Fischer was able to obtain oxazoles from the condensation of equimolar amounts of cyanohydrins and aromatic aldehydes in the presence of hydrochloric acid (Scheme 2.05).\textsuperscript{124} This synthesis involved the formation of acetimidoyl chloride followed by a sequence of substitution, isomerization and elimination reactions to afford 2,5 substituted oxazoles.

Scheme 2.05. Fischer’s oxazole synthesis.

Robinson\textsuperscript{125} and Gabriel\textsuperscript{126} discovered the use of 2-acetamidoketones in oxazole synthesis in 1909 and 1910, respectively. Being one oxidation level higher than that of the corresponding amino acid-derived precursors, 2-acylamido-ethanol undergoes cyclodehydration to directly give 2,5-di, 2,4,5-trialkyl, aryl, heteroaryl-, and aralkyl oxazoles without a subsequent oxidation step.
Since then, the Robinson-Gabriel dehydration method has been used extensively to assemble oxazole rings in the synthesis of natural products. Wipf and Lim’s synthesis of hennoxazole\textsuperscript{127} employed the Robinson-Gabriel dehydration strategy to construct the second ring of a bisoxazole moiety. Subsequent desilylation led to the target natural product.

Scheme 2.07. Wipf’s total synthesis of hennoxazole.

Another venerable method for oxazole synthesis was developed by Cornforth. The halogen replacement of $\alpha$-chloroacetoacetate with sodium benzoate in toluene gave an imine intermediate which was then transformed to 2-methyloxazole-4-carboxylate in the presence of ammonium acetate in acetic acid via O-N benzoyl migration.\textsuperscript{128,129} Cyclization and elimination of $\text{H}_2\text{O}$ furnished the substituted oxazole (Scheme 2.08).

Scheme 2.08. Cornforth’s oxazole synthesis.
In 1949, Cornforth\textsuperscript{130} observed that upon heating, 2-phenyl-5-ethoxyoxazole-4-carboxamide rearranged to 2-phenyl-5-aminoazole-4-carboxylate. This process now known as the Cornforth rearrangement, was further investigated by Dewar and Turchi\textsuperscript{131} who found that secondary and tertiary carboxamides were converted to the corresponding oxazoles generally in good to excellent yields.

\[ \text{Ar} = p\text{-tolyl, } p\text{-anisyl, } p\text{-BrC}_6\text{H}_4, p\text{-CF}_3\text{C}_6\text{H}_4 \]
\[ R^1 = \text{OCH}_3; R^2 = 1^\circ, 2^\circ, 3^\circ \text{ amines} \]
Cornforth (1949)
Dewar (1974)

**Scheme 2.09.** Dewar’s oxazole synthesis based on the Cornforth rearrangement.

A modified procedure of Sheehan’s methodology\textsuperscript{132} was tested for the construction of bifunctional oxazoles, which was successfully assembled by triflation of the oxazolone resulting from treatment of α-bromoacetyl bromide with diazomethane and silver isocyanate. Smith and coworkers further bridged this bifunctional oxazoles with two other fragments that ultimately led to the total synthesis of phorboxazole A.\textsuperscript{133}

**Scheme 2.10.** Sheehan’s preparation of oxazolone in Smith’s total synthesis of Phorboxazole A.

Many of total syntheses of oxazole-containing natural products mimic their biosynthesis, but attempts to oxidize the alcohol or to convert hydroxyl into chloride with SOCl\textsubscript{2} often lead to either unsatisfactory yields or extensive epimerization of the α-stereogenic center. This challenge was overcome by utilizing the Burgess reagent in the cyclodehydration step. The oxidation of
oxazoline was accomplished using CuBr$_2$ in the presence of HMTA and DBU. The epimerization was circumvented, and the oxazole was furnished in 67% yield in two steps (Scheme 2.11).$^{134}$

Scheme 2.11. Utility of the Burgess reagent in Smith’s total synthesis of Phorboxazole A.

A process developed by van Leusen$^{135}$ and coworkers allowed expedient access to 5-substituted oxazoles without the need of an external oxidant under mild basic conditions. Extension of this method was reported by Yu$^{136}$ for the high yielding preparation of 4,5-disubstituted oxazoles from aliphatic halides and various aldehydes in ionic liquids (Scheme 2.12).

Thus, the methods developed by van Leusen and Yu utilized the inherent polarity of the α-carbonyl carbon and constructed the key bond via a carbanion. Perusal of the literature indicates that the carbon-nitrogen bond can be made through umpolung$^1$ of the α-keto carbon although the later approach was only explored minimally in comparison to the former. The tin (IV) chloride-mediated Ritter reaction of α-halo ketones, which was demonstrated by Lora-Tamayo$^{137}$ 45 years
ago, exploits the mode of reverse polarity. Under the influence of the strong Lewis acid tin (IV) chloride, a putative $\alpha$-carbonyl carbocation is generated and the formation of various oxazoles can be accomplished satisfactorily (Scheme 2.13). However, the need for stoichiometric quantities of tin-based reagents together with the rather limited availability of $\alpha$-halo ketones appears to disfavor this method.

![Scheme 2.13. Lora-Tamayo’s oxazole synthesis.](image)

A related alternative, using $\text{Tl(OAc)}_3$ as an oxidizing reagent that precludes the need for a halogen on the $\alpha$ carbon of the keto group simplified the Lora-Tamayo tin-mediated procedure. However, it was found that only aliphatic nitriles were suitable substrates and benzonitrile resulted in low yields of the corresponding oxazole. Nevertheless, this suggests the attractive prospect of using simple ketones as precursors. This strategy was exploited by activating $\alpha$-keto carbons using iodine (III) and iron (III) promoters, oxidizing the $\alpha$-keto carbon to generate $\alpha$-oxo triflates or acetates in situ (Scheme 2.14).

Carbenes have been used in formal cycloaddition reactions to generate oxazole rings by Lewis acidic promoted methods in nitrile solvents. Ibata and Sato\textsuperscript{141} developed a BF\textsubscript{3}-catalyzed synthesis of oxazoles via diazo compounds as the carbene precursors, which were transformed to nitrilium intermediates, ultimately furnishing various oxazoles in the following step with good yields (Scheme 2.15).

Scheme 2.15. BF\textsubscript{3}-mediated oxazole synthesis.

Decomposition of diazo compounds to yield carbenes can be conveniently catalyzed by Rh\textsubscript{2}(OAc)\textsubscript{4} without affecting other functionalities. As a result, an efficient Rh\textsubscript{2}(OAc)\textsubscript{4} catalyzed cycloaddition between an alkynyl nitrile and diazomalonate to furnish an oxazole was accomplished in the total synthesis of leucascandrolide A by Kozmin and co-workers.\textsuperscript{142}
Scheme 2.16. Rh-catalyzed oxazole synthesis in Kozmin’s total synthesis of leucascandrolide A.

Diazocompounds can potentially be dangerous and explosive if they are not handled carefully. The use of oximes in place of diazo compounds for the synthesis of oxazoles was envisaged by Zhang and coworkers. Stable $\alpha$-diketone monooximes were obtained from the reaction of ketones and methyl nitrite in HCl-saturated ether. Exposure of $\alpha$-diketone monooximes and aldehydes in acidic media led to the formation of oxazole-derived N-oxides, which were reduced to 2,4,5-trisubstituted oxazoles with Zn/AcOH.

Scheme 2.17. Oxazole synthesis via oxime intermediates.

Nucleophilic substitution and cyclization are key steps of many useful oxazole syntheses. Strategies that combine these two reactions in one pot may provide practical advantages. Zhan and co-workers showcased a practical synthesis of substituted oxazoles from propargylic alcohols and amides by employing $p$-toluenesulfonic acid monohydrate (PTSA) as a proton shuffler. The oxazoles could be synthesized in good yields using a catalytic amount of PTSA, but a full equivalent of PTSA was required to reach full conversion.
Scheme 2.18. PTSA mediated oxazole synthesis from propargylic alcohol.

A three component reaction of an isonitrile, an aldehyde, a carboxylic acid to give an α-acyloxy amide was discovered by Passerini.\textsuperscript{145} This reaction and other multi-component reactions such as the Ugi reactions\textsuperscript{146,147} are applied broadly in heterocycle synthesis. Zhu and coworkers\textsuperscript{148} utilized the power of the Passerini reaction in the synthesis of oxazoles having an α-hydroxy-β-amino acid component (Scheme 2.19). A stereoselective variant involved the use of \(N, N\)-dibenzyl phenylalanal to couple with β-phenyl isocyanopropionamide, affording the anti adduct as the major product in up to 9:1 d.r. Hydrolysis under acidic conditions furnished the desired dipeptide with retention of stereochemical integrity.

Scheme 2.19. Stereospecific oxazole synthesis.

Several established methods for oxazole synthesis involve the oxidation of oxazolines derived from coupling of carboxylic acids with suitable amino-alcohols, or from oxo-amide intermediates.\textsuperscript{149} Graham\textsuperscript{150} of Merck Research Laboratories pointed out the disadvantages of this traditional approach, including the need to purify the intermediate and the requirement for moisture-sensitive reagents in the reaction. To overcome these limitations, a two step, one-pot procedure was developed, involving triethylamine-mediated condensation of serine methyl ester hydrochloride with aldehydes in the first step and DBU combined with \(\text{BrCCl}_3\) promoted global
oxidation of the ring in the second step (Scheme 2.20). This procedure was found to be general in terms of the selection of aldehydes, although serine methyl ester hydrochloride was the only amino ester component tested.

![Scheme 2.20](image)

**Scheme 2.20.** Graham’s approach to oxazole synthesis.

A tert-butyl hydroperoxide (TBHP)/I$_2$-mediated domino oxidative cyclization was developed by Jiang and co-workers$^{151}$ to conveniently give 2,5-disubstituted oxazoles. Various vinyl benzenes or naphthalenes with different substitution patterns and several benzylamines were employed in this transformation, but long chain aliphatic amines and 2-phenyl-propylene failed to yield oxazoles. Based on the isolation of α-iodo-acetophenone after mixing styrene, TBHP, and iodine, a mechanism involving the generation of oxo-phenylacetaldehyde via Kornblum oxidation$^{152}$ followed by condensation to α-imino phenone, enolization and cyclization was proposed (Scheme 2.21).

![Scheme 2.21](image)

**Scheme 2.21.** Oxazole synthesis via TBHP/I$_2$ mediated domino oxidative cyclization.
Wang and co-workers\(^{153}\) demonstrated that 2,5-disubstituted oxazoles can be derived from a wide range of aromatic aldehydes under basic conditions, a method similar to Jiang’s work. Efficient synthesis of tri-substituted oxazoles containing 4-carboxylate or 4-amido substituents from 1,3-dicarbonyl derivatives and benzyl amines was achieved by Cu catalyzed tandem TBHP oxidative cyclization.\(^{154}\) Only one regio-isomer was observed.

![Scheme 2.22. Oxazole synthesis from diketones and benzylamines.](image)

A mild base (Cs\(_2\)CO\(_3\))-mediated reaction of aromatic and unsaturated primary amides with 2,3-dibromopropene efficiently allows for the synthesis of 2-methyl-5-aryl-substituted oxazoles.\(^{155}\) It was speculated that allenes were formed through the elimination of bromide during the course of the reaction, therefore explaining the observed reactivity in the absence of metal catalysts.

![Scheme 2.23. Oxazole synthesis through allenamide intermediates.](image)

Metal catalyzed reactions have recently found popularity in building the oxazole moiety because they often offer milder conditions, produce less waste and are very often more efficient. A modular and practical method developed by Buchwald and coworkers\(^{156}\) involves copper-catalyzed amidation followed by iodine-promoted cyclization.
Scheme 2.24. Copper-catalyzed amidation in oxazole synthesis.

A mixture of AuCl$_3$ (10 mol%) and diruthenium complex (5 mol%) was applied by Uemura and co-workers$^{157}$ to the synthesis of oxazoles. A plausible mechanism was proposed by probing the actions of each catalyst and by studying the alleneamide intermediate by $^1$H NMR (Scheme 2.25). First, propargyl alcohol was converted to a propargylic amide by the diruthenium complex. Then, alleneamide formation was catalyzed by AuCl$_3$ which also assisted the cyclization to furnish the oxazoles. Liu and co-workers$^{158}$ found that Zn(OTf)$_2$, a more readily available metal reagent, could be used with the ruthenium cocatalyst (TpRuPPh$_3$) in the high yielding synthesis of oxazoles with a different 2,5-substitution pattern to those of Uemura’s and Zhan’s studies.

Scheme 2.25. Metal-catalyzed oxazole synthesis through alleneamide intermediates.
A similar structural propargylic amide can also be derived from the conversion of primary amide to an α-chloroglycinate followed by the addition of an alkynyl metal reagent. The cyclization step was induced by aqueous NaHCO₃ to form the desired oxazole. This strategy was used by Ciufolini and co-workers in the total synthesis of (-)-muscoride.

![Chemical structure]

R¹ = phenyl, methyl, iPr; R² = alkyl, TMS,

Ciufolini (2003)

**Scheme 2.26.** Ciufolini’s oxazole synthesis in the total synthesis of (-)-muscoride.

Relevant work by Müller describes the synthesis of substituted oxazol-5-ylethanones in a consecutive three-component sequence starting from the amidation of propargyl amine with an acid chloride, followed by cross-coupling with another acid chloride. Acid-mediated cycloisomerization of the 4-oxo-butynyl-benzamide afforded the desired oxazole motif (Scheme 2.27).

![Chemical structure]

R = aryl, heteroaryl, olefinic

**Scheme 2.27.** Multi-component oxazole synthesis.

An efficient, metal-catalyzed [2+2+1] approach to oxazoles has been developed. Zhang and co-workers continued from their previous work on gold carbene intermediates by avoiding the use of potentially hazardous diazo compounds as the substrates. Using Ph₃PAuNTf₂ as the catalyst and 8-methylquinoline N-oxide as the oxidant, alkynes were converted to α-oxo carbene
intermediates. A wide variety of 2,5-substituted aryl or alkyl oxazoles were available using only three equivalents of nitriles under the optimal conditions (Scheme 2.28). These mild conditions are advantageous such that many sensitive functional groups can be tolerated.

\[
\begin{align*}
\text{cat. Ph}_3\text{PAuNTf}_2, & \quad \text{oxidant} \\
R^1\equiv & \quad \text{R}^2\text{CN} \\
\quad & \quad \text{N} \quad \text{[Au]} \\
\quad & \quad \text{R}^2 \\
\quad & \quad \text{R}^1\equiv \text{O} \quad \text{R}_2 \\
\end{align*}
\]

\[R^1 = \text{aryl, alkyl}; \quad R^2 = \text{alkyl, benzyl, phenyl}
\]

Zhang (2011)

**Scheme 2.28.** Oxazole synthesis via [2+2+1] cycloaddition.

2.2.3 Substitution Reactions of Oxazoles

The syntheses discussed previously assemble the oxazole rings from either cheap commodities or readily available materials. Another important class of methods accomplish the functionalization or substitution of previously assembled oxazole starting materials.

\[
\begin{align*}
\text{i.e.} & \quad \text{R}^1\equiv\text{O} \quad \text{N} \quad \text{R}^3 \\
\quad & \quad \text{R}^1\equiv\text{O} \quad \text{N} \quad \text{R}^3 \\
\quad & \quad \text{R}^1\equiv\text{O} \\
\quad & \quad \text{R}^2\equiv\text{X} \\
\text{Modular} & \quad \text{Approach} \\
\quad & \quad \text{Direct} \\
\quad & \quad \text{Functionalization} \\
\quad & \quad \text{Approach} \\
\text{or} & \quad \text{or} \\
\text{or} & \quad \text{or}
\end{align*}
\]

**Scheme 2.29.** Two general approaches of oxazole synthesis.

At this point, it is useful to address the intrinsic properties of the carbons in the oxazole to be able to rationalize differences in reactivity. It was concluded from molecular orbital modeling and calculations\textsuperscript{162-165} that C\textsubscript{2} possesses the highest positive charge density of the carbons in oxazole. The calculated negative \(\pi\)-electronic charge densities are in the order \(q_5>q_4>q_2\) for the carbon atoms of oxazole.\textsuperscript{162-164} These computations seem to be consistent with the higher
reactivity of C₅ towards electrophilic aromatic substitution.¹⁴⁹ It can be inferred from these studies that the hydrogen of the C₂ is the most acidic, and that C₅ is more nucleophilic than the other carbons of the ring.

Upon the treatment of oxazole with n-BuLi at -75 °C followed by in D₂O quench, Hodges and coworkers¹⁶⁶ isolated 2-deurterio-oxazole. However, upon quenching with aldehydes, 4-substituted oxazolyl alcohols were the predominant products. Since the ring opened enolate could be trapped using TMSCl the equilibration between 2-lithio and 4-lithio species via the putative ring opened enolate was postulated (Scheme 2.30).

\[
\text{Scheme 2.30. } \text{C}_4\text{-lithiation of the oxazole heterocycle.}
\]

An ingenious idea of suppressing the ring opening process through the use of borane (BH₃) was implemented by Vedejs and Monahan¹⁶⁷ to effect metalation solely at C₂ of oxazole.

\[
\text{Scheme 2.31. } \text{C}_2 \text{ lithiumation of oxazole heterocycle through borane complexation.}
\]

The utilities of two complementary methods developed by Hodges and Vedejs to functionalize C₂ and C₄ of oxazole respectively were explored by Molinski and co-workers¹⁶⁸ in their total synthesis of Bengazole A. Lithiated oxazole was added to a chiral aldehyde to yield diastereomeric alcohols (1:3.5) in favor of undesired diastereomer, a problem that could be rectified by oxidation and selective reduction of the ketone. Silylation afforded 4-substituted
oxazole, which was subjected to the modified Vedejs’ borane metalation-addition with 5-oxazolecarboxaldehyde (Scheme 2.32).

Scheme 2.32. Total synthesis of Bengazole A.

Oxazoles have been used as substrates in transition metal-catalyzed cross-coupling reactions. Among the advances achieved in this regard are applications of Stille, Heck, Sonogashira, Negishi, and Suzuki protocols pioneered by Dondoni, Yamanaka, Panek, Anderson, and Greaney respectively (Scheme 2.33).
Scheme 2.33. Cross-coupling reactions of the oxazole heterocycle.

A variation of the Negishi cross-coupling reaction that employed 2-thioalkyloxazole established a reliable route to arylate, alkylate and to add alkyne groups at C2. 2,5-dithiomethyl oxazole can be prepared using Molinski’s protocol\textsuperscript{175} by two consecutive steps of lithiation and addition of dimethylsulfane (Scheme 2.34). The inhibitory effect exerted by the thiomehtyl group to open the oxazole ring during the course of lithiation was the rational for the preferred C5 regioselectivity of the second lithiation. 2,5-Disubstituted oxazoles were synthesized from 2,5-dithiomethyloxazole through consecutive addition of aryl zinc reagents to C2 followed a C5 arylation catalyzed by Ni catalyst in one pot. This selective manipulation was possible due to the fact that the Pd catalyst is less reactive toward the thiomethyl at C5, and the Ni catalyst, being more active, is used in the second cross-coupling reaction for the synthesis of unsymmetrical 2,5-
diarylated oxazoles. Other zinc reagents such as alkylzinc reagents were not presented in this study by Stambuli and coworkers.\textsuperscript{176}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme234.png}
\caption{Synthesis of 2,5-disubstituted oxazoles through Negishi cross coupling reactions of 2-thioxazole.}
\end{figure}

Because of the difficulty in achieving direct functionalization of C\textsubscript{4} in oxazole, 2,4-iodooxazole was tested as a linchpin to provide either the 4-aryl-2-iodooxazole or 2-aryl-4-iodooxazole. Strotman and co-workers\textsuperscript{177} demonstrated that the use of Xantphos can effect arylation at C\textsubscript{4} through a Suzuki-Miyaura coupling reaction whereas 1,3,5-triaza-7-phosphaadamantane was employed for coupling at C\textsubscript{2} (Scheme 2.35).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme235.png}
\caption{Regioselective synthesis of 2 or 4-substituted oxazoles.}
\end{figure}

\textsuperscript{176} Stambuli (2009)

\textsuperscript{177} Strotman (2010)
Cross coupling reactions of oxazoles with other functional groups allows for the assembly of multi-substituted oxazoles in a straightforward fashion. Employment of pre-functionalized oxazoles, however, detracts from the utility of this method since the synthesis of the precursors requires extra modifications, thus contributing to the cost of these methods. On the contrary, C-H activation seems to be the method of choice to directly prepare oxazoles that vary in the functional groups and the positions of the substituents.

In a seminal report by Miura and co-workers, the use of a copper oxidant resulted in the Pd-catalyzed C₂ functionalization of oxazoles to give 2,5-diphenyl oxazoles in excellent yield. Daugulis and Do later reported a method that employed only 10 mol% of CuI, albeit with a lower yield. Greaney and coworkers later described a Pd-catalyzed direct arylation of 5-substituted oxazoles on water to give various 2,5 disubstituted oxazoles, but the use of a stoichiometric quantity of Ag₂CO₃ was required. Piguel and co-workers adopted this knowledge to develop a palladium-catalyzed method for the direct arylation and alkenylation of oxazoles. 5-Phenyloxazole was the substrate in most of the reported arylation and alkenylation reactions, but this protocol was also applied to the C₂ functionalization of the parent oxazole ring (Scheme 2.36).

![Scheme 2.36. Functionalization of the oxazole heterocycle.](image)

Complementary methods for direct arylation of the oxazole with high regioselectivity at both C₅ and C₂ have been developed by Strotman and Chobanian and coworkers for a wide range of aryl and heteroaryl bromides, chlorides, iodides, and triflates. Using task-specific phosphine ligands, palladium-catalyzed C₅ arylation of oxazoles is preferred in polar solvents,
whereas C₂ arylation is preferred in nonpolar solvents. These observations suggest that C₅ arylation occurred through a concerted metalation-deprotonation (CMD) pathway due to greater stabilization of a polar CMD transition state by polar solvents such as DMA. Base dependent C₂ arylation was inferred to involve formal deprotonation at C₂. Thus, C₂ and C₅ functionalization of oxazoles can be effectively accomplished using this approach.

![Scheme 2.37](image.png)

**Scheme 2.37.** C₅ substitution of the oxazole heterocycle.

Metal-catalyzed decarboxylative cross coupling has emerged as a useful tool for the synthesis of unsymmetrical biaryls. Based on the collective efforts of several research groups, decarboxylative C-H coupling of azoles was accomplished by Pd catalysis using bis(dicyclohexylphosphino)ethane (dcpe). Formation of the desired products was described as the work of two catalytic cycles, involving C-H activation of the oxazole and decarboxylation of another azole. Under these anhydrous conditions, arrays of diazole and triazole compounds were prepared, although homocoupled products were also observed (**Scheme 2.38**).
Scheme 2.38. Greaney’s synthesis of bisoxazoles.

Olefination of oxazoles via C-H activation was accomplished by Antilla and coworkers who proposed that 2-methoxy-5-(p-methoxyphenyl)oxazole undergoes Pd catalyzed electrophilic C-H activation at C₄, migratory insertion onto the olefin, Pd-hydride elimination and reoxidation of Pd catalyst to the original oxidation state using Cu(OAc)$_2$ in CH$_3$CN to form the desired C₄ alkenyl oxazoles. α, β-Unsaturated esters or amides, styrenes and 1,3-dienes were found to be suitable substrates in this method, and substituents on the styrenes are well tolerated under these mild, base free conditions (Scheme 2.39).

Scheme 2.39. Olefination of oxazoles via C-H activation.

2.3 Research Objectives

It was illustrated in equation (1) of Scheme 1.38 that the reaction of an α-carbonyl tosylate and allyltrimethylsilane mediated by scandium (III) triflate in acetonitrile afforded a tri-substituted oxazole. The oxazole 2.3a was proposed to be derived from Ritter type reaction of α-carbonyl tosylate 2.2a and acetonitrile to give the nitrilium intermediate, followed by cyclization and rearomatization (see equation (1) of Scheme 1.38). A new carbon-nitrogen bond was formed through umpolung of α-carbonyl carbon as described in chapter 1. Our continuing interests in the umpolung chemistry of α-keto carbon prompted us to explore the lead result with the following
objectives: (1) to search for the optimal conditions for the synthesis of oxazoles from α-carbonyl tosylates, (2) to investigate the scope of the reaction, (3) to develop the synthetic applications of the oxazoles in the context of other heterocycle syntheses.

Results and Discussion

2.4 Substrate Synthesis and Optimization of Reaction Conditions for the Synthesis of Oxazoles

Substrates 2.2a-d were prepared from mandelic acid in a two-steps sequence. Fischer esterification of mandelic acid in the corresponding alcohol afforded mandelic esters in good yields. Alternatively, amide 2.2d was obtained by stirring 2-hydroxy-2-phenyl-1-(piperidin-1-yl)ethanone in a solution of trifluoroacetic anhydride and dichloromethane (see the experimental section). Conversion of the α-hydroxy-mandelic esters or amide to the corresponding α-toluenesulfonyl-mandelic esters were accomplished using toluenesulfonyl chloride or toluensulfonyl anhydride and N-methylimidazole or pyridine as tosylation and nucleophilic reagents respectively (Scheme 2.40). Desyl tosylate 2.2e was constructed from silver promoted tosylation of desyl bromide.
Scheme 2.40. Synthesis of substrates.

Optimization of the lead result is summarized in Table 6. In the search of optimal conditions, scandium triflate was not effective in the absence of allyl(trimethyl)silane (entry 1). This result may indicate that the in-situ generated trimethylsilyl triflate (TMSOTf) is responsible for promoting the reaction. As a result, Lewis acids such as aluminum chloride, titanium (IV) chloride, TMSOTf and boron trifluoride (BF$_3$•OEt$_2$) and Brønsted acids such as sulfuric acid were being tested for promoting oxazole formation. Only BF$_3$•OEt$_2$ and TMSOTf resulted in the formation of the oxazole; complete conversion was observed for the TMSOTf mediated reaction.
Variations in the stoichiometry of TMSOTf, the promoter of choice, revealed that 2.5 equivalents of this reagent were required to obtain high yields (entry 6-8). Several solvents were examined in order to use acetonitrile only as a reaction component and not as solvent (entry 9-14). As a result, 1,2-dichloroethane (DCE) was identified as a useful solvent and 12 equivalents of acetonitrile were necessary (entry 14).

![Chemical structure diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Promoter (equiv.)</th>
<th>Solvent</th>
<th>MeCN (equiv.)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sc(OTf)₃ (0.2)</td>
<td>MeCN</td>
<td>--</td>
<td>70</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>BF₃-OEt₂ (2.5)</td>
<td>MeCN</td>
<td>--</td>
<td>70</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃ (2.5)</td>
<td>MeCN</td>
<td>--</td>
<td>70</td>
<td>30</td>
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<td>4</td>
<td>TsOH (2.5)</td>
<td>MeCN</td>
<td>--</td>
<td>70</td>
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</tr>
<tr>
<td>5</td>
<td>TiCl₄ (2.5)</td>
<td>MeCN</td>
<td>--</td>
<td>70</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>TMSOTf (2.5)</td>
<td>MeCN</td>
<td>--</td>
<td>70</td>
<td>&gt;95</td>
</tr>
<tr>
<td>7</td>
<td>TMSOTf (1.5)</td>
<td>MeCN</td>
<td>--</td>
<td>70</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>TMSOTf (1)</td>
<td>MeCN</td>
<td>--</td>
<td>70</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>TMSOTf (2.5)</td>
<td>MeCN</td>
<td>--</td>
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<td>&gt;95</td>
</tr>
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<td>10</td>
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<td>THF</td>
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<td>70</td>
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<tr>
<td>11</td>
<td>TMSOTf (2.5)</td>
<td>DME</td>
<td>5</td>
<td>70</td>
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</tr>
<tr>
<td>12</td>
<td>TMSOTf (2.5)</td>
<td>DCE</td>
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<td>70</td>
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<tr>
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<td>DCE</td>
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<tr>
<td>14</td>
<td>TMSOTf (2.5)</td>
<td>DCE</td>
<td>12</td>
<td>80</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

*a Yield (0.2 mmol scale) determined by GC/MS using dodecane as a quantitative internal standard

Table 6. Optimization of reaction conditions for the synthesis of oxazoles.

### 2.5 Substrate Scope of the Oxazole Synthesis

With optimized conditions in hand, the scope of the reaction was investigated. Various 2-alkoxy and 2-amino oxazoles were conveniently prepared from the current method, and a range of cation stabilizing R² and nitrile substituents R³ were well tolerated. However, the preparation of α-oxo tosylates when R² is 4-methoxyphenyl or 3,4-(methylene dioxy)phenyl group and R³ is piperidinyl group was challenging. In these cases, the trifluoroacetate leaving group proved to
be a suitable replacement (entry 5, 8 and 9 of Table 7). The lower yields obtained for entries 4 and 9 were attributed to difficulties in isolation of electron-rich oxazoles by chromatography.

![Chemical reaction]

**Table 7.** Preparation of substituted oxazoles by the Ritter reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th># of substrate</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
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<td>OMe</td>
<td>Ph</td>
<td>2.2a</td>
<td>Me</td>
<td>2.3a</td>
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<td>OMe</td>
<td>Ph</td>
<td>2.2a</td>
<td>Ph</td>
<td>2.3b</td>
<td>65</td>
</tr>
<tr>
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<td>OEt</td>
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<td>2.2b</td>
<td>Ph</td>
<td>2.3c</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>O-i-Pr</td>
<td>Ph</td>
<td>2.2c</td>
<td>Ph</td>
<td>2.3d</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>piperidin-1-yl</td>
<td>Ph</td>
<td>2.2d</td>
<td>Ph</td>
<td>2.3e</td>
<td>75&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Ph</td>
<td>2.3f</td>
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<td>7</td>
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<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>2.2f</td>
<td>Ph</td>
<td>2.3g</td>
<td>77</td>
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<tr>
<td>8</td>
<td>OEt</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>2.2g</td>
<td>Ph</td>
<td>2.3h</td>
<td>89&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>OEt</td>
<td>3,4-(OCH&lt;sub&gt;2&lt;/sub&gt;O)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>2.2h</td>
<td>Ph</td>
<td>2.3i</td>
<td>65&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>Ph</td>
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<td>2.3m</td>
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<td>Ph</td>
<td>2.2e</td>
<td>vinyl</td>
<td>2.3n</td>
<td>82</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after recrystallization or column chromatography. See experimental section for details.

<sup>b</sup> Trifluoroacetate was used as the leaving group instead of tosylate.

Pimprinine, a natural product found in Streptomyces, is an indolyl-substituted oxazole.<sup>188</sup> Such heteroarene oxazoles are a class of targets that are well suited to this method. The Friedel-Crafts reaction of 1-methylindole with oxophenylacetaldehyde provided a precursor that underwent TMSOTf mediated Ritter reaction to furnish 5-indolyl oxazole 2.3o without prior O-sulfonylation. The precursor of the isomeric 4-indolyl-substituted oxazole 2.3p was prepared by base catalyzed isomerization of the Friedel-Crafts adduct followed by O-sulfonylation. This material was subjected to the conditions to afford 4-indolyl oxazole 2.3p (Scheme 2.41). The modest yields observed were the results of loss of materials in chromatography even though the conversion of substrate to oxazole was almost complete.
2.41. Synthesis of indolyl-phenyloxazoles.

2.6 Applications in Furan Synthesis

As described in the previous section, isolation of electron rich oxazoles can be challenging as they are prone to decomposition on silica gel. However, electron rich oxazoles 2.2a and 2.2b in this study are useful motifs in cycloaddition reaction with alkynes yielding furans 2.4a-b after expulsion of benzonitrile by a retro-[4+2] cycloaddition. Furans 2.4a and 2.4b were obtained in good yields from 2.2a in a two-step process without purification of the intermediate oxazole (Scheme 2.42).

2.7 Conclusions and Outlook

Oxazoles are important substructures of natural products and many groups contributed to the development of methods that afford this class of moiety. Our involvement in this field
stemmed from the observation of a trisubstituted oxazole as a byproduct of the scandium catalyzed reaction of an α-oxo tosylate with allyltrimethylsilane in acetonitrile. Further investigation revealed that TMSOTf was the ideal reagent to ionize α-oxo tosylates, generating cations that were trapped by the nitrile nucleophiles to furnish a wide range of tri-substituted oxazoles. Lower yields in some cases were attributed to the instabilities of electron-rich oxazoles on silica gel. Interesting heteroaryl oxazoles such as indolinyl substituted oxazoles can be prepared using this method, starting from inexpensive and readily available materials. 2-Alkoxy oxazoles were also used in cycloaddition reactions with dimethylacetylenedicarboxylate, providing fully substituted furans in good yields without the isolation of the intermediate oxazoles.

Since esters and amide motifs are readily converted to thioesters and thioamides by Lawesson’s reagent, one can envisage the current method can also be exploited for the synthesis of thiazoles which are substructures of many biological active natural products. Sanz-Cervera and coworkers\textsuperscript{189} prepared tri-substituted thiazole from 2-acetamidoketones, the common precursors for Robinson-Gabriel oxazole synthesis, by refluxing the 2-acetamidoketones with Lawesson’s reagent in THF (\textbf{Scheme 2.43}). Building on the ease of this protocol, the thiazole may be furnished in a two step sequence which may involve O→S transformation of α-toluenesulfonyl-mandelic esters 2.2a – 2.2h via the Lawesson’s reagent followed by the addition of various nitriles in our optimized conditions (\textbf{Scheme 2.43}).

\begin{center}
\textbf{Scheme 2.43.} The use of Lawesson’s reagent in thiazole and the proposed future work.
\end{center}
Experimental Details for Preparation of Substituted Oxazoles by Ritter Reactions of α-Oxo Tosylates

General procedure A. Preparation of Alkyl 2-hydroxy-2-phenylacetates.

To a dry flask containing mandelic acid (1.522 g, 10 mmol) in alcohol (30 mL) was added 1 drop of concentrated sulfuric acid. The resulting solution was stirred and refluxed for 14 hours. The whole solution was allowed to cool to 23 °C and concentrated in vacuo. Purification by flash chromatography on silica gel (10% EtOAc in n-pentane) yielded the alkyl 2-hydroxy-2-phenylacetate as a colorless solid.

Ethyl 2-hydroxy-2-phenylacetate (2.1b)

General procedure A was carried out on 10 mmol scale, using ethyl alcohol (30 mL) as solvent and mandelic acid (1.522 g, 10 mmol) as the starting material. After reflux and stirring at 78 °C, the reaction mixture was concentrated in vacuo. The residue was further purified by flash chromatography on silica gel (10% EtOAc in n-pentane) gave the title compound as a colorless solid (1.612 g, 89%). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.44-7.29 (m, 5H), 5.17 (d, J = 5.7 Hz, 1H), 4.32-4.12 (m, 2H), 3.48 (d, J = 5.7 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H). Characterization data were in agreement with literature values.$^{190}$

Isopropyl- 2-hydroxy-2-phenylacetate (2.1c)
General procedure A was carried out on 10 mmol scale, using isopropyl alcohol (30 mL) as solvent and mandelic acid (1.522 g, 10 mmol) as the starting material. After reflux and stirring at 82 °C, the reaction mixture was concentrated in vacuo. The residue was further purified by flash chromatography on silica gel (10% EtOAc in n-pentane) gave the title compound as a colorless solid (1.51 g, 78%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.43-7.31 (m, 5H), 5.12 (d, \(J = 6\) Hz, 1H), 5.10 (m, 1H), 3.44 (d, \(J = 6\) Hz, 1H), 1.29 (d, \(J = 6.4\) Hz, 3H), 1.12 (d, \(J = 6.4\) Hz, 3H). Characterization data were in agreement with literature values.\(^{191}\)

**Ethyl 2-(4-bromophenyl)-2-hydroxyacetate (2.1f)**

General procedure A was carried out on 3.5 mmol scale, using ethyl alcohol (10.5 mL) as solvent and 4-bromo-mandelic acid, (0.809 g, 3.5 mmol). After reflux and stirring at 78 °C, the reaction mixture was concentrated in vacuo. The residue was further purified by flash chromatography on silica gel (10% EtOAc in n-pentane) gave the title compound as a colorless solid (770 mg, 85%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.51 (d, \(J = 8.4\) Hz, 2H), 7.33 (d, \(J = 8.4\) Hz, 2H), 5.12 (d, \(J = 5.4\) Hz, 1H), 4.32-4.16 (m, 2H), 3.47 (d, \(J = 5.4\) Hz, 1H), 1.26 (t, \(J = 7.2\) Hz, 3H). Characterization data were in agreement with literature values.\(^{192}\)

**Ethyl 2-hydroxy-2-(4-methoxyphenyl)acetate (2.1g)**

General procedure A was carried out on 3.5 mmol scale, using ethyl alcohol (10.5 mL) as solvent and 4-methoxy-mandelic acid, (638 mg, 3.5 mmol). After reflux and stirring at 78 °C, the
reaction mixture was concentrated in vacuo. The residue was further purified by flash column chromatography on silica gel (10% EtOAc in n-pentane) gave the title compound as a colorless solid (618 mg, 84%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.34 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.11 (d, J = 5.6 Hz, 1H), 4.28-4.13 (m, 2H), 3.81 (s, 3H), 3.36 (d, J = 5.6 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H). Characterization data were in agreement with literature values.$^{192}$

**Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyacetate (2.1h)**

![Chemical structure of Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyacetate](image)

General procedure A was carried out on 1.32 mmol scale, using ethyl alcohol (4 mL) as solvent and 3,4-(methyleneedioxy)-mandelic acid (259 mg, 1.32 mmol). After reflux and stirring at 78 °C, the reaction mixture was concentrated in vacuo. The residue was further purified by flash chromatography on silica gel (10% EtOAc in n-pentane) gave the title compound as a colorless solid (264 mg, 89%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 6.90 (d, J = 6.6 Hz, 2H), 6.80 (d, J = 8.7 Hz, 1H), 5.96 (s, 2H), 5.06 (d, J = 5.7 Hz, 1H), 4.27-4.18 (m, 2H), 3.40 (d, J = 5.7 Hz, 1H), 1.26 (t, J = 6.9 Hz, 3H). Characterization data were in agreement with literature values.$^{192}$

**Preparation of 2-hydroxy-2-(1-methyl-1H-indol-3-yl)-1-phenylethanone (2.1i)**

![Chemical structure of 2-hydroxy-2-(1-methyl-1H-indol-3-yl)-1-phenylethanone](image)

Preparation of the title compound was conducted according to the method developed by Ivonin and coworkers.$^{193}$ To a reaction flask, 1-methylindole (0.763 mL, 6.11 mmol, 1.33 equiv) was added to a solution of phenylglyoxal (617 mg, 4.6 mmol, 1 equiv) in toluene (23 mL). The reaction mixture was then stirred for 22 hours at 70 °C and concentrated in vacuo. The residue was further purified by flash chromatography on silica (30% EtOAc in n-pentane) yielding the title compound as a colorless solid (993 mg, 81%). M.p. = 127 – 131 °C (EtOAc/n-pentane). $^1$H
NMR (300 MHz, CDCl₃) δ (ppm) 7.98 (d, J = 7.5 Hz, 2H), 7.74 (d, J = 8.1 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.28-7.13 (m, 3H), 6.95 (s, 1H), 6.30 (d, J = 6.3 Hz, 1H), 4.26 (d, J = 6.3 Hz, 1H), 3.69 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 199.4, 137.5, 134.1, 133.9, 129.2, 128.8, 128.4, 126.5, 122.5, 119.3, 113.2, 109.8, 69.1, 33.1; IR (cm⁻¹, neat) 3479 (m, br), 3059 (m), 2925 (m), 1676 (s), 1596 (m), 1476 (m), 1264 (s). MS (EI) m/z 265.11 (M⁺, 3), 158 (100), 144 (57), 160 (33); HRMS (EI) calcd for C₁₇H₁₅NO₂: 265.1103, found 265.1106. Characterization data were in agreement with literature values.

Preparation of 2-hydroxy-1-(1-methyl-1H-indol-3-yl)-2-phenylethanone (2.1j)

Preparation of the title compound was conducted according to the method developed by Ivonin and coworkers.²⁹⁴ To a reaction flask containing 2-hydroxy-2-(1-methyl-1H-indol-3-yl)-1-phenylethanone (361 mg, 1.36 mmol, 1 equiv) in acetonitrile (4.1 mL), triethylamine (0.28 mL, 2.04 mmol, 1.5 equiv) was added. The reaction mixture was then stirred for 12 hours (or until all of 2-hydroxy-2-(1-methyl-1H-indol-3-yl)-1-phenylethanone was consumed) at 70 °C and concentrated in vacuo. The residue was further purified by flash chromatography on silica (30% EtOAc in n-pentane) yielding the title compound as a colorless solid (260 mg, 72%). M.p. = 159 – 162 °C (EtOAc/n-pentane). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.43-8.40 (m, 1H), 7.48 (s, 1H), 7.44-7.41 (m, 2H), 7.37-7.27 (m, 6H), 5.66 (d, J = 5.7 Hz, 1H), 4.91 (d, J = 5.7 Hz, 1H), 3.74 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 192.8, 141.4, 137.3, 136.7, 129.2, 128.6, 127.9, 126.9, 124.1, 123.4, 122.8, 112.6, 110.0, 76.6, 33.9; IR (cm⁻¹, neat) 3393 (s, br), 3022 (w), 2941 (w), 1635 (s), 1365 (s). MS (EI) m/z 265.11 (M⁺, 3), 158 (100), 77 (30), 130 (11); HRMS (EI) calcd for C₁₇H₁₅NO₂: 265.1103, found 265.1096. Characterization data were in agreement with literature values.³⁸⁹

General procedure B. Preparation of Alkyl 2-phenyl-2-(tosyloxy)acetate.
Preparation of the title compound was conducted according to the method developed by Tanabe and coworkers.\textsuperscript{195} The reaction was carried out on 3 mmol scale. To a dry flask containing alkyl 2-hydroxyl-2-phenylacetate (1 equiv), $N$-methyl imidazole (1.5 equiv), triethylamine (1.5 equiv) in toluene (30 mL) was added $p$-toluenesulfonyl chloride (1.5 equiv) at 0 °C. The resulting solution was allowed to warm to 23 °C slowly and continued to stir at this temperature for 1 hour. The whole solution was diluted by addition of ethyl acetate. The solution mixture was partitioned between ethyl acetate and distilled water. The organic phase was separated, and the aqueous layer was then extracted twice with ethyl acetate (10 mL × 2) and extracted once with 0.5 M HCl (10 mL). The combined organic extracts were dried using Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (30% EtOAc in n-pentane) gave the resulting alkyl 2-phenyl-2-(tosyloxy)acetate as a colourless solid.

**Methyl 2-phenyl-2-(tosyloxy)acetate (2.2a)**

![Chemical structure of methyl 2-phenyl-2-(tosyloxy)acetate](image)

General procedure B described above was carried out on 12 mmol scale, using methyl mandelate (1.994 g, 12 mmol, 1 equiv), $N$-methyl imidazole (1.44 mL, 18 mmol, 1.5 equiv), triethylamine (2.5 mL, 18 mmol, 1.5 equiv), $p$-toluenesulfonyl chloride (3.43 g, 18 mmol, 1.5 equiv). After 1 hour at 23 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography (10% EtOAc in n-pentane) yielding the title compound as a colorless solid (3.05 g, 80%).\textsuperscript{1}H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.77-7.74 (m, 2H), 7.32-7.26 (m, 7H), 5.79 (s, 1H), 3.68 (s, 3H), 2.42 (s, 3H). Characterization data were in agreement with literature values.\textsuperscript{195}

**Ethyl 2-phenyl-2-(tosyloxy)acetate (2.2b)**
General procedure B described above was carried out on 3 mmol scale, using ethyl mandelate (536 mg, 3 mmol, 1 equiv), N-methyl imidazole (0.36 mL, 4.5 mmol, 1.5 equiv), triethylamine (0.62 mL, 4.5 mmol, 1.5 equiv), p-toluenesulfonyl chloride (858 mg, 4.5 mmol, 1.5 equiv). After 1 hour at 23 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography (10% EtOAc in n-pentane) yielding the title compound as a colorless solid (834 mg, 83%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.78 (d, J = 8.1 Hz, 2H), 7.37-7.29 (m, 7H), 5.77 (s, 1H), 4.20-4.06 (m, 2H), 2.42 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 167.6, 145.2, 133.7, 133.1, 129.9, 129.8, 129.0, 128.3, 127.7, 79.1, 62.3, 21.9, 14.1; IR (cm$^{-1}$, solid) 2990 (w), 2922 (w), 1747 (s), 1598 (m), 1460 (m), 1352 (s), 1206 (s), 1173 (s); HRMS (EI, M+ Na) calcd for C$_{17}$H$_{18}$O$_5$SNa: 357.0767, found 357.0770. Characterization data were in agreement with literature values.$^{196}$

**Isopropyl 2-phenyl-2-(tosyloxy)acetate (2.2c)**

General procedure B described above was carried out on 3 mmol scale, using isopropyl mandelate (583 mg, 3 mmol, 1 equiv), N-methyl imidazole (0.36 mL, 4.5 mmol, 1.5 equiv), triethylamine (0.62 mL, 4.5 mmol, 1.5 equiv), p-toluenesulfonyl chloride (858 mg, 4.5 mmol, 1.5 equiv). After 1 hour at 23 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography (10% EtOAc in n-pentane) yielding the title compound as a colorless oil (1.05 g, 100%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.79 (d, J = 8.4 Hz, 2H), 7.32-7.29 (m, 7H), 5.73 (s, 1H), 5.02-4.94 (m, 1H), 2.42 (s, 3H), 1.21 (d, J = 6 Hz, 3H), 1.12 (d, J = 6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 167.1, 145.2, 133.7, 133.2, 129.9, 129.7, 129.0, 128.3, 127.7, 79.2, 70.3, 21.9, 21.8, 21.5; IR (cm$^{-1}$, solid) 2952 (w), 2985 (w), 1727 (s), 1599 (m), 1453 (m), 1371 (s), 1277 (s); HRMS (ESI, M$^+$) calcd for C$_{18}$H$_{20}$O$_5$S: 349.1104, found 349.1094.
General procedure C. Preparation of Alkyl 2-aryl-2-(tosyloxy)acetate.

The reaction was carried out on 0.6 mmol. To a dry flask containing alkyl 2-hydroxyl-arylacetate (1 equiv), pyridine (1.5 equiv), triethylamine (1.5 equiv) in toluene was added p-toluenesulfonic anhydride (1.5 equiv) at 0 °C. The resulting solution was allowed to warm to 23 °C slowly and continued to stir at this temperature for 1 hour. The whole solution was diluted by addition of ethyl acetate. The solution mixture was partitioned between ethyl acetate (6 mL) and distilled water (3 mL). The organic phase was separated, and the organic layer was then extracted once with 0.5 M HCl (3 mL). The combined organic extracts were dried using Na$_2$SO$_4$ and concentrated in vacuo. Further purification by flash chromatography (10% EtOAc in n-pentane) gave the title compound as a colorless solid.

Ethyl 2-(4-bromophenyl)-2-(tosyloxy)acetate (2.2f)

General procedure C described above was carried out on 0.6 mmol scale, using ethyl 2-(4-bromophenyl)-2-hydroxyacetate (156 mg, 0.6 mmol, 1 equiv), pyridine (0.073 mL, 0.9 mmol, 1.5 equiv), triethylamine (0.125 mL, 0.9 mmol, 1.5 equiv), p-toluenesulfonic anhydride (294 mg, 0.9 mmol, 1.5 equiv). After 1 hour at 23 °C, the reaction mixture was worked up as described above. Further purification by flash chromatography (10% EtOAc in n-pentane) gave the title compound as a colorless oil (216 mg, 87%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.76 (d, $J =$ 8.4 Hz, 2H), 7.45 (d, $J =$ 8.4 Hz, 2H), 7.30 (d, $J =$ 8.4 Hz, 2H), 7.22 (d, $J =$ 8.4 Hz, 2H), 5.72 (s, 1H), 4.22-4.06 (m, 2H), 2.43 (s, 3H), 1.20 (t, $J =$ 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 167.1, 145.4, 133.5, 132.2, 130.0, 129.3, 129.3, 128.3, 128.3, 124.2, 78.3, 62.5, 21.9, 14.1; IR (cm$^{-1}$, solid) 2983 (w), 2922 (w), 1756 (s), 1596 (m), 1489 (m), 1369 (s); HRMS (ESI) calcd for C$_{17}$H$_{17}$O$_5$SBr: 413.0052, found 413.0048.
Preparation of 2-bromo-1,2-diphenylethanone (desyl bromide).

Preparation of the title compound was conducted according to the method developed by Stavber and coworkers.\textsuperscript{197} To a dry reaction flask containing deoxybenzoin (491 mg, 2.5 mmol, 1 equiv) was added N-bromosuccinimide (445 mg, 2.5 mmol, 1 equiv) and p-toluene sulfonic acid (48 mg, 0.25 mmol, 0.1 equiv). The resulting solution was heated to 80 °C for 10 minutes. The reaction solution was allowed to cool to 23 °C then diluted by addition of diethyl ether (5 mL). The solution mixture was partitioned between diethyl ether and distilled water. The organic phase was separated, and the aqueous layer was then extracted twice with diethyl ether (5 mL × 2). The combined organic extracts were dried using Na$_2$SO$_4$ and concentrated \textit{in vacuo}. Purification by recrystallization from ethanol gave the title compound as a colorless solid (593 mg, 86%). \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.00-7.98 (m, 2H), 7.59-7.52 (m, 3H), 7.47-7.43 (m, 2H), 7.39-7.31 (m, 3H), 6.38 (s, 1H). Characterization data were in agreement with literature values.\textsuperscript{198}

Preparation of 2-oxo-1,2-diphenylethyl 4-methylbenzenesulfonate (2.2e)

Preparation of the title compound was conducted according to the method developed by Sheehan and coworkers.\textsuperscript{199} To a dry reaction flask containing desyl bromide (500 mg, 1.817 mmol) in acetonitrile (3.6 mL) was added silver tosylate (527 mg, 1.89 mmol, 1.04 equiv). The resulting solution was heated to 70 °C and stirred for 15 minutes. The whole solution was allowed to cool to 23 °C. Silver bromide was removed by filtration, and the reaction mixture was concentrated \textit{in vacuo}. The residue was then dissolved in toluene and filtered to remove the last traces of silver bromide salts. Crude mixture was obtained by addition of \textit{n}-pentane to the filtrate. Further recrystallization from mixed solvent (30% \textit{n}-pentane in dichloromethane) gave
the title compound as a colorless solid (450 mg, 68%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.85 (d, \(J = 8\) Hz, 2H), 7.73 (d, \(J = 8.4\) Hz, 2H), 7.54-7.49 (m, 1H), 7.40-7.35 (m, 4H), 7.30-7.29 (m, 3H), 7.23 (d, \(J = 8\) Hz, 2H), 6.67 (s, 1H), 2.39 (s, 3H). Characterization data were in agreement with literature values.\(^{200}\)

2-(1-Methyl-1H-indol-3-yl)-2-oxo-1-phenylethyl 4-methylbenzenesulfonate (2.2f)

![Structure of the title compound](image)

General procedure C described above was carried out on 0.57 mmol scale, using 2-hydroxy-1-(1-methyl-1H-indol-3-yl)-2-phenylethanone (151 mg, 0.57 mmol, 1.0 equiv), pyridine (0.069 mL, 0.85 mmol, 1.5 equiv), triethylamine (0.118 mL, 0.85 mmol, 1.5 equiv), p-toluenesulfonic anhydride (277 mg, 0.85 mmol, 1.5 equiv). After 1 hour at 23 °C, the reaction mixture was worked up as described above. Further purification by flash chromatography (10% EtOAc in \(n\)-pentane) gave the title compound as a colorless solid which decomposes upon heating above 135 °C (238 mg, 100 %). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.32-8.30 (m, 1H), 7.90 (s, 1H), 7.72 (d, \(J = 8.4\) Hz, 2H), 7.43-7.40 (m, 2H), 7.30-7.26 (m, 6H), 7.16 (d, \(J = 8.1\) Hz, 2H), 6.27 (s, 1H), 3.81 (s, 3H), 2.31 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 187.2, 145.1, 137.2, 136.9, 134.6, 133.6, 129.8, 129.2, 128.9, 128.2, 127.6, 127.3, 124.0, 123.3, 123.0, 113.0, 109.8, 84.4, 34.0, 21.8; IR (cm\(^{-1}\), solid) 3119 (w), 3038 (w), 2937 (w), 1655 (s), 1532 (s), 1373 (m), 1330 (s); HRMS (ESI, M+H) calcd for C\(_{24}\)H\(_{22}\)N\(_2\)O\(_4\)S: 420.1264, found 420.1256.

**General procedure D. Preparation of 2-ethoxy-2-oxo-1-arylethyl 2,2,2-trifluoroacetate**

![Reaction scheme](image)
To a dry flask containing ethyl-2-hydroxy-2-arylacetate (1 equiv.) or 2-hydroxy-2-phenyl-1-(piperidin-1-yl)ethanone (1 equiv) in dichloromethane (DCM), trifluoroacetic anhydride (TFAA) (6.0 equiv.) was added at 0 °C. The resulting solution was allowed to warm to 23 °C slowly and continued to stir for 14 hours. The whole solution was concentrated in vacuo and the crude was used without further purification.

2-Oxo-1-phenyl-2-(piperidin-1-yl)ethyl 2,2,2-trifluoroacetate (2.2d)

General procedure D described above was carried out on 1.32 mmol scale, using 2-hydroxy-2-phenyl-1-(piperidin-1-yl)ethanone (290 mg, 1.32 mmol) and trifluoroacetic anhydride (1.1 mL, 7.92 mmol, 6 equiv) in 1 mL of dichloromethane. The solution mixture was concentrated in vacuo. The crude (311 mg, 75%) was used for the preparation of the oxazole without further purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.47-7.43 (m, 4H), 7.36-7.31 (m, 1H), 6.32 (s, 1H), 3.69-3.65 (m, 1H), 3.51-3.45 (m, 1H), 3.34-3.17 (m, 2H), 1.56 (m, 4H), 1.46 (m, 2H).

2-Ethoxy-1-(4-methoxyphenyl)-2-oxoethyl 2,2,2-trifluoroacetate (2.2g)

General procedure D described above was carried out on 0.6 mmol scale, using ethyl 2-hydroxy-2-(4-methoxyphenyl)acetate (125 mg, 0.6 mmol) and trifluoroacetic anhydride (0.5 mL, 3.6 mmol, 6 equiv) in 0.6 mL of DCM. The solution mixture was concentrated in vacuo. The crude (182 mg, 98%) was used for the preparation of the oxazole without further purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.41 (d, $J = 8.4$Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 6.02 (s, 1H), 4.28-4.18 (m, 2H), 3.82 (s, 3H), 1.25 (t, $J = 7.2$ Hz, 3H).
1-(Benzo[d][1,3]dioxol-5-yl)-2-ethoxy-2-oxoethyl 2,2,2-trifluoroacetate (2.2h)

General procedure D described above was carried out on 0.4 mmol scale, using ethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxyacetate (91 mg, 0.4 mmol) and trifluoroacetic anhydride (0.33 mL, 2.4 mmol, 6 equiv) in 0.4 mL of DCM. The solution mixture was concentrated in vacuo. The crude material (129 mg, 98%) was used for the preparation of the oxazole without further purification. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 6.96-6.92 (m, 2H), 6.84 (d, J = 7.6 Hz, 1H), 6.00 (s, 2H), 5.95 (s, 1H), 4.29-4.16 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H).

**General procedures E. Preparation of 2,4,5 tri-substituted oxazole.**

The reaction was carried out on 0.5 mmol scale. To a dry flask containing alkyl 2-aryl-2-(tosyloxy)acetate or 2-oxo-1,2-diphenylethyl 4-methylbenzenesulfonate (0.5 mmol, 1 equiv) were added 1,2-dichloroethane (DCE) (2.5 mL), the nitrile (6 mmol), and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.23 mL, 1.25 mmol) sequentially at 23 °C. The resulting solution was stirred and heated at 80 °C for 20 hours. The solution was allowed to cool to 23 °C then diluted with ethyl acetate (10 mL). The solution mixture was partitioned between ethyl acetate and distilled water. The organic phase was separated, and the aqueous layer was then extracted twice with ethyl acetate (10 mL × 2). The combined organic extracts were dried using Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel or on basic, activated alumina (10% EtOAc/n-pentane or 5% EtOAc/n-pentane) gave the resulting oxazole as a colourless solid.
General procedures F. Preparation of 2,4,5 tri-substituted oxazoles.

To a dry flask containing 2-ethoxy-1-aryl-2-oxoethyl 2,2,2-trifluoroacetate or 2-oxo-1-phenyl-2-(piperidin-1-yl)ethyl 2,2,2-trifluoroacetate (1 equiv) were added 1,2-dichloroethane (2.5 mL), the nitrile (12 equiv), and TMSOTf (2.5 equiv) sequentially at 23 °C. The resulting solution was stirred and heated at 80 °C for 20 hours. The solution was allowed to cool to 23 °C then diluted with ethyl acetate (10 mL). The solution mixture was partitioned between ethyl acetate and distilled water. The organic phase was separated, and the aqueous layer was then extracted twice with ethyl acetate (10 mL × 2). The combined organic extracts were dried using Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel or basic, activated alumina (10% EtOAc/n-pentane or 5% EtOAc/n-pentane) gave the resulting oxazole as a colourless solid.

5-Methoxy-2-methyl-4-phenyloxazole (2.3a)

General procedure E was carried out on 0.5 mmol scale, using acetonitrile (0.31 mL, 6 mmol, 12 equiv) and methyl 2-phenyl-2-(tosyloxy)acetate (160 mg, 0.5 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by the precipitation of the solid from the mixed solvent (10% EtOAc in n-pentane), yielding the title compound as a colorless solid (94 mg, 99%). M.p. = 79 – 82 °C (EtOAc/n-pentane). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.70 (m, 2H), 7.47-7.45 (m, 2H), 7.40-7.38 (m, 1H), 4.23 (s, 3H), 2.90 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 157.3, 154.2, 129.7, 129.6, 125.5, 123.5, 110.6, 62.2, 13.5; IR (cm⁻¹, solid): 3059 (m), 2983 (m), 1739 (w), 1629 (s), 1489 (s), 1381 (s); MS (EI) m/z 189.08 (M⁺, 3), 132.9 (100), 161.1 (62), 189.1 (49); HRMS (EI) calcd for C₁₁H₁₁NO₂: 189.0790, found 189.0790.
5-Methoxy-2,4-diphenyloxazole (2.3b)

![Chemical structure of 5-Methoxy-2,4-diphenyloxazole](image)

General procedure E was carried out on 0.5 mmol scale, using benzonitrile (0.62 mL, 6 mmol, 12 equiv) and methyl 2-phenyl-2-(tosyloxy) acetate **2.2a** (160 mg, 0.5 mmol). After 20 hours at 70 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane), yielding the title compound as an amorphous, colorless solid (82 mg, 65%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 8.03-8.00 (m, 2H), 7.91 (d, $J = 7.2$ Hz, 2H), 7.48-7.38 (m, 5H), 7.27-7.22 (m, 1H), 4.15 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 152.0, 131.6, 129.9, 128.8, 128.7, 127.9, 127.8, 126.7, 125.8, 125.3, 123.6, 60.3; IR (cm$^{-1}$, solid): 3063 (w), 2950 (m), 1624 (s), 1597 (s), 1498 (s), 1377 (s); MS (EI) m/z 251.09 (M$^+$, 3), 105.0 (100), 77 (64), 103.0 (35); HRMS (EI) calcd for C$_{16}$H$_{13}$NO$_2$: 251.0946, found 251.0944.

5-Ethoxy-2,4-diphenyloxazole (2.3c)

![Chemical structure of 5-Ethoxy-2,4-diphenyloxazole](image)

General procedure E described above was carried out on 0.5 mmol scale, using benzonitrile (0.62 mL, 6 mmol) and ethyl 2-phenyl-2-(tosyloxy)acetate **2.2b** (167 mg, 0.5 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane), yielding the title compound as an amorphous, colorless solid (109 mg, 82%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 8.03-8.00 (m, 2H), 7.88 (dd, $J = 6.3$, 0.9 Hz, 2H), 7.48-7.43 (m, 5H) 7.27-7.23 (m, 1H), 4.47 (q, $J$= 5.4 Hz, 2H), 1.54 (t, $J = 5.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 154.1, 152.2, 131.8, 129.9, 128.9, 128.7, 127.9, 126.7, 125.8, 125.3, 117.1, 70.0, 15.5; IR (cm$^{-1}$, neat) 3056 (w), 2919 (m),
2850 (m), 1596 (s), 1447 (s), 1330 (s); MS (EI) m/z 265.11 (M⁺, 3), 105.0 (100), 77.0 (18), 265.1 (14); HRMS (EI) calcd for C₁₇H₁₅NO₂: 265.1103, found 265.1104.

5-Isopropoxy-2,4-diphenyloxazole (2.3d)

![Structure of 5-Isopropoxy-2,4-diphenyloxazole (2.3d)](image)

General procedure E described above was carried out on 0.5 mmol scale, using benzonitrile (0.62 mL, 6 mmol) and isopropyl 2-phenyl-2-(tosyloxy)acetate 2.2c (174 mg, 0.5 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (10% EtOAc in n-pentane), yielding the title compound as an amorphous, colorless solid (77 mg, 55%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.95-7.92 (m, 2H), 7.88-7.86 (dd, J = 8.4, 1.2 Hz, 2H), 7.39-7.33 (m, 5H) 7.18-7.16 (m, 1H), 4.75-4.70 (m, 1H), 1.40 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 153.4, 152.5, 131.8, 129.9, 128.9, 128.7, 128.0, 126.7, 125.8, 125.4, 118.4, 78.5, 22.74; IR (cm⁻¹, solid) 3164 (w), 2983 (w), 1626 (s), 1446 (s), 1377 (s); MS (EI) m/z 279.13 (M⁺, 3), 77 (100), 103 (22), 105 (20); HRMS (EI) calcd for C₁₈H₁₇NO₂: 279.1259, found 279.1261.

2,4-Diphenyl-5-(piperidin-1-yl)oxazole (2.3e)

![Structure of 2,4-Diphenyl-5-(piperidin-1-yl)oxazole (2.3e)](image)

General procedure F described above was carried out on 0.5 mmol scale, using benzonitrile (0.62 mL, 6 mmol, 12 equiv) and 2-oxo-1-phenyl-2-(piperidin-1-yl)ethyl 2,2,2-trifluoroacetate 2.2d (158 mg, 0.5 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on basic activated alumina (5% EtOAc in n-pentane) yielding the title compound as an amorphous, colorless solid (114 mg,
75%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 8.01-7.96 (m, 4H), 7.44-7.35 (m, 5H), 7.23-7.19 (m, 1H), 3.13-3.09 (m, 4H), 1.75-1.69 (m, 4H), 1.63-1.55 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 155.4, 152.8, 132.7, 129.8, 128.8, 128.5, 128.3, 126.8, 126.2, 126.0, 124.1, 51.6, 26.2, 24.2; IR (cm$^{-1}$, solid): 3056 (w), 2939 (m), 2849 (m), 1607 (s), 1596 (s), 1447 (s), 1382 (s); MS (EI) m/z 304.16 (M$^+$, 3), 172.1 (100), 304.2 (92), 89 (84); HRMS (EI) calcd for C$_{20}$H$_{20}$N$_2$O: 304.1576, found 304.1569.

**2,4,5-Triphenyloxazole (2.3f)**

[Chemical structure image]

General procedure E described above was carried out on 0.5 mmol scale, using benzonitrile (0.62 mL, 6 mmol, 12 equiv) and 2-oxo-1,2-diphenylethyl 4-methylbenzenesulfonate 2.2e (183 mg, 0.5 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (10% EtOAc in n-pentane), yielding the title compound as a colorless solid (125 mg, 84%) M.p. = 116 – 120 °C (EtOAc/n-pentane). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 8.10-8.07 (m, 2H), 7.67 (dt, J = 6.8, 2.8, 1.6 Hz, 2H), 7.62 (dt, J = 6.8, 2.8, 1.6 Hz, 2H), 7.42-7.40 (m, 3H), 7.35-7.30 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 160.4, 145.8, 137.0, 132.8, 130.6, 129.2, 129.0, 128.9, 128.9, 128.8, 128.5, 128.4, 127.6, 126.8, 126.7; IR (cm$^{-1}$, solid) 3056 (w), 2921 (w), 1956 (w), 1704 (m), 1486 (s), 1326 (m); MS (EI) m/z 297.12 (M$^+$, 3), 165.0 (100), 297.0 (92), 89 (84); HRMS (EI) calcd for C$_{21}$H$_{15}$NO: 297.1154, found 297.1154.

**4-(4-Bromophenyl)-5-ethoxy-2-phenyloxazole (2.3g)**

[Chemical structure image]
General procedure E described above was carried out on 0.49 mmol scale, using benzonitrile (0.61 mL, 5.88 mmol, 12 equiv) and ethyl 2-(4-bromophenyl)-2-(tosyloxy)acetate 2.2f (203 mg, 0.49 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as a colorless solid (130 mg, 77%) M.p. = 98 – 102 °C (EtOAc/n-pentane). \[^1\]H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 8.00-7.97 (m, 2H), 7.80 (d, \(J = 8.7\) Hz, 2H), 7.53 (d, \(J = 8.7\) Hz, 2H), 7.45-7.43 (m, 3H), 4.48 (q, \(J = 7.2\) Hz, 2H), 1.53 (t, \(J = 7.2\) Hz, 3H); \[^13\]C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 152.2, 143.5, 131.8, 130.8, 130.0, 128.9, 127.7, 126.8, 125.8, 120.2, 116.1, 70.0, 15.4; IR (cm\(^{-1}\), solid) 3065 (w), 2949 (m), 2868 (w), 1625 (s), 1597 (s), 1488 (s), 1377 (s); MS (EI) m/z 343.02 (M\(^+\), 3), 105 (100), 77 (34), 183 (11); HRMS (EI) calcd for C\(_{17}\)H\(_{14}\)BrNO\(_2\): 343.0208, found 343.0209.

**5-Ethoxy-4-(4-methoxyphenyl)-2-phenyloxazole (2.3h)**

\[
\begin{align*}
\text{H}_3\text{C} & \text{O} \\
\text{H}_3\text{CO} & \\
\text{H}_2\text{C} & \\
\text{N} & \\
\text{O} & \\
\text{C} & \\
\text{C} & \\
\text{O} & \\
\text{H}_3\text{C} & \\
\end{align*}
\]

General procedure F described above was carried out on 0.5 mmol scale, using benzonitrile (0.62 mL, 6 mmol, 12 equiv) and 2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl 2,2,2-trifluoroacetate 2.2g (153 mg, 0.5 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as an amorphous, colorless solid (131 mg, 89%). \[^1\]H NMR (300 MHz, CDCl\(_3\)) \(\delta\) ppm 8.02-8.01 (m, 2H), 7.87 (d, \(J = 9\) Hz, 2H), 7.45-7.42 (m, 3H), 6.98 (d, \(J = 9\)Hz, 2 H), 4.44 (q, \(J = 7.2\) Hz, 2H), 3.84 (s, 3H), 1.52 (t, \(J = 7.2\) Hz, 3H); \[^13\]C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 158.6, 152.2, 129.8, 128.9, 128.0, 126.7, 125.8, 124.5, 117.4, 114.2, 112.5, 70.1, 55.5, 15.5; IR (cm\(^{-1}\), solid): 3054 (w), 2934 (m), 2835 (m), 1641 (s), 1511 (s), 1375 (s), 1243 (s). MS (EI) m/z 295.12 (M\(^+\), 3), 105.0 (100), 84.0 (39), 77 (18); HRMS (EI) calcd for C\(_{18}\)H\(_{17}\)NO\(_3\): 295.1208, found 295.1209.

**4-(Benzo[d][1,3]dioxol-5-yl)-5-ethoxy-2-phenyloxazole (2.3i)**
General procedure F described above was carried out on 0.3 mmol scale, using benzonitrile (0.62 mL, 3.6 mmol, 12 equiv) and 1-(benzo[d][1,3]dioxol-5-yl)-2-ethoxy-2-oxoethyl 2,2,2-trifluoroacetate \textbf{2.2h} (96 mg, 0.3 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in \(n\)-pentane) yielding the title compound as an amorphous, colorless solid (60 mg, 65%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.00-7.97 (m, 2H), 7.44-7.42 (m, 5H), 6.88 (d, J = 8.4 Hz, 1H), 5.98 (s, 2H), 4.45 (q, J = 6.9 Hz, 2H), 1.53 (t, J = 6.9 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 152.0, 148.0, 146.4, 129.8, 128.9, 127.9, 126.0, 125.8, 119.0, 117.1, 108.7, 106.1, 101.1, 78.2, 70.0, 15.4; IR (cm\(^{-1}\), solid): 2962 (w), 2919 (m), 2855 (m), 1631 (m), 1600 (s), 1500 (s), 1346 (s), 1248 (s). MS (EI) m/z 309.10 (M\(^+\), 3), 105.0 (100), 57.1 (29), 55.1 (22); HRMS (EI) calcd for C\(_{18}\)H\(_{15}\)NO\(_4\): 309.1001, found 309.1004.

\textbf{2-Methyl-4,5-diphenyloxazole (2.3j)}

General procedure E described was carried out on 0.5 mmol scale, using acetonitrile (0.31 mL, 6 mmol, 12 equiv) and 2-oxo-1,2-diphenylethyl 4-methylbenzenesulfonate \textbf{2.02e} (183 mg, 0.5 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (10% EtOAc in \(n\)-pentane) yielding the title compound as a colorless solid (108 mg, 92%) M.p. = 160 – 165 °C (EtOAc/\(n\)-pentane). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.62-7.58 (m 4H,), 7.52-7.46 (m, 6H), 3.05 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 164.4, 148.5, 131.6, 131.5, 129.9, 129.6, 128.4,
127.7, 127.1, 124.7, 123.6, 13.4; IR (cm$^{-1}$, solid) 2587 (m), 1606 (m), 1448 (m), 1301 (s); HRMS (ESI, M+H) calcd for $C_{16}H_{13}NO$: 236.1069, found 236.1070.

2-Ethyl-4,5-diphenyloxazole (2.03k)

General procedure E described above was carried out on 0.5 mmol scale, using propiononitrile (0.43 mL, 6 mmol, 12 equiv) and 2-oxo-1,2-diphenylethyl 4-methylbenzenesulfonate 2.2e (183 mg, 0.5 mmole). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (10% EtOAc in n-pentane) yielding the title compound as a colorless oil (95 mg, 76%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 7.66 (dt, J = 6.8, 3.6, 1.6 Hz, 2H), 7.60 (dt, J = 6.8, 3.6, 1.6 Hz, 2H), 7.39-7.30 (m, 6H), 2.92 (q, J = 7.6 Hz, 2 H), 1.45 (t, J = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 164.7, 145.3, 135.3, 132.9, 129.4, 128.8, 128.7, 128.7, 128.5, 128.2, 126.6, 22.0, 11.6; IR (cm$^{-1}$, solid) 3056 (w), 2979 (m), 1571 (s), 1445 (s), 1214 (s); MS (EI) m/z 249.12 (M$^+$, 3), 165.1 (100), 77.0 (91), 105 (44); HRMS (EI) calcd for $C_{17}H_{15}NO$: 249.1154, found 249.1158.

2-Heptyl-4,5-diphenyloxazole (2.3l)

General procedure E described above was carried out on 0.5 mmol scale, using heptanenitrile (0.92 mL, 6 mmol, 12 equiv) and 2-oxo-1,2-diphenylethyl 4-methylbenzenesulfonate 2.2e (183 mg, 0.5 mmole). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane)
yielding the title compound as a colorless oil (144 mg, 90%). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.66-7.63 (m, 2H), 7.60-7.57 (m, 2H), 7.39-7.31 (m, 6H), 2.87 (t, J = 7.5 Hz, 2 H), 1.91-1.81 (m, 2H), 1.35-1.30 (m, 8H), 0.91-0.87 (m, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 164.1, 145.2, 135.2, 132.9, 129.5, 128.8, 128.7, 128.5, 128.2, 126.6, 31.9, 29.4, 29.1, 28.5, 27.4, 22.8, 14.3; IR (cm$^{-1}$, neat) 3058 (w), 2925 (s), 1603 (m), 1444 (m), 1219 (m); MS (EI) m/z 319.19 (M$^+$, 3), 235.1(100), 105.0 (87), 69.0 (58); HRMS (EI) calcd for C$_{22}$H$_{25}$NO: 319.1936, found 319.1936.

2-Tert-butyl-4,5-diphenyloxazole (2.3m)

General procedure E described above was carried out on 0.5 mmol scale, using pivalonitrile (0.66 mL, 6 mmol, 12 equiv) and 2-oxo-1,2-diphenylethyl 4-methylbenzenesulfonate 2.2e (183 mg, 0.5 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless solid (134 mg, 97%). M.p. = 71 – 73 °C (EtOAc/n-pentane). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.67 (d, J = 6.3 Hz, 2H), 7.60 (d, J = 6.3 Hz, 2H), 7.39-7.30 (m, 6H), 1.48 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 170.0, 144.9, 135.1, 133.1, 129.6, 128.8, 128.8, 128.4, 128.3, 128.1, 126.6, 34.0, 28.9; IR (cm$^{-1}$, solid), 2974 (m), 1563 (m), 1458 (m), 1361 (m). MS (EI) m/z 277.15 (M$^+$, 3), 262.1 (100), 77.0 (99), 165.1 (73); HRMS (EI) calcd for C$_{19}$H$_{19}$NO: 277.1467, found 277.1461.

4,5-Diphenyl-2-vinylxazole (2.3n)
CAUTION! Acrylonitrile is a select carcinogen.

General procedure E described above was carried out on 0.5 mmol scale, using acrylonitrile (0.39 mL, 6 mmol, 12 equiv) and 2-oxo-1,2-diphenylethyl 4-methylbenzenesulfonate 2.2e (183 mg, 0.5 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless solid (102 mg 82%). M.p. = 75 – 78 °C (EtOAc/n-pentane).

The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless solid (102 mg 82%). M.p. = 75 – 78 °C (EtOAc/n-pentane). \( ^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.67-7.62 (m, 4H), 7.41-7.33 (m, 6H), 6.71 (dd, \( J = 13.2, 8.4 \) Hz, 1H), 6.30 (1H, \( J = 13.2, 0.6 \) Hz, dd), 5.70 (dd, \( J = 8.4, 0.6 \) Hz, 1H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 159.7, 145.5, 136.7, 132.6, 129.0, 128.9, 128.8, 128.7, 128.4, 128.2, 126.8, 123.6, 122.1. IR (cm\(^{-1}\), solid) 3066 (w), 1966 (w), 1862 (w), 1696 (w), 1602 (m), 1530 (m), 1444 (m), 1313 (m); MS (EI) m/z 247.10 (M\(^+\), 3), 247.1 (100), 165.1 (59), 219.1 (44); HRMS (EI) calcd for C\(_{17}\)H\(_{13}\)NO: 247.0997, found 247.0999.

2-Methyl-4-(1-methyl-1H-indol-3-yl)-5-phenyloxazole (2.3o)

To a dry flask containing 2-hydroxy-2-(1-methyl-1H-indol-3-yl)-1-phenylethanone (133 mg, 0.5 mmol) were added acetonitrile (2.5 mL) as solvent and TMSOTf (0.23 mL, 1.25 mmol) sequentially at –78 °C. The resulting solution was allowed to warm slowly to 23 °C and continued to stir at this temperature for 20 hours. The solution was then diluted with ethyl acetate (10 mL) and concentrated in vacuo. Purification of the residue by flash chromatography on basic, activated alumina (10% EtOAc in n-pentane) gave the resulting oxazole as an amorphous, yellow solid (61 mg, 42%). \( ^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) (ppm) 7.59-7.57 (m, 2H), 7.39-7.02 (m, 7H), 7.05 (t, \( J = 8.4 \) Hz, 1H), 3.84 (s, 3H), 2.57 (s, 3H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 159.9, 137.0, 129.4, 128.5, 128.4, 128.2, 127.5, 125.9, 125.7, 121.8, 121.3, 119.7, 109.3, 107.3,
33.0, 14.1; IR (cm⁻¹, solid) 3043 (w), 2921 (s), 2850 (m), 1584 (s), 1466 (s), 1336 (m), 1265 (s); HRMS (ESI, M+H) calcd for C₁₉H₁₇N₂O : 289.1335, found 289.1327.

5-(1-Methyl-1H-indol-3-yl)-2,4-diphenyloxazole (2.3p)

General procedure E described above was carried out on 0.22 mmol scale, using benzonitrile (0.28 mL, 2.6 mmol, 12 equiv) and 2-(1-methyl-1H-indol-3-yl)-2-oxo-1-phenylethyl 4-methylbenzenesulfonate 2.2f (93 mg, 0.22 mmol). After 20 hours at 80 °C, the reaction mixture was allowed to be cooled slowly to 23 °C and was worked up as described above. The residue was further purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as an amorphous, yellow solid (48 mg, 62%). ¹H NMR (300 MHz, CDCl₃) δ ppm 8.20-8.17 (m, 2H), 7.83-7.81 (m, 2H), 7.73 (d, J = 7.8 Hz, 1H), 7.53-7.49 (m, 3H), 7.41-7.29 (m, 6H), 7.21 (t, J = 8.1 Hz, 1H), 3.84 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 137.1, 135.3, 135.3, 133.2, 130.1, 129.0, 128.7, 128.2, 128.0, 127.8, 127.7, 126.4, 126.1, 122.8, 121.4, 120.8, 109.8, 104.4, 102.1, 33.4; IR (cm⁻¹, solid) 3055 (w), 2923 (m), 2853, 1630 (s), 1493 (s), 1336 (m). HRMS (ESI, M+H) m/z calcd for C₂₄H₁₉N₂O : 351.1491, found 351.1497.

General procedure G. Preparation of tetra-substituted furans via Diels-Alder reaction.

General procedure E described above was carried out on 0.25 mmol scale, using benzonitrile or acetonitrile (3 mmol, 12 equiv) and methyl 2-phenyl-2-(tosyloxy)acetate 2.2a (92 mg, 0.125 mmol). After 20 hours at 80 °C, the reaction mixture was worked up as described above. Without
further purification, toluene and dimethyl acetylenedicarboxylate (DMAD) (0.061 mL, 0.50 mmol, 2 equiv) were added to the residue. The reaction mixture was then stirred and heated at 110 °C for 14 hours. The solution mixture was partitioned between ethyl acetate and distilled water. The organic phase was separated, and the aqueous layer was then extracted twice with ethyl acetate (5 mL × 2). The combined organic extracts were dried using Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (10% ethyl acetate/n-pentane) gave the resulting furan as a colorless solid.

**Dimethyl 2-methoxy-5-phenylfuran-3,4-dicarboxylate (2.4a)**

General procedure G described above was carried out on 0.25 mmol scale, using methyl 2-phenyl-2-(tosyloxy)acetate (162 mg, 0.25 mmol), benzonitrile (0.62 mL, 3 mmol, 12 equiv) and DMAD (0.61 mL, 0.5 mmol, 2 equiv). Purification of the residue after extraction by flash chromatography on silica gel (10% EtOAc/n-pentane) gave the title compound as a colorless solid (107 mg, 73%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.60 (dd, J = 7.6 Hz, J = 1.6 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.34–7.32 (m, 1H), 4.19 (s, 3 H), 3.91 (s, 3H), 3.82 (s, 3H). Characterization data were in agreement with literature values.²⁰¹

**Dimethyl 2-methoxy-5-methylfuran-3,4-dicarboxylate (2.4b)**

General procedure G described above was carried out on 0.35 mmol scale, using methyl 2-phenyl-2-(tosyloxy)acetate (112 mg, 0.35 mmol), acetonitrile (0.22 mL, 4.2 mmol, 12 equiv) and DMAD (0.86 mL, 0.7 mmol, 2 equiv). Purification of the residue after extraction by flash chromatography on silica gel (10% EtOAc/n-pentane) gave the title compound as a colorless solid (55 mg, 69%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 4.06 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.38 (s, 3H). Characterization data were in agreement with literature values.²⁰²
References


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Chapter 3
Investigation of Anion-Arene Interactions in Asymmetric Organocatalysis

The introduction of this chapter provides an overview of anion-arene (or anion-\(\pi\)) interactions including their origin and study in gas, solid and solution phases. The main goal of our research, which will be described in the research objectives section, was to investigate this interaction in asymmetric enamine organocatalysis. In the ensuing section, the results of our efforts in the organocatalyzed aldol reactions and Michael addition to \(\beta\)-nitrostyrene will be discussed.

Introduction

3.1 Definition of Anion-\(\pi\) Interaction and Modes of Anion-\(\pi\) Interaction

Non-covalent forces play essential roles in chemistry.\(^1\) These forces include strong, directional interactions like hydrogen bonding, halogen bonding and cation-\(\pi\) complexation and less directional forces such as ion pairing, \(\pi-\pi\) stacking, solvophobic and van der Waals forces. Recently, attractive noncovalent interactions between anions and electron deficient \(\pi\)-systems have been explored.\(^2\) Studies have revealed anion-\(\pi\) interactions are dominated by electrostatic and anion-induced polarization contributions.\(^3\) The electrostatic component of the anion-\(\pi\) interaction is correlated to the permanent quadrupole moment, \(Q_{zz}\) which is a measure of the charge distribution of a molecule relative to a particular molecular axis. Figure 2 illustrates that a benzene ring can be dissected by a normal plane of symmetry into top and bottom hemispheres. In unsubstituted benzene, the electron clouds are evenly distributed above and below the plane of symmetry and therefore the \(Q_{zz}\) of benzene displays a negative value (\(Q_{zz} = -8.45\text{B}\)). For hexafluorobenzene (C\(_6\)F\(_6\)), the quadrupole moment is large and positive (\(Q_{zz} = +9.50\text{B}\)) because of the polarization of C-F bonds due to the high electronegativity of fluorine.
Figure 4. Representation of the quadrupole moment for (a) benzene and (b) hexafluorobenzene.

Anion-induced polarization, depicted in Figure 3, is another dominating factor that can give rise to anion-π interactions. As an anion approaches from one hemisphere of the π system, the π-electron density of the aromatic system may be inductively polarized and this induced polarization can contribute to the total interaction energy. The magnitude of the anion-induced polarization correlates with the molecular polarizability, $\alpha_{||}$ of the aromatic compound. When $Q_{zz}$ of the molecule is small, the molecular polarizability, $\alpha_{||}$ may prevail and the arene exhibits a dual behavior by binding to both anions and cations. In general, the anion-π interaction will be most pronounced if both $Q_{zz}$ and $\alpha_{||}$ of the aromatic compound are large.

Figure 5. Aromatic π-electron density polarizability.

Based on crystal structures and theoretical studies, anions are able to interact with arenes through three binding modes which are illustrated for Cl$^-$ complexes with 1,3,5-triazine. As shown in Figure 4, these are: (i) the centered mode in which the position of the anion is near the center of and above the plane of the ring; (ii) the off-centered mode where the σ-bonding occurs between the anion and any point (or atom) of the ring; (iii) hydrogen bonding where the anion binds to the hydrogen atom of the ring.
Figure 6. Illustration of three modes of anion-π interactions between 1,3,5-triazine and chloride (atom colors: carbon gray, hydrogen white, nitrogen blue and chloride green).

3.2 Anion-π Interactions in Gas, Solid and Solution Phases

The existence of anion-π interactions was suggested in an early study involving a combination of mass spectrometry experiments with theoretical modeling of the interaction of C₆F₆ with F⁻, Cl⁻, Br⁻ and I⁻. While a covalent σ complex was formed with F⁻, the other halides were bound noncovalently by C₆F₆ molecules with the ion at the intersection of the C₆ axes. This landmark study was followed by other mass spectrometry experiments indicating the feasibility of anion-arene interactions. An insightful investigation of the interactions of π-electron-deficient 1,4,5,8,9,12-hexaazatriphenylenehexacarbonitrile [HAT(CN)₆] with anions was carried out by Dunbar and coworkers. ESI-MS experiments indicated an anion-π interaction between halides and [HAT(CN)₆] as \([\text{[HAT(CN)₆]:[X]}]^-\) complex was observed.

Although gas phase studies allow for the observation of weak, non-covalent interactions, information about the strength and binding modes from gas phase studies may be limited. Complementary types of information may be obtained from the examination of the interaction in the solid and solution phases. For example, the X-ray crystal structure of the HAT(CN)₆ bromide complex indicates that the faces of [HAT(CN)₆] are closely associated with three anions on one side and a single anion and three benzene rings on the opposite side. Moreover, the anion-π interaction between [HAT(CN)₆] and halides was confirmed by UV/Vis, ¹³C and halogen NMR spectroscopy in THF. Dunbar's research team found a 2:3 stoichiometric ratio in the complex of
[HAT(CN)₆] with halides X⁻, suggesting an η², η²-mode of binding (Figure 5). The measured association constants in THF for Cl⁻, Br⁻ and I⁻ are 3780, 2200, 940 M⁻¹, respectively.

\[
\text{Figure 7. Schematic representation of } [\text{HAT(CN)}_6]_2[\text{X}^-]_3 \text{ complexes.}
\]

\[^1\text{H} \text{NMR was used by Johnson and coworkers}^7 \text{ to determine the association constants and binding modes of anions with uncharged } 2,4,6-\text{trisubstituted } 1,3,5-\text{triethylbenzene derivatives that differ in the position of their nitro substituents. They found that the magnitude of association constants for halides decreases in the order of } \text{Cl}^- > \text{Br}^- > \text{I}^- \text{ in deuterated benzene, ranging from 11 - 53 M}^{-1}. \text{ Depending on the position of the nitro substituents, either the hydrogen bonding mode or the off-centered binding mode was observed, based on striking differences in } \Delta \delta \text{ for receptors D and F versus that for receptor E (Figure 6). B3LYP/DZVP calculations suggested that the off-centered binding mode was preferred to the hydrogen bonding or centered mode for complexes of receptor E with anions.}
\]

\[
\text{Figure 8. Structural representations of receptor D, E and F.}
\]
Octamethyl calix[4]pyrrole was studied by Ballester and coworkers as a receptor for halides. The mode of anion binding involved hydrogen bonding with the four NH groups of the calix[4]pyrrole scaffold, placing the anion in the center of the cavity. X-ray crystal structures of solvated receptors revealed that the cone-conformation of the calix[4]pyrrole positions the anion above the planes of the π systems of the meso aryl substituents (Figure 7). The chemical shifts of protons in H₁, H², H³ and H⁴ were closely monitored to probe the effects of addition of chlorides in deuterated acetonitrile. Upon addition of chloride, upfield shifts of the aromatic protons and the existence of separate signals for free and bound calix[4]pyrrole receptor indicated that the included chloride is hydrogen bonded to the four pyrrolic NH groups with slow binding on the NMR time scale, and experiences anion-π interactions. It was found that association constant values for the Cl⁻: calix[4]pyrrole complex increased with the electron-withdrawing character of the R substituent. The estimated free energies of the chloride-π interaction indicate that the chloride-π interaction in this system is repulsive except for R = NO₂ which may reverse the Qzz of the phenyl ring, resulting a favorable anion-π interaction.

Figure 9. Structural representation of octamethyl calix[4]pyrrole and complex after addition of Cl⁻.

3.3 Research Objectives

As evidence for anion-arene interaction has become clearer, applications of these noncovalent interactions have begun to emerge. One such application is oligonaphthalenediimide (O-NDI)-based transmembrane transport developed by Matile and coworkers. In order to
achieve anion recognition and transport, a channel consisting of $\pi$-acidic, shape-persistent, rigid-rod O-NDI was synthesized to selectively mobilize chloride across lipid bilayers.

![Diagram of anion transport](image)

**Figure 10.** Application of anion-arene interactions in ion transport.

Although anion-\(\pi\) interactions continue to gain attention for their role in chemical and biological processes, their application in catalysis has not been demonstrated. On the contrary, several studies using cation-\(\pi\) interactions in asymmetric catalysis\(^{10-13}\) were reported. We hypothesized that incorporating electron-deficient aryl groups to organocatalysts might provide opportunities to use anion-arene interactions to influence reactivity and/or stereoselectivity in these systems. Our objectives were as follows: (1) to prepare catalysts that incorporate anion-stabilizing aromatic groups, (2) to investigate the utility of the catalysts in aldol reactions and conjugate additions to nitro – styrenes.

### Results and Discussion

#### 3.4 Synthesis of Organocatalysts

In early 1970s, (S)-proline was employed by Hajos and Parrish\(^{14,15}\) in the asymmetric intramolecular aldol reaction of 2-methyl-2-(3-oxobutyl)cyclopentane-1,3-dione to give the aldol adducts (the intermediates) in good enantioselectivity. Further sulfuric acid mediated hydrolysis would furnish the enone. The renaissance of proline as a chiral catalyst can be traced to the contributions of Barbas and List in aldol and Mannich reactions.\(^{16}\) Other proline derivatives have also been applied broadly in enamine catalysis with high enantioselectivity. Building on the aforementioned work, we aimed to develop a series of chiral pyrrolidine based
catalysts that utilize anion-\(\pi\) interaction to influence the stereochemical outcomes of polar addition reactions (Figure 9). In addition, electron deficient aryl groups such as dinitrobenzene and pentafluorobenzene in the catalysts could play important roles in magnifying the desired interaction to induce good selectivities, and we also envisaged that the catalysts would be consisted of ester or ether moieties to allow a quick access to this class of catalysts.

![Possible anion-\(\pi\) Stabilization](image)

**Figure 11.** Using anion-\(\pi\) interaction in asymmetric organocatalysis.

The synthesis of **3.3a-c** began with Boc protection of L-prolinol, followed by DMAP-catalyzed DIC coupling with carboxylic acids and subsequent TFA-mediated Boc deprotection, to furnish salts **3.3a-c** (Scheme 3.1). It is worthy of note that removal of the Boc group did not give rise to O→N acyl migration because the conditions are acidic. Another set of prolinol based organocatalysts **3.5a** and **3.5b** were obtained through a sequence of Mitsunobu reaction and TFA mediated Boc deprotection.
Scheme 3.01. Synthesis of electron-deficient arene-functionalized organocatalysts 3.3a-c, 3.5a and 3.5b.

Aldol reactions of p-nitro-benzaldehyde and acetone were tested using three different catalysts: 3.3a, 3.3b and L-proline. In the L-proline catalyzed reaction, the aldol adduct was furnished with high yield and the ee was not experimentally determined for this previously
published result. Both catalyst 3.3a and catalyst 3.3b afforded only the (E)-4-(4-nitrophenyl)but-3-en-2-one.

3.5 Organocatalyzed Aldol Reactions

Scheme 3.02. L-proline, 3.3a and 3.3b catalyzed reactions of p-nitro-benzaldehyde and acetone.

Further investigation of aldol reactions of p-nitro-benzaldehyde with acetone was conducted using the ether-linked catalysts 3.5a and 3.5b. Both aldol addition and condensation products were observed. $^1$H NMR spectra indicated that the reaction catalyzed by 3.5b was superior than that of 3.5a, as both the conversion and the ratio of addition to dehydration products were higher using 3.5b (Scheme 3.03). The enantiomeric ratios displayed from the
reaction of 3.5a and 3.5b were not determined due to the complication of the HPLC signals in the presence of dehydrating byproducts.

Scheme 3.03. 3.5a and 3.5b catalyzed reactions of p-nitro-benzaldehyde and acetone.

While reactions catalyzed by 3.3a, 3.3b, 3.5a and 3.5b afforded mixtures of aldol adduct and elimination product, Michael additions of β-nitro-styrene using these catalysts provided relatively clean conversion to the corresponding γ-nitro alkanone depending on the choice of the ketone or aldehyde pronucleophile. Representative results for additions of acetone to β-nitro-styrene using these catalysts are summarized in Scheme 3.04. Racemic proline was employed as the control catalyst for this reaction, resulting in only 35% yield and no ee (see experimental section). The catalysts tested all showed solvent-dependent activities and relatively low enantioselectivities. It is interesting to note that catalyst 3.3b and 3.3c displayed higher activity and ee than 3.3a in THF, and catalyst 3.5b displayed higher activity and ee than 3.5a in THF solvent. This may suggest that pentafluorobenzene may stabilize the transition state, lowering the activation barrier.
3.6 Organocatalyzed 1,4-Addition to β-Nitrostyrene

Scheme 3.04. Examination of catalysts in Michael addition of acetone to β-nitrostyrene.

Scheme 3.05 lists selected results for Michael additions of valeraldehyde to β-nitrostyrene catalyzed by 3.3a-c, 3.5a and 3.5b. Diethylamine was used in the control experiment and the desired product was isolated in 44% yield with low d.r. (see experimental information). Screening of several solvents indicated that dichloromethane and toluene could be employed to give good levels of enantioselectivity with satisfactory yields. It is interesting that the use of toluene resulted in high yields and diastereoselectivities. Comparison of 3.3a-c and 3.5a-b-catalyzed reactions reveals the effect of incorporating the anion-stabilizing groups into the catalysts. Catalyst 3.3b, which consists of pentafluorobenzene as an anion-stabilizing group, demonstrated 9% increase of ee over that of catalyst 3.3a. The same effects were also manifested in the 3.5a and 3.5b-catalyzed reactions as the pentafluorobenzyl ether catalyst 3.5b appears to
enhance ee to some extent in comparison to benzyl ether catalyst, **3.5a**. However, these differences are relatively small in terms of free energy, making them hard to interpret.

Scheme 3.05. Examination of catalysts in Michael addition of valeraldehyde to $\beta$-nitro styrene.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>d.r.</th>
<th>ee</th>
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</thead>
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<td><strong>3.3a</strong></td>
<td>(DCM)</td>
<td>64%</td>
<td>1:1.45</td>
<td>60%</td>
</tr>
<tr>
<td><strong>3.3b</strong></td>
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<td>1:1.45</td>
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<tr>
<td><strong>3.3c</strong></td>
<td>(DCM)</td>
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<td>1:2.64</td>
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<tr>
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<td>1:2.34</td>
<td>70%</td>
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<td><strong>3.5b</strong></td>
<td>(toluene)</td>
<td>69%</td>
<td>1:1.54</td>
<td>80%</td>
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</tbody>
</table>
3.7 Conclusions and Outlook

It is now clear from several distinct types of experimental data including mass spectrometry, X-ray crystallography, and solution-phase binding studies that interactions between anions and electron-deficient arenes are possible. This weak non-covalent interaction has been successfully applied in ion transport. This chapter has described our attempts to explore and expand the application of anion-π interactions in synthesis. The design of our catalysts involves prolinol derivatives with anion stabilizing groups such as pentafluorobenzene or dinitrobenzene. A selection of the catalysts were tested in aldol and Michael reactions of β-nitro styrene. Slight increases in ee for the 3.3b, 3.3c and 3.5b catalyzed reactions were indeed observed in comparison to those catalyzed by 3.3a or 3.5a. The low magnitude of these effects makes it challenging to ascribe them categorically to anion-arene interactions. Exploring catalysts that bear stronger anion-binding aryl groups (such as O-NDI pioneered by Matile and co-workers) or multiple arene moieties might be useful in giving rise to more significant effects (Scheme 3.06).

Scheme 3.06. Proposed structures of improved catalysts.

It was seen in this study that the yield and enantiomeric excess were both increased when changing the Michael donor from ketone to aldehyde in the 1,4-addition of β-NO₂ styrene. Alternatively, we could also implement changes in the Michael acceptor to examine the yields and ee’s of our currently developed catalyzed reactions. The intramolecular Michael reaction is another area that was not yet explored using our catalysts, and that could potentially yield interesting applications and higher selectivities (Scheme 3.07).
Scheme 3.07. Expansion of the substrate scope using anion stabilizing catalysts.
3.8 Experimental Details for Investigation of Anion-Arene Interactions in Asymmetric Organocatalysis

(S)-tert-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (3.1)

To a solution of 2-pyrrolidinemethanol in CH$_2$Cl$_2$ was added triethylamine via syringe followed by addition of di-tert-butyl dicarbonate in one portion. The reaction was stirred for 1 hour after which the resulting yellow solution was poured into 50 mL of distilled H$_2$O. The solution mixture was partitioned between CH$_2$Cl$_2$ and distilled water. The organic phase was separated, and the organic layer was then washed once with H$_2$O. The combined organic extracts were dried using Na$_2$SO$_4$ and concentrated in vacuo. Purification of the crude by column chromatography on silica gel (10% EtOAc in n-pentane) gave the title compound as a colorless solid (1.36g, 75%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) 4.72 (d, $J = 5.7$ Hz, 1H), 3.96 (br, s, 1H), 3.61-3.47 (m, 2H), 3.44-3.41 (m, 1H), 3.34-3.29 (m, 1H), 1.96 (dt, $J = 12.9, 7.5$ Hz, 1H), 1.86-1.75 (m, 2H), 1.79-1.47 (m, 9H). Characterization data were in agreement with literature values.$^{18}$

General procedure A. Esterification of substituted benzoic acid

To a stirred solution of substituted benzoic acid (1.5 equiv.), the 3.1 (1 equiv.) and DMAP (10 mol %) in CH$_2$Cl$_2$ (0.2 M) was added DIC (1.1 equiv.) at 0 $^\circ$C. The reaction mixture was then allowed to warm to room temperature. After stirring at room temperature for 24 hours (or judged completion by TLC), the reaction mixture was diluted with CH$_2$Cl$_2$ and quenched with water. The resulting solution was extracted with CH$_2$Cl$_2$ ($\times$2), and the combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification of the crude by column chromatography on silica gel gave the title compound.
(S)-tert-butyl 2-((benzoyloxy)methyl)pyrrolidine-1-carboxylate (3.2a)

![Chemical structure]

General procedure A described was carried out on 1.49 mmol scale, using benzoic acid (273 mg, 2.24 mmol, 1.5 equiv.), 3.1 (300 mg, 1.49 mmol), DMAP (18 mg, 0.15 mmol, 10 mol %) and DIC (346 µL, 2.24 mmol, 1.5 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless solid (412 mg, 91%) which was used to yield 3.3a after checking counts of hydrogens that were in agreement with the integration of hydrogens in \(^1\)H NMR spectrum. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 8.04 (s, 1H), 8.01 (d, \(J = 1.5\) Hz, 1H), 7.56 (t, \(J = 7.2\) Hz, 1H), 7.43 (t, \(J = 7.5\) Hz, 2H), 4.41 (dd, \(J = 10.8, 3.9\) Hz, 1H), 4.30 (br, s, 1H), 4.10 (br, s, 1H), 3.41 (br, s, 2H), 1.99-1.86 (m, 4H), 1.46 (s, 9H).

(S)-tert-butyl 2-(((perfluorobenzoyl)oxy)methyl)pyrrolidine-1-carboxylate (3.2b)

![Chemical structure]

General procedure A described was carried out on 2.5 mmol scale, using 2,3,4,5,6-pentafluorobenzoic acid (791 mg, 3.73 mmol, 1.5 equiv.), 3.1 (500 mg, 2.5 mmol), DMAP (31 mg, 0.25 mmol, 10 mol %) and DIC (577 µL, 3.73 mmol, 1.5 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless solid (1.07 g, >99%) which was used to yield 3.3b after checking counts of hydrogens that were in agreement with the integration of hydrogens in \(^1\)H NMR spectrum. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) 4.49-4.04 (m, 3H), 3.35 (br, s, 2H), 2.02-1.84 (m, 4H), 1.46 (s, 9H).

(S)-tert-butyl 2-(((3,5-dinitrobenzoyl)oxy)methyl)pyrrolidine-1-carboxylate (3.2c)
General procedure A described was carried out on 0.75 mmol scale, using 3,5-dinitro-benzoic acid (237 mg, 1.12 mmol, 1.5 equiv.), 3.1 (150 mg, 0.75 mmol), DMAP (9 mg, 0.07 mmol, 10 mol %) and DIC (173 µL, 1.12 mmol, 1.5 equiv.). After stirring for 24 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless solid (256 mg, 87%) which was used to yield 3.3c after checking counts of hydrogens that were in agreement with hydrogens in $^1$H NMR spectrum. $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 9.21 (s, br, 1H), 9.16 (s, br, 2H), 4.48 (br, s, 1H), 3.46 (d, J = 10.4 Hz, 2H), 3.41 (br, s, 2H), 2.09-1.63 (m, 4H), 1.41 (s, 9H).

**General procedure B. Mitsunobu reaction of N-Boc prolinol**

To a stirred solution of the triphenylphosphine, PPh$_3$ (2 equiv.) and Diisopropylazo dicarboxylate, DIAD (2 equiv.) in THF was added N-Boc-prolinol, 3.1 (1 equiv.). After a white precipitation was formed, a solution of alcohol (2 equiv.) in THF was added. After stirring at room temperature for 10 hours (or judged completion by TLC), the reaction mixture was diluted with Et$_2$O and filtered off solid residues. The filtrate was sequentially washed with distilled water, aqueous NaOH solution and brine. Combined organic layers were concentrated under reduced pressure. The crude was purified by column chromatography on silica gel.

**(S)-tert-butyl 2-(phenoxy methyl)pyrrolidine-1-carboxylate (3.4a)**
General procedure B described was carried out on 0.75 mmol scale, using N-Boc-prolinol, 3.1 (150 mg, 0.75 mmol), PPh₃ (393 mg, 1.5 mmol, 2 equiv.), phenol (141 mg, 1.5 mmol, 2 equiv.), DIAD (295 µL, 1.5 mmol, 2 equiv.). After stirring for 10 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless oil (90 mg, 43%) which was used to yield 3.5a after checking counts of hydrogens that were in agreement of the integration of hydrogens in $^1$H NMR spectrum. $^1$H NMR (300 MHz, CDCl₃) δ (ppm) 7.27 (t, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 3H), 4.13 (br, s, 2H), 3.85 (d, J = 4.6 Hz, 1H), 3.40 (br, s, 2H), 2.06-1.85 (m, 4H), 1.47 (s, 9H).

**(S)-tert-butyl 2-((perfluorophenoxy)methyl)pyrrolidine-1-carboxylate (3.4b)**

![Chemical Structure](image)

General procedure B described was carried out on 0.75 mmol scale, using N-Boc-prolinol, 3.1 (150 mg, 0.75 mmol), PPh₃ (393 mg, 1.5 mmol, 2 equiv.), 2,3,4,5,6-pentafluoro-phenol (276 mg, 1.5 mmol, 2 equiv.), DIAD (295 µL, 1.5 mmol, 2 equiv.). After stirring for 10 hours, the reaction mixture was worked up as described above. The residue was purified by flash chromatography on silica (5% EtOAc in n-pentane) yielding the title compound as a colorless oil (229 mg, 43%) which was used to yield 3.5b after checking counts of hydrogens that were in agreement with the integration of hydrogens in $^1$H NMR spectrum. $^1$H NMR (300 MHz, CDCl₃) δ (ppm) 4.25 (br, s, 1H), 4.00 (br, s, 2H), 3.37 (br, s, 2H), 2.12-1.88 (m, 4H), 1.43 (s, 9H).

**General procedure C. Removal of tert-butyl carbonate from N-Boc derivatives**

![Chloroformyl Derivative](image)

The N-Boc derivative is dissolved in a 1:1 mixture of trifluoroacetic acid and CH₂Cl₂ (0.2M). After the solution was stirring for 11 h at room temperature, the reaction mixture was diluted
with ethyl acetate and concentrated in vacuo under heating (50 °C) for 15 minutes. If the solid was not formed, excess of trifluoroacetic acid residual may be removed through dilution with ethyl acetate and concentration of the solution in vacuo.

(S)-2-((benzoyloxy)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.3a)

General procedure C described was carried out on 1.30 mmol scale, using 3.2a (398 mg, 1.30 mmol), trifluoroacetic acid (6.5 mL) and CH₂Cl₂ (6.5 mL). After stirring for 11 hours, the reaction mixture was worked up as described above yielding the title compound as a colorless solid (344 mg, 83%). M.p. = 98 – 100 °C (CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 10.52 (br, s, 1H), 9.56 (br, s, 1H), 8.02 (d, J = 7.5 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.8 Hz, 2H), 4.59-4.46 (m, 2H), 3.91 (br, s, 1H), 3.22 (d, J = 9.8 Hz, 2H), 2.22-1.84 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 166.0, 133.7, 130.0, 129.2, 128.7, 63.2, 58.7, 45.4, 45.4, 27.5, 23.8; IR (cm⁻¹, solid) 2964 (w, br), 2786 (w, br), 2535 (w, br); HRMS (ESI, M-C₂F₃O₂) calcd for C₁₂H₁₆NO₂: 206.1175, found 206.1185.

(S)-2-(((perfluorobenzoyl)oxy)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.3b)

General procedure C described was carried out on 2.63 mmol scale, using 3.2b (1.04 g, 2.63 mmol), trifluoroacetic acid (13 mL) and CH₂Cl₂ (13 mL). After stirring for 11 hours, the reaction mixture was worked up as described above yielding the title compound as a colorless solid (818 mg, 76%). M.p. = 95 – 97 °C (CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 10.27 (br, s, 1H), 9.82 (br, s, 1H), 4.77 (dd, J = 3.6, 3.3 Hz, 1H), 4.53 (dd, J = 12.6, 6Hz, 1H), 3.94-3.92 (m, 1H), 3.42 (m, 2H), 2.27-1.98 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 162.7, 162.3, 159.0, 159.0, 158.8, 64.1, 58.1, 45.7, 27.0, 24.0; IR (cm⁻¹, solid) 2968 (w, br), 2787 (w, br), 2465 (w,
br), 1732 (s), 1662 (s), 1495 (s); HRMS (ESI, M-C$_2$F$_3$O$_2$) calcd for C$_{12}$H$_{11}$N O$_2$F$_5$: 296.0704, found 296.0718.

(S)-2-(((3,5-dinitrobenzoyl)oxy)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.3c)

![Chemical structure of (S)-2-(((3,5-dinitrobenzoyl)oxy)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate](image)

General procedure C described was carried out on 0.64 mmol scale, using 3.2c (252 mg, 0.64 mmol), trifluoroacetic acid (3.2 mL) and CH$_2$Cl$_2$ (3.2 mL). After stirring for 11 hours, the reaction mixture was worked up as described above yielding the title compound as a colorless solid (259 mg, >99%). M.p. = 154 – 157 °C (CH$_2$Cl$_2$). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 10.40 (br, s, 1H), 9.86 (br, s, 1H), 9.20 (t, J = 2.1 Hz, 1H), 9.15 (d, J = 2.1 Hz, 2H), 4.85 (dd, J = 3.3, 3 Hz, 1H), 4.62 (dd, J = 8.1, 7.8 Hz, 1H), 4.02 (br, s, 1H), 3.43 (br, s, 2H), 2.35-1.94 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 162.6, 148.8, 133.0, 129.3, 122.9, 64.4, 58.6, 45.5, 26.9, 23.6; IR (cm$^{-1}$, solid) 2979 (w, br), 2788 (w, br), 2533 (w, br), 1717 (m), 1436 (s); HRMS (ESI, M-C$_2$F$_3$O$_2$) calcd for C$_{12}$H$_{14}$N$_3$O$_6$: 296.0698, found 296.0513.

(S)-2-(phenoxy)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.5a)

![Chemical structure of (S)-2-(phenoxy)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate](image)

General procedure C described was carried out on 0.29 mmol scale, using 3.4a (81 mg, 0.29 mmol), trifluoroacetic acid (1.5 mL) and CH$_2$Cl$_2$ (1.5 mL). After stirring for 11 hours, the reaction mixture was worked up as described above yielding the title compound as a yellow oil (81 mg, 95%). $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) 9.98 (br, s, 1H), 8.98 (br, s, 1H), 7.25 (t, 2H, J = 4.8 Hz), 6.96 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 2H), 4.11 (d, J = 4.8 Hz, 2H), 3.90 (br, s, 1H), 3.22 (br, s, 2H), 2.15-1.88 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm) 157.9, 129.8, 122.0, 114.8, 66.4, 59.0, 45.7, 26.9, 23.9; IR (cm$^{-1}$, solid) 2958 (w, br), 2588 (w, br), 1670 (m), 1481 (s); HRMS (ESI, M-C$_2$F$_3$O$_2$) calcd for C$_{11}$H$_{16}$N$_3$O: 178.1214, found 178.1202.
(S)-2-((perfluorophenoxy)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3.5b)

General procedure C described was carried out on 0.60 mmol scale, using 3.4b (220 mg, 0.60 mmol), trifluoroacetic acid (3 mL) and CH₂Cl₂ (3 mL). After stirring for 11 hours, the reaction mixture was worked up as described above yielding the title compound as a colorless solid (194 mg, 85%). M.p. = 58 – 62 °C (CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 10.4 (br, s, 1H), 9.80 (br, s, 1H), 4.49 (dd, J = 10.5, 4.2 Hz, 1H), 4.40 (dd, J = 10.5, 6.93 Hz, 1H), 4.00 (br, s, 1H), 3.39 (br, s, 2H), 2.30-1.93 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 162.8, 73.8, 58.7, 45.9, 27.0, 24.2; IR (cm⁻¹, solid) 2963 (w, br), 2533 (w, br), 2533 (w, br), 1659 (m), 1461 (s); HRMS (ESI, M-C₂F₃O₂) calcd for C₁₁H₁₁F₅N: 268.1877, found 268.1154.

4-Hydroxy-4-(4-nitrophenyl)butan-2-one

To a solution of anhydrous acetone (1.25 mL) was added the corresponding p-nitrobenzaldehyde (38 mg, 0.25 mmol) followed by L-proline (10 mg, 35 mol %) and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was treated with saturated ammonium chloride solution, the layers were separated. The aqueous layer was extracted several times with ethyl acetate, dried (MgSO₄) and evaporated. The pure aldol products were obtained by flash column chromatography on silica gel (10% EtOAc in n-pentane). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.20 (d, J = 7 Hz, 2H), 7.52 (d, J = 7 Hz, 2H), 5.25 (m, 1H), 3.56 (d, J = 3.2 Hz, 1H), 2.83 (m, 2H), 2.21 (s, 3H). Characterization data were in agreement with literature values.¹⁷

(E)-4-(4-nitrophenyl)but-3-en-2-one
To a solution of anhydrous acetone (0.5 mL) was added the corresponding p-nitrobenzaldehyde (15 mg, 0.10 mmol) followed by 3.3a (10 mg, 35 mol %) and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was treated with saturated ammonium chloride solution, the layers were separated. The aqueous layer was extracted several times with ethyl acetate, dried (MgSO₄) and evaporated. The pure aldol products were obtained by flash column chromatography on silica gel (10% EtOAc in n-pentane), yielding the title compound (9.7 mg, 51%). ¹H NMR (400 MHz, CDCl₃): δ (ppm) 8.26 (d, J = 8.9 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 16.3 Hz, 1H), 6.82 (d, J = 16.3 Hz, 1H), 2.42 (s, 3H). Characterization data were in agreement with literature values.¹⁹

5-Nitro-4-phenylpentan-2-one

To a solution of β-NO₂ styrene (15 mg, 1 mmol) in anhydrous MeOH (0.5 mL) was added the acetone (73 µL, 1 mmol) and DL-proline (23 mg, 0.02 mmol, 20 mol %) and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was treated with saturated ammonium chloride solution, the layers were separated. The aqueous layer was extracted several times with ethyl acetate, dried (MgSO₄), and evaporated. The pure products (7.2 mg, 35%) were obtained by flash column chromatography on silica gel (50% EtOAc in n-pentane). ¹H NMR (300 MHz, CDCl₃): δ 7.36-7.20 (m, 5H), 4.73-4.57 (m, 2H), 4.03 (q, J = 7.2 Hz, 1H), 2.92 (d, J = 6.9 Hz, 2H), 2.12 (s, 3H). Characterization data were in agreement with literature values.²⁰

Trans-2-(2-nitro-1-phenylethyl)pentanal
To a solution of $\beta$-NO$_2$ styrene (112 mg, 0.75 mmol, 1.5 equiv.) in anhydrous toluene (2.5 mL) was added the valeraldehyde (53 µL, 0.5 mmol) and diethylamine (10 µL, 0.1 mmol, 20 mol %) and the resulting mixture was stirred at 80 °C for 24 h. The reaction mixture was treated with saturated ammonium chloride solution, the layers were separated. The aqueous layer was extracted several times with ethyl acetate, dried (MgSO$_4$), and evaporated. The pure products (52 mg, syn/anti = 1.13:1, 44%) were obtained by flash column chromatography on silica gel (10% EtOAc in $n$-pentane). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 9.49 (d, $J$ = 4 Hz, 1H), 7.33-7.30 (m, 3H), 7.17 (dd, $J$ = 10.8, 2.4 Hz, 2H), 4.85-4.75 (m, 2H), 3.83 (q, $J$ = 10 Hz, 1H), 2.72-2.59 (m, 1H), 1.73-1.63 (m, 1H), 1.57-1.49 (m, 1H), 1.40-1.35 (m, 2H), 0.93 (t, $J$ = 10 Hz, 3H). Characterization data were in agreement with literature values.$^{21}$

**Cis-2-(2-nitro-1-phenylethyl)pentanal**

\[
\begin{align*}
\text{Ph} & \quad \text{C}_3\text{H}_7 \\
\text{NO}_2 & \quad \text{C}_3\text{H}_7
\end{align*}
\]

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) 9.71 (d, $J$ = 3.6 Hz, 1H), 7.38-7.30 (m, 3H), 7.19 (dd, $J$ = 10.8, 2.4 Hz, 2H), 4.81-4.61 (m, 2H), 3.81-3.73 (m, 1H), 2.73-2.67 (m, 1H), 1.54-1.20 (m, 4H), 0.80 (t, $J$ = 7.2 Hz, 3H). Characterization data were in agreement with literature values.$^{21}$
Table 8. Examination of factors in Michael addition of β-nitro styrene with acetone.

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<sup>a</sup> Isolated yield is 36%
Table 9. Examination of factors in Michael addition of β-nitro styrene with valeraldehyde.

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<th>ee (syn, %)</th>
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$\alpha$ – Using 1.5 equiv. nitro styrene and isolated yield is 44%
References


Appendices

1.2a

Ph

O

Me

1.2a

Me

ppm (t1)

ppm (t1)
$\text{Ph} \quad OMe$

$\text{MeO} \quad OMe$

$\text{MeO} \quad OMe$

$\text{OMe}$

$1.2b$

$\text{ppm (t1)}$

$0 \quad 50 \quad 100 \quad 150 \quad 200$

$1.2b$

$\text{Ph} \quad OMe$

$\text{MeO} \quad OMe$

$\text{MeO} \quad OMe$

$\text{OMe}$

$\text{ppm (t1)}$

$0 \quad 200 \quad 150 \quad 100 \quad 50 \quad 0$
1.2g
$ppm_{(t1)}$

1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 1.5

$N$

$O$
1.5b
d.r. = 1.4:1

1.8c
d.r. = 1.1:1

1.10a
d.r. = 1.7:1

Major diastereomer
d.r. = 1.7:1

1.10 b
$\beta/\alpha = 62:38$

1.19
2.3I
2.3 m

2.3 m
2.3n

ppm (t1)

2.3n

ppm (t1)
2.4a

MeO

O

$\text{O PhMeO CO}_2\text{MeMeO}_2\text{C}$

ppm (t1)
3.3a
3.5a

ppm (t1)

3.5a

ppm (t1)
(±)-Proline catalyzed Michael reaction of β-NO₂ styrene with acetone

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### 3.3b catalyzed Michael reaction of β-NO₂ styrene with acetone in THF

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### HNEt₂ mediated syn Michael reaction of β-NO₂ styrene with valeraldehyde in toluene

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HNEt$_2$ mediated syn Michael reaction of β-NO$_2$ styrene with valeraldehyde in toluene

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### 3.3b catalyzed syn Michael reaction of β-NO₂ styrene with valeraldehyde in DCM

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### 3.3b catalyzed anti Michael reaction of β-NO₂ styrene with valeraldehyde in DCM

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Copyright Acknowledgements

The work presented in this thesis was conducted by the author under the supervision of Professor Mark S. Taylor in the Department of Chemistry at University of Toronto.

The following is a list of new compounds prepared using new methodology in the course of this work: 1.2a-h, 1.3a-f, 1.5a-h, 1.8a-d, 1.10a, 1.10b, 2.3a-p.

The following is a list of new catalysts prepared to investigate anion-π interactions in asymmetric organocatalysis: 3.3a-c, 3.5a, 3.5b.