Title
STUDIES CONCERNING NUCLEOPHILIC PHOSPHINE CATALYSIS AND DESIGNS OF NEW CHIRAL AMINOPHOSPHINES TOWARD ASYMMETRIC PHOSPHINE-CATALYzed REACTIONS

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Studies Concerning Nucleophilic Phosphine Catalysis and Designs of new Chiral Aminophosphines toward Asymmetric Phosphine-Catalyzed Reactions

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

San Ngoc Khong

2013
ABSTRACT OF THE DISSERTATION

Studies Concerning Nucleophilic Phosphine Catalysis and Designs of new Chiral Aminophosphines toward Asymmetric Phosphine-Catalyzed Reactions

by

San Ngoc Khong

Doctor of Philosophy in Chemistry
University of California, Los Angeles, 2013

Phosphinocatalysis has been used among us as a short term for nucleophilic phosphine catalysis. The information in chapter 1 will focus on how phosphinocatalysis was discovered, who contributed to the early-day developments of this field, and what have been achieved in the field. Chapter 2 will cover phosphine–allene chemistry in which the equilibrium between phosphonium dienolate and vinylogous ylide was reaffirmed. Two new phosphine-mediated transformations were discovered in this chemistry: vinylogous aldol/P-to-C aryl migration by reaction of phosphonium dienolate
with an aromatic aldehyde and vinylogous Wittig olefination by reaction of vinylogous ylide with an aromatic aldehyde. Chapter 3 will discuss the development of a one-pot procedure for phosphine-initiated general base-catalyzed quinoline synthesis and of its variation to quinolone synthesis. A number of 3-substituted and 3,4-disubstituted quinolines, as well as 3-substituted 4-quinolones have been generated from this methodology. Chapter 4 involves the designs of new chiral aminophosphines toward the asymmetric version of phosphine-catalyzed double Michael reaction. The aminophosphines were particularly designed based on the presumption that the anchimeric assistance of the amino group onto the phosphonium phosphorous was essentially significant to the reaction’s success. The chiral element was designed to be on the amino group, which would endow the asymmetric environment to the reactive center via anchimeric assistance during the reaction. A small collection of chiral aminophosphines were eventually prepared based on this design. Chapter 5 was an extension on the design of chiral aminophosphines. However, the new design of chiral aminophosphines was not based on any specific asymmetric chemical transformations. This design was centered on the steric-directing mode of asymmetric induction and then would be tested toward various phosphinocatalysis reactions.
The dissertation of San Ngoc Khong is approved.

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Leonard H. Rome

Yves F. Rubin

Ohyun Kwon, Committee Chair

University of California, Los Angeles

2013
To my parents, my wife, and my children
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Publications and Presentations


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This dissertation would absolutely not be possible without the support, love and encouragement from my family. I am endlessly indebted to my parents for their unconditional support and love. Whichever path that I have chosen, I could feel that they were there with me. I want to give many thanks to my sisters and brothers, who have been always listening to me and constantly providing support and encouragement. Marrying my wife, Uyen Dinh, was definitely the best decision that I have ever made in my life. I am extremely grateful for having Uyen by my side and immeasurably thankful to her for giving births to my adorable daughter, Quynh Khong, and my cute little son, Khang Khong. I am indefinitely grateful to God for sending them to my life, who have made my life so colorful. Their love to me and the happy family time have given me strength and motivation to get through my graduate school. I want to give special thanks to my wife, who has been caring for me with delicious home-cooked food and to my kids, who have been bringing joys and laughs to my life. Finally, I would like to express my deep gratitude to every single one in my family for support and love and for walking with me through every single step in my graduate career.
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CHAPTER ONE

History of Phosphine and Phosphinocatalysis

1.1. Introduction

Phosphinocatalysis, also known as nucleophilic phosphine catalysis, has emerged in the past decade as a powerful tool in organic synthesis. In particular, recent years have witnessed explosive growth in the number of new phosphine-catalyzed reactions and their asymmetric variations.\(^1\) Since the initial disclosure of the allene–imine [4 + 2] annulation, our group has been actively engaged in uncovering new reaction modalities in phosphinocatalysis.\(^2\) Understanding the previously reported reactivity patterns of phosphinocatalysis is an essential part of designing new reactions, which instigated us to launch an in-depth search into literature. The search finally unveiled fascinating details that, as far as we are aware, have not been acknowledged previously by the phosphinocatalysis community, and we feel thrilled to share such details with the chemistry community.

The classical nucleophilic phosphine-catalyzed reactions that are regularly mentioned as representative examples are the Rauhut–Currier (RC) and Morita–Baylis–Hillman (MBH) reactions. The broad scope and general applicability of these two reactions have undoubtedly contributed to the significant attention that they have garnered from synthetic chemists. This focus has, however, overshadowed other active research into the nucleophilic behavior of tertiary phosphines—including studies that were performed prior to and contemporaneously with the invention of the RC and MBH
reactions. Herein, we shine a light on other early and important contributions that led to expansion of the field of nucleophilic additions of phosphines to activated olefins.

1.2 Discovery of Tertiary Phosphines

The first tertiary phosphine, trimethylphosphine, was synthesized, isolated and reported in 1847 by Paul Thénard from the reaction between methyl chloride and calcium phosphide at high temperature.\textsuperscript{3} Later, triethylphosphine was also synthesized by the same process and briefly disclosed by the same author. Surprisingly, trimethylphosphine and triethylphosphine were discovered before aliphatic amines were made, and they received much less attention than they should have deserved at the time of publication. Numerous obstacles and dangers in the preparation of these phosphines rendered the researches on them incomplete. Fortunately, the subsequent discovery and extensive studies of amines by Hofmann and Cahours established a connection between amines and phosphines that revived the field of phosphine. A decade after Thénard abandoned his studies on phosphines, Hofmann and Cahours reported a new preparation of trimethylphosphine and triethylphosphine with easy isolation at perfect purity from the reaction between methyl or ethyl zinc and phosphorous trichloride.\textsuperscript{4}
1.3 Nucleophilic Addition of Tertiary Phosphines to Carbon-Centered Electrophiles: Structural Determination

1.3.1 1,2-Addition to Carbon Disulfide

A few years later, in 1860 the first nucleophilic addition of a tertiary phosphine, specifically triethylphosphine, to a carbon-centered electrophile, namely carbon disulfide, was carried out by Hofmann. Triethylphosphine was considered, by Hofmann, as the most sensitive reagent to carbon disulfide, for it reacted instantly to form a beautiful red crystalline adduct at the ratio of 1:1 with carbon disulfide. Triethylphosphine was also useful to test the presence of and estimate the minute quantity of carbon disulfide in coal gas. Nevertheless, the structure of the red crystalline adduct was not determined but surmised as phosphinyl dithioester 1 by Hofmann (Figure 1.3.1). In 1907, Hantzsch reasoned that phosphorous, unlike nitrogen, was able to make five covalent bonds, hence proposed the pentavalent phosphorous cyclic adduct 2 as the product of triethylphosphine to carbon disulfide. Davies, however, argued that it was “difficult to assign a space structure” to the pentavalent phosphorus atom in a strained thiaphosphiranethione ring and alternatively suggested inner-salt 3 as the structure of the adduct formed between an dialkylarylphosphine and carbon disulfide, which was later verified by X-ray crystallography in 1961.
1.3.2 Addition to p-Benzophenones and Similar Systems

1.3.2.1 1,2-Addition and Schönberg’s P-to-O Addition

Believing that the mode of phosphine addition to carbon disulfide would apply to other similar electrophilic systems, Davies assigned structure 4 to the adducts of p-benzoquinone with triethylphosphine, tributylphosphine, and dimethyl(p-tolyl)phosphine (Figure 1.3.2). In the following year, Schönberg revised the adduct between triphenylphosphine and p-benzoquinone to structure 5, which was later known as “Schönberg adduct,” based on the fact that its hydrolysis in NaOH solution produced dihydroquinone and triphenylphosphine oxide. In addition to p-benzoquinone, maleic anhydride (and some of its substituted derivatives) also exhibited similar reactivity toward triphenylphosphine, forming an adduct assigned to structure 6. Schönberg reported that addition of as little as a single crystal of maleic anhydride or p-benzoquinone into a dilute solution of triphenylphosphine in chloroform immediately provided an orange-red or reddish brown solution, respectively. Although these processes were characterized as “sensitive color reactions,” the crystalline “Schönberg adduct” was almost colorless, and the major amorphous solid responsible for the color of the reaction was not identifiable.
1.3.2.2 Proof of 1,4-Addition by Ramirez

In 1956, Ramirez investigated triphenylphosphine addition to \( p \)-benzoquinones and reported that while \( p \)-chloranil formed only Schönberg adduct and 2,5-dichloro-\( p \)-benzoquinone formed a mixture of Schönberg adduct and the 1,4-conjugate addition product, \( p \)-benzoquinone itself exclusively provided 1,4-addition product 7 (Figure 1.3.2).\(^{14}\) Knowing the fact that an all-carbon quaternary phosphonium species would generate phosphine oxide upon alkaline hydrolysis,\(^ {15}\) Ramirez believed that hydrolysis of the “Schönberg adduct” in aqueous NaOH insufficiently support the structure 5. Structural reassignment thus resulted in the 1,4-conjugate addition product 7 (after aromatization). To support the new structure, Ramirez proved the absence of a P–O bond in the structure by observing alkylation of the free phenolic hydroxyl groups. Indeed, when the phosphonium adduct 7 was treated sequentially with an excess of ethyl iodide and then subjected to hydrolysis in NaOH solution, the hydrolytic products contained, as expected, hydroquinone diethyl ether (9) and triphenylphosphine oxide (Scheme 1.3.1).\(^ {14}\)
1.3.2.3 Proof of 1,4-Addition by Horner

Horner, on the other hand, employed a more direct approach by comparing the hydroiodide salt of the phosphonium species 7 (the phosphonium iodide 12) with another sample of 12 prepared in an alternative route. In 1958, Horner made (2,5-dimethoxyphenyl)triphenylphosphonium iodide (11) from 2,5-dimethoxyphenyl bromide (10) employing his “cobalt salt method”\(^\text{16}\) for radical arylation of triphenylphosphine (Scheme 1.3.2).\(^\text{17}\) Global methyl deprotection of intermediate 11, followed by treatment with sodium iodide, resulted in phosphonium iodide 12, which exhibited identical IR spectrum to that of the iodide salt prepared through treatment of the phosphonium species 7 with hydroiodide. This experiment unambiguously confirmed, again, the structure 7 of the adduct between a phosphine and \(p\)-benzoquinone.

\[\text{Scheme 1.3.2}\]
1.3.3 Schönberg’s Adducts

Although Schönberg adduct was proved incorrect, by Ramirez and Horner, in the case of triphenylphosphine and \( p \)-benzoquinone,\(^{14,17} \) it was correct in some other cases. In 1955, Horner investigated the addition of triphenylphosphine to \( o \)-benzoquinone and \( o \)-chloranil and arrived with the structures of the corresponding Schönberg adducts 13 and 14 (Figure 1.3.3).\(^{18} \) The 1:1 adduct 13 of triphenylphosphine and \( o \)-benzoquinone, however, had not been isolated for full characterization.\(^{19} \) In the following years, Ramirez extended his investigation to study the reaction of trialkylphosphites with \( p \)-benzoquinone systems. Ramirez indicated that \( p \)-chloranil formed only Schönberg adduct with either triphenylphosphine or a phosphite (e.g. trimethylphosphite, triethylphosphite, and triphenylphosphite).\(^{20} \) While \( p \)-benzoquinone exclusively formed Horner’s 1,4-addition adduct with triphenylphosphine, it provided the Schönberg adduct with a trialkylphosphite (trimethylphosphite and triethylphosphite).\(^{21} \) Unlike the case of triphenylphosphite, the addition of trialkylphosphite to \( p \)-quinone systems did not stop at the Schönberg zwitterion adducts 15; it was followed by Arbuzov rearrangement to form dialkyl(4-alkoxyphenyl)phosphate 16.\(^{20,21} \) Another conjugated dicarbonyl system that gave the Schönberg adduct with a phosphite was presented by Kukhtin in 1958 as an \( \alpha,\beta \)-diketone.\(^{22} \) Kukhtin reacted a trialkylphosphite (such as triethylphosphite, tri-\( n \)-propylphosphite, and tri-\( n \)-butyl-phosphite) with diacetyl to first form the Schönberg adduct 17, which then underwent Arbuzov rearrangement to form dialkyl(3-alkoxybut-2-en-2-yl)phosphate 18. Mukaiyama recently disclosed a new methodology in preparing ethers and esters in which the phosphinite was activated in the form of a Schönberg adduct 19 with a \( p \)-benzoquinone system (e.g. unsubstituted \( p \)-benzoquinone, partially
substituted 2,5-dimethyl \( p \)-benzoquinone and 2,6-dimethyl \( p \)-benzoquinone, and fully substituted 2,3,5,6-tetramethyl \( p \)-benzoquinone). Followed was the formation of ether (R'OR) or ester (R'COOR) with an external reagent (R'OH or R'COOH) via Arbuzov rearrangement, together with the byproduct phosphate 20.\(^{23}\)

**Figure 1.3.3**

![Scheme of reactions](image)

**1.3.4 Other Early Phosphine-Related Discoveries**

For a better perspective on early phosphine discoveries, it would be worthwhile to mention the Michaelis–Arbuzov rearrangement. Michaelis reported the original reaction of triethylphosphate and triphenylphosphate with methyl iodide in 1898 (Scheme 1.3.4.1).\(^{24}\) In this report, triphenylphosphate reacted with methyl iodide to first form a crystalline adduct, which then generated diphenyl methylphosphonate, phenol, and hydroiodide under the action of water; whereas, triethylphosphate slowly reacted with
methyl iodide at 220 °C to release methylphosphonic acid, ethylene, and ethyl iodide. Later in 1905, Arbuzov reported the corrected version of the reactions after repeating them with pure phosphites and eventually established the venerable Michaelis–Arbuzov rearrangement.\textsuperscript{25} Triethylphosphite was reported to react easily with methyl iodide to form an unstable salt-like intermediate, which decomposed under the experimental condition into diethyl methylphosphonate and ethyl iodide. Similarly, the addition of triphenylphosphite to methyl iodide on heating would undergo the thermal decomposition to give iodobenzene and diphenyl methylphosphonate. Of other events on nucleophilic phosphine addition, Hofmann’s report\textsuperscript{5} on the addition of triethylphosphine and trimethylphosphine to phenyl isothiocyanate in 1860 and Staudinger’s report\textsuperscript{26} on the addition of triethylphosphine onto diphenylketene in 1919 constituted early examples of phosphine addition to carbon-centered electrophiles (Scheme 1.3.4.1).
1.4 Phosphinocatalysis: Early Stage

1.4.1 Horner's Adducts

The two independent studies by Ramirez and Horner confirmed that tertiary phosphines often added to \( \alpha,\beta \)-enones through 1,4-addition rather than 1,2-addition (Schönberg’s P-to-O addition would also occur in some cases). In fact, it had been known from a study by Horner a few years earlier, that tertiary phosphines react with activated olefins through 1,4-conjugate addition—a finding that may have influenced both Ramirez and Horner to consider 1,4-addition of phospine to \( \rho \)-benzoquinone. In 1955, Horner reported that a tertiary phosphine smoothly added to sufficiently
polarized olefinic bonds in a ratio of 1:1 to provide stable, crystalline zwitterionic “Horner adducts”—for example, the phosphonium zwitterions 21 and 22 (Figure 1.4.1.1).

In addition to the historical value of these first examples of phosphine 1,4-addition to conjugated systems, the resultant zwitterionic phosphonium adducts were also of significant value to synthetic chemistry.

*Figure 1.4.1.1*

1.4.2 The First Phosphine-Initiated Reaction: Polymerization

In the same year, shortly after reporting the first example of the “Horner adduct,” Horner reported the phosphine-initiated polymerization of electron-deficient olefins. For example, the polymerization of acrylonitrile was initiated through conjugate addition of triethylphosphine to acrylonitrile to generate the “Horner adduct” 23, which underwent chain elongation by adding, in a head-to-tail fashion, to additional molecules of acrylonitrile, ultimately forming the polymeric zwitterion which, after quenching with water, released the acrylonitrile polymer 25 (Scheme 1.4.2.1). That study revealed the remarkable potential of “Horner adducts” as reactive intermediates to form new C–C bonds. Accordingly, in 1961 Ford attempted to perform α-methylation of preformed phosphonium malononitrile Horner adducts 26 with methyl iodide in methanol; these reactions failed, however, to generate the new C–C bonds, instead regenerating the aryldinemalononitriles 27 through β-elimination of tributylphosphine.
1.4.3 First Phosphinocatalysis: Hexamerization of Acrylonitrile

In 1962, Price reported a novel hexamerization of acrylonitrile catalyzed by triphenylphosphine (Scheme 1.4.3.1)\(^\text{30}\)—the first time a tertiary phosphine had been employed to catalyze a reaction. To explain the formation of the unexpected hexameric adduct 32, Price proposed, for the first time, interconversion of the phosphonium zwitterion 28 and the phosphonium ylide 29 through proton transfer in the protic solvent ethanol. The addition of the phosphonium ylide 29 to another molecule of acrylonitrile, he suggested, led to the tail-to-tail dimer 31, based on the fact that this dimer, when prepared independently, could be converted to the hexameric product 32 in a solution of acrylonitrile in tert-butyl alcohol featuring a catalytic quantity of triphenylphosphine. Although the structure of the hexameric product 32 was assigned correctly with the support of X-ray crystallographic data,\(^\text{31}\) the structure of the dimeric precursor 31 was assigned incorrectly. The correct structure was later put forth by Baizer and Anderson (see 1.4.3).
1.5 Phosphinocatalysis: Development Stage

A number of reactions utilizing nucleophilic phosphine catalysis have been independently studied and developed. Depending on the reaction condition, either phosphonium zwitterion 33 or phosphonium ylide 34, or both, would be selected to react and lead to different transformations (Scheme 1.5.1).
Scheme 1.5.1

1.5.1 Rauhut-Currier Reaction

The year 1963 saw the arrival of the venerable Rauhut–Currier dimerization of alkyl acrylates catalyzed by trialkylphosphines (Scheme 1.5.1).\textsuperscript{32} Although it was not the first report of a nucleophilic phosphine-catalyzed reaction, it could be considered as the first successful example of the trapping of the zwitterionic Horner adduct to form a new C–C bond in a controlled manner (unlike the multiple bonds formed in Horner's polymerization).
1.5.2 Oda Reaction

In the following year, Oda successfully trapped the phosphonium ylide 34 in Wittig reactions with aldehydes, validating the existence of the phosphonium ylide that Price had initially suggested (Scheme 1.5.1). Price had assumed that the formation of the phosphonium ylide 34 was facilitated by the protic solvent (ethanol); a protic solvent was, however, not necessary: the product yields for Oda’s olefination were comparable in the presence or absence of an alcoholic solvent. One other significant feature of Oda’s reaction was that the Wittig reaction was performed with the ylide generated in situ directly from triphenylphosphine and the activated olefin.

1.5.3 McClure–Baizer–Anderson Reaction

Baizer and Anderson found in 1965 that the structure of the dimeric intermediate proposed in Price’s work had been misassigned; they reassigned the dimer to its regioisomer, which also led to the same product as Price’s hexamer under the influence of catalytic triphenylphosphine (Scheme 1.5.1). Later that same year, a patent was issued to McClure for developing conditions for the synthesis of this new dimer. The McClure–Baizer–Anderson (MBA) reaction differs mechanistically from the RC reaction only at the entering nucleophile: it begins with the ylide 34, whereas the RC reaction begins with the phosphonium zwitterion 33. The endgames of both reactions are identical, with elimination of the phosphine to release the dimeric product being preceded by deprotonation (through proton transfer) α to the electron-withdrawing group. Notably, the tail-to-tail MBA dimerization remains underutilized, mainly because of poor yields resulting from the competing RC reaction in the same pot; in contrast, the
head-to-tail dimerization through the RC reaction has been adopted widely by the synthesis community.  

1.5.4 Morita Reaction

In 1968, Morita reported the union of alkyl acrylates and aldehydes in the presence of a catalytic amount of tricyclohexylphosphine—a transformation that is now widely recognized as the Morita–Baylis–Hillman reaction (Schem 1.5.1). Unlike Oda’s reaction, Morita could successfully trap the phosphonium enolate 33 with aldehydes, facilitating the eventual catalysis. Morita suggested that the equilibrium between the phosphonium zwitterion 33 and the phosphonium ylide 34 favored the latter when using the relatively electron-deficient triphenylphosphine and favored the former when using relatively electron-rich trialkylphosphines. In fact, both MBH and RC reactions occurred when employing the trialkylphosphine-derived phosphonium zwitterion 33 as the reactive intermediate, while MBA and Oda’s reactions resulted when the triphenylphosphine-derived phosphonium ylide 34 was the reactive intermediate.

1.5.5 Winterfeldt Reaction: First Phosphine-Catalyzed Annulation

The year 1966 was marked by the first nucleophilic phosphine-catalyzed union of two different species of molecules. In Winterfeldt’s annulation, a fully substituted lactone was produced by mixing dimethyl acetylenedicarboxylate (DMAD), benzaldehyde, and a substoichiometric amount of triphenylphosphine in dioxane (Scheme 1.5.5.1). Unfortunately, the triphenylphosphine-catalyzed formation of the lactone 39 from DMAD was reported merely as an isolated example of applying DMAD in heterocycle
syntheses and was not widely considered as a new phosphine-catalyzed reaction for further development.

Scheme 1.5.5.1

1.6 Phosphinocatalysis: Current Development

1.6.1 Michael Addition

Phosphinocatalysis was also featured in Michael addition and gamma-umpolung addition that were developed in the early 1970s and 1990s, respectively. In 1973, White and Baizer at Monsanto reported that a weak base such as tertiary phosphine was able to catalyze the Michael addition of a carbon-centered pronucleophile to an activated olefin—a strong base was normally required to catalyze this type of reaction.\(^{39}\) In particular, tributylphosphine was found as an effective catalyst for the Michael reaction between 2-nitropropane and ethyl acrylate (Scheme 1.6.1.1). Besides, Michael reaction was also observed for other pronucleophiles (e.g., nitromethane, dimethyl malonate, diphenylacetonitrile, and acetylacetone) and other activated olefins (e.g., methyl vinyl ketone, acrylo-, crotono-, and methacrylonitrile). It was suggested that the strong base was indeed generated in situ from the nucleophilic addition of phosphine onto the activated olefin. This strong base would then activated the carbon-centered pronucleophile (at acidic carbon) via deprotonation. The Michael addition of the
resultant nucleophile onto the activated olefin led to another strong base, which in turn deprotonated another pronucleophile and released the Michael adduct. Three decades later, Bergman and Toste studied a similar trimethylphosphine-catalyzed Michael reaction of oxygen nucleophiles (water and alcohols) to a variety of activated olefins.\(^{40}\) Investigation on the reaction mechanism further verified White and Baizer’s reaction mechanism in which the phosphonium zwitterion generated in situ from the addition of phosphine to the activated olefin acted as a strong base to drive the reaction. In 1993, Inanaga showed that phosphines (e.g. tributylphosphine and triphenylphosphine) could efficiently catalyze the Michael addition of aliphatic alcohols onto methyl propiolate to afford methyl 3-alkoxyacrylates (Scheme 1.6.1.1).\(^{41}\) In this reaction, Inanaga suggested that phosphine was the active form of catalyst and was regenerated through the catalytic cycle and that the phosphonium zwitterion activated the pronucleophile and participated in bond formation via addition/elimination.

**Scheme 1.6.1.1**

![Diagram of the Michael reaction catalyzed by phosphines.](image)
1.6.2 γ-Umpolung Addition

Phosphine-catalyzed γ-umpolung addition of nucleophiles onto γ-carbon of 2-butynoates was first reported by Trost in 1994. Trost disclosed that triphenylphosphine at a correct pH would effectively facilitate the novel “umpolung” electrophilicity at γ-carbon of 2-butynoates. For example, dimethyl malonate was able to perform umpolung addition to γ-carbon of 2-butynoates in the presence of a catalytic amount of triphenylphosphine and a stoichiometric amount of the buffer NaOAc/HOAc at reflux (Scheme 1.6.2.1). In 1995, Lu employed 2,3-allenoates for the reaction with a nucleophile in the presence of a catalytic amount of triphenylphosphine. Another γ-umpolung addition of dimethyl malonate was observed at γ-carbon of 2,3-allenoate for this reaction system. The product from Trost’s and Lu’s reactions, for examples shown in Scheme 1.6.2.1, were identical because the interaction of either 2-butynoate or 2,3-dienolate with triphenylphosphine would lead to the same vinylphosphonium intermediate A.

Scheme 1.6.2.1
1.6.3 Annulation of Allenes

Despite the sporadic yet steady stream of discoveries, phosphinocatalysis reactions remained as novelty rather than an established field of studies. Why is it then only in the past decade that we have witnessed the surge in nucleophilic phosphinocatalysis? Our hypothesis is that the upsurge came from the incorporation of new electrophiles featuring carbon–carbon multiple bonds—namely, allenoates—\(^44\) that allowed annulation reactions to be performed. Although Winterfeldt’s DMAD-aldehyde annulation had been reported even before the Morita reaction, DMAD as a building block does not leave a room for structural variation to allow exploration of different reactivity patterns. One of the most amazing features of phosphinocatalysis is the wide structural diversity in the dizzying array of annulation products stemming from the many newly developed reactions. The first phosphine-catalyzed annulation of an allenoate was Lu’s \([3 + 2]\) process, reported in 1995 (Scheme 1.6.3.1).\(^45\) Still, it went relatively unnoticed until in 2003,\(^46\) when we reported our first allene–imine \([4 + 2]\) annulation illustrating that allene can act as a plastic core for allowing different reaction patterns.\(^2\) In an effort to expand Lu’s \([3 + 2]\) annulation to the union of an allene and an aldehyde, we also unearthed three different allene–aldehyde annulations, further demonstrating that multiple reaction pathways are available to even a single combination of starting materials.\(^47\) Looking back, such discoveries mirror those from the 1960s—diversity in reaction modalities is the hallmark of nucleophilic phosphinocatalysis. Remarkable advances have also been made in enantioselective phosphinocatalysis, especially in the development of chiral phosphines designed specifically for organocatalysis, but that would be a topic for another perspective.\(^48\)
1.7 Conclusion

For today's chemists it is often easy to disregard or take for granted matters that were once the subject of intense debate. While the histories of some scientific debates, such as the structural assignment of benzene, are well known and even taught in undergraduate chemistry courses, many have not been addressed satisfactorily, even by active practitioners in those specific fields. The historical debate evolving around the preferential 1,4-addition over 1,2-addition of tertiary phosphines to $\alpha,\beta$-unsaturated carbonyl systems is one such example. The conjugate addition of phosphines to $\alpha,\beta$-unsaturated carbonyl systems is casually employed in the current literature of nucleophilic phosphinocatalysis, yet it took more than 20 years to conclude that 1,4-addition of triphenylphosphine occurred to the conjugated system of $p$-benzoquinone. Furthermore, Horner’s contributions—reporting the first conjugate addition products formed between tertiary phosphines and activated olefins and using the “Horner adduct” in polymerization—have not been widely acknowledged, nor has Price’s first proposal of the phosphonium “Horner adduct” undergoing interconversion, through proton transfer, into a phosphonium ylide to explain the unusual formation of the acrylonitrile hexamer.
These findings laid the conceptual and experimental foundations for the development of many subsequent reactions—namely the RC, MBH, MBA, and Oda reactions.

Understanding the history of a specific field is always essential and valuable to those seeking to innovate within it. With the current resurgence of nucleophilic phosphine-catalyzed and -mediated reactions, the lessons in this perspective should be relevant and, hopefully, will guide continuing innovations in the development of nucleophilic phosphinocatalysis.

1.8 Notes and References


(46) By the end of 2002, reference 21 had been cited 29 times. Today, Lu’s 1995 report has 210+ citations.


CHAPTER TWO

Equilibrium between a Vinylogous Ylide and a Phosphonium Dienolate Zwitterion: Vinylogous Wittig Olefination versus Vinylogous Aldol-Type Reaction

2.1 Background

2.1.1 Equilibrium between Enolate and Ylide

In 1962, Takashina and Price, while studying the nucleophilic polymerization of electron-poor olefins,\(^1\) reported the formation of a crystalline hexameric adduct of acrylonitrile when they used triphenylphosphine as a catalyst in alcoholic solvents.\(^2\) Because the same product could be prepared through the reaction of 1,4-dicyano-trans-2-butene with acrylonitrile in the presence of a base, the initial dimerization of acrylonitrile to 1,4-dicyano-trans-2-butene was proposed as the key step (Scheme 2.1.1.1).

Scheme 2.1.1.1

![Scheme 2.1.1.1](image)

This head-to-head dimerization would, however, be a very unlikely event in conventional base-catalyzed polymerization. Consequently, Price invoked the formation of an ylide intermediate B from the immediate zwitterionic intermediate A to explain the reaction sequence of acrylonitrile hexamerization (Scheme 2.1.1.2).
2.1.2 Enolate and Ylide in Reactions

Shortly after the proposal of the ylide B as an alternative intermediate from zwitterion A, Rauhut and Currier successfully trapped the enolate A (E = CO$_2$R) in the synthesis of dialkyl 2-methyleneglutarates from alkyl acrylates when using tributylphosphine as the nucleophilic catalyst (Scheme 2.1.1.2). In the following year (1964), Oda and coworkers succeeded in trapping ylide B with an aromatic aldehyde, using triphenylphosphine as the nucleophilic trigger in alcoholic solvents. The resulting transformation was a Wittig olefination. Although not catalytic with respect to the phosphine, this transformation was the first phosphine-mediated reaction between an olefin and an aldehyde. One interesting feature in Oda’s experiment was that the ylide was generated in situ directly from a phosphine and an activated olefin in the presence of an aldehyde, rather than from a preformed phosphonium salt. In 1968, Morita and
coworkers reacted the enolate A with an aldehyde, creating a novel aldol-type product. Credit was granted to Morita, together with Baylis and Hillman, for efficiently trapping the enolate A in the first phosphine-catalyzed aldol-type reaction. Notably, electron-donating trialkylphosphines preferred forming (and/or facilitated the reactions of) intermediate A, whereas electron-poor triarylphosphines favored the ylide intermediate B. In addition, alcoholic solvents would facilitate the conversion of the enolate A to the ylide B via proton transfer, as suggested by Price. In contrast, it was later proved by Oda that the alcoholic solvent was unnecessary for such conversion.

2.1.3 Equilibrium between Dienolate and Vinylogous Ylide

While the Morita–Baylis–Hillman (MBH)–type of reaction modality has continued to garner attention from the organic synthesis community, especially during the last two decades, the intricate equilibrium between the phosphonium enolate A and ylide B or reactions proceeding through the ylide intermediate B have been observed only recently. In 2007, we reported the equilibrium between the phosphonium dienolate (vinylogous enolate) A1 and the alternative extended ylide (vinylogous ylide) B1 and their reactions with activated olefins to form two regioisomeric cyclohexenes (Scheme 2.1.3). In agreement with Price’s and Rauhur-Currier’s observations, the electron-donating/nucleophilic hexamethylphosphorus triamide (HMPT) favored the reaction through the phosphonium enolate A1, whereas electron-poor triarylphosphines facilitated reactions proceeding through the vinylogous ylide B1. Based on the reactions of intermediates A and B with aldehydes, we hypothesized the possibility of performing selective vinylogous MBH or Wittig reactions of the intermediates A1 or B1 with aldehydes, depending on the electronic nature of the phosphines used. Herein, we
report two such transformations: tandem vinylogous aldol/phosphorus-to-carbon aryl migration and vinylogous Wittig olefination.\textsuperscript{13}

\textit{Scheme 2.1.3.1}

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\begin{minipage}{0.4\textwidth}
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      \includegraphics[width=\textwidth]{scheme.png}
    \end{center}
  \end{minipage}};
  \node (B) at (3,0) {\begin{minipage}{0.4\textwidth}
    \begin{center}
      \includegraphics[width=\textwidth]{scheme.png}
    \end{center}
  \end{minipage}};
  \node (C) at (1.5,1.5) {\begin{minipage}{0.2\textwidth}
    \begin{center}
      \includegraphics[width=\textwidth]{scheme.png}
    \end{center}
  \end{minipage}};
  \node (D) at (1.5,-1.5) {\begin{minipage}{0.2\textwidth}
    \begin{center}
      \includegraphics[width=\textwidth]{scheme.png}
    \end{center}
  \end{minipage}};
  \node (E) at (-1.5,1.5) {\begin{minipage}{0.2\textwidth}
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    \end{center}
  \end{minipage}};
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  \end{minipage}};
  \node (G) at (4,0) {\begin{minipage}{0.4\textwidth}
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    \end{center}
  \end{minipage}};
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    \end{center}
  \end{minipage}};
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    \end{center}
  \end{minipage}};
  \node (J) at (4.5,-1.5) {\begin{minipage}{0.2\textwidth}
    \begin{center}
      \includegraphics[width=\textwidth]{scheme.png}
    \end{center}
  \end{minipage}};

\end{tikzpicture}
\end{center}

\subsection*{2.2 Results and Discussion}

\subsubsection*{2.2.1 Reaction of Dienolate}

We initially examined the reaction of benzaldehyde in benzene under reflux (Table 2.2.1.1).\textsuperscript{14} Using alkylphosphines (PMe$_3$, PBu$_3$, PBn$_3$, and PCy$_3$) or HMPT in the reaction resulted in only oligomerization of the allenic ester without incorporation of benzaldehyde; in contrast, triphenylphosphine facilitated the anticipated MBH-type reaction.\textsuperscript{15} The reactions performed in benzene, toluene, or ethyl acetate under reflux provided in the same yield of product 3a (entries 1–3). In the absence of solvent, the reaction was complete within 2 h with a slightly diminished yield of product 3a (entry 4). As we have observed consistently for the reactions between allenoates and
aldehydes,\textsuperscript{16} the enolate A1 reacted with the aldehyde preferably at its $\gamma$ carbon atom. In addition, for this reaction we observed a rare 1,2-aryl migration from the aryl phosphonium moiety to the neighboring $\alpha$ carbon atom.\textsuperscript{17} We established the structures of the aldol-type products 3 using $^1$H NMR, $^{13}$C NMR, and 2D-NMR spectroscopy and X-ray crystallographic analysis (Figure 2.2.1.1, 3c).\textsuperscript{18}

\textit{Table 2.2.1.1}

\begin{center}
\begin{tabular}{cccccc}
\hline
entry & Ar & R & solvent & time (h) & temp ($^\circ$C) & yield (%)\textsuperscript{b} \\
\hline
1 & C\textsubscript{6}H\textsubscript{5} & C\textsubscript{6}H\textsubscript{5} & benzene & 24 & reflux & 28 (3a) \\
2 & C\textsubscript{6}H\textsubscript{5} & C\textsubscript{6}H\textsubscript{5} & toluene & 24 & reflux & 28 (3a) \\
3 & C\textsubscript{6}H\textsubscript{5} & C\textsubscript{6}H\textsubscript{5} & EtOAc & 24 & reflux & 28 (3a) \\
4\textsuperscript{c} & C\textsubscript{6}H\textsubscript{5} & C\textsubscript{6}H\textsubscript{5} & neat & 2 & 160 & 25 (3a) \\
5 & 4-CF\textsubscript{3}C\textsubscript{6}H\textsubscript{4} & C\textsubscript{6}H\textsubscript{5} & benzene & 24 & reflux & 33 (3b) \\
6 & 4-NCC\textsubscript{6}H\textsubscript{4} & C\textsubscript{6}H\textsubscript{5} & toluene & 24 & reflux & 33 (3c) \\
7 & 4-NCC\textsubscript{6}H\textsubscript{4} & C\textsubscript{6}H\textsubscript{5} & toluene & 24 & rt & trace (3c) \\
8 & 4-NCC\textsubscript{6}H\textsubscript{4} & C\textsubscript{6}H\textsubscript{5} & MeOH & 24 & rt & 0 \\
\hline
\end{tabular}
\end{center}
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<tr>
<th></th>
<th>Reaction Components</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Reflux</th>
<th>Yield</th>
</tr>
</thead>
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<td>9</td>
<td>4-BrC₆H₄ C₆H₅</td>
<td>benzene</td>
<td>24</td>
<td>reflux</td>
<td>21 (3d)</td>
</tr>
<tr>
<td>10</td>
<td>3-HOC₆H₄ C₆H₅</td>
<td>benzene</td>
<td>24</td>
<td>reflux</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>4-Me₂NC₆H₄ C₆H₅</td>
<td>toluene</td>
<td>54</td>
<td>160</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>4-Me₂NC₆H₄ C₆H₅</td>
<td>neat</td>
<td>48</td>
<td>160</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>4-NCC₆H₄ 4-MeC₆H₄</td>
<td>toluene</td>
<td>24</td>
<td>reflux</td>
<td>21 (3e)</td>
</tr>
<tr>
<td>14</td>
<td>4-NCC₆H₄ C₆H₅</td>
<td>toluene</td>
<td>24</td>
<td>reflux</td>
<td>37 (4a)</td>
</tr>
</tbody>
</table>

*a* Allenic ester in solvent (10 mL) was added slowly (over 2 h) via a syringe pump into the mixture of the other reaction components in solvent (5 mL). *b* Isolated yield of product. *c* Reaction was performed in a sealed tube. *d* Total volume of solvent: 2 mL. *e* BF₃·Et₂O (10 mol %) was added to the reaction mixture.

*Figure 2.2.1.1*
The presence of an electron-withdrawing substituent in the aromatic aldehyde slightly increased the yields of products 3b and 3c (Table 2.2.1.1, entries 5 and 6). When performed in toluene at room temperature, however, the reaction afforded only a trace amount of product 3c (entry 7). We suspect that high temperature was required to facilitate the 1,2-aryl migration, but it also accelerated the phosphine-catalyzed oligomerization of the allenic ester, thereby resulting in moderate overall reaction efficiency. At room temperature in methanol, we did not detect the formation of product 3c (entry 8). Although p-bromobenzaldehyde provided moderate reaction efficiency (product 3d, entry 9), hydroxy- and amino-substituted benzaldehydes did not yield any aldol-like products under any of the tested conditions (entries 10–12). Using tris(p-tolyl)phosphine under the working conditions afforded product 3e, verifying that triphenylphosphine was the source of the phenyl group in products 3a–d (entry 13). Tris(p-tolyl)phosphine afforded lower yield of 3e than did triphenylphosphine, presumably because a phosphine of stronger nucleophilicity led to increased oligomerization of the allenic ester and/or because of the poorer migratory aptitude of the electron-rich p-tolyl group (see 2.2.3).

2.2.2 Reaction of Vinylogous Ylide

2.2.2.1 Optimization of Reaction Condition

Aromatic aldehydes might not have been active enough for the nucleophilic addition of the dienolate and, therefore, it was susceptible to competition from the oligomerization of the allenic ester. Lewis acids are commonly used to activate carbonyl compounds toward nucleophilic addition.\textsuperscript{19} Therefore, we added a catalytic amount (0.1
equiv) of boron trifluoride etherate in an attempt to enhance the efficiency of the desired reactions between the enolate and the aromatic aldehydes. Surprisingly, the formation of product 3a was inhibited while the yield of the Wittig-type product 4a increased significantly (Table 2.2.1.1, entry 14). Notably, the Lewis basic phosphine and Lewis acidic boron trifluoride etherate were compatible in this instance. We postulate three possible functions for the catalytic Lewis acid in the formation of 4a: (1) enhancing the electrophilicity of the carbonyl group of the aromatic aldehyde, (2) suppressing enolate formation from enolizable carbonyl compounds, much like CeCl₃,[20] and (3) facilitating the addition at the β’ carbon atom via simultaneous coordination to the carbonyl groups of both the aldehyde and the allenic ester (see 2.2.3).

*Table 2.2.1.1*

<table>
<thead>
<tr>
<th>entry</th>
<th>1 (equiv)</th>
<th>2a (equiv)</th>
<th>PAr₃ (equiv)</th>
<th>t (h)</th>
<th>T (°C)</th>
<th>yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>1</td>
<td>PPh₃ (1)</td>
<td>36</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>1</td>
<td>PPh₃ (1)</td>
<td>36</td>
<td>rtc</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>1</td>
<td>PPh₃ (1)</td>
<td>36</td>
<td>rt</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>1</td>
<td>PPh₃ (1)</td>
<td>36</td>
<td>40</td>
<td>37</td>
</tr>
</tbody>
</table>
Among the series of organic solvents tested, acetonitrile was most efficacious for the Wittig reaction (Table 2.2.2.1.1). We obtained the diene 4a as a mixture of four possible isomers, as was the case also in Corey’s diene synthesis via a vinylogous Wittig reaction. In an attempt to reduce the yield of the minor isomers of product 4a, we ran the reaction at 0 °C, but did not detect any product 4a (entry 1). The Wittig reaction was sensitive to the temperature, providing a greater yield of product 4a at elevated temperatures (entries 1–5). Increasing the amount of allenic ester in the reaction did not improve the reaction efficiency; it only increased the oligomerization of the allenic ester (entries 2 and 3). Elevating the reaction temperature resulted in an increase in the reaction rate and the reaction yield of 4a (entries 4 and 5). The use of 5.0 equivalents of the aldehyde surprisingly lowered the reaction yield of product 4a (entry 6), presumably because the relatively small amount (0.1 equiv.) of BF₃·Et₂O was no longer effective to activate a large excess of aldehydes in the reaction mixture. The addition of more triphenylphosphine, on the other hand, increased the product yield significantly (entry 7). In a previous study, we found that tris(4-fluorophenyl)phosphine
preferentially facilitated reactions via the vinylogous ylide $\text{B1}$. Indeed, the use of tris(4-fluorophenyl)phosphine increased the yield of the reaction from 30% (entry 2) to 47% (entry 8) under otherwise identical reaction conditions. Nevertheless, because tris(4-fluorophenyl)phosphine is a weaker nucleophile, the reaction took longer to complete at room temperature.

### 2.2.2.2 Lewis-Acid Additives

Next, we examined the effects of further modifications of the reaction conditions. At elevated temperature and using tris(4-fluorophenyl)phosphine, the desired transformation occurred within a reasonable amount of time with an increased yield of the isolated diene product (Table 2.2.2.2.1, entry 1). In the absence of the BF$_3$·Et$_2$O catalyst, however, even the use of tris(4-fluorophenyl)phosphine did not afford a good yield on the reaction product (entry 2). Increasing the loading of BF$_3$·Et$_2$O (from 10 to 20 mol %) lowered the reaction yield (entry 3), whereas a slight increase in the loadings of both the phosphine and BF$_3$·Et$_2$O resulted in a slight increase in the reaction yield of product 4a (entry 4). The reaction could not tolerate a stoichiometric amount of BF$_3$·Et$_2$O (entry 5), even in the presence of an increased amount of phosphine (entry 6).

Although trace amounts of water or alcohol can be useful for catalyzing stepwise proton transfers in some phosphine-mediated reactions, we found that an excess of a protic solvent lowered the reaction yield of 4a in this reaction system (entry 7). When we used TiCl$_4$ as the Lewis acid additive, rather than BF$_3$·Et$_2$O, the yield of product 4a remained unchanged (cf. entries 1 and 8). The introduction of TBAF as an additive did not improve the reaction (entry 9).
### Table 2.2.2.2.1

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>equiv (PAR₃)</th>
<th>additive</th>
<th>mol % (additive)</th>
<th>yield [%]⁺</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>4-FC₆H₄</td>
<td>1</td>
<td>BF₃•Et₂O</td>
<td>10</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>4-FC₆H₄</td>
<td>1</td>
<td>none</td>
<td>N/A</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>4-FC₆H₄</td>
<td>1</td>
<td>BF₃•Et₂O</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>4-FC₆H₄</td>
<td>1.3</td>
<td>BF₃•Et₂O</td>
<td>30</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>1</td>
<td>BF₃•Et₂O</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>2</td>
<td>BF₃•Et₂O</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>7ᵇ</td>
<td>4-FC₆H₄</td>
<td>1</td>
<td>BF₃•Et₂O</td>
<td>10</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>4-FC₆H₄</td>
<td>1</td>
<td>TiCl₄</td>
<td>10</td>
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<td>9</td>
<td>Ph</td>
<td>1</td>
<td>TBAF</td>
<td>10</td>
<td>28</td>
</tr>
</tbody>
</table>

⁺ Isolated yield. ᵇ MeOH (2 drops) was added.

### 2.2.2.3 Scope of Aldehyde Substrates

Next, we examined the effects that electron-withdrawing substituents at various positions on the aromatic ring of the benzaldehydes had on the vinylogous Wittig
reactions (Table 2.2.2.3.1). Cyano groups (entries 1–3), in general, afforded greater yields of the diene 4 than did nitro substituents (entries 4–6). These electron-withdrawing groups were most effective at the meta positions of the aromatic aldehydes (entries 2 and 5). Introducing the substituent at the ortho position lowered the reaction yields of the dienes 4 (entries 3 and 6), presumably because steric hindrance negatively affected the nucleophilic addition step during the vinylogous Wittig reaction. Installing a weaker electron-withdrawing group (fluorine atom) on the aromatic ring lowered the reaction yield (entry 7). The presence of the various electron withdrawing groups slightly affected the E:Z ratios of the newly formed bonds in the product mixtures (see 2.2.4); in all cases, the E configuration of the new double bond was favored over the Z configuration (from 2:1 to 5:1, Table 2.2.2.3.1).

Table 2.2.2.3.1

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>E:Z ratio&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-NCC₆H₄</td>
<td>4a</td>
<td>63</td>
<td>5:2</td>
</tr>
<tr>
<td>2</td>
<td>3-NCC₆H₄</td>
<td>4b</td>
<td>65</td>
<td>5:2</td>
</tr>
<tr>
<td>3</td>
<td>2-NCC₆H₄</td>
<td>4c</td>
<td>60</td>
<td>5:1</td>
</tr>
<tr>
<td>4</td>
<td>4-O₂NC₆H₄</td>
<td>4d</td>
<td>51</td>
<td>4:1</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>---</td>
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<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>3-O&lt;sub&gt;2&lt;/sub&gt;NC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4e</td>
<td>57</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td>2-O&lt;sub&gt;2&lt;/sub&gt;NC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4f</td>
<td>50</td>
<td>7:2</td>
</tr>
<tr>
<td>7</td>
<td>3-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4g</td>
<td>49</td>
<td>5:2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Allenic ester in CH<sub>3</sub>CN (5 mL) was added in one portion to the mixture of the other components in CH<sub>3</sub>CN (10 mL).  
<sup>b</sup> Isolated yield.  
<sup>c</sup> Relating to the geometry around the newly formed double bond; the ratio was determined after integration of the signals of protons H<sup>a</sup> and H<sup>b</sup> in the ¹H NMR spectrum of the crude reaction product.

### 2.2.3 Mechanism

Scheme 2.2.3.1 presents a suggested mechanism for the formation of 3 and 4. The phosphine first underwent a Michael addition to the allenic ester 1 to form the enolate zwitterion 5. Subsequent stepwise proton transfers established the equilibrium between the dienolate 5 and the vinylogous ylide 6.¹¹ Dependent upon the nature of the phosphine in use, as well as the presence/absence of a Lewis acid, either the dienolate or the vinylogous ylide became the dominant species for reaction with the aldehyde. For the vinylogous aldol/1,2-aryl migration pathway, the dienolate 5 added to the aldehyde 2 to form the alkoxide 7. Stepwise proton transfers then occurred to form the ylide 8,²⁴ which underwent a net 1,2-aryl migration, through an intramolecular S<sub>N</sub>Ar reaction, to generate the phosphine 9. The oxophilicity of the alkylidiphenylphosphine 9 accounts for the formation of the phosphinite 10, which eventually hydrolyzed during purification to form the alcohol 3. ³¹P NMR spectra of the reaction mixture in C<sub>6</sub>D<sub>6</sub> heated under reflux for 10 min, 2 h, 5 h, 10 h, and 24 h revealed a peak at δ 113.3 ppm of increasing intensity (Figure 2.2.3.1), indicative of the accumulation of the phosphinite 10.²⁵ For the
vinyllogous Wittig pathway, the vinyllogous ylide added to the Lewis acid–activated aldehyde 2 to form the phosphonium alkoxide 11. Stepwise proton transfers led to isomerization of the vinyl phosphonium 11 to the allylic phosphonium 12, which cyclized to form a six-membered-ring product, the 3,6-dihydro-2,2,2-triphenyl-1,2-oxaphosphonine 13. Through a retro-Diels–Alder (rDA) process, triphenylphosphine oxide was formed from 13, resulting in the diene 4 being formed as a mixture of isomers.\textsuperscript{13}
Scheme 2.2.3.1

1. Reaction of 1 with PPh₃ to form 5 and 6.

2. Conversion of 5 to 7 through H⁺ transfer and 1,2-phenyl migration.

3. Formation of 8 from 7.

4. Acylation of 8 to form 9.

5. Conversion of 9 to 10 through silica gel.

6. Conversion of 10 to 3 through vinylogous Aldol / aryl migration.

7. Conversion of 1 to 6 through vinylogous ylide.

8. Conversion of 6 to 11 through H⁺ transfer.

9. Conversion of 11 to 12 through H⁺ transfer.

10. Conversion of 12 to 13 through aryl migration.

11. Conversion of 13 to 4 through vinylogous Wittig.
2.2.4 Discussion

Unlike regular Wittig reactions, which favor formation of Z olefins, the configurations of our newly formed olefins from these vinylogous Wittig reactions were determined by their steric surroundings. The proposed 3,6-dihydro-2,2,2-triphenyl-1,2-oxaphosphonine intermediate 13 is assembled into a boat conformation so that the π and σ* orbitals are aligned properly for the rDA process. Scheme 2.2.4.1 presents four possible relative arrangements for the substituents at C3 and C6. We would expect the intermediate 13.4 to be the most favorable, due to its limited degree of steric congestion; accordingly, intermediate 13.1 would be the least likely to form. Even
though an aryl group is larger than a methyl group, its flat and rigid ring can orient itself to minimize the van der Waals repulsion with other groups.\textsuperscript{27} We would also expect the intermediate 13.2 to be more favorable than 13.3; indeed, the corresponding Z olefin generated from 13.2 was the second most abundant product, as determined through \textsuperscript{1}H NMR spectroscopic analysis. The pseudoaxial aryl group in the boat conformation of 13.2 is oriented in such a manner to minimize van der Waals repulsion of the pseudoaxial allylic hydrogen atom. The methyl group, in contrast, with its tetrahedral configuration, suffers severe van der Waals repulsion with the proximal pseudoaxial allylic proton in the boat conformation 13.3. The significant degree of Z olefin formation presumably arose because the flat structure of the aromatic ring could minimize the extent of flagpole interactions with the hydrogen atom in structure 13.2.

\textit{Scheme 2.2.4.1}

![Scheme 2.2.4.1](image-url)
2.3 Conclusion

We have observed a classic case of equilibrium between phosphonium dienolates and vinylogous phosphorus ylides during the phosphine-mediated reactions of an α-methyl allenic ester with various aldehydes. When we exposed the α-methyl allenic ester to the aldehydes in the presence of a tertiary phosphine, both aldol-type and Wittig reactions ensued. Specifically, triphenylphosphine facilitated a tandem vinylogous aldol/1,2-aryl phosphorus-to-carbon migration reaction between the α-methyl allenic ester and electron-poor aromatic aldehydes. In the presence of sub-stoichiometric amounts of a Lewis acid, such as BF$_3$·Et$_2$O or TiCl$_4$, rare vinylogous Wittig olefinations occurred between the α-methyl allenic ester and electron-poor aromatic aldehydes. The vinylogous Wittig reaction was best facilitated in the presence of the electron-poor tris(p-fluorophenyl)phosphine. Products featuring thermodynamically more stable E configurations were formed preferentially in the vinylogous Wittig reaction, in contrast to the Z olefin formation traditionally observed for normal Wittig olefinations.

2.4 Experimental Section

2.4.1 Materials and Methods

All reactions were performed under argon atmosphere with dry solvents and anhydrous conditions, unless otherwise indicated. Benzene, toluene and acetonitrile were freshly used from the distillation on CaH$_2$. BF$_3$·Et$_2$O was freshly distilled from CaH$_2$. All other reagents were used as received from commercial sources. All allenic esters and other allenic compounds 1 were synthesized according to procedures
Reactions were monitored by using thin layer chromatography (TLC) performed on 0.25-mm SiliCycle silica gel plates and visualized under UV light, with permanganate staining. Flash column chromatography (FCC) was performed using SiliCycle Silica-P Flash silica gel (60 Å pore size, 40–63 μm). IR spectra were recorded on a Perkin–Elmer pargon 1600 FT-IR spectrometer. NMR spectra were obtained on Bruker Avance-500 instruments, calibrated using residual chloroform as an internal reference (7.26 and 77.0 ppm for 1H and 13C NMR spectra, respectively). $^1$H NMR spectral data are reported as follows: chemical shift ($\delta$, ppm), multiplicity, coupling constant (Hz), and integration. 13C spectral data are reported in terms of the chemical shift. The following abbreviations are used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; MALDI mass spectrometric data were obtained using an Applied Biosystems Voyager-DE-STR MALDI-TOF instrument, samples dissolved in DCM, and 2,5-dihydroxybenzoic acid as the matrix. GC-MS data were obtained using Agilent 6890-5975 GC-MS with autosampler instrument installed with HP5 column, samples dissolved in DCM.

2.4.2 Preparative procedures

General Procedure for 3

A flame-dried round-bottom flask was charged with triphenylphosphine (1.0 equiv), an aldehyde (1.0 equiv), and dry toluene (5 mL). The mixture was heated under reflux and then ethyl 2-methyl-2,3-butadienoate (1.2 equiv) was added slowly via a syringe pump over 2 h. The mixture was then heated under reflux for 24 h before being
concentrated. The crude residue was purified through FCC (SiO$_2$; hexanes/ethyl acetate, 8:3) to afford the alcohol 3.

**General Procedure for 4**

A flame-dried round-bottom flask was charged with tris(4-fluorophenyl)phosphine (1.0 equiv), an aldehyde (1.0 equiv), and dry acetonitrile (10 mL). The mixture was stirred and heated to 80 °C in an oil bath and then a solution of ethyl 2-methyl-2,3-butadienoate in dry acetonitrile (5 mL) was added to the mixture in one portion. After the reaction had reached completion (ca. 48 h), the mixture was concentrated and the crude residue purified through FCC (SiO$_2$; hexanes/ethyl acetate, 5:1) to provide a mixture of isomeric dienes. The number of isomers in the mixture was determined by GC-MS; the ratio of isomers was calculated from $^1$H NMR spectral data of the crude product.

**2.4.3 Spectral Data**

**Spectral Data of 3**

(Z)-Ethyl 5-hydroxy-2-methyl-3,5-diphenyl-2-pentenoate (3a). 27% yield as a pale yellow oil. IR (film) $\nu_{\text{max}}$ 3460, 3059, 3028, 2980, 2927, 1705, 1311, 1244, 1140 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.29-7.11 (m, 10H), 4.58 (ddd, $J = 1.8, 5.1, 5.8$ Hz, 1H),
3.81 (q, J = 7.5 Hz, 2H), 3.04 (dd, J = 8.5, 14.0 Hz, 1H), 2.80 (dd, J = 5.0, 14.0 Hz, 1H), 1.95 (s, 3H), 0.80 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.6, 143.7, 142.1, 142.0, 129.6, 128.3, 128.1, 127.6, 127.1, 125.6, 72.2, 60.2, 44.5, 16.2, 13.4; MS (MALDI) calcd for C₂₀H₂₂NaO₃ [M+Na]⁺ 333.15, found 333.14.

(Z)-Ethyl 5-((p-Trifluoromethylphenyl)-5-hydroxy-3-phenyl-2-methyl-2-pentenoate (3b). 33% yield; pale yellow oil. IR (film) νmax 3460, 3057, 2983, 2929, 1706, 1326, 1164, 1125, 1067 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.47 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.18–7.25 (m, 3H), 7.07–7.09 (m, 2H), 4.56–4.57 (m, 1H), 3.74 (q, J = 7.0 Hz, 2H), 2.94 (dd, J = 9.0, 14 Hz, 1H), 2.69 (dd, J = 5.0, 13.5 Hz, 1H), 1.89 (s, 3H), 0.72 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.5, 147.6, 141.6, 141.3, 130.0, 129.7(q, J = 32.3 Hz), 128.2, 127.5, 127.3, 125.9, 125.2 (q, J = 3.7 Hz), 124.0 (q, J = 272.3 Hz), 71.5, 60.3, 44.4, 16.2, 13.3; MS (MALDI) calcd for C₂₁H₂₁F₃NaO₃ [M + Na]⁺ 401.13, found 401.22.

(Z)-Ethyl 5-((p-Cyanophenyl)-5-hydroxy-2-methyl-3-phenyl-2-pentenoate (3c). 33%
yield; colorless oil. IR (film) $\nu_{\text{max}}$ 3474, 3051, 2978, 2925, 2229, 1705, 1311, 1245, 1140, 1067 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.50 (d, $J = 8.5$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.19–7.25 (m, 3H), 7.08 (d, $J = 6.5$ Hz, 2H), 4.54–4.56 (m, 1H), 3.74 (q, $J = 7.0$ Hz, 2H), 2.92 (dd, $J = 14.0$, 8.5 Hz, 1H), 2.68 (dd, $J = 14.0$, 5.0 Hz, 1H), 2.51 (s, 1H), 1.84 (s, 3H), 0.72 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.5, 149.1, 141.5, 141.0, 132.1, 130.1, 128.2, 127.5, 127.4, 126.3, 118.7, 111.1, 60.3, 44.3, 16.3, 13.3; MS (MALDI) calcd for C$_{21}$H$_{21}$NO$_3$Na [M + Na]$^+$ 358.14, found 358.12.

(Z)-Ethyl 5-($p$-Bromophenyl)-5-hydroxy-3-phenyl-2-methyl-2-pentenoate (3d). 21% yield; colorless oil. IR (film) $\nu_{\text{max}}$ 3468, 3050, 3018, 2981, 2927, 1707, 1311, 1242, 1141 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.38 (d, $J = 6.5$ Hz, 2H), 7.25–7.28 (m, 3H), 7.09–7.12 (m, 4H), 4.47 (dd, $J = 5.0$, 8.0 Hz, 1H), 3.77 (q, $J = 7.0$ Hz, 2H), 2.96 (dd, $J = 8.5$, 13.5 Hz, 1H), 2.73 (s, 1H), 2.71 (dd, $J = 5.5$, 14.5 Hz, 1H), 1.89 (s, 3H), 0.77 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.7, 142.8, 141.8, 141.7, 131.3, 129.6, 128.1, 127.6, 127.4, 127.2, 121.2, 71.4, 60.3, 44.3, 16.2, 13.3.
(Z)-Ethyl 5-(p-Cyanophenyl)-5-hydroxy-2-methyl-3-(p-tolyl)-2-pentenoate (3e).  
21% yield; pale yellow oil. IR (film) $\nu_{\text{max}}$ 3472, 3055, 2980, 2302, 1706, 1312, 1245, 1141, 1067 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.60 (d, $J = 8.0$ Hz, 2), 7.50 (d, $J = 7.5$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.06 (d, $J = 8.5$ Hz, 2H), 4.64 (dd, $J = 4.0$, 8.5 Hz, 1H), 3.86 (q, $J = 7.0$ Hz, 2H), 2.97 (dd, $J = 8.5$, 14.0 Hz, 1H), 2.75 (dd, $J = 4.0$, 14.0 Hz, 1H), 2.35 (s, 3H), 1.94 (s, 3H), 0.86 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.5, 149.0, 140.8, 138.3, 137.3, 132.1, 130.0, 129.0, 127.4, 126.3, 118.7, 111.2, 71.5, 60.3, 43.3, 21.1, 16.3, 13.4.  

Spectral Data of 4

Ethyl 2-(4-Cyanostyryl)-2-butoanoate (4a). 63% yield; colorless oil. IR (film) $\nu_{\text{max}}$ 3047, 2982, 2938, 2226, 1713, 1603, 1054, 1249, 1141 cm$^{-1}$; (major isomer) $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.60 (d, $J = 8.4$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 16.4$ Hz, 1H), 7.00 (d, $J = 16.4$ Hz, 1H), 6.96 (q, $J = 7.2$ Hz, 1H), 4.26 (q, $J = 7.2$ Hz, 2H), 2.02 (d, $J = 7.4$ Hz, 3H), 1.33 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.5, 142.0, 140.2, 132.3, 131.4, 130.4, 126.8, 124.0, 118.9, 110.7, 60.7, 14.7, 14.1; (second most
abundant isomer) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.50 (d, \(J = 8.4\) Hz, 2H), 7.34 (d, \(J = 8.3\) Hz, 2H), 6.88 (q, \(J = 7.0\) Hz, 1H), 6.63 (d, \(J = 11.8\) Hz, 1H), 6.36 (d, \(J = 12.2\) Hz, 1H), 4.08 (q, \(J = 7.3\) Hz, 2H), 1.59 (d, \(J = 7.3\) Hz, 3H), 1.16 (t, \(J = 6.99\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 166.5, 142.1, 140.6, 132.0, 131.1, 130.1, 128.7, 126.3, 118.7, 110.5, 30.8, 15.3, 14.0; MS (Agilent GC-MS) calcd for C\(_{15}\)H\(_{15}\)NO\(_2\) [M\(^+\)] 241.11, found 241.1.

**Ethyl 2-(3-Cyanostyryl)-2-butenoate (4b).** 65% yield; colorless oil. IR (film) \(\nu_{\text{max}}\) 3063, 2982, 2916, 2849, 2230, 1714, 1576, 1477, 1256, 1139 cm\(^{-1}\); (major isomer) \(^1\)H NMR (500 MHz, CDCl\(_3\); non-aromatic protons) \(\delta\) 7.07 (d, \(J = 16.5\) Hz, 1H), 6.96 (d, \(J = 16.5\) Hz, 1H), 6.95 (q, \(J = 7.5\) Hz, 1H), 4.27 (q, \(J = 7.2\) Hz, 2H), 2.03 (d, \(J = 7.4\) Hz, 3H), 1.34 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 166.6, 142.1, 140.8, 139.8, 138.8, 132.8, 130.9, 130.7, 130.6, 129.7, 129.3, 118.7, 112.8, 60.7, 14.7, 14.2; (second most abundant isomer) \(^1\)H NMR (500 MHz, CDCl\(_3\); non-aromatic protons) \(\delta\) 6.77 (d, \(J = 16.5\) Hz, 1H), 6.59 (d, \(J = 16.5\) Hz, 1H), 6.22 (q, \(J = 7.3\) Hz, 1H), 4.36 (q, \(J = 7.1\) Hz, 2H), 1.99 (d, \(J = 7.3\) Hz, 3H), 1.39 (t, \(J = 7.1\) Hz, 3H); (third most abundant isomer) \(^1\)H NMR (500 MHz, CDCl\(_3\); non-aromatic protons) \(\delta\) 6.42 (d, \(J = 12.0\) Hz, 1H), 6.34 (dt, \(J = 12.0, 1.3\) Hz, 1H), 6.17 (qd, \(J = 7.3, 1.1\) Hz, 1H), 3.87 (q, \(J = 7.2\) Hz, 2H), 1.96 (dd, \(J = 7.3, 1.2\) Hz, 3H), 1.12 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 166.5, 139.8, 138.5, 136.3, 131.9, 130.35, 140.31, 130.26, 128.8, 127.6, 118.7, 112.2, 60.4, 15.5, 13.8; MS (Agilent GC-MS) calcd for C\(_{15}\)H\(_{15}\)NO\(_2\) [M\(^+\)] 241.11, found 241.1.
Ethyl 2-(2-Cyanostyryl)-2-butoenate (4c). 60% yield; colorless oil. IR (film) $\nu_{\text{max}}$ 3066, 2982, 2873, 2851, 2223, 1714, 1633, 1595, 1478, 1447, 1385, 1244, 1141, 1025 cm$^{-1}$; (major isomer) $^1$H NMR (500 MHz, CDCl$_3$; non-aromatic protons) $\delta$ 7.36 (d, $J$ = 16.6 Hz, 1H), 7.10 (d, $J$ = 16.6 Hz, 1H), 7.03 (q, $J$ = 7.5 Hz, 1H), 4.29 (q, $J$ = 7.3 Hz, 2H), 2.06 (d, $J$ = 7.5 Hz, 3H), 1.36 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.6, 140.8 (two peaks), 133.0, 132.7, 131.9, 130.5, 129.1, 127.6, 125.5, 117.8, 111.2, 60.9, 15.0, 14.1; (second most abundant isomer) $^1$H NMR (500 MHz, CDCl$_3$; non-aromatic protons) $\delta$ 7.00 (d, $J$ = 16.2 Hz, 1H), 6.92 (d, $J$ = 16.2 Hz, 1H), 6.33 (q, $J$ = 7.4 Hz, 1H), 4.37 (q, $J$ = 7.1 Hz, 2H), 2.03 (d, $J$ = 7.4 Hz, 3H), 1.41 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.3, 141.6, 141.0, 132.5, 132.1, 131.2, 130.6, 129.5, 127.4, 125.8, 117.8, 111.9, 60.3, 15.5, 13.7; MS (Agilent GC-MS) calcd for C$_{15}$H$_{15}$NO$_2$ [M$^+$] 241.11, found 241.1.

Ethyl 2-(4-Nitrostyryl)-2-butoenate (4d). 51% yield; yellow oil. IR (film) $\nu_{\text{max}}$ 2984, 2916, 2848, 1714, 1593, 1513, 1343, 1256, 1143 cm$^{-1}$; (major) $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.20 (d, $J$ = 8.5 Hz, 2H), 7.58 (d, $J$ = 8.5 Hz, 2H), 7.19 (d, $J$ = 16.5 Hz, 1H), 7.07 (d, $J$ = 16.5 Hz, 1H), 7.00 (q, $J$ = 7.5 Hz, 1H), 4.28 (q, $J$ = 7.0 Hz, 2H), 2.05 (d, $J$ = 7.5 Hz, 3H), 1.35 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.7, 144.1, 140.9,
Ethyl 2-(3-Nitrostyryl)-2-butenoate (4e). 57% yield; yellow oil. IR (film) \( \nu_{\max} \) 3089, 2980, 2916, 2849, 1712, 1529, 1530, 1253 cm\(^{-1}\); (major) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \):
8.31 (s, 1H), 8.10 (dd, \( J = 8.1, 1.2 \) Hz, 1H), 7.74 (d, \( J = 7.9 \) Hz, 1H), 7.50 (t, \( J = 7.9 \) Hz, 1H), 7.15 (d, \( J = 16.5 \) Hz, 1H), 7.03 (d, \( J = 16.5 \) Hz, 1H), 6.98 (q, \( J = 7.4 \) Hz, 1H), 4.28 (q, \( J = 7.1 \) Hz, 2H), 2.05 (d, \( J = 7.4 \) Hz, 3H), 1.35 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 166.8, 148.9, 140.2, 139.5, 132.4, 130.9, 130.4, 129.4, 123.5, 122.1, 120.8, 60.8, 14.8, 14.2; (second most abundant isomer) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \):
8.12 (s, 1H), 8.06 (d, \( J = 8.4 \) Hz, 1H), 7.58 (d, \( J = 7.6 \) Hz, 1H), 7.45 (t, \( J = 7.8 \) Hz, 1H), 6.49 (d, \( J = 12.0 \) Hz, 1H), 6.38 (d, \( J = 12.0 \) Hz, 1H), 6.20 (d, \( J = 7.2 \) Hz, 1H), 3.87 (q, \( J = 7.2 \) Hz, 2H), 1.97 (d, \( J = 7.2 \) Hz, 3H), 1.11 (t, \( J = 7.2 \) Hz, 3H); MS (Agilent GC-MS) calcd for C\(_{14}\)H\(_{15}\)NO\(_4\) [M\(^+\)] 261.10, found 261.1.

Ethyl 2-(2-Nitrostyryl)-2-butenoate (4f). 50% yield; yellow oil. IR (film) \( \nu_{\max} \) 3067, 2982, 2937, 2849, 1716, 1606, 1570, 1521, 1346, 1250, 1146, 1027 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \):
8.00 (d, \( J = 8.1 \) Hz, 1H), 7.75 (d, \( J = 8.1 \) Hz, 1H), 7.64 (t, \( J = 7.6 \) Hz, 1H), 7.48 (d, \( J = 16.3 \) Hz, 1H), 7.45–7.47 (m, 1H), 7.07 (q, \( J = 7.4 \) Hz, 1H), 6.92 (d, \( J =
16.3 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 2.10 (d, J = 7.4 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 166.6, 140.4, 133.3, 133.0, 132.9, 130.6, 128.7, 128.2, 128.0, 125.8, 124.5, 60.8, 14.9, 14.1; methyl and ethoxy protons of other minor isomers: (500 MHz, CDCl3) δ 3.76 (q, J = 7.1 Hz, 2H), 1.92 (d, J = 7.5 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H); δ 4.40 (q, J = 7.1 Hz, 2H), 2.07 (d, J = 7.5 Hz, 3H), 1.44 (t, J = 7.1 Hz, 3H); δ 4.11 (q, J = 7.1 Hz, 2H), 1.60 (dd, J = 1.4, 7.4 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); MS (Agilent GC-MS) calcd for C14H15NO4 [M]+ 261.10, found 261.1.

49% yield; colorless oil. IR (film) νmax 3037, 2981, 2928, 2855, 1711, 1609, 1581, 1486, 1446, 1263, 1240, 1143 cm⁻¹; (major) 1H NMR (500 MHz, CDCl3) δ 7.26–7.30 (m, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.14–7.18 (m, 1H), 7.03 (d, J = 16.4 Hz, 1H), 6.93–6.97 (m, 1H), 6.902 (d, J = 16.4 Hz, 1H), 6.903 (q, J = 7.5 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 2.01 (d, J = 7.5 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 167.0, 163.1 (d, J = 239.3 Hz), 139.9 (d, J = 8.0 Hz), 138.8, 132.1 (d, J = 3.2 Hz), 130.7, 129.9 (d, J = 8.5 Hz), 122.4 (d, J = 3.1 Hz), 121.9, 114.4 (d, J = 21.6 Hz), 112.6 (d, J = 21.8 Hz), 60.6, 14.7, 14.2; MS (Agilent GC-MS) calcd for C14H15O2F [M]+ 234.11, found 234.1.
2.5 Notes and References


(10) After our reports on the reactions between $\alpha$-alkyl allenoates and imines (Ref. 28) and olefins (Ref. 11), He's group published a series of papers on the reactions between $\alpha$-alkyl allenoates and aldehydes; see: (a) He, Z.; Tang, X.; He, Z. Phosphorus, Sulfur Silicon Relat. Elem. 2008, 183, 1518. (b) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. Org. Lett. 2010, 12, 544; For examples of reactions between $\alpha$-alkyl allenoates and aldehydes, see: (c) Xu, S.; Zhou, L.; Ma, R.;


(14) The reactions performed at room temperature did not provide any identifiable products derived from the allenoate and benzaldehyde.

(15) No alkyl migration occurred with these phosphines (only oligomerization of the allenoate): PMe$_3$, PBu$_3$, HMPT, PBn$_3$, and PCy$_3$.


(18) Crystallographic data for 3c has been deposited with the Cambridge Crystallographic Data Centre as supplementary number CCDC 763343. The data can be obtained online free of charge [or from the Cambridge Crystallographic


(21) Solvents tested: toluene, benzene, xylene, neat (no solvent), DCM, 1,2-dichloroethane (DCE), chloroform, acetone, diethyl ether, THF, dioxane, DMSO, methanol, isopropanol, tert-butanol, and acetonitrile.


(23) Other additives tested that were not as efficient as BF$_3$Et$_2$O: AgOAc, CeCl$_3$, AlCl$_3$, CsF, LiCl, KF, FeCl$_3$, CrCl$_3$, and ZnCl$_2$.

(24) Under the same conditions, the reaction of the parent allenic ester, ethyl 2,3-butadienoate, provided no aryl migration product.

(25) Selected $^{31}$P NMR spectroscopic data of the alkyl diphenylphosphinite: δ 115.6 (Ph$_2$OMe), 109.8 (Ph$_2$POEt), 111.1 (Ph$_2$POBu), 104.0 (Ph$_2$POc-Hex), 117.0 (Ph$_2$POCH$_2$-Hex), 113.4 (Ph$_2$POCH$_2$CH=CH$_2$) ppm. Platt, A. W. G.; Kleemann,
S. G. $^{31}$P NMR data of three coordinate ($\lambda^3 \sigma^3$) phosphorus compounds containing bonds to chalcogenides (O, S, Se, Te) but no bonds to halogen in *Handbook of Phosphorus-31 Nuclear Magnetic Resonance Data*; Tebby, J. C., Ed.; CRC: Boca Raton, FL, 1991; p 85.


APPENDIX ONE

Spectra Relevant to Chapter Two:

Equilibrium between a Vinylogous Ylide and a Phosphonium Dienolate Zwitterion: Vinylogous Wittig Olefination versus Vinylogous Aldol-Type Reaction
A1.1 Structure Analysis of 3c Based on 1D and 2D NMR Spectra

The structure of 3c was determined based on MS (MALDI), 1H, 13C, 13C-DEPT, 2DCOSY, HMHC, HMBC, and NOESY NMR spectra, and further confirmed through single crystal X-ray crystallographic analysis. MS (MALDI) of 3c provided the molecular ion at $m/z$ 358.12 [M + Na]+, in accordance with the molecular structure of 3c (C21H21NO3) bound to a Na ion. 1H NMR spectroscopy indicated a total of 21 protons in the molecule, including four aromatic protons of a $p$-substituted phenyl ring [7.5 (d) and 7.3 (d) ppm], five aromatic protons of a monosubstituted phenyl ring (7.25–7.07 ppm), two geminal diastereotopic protons at C7 [2.9 (dd) and 2.7 (dd) ppm], one benzylic proton (4.6–4.5 ppm), one alcoholic proton (2.5 ppm), and five protons for the ethyl group of the carboxylic ester [3.7 (q) and 0.7 (t) ppm]. 13C DEPT and 13C NMR spectra indicated a total of 21 carbon atoms in the molecule, of which two were aliphatic methylene carbon atoms and one was an aliphatic methine carbon atom. 2D-COSY spectroscopy validated the couplings throughout the carbon chain: homoallylic coupling of C7H–C10H, geminal coupling of C7H–C7H, and vicinal coupling of C6H–C7H+OH. 2D-HMQC spectroscopy verified that the geminal diastereotopic protons belonged to C7, and that no cross peak appeared for the alcoholic proton. 2D-NOESY spectroscopy validated the geometry of the molecule, via the spatial couplings of C7H–C10H, OH–C10H, and C14–17H–C12H as cross peaks in the spectrum.
Figure A1.1 $^1$H NMR (500 MHz, CDCl$_3$) of compound 3c
Figure A1.2 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 3c

Figure A1.3 DEPT45 (500 MHz, CDCl$_3$) of compound 3c
Figure A1.4 DEPT90 (500 MHz, CDCl₃) of compound 3c

Figure A1.5 DEPT135 (500 MHz, CDCl₃) of compound 3c
Figure A1.6 COSY (500 MHz, CDCl₃) of compound 3c
Figure A1.7 HMQC (500 MHz, CDCl$_3$) of compound 3c
Figure A1.8 NOESY (500 MHz, CDCl₃) of compound 3c
Figure A1.9 $^1$H NMR (500 MHz, CDCl$_3$) of compound 3a
Figure A1.10 $^{13}\text{C}$ NMR (500 MHz, CDCl$_3$) of compound 3a
Figure A1.11 $^1$H NMR (500 MHz, CDCl$_3$) of compound 3b
Figure A1.12 $^1$H NMR (500 MHz, CDCl$_3$) of compound 3b
Figure A1.13 $^1$H NMR (500 MHz, CDCl$_3$) of compound 3c
Figure A1.14 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 3c
Figure A1.15 $^1$H NMR (500 MHz, CDCl$_3$) of compound 3d
Figure A1.16 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 3d
Figure A1.17 $^1$H NMR (500 MHz, CDCl$_3$) of compound 3e
Figure A1.18 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 3e
Structure Analysis of 4e Based on 1D and 2D NMR Spectra

The structure of 4e was determined based on MS (Agilent GC-MS), 1H, 13C, 2D-COSY, and 2D-NOESY NMR spectroscopy. MS (Agilent GC-MS) of 4e provided the molecular ion at $m/z$ 261.1 [M+], in accordance with the molecular structure of 44 (C14H15NO4) by itself. 1H NMR spectroscopy indicated a total of 15 protons in the molecule: four aromatic protons of the disubstituted phenyl ring [major: $\delta$ 8.31 (s, 1H), 8.10 (dd, 1H), 7.74 (d, 1H), 7.50 (t, 1H); minor: 8.12 (s, 1H), 8.06 (d, 1H), 7.58 (d, 1H), 7.45 (t, 1H) ppm], two adjacent vinylic protons [major: two trans ($J_{\text{trans}} = 16.5$ Hz) vinylic protons at $\delta$ 7.15 (d) and 7.03 (d) ppm; minor: two cis ($J_{\text{cis}} = 12.0$ Hz) vinylic protons at $\delta$ 6.63 (d) and 6.36 (d) ppm] and another vinylic proton [major: $\delta$ 6.98 (q) ppm; minor: 6.20 (q) ppm] adjacent to a methyl group [major: $\delta$ 2.05 (d) ppm; minor: 1.97 (d) ppm], and five protons for the ethyl group of the carboxylic ester [major: $\delta$ 4.28 (q) and 1.35 (t) ppm; minor: 3.87 (q) and 1.11 (t) ppm]. Fourteen carbon atoms of the major product were detected in the 13C NMR spectrum. 2D-COSY spectroscopy validated the couplings throughout the carbon chain of the vinylic protons (in both the cis and trans isomers) Ha–Hb and the vicinal coupling of Hc–Hd. 2D-NOESY spectroscopy clearly confirmed that the methyl group was cis to the ethyl ester group in the major trans isomer: the cross-peak indicated short-distance interactions between the methyl and ethyl protons through space.
Figure A1.19 $^1$H NMR of compound 4e
Figure A1.20 $^{13}$C NMR of compound 4e
Figure A1.21 COSY (500 MHz, CDCl$_3$) of compound 4e
Figure A1.22 NOESY (500 MHz, CDCl$_3$) of compound 4e
Figure A1.23 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4a
Figure A1.24 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4a
Figure A1.24 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4b
Figure A1.25 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4b
Figure A1.26 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4c
Figure A1.27 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4c
Figure A1.28 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4d
Figure A1.29 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4d
Figure A1.30 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4e
Figure A1.31 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4e
Figure A1. $^{1}$H NMR (500 MHz, CDCl$_3$) of compound 4f
Figure A1. $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4f
Figure A1.34 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4g
Figure A1.35 $^{13}$C NMR (500 MHz, CDCl$_3$) of compound 4g
APPENDIX TWO

X-ray Crystallography Data Relevant to Chapter Two: Equilibrium between a Vinylogous Ylide and a Phosphonium Dienolate Zwitterion: Vinylogous Wittig Olefination versus Vinylogous Aldol-Type Reaction
X-ray Crystal Structure Analysis of 3c

![Chemical structure of 3c](image)

**Table 1.** Crystal data and structure refinement for kw1808sa.

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Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$ x $10^3$) for kw1808sa. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å\(^2\times 10^3\)for kw1808sa. The anisotropic displacement factor exponent takes the form: \(-2p^2[\ h^2a^*2U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12} \]

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Table 6. Torsion angles [°] for kw1808sa.

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C(20)-O(2)-C(17)-O(3)   -6.94(18)
C(20)-O(2)-C(17)-C(16)  176.17(11)
C(9)-C(16)-C(17)-O(3)   133.09(14)
C(18)-C(16)-C(17)-O(3)  -48.06(17)
C(9)-C(16)-C(17)-O(2)   -50.09(15)
C(18)-C(16)-C(17)-O(2)  128.77(11)
C(17)-O(2)-C(20)-C(21)  -166.83(13)

Symmetry transformations used to generate equivalent atoms:
CHAPTER THREE

One-Pot Phosphine-Catalyzed Quinoline Syntheses

3.1 Background and Introduction

3.1.1 Available Quinoline Syntheses

The quinoline unit is found in a wide variety of pharmacologically and biologically active compounds.¹ Not surprisingly, quinoline derivatives continue to attract the attention of medicinal chemists, and strategies for accessing new scaffolds of quinoline derivatives are of great interest to synthetic chemists. In recent years, many transition metal–catalyzed processes have been developed for mild and efficient syntheses of quinolines.² Notably, the number of conventional metal-free paths for quinoline syntheses have also been growing.³ Several classical methods for targeting the quinoline core—including the Skraup, Doebner–von Miller, Friedländer, Pfitzinger, Conrad–Limpach, and Combes syntheses⁴a,b—remain relevant today for the preparation of quinoline-containing materials, ligands, and pharmaceutical agents.⁴a Nevertheless, such reactions are often performed under unfavorably harsh conditions, typically with either a strong acid or base and thermal assistance.⁴a,b For example, the Friedländer quinoline synthesis, a particularly powerful tool for generating quinoline core systems, is performed at high temperature in the presence of either a strong acid or base.⁴ In addition to unattractive reaction conditions, the instability of the coupling partners in the Friedländer quinoline synthesis further limits its synthetic potential.⁴,⁵ In particular, when the synthesis of 3-substituted quinolines is attempted using Friedländer methodology
(R² = R³ = H), self-condensation of both aldehyde coupling partners can lower the reaction efficiency and complicate the product's purification (Scheme 3.1.1.1). To prevent self-condensation of aminobenzaldehydes in Friedländer methodology, several classical approaches, namely the Borsche, Pfitzinger, and Niemantowski quinoline syntheses, were developed employing alternative starting materials. In a recent report, for example, aminobenzaldehydes were generated in situ from corresponding nitrobenzaldehydes and subsequently used in the Friedländer synthesis.

Scheme 3.1.1.1

3.1.2 3-Substituted Quinolines

For the synthesis of 3-substituted quinolines in particular, in 2009 Verpoort reported a one-pot methodology to avoid self-condensation of the aminobenzaldehyde by employing an aminobenzyl alcohol as a precursor; they also prevented self-condensation of the other coupling partner through late introduction of the strong base. This approach, however, requires an elevated temperature and a stoichiometric amount of the strong base. More recently, Li reported an alternative approach to 3-substituted quinolines by coupling alkynones with aminobenzaldehyde in the presence of a catalytic amount of Lewis acid as the activator. Despite the use of a mild Lewis acid, this approach requires thermal assistance, long reaction times, and the use of unstable aminobenzaldehydes. The difficulty of synthesizing 3-substituted quinolines is generally encountered also when using other methods. Herein, we report a simple and efficient method...
one-pot phosphine-catalyzed procedure for the synthesis of 3-substituted quinolines under mild conditions from stable starting materials.

3.1.3 Development of 3-Substituted Quinoline Synthesis

We developed the title quinoline synthesis during an expansion of our original double-Michael reaction.\textsuperscript{9,10} We attempted to develop alternative modes of this tandem reaction to generate a variety of heterocyclic scaffolds (Scheme 3.1.3.1). The double-Michael reaction requires two pronucleophilic groups in one of the starting materials to undergo the two successive Michael additions. Replacing one pronucleophilic group with an electrophilic group would alter the nature of the reaction to a cascade of nucleophilic additions (Michael addition followed by an aldol reaction, or vice versa). The presence of an $N$-tosyl group in the substrates not only activated the pronucleophile but also completely inhibited the self-condensation normally observed for Friedländer substrates. In fact, $N$-tosylated $o$-aminobenzaldehydes are bench-stable at room temperature for months of storage without any deterioration. The activated acetylenes are likewise very stable under storage and during the reaction.

\textit{Scheme 3.1.3.1}
3.2 Synthesis of Quinolines

3.2.1 Results

3.2.1.1 Preliminary Result and Reaction Optimization

In a preliminary study of the reaction, we reacted 0.1 M of \(N\)-tosyl-2-aminobenzaldehyde (1a) with 2.0 equivalents of 3-butyne-2-one (2a) in THF in the presence of 20 mol% PPh\(_3\) as the catalyst. We stopped the reaction prior to completion, after 17 h, for a quick evaluation of its feasibility, identifying the dihydroquinoline 3a as the product in 28% yield (Table 3.2.1.1.1, entry 1). We suspected that the long reaction time might have caused 2a to oligomerize in the presence of the nucleophilic catalyst PPh\(_3\), thereby explaining the poor reaction yield. Therefore, we tested the slow addition (syringe pump, 2 h) of 2a to the reaction mixture, but the yield was unchanged (entry 2). We observed \(^1\)H NMR spectra almost no oligomerization in a mixture of 2a and 20 mol% PPh\(_3\) after several days. Increasing the reaction time from 17 to 24 h barely increase the reaction yield (entry 3), implying that a significantly longer time might be required for the reaction to reach completion. Surprisingly, the addition of a stoichiometric amount of PPh\(_3\) did not accelerate the reaction; indeed, it completely shut down the reaction and yielded no product (entry 4). \(^1\)H NMR spectra revealed the complete destruction of 2a within 5 min in the presence of a stoichiometric amount of PPh\(_3\). When the reaction concentration was greater than 0.2 M, the reaction yield improved significantly (entries 1 and 5–7). Among the solvents tested for the reaction, MeCN provided the best performance (entry 8).\(^{11}\) The reactions of 1a in THF at concentrations of 0.4 and 0.2 M resulted in the same yields (entries 6 and 7). In MeCN,
1a is not soluble at a concentration of 0.4 M; therefore, we considered the optimal concentration of 1a in MeCN to be 0.2 M. Decreasing the loading of the catalyst PPh₃ to 10 mol% improved the reaction yield by 4% (entry 10). The reaction yield decreased, however, after decreasing the catalyst loading of 5 mol% (entry 11). Increasing the number of equivalents of the activated acetylene 2a did not improve the reaction performance (entry 12). Careful monitoring revealed that the reaction required only 4 h to reach completion in MeCN (entry 13). Finally, decreasing the amount of 2a to 1.5 equivalents did not change the reaction yield (entry 14), but it did drop dramatically to 14% when we used 1.2 equivalents of 2a (entry 15).

Table 3.2.1.1.1

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<thead>
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<th>entry</th>
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<th>PPh₃ (mol%)</th>
<th>solvent</th>
<th>concentration b (M)</th>
<th>time (h)</th>
<th>yield (%)</th>
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<td>10</td>
<td>MeCN</td>
<td>0.2</td>
<td>4</td>
<td>14</td>
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</table>

\(^a\) Butynone 2a was added in one portion to a solution of 1a and PPh₃ in the indicated solvent. \(^b\) Concentration of the aldehyde 1a. \(^c\) Addition of butynone 2a over 2 h via syringe pump. \(^d\) Not available.

### 3.2.1.2 One-Pot Procedure of Quinoline Synthesis

The isolated dihydroquinoline adduct 3a was unstable and readily decomposed at room temperature.\(^5a\) Treating the vinylogous hemiaminal with acetyl chloride and
pyridine resulted in the clean production of the stable quinoline 4a in excellent yield (Scheme 3.2.1.2.1).

Scheme 3.2.1.2.1

In this two-pot procedure, decomposition of the unstable dihydroquinoline 3a during its isolation resulted in a lower yield of the quinoline product 4a. Such loss could be avoided through a one-pot procedure to directly convert the unstable dihydroquinoline intermediate into the corresponding quinoline. The ideal reagent for such a procedure would necessarily contain a “chloride” to trap the tosyl group in the form of the byproduct TsCl; in addition, it should transform the OH group into a good leaving group. Hydrogen chloride met these requirements; simply quenching the reaction with 1 M aqueous HCl provided the quinoline 4a in 88% yield together with TsCl as a byproduct (Scheme 3.2.1.2.2). This higher yield for the isolated quinoline relative to that of the isolated dihydroquiniline confirmed the loss of the latter product through decomposition in the two-pot procedure.

Scheme 3.2.1.2.2
3.2.1.3 Substrate Scope

Variations on substrate 1

Having optimized the one-pot procedure for the synthesis of the 3-substituted quinoline, we further examined the scope of this reaction for the synthesis of 3-acetylquinolines (Table 3.2.1.3.1). Regardless of the electron-donating or -withdrawing ability of the substituents on the aminobenzaldehyde, the reactions were highly efficient, generating the desired quinolines in high yields. Nevertheless, the nature of the substituents had a significant impact on the rate of the reaction. The reaction of the non-substituted \(N\)-tosyl-2-aminobenzaldehyde (1a) reached completion within 4 h in 88% yield (entry 1). The electronically similar \(N\)-tosyl-3-amino-2-naphthaldehyde (1b) was converted into the quinoline 4b in a comparable yield of 89% after a similar reaction time of 5 h (entry 2). The presence of electron-withdrawing groups significantly slowed the rates of the reactions (entries 3–5), whereas electron-donating groups accelerated them (entries 6 and 7). In general, the presence of a substituent, regardless of its electronic nature, had a positive impact on the yield of the reaction (entry 1 vs. entries 2–7).

Table 3.2.1.3.1

![Table 3.2.1.3.1](image)
<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>time (h)</th>
<th>yield (%)$^b$</th>
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<td>96</td>
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<tr>
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<td><img src="1e.png" alt="image" /></td>
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<td>11</td>
<td>95</td>
</tr>
<tr>
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<td>1.5</td>
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<td>1.5</td>
<td>92</td>
</tr>
</tbody>
</table>

$^a$ 2a (1.5 equiv.) was added in one portion to a solution of 1 (0.2 M) and PPh$_3$ (10 mol%) in MeCN. $^b$ Isolated yield.
Variations on Substrate 2

The successful syntheses of the 3-acetylquinolines encouraged us to expand the scope of the reaction to include other 3-substituted quinolines (Table 3.2.1.3.2). In general, the reaction was highly efficient for acetylenic ketones, but much less efficient for other activated alkynes (entries 1–10 vs. entries 12 and 13). We obtained lower yields for the reactions performed with methyl propiolate or an acetylenic sulfone, due to formation of the corresponding simple Michael adducts with the aldehyde functionality intact (entries 12 and 13). With regard to the acetylenic ketone, the reaction was faster and provided higher yields for aryl acetylenyl ketones than was the case for alkyl acetylenyl ketones (entry 1 vs. entries 2–9). The electronic nature of the aryl group of the acetylenic ketone greatly impacted the reaction rate and yield. With electron-deficient aryl groups, the reactions required only a few minutes to reach completion in excellent yields (entry 2 vs. entries 3–8 and 11). In contrast, electron-rich aryl groups prolonged the reaction and resulted in excellent but lower yields (entry 2 vs. entries 9 and 10). We also examined the versatility of the reaction when using a multifunctional acetylenic ketone, namely a bis(acetylenic ketone); here, the reaction proceeded smoothly to form the bisquinoline product in good yield (entry 11).

Table 3.2.1.3.2
<table>
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<tr>
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<th>product</th>
<th>time (min)</th>
<th>yield (%)</th>
</tr>
</thead>
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<td>88</td>
</tr>
<tr>
<td>2</td>
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<td><img src="image4.png" alt="product2" /></td>
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<td>95</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="substrate3" /></td>
<td><img src="image6.png" alt="product3" /></td>
<td>20</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="substrate4" /></td>
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<td>5</td>
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</tr>
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<td>5</td>
<td>98</td>
</tr>
<tr>
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<td><img src="image11.png" alt="substrate6" /></td>
<td><img src="image12.png" alt="product6" /></td>
<td>5</td>
<td>97</td>
</tr>
<tr>
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<td><img src="image13.png" alt="substrate7" /></td>
<td><img src="image14.png" alt="product7" /></td>
<td>5</td>
<td>96</td>
</tr>
</tbody>
</table>
(1.5 equiv.) was added in one portion to a solution of 1a (0.2 M) and PPh₃ (10 mol%) in MeCN. b Isolated yield. c 2 (1.0 equiv.) was added to a solution of 2.1 Equivalent of 1a (0.21 M) and PPh₃ (20 mol%) in MeCN.
3,4-Disubstituted Quinolines

We further expanded the scope of the reaction to include less reactive o-aminophenones as partners for the syntheses of 3,4-disubstituted quinoline. The reactions afforded the desired products, albeit in lower yields after longer reaction times (Table 3.2.1.3.2, entry 2 vs. Table 3.2.1.3.2). Longer reaction times were expected because of the lower reactivity of ketones relative to corresponding aldehydes. Among the selected o-aminophenones, those with larger R groups required the longest reaction times (entry 3 vs. entries 1, 2 and 4), although the size of the R group had only a minor impact on the reaction yield (entries 1–4).

\textit{Table 3.2.1.3.3}

\[ \begin{align*}
& \text{R} \\
1 & \text{NHTs} \\
2b & \text{Ph} \\
1. \text{PPh}_3 (10 \text{ mol\%}) \quad \text{MeCN, rt, time} \\
2. \text{1 N HCl, 5 min} \\
4 & \text{R} \\
& \text{Ph} \\
\end{align*} \]
<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>time (h)</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td><img src="4t.png" alt="image" /></td>
<td>3.5</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
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<td><img src="4u.png" alt="image" /></td>
<td>3.5</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td><img src="1v.png" alt="image" /></td>
<td><img src="4v.png" alt="image" /></td>
<td>6.5</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td><img src="1w.png" alt="image" /></td>
<td><img src="4w.png" alt="image" /></td>
<td>2.5</td>
<td>67</td>
</tr>
</tbody>
</table>

$^a$ 2b (1.5 equiv.) was added in one portion to a solution of 1 (0.2 M) and PPh$_3$ (10 mol%) in MeCN.  $^b$ Isolated yield.
3.3.1 Mechanistic Study on Quinoline Synthesis

3.3.1.1 NMR Study: Insight into the Reaction

In the hopes of seeing reaction intermediates and knowing more detail about the reaction, we used NMR spectroscopy to monitor the reaction between 1a and 2a in the presence of 10 mol% PPh\textsubscript{3} in CD\textsubscript{3}CN; no intermediates were evident at any time during the course of the reaction. The $^1$H NMR spectra of the reaction mixture revealed that the signal for the NH unit of reactant 1a disappeared within 10 min (Figure 3.3.1.1.1). Apparently, the reaction was initiated rapidly in MeCN with partial deprotonation of the NH group; fast proton exchange made the NH proton undetectable on the time scale of $^1$H NMR spectroscopy at 10.83 ppm (the presence of N-tosylaminobenzaldehyde 1a was verified through TLC analysis during the reaction period). At the same time, two new signals, corresponding to protons H\textsuperscript{a} and H\textsuperscript{b} of the dihydroquinoline adduct, were growing (see NMR from 10 min to 4 h). Because of rapid proton exchange, the proton of the OH group of the dihydroquinoline product was also undetectable in the $^1$H NMR spectra recorded throughout the course of the reaction. In general, only the starting materials and the final dihydroquinoline products were evident (i.e., no intermediates were observed) at any time during the reactions monitored using $^1$H NMR spectroscopy.
Figure 3.3.1.1.1

\[
1a \quad \text{NHTs} + 2a \quad \text{PPh}_3 (10 \text{ mol%}) \quad \text{CD}_2\text{CN, rt, time} \rightarrow 3a
\]

Control 1
4 h

Control 2
4 h
3.3.1.2 Possible Mechanisms

Three possible mechanistic scenarios are suggested. Mechanism 1 involves a general base catalysis (Scheme 3.3.1.2.1). Nucleophilic addition of the free phosphine to the activated alkyne results in the phosphonium allenolate A, which acts as a base to activate the pronucleophile through deprotonation, resulting in a subsequent general base-catalyzed Michael/aldol reaction.
Mechanism 2 (Scheme 3.3.1.2.2) is based on a nucleophilic phosphine catalysis, in which the phosphine is consumed and regenerated along the catalytic cycle; the ion pair B, which is also generated in mechanism 1, is presumably associated in a sufficiently tight manner to enforce the nucleophilic addition within the ion pair.\(^9\) Mechanism 3 (Scheme 3.3.1.2.3) is also based on a nucleophilic phosphine catalysis, where the aldol addition occurs immediately after the formation of the phosphonium allenolate A; hence, the ion pair B is not formed.
Scheme 3.3.1.2.2

Mechanism 2

Scheme 3.3.1.2.3

Mechanism 3
3.3.1.3 General Base Catalysis

Because we isolated the Michael adduct together with the quinoline product in the reaction of methyl propiolate,\textsuperscript{12} we speculate that mechanism 3 was most unlikely to operate. As indicated in Table 3.3.1.3.1, the reaction proceeded to form the quinoline product in the presence of a catalytic amount of a non-nucleophilic base. This result supports the general base catalysis mechanism as operating in this reaction.

Table 3.3.1.3.1

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{b}</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>69</td>
</tr>
<tr>
<td>2\textsuperscript{b}</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>1 M aq. NaOH</td>
<td>58</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield. \textsuperscript{b} Heterogeneous reaction mixture.

3.5 Conclusion

We have developed an efficient one-pot procedure for the syntheses of 3-substituted and 3,4-disubstituted quinolines from the reactions of activated acetylenes with N-tosyl-2-aminobenzaldehydes and N-tosyl-2-aminobenzophenones, respectively. This approach provides a convenient and direct route toward 3-substituted quinolines,
which are challenging to prepare using other methods. The reaction conditions are mild and many different substituents can be introduced without compromising yields.

3.6 Experimental Section

3.6.1 Materials and Methods

All reactions were performed in dry solvents under an Ar atmosphere and anhydrous conditions, unless otherwise indicated. DCM, THF, and MeCN were freshly distilled over CaH$_2$ prior to use. Anhydrous DMSO was used as received from a commercial source. All other reagents were used as received from commercial sources. Reactions were monitored through thin layer chromatography (TLC) on 0.25-mm SiliCycle silica gel plates and visualized under UV light and with permanganate or 2,4-dinitrophenylhydrazine (DNP) staining. Flash column chromatography (FCC) was performed using SiliCycle Silica-P Flash silica gel (60-Å pore size, 40–63 μm). IR spectra were recorded using a Jasco FT-IR 4100 spectrometer. NMR spectra of the dihydroquinoline 3a were obtained using Bruker Avance-500 instruments, calibrated to residual THF-d$_8$ as the internal reference (1.73 and 3.58 ppm for 1H NMR spectra; 25.4 and 67.6 ppm for 13C NMR spectra). NMR spectra of the quinolines 4 were recorded using Bruker Avance-500 instruments, calibrated to CD(H)Cl$_3$ as the internal reference (7.26 and 77.0 ppm for 1H and 13C NMR spectra, respectively). $^1$H NMR spectral data are reported in terms of chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. $^{13}$C NMR spectral data are reported in terms of chemical shift (δ, ppm) and multiplicity, with the coupling constant (Hz) in the case of J$_{CF}$ coupling. The following abbreviations indicate the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m,
A multiplet; br, broad. High resolution mass spectra were recorded using a Waters LCT Premier XE time-of-flight instrument controlled by MassLynx 4.1 software. Samples were infused using direct loop injection from a Waters Acquity UPLC into the multi-mode ionization source. The lock mass standard for accurate mass determination was leucine enkephalin (Sigma L9133).

3.6.2 Preparative Procedures

General Procedure for Substrates 1

The N-tosylbenzaldehydes 1a–g were prepared from the corresponding anthranilic acids in three steps without purification of any intermediates. The N-tosyl-o-aminophenones 1t and 1u were prepared directly from the corresponding o-aminophenones through a single tosylation step. The N-tosyl-o-aminophenones 1v and 1w were prepared from the corresponding 2-aminobenzonitriles in two steps, without purification of any intermediates.

General Procedure for Substrates 2

The activated alkynes 2h–s were prepared in two steps, without purification of any intermediates, according to reported procedures.

General Procedure for Quinolines 4

O-Aminobenzaldehyde (1, 0.2 mmol), PPh₃ (5.3 mg, 10 mol%), and MeCN (1 mL) were added sequentially to a flame-dried flask (10 mL); unless otherwise noted, the mixture was stirred until complete dissolution occurred. The activated acetylene 2 (0.3
was added in one portion and then the mixture was stirred under Ar at room
temperature. Upon completion of the reaction, 1 M aqueous HCl (1 mL) was added and
then the mixture was stirred for 5 min before saturated aqueous NaHCO₃ (1 mL) was
added to neutralize the mixture. The mixture was poured into a separatory funnel along
with DCM (10 mL) and saturated aqueous NaHCO₃ (10 mL). The aqueous phase was
separated and extracted with DCM (2 mL). The combined organic phases were dried
(Na₂SO₄) and concentrated in vacuo; the residue was purified through FCC.

3.6.3 Spectral Data

1-(1-Tosyl-1,4-dihydroquinolin-3-yl)ethanone (3a). 1-(1-Tosyl-1,4-dihydroquinolin-3-yl)ethanone (3a). To a flame-dried flask (10 mL) were sequentially added N-tosyl 2-
aminobenzaldehyde (1a) (0.2 mmol), PPh₃ (5.3 mg, 10 mol%), and MeCN (1 mL). The
mixture was stirred until complete dissolution and then 3-butyn-2-one (2) (23.5 μL, 0.3
mmol) was added in one portion. The mixture was stirred under argon at room
temperature; upon completion of the reaction (4.0–4.5 h), the mixture was concentrated
in vacuo and purified through flash column chromatography (gradient EtOAc/Hex, 3:7 to
1:1) to furnish a slightly yellow solid (52.1 mg, 76% yield). ¹H NMR (500 MHz, THF-d₈) δ
7.81 (d, J = 8.1 Hz, 1H), 7.41–7.37 (m, 4H), 7.32 (s, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.15
(d, J = 8.2 Hz, 2H), 6.81 (d, J = 6.1 Hz, 1H), 5.85 (d, J = 6.1 Hz, 1H), 2.32 (s, 3H), 2.26
(s, 3H); ¹³C NMR (125 MHz, THF-d₈) δ 194.2, 143.3, 137.0, 135.0, 134.2, 132.2, 130.0,
128.9, 128.8, 126.5, 125.6, 124.8, 124.6, 73.3, 24.1, 20.2; HRMS (ESI-TOF) \( m/z \) [M – OH]^+ Calcd for C\(_{18}\)H\(_{16}\)NO\(_3\)S 326.0851, found 326.0847

1-(Quinolin-3-yl)ethanone (4a).\(^{16}\) 88% yield; slightly yellow solid. M.p. 98–99 °C. IR (film) \( \nu \)\(_{\text{max}} \) 3065, 3009, 2920, 1681, 1615, 1587, 1571, 1493, 1371 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.42 (s, 1H), 8.69 (s, 1H), 8.15 (d, \( J = 8.5 \) Hz, 1H), 7.93 (d, \( J = 8.0 \) Hz, 1H), 7.83 (t, \( J = 7.5 \) Hz, 1H), 7.62 (t, \( J = 7.5 \) Hz, 1H), 2.73 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 196.5, 149.5, 149.0, 137.3, 131.9, 129.22, 129.19, 129.1, 127.5, 126.7, 26.7; HRMS (ESI-TOF) \( m/z \) [M + H]^+ Calcd for C\(_{11}\)H\(_{10}\)NO 172.0762, found 172.0762.

1-(Benzo[g]quinolin-3-yl)ethanone (4b). 89% yield; bright yellow solid. M.p. 150–152 °C. IR (film) \( \nu \)\(_{\text{max}} \) 3046, 2998, 2922, 1676, 1612, 1532, 1352, 1215 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.47 (s, 1H), 8.84 (s, 1H), 8.70 (s, 1H), 8.51 (s, 1H), 8.10 (d, \( J = 8.5 \) Hz, 1H), 8.06 (d, \( J = 8.5 \) Hz, 1H), 7.62–7.55 (m, 2H), 2.76 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 196.5, 149.5, 149.0, 137.3, 131.9, 129.22, 129.19, 129.1, 127.5, 126.7, 26.7; HRMS (ESI-TOF) \( m/z \) [M + H]^+ Calcd for C\(_{15}\)H\(_{12}\)NO 222.0919, found 222.0921.
1-[7-(Trifluoromethyl)quinolin-3-yl]ethanone (4c). 94% yield; white crystalline solid. M.p. 126–127 °C. IR (film) \( \nu_{\text{max}} \) 3059, 3020, 2929, 1689, 1594, 1464, 1124 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.50 (s, 1H), 8.75 (s, 1H), 8.45 (s, 1H), 8.08 (d, \( J = 8.5 \) Hz, 1H), 7.80 (d, \( J = 8.5 \) Hz, 1H), 2.77 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 196.1, 150.4, 148.7, 138.3, 133.2 (q, \( J = 32.9 \) Hz), 130.5, 130.4, 128.3, 127.2 (q, \( J = 4.4 \) Hz), 123.5 (q, \( J = 271.0 \) Hz), 123.1 (q, \( J = 4.5 \) Hz), 26.8; HRMS (ESI-TOF) \( m/z \) [M + H]\(^+\) Calcd for C\(_{12}\)H\(_9\)F\(_3\)NO 240.0636, found 240.0632.

![4c](image)

1-(7-Fluoroquinolin-3-yl)ethanone (4d). 96%; white solid. M.p. 116–118 °C. IR (film) \( \nu_{\text{max}} \) 3051, 2923, 1670, 1619, 1602, 1579, 1274, 1193 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.42 (s, 1H), 8.70 (s, 1H), 7.95 (dd, \( J = 8.9, 5.1 \) Hz, 1H), 7.77 (dd, \( J = 9.8, 2.3 \) Hz, 1H), 7.42 (dt, \( J = 8.7, 2.5, 1 \) Hz), 2.73 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 196.2, 164.5 (d, \( J = 254.8 \) Hz), 150.9 (d, \( J = 12.7 \) Hz), 150.2, 140.0, 131.5 (d, \( J = 10.5 \) Hz), 128.8, 123.8, 118.2 (d, \( J = 25.7 \) Hz), 113.3 (d, \( J = 20.7 \) Hz), 26.7; HRMS (ESI-TOF) \( m/z \) [M + H]\(^+\) Calcd for C\(_{11}\)H\(_9\)FNO 190.0668, found 190.0670.

![4d](image)

1-(6,7-Difluoroquinolin-3-yl)ethanone (4e). 95% yield; white solid. M.p. 151–153 °C. IR (film) \( \nu_{\text{max}} \) 3061, 2923, 1682, 1595, 1505, 1475, 1347, 1253, 1234 cm\(^{-1}\); \(^1\)H NMR
(500 MHz, CDCl$_3$) $\delta$ 9.39 (s, 1H), 8.65 (s, 1H), 8.45 (s, 1H), 7.90 (dd, $J = 7.7, 7.7$ Hz, 1H), 7.68 (dd, $J = 8.3, 8.3$ Hz, 1H), 2.74 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 196.0, 153.7 (dd, $J = 257.0, 17.8$ Hz), 150.6 (dd, $J = 257.0, 17.8$ Hz), 147.1 (d, $J = 11.2$ Hz), 136.2, 129.3, 123.8 (d, $J = 7.1$ Hz), 115.9 (d, $J = 17.2$ Hz), 114.3 (d, $J = 17.2$ Hz), 26.7; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for C$_{11}$H$_8$F$_2$NO 208.0574, found 208.0584.

1-(6,7-Dimethoxyquinolin-3-yl)ethanone (4f). $^{17}$ 99% yield; white solid. M.p. 160–163 $^\circ$C. IR (film) $\nu_{\text{max}}$ 3008, 2960, 2925, 2831, 1667, 1597, 1504, 1438, 1427, 1228, 1144, 1003 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.24 (s, 1H), 8.56 (s, 1H), 7.46 (s, 1H), 7.14 (s, 1H), 4.06 (s, 3H), 4.03 (s, 3H), 2.71 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 196.6, 154.4, 150.4, 147.4, 147.3, 135.0, 127.9, 122.4, 107.8, 106.0, 56.2, 56.0, 26.6; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for C$_{13}$H$_{14}$NO$_3$ 232.0974, found 232.0964.

1-(6-Methoxyquinolin-3-yl)ethanone (4g). 92% yield; light-yellow solid. M.p. 122–124 $^\circ$C. IR (film) $\nu_{\text{max}}$ 2956, 2923, 2852, 1682, 1619, 1595, 1503, 1368, 1227, 1023 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.25 (s, 1H), 8.57 (s, 1H), 8.02 (d, $J = 9.0$ Hz, 1H), 7.45 (dd, $J = 9.0, 2.5$ Hz, 1H), 7.14 (d, $J = 2.5$ Hz, 1H), 3.93 (s, 3H), 2.71 (s, 3H); $^{13}$C NMR (125
MHz, CDCl$_3$) δ 196.8, 158.3, 146.7, 146.0, 135.8, 130.6, 129.4, 127.9, 127.8, 124.8, 55.5, 26.8; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for C$_{12}$H$_{12}$NO$_2$ 202.0868, found 202.0870.

Phenyl(quinolin-3-yl)methanone (4h). 7 95% yield; crystalline yellow solid. M.p. 73–75 °C. IR (film) $\nu_{\text{max}}$ 3052, 1647, 1616, 1597, 1571, 1287, 1243 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 9.33 (s, 1H), 8.56 (s, 1H), 8.20 (d, $J = 8.0$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.88–7.86 (m, 3H), 7.69–7.63 (m, 2H), 7.58–7.48 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 194.8, 150.3, 149.4, 138.7, 136.9, 133.0, 131.8, 129.97, 129.95, 129.4, 129.1, 128.6, 127.5, 126.5; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for C$_{16}$H$_{12}$NO 234.0919, found 234.0915.

Naphth-1-yl(quinolin-3-yl)methanone (4i). 7 99% yield; pale yellow oil. IR (film) $\nu_{\text{max}}$ 3051, 1652, 1616, 1589, 1568, 1493, 1286, 1237, 1186 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 9.43 (s, 1H), 8.54 (s, 1H), 8.21–8.19 (m, 2H), 8.08 (d, $J = 8.2$ Hz, 1H), 7.96 (d, $J = 8.2$ Hz, 1H), 7.87–7.84 (m, 2H), 7.66 (d, $J = 7.1$ Hz, 1H), 7.62–7.53 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 196.3, 150.4, 149.7, 139.5, 135.2, 133.8, 132.0, 130.8, 130.7,
129.4, 129.3, 128.5, 128.4, 127.6, 127.5, 126.7, 126.6, 125.4, 124.3; HRMS (ESI-TOF) m/z [M + H]^+ Calcd for C_{20}H_{14}NO 284.1075, found 284.1072.

![4j](image)

**2-Fluorophenyl(quinolin-3-yl)methanone (4j).** 98% yield; light yellow solid. M.p. 84–86 °C. IR (film) ν_{max} 3086, 1664, 1610, 1595, 1568, 1448, 1296, 1213 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 9.33 (s, 1H), 8.54 (s, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 14.1 Hz, 1H), 7.62–7.59 (m, 2H), 7.33 (t, J = 7.9 Hz, 1H), 7.20 (t, J = 8.5 Hz, 1H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) δ 191.7, 160.1 (d, J = 253.6 Hz), 149.7, 138.9, 133.9 (d, J = 8.4 Hz), 132.1, 130.9 (d, J = 2.7 Hz), 129.9, 129.4 (d, J = 10.1 Hz), 127.5, 126.6, 126.0 (d, J = 14.4 Hz), 124.6 (d, J = 3.8 Hz), 116.4 (d, J = 21.8 Hz); HRMS (ESI-TOF) m/z [M + H]^+ Calcd for C_{16}H_{11}FNO 252.0825, found 252.0829.

![4k](image)

**4-Bromophenyl(quinolin-3-yl)methanone (4k).** 98% yield; white crystalline solid. M.p. 115–117 °C. IR (film) ν_{max} 3090, 3056, 1645, 1618, 1584, 1566, 1491, 1366, 1231, 1168, 1069 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 9.30 (s, 1H), 8.53 (s, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.87 (t, J = 8.1 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.65 (t, J = 8.1 Hz, 1H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) δ 193.7,
3,4-Dichlorophenyl(quinolin-3-yl)methanone (4l). 97% yield; light yellow solid. M.p. 112–113 °C. IR (film) νmax 3076, 1637, 1617, 1577, 1385, 1293, 1238 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.28 (d, J = 1.9 Hz, 1H), 8.52 (d, J = 1.9 Hz, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.95–7.92 (m, 2H), 7.87 (ddd, J = 8.5, 7.0, 1.3 Hz, 1H), 7.69–7.61 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 192.4, 149.8, 149.6, 138.7, 136.5, 133.4, 132.1, 131.6, 130.7, 129.5, 129.12, 129.10, 128.9, 127.8, 126.4; HRMS (ESI-TOF) m/z [M + H]⁺ Calcd for C₁₆H₁₁BrNO 312.0024, found 312.0013.

3-(Quinoline-3-carbonyl)benzonitrile (4m). 96% yield; off-white crystalline solid. M.p. 105–107 °C. IR (film) νmax 3067, 2227, 1653, 1616, 1596, 1567, 1291, 1179 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.30 (d, J = 2.7 Hz, 1H), 8.53 (d, J = 2.7 Hz, 1H), 8.21 (d, J = 10.6 Hz, 1H), 8.14 (s, 1H), 8.09 (dt, J = 9.8, 1.9 Hz, 1H), 7.95–7.92 (m, 2H), 7.89 (t, J = 9.7 Hz, 1H), 7.69 (q, J = 10.1 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 192.6, 149.74, 149.66, 138.9, 137.9, 135.8, 133.7, 133.2, 132.4, 129.6, 129.5, 129.2, 128.7, 127.9,
126.3, 117.6, 113.2; HRMS (ESI-TOF) m/z [M + H]^+ Calcd for C_{17}H_{11}N_{2}O 259.0871, found 259.0882.

3-Nitrophenyl(quinolin-3-yl)methanone (4n). 98% yield; white solid. M.p 138–140 °C. IR (film) ν_{max} 3086, 1642, 1612, 1527, 1491, 1346, 1285 cm^{-1}; ^1H NMR (500 MHz, CDCl₃) δ 9.31 (s, 1H), 8.69 (s, 1H), 8.56 (s, 1H), 8.50 (d, J = 8.5 Hz, 1H), 8.20 (t, J = 7.3 Hz, 2H), 7.94 (d, J = 8.5 Hz, 1H), 7.90 (t, J = 7.3 Hz, 1H), 7.77 (t, J = 7.3 Hz, 1H), 7.67 (t, J = 7.3 Hz, 1H); ^13C NMR (125 MHz, CDCl₃) δ 192.4, 149.71, 149.70, 148.2, 138.9, 138.3, 135.3, 132.4, 129.9, 129.5, 129.2, 128.7, 127.9, 127.2, 126.4, 124.5; HRMS (ESI-TOF) m/z [M + H]^+ Calcd for C_{16}H_{11}N_{2}O 279.0770, found 279.0776.

3,4-Dimethoxyphenyl(quinolin-3-yl)methanone (4o). 93% yield; white solid. M.p 93–95 °C. IR (film) ν_{max} 3042, 2995, 2934, 1637, 1592, 1580, 1513, 1418, 1295, 1264, 1247, 1228, 1143, 1113, 1020 cm^{-1}; ^1H NMR (500 MHz, CDCl₃) δ 9.28 (d, J = 1.3 Hz, 1H), 8.54 (d, J = 1.3 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.85 (t, J = 8.2 Hz, 1H), 7.65 (t, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.42 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H); ^13C NMR (125 MHz, CDCl₃) δ 196.1, 150.4, 148.7, 136.8, 131.9, 129.22, 129.19, 129.1, 127.5, 126.7, 26.7; HRMS (ESI-TOF) m/z [M + H]^+ Calcd for C_{18}H_{16}NO_{3} 294.1130, found 294.1130.
Quinolin-3-yl(thien-2-yl)methanone (4p). 786% yield; white solid. M.p. 89–91 °C. IR (film) \( \nu_{\text{max}} \) 3102, 3065, 1629, 1617, 1588, 1517, 1492, 1410, 1366, 1292, 1251, 1062 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\) \( \delta \) 9.33 (s, 1H), 8.64 (s, 1H), 8.18 (d, \( J = 8.9 \) Hz, 1H), 7.93 (d, \( J = 8.9 \) Hz, 1H), 7.84 (t, \( J = 7.2 \) Hz, 1H), 7.79 (d, \( J = 5.0 \) Hz, 1H), 7.70 (d, \( J = 5.0 \) Hz, 1H), 7.64 (t, \( J = 7.5 \) Hz, 1H), 7.21 (t, \( J = 5.0 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\) \( \delta \) 186.1, 149.5, 149.3, 143.1, 137.7, 135.01, 134.99, 131.7, 130.6, 129.4, 129.0, 128.3, 127.6, 126.6; HRMS (ESI-TOF) \( m/z \) [M + H]\(^+\) Calcd for C\(_{14}\)H\(_{10}\)NOS 240.0483, found 240.0494.

1,4-Phenylenebis(quinolin-3-yl)methanone (4q). 63% yield; pale yellow powder. M.p. 237–239 °C. IR (film) \( \nu_{\text{max}} \) 3023, 1641, 1614, 1595, 1571, 1366, 1290, 1246, 1122 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\) \( \delta \) 9.38 (s, 2H), 8.61 (s, 2H), 8.22 (d, \( J = 8.2 \) Hz, 2H), 8.03 (s, 4H), 7.96 (d, \( J = 8.2 \) Hz, 2H), 7.89 (t, \( J = 8.2 \) Hz, 2H), 7.68 (t, \( J = 8.2 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\) \( \delta \) 194.0, 150.0, 149.6, 140.4, 139.1, 132.2, 130.0, 129.5, 129.22, 129.18, 127.8, 126.5; HRMS (ESI-TOF) \( m/z \) [M + H]\(^+\) Calcd for C\(_{26}\)H\(_{17}\)N\(_2\)O\(_2\) 389.1290, found 389.1291.
Methyl quinoline-3-carboxylate (4r).\textsuperscript{18} 60\% yield; white crystalline solid. M.p. 69–70 °C. IR (film) $\nu_{\text{max}}$ 3056, 2948, 2924, 2849, 1714, 1618, 1572, 1433, 1367, 1290, 1240, 1193, 1100 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.44 (s, 1H), 8.84 (s, 1H), 8.16 (d, $J$ = 7.9 Hz, 1H), 7.93 (d, $J$ = 7.9 Hz, 1H), 7.83 (t, $J$ = 7.9 Hz, 1H), 7.62 (t, $J$ = 7.9 Hz, 1H), 4.01 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.7, 149.9, 149.7, 138.7, 131.8, 129.4, 129.0, 127.3, 126.7, 122.9, 52.4; HRMS (ESI-TOF) $m/z$ [M + H]$^+$ Calcd for C$_{11}$H$_{10}$NO$_2$ 188.0712, found 188.0709.

Quinolin-3-yl(tosyl)methanone (4s).\textsuperscript{19} 30\% yield; yellow crystalline solid. M.p. 165–170 °C. IR (film) $\nu_{\text{max}}$ 3068, 3056, 2925, 2851, 1616, 1593, 1585, 1497, 1312, 1304, 1290, 1153, 1140, 1091 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.25 (d, $J$ = 1.7 Hz, 1H), 8.79 (d, $J$ = 1.8 Hz, 1H), 8.14 (d, $J$ = 8.5 Hz, 1H), 7.95 (d, $J$ = 8.5 Hz, 1H), 7.90 (d, $J$ = 8.2 Hz, 2H), 7.86 (t, $J$ = 8.4 Hz, 3H), 7.67 (t, $J$ = 8.4 Hz, 1H), 7.32 (d, $J$ = 8.3 Hz, 2H), 2.39 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 149.2, 147.0, 144.8, 137.9, 136.5, 135.0, 132.5, 130.1, 129.5, 129.1, 128.2, 127.8, 126.3, 21.5; HRMS (ESI-TOF) $m/z$ [M + H]$^+$ Calcd for C$_{16}$H$_{14}$NO$_2$S 284.0745, found 284.0753.
4-Methylquinolin-3-yl(phenyl)methanone (4t).\(^7\) 82\% yield; yellow crystalline solid. M.p. 82–86 °C. IR (film) \(v_{\text{max}}\) 3059, 3030, 2918, 1658, 1645, 1581, 1494, 1449, 1248, 1161 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.82 (s, 1H), 8.17 (d, \(J = 8.3\) Hz, 1H), 8.12 (d, \(J = 8.5\) Hz, 1H), 7.85–7.78 (m, 3H), 7.68–7.61 (m, 2H), 7.49 (t, \(J = 7.8\) Hz, 2H), 2.67 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 196.9, 148.5, 148.0, 143.5, 137.4, 133.8, 131.8, 130.3, 130.1, 130.0, 128.7, 127.5, 127.2, 124.3, 15.8; HRMS (ESI-TOF) \(m/z\) [M + H]\(^+\) Calcd for C\(_{17}\)H\(_{14}\)NO 248.1075, found 248.1064.

Phenyl(4-phenylquinolin-3-yl)methanone (4u).\(^7\) 72\% yield; yellow crystalline solid. M.p. 108–110 °C. IR (film) \(v_{\text{max}}\) 3062, 1654, 1570, 1486, 1324 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.00 (s, 1H), 8.24 (d, \(J = 8.5\) Hz, 1H), 7.83–7.78 (m, 2H), 7.63–7.61 (m, 2H), 7.57–7.54 (m, 1H), 7.46–7.42 (m, 1H), 7.30–7.25 (m, 7H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 196.7, 148.8, 148.4, 146.9, 137.3, 134.8, 133.1, 131.7, 130.4, 130.0, 129.7, 129.6, 128.4, 128.14, 128.12, 127.4, 126.7, 126.3; HRMS (ESI-TOF) \(m/z\) [M + H]\(^+\) Calcd for C\(_{22}\)H\(_{16}\)NO 310.1232, found 310.1230.
4-Cyclohexylquinolin-3-yl(phenyl)methanone (4v). 75% yield; pale-yellow oil. IR (film) ν\textsubscript{max} 3066, 2927, 2853, 1665, 1577, 1498, 1448, 1282, 1241 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 8.64 (s, 1H), 8.34 (br s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 6.3 Hz, 2H), 7.75 (t, J = 7.1 Hz, 1H), 7.61 (q, J = 7.3 Hz, 2H), 7.46 (t, J = 7.3 Hz, 2H), 3.25 (br s, 1H), 1.97 (br s, 2H), 1.85–1.77 (m, 4H), 1.26 (br s, 4H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 198.2, 150.7, 148.7, 148.1, 137.6, 133.8, 132.0, 130.7, 130.1, 129.6, 128.9, 128.6, 126.7, 126.6, 32.0, 27.0, 25.7; HRMS (ESI-TOF) m/z [M + H]\textsuperscript{+} Calcd for C\textsubscript{22}H\textsubscript{22}NO 316.1701, found 316.1699.

4-Cyclopropylquinolin-3-yl(phenyl)methanone (4w). 67% yield; pale-yellow oil. IR (film) ν\textsubscript{max} 3064, 3005, 2922, 1654, 1596, 1567, 1499, 1447, 1322, 1279, 1241, 1226, 1170 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 8.83 (s, 1H), 8.51 (d, J = 8.5 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.85–7.79 (m, 3H), 7.68–7.66 (m, 1H), 7.65–7.59 (m, 1H), 7.59–7.46 (m, 2H), 2.11–2.08 (m, 1H), 0.95–0.93 (m, 2H), 0.59–0.57 (m, 2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 197.2, 148.9, 148.5, 147.4, 138.0, 133.4, 132.7, 130.3, 130.0, 129.6, 128.6, 128.3, 127.1, 125.5, 12.8, 8.2; HRMS (ESI-TOF) m/z [M + H]\textsuperscript{+} Calcd for C\textsubscript{19}H\textsubscript{16}NO 274.1232, found 274.1230.
3.7 Notes and References


(11) The Michael adduct was isolated in 30% yield as a mixture of cis and trans isomers.


APPENDIX THREE

Substrates and Quinoline Products in Chapter Three:

One-Pot Phosphine-Catalyzed Quinoline Syntheses
Figure A3.1 Preparation of Substrate 1

Figure A3.2 Preparation of Substrate 2
Figure A3.3 Substituted 3-Acetylquinolines

Figure A3.4 3-Substituted Quinolines
Figure A3.5 3,4-Disubstituted Quinolines
APPENDIX FOUR

Spectra Relevant to Chapter Three:

One-Pot Phosphine-Initiated General Base-Catalyzed Quinoline Synthesis
Figure A4.1 $^1$H NMR (500 MHz, CDCl$_3$) of compound $3a$

Figure A4.2 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound $3a$
Figure A4.3 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4a

Figure A4.4 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4a
Figure A4.5 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4b

Figure A4.6 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4b
Figure A4.7 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4c

Figure A4.8 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4c
Figure A4.9 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4d

Figure A4.10 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4d
Figure A4.11 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4e

Figure A4.12 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4e
Figure A4.13 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4f

Figure A4.14 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4f
Figure A4.15 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4g

Figure A4.16 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4g
Figure A4.17 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4h

Figure A4.18 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4h
Figure A4.19 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4i

Figure A4.20 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4i
Figure A4.21 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4j

Figure A4.22 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4j
Figure A4.23 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4k

Figure A4.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4k
Figure A4.25 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4I

Figure A4.26 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4I
Figure A4.27 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4m

Figure A4.28 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4m
Figure A4.29 $^1$H NMR (500 MHz, CDCl₃) of compound 4n

Figure A4.30 $^{13}$C NMR (125 MHz, CDCl₃) of compound 4n
Figure A4.31 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4o

Figure A4.32 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4o
Figure A4.33 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4p

Figure A4.34 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4p
**Figure A4.35** $^1$H NMR (500 MHz, CDCl$_3$) of compound 4q

**Figure A4.36** $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4q
Figure A4.37 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4r

Figure A4.38 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4r
Figure A4.39 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4s

Figure A4.40 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4s
Figure A4.41 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4t

Figure A4.42 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4t
Figure A4.43 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4u

Figure A4.44 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4u
Figure A4.45 $^1$H NMR (500 MHz, CDCl$_3$) of compound 4v

Figure A4.46 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 4v
Figure A4.47 $^1$H NMR (500 MHz, CDCl$_3$) of compound $4w$

Figure A4.48 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound $4w$
4.1 Introduction

Since the discovery of antibiotic Nalidixic acid in 1962,\textsuperscript{1} 3-substituted 4-quinolones has attracted extensive studies and modifications to deliver new generations of quinolone-based drugs with enhanced activity against microorganism.\textsuperscript{2} The therapeutic quinolones were known not modeled based on any natural sources; they were entirely of synthetic origin.\textsuperscript{3} As of now, four generations of clinically approved 3-substituted 4-quinolones have been developed and put in highly profitable market. For example, ciprofloxacin\textsuperscript{4a} and levofloxacin\textsuperscript{4b} have been well known as the billion-dollar antimicrobial agents (Figure 4.1.1).
Among a number of conventional methods that can build the quinolone core structure, Gould-Jacobs reaction\(^5\) and Grohe-Heitzer reaction\(^6\) remain the two most effective methods to approach 3-substituted 4-quinolones.\(^{3a}\) Despite the interesting medicinal activity of quinolones, especially 3-substituted-4-quinolones, limited number of synthetic methods on 4-quinolone core have been developed.\(^7\) In light of our previous studies that phosphine catalysis quickly and efficiently gave access to 3-substituted and 3,4-disubstituted quinolines,\(^8\) we have envisioned that 3-substituted-4-quinolone structures could also be achieved by phosphine catalysis\(^9\) (Scheme 4.1.1). In the case that R' is a non-leaving group (R' = H, alkyl or aryl), the hemi-aminal motif in 4-hydroxy-1,4-dihydroquinoline 4 allows a facile detosylation under acidic work up to furnish quinoline 5. In contrast, intermediate 4 can be converted immediately into 3-substituted 4-quinolone 3 when R' is ejected as a good leaving group. This new method would provide a quick access to a new scaffold of N-tosylated 3-substituted 4-quinolones 3.
4.2 Results and Discussion

We began to test the viability of quinolone synthesis with the reaction between phenyl thiobenzoate 1a and alkynone 2a under the same reaction condition that was used for the quinoline synthesis. Under such condition, 1.5 equivalent of alkynone 2a was mixed with thiobenzoate 1a and 0.1 equivalent of triphenylphosphine in a volume of acetonitrile that would make 0.2 M of 1a at room temperature. The reaction could afford the desired quinolone adduct 3aa albeit in low yield. Notably, the supposedly excess coupling partner 2a was completely consumed whereas substrate 1a was still available after the reaction. Doubling the amount of the alkynone 2a could eventually lead to complete consumption of 1a in the reaction and conveniently provide twofold increase in the yield of quinolone product 3aa (Scheme 4.2.1). However, the reaction yield was obtained only within a fairly good range due to the steric hindrance of the leaving group thiophenolate affecting the acylation/cyclization, as we had witnessed similar steric
hindrance lowering the reaction yields in the synthesis of 3,4-disubstituted quinolines from our previous study.\(^8\)

Scheme 4.2.1

Screening the reaction with other aryl acetylenyl ketones 2, a number quinolone structures were generated (Table 4.2.1). In general, the reaction yields varied slightly for different substituents at different positions on the aromatic ring (3aa vs. 3ab–3ai). The general trend of reaction yields corresponding to various aromatic rings was not easily discernable. Electron-deficient aromatic rings indicated a tendency to lower the reaction yields (3aa vs. 3ab–3ag) while electron-rich aromatic rings provided slightly better yields (3aa vs. 3ah and 3ai). Comparing the electron-withdrawing effects of halide substituents at meta position in particular showed a contradictory trend that more electron-withdrawing halides increased the yields of quinolone formation (3ae–3ag).
Various substituents at different positions on substrate 1 also affected the reaction yields (Table 4.2.2). Napthalene ring, with similar electronic property to benzen ring, illustrated comparable yield to the corresponding quinolone product (3aa vs. 3ba). Having substitutions at both C4 and C5 on substrate 1, regardless of electronic property, provided lower yields (3aa vs. 3ca and 3da). The presence of either an electron-donating or electron-withdrawing substituent at C4-position in substrate 1 could afford higher yields (3aa vs. 3ea-3ha) whereas substitution at C5-position lowered the reaction yield (3ia).
Table 4.2.2 \(^a\)

<table>
<thead>
<tr>
<th>R</th>
<th>O</th>
<th>O</th>
<th>Ph</th>
<th>Ts</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>Ph</td>
<td>SPh</td>
<td>N(\text{H})</td>
</tr>
</tbody>
</table>

\[
\text{Ph} - \text{SO}_2 - \text{Ph} + \text{Ph} - \text{CH} = \text{C} - \text{Ph} \xrightarrow{\text{PPh}_3 (10 \text{ mol\%})} \text{Ph} - \text{N} - \text{C} = \text{O} - \text{Ph}
\]

\[
\text{MeCN, rt, 6 h}
\]

\[
\text{1a, 78%}
\]

\[
\text{3aa, 78%}
\]

\[
\text{3ba, 80%}
\]

\[
\text{3ca, 69%}
\]

\[
\text{3ea, 79%}
\]

\[
\text{3fa, 86%}
\]

\[
\text{3ga, 87%}
\]

\[
\text{3ha, 79%}
\]

\[
\text{3ia, 69%}
\]

\[^a\text{Isolated yield.}\]

Quinolone-based drugs were known to contain the structural unit of 4-quinolone-3-carboxylic acid.\(^{10}\) As a result, we turned our attention toward the formation of methyl 4-quinolone-3-carboxylic ester 3\(\text{ak}\) from the reaction between phenyl thiobenzoate 1\(\text{a}\) and methyl propiolate (2\(\text{k}\)). The current reaction condition, however, could only provide an unsatisfactory yield of 3\(\text{ak}\) (Table 4.2.3).\(^{11}\) Due to its potential access to therapeutic quinolone reagents, the formation of 3\(\text{ak}\) was subjected to the optimization process. Triphenylphosphine and acetonitrile were again selected, respectively, as the catalyst and solvent for this transformation.\(^{12}\) As shown in Table 4.2.3, other reaction
parameters were also screened for improvement in the yield of 3ak. It was found that the reaction yields were affected by changing the concentration of substrate 1a (entries 2–6). The reaction provided no quinolone product under neat condition (entry 2). Diluting substrate 1a in the reaction mixture, the yield of quinolone product 3ak was increasingly improved until it reached the concentration of 0.1 M (entries 3 and 4) and decreasing at further dilutions (entries 5 and 6). The reaction yield improved slightly at elevated temperature under microwave-assisted condition (entry 1 vs. entry 3). Longer reaction time resulted in unchanged reaction yield (entry 7 vs. entry 8), indicating no decomposition of the quinolone product under the reaction condition. Loading more triphenylphosphine catalyst was nonbeneficial to the reaction yield while less catalyst loading slightly lowered the product formation (entry 7 vs. entries 9 and 10).

Table 4.2.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration (M) a</th>
<th>Temp (°C) b</th>
<th>Time (h)</th>
<th>PPh3 (%)</th>
<th>Yield (%) c</th>
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<tr>
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<td>rt</td>
<td>12</td>
<td>10</td>
<td>30</td>
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<tr>
<td>2</td>
<td>Neat</td>
<td>72</td>
<td>2</td>
<td>10</td>
<td>0</td>
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<tr>
<td>3</td>
<td>0.2</td>
<td>72</td>
<td>2</td>
<td>10</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>72</td>
<td>2</td>
<td>10</td>
<td>55</td>
</tr>
</tbody>
</table>
It has been known, in making 3,4-disubstituted quinolines, that the steric effect of the R’ group lowered the efficiency of the cyclization to form the quinoline ring and therefore could only sustain a reasonable range of the reaction yield (Scheme 4.1.1). The quinolone formation was not only influenced by the steric effect of R’ but also affected by its leaving ability (R’ = X). Consequentially, a set of substrates 1j–p were prepared and screened to study the effect of the leaving group X on quinolone formation. As expected, substrate 1j with the poor methoxide leaving group provided quinolone product only in a trace amount, while substrate 1k and 1l having the slightly better leaving group of electron-deficient phenoxide and ethanethiolate, respectively, provided slightly better yields (15% and 20% respectively). Accordingly, substrates 1m and 1n containing electron-deficient benzenethiolates were prepared. While substrate 1m exhibited a slight improvement in the reaction yield (61% vs. 65%), substrate 1n with even better leaving group than substrate 1m could only lead to low product yield (22%). The dimerization of 1n under basic reaction condition was the suspected reason

<table>
<thead>
<tr>
<th></th>
<th>Concentration of substrate 1a.</th>
<th>Elevated temperature by microwave.</th>
<th>Isolated yield.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.075</td>
<td>72</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
<td>72</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>82</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>0.1</td>
<td>82</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>0.1</td>
<td>82</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>0.1</td>
<td>82</td>
<td>5</td>
</tr>
</tbody>
</table>

The exact concentration of substrate 1a, elevated temperature by microwave, and isolated yield are provided in the table.
responsible for the low reaction yield.\textsuperscript{13} Substrates 1\textit{o} and 1\textit{p} containing excellent leaving groups and highly reactive carbonyls, surprisingly resulted in no reaction. Although substrate 1\textit{m} was observed to provide a slightly better yield than substrate 1\textit{a} in quinolone synthesis, derivatives of thioester 1\textit{a} was opted for the generation of 4-quinolone-3-carboxylates due to the easy access to thiophenol.

\textit{Table 4.2.4} \textsuperscript{a}

\begin{center}
\begin{tabular}{l}
\textbf{1} & \textbf{2k} & \textbf{3ak} \\
\text{O} & \text{CO}_2\text{Me} & \text{PPh}_3 (10 \text{ mol\%}) \\
\text{MeCN, microwave (82 °C), 2 h} & & \\
\end{tabular}
\end{center}

\begin{tabular}{llll}
\textbf{1a} & \textbf{1j} & \textbf{1k} & \textbf{1l} \\
\text{NHTTs} & \text{NHTTs} & \text{NHTTs} & \text{NHTTs} \\
\text{61\%} & \text{trace} & \text{15\%} & \text{20\%} \\
\end{tabular}

\begin{tabular}{llll}
\textbf{1m} & \textbf{1n} & \textbf{1o} & \textbf{1p} \\
\text{NHTTs} & \text{NHTTs} & \text{no reaction} & \text{no reaction} \\
\text{66\%} & \text{22\%} & \text{no reaction} & \text{no reaction} \\
\end{tabular}

\textsuperscript{a} Isolated yields of quinolone 3\textit{ak} shown in parentheses.

Available substrates 1 from Table 4.2.2 were again utilized in the reaction with methyl propiolate (2\textit{k}) for access to various methyl 4-quinolone-3-carboxylic esters (Table 4.2.5). In general, similar trend to Table 4.2.2 was observed in the reactivity of the substrates toward formation of the new set of quinolones. Similar electronic property of naphthalene ring to benzen ring could lead to comparable yield of the quinolone product (Table 4.2.5, 3\textit{ak} vs. 3\textit{bk}). The presence of substitutions at both C4 and C5 on
substrate 1, regardless of the electronic property, lowered the reactions yields (3ak vs. 3ck and 3dk). Again, the general trend was that better yields would be obtained in the presence of a substituent at C4-position in substrate 1 (3ek, 3gk and 3hk) although the electron-donating methoxy group at C4-position followed the opposite trend to give slightly lower yield (3fk). Similar to table 4.2.2, substitution at C5-position provided lower reaction yield (3ik). Notably, electron-deficient substrates 1 exhibited lower reactivity by requiring longer reaction times (for 3ck and 3ik).

Table 4.2.5

<table>
<thead>
<tr>
<th>Substrate 1</th>
<th>Substrate 2</th>
<th>Conditions</th>
<th>Product 3</th>
<th>Yield</th>
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<tr>
<td><img src="image1.png" alt="Substrate 1 Image" /></td>
<td><img src="image2.png" alt="Substrate 2 Image" /></td>
<td>PPh₃ (10 mol%), MeCN, microwave (82 °C), 2 h</td>
<td><img src="image3.png" alt="Product Image" /></td>
<td>61%</td>
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<td><img src="image37.png" alt="Product Image" /></td>
<td><img src="image38.png" alt="Product Image" /></td>
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</tbody>
</table>

\(^[a]\) Isolated yield. \(^[b]\) Reaction time of 4 h.
Similar to quinoline synthesis from our previous study, quinolone formation was believed to take place through a general base catalysis (Figure 4.2.1). Nucleophilic addition of triphenylphosphine onto activated alkyne 2 would generate the phosphonium zwitterion A which then acted as a strong base to deprotonate and activate the pronucleophile 1. The resulting nucleophile in B now added to activated alkyne 2 to generate the ion pair C. Whereas the subsequent cyclization outcompeted the protonation in the case of dihydroquinoline formation (X = H, alkyl or aryl), the cyclization/acyl substitution (X = SPh) to form the corresponding quinolone 3 was challenged by protonation interruption leading to Michael adduct 7. Upon formation of quinolone 3, the leaving group X would be released into the reaction mixture in the form of the ion pair D, which then added to the free activated acetylene 2 to regenerate the base (in form of the ion pair E) for the continuation of the catalytic cycle. Alternatively, the leaving group X might, by itself, work as a base to activate another molecule of pronucleophile 1. In such case, the generation of proton-donor HX would possibly facilitate the proton transfer, leading to more byproduct 7.
4.3 Conclusion

We successfully generated an array of S-phenyl 2-(N-tosylamide)benzothioates that provided direct access to the structures of 3-aroyl-4-quinolones and 4-quinolone-3-carboxylates. Formation of quinolones in the presence of a phosphine is believed to happen through general base catalysis which is initiated by nucleophilic addition of phosphine to the activated acetylenes.
4.4 Experimental Section

4.4.1 Materials and Methods

All reactions were performed under argon atmosphere with dry solvents and anhydrous conditions, unless otherwise indicated. DCM, THF, toluene, and acetonitrile were freshly distilled over CaH2 before use. DCE, EtOAc, and chlorobenzene were dried over molecular sieve (1:5 w/v) at least two days before use. Anhydrous DMSO and DMF were used as received from a commercial source. All other reagents were used as received from commercial sources. Reactions were monitored by using thin layer chromatography (TLC) performed on 0.25-mm SiliCycle silica gel plates and visualized under UV light, with permanganate and ceric ammonium molybdate (CAM) staining. Flash column chromatography (FCC) was performed using SiliCycle Silica-P Flash silica gel (60 Å pore size, 40–63 μm). IR spectra were recorded on Jasco FT-IR 4100 spectrometer. NMR spectra of quinolone 5 were obtained on Bruker Avance-500 instruments, calibrated using residual chloroform as an internal reference (7.26 and 77.0 ppm for 1H and 13C NMR spectra, respectively). 1H NMR spectral data are reported in terms of chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. 13C NMR spectral data are reported in terms of chemical shift (δ, ppm), multiplicity, and coupling constant (Hz) in the case of JCF coupling. The following abbreviations are used to indicate multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet.
4.4.2 Preparative Procedures

Procedure for Substrates 1

Preparation of substrates 1a–1i and 1k–1n. These substrates were prepared from the corresponding anthranilic acids in three steps. First, the anthranilic acid was mixed with 1/3 equivalents of triphosgene in MeCN/DCM and heated to 50–55 °C before 2 equivalents of pyridine was added. After stirring overnight, the reaction was cooled to room temperature and water was added. The product of isatoic anhydride was filtered and air dried completely before use.\textsuperscript{14} Isatoic anhydride obtained from the previous step was treated with 1 equivalent of either the alcohol (for substrate 1k) or the thiol (for the other substrates) and 10 mol\% NaOH in dry 1,4-dioxane, and the mixture was heated to 90–100 °C until gas evolution ceased. The reaction was cooled to room temperature and water was added. Extraction with EtOAc, followed by concentration under reduced pressure provided the crude product.\textsuperscript{15} The purification at this step was unnecessary for the performance of the next step; however, it could be purified through column chromatography (EtOAc/Hexanes). The crude product was then treated with 1.3 equivalents of TsCl in DCM and pyridine (1 mL/1 mmol), and the reaction was stirred at room temperature until completion. Chromatographic purification provided the clean substrates 1a–1i and 1k–1n.

Substrate 1j was prepared following a known procedure.\textsuperscript{16}

The o-tosylamidobenzoic anhydride 1o and o-tosylamidobenzoic chloride 1p were prepare from N-tosyl anthranilic acid. N-tosyl anthranilic acid was prepared from the
corresponding anthranilic acid following a known procedure. It was recrystallised from 95 °C EtOH for use in the following procedures.

**Preparation of substrate 1o.** To a flame-dried 100 mL round-bottom flask, N-tosyl anthranilic acid (1.0 g, 3.43 mmol) was mixed with benzoyl chloride (0.4 mL, 3.43 mmol) in 30 mL dry Et₂O, and the reaction mixture was then cooled to 0 °C in an ice bath. Pyridine (0.5 mL) was slowly added, and the reaction mixture was stirred vigorously for 2 hours at the same temperature. The white solid was formed, filtered, and washed a few times with cold Et₂O. The solid was dissolved back in benzene and washed with ice-cold concentrated HCl (2x2.5 mL) with the addition of a small portion of ice. It was finally washed with ice-cold water and then dried over Na₂SO₄. The removal of the solvent under reduced pressure afforded the title product 1o as white solid (1.3 g, 96%).

**Preparation of substrate 1p.** To a flame-dried round-bottom flask was added N-tosyl anthranilic acid (3.0 g). To the reaction flask secured under argon was added thionyl chloride (9.0 mL). The reaction mixture was reflux for 2 hours and the excess thionyl chloride was removed under reduced pressure. The crude solid was dissolved in hot benzene and filtered, if necessary, to remove any insoluble particles. The product was precipitated out upon addition of petroleum ether. The solid was then washed with benzene–pentane to afford the clean product 1p as a white solid (2.48 g, 78%).

**Syntheses of Substrates 2**

**Preparation of substrates 2a–2i.** These substrates were prepared following a known procedure.
General procedure for aryl 3-aryloyl-4-quinolones (Table 4.2.1 and 4.2.2)

S-phenyl thiobenzoate (1, 0.3 mmol), PPh₃ (7.9 mg, 10 mol %), MeCN (3 mL), and aryl acetylenyl ketone 2 (0.9 mmol) were added sequentially to an oven-dried round-bottom flask. The mixture was stirred at room temperature over 6 hours before it was concentrated under reduced pressure and purified by flash column chromatography (gradient EtOAc/Hexanes 20% to 30%) to afford quinolone 3.

General procedure for methyl 4-quinolone-3-carboxylic esters (Table 4.2.5)

S-phenyl thiobenzoate (1, 0.3 mmol), PPh₃ (7.9 mg, 10 mol %), MeCN (3 mL), and methyl propiolate 2k (81 µL, 0.9 mmol) were added sequentially to an oven-dried microwave vessel; unless otherwise noted, the mixture was microwaved at 82 °C for 2 hours before it was concentrated under reduced pressure and purified by flash column chromatography (gradient EtOAc/Hexanes 30% to 50%) to afford quinolone 3.

4.4.3 Spectral Data

![S-phenyl 2-(4-methylphenylsulfonamido)benzothioate (1a)](image)

S-phenyl 2-(4-methylphenylsulfonamido)benzothioate (1a). White crystalline solid. M.p. 113–115 °C. IR (film) νₘₐₓ 3201, 1639, 1595, 1577, 1481, 1385, 1331, 1159, 1087 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.19 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.73–7.67 (m, 3H), 7.54–7.47 (m, 4H), 7.45–7.42 (m, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.13 (t, J = 7.7 Hz, 1H), 2.38 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 193.8, 144.0, 138.0, 136.4, 135.3, 134.9,
S-phenyl 3-(4-methylphenylsulfonamido)naphthalene-2-carbothioate (1b). Yellow solid. M.p. 118–120 °C. IR (film) ν\text{max} 3205, 3062, 3032, 1644, 1598, 1505, 1467, 1417, 1352, 1326, 1246, 1169, 1148, 1109, 1088 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 9.73 (s, 1H), 8.66 (s, 1H), 8.14 (s, 1H), 7.92 (d, \(J = 8.1\) Hz, 1H), 7.85 (d, \(J = 8.3\) Hz, 1H), 7.71–7.63 (m, 3H), 7.58–7.48 (m, 6H), 7.22 (d, \(J = 8.3\) Hz, 2H), 2.39 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ 193.8, 143.8, 136.3, 136.0, 135.2, 132.9, 132.3, 130.2, 129.9, 129.7, 129.5, 129.07, 129.04, 127.6, 127.3, 126.6, 126.4, 124.6, 119.0, 21.6. GCMS (EI+) and MALDI-TOF: Decomposition.

S-phenyl 4,5-difluoro-2-(4-methylphenylsulfonamido)benzothioate (1c). White crystalline solid. M.p. 133–135 °C. IR (film) ν\text{max} 3132, 3096, 1644, 1600, 1512, 1418, 1349, 1305, 1152, 1119, 1085 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)) 10.23 (s, 1H), 7.94 (dd, \(J = 10.5, 8.3\) Hz, 1H), 7.72 (d, \(J = 8.3\) Hz, 2H), 7.67 (dd, \(J = 12.2, 7.1\) Hz, 1H), 7.60–7.51 (m, 3H), 7.50–7.45 (m, 2H), 7.30 (d, \(J = 8.5\) Hz, 2H), 2.45 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ 192.1, 154.0 (dd, \(J_{C-F} = 259.2, 13.6\) Hz), 145.7 (dd, \(J_{C-F} = 249.0, 11.9\) Hz), 144.5, 135.9 (dd, \(J_{C-F} = 9.9, 2.5\) Hz), 135.8, 135.2, 130.5, 129.9, 129.6, 127.3,
125.7, 119.2 (dd, $J_{CF} = 7.6, 3.9$ Hz), 118.6 (dd, $J_{CF} = 19.7, 2.7$ Hz), 109.5 (d, $J_{CF} = 22.9$ Hz), 21.6. GCMS (EI+) and MALDI-TOF: Decomposition.

![Structure 1d](image1)

**S-phenyl 4,5-dimethoxy-2-(4-methylphenylsulfonamido)benzothioate (1d).** White solid. M.p. 134–135 °C. IR (film) $\nu_{\max}$ 3127, 3112, 3067, 1615, 1576, 1518, 1442, 1397, 1348, 1287, 1266, 1157, 1128, 1089 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 10.2 (s, 1H), 7.66 (d, $J = 7.9$ Hz, 2H), 7.54–7.50 (m, 3H), 7.47–7.42 (m, 3H), 7.33 (s, 1H), 7.25 (d, $J = 7.9$ Hz, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 2.42 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 191.8, 154.4, 145.0, 144.0, 136.1, 135.3, 133.7, 130.0, 129.7, 129.4, 127.3, 126.7, 115.7, 111.3, 103.9, 56.34, 56.28, 21.6. GCMS (EI+) and MALDI-TOF: Decomposition.

![Structure 1e](image2)

**S-phenyl 5-methyl-2-(4-methylphenylsulfonamido)benzothioate (1e).** White crystalline solid. M.p. 116–119 °C. IR (film) $\nu_{\max}$ 3226, 3191, 3060, 2924, 1636, 1595, 1580, 1488, 1383, 1333, 1243, 1157, 1089 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 10.0 (s, 1H), 7.88 (s, 1H), 7.69–7.66 (m, 3H), 7.55–7.53 (m, 3H), 7.48–7.44 (m, 2H), 7.36 (d, $J = 8.1$ Hz, 1H), 7.26 (d, $J = 8.1$ Hz, 2H), 2.42 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 193.6, 143.9, 136.4, 135.7, 135.3, 135.2, 133.4, 130.1, 129.7, 129.4, 127.3, 126.6, 123.5, 120.8, 21.6, 20.7. Notice, one aromatic carbon was not seen. GCMS (EI+) and MALDI-TOF: Decomposition.
**S-phenyl 5-methoxy-2-(4-methylphenylsulfonamido)benzothioate (1f).** White solid. M.p. 125–126 °C. IR (film) \( \nu_{\text{max}} \) 3279, 3254, 1660, 1609, 1573, 1489, 1389, 1334, 1293, 1277, 1266, 1152, 1092, 1033 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.47 (s, 1H), 7.74 (d, \( J = 9.0 \) Hz, 1H), 7.59 (d, \( J = 8.3 \) Hz, 2H), 7.54–7.51 (m, 4H), 7.43–7.38 (m, 2H), 7.24 (d, \( J = 8.1 \) Hz, 2H), 7.14 (dd, \( J = 9.1, 2.9 \) Hz, 1H), 3.88 (s, 3H), 2.43 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 192.8, 144.3, 137.6, 136.9, 136.1, 135.2, 132.5, 130.4, 129.9, 129.6, 127.3, 125.9, 124.6, 121.9, 116.0, 21.6. GCMS (EI+) and MALDI-TOF: Decomposition.

**S-phenyl 5-bromo-2-(4-methylphenylsulfonamido)benzothioate (1g).** White solid. M.p. 128–130 °C. IR (film) \( \nu_{\text{max}} \) 3194, 3054, 3026, 2923, 1642, 1595, 1563, 1480, 1394, 1345, 1286, 1177, 1154, 1126, 1085 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 10.1 (s, 1H), 8.20 (s, 1H), 7.70 (d, \( J = 8.1 \) Hz, 2H), 7.66 (s, 1H), 7.64 (d, \( J = 2.0 \) Hz, 1H), 7.56–7.53 (m, 3H), 7.49–7.45 (m, 2H), 7.28 (d, \( J = 8.5 \) Hz, 1H), 2.43 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 192.8, 144.3, 137.6, 136.9, 136.1, 135.2, 132.5, 130.4, 129.9, 129.6, 127.3, 125.9, 124.6, 121.9, 116.0, 21.6. GCMS (EI+) and MALDI-TOF: Decomposition.
S-phenyl 5-iodo-2-(4-methylphenylsulfonamido)benzothioate (1h). Yellowish brown solid. M.p. 133–134 °C. IR (film) \( \nu_{\text{max}} \) 3177, 3059, 1638, 1560, 1479, 1472, 1440, 1408, 1388, 1343, 1282, 1183, 1159, 1128, 1089 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 10.14 (s, 1H), 8.37 (d, \( J = 2.0 \) Hz, 1H), 7.80 (dd, \( J = 8.7, 2.0 \) Hz, 1H), 7.72 (d, \( J = 8.2 \) Hz, 2H), 7.56–7.52 (m, 4H), 7.48 (d, \( J = 1.9 \) Hz, 1H), 7.47–7.45 (m, 1H), 7.29 (d, \( J = 8.0 \) Hz, 2H), 2.43 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 192.7, 144.4, 143.4, 138.4, 137.6, 136.1, 135.2, 130.4, 129.9, 129.6, 127.3, 125.9, 124.7, 121.8, 85.8, 21.7. GCMS (EI+) and MALDI-TOF: Decomposition.

S-phenyl 4-fluoro-2-(4-methylphenylsulfonamido)benzothioate (1i). White solid. M.p. 116–117 °C. IR (film) \( \nu_{\text{max}} \) 3195, 3092, 3061, 1639, 1609, 1581, 1495, 1426, 1402, 1339, 1288, 1189, 1155, 1089 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 10.6 (s, 1H), 8.15 (dd, \( J = 8.8, 6.0 \) Hz, 1H), 7.77 (d, \( J = 8.3 \) Hz, 2H), 7.56–7.53 (m, 3H), 7.51–7.47 (m, 3H), 7.30 (d, \( J = 7.9 \) Hz, 2H), 6.86–6.80 (m, 1H), 2.44 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 192.9, 166.2 (d, \( J_{\text{C-F}} = 256.9 \) Hz), 144.4, 140.9 (d, \( J_{\text{C-F}} = 12.2 \) Hz), 136.1, 135.4, 132.8 (d, \( J_{\text{C-F}} = 11.1 \) Hz), 130.3, 129.9, 129.5, 127.3, 126.2, 118.7 (d, \( J_{\text{C-F}} = 2.9 \) Hz), 110.3 (d, \( J_{\text{C-F}} = 22.5 \) Hz), 106.2 (d, \( J_{\text{C-F}} = 27.1 \) Hz), 21.6. GCMS (EI+) and MALDI-TOF: Decomposition.
4-fluorophenyl 2-(4-methylphenylsulfonamido)benzoate (1k). White solid. M.p. 113–115 °C. IR (film) \( \nu_{\text{max}} \) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 10.40 (s, 1H), 8.19 (dd, \( J = 8.0, 1.5 \) Hz, 1H), 7.81–7.78 (m, 3H), 7.58 (ddd, \( J = 8.7, 7.5, 1.5 \) Hz, 1H), 7.28 (d, \( J = 8.0 \) Hz, 2H), 7.19–7.12 (m, 5H), 2.42 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 166.6, 160.4 (d, \( J_{C-F} = 251.7 \) Hz), 145.8 (d, \( J_{C-F} = 2.9 \) Hz), 144.1, 141.1, 136.2, 135.3, 131.6, 129.6, 127.2, 123.0 (d, \( J_{C-F} = 8.6 \) Hz), 122.96, 119.0, 116.2 (d, \( J_{C-F} = 23.7 \) Hz), 114.7, 21.4. GCMS (EI+) and MALDI-TOF: Decomposition.

S-ethyl 2-(4-methylphenylsulfonamido)benzothioate (1m). Brownish solid. M.p. 119–121 °C. IR (film) \( \nu_{\text{max}} \) 3135, 2982, 2940, 1616, 1595, 1575, 1488, 1449, 1400, 1338, 1289, 1189, 1160, 1089 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 10.44 (s, 1H), 7.90 (dd, \( J = 8.0, 1.4 \) Hz, 1H), 7.69 (app d, \( J = 8.4 \) Hz, 3H), 7.45 (dt, \( J = 8.7, 1.5 \) Hz, 1H), 7.21 (d, \( J = 8.6 \) Hz, 2H), 7.06 (dt, \( J = 8.1, 1.1 \) Hz, 1H), 2.99 (q, \( J = 7.5 \) Hz, 2H), 2.35 (s, 3H), 1.31 (t, \( J = 7.5 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 195.6, 144.0, 137.4, 136.3, 134.4, 129.9, 129.7, 127.2, 124.0, 123.4, 120.1, 23.9, 21.5, 14.4. GCMS (EI+) and MALDI-TOF: Decomposition.
S-(4-chlorophenyl) 2-(4-methylphenylsulfonamido)benzothioate (1n). Yellowish crystalline solid. M.p. 123–125 °C. IR (film) $\nu_{\text{max}}$ 3187, 2924, 1635, 1599, 1574, 1490, 1474, 1454, 1410, 1348, 1291, 1178, 1155, 1087, 1015 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.19 (s, 1H), 8.07 (dd, $J = 8.1, 1.3$ Hz, 1H), 7.77–7.71 (m, 3H), 7.57–7.48 (m, 3H), 7.42–7.37 (m, 2H), 7.26 (d, $J = 8.1$ Hz, 2H), 7.16 (ddd, $J = 8.2, 7.5, 1.1$ Hz, 1H), 2.41 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 193.2, 144.1, 138.1, 136.7, 136.5, 136.3, 135.2, 130.1, 129.8, 129.7, 127.3, 124.9, 123.3, 122.7, 119.9, 21.6. GCMS (EI+) and MALDI-TOF: Decomposition.

S-(4-nitrophenyl) 2-(4-methylphenylsulfonamido)benzothioate (1n). White crystalline solid. M.p. 125–126 °C. IR (film) $\nu_{\text{max}}$ cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.1 (s, 1H), 8.36 (d, $J = 8.9$ Hz, 2H), 8.07 (dd, $J = 8.1, 1.4$ Hz, 1H), 7.77–7.72 (m, 3H), 7.68 (d, $J = 8.9$ Hz, 2H), 7.58 (ddd, $J = 8.6, 7.4, 1.4$ Hz, 1H), 7.28 (d, $J = 8.1$ Hz, 2H), 7.19 (ddd, $J = 8.2, 7.5, 1.1$ Hz, 1H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 191.5, 148.6, 144.2, 138.3, 136.3, 135.8, 135.6, 134.9, 130.1, 129.8, 127.3, 124.1, 123.4, 122.3, 119.9, 21.6. GCMS (EI+) and MALDI-TOF: Decomposition.
Benzoic 2-(4-methylphenylsulfonamido)benzoic anhydride (1p). White solid. M.p. 128–130 °C. IR (film) $\nu_{\text{max}}$ 3229, 3062, 1768, 1701, 1599, 1579, 1488, 1453, 1394, 1343, 1202, 1161, 1034 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.27 (s, 1H), 8.09 (d, $J$ = 8.2 Hz, 2H), 8.02 (d, $J$ = 7.9 Hz, 1H), 7.80–7.77 (m, 3H), 7.70 (t, $J$ = 7.4 Hz, 1H), 7.58–7.52 (m, 3H), 7.25 (d, $J$ = 7.9 Hz, 2H), 7.10 (t, $J$ = 7.9 Hz, 1H), 2.37 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 164.2, 161.4, 144.2, 141.9, 136.2, 136.1, 134.9, 131.7, 130.6, 129.7, 128.9, 128.1, 127.3, 122.8, 118.9, 114.3, 21.5. GCMS (El+) and MALDI-TOF: Decomposition.

2-(4-methylphenylsulfonamido)benzoyl chloride (1q). White crystalline solid. M.p. 117–118 °C. IR (film) $\nu_{\text{max}}$ 3277, 1687, 1596, 1576, 1488, 1458, 1400, 1342, 1292, 1198, 1156, 1089 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.58 (s, 1H), 8.18 (d, $J$ = 8.1 Hz, 1H), 7.73–7.71 (m, 3H), 7.57 (t, $J$ = 7.4 Hz, 1H), 7.26 (d, $J$ = 7.8 Hz, 2H), 7.14 (t, $J$ = 7.7 Hz, 1H), 2.38 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.0, 144.5, 140.3, 136.8, 135.7, 135.3, 129.8, 127.2, 123.4, 119.6, 119.1, 21.5. GCMS (El+) and MALDI-TOF: Decomposition.
3-Benzoyl-1-tosylquinolin-4(1H)-one (3aa). 72% yield; slightly yellow crystalline solid. M.p. 147–157 °C. IR (film) ν\text{max} \, 3083, 2922, 2851, 1670, 1626, 1595, 1562, 1467, 1400, 1363, 1338, 1167, 1138, 1084 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 9.04 (s, 1H), 8.36 (d, \(J= 7.8\) Hz, 1H), 8.23 (d, \(J= 8.7\) Hz, 1H), 7.86 (d, \(J= 8.0\) Hz, 2H), 7.84 (d, \(J= 9.2\) Hz, 2H), 7.64 (t, \(J= 7.9\) Hz, 1H), 7.58 (t, \(J= 7.6\) Hz, 1H), 7.48–7.43 (m, 3H), 7.36 (d, \(J= 8.0\) Hz, 2H), 2.42 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 192.8, 175.4, 147.0, 141.2, 137.4, 136.3, 133.3, 133.2, 133.1, 130.5, 129.5, 128.2, 127.7, 127.3, 126.2, 123.0, 118.2, 21.7; GCMS (El+) calcd for C\(_{16}\)H\(_{11}\)NO\(_2\) [M – Ts + H]\(^+\), m/z 249.08, found 249.1.

3-(1-Naphthoyl)-1-tosylquinolin-4(1H)-one (3ab). 68% yield; light brown oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 9.25 (s, 1H), 8.47 (d, \(J= 8.0\) Hz, 1H), 8.29 (d, \(J= 8.0\) Hz, 1H), 8.23 (d, \(J= 8.8\) Hz, 1H), 8.01 (d, \(J= 8.1\) Hz, 1H), 7.91 (d, \(J= 8.2\) Hz, 1H), 7.82 (d, \(J= 8.2\) Hz, 2H), 7.71 (d, \(J= 7.0\) Hz, 1H), 7.61 (t, \(J= 8.8\) Hz, 1H), 7.57–7.47 (m, 4H), 7.39 (t, \(J= 7.8\) Hz, 1H), 7.34 (d, \(J= 8.1\) Hz, 2H), 2.40 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 200.2, 174.4, 148.2, 141.7, 140.0, 139.8, 137.1, 135.2, 133.8, 133.5, 131.5, 129.9, 129.2, 129.1, 128.8, 128.6, 128.2, 127.1, 125.7, 124.8, 124.6, 124.3, 121.7, 111.6, 21.2. GCMS (El+) calcd for C\(_{20}\)H\(_{13}\)NO\(_2\) [M – Ts + H]\(^+\), m/z 299.09, found 299.1.
3-([1,1'-biphenyl]-4-carbonyl)-1-tosylquinolin-4(1H)-one (3ac). 71% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.13 (s, 1H), 8.43 (dd, $J$ = 8.0, 1.6 Hz, 1H), 8.29 (d, $J$ = 8.7 Hz, 1H), 7.99 (d, $J$ = 8.5 Hz, 2H), 7.89 (d, $J$ = 8.5 Hz, 2H), 7.72 (d, $J$ = 8.4 Hz, 2H), 7.69–7.66 (m, 3H), 7.53–7.44 (m, 4H), 7.40 (d, $J$ = 8.1 Hz, 2H), 2.45 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 192.5, 175.6, 147.1, 146.0, 141.4, 140.1, 136.5, 136.2, 133.4, 133.3, 130.7, 130.3, 128.9, 128.2, 127.90, 127.88, 127.44, 127.37, 127.1, 126.4, 123.3, 118.4, 21.8. GCMS (EI+) calcd for C$_{22}$H$_{15}$NO$_2$ [M – Ts + H]$^+$, m/z 325.11, found 325.1.

1-Tosyl-3-(4-(trifluoromethyl)benzoyl)quinolin-4(1H)-one (3ad). 75% yield; light brown solid. M.p. ???. IR (film) $\nu_{\text{max}}$ 3036, 2958, 2924, 1670, 1503, 1466, 1406, 1322, 1311, 1166, 1122, 1064 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.17 (s, 1H), 8.34 (d, $J$ = 8.0 Hz, 1H), 8.24 (d, $J$ = 8.9 Hz, 1H), 7.92 (d, $J$ = 8.0 Hz, 2H), 7.86 (d, $J$ = 8.3 Hz, 2H), 7.72 (d, $J$ = 8.0 Hz, 2H), 7.66 (dt, $J$ = 8.5, 1.3 Hz, 1H), 7.46 (t, $J$ = 7.7 Hz, 1H), 7.38 (d, $J$ = 8.2 Hz, 2H), 2.43 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 192.2, 175.3, 147.1, 142.4, 140.5, 136.3, 134.0 (q, $J_{C,F}$ = 32.4 Hz), 133.3, 133.1, 130.6, 129.5, 127.8, 127.7, 127.4, 126.5, 125.2 (q, $J_{C,F}$ = 3.7 Hz), 123.6 (q, $J$ = 273.3 Hz), 121.9, 118.3, 21.7. GCMS (EI+) calcd for C$_{17}$H$_{10}$F$_3$NO$_2$ [M – Ts + H]$^+$, m/z 317.1, found 317.1.
3-(2-fluorobenzoyl)-1-tosylquinolin-4(1H)-one (3ae). 98.3 mg, 79% yield; brownish crystalline solid. M.p. 139–150 °C. IR (film) ν max 3083, 2927, 2845, 1670, 1644, 1586, 1561, 1406, 1331, 1288, 1224, 1140, 1121, 1032, 1010 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.11 (s, 1H), 8.38 (dd, J = 8.0, 1.4 Hz, 1H), 8.27 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.71–7.63 (m, 2H), 7.59–7.55 (m, 1H), 7.50–7.44 (m, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.34–7.27 (m, 1H), 2.45 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 191.9 (d, J C-F = 2.5 Hz), 175.4, 162.6 (d, J C-F = 246.1 Hz), 147.2, 141.8, 139.7 (d, J C-F = 6.2 Hz), 136.4, 133.4, 133.2, 130.7, 130.0 (d, J C-F = 7.2 Hz), 127.9, 127.8, 127.4, 126.5, 125.4 (d, J C-F = 3.0 Hz), 122.5, 120.1 (d, J C-F = 20.5 Hz), 118.4, 116.6 (d, J C-F = 22.2 Hz), 21.8. GCMS (EI+) calcd for C₁₆H₁₀FNO₂ [M – Ts + H]⁺, m/z 267.07, found 267.1.

3-(3-chlorobenzoyl)-1-tosylquinolin-4(1H)-one (3af). 68% yield; yellowish orange solid. IR (film) ν max 3073, 2920, 2853, 1670, 1645, 1626, 1585, 1465, 1440, 1408, 1332, 1310, 1158, 1148, 1124, 1085 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.11 (s, 1H), 8.39 (dd, J = 8.0, 1.7 Hz, 1H), 8.27 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), (t, J = 1.8 Hz, 1H), 7.75–7.65 (m, 2H), 7.57 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.50–7.40 (m, 4H), 2.46 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 191.9, 175.4, 147.2, 141.9, 139.3, 136.4, 134.5,
133.4, 133.3, 133.0, 130.7, 129.6, 129.3, 127.91, 127.7, 127.4, 126.5, 122.4, 118.4, 21.8. GCMS (EI+) calcd for C\textsubscript{16}H\textsubscript{10}ClNO\textsubscript{2} [M – Ts + H]\textsuperscript{+}, m/z 283.04, found 283.0.

![Diagram of 3-ag](image)

3-(3-bromobenzoyl)-1-tosylquinolin-4(1H)-one (3ag). 66% yield; yellowish solid. M.p. 188-191 °C. IR (film) \( \nu_{\text{max}} \) 3229, 3065, 2980, 2914, 1667, 1645, 1586, 1560, 1406, 1331, 1287, 1223, 1140, 1122, 1032, 1010 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 9.10 (s, 1H), 8.38 (dd, \( J = 8.1, 1.7 \text{ Hz}, 1\)H), 8.26 (d, \( J = 8.8 \text{ Hz}, 1\)H), 8.00 (t, \( J = 1.8 \text{ Hz}, 1\)H), 7.88 (d, \( J = 8.4 \text{ Hz}, 2\)H), 7.79–7.65 (m, 3H), 7.48 (ddd, \( J = 8.0, 7.1, 0.8 \text{ Hz}, 1\)H), 7.41 (d, \( J = 8.3 \text{ Hz}, 2\)H), 7.36 (t, \( J = 7.9 \text{ Hz}, 1\)H), 2.46 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 191.7, 175.4, 147.2, 141.9, 139.5, 136.4, 135.9, 133.4, 133.2, 132.2, 130.7, 129.9, 128.2, 127.92, 127.87, 127.4, 126.5, 122.6, 122.3, 118.4, 21.8. GCMS (EI+) calcd for C\textsubscript{16}H\textsubscript{10}BrNO\textsubscript{2} [M – Ts + H]\textsuperscript{+}, m/z 327.0 and 329.0, found 327.0 and 329.0.

![Diagram of 3-ah](image)

3-(Thiophene-2-carbonyl)-1-tosylquinolin-4(1H)-one (3ah). 79% yield; brown solid. IR (film) \( \nu_{\text{max}} \) 3152, 3107, 1704, 1632, 1617, 1578, 1556, 1494, 1411, 1303, 1240, 1222, 1209, 1144, 1116, 1028, 1004 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 9.89 (s, 1H), 8.52 (d, \( J = 8.3 \text{ Hz}, 1\)H), 8.36 (d, \( J = 8.4 \text{ Hz}, 1\)H), 8.19 (d, \( J = 3.1 \text{ Hz}, 1\)H), 8.08 (t, \( J = 7.5 \text{ Hz}, 1\)H), 7.91 (d, \( J = 4.5 \text{ Hz}, 1\)H), 7.83 (t, \( J = 7.9 \text{ Hz}, 1\)H), 7.79 (d, \( J = 7.9 \text{ Hz}, 2\)H), 7.31 (t, \( J = 7.9 \text{ Hz}, 1\)H), 7.19 (d, \( J = 7.9 \text{ Hz}, 2\)H), 7.17 (d, \( J = 7.9 \text{ Hz}, 1\)H)
= 4.5 Hz, 1H), 7.13 (d, J = 7.8 Hz, 2H), 2.31 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 188.0, 174.2, 147.2, 141.1, 140.5, 139.6, 137.8, 137.3, 137.1, 130.0, 129.4, 128.8, 127.7, 125.9, 124.8, 121.6, 119.8, 109.7, 21.2. GCMS (EI+) calcd for C$_{14}$H$_9$NO$_2$S [M – Ts + H]$^+$, m/z 255.0, found 255.0.

3-(4-(Benzyloxy)benzoyl)-1-tosylquinolin-4(1H)-one (3ai). 83% yield; off-white solid. IR (film) $v_{\text{max}}$ 3055, 3035, 2916, 1666, 1645, 1601, 1407, 1385, 1334, 1312, 1231, 1171, 1148, 1121, 1032, 1009 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.99 (s, 1H), 8.37 (dd, J = 8.0, 1.5 Hz, 1H), 8.23 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.63 (ddd, J = 8.8, 7.1, 1.6 Hz, 1H), 7.44–7.34 (m, 8H), 7.02 (d, J = 8.8 Hz, 2H), 5.13 (s, 2H), 2.40 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 196.7, 174.6, 164.0, 147.8, 144.9, 140.1, 139.7, 137.0, 135.5, 132.4, 129.2, 128.73, 128.66, 128.3, 127.5, 127.1, 125.9, 124.8, 121.7, 120.8, 115.7, 110.0, 70.4, 21.2. GCMS (EI+) calcd for C$_{23}$H$_{17}$NO$_3$ [M – Ts + H]$^+$, m/z 355.1, found 355.1.

3-Benzoyl-1-tosylbenzo[g]quinolin-4(1H)-one (3ba). 80% yield; light brown solid. IR (film) $v_{\text{max}}$ 3035, 2955, 2928, 1644, 1622, 1595, 1320, 1291, 1237, 1169, 1147, 1107, 1029, 1004 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 9.14 (s, 1H), 8.89 (s, 1H), 8.69 (s, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.88 (app t, J = 9.2 Hz, 4H), 7.58 (t, J
= 7.4 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.46 (app t, J = 7.7 Hz, 3H), 7.32 (d, J = 8.2 Hz, 2H), 2.35 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 192.8, 176.3, 146.8, 142.8, 137.6, 134.8, 134.7, 133.1, 132.4, 130.9, 130.2, 129.5, 129.2, 129.0, 128.2, 128.0, 127.8, 127.1, 126.0, 125.0, 121.2, 116.7, 21.6. GCMS (EI+) calcd for C$_{20}$H$_{13}$NO$_2$ [M – Ts + H]$^+$, m/z 299.09, found 299.1.

3-benzoyl-6,7-difluoro-1-tosylquinolin-4(1H)-one (3ca). IR (film) $\nu_{\text{max}}$ 3079, 3070, 3021, 2967, 1635, 1618, 1590, 1529, 1495, 1414, 1384, 1362, 1283, 1203, 1186, 1145 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.99 (s, 1H), 8.16 (dd, J = 12.3, 6.4 Hz, 1H), 8.12 (app t, J = 9.4 Hz, 1H), 7.83 (d, J = 8.1 Hz, 4H), 7.59 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 192.2, 173.7, 153.1 (dd, $J_{C-F}$ = 256.9, 14.2 Hz), 148.9 (dd, $J_{C-F}$ = 254.8, 14.2 Hz), 147.5, 141.5, 137.0, 134.6, 133.4, 132.6, 130.8, 129.4, 128.3, 127.7, 124.9 (dd, $J_{C-F}$ = 4.7, 2.5 Hz), 122.7, 115.5 (dd, $J_{C-F}$ = 18.6, 2.3 Hz), 108.1 (d, $J_{C-F}$ = 25.0 Hz), 21.7. GCMS (EI+) calcd for C$_{16}$H$_9$F$_2$NO$_2$ [M – Ts + H]$^+$, m/z 285.06, found 285.1.

3-Benzoyl-6,7-dimethoxy-1-tosylquinolin-4(1H)-one (3da). 41% yield; light brown crystalline solid. IR (film) $\nu_{\text{max}}$ 3021, 2955, 2925, 2853, 1650, 1637, 1626, 1509, 1392, 1289, 1236, 1221, 1146, 1112 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.99 (s, 1H), 8.09 (s,
1H), 7.80 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.71 (t, J = 7.8 Hz, 1H), 7.65 (s, 1H), 7.60 (t, J = 7.8 Hz, 2H), 7.14 (d, J = 7.8 Hz, 2H), 4.11 (s, 3H), 4.08 (s, 3H), 2.32 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 199.2, 170.9, 158.8, 151.7, 144.8, 142.0, 140.0, 138.2, 134.8, 134.0, 129.3, 129.2, 128.7, 125.9, 115.1, 109.1, 101.8, 101.6, 57.8, 56.6, 21.2. GCMS (EI+) calcd for C18H15NO4 [M – Ts + H]+, m/z 309.1, found 309.1.

3-Benzoyl-6-methyl-1-tosylquinolin-4(1H)-one (3ea). 79% yield; light brown crystalline solid. IR (film) νmax 3073, 3057, 3042, 2956, 2921, 1650, 1609, 1571, 1505, 1398, 1375, 1247, 1153, 1116, 1027, 1004 cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 9.01 (s, 1H), 8.14 (d, J = 1.7 Hz, 1H), 8.12 (d, J = 8.9 Hz, 1H), 7.85 (dd, J = 8.4, 1.5 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.57 (tt, J = 7.4, 1.3 Hz, 1H), 7.45 (tt, J = 7.9, 2.2 Hz, 3H), 7.35 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H), 2.39 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 193.0, 175.5, 146.8, 141.0, 137.4, 136.5, 134.3, 134.2, 133.2, 133.1, 130.5, 129.5, 128.2, 127.7, 127.3, 127.2, 122.8, 118.1, 21.7, 20.7. GCMS (EI+) calcd for C17H13NO2 [M – Ts + H]+, m/z 263.09, found 263.1.

3-benzoyl-6-methoxy-1-tosylquinolin-4(1H)-one (3fa). 86% yield; light brown oil. IR (film) νmax 3067, 3050, 2966, 2924, 1661, 1610, 1583, 1504, 1444, 1398, 1377, 1292, 1221, 1148, 1128, 1029 cm⁻¹; 1H NMR (500 MHz, CDCl3) δ 9.05 (s, 1H), 8.22 (d, J = 9.4
Hz, 1H), 7.90–7.83 (m, 4H), 7.79 (d, J = 3.1 Hz, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (d, J = 7.7 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.25 (dd, J = 9.4, 3.3 Hz, 1H), 3.87 (s, 3H), 2.45 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 198.6, 172.7, 159.8, 145.1, 141.7, 140.1, 135.1, 134.9, 134.0, 129.5, 129.2, 129.0, 128.7, 127.0, 125.8, 123.2, 110.3, 102.5, 56.1, 21.2. GCMS (EI+) calcd for C$_{17}$H$_{13}$NO$_3$ [M – Ts + H]$^+$, m/z 279.09, found 279.1.

3-Benzoyl-6-bromo-1-tosylquinolin-4(1H)-one (3ga). 87% yield; slight brown crystalline solid. IR (film) $\nu_{\text{max}}$ 3075, 1638, 1615, 1556, 1530, 1463, 1372, 1293, 1162, 1122, 1003 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.02 (s, 1H), 8.47 (s, 1H), 8.14 (d, J = 9.3 Hz, 1H), 7.84 (d, J = 9.3 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 9.2 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 2.44 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 192.4, 174.1, 147.2, 141.3, 137.1, 136.0, 135.1, 133.3, 132.9, 130.6, 130.4, 129.5, 128.7, 128.3, 127.7, 123.2, 120.5, 120.1, 21.7. GCMS (EI+) calcd for C$_{16}$H$_{10}$BrNO$_2$ [M – Ts + H]$^+$, m/z 327.0 and 329.0, found 327.0 and 329.0.

3-Benzoyl-6-iodo-1-tosylquinolin-4(1H)-one (3ha). 86% yield; white crystalline solid. IR (film) $\nu_{\text{max}}$ 3084, 3070, 3029, 1672, 1624, 1588, 1465, 1442, 1382, 1331, 1171, 1136, 1119, 1078 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.02 (s, 1H), 8.66 (d, J = 2.2 Hz, 1H), 7.99 (d, J = 9.3 Hz, 1H), 7.89 (dd, J = 9.2, 2.2 Hz, 1H), 7.84 (s, 1H), 7.83 (d, J = 1.2 Hz,
1H), 7.82 (s, 1H), 7.80 (s, 1H), 7.59 (tt, \( J = 7.4 \), 1.2 Hz, 1H), 7.46 (t, \( J = 8.0 \) Hz, 2H), 7.38 (d, \( J = 8.0 \) Hz, 2H), 2.43 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 192.4, 174.0, 147.2, 141.6, 141.3, 137.1, 136.6, 135.7, 133.3, 132.9, 130.6, 129.5, 128.7, 128.3, 127.7, 123.3, 120.0, 91.3, 21.7. GCMS (EI+) calcd for C\(_{16}\)H\(_{10}\)INO\(_2\) [M – Ts + H]\(^+\), m/z 375.0, found 375.0.

![3ia](image)

**3-benzoyl-7-fluoro-1-tosylquinolin-4(1H)-one (3ia).** 69% yield; slightly yellow crystalline solid. IR (film) \( \nu_{\text{max}} \) 3085, 3055, 2923, 1672, 1631, 1609, 1596, 1445, 1389, 1369, 1309, 1248, 1213, 1171, 1085 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.03 (s, 1H), 8.43 (dd, \( J = 9.0 \), 6.6 Hz, 1H), 8.01 (dd, \( J = 11.2 \), 2.2 Hz, 1H), 7.90–7.87 (m, 4H), 7.63 (tt, \( J = 7.5 \), 1.3 Hz, 1H), 7.50 (app t, \( J = 7.8 \) Hz, 2H), 7.43 (d, \( J = 8.3 \) Hz, 2H), 7.2 (ddd, \( J = 9.1 \), 7.6, 2.2 Hz, 1H), 2.48 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 192.6, 174.7, 165.1 (d, \( J_{\text{C-F}} = 253.5 \) Hz), 147.4, 141.4, 137.7 (d, \( J_{\text{C-F}} = 12.4 \) Hz), 137.3, 133.4, 133.0, 130.8, 130.6, 129.6, 128.4, 127.9, 124.1 (d, \( J_{\text{C-F}} = 2.2 \) Hz), 123.5, 114.9 (d, \( J_{\text{C-F}} = 22.8 \) Hz), 105.6 (d, \( J_{\text{C-F}} = 29.3 \) Hz), 21.8. GCMS (EI+) calcd for C\(_{16}\)H\(_{10}\)FNO\(_2\) [M – Ts + H]\(^+\), m/z 267.07, found 267.1.

![3ak](image)

**Methyl 1-tosyl-4-quinolone-3-carboxylate (3ak).** 61% yield; slightly yellow crystalline solid. M.p. 179–190 °C. IR (film) \( \nu_{\text{max}} \) 3049, 3027, 2958, 1678, 1637, 1587, 1505, 1464,
1433, 1314, 1234, 1219, 1132, 1100, 1027 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.42 (s, 1H), 8.39 (dd, J = 8.0, 1.7 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.59 (ddd, J = 8.9, 7.2, 1.7 Hz, 1H), 7.41 (ddd, J = 7.2, 6.2, 0.8 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 3.96 (s, 3H), 2.40 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 174.4, 164.7, 147.1, 144.0, 135.9, 133.2, 133.1, 130.6, 128.1, 127.9, 127.8, 126.5, 118.2, 113.7, 52.5, 21.8.

GCMS (EI⁺) calcd for C₁₈H₁₅NO₅S [M – Ts + H]⁺, m/z 203.06, found 203.1.

Methyl 4-oxo-1-tosyl-1,4-dihydrobenzo[g]quinoline-3-carboxylate (3bk). 58% yield; slight brown solid. IR (film) ν_max 3103, 3025, 1735, 1649, 1623, 1592, 1456, 1403, 1358, 1320, 1239, 1194, 1148, 1170, 1126, 1065 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.51 (s, 1H), 8.93 (s, 1H), 8.62 (s, 1H), 7.98 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.6 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 3.98 (s, 3H), 2.35 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 175.1, 164.6, 146.9, 145.2, 134.6, 133.0, 132.0, 130.4, 130.3, 129.23, 129.19, 129.05, 127.9, 127.7, 127.0, 125.4, 116.6, 112.0, 52.4, 21.6. GCMS (EI⁺) calcd for C₁₅H₁₃NO₃ [M – Ts + H]⁺, m/z 253.1, found 253.1.

Methyl 6,7-difluoro-4-oxo-1-tosyl-1,4-dihydroquinoline-3-carboxylate (3ck). 40% yield; off-white crystalline solid. IR (film) ν_max 3112, 3064, 2962, 2925, 1697, 1682,
1620, 1605, 1563, 1492, 1382, 1287, 1169, 1143, 1116, 1083 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.38 (s, 1H), 8.16 (dd, \(J = 9.8, 8.9\) Hz, 1H), 8.09 (dd, \(J = 12.1, 6.4\) Hz, 1H), 7.79 (d, \(J = 8.5\) Hz, 2H), 7.39 (d, \(J = 8.4\) Hz, 2H), 3.96 (s, 3H), 2.44 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 172.7, 164.2, 153.1 (dd, \(J = 253.7, 13.6\) Hz), 149.1 (dd, \(J = 253.7, 13.6\) Hz), 147.7, 144.3, 132.6, 132.4 (d, \(J = 2.4\) Hz), 130.9, 127.8, 125.5 (dd, \(J = 5.1, 2.5\) Hz), 115.9 (dd, \(J = 18.9, 2.5\) Hz), 113.5, 108.1 (d, \(J = 24.8\) Hz), 52.6, 21.8. GCMS (EI+) calcd for C\(_{11}\)H\(_7\)F\(_2\)NO\(_3\) [M – Ts + H]\(^+\), m/z 239.0, found 239.0.

**Methyl 6,7-dimethoxy-4-oxo-1-tosyl-1,4-dihydroquinoline-3-carboxylate (3dk).** 44% yield; white crystalline solid. IR (film) \(\nu_{\text{max}}\) 3083, 2963, 2924, 1853, 1697, 1637, 1607, 1512, 1429, 1279, 1228, 1171, 1132, 1087, 1035 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.33 (s, 1H), 7.75 (d, \(J = 8.1\) Hz, 2H), 7.747 (s, 1H), 7.61 (s, 1H), 7.34 (d, \(J = 8.2\) Hz, 2H), 3.95 (s, 3H), 3.92 (s, 6H), 2.41 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 173.5, 164.8, 153.0, 148.2, 147.1, 142.7, 133.2, 130.9, 130.5, 127.6, 122.1, 113.3, 107.2, 100.4, 56.14, 56.07, 52.3, 21.7. GCMS (EI+) calcd for C\(_{13}\)H\(_{13}\)NO\(_5\) [M – Ts + H]\(^+\), m/z 263.1, found 263.1.

**Methyl 6-methyl-4-oxo-1-tosyl-1,4-dihydroquinoline-3-carboxylate (3ek).** 68% yield; light yellow solid. IR (film) \(\nu_{\text{max}}\) 3094, 2956, 2923, 1699, 1651, 1593, 1486, 1434, 1362,
1300, 1172, 1135, 1085 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.37 (s, 1H), 8.15 (s, 1H), 8.02 (d, $J = 8.5$ Hz, 1H), 7.76 (d, $J = 7.7$ Hz, 2H), 7.37 (d, $J = 8.5$ Hz, 1H), 7.32 (d, $J = 7.7$ Hz, 2H), 3.93 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.4, 164.6, 146.9, 143.6, 136.6, 134.1, 133.6, 133.1, 130.5, 127.7, 127.5, 127.4, 117.9, 113.3, 52.3, 21.6, 20.7. GCMS (El$^+$) calcd for C$_{12}$H$_{11}$NO$_3$ [M – Ts + H]$^+$, m/z 217.1, found 217.1.

Methyl 6-methoxy-4-oxo-1-tosyl-1,4-dihydroquinoline-3-carboxylate (3fk). IR (film) $\nu_{\text{max}}$ 2957, 2924, 2852, 1675, 1620, 1589, 1504, 1448, 1429, 1292, 1230, 1213, 1158, 1118, 1030, 1007 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.37 (s, 1H), 8.11 (d, $J = 9.4$ Hz, 1H), 7.79 (d, $J = 3.0$ Hz, 1H), 7.77 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.16 (dd, $J = 9.4$, 3.1 Hz, 1H), 3.95 (s, 3H), 3.84 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.2, 168.3, 159.9, 143.1, 141.6, 140.2, 135.5, 128.8, 128.7, 125.9, 123.3, 121.4, 104.3, 102.0, 55.1, 53.9, 21.2. GCMS (El$^+$) calcd for C$_{12}$H$_{11}$NO$_4$ [M – Ts + H]$^+$, m/z 233.1, found 233.1.

Methyl 6-bromo-4-oxo-1-tosyl-1,4-dihydroquinoline-3-carboxylate (3gk). 66% yield; light yellow crystalline solid. IR (film) $\nu_{\text{max}}$ 3078, 2956, 1692, 1610, 1524, 1462, 1434, 1290, 1187, 1153, 1110 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.39 (s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 7.85 (d, $J = 7.7$ Hz, 1H), 7.72 (d, $J = 7.7$ Hz, 1H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.37 (d, $J = 7.7$ Hz, 1H), 7.32 (d, $J = 7.7$ Hz, 1H), 3.95 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.4, 164.6, 146.9, 143.6, 136.6, 134.1, 133.6, 133.1, 130.5, 127.7, 127.5, 127.4, 117.9, 113.3, 52.3, 21.6, 20.7. GCMS (El$^+$) calcd for C$_{12}$H$_{11}$NO$_4$ [M – Ts + H]$^+$, m/z 249.1, found 249.1. 

Methyl 6-bromo-4-oxo-1-tosyl-1,4-dihydroquinoline-3-carboxylate (3gk). 66% yield; light yellow crystalline solid. IR (film) $\nu_{\text{max}}$ 3078, 2956, 1692, 1610, 1524, 1462, 1434, 1290, 1187, 1153, 1110 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.39 (s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 7.85 (d, $J = 7.7$ Hz, 1H), 7.72 (d, $J = 7.7$ Hz, 1H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.37 (d, $J = 7.7$ Hz, 1H), 7.32 (d, $J = 7.7$ Hz, 1H), 3.95 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.4, 164.6, 146.9, 143.6, 136.6, 134.1, 133.6, 133.1, 130.5, 127.7, 127.5, 127.4, 117.9, 113.3, 52.3, 21.6, 20.7. GCMS (El$^+$) calcd for C$_{12}$H$_{11}$NO$_4$ [M – Ts + H]$^+$, m/z 249.1, found 249.1.
8.05 (d, $J = 9.1$ Hz, 1H), 7.77 (d, $J = 7.8$ Hz, 2H), 7.66 (d, $J = 8.7$ Hz, 1H), 7.35 (d, $J = 7.7$ Hz, 2H), 3.95 (s, 3H), 2.41 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.0, 164.2, 147.3, 144.0, 135.9, 134.6, 132.7, 130.6, 130.5, 129.1, 127.7, 120.7, 119.9, 113.7, 52.5, 21.7. GCMS (EI+) calcd for C$_{11}$H$_8$BrNO$_3$ [M – Ts + H]$^+$, m/z 281.0 and 283.0, found 281.0 and 283.0.

Methyl 6-iodo-4-oxo-1-tosyl-1,4-dihydroquinoline-3-carboxylate (3hk). 67% yield; yellowish solid. IR (film) $\nu_{\text{max}}$ 3252, 3160, 3065, 2985, 1691, 1618, 1562, 1460, 1186, 1162, 1119 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.38 (s, 1H), 8.65 (s, 1H), 7.90 (d, $J = 8.9$ Hz, 1H), 7.83 (d, $J = 9.0$ Hz, 1H), 7.77 (d, $J = 6.7$ Hz, 2H), 7.35 (d, $J = 6.8$ Hz, 2H), 3.94 (s, 3H), 2.40 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.5, 168.1, 146.4, 145.4, 140.9, 140.6, 139.4, 133.0, 128.8, 125.9, 123.2, 121.0, 104.9, 95.3, 54.2, 21.3. GCMS (EI+) calcd for C$_{11}$H$_8$IINO$_3$ [M – Ts + H]$^+$, m/z 329.0, found 329.0.

Methyl 7-fluoro-4-oxo-1-tosyl-1,4-dihydroquinoline-3-carboxylate (3ik). 49% yield. IR (film) $\nu_{\text{max}}$ 3064, 2955, 1694, 1626, 1586, 1494, 1457, 1256, 1227, 1147 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.37 (s, 1H), 8.42–8.38 (m, 1H), 7.89 (d, $J = 11.0$ Hz, 1H), 7.80 (d, $J = 8.1$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H), 7.15–7.10 (m, 1H), 3.95 (s, 3H), 2.42 (s, 3H); $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ 173.4, 164.8 (d, $J_{C-F} = 255$ Hz), 164.3, 147.3,
144.1, 137.0 (d, $J_{CF} = 12$ Hz), 132.6, 130.8 (d, $J_{CF} = 11$ Hz), 130.7, 127.8, 124.3, 114.8 (d, $J_{CF} = 22.6$ Hz), 114.0, 105.3 (d, $J_{CF} = 29.3$ Hz), 52.4, 21.7. GCMS (EI+) calcd for C$_{11}$H$_8$FNO$_3$ [M – Ts + H]$^+$, m/z 221.1, found 221.0.

4.5 Notes and References


(11) Methyl propiolate showed inferior reactivity to alkynone, as observed in quinoline synthesis.  

(12) Other solvents were also screened: THF, toluene, DCE, ethyl acetate, chlorobenzene, and DMF. Few other phosphines were also tested with the reaction, including PBN₃, Ph₂Pë, P(4-FC₆H₄)₃, and P(4-MeOC₆H₄)₃.

(13) Significant dimerization of substrate 1n was observed during its preparation under basic condition. Careful control and reduced basicity would enable the formation of 1n.


APPENDIX FIVE

Substrates and Quinolone Products in Chapter Four:

Phosphine-Initiated General Base-Catalyzed Quinolone Syntheses
Figure A5.1 Preparation of substrate 1

Figure A5.2 All substrates 1

Figure A5.2 Preparation of Substrate 2
Figure A5.3 List of 3-arylated 4-quinolones

Figure A5.4 List of 3-phenylated 4-quinolones
Figure A5.5 List of 4-quinolone-3-carboxylic methyl esters
APPENDIX SIX

Spectra Relevant to Chapter Four:

Phosphine-Initiated General Base-Catalyzed Quinolone Syntheses
Figure A6.1 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1a

Figure A6.2 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1a
Figure A6.3 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1b

Figure A6.4 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1b
Figure A6.5 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1c

Figure A6.6 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1c
Figure A6.7 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1d

Figure A6.8 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1d
Figure A6.9 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1e

Figure A6.10 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1e
Figure A6.11 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1f

Figure A6.12 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1f
$\text{Br} \quad \text{O} \\
\text{PH} \quad \text{NHTs}$

Figure A6.13 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1g

Figure A6.14 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1g
Figure A6.15 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1h

Figure A6.16 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1h
Figure A.6.17 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1i

Figure A.6.18 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1i
Figure A.6.19 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1k

Figure A.6.20 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1k
Figure A6.21 $^1$H NMR (300 MHz, CDCl$_3$) of compound 11

Figure A6.22 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 11
Figure A6.23 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1m

Figure A6.24 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1m
Figure A6.25 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1n

Figure A6.26 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1n
Figure A6.27 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1o

Figure A6.28 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1o
Figure A6.29 $^1$H NMR (300 MHz, CDCl$_3$) of compound 1p

Figure A6.30 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 1p
Figure A6.31 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3aa

Figure A6.32 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3aa
Figure A6.33 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ab

Figure A6.34 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ab
Figure A6.35 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ac

Figure A6.36 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ac
Figure A6.37 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ad

Figure A6.38 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ad
Figure A6.39 ^1^H NMR (300 MHz, CDCl\textsubscript{3}) of compound 3ae

Figure A6.40 ^1^3^C NMR (75 MHz, CDCl\textsubscript{3}) of compound 3ae
Figure A6.41 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3af

Figure A6.42 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3af
Figure A6.43 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ag

Figure A6.44 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ag
Figure A6.45 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ah

Figure A6.46 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ah
Figure A6.47 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ai

Figure A6.48 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ai
Figure A6.49  $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ba

Figure A6.50  $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ba
Figure A6.51 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ca

Figure A6.52 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ca
Figure A6.53 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3da

Figure A6.54 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3da
Figure A6.55 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ea

Figure A6.56 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ea
Figure A6.57 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3fa

Figure A6.58 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3fa
Figure A6.59 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ga

Figure A6.60 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ga
Figure A6.61 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ha

Figure A6.62 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ha
Figure A6.63 ¹H NMR (300 MHz, CDCl₃) of compound 3ia

Figure A6.64 ¹³C NMR (75 MHz, CDCl₃) of compound 3ia
Figure A.65 ¹H NMR (300 MHz, CDCl₃) of compound 3ak

Figure A.66 ¹³C NMR (75 MHz, CDCl₃) of compound 3ak
Figure A6.67 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3bk

Figure A6.68 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3bk
Figure A6.69 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ck

Figure A6.70 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ck
Figure A6.71 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3dk

Figure A6.72 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3dk
Figure A6.73 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ek

Figure A6.74 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ek
Figure A6.75 ¹H NMR (300 MHz, CDCl₃) of compound 3fk

Figure A6.76 ¹³C NMR (75 MHz, CDCl₃) of compound 3fk
Figure A6.77 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3gk

Figure A6.78 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3gk
Figure A6.79 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3hk

Figure A6.80 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3hk
Figure A6.81 $^1$H NMR (300 MHz, CDCl$_3$) of compound 3ik

Figure A6.82 $^{13}$C NMR (75 MHz, CDCl$_3$) of compound 3ik
5.1 Background and Introduction

5.1.1 History of Asymmetric Catalysis

5.1.1.1 Initial Attempts on Asymmetric Catalysis

Most chiral natural products exist in enantiomerically pure forms, synthesized in Nature mostly through enzyme-mediated catalysis.¹ Not surprisingly, enantioselective catalysis processes were long believed, up until the early 1900s, to be accessible using only natural enzymes, until Bredig's attempts at (i) kinetic resolution of racemic camphorcarboxylic acid through selective decarboxylation in a chiral medium (e.g., L- or D-limonene) or in the presence of a chiral alkaloid catalyst (e.g., nicotine or quinidine)²–⁵ and (ii) asymmetric synthesis of mandelonitrile through the addition of HCN to benzaldehyde in the presence of a cinchona alkaloid catalyst (e.g., quinidine or quinine)²,³,⁶. Although these effortful studies were conceptually groundbreaking, the enantioselectivity achieved was synthetically impractical (<10% ee). A synthetically useful enantiomeric excess of 74% was first achieved by Pracejus in the synthesis of (−)-methyl α-phenylpropionate from methyl phenyl ketene and methanol with O-acetylquinine as the catalyst.⁷
5.1.1.2 Advent of Asymmetric Organometallic Catalysis

Catalytic asymmetric synthesis was established as a reliable and practical approach when Knowles reported, in the late 1960s and early 1970s, the first asymmetric hydrogenations catalyzed by transition metals bearing chiral phosphine ligands.\textsuperscript{8–13} Shortly afterward, a great number of chiral phosphine ligands were developed to provide excellent enantioselectivity in transition metal-catalyzed hydrogenations.\textsuperscript{14,15} The major disadvantage of transition metal catalysis, however, is that traces of toxic heavy metals can be left behind in the final products.

5.1.1.3 Early Asymmetric Organocatalysis

In the early 1970s, L-proline-mediated asymmetric Robinson annulation was first reported,\textsuperscript{16–19} although the synthesis community paid very little attention to it because the reaction was considered a novelty. Since the concept of organocatalysis—the utilization of metal-free small organic molecules as catalysts for organic transformations—was developed and recognized in the late 1990s, there has been an explosion of research in the field of organocatalysis,\textsuperscript{20–22} which is now widely considered as a third main branch of research in asymmetric synthesis, beside enzymatic catalysis and organometallic catalysis.
5.1.2 Asymmetric Induction Modes in Organocatalysis

A chiral organocatalyst can render enantioinduction (asymmetric induction) through a few modes, including covalent bonding, ionic bonding, and hydrogen bonding (Figure 5.1.2.1).\textsuperscript{21}

*Figure 5.1.2.1*

**Covalent bonding**

\[
\begin{align*}
\text{substrate} & : \quad \text{Ph} - \text{N} - \text{t-Bu} \\
\text{catalyst} & : \quad \text{Ph} - \text{N} - \text{t-Bu}
\end{align*}
\]

**Ionic bonding**

\[
\begin{align*}
\text{substrate} & : \quad \text{R}^2 \text{Cl} \\
\text{catalyst} & : \quad \text{n-C}_5\text{H}_{11} - \text{N} - \text{t-Bu} - \text{S} - \text{N} - \text{t-Bu} - \text{N} - \text{t-Bu}
\end{align*}
\]
5.1.3 Feature of Phosphine-Catalyzed Double-Michael Reaction

In 2007, we reported a phosphine-catalyzed double-Michael addition in which a bisphosphine was the best catalyst.\textsuperscript{23–25} We suggested that anchimeric assistance by the other tethered phosphino group stabilized the resultant phosphonium cation in the transitional intermediates, leading to a higher yield of the double-Michael adduct. Because of the rigid architecture provided by intramolecular anchimeric assistance, we suspected that a chiral element at the terminus of the non-reactive phosphino group would be likely to endow the reactive phosphonium center with steric bias, potentially leading to a new mode of enantioinduction (Figure 5.1.3.1). Practically, the synthesis of chiral bisphosphines is often challenging because it requires careful handling of pyrophoric and air-sensitive phosphorus-containing intermediates.
5.1.4 Aminophosphine vs. Bisphosphine

As a variant of the bisphosphine catalyst, we sought an equivalent to a phosphino group that would be easy to handle yet stabilize the tethered phosphonium cation through anchimeric assistance. In Verkade’s proazaphosphatrane, the nitrogen atom could efficiently stabilize the resultant protonated phosphonium center, making it a super base (Figure 5.1.4.1).

Therefore, we expected an aminophosphine—with an amino group replacing a tethered phosphino group in the bisphosphine—to function much like a bisphosphine when catalyzing double-Michael additions (Figure 5.1.4.2). Less toxic and more air-stable than phosphines, amines also have advantages in terms of their synthesis and storage. Furthermore, many diverse chiral amines are readily available commercially.
from natural sources. Appending a customized chiral element to an achiral amine is also easy to achieve through simple alkylation, imine reduction, or peptide coupling/reduction. Therefore, we proceeded to synthesize a variety of chiral aminophosphines to determine if they could result in enantioinduction via anchimeric assistance and concurrently to develop an asymmetric variant of the double-Michael reaction.

Figure 5.1.4.2

5.1.5 Double-Michael Reaction: Proposed Mechanism

We propose a reaction mechanism for the double-Michael reaction that occurs via pathway A, in which the cyclization is accomplished through direct intramolecular S_n2 displacement of the phosphonium cation (Scheme 5.1.5.1). Alternatively, the reaction could possibly follow mechanistic pathway B, in which the intermediate phosphonium zwitterions serve as a Brønsted base and the resulting phosphonium species as a counter cation of the reactive intermediate anions. In either case, the most important factor affecting the success of cyclization would be the stability of the phosphonium species generated along the pathway. If the reaction employed a chiral aminophosphine catalyst, the enantioselectivity would probably be
induced via anchimeric assistance of the amine in stabilizing the quaternary phosphonium center.

Scheme 5.1.5.1

5.2 Results and Discussion

5.2.1 Commercially Available Chiral Bisphosphines

Chiral bisphosphines featuring $C_2$- or local $C_2$-symmetry, obtained directly from commercial sources, were tested in the double-Michael reaction between $o$-$(p$-tosylamido)phenylmalonate (1a) and 3-butyn-2-one (2a) to form the indoline product 3aa (Table 5.2.1.1). The optimal conditions for the reaction catalyzed by diphenylphosphinopropane (DPPP) required an elevated temperature (entry 1). Employing chiral bisphosphines as catalysts, the double-Michael reaction at elevated
temperature exhibited no enantioinduction (entries 2, 4, and 6). At room temperature, however, the reactions exhibited low levels of enantioselectivity (entries 3, 5, 7, and 8). Employing \((S,S)\)-DIOP as a chiral catalyst resulted in no desired product (entry 9). The use of chiral bisamine \((DHQ)_2PHAL\) provided a lower yield, with no improvement in enantioselectivity (entry 10). Catalysis by the \((R,R)\)-DACH-naphthyl Trost ligand, a chiral bisamidophosphine, resulted in a much inferior yield, with no enantioselectivity (entry 11). Surprisingly, the aminophosphine 42, which has the same rigid carbon framework and distance between the two functional groups as those in DIOP, catalyzed the reaction successfully, providing a good yield and a slightly improved enantioselectivity (entries 9 and 12). This result offered us a hope that we could develop an asymmetric variant of the double-Michael addition using a chiral aminophosphine as the catalyst.

*Table 5.2.1.1*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)$^a$</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DPPP</td>
<td>80</td>
<td>9</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>((S,S))-DIPAMP</td>
<td>80</td>
<td>7</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>rt$^b$</td>
<td></td>
<td>48</td>
<td>87</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>((R,R))-Et-DuPHOS</td>
<td>80</td>
<td>9</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rt</td>
<td>9</td>
<td>58</td>
<td>5</td>
</tr>
<tr>
<td>---</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>6</td>
<td>(S,S)-Me-BPE</td>
<td>80</td>
<td>7</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>(R)-BINAP</td>
<td>rt</td>
<td>9</td>
<td>78</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>(S,S)-DIOP</td>
<td>rt</td>
<td>24</td>
<td>n/r$^c$</td>
<td>n/a$^d$</td>
</tr>
<tr>
<td>9</td>
<td>(DHQ)$_2$PHAL</td>
<td>rt</td>
<td>9</td>
<td>46</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>(R,R)-DACH-napthyl Trost ligand</td>
<td>rt</td>
<td>16</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>(4S,5R)-42$^e$</td>
<td>rt</td>
<td>24</td>
<td>86</td>
<td>6</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield. $^b$ rt = Room temperature. $^c$ n/r = No reaction. $^d$ n/a = Not applicable. $^e$ Synthetically prepared phosphine:

```
(4S,5R)-42
```

### 5.2.2 Designs of Chiral Aminophosphines

#### 5.2.2.1 Synthesis of Aminophosphines

Scheme 5.2.2.1.1 outlines our approach for the syntheses of three-carbon-tethered aminophosphines. It starts with acylation of a primary or secondary amine with
acryloyl chloride to form the corresponding acrylamide, followed by Michael addition of diphenylphosphine to generate an amidophosphine, which would eventually be converted to the aminophosphine through LiAlH₄-mediated reduction. Because the chirality of the amine would be endowed to the reactive phosphonium center, our goal was to identify potential chiral amines from either commercial or synthetic sources. Notably, we could also test the amidophosphine, an immediate precursor of the aminophosphine, for its enantioinduction ability in double-Michael reactions.

Scheme 5.2.2.1.1

5.2.2.2 Chiral Aminophosphines Derived from a Simple Chiral Amine

To test the viability of the proposed synthetic route, we employed an inexpensive chiral amine 1 to synthesize the chiral aminophosphine 5 (Scheme 5.2.2.2.1). The chiral amine 1 was first N-methylated via formylation followed by LiAlH₄-mediated reduction to furnish the chiral amine 2, which we then treated it with acryloyl chloride to prepare the acrylamide substrate 3 for the subsequent Michael addition of diphenylphosphine. We obtained our target aminophosphine 5 after LiAlH₄-mediated reduction of the Michael adduct amidophosphine 4. This synthetic route was reliable and the purification of the products was straightforward.
When testing the chiral aminophosphine 5 in the double-Michael addition, we detected an enantioselectivity of 5% ee. The reaction yield was, however, low, due to our early termination of the reaction to determine the enantioselectivity (Table 5.2.2.2.1, entry 1).

Table 5.2.2.2.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aminophosphine</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5</td>
<td>46</td>
<td>5</td>
</tr>
</tbody>
</table>
Isolated yield. \(^b\) Reaction time was 6 h.

Shortening the tether length in the aminophosphine would bring the two functional groups in closer proximity, potentially enhancing the interaction between amino and phosphino centers and therefore forming more-rigid reaction intermediates. Accordingly, we synthesized the aminophosphine 7 from the amine 2 through coupling with bromoacetyl bromide, substitution with potassium diphenylphosphide, and LiAlH\(_4\)-mediated reduction of the amidophosphine 6 (Scheme 5.2.2.2.2). To our dismay, when
we employed this chiral aminophosphine 7 in the double-Michael reaction, the enantioselectivity of the reaction was barely detectable (Table 5.2.2.2.1, entry 3).

**Scheme 5.2.2.2.2**

We surmised that it might be more advantageous to feature a free N–H group in the aminophosphine to provide a site for hydrogen bonding to the C=O oxygen atom of the alkynone substrate.\(^{31-35}\) such hydrogen bonding would bring the two functional groups closer together in the transitional intermediate (Figure 5.2.2.2.1).

**Figure 5.2.2.2.1**

As a result, we treated the chiral amine 1 with acryloyl chloride to prepare the acrylamide 8; Michael addition with diphenylphosphine under basic conditions furnished the amidophosphine 9, which underwent LiAlH₄-mediated reduction to generate the target chiral aminophosphine 10 (Scheme 5.2.2.2.3). The enantioinduction in the double-Michael reaction catalyzed by the aminophosphine 10 was similarly low to that induced by the aminophosphine catalyst 5, which features no N–H bond (Table 5.2.2.2.1, entry 3).
Interestingly, the amidophosphines 4, 6, and 9 also catalyzed the double-Michael reaction, with yields and enantioselectivities comparable to those of their corresponding aminophosphines (cf. entries 1–6).

Scheme 5.2.2.2.3

5.2.2.3 Chiral Aminophosphines Derived from L-Proline

Because our simple versions of aminophosphines with acyclic chiral amine motifs did not work well as catalysts for the asymmetric double-Michael additions, we decided to insert a more-rigid chiral amine motif derived from L-proline, which has been employed frequently in asymmetric reactions.\textsuperscript{36,37} O-Benzyl aminophosphine 17 became our first synthetic target (Scheme 5.2.2.3.1). After a simple sequence of LiAlH\textsubscript{4}-mediated reduction, N-Boc protection, and O-benzylation, we obtained the globally protected L-prolinol 14. The Boc group of 14 was released under acidic conditions and the resulting free amine was converted to the acrylamide 15 upon treatment with acryloyl chloride. Michael addition of diphenylphosphine to the acrylamide 15 under basic conditions cleanly afforded the amidophosphine 16, which underwent LiAlH\textsubscript{4}-mediated reduction to yield the target aminophosphine 17.
Unfortunately, we detected only 3% ee when applying the aminophosphine 17 to catalyze the double-Michael reaction. The corresponding amidophosphine 16 provided undetectable enantioselectivity, although the product yield was higher than that obtained with the aminophosphine 17 (Table 5.2.2.3.1, entries 1 and 2).

Table 5.2.2.3.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aminophosphine</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
</table>

---

<sup>a</sup> Yield of product after isolation and purification.

<sup>b</sup> Enantiomeric excess determined by chiral HPLC.
We suspected that unmasking the OH group in the aminophosphine 17 might potentially provide hydrogen bonding to the C=O oxygen atom in the alkynone substrate, possibly helping to lock the reaction intermediates into a more-rigid conformation and, hopefully, create a more-asymmetric environment in the subsequent steps toward the Michael adduct (Figure 5.2.2.3.1).\textsuperscript{31–35} The hydroxymethyl aminophosphine 19 was quickly accessible from the unprotected L-prolinol 12 through
the sequence of N-acryloylation, Michael addition of diphenylphosphine, and LiAlH₄-mediated reduction (Scheme 5.2.2.3.2).

Scheme 5.2.2.3.2

The resulting enantioselectivities were slightly increased and encouraging: 6% ee for the aminophosphine 19 and 9% ee for the corresponding amidophosphine 18 (Table 5.2.2.3.1, entries 3 and 4). Notably, the yield and enantioselectivity provided by the amidophosphine 18 were superior to those induced by the aminophosphine 19 in the double-Michael addition.

Figure 5.2.2.3.1

Another scaffold of amino acid-derived phosphines has recently been successfully employed in asymmetric nucleophilic catalysis. In this scaffold, the two functional groups are tethered through two carbon atoms, with the chiral element residing on the tether bridge. The aminophosphines 21 and 23–25 are derived accordingly from L-proline (Scheme 5.2.2.3.3).
The \textit{N}-Tosyl aminophosphine 21 was quickly prepared from \textit{L}-prolinol 12 after global tosylation and subsequent direct displacement of the tosyl group with potassium diphenylphosphide. The aminophosphines 24 and 25 were both obtained from the aminophosphine 23, through LiAlH\textsubscript{4}-mediated reduction and acidic Boc-deprotection, respectively; the aminophosphine 23 itself was quickly accessible through tosylation of \textit{N}-Boc-\textit{L}-prolinol 13 and subsequent substitution with potassium diphenylphosphide. To our dismay, these \textit{L}-proline-derived aminophosphines provided generally unsatisfactory levels of enantioselectivity in the double-Michael reaction, with the exception of 23 (Table 5.2.2.3.2, entries 1–4).
Introduction of more substituents to the chiral element in a L-proline-derived aminophosphine could possibly enhance the catalyst enantioinduction. Aminophosphine 31 and 32 were thus synthesized as illustrated in Scheme 5.2.2.3.4.
α,α-Diphenyl L-prolinol trimethylsilyl ether 28, which was easily prepared from L-proline (11) using a reported procedure, was subjected to the aforementioned route of phosphine synthesis including acryloylation and Michael-addition of diphenylphosphine. Unexpectedly, TMS protecting group was cleaved under basic Michael-addition condition to yield the hydroxy amidophosphine 30. The reintroduction of the silyl protecting group to amidophosphine 30 was not achievable due to the hydrolysis of the product during chromatography. Amidophosphine 30 was then set forward to LAH reduction to provide aminophosphine 31 which could be silylated to furnish O-TMS aminophosphine 32. Yet, the application of aminophosphine 31 and 32 to the double-
Michael reaction only provided lower reaction yield and enantioselectivity (Table 5.2.2.3.3, entries 2 and 3). Likewise, amidophosphine 30 resulted in no enantioinduction despite higher yield than the corresponding aminophosphine 31 in the double-Michael reaction (entry 1).

Table 5.2.2.3.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aminophosphine</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Aminophosphine 30" /></td>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Aminophosphine 31" /></td>
<td>74</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Aminophosphine 32" /></td>
<td>73</td>
<td>2</td>
</tr>
</tbody>
</table>
*Isolated yield.* \(^b\) Reaction time was 6 h.

### 5.2.2.4 Chiral Aminophosphines Derived from (S)-Binol

Because the L-proline-derived aminophosphines were not satisfactory sources of asymmetric induction in the double-Michael reaction, we sought to prepare binol-derived aminophosphines featuring local $C_2$ symmetry on the amino moiety. Chiral binol and its derivatives have been used as sources of asymmetry in several chiral catalysts,\(^{38–41}\) therefore, we selected binol as our first choice for the preparation of $C_2$-symmetric amine-containing aminophosphines. Scheme 5.2.2.4.1 outlines our synthesis of the aminophosphine 41. Within five steps, using a known procedure, we obtained the local $C_2$-symmetric amine 38 from commercially available (S)-binol (33). We subjected the crude product of the amine 38 directly to acryloylation to cleanly yield the acrylamide 39. Subsequent Michael addition of diphenylphosphine and LiAlH\(_4\)-mediated reduction afforded the amidophosphine 40 and the aminophosphine 41, respectively.
Our earlier version of the binol-derived aminophosphine 42 (Table 4.2.1.1, entry 12) is distinct from aminophosphine 41 in that the latter possesses a shorter, more-flexible tethering carbon atom chain. The aminophosphine 41 provided better enantioselectivity toward the double-Michael reaction, albeit with lower yield, than the aminophosphine 42 (cf. Table 5.2.1.1, entry 12 with Table 5.2.2.4.1, entry 1). The amidophosphine 40, however, provided undetectable enantioselectivity in the double-Michael reaction, even though its reaction yield was higher than that of the aminophosphine 41 (entry 2).
Table 5.2.2.4.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aminophosphine</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>69</td>
<td>10</td>
</tr>
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<td>2</td>
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<td>81</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Aminophosphine 3" /></td>
<td>90</td>
<td>3</td>
</tr>
</tbody>
</table>
Encouraged by a slight improvement in enantioselectivity, we considered modifying the aminophosphine 41 to, hopefully, further enhance the enantioselectivity of the double-Michael addition. The introduction of an aryl group to binaphthyl systems at the 3 and 3'-positions is commonly applied to enhance the steric bias of the molecule and increase the reaction’s enantioselectivity.\textsuperscript{42,43} We decided to install naphthyl groups on the binaphthyl framework because of the ready availability of the requisite reagent and the medium size of the naphthyl group (Scheme 5.2.2.4.2). Using a reported multistep synthesis, we installed naphthyl substituents at the desired 3,3'-positions to obtain the intermediate amine 43. Subjecting the crude amine 43 to the aforementioned conditions for aminophosphine synthesis, we eventually isolated the amidophosphine 45 and the aminophosphine 46. Surprisingly, the aminophosphine 46 provided only 3% ee, lower than the enantioselectivity obtained when using the unmodified aminophosphine 41 (Table 5.2.2.4.1, entries 1 and 3). Similarly, application of the amidophosphine 45 to the double-Michael reaction gave a yield of 88% and an enantioselectivity of only 3% ee (entry 4).

\textsuperscript{a} Isolated yield. \textsuperscript{b} Reaction time was 6 h.
5.3 Conclusions

Because the bisphosphine-catalyzed double-Michael reaction is an efficient methodology for synthesizing 5- and 6-membered heterocycles, we sought an asymmetric variant of the reaction, employing a chiral bisphosphine catalyst. Several common and commercially available bisphosphines were only marginally successful at catalyzing a double-Michael indoline synthesis. After establishing that the aminophosphine 42 was as efficient as bisphosphine at facilitating the double-Michael reaction, we prepared a series of chiral aminophosphines.

The synthesis of a chiral aminophosphine is simpler than that of a chiral bisphosphine because of the availability of a wide variety of chiral amines found in Nature and the ease of preparing and handling chiral amines. We prepared a series of aminophosphines featuring tethers of two or three carbon atoms, derived from an acyclic chiral amine, L-proline, and (S)-binol, and employed them as catalysts in the
double-Michael indoline synthesis. Despite the impractical enantioselectivities provided by these aminophosphines, we are encouraged by some slight improvements in enantioinduction relative to those of bisphosphines. Notably, however, we obtained these poor levels of enantioinduction using only one type of substrate under one specific set of conditions; therefore, we should not dismiss the use of chiral aminophosphines in double-Michael indoline syntheses until we have subjected the systems to further investigation. To the best of our knowledge, no literature precedent exists for chiral induction through intramolecular anchimeric assistance. Therefore, it remains a novel and a very challenging task to discover an appropriate aminophosphine for the asymmetric variant of the double-Michael addition and to verify the feasibility of chiral induction through intramolecular anchimeric assistance.

5.4 Experimental Section

5.4.1 Materials and Methods

5.4.1.1 General Information

All reactions were performed in flamed-dried round-bottom flasks under an atmosphere of Ar with dry solvents, unless otherwise noted. A glass water condenser, fitted with a rubber septum, was attached to each flask in the cases of reactions performed under reflux. A syringe pump and stainless-steel needles were used for slow addition of reagents into the reaction mixtures. Reactions were monitored through thin-layer chromatography (TLC) on 0.25-mm SiliCycle silica gel plates, visualizing under UV light or staining with iodine, p-anisaldehyde, or potassium permanganate. Flash column chromatography (FCC) was performed using SiliCycle Silica-P Flash silica gel (60 Å
pore size, 40–63 μm) and compressed air. Purification of phosphines was performed through quick FCC; phosphine-containing fractions were collected immediately into a flask secured under Ar. Organic solvents were evaporated in rotary evaporators under reduced pressure; the flasks were refilled with Ar when isolating phosphines. Phosphine products were stored under Ar at all times.

5.4.1.2 Materials and Reagents

Reagents were used as received from commercial sources, unless otherwise noted. Acryloyl chloride and potassium phosphate tribasic n-hydrate were purchased from Fluka. Tetraethylammonium hydroxide (37% w/w, aqueous solution), trifluoroacetic anhydride, N,N-dimethylbarbituric acid, methyl iodide, and (R)-(+)1-phenylethylamine were purchased from Alfa Aesar. Bromoacetyl bromide, lithium aluminum hydride (LAH), potassium diphenylphosphide (0.5 M in THF), methylmagnesium bromide (3.0 M in diethyl ether), hydrogen peroxide (30–32 wt %, solution in water), n-butyllithium (1.6 M in hexanes), sodium hydride (60% dispersion in mineral oil), methoxymethyl chloride, methyl magnesium iodide (3.0 M in diethyl ether), azobisisobutyronitrile (AIBN), boron tribromide, allylamine, and L-proline (11) were purchased from Aldrich. Trimethyl borate, ethyl formate, and NiCl₂(dppp) were purchased from Acros Organics. Palladium(II) acetate was purchased from Strem Chemicals. 2-Naphthaleneboronic acid and (S)-(−)-1,1′-bi-2-naphthol (33) were purchased from Combi-Blocks. Trifluoromethanesulfonyl anhydride was purchased from Oakwood. Phenylmagnesium bromide was freshly prepared before use. N-Bromosuccinimide was recrystallized from distilled water. TMSOTf was prepared using a published procedure [44,45]. Diphenylphosphine was prepared and purified using published procedures [46,47]. Allylamine was redistilled.
prior to use. Acetonitrile (MeCN), dichloromethane (DCM), and triethylamine (TEA) were distilled from CaH$_2$ under Ar atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et$_2$O) were distilled from Na and benzophenone under Ar atmosphere. Dry MeCN and dry DCM were deoxygenated using three freeze/pump/thaw degassing cycles.

### 5.4.1.3 Instrumentation

IR spectra were recorded using a Perkin–Elmer Paragon 1000 FTIR spectrometer. NMR spectra were recorded using Bruker Avance-500, ARX-500, or Avance-300 instruments, calibrated to signals from the solvent as an internal reference [7.26 (residual CHCl$_3$) and 77.00 (CDCl$_3$) ppm for $^1$H and $^{13}$C-NMR spectra, respectively]. Data for $^1$H-NMR spectra are reported in terms of chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. Data for $^{13}$C-NMR spectra are reported in terms of chemical shift (δ, ppm), multiplicity, and coupling constants (Hz) in the case of J$_{CP}$ coupling. The following abbreviations are used to denote multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; qi = quintet; m = multiplet; br = broad; app = apparent. Mass spectra were analyzed using instrument-supplied software. Gas chromatography/mass spectrometry (GC–MS) data were obtained using an Agilent 6890–5975 GC–MS system equipped with an autosampler and an HP5 column; samples were dissolved in DCM.

### 5.4.2 Preparative Procedures

The amine 2,$^{48}$ and the acrylamide 8,$^{49}$ were prepared following reported procedures. Compounds 12,$^{50}$ 13,$^{51}$ 14,$^{52}$ 20,$^{53}$ 21,$^{54}$ 22,$^{23}$ 25,$^{55}$, and 24,$^{56}$ provided spectral data matching those reported in the literature. Compounds 26, 27,$^{57}$ and 28,$^{58}$...
were prepared following reported procedures. Compounds 34–38 and 43–55 were prepared following published procedures.\(^{43}\)

\[
\text{(R)-3-(Diphenylphosphino)-N-methyl-N-(1-phenylethyl)propanamide (4).}
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The acrylamide 3 (568 mg, 3 mmol) and Ph\(_2\)PH (783 \(\mu\)L, 4.5 mmol) were placed in a flask containing deoxygenated MeCN (15 mL). Aqueous 1 N NaOH (13 drops) was added and then the mixture was heated under reflux overnight. After cooling, the reaction mixture was washed with water, dried (Na\(_2\)SO\(_4\)), and concentrated. The residue was purified through column chromatography (SiO\(_2\); 30% EtOAc/Hex) to afford a colorless oil 4 (788.4 mg, 70\%). \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) (both rotamers) 7.52 (br s, 5H), 7.38 (br s, 9H), 7.3 (br s, 4H), 7.18 (br s, 0.8H), 6.13 (q, \(J = 7.3\) Hz, 0.7H), 4.99 (q, \(J = 7.3\) Hz, 0.3H), 2.73 (br s, 1H), 2.57 (br s, 3H), 2.53–2.48 (m, 4H), 1.56 (d, \(J = 7.2\) Hz, 1H), 1.51 (d, \(J = 7.2\) Hz, 3H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.1 (d, \(J = 14.4\) Hz), 140.5, 138.2, 138.1, 138.05, 138.00, 132.7 (d, \(J = 6.5\) Hz), 132.6 (d, \(J = 6.5\) Hz), 128.60, 128.58, 128.4, 128.35, 128.3, 127.2, 127.1, 50.3, 30.2 (d, \(J = 20.5\) Hz), 29.2, 23.0 (d, \(J = 10.9\) Hz), 15.5 (rotamer) 172.1 (d, \(J = 14.4\) Hz), 140.1, 138.3, 138.2, 138.0, 137.9, 132.6, 132.5, 127.3, 126.2, 54.4, 29.6 (d, \(J = 20.5\) Hz), 28.0, 23.4 (d, \(J = 10.9\) Hz), 17.6; \(^{31}\)P-NMR (202 MHz, CDCl\(_3\)) \(\delta\) –14.0, (rotamer) –14.2.
(R)-3-(Diphenylphosphino)-N-methyl-N-(1-phenylethyl)propan-1-amine (5). A solution of the amidophosphine 4 (750.8 mg, 2 mmol) in dry THF (10 mL) was cannulated into a slurry of LAH (379.5 mg, 10 mmol) in dry THF (10 mL) at 0 °C. The mixture was then stirred at room temperature overnight before being cooled at 0 °C and having the reaction quenched through slow addition of 1 N NaOH (5 mL, 5 mmol). The reaction mixture was dried with Na₂SO₄ (vigorous stirring for 20 min), then filtered through Celite and washed with Et₂O (3 × 10 mL). After concentrating the filtrate, the residue was purified through column chromatography (SiO₂; 3% Et₃N in 10% EtOAc/Hex) to afford a colorless oil 5 (585.5 mg, 81%). ¹H-NMR (500 MHz, CDCl₃) δ 7.46–7.42 (m, 5H), 7.36–7.32 (m, 10H), 3.57 (q, J = 6.7 Hz, 1H), 2.56–2.50 (m, 1H), 2.42–2.37 (m, 1H), 2.17 (s, 3H), 2.10–1.98 (m, 2H), 1.66–1.58 (m, 2H), 1.37 (d, J = 6.7 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ 143.9, 138.93 (d, J = 13.3 Hz), 138.87 (d, J = 13.3 Hz), 132.7 (d, J = 4.4 Hz), 132.6 (d, J = 4.4 Hz), 128.4, 128.3, 128.2, 128.0, 127.6, 126.6, 63.1, 55.2 (d, J = 13.5 Hz), 38.3, 25.5 (d, J = 11.0 Hz), 23.5 (d, J = 16.0 Hz), 18.3; ³¹P-NMR (202 MHz, CDCl₃) δ –15.1; GCMS (EI+) calcd for [C₉H₄Cl₂O]: m/z 361.2, found 361.3.

(R)-2-(Diphenylphosphino)-N-methyl-N-(1-phenylethyl)acetamide (6). The amine 2 (676 mg, 5 mmol) was added to a solution of DMAP (733 mg, 6 mmol) in dry THF (50 mL).
The mixture was cooled to 0 °C and then bromoacetyl bromide (1.21 g, 6 mmol) in dry THF (20 mL) was added slowly. After stirring at room temperature for 2 h, the mixture was filtered through a short pad of silica gel, which was washed with Et₂O until the product had completely eluted out. The filtrate was concentrated and then replenished with dry THF (50 mL). The mixture was cooled to –78 °C and then Ph₂PK (0.5 N in THF, 7.5 mmol, 15 mL) was added slowly. The mixture was stirred overnight at room temperature and then it was quenched (saturated NH₄Cl), washed (water), dried (Na₂SO₄), and concentrated. The residue was purified through column chromatography (SiO₂; gradient 20–50% EtOAc/Hex) to afford a colorless oil 6 (513 mg, 40%). ¹H-NMR (300 MHz, CDCl₃) δ (both rotamers) 7.54–7.47 (m, 6H), 7.35–7.19 (m, 15H), 6.03 (q, J = 7.1 Hz, 1H), 5.33 (q, J = 7.1 Hz, 0.4H), 3.32 (s, 0.8H), 3.23 (s, 2H), 2.67 (s, 1.2H), 2.65 (s, 3H), 1.56 (d, J = 7.0 Hz, 1.2H), 1.42 (d, J = 7.0 Hz, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ (both rotamers) 169.84 (d, J = 7.8 Hz), 169.8 (d, J = 7.8 Hz), 140.6, 140.3, 138.2 (d, J = 14.3 Hz), 138.0 (d, J = 14.3 Hz), 133.0, 132.7, 128.9, 128.7, 128.6, 128.5, 127.5, 127.3, 127.2, 126.5, 50.5, 35.7, 35.4, 30.4, 30.3, 28.2, 17.9, 15.5; ³¹P-NMR (121 MHz, CDCl₃) δ –18.8, (rotamer) –18.7.

(R)-2-(Diphenylphosphino)-N-methyl-N-(1-phenylethyl)ethanamine (7). Using the procedure described for the synthesis of the aminophosphine 5, the aminophosphine 7 (67%) was obtained as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ (both rotamers) 7.40–7.34 (m, 4H), 7.33–7.19 (m, 11H), 3.56 (q, J = 6.8 Hz, 1H), 2.67–2.43 (m, 2H),
2.31–2.16 (m, 5H), 1.30 (d, J = 6.8 Hz, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 144.0, 138.7 (d, J = 12.6 Hz), 138.6 (d, J = 12.6 Hz), 132.8 (d, J = 1.9 Hz), 132.5 (d, J = 1.9 Hz), 128.5, 128.48, 128.44, 128.35, 128.2, 127.6, 126.8, 63.1, 51.0 (d, J = 22.9 Hz), 38.5, 25.9 (d, J = 12.0 Hz), 18.9; $^{31}$P-NMR (121 MHz, CDCl$_3$) $\delta$−19.9.

(R)-3-(Diphenylphosphino)-N-(1-phenylethyl)propanamide (9). Using the procedure described for the synthesis of the aminophosphine 10, but stopping at the first step, the amidophosphine 9 was obtained as a colorless oil. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.45–7.39 (m, 4H), 7.36–7.27 (m, 11H), 5.64 (d, J = 7.3 Hz, 1H), 5.10 (app qi, J = 7.3 Hz, 1H), 2.43–2.36 (m, 2H), 2.29–2.19 (m, 2H), 1.46 (d, J = 6.9 Hz, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 171.2 (d, J = 12.8 Hz), 143.1, 137.9 (d, J = 12.6 Hz), 132.9, 132.6, 128.7 (d, J = 7.1 Hz), 128.5 (d, J = 6.6 Hz), 127.4, 126.2, 48.9, 32.9 (d, J = 18.3 Hz), 23.4 (d, J = 12.1 Hz), 21.7; $^{31}$P-NMR (121 MHz, CDCl$_3$) $\delta$−15.4.

(R)-3-(Diphenylphosphino)-N-(1-phenylethyl)propan-1-amine (10). Ph$_2$PH (0.7 mL, 4 mmol) was added to a solution of the acrylamide 8 (350 mg, 2 mmol) in dry MeCN (10 mL). Et$_4$NOH·H$_2$O (37% aqueous solution, 0.5 mL) was added and then the mixture was stirred at room temperature overnight before being concentrated. The residue was dissolved in DCM (20 mL), washed with water (5 mL), dried (Na$_2$SO$_4$), and
concentrated. The residue was dissolved in dry THF (5 mL) and then cannulated into a flask containing a slurry of LAH (380 mg, 10 mmol) in dry THF (10 mL) under Argon. After overnight stirring at room temperature, the reaction mixture was cooled to 0 °C and 1N NaOH (4 mL, 4 mmol) was added to quench the reaction. Na$_2$SO$_4$ was added and the mixture was stirred vigorously for 20 min, then filtered through Celite and washed with Et$_2$O (3 × 10 mL). The filtrate was concentrated under vacuo and the residue was purified through column chromatography (SiO$_2$; 5% Et$_3$N in 30% EtOAc/Hex) to afford a colorless oil 10 (569.8 mg, 82%). $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.48–7.44 (m, 4H), 7.39–7.27 (m, 11H), 3.77 (q, $J = 6.5$ Hz, 1H), 2.67–2.55 (m, 2H), 2.15–2.03 (m, 2H), 1.72–1.57 (m, 2H), 1.38 (d, $J = 6.5$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 145.6, 138.7 (d, $J = 12.3$ Hz), 138.6 (d, $J = 12.3$ Hz), 132.7 (d, $J = 4.2$ Hz), 132.5 (d, $J = 4.2$ Hz), 128.4, 128.3, 128.2, 126.7, 126.4, 58.0, 48.7 (d, $J = 13.6$ Hz), 26.5 (d, $J = 16.0$ Hz), 25.6 (d, $J = 11.5$ Hz), 24.2; $^{31}$P-NMR (202 MHz, CDCl$_3$) $\delta$ –14.6.

(S)-1-(2-((Benzyloxy)methyl)pyrrolidin-1-yl)prop-2-en-1-one (15). TFA (25 mL) was added to a solution of 14 (1.19 g, 6.6 mmol) in DCM (25 mL) and then the mixture was stirred for 5 h at room temperature. The solution was concentrated and the residue poured into a premixed solid comprising NaHCO$_3$ and a few pieces of ice; the aqueous phase was extracted with DCM, dried (Na$_2$SO$_4$), and concentrated. The residue was dissolved in dry DCM (50 mL); TEA (1.4 mL, 10 mmol) was added to the solution, which
was then cooled to 0 °C. Acryloyl chloride (0.66 mL, 8.2 mmol) was added and then the mixture was stirred at room temperature overnight before being filtered through a short pad of silica gel and washed with DCM (4×) until the product had eluted completely. The filtrate was concentrated and the residue purified through column chromatography (SiO₂; 30% EtOAc/Hex) to afford 15 (1.44 g, 89%) as a pale yellow oil. ¹H-NMR (300 MHz, CDCl₃) δ (both rotamers) 7.37–7.28 (m, 5H), 6.56–6.32 (m, 2H), 5.68–5.59 (m, 1H), 4.53 (s, 0.5H), 4.51 (s, 1.5H), 4.42–4.36 (m, 0.5H), 4.18–4.11 (m, 0.5H), 3.70 (dd, J = 9.4, 3.1 Hz, 0.5H), 3.61–3.32 (m, 3.5H), 2.12–1.97 (m, 2H), 1.94–1.84 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃) δ (both rotamers) 164.9, 164.7, 138.6, 137.8, 129.1, 128.8, 128.5, 128.3, 127.8, 127.6, 127.5, 127.4, 73.4, 73.2, 71.7, 70.1, 56.9, 56.8, 47.4, 46.0, 29.0, 27.5, 24.2, 21.9.

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\text{(S)-1-(2-((Benzyloxy)methyl)pyrrolidin-1-yl)-3-(diphenylphosphino)propan-1-one (16).}
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Ph₂PH (1.2 mL, 6.9 mmol) and 1 M NaOH (10–15 drops) were added to a solution of 15 (1.35 g, 5.5 mmol) in dry MeCN (10 mL) and dry DCM (10 mL). The mixture was stirred at room temperature overnight before being concentrated and purified through column chromatography (SiO₂; 50% EtOAc/Hex) to afford 16 (1.42 g, 60%) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃) δ (both rotamers) 7.47–7.40 (m, 4H), 7.36–7.23 (m, 11H), 4.54 (d, J = 12.0 Hz, 0.7H), 4.47 (d, J = 12.0 Hz, 0.7H), 4.41 (d, J = 12.0 Hz, 0.3H), 4.35 (d, J = 12.0 Hz, 0.3H), 4.30–4.23 (m, 0.7H), 3.93–3.85 (m, 0.3H), 3.65 (d, J = 3.3 Hz,
0.3H), 3.62 (d, J = 3.3 Hz, 0.7H), 3.50 (d, J = 6.88 Hz, 0.6H), 3.47 (d, J = 6.88 Hz, 0.4H), 3.31–3.18 (m, 2H), 2.52–2.27 (m, 4H), 2.05–1.82 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ (both rotamers) 171.1 (d, J = 14.5 Hz), 138.6, 138.4 (d, J = 16.7), 138.2 (d, J = 16.7 Hz), 132.9, 132.9 (d, J = 3.8 Hz), 132.7, 132.6 (d, J = 3.8 Hz), 128.72, 128.70, 128.53, 128.5, 128.4, 128.3, 127.54, 127.5, 73.3, 73.2, 71.4, 70.1, 56.9, 56.7, 47.2, 47.8, 31.4, 31.2, 28.8, 27.6, 24.1, 23.4, 22.8, 22.7, 21.9; $^{31}$P-NMR (121 MHz, CDCl$_3$) $\delta$ – 15.2, (rotamer) – 15.3.

(S)-2-((Benzyloxy)methyl)-1-(3-(diphenylphosphino)propyl)pyrrolidine (17). Using the procedure described for the synthesis of the aminophosphine 5, the aminophosphine 17 (76%) was obtained as a colorless oil. $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.44–7.40 (m, 4H), 7.33 (br s, 11H), 4.52 (s, 2H), 3.50–3.46 (m, 1H), 3.37–3.13 (m, 1H), 3.05–3.03 (m, 1H), 2.97–2.91 (m, 1H), 2.64–2.62 (m, 1H), 2.41–2.35 (m, 1H), 2.14–2.09 (m, 2H), 2.05–1.98 (m, 1H), 1.95–1.84 (m, 1H), 1.72–1.60 (m, 5H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 139.1 (d, J = 20.1 Hz), 138.9 (d, J = 19.9 Hz), 138.6, 132.9 (d, J = 15.8 Hz), 132.6 (d, J = 15.5 Hz), 128.5, 128.4, 128.3, 127.7, 127.5, 74.0, 73.3, 63.6, 56.8 (d, J = 13.8 Hz), 54.4, 28.6, 25.9 (d, J = 11.3 Hz), 25.4 (d, J = 16.1 Hz), 23.0; $^{31}$P-NMR (121 MHz, CDCl$_3$) $\delta$ – 15.9.
(S)-3-(Diphenylphosphino)-1-(2-(hydroxymethyl)pyrrolidin-1-yl)propan-1-one (18). Using the procedures described for the syntheses of 3 and 4, 18 was obtained as a colorless oil. IR (film) $\nu_{\text{max}}$ 3385, 3051, 2951, 2875, 1621, 1434, 1313, 1188, 1052 cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.46–7.42 (m, 4H), 7.35–7.32 (m, 6H), 4.97 (br s, 1H), 4.19–4.14 (m, 1H), 3.65–3.64 (m, 1H), 3.55–3.51 (m, 1H), 3.37–3.28 (m, 2H), 2.42–2.35 (m, 4H), 2.01–1.95 (m, 1H), 1.91–1.83 (m, 1H), 1.83–1.75 (m, 1H), 1.59–1.52 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 173.4 (d, $J = 14.3$ Hz), 137.8 (d, $J = 12.1$ Hz), 137.8 (d, $J = 12.1$ Hz), 132.7, 132.5, 128.7, 128.4 (d, $J = 6.5$ Hz), 67.2, 61.2, 47.8, 31.3 (d, $J = 20.3$ Hz), 28.1, 24.2, 22.7 (d, $J = 10.6$ Hz); $^{31}$P-NMR (202 MHz, CDCl$_3$) $\delta$ 14.3.

(S)-(1-(3-(Diphenylphosphino)propyl)pyrrolidin-2-yl)methanol (19). Using the procedure described for the synthesis of the aminophosphine 5, the aminophosphine 19 (76%) was obtained as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.44–7.39 (m, 4H), 7.32 (br s, 6H), 3.62 (dd, $J = 10.5, 3.2$ Hz, 1H), 3.37 (d, $J = 10.5$ Hz, 1H), 3.05–3.01 (m, 1H), 2.85–2.79 (m, 1H), 2.54–2.51 (m, 1H), 2.36–2.31 (m, 1H), 2.17–2.11 (m, 2H), 2.05–1.99 (m, 1H), 1.88–1.81 (m, 1H), 1.79–1.73 (m, 1H), 1.71–1.66 (m, 2H), 1.64–1.58 (m, 2H);
\(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) 138.6 (d, \(J = 21.5\) Hz), 138.5 (d, \(J = 21.5\) Hz), 132.7, 132.6, 132.4, 128.5, 128.4, 128.3 (d, \(J = 6.9\) Hz), 128.27 (d, \(J = 6.9\) Hz), 64.6, 61.7, 55.0 (d, \(J = 13.1\) Hz), 53.8, 27.4, 25.6 (d, \(J = 11.1\) Hz), 25.1 (d, \(J = 15.6\) Hz), 23.4; \(^{31}\)P-NMR (202 MHz, CDCl\(_3\)) \(\delta\) –15.4.

(S)-1-(2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidin-1-yl)prop-2-en-1-one (29). Using the procedure described for the synthesis of the acrylamide 15, the acrylamide 29 (81%) was obtained as a colorless oil. \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\) (both rotamers) 7.47–7.25 (m, 10H), 6.81 (dd, \(J = 16.8, 12.3\) Hz, 0.7H), 6.29 (dd, \(J = 16.8, 2.0\) Hz, 0.7H), 6.25 (dd, \(J = 16.8, 12.3\) Hz, 0.3H), 6.12 (dd, \(J = 16.8, 2.0\) Hz, 0.3H), 5.63–5.52 (m, 1H), 5.39 (dd, \(J = 12.3, 2.0\) Hz, 0.7H), 5.10 (dd, \(J = 12.3, 2.0\) Hz, 0.3H), 3.77–3.76 (m, 0.7H), 3.42–3.39 (m, 0.3H), 3.89–3.87 (m, 0.3H), 2.19–2.15 (m, 0.7H), 2.09–2.07 (m, 0.7H), 1.92–1.88 (m, 0.3H), 1.86 (br s, 1H), 1.62–1.58 (m, 0.3H), 1.51–1.46 (m, 0.7H), 1.35–1.29 (m, 0.3H), 1.20–1.14 (m, 0.7H), –0.13 (s, 2.7H), –0.25 (s, 6.3H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)) \(\delta\) (both rotamers) 166.01, 166.00, 144.3, 144.2, 142.3, 141.0, 130.4, 129.6, 129.3, 129.2, 128.8, 128.1, 127.6, 127.4, 127.3, 127.2, 127.0, 126.4, 125.7, 84.4, 65.9, 62.4, 48.2, 46.3, 28.3, 27.1, 23.8, 21.8, 1.8.
(S)-3-(Diphenylphosphino)-1-(2-(hydroxydiphenylmethyl)pyrrolidin-1-yl)propan-1-one (30). Using the procedure described for the synthesis of the amidophosphine 18, the amidophosphine 30 (94%) was obtained as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.43–7.25 (m, 20H), 6.92 (s, 1H), 5.16–5.13 (m, 1H), 3.19–3.17 (m, 1H), 2.78–2.77 (m, 1H), 2.34–2.30 (m, 3H), 2.23–2.21 (m, 1H), 2.04–2.02 (m, 1H), 1.93–1.92 (m, 1H), 1.50–1.43 (m, 1H), 0.94–0.91 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 174.8 (d, J = 15.0 Hz), 146.0, 143.3, 137.8 (d, J = 12.6 Hz), 132.7 (d, J = 11.9 Hz), 132.5 (d, J = 11.8 Hz), 128.74, 128.71, 128.5, 128.4, 128.0, 127.8, 127.6, 127.3, 127.14, 127.12, 81.9, 66.8, 48.4, 31.5 (d, J = 19.9 Hz), 29.4, 23.1, 22.9 (d, J = 11.3 Hz); $^{31}$P-NMR (202 MHz, CDCl$_3$) $\delta$–14.3.

(S)-(1-(3-(Diphenylphosphino)propyl)pyrrolidin-2-yl)diphenylmethanol (31). Using the procedure described for the synthesis of the aminophosphine 19, the aminophosphine 31 (85%) was obtained as a white crystalline solid. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.63 (d, J = 7.9 Hz, 2H), 7.56 (d, J = 7.9 Hz, 2H), 7.42–7.30 (m, 12H), 7.26 (t, J = 7.9 Hz, 2H), 7.21–7.16 (m, 2H), 4.85 (s, 1H), 3.85–3.83 (m, 1H), 3.13–3.10 (m, 1H), 2.34–2.29 (m,
1H), 2.26–2.21 (m, 1H), 2.00–1.87 (m, 2H), 1.82–1.60 (m, 5H), 1.56–1.50 (m, 1H), 1.39–1.31 (m, 2H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 148.0, 146.4, 138.7 (d, $J = 16.7$ Hz), 138.6 (d, $J = 16.7$ Hz), 132.7, 132.5 (d, $J = 5.0$ Hz), 132.3, 128.4, 128.29, 128.27, 128.22, 128.18, 127.9 (d, $J = 4.4$ Hz), 126.0, 125.6, 125.5, 77.8, 71.0, 57.4 (d, $J = 14.2$ Hz), 55.1, 29.4, 25.2 (d, $J = 10.7$ Hz), 24.9 (d, $J = 15.6$ Hz), 24.4; $^{31}$P-NMR (202 MHz, CDCl$_3$) $\delta$–14.6.

(S)-2-(Diphenyl((trimethylsilyl)oxy)methyl)-1-(3-(diphenylphosphino)propyl)pyrrolidine (32). TMSOTf (255 $\mu$L, 1.4 mmol) was added to a solution of the aminophosphine 31 (335.7 mg, 0.7 mmol) and TEA (0.3 mL, 2.1 mmol) in dry DCM (5 mL) at 0 °C. The mixture was stirred overnight and then concentrated. The residue was purified through column chromatography (SiO$_2$; 15% EtOAc/Hex) to afford 32 (266.5 mg, 69%) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.61–7.58 (m, 2H), 7.53–7.50 (m, 2H), 7.46–7.42 (m, 4H), 7.41–7.37 (m, 6H), 7.34–7.31 (m, 3H), 7.29–7.27 (m, 3H), 3.75 (dd, $J = 9.7, 3.2$ Hz, 1H), 2.95 (q, $J = 9.7$ Hz, 1H), 2.66 (dt, $J = 8.9, 2.2$ Hz, 1H), 2.52 (dt, $J = 11.3, 5.6$ Hz, 1H), 2.13–2.08 (m, 2H), 1.94–1.86 (m, 1H), 1.79–1.70 (m, 2H), 1.52–1.44 (m, 2H), 1.36–1.30 (m, 1H), 0.67–0.57 (m, 1H), –0.12 (s, 9H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 144.4, 143.7, 139.2 (d, $J = 13.6$ Hz), 139.0 (d, $J = 13.6$ Hz), 132.7, 132.6, 132.4, 129.6 (d, $J = 4.8$ Hz), 128.3, 128.2, 128.16, 126.74, 126.71, 84.5, 72.1, 59.0 (d, $J = 14.5$ Hz), 54.5, 28.7, 25.5, 25.3, 23.7, 2.0; $^{31}$P-NMR (202 MHz, CDCl$_3$) $\delta$–14.4.

\[\text{Ph} \]
\[\text{OTMS} \]
\[\text{32} \]

\[\text{PPh}_2 \]
Using the procedure described for the synthesis of the acrylamide 29, the acrylamide 39 (75%) was obtained as a light-yellow foam. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 8.00–7.95 (m, 4H), 7.65 (d, $J$ = 8.4 Hz, 1H), 7.52–7.44 (m, 5H), 7.30 (q, $J$ = 7.0 Hz, 2H), 6.71 (dd, $J$ = 16.9, 10.6 Hz, 1H), 6.35 (dd, $J$ = 16.9, 1.4 Hz, 1H), 5.77 (dd, $J$ = 10.6, 1.4 Hz, 1H), 5.45 (d, $J$ = 13.7 Hz, 1H), 4.79 (d, $J$ = 12.8 Hz, 1H), 4.01 (d, $J$ = 12.8 Hz, 1H), 3.60 (d, $J$ = 13.7 Hz, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 164.9, 135.2, 134.9, 133.9, 133.3, 132.8, 132.0, 131.3, 131.2, 129.2, 128.6, 128.3, 128.2, 127.9, 127.7, 127.4, 127.2, 126.7, 126.1, 126.0, 125.8, 49.7, 46.5.

Using the procedure described for the synthesis of the amidophosphine 30, the amidophosphine 40 (85%) was obtained as a white solid. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 8.00 (t, $J$ = 9.2 Hz, 4H), 7.68 (d, $J$ = 8.4 Hz, 1H), 7.56–7.52 (m, 7H), 7.50–7.47 (m, 1H), 7.43–7.39 (m, 7H), 7.35–7.31 (m, 2H), 5.53 (d, $J$ = 13.5 Hz, 1H), 4.51 (d, $J$ = 12.9 Hz,
(S)-4-(3-(Diphenylphosphino)propyl)-4,5-dihydro-3H-dinaphtho[2,1-c:1´,2´-e]azepine (41). Using the procedure described for the synthesis of the aminophosphine 31, the aminophosphine 41 (83%) was obtained as a white solid. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 7.99 (t, $J = 8.0$ Hz, 4H), 7.51 (q, $J = 8.0$ Hz, 10H), 7.39 (t, $J = 6.2$ Hz, 6H), 7.31 (t, $J = 7.6$ Hz, 2H), 3.67 (d, $J = 12.4$ Hz, 2H), 3.19 (d, $J = 12.4$ Hz, 2H), 2.76–2.70 (m, 1H), 2.56–2.50 (m, 1H), 2.18 (t, $J = 7.7$ Hz, 2H), 1.83–1.76 (m, 2H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 138.7 (d, $J = 22.4$ Hz), 138.6 (d, $J = 22.4$ Hz), 134.8, 133.5, 133.0, 132.7 (d, $J = 4.5$ Hz), 132.6 (d, $J = 4.5$ Hz), 131.3, 128.4, 128.32, 128.27, 128.15, 128.11, 127.6, 127.3, 125.6, 125.2, 56.3 (d, $J = 13.9$ Hz), 55.2, 25.7 (d, $J = 11.5$ Hz), 24.4 (d, $J = 16.5$ Hz); $^{31}$P-NMR (202 MHz, CDCl$_3$) $\delta$ –14.7.
1-(2,6-Di(naphthalen-2-yl)-3H-dinaphtho[2,1-c:1’,2’-e]azepin-4(5H)-yl)-3-(diphenylphosphino)propan-1-one (45). Using the procedure described for the synthesis of the amidophosphine 40, the amidophosphine 45 was obtained as a light-yellow foam (63%).

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 8.06 (s, 1H), 8.03–8.01 (m, 4H), 7.98–7.89 (m, 10H), 7.72 (app t, $J = 7.7$ Hz, 2H), 7.63–7.55 (m, 6H), 7.43–7.39 (m, 3H), 7.35–7.31 (m, 6H), 7.28–7.25 (m, 2H), 7.15 (d, $J = 8.5$ Hz, 1H), 5.00 (app t, $J = 4.6$ Hz, 1H), 4.50 (app dd, $J = 13.9$, 5.6 Hz, 1H), 4.17 (app dd, $J = 14.1$, 3.9 Hz, 1H), 1.83–1.77 (m, 2H), 1.62–1.53 (m, 2H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 170.4 (d, $J = 15.3$ Hz), 141.3, 140.8, 139.4, 138.4 (d, $J = 10.0$ Hz), 134.8, 133.23, 133.16, 133.1, 132.9, 132.6 (d, $J = 4.5$ Hz), 132.5 (d, $J = 4.5$ Hz), 132.4, 132.3, 131.9, 131.8, 129.7, 129.0, 128.54, 128.52, 128.33, 128.31, 128.25, 127.98, 127.96, 127.88, 127.7, 127.6, 127.5, 127.3, 126.7, 126.6, 126.42, 126.39, 126.2, 126.13, 126.07, 125.9, 125.5, 125.0, 40.2, 31.9 (d, $J = 18.1$ Hz), 22.8 (d, $J = 12.0$ Hz); $^{31}$P-NMR (202 MHz, CDCl$_3$) $\delta$–14.2.
4-(3-(Diphenylphosphino)propyl)-2,6-di(naphthalen-2-yl)-4,5-dihydro-3H-dinaphtho[2,1-c:1',2'-e]azepine (46). Using the procedure described for the synthesis of the aminophosphine 41, the aminophosphine 46 (55%) was obtained as a light-yellow foam. $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 8.11 (br s, 2H), 8.08 (s, 2H), 8.01 (d, $J = 8.1$ Hz, 2H), 7.90–7.82 (m, 7H), 7.58 (d, $J = 8.6$ Hz, 2H), 7.56–7.49 (m, 7H), 7.34 (app t, $J = 7.4$ Hz, 2H), 7.31–7.27 (m, 3H), 7.22 (app t, $J = 7.3$ Hz, 5H), 7.14 (app t, $J = 7.1$ Hz, 2H), 3.99 (d, $J = 12.4$ Hz, 2H), 3.15 (d, $J = 11.8$ Hz, 2H), 2.19–2.15 (m, 1H), 2.07–2.01 (m, 1H), 1.67 (br s, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ 140.3, 138.9, 136.2, 133.2, 132.6, 132.5, 132.4, 132.3, 131.9, 130.8, 129.3, 128.6, 128.4, 128.3, 128.1, 128.09, 128.08, 128.0, 127.7, 127.5, 126.2, 125.9, 125.8, 125.7, 55.0 (d, $J = 13.2$ Hz), 50.6, 25.2 (d, $J = 11.4$ Hz), 23.5 (d, $J = 15.6$ Hz); $^{31}$P-NMR (202 MHz, CDCl$_3$) $\delta$ –14.3.

5.5 Notes and References


APPENDIX SEVEN

Spectra Relevant to Chapter Five:

Chiral Aminophosphines: Designs, Syntheses, and Applications Toward Asymmetric Phosphine-Catalyzed Reactions (Part 1)
Figure A7.1 $^1$H NMR (500 MHz, CDCl$_3$) of diphenylphosphine
Figure A7. 2,13C NMR (125 MHz, CDCl₃) of diphenylphosphine
Figure A7.3. 31P NMR (121 MHz, CDCl3) of diphenylphosphine
Figure A7.4: $^{13}$C NMR (125 MHz, CDCl$_3$) of amidophosphine 4.
Figure A7.5 $^{31}$P NMR (121 MHz, CDCl$_3$) of amidophosphine 4
Figure A7.6 $^1$H NMR (500 MHz, CDCl$_3$) of aminophosphine 5
Figure A7.7 13C NMR (125 MHz, CDCl₃) of aminophosphine 5

Default parameters for C-13 with proton decoupling

Current Data Parameters
NAME TMI
EXPDM 2
PROCNO 1

F2 - Acquisition Parameters
Date 2010/01/18
Time 16.56
INSTRUM avx500
PROBHD 5 mm broadhan
FUPROP zgc30
TD 65536
SOLVENT CDC13
NS 64
DS 0
SWW 35714.285 Hz
FDRES 0.54/497 Hz
AG 0.3175540 sec
FG 25800
DM 14.000 usec
DE 20.000 usec
TE 300.0 K
D12 0.000000 sec
DLS 17.70 dB
CCPMAG valtol5
PFI 500.00 usec
DI 2.0000000 sec
F1 6.80 usec
SF01 125.7576990 MHz
MNUCEX 13C
D11 0.0300000 sec

F2 - Processing parameters
SI 30720
SF 125.7576990 MHz
WDW EM
GSS 0
LB 1.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
FP 261.096 ppm
F1 32908.09 Hz
FP 251.986 ppm
F2 -766.20 Hz
FPCH 14.1995 ppm/cm
HCHM 1785.7143 Hz/cm
Figure A7.8 $^{31}$P NMR (121 MHz, CDCl$_3$) of aminophosphine 5
Figure A.7.9 13C NMR (125 MHz, CDCl₃) of amidophosphine
Figure A7.10 31P NMR (121 MHz, CDCl₃) of amidophosphine.
H NMR (300 MHz, CDCl₃) of aminophosphine.
Figure A7.12. $^{13}$C NMR (75 MHz, CDCl$_3$) of aminophosphine.
Figure A7.13 $^{31}\text{P}$ NMR (121 MHz, CDCl$_3$) of aminophosphine 7
Figure A7.14 ¹H NMR (500 MHz, CDCl₃) of aminophosphine 10
Figure A7.15 $^{13}$C NMR (75 MHz, CDCl$_3$) of aminophosphine 10
Figure A7.16 \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) of compound 15
Figure A7.17. $^{13}$C NMR (75 MHz, CDCl$_3$) of amidophosphine
Figure A.7.18. $^{31}P$ NMR (121 MHz, CDCl$_3$) of amidophosphate 16.
Figure A7.19. $^1$H NMR (300 MHz, CDCl$_3$) of aminophosphine 17
Figure A7.20 $^{13}$C NMR (75 MHz, CDCl$_3$) of aminophosphine 17
Figure A.7. 21 $^3$P NMR (121 MHz, CDCl$_3$) of aminophosphine.
Figure A.7.22 1H NMR (500 MHz, CDCl₃) of amidophosphine 18.

Current Data Parameters
NAME  SK113
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Data_  20100419
Time  15.39
INSTRUM  a=×500
PROBD  5 mm broadband
PULPROG  zg30
TD  55936
SOLVENT  CDCl₃
NS  8
DS  0
SNH  10000.000 Hz
FIDRES  0.152588 Hz
AQ  3.2768520 sec
RS  715
DN  50.000 use
DE  71.43 use
TE  300.0 K
DI  2.0000000 sec
P1  11.00 use
SF01  500.133008 MHz
NUCLEUS  1H

F2 - Processing parameters
SI  32768
SF  500.130024 MHz
MDW  EM
SSB  6
LB  0.30 Hz
GB  0
PC  1.00

1D NMR plot parameters
CX  20.00 cm
F1P  9.400 ppm
F1  4701.0 Hz
FDP  -0.600 ppm
F2  -300.0 Hz
PPMCH  0.50000 ppm
HIZM  250.06502 Hz/
$^{13}$C NMR (125 MHz, CDCl$_3$) of amidophosphine
Figure A.7.24 

$^{31}$P NMR (121 MHz, CDCl$_3$) of amidophosphine 18

Current Data Parameters
NAME 5K113
EXPNO 3
PROCNO 1

$^{31}$P NMR Parameters

- Frequency: 121 MHz
- Solvent: Aceton
- Sample: Amidophosphine 18

The NMR spectrum shows a peak at around -30 ppm, indicating the presence of the phosphorus atom in the amidophosphine 18 molecule.

Additionally, there is a note on the page: "may be the crystal formed during the preparation of NMR sample."
Figure A7.25 $^1$H NMR (500 MHz, CDCl$_3$) of aminophosphine 19
Figure A7.26.13 C NMR (125 MHz, CDCl₃) of aminophosphine.
Figure A7.27 P NMR (121 MHz, CDCl₃) of aminophosphine

Current Data Parameters
NAME  5k114
EXPMOD  3
PROCNO  1

F2 - Acquisition Parameters
Date_  20100420
Time  21.20
INSTRUM  av550
PROBNO  5 mm broaden
PULPROG  zpg30
TD  65536
SOLVENT  Acetone
NS  16
DS  4
DMH  83333.336 Hz
FORES  1.271566 Hz
AS  0.3952660 sec
RG  32768
DM  6.000 usec
DE  4.97 usec
TE  300.0 K
DS2  0.00000000 sec
DLS  21.000 usec
D1  2.00000000 sec
CPDMPG  wait216
PS1  105.00 usec
D11  0.0300000 sec
DLS  21.000 usec
P1  4.00 usec
SF01  202.4459621 MHz
NUCLEUS  31P

F2 - Processing parameters
SI  32768
SF  202.456650 MHz
MOD  EM
SSB  0
LB  1.00 Hz
GB  0
PC  1.00

13C NMR plot parameters
CK  20.00 cm
FSP  100.000 ppm
F1  20245.61 Hz
F2  -100.000 ppm
F2P  -35442.09 Hz
PRMCW  14.000000 ppm/cm
H2CM  12934.38504 Hz/cm
Figure A7.28 $^1$H NMR (600 MHz, CDCl$_3$) of compound 29

rotamers observed well in this molecule
Figure A7.29 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 29
Figure A7.30 $^1$H NMR (500 MHz, CDCl$_3$) of amidophosphine 30
Figure A7.31 $^{13}$C NMR (125 MHz, CDCl$_3$) of amidophosphine 30
Figure A.7.32 31P NMR (121 MHz, CDCl₃) of amidophosphine.
Figure A7.33 $^1$H NMR (500 MHz, CDCl$_3$) of aminophosphine 31
Figure A7. 34 $^{13}$C NMR (125 MHz, CDCl$_3$) of aminophosphine

Default parameters for C-13 with proton decoupling

Current Data Parameters
NAME: 203
EXPN: 0
PROCNO: 1

F2 - Acquisition Parameters
Data: 2065004
Time: 16.23
INSTRUM: arx500
RBOBD: 5 mm broadband
PULPROG: zpg40
TD: 89356
SOLVENT: CDCl$_3$
NS: 304
DG: 0
SMH: 3574.205 Hz
FIDRES: 0.844957 Hz
AM: 0.0175548 sec
AG: 32768
DN: 14.000 usec
DE: 20.000 usec
TE: 100.00 K
DI: 0.0000000 sec
DL: 8.00 dB
DP: 1.000 Hz
SP1: 357.7200000 MHz
NUCLEUS: 13C
D1: 0.03000000 sec

F2 - Processing parameters
SI: 32768
SF: 125.7500000 MHz
WMN: EM
SSB: 2
LB: 1.00 Hz
GB: 0
PC: 4.00

1D NMR plot parameters
C1: 0.00 cm
F1P: 261.996 ppm
F1: 3278.460 Hz
F2P: -21.996 ppm
F2: 2766.20 Hz
FWHM: 14.01093333 ppm/cm
HZCM: 1785.713491 Hz/cm
Figure A7.35 $^{31}$P NMR (121 MHz, CDCl$_3$) of aminophosphine 31
Figure A7.36 1H NMR (500 MHz, CDCl₃) of aminophosphine 32

Current Data Parameters
NAME  SK331
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date  20100506
Time  22:25
INSTRUM  arX500
PROBNO  50 mm broadband
F1PROD  zg30
TD  65536
SOLVENT  CDC13
NS  8
DS  0
SWH  10000.000 Hz
FIDRES  0.152588 HZ
AG  2.3768500 sec
RG  256
DM  50.000 use
DE  71.43 use
TE  300.00 K
D1  2.000000000 sec
P1  11.00 use
SFDM  500.1330000 MHz
NUCLEUS  1H

F2 - Processing parameters
SI  32768
SF  500.1300000 MHz
WDM  EM
SSB  0
LB  0.30 Hz
GB  0
PC  1.00

1D NMR plot parameters
CX  20.00 cm
FSI  9.400 ppm
F16  4701.22 Hz
F26  -0.000 ppm
F2  -300.00 Hz
PPMCM  0.50000 ppm
HZCM  250.00000 Hz/
Figure A7.37 $^{13}$C NMR (125 MHz, CDCl$_3$) of aminophosphine 32
Figure A7.38 $^{31}$P NMR (121 MHz, CDCl$_3$) of aminophosphine 32
Figure A7.39 $^1\text{H}$ NMR (500 MHz, CDCl$_3$) of compound 39
Figure A7.40 $^1$H NMR (500 MHz, CDCl$_3$) of amidophosphine 40
Figure A.41: $^{13}$C NMR (125 MHz, CDCl$_3$) of amidophosphine.
Figure A7.42 $^{31}$P NMR (121 MHz, CDCl₃) of amidophosphine 40
Figure A7.43 $^1$H NMR (500 MHz, CDCl$_3$) of aminophosphine 41
Figure A7.44  $^{13}$C NMR (125 MHz, CDCl$_3$) of aminophosphine.
Figure A7.45 $^{31}\text{P}$ NMR (121 MHz, CDCl$_3$) of aminophosphine 41
Figure A7.46 $^1$H NMR (500 MHz, CDCl$_3$) of amidophosphine 45
Figure A7.48 $^{31}$P NMR (121 MHz, CDCl$_3$) of amidophosphine 45
Figure A7.46 1H NMR (500 MHz, CDCl₃) of aminophosphine 46.

Current Data Parameters
NAME      SH168_1
EXPNO     1
PROCNO    1

F2 - Acquisition Parameters
Date       20100913
Time       12.50
INSTRUM    any500
POW250D    5 mm broadband
PULPROG    r950
TD         65536
SOLVENT    CDCl₃
NS         8
DG         10000.000 Hz
FIDRES     0.152568 Hz
AQ         3.2768500 sec
AG         256
DW         50.000 use
DE         71.43 use
TE         300.00 K
DT         2.000000000 sec
P1         11.00 use
SF01       500.1330000 MHz
NUCLEUS    1H

F2 - Processing parameters
SI         32768
SF         500.1300238 MHz
MOM        EM
SBB        0
LB         0.30 Hz
GB         0
PC         1.00

1D NMR plot parameters
CX         20.00 cm
F1P        9.400 ppm
F1         4701.22 Hz
F2P        0.600 ppm
F2         -300.08 Hz
PPMCM      0.50000 ppm
HZCM       250.08562 Hz
Figure A7.50 $^{13}$C NMR (125 MHz, CDCl$_3$) of aminophosphine 46
Figure A7.5 31P NMR (121 MHz, CDCl3) of aminophosphine 46
CHAPTER SIX

Chiral Aminophosphines: Designs, Syntheses, and Applications
Toward Asymmetric Phosphinocatalysis (Part 2)

6.1 Background and Introduction

6.1.1 Source of Chirality on Phosphine

Due to the importance of asymmetric catalysis in organic synthesis, a vast number of chiral phosphine ligands have been developed and great effort in developing asymmetric catalysis was centered in the last few decades. One interesting feature of chiral phosphines is the center of chirality on them. The chirality on a phosphine may reside on the phosphorous center, in the carbon backbone, or result from the entire phosphine molecule framework.\(^1\)

6.1.1.1 P-Stereogenic Center

If the lone pair on the phosphorous is considered as one substituent, the tetrahedral geometry of a tertiary phosphine will cause a chiral center at the phosphorous. Unlike its close relative tertiary amines, the phosphine features a high inversion barrier that prevents the racemization at room temperature and sustain the chirality on the phosphorous center (Figure 6.1.1.1.1).\(^2\) The racemization half-life for a phosphine was also determined as a couple of day at 115 °C as noted by Horner and Mislow.\(^3\)
Early methods for preparing P-chiral phosphines were independently developed by Horner and Mislow in the 1960s while studying the stereochemistry of substitution reaction on chiral phosphorous compounds. Horner approached the preparation of chiral phosphine via electrochemical reduction of a chiral tetravalent phosphonium salt that was resolved by fractional crystallization. Mislow, on the other hand, prepared the chiral phosphine by treating the resolved chiral menthyl phosphinate with a Grinard reagent and reducing the resulting chiral phosphine oxide to the chiral phosphine. A few examples of P-chiral phosphines are listed in Figure 6.1.1.2.
6.1.1.2 Stereogenic Center on the Carbon Backbone

Although the chirality directly placed on the phosphorous center seems to be more desirable to induce an asymmetry,\(^6\) the chiral center residing on the carbon backbone is not less efficient in asymmetric induction. In 1971, Kagan developed the chiral phosphine ligand DIOP that showed comparable enantioinduction to CAMP in the Rh-catalyzed hydrogenation of an enamide system.\(^6,7\)

Due to the flexibility and availability of the chiral carbon backbone, following the discovery of DIOP was a whole series of chiral phosphines with asymmetry on the carbon backbone. A few examples of the early chiral phosphines with the asymmetry on the carbon backbone are listed in Figure 6.1.1.2.1.\(^7\)–\(^9\)

*Figure 6.1.1.2.1*

![DIOP, BPPM, CHIRAPHOS, PROPHOS](image)

6.1.1.3 Chirality from Molecular Framework

It is obvious to possess a chiral center on the molecule in order to induce an asymmetry from it. However, another type of chirality, which does not require any chiral centers in the molecule, can arise from the arrangement of the entire molecular framework. One such type of chirality, known as axial chirality,\(^{10}\) has been extensively employed in the designs of new chiral phosphines after Noyori reported the first axially chiral phosphine, BINAP, and its excellent enantioinduction in Rh-catalyzed
hydrogenation of an enamide. Figure 6.1.1.3.1 below displays a few examples of the axially chiral phosphines.

**Figure 6.1.1.3.1**

It is fortunate for the later field of phosphinocatalysis to inherit thousands of great designs of chiral phosphines that have been specifically developed toward the asymmetric transition metal-catalyzed reactions. Since phosphinocatalysis has different mode of reactivity from the transition metal catalysis, designing phosphines for phosphinocatalysis is very likely to be different from designing phosphine ligands for transition metal catalysis. However, the knowledge about chiral phosphine ligands is still of great benefit to the development of asymmetric phosphinocatalysis. The chiral catalysts developed for asymmetric phosphine-catalyzed reactions include monofunctional and bifunctional phosphine catalysts. In section 6.1.2, a brief review will focus on the types of chiral phosphine catalysts (with representative ones) and the achievements in asymmetric catalysis rather than attempting to provide details of each type of reaction.
6.1.2 Mono-functional Phosphine Catalyst

6.1.2.1 Rigid Bicyclic Phosphine Catalyst

Lu first reported the phosphine-catalyzed [3 + 2] annulation between an allenoate and an activated olefin to generate a functionalized cyclopentene in 1995.\textsuperscript{14} Two years later, Zhang successfully operated the asymmetric version of Lu’s [3 + 2] annulation with high enantioselectivity by employing a novel rigid bicyclic phosphine catalyst \textsuperscript{1} (Figure 6.1.2.1.1).\textsuperscript{15} In this design, the fused bicyclic [2.2.1] phosphine features a rigid structure together with a local \(C_2\)-symmetry that are responsible for high enantioinduction in the reaction.

In 1993, Vedejs first reported that the acylation of alcohols with carboxylic anhydrides could be catalyzed by tributylphosphine, being catalytically similar to DMAP.\textsuperscript{16} In 1996, also reported from the same group was the first kinetic resolution of secondary alcohols using chiral phosphines.\textsuperscript{17a} In this report, the best selectivity achieved from using Burk’s trans-2,5-dimethyl-1-phenylphospholane catalyst\textsuperscript{18} was still unsatisfactory; and starting from the structure of Burk’s catalyst, a new chiral phosphine 2 was designed based on 2-phosphabicyclo-[3.3.0]octane skeleton in 1999 (Figure 6.1.2.1.1). Vedejs reported that the new catalyst made a significant improvement to the enantioselective acylation.\textsuperscript{17b} In this phosphine, the bicyclic framework played a key role to the reactivity of the catalyst, adding a conformational effect to make the lone pair on phosphorous more accessible.\textsuperscript{19}
Recently, Kwon has developed new chiral bicyclic phosphines that are derived from L-hydroxyproline (L-HYP) and enantiomeric carvone (both R and S enantiomers are abundant), respectively (Figure 6.1.2.1.2). These rigid bicyclic phosphines have shown excellent enantioinduction in [3 + 2] annulation between gamma-substituted allenoates and activated imines.\textsuperscript{20a} Excellent enantioselectivity of chiral phosphine 3 was illustrated in the application toward the enantioselective total synthesis of (+)-Ibophyllidine.\textsuperscript{20b}

**Figure 6.1.2.1.2**

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig61212.png}
\caption{Axially Chiral Phosphine Catalyst}
\end{figure}

\begin{itemize}
\item [3 + 2] annulation, dihydropyrrrole\textsuperscript{20a}
\item Total synthesis of (+)-Ibophyllidine\textsuperscript{20b}
\end{itemize}

Kwon, Unpublished

### 6.1.2.2 Axially Chiral Phosphine Catalyst

In 2003, Kwon reported an access to tetrahydropyridine via the novel phosphine-catalyzed [4 + 2] annulation between the alpha-substituted allenoates and activated imines.\textsuperscript{21} In 2005, Fu employed Gadiali’s phosphine 6, developed in 1994,\textsuperscript{22} to
catalyze the asymmetric version of Kwon’s [4 + 2] annulation (Figure 6.1.2.2.1).\textsuperscript{23a} In the following year, Fu applied again phosphepine 6 to the asymmetric [3 + 2] annulation between an unsubstituted allenoate and an α,β-unsaturated ketone and successfully generate a functionalized cyclopentene with high enantioselectivity.\textsuperscript{23b} Not listed here are many of other applications of Gladiali’s phosphepines in phosphine-catalyzed reactions, being reported afterward.\textsuperscript{24} In 2009, Fu employed another axially chiral phosphine developed by Zhou in 2005, namely spiro phosphepine 7,\textsuperscript{25} to conduct the asymmetric version of Trost’s gamma-umpolung addition.\textsuperscript{26} The reaction was successfully catalyzed by spiro phosphepine to provide high yield and good to excellent enantioselectivity.\textsuperscript{23c,d}

Another example of axially chiral phosphine, successfully applied toward a phosphine-catalyzed reaction, has been illustrated in Marinetti’s work in 2008. In this work, ferrocene was employed as the axial chiral backbone to design a family of the chiral phosphine of FerroPHANE. The subsequent application of TMS-FerroPHANE (8), as shown in Figure 6.1.2.2.1, toward the asymmetric [3 + 2] annulation between the unsubstituted ethyl allenoate and activated olefins has proven successful with high enantioselectivity.\textsuperscript{27} Since then, TMS-FerroPHANE (8) has shown its catalytic prowess in the [3 + 2] annulation between various activated olefins and allene substrates.\textsuperscript{28}
6.1.3 Bifunctional Phosphine Catalyst

The concept of bifunctional catalyst has been applied to the new design of chiral phosphine. In general, the presence of the chiral element in the molecule is further assisted by the hydrogen bonds from the second functionality to the substrate in order to lock the transitional intermediate in a rigid structure. A few examples of the chiral bifunctional phosphines and early contributions to this area of phosphinocatalysis will be briefly discussed here.

6.1.3.1 Axially Chiral Catalyst

In 2003, Shi reported that the asymmetric version of aza-Morita–Baylis–Hillman (aza-MBH) reaction could be achieved by a chiral bifunctional phosphine catalyst derived from the axially chiral binol. With chiral phosphine 9 (Figure 6.1.3.1.1), high enantioselectivity of aza-MBH reaction, even with the simple Michael acceptor MVK, could be realized (ee’s above 90%). The key factor for the achievement of high enantiselectivity in aza-MBH reaction is the presence of the second functionality hosting the hydrogen-bonding site. Many other asymmetric phosphine-catalyzed reactions
could be achieved with high enantioselectivity by tuning the hydrogen-bonding site of the bifunctional phosphine catalyst: aza-MBH reaction, [3 + 2] allene-alkene annulation, nucleophilic substitution of Morita–Baylis–Hillman adducts (MBHADs).29

Figure 6.1.3.1.1

![Diagram of chiral amino-phosphine catalyst]

6.1.3.2 Chiral Amino-phosphine Catalyst

Chiral amino acids have long been exploited as a chiral pool for asymmetric organocatalysis. While investigating catalytic peptide, Miller has come across the idea of putting a phosphino group in the peptide backbone to enrich the functionality. A simple derivatives from Gilbertson’s phosphines30 were thus employed and simply tested, without further elaboration into a peptide, to catalyze the asymmetric [3 + 2] allene-alkene annulation. In the report, Miller found that the presence of the hydrogen-bond donor N–H is essential to the effective enantioinduction of the catalyst and any
changes to the hydrogen-bond donor property will deviates the enantioselectivity and efficiency of the reaction (Figure 6.1.3.2.1). 31

After Jacobsen’s report of thiourea catalyst in 1998, hydrogen bonding in catalysis and asymmetric catalysis has gained popularity in organocatalysis. 32 Having witnessed the success of Miller’s bifunctional amino-phosphine catalyst in the asymmetric [3 + 2] allene-alkene annulation, Jacobsen has devised the new design of chiral bifunctional phosphine by incorporating the superb hydrogen-bonding motif of thiourea into the structure (Figure 6.1.3.2.1). In 2008, Jacobsen reported that this new chiral catalyst of thiourea-phosphine resulted in excellent enantioselectivity in asymmetric [3 + 2] allene-imine annulation. 33

Figure 6.1.3.2.1

The successful application of the chiral bifunctional phosphine to asymmetric [3 + 2] annulation by Miller has opened a new avenue for the extensive research program on chiral amino acid-derived phosphines in phosphinocatalysis. In 2010, Zhao started to develop this idea in a systematic manner. The phosphine was directly derived from the corresponding amino acid, in which the carboxylic acid functional group would be reduced to alcohol and then replaced by a phosphino group. The chiral backbone can be varied by utilizing different amino acids while the amino functional group was used
for hydrogen bonding (Figure 6.1.3.2.2). Employing this strategy, Zhao systematically built a small collection of chiral aminophosphines to screen for a reaction. In Zhao's report in 2010, chiral aminophosphine 14 stood out as an effective catalyst and provided high enantioselectivity in [3 + 2] allene-alken annulation.34

*Figure 6.1.3.2.2*

Having been actively studying asymmetric catalysis by primary amino acids, Lu began to expand the research into chiral amino acid-derived phosphines in asymmetric phosphinocatalysis. Utilizing the same strategy that Zhao has disclosed, Lu has built up a collection of chiral aminophosphines. Although a simple amino acid was still considered for the chiral backbone in some of Lu's chiral phosphines (Figure 6.1.3.2.2), dipeptide chiral backbone was central in Lu's designs of chiral phosphines (Figure 6.1.3.2.3). The dipeptide backbone was believed to provide more hydrogen bondings and hence more effective chiral communication of the catalyst to the substrate. For the

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same reason, Lu has also added the thiourea motif to the chiral amino acid backbone in order to enhance such effect. Utilizing variants of chiral catalysts from his library of chiral aminophosphines, Lu has developed a variety of asymmetric transformations, including [3 + 2] allene-alkene annulation, [3 + 2] allene-imine annulation, [4 + 2] allene-alkene annulation, [3 + 2] MBHADs-alkene annulation, and Michael addition.

Figure 6.1.3.2.3

![Diagram of chiral catalysts](image)

6.1.4 Design of Chiral Phosphines

6.1.4.1 Source of Chirality

Chiral amino acids, both proteinogenic and nonproteinogenic variants, have proven to be wonderful resources for asymmetric catalysis. The abundancy and ready availability of chiral amino acids have made them desirable sources of chirality. Proline,
unique in both the cyclic structure and the secondary amine, has attracted great attention in the past decades for its catalytic versatility.\textsuperscript{36} Despite the popularity of proline in catalysis, it has been left out in designing new chiral amino acid-derived phosphines for phosphinocatalysis.\textsuperscript{31–33} Perhaps it is due to the fact that functionalization of proline’s secondary amine will obviate the possibility of hydrogen bonding. As illustrated in Figure 6.1.4.1.1, tuning substituent at the site of secondary amine would remove the hydrogen bonding unless a thiourea or carbamate motif was employed.

\textit{Figure 6.1.4.1.1}

![Diagram](image)

Apparently, the recent successes in asymmetric phosphinocatalysis has required the presence of hydrogen bonding for chiral amino acid-derived phosphines. However, progress in the field of enamine and iminium catalysis has taught a lesson that steric direction was later realized as another mode of asymmetric induction besides hydrogen bonding direction (Figure 6.1.4.1.2).\textsuperscript{37,38}
Since hydrogen-bonding direction has been centered in designing recent chiral aminophosphines for asymmetric catalysis,\textsuperscript{31,33–35} steric direction has not been considered as a promising platform for aminophosphine designs. With our general interest in phosphinocatalysis and its applications toward natural product synthesis, and recently in asymmetric phosphinocatalysis and chiral phospine designs, we became interested in the possibility of sterically driven asymmetric phosphinocatalysis, and have chosen to create chiral aminophosphines from chiral L-hydroxyproline (L-HYP), an abundant nonproteinogenic amino acid with the proline skeleton and an additional hydroxy group for further steric tuning (Figure 6.1.4.1.3).
6.1.4.2 Synthetic Plans

We have envisioned that two sets of phosphines could be obtained from L-HYP by installing diphenylphosphino group either at the secondary alcohol carbon or at carboxylic acid carbon (Figure 6.1.4.2.1). Accordingly, aminophosphines 20 could be obtained from the common intermediate mesylate 19 via displacement of the mesylate by the diphenylphosphino group and functional group manipulations. The syntheses of phosphines 25 were straightforward; starting from the commercially available L-HYP, various protecting groups could be installed before the substitution of the mesylate by diphenylphosphino group.
6.2 Synthesis of Chiral L-HYP-Derived Phosphines

Implementation of the synthetic route was illustrated in Scheme 6.2.1. First, the Boc-protection of L-HYP (18) proceeded to provide a quantitative yield of N-Boc L-HYP 26. Benzylolation of the free alcohol followed by borane reduction of carboxylic acid resulted in primary alcohol precursor 28, mesylation of which led to the starting material
19 for phosphine synthesis.\textsuperscript{39} Preparation of 19 was quickly achievable in multi-gram scale (9.0 g scale) from L-HYP (18) within 4 reaction steps. Only two chromatographic columns were necessary to achieve clean material 19 for the next important step of phosphine formation.

Scheme 6.2.1

Mesylate 19 then could be converted into phosphine 20a by slow addition of excess potassium diphenylphosphide at low temperature. Under air free condition, displacement of the mesylate by diphenylphosphide was performed at low temperature and resulted in high yield of phosphine 20a (Scheme 6.2.2).

Scheme 6.2.2
Now that aminophosphine 20a was successfully prepared, other variants were also considered to form a small collection of chiral phosphines to screen a variety of phosphine-catalyzed reactions. A few variants of chiral aminophoshines 20, varying at N-substituents, has been summerized in Table 6.2.1. Removal of the Boc group from aminophosphine 20a by trifluoroacetic acid (TFA) in DCM has resulted in low isolated yield of the corresponding free-amino phosphine; as a result, a one-pot procedure, removing the Boc group and replacing with another substituent, was formulated to avoid the unwanted loss of material. After the Boc-deprotection, excess amount of triethylamine was added to neutralize the acid TFA in the previous step and mediate the acylation with an acyl chloride reagent. With the one-pot procedure, four aminophosphines 20b–e have been generated and isolated in high purity.
Table 6.2.1

![Diagram of the reaction with formulas and conditions]

2. Preliminary Results in Phosphine-Catalyzed [4 + 2] Annulation

The first three chiral phosphines became available and were immediately applied toward our [4 + 2] annulation. Displayed in Table 6.3.1 were very promising values of enantioselectivity. Even though the reaction was slow and could not reach completion over 3 days, the first attempts in asymmetric [4 + 2] allene-alkene annulation have already provided enantioselectivities of more than 50%. From the preliminary results, the enantioselectivity has seemingly increased with the increasing bulkiness of N-substituents, and the model of steric control has seemed to follow.
The catalysts were also checked with the more activated allene in [4 + 2] allene-alken annulation.\textsuperscript{23a} Table 6.3.2 has summarized the preliminary results of the reaction. As expected, the more activated allene allowed the reaction to reach completion within 36 hours. The yields and diastereoselectivities were fair, and the enantioselectivities were reasonable. However, the preliminary values under unoptimized reaction conditions have been very promising for further development in this model of steric control.

Table 6.3.2
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<th>complete</th>
<th>yield (%)</th>
<th>dr</th>
<th>ee (%)</th>
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<td>yes</td>
<td>59</td>
<td>80:20</td>
<td>33</td>
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<tr>
<td>2</td>
<td>20b</td>
<td>20</td>
<td>yes</td>
<td>74</td>
<td>78:22</td>
<td>46</td>
</tr>
<tr>
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<td>20c</td>
<td>10</td>
<td>no</td>
<td>62</td>
<td>76:24</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>20d</td>
<td>10</td>
<td>no</td>
<td>42</td>
<td>77:23</td>
<td>46</td>
</tr>
</tbody>
</table>

6.4 Conclusion

Taking advantage of the ready availability of naturally occurring chiral amino acids, we have chosen L-HYP, a nonproteinogenic but abundantly available amino acid for our designs of phosphines. Trying to employ the steric direction in enantioinduction, we have developed a synthetic route to a number of L-HYP-derived phosphines. The preliminary applications of these phosphines toward the [4 + 2] allene-imine annulation has proved moderately successful for enantioselectivities. It is, however, still at the very early stage of realizing the true potential of the sterically directed chiral phosphines, and there are still plenty of rooms for further optimizations to reach the goal of excellent enantioselectivities in the [4 + 2] annulation.
6.5 Experimental Section

6.5.1 Materials and Methods

6.5.1.1 General Information

All reactions were performed in flamed-dried round-bottom flasks under an atmosphere of Ar with dry solvents, unless otherwise noted. A syringe pump and stainless-steel needles were used for slow addition of reagents into the reaction mixtures. Reactions were monitored by thin-layer chromatography (TLC) on 0.25-mm SiliCycle silica gel plates, visualizing under UV light or staining with iodine, p-anisaldehyde, or potassium permanganate. Flash column chromatography (FCC) was performed using SiliCycle Silica-P Flash silica gel (60 Å pore size, 40–63 μm) and compressed air. Purification of phosphines was performed through quick FCC; phosphine-containing fractions were collected immediately into a flask secured under Ar. Organic solvents were evaporated in rotary evaporators under reduced pressure; the flasks were refilled with Ar when isolating phosphines. Phosphine products were stored under Ar at all times.

6.5.1.2 Materials and Reagents

Reagents were used as received from commercial sources, unless otherwise noted. Acetonitrile (MeCN), dichloromethane (DCM), and triethylamine (TEA) were distilled from CaH₂ under Ar atmosphere. Tetrahydrofuran (THF) was distilled from Na and benzophenone under Ar atmosphere.
6.5.1.3 Instrumentation

NMR spectra were recorded using Bruker Avance-500 or Avance-300 instruments, calibrated to signals from the solvent as an internal reference [7.26 (residual CHCl₃) and 77.00 (CDCl₃) ppm for ¹H and ¹³C-NMR spectra, respectively]. Data for ¹H-NMR spectra are reported in terms of chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. Data for ¹³C-NMR spectra are reported in terms of chemical shift (δ, ppm), multiplicity, and coupling constants (Hz) in the case of JCP coupling. The following abbreviations are used to denote multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; q₁ = quintet, sx = sextet, sp = septet; m = multiplet; br = broad; app = apparent.

6.5.2 Preparative Procedures

4-Benzylxoy-2-methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid t-butyl ester (19).³⁰ To a solution of L-HYP (5.08 g, 38.77 mmol) in 40 mL 1,4-dioxane and 40 mL 1N aqueous NaOH at 0 °C was slowly added Boc₂O (9.3 g, 42.6 mmol). The reaction mixture was stirred for 8 h at room temperature. After the reaction was confirmed complete by TLC, it was concentrated under reduced pressure and then acidified to pH 1 and extractracted with EtOAc. The extract was washed with brine and dried over Na₂SO₄ before concentrated to provide a quantitative yield of clear viscous oil Boc-protected L-HYP.³¹ Boc-protected L-HYP was dissolved in dry 50 mL THF and then
cannulated into the mixture of NaH (7g, 155 mmol) in 100 mL dry THF at 0 °C. Benzyl bromide (5.4 mL, 45 mmol) was then added dropwise to the reaction mixture. The reaction flask was warmed to room temperature before being refluxed over 6 h. The reaction was cooled down and poured over ice. Organic solvent was removed under reduced pressure and the aqueous solution was washed with EtOAc. The aqueous layer was acidified with 2N HCl until pH of 2, and then extracted with EtOAc. The organic layer was concentrated under reduced pressure to yield a brownish yellow oil. This brownish yellow oil was dissolved back in 150 mL dry THF and cooled to 0 °C. BH$_3$ DMS (5.7 mL, 58 mmol) was added dropwise to the reaction mixture, and then kept stirred at 0 °C for an additional 1 h. The reaction flask was then removed from the ice bath, and the reaction was stirred overnight at room temperature. The reaction mixture was poured over ice and sequentially extracted with EtOAc, washed with brine, washed with saturated sodium bicarbonate solution, and dried over Na$_2$SO$_4$. The final solution was concentrated under reduced pressure and purified by liquid chromatography (gradient EtOAc/Hexanes 30% to 50%) to yield a slightly yellow oil (8.1 g, 68% over 3 steps). The slightly yellow oil from previous step (7.8 g, 25.3 mmol) was dissolved in dry DCM and cooled to 0 °C. To the solution was added Et$_3$N (3.9 mL, 28 mmol) and slowly added MsCl (2.06 mL, 26.6 mmol). After the reaction was checked via TLC and reached completion, the solvent was removed under reduced pressure. The residue was dissolved back in EtOAc and washed sequentially with water, saturated sodium bicarbonate solution, brine and then dried over Na$_2$SO$_4$. The product was isolated via FCC (EtOAc/Hexanes 30%) to provide product 19 (8.99 g, 92%) as a slightly yellow viscous oil.
(2S,4R)-tert-butyl 4-(benzyloxy)-2-((diphenylphosphino)methyl)pyrrolidine-1-carboxylate (20a). To a carefully flame dried round bottom flask containing a stir bar was added 19 (771 mg, 2 mmol). To the flask was added 20 mL dry THF via a syringe while it was kept under argon. The flask was then cooled down to –40 °C before 0.5 N Ph2PK solution in THF (6 mL, 3 mmol) was added over 2 h via syringe pump. After the addition was done, the reaction mixture was stirred at the same temperature for an additional 7 h. The reaction was then warmed to room temperature before the addition of H2O (1–1.5 mL) until the disappearance of the reaction color. To the mixture was added DCM (20 mL) and the organic layer was collected. The aqueous layer was then extracted twice with DCM. The combined organic layer was dried over Na2SO4 and concentrated under reduced pressure. The crude residue was purified through column chromatography (EtOAc/Hexanes 1:10 to 1:5) to afford a clear viscous oil 20a (846 mg, 89%). 1H-NMR (500 MHz, CDCl3) δ 7.61 (br s, 1H), 7.54 (br s, 1H), 7.46 (app t, J = 6.6 Hz, 2H), 7.38–7.30 (m, 11H), 4.49 (br s, 2H), 4.27 – 4.10 (m, 2H), 3.90 –3.43 (m, 2H), 3.04 – 2.88 (m, 1H), 2.33 – 2.12 (m, 3H), 1.49 (s, 9H); 13C-NMR (125 MHz, CDCl3) δ 154.4, 137.8, 132.7 (J = 19.2 Hz), 132.3 (J = 19.5 Hz), 128.6, 128.3 (d, J = 7.1 Hz), 128.2, 127.4, 127.3, 79.4, 70.6, 54.1 (d, J = 18.9 Hz), 53.2, 38.6, 35.0 (d, J = 10.8 Hz), 33.5 (br s), 28.3; 31P-NMR (202 MHz, CDCl3) δ –22.9.
General Procedure for preparing 20b–e: To a flame-dried round bottom flask, with a stir bar inside, was added phosphine 20a (1.5–1.6 mmol) and 1.5 mL of dry DCM. 1.5 mL TFA was added dropwise to the solution at 0 °C and the reaction mixture was stirred at room temperature for 1 h. After 1 h, the reaction mixture was diluted with 3.5 mL dry DCM and cooled to 0 °C. 3.5 mL Et₃N was then added dropwise to the reaction mixture before an acyl chloride reagent (1.2 eq) was slowly added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was washed with H₂O and the organic layer was dried over Na₂SO₄. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography.

![Chemical Structure](image)

1-((2S,4R)-4-(benzyloxy)-2-((diphenylphosphino)methyl)pyrrolidin-1-yl)-2,2-dimethylpropan-1-one (20b). Obtained as a white solid (70%). ¹H-NMR (500 MHz, CDCl₃) δ 7.60 (t, J = 7.5 Hz, 2H), 7.44–7.41 (m, 2H), 7.37 (app t, J = 7.0 Hz, 2H), 7.34–7.26 (m, 9H), 4.52–4.43 (m, 3H) (apparent overlapping peaks), 4.17 (app s, 1H), 3.90 (d, J = 11.4 Hz, 1H), 3.56 (dd, J = 11.4, 4.4 Hz, 1H), 2.91 (d, J = 13.9 Hz, 1H), 2.24–2.19 (m, 2H), 2.16–2.10 (m, 1H), 1.17 (s, 9H); ¹³C-NMR (125 MHz, CDCl₃) δ 176.7, 137.8, 132.8 (d, J = 18.8 Hz), 132.7 (d, J = 19.4 Hz), 128.6, 128.5 (d, J = 7.0 Hz), 128.35 (d, J = 7.0 Hz), 128.32, 127.6, 127.3, 77.4, 70.6, 55.7 (d, J = 17.5 Hz), 53.1, 38.8, 35.5 (d, J = 9.3 Hz), 32.8 (d, J = 13.7 Hz), 27.5; ³¹P-NMR (202 MHz, CDCl₃) δ –23.5.
1-((2S,4R)-4-(benzyloxy)-2-((diphenylphosphino)methyl)pyrrolidin-1-yl)-2,2-
diphenylethanoine (20c). Obtained as a white solid (80%). $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ (on aliphatic region, major rotamer) 5.00 (s, 1H), 4.52–4.50 (m, 1H) (overlapping peaks), 4.25 (d, $J = 12.2$ Hz, 1H), 4.17 (d, $J = 11.9$ Hz, 1H), 4.13–4.10 (m, 1H), 3.66 (d, $J = 10.2$ Hz, 1H), 3.49 (dd, $J = 11.0$, 4.7 Hz, 1H), 3.26 (dt, $J = 13.5$, 4.5 Hz, 1H), 2.24–2.14 (m, 2H), 2.05–2.00 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$) $\delta$ (major rotamer) 170.3, 139.4, 138.9, 137.7, 133.0 (d, $J = 19.3$ Hz), 132.7 (d, $J = 19.3$ Hz), 129.1, 128.9, 128.8, 128.6, 128.59, 128.56, 128.43, 128.41, 128.35, 128.32, 127.6, 127.5, 126.9 (d, $J = 8.0$ Hz), 76.5 (d, $J = 1.8$ Hz), 70.7, 57.0, 54.9 (d, $J = 19.2$ Hz), 51.9, 36.9 (d, $J = 9.8$ Hz), 32.7 (d, $J = 12.5$ Hz); $^{31}$P-NMR (202 MHz, CDCl$_3$) $\delta$ –22.5 (major rotamer), –23.2 (minor rotamer).

((2S,4R)-4-(benzyloxy)-2-((diphenylphosphino)methyl)pyrrolidin-1-yl)(3,5-
bis(trifluoromethyl)phenyl)methanone (20c). Obtained as a white solid (69%). $^1$H-NMR
(500 MHz, CDCl₃) δ 7.87 (s, 1H), 7.60 (s, 2H), 7.57–7.53 (m, 4H), 7.38–7.16 (m, 11H), 4.78–4.70 (m, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.30 (d, J = 11.9 Hz, 1H), 4.14 (br s, 1H), 3.53 (dd, J = 11.3, 3.3 Hz, 1H), 3.32 (d, J = 11.3 Hz, 1H), 2.84–2.76 (m, 2H), 2.48 (dd, J = 13.2, 7.9 Hz, 1H), 2.34 (br s, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 167.1, 138.4, 137.6, 137.5, 137.49, 132.8 (d, J = 21.3 Hz), 132.4 (d, J = 18.6 Hz), 131.5 (q, J = 33.7 Hz), 129.1, 128.63, 128.56 (d, J = 7.5 Hz), 128.54 (d, J = 6.8 Hz), 128.4, 127.7, 127.6 (br s), 127.4, 123.6 (sp, J = 3.6 Hz), 122.8 (q, J = 273.7 Hz), 77.1, 70.8, 55.6, 55.0 (d, J = 16.9 Hz), 36.9 (d, J = 10.6 Hz), 32.3 (d, J = 12.9 Hz); ³¹P-NMR (202 MHz, CDCl₃) δ –26.4.

(1s,3R)-adamantan-1-yl((2S,4R)-4-(benzyloxy)-2-((diphenylphosphino)methyl)pyrrolidin-1-yl)methanone (20e). Obtained as a white solid (88%). ¹H-NMR (500 MHz, CDCl₃) δ 7.60 (t, J = 7.3 Hz, 2H), 7.44–7.41 (m, 2H), 7.39–7.28 (m, 11H), 4.54–4.50 (m, 2H) (overlapping peaks), 4.44 (d, J = 12 Hz, 1H), 4.19 (br s, 1H), 3.99 (d, J = 11.2 Hz, 1H), 3.62 (dd, J = 11.3, 4.4 Hz, 1H), 2.88 (d, J = 13.3 Hz, 1H), 2.19 (dd, J = 13.4, 9.5 Hz, 2H), 2.12 (br s, 1H), 1.99 (s, 3H), 1.87 (s, 6H), 1.71–1.65 (app q, J = 12.4 Hz, 6H); ¹³C-NMR (125 MHz, CDCl₃) δ 176.1, 137.9, 132.8 (d, J = 18.8 Hz), 132.7 (d, J = 19.6 Hz), 128.53, 128.48, 128.34, 128.30, 127.6, 127.5, 77.6, 70.8, 55.9 (d, J = 16.3 Hz), 53.1, 41.6, 38.0, 36.5, 35.2 (d, J = 8.2 Hz), 32.9 (d, J = 12.0 Hz), 28.3; ³¹P-NMR (202 MHz, CDCl₃) δ –21.8.
6.6 Notes and References


APPENDIX EIGHT

Spectra Relevant to Chapter Six:

Chiral Aminophosphines: Designs, Syntheses, and Applications Toward Asymmetric Phosphine-Catalyzed Reactions (Part 2)
Figure A8.1 $^1$H NMR (500 MHz, CDCl$_3$) of compound 20a
Figure A8.2 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 20a
Figure A8.3 $^{31}$P NMR (121 MHz, CDCl$_3$) of compound 20a
Figure A8.4 $^1$H NMR (500 MHz, CDCl$_3$) of compound 20b
Figure A8.5 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 20b
Figure A8.6 $^{31}$P NMR (121 MHz, CDCl$_3$) of compound 20b
Figure A8.7 $^1$H NMR (500 MHz, CDCl$_3$) of compound 20c
Figure A8.8 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 20c
Figure A8.9 $^{31}$P NMR (121 MHz, CDCl$_3$) of compound 20c
Figure A8.10 $^1$H NMR (500 MHz, CDCl$_3$) of compound 20d
Figure A8.11 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 20d
Figure A8.12 $^{31}$P NMR (121 MHz, CDCl$_3$) of compound 20d
Figure A8.13 $^1$H NMR (500 MHz, CDCl$_3$) of compound 20e
Figure A8.14 $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 20e
Figure A8.15 $^{31}$P NMR (121 MHz, CDCl$_3$) of compound 20e
Figure A8.16 SFC profile of [4 + 2] allene-imine adduct by catalyst 20a
Figure A8.17 SFC profile of [4 + 2] allene-imine adduct by catalyst 20b
Figure A.18 SFC profile of [4 + 2] allene-imine adduct by catalyst 20c