CHAPTER 4

Benzannulated Bicycles by Three-Component Aryne Reactions

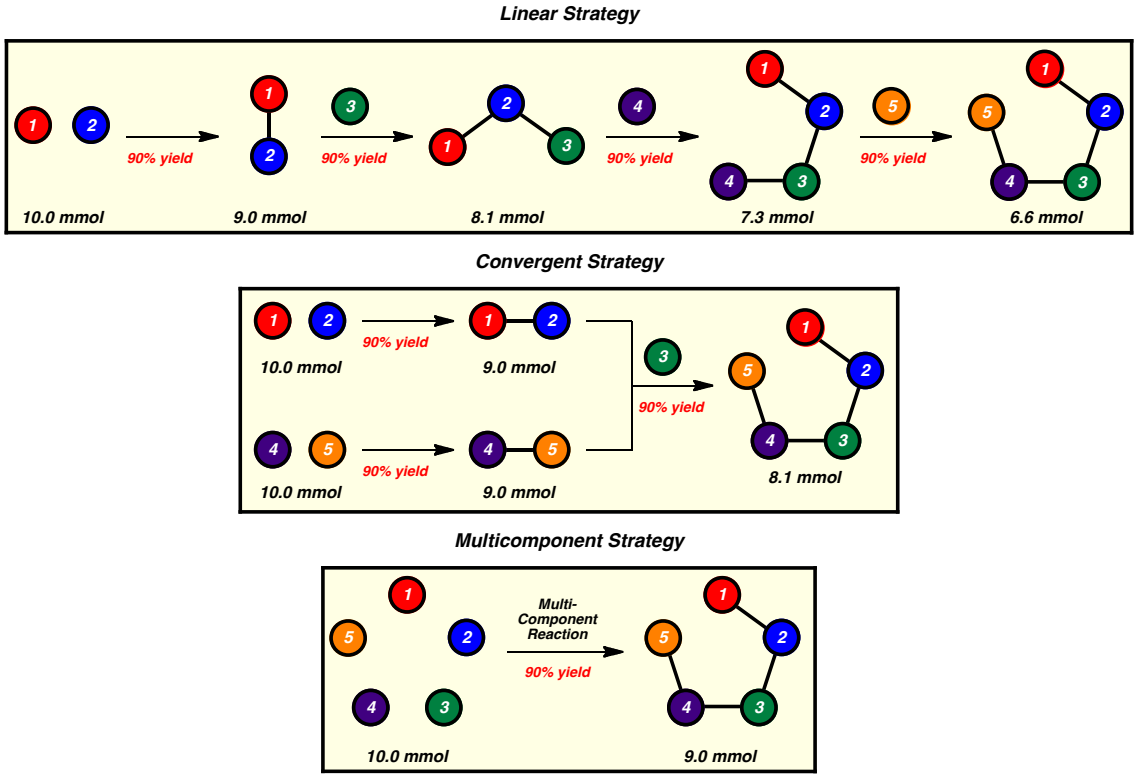
4.1 INTRODUCTION AND BACKGROUND

4.1.1 Multicomponent Reactions

Multicomponent reactions involve sequential transformations between three or more compounds existing simultaneously within a reaction mixture, resulting in a product that contains all or segments of each participant.[1] The mechanisms of these processes are understandably complex, requiring well-tuned collections of molecules capable of reacting in a specific sequence with one another to create the desired product. Because the possibilities of combining multiple reaction partners under the right conditions are effectively without limit, the field of multicomponent organic synthesis now encompasses a diversity of product structures generated by the combination of between three and seven distinct substances.[2] Not surprisingly, this has led to an abundant use of multicomponent chemistry in the preparation of combinatorial libraries for bioactivity screening and pharmaceutical discovery.[3]

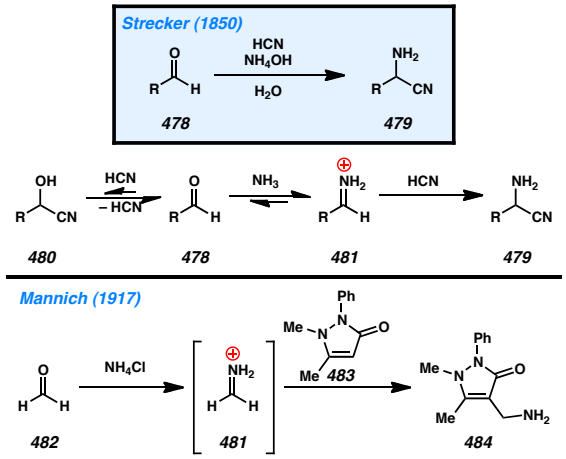
From a technical perspective, the ability to generate structural diversity in a single synthetic step is one of the most appealing aspects of muticomponent chemistry. For instance, a linear approach to incorporate five components into a reaction will require 4 consecutive steps, each with a certain yield, and likely some purification and work-up (Scheme 4.1). If each of these 4 steps yields 90% of the product, the maximum theoretical yield of these relatively high-yielding processes is less than 66% of the original amount. A convergent approach attaining similar product yields, using a three-component union of intermediates, would have a theoretical maximum output of 81%. In contrast, a multicomponent strategy with this efficiency will generate the product in a single transformation, in 90% overall yield. Consequently, developing multicomponent tactics for chemical synthesis is an undeniably attractive area for further exploration.

Scheme 4.1. *Strategic advantages of multicomponent synthesis*



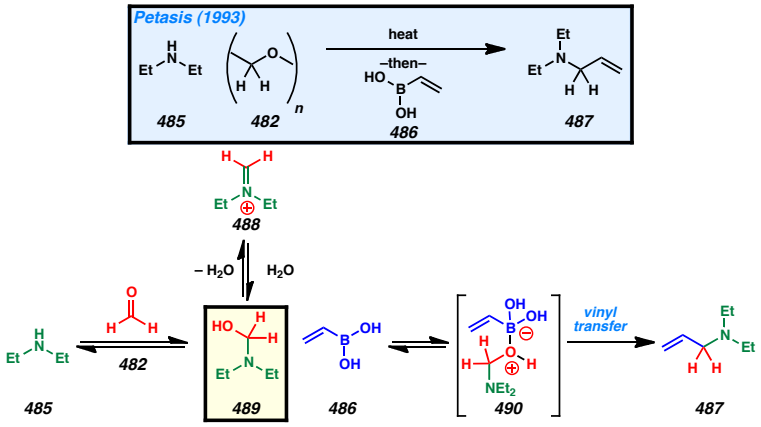
Any multicomponent reaction requires a set of specifically tuned reaction partners that are capable of either neutrally combining with one another, or transferring charge in a specific, often reversible, order that culminates in a final, irreversible transformation.[1] Because of the mechanistic complexity of these reactions—multiple steps are required to form multiple bonds—the reagents used are not typically very reactive when alone. A characteristic feature of multicomponent operations, though, is a pair of reagents that, when combined, form a specific, reactive intermediate to facilitate the reaction. This partnered activation is apparent in one of the first multicomponent reactions reported,[4] the Strecker synthesis of α-amino nitriles (**479**) from ammonium hydroxide, hydrogen cyanide, and aldehydes (**478**) in one pot (Scheme 4.2).[5] Mechanistically, the direct addition of cyanide to an aldehyde (**478**) is a highly reversible process that favors the starting materials. However, condensation of ammonia with the aldehyde creates a reactive intermediate iminium species (**481**) that is capable of suffering irreversible cyanide addition to furnish the product α-amino nitrile **479**. The Strecker synthesis is the earliest of many examples that illustrate improved reactivity via a multicomponent process. The same cooperative effect was later exploited in the development of the Mannich reaction (**482→484**), which proceeds through intermediate iminium **481**, and has proven an indispensable multicomponent approach to organic synthesis.[6,7]

Scheme 4.2. *Early multicomponent reactions*



By extending this basic design principle, seemingly incompatible reaction partners are readily coupled to form interesting structures, as in the case of the Petasis synthesis of allylic amines (Scheme 4.3).[8] In this reaction, an amine (**485**), an aldehyde (**482**) and a vinyl boronic acid (**486**) produce the targeted allylic amine (**487**). Like the Strecker reaction, the Petasis initiates with amine activation of the aldehyde (**489**), but not through the anticipated iminium **488**; these have proven to be unreactive to boronic acid addition. In this specific case, a putative hemiaminal (**489**)—the intermediate species in iminium formation—coordinates the boronic acid, assembling an activated boronate intermediate **490**. Subsequent to this step, vinyl group transfer yields the allyl amine (**487**) and boronic acid. Importantly, in the Petasis reaction a neutral reactive intermediate (**489**) is generated, permitting an otherwise passive reagent (vinyl boronic acid **486**) to react efficiently and irreversibly to yield the product (**487**).

Scheme 4.3. *Aminal relay intermediate* ***489*** *in Petasis reaction*

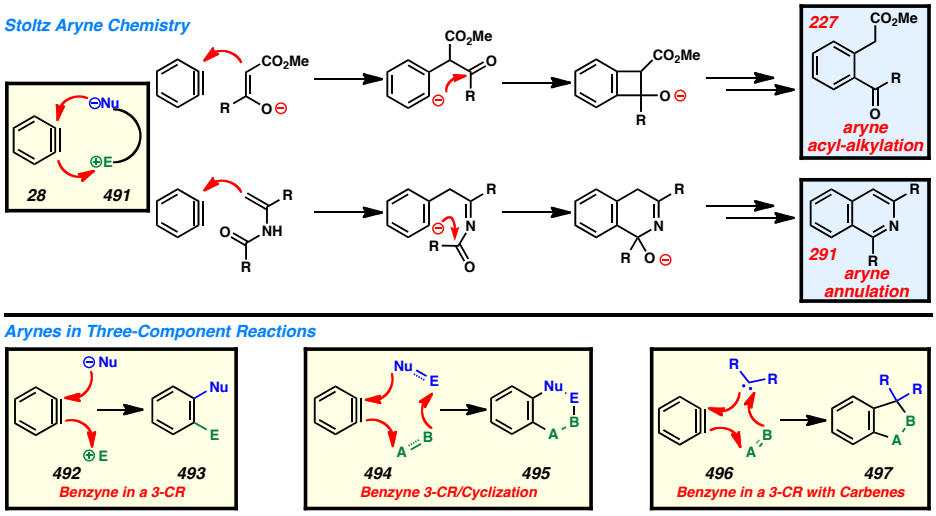


The Strecker and Petasis reactions both illustrate the importance of having a competent intermediate partner in multicomponent transformations. In general, such a transient species must be sufficiently active to undergo addition by an external nucleophile, while similarly selective to prohibit promiscuous reactivity with other nucleophiles in solution. The electophilic behavior required for these intermediates (e.g., **488**) to initiate these operations is typically followed by some sort of nucleophilic behavior, as in the coordinaton of boronic acid **486** by the aminal **489**. This property—displaying limited character as both a nucleophile and an electrophile—is known as ambiphilicity.[9] The ambiphilic partners in multicomponent reactions are crucial for charge transfer from a specific nucleophile (e.g., amine **485**) to another, less reactive electrophile (e.g., boronic acid **486**), behaving as relay intermediates for the completion of the operation. Because the charge transfer process is central to the bond-forming steps that occur during a multicomponent reaction, careful selection of a relay intermediate is critical for the success of a new methodology.

4.1.2 Multicomponent Aryne Reactions

Benzyne is ideally suited for multicomponent synthesis because it functions as a neutral agent to transfer charge between nucleophiles and electrophiles in the majority of its known applications (Scheme 4.4).[10] Previous research efforts in our group used these reactive intermediates to transfer electrons across the aryne bond in two-component reactions (e.g., **28** + **491**), revealing 1,2-disubstituted arene products resulting from C–C bond insertion (**227**)[11] and heterocyclization reactions (**291**).[12] In these examples, the initial nucleophile and terminal electrophile are within the same molecule. The most simple aryne three-component reaction (3-CR) would initiate by addition of a nucleophile into benzyne and quench the resulting aryl anion with an external electrophile (e.g., **492→493**). If other relay species are used, additional charge transfer can be employed to extend this method to the synthesis of polycycles (**494→495**). For cyclizations to occur, a component that both participates in the nucleophilic attack of benzyne and behaves as an electrophile for an irreversible ring closure is essential. Carbene equivalents—specifically, isocyanides—have often been used in multicomponent synthesis for those particular properties (**496→497**).

Scheme 4.4. *Benzyne is an effective electron relay intermediate*

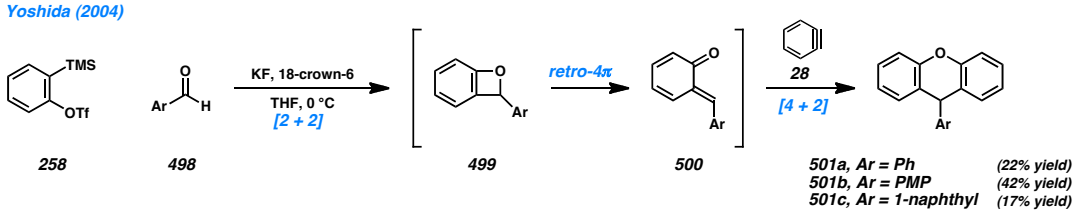


4.1.2.1 Three-Component Reactions

In the past 20 years, numerous methods have been published that also use arynes as relay species in these reactions. What follows is a brief summary of published work. Kobayashi's development of the *ortho*-silyl aryl triflate precursor to benzyne, which requires very mild conditions to generate the strained triple bond, has led to a broad-based examination of aryne participation in multicomponent reactions.[13] While previous examples exist, the bulk of research toward new multicomponent aryne reactions has taken place within the past decade.[14,15,16–18] The simplest examples involve two equivalents of an aryne and a third reagent.[19] Yoshida and Kunai have been active contributors to multicomponent aryne transformations over this period. In 2004, they disclosed a method to generate 9-arylxanthenes (**501a–c**) from aldehydes (**498**) and *ortho*-silyl aryl triflates (**258**).[20] In the presence of a potassium fluoride/18-Crown-6 complex, **258** generates benzyne, which performs a formal [2 + 2] cycloaddition with the aldehyde to give benzoxetane **499**. Retro-4π cyclization opens the four-membered ring

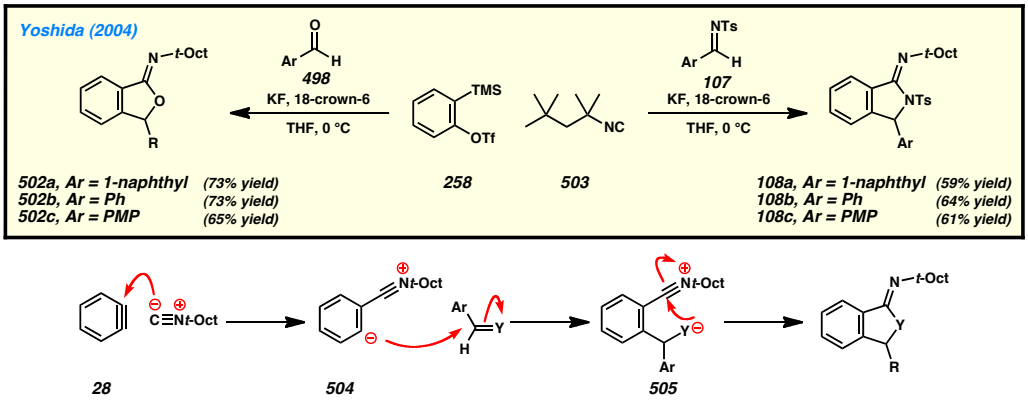
to an *ortho*-quinone methide **500**, which is capable of participating in a [4 + 2] cycloaddition with a second equivalent of benzyne to form the xanthene (**501**). The group went on to show that the reaction proceeds with most electron-rich, electron-deficient, and polycyclic aryl aldehydes to provide the corresponding 9-arylxanthenes in 17–70% yield.

Scheme 4.5. *Three-component synthesis of xanthenes (**501**) with two aryne equivalents*



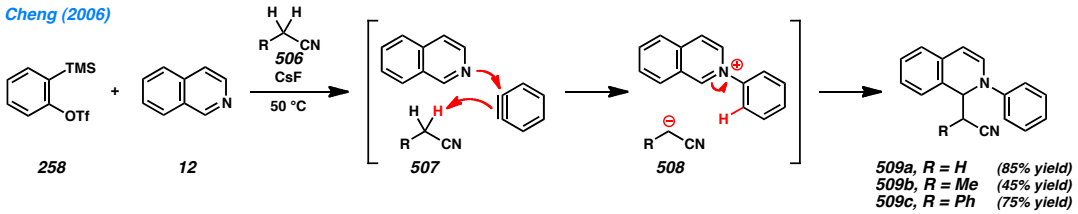
Yoshida expanded the scope of these aryne 3-CR processes in describing reaction of ortho-silyl aryl triflates (**258**), isocyanides (**503**), and either aldehydes (**498**) or aldimines (**107**), to construct iminoisobenzofurans[21] (**502a–c**) and iminoisoindoles[22] (**108a–c**) respectively (Scheme 4.6).[23] The isocyanide functions as a carbene equivalent, acting a nucleophile and an electrophile at different points in the mechanism. Addition of the isocyanide to the aryne generates zwitterion **504**.[24] The *ortho*-anionic aryl species (**504**) adds to the carbonyl component to relay the electrons, and effect ring closure by addition of the resulting anion (**505**) to the *N*-alkyl nitrilium ion, to give the product (**108** or **502**). Most substrates were aryl aldehydes, but both propionaldehyde and pivaldehyde participate in the three-component reaction to form alkyl-substituted iminoisobenzofurans.

Scheme 4.6. *Yoshida's three-component reactions of arynes with isocyanides to form heterocycles*



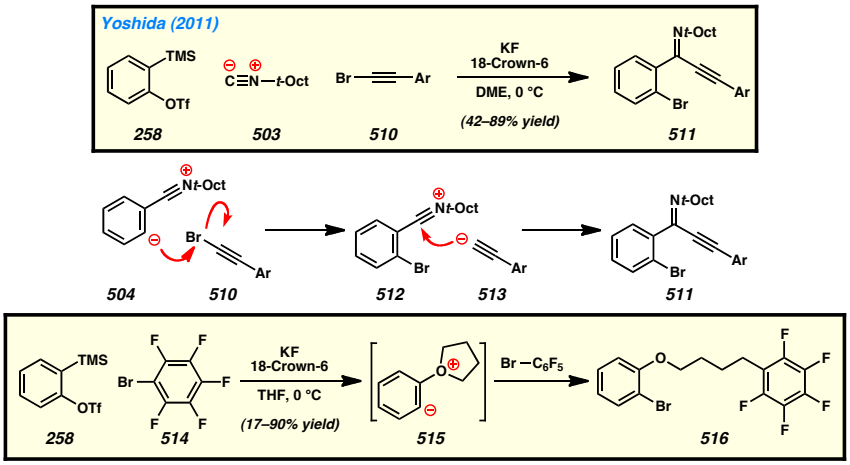
In addition to isocyanides, heterocycles can be used as both the initiating and terminating residue in 3-CRs by activation through addition to the aryne. Cheng developed a reaction using arynes, isoquinolines (**12**), and nitriles (**506**) by exploiting this mechanism (Scheme 4.7).[25,26] In this case, the aryne functions as an arylating agent, producing *N*-aryl isoquinolinium ion **508** after deprotonating the nitrile. Addition of the resulting anion (**508**) to the activated heteroaromatic system then yields an *N*-aryl dihydroisoquinoline (**509a–c**) bearing various substitution at C(1). The group has reported similar reactivity with pyridines in place of isoquinolines.[27] In general, aromatic ring systems are exceptional targets for approach by aryne three-component reactions. Reports of benzoxazinone,[28] naphthalene,[29] anthranilic acid,[30] *ortho*-aminobenzyl alcohol[31] and amine[32] syntheses using this strategy have underscored the versatility of this important reactive intermediate.[13]

Scheme 4.7. *Cheng's synthesis of 1,2-dihydroisoquinolines via aryne three-component reaction*



Yoshida has recently disclosed a unique coupling of isocyanides, alkynyl bromides (**510**) and arynes to form bromoarenes (**511**, Scheme 4.8). Interestingly, this reactivity involves a halogen transfer (**504→512**) to form an acetylide (**513**) to quench the nitrilium cation.[33] Similarly, THF and electron-poor perfluorobromoarenes (**514**) display very similar reactivity with benzyne (**28**), to yield bromoaryl ether ring-opened products (**516**) by proceeding through oxonium zwitterion **515**.

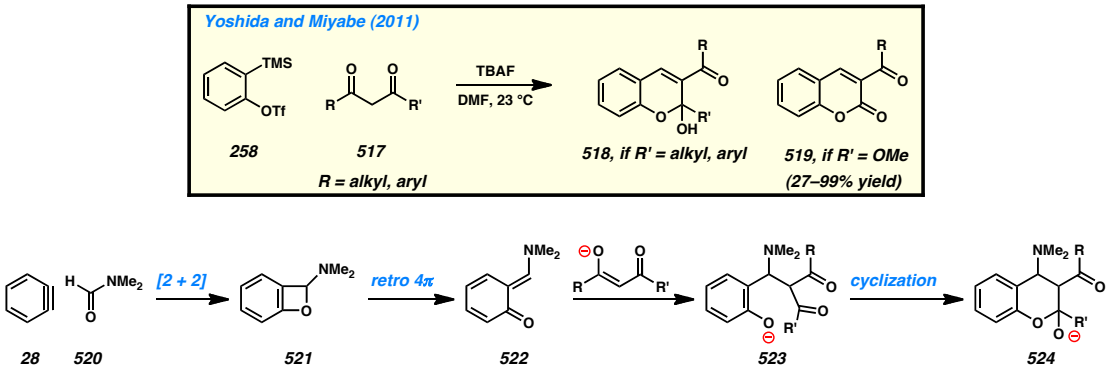
Scheme 4.8. *Yoshida's three-component coupling of alkynyl and aryl bromides*



Yoshida[34] and Miyabe[35] have independently reported an interesting transition from aryne reactive intermediates to similarly active *ortho*-quinone methides through a

multicomponent approach. In both cases, dimethyl formamide (**520**) is reacted with benzyne (**28**) to perform a formal [2 + 2] cycloaddition, generating strained cyclic aminal **521**, which rapidly undergoes a 4π retrocyclization to unveil the *ortho*-quinone methide (**522**, Scheme 4.9). At this point, a 1,3-diketone or β-ketoester derivative (**517**) adds to the reactive quinone methide to furnish 2-*H*-chromenes (**518**) or coumarines (**519**), respectively, following cyclization.

Scheme 4.9. *Aryne three-component reaction to form chromenes (**518**) and coumarines (**519**)*



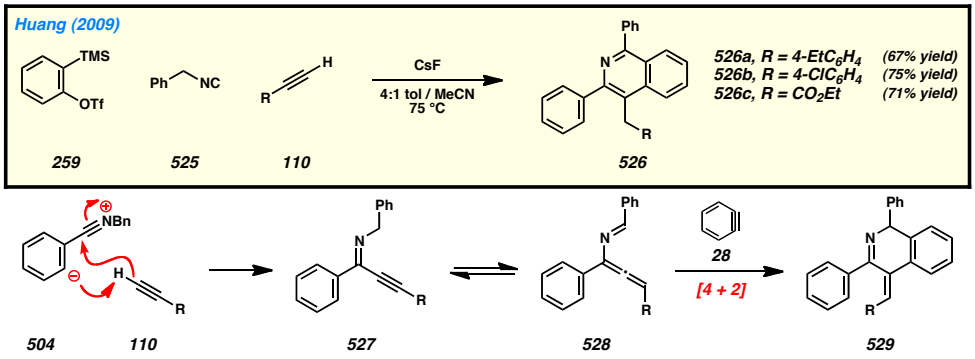
In addition to the metal-free three-component aryne reactions discussed above, there have been a number of transition metal-catalyzed transformations reported in recent years.[36–38,39,40,41,42,43,44] Such reactions have focused on benzannulated carbocycle synthesis through aryne intermediates, and thus fall beyond the immediate scope of interest for this survey.

4.1.2.2 Four-Component Reactions

In comparison to the array of three-component aryne reactions described above, the field of four-component transformations is still very much in its infancy. Typical

four-component methodologies forms compounds derived from multiple equivalents of the aryne.[45] Huang disclosed an illustrative example in a novel approach to polyfunctionalized isoquinolines (**526a-c**) using arynes, isocyanides, and terminal alkynes (Scheme 4.10).[46] The purported mechanism of formation begins with an addition of isocyanide **525** to benzyne to form zwitterion **504**. Deprotonation of the alkyne is then followed by addition to the nitrilium ion to generate propargylic imine **527**, which is envisioned to be in equilibrium with allene **528**. This intermediate undergoes a [4 + 2] cycloaddition with a second equivalent of benzyne to form dihydroisoquinoline **529**, which equilibrates to the isolated product (**526**). Interestingly, if the alkyne component was used in excess, the second [4 + 2] cycloaddition gives rise to pyridine products instead of isoquinolines.

Scheme 4.10. *Four-component synthesis of isoquinolines (**526**) using two aryne equivalents*



The possibility for developing innovative strategies for the synthesis of benzannulated heterocycles via aryne-based multicomponent reactions makes this methodology exceedingly appealing for further development. With this thought in mind,

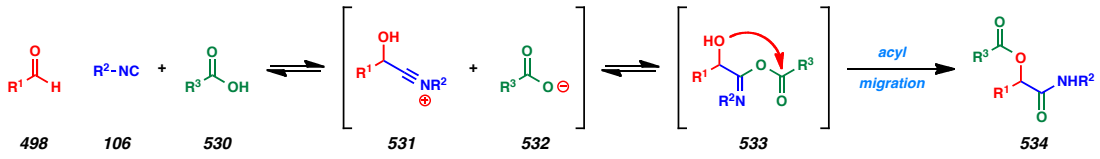
we turned our attention to the development of new heterocyclic systems by multicomponent aryne reactions.

4.2 SYNTHESIS OF PHENOXY IMINOISOBENZOFURANS AND IMINOINDENONES VIA THREE-COMPONENT REACTION OF ARYNES, ISOCYANIDES, AND ESTERS OR ALKYNES[47,48,†]

4.2.1 A Strategic Approach to New Three-Component Reactions

Our inspiration for a new multicomponent aryne reaction came from considering the mechanisms involved in more classical multicomponent transformations. In particular, we were interested in the Passerini reaction, a method used to prepare α-acyloxyamides (**534**) through the three-component coupling of aldehydes (**498**), isocyanides (**106**), and carboxylic acids (**530**) (Scheme 4.11).[49] The reaction proceeds through an initial combination of the aldehyde and isocyanide substrates to form a hydroxy nitrilium intermediate (**531**).[50] Nucleophilic addition of the carboxylate (**532**) then produces a neutral imidate (**533**), which undergoes acyl migration to the free alcohol to form the amide product (**534**).

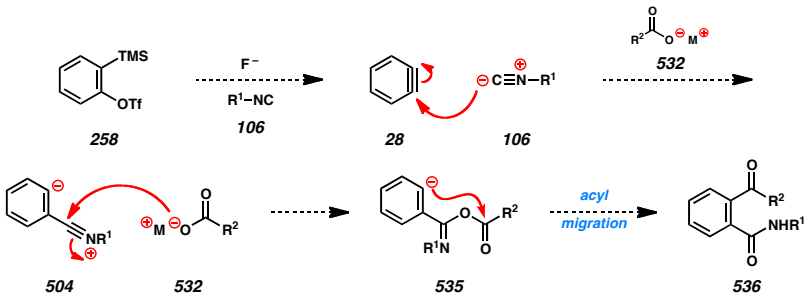
Scheme 4.11. *Passerini three-component synthesis of α-acyloxyamides*



† This work was performed in collaboration with Dr. Kevin M. Allan, a fellow graduate student in the Stoltz research group.

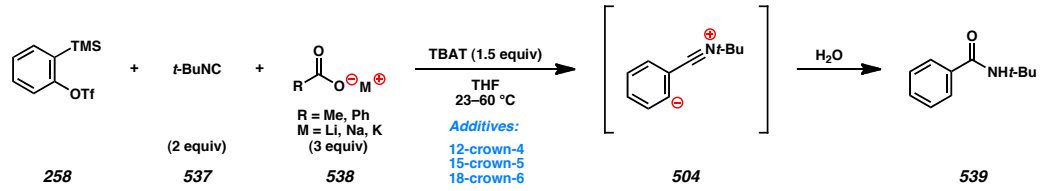
Within this mechanism, we recognized that the aldehyde plays the part of the relay component over the course of the reaction. Since benzyne is known to act in a similar capacity, we foresaw the viability of an aryne-containing analogue of the Passerini reaction. In this process, benzyne would take the place of the aldehyde to generate *ortho*-ketobenzamides (**536**) (Scheme 4.12). Considering the mechanism in a stepwise sense, we anticipated an initial addition of the isocyanide (**106**) to benzyne (**28**) to form zwitterion **504**.[24] Then, nucleophilic addition of a carboxylate (**532**) to the nitrilium ion would produce *ortho*-anionic acyl imidate **535**. The specific use of the carboxylate salt was viewed as a necessity in light of the expectation that a carboxylic acid would simply protonate the aromatic ring. In the final step, acyl migration from oxygen to carbon would produce *ortho*-ketobenzamide **536**.[51] In line with our previous development of the aryne acyl-alkylation reaction,[11] we expected this method would provide a useful new addition to the arsenal of aryne 1,2-disubstitution reactions.

Scheme 4.12. *Desired aryne analogue of the Passerini three-component reaction*



At the outset of our efforts to explore this proposed Passerini analog, we decided to react *ortho*-silyl aryl triflate **258**, *tert*-butyl isocyanide (**537**), and various alkali salts of acetic and benzoic acid (**538**) (Scheme 4.13). When these reagents are combined with tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) in tetrahydrofuran, the only product isolated from the reaction mixture was *N*-*tert*-butyl benzamide (**539**), even at elevated temperatures. This outcome presumably results from addition of the isocyanide to benzyne and by quenching of the nitrilium (**504**) with adventitious water. Due to the insolubility of the salt, we added the appropriate crown ethers. Unfortunately, these additives had no effect upon the outcome; they often resulted in a lower yield of **539**.

Scheme 4.13. *Initial investigation of three-component reaction with benzyne, tert-butyl isocyanide, and carboxylate salts*

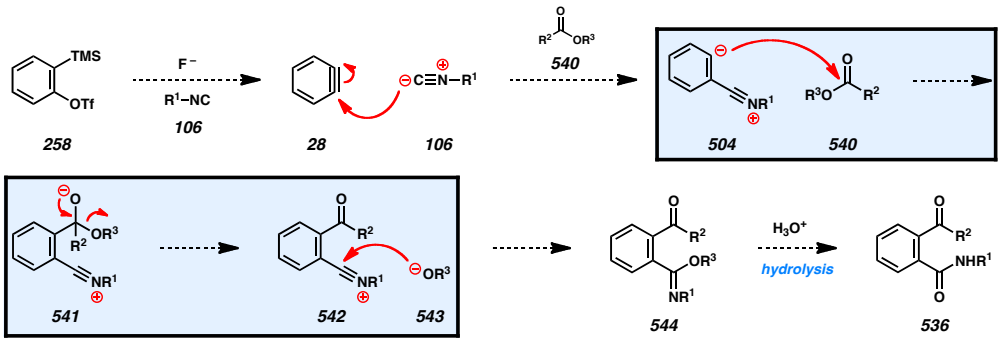


4.2.2 Synthesis of Phenoxy Iminoisobenzofurans

Our unsuccessful application of carboxylate salts led us to modify our initial mechanistic design to employ the aryl anion nucleophile (**504**) as a means to attack the carboxylic component (Scheme 4.14). By exchanging the carboxylate for an ester (**540**), we expected this to suffer nucleophilic addition by the aryl anion, generating a tetrahedral alkoxy intermediate (**541**). Ejection of the alkoxide (**543**) from tetrahedral ketal **541** and

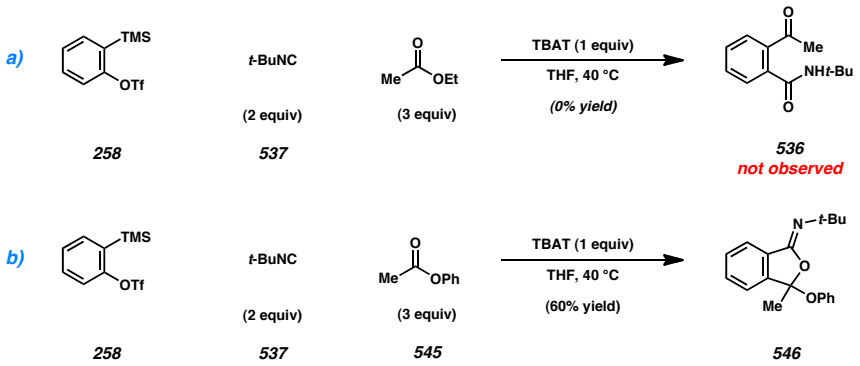
reaction termination by addition of **543** to the nitrilium (**542**) would furnish a neutral imidate (**544**). Finally, this compound could be hydrolyzed upon work-up or in a subsequent step in order to intercept the targeted *ortho*-ketobenzamide (**536**).

Scheme 4.14. *A revision to the proposed aryne Passerini-type reaction using esters*



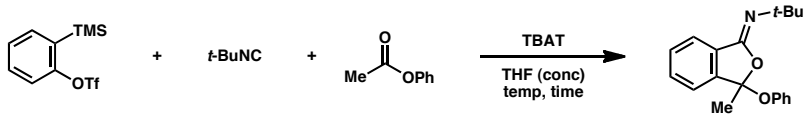
Ethyl acetate was chosen for the first trial due to its availability as an organic solvent, but when the reaction was performed by the aforementioned method at 40 °C, none of the desired ketobenzamide (**536**) was observed (Scheme 4.15a). Since similar additions have been established using aldehydes[21,31] and aldimines,[22,32] we investigated a more electrophilic ester, phenyl acetate (**545**).[52] When the reaction was performed under identical conditions, however, we were surprised to find that instead of generating the expected ketobenzamide (**536**), phenoxy iminoisobenzofuran **546** was isolated in 60% yield (Scheme 4.15b). This product most likely forms through intramolecular attack of the nitrilium ion by an alkoxide intermediate similar to **541**. Accordingly, closure of the five-membered ring is more rapid than expulsion of the alkoxide. This is the first preparation of a stable ether-substituted iminoisobenzofuran.[53]

Scheme 4.15. *Attempted acyl benzamide synthesis by three-component coupling with benzyne, tert-butyl isocyanide, a) ethyl acetate and b) phenyl acetate*



The unexpected phenoxy iminoisobenzofuran **546** produced in the reaction was an interesting structure worth further examination, so we next set about optimizing for its synthesis (Table 4.1). With the aryne as the limiting reagent, we explored the impact of excess phenyl acetate relative to the isocyanide based on the poor reactivities of prior carbonyl components. Subsequent trials using the original stoichiometric ratios at room temperature (entry 2) and 60 °C (entry 3), did not provide the product in greater than 60% yield. We then evaluated conditions in which the isocyanide (entry 4) and the phenyl ester (entry 5) were each used in limiting quantities. Interestingly, we discovered that the phenyl ester stoichiometry had nearly the same effect on the yield as the aryne (entry 1), and we decided to use the ester as the limiting reagent. As in the previous optimization of our aryne annulation method,[12] we diluted the reaction solution to 0.1 M (entry 6). While this had a modest attenuating effect on the rate of product formation, it was accompanied by an appreciable increase in yield. Further attempts to decrease the reaction temperature (entry 7) and the amount of excess material used (entry 8) only diminished yields.

***Table 4.1**. Optimization of the three-component reaction with benzyne, tert-butyl isocyanide, and phenyl acetate*



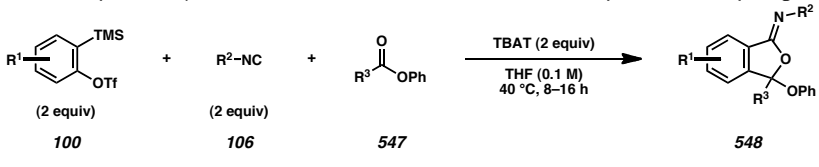
258 ***537*** ***545*** ***546***

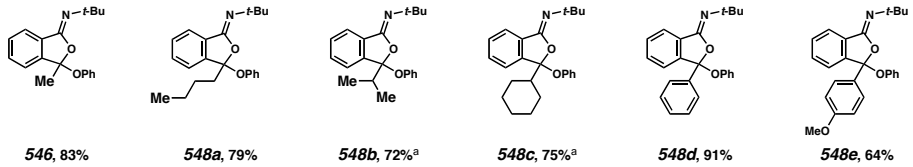
entry	*aryne equiv*	*TBAT equiv*	*t-BuNC equiv*	*PhOAc equiv*	*[258] (M)*	*temp. (°C)*	*time (h)*	*yield*
1	1	1	2	3	0.2	40	8	60%
2	1	1	2	3	0.2	23	24	35%
3	1	1	2	3	0.2	60	6	44%
4	2	2	1	3	0.2	40	8	49%
5	2	2	2	1	0.2	40	8	57%
6	**2**	**2**	**2**	**1**	**0.1**	**40**	**12**	**83%**
7	2	2	2	1	0.1	23	24	69%
8	1	1	1	1	0.1	40	12	40%

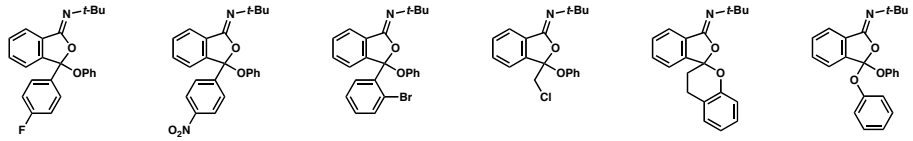
With an optimal set of conditions to prepare the phenoxy iminoisobenzofuran (**546**) in hand, we were determined explore the reaction's potential scope. A number of differentially substituted phenyl esters were prepared from the corresponding carboxylic acids in a single step proved very effective substrates (Table 4.2). Esters with linear (**546** and **548a**), branched (**548b**), and cyclic (**548c**) alkyl substituents performed well under the established reaction conditions. Benzoic esters (e.g., **548d**) fared well, though electron-withdrawing substituents (**548f**–**h**) were more reactive than electron-donating arenes (**548e**). Notably, an α-haloester does not detrimentally interact with *tert*-butyl isocyanide (**537**), because phenyl chloroacetate produced the expected three-component adduct (**548i**) in good yield. To our delight, dihydrocoumarin and phenyl carbonate formed interesting spirocyclic (**548j**) and masked orthoester products (**548k**), respectively. In further investigations, we evaluated the isocyanide component by

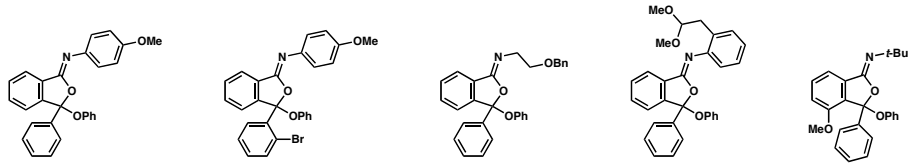
replacing *tert*-butyl isocyanide (**537**) with 4-methoxyphenyl isocyanide (**548l** and **548m**) and 2-benzyloxyethyl isocyanide (**548n**) to form *N*-functionalized imidates. The *ortho*-(dimethoxyethyl)phenyl isocyanide, designed by Kobayashi as a convertible functional handle for Ugi reactions,[54] produced iminoisobenzofuran **548o** in a reasonable yield despite the steric bulk of the nucleophile. Finally, the three-component coupling with a series of heteroatom-functionalized aryne precursors furnished aryl-substituted adducts **548p–u**. Importantly, when unsymmetrical arynes were used, the reaction generated the single isomer of the expected *tert*-butyl isocyanide addition of to the activated position *meta* to the heteroatom (**548p–r**).[55,56]

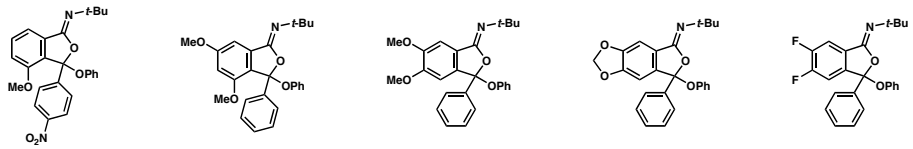
Table 4.2. *Synthesis of phenoxy iminoisobenzofurans via three-component coupling*







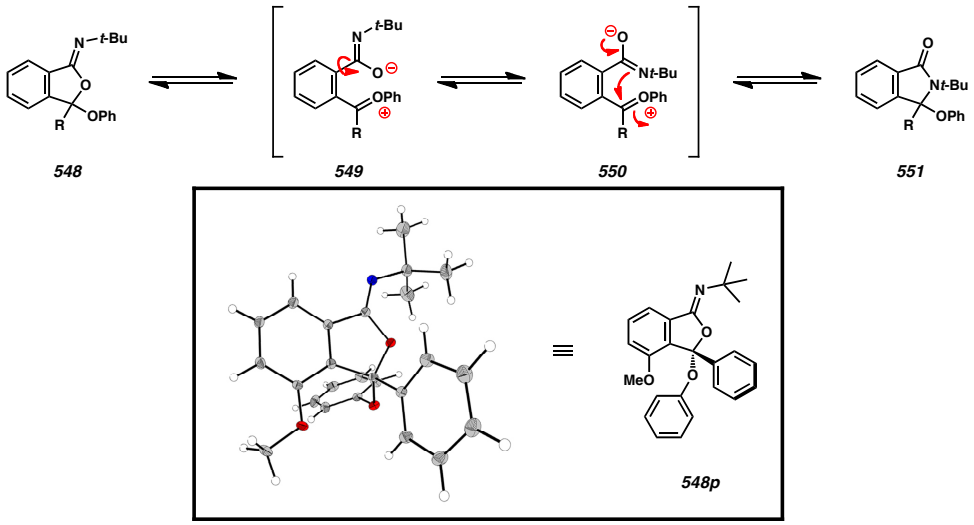




[a] Reaction performed at 60 °C

Our original structural assignment of the phenoxy iminoisobenzofurans was determined by analogy to Yoshida's earlier work with iminoisobenzofurans[21] and iminoisoindoles.[22] However, a structural rearrangement pathway is available to our products (Scheme 4.16). Lone pair donation by the phenoxy substituent would form a ring opened oxocarbenium species (**549**), and addition of the imidate nitrogen to the activated carbonyl could produce the isomeric isoindolinone (**551**). The close structural similarity between iminoisobenzofuran **548** and lactam **551**, made definitive assignment based on NMR and IR data difficult. We therefore obtained a crystal of adduct **548p** suitable for X-ray diffraction, which unambiguously confirmed our structural assignment.

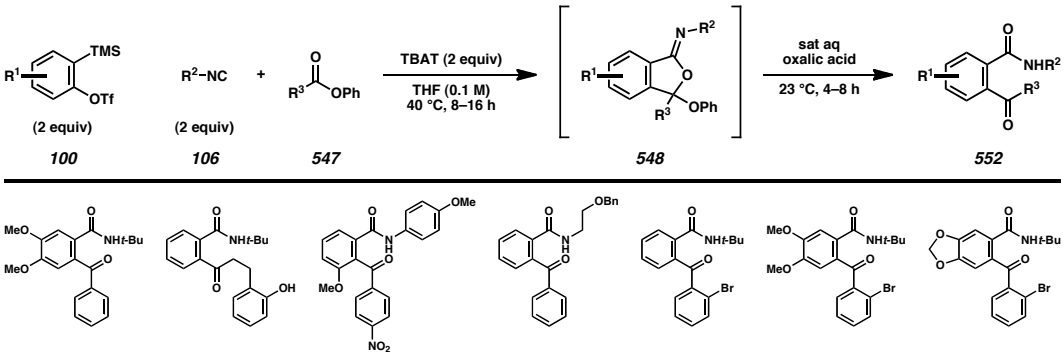
Scheme 4.16. *Potential equilibration between iminoisobenzofuran and isoindolinone isomers and X-ray crystal structure of phenoxy iminoisobenzofuran* ***548p***



We anticipated that our originally targeted *ortho*-ketobenzamides (e.g., **552**) might still be accessible from the phenoxy iminoisobenzofurans (**548**) by a ring-opening hydrolysis (Table 4.3). We began examining conditions for hydrolysis with a thorough

screen of protic acids, and discovered that oxalic acid was optimally functional (Table 4.3). Thus, a one-pot procedure for the synthesis of *ortho*-ketobenzamides was developed. Upon completion of the three-component coupling, saturated aqueous oxalic acid is added to the crude reaction and the biphasic mixture is allowed to stir a room temperature until the phenoxy iminoisobenzofuran is fully consumed. Thus, we can access di- (**552b**, **d**, and **e**), tri- (**552c**), and tetrasubstituted (**552a**, **f**, and **g**) *ortho*-ketobenzamides in good yield from *ortho*-silyl aryl triflate (**100**), isocyanide (**106**), and phenyl ester (**547**) starting materials.[57]

Table 4.3. *One-pot procedure for ortho-ketobenzamides via three-component coupling/hydrolysis*

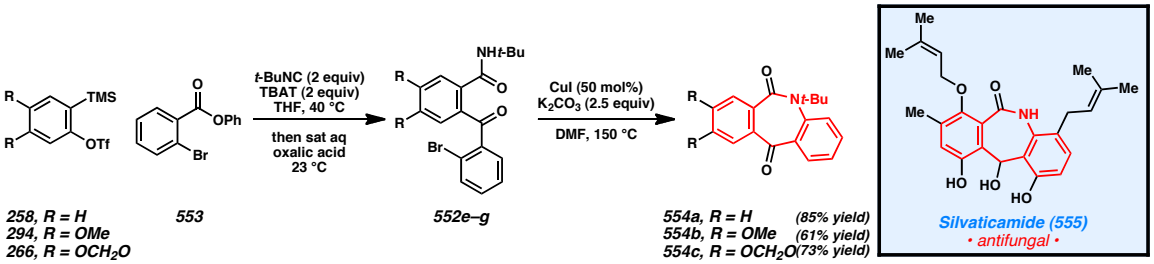


[a] Reaction performed at 60 °C.

By developing this procedure for *ortho*-ketobenzamide generation, we anticipated that the potential synthetic utility of the otherwise unique iminoisobenzofuran intermediates might be untapped by further application. As a demonstration, we decided to examine an intramolecular coupling between the amide nitrogen and an aryl bromide contained within 2-(*ortho*-bromobenzoyl)benzamides **552e**–**g**, which form caprolactams (Scheme 4.17). Preliminary attempts employing **552e** in the presence of several

transition metal catalysts[58,59] complexes failed to produce the desired seven-membered ring, which can likely be attributed to the steric bulk of the *tert*-butyl amide. Eventually, copper(I) iodide used in the absence of an added ligand did succeed in catalyzing the reaction, forming dibenzoketocaprolactams **554a–c**. This structure is found in many natural products, such as silvaticamide[60] (**555**), indicating that an extension of our multicomponent methodology has greater synthetic utility for potentially broader impact.

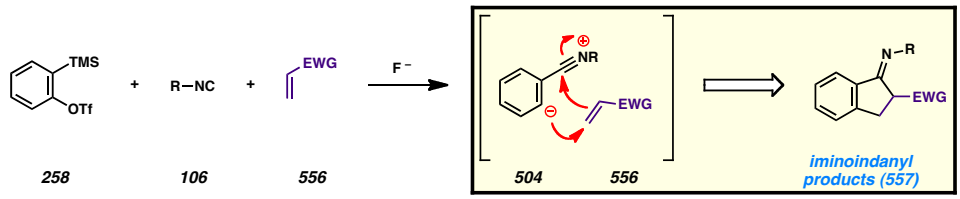
Scheme 4.17. *Two-step synthesis of dibenzoketocaprolactams*



4.2.3 Synthesis of Iminoindenones

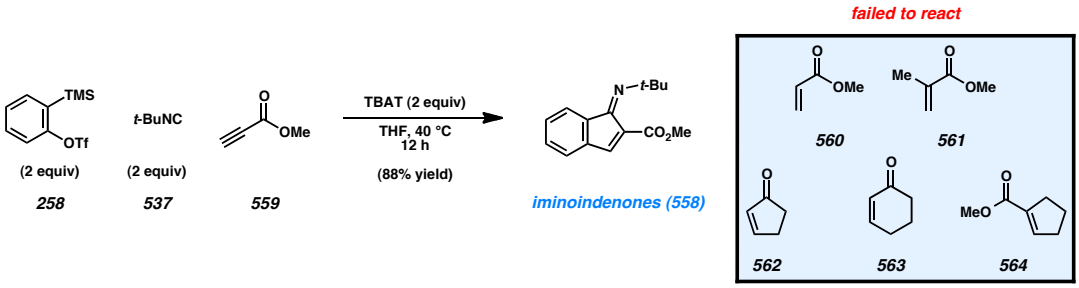
In order to expand the utility of our general aryne multicomponent reaction strategy, we began to examine substrates other than phenyl esters capable of fulfilling the role as a secondary relay species. Specifically, we wanted to exploit the first step of the reaction mechanism, which forms zwitterion **504** (Scheme 4.18). In the other cases, this next added to the relay component, through which the negative charge was conveyed back to the nitrilium ion. A conjugate acceptor (**556**) should fill this relay role by acting as both a β-electrophile and α-nucleophile.

Scheme 4.18. *Proposed carbocycle synthesis by aryne three-component reaction with isocyanides*



Accordingly, we examined α,β-unsaturated carbonyl compounds (**559**–**564**) under the previously optimized reaction conditions to form carbocyclic adducts like **557**. We found that methyl propiolate (**559**) furnished iminoindenone **558** in 88% yield after 12 h while compounds **560**–**564** failed to react (Scheme 4.19).

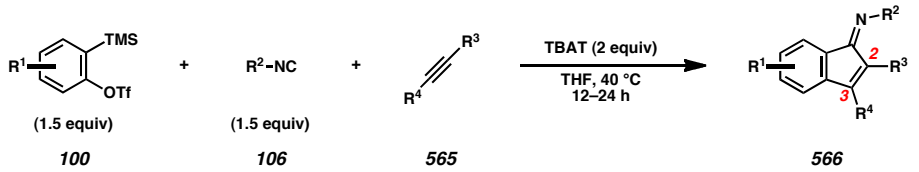
Scheme 4.19. *Three-component coupling of benzyne, tert-butyl isocyanide, and methyl propiolate*

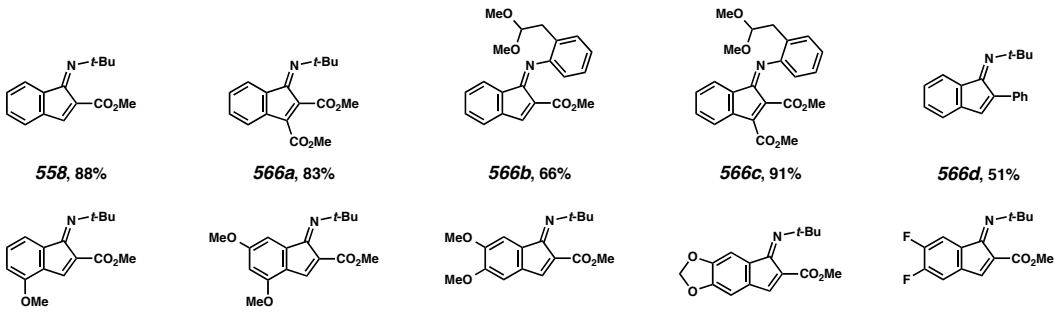


Exploration of the substrate scope showed that substitution at the β-position of the propiolate framework provided access to 2,3-disubstituted iminoindenone **558** without significantly impacting the yield (Table 4.4). The reaction also proved amenable to the replacement of *tert*-butyl isocyanide with Kobayashi's *ortho*-(dimethoxyethyl)phenyl isocyanide,[54] generating compounds **566b** and **566c** in 66% and 91% yield, respectively. Phenylacetylene also proved a competent partner for this reaction, producing 2-phenyl-

iminoindenone **566d**. Finally, we examined the effects of aryne substitution upon product distribution. As with the phenoxy iminoisobenzofurans, we found that both symmetrical and unsymmetrical heteroatom-functionalized arynes of diverse electronic character formed the expected three-component adducts (**566e–i**) in good yield as single isomers.

Table 4.4. *Three-component coupling of arynes, isocyanides, and alkynes*



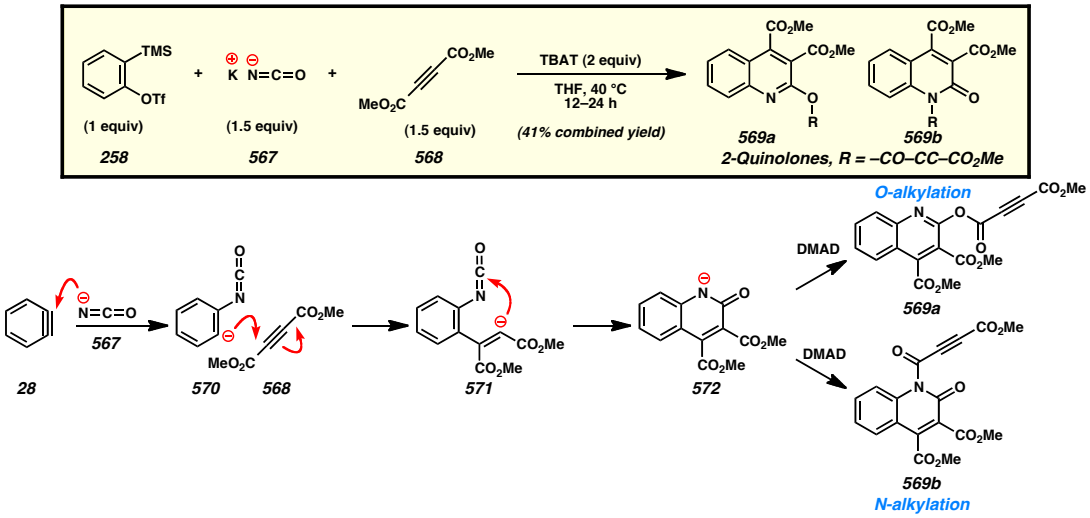


4.2.4 Quinolone Synthesis Using Potassium Isocyanate

Our early success with multicomponent reactions using arynes has led us to a broad-based investigation of similar reaction systems that differ more substantially from the literature reports. Several preliminary investigations have been initiated using the unprecedented base potassium cyanate (**567**). In particular, we have found that dimethyl acetylene dicarboxylate (**568**) (DMAD) reacts with an equivalent of the isocyanate and an equivalent of benzyne to form the 2-quinolone products **569** in modest yield (Figure

4.20). We speculate that the mechanism of this reaction initiates with cyanate addition to the aryne (**28**), generating *ortho*-anionic aryl isocyanate **570**, which next proceeds through a formal [4 + 2] reaction affording the 2-quinolone (**572**). The presence of DMAD has led to the isolation of a 1:1 ratio of *O*- and *N*-alkylated quinolines (**569a-b**), formed by alkylation of cyclized product **572**. Attempts to isolate the protonated **572** without secondary alkylation have thus far failed. As in the isoquinolone synthesis, the reaction appears to be highly sensitive to over-arylation of the products, a problem that has severely hindered optimization of reaction yields. This direct method to produce a quinolone, however, is directly complementary to our previously reported aryne annulation strategy for the formation of isoquinolines and indolines, and thus highly desirable. For this reason, it continues to be the subject of interest for ongoing research in the group.

Scheme 4.20. *2-Quinolones* ***569a–b*** *by reaction of benzyne, DMAD, and potassium isocyanate*



4.3 CONCLUDING REMARKS

Our interest in multicomponent processes that use arynes as relay intermediates stems from our fundamental desire to discover new reactivity in chemical synthesis. In this way, we have used our mechanistic understanding of a classical reaction pathway (the Passerini reaction) to adapt the transformation for arynes, ultimately yielding an entirely novel structural class of benzannulated heterocycles. Furthermore, we have been able to extend our efforts to make phenoxy iminoisobenzofurans to the production of intermediates with potential utility in broader synthetic goals. From a single unanticipated result, we have been able to target iminoisobenzofurans, *ortho*-acyl benzamides, and caprolactams. Moreover, this new mode of reactivity inspired us to make entirely unique compounds, allowing a three-component approach to iminoindenone carbocyclic products, carrying our interests in aryne chemistry in a new direction. This early success has inspired ongoing research efforts in our group to further exploit the highly reactive aryne intermediate in multi-component reactions for continued development.

4.4 EXPERIMENTAL SECTION

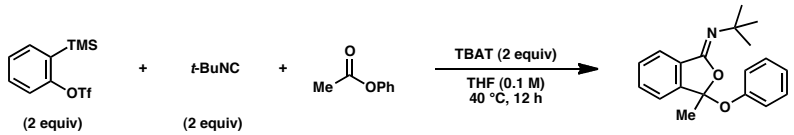
4.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) was azeotropically dried from acetonitrile prior to use. 3-Methoxy-2-(trimethylsilyl)phenyl triflate (**264**),[61] 3,5-dimethoxy-2-(trimethylsilyl) phenyl triflate (**293**),[62] 4,5-dimethoxy-2-(trimethylsilyl) phenyl triflate (**294**),[63] 6-(trimethylsilyl)benzo[*d*][1,3]dioxol-5-yl triflate (**266**),[64] and 4,5-difluoro-2-(trimethylsilyl)phenyl triflate (**296**)[65] were prepared according to literature procedures. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or ceric ammonium molybdate staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or

mixed (MM) ionization mode, or obtained from the Caltech Mass Spectral Facility (EI+ or FAB+).

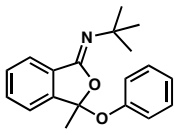
4.4.2 4.4.2 Preparative Procedures and Spectroscopic Data

4.4.2.1 Representative Procedure for the Three-Component Synthesis of Phenoxy Iminoisobenzofurans from Arynes, Isocyanides, and Phenyl Esters



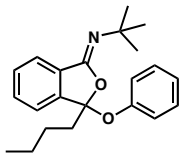
A flame-dried 50 mL round bottomed flask with a magnetic stir bar was charged with TBAT (1.70 g, 3.15 mmol, 2.0 equiv) and THF (16 mL). To this solution was added phenyl acetate (**545**) (0.20 mL, 1.57 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**258**) (0.765 mL, 3.15 mmol, 2.0 equiv), and *tert*-butylisocyanide (**537**) (0.356 mL, 3.15 mmol, 2.0 equiv), each via syringe. The reaction was heated to 40 °C under argon for 12 h, at which point TLC analysis showed complete consumption of phenyl acetate. The reaction was cooled to room temperature and passed over a plug of silica (3 cm diam. x 5 cm length) eluting with 15:85 EtOAc/hexanes in order to remove excess TBAT from solution. The solvents were removed under reduced pressure and the crude residue was purified by flash chromatography over silica gel.

4.4.2.2 Spectroscopic Data for Phenoxy Iminoisobenzofurans



Phenoxy iminoisobenzofuran 546

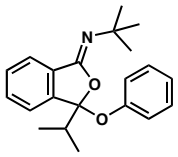
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (83% yield). R_f = 0.46 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{19}H_{21}NO_2$ $[M+H]^+$: 296.1651, found 296.1650.



Phenoxy iminoisobenzofuran 548a

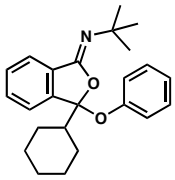
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (79% yield). R_f = 0.43 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 7.6 Hz, 1H), 7.50–7.42 (comp m, 2H), 7.37 (dt, J = 7.8, 2.0 Hz, 1H), 7.08 (t, J = 7.6 Hz, 2H), 6.94 (t, J = 7.3 Hz, 1H), 6.86 (d, J = 7.6 Hz, 2H), 2.42 (ddd, J = 13.9, 12.0, 4.6 Hz, 1H), 2.20 (ddd, J = 13.9, 12.0, 4.6 Hz, 1H), 1.51–1.40 (m, 1H), 1.44 (s, 9H), 1.39–1.26 (m, 2H), 1.22–1.11 (m, 1H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 153.7, 153.0, 142.5, 136.6, 130.0, 129.0, 128.3, 124.3, 123.4, 122.9, 122.6, 112.8, 54.0, 39.2, 30.4, 25.7, 22.8, 14.2; IR (Neat Film, NaCl) 2963, 2871, 1706, 1592, 1491, 1214 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{22}H_{27}NO_2$ $[M+H]^+$: 338.2120, found 338.2125.



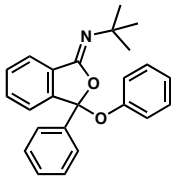
Phenoxy iminoisobenzofuran 548b

Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (72% yield). R_f = 0.54 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (dt, J = 7.6, 1.0 Hz, 1H), 7.43 (dd, J = 4.4, 1.2 Hz, 1H), 7.41 (d, J = 5.1 Hz, 1H), 7.34 (ddd, J = 7.8, 6.1, 2.4 Hz, 1H), 7.03 (dd, J = 8.3, 7.3 Hz, 2H), 6.90 (tt, J = 7.3, 1.2 Hz, 1H), 6.78 (dd, J = 8.8, 1.2 Hz, 2H), 2.62 (septet, J = 6.8 Hz, 1H), 1.42 (s, 9H), 1.22 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 153.4, 141.6, 134.1, 131.2, 130.0, 129.0, 124.2, 123.3, 123.0, 122.9, 114.9, 54.0, 37.4, 30.4, 17.3, 16.8; IR (Neat Film, NaCl) 2968, 1706, 1592, 1491, 1214, 1070 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{21}H_{25}NO_2$ $[M+H]^+$: 324.1964, found 324.1959.



Phenoxy iminoisobenzofuran 548c

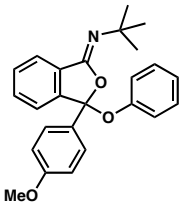
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (75% yield). R_f = 0.46 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ□7.61 (d, J = 7.6 Hz, 1H), 7.43–7.40 (comp m, 2H), 7.34 (dd, J = 7.8, 2.4 Hz, 1H), 7.03 (t, J = 7.6 Hz, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 7.6 Hz, 2H), 2.29 (td, J = 12.0, 3.2 Hz, 2H), 1.86 (br d, J = 12.9 Hz, 1H), 1.71 (br s, 1H), 1.50–1.41 (m, 1H), 1.43 (s, 9H), 1.38–1.14 (comp m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 153.3, 141.7, 136.6, 134.1, 131.1, 129.9, 129.0, 128.3, 124.2, 123.3, 123.0, 122.9, 114.3, 54.0, 47.0, 30.4, 27.2, 26.8, 26.6, 26.3, 26.2; IR (Neat Film, NaCl) 2931, 1706, 1593, 1491, 1213 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{29}NO_2$ $[M+H]^+$: 364.2271, found 364.2273.



Phenoxy iminoisobenzofuran 548d

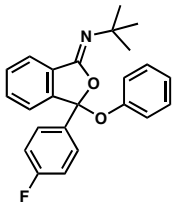
Purified by flash chromatography (SiO_2, 3:97 EtOAc/hexanes) to yield a white solid (91% yield). R_f = 0.40 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dt, J = 7.6, 1.0 Hz, 1H), 7.64 (dd, J = 7.1, 1.5 Hz, 2H), 7.45-7.33 (comp m, 6H), 7.13 (dd, J = 8.5, 7.3 Hz, 2H), 6.99 (dd, J = 7.6, 1.2 Hz, 2H), 6.95 (t, J = 7.3 Hz, 1H), 1.47 (s, 9H););

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 152.8, 144.5, 139.8, 131.8, 131.7, 130.1, 129.2, 129.0, 128.9, 126.0, 123.6, 123.5, 123.3, 121.5, 110.4, 54.3, 30.5; IR (Neat Film, NaCl) 2968, 1709, 1590, 1491, 1213 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{24}NO_2$ $[M+H]^+$: 358.1807, found 358.1798.



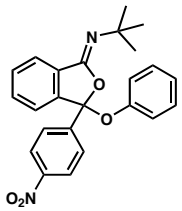
Phenoxy iminoisobenzofuran 548e

Purified by flash chromatography (SiO_2, 4:96 EtOAc/hexanes) to yield a colorless oil (64% yield). R_f = 0.30 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.44 (dd, J = 7.3, 6.6 Hz, 1H), 7.41–7.36 (comp m, 2H), 7.13 (dd, J = 8.5, 7.3 Hz, 2H), 6.99 (d, J = 7.8 Hz, 2H), 6.95 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 154.1, 152.9, 144.7, 131.9, 131.7, 131.3, 130.0, 129.1, 128.7, 127.4, 126.9, 123.6, 123.2, 121.6, 114.2, 55.5, 54.3, 30.5; IR (Neat Film, NaCl) 2967, 1708, 1661, 1513, 1490, 1254, 1213, 1173 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{25}H_{25}NO_3$ $[M+H]^+$: 388.1913, found 388.1923.



Phenoxy iminoisobenzofuran 548f

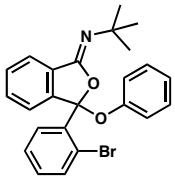
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (86% yield). R_f = 0.43 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dt, J = 7.3, 1.0 Hz, 1H), 7.61 (dd, J = 9.0, 5.1 Hz, 2H), 7.45 (td, J = 7.3, 1.2 Hz, 1H), 7.40 (dd, J = 7.3, 1.2 Hz, 1H), 7.38 (tt, J = 7.3, 1.0 Hz, 1H), 7.13 (dd, J = 8.8, 7.1 Hz, 2H), 7.07 (t, J = 8.8 Hz, 2H), 6.97 (d, J = 7.1 Hz, 2H), 6.96 (tt, J = 7.1, 1.2 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 161.9, 153.6, 152.1, 143.9, 136.4, 131.7, 131.5, 130.1, 129.9, 129.0, 128.1, 127.8 (d, $J_{C–F}$ = 8.6 Hz), 123.6 (d, $J_{C–F}$ = 21.9 Hz), 123.0, 121.5, 115.6 (d, $J_{C–F}$ = 21.5 Hz), 109.9, 54.1, 30.2; ^{19}F NMR (282 MHz, $CDCl_3$) d –113.0 (app septet, J = 5.1 Hz); IR (Neat Film, NaCl) 2968, 1710, 1590, 1509, 1491, 1211, 1158 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{22}FNO_2$ $[M+H]^+$: 376.1713, found 376.1747.



Phenoxy iminoisobenzofuran 548g

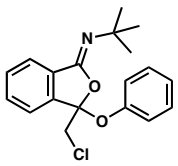
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a white solid (90% yield). R_f = 0.37 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 9.0 Hz, 2H), 7.76 (dt, J = 7.6, 1.0 Hz, 1H), 7.47 (td, J = 7.3,

1.2 Hz, 1H), 7.42 (td, J = 7.6, 1.2 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.15 (dd, J = 8.5, 7.3 Hz, 2H), 7.00 (tt, J = 7.3, 1.2 Hz, 1H), 6.97 (d, J = 7.6 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 151.6, 148.2, 146.6, 142.9, 135.1, 131.8, 130.5, 129.2, 127.9, 127.0, 124.1, 124.0, 123.8, 123.0, 121.6, 109.3, 54.4, 30.3; IR (Neat Film, NaCl) 2969, 1712, 1590, 1525, 1490, 1350, 1210 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{22}N_2O_4$ $[M+H]^+$: 403.1658, found 403.1670.



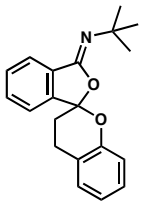
Phenoxy iminoisobenzofuran 548h

Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (77% yield). R_f = 0.40 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.1, 1.7 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.62 (td, J = 7.9, 1.2 Hz, 2H), 7.46 (td, J = 7.9, 1.2 Hz, 1H), 7.45–7.38 (comp m, 2H), 7.25 (td, J = 7.6, 1.7 Hz, 1H), 7.11 (t, J = 7.3 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 7.6 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 152.4, 142.5, 137.2, 136.4, 135.4, 135.0, 131.2, 130.5, 130.1, 129.7, 128.8, 128.1, 127.9, 127.2, 123.9, 123.1, 123.0, 122.5, 109.5, 54.2, 30.3; IR (Neat Film, NaCl) 2968, 1711, 1589, 1490, 1429, 1289, 1209 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{24}H_{22}BrNO_2$ $[M+H]^+$: 438.0889, found 438.0881.



Phenoxy iminoisobenzofuran 548i

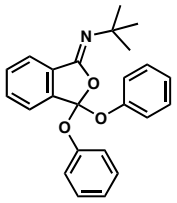
Purified by flash chromatography (SiO_2, 3:97 EtOAc/hexanes) to yield a pale yellow oil (76% yield). R_f = 0.55 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 7.6 Hz, 1H), 7.56 (dt, J = 7.6, 1.0 Hz, 1H), 7.48 (dt, J = 7.6, 1.0 Hz, 1H), 7.42 (dt, J = 7.6, 1.0 Hz, 1H), 7.10 (t, J = 7.6 Hz, 2H), 6.98 (tt, J = 7.3, 1.0 Hz, 1H), 6.90 (dd, J = 7.6, 1.0 Hz, 2H), 4.14 (d, J = 11.7 Hz, 1H), 4.07 (d, J = 11.7 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 151.7, 139.7, 134.1, 131.5, 130.8, 129.3, 124.9, 123.6, 123.2, 122.7, 109.6, 54.4, 47.9, 30.3; IR (Neat Film, NaCl) 2968, 1788, 1709, 1591, 1490, 1210 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{19}H_{20}ClNO_2$ $[M+H]^+$: 330.1255, found 330.1271.



Phenoxy iminoisobenzofuran 548j

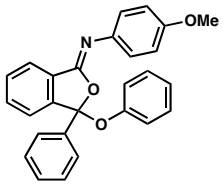
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a white solid (86% yield). R_f = 0.37 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ□7.86 (d, J = 7.6 Hz, 1H), 7.55 (dd, J = 7.3, 1.5 Hz, 1H), 7.51 (ddd, J = 7.3, 1.5, 1.2 Hz, 1H), 7.39 (td, J = 7.3, 1.2 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 8.1 Hz, 1H), 7.00 (td, J = 7.3, 1.2 Hz, 1H), 6.87 (dd, J = 8.1, 1.2 Hz, 1H), 3.29 (ddd, J = 13.7, 13.4, 5.6 Hz, 1H),

2.95 (ddd, J = 16.4, 5.6, 1.7 Hz, 1H), 2.43 (td, J = 13.7, 5.9 Hz, 1H), 2.19 (ddd, J = 13.4, 5.9, 2.0 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 152.7, 143.7, 136.1, 135.0, 131.4, 130.3, 129.2, 127.7, 123.6, 121.7, 121.5, 117.0, 105.9, 54.1, 30.0, 28.0, 22.0; IR (Neat Film, NaCl) 2967, 1706, 1586, 1489, 1362, 1228, 1044 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{20}H_{21}NO_2$ $[M+H]^+$: 308.1651, found 308.1661.



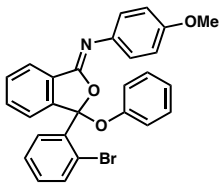
Phenoxy iminoisobenzofuran 548k

Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (71% yield). R_f = 0.43 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.6, 1.0 Hz, 1H), 7.62 (d, J = 8.1, 1.5 Hz, 2H), 7.48 (tt, J = 7.3, 1.5 Hz, 1H), 7.43 (dd, J = 6.8, 1.2 Hz, 1H), 7.38 (td, J = 7.6, 1.0 Hz, 1H), 7.20 (dd, J = 8.5, 7.6 Hz, 2H), 7.12 (td, J = 7.6, 1.2 Hz, 1H), 7.05 (ddd, J = 7.3, 1.2, 1.0 Hz, 2H), 6.94 (dd, J = 8.5, 1.0 Hz, 2H), 6.36 (dt, J = 7.6, 1.0 Hz, 1H), 1.77 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 153.6, 139.1, 138.2, 136.4, 134.2, 132.4, 132.3, 131.6, 131.1, 130.3, 130.1, 129.1, 128.1, 124.1, 123.2, 123.0, 121.9, 121.3, 113.4, 57.1, 28.4; IR (Neat Film, NaCl) 2966, 1713, 1589, 1489, 1357, 1323, 1202, 1128, 1016 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{24}H_{23}NO_3$ $[M+H]^+$: 374.1756, found 374.1763.



Phenoxy iminoisobenzofuran 548l

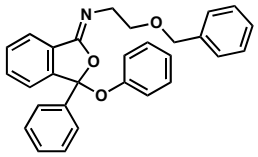
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 4:96 EtOAc/hexanes) to yield a white solid (68% yield). R_f = 0.35 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ□7.85 (ddd, J = 7.6, 1.2, 1.0 Hz, 1H), 7.65 (ddd, J = 8.1, 1.2 Hz, 2H), 7.50–7.45 (comp m, 3H), 7.49 (d, J = 9.0 Hz, 2H), 7.42–7.35 (comp m, 3H), 7.12 (dd, J = 8.8, 7.3 Hz, 2H), 6.98 (dd, J = 8.8, 1.2 Hz, 2H), 6.97 (dd, J = 6.1, 1.0 Hz, 1H), 6.92 (d, J = 9.3 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 153.9, 153.6, 144.4, 138.9, 138.6, 135.0, 131.9, 131.2, 130.2, 130.1, 129.0, 129.0, 128.7, 127.9, 125.9, 125.9, 123.8, 123.5, 123.3, 121.8, 113.9, 55.4; IR (Neat Film, NaCl) 3062, 2928, 2833, 1685, 1591, 1506, 1488, 1292, 1245, 1208, 1030 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{27}H_{21}NO_3$ $[M+H]^+$: 408.1594, found 408.1608.



Phenoxy iminoisobenzofuran 548m

Purified by flash chromatography (SiO_2, 2:98→ 4:96 EtOAc/hexanes) to yield a white solid (62% yield). R_f = 0.37 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ□8.16 (dd, J = 7.8, 1.5 Hz, 1H), 7.77 (dd, J = 7.3, 1.0 Hz, 1H), 7.62 (dd, J = 7.8, 1.2 Hz, 1H), 7.51 (td, J = 7.3, 1.2 Hz, 1H), 7.47 (dd, J = 7.3, 1.2 Hz, 1H), 7.44–7.41 (comp m,

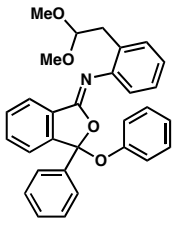
2H), 7.43 (d, J = 9.0 Hz, 2H), 7.26 (ddd, J = 0.5, 1.7, 8.1 Hz, 1H), 7.09 (dd, J = 8.6, 7.3 Hz, 2H), 6.99 (ddd, J = 7.3, 1.2, 1.0 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 6.87 (dd, J = 8.6, 1.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 154.3, 152.4, 142.7, 138.7, 136.4, 135.4, 135.0, 133.3, 131.7, 130.7, 130.4, 130.1, 129.6, 128.9, 127.9, 127.3, 125.6, 124.4, 123.2, 123.1, 123.0, 121.4, 113.9, 55.4; IR (Neat Film, NaCl) 3062, 2928, 2833, 1692, 1590, 1506, 1490, 1466, 1293, 1244, 1202, 1034 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{27}H_{20}BrNO_3$ $[M+H]^+$: 488.0684, found 488.0714.



Phenoxy iminoisobenzofuran 548n

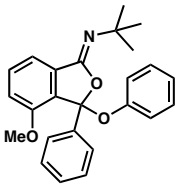
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98→ 8:92 EtOAc/hexanes) to yield a pale yellow solid (67% yield). R_f = 0.30 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ□7.74 (dt, J = 7.8, 1.0 Hz, 1H), 7.65–7.62 (comp m, 2H), 7.46 (dd, J = 6.8, 1.0 Hz, 1H), 7.44 (dd, J = 7.6, 0.7 Hz, 1H), 7.41 (ddd, J = 7.6, 1.7, 1.0 Hz, 1H), 7.40–7.37 (comp m, 2H), 7.36–7.33 (comp m, 5H), 7.28 (tt, J = 7.3, 1.0, 1H), 7.10 (dd, J = 8.8, 7.3 Hz, 2H), 6.99 (dd, J = 7.6, 1.2 Hz, 2H), 6.94 (tt, J = 7.3, 1.2 Hz, 1H), 4.64 (s, 2H), 3.98 (dt, J = 13.7, 6.3 Hz, 1H), 3.88 (ddd, J = 13.7, 6.3, 5.4 Hz, 1H), 3.80 (ddd, J = 6.6, 6.3, 1.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 153.5, 144.9, 138.9, 138.5, 135.3, 131.6, 130.3, 129.9, 128.9, 128.8, 128.5, 128.3, 127.7, 127.4, 125.8, 123.7, 123.2, 123.1, 121.8, 73.0, 70.1, 47.8; IR (Neat Film, NaCl)

3057, 2858, 1707, 1589, 1490, 1449, 1293, 1208, 1100 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{29}H_{25}NO_3$ $[M+H]^+$: 436.1907, found 436.1893.



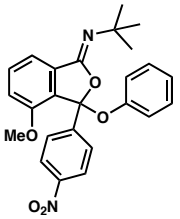
Phenoxy iminoisobenzofuran 548o

Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 5:95 EtOAc/hexanes) to yield a yellow oil (58% yield). R_f = 0.40 (25:75 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ□8.46 (dd, J = 7.3, 1.0 Hz, 1H), 7.74 (ddd, J = 7.3, 1.2, 1.0 Hz, 1H), 7.65 (dd, J = 8.1, 1.5 Hz, 2H), 7.57 (ddd, J = 7.6, 1.5, 1.0 Hz, 1H), 7.45 (dd, J = 7.3, 1.5 Hz, 2H), 7.40 (ddd, J = 7.57, 1.5, 1.2 Hz, 2H), 7.27 (m, 1H), 7.26 (tt, J = 7.3, 1.5 Hz, 1H), 7.22 (dd, J = 7.8, 7.3 Hz, 2H), 7.12 (dd, J = 7.8, 1.2 Hz, 2H), 6.99 (dd, J = 7.8, 1.0 Hz, 1H), 6.82 (td, J = 7.6, 1.2 Hz, 1H), 6.62 (td, J = 8.1, 1.5 Hz, 1H), 5.23 (dd, J = 7.8, 1.2 Hz, 1H), 3.66 (t, J = 5.4 Hz, 1H), 3.01 (s, 6H), 2.98 (t, J = 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 144.7, 142.9, 138.1, 138.0, 135.8, 135.6, 134.7, 133.5, 133.2, 131.2, 130.2, 130.1, 129.8, 128.8, 128.6, 128.5, 127.9, 127.6, 127.4, 127.3, 125.0, 124.2, 121.4, 102.9, 51.7, 31.3; IR (Neat Film, NaCl) 3067, 2935, 1617, 1597, 1429, 1303, 1121, 1068, 1048 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{30}H_{27}NO_4$ $[M+H]^+$: 466.2013, found 466.2008.



Phenoxy iminoisobenzofuran 548p

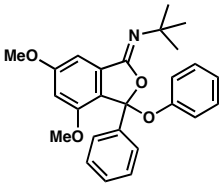
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 4:96 EtOAc/hexanes) to yield a white solid (75% yield). X-ray diffraction crystals were grown via slow evaporation of a solution of the white solid (20 mg) in $CDCl_3$ (0.6 mL) on the bench top at 23 °C over 3 days; mp 101–104 °C. R_f = 0.30 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ□7.68 (d, J = 6.6 Hz, 2H), 7.40–7.34 (comp m, 3H), 7.32 (t, J = 7.8 Hz, 2H), 7.11 (dd, J = 8.6, 7.1 Hz, 2H), 7.06 (dd, J = 7.6, 1.2 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.83 (d, J = 8.6 Hz, 1H), 3.78 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 154.0, 153.1, 139.2, 135.1, 134.6, 132.3, 130.6, 129.0, 128.7, 128.1, 126.9, 124.4, 122.4, 115.5, 113.6, 55.7, 54.3, 30.4; IR (Neat Film, NaCl) 2967, 1699, 1612, 1489, 1271, 1213, 1049 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{25}H_{25}NO_3$ $[M+H]^+$: 388.1907, found 388.1925.



Phenoxy iminoisobenzofuran 548q

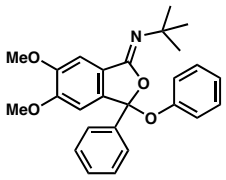
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 6:94 EtOAc/hexanes) to yield a pale yellow solid (96% yield). R_f = 0.10 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 9.0

Hz, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.28 (dd, J = 7.8, 0.7 Hz, 1H), 7.13 (dd, J = 8.5, 7.3 Hz, 2H), 7.02 (dd, J = 8.8, 1.2 Hz, 2H), 6.99 (ddd, J = 7.3, 1.2, 1.0 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 3.79 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 153.2, 151.6, 147.9, 146.1, 134.4, 132.7, 129.2, 128.9, 127.8, 124.7, 123.2, 122.2, 115.4, 113.4, 109.8, 55.5, 54.2, 30.2; IR (Neat Film, NaCl) 2968, 1700, 1613, 1524, 1490, 1349, 1271, 1211, 1044 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{25}H_{24}N_2O_5$ $[M–H]^-$: 431.1612, found 431.1621.



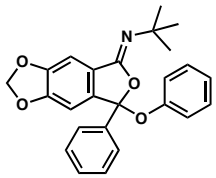
Phenoxy iminoisobenzofuran 548r

Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 2:98 → 4:96 EtOAc/hexanes) to yield a white solid (68% yield). R_f = 0.27 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.8, 1.7 Hz, 2H), 7.36 (dd, J = 7.8, 1.7 Hz, 2H), 7.35 (tt, J = 7.8, 1.7 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 7.04 (dd, J = 8.3, 1.2 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.38 (d, J = 2.0 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 155.1, 153.8, 152.9, 139.4, 135.5, 128.7, 128.4, 128.1, 127.8, 126.5, 124.1, 123.8, 122.4, 102.7, 97.0, 55.8, 55.4, 54.0, 30.2; IR (Neat Film, NaCl) 2964, 1695, 1619, 1599, 1355, 1204, 1146, 1037 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{26}H_{27}NO_4$ $[M+H]^+$: 418.2013, found 418.2020.



Phenoxy iminoisobenzofuran 548s

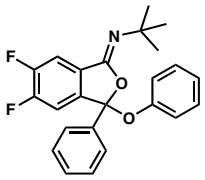
Purified by flash chromatography (SiO_2, 5:95 → 10:90 EtOAc/hexanes) to yield a white solid (85% yield). R_f = 0.23 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 6.8 Hz, 2H), 7.40 (dd, J = 7.1, 6.8 Hz, 2H), 7.35 (tt, J = 7.1, 1.5 Hz, 1H), 7.14 (dd, J = 8.5, 7.1, 2H), 7.12 (s, 1H), 7.00–6.95 (comp m, 3H), 6.77 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 153.0, 152.6, 151.0, 139.8, 137.4, 129.8, 128.9, 128.7, 128.6, 128.2, 125.7, 123.5, 121.5, 104.5, 104.4, 56.3, 56.2, 54.0, 30.3; IR (Neat Film, NaCl) 2966, 1701, 1595, 1501, 1491, 1317, 1214 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{26}H_{27}NO_4$ $[M+H]^+$: 418.2013, found 418.2016.



Phenoxy iminoisobenzofuran 548t

Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (76% yield). R_f = 0.30 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 7.1 Hz, 2H), 7.39 (dd, J = 7.6, 6.8 Hz, 2H), 7.34 (tt, J = 7.1, 1.0 Hz, 1H), 7.16 (dd, J = 8.5, 7.6 Hz, 2H), 7.06 (s, 1H), 7.00 (dd, J = 8.5, 1.0 Hz, 2H), 6.98 (t, J= 7.3 Hz, 1H), 6.74 (s, 1H), 6.02 (d, J = 1.2 Hz, 1H), 5.97 (d, J = 1.2 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.2, 151.2, 149.7, 139.7, 139.3, 136.0, 135.0, 129.0, 128.8,

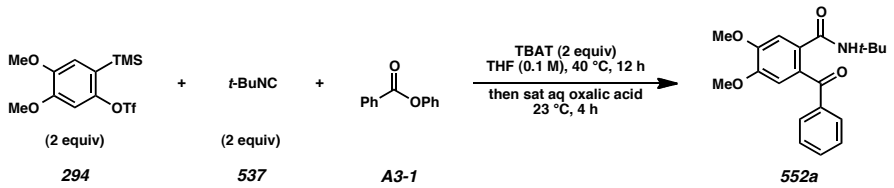
128.7, 125.7, 123.4, 121.4, 102.8, 102.6, 102.2, 53.9, 30.3; IR (Neat Film, NaCl) 2967, 1707, 1473, 1307, 1213, 1059, 1037 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{25}H_{23}NO_4$ $[M+H]^+$: 402.1700, found 402.1684.



Phenoxy iminoisobenzofuran 548u

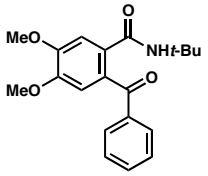
Purified by flash chromatography (SiO_2, 0:100 → 2:98 EtOAc/hexanes) to yield a pale yellow oil (62% yield). R_f = 0.50 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J = 6.6, 1.5 Hz, 2H), 7.48 (dd, J = 8.8, 7.1 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.39 (dd, J = 8.3, 6.8 Hz, 1H), 7.17 (tt, J = 7.6, 1.5 Hz, 1H), 7.15 (d, J = 7.6 Hz, 2H), 6.99 (t, J = 7.6 Hz, 1H), 6.98 (dd, J = 7.6, 7.1 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0 (d, $J_{C–F}$ = 14.7 Hz), 153.5, 153.1 (d, $J_{C–F}$ = 14.3 Hz), 151.9 (d, $J_{C–F}$ = 14.3 Hz), 151.1 (d, $J_{C–F}$ = 14.3 Hz), 150.3, 140.3, 138.8, 129.2, 129.1, 128.9, 125.6, 123.8, 121.3, 111.0 (dd, $J_{C–F}$ = 19.8, 4.1 Hz), 109.4, 54.3, 30.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ –130.3 (ddd, J = 18.9, 7.9, 7.6 Hz), –133.7 (ddd, J = 18.9, 7.1, 6.8 Hz); IR (Neat Film, NaCl) 2968, 1711, 1498, 1451, 1343, 1211 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{24}H_{21}F_2NO_2$ $[M–H]^–$: 392.1468, found 392.1479.

4.4.2.3 Representative Procedure for the One-Pot Synthesis of Ortho-Ketobenzamides via Three-Component Synthesis and Hydrolysis of Phenoxy Iminoisobenzofurans



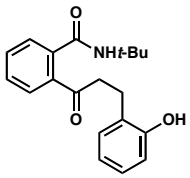
A flame-dried 15 mL long reaction tube with a magnetic stir bar was charged with TBAT (0.545 g, 1.01 mmol, 2 equiv), phenyl benzoate (**A3-1**) (0.100 g, 0.504 mmol), and THF (5 mL). To this solution was added silyl aryl triflate **294** (0.362 g, 1.01 mmol, 2 equiv) and *tert*-butylisocyanide (**537**) (0.114 mL, 1.01 mmol, 2 equiv), each via syringe. The reaction was heated to 40 °C under argon for 12 h, at which point TLC analysis showed complete consumption of phenyl benzoate (**A3-1**) (NOTE: at this point, the major component of the reaction is phenoxy iminoisobenzofuran **552a**). The reaction was cooled to room temperature and a saturated aqueous solution of oxalic acid (5 mL) was added via syringe. The mixture was vigorously stirred at room temperature for 4 h, at which point TLC analysis showed complete comsumption of the intermediate iminoisobenzofuran. The reaction was quenched by the slow addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was stirred until bubbling ceased and then extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel.

4.4.2.4 Spectroscopic Data for Ortho-Ketobenzamides



ortho-Ketobenzamide 552a

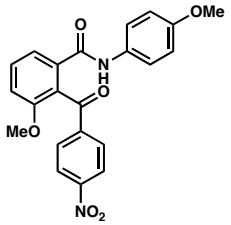
Purified by flash chromatography (SiO_2, 15:85 → 40:60 EtOAc/hexanes) to yield a white solid (81% yield). R_f = 0.37 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 8.3, 1.2 Hz, 2H), 7.57 (tt, J = 7.6, 1.2 Hz, 1H), 7.45 (dd, J = 8.1, 7.6 Hz, 2H), 7.24 (s, 1H), 6.95 (s, 1H), 5.59 (br s, 1H), 4.00 (s, 3H), 3.92 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 166.7, 150.4, 150.3, 137.5, 133.5, 130.7, 129.8, 128.6, 127.8, 111.1, 110.7, 56.3, 56.2, 51.8, 28.0; IR (Neat Film, NaCl) 3318, 2965, 1654, 1648, 1596, 1502, 1449, 1348, 1293, 1273, 1215 1084 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{20}H_{23}NO_4$ $[M–H]^-$: 340.1554, found 340.1556.



ortho-Ketobenzamide 552b

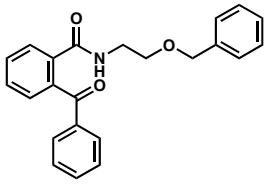
Purified by flash chromatography (SiO_2, 10:90 → 25:75 EtOAc/hexanes) to yield a white solid (75% yield). R_f = 0.10 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.42 (comp m, 4H), 7.12–7.08 (comp m, 2H), 6.88 (dd, J = 8.5, 1.2 Hz, 1H), 6.84 (td, J = 7.3, 1.2 Hz, 1H), 5.72 (br s, 1H), 3.26 (t, J = 6.4 Hz, 2H), 3.02 (t, J = 6.4 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 168.4, 154.5, 138.5, 136.8, 131.1,

130.4, 130.2, 129.9, 127.6, 127.5, 127.3, 120.5, 117.2, 52.2, 43.2, 28.6, 24.2; IR (Neat Film, NaCl) 3315, 2970, 1681, 1644, 1593, 1532, 1456, 1366, 1230 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{20}H_{23}NO_3$ $[M–H]^-$: 324.1605, found 324.1620.



***ortho*-Ketobenzamide 552c**

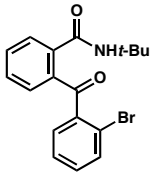
Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes) to yield a yellow solid (84% yield). R_f = 0.10 (25:75 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 11.7 Hz, 1H), 8.33 (d, *J* = 1.7 Hz, 1H), 7.88 (m, 1H), 7.45 (d, *J* = 9.0 Hz, 2H), 7.28 (br s, 1H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 158.8, 157.7, 156.7, 129.9, 129.5, 121.8, 121.7, 114.9, 114.2, 55.6, 55.5; IR (Neat Film, NaCl) 3270, 3127, 3062, 1684, 1603, 1512, 1412, 1301, 1247, 1032 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{22}H_{18}N_2O_6$ $[M+H]^+$: 407.1238, found 407.1233.



***ortho*-Ketobenzamide 552d**

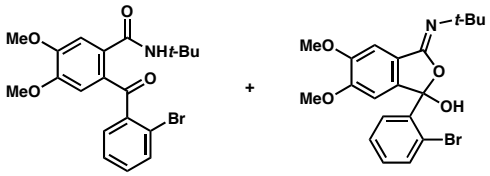
Reaction performed at 60 °C. Purified by flash chromatography (SiO_2, 5:95 → 15:85 EtOAc/hexanes) to yield a white solid (59% yield). R_f = 0.27 (25:75 EtOAc/hexanes); ^1H

NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.48 (td, *J* = 7.3, 1.5 Hz, 1H), 7.45 (ddd, *J* = 7.3, 1.5, 0.5 Hz, 1H), 7.39 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.38–7.31 (comp m, 7H), 7.29 (dd, *J* = 8.1, 1.5 Hz, 2H), 6.09 (t, *J* = 5.4 Hz, 1H), 4.38 (s, 2H), 3.15 (t, *J* = 5.1 Hz, 2H), 2.97 (dt, *J* = 5.4, 5.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 169.4, 143.2, 139.2, 138.0, 136.1, 135.7, 134.0, 129.8, 129.7, 129.0, 128.5, 127.8, 127.7, 127.6, 126.6, 72.9, 68.4, 39.4; IR (Neat Film, NaCl) 3284, 3067, 2860, 1634, 1631, 1536, 1427, 1300, 1107 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{23}H_{21}NO_3$ $[M+H]^+$: 360.1594, found 360.1588.



***ortho*-Ketobenzamide 552e**

Purified by flash chromatography (SiO_2, 20:80 → 30:70 EtOAc/hexanes) to yield a colorless oil (77% yield). R_f = 0.20 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.56–7.54 (comp m, 2H), 7.49 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.46–7.44 (comp m, 2H), 7.38 (td, *J* = 7.6, 1.5 Hz, 1H), 7.34 (td, *J* = 7.8, 2.0 Hz, 1H), 5.74 (br s, 1H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.1, 167.9, 139.4, 138.7, 137.3, 133.8, 132.3, 131.8, 131.7, 130.3, 129.6, 127.9, 127.3, 120.8, 51.9, 28.5; IR (Neat Film, NaCl) 3320, 2969, 1663, 1534, 1452, 1297, 1248, 1220 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{18}H_{18}BrNO_2$ $[M+H]^+$: 360.0594, found 360.0594.



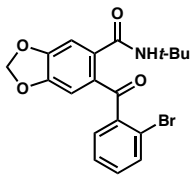
***ortho*-Ketobenzamide 552f and cyclic imidate A3-2**

Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes) to yield a colorless oil (69% yield). R_f = 0.10 (25:75 EtOAc/hexanes). Product was isolated as a 2:1 mixture of inseparable ketobenzamide and cyclic imidate isomers. ^{1}H and ^{13}C NMR data are reported for individual isomers; IR and HRMS data are reported for the mixture.

***ortho*-Ketobenzamide** (**552f**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.46 (dd, *J* = 7.3, 2.0 Hz, 1H), 7.40 (td, *J* = 7.6, 1.5 Hz, 1H), 7.34 (td, *J* = 7.8, 2.0 Hz, 1H), 7.08 (s, 1H), 6.96 (s, 1H), 5.70 (br s, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 167.6, 151.9, 149.4, 139.7, 135.2, 133.8, 133.1, 132.2, 131.5, 127.4, 120.7, 113.1, 111.2, 56.3, 56.2, 51.9, 28.3.

Cyclic imidate (**A3-2**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.43 (ddd, *J* = 8.1, 7.3, 1.2 Hz, 1H), 7.23 (s, 1H), 7.19 (ddd, *J* = 7.8, 7.3, 1.7 Hz, 1H), 6.37 (s, 1H), 3.94 (s, 3H), 3.77 (s, 3H), 2.87 (br s, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 153.0, 150.7, 140.4, 139.0, 129.9, 129.7, 129.0, 127.3, 126.0, 121.0, 104.3, 103.6, 91.8, 57.0, 56.3, 56.2, 28.8.

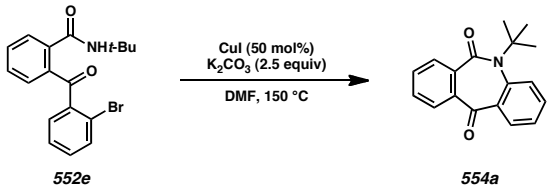
IR (Neat Film, NaCl) 3357, 2966, 2936, 1664, 1593, 1507, 1502, 1463, 1349, 1289, 1272, 1212, 1089 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{20}H_{22}BrNO_4$ $[M+H]^+$: 420.0805, found 420.0817.



***ortho*-Ketobenzamide 552g**

Purified by flash chromatography (SiO_2, 5:95 → 20:80 EtOAc/hexanes) to yield a white solid (64% yield). R_f = 0.10 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1H), 7.33 (td, *J* = 7.8, 2.0 Hz, 1H), 7.01 (s, 1H), 6.86 (s, 1H), 6.07 (s, 2H), 5.63 (br s, 1H), 1.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 167.4, 150.5, 148.3, 139.7, 135.1, 133.6, 132.1, 131.3, 127.4, 121.4, 120.5, 110.4, 108.7, 102.3, 51.9, 28.4; IR (Neat Film, NaCl) 3317, 2969, 2907, 1654, 1650, 1607, 1503, 1482, 1453, 1367, 1285, 1259, 1226, 1035 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{19}H_{18}BrNO_4$ $[M+H]^+$: 404.0492, found 404.0505.

4.4.2.5 Representative Procedure for the Copper-Catalyzed Intramolecular Coupling of 2-(*ortho*-Bromobenzoyl)benzamides

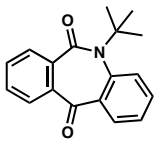


552e *554a*

A flame-dried 1.5 dram vial containing a magnetic stir bar and sealed with a PTFE/silicone septum and screw cap was charged with copper(I) iodide (0.005 g, 0.028 mmol, 0.5 equiv) and potassium carbonate (0.019 g, 0.137 mmol, 2.5 equiv). The vial was evacuated and backfilled with argon twice. Then ketobenzamide **552e** (0.020 g,

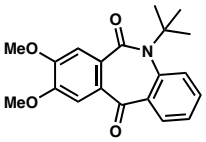
0.056 mmol) in DMF (0.6 mL) was added and the mixture was heated to 150 °C. The solution started as a pale yellow and became progressively brighter yellow over the course of the reaction. After stirring for 24 h, the reaction was cooled to room temperature and filtered through a pad of silica under EtOAc elution. The solvents were removed under reduced pressure and the resulting yellow residue was purified via flash chromatography over silica gel.

4.4.2.6 Spectroscopic Data for Dibenzoketocaprolactams



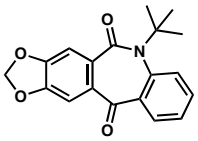
Dibenzoketocaprolactam 554a

Purified by flash chromatography (SiO_2, 5:95 → 10:90 EtOAc/hexanes) to yield a white solid (85% yield). R_f = 0.50 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (ddd, *J* = 7.8, 1.2, 0.7 Hz, 1H), 7.57 (ddd, *J* = 7.8, 6.4, 2.5 Hz, 1H), 7.53 (d, *J* = 1.7 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.42–7.37 (comp m, 2H), 7.40 (dd, *J* = 6.1, 1.5 Hz, 1H), 7.31–7.27 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 166.9, 142.1, 141.1, 137.3, 133.5, 132.2, 131.9, 131.8, 130.1, 127.9, 127.3, 126.0, 125.8, 60.9, 30.0; IR (Neat Film, NaCl) 2974, 1689, 1647, 1592, 1483, 1446, 1340, 1280, 1188 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{18}H_{17}NO_2$ $[M+H]^+$: 280.1332, found 280.1340.



Dibenzoketocaprolactam 554b

Purified by flash chromatography (SiO_2, 5:95 → 10:90 EtOAc/hexanes) to yield a pale yellow oil (61% yield). R_f = 0.30 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.44 (ddd, *J* = 7.6, 1.5, 0.5 Hz, 1H), 7.42 (ddd, *J* = 7.6, 1.7, 1.5 Hz, 1H), 7.39 (app td, *J* = 6.8, 1.7 Hz, 1H), 7.29 (ddd, *J* = 7.6, 6.8, 1.7 Hz, 1H), 7.08 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 166.7, 151.8, 151.5, 141.6, 137.2, 134.6, 130.0, 127.6, 127.4, 127.0, 126.3, 113.9, 108.4, 60.9, 56.3, 56.2, 30.1; IR (Neat Film, NaCl) 2969, 2935, 1674, 1645, 1589, 1514, 1447, 1360, 1331, 1286, 1219, 1185, 1077 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{21}NO_4$ $[M^{\bullet}]^+$: 339.1471, found 339.1484.

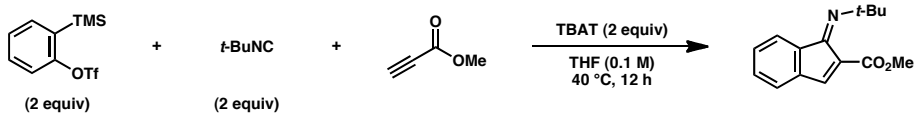


Dibenzoketocaprolactam 554c

Purified by flash chromatography (SiO_2, 5:95 EtOAc/hexanes) to yield a yellow oil (73% yield). R_f = 0.40 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.39 (app dd, *J* = 2.7, 1.0 Hz, 2H), 7.38 (dd, *J* = 5.9, 1.5 Hz, 1H), 7.29 (t, *J* = 3.7 Hz, 1H), 7.00 (s, 1H), 6.05 (d, *J* = 9.5 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 166.1, 150.8, 150.4, 141.7, 137.1, 136.8, 129.9, 127.7, 127.1, 126.1, 111.6, 105.9, 102.4, 60.9, 30.0; IR (Neat Film, NaCl) 2973, 2909, 1679, 1645, 1608, 1593, 1483, 1448, 1373,

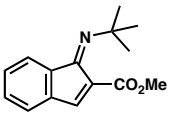
1332, 1282, 1187, 1037 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{17}NO_4$ $[M+H]^+$: 324.1230, found 324.1241.

4.4.2.7 Representative Procedure for the Three-Component Synthesis of Iminoindenones from Arynes, Isocyanides, and Alkynes



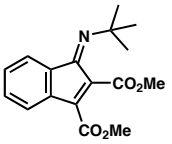
A flame-dried 15 mL round bottomed flask with a magnetic stir bar was charged with TBAT (0.607 g, 1.124 mmol, 2.0 equiv) and THF (3 mL). To this solution was added methyl propiolate (**559**) (0.05 mL, 0.562 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**258**) (0.204 mL, 0.843 mmol, 1.5 equiv), and *tert*-butylisocyanide (**537**) (0.095 mL, 0.843 mmol, 1.5 equiv), each via syringe. The reaction was heated to 40 °C under argon for 12 h, at which point TLC analysis showed complete consumption of aryne precursor. The reaction was cooled to room temperature, and then concentrated on celite. The crude suspension was purified by flash chromatography over silica gel.

4.4.2.8 Spectroscopic Data for Iminoindenones



Iminoindenone 558

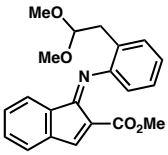
Purified by flash chromatography (SiO_2, 5:95 EtOAc/hexanes) to yield a yellow solid (88% yield). R_f = 0.66 (20:80 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{15}H_{17}NO_2$ [M+]: 243.1259, found 243.1260.



Iminoindenone 566a

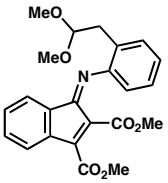
Purified by flash chromatography (SiO_2, 10:90 EtOAc/hexanes) to yield a white solid (83% yield). R_f = 0.38 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6,

54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{17}H_{19}NO_4$ $[M]^+$: 301.1314, found 301.1315.



Iminoindenone 566b

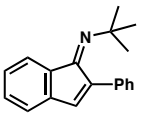
Purified by flash chromatography (SiO_2, 15:85 EtOAc/hexanes) to yield a yellow oil (66% yield). R_f = 0.39 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 8.75 Hz, 2H), 7.56-7.50 (m, 3H), 7.35 (d, J = 7.24 Hz, 1H), 7.28 (t, J = 7.83 Hz, 1H), 7.19 (t, J = 7.24 Hz, 1H), 7.02 (d, J = 7.24 Hz, 1H) 4.53 (t, J = 5.85 Hz, 1H), 3.79 (s, 3H), 3.29 (s, 6H), 2.97 (d, J = 5.85); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.00, 149.04, 147.04, 135.96, 131.79, 130.88, 129.21, 128.64, 127.99, 126.96, 126.02, 118.65, 104.82, 85.55, 77.74, 53.74, 53.11, 35.85; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{21}H_{21}NO_4$ $[M]^+$: 351.1471, found 351.1457.



Iminoindenone 566c

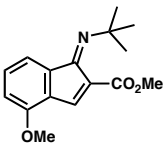
Purified by flash chromatography (SiO_2, 15:85 EtOAc/hexanes) to yield a yellow solid (91% yield). R_f = 0.57 (20:80 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 6.51 Hz, 1H), 7.68-7.61 (m, 3H), 7.31 (d, J = 7.50 Hz, 1H), 7.26 (t, J = 6.51 Hz, 2H) 7.11 (t, J = 6.93 Hz, 1H), 4.62 (t, J = 4.98, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.31 (s, 3H),

3.30 (s, 3H), 3.04 (t, J = 7.07 Hz, 2H; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2939, 2832, 1722, 1598, 1489, 1435, 1337, 1281, 1258, 1088, 1060, 982, 1060, 758 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{23}H_{23}NO_6$ $[M+H]^+$: 409.1525, found 410.1524.



Iminoindenone 566d

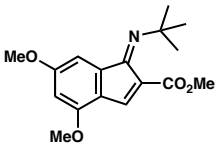
Purified by flash chromatography (SiO_2, 5:95 CH_2Cl_2/hexanes) to yield a pale yellow oil (51% yield). R_f = 0.60 (5:95 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 2.4 Hz, 1H), 8.08 (d, *J* = 3.7, 1.2 Hz, 1H), 7.61–7.58 (comp m, 2H), 7.46–7.38 (comp m, 6H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 147.0, 139.5, 136.9, 131.6, 130.0, 129.6, 128.6, 128.1, 127.2, 122.0, 98.9, 84.1, 57.0, 29.5; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{19}N$ $[M+H]^+$: 262.1590, found 262.1592.



Iminoindenone 566e

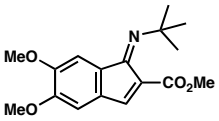
Purified by flash chromatography (SiO_2, 15:85 EtOAc/hexanes) to yield a yellow oil (66% yield). R_f = 0.41 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 7.97 Hz, 1H), 7.54 (s, 1H), 7.37 (t, J = 7.97 Hz, 1H), 6.98 (d, J = 7.97 Hz, 1H), 3.88 (s,

3H), 3.86 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.63, 153.55, 144.13, 139.43, 129.31, 119.96, 116.74, 111.76, 87.92, 78.63, 57.75, 55.35, 53.14, 29.61; IR (Neat Film, NaCl) 2969, 215, 1720, 1602, 1576, 1486, 1466, 1433, 1362, 1275, 1252, 1206, 1175, 1043, 983, 914, 879, 790, 748 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{16}H_{19}NO_3$ $[M+H]^+$: 274.1365, found 274.1454



Iminoindenone 566f

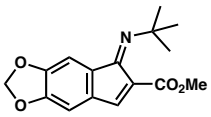
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (79% yield). R_f = 0.41 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{17}H_{21}NO_4$ $[M+H]^+$: 304.1471, found 304.1560.



Iminoindenone 566g

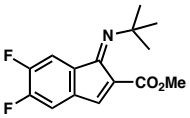
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (54% yield). R_f = 0.22 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dt, J = 7.6, 1.0 Hz, 1H), 7.49 (d, J = 1.0 Hz, 1H), 7.48 (dd, J = 2.0, 1.0 Hz, 1H), 7.39 (ddd, J =

8.3, 5.1, 3.2 Hz, 1H), 7.12 (dd, J = 8.3, 7.3 Hz, 2H), 6.97 (tt, J = 7.3, 1.2 Hz, 1H), 6.92 (dd, J = 8.8, 1.2 Hz, 2H), 1.97 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 143.6, 136.6, 132.9, 131.4, 130.1, 129.1, 128.3, 124.4, 123.4, 122.8, 122.3, 110.6, 54.1, 30.4, 26.3; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{17}H_{21}NO_4$ $[M+H]^+$: 304.1471, found 304.1552.



Iminoindenone 566h

Purified by flash chromatography (SiO_2, 10:90 EtOAc/hexanes) to yield a white solid (56% yield). R_f = 0.46 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.51 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 6.00 (s, 2H), 3.88 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 148.0, 143.3, 132.9, 122.6, 110.0, 107.7, 106.7, 101.5, 87.7, 78.3, 57.4, 53.1, 29.7; IR (Neat Film, NaCl) 2697, 2217, 1718, 1576, 1504, 1488, 1444, 1362, 1275, 1257, 1207, 1117, 1039, 980, 937, 918, 812, 748 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{16}H_{17}NO_4$ $[M+H]^+$: 288.1158, found 288.1227.

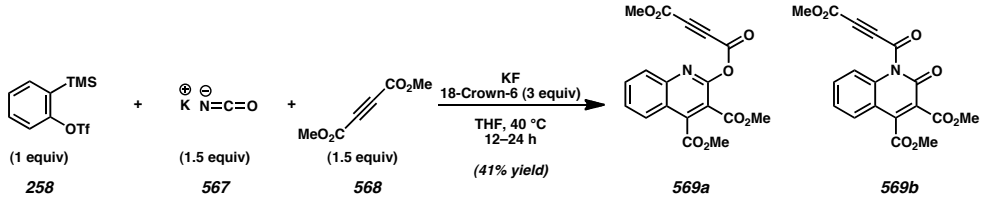


Iminoindenone 566i

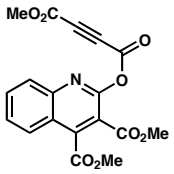
Purified by flash chromatography (SiO_2, 2:98 EtOAc/hexanes) to yield a colorless oil (80% yield). R_f = 0.46 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dq, *J* = 8.0, 2.2 Hz, 1H), 7.73 (d, *J* = 2.2 Hz, 1H), 7.19 (q, *J* = 8.0 Hz, 1H), 3.90 (s, 3H), 1.48

(s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 142.0, 136.3, 128.3, 123.7, 117.0, 116.9, 116.0, 115.8, 88.24, 58.0, 53.3, 29.6; IR (Neat Film, NaCl) 2968, 1778, 1704, 1662, 1490, 1215, 1114 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{15}F_2NO_2$ $[M+H]^+$: 280.1144, found 280.1162.

4.4.2.9 Representative Procedure for the Three-Component Synthesis of 2-Quinolones from Arynes, Potassium Cyanate, and DMAD

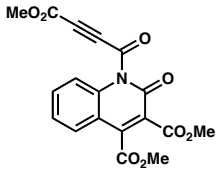


A 15 mL round bottomed flask with a magnetic stir bar was charged with KF (0.024 g, 0.407 mmol, 1.5 equiv) and flame dried. To the flask was added a solution of DMAD (**568**) (0.05 mL, 0.407 mmol), 18-Crown-6 (215 mg, 0.814 mmol, 3 equiv), and potassium cyanate (33 mg, 0.407 mmol) in THF (4mL). This was allowed to stir at room temperature for 10 m under a nitrogen atmosphere. Next, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**258**) (0.066 mL, 0.271 mmol, 1.0 equiv), was added via syringe. The reaction was heated to 40 °C under nitrogen for 12 h, at which point TLC analysis showed complete consumption of aryne precursor. The reaction was cooled to room temperature, and then concentrated on celite. Purified by flash chromatography (SiO_2, 30:70 EtOAc/hexanes) to yield **569a** and **569b** as colorless solids (30 mg, 57% combined yield).



Quinolone 569a

R_f = 0.29 (40:60 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.2 Hz, 1H), 7.78 (d *J* = 8.5 Hz, 1H), 7.68 (q, *J* = 7.7, 1.2 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 142.0, 136.3, 128.3, 123.7, 117.0, 116.9, 116.0, 115.8, 88.24, 58.0, 53.3; IR (Neat Film, NaCl) 2956, 2924, 1734, 1700, 1603, 1437, 1266, 1165, 1091, 1053, 976, 758 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{14}NO_8$ $[M+H]^+$: 372.0719, found 372.0671.



Quinolone 569b

R_f = 0.42 (40:60 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.85 (ddd, *J* = 7.9, 2.2, 1.5 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.5 (t, *J* = 7.5 Hz, 1H), 4.11 (s, 3H), 4.04 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 142.0, 136.3, 128.3, 123.7, 117.0, 116.9, 116.0, 115.8, 88.24, 58.0, 53.3; IR (Neat Film, NaCl) 1740, 1734, 1670, 1560, 1465, 1246, 1222, 1146, 1003, 773 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{18}H_{14}NO_8$ $[M+H]^+$: 372.0719, found 372.0666.

4.5 REFERENCES AND NOTES

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(2) For a review of multicomponent reaction strategies in natural product total synthesis, see: Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486.

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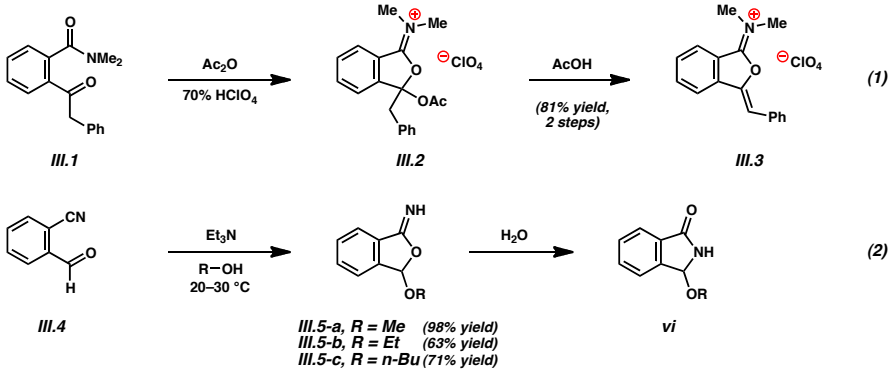

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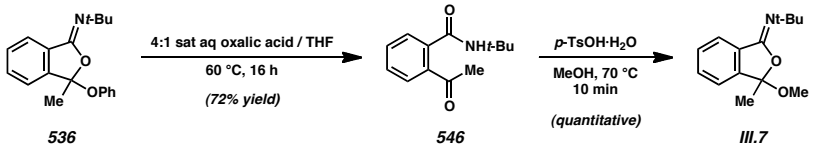

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