Regio and diastereoselective synthesis of allylic amine through hydrocupration of terminal alkynes

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Abstract

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Allylic amines play a crucial role in organic synthesis, owing to their versatility and unique chemical reactivity resulting from the allylic double bond. Their significance is further evident in their incorporation as structural backbones in natural products and drug molecules. Allylic amines can be synthesized using various strategies, including C-N bond formation via allylic substitution, C-H bond amination, and C-C bond formation by adding alkenyl metal to imine or by reductive cross-coupling reactions. Herein, we develop an innovative approach to allylic amine synthesis based on copper-catalyzed stereoselective reductive cross-coupling between alkynes and α-Cl phthalimide. We demonstrate that the reaction is compatible with various functional groups under mild conditions. Interestingly, different from our proposed mechanism, the preliminary mechanistic study shows that the process does not involve the generation of a radical at the α-nitrogen position

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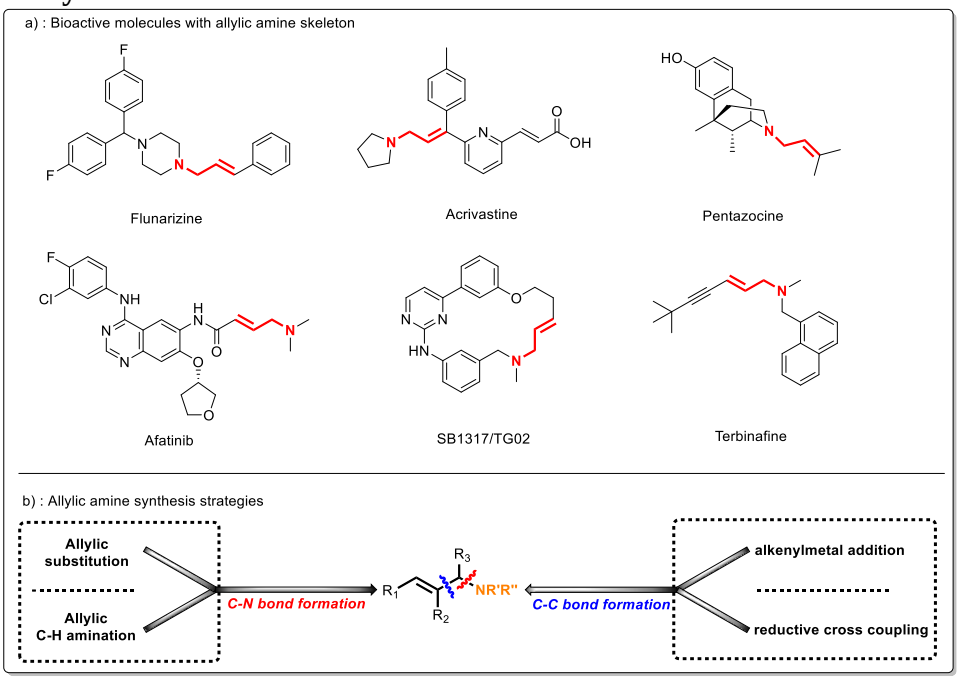
Chapter 1. INTRODUCTION

Allylic amines are a versatile and important class of compounds in organic synthesis, owing to their chemical reactivity resulting from the double bond. This functional group offers diverse transformations, including oxidation, reduction, and addition reactions, which significantly expand the synthetic utility of allylic amines. Additionally, the amino group on the allylic carbon atom provides an additional functionalization site, making these molecules indispensable in modern organic chemistry. The significance of allylic amines is further evident in their incorporation as structural backbones in natural products and drug molecules, underscoring their relevance in medicinal chemistry (Scheme 1. a). Over the last few decades, the scientific community has made remarkable strides in devising an array of methods for the synthesis of allylic amines. These strategies can largely be grouped into two categories: C-N and C-C bond formation (Scheme 1. b).

Scheme 1. Selected examples of bioactive molecules with allylic amine skeleton; synthetic strategies to allylic amine.



Chapter 2. ALLYLIC AMINE SYNTHESIS THROUGH C-N BOND FORMATION

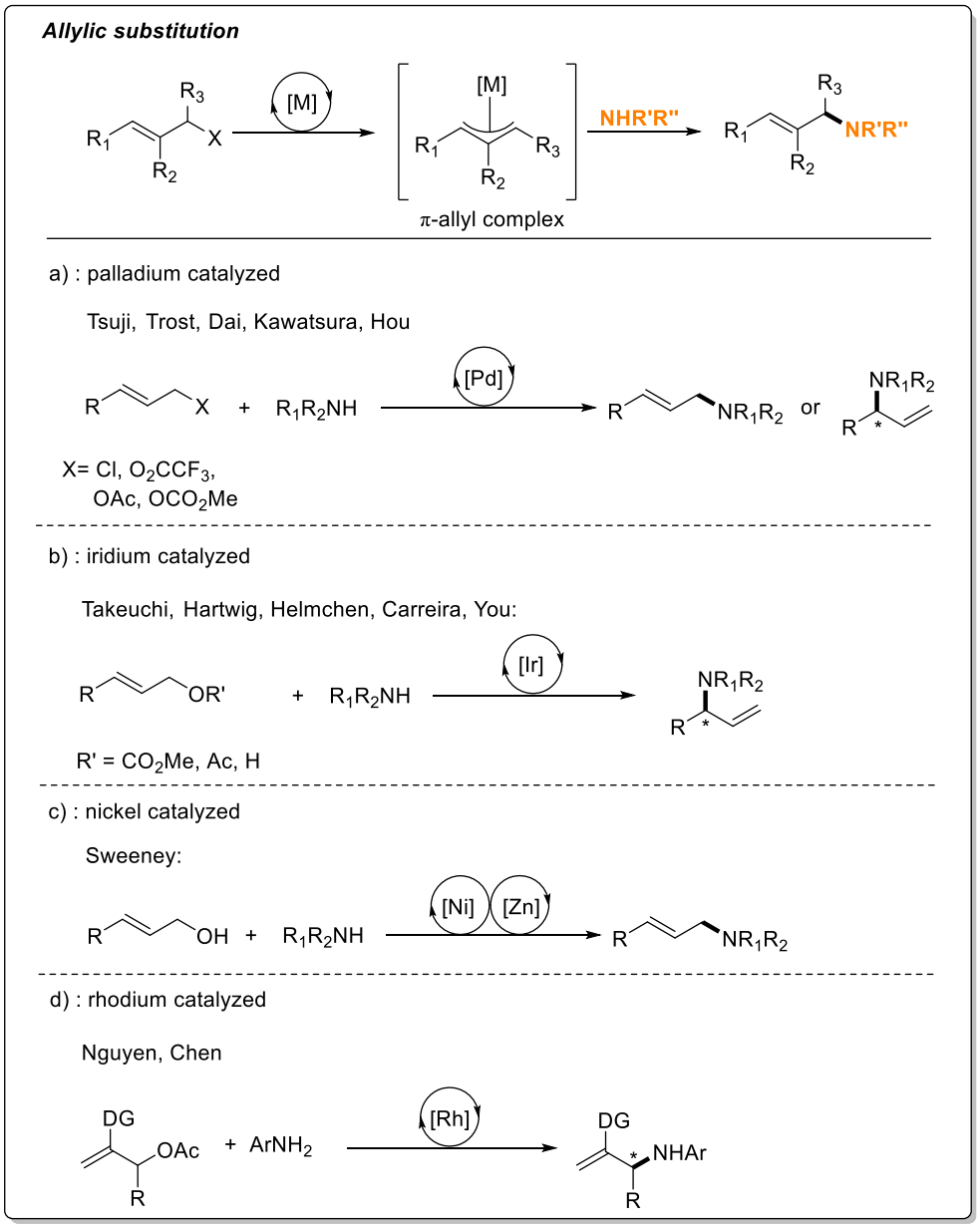
In the broadest sense, the synthesis of allylic amines via C-N bond formation is about introducing an amine group onto an allylic position, which is a carbon atom adjacent to a carbon-carbon double bond. There are numerous strategies for the creation of this C-N bond, each with its own set of conditions, catalysts, and substrates. These strategies can range from direct nucleophilic substitution methods to transition metal-catalyzed reactions, and they can involve different types of starting materials such as allylic halides, allylic esters and alkenes.

2.1 ALLYLIC SUBSTITUTION

Ever since the advent of the Tsuji-Trost reaction, many catalytic systems have been developed for metal-catalyzed allylic substitutions. Due to their ubiquity and potent nucleophilic properties, amines have emerged as ideal agents for synthesizing allylic amines via the Tsuji-Trost reaction. Over the past several decades, a wide array of nucleophilic amines has been successfully employed in the synthesis of both linear and branched allylic amines, demonstrating high levels of regio- and enantioselectivity. The groundbreaking contributions by Tsuji and Trost paved the way for understanding the pivotal role of the nucleophilic attack from an amine to the palladium-allyl intermediate. This interaction, leading to the formation of a π-allyl intermediate, was later validated as a critical step in the sequence of allylic substitution reactions. Since then, palladium-catalyzed allylic amine synthesis via Tsuji-Trost type reaction became an attractive field (Scheme 2. a). [1-6] Furthering this field of study, a wave of research led by Takeuchi, Helmchen, Hartwig, Carreira, and You, introduced an expansive array of phosphorous ligands in Ir-catalyzed allylic amination reactions (Scheme 2. b).[7-24] Their work contributed significantly to the control of

enantioselectivity in these processes. Subsequent investigations uncovered that other metals, specifically nickel and rhodium, could similarly facilitate these reactions (Scheme 2. c-d).[25-29] Overall, this approach has been highly effective, and the development of new catalysts and ligands has dramatically expanded the scope of these reactions, enabling the use of a broader range of amines and allylic substrates.

Scheme 2. Selected examples of allylic amine synthesis through allylic substitution reactions.



2.2 ALLYLIC C-H BOND AMINATION

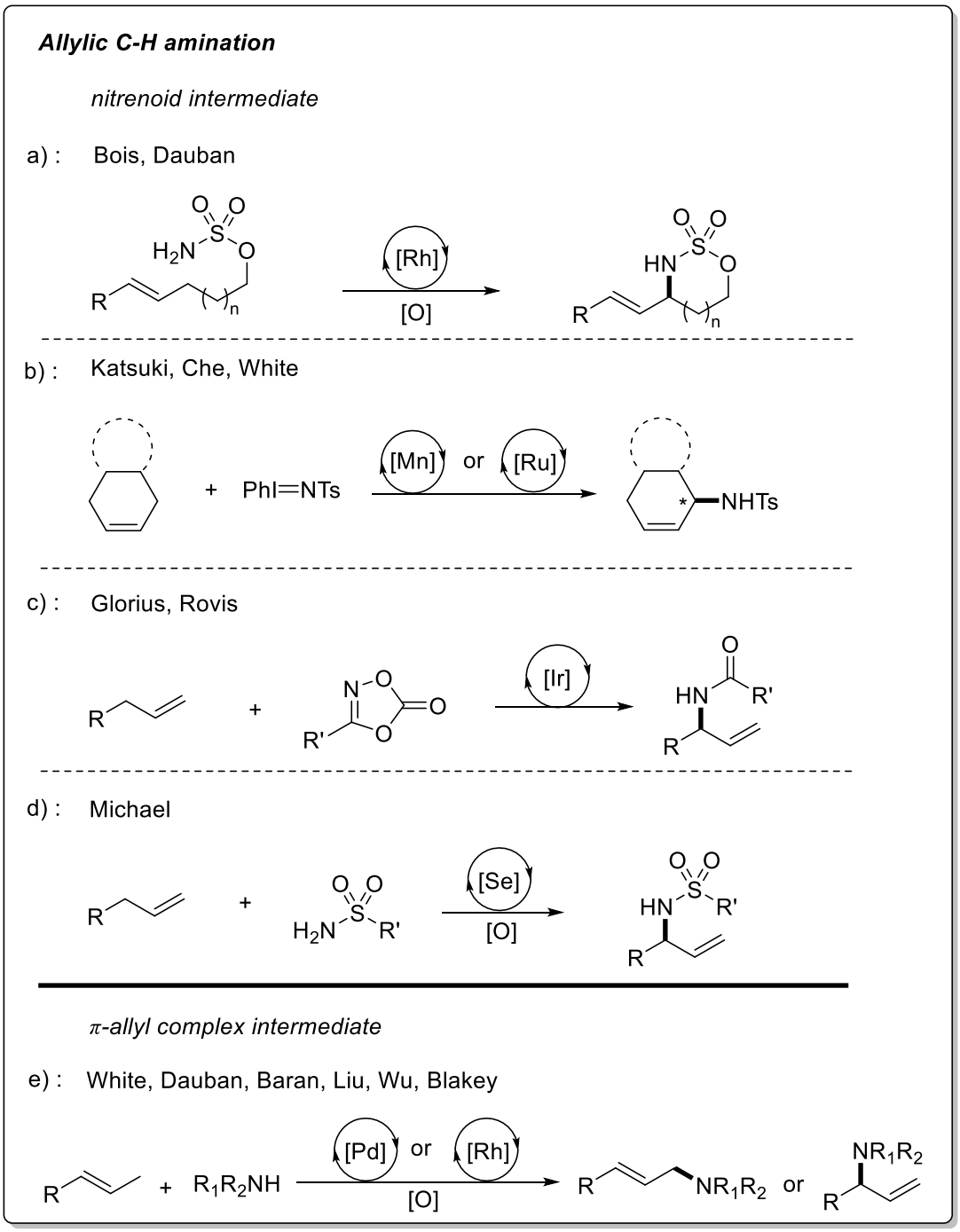
Allylic C-H amination is an efficient synthetic method that circumvents the need for pre-formed allylic substituted precursors, greatly simplifying the synthesis process. In a typical procedure, a transition metal catalyst prompts the formation of a metal nitrenoid from a suitable nitrogen source, such as an azide or a nitrene precursor. This nitrenoid then inserts into the allylic C-H bond, effectively creating the desired C-N bond and producing the allylic amine. Over the past two decades, specific metal-based systems, including manganese, rhodium, ruthenium and iridium, have been developed and optimized to facilitate allylic C-H bond amination (Scheme 3.a-c).[30-35] Innovations in this field have also led to alternative approaches. Notably, the Michael group(there are others as well, you can find them in their paper) has developed an innovative selenium-based, metal-free system for allylic amination. This unique method offers distinct regioselectivity, expanding the synthetic toolbox to allylic amines (Scheme 3.d).[36] Another intriguing method involves the formation of a π-allyl complex. However, this approach varies from the standard Tsuji-Trost reaction. Here, the allylic-non-substituted alkenes form the intermediate via an oxidation process, typically in the presence of palladium or rhodium catalysts. This alternative pathway provides another effective strategy for allylic amine synthesis (Scheme 3.e).[37-42]

Chapter 3. ALLYLIC AMINE SYNTHESIS THROUGH C-C BOND FORMATION

Contrary to C-N bond formation, the synthesis of allylic amines via C-C bond formation typically necessitates an α-electrophilic nitrogen source and a nucleophilic sp^2 hybridized carbon source. This process can be categorized primarily into two main routes. The first involves directly adding

an alkenyl metal species to an imine, while the second route involves a reductive cross-coupling reaction between an alkyne and an imine.

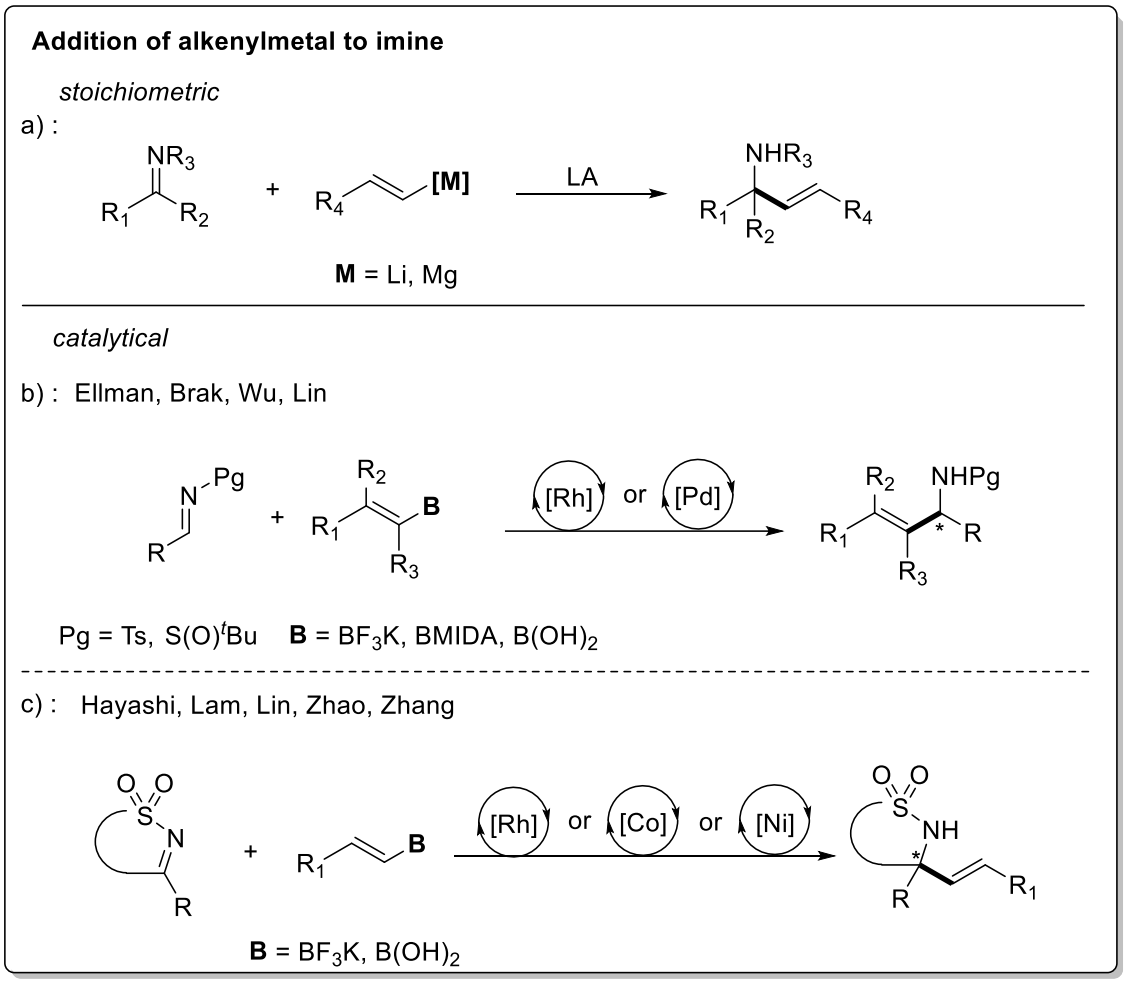
Scheme 3. Selected examples of allylic amine synthesis through allylic C-H bond amination.



3.1 Direct addition of alkenyl metal to imine

Alkenyl metal reagents serve as an excellent nucleophilic source of sp^2 hybridized carbon, which are instrumental in forming carbon-carbon bonds through coupling reactions with various electrophilic counterparts. These reagents are conveniently generated through transmetallation, which involves an exchange between alkenyl halides or tosylates and transition metals such as palladium, nickel, copper, or main group metals like lithium, magnesium, and zinc. The strategic addition of alkenyl metal to imine provides a streamlined and practical approach to the synthesis of allylic amines. During the early 20th century, stoichiometric reactions between alkenyl lithium, Grignard reagents and imine were documented (Scheme 4.a). However, the highly alkaline nature of organolithium or Grignard reagents restricted the scope of these reactions. These issues were addressed by employing a softer metal while maintaining the desired nucleophilicity of the alkenyl metal reagent and making the process catalytical. A breakthrough came with the discovery of arylboronic acids, incredibly versatile organometallic reagents, due to their stability, functional group tolerance, ease of preparation, and wide commercial availability. Despite being weak nucleophiles, arylboronic acids have shown impressive reactivity when catalyzed by rhodium or palladium phosphine complexes in their addition to protected imines (Scheme 4.b).[43-51] Later research revealed that alkenyl boron reagents and transition metal like nickel and cobalt also exhibited this capacity, expanding the synthetic strategy for coupling reactions with imines (Scheme 4.c).[52-57]

Scheme 4. Selected examples of allylic amine synthesis through addition of alkenyl metal to imine.



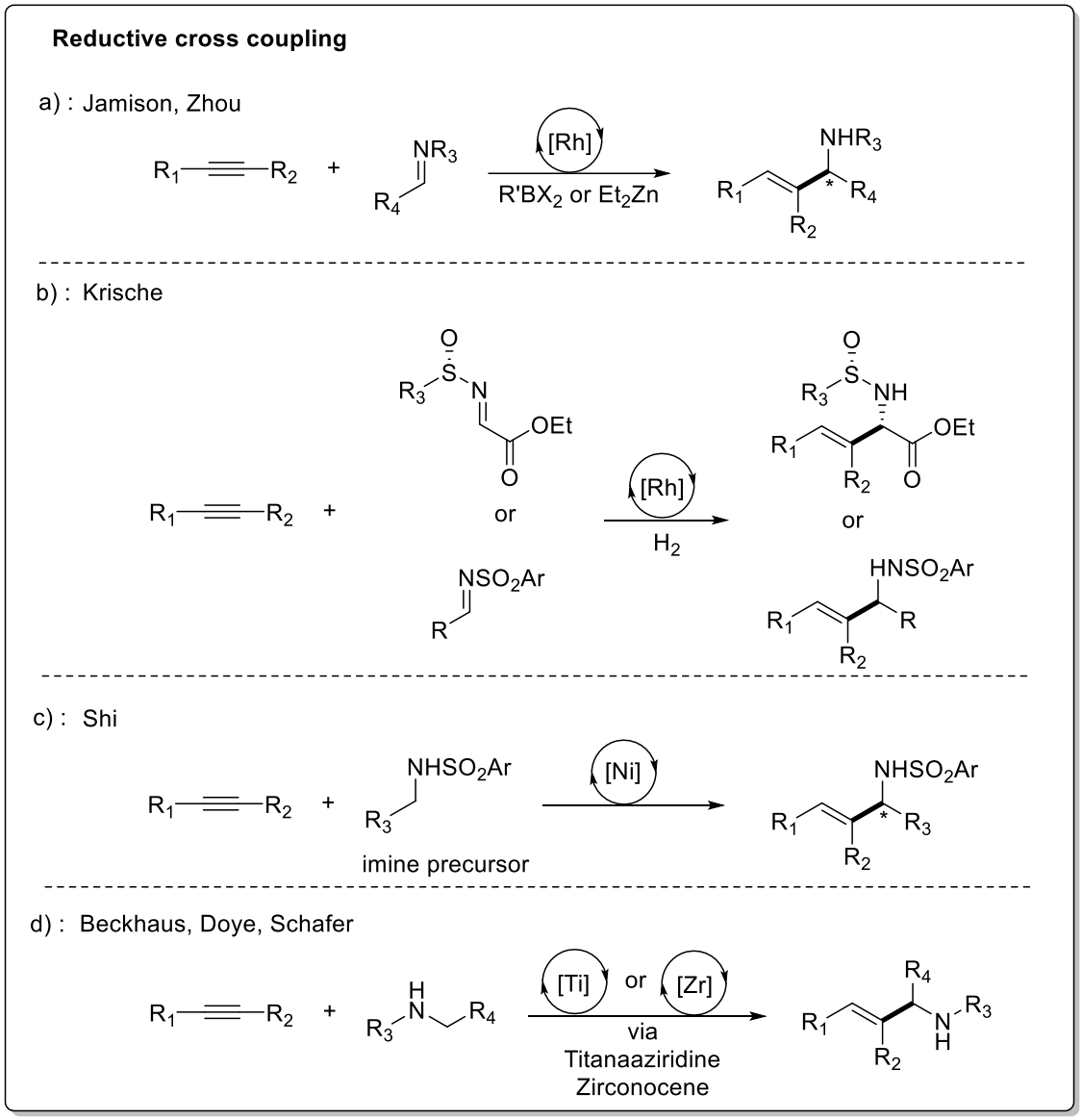
3.2 REDUCTIVE CROSS COUPLING OF ALKYNE WITH IMINE

Alkenyl boron species are usually made from alkynes through hydroboration sometimes encountering regioselectivity and cis-trans selectivity issues. Despite recent advances in allylic amine synthesis, a high regioselective cross-coupling reaction between alkyne and imine that selectively forms E or Z isomer of an allylic amine is desirable. Although hydroalkylation of alkynes using transition metals like nickel, cobalt, copper, silver, gold, rhodium, ruthenium, palladium, and iridium are widely reported,[58-76] the alkylation partner could rarely be imine due to

its lower electrophilicity compared with commonly used electrophiles, such as aldehydes or alkyl halides. In some cases, allylic amine products will even deactivate catalysts. Therefore, the reductive catalytical coupling reaction of alkynes with imines remained challenging until Jamison and his team accomplished the initial pioneering development. They successfully executed the alkylative coupling of disubstituted alkynes, N-alkyl imines, and organoboron reagents, generating allylic amines. The results showed excellent yields, high regioselectivities, and moderate to impressive enantioselectivities. By switching the reductant to alkyl zinc reagents Zhou developed an innovative system of this reductive coupling reaction and afforded allylic amines with high chemoselectivity (Scheme 5.a).[77-79] In 2005, Krische introduced rhodium-catalyzed diastereoselective couplings of 1,3-enynes and 1,3-diynes with ethyl N-sulfinyliminoacetates using H_2 as a reductant. Years later, the same research group developed highly enantioselective iridium-catalyzed reductive coupling of dialkyl-substituted alkynes with N-sulfonyl-imines and rhodium-catalyzed couplings of acetylene and imines (Scheme 5.b).[80-83] In recent years, Shi reported a nickel-catalyzed enantioselective α-alkenylation of N-sulfonyl amines with alkynes affording a wide variety of allylic amines, in which imine is formed in situ (Scheme 5.c).[60] Inspired by Buchwald's pioneering work,[84-85] catalytical hydroaminoalklation of alkynes using zirconium and titanium (through zirconocene or titanaaziridine intermediate) were also reported (Scheme 5.d).[86-87] The alkyne scope in the few reported methods is all internal ones. Because the oxidative addition from the alkyne to metal catalyst forming the alkenyl metal intermediate is the crucial step in these reactions, and internal alkynes are better π electron donors than terminal alkynes, thus, more active in that oxidative addition process. Additionally, the 1,2-disubstituted alkenyl metal intermediates are generally more stable than monosubstituted ones due to the stereo-hindrance that prevent attack from nucleophiles. However, the regioselectivity problem occurs when asymmetric

internal alkynes are used. To circumvent this issue, they used symmetric internal alkynes or alkynes with two functional groups with significantly different electron properties (phenyl, and methyl) on each side of the triple bond. With these restrictions, the alkyne scope becomes limited. So far, the only reported example of allylic amine synthesis from terminal alkynes with anti-Markovnikov selectivity used a stoichiometric amount of zirconium catalyst and alkyl zinc reagent.[88] Overall, catalytic anti-Markovnikov hydroalkylation for making allylic amines remains challenging.

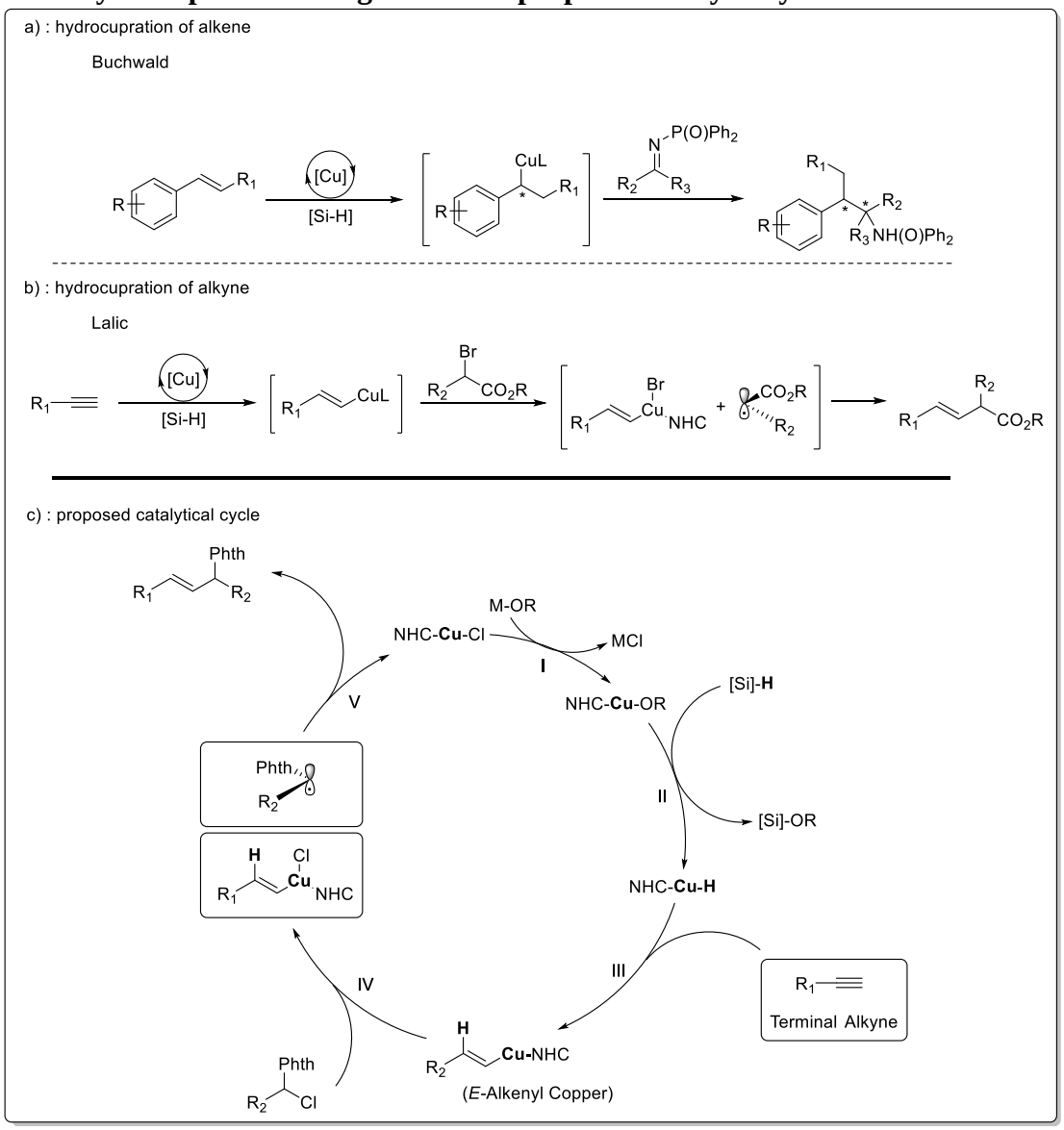
Scheme 5. Selected examples of allylic amine synthesis through reductive cross coupling.



3.3 PROJECT PROPOSAL

Our group has long been studying the hydroalkylation of terminal alkynes through copper hydride mediated transformations . During the past few years, we have developed many differential dihydrofunctionalization reactions with terminal alkynes, enabling the formation of allylic boronate esters, benzylic alkyl boronates, skipped dienes and trisubstituted alkenes in high regio- and stereoselectivity.[89-91] Buchwald group is also interested in discovering new processes and applications catalyzed by copper (I) hydride complexes. They have disclosed many synthetic approaches to various products through hydrocupration followed by an electrophilic functionalization. Their success in amine synthesis with Cu-H complex demonstrates the alkyl copper intermediate can react directly with imines (Scheme 6.a).[92] Inspired by Buchwald's work, we proposed that our alkenyl copper (I) species from hydrocupration of terminal alkynes could lead to regioselective formation of (*E*-) allylic amines. The most straightforward choice of coupling partner with alkenyl copper (I) are imines. Unfortunately, in our preliminary study, imines cannot survive the presence of Cu-H complex, giving mainly the undesired reduced amine products. The alternative electrophile should be a synthon of imines, which provides an electrophilic carbon at the α position to nitrogen. In 2019, our group reported the coupling reaction between terminal alkynes and α-bromo esters through a single electron transfer (SET) process (Scheme 6.b).[93] Therefore, we proposed that α-halo amines could be an ideal substitutive choice of imine and form allylic amine in a SET pathway (Scheme 6.c). This idea was strongly encouraged by Fu's recent work on coupling reactions between alkyl zinc and α-Cl-phthalimide.[94]

Scheme 6. Hydrocupration background and proposed catalytic cycle.

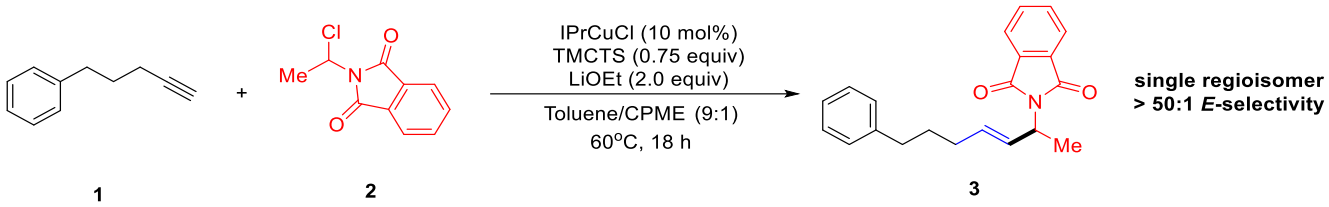


Chapter 4. EXPERIMENTAL SECTION

4.1 REACTION DEVELOPMENT AND OPTIMIZATION

We carried out the preliminary experiments using the conditions developed for the reductive coupling of terminal alkynes with α-bromo esters. Encouragingly, we could obtain a 28 % yield of the desired product **3** with most of the starting materials left. After optimization of reaction conditions, the best results were obtained with IPrCuCl as the catalyst, LiOEt as the turnover reagent and TMCTS as the hydride source. The stoichiometry of alkyne and α-Cl phthalimide are 1.5 equivalent and 1.0 equivalent, respectively. The reaction is performed in a mixture of toluene and CPME (9:1, v:v) at 60 ^{o}C with 10 mol% of catalyst, 75 mol% of TMCTS and 200 mol% of turnover reagent LiOEt. During the reaction conditions optimization, we observed some interesting results listed below (Table 1). SIPrCuCl also gave a good yield of product while other NHC-supported catalysts, such as IMes-supported one failed. The combination of CuCl and various nitrogen ligands also did not work in our reaction system. Silanes with alkoxy ligands worked better than alkyl or phenyl silanes, while the closely related PHMS performed slightly worse than TMCTS. The turnover reagent should precisely be LiOEt. Either switching the cation or the anion significantly lowers the yield. Among all screened solvents, aprotic ones with low polarity worked well, and the optimal solvent combination was toluene: CPME = 9:1. Other ratio of these two or other mixtures resulted in lower yields.

Table 1. reaction development.



1 2 3

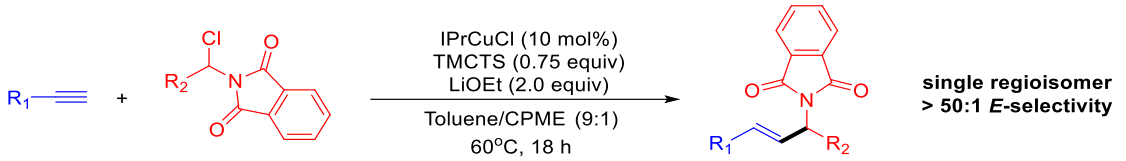
entry	change from standard conditions	yield(%)
1	none	83
2	SIPrCuCl instead of IPrCuCl	80
3	IMesCuCl instead of IPrCuCl	7
4	CuCl + Ligands	<5
5	PHMS instead of TMCTS	73
6	Ph_3SiH instead of TMCTS	41
7	$(EtO)_3SiH$ instead of TMCTS	67
8	NaOEt instead of LiOEt	7
9	KOEt instead of LiOEt	42
10	LiOMe instead of LiOEt	<5
11	toluene instead of toluene/CPME (9:1)	75
12	toluene/CPME (1:1) instead of toluene/CPME (9:1)	56
13	benzene instead of toluene/CPME (9:1)	74

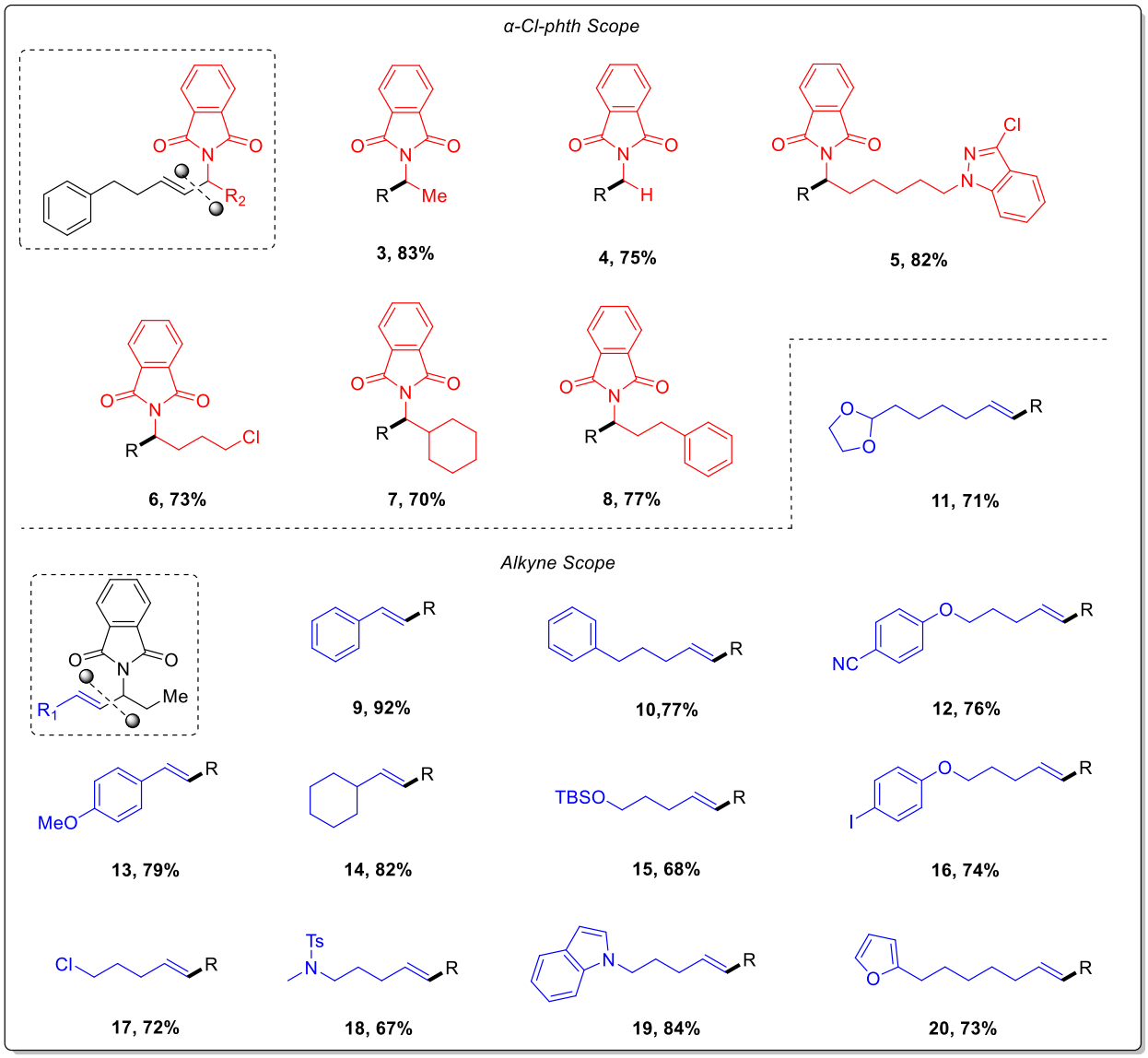
4.2 Substrate scope

Using the optimized reaction conditions, we were able to form a variety of allylic amines with the *E* to *Z* ratio greater than 50 to 1. The substrate scope showed our reaction's good functional group tolerance. The reaction could be accomplished in the presence of protected alcohol (**15**), protected amine (**18**), protected phenol (**13**), chlorides (**6, 17**), iodides (**16**), indole (**19**), furan (**20**) and

chloroindazole (**5**). We found that conjugated alkynes also worked quite well, even if an electron-donating group is involved in the conjugation (**13**). However, an electron-withdrawing group dramatically depressed the yield. The α α'-chloro, aryl phthalimide gave moderate yield, but it decreased if an electron-withdrawing group is introduced at the aryl group.

Table 2. Substrate scope.

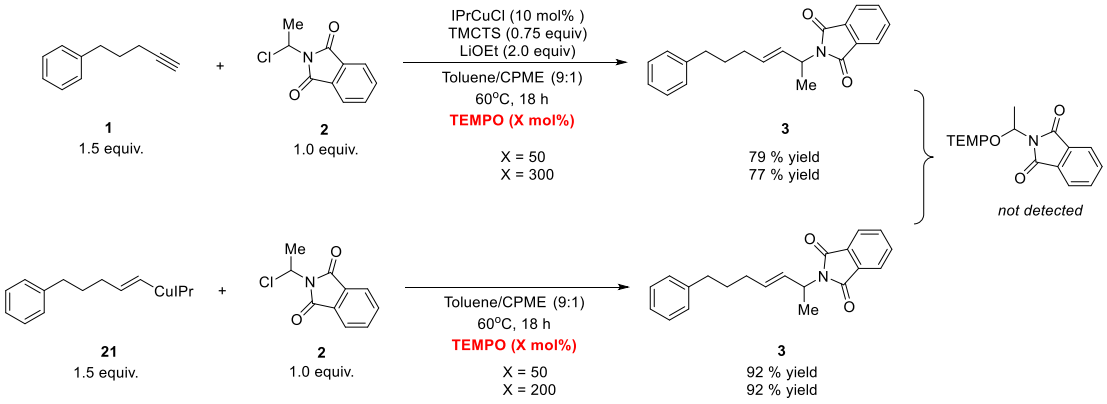




4.3 MECHANISTIC STUDY

We began our mechanistic study with the radical trap experiment. According to our proposed reaction pathway (scheme 6.c), the addition of TEMPO will inhibit the SET process, thus, giving out our product with a much lower yield. Surprisingly, neither the catalytical nor the stoichiometric radical trap experiment showed a significant decrease in yield; even when more than 200 mol% of TEMPO was added. Furthermore, the corresponding TEMPO-radical adduct was not observed on GC-MS.

Scheme 7. Radical probe.



4.4 CONCLUSION

In conclusion, we develop an innovative approach to *E*-allylic amine synthesis based on copper-catalyzed stereoselective reductive cross-coupling between alkynes and α-Cl phthalimide. We demonstrate that the reaction is compatible with various functional groups under mild conditions. and the preliminary mechanistic study shows that the process does not involve the generation of a radical at the α-nitrogen position.

Chapter 5. SUPPLYMENTARY INFORMATION

5.1 General Information

All reactions were performed under a nitrogen atmosphere with flame or oven-dried (120 °C) glassware, using standard Schlenk techniques, or in a glovebox (Nexus II from Vacuum Atmospheres). Column chromatography was performed using a Biotage Iso-1SV flash purification system with silica gel from Agela Technologies Inc. (60Å, 40-60 µm, 230-400 mesh. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum RX I spectrometer. IR peak absorbencies are represented as follows: s = strong, m = medium, w = weak, br = broad. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-300, AV-301 or GG-500 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS and are referenced relative to residual solvent peak ($CDCl_3$ (7.26 ppm), or C_6D_6 (7.16 ppm)). ^{13}C chemical shifts are reported in parts per million downfield of TMS and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.2 ppm, C_6D_6: δ 128.1 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hept = heptet, m = multiplet), integration, and coupling constants in Hertz (Hz). GC analysis was performed on a Shimadzu GC-2010 instrument with a flame ionization detector and a SHRXI-5MS column (15 m, 0.25 mm inner diameter, 0.25 µm film thickness). The following temperature program was used: 2 min @ 60 °C, 13 °C/min to 160 °C, 30 °C/min to 250 °C, 5.5 min @ 250 °C.

Materials: THF, CH_2Cl_2, acetonitrile, DMF, and toluene were degassed and dried by passing through columns of neutral alumina. 1,4-dioxane was distilled over calcium hydride, degassed, and stored over 3Å (1-2 mm beads) molecular sieves. Isooctane, chlorobenzene, DCE and heptane were degassed and stored over 3Å (1-2 mm beads) molecular sieves. Deuterated solvents were

purchased from Cambridge Isotope Laboratories, Inc. and used as received. Commercial reagents were purchased from Sigma-Aldrich, TCI America, GFS-Chemicals, and AK-Scientific. NHC ligands were synthesized using known procedures. All commercial alkynes were distilled over $NaBH_4$ and stored over 3Å (1-2 mm beads) molecular sieves.

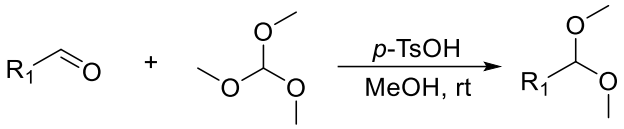
5.2 STARTING MATERIALS, CATALYSTS AND STANDARD PRODUCT SYNTHESIS

5.2.1 Reaction conditions optimization General procedures

General procedure A (hydroalkylation):

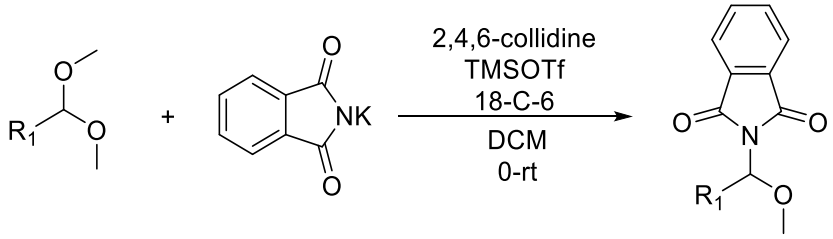
In a nitrogen-filled glovebox, a 20 mL scintillation vial was charged with IPrCuCl (0.05 mmol, 0.1 equiv.), LiOEt (1 mmol, 2.0 equiv.) and a stir bar. To the vial was added cyclopentyl methyl ether (CPME) and toluene (v:v = 1:9, 0.1 M). Then 2，4，6，8-tetramethylcyclotetrasiloxane (TMCTS) (0.325 mmol, 0.75 equiv.) was added. A bright yellow color was immediately observed. Alkyne (0.75 mmol, 1.5 equiv.) was then added, and the mixture was stirred at room temperature until the yellow color disappeared. α-Cl-phthalimide (0.5 mmol, 1.0 equiv.) was then added and the reaction mixture was stirred at 60 ^{o}C overnight. After reaction completion, the vial was brought out of the glovebox and opened. The reaction mixture was passed through a plug of Celite and the Celite cake was washed with 100 mL EtOAc. Filtrate was concentrated, and loaded onto an alumina flash chromatography column (neutral, Brockman I). The column was flushed with ten to fifteen column volumes of hexanes for silane removal before the product was eluted with a Hexanes/EtOAc mixture.

General procedure B (acetalization):



A flame dried 20 mL scintillation vial was charged with aldehyde (1.0 equiv.) and astir bar. Then, methanol (1 M) was added to the mixture, followed by trimethyl orthoformate (1.5 equiv.). To the mixture, *p*-toluenesulfonic acid mono hydride (0.01 equiv.) was added. The resulting reaction mixture was stirred at room temperature overnight. Upon reaction completion, the reaction mixture was transferred into a separatory funnel, 50 mL Et_2O was added, and the organic phase was washed with 30 mL water three times, dried over $MgSO_4$. Upon the removal of the solvent under the reduced pressure, the crude product was used directly in the next step.

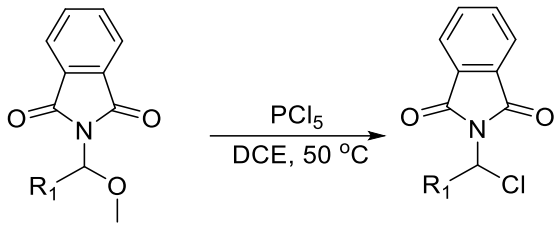
General procedure C (α-methoxyl phthalimide formation):



A flame fried Schlenk flask was charged with acetal (1.0 equiv.) and a stir bar. Anhydrous DCM was added to the flask (0.3 M) followed by the addition of 2,4,6-trimethylpyridine (3.0 equiv.). Then the mixture was cooled to 0 ^oC in the ice bath, and trimethylsilyl triflate (2.0 equiv.) was added dropwise to the solution. The reaction mixture was then stirred at 0 ^oC for 30 minutes, and potassium phthalimide (3.0 equiv.), 18-crowm-6 (3.0 equiv.) were added in one portion to the mixture. Upon addition, the reaction mixture was stirred at room temperature overnight. The reaction was diluted with DCM and quenched with 2 M hydrochloric acid. The organic phase was separated and aqueous phase was extracted with DCM three times. The combined organic phase

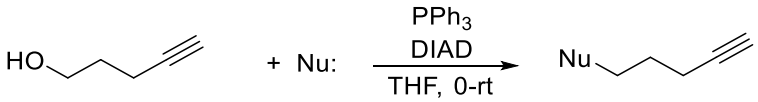
was then washed with brine twice and dried over $MgSO_4$. The reaction mixture was loaded onto a silica gel chromatography column after the removal of solvent, and 0-15% EtOAc in hexanes mixture was used to elute product.

General procedure D (α-Cl-phthalimide formation):



A flame dried round bottom flask was charged with α-methoxyl phthalimide (1.0 equiv.) and a stir bar followed by the addition of 1,2-dichloroethane (1 M). The mixture was stirred at room temperature until it become homogenous. Phosphorus pentachloride (1.5 equiv.) was added and the reaction mixture was stirred at 50 °C overnight. The reaction mixture was cooled down to room temperature and diluted with DCM. Saturated sodium bicarbonate solution was then added to the mixture, and the solution was stirred vigorously until no bubbles were forming. The aqueous phase was extracted with DCM twice and the combined organic phase was washed with brine twice and dried over $MgSO_4$. After the removal of solvent, the crude product was further purified via recrystallization or column chromatography.

General procedure E (alkyne synthesis):



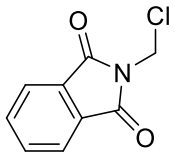
Nu: = substituded phenol or protected amine

To a flame dried Schlenk flask equipped with a stir bar, PPh_3 (1.2 equiv.), nucleophile (1.0 equiv.), 4-pentyn-1-ol (1.0 equiv.) and anhydrous THF (0.6 M) were added. The mixture was cooled to 0 °C through ice bath. Then DIAD (1.2 equiv.) was added dropwise. The reaction mixture was stirred

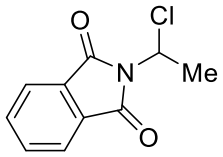
at room temperature overnight. Upon conversion of the starting material, solvent was removed under vacuum. The reside was suspended in hexanes and stirred vigorously for 30 minutes, filtered through celite and the filtrate was concentrated. The crude product was purified via flash silica gel column chromatography.

5.2.2 α-Cl-phthalimide starting materials synthesis

All synthesized products match the reported ^{1}H NMR.[94]

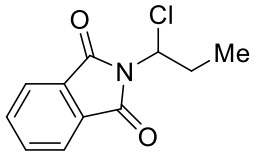


2-(chloromethyl)isoindoline-1,3-dione (S1), was purchased from Combi-Blocks and was used directly without further purification.

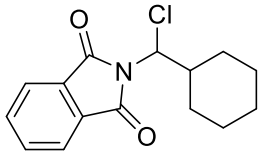


2-(1-chloroethyl)isoindoline-1,3-dione (2):

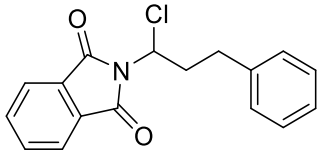
To a round bottom flask, 2-vinylisoindoline-1,3-dione (1.0 equiv.) was added, followed by the addition of HCl (4 M solution in dioxane, 4.0 equiv.). The reaction mixture was stirred at room temperature for 3 hours. Then, the solvent was removed under vacuum and the crude product was purified via recrystallization.



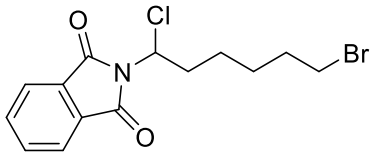
2-(1-chloropropyl)isoindoline-1,3-dione (S2), was synthesized according to General procedure C, D, from 1,1-dimethoxypropane.



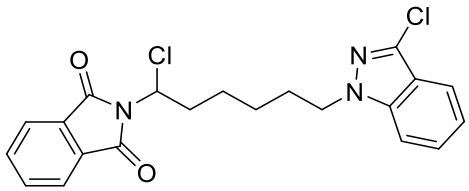
2-(chloro(cyclohexyl)methyl)isoindoline-1,3-dione (S3), was synthesized according to General procedure B ,C, D from cyclohexanecarbaldehyde.



2-(1-chloro-3-phenylpropyl)isoindoline-1,3-dione (S4), was synthesized according to General procedure B,C,D from 3-phenylpropanal.



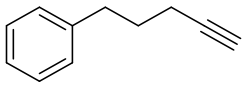
2-(6-bromo-1-chlorohexyl)isoindoline-1,3-dione (S5), was synthesized according to General procedure B, C, D from 6-bromohexanal.



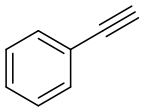
2-(1-chloro-6-(3-chloro-1H-indazol-1-yl)hexyl)isoindoline-1,3-dione (S6), was synthesized according to General procedure B,C from, 6-bromohexanal. Then to a round bottom flask, 2-(6-bromo-1-methoxyhexyl) isoindoline-1,3-dione (1.0 equiv.), 3-chloro-1H-indazole (1.2 equiv.), K_2CO_3 (1.3 equiv.) and DMF (1 M). The reaction mixture was heated to 50 ^oC and stirred overnight. Then the reaction mixture was cooled to room temperature and H_2O was added. The mixture was extracted with EtOAc three times. The combined organic phase was washed with brine and dried over $MgSO_4$. The crude product was purified via flash silica gel column chromatography. Then final product was obtained followed General procedure D.

5.2.3 Alkyne starting materials synthesis

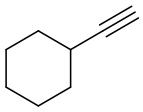
All synthesized products match reported ^1H NMR.[93]



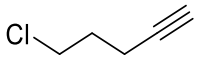
5-phenyl-1-pentyne (1), was purchased from Combi-Blocks, and was distilled over calcium hydride before use.



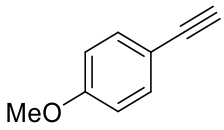
ethynylbenzene (S7), was purchased from Combi-Blocks, and was distilled over calcium hydride before use.



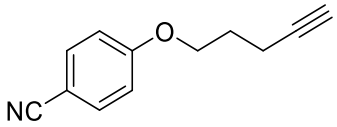
ethynylcyclohexane (S8), was purchased from Combi-Blocks, and was distilled over calcium hydride before use.



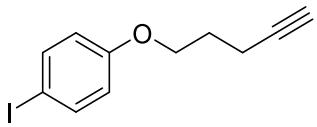
5-chloro-1-pentyne (S9), was purchased from Combi-Blocks, and was distilled over calcium hydride before use.



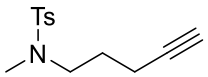
1-ethynyl-4-methoxybenzene (S10), was purchased from Combi-Blocks, and was used directly without further purification.



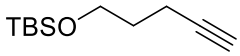
4-(pent-4-yn-1-yloxy)benzonitrile (S11), was synthesized according to General procedure E from 4-hydroxybenzonitrile.



1-iodo-4-(pent-4-yn-1-yloxy)benzene (S12), was synthesized according to General procedure E from 4-iodophenol.

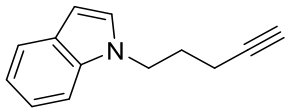


N,4-dimethyl-N-(pent-4-yn-1-yl)benzenesulfonamide (S13), was synthesized according to General procedure E from N,4-dimethylbenzenesulfonamide.



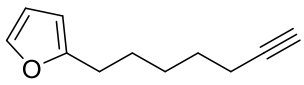
tert-butyldimethyl(pent-4-yn-1-yloxy)silane (S14)

To a round bottom flask, pent-4-yn-1-ol (1.0 equiv.), and DCM (0.2 M) were added. The mixture was cooled to 0^{o}C in the ice bath. Imidazole (1.2 equiv.) was then added to the mixture followed by the dropwise addition of TBSCl (1.2 equiv. pre-dissolved in DCM). The reaction mixture was stirred at room temperature overnight. Upon completion, the reaction was quenched with H_2O and extracted with DCM three times. The combined organic phase was washed with brine and concentrated under vacuum. Crude product was purified via flash silica gel column chromatography.



1-(pent-4-yn-1-yl)-1H-indole (S15):

To a round bottom flask, indole (1.0 equiv.), KOH (1.3 equiv.) and DMF (0.5 M) were added. The mixture was stirred at room temperature for 15 minutes. Then 5-chloro-1-pentyne (1.1 equiv.) was added. The reaction mixture was heated to 50 ^{o}C and stirred overnight. Upon fully conversion of indole, H_2O was added to the reaction mixture and the mixture was extracted with Et_2O three times. The combined organic phase was washed with brine twice and dried over $MgSO_4$. The product was purified by flash silica gel column chromatography.



2-(hept-6-yn-1-yl)furan (S16):

Preparation of 7-(trimethylsilyl)hept-6-yn-1-ol:

To a flame dried Schlenk flask, hept-6-yn-1-ol (1.0 equiv.) and anhydrous THF (0.4 M) were added. The solution was cooled to -78 ^{o}C through dry ice-acetone bath, and nBuLi (2.5 M solution in hexanes, 2.0 equiv.) was added dropwise. The mixture was stirred at -78 ^{o}C for 1 hour and TMSCl (3.0 equiv.) was added slowly. Then the reaction mixture was warmed to room temperature and stirred overnight. Upon completion, the reaction mixture was cooled to 0 ^{o}C through ice bath and quenched with HCl (1 M solution in H_2O), stirred until no bis silylated product exist. The mixture was extracted with Et_2O three times and the combined organic phase was washed with brine, dried over $MgSO_4$. The product was purified by flash silica gel column chromatography.

Preparation of (7-bromohept-1-yn-1-yl) trimethylsilane:

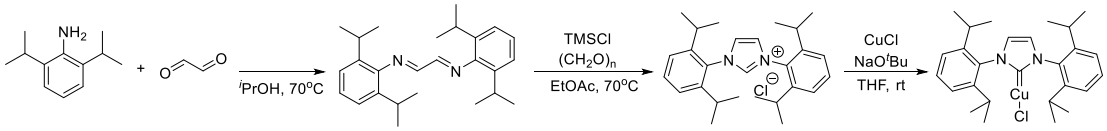
To a flame dried Schlenk flask, 7-(trimethylsilyl)hept-6-yn-1-ol (1.0 equiv.), PPh_3 (1.2 equiv.) and DCM (0.4 M) were added. The mixture was cooled to -30^{o} C using dry ice-acetone bath. Then, NBS was added slowly and the mixture was warmed to room temperature and stirred overnight. Upon completion, the mixture was diluted with Et_2O and washed with saturated $NaHCO_3$ solution twice, and brine once. Organic phase was then dried over $MgSO_4$. After removal of the solvent, the residue was suspended in hexanes and stirred vigorously for 30 minutes. Then, the mixture was filtered through celite and concentrated under vacuum. The product was purified by flash silica gel column chromatography.

Synthesis of 2-(hept-6-yn-1-yl)furan:

To a flame dried Schlenk flask, furan (3.5 equiv.) and anhydrous THF (1 M) were added. The solution was cooled to 0 ^{o}C in the ice bath. Then nBuLi (2.5 M solution in hexanes, 3.0 equiv.) was added dropwise. The mixture was stirred at 0^{o}C for 1 hour, followed by the slowly addition of (7-bromohept-1-yn-1-yl) trimethylsilane. The reaction mixture was then stirred at room temperature overnight. Then, the reaction was quenched with saturated NH_4Cl solution and extracted with Et_2O three times. The combined organic phase was washed with brine twice and dried over $MgSO_4$. The product was purified by flash silica gel column chromatography.

5.2.4 Copper catalysts synthesis

All synthesized products match the reported ^{1}H NMR.[93]



IPrCuCl synthesis:

Synthesis of *N*^{1},*N*^{2}-bis(2,6-diisopropylphenyl)ethane-1,2-diimine:

To a round bottom flask, 2,6-diisopropyl aniline (1.0 equiv.) and ^{i}PrOH (1 M) were added, followed by the addition of glyoxal (40 wt% in H_2O, 1.2 equiv.). The reaction mixture was heated to 70 ^{o}C for 3 hours. Then the mixture was cooled through dry ice- acetone bath to precipitate product. Precipitate was filtered and washed with cooled ^{i}PrOH three times and dried under high vacuum.

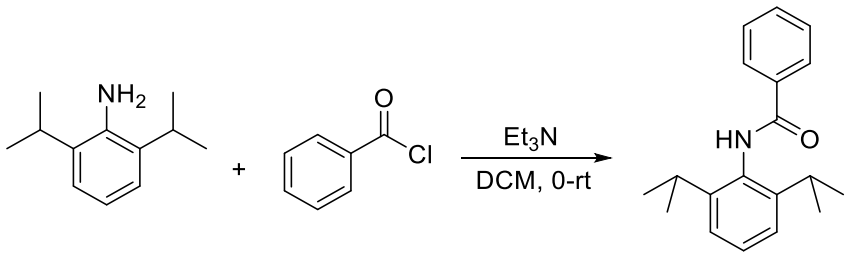
Synthesis of 1*H*-Imidazolium, 1,3-bis[2,6-bis(1-methylethyl)phenyl]-, chloride

To a round bottom flask, diamine (1.0 equiv.), polyoxymethylene (1.0 equiv.) and EtOAc (0.25 M) were added. The mixture was stirred at room temperature and TMSCl was added dropwise. Upon addition, the reaction mixture was heated to reflux for 3 hours. Then the mixture was cooled down to room temperature and filtered through filter funnel. Filtrate was washed with cooled EtOAc and Et_2O three times and dried under high vacuum overnight.

Synthesis of (1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene) copper(I) chloride:

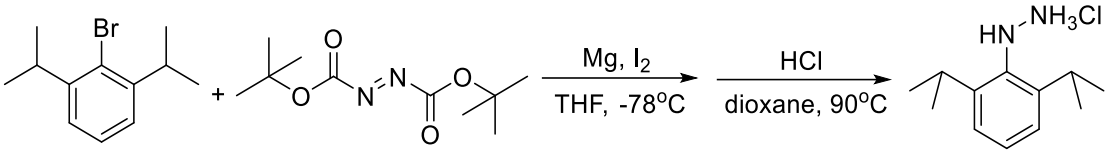
In a nitrogen filled glovebox, a scintillation vial was charged with NHC-HCl (1.0 equiv.), CuCl (1.01 equiv.) and anhydrous THF (0.075 M). Then NaO^{t}Bu (1.01 equiv.) was weighted out in a shell vial and dissolved in anhydrous THF (0.075 M). The NaO^{t}Bu solution was added to the reaction mixture dropwise over 5 minutes. Upon addition, the reaction mixture was stirred at room temperature for 3 hours. Then THF was removed under high vacuum, and the reside was dissolved in a minimal amount of DCM. The product was precipitated with large excessive amount of pentane, filtered, washed with pentane and dried under high vacuum. The ^{1}H NMR matches the reported.

TriCuCl synthesis:



Synthesis of N-(2,6-diisopropylphenyl) benzamide:

To a round bottom flask, 2,6-diisopropylaniline (1.0 equiv.), triethylamine (1.5 equiv.) and DCM (0.2 M) were added. The mixture was cooled to 0 ^{o}C through ice bath and benzoyl chloride was added dropwise to the mixture over 5 minutes. The reaction mixture was stirred at room temperature overnight. Upon full conversion of starting material, the reaction was quenched with brine. The mixture was extracted with DCM three times, and the combined organic phase was washed with brine. Crude product was purified by recrystallization.



Synthesis of 2,6-diisopropylphenylhydrazine hydrochloride:

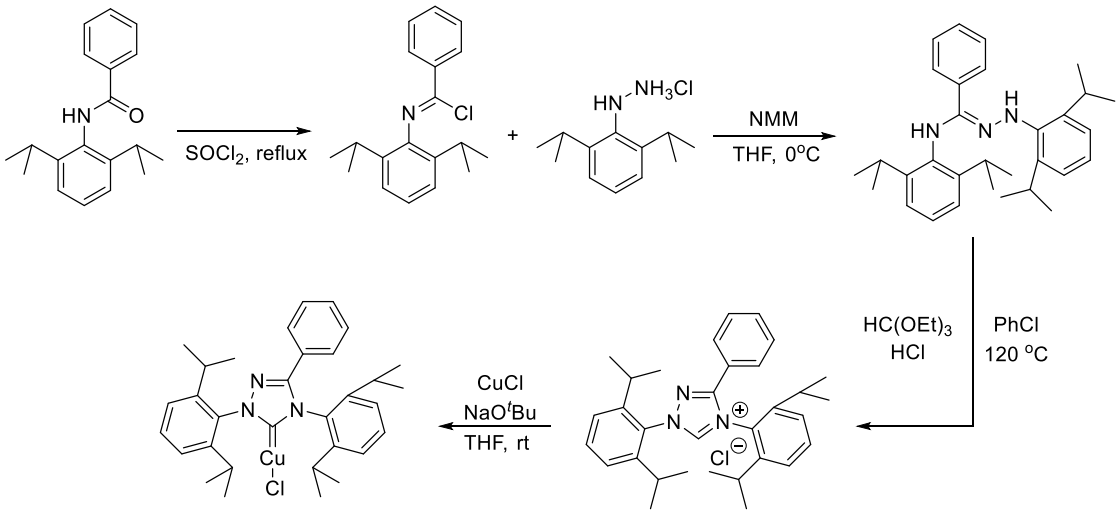
Grignard Reagent preparation:

To a flame dried Schlenk flask, Mg (3.0 equiv.) I_2 crystal (catalytical amount) and anhydrous THF (0.6 M) were added. Then a small portion of 2-bromo-1,3-diisopropylbenzene was added to initialize the reaction. Then the remaining 2-bromo-1,3-diisopropylbenzene (1.0 equiv.) was added. The reaction mixture was stirred at 70 ^{o}C for 3 hours and cooled down to room temperature.

A flame dried Schlenk flask was charged with DBAD (1.0 equiv.) and anhydrous THF (0.3 M). The solution was cooled down to -78 ^{o}C through dry ice-acetone bath. The premade Grignard reagent was then added dropwise to the reaction mixture through cannula. The mixture was stirred at -78 ^{o}C for 1 hour, quenched with acetic acid and warmed up to room temperature. H_2O was added to the reaction mixture and the mixture was extracted with Et_2O three times. The combined organic phase was then washed with brine twice and dried over $MgSO_4$. After the removal of solvent, ^{i}PrOH and HCl (4 M solution in dioxane) were added to the residue, the mixture was

heated to 90 °C and stirred for 30 minutes. Then the reaction mixture was cooled down to -20 °C (kept in a freezer) and Et_2O was added to precipitate product. Precipitant was filtered and washed with cooled Et_2O.

Synthesis of TriCuCl:



N-(2,6-diisopropylphenyl) benzimidoyl chloride preparation:

To a flame dried round bottom flask, N-(2,6-diisopropylphenyl) benzamide (1.0 equiv.) and $SOCl_2$ (2.5 M) were added. The reaction mixture was stirred under reflux for 3 hours. Then the excessive $SOCl_2$ was removed through vacuum distillation. The crude product was used directly into next step without further purification. The ^1H NMR matches the reported.

N,N'-bis(2,6-diisopropylphenyl)benzohydrazonamide preparation:

To a flame dried round bottom flask, 2,6-diisopropylphenylhydrazine hydrochloride (1.0 equiv.) and anhydrous THF (0.15 M) were added. Crude product from last step was dissolved in anhydrous THF and transferred to the reaction mixture. The mixture was then cooled to 0°C through ice bath and 4-Methylmorpholine (1.05 equiv.) was added dropwise. The mixture was stirred at 0 °C for 3

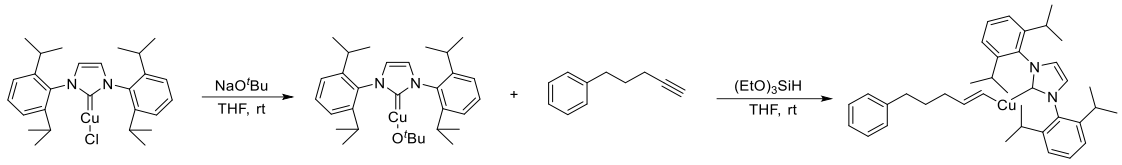
hours before warming to room temperature and stirred overnight. H_2O was added to the mixture upon reaction completion. The reaction mixture was extracted with DCM three times and the combined organic phase was washed with brine and dried over $MgSO_4$. The crude product was obtained after the removal of solvent, and was used directly into next step without further purification.

To a round bottom flask, crude N,N'-bis(2,6-diisopropylphenyl)benzohydrazonamide (1.0 equiv.) and chlorobenzene (0.25 M), HCl (4 M solution in dioxane, 10 equiv.) and triethyl orthoformate (6 equiv.) were added. The reaction mixture was stirred under reflux for 2 hours. Then the solvent was removed under vacuum and the residue was filtered and washed with pentane and EtOAc.

Synthesis of (2,4-bis(2,6-diisopropylphenyl)-5-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-ylidene) copper(I) chloride:

In a nitrogen filled glovebox, a scintillation vial was charged with NHC-HCl (1.0 equiv.), CuCl (1.01 equiv.) and anhydrous THF (0.075 M). Then NaO^tBu (1.01 equiv.) was weighted out in a shell vial and dissolved in anhydrous THF (0.075 M). The NaO^tBu solution was added to the reaction mixture dropwise over 5 minutes. Upon addition, the reaction mixture was stirred at room temperature for 3 hours. Then THF was removed under high vacuum, and the reside was dissolved in a minimal amount of DCM. The product was precipitated with large excessive amount of pentane, filtered, washed with pentane and dried under high vacuum.

Alkenyl copper synthesis:



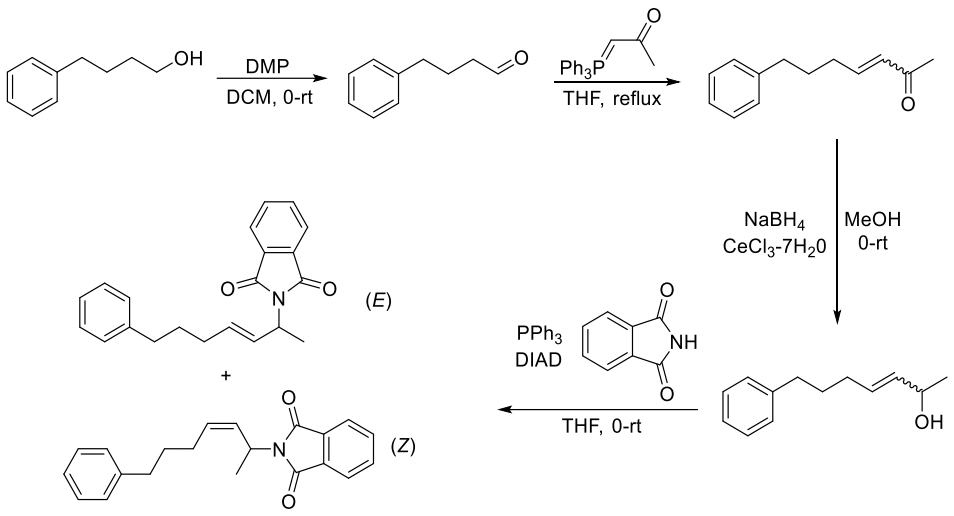
Preparation of IPrCuO^{t}Bu:

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, IPrCuCl (1.0 equiv.), and anhydrous THF (0.2 M). Then NaO^{t}Bu (1.1 equiv.) was weighted out and dissolved with THF (0.2 M) in a shell vial. The NaO^{t}Bu solution was transferred into the reaction mixture dropwise, and the reaction mixture was stirred at room temperature overnight. Upon the completion of the reaction, THF was removed under high vacuum and the residue was dissolved in large excess amount of toluene, filtered through a plug of celite. Filtrate was concentrated under high vacuum and redissolved in minimize amount of DCM followed by large excess of pentane. After precipitation, product was filtered and washed with pentane twice and vacuum dried overnight.

Synthesis of alkenyl copper (21):

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, IPrCuO^{t}Bu (1.0 equiv.), and anhydrous THF (0.2 M). Then triethoxyl silane stock solution (0.2 M in THF, 1.0 equiv.) was added dropwise. The reaction mixture turned yellow immediately after the addition of silane. 5-phenyl-1-pentyne (0.2 M in THF, 1.0 equiv.) was then added dropwise to the reaction mixture, and the mixture was stirred at room temperature until yellow color disappeared. Solvent was removed under high vacuum and residue was dissolved in minimize amount of DCM followed by the addition of large excess of pentane. The mixture was kept in a -25 ^{o}C freezer overnight. After precipitation, product was filtered and washed with cooled pentane twice and vacuum dried overnight.

5.2.5 Standard product synthesis and NMR, GC analysis



Synthesis of Benzenebutanal:

A round bottom flask was charged with a stir bar and benzenebutanol (1.0 equiv.), DCM was then added (0.2 M) and the mixture was cooled down to 0 ^{o}C through ice bath. Then Dess-Martin periodinane (1.5 equiv.) was added in three portions. The reaction mixture was then stirred at room temperature overnight. Upon completion, the mixture was cooled down to 0 ^{o}C through ice bath and filtered through celite. Celite cake was washed with DCM three times. Then saturated sodium bicarbonate solution (mixed with 2.5wt% sodium thiosulfate) was then added to the reaction mixture and the mixture was stirred vigorously for 1 hour. The aqueous phase was extracted with DCM twice and the combined organic phase was washed with brine twice, dried over $MgSO_4$. The mixture was purified by flash silica column chromatography with 20% Et_2O in Pentane.

Synthesis of 7-phenylhept-3-en-2-one:

A flame dried Schlenk flask was filled with nitrogen, charged with a stir bar and benzenebutanal (1.0 equiv.). Anhydrous THF (0.2 M) was then added to the flask followed by the addition of 1-(triphenylphosphoranylidene)-2-propanone (1.05 equiv.). The reaction mixture was heated to reflux overnight. After reaction, the mixture was cooled down to room temperature, and solvent was removed under vacuum. Hexanes was added to the residue and the mixture was stirred vigorously for 30 minutes. Then the mixture was filtered through celite. The crude product was purified by flash silica column chromatography with 10% EtOAc in Hexanes.

Synthesis of 7-phenylhept-3-en-2-ol:

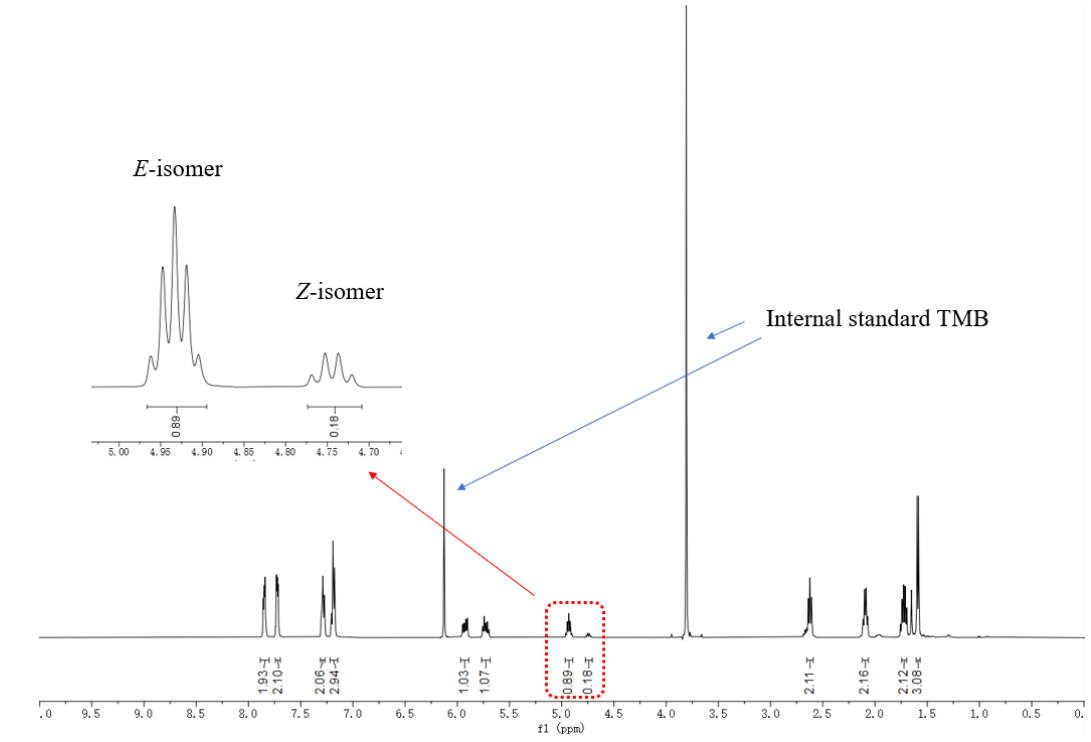
A round bottom flask was charged with a stir bar and 7-phenylhept-3-en-2-one (1.0 equiv.). Methanol (1 M) was then added to the flask, and the mixture was cooled to 0 ^{o}C through ice bath. $CeCl_3$-$7H_2O$ (1.0 equiv.) and $NaBH_4$ (1.0 equiv.) was then added to the mixture, and the reaction mixture was stirred at room temperature for 10 minutes. The reaction was quenched with saturated NH_4Cl solution and extracted with Et_2O three times. The combined organic phase was washed with brine twice and dried over $MgSO_4$. The crude product was purified by flash silica column chromatography with 20% Et_2O in Pentane.

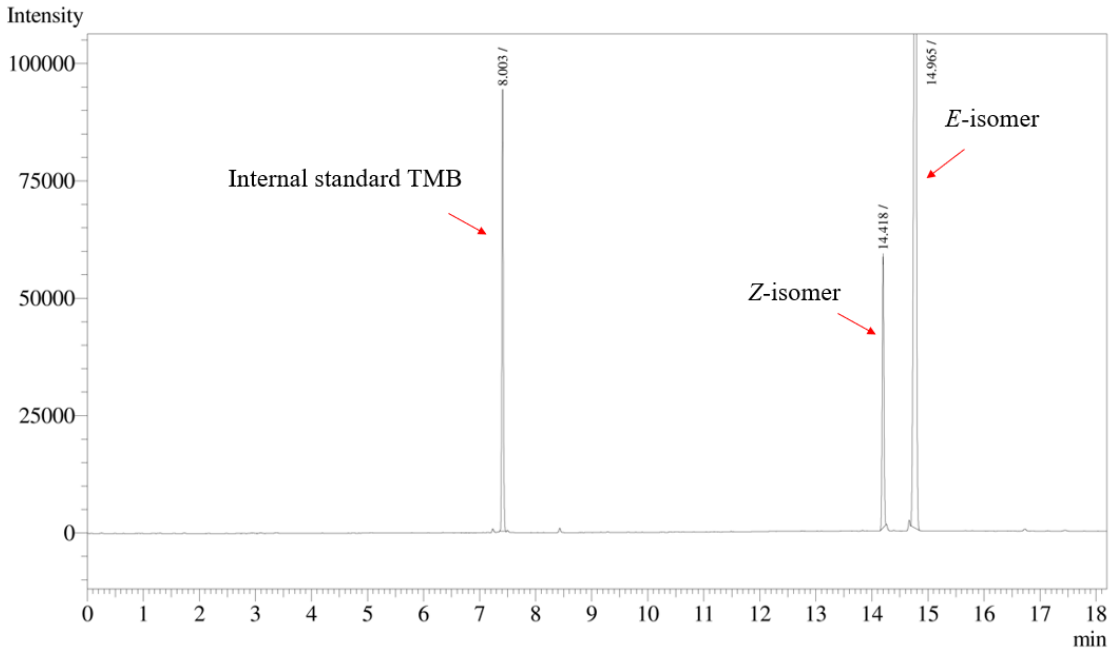
Synthesis of 2-(7-phenylhept-3-en-2-yl) isoindoline-1,3-dione:

A flame dried Schlenk flask was charged with a stir bar, 7-phenylhept-3-en-2-ol (1.0 equiv.), PPh_3 (1.2 equiv.), phthalimide (1.0 equiv.) and anhydrous THF (0.5 M). The mixture was them cooled down to 0 ^{o}C through ice bath, and DIAD (1.2 equiv.) was added dropwise to the mixture. After addition, the reaction mixture was stirred at room temperature overnight. After reaction, the

solvent was removed under vacuum. Hexanes was added to the residue and the mixture was stirred vigorously for 30 minutes. Then the mixture was filtered through celite. The mixture was purified by flash silica column chromatography with 10% EtOAc in Hexanes.

Scheme 7. NMR spectrum and GC spectrum of standard product and its Z-isomer.

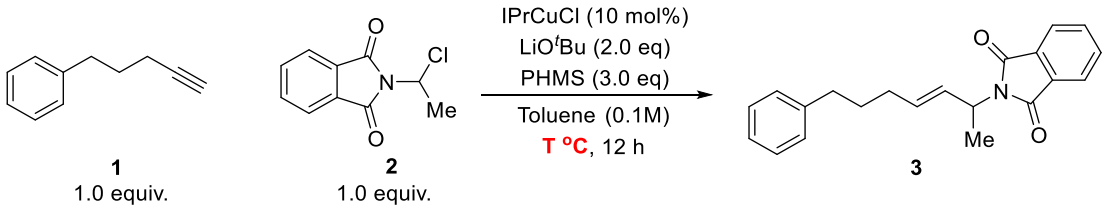




5.3 REACTION CONDITIONS OPTIMIZATION

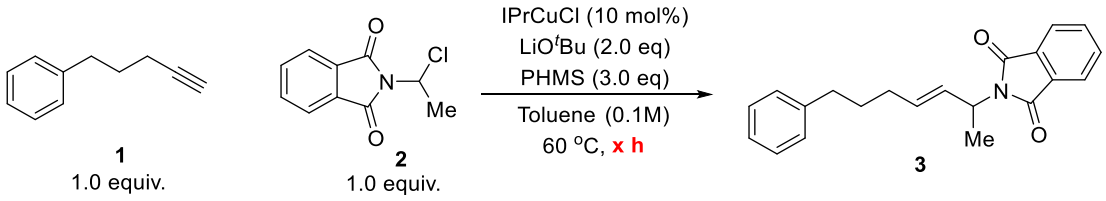
All the reactions shown in table S1 to table S13 were performed on a 0.1 mmol scale. In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, copper catalyst, base, solvent, silane, alkyne respectively. The reaction mixture was stirred at room temperature until the yellow color disappeared. Then, α-Cl-phthalimide was added, and the reaction mixture was stirred at the indicated temperature for indicated time. Silane, alkyne and α-Cl-phthalimide were prepared in stock solutions with internal standard trimethoxybenzene (TMB) in either alkyne stock solution or α-Cl-phthalimide stock solution.

Table S1: Temperature screen



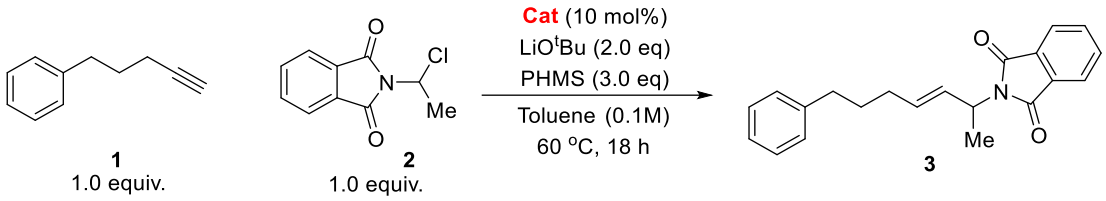
Entry	Temperature °C	Yield (%)
1	23	21
2	45	28
3	60	36

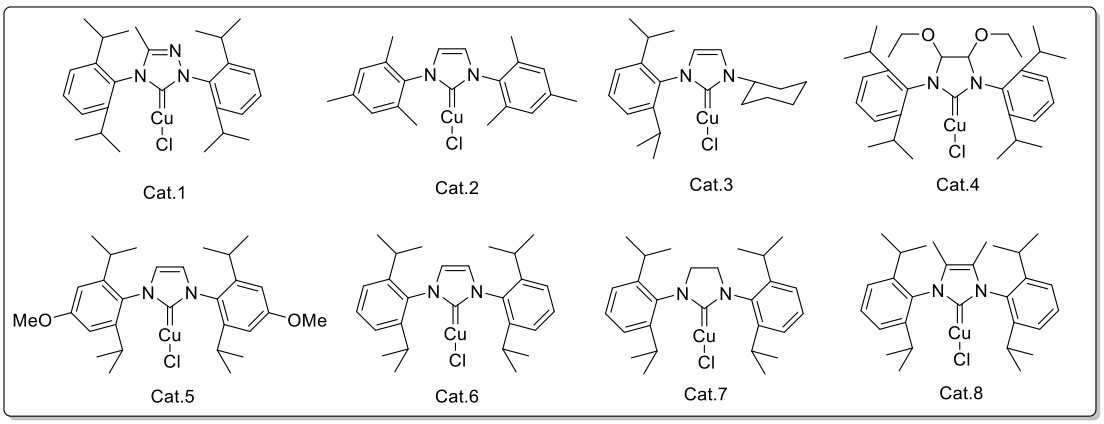
Table S2: Reaction time screen



Entry	Reaction time (h)	Yield (%)
1	12	36
2	18	39
3	24	39
4	48	39

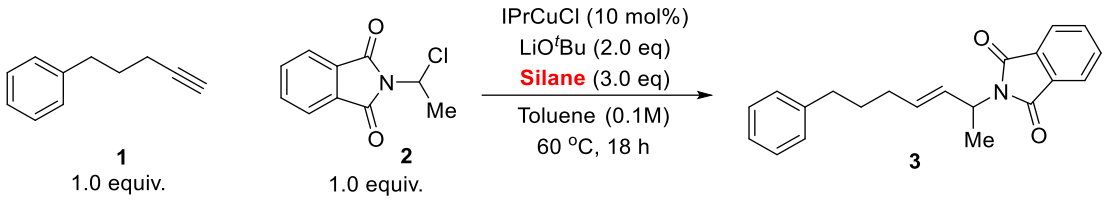
Table S3: Catalyst screen





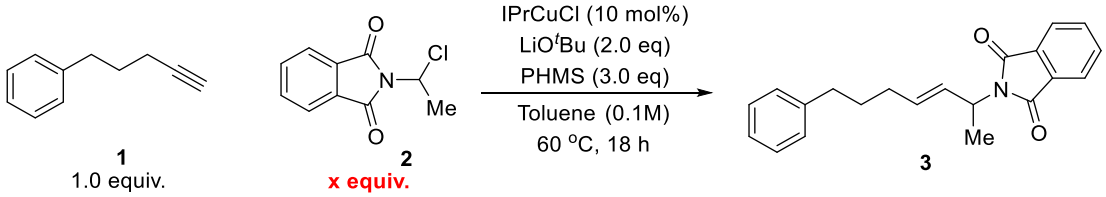
Entry	Catalyst	Yield (%)
1	Cat.1	5
2	Cat.2 (IMesCuCl)	8
3	Cat.3	7
4	Cat.4	19
5	Cat.5	36
6	Cat.6 (IPrCuCl)	39
7	Cat.7 (SIPrCuCl)	38
8	Cat.8	15

Table S4: Silane screen



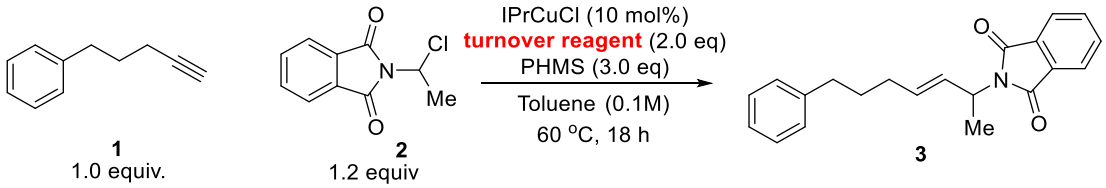
Entry	Silane	Yield (%)
1	Ph_3SiH	4
2	$Me(OMe)_2SiH$	21
3	$Me(OEt)_2SiH$	8
4	$^tBu_2SiH_2$	16
5	$(OEt)_3SiH$	11
6	$PhSiH_3$	4
7	Ph_2MeSiH	5
8	$^iPrMe_2SiH$	4
9	TMDSO	16
10	PHMS	39

Table S5: α-Cl-phthalimide stoichiometry



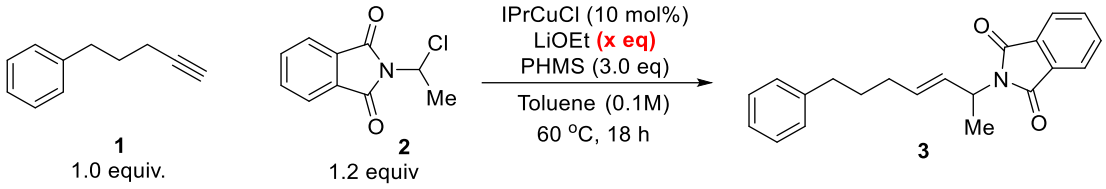
Entry	Equiv.	Yield (%)
1	1.0	39
2	1.2	48
3	1.5	43
4	2.0	23
5	3.0	13

Table S6: Turnover reagent



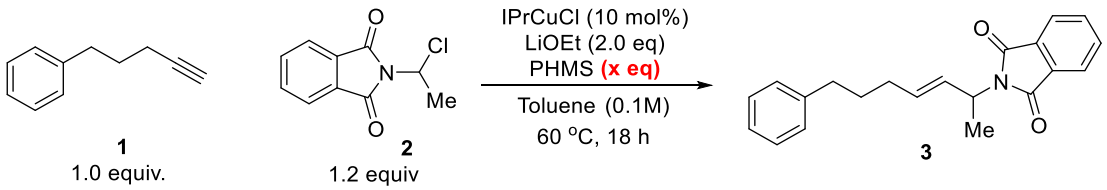
Entry	Turnover reagent	Yield (%)
1	LiOMe	0
2	LiOEt	61
3	LiO^{i}Pr	35
4	LiO^{t}Bu	48
5	LiOTMS	19
6	LiHMDS	5
7	NaOEt	12
8	NaO^{i}Pr	2
9	NaO^{t}Bu	7
10	NaOTMS	7
11	NaO^{t}Am	8
12	KOEt	5
13	KO^{t}Bu	0
14	KHMDS	3
15	KOTMS	3
16	KO^{t}Am	0

Table S7: Turnover reagent stoichiometry



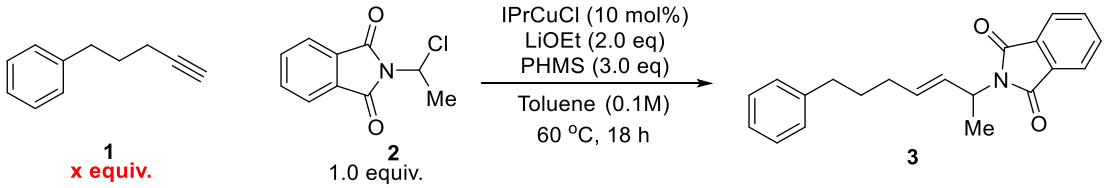
Entry	Equiv.	Yield (%)
1	1.0	21
2	1.5	43
3	2.0	61
4	2.5	47
5	3.0	42

Table S8: Silane stoichiometry



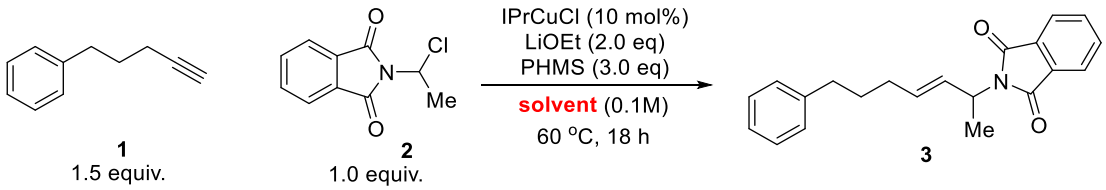
Entry	Equiv.	Yield (%)
1	1.0	45
2	1.5	57
3	2.0	57
4	2.5	57
5	3.0	61
6	4.0	39
7	5.0	35

Table S9: Alkyne stoichiometry



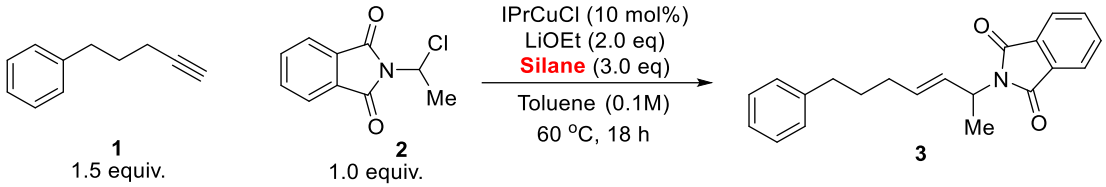
Entry	Equiv.	Yield (%)
1	1.0	57
2	1.2	66
3	1.5	71
4	2.0	71
5	2.5	70

Table S10: Solvent screen



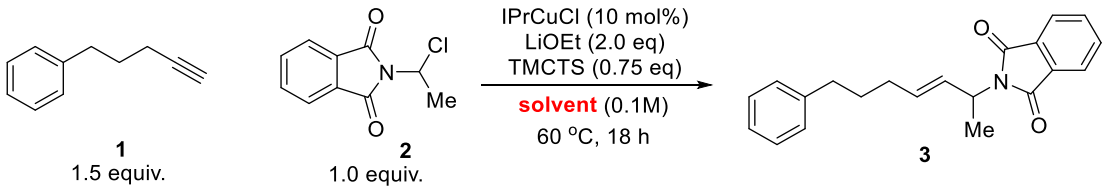
Entry	Solvent	Yield (%)
1	DME	3
2	DMA	0
3	dioxane	28
4	pyridine	0
5	MeCN	0
6	CPME	69
7	CCl_4	0
8	cyclohexane	58
9	dodecane	40
10	PhF	55
11	PhCl	62
12	$PhCF_3$	48
13	benzene	70
14	toluene	71
15	xylenes	58
16	mesitylene	66
17	THF	16

Table S11: Silane screen



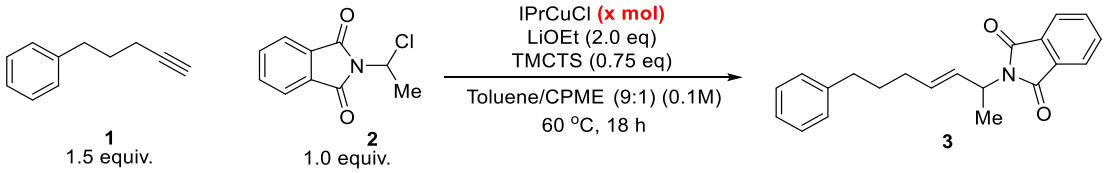
Entry	Silane	Yield (%)
1	$Me_2(OMe)SiH$	29
2	$^nPr_3SiH$	0
3	$(HSiMe_2O)_3SiMe$	24
4	TMCTS	76

Table S12: Solvent screen



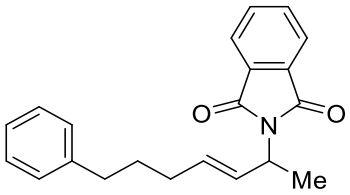
Entry	Solvent (v:v)	Yield (%)
1	Toluene/THF (9:1)	44
2	Toluene/THF (7:3)	21
3	Toluene/THF (1:1)	12
4	Toluene/CPME (9:1)	83
5	Toluene/CPME (7:3)	66
6	Toluene/CPME (1:1)	56

Table S13: Catalyst stoichiometry



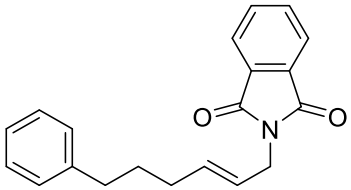
Entry	Equiv.	Yield (%)
1	2%	74
2	5%	77
3	10%	83
4	15%	83
5	20%	81

5.4 PRODUCT CHARACTERIZATION

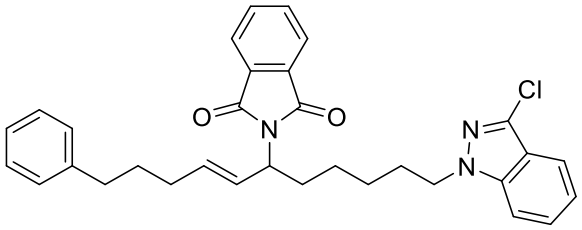


(*E*)-2-(7-phenylhept-3-en-2-yl)isoindoline-1,3-dione (3), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-8% EtOAc in

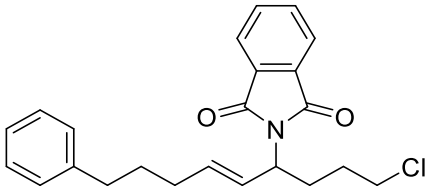
hexanes and was isolated as a colorless oil (133 mg, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.31 – 7.10 (m, 5H), 5.89 (dd, *J* = 15.5, 7.4 Hz, 1H), 5.77 – 5.61 (m, 1H), 4.90 (p, *J* = 7.2 Hz, 1H), 2.64 – 2.53 (m, 2H), 2.06 (q, *J* = 6.9 Hz, 2H), 1.69 (p, *J* = 7.6 Hz, 2H), 1.55 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 142.4, 133.9, 132.9, 132.3, 129.2, 128.6, 128.4, 125.8, 123.2, 48.9, 35.4, 31.7, 30.8, 19.1. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{21}H_{22}NO_2$, 320.2 ; found 320.0. FTIR (neat, cm^{-1}): 3084.3 (w), 3025.7 (m), 2934.0 (s), 2856.3 (m), 1774.0 (s), 1704.9 (s), 1603.0 (m), 1386.3 (s), 1171.7 (m), 910.6 (s), 699.6 (s).



(*E*)-2-(6-phenylhex-2-en-1-yl)isoindoline-1,3-dione (4), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-10% EtOAc in hexanes and was isolated as a white solid (115 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.31 – 7.10 (m, 5H), 5.86 – 5.64 (m, 1H), 5.60 – 5.44 (m, 1H), 4.24 (d, *J* = 4.8 Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.05 (q, *J* = 7.2 Hz, 2H), 1.69 (p, *J* = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 142.4, 134.8, 134.0, 132.3, 128.5, 128.4, 125.8, 123.7, 123.3, 39.7, 35.4, 31.7, 30.7. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{20}H_{20}NO_2$, 306.1 ; found 306.0. FTIR (neat, cm^{-1}): 3025.3 (m), 2929.7 (m), 2855.6 (m), 1771.5 (s), 1713.5 (s), 1615.4 (w), 1429.1 (s), 1393.5 (s), 1113.4 (m), 792.6 (w), 699.7 (s).

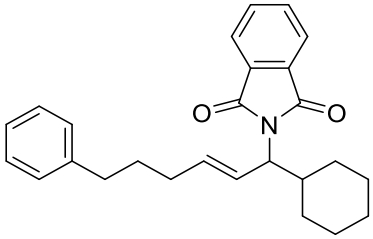


(*E*)-2-(11-(3-chloro-1H-indazol-1-yl)-1-phenylundec-4-en-6-yl)isoindoline-1,3-dione (5), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-10% EtOAc in hexanes and was isolated as a colorless oil (216 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.29 (m, 2H), 7.29 – 7.09 (m, 7H), 5.86 (dd, *J* = 15.4, 8.2 Hz, 1H), 5.74 – 5.59 (m, 1H), 4.64 (q, *J* = 8.0 Hz, 1H), 4.27 (t, *J* = 7.1 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), (2.02 - 1.87 m, 6H), 1.67 (p, *J* = 7.6 Hz, 2H), 1.41 – 1.20 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 142.3, 140.8, 134.0, 133.9, 132.5, 132.0, 128.5, 128.3, 127.9, 127.4, 125.8, 123.2, 121.1, 121.0, 119.8, 109.4, 53.8, 49.1, 35.4, 32.4, 31.7, 30.8, 29.7, 26.4, 26.2. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{32}H_{33}N_3O_2Cl$, 526.2 ; found 526.1. FTIR (neat, cm^{-1}): 3060.6 (w), 3025.6 (w), 2932.5 (s), 2857.5 (m), 1770.4 (s), 1716.4 (s), 1615.9 (m), 1385.9 (s), 1171.9 (m), 909.9 (m), 719.5 (s).

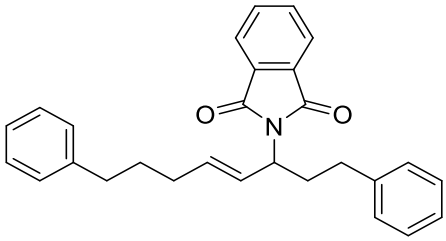


(*E*)-2-(1-chloro-9-phenylnon-5-en-4-yl)isoindoline-1,3-dione (6), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-10% EtOAc in hexanes and was isolated as a colorless oil (139 mg, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.32 – 7.05 (m, 5H), 5.90 (dd, *J* = 15.4, 8.1 Hz, 1H), 5.73 (dt, *J* = 14.8, 6.5 Hz, 1H), 4.70 (q, *J* = 8.0 Hz, 1H), 3.54 (t, *J* = 6.6

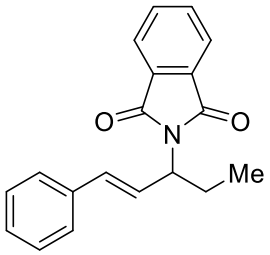
Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.22 – 1.98 (m, 4H), 1.83 – 1.61 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 142.2, 134.5, 134.0, 131.9, 128.5, 127.5, 125.8, 123.2, 53.1, 44.3, 35.4, 31.7, 30.7, 30.0, 29.7. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{23}H_{25}NO_2Cl$, 382.2 ; found 382.0. FTIR (neat, cm^{-1}): 3084.5 (w), 3025.0 (s), 2918.9 (m), 2856.5 (s), 1770.4 (s), 1732.8 (m), 1699.0 (s), 1495.3 (s), 1111.0 (s), 875.6 (s), 696.1 (s).



(*E*)-2-(1-cyclohexyl-6-phenylhex-2-en-1-yl)isoindoline-1,3-dione (7), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-8% EtOAc in hexanes and was isolated as a colorless oil (136 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.33 – 7.04 (m, 5H), 5.94 (dd, *J* = 15.4, 9.2 Hz, 1H), 5.76 – 5.61 (m, 1H), 4.32 (t, *J* = 9.9 Hz, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.21 – 1.99 (m, 3H), 1.92 – 1.37 (m, 7H), 1.35 – 1.07 (m, 3H), 0.95-0.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 142.4, 135.4, 133.9, 132.1, 128.6, 128.4, 127.2, 125.8, 123.2, 59.8, 38.4, 35.5, 31.9, 31.0, 30.0, 26.3, 25.8, 25.8. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{26}H_{30}NO_2$, 388.2 ; found 388.1. FTIR (neat, cm^{-1}): 3060.8 (w), 3025.9 (m), 2926.6 (s), 2851.7 (s), 1770.4 (s), 1708.0 (s), 1611.4 (s), 1385.3 (s), 1086.1 (m), 909.7 (s), 699.8 (s).

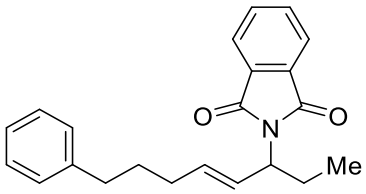


(*E*)-2-(1,8-diphenyloct-4-en-3-yl)isoindoline-1,3-dione (8), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-10% EtOAc in hexanes and was isolated as a colorless oil (158 mg, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.32 – 7.03 (m, 10H), 5.91 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.79 – 5.63 (m, 1H), 4.74 (q, *J* = 7.8 Hz, 1H), 2.75 – 2.34 (m, 4H), 2.56 – 2.34 (m, 1H), 2.32 – 2.11 (m, 1H), 2.06 (q, *J* = 7.2 Hz, 2H), 1.69 (p, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 142.1, 140.9, 134.0, 133.6, 131.9, 128.3, 128.2, 128.2, 128.2, 127.8, 125.8, 125.6, 122.9, 53.5, 35.2, 33.9, 32.9, 31.6, 30.6. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{28}H_{28}NO_2$, 410.2 ; found 410.0. FTIR (neat, cm^{-1}): 3084.4 (w), 3060.7 (m), 3025.8 (m), 2930.4 (s), 2856.8 (m), 1769.8 (s), 1719.7 (s), 1602.5 (m), 1385.8 (s), 1171.4 (w), 699.1 (s).

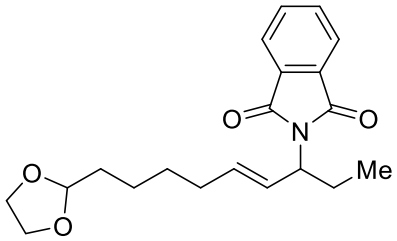


(*E*)-2-(1-phenylpent-1-en-3-yl)isoindoline-1,3-dione (9), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-8% EtOAc in hexanes and was isolated as a white solid (134 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.43 – 7.17 (m, 5H), 6.72 – 6.54 (m, 2H), 4.80 (q, *J* = 7.4 Hz, 1H), 2.26 – 1.94 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz,

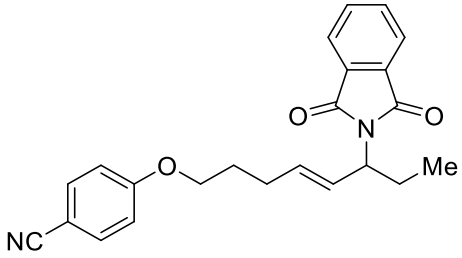
$CDCl_3$) δ 168.3, 136.5, 134.0, 133.2, 132.1, 128.6, 128.0, 127.1, 126.7, 123.3, 55.7, 25.9, 11.2. MS-ESI (m/z): $[M+Na]^+$ calculated for $C_{19}H_{17}NO_2Na$, 314.1 ; found 314.1. FTIR (neat, cm^{-1}): 3053.6 (m), 2985.1 (w), 1768.2 (w), 1711.1 (s), 1652.7 (w), 1419.5 (w), 1387.6 (m), 1086.6 (w), 966.1 (w), 894.4 (w), 703.2 (s).



(*E*)-2-(8-phenyloct-4-en-3-yl)isoindoline-1,3-dione (10), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-8% EtOAc in hexanes and was isolated as a colorless oil (128 mg, 77% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.31 – 7.10 (m, 5H), 5.89 (dd, *J* = 15.5, 8.2 Hz, 1H), 5.78 – 5.62 (m, 1H), 4.59 (q, *J* = 8.0 Hz, 1H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.14 – 1.84 (m, 4H), 1.69 (p, *J* = 7.6 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 142.4, 134.1, 133.9, 132.2, 128.5, 128.4, 128.0, 125.8, 123.2, 55.6, 35.4, 31.8, 30.8, 25.9, 11.2. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{22}H_{24}NO_2$, 334.2 ; found 334.2. FTIR (neat, cm^{-1}): 3060.9 (w), 3025.9 (m), 2965.9 (m), 2874.9 (m), 1770.4 (s), 1712.9 (s), 1611.6 (w), 1467.0 (m), 1385.9 (s), 1171.8 (m), 699.3 (s).

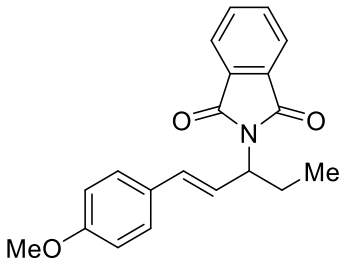


(*E*)-2-(9-(1,3-dioxolan-2-yl)non-4-en-3-yl)isoindoline-1,3-dione (11), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-15% EtOAc in hexanes and was isolated as a colorless oil (122 mg, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.87 (dd, *J* = 15.4, 8.4 Hz, 1H), 5.75 – 5.60 (m, 1H), 4.81 (t, *J* = 4.8 Hz, 1H), 4.58 (q, *J* = 8.0 Hz, 1H), 4.01 – 3.73 (m, 4H), 2.12 – 1.81 (m, 4H), 1.62 (t, *J* = 6.6 Hz, 2H), 1.48 – 1.34 (m, 4H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 134.3, 133.9, 132.2, 127.7, 123.2, 104.7, 64.9, 55.6, 33.8, 32.2, 29.0, 25.9, 23.7, 11.2. FTIR (neat, cm^{-1}): 3062.4 (w), 2888.3 (s), 2858.6 (m), 2766.4 (w), , 1770.5 (s), 1612.4 (m), 1464.4 (s), 1386.9 (s), 1128.4 (s), 795.7 (m), 719.5 (s).

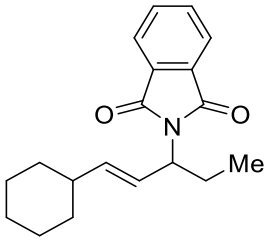


(*E*)-4-((6-(1,3-dioxoisoindolin-2-yl)oct-4-en-1-yl)oxy)benzonitrile (12), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-15% EtOAc in hexanes and was isolated as a light yellow oil (142 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 5.91 (dd, *J* = 15.5, 8.0 Hz, 1H), 5.70 (dt, *J* = 15.4, 6.7 Hz, 1H), 4.59 (q, *J* = 7.9 Hz, 1H), 3.96 (t, *J* = 6.3 Hz, 2H), 2.22 (q, *J* = 7.1 Hz, 2H), 2.12 – 1.79 (m, 4H),

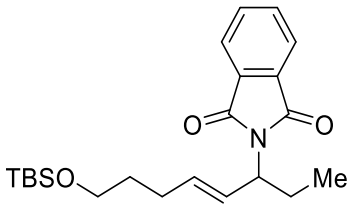
0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 162.3, 134.0, 133.9, 132.6, 131.9, 128.9, 123.1, 119.3, 115.2, 103.7, 67.4, 55.2, 28.5, 28.1, 25.6, 11.1. FTIR (neat, cm^{-1}): 3055.3 (w), 2965.9 (m), 2934.9 (m), 2875.6 (m), 2224.3 (s), 1770.3 (s), 1716.3 (s), 1605.5 (s), 1388.8 (s), 1171.3 (s), 719.6 (s).



(*E*)-2-(1-(4-methoxyphenyl)pent-1-en-3-yl)isoindoline-1,3-dione (13), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-10% EtOAc in hexanes and was isolated as a light yellow oil (127 mg, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.7, 3.0 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.62 – 6.42 (m, 2H), 4.77 (q, *J* = 7.7 Hz, 1H), 3.79 (s, 3H), 2.22 – 1.95 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 159.5, 133.9, 132.7, 132.1, 129.3, 127.9, 124.9, 123.2, 114.0, 55.9, 55.4, 26.0, 11.2. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{20}H_{20}NO_3$, 322.1 ; found 322.0. FTIR (neat, cm^{-1}): 3033.5 (w), 2965.5 (m), 2932.7 (m), 2835.9 (m), 1768.1 (s), 1715.0 (s), 1606.9 (s), 1387.5 (s), 1175.3 (s), 1036.0 (s), 719.6 (s).

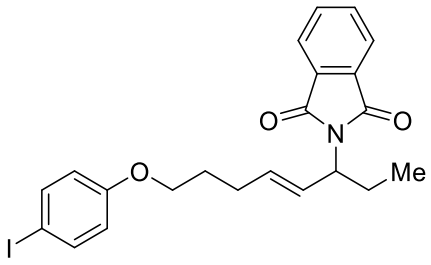


(*E*)-2-(1-cyclohexylpent-1-en-3-yl)isoindoline-1,3-dione (14), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-8% EtOAc in hexanes and was isolated as a colorless oil (122 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.83 (ddd, *J* = 15.6, 8.3, 1.2 Hz, 1H), 5.63 (dd, *J* = 15.6, 6.5 Hz, 1H), 4.56 (q, *J* = 8.0 Hz, 1H), 2.11 – 1.80 (m, 3H), 1.68 (d, *J* = 12.1 Hz, 5H), 1.34 – 0.94 (m, 5H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 140.4, 133.9, 132.2, 124.9, 123.2, 55.8, 40.4, 32.8, 26.2, 26.0, 26.0, 11.2. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{19}H_{24}NO_2$, 298.2 ; found 298.1. FTIR (neat, cm^{-1}): 2965.9 (m), 2925.0 (s), 2850.5 (s), 1770.2 (s), 1712.5 (s), 1612.1 (m), 1385.5 (s), 1171.4 (m), 1085.9 (m), 973.4 (m), 648.4 (w).

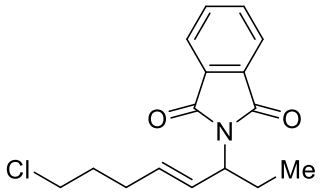


(*E*)-2-(8-((tert-butyldimethylsilyl)oxy)oct-4-en-3-yl)isoindoline-1,3-dione (15), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-8% EtOAc in hexanes and was isolated as a colorless oil (132 mg, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.87 (dd, *J* = 15.5, 8.1 Hz, 1H), 5.67 (dt, *J* = 15.3, 6.6 Hz, 1H), 4.58 (q, *J* = 8.0 Hz, 1H), 3.57 (t, *J* = 6.3 Hz, 2H), 2.12

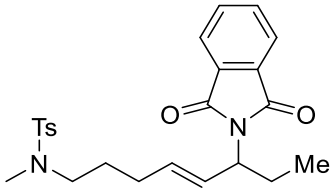
– 1.81 (m, 4H), 1.57 – 1.30 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 134.4, 133.9, 132.1, 127.7, 123.2, 63.1, 55.6, 32.4, 32.0, 26.1, 25.9, 25.4, 18.4, 11.2, -5.2. FTIR (neat, cm^{-1}): 2930.3 (s), 2856.7 (s), 1771.4 (s), 1716.1 (s), 1612.5 (w), 1468.1 (m), 1255.6 (s), 1099.8 (s), 835.5 (m), 775.9 (m), 719.5 (s).



(*E*)-2-(8-(4-iodophenoxy)oct-4-en-3-yl)isoindoline-1,3-dione (16), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-10% EtOAc in hexanes and was isolated as a colorless oil (176 mg, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.54 – 7.43 (m, 2H), 6.67 – 6.55 (m, 2H), 5.91 (dd, *J* = 15.5, 8.1 Hz, 1H), 5.78 – 5.62 (m, 1H), 4.60 (q, *J* = 8.0 Hz, 1H), 3.88 (t, *J* = 6.3 Hz, 2H), 2.20 (q, *J* = 6.9 Hz, 2H), 2.13 – 1.76 (m, 4H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 158.9, 138.2, 134.0, 133.0, 132.0, 128.6, 123.2, 117.0, 82.6, 67.2, 55.4, 28.6, 25.7, 11.2. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{22}H_{23}NO_3I$, 476.1 ; found 476.0. FTIR (neat, cm^{-1}): 3061.5 (w), 2932.4 (s), 2874.4 (m), 1767.0 (s), 1698.9 (s), 1586.0 (m), 1488.5 (s), 1362.0 (m), 1173.8 (m), 972.7 (w), 719.6 (m).

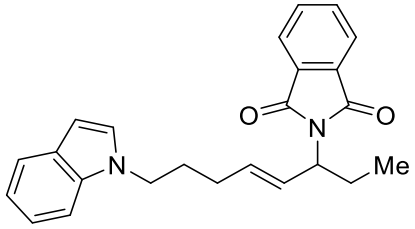


(*E*)-2-(8-chlorooct-4-en-3-yl)isoindoline-1,3-dione (17), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-8% EtOAc in hexanes and was isolated as a colorless oil (105 mg, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.93 (dd, *J* = 15.5, 8.2 Hz, 1H), 5.65 (dt, *J* = 14.6, 6.8 Hz, 1H), 4.60 (q, *J* = 8.0 Hz, 1H), 3.51 (t, *J* = 6.6 Hz, 2H), 2.19 (q, *J* = 7.1 Hz, 2H), 2.12 – 1.76 (m, 4H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 134.0, 132.3, 132.1, 129.0, 123.3, 55.4, 44.4, 31.9, 29.4, 25.8, 11.2. FTIR (neat, cm^{-1}): 2965.6 (s), 2933.7 (m), 2875.1 (m), 1771.4 (s), 1716.0 (s), 1612.1 (m), 1467.2 (m), 1386.4 (m), 1171.9 (w), 973.5 (m), 649.9 (w).

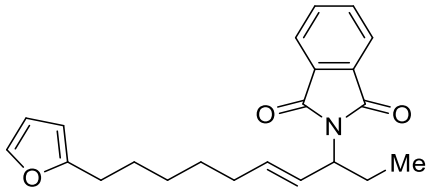


(*E*)-N-(6-(1,3-dioxoisoindolin-2-yl)oct-4-en-1-yl)-N,4-dimethylbenzenesulfonamide (18), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-15% EtOAc in hexanes and was isolated as a colorless oil (148 mg, 67% yield).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.68 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 5.88 (ddd, *J* = 15.4, 8.1, 1.5 Hz, 1H), 5.65 (dt, *J* = 15.3, 6.6 Hz, 1H), 4.57 (q, *J* = 7.9 Hz, 1H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.67 (s, 3H), 2.40 (s, 3H), 2.14 – 1.74 (m, 4H), 1.58 (p, *J* = 7.4 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$)

δ 168.2, 143.2, 134.6, 133.9, 132.8, 132.0, 129.7, 128.5, 127.4, 123.1, 55.3, 49.6, 34.8, 29.1, 27.0, 25.7, 21.5, 11.1. ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 143.2, 134.6, 133.9, 132.8, 132.0, 129.7, 128.5, 127.4, 123.1, 55.3, 49.6, 34.8, 29.1, 27.0, 25.7, 21.5, 11.1. FTIR (neat, cm^{-1}): 3061.8 (w), 2967.9 (m), 2932.5 (w), 2874.8 (m), 2255.9 (w), 1770.3 (m), 1597.8 (m), 1463.4 (m), 1385.9 (s), 1160.5 (s), 719.5 (s).



(*E*)-2-(8-(1H-indol-1-yl)oct-4-en-3-yl)isoindoline-1,3-dione (19), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-10% EtOAc in hexanes and was isolated as a light yellow oil (156 mg, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.7, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.46 (d, *J* = 3.1 Hz, 1H), 5.90 (dd, *J* = 15.3, 7.9 Hz, 1H), 5.66 (dt, *J* = 14.6, 6.5 Hz, 1H), 4.60 (q, *J* = 7.8 Hz, 1H), 4.10 (t, *J* = 6.9 Hz, 2H), 2.09 – 1.83 (m, 6H), 0.89 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 136.0, 134.0, 132.7, 132.1, 128.9, 128.7, 127.9, 123.3, 121.4, 121.0, 119.3, 109.4, 101.1, 55.3, 45.6, 29.5, 29.4, 25.8, 11.2. FTIR (neat, cm^{-1}): 3061.4 (m), 2927.4 (s), 2855.1 (s), 1869.5 (w), 1700.0 (w), 1603.3 (m), 1496.4 (m), 1452.2 (s), 1144.9 (m), 746.3 (w), 697.1 (s).



(*E*)-2-(10-(furan-2-yl)dec-4-en-3-yl)isoindoline-1,3-dione (20), compound was prepared according to general procedure A and was purified by alumina column chromatography, 0-12% EtOAc in hexanes and was isolated as a colorless oil (128 mg, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.28 – 7.26 (m, 1H), 6.29 – 6.21 (m, 1H), 5.97 – 5.92 (m, 1H), 5.87 (dd, *J* = 15.4, 8.2 Hz, 1H), 5.75 – 5.59 (m, 1H), 4.58 (q, *J* = 8.0 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.10 – 1.81 (m, 4H), 1.69 – 1.53 (m, 2H), 1.46 – 1.23 (m, 4H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4, 156.6, 140.8, 134.5, 133.9, 132.2, 127.6, 123.2, 110.1, 104.7, 55.7, 32.2, 28.8, 28.8, 28.0, 27.9, 25.9, 11.2. MS-ESI (m/z): $[M+H]^+$ calculated for $C_{22}H_{26}NO_3$, 352.2 ; found 352.1. FTIR (neat, cm^{-1}): 3114.5 (w), 2965.9 (m), 2931.4 (s), 2856.4 (m), 1770.4 (m), 1711.6 (s), 1506.3 (m), 1466.7 (m), 1331.9 (m), 973.3 (m), 719.1 (s).

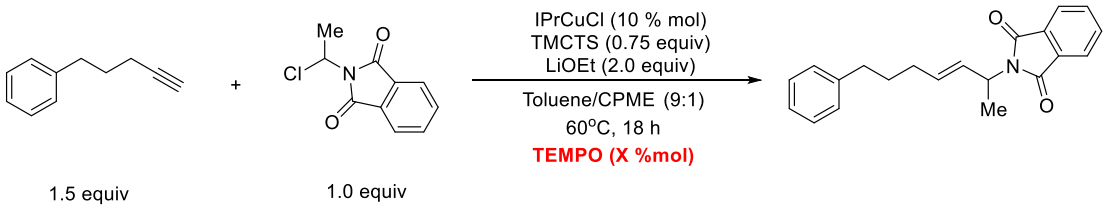
5.5 MECHANISTIC EXPERIMENTS

Radical trap probe

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, IPrCuCl (4.9 mg, 0.01 mmol, 0.1 equiv.), LiOEt (10.4 mg, 0.2 mmol, 2 equiv.) and toluene/CPME (9:1). Then stock solution of TMCTS (0.75 M in toluene, 100 μL, 0.75 equiv.) was added, followed by the addition of alkyne stock solution (1 M in toluene, 150 μL, 1.5 equiv.). The solution was stirred at room temperature until the yellow color disappeared. α-Cl-phthalimide stock solution (0.5 M in toluene with 0.4 M TMB, 200 μL, 1.0 equiv.) and required amount of TEMPO were added. The reaction was stirred

overnight and a 50 µL aliquot from the reaction mixture was passed through a plug of silica with ethyl acetate, and analyzed by GC.

Table S14: Radical trap probe experiments.

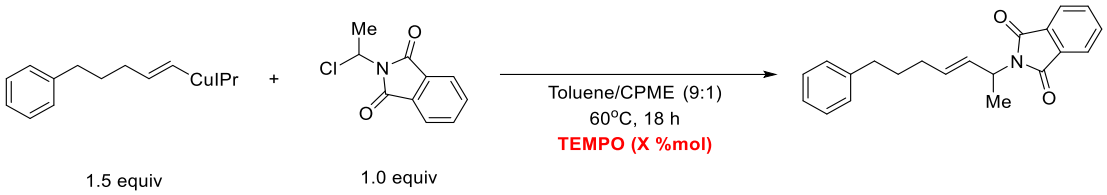


Entry	Equiv. of TEMPO	Yield (%)
1	0 %	80
2	20 %	79
3	50 %	79
4	80 %	78
5	150 %	81
6	300 %	77

Stoichiometric experiment with TEMPO

In a nitrogen-filled glovebox, a dram vial was charged with a stir bar, alkenylcopper (44.6 mg, 0.05 mmol, 1.5 equiv.) and toluene/CPME (9:1). Then α-Cl-phthalimide stock solution (0.5 M in toluene with 0.4 M TMB, 100 µL, 1.0 equiv.) and required amount of TEMPO were added. The reaction was stirred overnight and a 50 µL aliquot from the reaction mixture was passed through a plug of silica with ethyl acetate, and analyzed by GC.

Table S15: Stoichiometric experiment with TEMPO.



1.5 equiv

1.0 equiv

Entry	Equiv. of TEMPO	Yield (%)
1	0 %	92
2	50 %	92
3	200 %	96

CHAPTER 6. REFERENCE

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(2) Granberg, K. L.; Baeckvall, J. E. Isomerization of (.pi.-allyl)palladium complexes via nucleophilic displacement by palladium(0). A common mechanism in palladium(0)-catalyzed allylic substitution. *Journal of the American Chemical Society* **1992**, *114* (17), 6858-6863. DOI: 10.1021/ja00043a034.

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