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Article

Di-tert-butyl Ethynylimidodicarbonate as a General Synthon for the #-Aminoethylation of Organic Electrophiles: Application to the Formal Synthesis of Pyrrolidinoindoline Alkaloids (±)-CPC-1 and (±)-Alline

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Di-*tert*-butyl Ethynylimidodicarbonate as a General Synthon for the β-Aminoethylation of Organic Electrophiles: Application to the Formal Synthesis of Pyrrolidinoindoline Alkaloids (±)-CPC-1 and (±)-Alline

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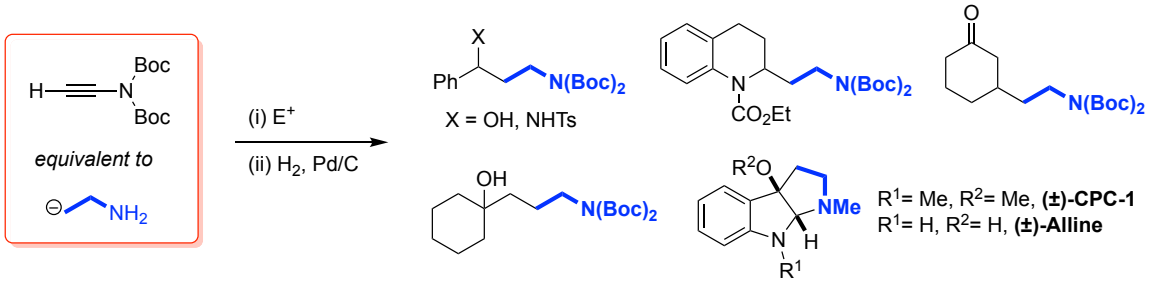


Abstract:

The reagent di-*tert*-butyl ethynylimidodicarbonate is demonstrated as a β-aminoethyl anion synthetic equivalent. It can be used to install ethyleneamine groups by exploiting its terminal alkyne reactivity with common organic electrophiles. Reactions exemplified with this terminal ynimide reagent include additions to imines, aldehydes, ketones, pyridinium salts, Michael acceptors, epoxides, as well as Pd-catalyzed Sonogoshira couplings. Subsequent regioselective [3+2] cycloadditions of the alkynyl-imides (ynimides) generate *N*,*N*-di-Boc imide functionalized triazole and isoxazole heterocycles. Reduction of the ynimides with Pd-catalyzed hydrogenation generates ethyleneimides with easily removable *N*,*N*-di-Boc-carbamate protecting groups allowing for a flexible ynimide based approach to ethyleneamine installation. The utility of this two-step aminoethylation strategy was demonstrated in the short formal syntheses of pyrrolidinoindoline alkaloids (±)-CPC-1 and (±)-alline. Analogously, the reagent (*N*,*N*,*N'*)-tri-Boc 2-ethynylhydrazine, serves as a β-hydrazinoethyl anion synthetic equivalent.

Introduction:

β-Substituted ethylamines are a common structural motif found in natural products and a privileged scaffold in pharmaceutical development. Acyclic examples include neurotransmitters such as dopamine and serotonin, the serotonin/norepinephrine reuptake inhibitors duloxetine, fluoxetine, and atomoxetine, and the beta-3 adrenergic receptor agonist mirabegron (Figure 1). More commonly, the β-substituted ethylamine motif is embedded within a ring, such as in the tetrahydroquinoline VMAT2 inhibitor valbenazine, the pyrroloiminoquinone discorhabdin B, the antiplatelet clopidogrel, or in complex alkaloids such as ibogamine, ibogaine, cephalotaxine, lamellarin L, galanthamine, and strychnine. In addition, there are many examples of targets incorporating further substitution at either the α- or β-positions of the β-ethyleneamine fragment.

The de novo synthesis of β-substituted ethylamines **1** typically relies upon one of three key disconnections (Figure 2a). C–N bond disconnection is a powerful approach, through for example reductive amination,[1] Gabriel amination,[2] or hydroamination[3] strategies. However, this disconnection does not readily allow for diversification of the β-substituent. Disconnection of the α-C–C bond can be achieved, for example, through the use of α-amino anion equivalents such as cyanide[4] or nitromethane anion[5] followed by subsequent reduction. Disconnection of the β-C–C bond can occur through the use of either electrophilic or nucleophilic β-ethyleneamine fragments. For example, the metallated intermediate **2** serves as an equivalent to the nucleophilic synthon **3**. The challenge in the latter case is that fragmentation via $E1_{cB}$ elimination of the protected amino group can occur (i.e., **4**) for Mg based intermediates **2**.[6] More stable versions of type **2** reagents include alkylboronate[7] and alkylzinc[8] aminoethylation examples but these species are mostly limited to the generation of phenethylamine products. To overcome these issues, we envisaged the use of β-anionic or metallated ynamides **5** (which are incapable of $E1_{cB}$ elimination) as stable and versatile reagents for β-ethyleneamine installation. Such intermediates would be accessible from the corresponding terminal ynamides, and act as synthetic equivalents to either the reduced nucleophilic β-aminoethylene synthon **3** (following reduction) or unsaturated synthon **6** (Figure 2b).

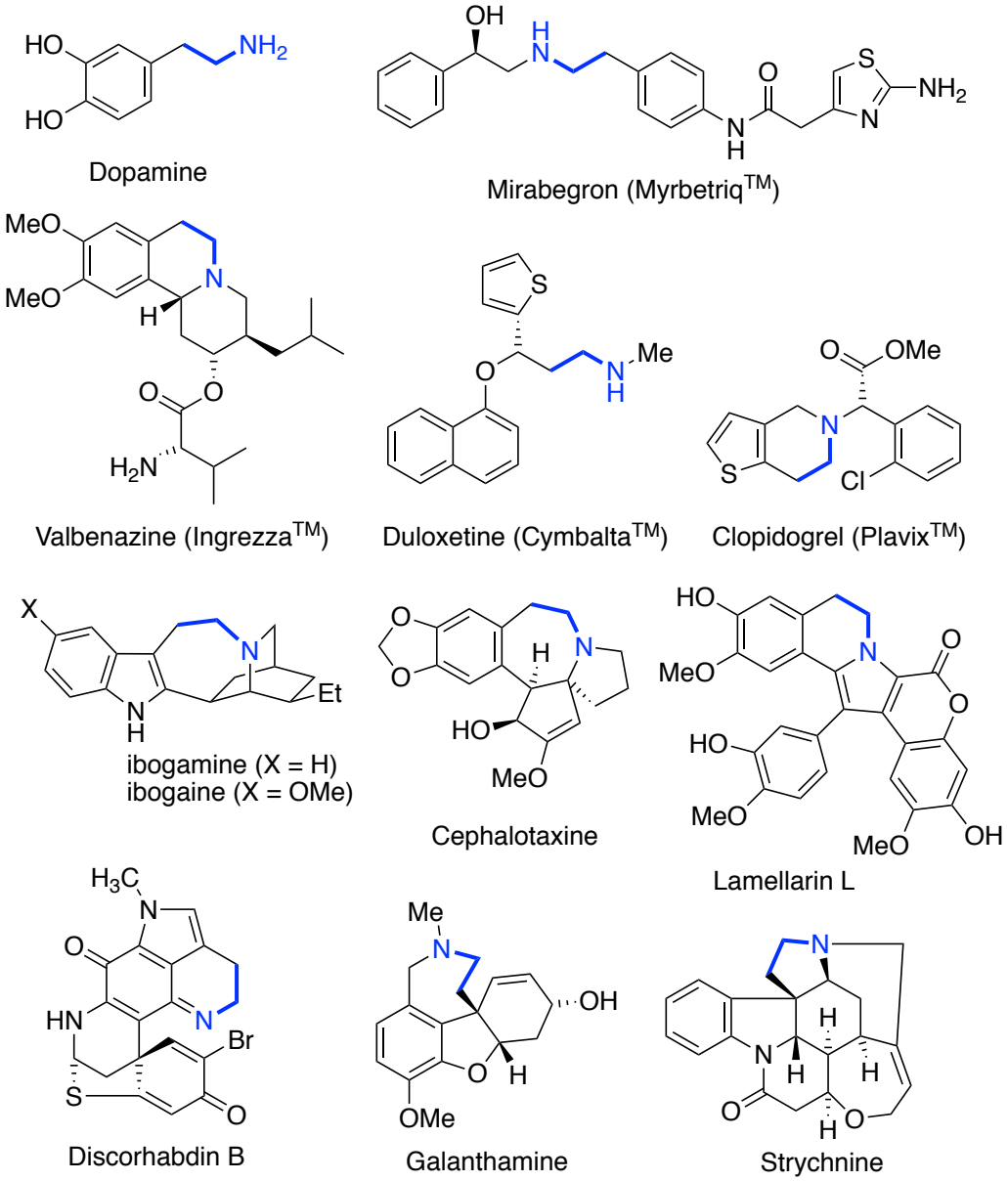


Figure 1. Representative β-substituted ethylamine natural product and pharmaceutical molecules containing ethyleneamine fragments.

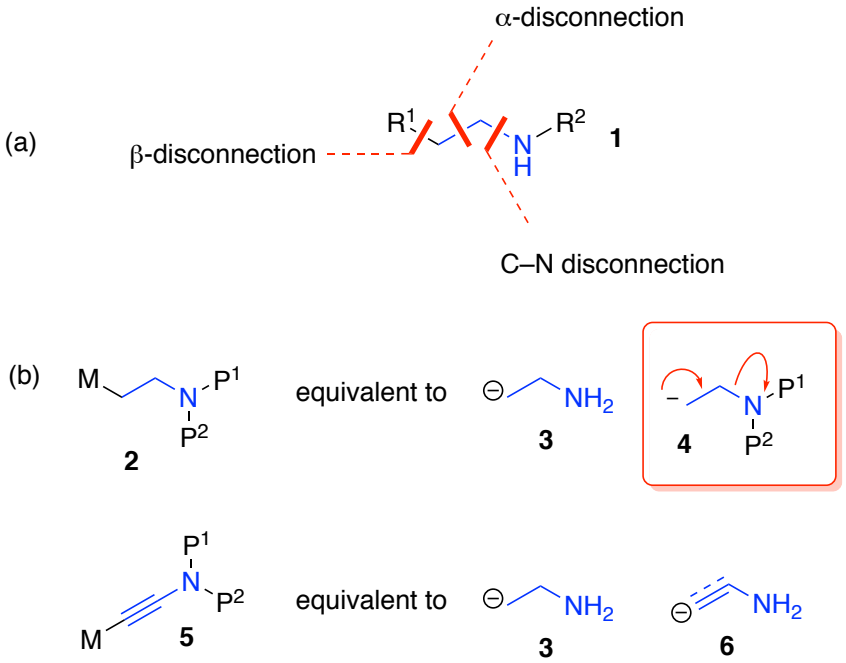
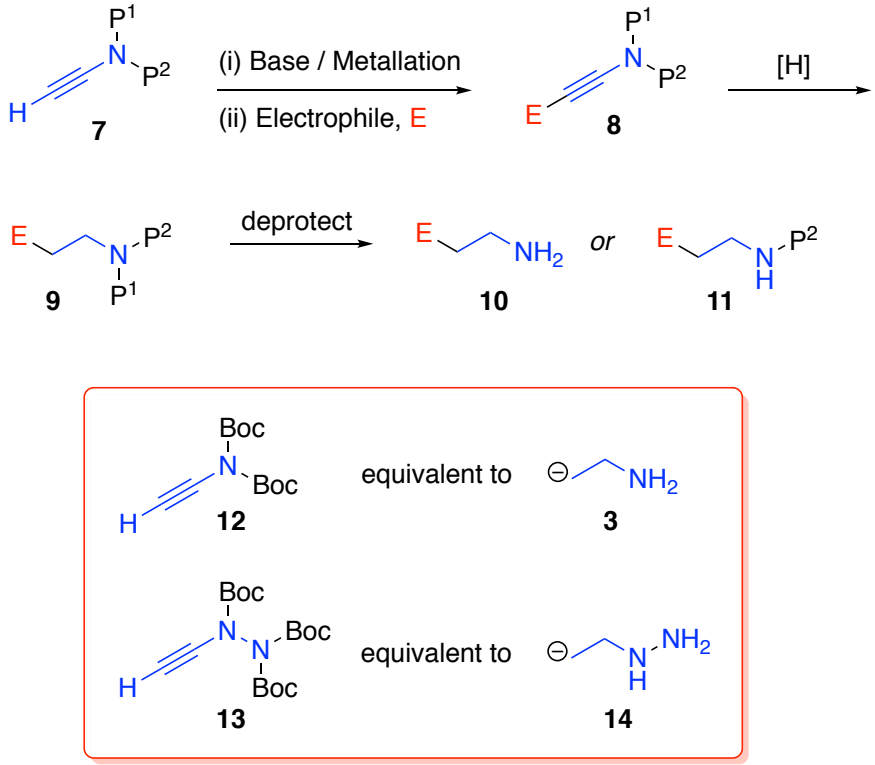


Figure 2. (a) Three disconnections for β-substituted ethylamine synthesis. (b) Nucleophilic β-aminoethylene synthetic equivalents **2** and **5**.

Ynamides are stable *N*-substituted alkynes which have become popular reagents for selectively incorporating amine functional groups in organic molecules.[9] In particular, the utility of these polarized 1-amido-alkynes have been exemplified in natural product total synthesis applications via *N*-alkynyl cycloaddition and cyclization reactions.[10] In contrast to the familiar use of ynamides in ring-forming reactions, terminal ynamide species, required for the formation of **5**, remain surprisingly under-utilized in additions to common organic electrophiles. Previous work in this area includes ynamide Sonogashira couplings,[11] ynamide-acetylide addition to carbonyl groups,[12,13] and copper-catalyzed ynamide addition to acid-chlorides and pyridinium salts.[14] More recently, a powerful copper-catalyzed enantioselective addition of *N*-sulfonamide protected terminal ynamides to isatins was disclosed while this manuscript was in preparation.[15] While useful, these examples have the limitation of using *N*-substituted alkynes possessing urethane, sulfonamide or indole groups on nitrogen which are not easily deprotected or transformed into other amine functional groups (e.g., primary amines). Furthermore, there appear to be no examples of terminal ynamide nucleophiles reacting with other common electrophiles such as epoxides and Michael acceptors.

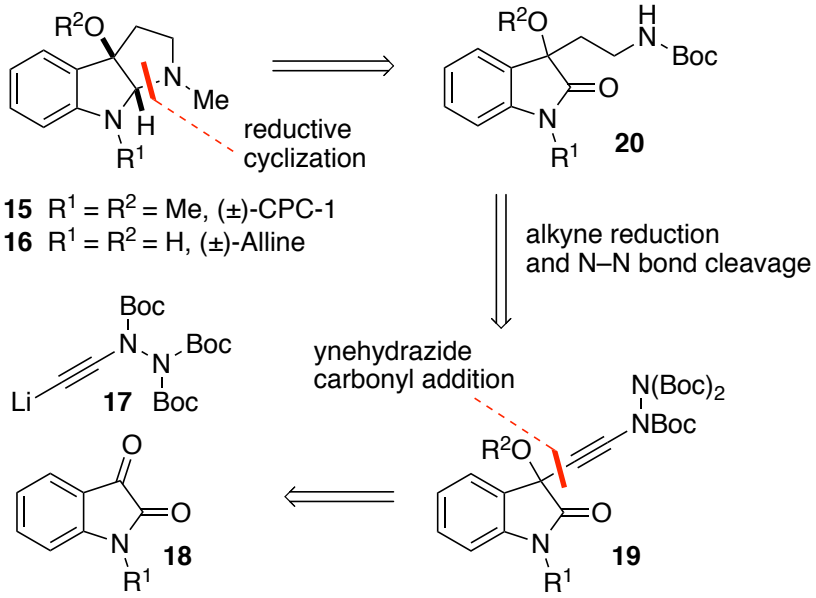
We envisaged the use of a terminal ynamide **7** which on deprotonation and trapping with an electrophile or cross-coupling would form the ynamide **8**. Subsequent reduction to **9** and deprotection would lead to the formation of the primary amine **10** or the substituted variant **11**. This would represent both a powerful approach to functionalized ynamide synthesis, and when combined with subsequent alkyne reduction would serve as a general route to install β-ethyleneamine groups (Scheme 1). Our prior studies on the use of Boc-protected ynehydrazides[16] suggested that the use of di-Boc protected precursors **12** or **13** could potentially serve as synthetic equivalents to the β-ethyleneamine synthon **3** or β-ethylenehydrazine synthon **14**, respectively. Herein, we describe our initial investigation into the utility of terminal ynamide and ynehydrazide reagents **12** or **13**, including a general exploration of their reactivity. The di-*tert*-butyl ethynylimidodicarbonate **12** is demonstrated to be a general β-aminoethyl anion synthon and is applied to the total syntheses of two pyrrolidinoindoline alkaloids.



Scheme 1. General concept of Boc-protected ynamide acetylide anions as β-ethyleneamine and β-ethylenehydrazine synthetic equivalents.

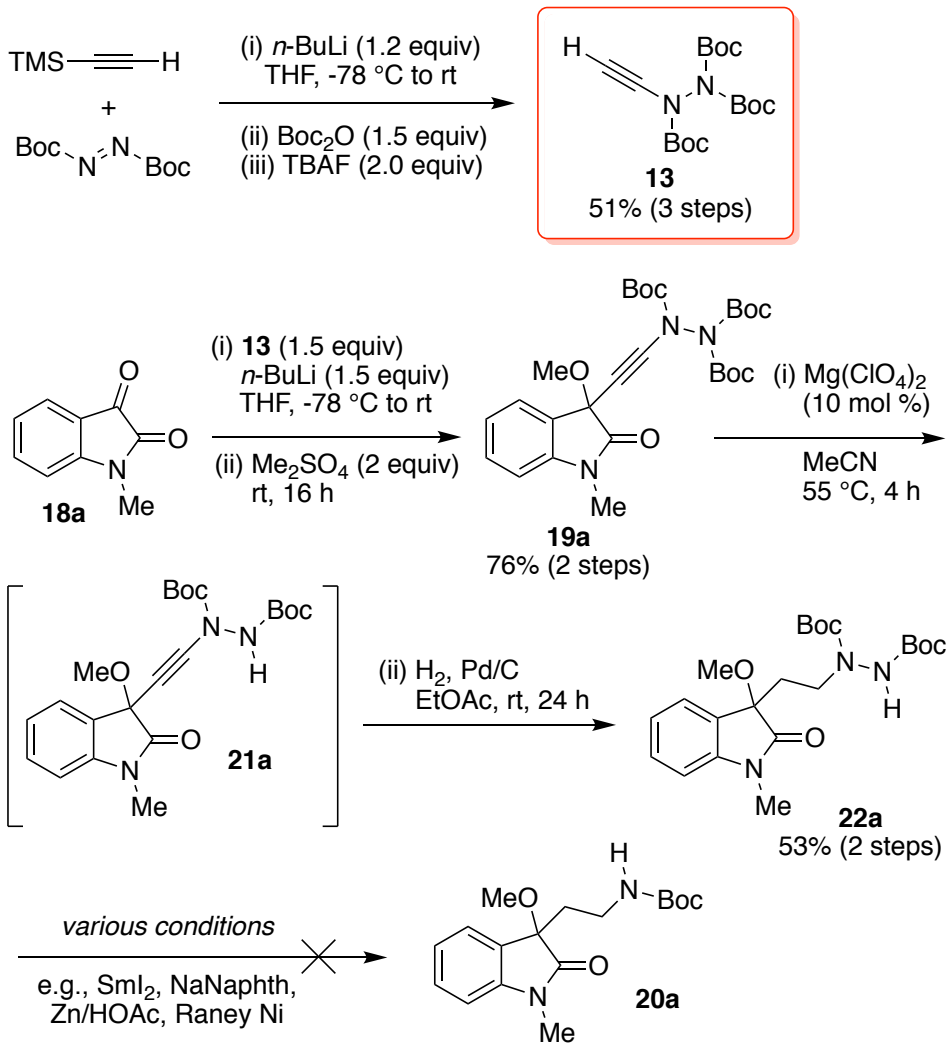
Results and Discussion:

Initial studies on the use of ynehydrazides, formed by the addition of acetylides to di-*t*-butylazodicarboxylate (DBAD), had revealed that the Boc groups provided stable *N*-substituted alkyne species and could be readily deprotected after manipulation of the alkyne.[16] We similarly reasoned that the tri-Boc protected terminal ynehydrazide **13** could serve as an equivalent to either of the synthons **3** or **14** (following alkyne reduction and, in the former case, reductive cleavage of the N–N bond). To evaluate the terminal ynehydrazide approach to aminoethylation, the pyrrolidinoindoline alkaloids[17] (±)-CPC-1 **15**[18,19] and (±)-alline **16**[20,21] were chosen as targets. Briefly, we envisaged an approach utilizing addition of the lithium acetylide **17** (formed by deprotonation of **13**) to an *N*-protected isatin **18** (Scheme 2). Subsequent alkyne reduction and hydrazine N–N bond cleavage of **19** to **20**, followed by a reductive cyclization was envisaged to then afford **15** or **16**.



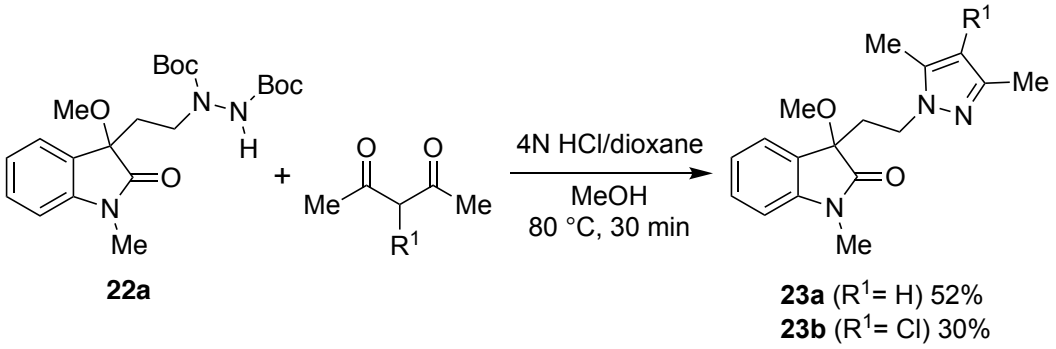
Scheme 2. Proposed ynehydrazide aminoethylation approach to pyrrolidinoindoline alkaloids

Toward this goal, we were pleased to observe that the tri-Boc-protected terminal ynehydrazide **13** could be easily prepared in gram-scale quantities through the addition of lithiated trimethysilylethyne to di-*tert*-butylazodicarboxylate (DBAD), and subsequent trapping with $(Boc)_2O$ and TBAF deprotection (Scheme 3). Addition of **13** as its lithium acetylide to *N*-Me isatin ketone **18a** followed by methylation afforded **19a** in good yield. Isatin ynehydrazide **19a** could be mono-deprotected to **20a** using catalytic magnesium perchlorate.[22] Reduction of the alkyne group of **20a** occurred to give hydrazide **22a**. However, attempts to then cleave the N–N bond under a variety of conventional conditions were unsuccessful. A major side product observed in many of the reduction reactions attempted was the undesired reductive cleavage of the methyl ether α- to the isatin amide.



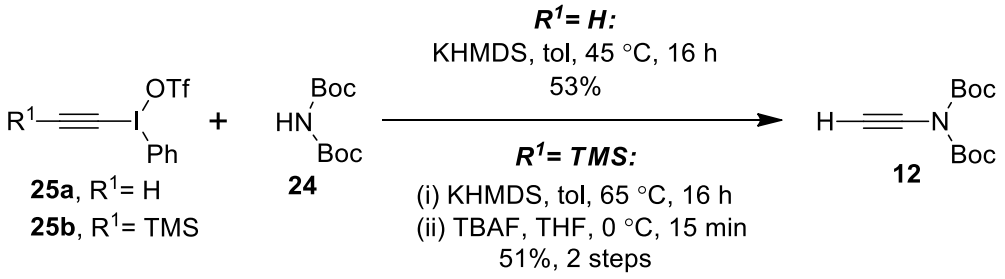
Scheme 3. Unsuccessful ynehydrazide approach to (±)-CPC-1

Although unsuccessful in the synthesis of the target alkaloid CPC-1 **15**, these results provided a proof-of-concept for using ynehydrazide **13** as a reagent for hydrazinoethylation which may be valuable for other applications including heterocycle generation. To illustrate this concept, compound **22a** was directly elaborated to pyrazoles[23] **23a** and **23b**, demonstrating how reagent **13** can further function as an ethylenepyrazole building block (Scheme 4).



Scheme 4. Conversion of compound **22a** to ethylenepyrazoles **23a** and **23b**

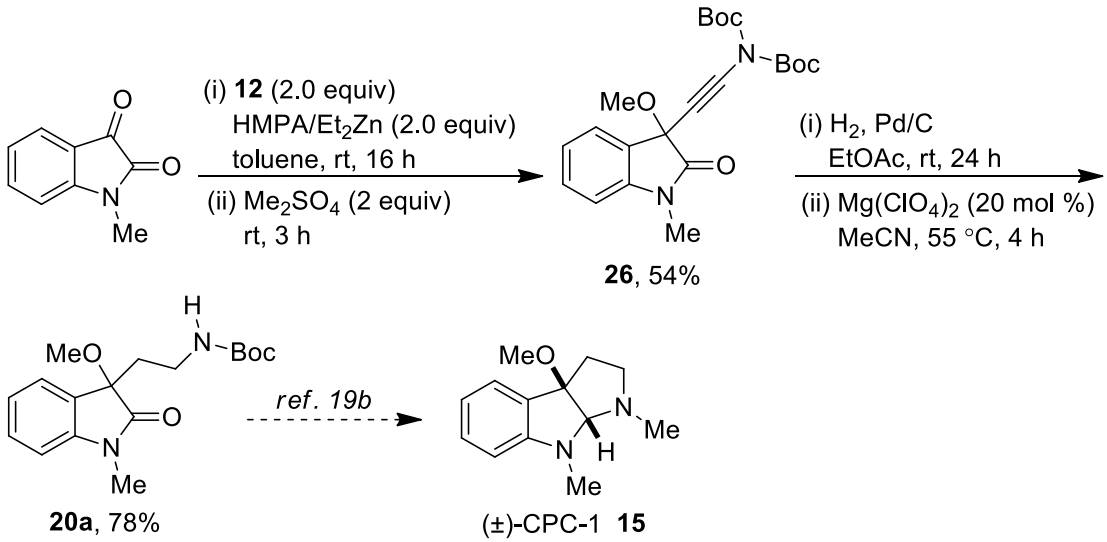
We next revisited our pyrrolidinoindoline synthetic strategy with the goal of using an alternative ynamide derivative for the key aminoethylation. Drawing a parallel with Gabriel amination[2] strategies which utilize phthalimide or di-Boc-imide nucleophiles as masked amines, our efforts focused on investigating imide functionalized alkynes as ethyleneamine synthons. In this regard, we were particularly attracted to the previously reported *N*,*N*-di-Boc terminal ynimide **12**[24] because it appeared straightforward to prepare, and possessed flexible Boc carbamate protecting groups which should be easy to remove or manipulate.[25] Under slightly modified conditions to those described previously,[24] ynimide **12** was prepared in synthetically useful quantities via addition of di-*tert*-butyl-iminodicarboxylate **24** to alkynyl-iododium triflate reagents **25** with mild heating (Scheme 5).



Scheme 5. Synthesis of di-*tert*-butyl ethynylimidodicarbonate ynimide reagent **12** from alkynyliodonium triflate reagents **25**

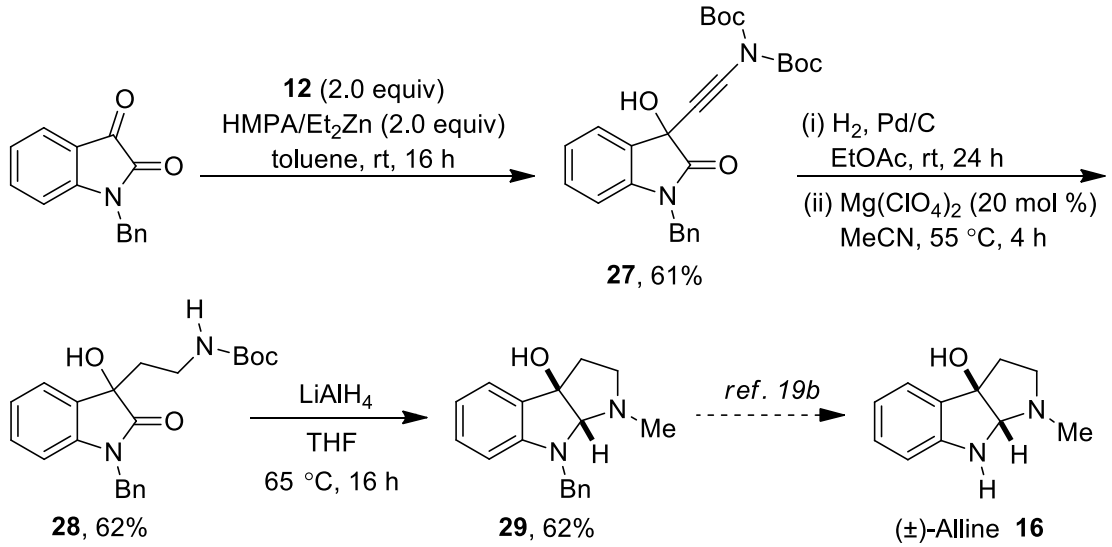
With ynimide **12** in hand, we revisited our terminal *N*-linked alkyne aminoethylation concept in additions to protected isatins toward the synthesis of the alkaloids (±)-CPC-1

15 and (±)-alline **16**. In contrast to our prior ynehydrazide results in this area, attempts to generate the lithium-acetylide of **12** with *n*-BuLi or LDA followed by trapping with *N*-Me-isatin resulted in unsatisfactory carbonyl addition. Ultimately, a slight modification of literature conditions for room temperature formation of Zn-acetylides using a Et_2Zn/HMPA mixture[26] was found to allow for clean addition of **12**. Functionalized ynimide **26** was obtained after tertiary alcohol methylation (Scheme 6). Importantly, this ynimide strategy was successful in completing the formal total synthesis of pyrrolidinoindoline (±)-CPC-1 **15** via hydrogenation and $Mg(ClO_4)_2$ catalyzed imide mono-Boc deprotection[22] to provide ethyleneamine compound **20a** which is known to undergo reductive cyclization to the target alkaloid.[19b]



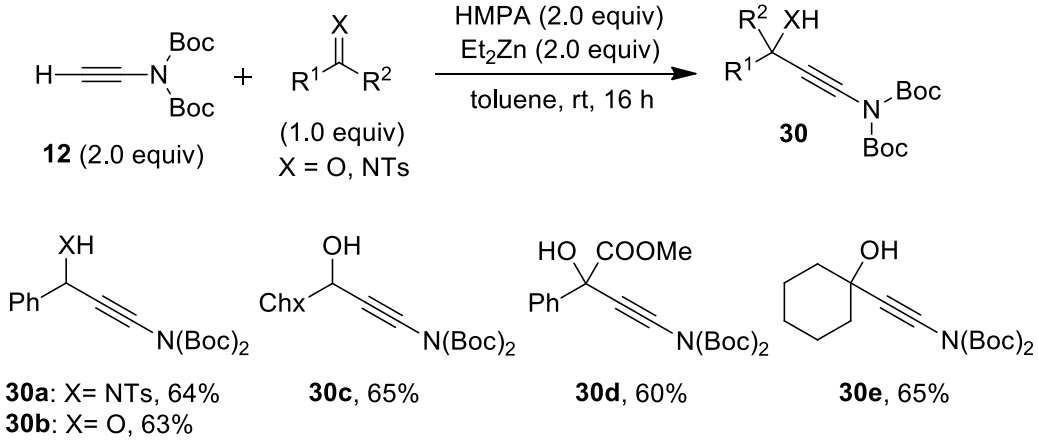
Scheme 6. Formal synthesis of (±)-CPC-1 using an ynimide aminoethylation approach

The related alkaloid (±)-alline **16** was then accessed in a similar fashion via Zn-acetylide addition of ynimide **12** to *N*-benzyl isatin to give **27** (Scheme 7). Subsequent hydrogenation/deprotection afforded intermediate **28**. The formal synthesis was realized by reductive cyclization with $LiAlH_4$ to provide compound **29** which is known to undergo benzyl deprotection to provide the target alkaloid.[19b]



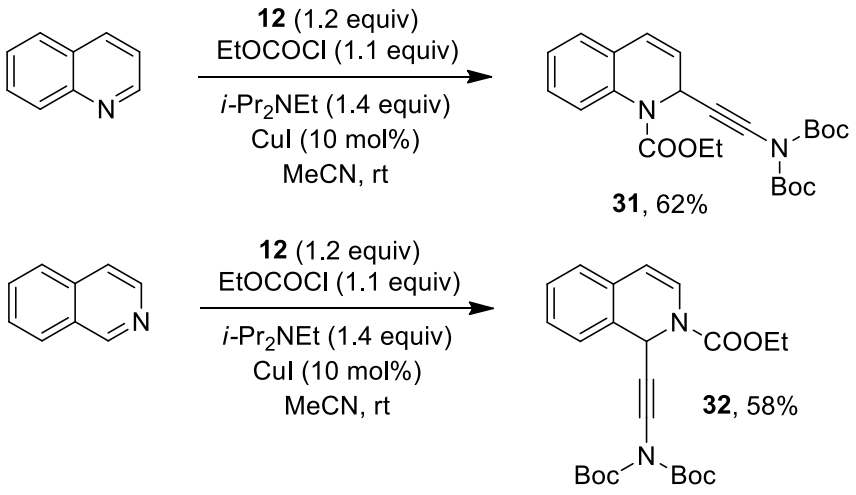
Scheme 7. Formal synthesis of (±)-alline using an ynimide aminoethylation approach

These results illustrate how the *N*,*N*-di-boc imide group is a superior ynamide alkyne substituent versus other commonly used sulfonamide or urethane groups, because its flexibility toward deprotection or conversion to other amine functional groups. Based on these results, we investigated the generality of this ynimide based aminoethylation strategy using **12** as an acetylide nucleophile with a variety of other common electrophiles. The Zn-acetylide of **12** was found to undergo reaction with other carbonyl species including aldehydes, ketones and imines (Scheme 8). Only activated imines like those possessing an *N*-sulfonyl group were found to be reactive with the Zn-acetylide of **12**, and attempts to alkynylate aldehydes with **12** under catalytic conditions[27] were unsuccessful.



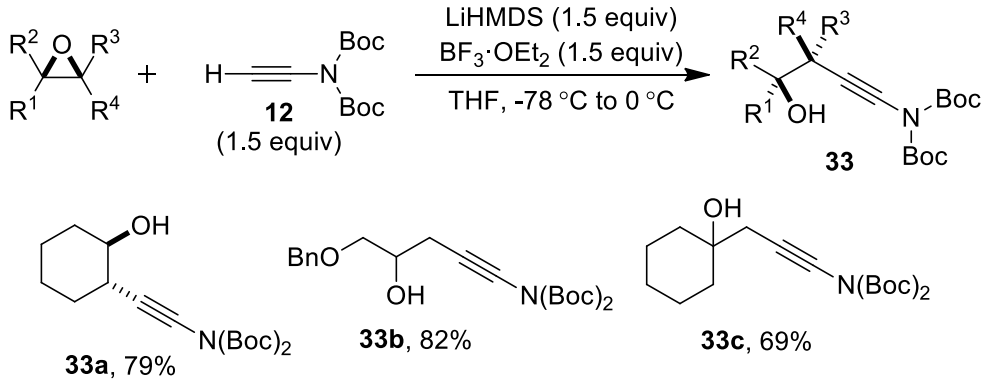
Scheme 8. Reaction of di-*tert*-butyl ethynylimidodicarbonate ynimide **12** with carbonyl and sulfonylimine electrophiles

Di-*tert*-butyl ethynylimidodicarbonate **12** was also found to participate in a copper-catalyzed multicomponent *N*-acyl pyridinium salt reaction[28] providing access to interesting ynimide functionalized dihydroquinoline **31** and dihydroisoquinoline **32** compounds (Scheme 9). Although two regioisomeric addition sites exist in the quinoline case, only the 1,2-addition product **31** was observed which is consistent with previous observations using other alkyne additions.[28]

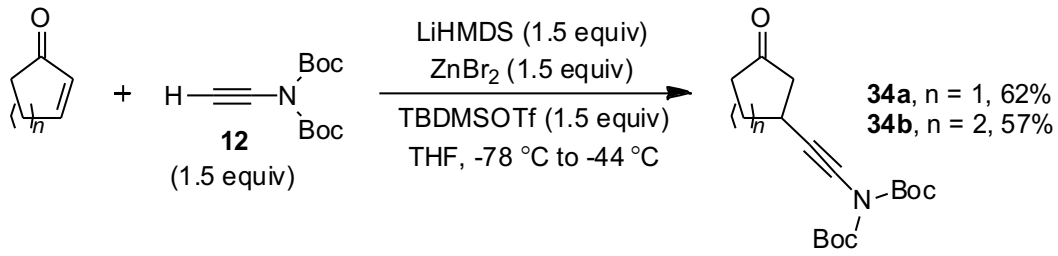


Scheme 9. Copper-catalyzed reaction of di-*tert*-butyl ethynylimidodicarbonate ynimide **12** with heteroaromatic *N*-acyliminium ions

The first examples of terminal ynamide addition to epoxide and Michael acceptor electrophiles were also achieved with ynimide reagent **12** (Schemes 10 and 11). For addition of **12** to epoxides, the Yamaguchi conditions[29] were found to be generally optimal for formation of **33**. Poor regioselectivity (~1:1) was observed with styrene oxide which did not improve using alternative conditions. In addition, attempts to facilitate a Michael addition of ynimide **12** using rhodium catalysis were unsatisfactory and resulted in a complex mixture of products. However, 1,4-addition of **12** could be achieved via reaction of the Zn-acetylide in combination with TBDMSOTf activation of the Michael acceptor.[30] In order to reveal the desired ketone products **34**, tetrabutylamonnium fluoride was used to cleave the silyl-enol ether intermediates due to the acidic sensitivity of the ynimide fragment.

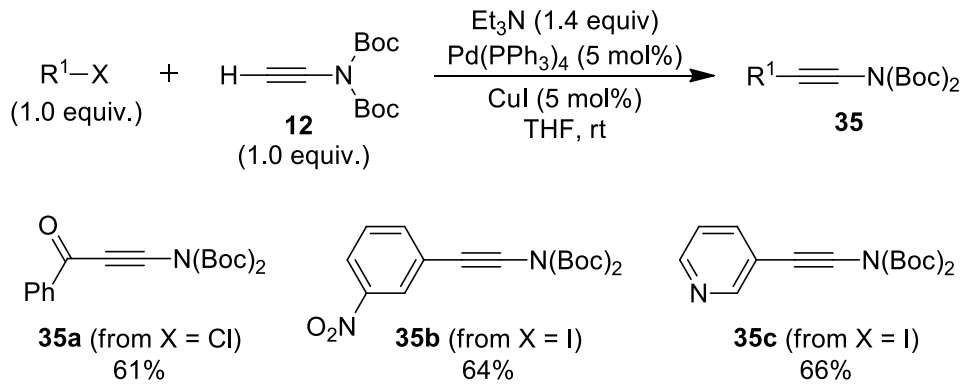


Scheme 10. Reaction of di-*tert*-butyl ethynylimidodicarbonate ynimide **12** with epoxides



Scheme 11. Reaction of di-*tert*-butyl ethynylimidodicarbonate ynimide **12** with enones

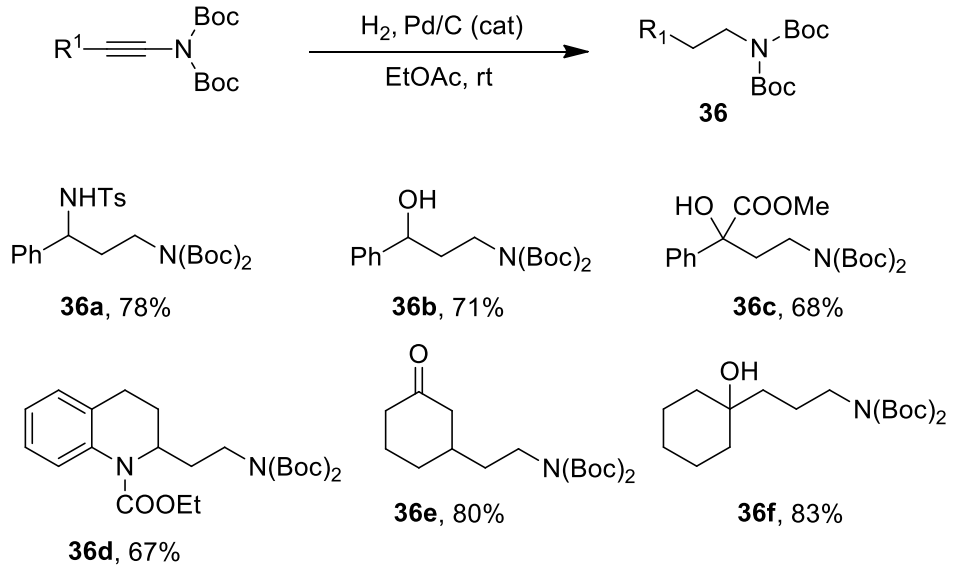
Ynimide **12** was also functionalized with acyl and aryl groups using metal-catalyzed Sonogashira conditions to give the coupled products **35** (Scheme 12). Efficient ynimide arylation was only observed using aryl iodides as coupling partners as the use of aryl-bromides resulted in low amounts of desired aryl-coupled ynimide product, possibly as a result of competing metal facilitated oxazolinone cyclization of *N*-Boc alkyne **12**.[24]



Scheme 12. Sonogoshira couplings with di-*tert*-butyl ethynylimidodicarbonate ynimide **12**

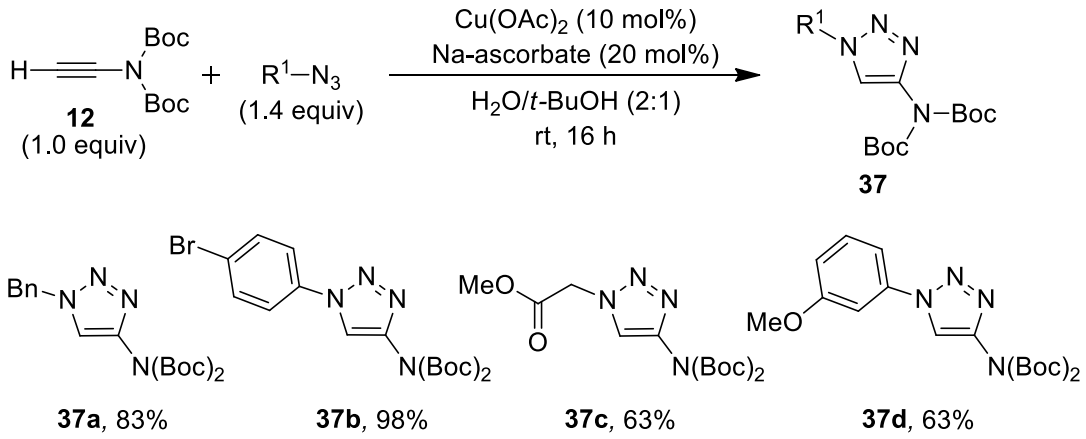
To exemplify the generality of an alkynyl-imide aminoethylation strategy, a variety of the functionalized alkynyl-imides prepared above were reduced using simple Pd/C hydrogenation conditions. This approach afforded the corresponding ethyleneamine products **36** (Scheme 13). Importantly, expanded access to aminoethyl structures including valuable diamine and amino-alcohol products demonstrates how this ynimide reaction sequence is differentiated from other aminoethylation strategies which typically only provide access to aryl-functionalized ethyleneamines.[7,8] In addition, the di-Boc group can be readily deprotected into the fully deprotected amine, or the mono-Boc

carbamates using catalytic $Mg(ClO_4)_2$, which in turn can be converted into N-methylamines by reduction with $LiAlH_4$, *vide supra*.

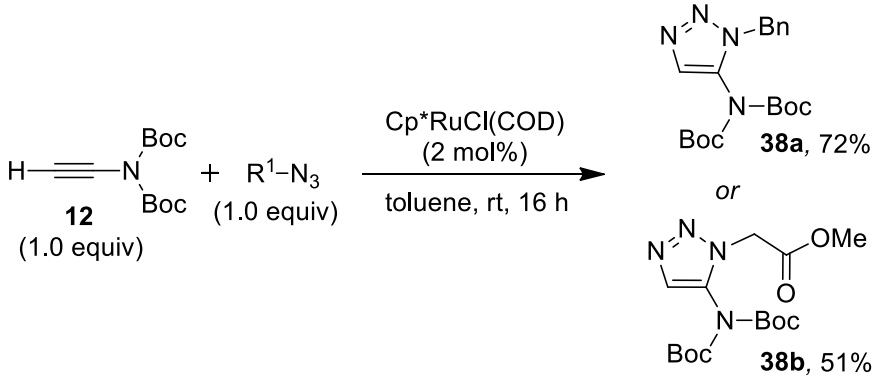


Scheme 13. Aminoethylation products **36** derived from di-*tert*-butyl ethynylimidodicarbonate ynimide reagent **12**

In addition to aminoethylation, the ynimide reagent **12** can also be used to incorporate the convenient and flexible Boc-imide group in pharmaceutically relevant heterocycles through the use of subsequent [3+2] cycloadditions. For example, copper-catalyzed [3+2] cycloaddition reaction of **12** with azides,[31] affords 4-substituted 1,2,3-triazoles **37** functionalized with the easily de-blocked di-Boc imide group (Scheme 14). Furthermore, application of Fokin's ruthenium catalyzed conditions[32] results in a complete regioselectivity switch to provide 5-imide substituted 1,2,3-triazoles **38** (Scheme 15). This interesting electronically biased regioselectivity outcome with ruthenium is consistent with Fokin's observations and other related [3+2] results.[16a]

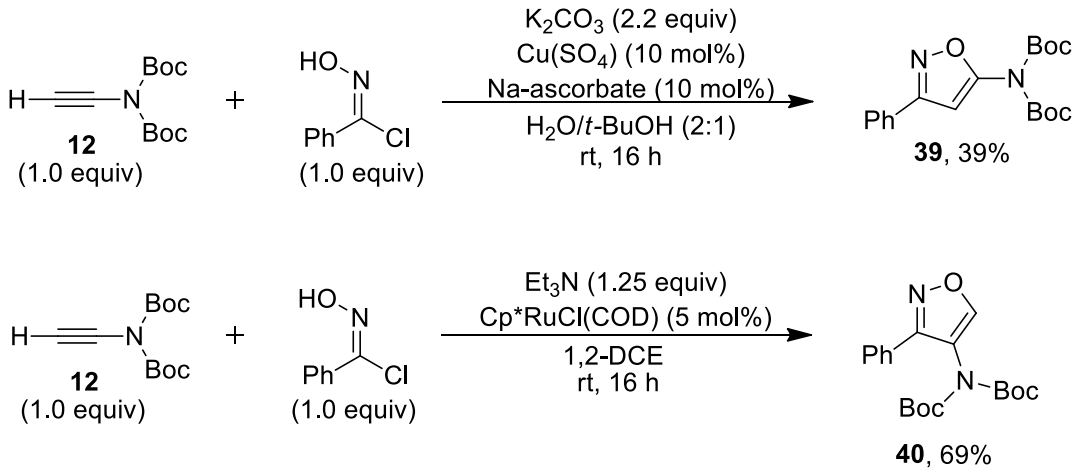


Scheme 14. Cu-catalyzed synthesis of 4-imide-functionalized triazoles from di-*tert*-butyl ethynylimidodicarbonate ynimide **12**



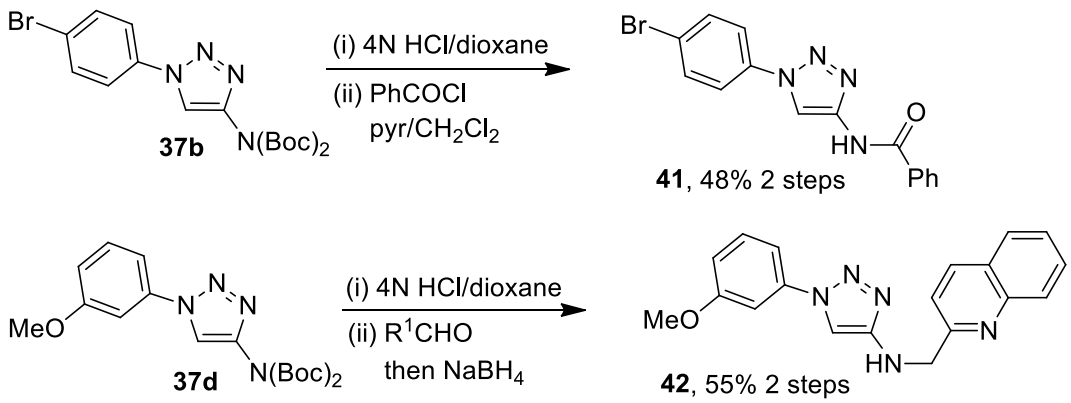
Scheme 15. Ru-catalyzed synthesis of 5-imide functionalized triazoles from di-*tert*-butyl ethynylimidodicarbonate ynimide **12**

In a related fashion, di-Boc ynimide **12** can also be used to generate imide functionalized isoxazoles such as **39** (Scheme 16). Again, a complete regioselectivity switch in isoxazole formation is observed using Fokin's ruthenium catalyzed conditions[33] versus copper-catalysis, to afford the regioisomeric adduct **40**.



Scheme 16. Catalytic synthesis of imide-functionalized isoxazoles from di-*tert*-butyl ethynylimidodicarbonate ynimide **12**

As an illustration of the simplicity with which these di-Boc imide functionalized heterocycles can be deprotected and exploited, amide and amine functionalized triazoles **41** and **42** were synthesized via a Boc-group deprotection / acylation or reductive amination strategy, respectively (Scheme 17). In this regard, ynimide **12** is shown to be a more flexible reagent for heterocycle amine-functionalization via introduction of the di-Boc imide group versus conventional ynamide cycloadducts possessing sulfonamide or urethane nitrogen-functionality.



Scheme 17. Deprotection and reaction of Boc-imide functionalized triazoles

Conclusion

Di-*tert*-butyl ethynylimidodicarbonate reagent **12** is a useful precursor to generate functionalized internal ynimides as well as di-Boc imide functionalized triazole and isoxazole heterocycles. The ynimide products included in this report were constructed using new examples of ynamide acetylide reactivity with carbonyl groups, imines, epoxides, Michael acceptors, and pyridinium ions. Importantly, ynimide **12** is demonstrated to function as an ethyleneamine building block via simple hydrogenation of internal ynimide products resulting in straightforward access to useful aminoethylated structures including alkaloid natural products. Future work in this area includes the investigation of asymmetric ynimide carbonyl alkynylations as well as using reagent **12** to prepare other alkaloids through possible epoxide opening or 1,4-addition strategies. Analogous chemistry is also possible using the tri-Boc protected terminal ynehydrazide **13**, which serves as a synthetic equivalent to a nucleophilic β-hydrazinoethyl anion synthon. Overall, we hope that this study will encourage others to consider terminal ynamide acetylide disconnections in complex molecule syntheses.

Experimental Section:

THF was dried over sodium benzophenone-ketyl and toluene and acetonitrile were dried over calcium hydride and distilled fresh under nitrogen atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. The following reagents were prepared according to previously reported literature conditions: *N*-hydroxybenzimidoyl chloride,[34] 1-methylindoline-2,3-dione[35] and 1-benzylindoline-2,3-dione,[36] 1-oxaspiro[2.5]octane,[37] (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide,[38] methyl 2-azidoacetate,[39] and aryl-azides.[40] All other reagents including catalysts, LiHMDS (1.0 M in THF), KHMDS (0.5 M in toluene), Tf_2O (1.0 M in CH_2Cl_2), Et_2Zn (1.0 M in hexanes), alkynes, di-*tert*-butyl-azodicarboxylate, epoxides, Michael acceptors, benzoyl-chloride, aryl-halides, aldehydes (passed through short plug of basic Al_2O_3 immediately prior to use), ketones and benzyl azide were purchased from Aldrich or VWR and used as received unless otherwise stated. NMR solvent ($CDCl_3$ with TMS internal standard) was purchased from Cambridge Isotopes Lab Inc. and used as received.

All products were characterized by ^{1}H NMR and ^{13}C NMR, IR and HRMS. ^{1}H NMR and ^{13}C NMR were recorded on Varian Mercury 300 MHz, Varian Mercury 400 MHz, and Bruker 500 MHz spectrometers. Chemical shifts are expressed in ppm values and ^{1}H NMR spectra are referenced to 0.00 ppm for Me_4Si (TMS) and solvent residual peak of 2.50 ppm for d_6-DMSO. ^{13}C NMR spectra are referenced to 77.00 ppm for $CDCl_3$ and 39.52 ppm for d_6-DMSO. Peak multiplicities are designated by the following abbreviations: s, singlet; br.s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; r, rotomers; *J*, coupling constant in Hz. If a coupling pattern can be assigned as a combination of multiplicities, then the listed abbreviations are combined to provide an appropriate descriptor for the observed patterns (e.g., dt–doublet of triplets). IR spectra were obtained on a Shimadzu FTIR-8400S with samples loaded as thin films on NaCl plates neat or with CH_2Cl_2 as indicated. Mass spectra were obtained by the University of Toronto mass spectral facility (AIMS); high resolution mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Flash column chromatography was performed on silica gel (60 Å, 230-400 mesh, obtained from Silicycle Inc.) using reagent grade EtOAc and hexanes as eluent (gradient elution 0-100% EtOAc unless otherwise stated). Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL G/UV254 purchased from Silicycle Inc.) and visualized with a UV lamp (254 nm) or $KMnO_4$ stain and heating.

Tri-*tert*-butyl 2-ethynylhydrazine-1,1,2-tricarboxylate (13)

In a nitrogen flushed 250 mL flask capped with a rubber septa was charged THF (30 mL) and ethynyltrimethylsilane (1.42 mL, 10.0 mmol, 1.0 eq.) under N_2 and cooled to -78 °C in a dry ice/acetone bath. A solution of *n*-BuLi (4.80 mL of a 2.5 M solution in hexanes, 12.0 mmol, 1.2 eq.) was then added dropwise over 1-2 min and the resulting mixture stirred at -78 °C for 15 min. A solution of DBAD (di-*t*-butyl-azodicarboxylate, 3.45 g, 15.0 mmol, 1.5 eq.) in THF (15 mL) was then added over 1-2 min and the cooling bath removed and the mixture allowed to warm to room temperature and stirred at room temperature for 30 min. The reaction mixture was then re-cooled to -78 °C and Boc_2O (1.83 g, 15.0 mmol, 1.5 eq.) in THF (6 mL) added and the cooling bath removed and the

mixture allowed to warm to room temperature and stirred at room temperature for 30 min. The reaction mixture was then quenched by addition of saturated NH_4Cl (aq.) (30 mL) and diluted with EtOAc (100 mL) and water (20 mL) and the layers separated. The organic extract was dried ($MgSO_4$), filtered through a Si plug topped with Celite (2" tall x 1" wide) using EtOAc (50 mL) to wash/elute and the filtrate concentrated under reduced pressure to provide 3.90 g of a yellow oil. The resulting crude residue was dissolved in THF (20 mL) and cooled to 0 °C and treated with tetra-*n*-butyl-ammonium fluoride (TBAF, 18.2 mL of a 1M solution in THF, 18.2 mmol, ~2.0 eq.) and stirred for 45 min in the ice/water bath. The reaction mixture was then diluted with water (100 mL) and extracted with Et_2O (2 x 300 mL). The organic extracts were combined, washed with water (50 mL) then saturated NaCl (aq.) (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was then purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **13** (1.80 g, 51% yield over 2 steps) as a yellow oil. R_f = 0.37 (20% EtOAc/hexanes); IR (neat, cm^{-1}) 3272, 2981, 2936, 2148, 1807, 1750, 1478, 1456, 1393, 1146, 1002, 847; ^1H NMR (400 MHz, $CDCl_3$) δ 3.08 – 2.93 (1H, r, m), 1.43–1.60 (27H, m); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.0, 148.7, 84.4, 74.3, 60.7, 60.1, 27.90, 27.84; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{28}N_2O_6Na$, 379.1839; Found, 379.1852.

Tri-*tert*-butyl-2-((3-methoxy-1-methyl-2-oxoindolin-3-yl)ethynyl)hydrazine-1,1,2-tricarboxylate (19a)

Terminal ynehydrazide **13** (535 mg, 1.5 mmol, 1.5 eq.) was dissolved in THF (5 mL) and cooled to -78 °C in a dry ice/acetone bath. A solution of *n*-BuLi (0.60 mL of a 2.5 M solution in hexanes, 1.5 mmol, 1.5 eq.) was then added dropwise over 1-2 min and the resulting mixture stirred at -78 °C for 15 min. A solution of *N*-Me isatin (161 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was then added and the cooling bath removed and the mixture allowed to warm to room temperature. After stirring for 1 h at room temperature dimethylsulfate (0.24 mL, 2.5 mmol, 2.5 eq.) was added and the mixture stirred at room temperature for a further 3 h. The reaction mixture was then diluted with water (25 mL) and EtOAc (75 mL) and the phases separated. The aqueous phase was extracted again

with EtOAc (50 mL) and the organic extracts combined and washed with saturated NaCl (aq.) (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was then purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **19a** (407 mg, 76% yield over 2 steps) as an orange oil after vacuum line drying to remove residual dimethylsulfate. R_f = 0.38 (40% EtOAc/hexanes); IR (neat, cm^{-1}) 3059, 2981, 2935, 2258, 1801, 1730, 1700, 1622, 1478; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.50 (1H, m), 7.29–7.37 (1H, m), 7.02–7.12 (1H, m), 6.78–6.85 (1H, m), 3.58–3.66 (3H, r, m), 3.12–3.23 (3H, r, m), 1.40–1.55 (27H, m); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.3, 151.0, 148.86, 148.79, 143.1, 130.4, 128.0, 124.8, 123.1, 108.6, 84.7, 84.51, 84.46, 80.3, 74.3, 67.5, 52.9, 28.1, 27.9, 27.8, 26.3; HRMS (EI) *m/z*: $[M + NH_4]^+$ Calcd for $C_{27}H_{41}N_4O_8$, 549.2924; Found, 549.2910.

Di-*tert*-butyl 1-(2-(3-methoxy-1-methyl-2-oxoindolin-3-yl)ethyl)hydrazine-1,2-dicarboxylate (22a)

Compound **19a** (215 mg, 0.405 mmol, 1.0 eq.) was dissolved in MeCN (5 mL) and $Mg(ClO_4)_2$ (9 mg, 0.04 mmol, 0.1 eq.) was added and the flask fitted with a reflux condenser and placed in a 55 °C oil bath. After 4 h, ^1H NMR of an aliquot showed conversion to the imide mono-Boc deprotected product. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude residue was dissolved in EtOAc (40 mL) and filtered through a Celite pad and concentrated under reduced pressure again to provide 180 mg (quant. yield) of the crude mono imide-Boc deprotected intermediate. The crude residue thus obtained was dissolved in EtOAc (10 mL) and Pd/C added (90 mg 10% w/w, ~0.2 eq. Pd). The flask was capped with a rubber septa and purged with N_2 for 2 min. then a balloon of H_2 attached and purged for 5 min before a fresh H_2 balloon attached and the mixture stirred at room temperature overnight. After 24 h, the reaction mixture was filtered through Celite using EtOAc (40 mL) to wash/elute and concentrated under reduced pressure. The crude residue was then purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **22a** (94 mg, 53% yield over 2 steps) as a yellow oil. R_f= 0.36 (40% EtOAc/hexanes); IR (neat, cm^{-1}) 3322, 3057, 3001, 2938, 2828, 2253, 1743, 1662, 1603,

1476; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.44 (2H, m), 7.00–7.21 (1H, m), 6.84 (1H, d, *J* = 6.0 Hz), 6.28–6.58 (1H, r, m), 3.26–3.65 (2H, m), 3.18 (3H, s), 2.99 (3H, s), 2.28–2.48 (1H, m), 2.07–2.26 (1H, m), 1.28–1.52 (18H, m); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.1, 155.0, 154.6, 144.2, 130.1, 128.0, 124.2, 123.2, 108.5, 81.7, 80.8, 77.2, 52.5, 43.4, 34.3, 28.2, 28.1, 26.1; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{34}N_3O_6$, 436.2448; Found, 436.2441.

3-(2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)ethyl)-3-methoxy-1-methylindolin-2-one (23a)

Compound **22a** (45 mg, 0.103 mmol, 1.0 eq.) was dissolved in MeOH (1 mL) in a capped microwave vial and 2,4-pentanedione added (15.5 mg, 0.016 mL, 0.154 mmol, 1.5 eq.) followed by addition of 4N HCl in dioxane (0.5 mL). The mixture was stirred at room temperature for 30 min then placed in an 80 °C oil bath for 30 min. The reaction was cooled to room temperature and the volatiles removed under an air stream. The crude residue was then partitioned between CH_2Cl_2 (40 mL) and saturated $NaHCO_3$ (aq.) (10 mL) and the phases separated. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure and the crude residue purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **23a** (16.2 mg, 52% yield) as a yellow oil. R_f = 0.09 (60% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3091, 2981, 2930, 2827, 1720, 1612, 1553, 1471, 1372, 1347, 1121, 1094, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, app td, *J* = 7.5, 1.0 Hz), 7.28 (1H, d, *J* = 7.0 Hz), 7.10 (1H, app t, *J* = 7.5 Hz), 6.84 (1H, d, *J* = 8.0 Hz), 5.71 (1H, s), 4.10–4.30 (2H, m), 3.21 (3H, s), 3.03 (3H, s), 2.40 (1H, ddd, *J* = 14.0, 10.5, 6.0 Hz), 2.27 (1H, ddd, *J* = 14.0, 10.0, 5.5 Hz), 2.20 (3H, s), 2.15 (3H, s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.4, 147.2, 143.7, 138.8, 130.0, 126.7, 124.3, 123.1, 108.4, 104.8, 81.0, 53.0, 42.8, 37.8, 26.1, 13.4, 10.9; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3O_2$, 300.1712; Found, 300.1711.

3-(2-(4-Chloro-3,5-dimethyl-1*H*-pyrazol-1-yl)ethyl)-3-methoxy-1-methylindolin-2-one (23b)

An identical procedure used for the preparation of compound **23a** using compound **22a** (39 mg, 0.090 mmol, 1.0 eq.) and 3-chloro-2,4-pentanedione (17 mg, 0.014 mL, 0.127 mmol, 1.4 eq.) provided compound **6** (9.2 mg, 30% yield) as a yellow wax. R_f = 0.17 (60% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3080, 2931, 2828, 1722, 1612, 1471, 1373, 1348, 1124, 1092, 753; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, app td, *J* = 7.5, 1.5 Hz), 7.26–7.29 (1H, m), 7.10 (1H, app td, *J* = 7.5, 1.0 Hz), 6.84 (1H, d, *J* = 8.0 Hz), 4.11–4.31 (2H, m), 3.21 (3H, s), 3.02 (3H, s), 2.39 (1H, ddd, *J* = 14.0, 10.0, 6.0 Hz), 2.24 (1H, ddd, *J* = 14.0, 10.0, 6.0 Hz), 2.18 (3H, s), 2.13 (3H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.3, 144.2, 143.7, 135.1, 130.1, 126.6, 124.2 (2C), 123.1, 108.5, 80.8, 53.0, 43.9, 37.7, 26.2, 11.2, 9.2; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{21}ClN_3O_2$, 334.1322; Found, 334.1327.

Di-*tert*-butyl-iminodicarboxylate (24)

Di-*tert*-butyl-iminodicarboxylate is commercially available but can also be conveniently prepared according to the following adaptation of a literature protocol:[41] NH_4Cl (1.07 g, 20.0 mmol, 1.0 eq.) was added to a 0 ºC solution of Boc_2O (18.70 g, 85.78 mmol, 4.29 eq.) in MeCN (20 mL) and a solution of DMAP (4.90 g, 40.0 mmol, 2.0 eq.) in MeCN (65 mL) was added dropwise by addition funnel over 30 min under N_2 and the mixture was allowed to stir overnight, warming to room temperature. After 18 h, the reaction mixture was concentrated under reduced pressure and the resulting residue was partitioned between Et_2O (150 mL) and 5% aqueous citric acid solution (50 mL) and separated. The organic extract was washed again with 5% aqueous citric acid (50 mL) then with saturated $NaHCO_3$ (aq.) (2 x 50 mL) followed by saturated NaCl (aq.) (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide *N*,*N*,*N*-tri-*tert*-butyl iminotricarboxylate (4.98 g, 79% yield) as a waxy solid. *N*,*N*,*N*-Tri-*tert*-butyl-tri-iminocarboxylate (4.90 g, 15.46 mmol, 1.0 eq.) was dissolved in MeOH (20 mL) and hydrazine-monohydrate (3.0 mL, 61.8 mmol, 4.0 eq.) was added under N_2 at room temperature. The reaction mixture was stirred for 4 h at room temperature then diluted

with Et_2O (100 mL) and washed with 10% HCl (aq.) (2 x 25 mL) followed by saturated $NaHCO_3$ (aq.) (2 x 25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to provide compound **9** (3.05 g, 91% yield) as a white solid.

Di-*tert*-butyl ethynylimidodicarbonate (12)

From terminal alkynyl iodonium salt 25a: A suspension of $PhI(OAc)_2$ (5.96 g, 18.5 mmol, 1.0 eq.) in CH_2Cl_2 (10 mL) at 0 ºC was treated with Tf_2O (9.25 mL of a 1.0 M solution in CH_2Cl_2, 9.25 mmol, 0.5 eq.) under N_2. This mixture was stirred for 30 min in the ice bath then tributyl(ethynyl)stannane (5.80 g, 18.5 mmol, 1.0 eq.) was added by syringe and the reaction mixture stirred for 90 min in the cooling bath. The volatiles were then removed on a rotary evaporator followed by brief vacuum line drying (5 min). The residue thus obtained was slurried in Et_2O (5 mL) and the solids filtered off using Et_2O (25 mL) to wash to provide the terminal alkynyl iodonium salt **25a** (6.19 g, 88% yield) as a white solid which should be reacted within 2-3 h of preparation.

Di-*tert*-butyl-iminodicarboxylate **24** (868 mg, 4.0 mmol, 1.0 eq.) in a N_2 flushed flask was dissolved in toluene (118 mL) and cooled to 0 ºC and KHMDS (8.40 mL of a 0.5 M solution in toluene, 4.20 mmol, 1.05 eq.) was added. After stirring for 30 min, freshly prepared terminal alkynyl iodonium salt **25a** (2.72 g, 7.20 mmol, 1.8 eq.) was added in one portion and the mixture was removed from the cooling bath and after warming to room temperature (20 min) the flask was placed in a 45 ºC oil bath with a reflux condenser. After 16 h, the reaction mixture was cooled to room temperature and filtered through a short plug of Celite using toluene (75 mL) to wash/elute and the filtrate was concentrated under reduced pressure. The resulting crude residue was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **12** (525 mg, 55% yield) as a yellow oil.

From TMS-alkynylphenyliodonium triflate 25b: TMS-alkynylphenyliodonium triflate was prepared following a literature protocol,[42] the following is representative: a suspension of $PhI(OAc)_2$ (12.9 g, 40.0 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) at 0 ºC was

treated with Tf_2O (20.0 mL of a 1.0 M solution in CH_2Cl_2, 20.0 mmol, 0.5 eq.) under N_2. This mixture was stirred for 30 min in an ice bath then bis-trimethylsilylacetylene (6.8 g, 9.08 mL, 40.0 mmol, 1.0 eq.) was added by syringe and stirred for 1 h in an ice bath, then the volatiles were removed under reduced pressure followed by brief vacuum line drying (5 min). The residue thus obtained was slurried in Et_2O (20 mL) and the solids filtered off using Et_2O (25 mL) to wash to provide TMS-alkynylphenyliodonium salt **25b** (14.8 g, 82% yield) as a white solid.

Di-*tert*-butyl-iminodicarboxylate **24** (2.65 g, 12.21 mmol, 1.0 eq.) in a N_2 flushed 1-L flask was dissolved in toluene (400 mL) and cooled to 0 ºC and KHMDS (25.6 mL of a 0.5 M solution in toluene, 12.8 mmol, 1.05 eq.) was added. After stirring for 30 min, TMS-alkynylphenyliodonium salt **25b** (13.74 g, 30.5 mmol, 2.5 eq.) was added in two equal portions over 30 min and the mixture was removed from the cooling bath and after warming to room temperature (20 min) the flask was placed in a 65 ºC oil bath with an attached reflux condenser. After 15 h, the reaction mixture was cooled to room temperature and filtered through a short plug of Celite and the filtrate was concentrated under reduced pressure. The resulting crude residue was dissolved in THF (10 mL) and cooled to 0 ºC and treated with tetra-*n*-butyl-ammonium fluoride (TBAF, 24.4 mL of a 1M solution in THF, 24.4 mmol, ~2 eq.) and stirred for 15 min in the cooling bath then stirred for 1 h at room temperature. The reaction mixture was then diluted with water (100 mL) and extracted with Et_2O (2 x 200 mL). The organic extracts were combined, washed with water (3 x 50 mL) then with saturated NaCl (aq.) (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was then purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **12** (1.52 g, 51% yield) as a yellow oil. R_f = 0.45 (20% EtOAc/hexanes); IR (neat, cm^{-1}) 3281, 2982, 2937, 2156, 1805, 1766, 1479, 1456, 1396, 1371, 1348, 1309, 1244, 1138, 846; ^1H NMR (300 MHz, $CDCl_3$) δ 2.99 (1H, s), 1.54 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.6, 85.0, 71.6, 62.6, 27.7; HRMS (EI) *m/z*: $[M + NH_4]^+$ Calcd for $C_{12}H_{23}N_2O_4$, 259.1658; Found, 259.1655.

Di-*tert*-butyl-((3-methoxy-1-methyl-2-oxoindolin-3-yl)ethynyl)-imidocarbonate (26)

A N_2 purged flask containing di-*tert*-butyl ethynylimidodicarbonate **12** (96 mg, 0.40 mmol, 2.0 eq.) and HMPA (72 mg, 0.07 mL, 0.40 mmol, 2.0 eq.) in toluene (1.0 mL) was treated with Et_2Zn (0.40 mL of a 1 M solution in hexanes, 0.40 mmol, 2.0 eq.) at room temperature. After stirring for 2 h, 1-methylindoline-2,3-dione (32 mg, 0.20 mmol, 1.0 eq.) in toluene (1.0 mL) was added and the reaction mixture was stirred at room temperature overnight. After 14 h, dimethyl sulfate (50 mg, 0.038 mL, 0.40 mmol, 2.0 eq.) was added and the reaction mixture stirred at room temperature for 3 h. Then, saturated NH_4Cl (aq.) (5 mL) and H_2O (5 mL) were added in that order and organics were extracted with EtOAc (50 mL). The organic extract was washed with 1M NaOH (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified through silica gel chromatography (pre-treated with 1% Et_3N in hexanes, using gradient elution 0-100% EtOAc in hexanes) to provide compound **26 (**45 mg, 54% yield) as a yellow oil. R_f= 0.48 (40% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 2982, 2938, 2829, 2268, 1809, 1770, 1728, 1614, 1471, 1371, 1238, 1136, 1105, 1018, 845; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.46 (1H, m), 7.34 (1H, app td, J = 8.0, 1.0 Hz), 7.05–7.11 (1H, m), 6.82 (1H, d, J = 8.0 Hz), 3.64 (3H, s), 3.19 (3H, s), 1.49 (18H, s); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.3, 148.8, 143.1, 130.4, 127.8, 124.7, 123.1, 108.6, 85.0, 76.9, 74.2, 69.5, 53.2, 27.7, 26.2; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{28}N_2O_6Na$, 439.1839; Found, 439.1846.

***tert*-Butyl (2-(3-methoxy-1-methyl-2-oxoindolin-3-yl)ethyl)carbamate (20a)**

To a solution of compound **26** (18 mg, 0.043 mmol, 1.0 eq.) dissolved in EtOAc (5 mL) was added Pd/C (9.0 mg of 10% w/w dry) and the flask was capped with a rubber septa and purged with N_2 then purged with a balloon of H_2 (5 min) and stirred at room temperature under a balloon of H_2 for 12 h. The reaction flask was then purged with N_2 and the reaction mixture filtered through Celite using EtOAc (40 mL) to wash/elute and the filtrate concentrated under reduced pressure. The resulting crude residue (18 mg) was dissolved in MeCN (3 mL) and $Mg(ClO_4)_2$ (2.1 mg, 0.0086 mmol, 0.2 eq.) was added and the flask was placed in a 55 ºC oil bath with a reflux condenser under N_2 for 2.5 h.

The reaction mixture was cooled to room temperature and the volatiles removed under reduced pressure and the crude residue was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **20a** (10.8 mg, 78% yield) as a gum. R_f = 0.31 (40% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3364, 2976, 2933, 2828, 1713, 1614, 1500, 1472, 1367, 1348, 1250, 1173; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.39 (2H, m), 7.10–7.15 (1H, m), 6.85 (1H, d, *J* = 8.0 Hz), 4.92 (1H, br s), 3.23–3.33 (2H, m), 3.21 (3H, s), 3.01 (3H, s), 2.08 (2H, t, *J* = 6.5 Hz), 1.41 (9H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 175.8, 155.8, 143.7, 130.0, 126.8, 124.4, 123.2, 108.6, 81.9, 79.0, 53.0, 37.4, 35.4, 28.4, 26.2; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{25}N_2O_4$, 321.1814; Found, 321.1822.

Di-*tert*-butyl ((3-hydroxy-1-benzyl-2-oxoindolin-3-yl)ethynyl)-imidocarbonate (27)

A N_2 purged flask containing di-*tert*-butyl ethynylimidodicarbonate compound **12** (96 mg, 0.40 mmol, 2.0 eq.) and HMPA (0.07 mL, 0.40 mmol, 2.0 eq.) in toluene (1.0 mL) was treated with Et_2Zn (0.40 mL of a 1 M solution in hexanes, 0.40 mmol, 2.0 eq.) at room temperature. After stirring for 2 h, 1-benzylindoline-2,3-dione (47 mg, 0.20 mmol, 1.0 eq.) in toluene (1.0 mL) was added and the reaction mixture was stirred at room temperature overnight. After 16 h, saturated NH_4Cl (aq.) (5 mL) and then H_2O (5 mL) were added and the organics extracted with EtOAc (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **27** (59 mg, 61% yield) as a yellow oil. R_f = 0.37 (40% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3379, 3063, 2982, 2933, 2268, 1809, 1778, 1738, 1614, 1489, 1468, 1373, 1267, 1240, 1170, 1138, 1109, 982; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, *J* = 7.6, 1.0 Hz), 7.27–7.36 (5H, m), 7.22 (1H, app td, *J* = 7.8, 1.2 Hz), 7.03–7.11 (1H, m), 6.71 (1H, d, *J* = 7.8 Hz), 4.80–4.98 (2H, m), 3.60 (1H, s), 1.49 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.7, 148.8, 142.0, 135.1, 130.3, 128.84, 128.80, 127.8, 127.1, 124.6, 123.5, 109.8, 85.1, 75.6, 71.8, 69.3, 44.0, 27.7; HRMS (EI) *m/z*: $[M + NH_4]^+$ Calcd for $C_{27}H_{34}N_3O_6$, 496.2448; Found, 496.2453.

tert-Butyl-(2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)ethyl)carbamate (28)

To compound **27** (35 mg, 0.073 mmol, 1.0 eq.) dissolved in EtOAc (5 mL) was added Pd/C (16 mg of 10% w/w dry) and the flask was capped with a rubber septa and purged with N_2, then purged with a balloon of H_2 (5 min) and stirred at room temperature under a balloon of H_2 for 32 h. Then, the reaction flask was purged with N_2 and the reaction mixture filtered through Celite using EtOAc (40 mL) to wash/elute and the filtrate concentrated under reduced pressure. The resulting crude residue (29 mg) was dissolved in MeCN (3 mL) and $Mg(ClO_4)_2$ (1.3 mg, 0.006 mmol, 0.1 eq.) was added and the flask was placed in a 55 º oil bath with a reflux condenser under N_2 for 3 h then a further portion of $Mg(ClO_4)_2$ (1.3 mg, 0.006 mmol, 0.1 eq.) was added and heating continued for 2 h. The reaction mixture was then cooled to room temperature, the volatiles removed under reduced pressure and then the crude residue was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **28** (17.2 mg, 62% yield) as a white wax. R_f = 0.27 (40% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3366, 3061, 2976, 2930, 1720, 1614, 1489, 1468, 1367, 1251, 1175; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (1H, dd, J = 7.4, 0.8 Hz), 7.26–7.35 (5H, m), 7.21 (1H, app td, J = 7.8, 1.2 Hz), 7.02–7.11 (1H, m), 6.73 (1H, d, J = 7.8 Hz), 4.74–5.01 (3H, m), 3.26–3.38 (2H, m), 3.22 (1H, br s), 2.08–2.26 (2H, m), 1.43 (9H, s); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 177.8, 156.0, 142.2, 135.4, 129.8, 128.9, 127.8, 127.3, 127.2, 124.1, 123.3, 109.7, 79.4, 75.4, 43.8, 38.3, 35.6, 28.4; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{26}N_2O_4Na$, 405.1784; Found, 405.1785.

8-Benzyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-3a-ol (29)

Compound **28** (15.5 mg, 0.0406 mmol, 1.0 eq.) was charged to a flask and N_2 purged for 5 min, then dissolved in THF (3 mL) and cooled to 0 ºC in an ice/water bath. $LiAlH_4$ was then added under N_2 (0.14 mL of a 2.0 M solution in THF, 0.28 mmol, 7.0 eq.) and the reaction mixture was stirred 15 min, then placed in a 65 ºC oil bath with a reflux condenser under N_2 for 14 h. The mixture was then cooled to room temperature and quenched by addition of MeOH (1.0 mL) followed by stirring for 30 min. H_2O (1.0 mL) was then added and the mixture stirred for an additional 30 min. The resulting slurry was

diluted with EtOAc (30 mL) and filtered through Celite using EtOAc (50 mL) to wash/elute and the resultant mixture concentrated under reduced pressure. The crude residue was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes, followed by elution with 5% MeOH in EtOAc) to provide compound **29** (7.1 mg, 62% yield) as a yellow oil. R_f = 0.18 (2% MeOH/EtOAc); IR (CH_2Cl_2, cm^{-1}) 3354 (br), 2930, 2870, 1610, 1495, 1159, 1053; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.36 (6H, m), 7.12 (1H, app td, *J* = 7.7, 1.2 Hz), 6.76 (1H, app td, *J* = 7.5, 0.5 Hz), 6.40 (1H, d, *J* = 8.1 Hz), 4.59 (1H, s), 4.55 (1H, s), 4.40–4.47 (2H, m), 2.83–2.90 (1H, m), 2.76–2.82 (1H, m), 2.47 (3H, s), 2.32–2.40 (1H, m), 2.22–2.29 (1H, m); ^{13}C NMR{^1H} (126 MHz, $CDCl_3$) δ 151.4, 138.6, 132.2, 129.9, 128.6, 127.00, 126.99, 123.2, 118.4, 108.3, 96.8, 88.5, 53.4, 53.1, 40.2, 38.8; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{26}N_2O_4Na$, 405.1784; Found, 405.1785.

(3-(4-Methylphenylsulfonamido)-3-phenylprop-1-yn-1-yl)imidocarbonate (30a):

A N_2 purged flask containing di-*tert*-butyl ethynylimidodicarbonate compound **12** (48 mg, 0.20 mmol, 2.0 eq.) and HMPA (36 mg, 0.035 mL, 0.20 mmol, 2.0 eq.) in toluene (0.5 mL) was treated with Et_2Zn (0.20 mL of a 1 M solution in hexanes, 0.20 mmol, 2.0 eq.) at room temperature and after 2 h (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide[2] (26 mg, 0.10 mmol, 1.0 eq.) in toluene (0.5 mL) was added and the reaction mixture was stirred at room temperature overnight. After 14 h, saturated NH_4Cl (aq.) (5 mL) and H_2O (5 mL) were then added in that order and organics extracted with EtOAc (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **30a** (32 mg, 64% yield) as a white solid. R_f = 0.51 (40% EtOAc/hexanes); m.p. = 123–126 ºC; IR (CH_2Cl_2, cm^{-1}) 3273, 3064, 3032, 2982, 2933, 2274, 1809, 1740, 1599, 1456, 1371, 1329, 1242, 1138, 1045; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.5 Hz), 7.43 -7.51 (2H, m), 7.24–7.33 (5H, m), 5.50 (1H, d, *J* = 8.5 Hz), 4.89 (1H, d, *J* = 8.0 Hz), 2.41 (3H, s), 1.51 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1, 143.4, 137.7, 137.6, 129.4, 128.6, 128.4, 127.35 (2C), 85.0, 75.7, 71.2, 49.6, 27.8, 21.5; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{32}N_2O_6SNa$, 523.1873; Found, 523.1887.

Di-*tert*-butyl (3-hydroxy-3-phenylprop-1-yn-1-yl)imidocarbonate (30b)

Prepared following the procedure used for compound **30a** using benzaldehyde (11 mg, 0.10 mmol, 1.0 eq.) in toluene (0.5 mL) to provide compound **30b** (22 mg, 63% yield) as a yellow oil. R_f = 0.49 (40% EtOAc/hexanes); IR (neat, cm^{-1}) 3450 (br), 2982, 2935, 2272, 2227, 1805, 1774, 1494, 1456, 1371, 1240, 1138, 844; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.64 (2H, m), 7.29–7.43 (3H, m), 5.65 (1H, d, *J* = 6.0 Hz), 2.32 (1H, d, *J* = 6.5 Hz), 1.53 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.5, 140.7, 128.5, 128.4, 126.8, 85.0, 76.1, 74.1, 64.9, 27.8; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{25}NO_5Na$, 370.1624; Found, 370.1633.

Di-*tert*-butyl (3-cyclohexyl-3-hydroxyprop-1-yn-1-yl)imidocarbonate (30c)

Prepared following the procedure used for compound **30a** using cyclohexane carboxaldehyde (11 mg, 0.10 mmol, 1.0 eq.) in toluene (0.5 mL) to provide compound **30c** (23 mg, 65% yield) as a clear oil. R_f = 0.21 (40% EtOAc/hexanes); IR (neat, cm^{-1}) 3470 (br), 2982, 2930, 2852, 2272, 1805, 1767, 1460, 1394, 1371, 1240, 1140, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ 4.33 (1H, dd, *J* = 5.5, 5.5 Hz), 1.88 (2H, d, *J* = 11.5 Hz), 1.74–1.81 (2H, m), 1.65–1.71 (1H, m), 1.59–1.62 (1H, m), 1.46–1.56 (18H, m), 1.06–1.30 (6H, m); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.6, 84.8, 82.0, 74.2, 67.4, 44.2, 28.5, 27.8, 26.3, 25.8; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{31}NO_5Na$, 376.2094; Found, 376.2108.

Methyl 4-(di-*tert*-butoxycarbonylamino)-2-hydroxy-2-phenylbut-3-ynoate (30d)

Prepared following the procedure used for compound **30a** using methyl 2-oxo-2-phenylacetate (16 mg, 0.10 mmol, 1.0 eq.) in toluene (0.5 mL) to provide compound **30d** (24 mg, 60% yield) as a yellow oil. R_f = 0.17 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3474, 2955, 2276, 1809, 1767, 1734, 1371, 1240, 1138, 844; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.73 (2H, m), 7.32–7.39 (3H, m), 4.17 (1H, s), 3.78 (3H, s), 1.54 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.4, 148.9, 139.2, 128.7, 128.3, 126.4, 85.0, 75.8,

73.2, 72.8, 54.1, 27.8; HRMS (EI) *m/z*: $[M + NH_4]^+$ Calcd for $C_{21}H_{31}N_2O_7$, 423.2131; Found, 423.2134.

Di-*tert*-butyl ((1-hydroxycyclohexyl)ethynyl)imidocarbonate (30e)

Prepared following the procedure used for compound **30a** using cyclohexanone (10 mg, 0.10 mmol, 1.0 eq.) in toluene (0.5 mL) to provide compound **30e** (22 mg, 65% yield) as a clear oil. R_f = 0.14 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3447, 2980, 2936, 2858, 2270, 1805, 1770, 1456, 1371, 1244, 1140, 966, 847; ^1H NMR (400 MHz, $CDCl_3$) δ 2.00–2.06 (1H, m), 1.89–1.97 (2H, m), 1.65–1.74 (2H, m), 1.56–1.64 (4H, m), 1.53 (18H, s), 1.46–1.50 (1H, m), 1.17–1.31 (1H, m); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.6, 84.5, 73.9, 71.7, 69.1, 39.9, 27.8, 25.2, 23.4; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{29}NO_5Na$, 362.1937; Found, 362.1941.

Ethyl-2-(di-*tert*-butyl ethynylimidocarbonate) quinoline-1(*2H*)-carboxylate (31)

To a solution of quinoline (25.8 mg, 0.20 mmol, 1.0 eq.) in MeCN (0.5 mL) was added a solution of $EtCO_2Cl$ (24 mg, 0.22 mmol, 1.1 eq.) in MeCN (0.5 mL) followed by addition of a solution of di-*tert*-butyl ethynylimidodicarbonate **12** (54 mg, 0.24 mmol, 1.2 eq.) in MeCN (0.5 mL). This mixture was then added by pipette to a pre-stirred mixture of CuI (3.8 mg, 0.02 mmol, 0.1 eq.) and *i*-Pr_2NEt (36 mg, 0.28 mmol, 1.4 eq.) in MeCN (1.0 mL) using MeCN (0.5 mL) to complete the transfer and the mixture stirred at room temperature overnight. After 14 h, the volatiles were removed under an air stream and the crude residue purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **31** (55 mg, 62% yield) as a yellow oil. R_f = 0.23 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3057, 2983, 2936, 2258, 1809, 1774, 1705, 1371, 1265, 1138; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, *J* = 6.5 Hz), 7.19–7.26 (1H, m), 7.00–7.12 (2H, m), 6.48–6.54 (1H, m), 5.98–6.09 (2H, m), 4.16–4.40 (2H, m, r), 1.39 (18H, s), 1.34 (3H, t, *J* = 7.0 Hz); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 153.7, 149.3, 134.4, 127.8, 126.6, 126.5, 125.6, 125.1, 124.3, 124.2, 84.5, 72.7, 70.9, 62.5, 44.2, 27.6, 14.5; HRMS (EI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}N_2O_6$, 443.2182; Found, 443.2186.

Ethyl-1-(di-*tert*-butyl-ethynylimidocarbonate)isoquinoline-2(1*H*)-carboxylate (32)

Prepared according to the procedure for compound **31** using isoquinoline (25.8 mg, 0.20 mmol, 1.0 eq.) to provide compound **32** (51 mg, 58% yield) as a yellow oil. R_f = 0.30 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 2982, 2935, 2270, 1809, 1770, 1712, 1635, 1456, 1371, 1325, 1242, 1138, 846; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.25 (3H, m), 7.07 (1H, d, *J* = 6.5 Hz), 6.79–7.01 (1H, m), 6.15–6.39 (1H, m), 5.83–6.00 (1H, m), 4.21–4.38 (2H, m), 1.37–1.49 (18H, m), 1.30–1.37 (3H, m); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 152.6, 149.1, 129.9, 129.6, 128.2, 127.2, 126.0, 124.9, 124.3, 108.3, 84.3, 72.8, 72.5, 62.6, 47.2–46.6 (1C, r), 27.6, 14.5; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{31}N_2O_6$, 443.2182; Found, 443.2185.

Di-*tert*-butyl 2-(*anti*-(2-hydroxycyclohexyl) ethynyl)imidocarbonate (33a)

A N_2 purged flask containing di-*tert*-butyl ethynylimidodicarbonate compound **12** (36 mg, 0.15 mmol, 1.5 eq.) in THF (1 mL) was cooled to -78 ºC in a dry ice/acetone bath and LiHMDS (0.15 mL of a 1.0 M solution in THF, 0.15 mmol, 1.5 eq.) was added and stirred for 5 min. Then, cyclohexene oxide (10 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL) was added followed immediately by addition of $BF_3{\cdot}OEt_2$ (21 mg, 0.018 mL, 0.15 mmol, 1.5 eq.). The reaction mixture was removed from the dry ice/acetone bath and placed in a 0 ºC ice/water bath and stirred for 3 h then diluted with saturated NH_4Cl (aq.) (5 mL), EtOAc (50 mL) and H_2O (5 mL) in that order and the phases were separated. The organic extract was dried ($MgSO_4$), filtered, concentrated under reduced pressure and the crude residue obtained was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **33a** (27 mg, 79% yield) as a white solid. R_f = 0.17 (20% EtOAc/hexanes); m.p. = 68–72 ºC; IR (CH_2Cl_2, cm^{-1}) 3493 (br), 2980, 2933, 2860, 2274, 2232, 1809, 1737, 1456, 1371, 1240, 1114, 1016, 1037, 848; ^1H NMR (400 MHz, $CDCl_3$) δ 3.46 (1H, td, *J* = 9.5, 4.0 Hz), 2.55 (1H, s), 2.37 (1H, ddd, *J* = 11.5, 9.5, 3.5 Hz), 1.92–2.09 (2H, m), 1.73–1.83 (1H, m), 1.65–1.71 (1H, m), 1.53 (18H, s), 1.21–1.44 (4H, m); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.8, 84.7, 75.0, 73.9, 71.8, 39.0, 32.7, 30.5, 27.8, 24.8, 24.2; HRMS (EI) *m/z*: $[M + NH_4]^+$ Calcd for $C_{18}H_{33}N_2O_5$, 357.2390; Found, 357.2393.

Di-*tert*-butyl (5-(benzyloxy)-4-hydroxypent-1-yn-1-yl)imidocarbonate (33b)

Prepared according to the procedure for compound **33a** using 2-((benzyloxy)methyl)oxirane (16 mg, 0.10 mmol, 1.0 eq.) and stirring for 90 min at 0 ºC instead of 3 h before work-up to provide compound **33b** (33 mg, 82% yield) of a 94:6 ratio of regioisomers (^{1}H NMR) in favour of the one shown as a clear oil. R_f = 0.38 (40% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3470 (br), 2980, 2934, 2868, 2280, 1805, 1766, 1738, 1456, 1371, 1240, 1140, 848; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.40 (5H, m), 4.58 (2H, s), 3.90–4.06 (1H, m), 3.63 (1H, dd, *J* = 9.5, 4.5 Hz), 3.53 (1H, dd, *J* = 9.5, 6.5 Hz), 2.60 (2H, dd, *J* = 6.5, 2.0 Hz), 2.50 (1H, d, *J* = 4.5 Hz), 1.52 (18H, s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.0, 137.9, 128.4, 127.8, 127.7, 84.6, 73.4, 73.0, 71.7, 69.6, 69.0, 27.8, 23.8; HRMS (EI) *m/z*: $[M + NH_4]^+$ Calcd for $C_{22}H_{35}N_2O_6$, 423.2495; Found, 423.2510.

Di-*tert*-butyl (3-(1-hydroxycyclohexyl)prop-1-yn-1-yl)imidocarbonate (33c)

Prepared according to the procedure for compound **33a** using 1-oxaspiro[2.5]octane (11 mg, 0.10 mmol, 1.0 eq.) and stirring for 90 min at 0 ºC instead of 3 h before work-up to provide compound **33c** (24 mg, 69% yield) as a clear oil. R_f = 0.25 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3516 (br), 2982, 2933, 2860, 2276, 1805, 1766, 1456, 1371, 1240, 1140, 982, 848; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (2H, s), 1.96 (1H, s), 1.55–1.73 (6H, m), 1.53 (18H, s), 1.42–1.51 (4H, m); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.0, 84.6, 72.4, 70.7, 70.0, 36.9, 32.9, 27.8, 25.6, 22.2; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{32}NO_5$, 354.2280; found, 354.2277.

Di-*tert*-butyl 2-((3-oxocyclopentyl)ethynyl)imidocarbonate (34a)

A N_2 purged flask containing di-*tert*-butyl ethynylimidodicarbonate **12** (36 mg, 0.15 mmol, 1.5 eq.) in Et_2O (0.5 mL) was cooled to -78 ºC in a dry ice/acetone bath and LiHMDS (0.15 mL of a 1.0 M solution in THF, 0.15 mmol, 1.5 eq.) was added. After stirring for 5 min, a solution of $ZnBr_2$ (34 mg, 0.15 mmol, 1.5 eq.) in THF (0.5 mL) was added and the reaction mixture transferred to a -44 ºC dry ice/MeCN bath. After 20 min, a solution of cyclopent-2-enone (9.0 mg, 0.1 mmol, 1.0 eq.) in THF (0.5 mL) was added

followed immediately by addition of TBSOTf (40 mg, 0.035 mL, 0.15 mmol, 1.5 eq.). After 2 h in the dry ice/MeCN bath, the reaction mixture was treated with saturated NH_4Cl (aq.) (5 mL) and warmed to room temperature then diluted with H_2O (5 mL) and EtOAc (50 mL) and the layers were separated. The organic phase was dried ($MgSO_4$), filtered through a Celite plug and concentrated under reduced pressure. The crude silyl enol-ether product thus obtained was dissolved in THF (3 mL) and treated with TBAF (tetrabutylammonium fluoride, 0.20 mL of a 1 M solution in THF, 0.2 mmol, 2.0 eq.) at room temperature under N_2. After 15 min, H_2O (20 mL) was added and the mixture was extracted with Et_2O (2 x 40 mL). The organic extracts were combined and washed with H_2O (4 x 10 mL) then with saturated NaCl (aq.) (10 mL), dried ($MgSO_4$), filtered, concentrated under reduced pressure and purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **34a** (20 mg, 62% yield) as a clear oil. R_f = 0.20 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 2980, 2935, 2276, 1805, 1768, 1743, 1371, 1240, 1138, 848; ^1H NMR (400 MHz, $CDCl_3$) δ 3.23 (1H, app quin, J = 7.0 Hz), 2.36–2.57 (2H, m), 2.14–2.34 (3H, m), 1.99–2.12 (1H, m), 1.52 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 217.1, 149.9, 84.6, 74.9, 70.9, 45.1, 37.2, 30.2, 27.8, 27.4; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{25}NO_5Na$, 346.1624; Found, 346.1627.

Di-*tert*-butyl 2-((3-oxocyclohexyl)ethynyl)imidocarbonate (34b)

Prepared according to the procedure for compound **34a** using cyclohexenone (9.6 mg, 0.1 mmol, 1.0 eq.) and stirring for 1 h instead of 2 h in the dry ice/MeCN bath before work-up to provide compound **34b** (19.3 mg, 57% yield) as a clear oil. R_f= 0.18 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 2980, 2939, 2272, 1805, 1770, 1716, 1456, 1371, 1242, 1140, 1105, 847; ^1H NMR (400 MHz, $CDCl_3$) δ 3.04–3.12 (1H, m), 2.58 (1H, dd, J = 14.5, 5.0 Hz), 2.44 (1H, dd, J = 14.5, 8.0 Hz), 2.34 (2H, app t, J = 6.5 Hz), 2.09–2.20 (1H, m), 1.98–2.06 (1H, m), 1.73–1.90 (2H, m), 1.52 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 209.0, 149.8, 84.5, 74.5, 71.8, 46.9, 41.2, 30.8, 29.9, 27.8, 23.8; HRMS (EI) *m/z*: $[M + NH_4]^+$ Calcd for $C_{18}H_{31}N_2O_5$, 355.2233; found, 355.2230.

Di-*tert*-butyl 2-(3-oxo-3-phenylprop-1-yn-1-yl)imidocarbonate (35a)

A flask containing $Pd(PPh_3)_4$ (8.7 mg, 0.0075 mmol, 0.05 eq.) and CuI (1.4 mg, 0.0075 mmol, 0.05 eq.) was sealed with a rubber septum and purged with N_2 for 5 min. This flask was then charged with benzoyl chloride (21 mg, 0.15 mmol, 1.0 eq.) in THF (0.5 mL), followed by addition of Et_3N (21.3 mg, 0.029 mL, 0.21 mmol, 1.4 eq.) then a solution of di-*tert*-butyl ethynylimidodicarbonate compound **12** (36 mg, 0.15 mmol, 1.0 eq.) in THF (0.5 mL) was added. The reaction mixture was stirred at room temperature under N_2 for 2 h then diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (aq.) (10 mL). The organic extract was dried ($MgSO_4$), filtered through a Celite pad and concentrated under reduced pressure. The crude residue obtained was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **35a** (32 mg, 61% yield) as a light yellow oil. R_f = 0.37 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3055, 2987, 2227, 1813, 1782, 1643, 1421, 1373, 1265, 1132, 896; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (2H, dd, J = 8.5, 1.5 Hz), 7.55–7.64 (1H, m), 7.42–7.53 (2H, m), 1.58–1.66 (18H, m); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 177.2, 148.3, 136.9, 133.8, 129.4, 128.4, 86.4, 84.0, 77.2, 27.8; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{24}NO_5$, 346.1654; Found, 346.1651.

Di-*tert*-butyl 2-((3-nitrophenyl)ethynyl)imidocarbonate (35b)

A flask containing $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol, 0.05 eq.) and CuI (1.0 mg, 0.005 mmol, 0.05 eq.) was sealed with a rubber septum and purged with N_2 for 5 min. This flask was then charged with a solution of 1-iodo-3-nitrobenzene (25 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL), followed by addition of Et_3N (14.2 mg, 0.020 mL, 0.14 mmol, 1.4 eq.) then a solution of di-*tert*-butyl ethynylimidodicarbonate compound **12** (24 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL) was added. The reaction mixture was stirred at room temperature under N_2 for 24 h then diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (aq.) (10 mL). The organic extract was dried ($MgSO_4$), filtered through a Celite pad and concentrated under reduced pressure. The crude residue obtained was purified through silica gel chromatography (gradient elution 0-100 %

EtOAc in hexanes) to provide compound **35b** (23 mg, 64% yield) as a brown solid. R_f = 0.45 (20% EtOAc/hexanes); m.p. > 220 ºC; IR (CH_2Cl_2, cm^{-1}) 2980, 2935, 2260, 1813, 1780, 1740, 1533, 1370, 1238, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, dd, *J* = 2.0, 2.0 Hz), 8.13 (1H, ddd, *J* = 8.5, 2.0, 1.0 Hz), 7.70 – 7.66 (1H, m), 7.49 (1H, dd, *J* = 8.0, 8.0 Hz), 1.59 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1, 136.4, 129.3, 128.5, 125.5, 125.0, 122.4, 85.3, 81.1, 72.7, 27.8; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{22}N_2O_6Na$, 385.1370; Found, 385.1379.

Di-*tert*-butyl 2-((3-pyridinyl)ethynyl)imidocarbonate (35c)

A flask containing $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol, 0.05 eq.) and CuI (1.0 mg, 0.005 mmol, 0.05 eq.) was sealed with a rubber septum and purged with N_2 for 5 min. This flask was then charged with a solution of 3-iodopyridine (20 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL), followed by addition of Et_3N (14.2 mg, 0.020 mL, 0.14 mmol, 1.4 eq.) and then a solution of di-*tert*-butyl ethynylimidodicarbonate compound **12** (24 mg, 0.10 mmol, 1.0 eq.) in THF (0.5 mL) was added. The reaction mixture was stirred at room temperature under N_2 for 16 h then diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3$ (aq.) (10 mL). The organic extract was dried ($MgSO_4$), filtered through a Celite pad and concentrated under reduced pressure. The crude residue obtained was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **35c** (21 mg, 66% yield) as a yellow solid. R_f = 0.08 (20% EtOAc/hexanes); m.p. = 62–67 ºC; IR (CH_2Cl_2, cm^{-1}) 2976, 2932, 2264, 1801, 1774, 1564, 1456, 1369, 1238, 1134, 1103, 845; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38–8.82 (2H, m), 7.68 (1H, d, *J* = 8.0 Hz), 7.15–7.35 (1H, m), 1.57 (18H, s); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 151.5, 149.2, 148.1, 137.6, 132.1, 128.4, 85.1, 81.6, 71.5, 27.8; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{23}N_2O_4$, 319.1658; Found, 319.1667.

Di-*tert*-butyl-(3-(4-methylphenylsulfonamido)-3-phenylpropyl)-imidocarbonate (36a)

To a solution of compound **30a** (15 mg, 0.03 mmol, 1.0 eq.) in EtOAc (3 mL) was added Pd/C (3.0 mg of 10% w/w dry) and the flask was capped with a rubber septa and purged

with N_2 then purged with a balloon of H_2 (5 min) and stirred at room temperature under a balloon of H_2 for 18 h. The reaction flask was then purged with N_2 and the reaction mixture was filtered through Celite using EtOAc (40 mL) to wash/elute and the filtrate concentrated under reduced pressure. The resulting crude residue was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **36a** (11.7 mg, 78% yield) as a white solid. R_f = 0.12 (20% EtOAc/hexanes); m.p. = 118–121 ºC; IR (CH_2Cl_2, cm^{-1}) 3273, 2980, 2932, 1778, 1747, 1693, 1599, 1456, 1367, 1161, 1116; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 8.5 Hz), 7.10–7.20 (5H, m), 7.03–7.09 (2H, m), 5.25 (1H, d, *J* = 7.0 Hz), 4.32 (1H, dt, *J* = 7.0, 7.0 Hz), 3.32–3.59 (2H, m), 2.36 (3H, s), 1.91–2.12 (2H, m), 1.46 (18H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 152.4, 143.0, 140.4, 137.7, 129.3, 128.5, 127.4, 127.0, 126.3, 82.6, 56.2, 43.2, 36.2, 28.0, 21.4; HRMS (EI) *m/z*: $[M + NH_4]^+$ Calcd for $C_{26}H_{40}N_3O_6S$, 522.2638; Found, 522.2646.

Di-*tert*-butyl (3-hydroxy-3-phenylpropyl)-imidocarbonate (36b)

Prepared according to the procedure for compound **36a** using compound **30b** (14 mg, 0.04 mmol, 1.0 eq.) and Pd/C (3.0 mg of 10% w/w dry) in EtOAc (3 mL) and stirring under a balloon of H_2 for 16 h to provide compound **36b** (10.0 mg, 71% yield) as a clear oil. R_f = 0.23 (20% EtOAc/hexanes); IR (neat, cm^{-1}) 3466 (br), 3063, 2980, 2933, 1737, 1674, 1456, 1352, 1140; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.44 (5H, m), 4.68 (1H, dt, *J* = 9.5, 3.5 Hz), 3.67–3.90 (2H, m), 3.28 (1H, d, *J* = 3.5 Hz), 1.96–2.11 (1H, m), 1.81–1.95 (1H, m), 1.51 (18H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 153.2, 144.0, 128.4, 127.3, 125.6, 82.8, 70.8, 43.2, 38.5, 28.0; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{29}NO_5Na$, 374.1937; Found, 374.1943.

Methyl 4-((di-*tert*-butoxycarbonyl)amino)-2-hydroxy-2-phenylbutanoate (36c)

Prepared according to the procedure for compound **36a** using compound **30d** (24 mg, 0.059 mmol, 1.0 eq.) and Pd/C (7.0 mg of 10% w/w dry) in EtOAc (3 mL) and stirring under a balloon of H_2 for 18 h to provide compound **36c** (16.3 mg, 68% yield) as a yellow oil. R_f = 0.22 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3500 (br), 2980, 2933,

1790, 1732, 1699, 1448, 1394, 1367, 1222, 1155, 1128, 856; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.65 (2H, m), 7.27–7.40 (3H, m), 4.17 (1H, s), 3.72–3.83 (4H, m), 3.62 (1H, ddd, *J* = 14.0, 9.0, 4.5 Hz), 2.54 (1H, ddd, *J* = 13.5, 8.5, 6.5 Hz), 2.30 (1H, ddd, *J* = 13.5, 8.5, 4.5 Hz), 1.50 (18H, s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.1, 152.6, 141.3, 128.3, 127.8, 125.4, 82.5, 76.8, 53.3, 42.0, 38.3, 28.1; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{31}NO_7Na$, 432.1992; Found, 432.1987.

Ethyl-2-(2-(di-*tert*-butyl-imidocarbonate)ethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (36d)

Prepared according to the procedure for compound **36a** using compound **31** (22 mg, 0.05 mmol, 1.0 eq.) and Pd/C (6.0 mg of 10% w/w dry) in EtOAc (5 mL) and stirring under a balloon of H_2 for 36 h to provide **36d** (14.8 mg, 67% yield) as a yellow oil. R_f = 0.30 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3435, 2980, 2933, 1790, 1747, 1699, 1492, 1456, 1394, 1367, 1315, 1122, 855; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* = 8.0 Hz), 7.12–7.19 (1H, m), 7.05–7.11 (1H, m), 6.98–7.05 (1H, m), 4.60 (1H, app quin, *J* = 6.5 Hz), 4.10–4.33 (2H, m), 3.50–3.69 (2H, m), 2.61–2.81 (2H, m), 2.13–2.27 (1H, m), 1.76–1.88 (1H, m), 1.63–1.75 (2H, m), 1.37–1.52 (18H, m), 1.30 (3H, t, *J* = 7.0 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.8, 152.3, 136.5, 130.8, 128.0, 126.0, 125.6, 124.1, 82.1, 61.8, 51.1, 43.8, 32.2, 28.3, 28.0, 24.5, 14.5; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{36}N_2O_6Na$, 471.2465; Found, 471.2466.

Di-*tert*-butyl (2-(3-oxocyclohexyl)ethyl)imidocarbonate (36e)

Prepared according to the procedure for compound **36a** using compound **34b** (14 mg, 0.0415 mmol, 1.0 eq.) and Pd/C (9.0 mg of 10% w/w dry) in EtOAc (3 mL) and stirring under a balloon of H_2 for 20 h to provide compound **36e** (11.3 mg, 80% yield) as a clear oil. R_f = 0.19 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 2978, 2933, 2866, 1791, 1747, 1716, 1695, 1456, 1394, 1367, 1294, 1257, 1228, 1176, 1141, 1120; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (2H, t, *J* = 8.0 Hz), 2.41–2.48 (1H, m), 2.32–2.40 (1H, m), 2.19–2.31 (1H, m), 2.00–2.11 (2H, m), 1.90–1.99 (1H, m), 1.73–1.85 (1H, m), 1.58–1.68 (2H, m), 1.49 (18H, s), 1.23–1.43 (2H, m); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 211.2, 152.5, 82.3,

48.0, 44.1, 41.4, 36.9, 35.6, 31.1, 28.1, 25.2; HRMS (EI) *m/z*: $[M + NH_4]^+$ Calcd for $C_{18}H_{35}N_2O_5$, 359.2546; Found, 359.2545.

Di-*tert*-butyl (3-(1-hydroxycyclohexyl)propyl)imidocarbonate (36f)

Prepared according to the procedure for compound **36a** using compound **33c** (21 mg, 0.0594 mmol, 1.0 eq.) and Pd/C (14 mg of 10% w/w dry) in EtOAc (3 mL) and stirring under a balloon of H_2 for 21 h to provide compound **36f** (17.8 mg, 83% yield) as a clear oil. R_f = 0.16 (20% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3520 (br), 2980, 2933, 2862, 1784, 1734, 1695, 1456, 1394, 1367, 1174, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 3.58 (2H, t, *J* = 7.0 Hz), 1.62–1.72 (2H, m), 1.54–1.61 (4H, m), 1.47–1.53 (21H, m), 1.38–1.46 (4H, m), 1.22–1.31 (2H, m); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 152.8, 82.1, 71.2, 46.8, 39.1, 37.4, 28.1, 25.8, 22.7, 22.2; HRMS (EI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{35}NO_5Na$, 380.2407; Found, 380.2412.

Di-*tert*-butyl (1-benzyl-1*H*-1,2,3-triazol-4-yl)imidocarbonate (37a)

Di-*tert*-butyl ethynylimidodicarbonate compound **12** (48 mg, 0.2 mmol, 1.0 eq.) was dissolved in a mixture of water (2 mL) and *t*-BuOH (1 mL) in a 20-dram scintillation vial. Benzyl azide (38 mg, 0.03 mL, 0.28 mmol, 1.4 eq.) was then added followed by addition of anhydrous $Cu(OAc)_2$ (3.6 mg, 0.02 mmol, 0.1 eq.) and sodium-(L)-ascorbate (8 mg, 0.04 mmol, 0.2 eq.) and the resulting cloudy mixture stirred for 16 h at room temperature. The volatiles were removed under a stream of air and the resulting residue was partitioned between EtOAc (100 mL) and water (20 mL) and the layers were separated. The organic layer was washed with saturated NaCl(aq.) (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **37a** (62 mg, 83% yield) as a beige solid. R_f = 0.17 (10% MeOH/CH_2Cl_2); m.p. = 97–100 ºC; IR ($CDCl_3$, cm^{-1}) 3155, 2984, 2934, 2253, 1794, 1751, 1717, 1564, 1456, 1371, 1275, 1252, 1151, 1121, 1105, 908 ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.42 (4H, m) 7.15–7.26 (2H, m) 5.54 (2H, s) 1.42 (18H, s); $^{13}C\{^1H\}$

NMR (101 MHz, $CDCl_3$) δ 150.6; 143.5; 134.6; 129.1; 128.8; 127.7; 119.9; 83.5; 54.6; 27.8; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{27}N_4O_4$, 375.2026; Found, 375.2039.

Di-*tert*-butyl (1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)imidocarbonate (37b)

Prepared according to the procedure for compound **37a** using 1-azido-4-bromobenzene (55 mg, 0.28 mmol, 1.4 eq.) to provide compound **37b** (86 mg, 98% yield) as a yellow solid. R_f = 0.53 (40% EtOAc/hexanes); m.p. = 196–199 ºC; IR (CH_2Cl_2, cm^{-1}) 3055, 2986, 2305, 1798, 1740, 1724, 1501, 1421, 1369, 1150, 1120, 897; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, s) 7.60–7.70 (4H, m) 1.49 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.7; 143.9; 136.0; 132.9; 122.6; 121.7; 117.7; 84.0; 27.9; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{24}BrN_4O_4$, 439.0981; Found, 439.0970.

Methyl 2-(4-((di-*tert*-butoxycarbonyl)amino)-1*H*-1,2,3-triazol-1-yl)acetate (37c)

Prepared according to the procedure for compound **37a** using di-*tert*-butyl ethynylimidodicarbonate compound **12** (43 mg, 0.18 mmol, 1.0 eq.) and methyl 2-azidoacetate (29 mg, 0.25 mmol, 1.4 eq.) to provide compound **37c** (36.2 mg, 63% yield) as a white solid. R_f = 0.06 (20% EtOAc/hexanes); m.p. = 76–79 ºC; IR (CH_2Cl_2, cm^{-1}) 3055, 2986, 2306, 1784, 1759, 1720, 1566, 1369, 1150, 1121, 1105, 1040, 897; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, s), 5.17 (2H, s), 3.81 (3H, s), 1.44 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 150.5, 143.4, 121.4, 83.6, 53.1, 51.2, 27.8; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{25}N_4O_6$, 357.1774; Found, 357.1779.

Di-*tert*-butyl-(1-(3-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)imidocarbonate (37d)

Prepared according to the procedure for compound **37a** using 1-azido-3-methoxybenzene (42 mg, 0.28 mmol, 1.4 eq.) to provide compound **37d** (49 mg, 63% yield) as a white solid. R_f = 0.36 (20% EtOAc/hexanes); m.p. = 153–155 ºC; IR (CH_2Cl_2, cm^{-1}) 3055, 2984, 2938, 2225, 1794, 1759, 1720, 1610, 1369, 1265, 1151, 1121; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, s), 7.42 (1H, app t, J = 8.0 Hz), 7.36 (1H, app t, J = 2.0 Hz), 7.27-7.25 (1H, m), 6.98 (1H, dd, J = 8.5, 2.5 Hz), 3.89 (3H, s), 1.49 (18H, s); $^{13}C\{^1H\}$ NMR

(101 MHz, $CDCl_3$) δ 160.6, 150.7, 143.7, 138.1, 130.6, 118.0, 114.8, 112.2, 106.2, 83.8, 55.7, 27.9; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{27}N_4O_5$, 391.1981; Found, 391.1992.

Di-*tert*-butyl (1-benzyl-1*H*-1,2,3-triazol-5-yl)imidocarbonate (38a)

Cp*RuCl(COD) (1.5 mg, 0.004 mmol, 0.02 eq.) was charged to a vial capped with a septa and purged with nitrogen for 5 min then a solution of di-*tert*-butyl ethynylimidodicarbonate compound **12** (48 mg, 0.2 mmol, 1.0 eq.) in toluene (0.5 mL) was added followed by addition of a solution of benzyl azide (27 mg, 0.2 mmol, 1.0 eq.) in toluene (0.5 mL) and the mixture stirred at room temperature. After 16 h, the reaction mixture was loaded directly onto silica gel and purified by flash column chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **38a** (54 mg, 52% yield) as a white solid. R_f = 0.38 (20% EtOAc/hexanes); m.p. = 123–125 ºC; IR (CH_2Cl_2, cm^{-1}) 3055, 2986, 2306, 1801, 1769, 1456, 1421, 1371, 1148, 1103, 897; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, s), 7.28–7.40 (5H, m), 5.36 (2H, s), 1.30 (18H, s); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.9; 133.8; 133.4; 131.2; 129.0; 128.6; 128.1; 84.6; 51.5; 27.6; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{27}N_4O_4$, 375.2026; Found, 375.2038.

Methyl 2-(5-((di-*tert*-butoxycarbonyl)amino)-1*H*-1,2,3-triazol-1-yl)acetate (38b)

Prepared according to the procedure for compound **38a** using methyl 2-azidoacetate (23 mg, 0.2 mmol, 1.0 eq.) to provide compound **38b** (36 mg, 51% yield) as a yellow solid. R_f = 0.31 (40% EtOAc/hexanes); m.p. = 111–113 ºC; IR (CH_2Cl_2, cm^{-1}) 3055, 2986, 2306, 1801, 1767, 1728, 1574, 1460, 1439, 1371, 1267, 1146, 1105; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, s), 5.01 (2H, s), 3.78 (3H, s), 1.44 (18H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.8, 149.0, 133.9, 131.2, 85.0, 52.9, 48.2, 27.7; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{25}N_4O_6$, 357.1774; Found, 357.1777.

5-(Di-*tert*-butylimidocarbonate)-3-phenylisoxazole (39)

Compound **12** (48 mg, 0.2 mmol, 1.0 eq.) and *N*-hydroxybenzimidoyl chloride (44 mg, 0.28 mmol, 1.4 eq.) were combined in a mixture of water (2 mL) and *t*-BuOH (1 mL) in a

20-dram scintillation vial. Sodium-(L)-ascorbate (4.0 mg, 0.02 mmol, 0.1 eq.) was then added followed by K_2CO_3 (61 mg, 0.44 mmol, 2.2 eq.) and Cu(II)SO_4-anhydrous (3.0 mg, 0.02 mmol, 0.1 eq.) and the resulting cloudy mixture stirred for 16 h at room temperature. The volatiles were then removed under a stream of air and the resulting residue was partitioned between EtOAc (75 mL) and water (25 mL) and the layers were separated. The organic layer was washed with saturated NaCl (aq.) (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **39** (28 mg, 39% yield) as a pale yellow solid. R_f = 0.28 (20% EtOAc/hexanes); m.p. = 147–150 ºC; IR (CH_2Cl_2, cm^{-1}) 3055, 2988, 2305, 1801, 1653, 1636, 1421, 739; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.89 (2H, m), 7.40–7.52 (3H, m), 6.43 (1H, s), 1.48 (18H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.3, 161.4, 148.8, 130.2, 129.0, 128.9, 126.5, 97.3, 84.7, 27.8; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{25}N_2O_5$, 361.1757; Found, 361.1762.

4-(Di-*tert*-butylimidocarbonate)-3-phenylisoxazole (40)

Compound **12** (48 mg, 0.2 mmol, 1.0 eq.) and *N*-hydroxybenzimidoyl chloride (34 mg, 0.22 mmol, 1.1 eq.) and Cp*RuCl(COD) (3.8 mg, 0.01 mmol, 0.05 eq.) and Et_3N (25 mg, 0.034 mL, 0.25 mmol, 1.25 eq.) were combined in 1,2-dichloroethane (1.0 mL) in that order. The reaction vial was sealed and purged with N_2 for 5 min then stirred at room temperature for 16 h. The reaction mixture was then loaded directly onto silica gel and purified by flash column chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **40** (50 mg, 69% yield) as a grey solid. R_f = 0.27 (20% EtOAc/hexanes); m.p. = 57–59 ºC; IR (neat, cm^{-1}) 3111, 3068, 2982, 2342, 1798, 1755, 1713, 1622, 1464, 1362, 1246, 1159, 1116; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (1H, s), 7.62–7.68 (2H, m), 7.44–7.49 (3H, m), 1.30 (18H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.8, 155.2, 150.2, 130.1, 129.0, 127.8, 127.2, 119.2, 83.8, 27.6; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{25}N_2O_5$, 361.1764; Found, 361.1776.

_N_-(1-(4-Bromophenyl)-1_H_-1,2,3-triazol-4-yl)benzamide (41)

Compound **37b** (35 mg, 0.08 mmol, 1.0 eq.) was suspended in EtOAc (4 mL) and treated with 4N HCl in dioxanes (0.5 mL) and stirred at room temperature. After 1 h, a further portion of 4N HCl in dioxanes (1.0 mL) was added and stirring continued. After a further 1 h, another portion of 4N HCl in dioxanes (1.0 mL) was added and stirred at room temperature overnight. After 16 h, the volatiles were removed on a rotary evaporator and the resulting crude residue was re-dissolved in CH_2Cl_2 (1 mL) and pyridine (1 mL) and cooled to 0 °C in an ice/water bath. A solution of benzoyl chloride (13 mg, 0.096 mmol, 1.2 eq.) in CH_2Cl_2 (0.5 mL) was then added and the reaction mixture was stirred for 4 h. Then, the reaction mixture was partitioned between CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ (aq.) (15 mL) and the phases were separated. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography through silica gel chromatography (gradient elution 0-100 % EtOAc in hexanes) to provide compound **41** (13 mg, 48% yield over 2 steps) as a brown solid. R_f = 0.18 (40% EtOAc/hexanes); m.p > 200 ºC; IR (CH_2Cl_2, cm^{-1}) 3252, 2955, 2924, 2852, 2228, 1720, 1659, 1593, 1497, 1402, 1159; ^1H NMR (300 MHz, DMSO-d_6) δ 11.49 (1H, s), 8.92 (1H, s), 8.02–8.11 (2H, m), 7.91–7.99 (2H, m), 7.74–7.82 (2H, m), 7.46–7.64 (3H, m); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 164.8, 145.2, 136.4, 133.5, 133.2, 132.5, 129.0, 128.4, 122.4, 121.7, 112.8; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{12}BrN_4O$, 343.0188; Found, 343.0191.

1-(3-Methoxyphenyl)-_N_-(quinolin-2-ylmethyl)-1_H_-1,2,3-triazol-4-amine (42)

Compound **37d** (30 mg, 0.077 mmol, 1.0 eq.) was dissolved in MeOH (1 mL) and treated with 4N HCl in dioxanes (0.5 mL) and stirred at room temperature overnight. After 18 h, the volatiles were removed under an air stream and the crude residue partitioned between CH_2Cl_2 (40 mL) and saturated $NaHCO_3$ (aq.) (15 mL) and the phases were separated. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 13 mg (89%) of crude Boc deprotected material. The resulting crude free amine (13 mg, 0.068 mmol, 1.0 eq.) was re-dissolved in CH_2Cl_2 (3 mL) and 2-quinoline

carboxaldehyde (10.8 mg, 0.068 mmol, 1.0 eq.) was added followed by $MgSO_4$ (25 mg) and the mixture stirred at room temperature overnight. After 16 h, the reaction mixture was diluted with CH_2Cl_2 (40 mL) and filtered through Celite and concentrated under reduced pressure. The resulting crude imine was re-dissolved in MeOH (3 mL) and treated with $NaBH_4$ (5.3 mg, 0.14 mmol, 2.0 eq.) and stirred at room temperature for 45 min then volatiles removed on a rotary evaporator. MeOH (5 mL) was then added and the volatiles removed again on a rotary evaporator. The crude residue obtained was then partitioned between CH_2Cl_2 (30 mL) and saturated $NaHCO_3$(aq.) (15 mL) and the phases were separated. The aqueous phase was extracted again with CH_2Cl_2 (30 mL) and the organic extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography through silica gel (10% MeOH in EtOAc) to provide compound **42** (14 mg, 55% over 2 steps) as a yellow waxy semi-solid. R_f = 0.34 (60% EtOAc/hexanes); IR (CH_2Cl_2, cm^{-1}) 3344, 3142, 3063, 2959, 2926, 2855, 1747, 1589, 1263, 1163, 1038; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 8.5 Hz), 8.09 (1H, d, J = 8.0 Hz), 7.82 (1H, d, J = 8.5 Hz), 7.73 (1H, ddd, J = 8.5, 7.0, 1.5 Hz), 7.47–7.58 (2H, m), 7.15–7.39 (4H, m), 6.86–6.94 (1H, m), 5.27 (1H, br.s.), 4.71 (2H, s), 3.85 (3H, s); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.5; 158.1; 154.8; 147.5; 138.4; 136.9; 130.3; 129.8; 128.8; 127.6; 127.4; 126.4; 119.7; 114.1; 111.8; 105.7; 103.7; 55.6; 51.2; HRMS (EI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}N_5O$, 332.1511; Found, 332.1507.

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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References

[1] Selected reviews: (a) Afanasyev, O. I.; Kuchuk, E.; Usanov, D. L.; Chusov, D. Reductive Amination in the Synthesis of Pharmaceuticals. *Chem. Rev.* **2019**, *119*, 11857–11911. (b) Legnani, L.; Bhawal, B. N.; Morandi, B. Recent Developments in the Direct Synthesis of Unprotected Primary Amines. *Synthesis* **2017**, *49*, 776–789. (c) Abdel-Magid, A. F.; Mehrman, S. J. A Review on the Use of Sodium Triacetoxyborohydride in the Reductive Amination of Ketones and Aldehydes. *Org. Proc. Res. Dev.* **2006**, *10*, 971–1031. (d) Tararov, V. I.; Moerner, A. Approaching Highly Enantioselective Reductive Amination. *Synlett* **2005**, 203–211. (e) Gomez, S.; Peters, J. A.; Maschmeyer, T. The Reductive Amination of Aldehydes and Ketones and the Hydrogenation of Nitriles: Mechanistic Aspects and Selectivity Control. *Adv. Synth. Catal.* **2002**, *344*, 1037–1057. (f) Baxter, E. W.; Reitz, A. B. Reductive Aminations of Carbonyl Compounds with Borohydride and Borane Reducing Agents. *Org. React.* **2001**, *59*, 1–714.

[2] Selected reviews: (a) Gibson, M. S.; Bradshaw, R. W. The Gabriel Synthesis of Primary Amines. *Angew. Chem. Int. Ed.* **1968**, *7*, 919–930. (b) Ragnarsson, U.; Grehn, L. Novel Gabriel Reagents. *Acc. Chem. Res.* **1991**, *24*, 285–289. (c) See also ref. 1b.

[3] Selected reviews: (a) Mueller, T. E.; Hultzsch, K. C; Yus, M.; Foubelo, F.; Tada, M. Hydroamination: Direct Addition of Amines to Alkenes and Alkynes. *Chem. Rev.* **2008**, *108*, 3795–3892. (b) Kalck, P.; Urrutigoity, M. Tandem Hydroaminomethylationi Reaction to Synthesize Amines from Alkenes. *Chem. Rev.* **2018**, *118*, 3833–3861. (c) Hesp, K. D.; Stradiotto, M. Rhodium- and Iridium-Catalyzed Hydroamination of Alkenes. *ChemCatChem* **2010**, *2*, 1192–1207.

[4] (a) Fatiadi, A. J. In Preparation and Synthetic Applications of Cyano Compounds; Patai, S., Rappoport, Z., Eds.; Wiley-VCH: New York, 1983. (b) Rappoport, Z. In Chemistry of the Cyano Group; Wiley: London, 1970; pp 121–312.

[5] (a) Noboro, O (2001). The Nitro Group in Organic Synthesis; Wiley-VCH: New York, NY, 2001. (b) Luzzio, F. A. The Henry Reaction: Recent Examples. *Tetrahedron* **2001**, *57*, 915–945.

[6] Steinborn, D. Synthesis and Stability of *N*,*N*-disubstituted (β-aminoethyl)magnesium bromides; the first β-heteroatom-substituted Grignard compounds of the type $R_2NCH_2CH_2MgX$. *J. Organomet. Chem.* **1979**, *182*, 313–322.

[7] Phenethylamines via a β-aminoethylboronate Suzuki-Miyaura coupling approach: (a) Molander, G. A.; Jean-Gerard, L. Scope of the Suzuki-Miyaura Aminoethylation Reaction Using Organotrifluoroborates. *J. Org. Chem.* **2007**, *72*, 8422–8426. (b) Molander, G. A.; Vargas, F. β–Aminoethyltrifluoroborates: Efficient Aminoethylations via Suzuki-Miyaura Cross-Coupling. *Org. Lett.* **2007**, *9*, 203–206. (c) Kamatani, A.; Overman, L. E. A Suzuki Coupling Method for Directly Introducing a Protected β–Aminoethyl Group into Arenes and Alkenes. Convenient Synthesis of Phenethyl and Homoallylic Amines. *J. Org. Chem.* **1999**, *64*, 8743–8744. (d) Kamatani, A.; Overman, L. E. A New Asymmetric Synthesis of *trans*-Hydroisoquinolones. *Org. Lett.* **2001**, *3*, 1229–1232. (e) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. Sequential Catalytic Asymmetric Heck-Iminium Ion Cyclization: Enantioselective Total Synthesis of the *Strychnos* Alkaloid Minfiensine. *J. Am. Chem. Soc.* **2005**, *127*, 10186–10187. (f) Fuchs, J. R.; Funk, R. L.; Indol-2-one Intermediates: Mechanistic Evidence and Synthetic Utility. Total Syntheses of (±)-Flustramines A and C. *Org. Lett.* **2005**, *7*, 677–680.

[8] β-aminoethyl organozinc reagents undergo Negishi couplings to generate phenethylamines and are also reported to install aminoethyl groups via reaction with allylic electrophiles: (a) Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H. P.; Berger, S.;

Knochel, P. Preparation and Reactivity of Chiral β–Amido-Alkylzinc Iodides and Related Configurationally Stable Zinc Organometallics. *Tetrahedron*, **1994**, *50*, 2415–2432. (b) Hunter, C.; Jackson, R. F. W.; Rami, H. K. Efficient Synthesis of Protected –Phenylethylamines and β–Phenyl-α-isopropylethylamines using Organozinc Chemistry. *J. Chem. Soc., Perkin Trans.* 1 **2000**, *2*, 219–223. (c) Rilatt, I.; Caggiano, L.; Jackson, R. F. Development and Applications of Amino Acid Derived Organometallics. *Synlett* **2005**, 2701–2719.

[9] General ynamide reviews: (a) Evano, G.; Coste, A.; Jouvin, K. Ynamides: Versatile Tools in Organic Synthesis. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840–2859. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. Ynamides: a Modern Functional Group for the New Millennium. *Chem. Rev.* **2010**, *110*, 5064–5106. (c) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L-L. Recent Advances in the Chemistry of Ynamines and Ynamides. *Tetrahedron* **2001**, *57*, 7575–7606.

[10] Selected examples of ynamide applications in natural product total synthesis: (a) Alayrac, C.; Schollmeyer, D.; Witulski, B. First Total Synthesis of Antiostatin A_1, a Potent Carbazole-Based Naturally Occurring Antioxidant. *Chem. Commun.* **2009**, 1464–1466. (b) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. Synthesis of 3-(arylmethylene)isoindolin-1-ones from Ynamides by Heck-Suzuki-Miyaura Domino Reactions. Application to the Synthesis of Lennoxamine. *Tetrahedron* **2006**, *62*, 3882–3895. (c) Nissen, F.; Richard, V.; Alayrac, C.; Witulski, B. Synthesis of β– and γ–Carbolines via Ruthenium and Rhodium Catalyzed [2+2+2] Cycloadditions of Yne-Ynamides with Methylcyanoformate. *Chem. Commun.* **2011**, *47*, 6656–6658. (d) Nissen, F.; Detert, H. Total Synthesis of Lavendamycin by a [2+2+2] Cycloaddition. *Eur. J. Org. Chem.* **2011**, 2845–2853. (e) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. Brønsted Acid-Catalyzed Highly Stereoselective Arene-Ynamide Cyclizations. A Novel Keteniminium Pictet-Spengler Cyclization in Syntheses of (±)-Desbromoarborescidines A and C. *Org. Lett.* **2005**, *7*, 1047–1050. (f) Saito, N.; Ichimaru, T.; Sato, Y. Total Synthesis of (-)-Herbindoles A, B, and C via Transition-Metal-

Catalyzed Intramolecular [2+2+2] Cyclization between Ynamide and Diynes. *Org. Lett.* **2012**, *14*, 1914–1917. (g) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. Synthesis of Polycyclic Benzofused Nitrogen Heterocycles via a Tandem Ynamide Benzannulation/Ring-Closing Metathesis Strategy. Application in a Formal Total Synthesis of (+)-FR900482. *J. Org. Chem.* **2011**, *76*, 1852–1873. (h) Gourdet, B.; Lam, H-W. Catalytic Asymmetric Dihydroxylation of Enamides and Application to the Total Synthesis of (+)-Tanikolide. *Angew. Chem. Int. Ed.* **2010**, *49*, 8733–8737.

[11] (a) Wakamatsu, H.; Takeshita, M. Copper-Free Sonogashira Cross-Coupling of Ynamides: Easy Access to Various Substituted Ynamides from Nonsubstituted Ynamides. *Synlett* **2010**, 2322–2324. (b) Dooleweerdt, K.; Ruhland, T.; Skrydstrup, T. Application of Ynamides in the Synthesis of 2-Amidoindoles. *Org. Lett.* **2009**, *11*, 221–224. (c) Tracey, M-R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. Sonogashira Cross-Couplings of Ynamides. Syntheses of Urethane- and Sulfonamide-Terminated Conjugated Phenylacetylenic Systems. *Org. Lett.* **2004**, *6*, 2209–2212.

[12] (a) Wang, X-N.; Hsung, R. P.; Rui, Q.; Fox, S. K.; Lv, M-C. A Highly Stereoselective Addition of Lithiated Ynamides to Ellman-Davis Chiral *N-tert*-Butanesulfinyl Imines. *Org. Lett.* **2013**, *15*, 2514–2517. (b) Cook, A. M.; Wolf, C. Catalytic Enantioselective Nucleophilic Addition of Ynamides to Aldehydes. *Chem. Commun.* **2014**, *50*, 3151–3154.

[13] Indirect ynamide carbonyl addition examples: (a) A sulfonamide β,β-dichloroenamide reacted with benzaldehyde to produce a propargylic ynamide presumably through a lithium-acetylide ynamide intermediate: Rodriguez, D.; Fernanda Martinez-Esperon, M.; Castedo, L.; Saa, C. Synthesis of Disubstituted Ynamides from β,β-Dichloroenamides and Electrophiles. *Synlett* **2007**, 1963–1965. (b) Internal sulfonamide ynamide titanium complexes react with aldehydes producing enamides: (i) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. Practical Preparation of *N*-(1-Alkynyl)sulfonamides and Their Remote Diastereoselective Addition to Aldehydes via

Titanation. *Org. Lett.* **2004**, *6*, 727–729. (ii) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. Concise and Stereoselective Synthesis of Enamides and Dienamides by a Titanium-Mediates Coupling Method. *Org. Lett.* **2003**, *5*, 67–70. (c) Terminal sulfonamide ynamides have been described to undergo a hydroboration/zinc-transmetallation/carbonyl addition sequence to produce enamides: Valenta, P.; Carroll, P. J.; Walsh, P. J. Stereoselective Synthesis of β–Hydroxy Enamines, Aminocyclopropanes, and 1,3-Amino Alcohols via Asymmetric Catalysis. *J. Am. Chem. Soc.* **2010**, *132*, 14179–14190.

[14] Zhang, P.; Cook, A. M.; Liu, Y.; Wolf, C. Copper(I)-Catalyzed Nucleophilic Addition of Ynamides to Acyl Chlorides and Activated *N*-Heterocycles. *J. Org. Chem.* **2014**, *79*, 4167–4173.

[15] Moskowitz, M.; Wolf, C. Catalytic Enantioselective Ynamide Additions to Isatins: Concise Access to Oxindole Alkaloids. *Angew. Chem. Int. Ed.* **2019**, *58*, 3402–3406.

[16] (a) Beveridge, R. E.; Batey, R. A. Terminal Alkyne Addition to Diazodicarboxylates: Synthesis of Hydrazide Linked Alkynes (Ynehydrazides). *Org. Lett.* **2012**, *14*, 540–543. (b) Beveridge, R. E.; Batey, R. A. Total Synthesis of the Cytotoxic Enehydrazide Natural Products Hydrazidomycins A and B by a Carbazate Addition/Peterson Olefination Approach. *Org. Lett.* **2013**, *15*, 3086–3089.

[17] For reviews on pyrroloindoline alkaloids, see: (a) Ruiz-Sanchis, P.; Savina, S. A.; Albericio, F.; Alvarez, M. Structure, Bioactivity and Synthesis of Natural Products with Hexahydropyrrolo[2,3-b]indole. *Chem. Eur. J.* **2011**, 1388–1408. (b) Crich, D.; Banerjee, A. Chemistry of the Hexahydropyrrolo[2,3-b]indoles: Configuration, Conformation, Reactivity, and Applications in Synthesis. *Acc. Chem. Res.* **2007**, *40*, 151–161.

[18] CPC-1 isolation and characterization: Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. Two new tryptamine-derived alkaloids from Chimonanthus praecox f. concolor. *Tetrahedron Lett.* **2006**, *47*, 3199–3202.

[19] CPC-1 syntheses: (a) Kajiyama, D.; Saitoh, T.; Yamaguchi, S.; Nishiyama, S. Oxidative Cyclization Reactions of Tryptamine Utilizing Hypervalent Iodobenzene in Routes for Pyrroloindole Alkaloid Synthesis. *Synthesis* **2012**, 1667–1671. (b) Singh, A.; Roth, G. P. A [3+2] Dipolar Cycloaddition Route to 3-Hydroxy-3-alkyl Oxindoles: An Approach to Pyrrolidinoindoline Alkloids. *Org. Lett.* **2011**, *13*, 2118–2121. (c) Itoh, T.; Ishikawa, H.; Hayashi, Y. Asymmetric Aldol Reaction of Acetaldehyde and Isatin Derivatives for the Total Syntheses of *ent*-Convolutamydine E and CPC-1 and a Half Fragment of Madindoline A and B. *Org. Lett.* **2009**, *11*, 3854–3857.

[20] Alline isolation and characterization: (a) Samikov, K.; Shakirov, R.; Antsupova, T. P.; Yunusov, S. Y. Allium alkaloids. *Khim. Prirod. Soed.* **1986**, 383. (b) Tashkhodzhaev, B.; Samikov, K.; Yagudaev, M. R.; Antsupova, T. P.; Shakirov, R.; Yunusov, S. Y. Structure of Alline. *Khim. Prirod. Soed.* **1985**, 687–691.

[21] Alline syntheses: Kawasaki, T.; Takamiya, W.; Okamoto, N.; Nagaoka, M.; Hirayama, T. Silyl-enolization-asymmetric Claisen rearrangement of 2-allyloxyindolin-3-one: enantioselective total synthesis of 3a-hydroxypyrrolo[2,3-b]indoline alkaloid alline. *Tetrahedron Lett.* **2006**, *47*, 5379–5382. See also ref. 19b.

[22] Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. A highly selective protocol for the deprotection of Boc-protected amides and carbamates. *Tetrahedron Lett.* **1993**, *34*, 7873–7876.

[23] For related one-pot conversion of di-Boc hydrazides to heterocycles see, (a) Beveridge, R. E.; Fernando, D.; Gerstenberger, B. S. One-pot copper-catalyzed synthesis of *N*-functionalized pyrazoles from boronic acids. *Tetrahedron Lett.* **2010**, *51*, 5005–5008. (b) Gerstenberger, B. S., Rauckhorst, M. R., Starr, J. T. One-Pot Synthesis of *N*-Arylpyrazoles from Aryl Halides. *Org. Lett.* **2009**, *11*, 2097–2100. (c) Beveridge, R. E.; Gerstenberger, B. S. A direct copper-catalyzed route to pyrrolo-fused heterocycles from boronic acids. *Tetrahedron Lett.* **2012**, *53*, 564–569. (d) Inman, M.; Carbone, A.; Moody,

C. J. Two-Step Route to Indoles and Analogues from Haloarenes: A Variation on the Fischer Indole Synthesis. *J. Org. Chem.* **2012**, *77*, 1217–1232. See also ref. 16a.

[24] The di-*tert*-butyl ethynylimidodicarbonate ynimide **10** has been prepared once in low yield (23%) and applied only to a gold-catalyzed oxazolinone formation: Hashmi, S.; Salathe, R.; Frey, W. Gold-Catalyzed Cyclization of *N*-Alkynyl Carbamates. *Synlett* **2007**, 1763–1766.

[25] For the synthesis of a terminal phthaloyl-ynimide reagent, see: Sueda, T.; Oshima, A.; Teno, N. *N*-Alkynyl Imides (Ynimides): Synthesis and Use as a Variant of Highly Labile Ethynamine. *Org. Lett.* **2011**, *13*, 3996–3999.

[26] Gao, G.; Xie, R.-G.; Pu, L. Highly enantioselective alkyne additions to aldehydes in the presence of 1,1'-bi-2-naphthol and hexamethylphosphoramide. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5417–5420.

[27] Frantz, D. E.; Fassler, R.; Carreira, E. M. Facile Enantioselective Synthesis of Propargylic Alcohols by Direct Addition of Terminal Alkynes to Aldehydes. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.

[28] Black, D. A.; Beveridge, R. E.; Arndtsen, B. A. Copper-Catalyzed Coupling of Pyridines and Quinolines with Alkynes: A One-Step, Asymmetric Route to Functionalized Heterocycles. *J. Org. Chem.* **2008**, *73*, 1906–1910. See also ref. 14 for a related reaction with ynamides.

[29] Yamaguchi, M.; Hirao, I. An efficient method for the alkynylation of oxiranes using alkynyl boranes. *Tetrahedron Lett.* **1983**, *24*, 391–394.

[30] Kim, S.; Lee, J. M. Trialkylsilyl triflate promoted conjugate addition of alkynylzinc compounds to α,β-enones. *Tetrahedron Lett.* **1990**, *31*, 7627–7630.

[31] Selected reviews: (a) Hein, J. E.; Fokin, V. V. Copper-catalyzed azide-alkyne cycloaddition (CuAAC) and beyond: new reactivity of copper(I) acetylides. *Chem. Soc. Rev.* **2013**, *39*, 1302–1315. (b) Meldal, M.; Tornoe, C. W. Cu-Catalyzed Azide-Alkyne Cycloaddition. *Chem. Rev.* **2008**, *108*, 2952–3015.

[32] Boren, B. C.; Naravan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. Ruthenium-Catalyzed Azide-Alkyne Cycloaddition: Scope and Mechanism. *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930.

[33] Grecian, S.; Fokin, V. V. Ruthenium-Catalyzed Cycloaddition of Nitrile Oxides and Alkynes: Practical Synthesis of Isoxazoles. *Angew. Chem. Int. Ed.* **2008**, *47*, 8285–8287.

[34] Liu, K.-C.; Shelton, B. R.; Howe, R. K. A particularly convenient preparation of benzohydroximinoyl chlorides (nitrile oxide precursors). *J. Org. Chem.* **1980**, *45*, 3916–3918.

[35] Jie, H.; Li, J.; Li, C.; Jia, X. Isocyanide-Based Multicomponent [2+2+1]-Cycloaddition Strategy to Construct Functionalized Spirocyclic Oxindoles. *Synlett* **2012**, 2274–2278.

[36] Cassani, C.; Melchiorre, P. Direct Catalytic Enantioselective Vinylogous Aldol Reactions of α-Branched Enals with Isatins. *Org. Lett.* **2012**, *14*, 5590–5593.

[37] Elenkov, M. M.; Primozic, I.; Hrenar, T.; Smolko, A.; Dokli, I.; Salopek-Sondi, B.; Tang, L. Catalytic activity of halohydrin dehalogenases towards spiroepoxides. *Org. Biomol. Chem.* **2012**, *10*, 5063–5072.

[38] Duran-Galvan, M.; Connell, B. T. Synthesis of 2-amino-1,3-dienes by chromium-catalyzed addition of silylated propargyl bromides to imines. *Tetrahedron* **2011**, *67*, 7901–7908.

[39] McNulty, J.; Keskow, K.; Vemula, R. The First Well-Defined Silver(I)-Complex-Catalyzed Cycloaddition of Azides onto Terminal Alkynes at Room Temperature. *Chem. Eur. J.* **2011**, *17*, 14727–14730.

[40] Kwok, S. W.; Fotsing, J. R.; Fraser, R. J.; Rodionov, V. O.; Fokin, V. V. Transition-Metal-Free Catalytic Synthesis of 1,5-Diaryl-1,2,3-triazoles. *Org. Lett.* **2010**, *12*, 4217–4219.

[41] (a) Degerbeck, F.; Grehn, L.; Ragnarsson, U. Synthesis, Properties and Use of Nitridotricarbonic Acid Tri-*tert*-Butyl Ester. *Acta Chem. Scand.* **1993**, *47*, 896–898. (b) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. Selective Cleavage of Boc-acylamides. A Novel Approach to Deacylation of Carboxamides. *Acta. Chem. Scand.* **1987**, *41*, 18–23.

[42] (a) Kitamura, T.; Kotani, M.; Fujiwara, Y. An Alternative Synthesis of Alkynyl(phenyl)iodonium Triflates Using (Diacetoxyiodo)benzene and Alkynylsilanes. *Synthesis* **1998**, 1416–1418. For reviews on alkynyl-iodonium triflates, see: (b) Stang, P. J.; Zhdankin, V. V. Organic Polyvalent Iodine Compounds. *Chem. Rev.* **1996**, *96*, 1123–1178. (c) *Modern Acetylene Chemistry*, (Eds: P. J. Stang, F. Diederich), VCH, Weinheim, 1995.