Synthesis of N-heterocycles through cyclization-triggered tandem additions to alkynes and the study of promoters in ionic reactions.

Junbin Han

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SYNTHESIS OF N-HETEROCYCLES THROUGH CYCLIZATION-TRIGGERED TANDEM ADDITIONS TO ALKYNES AND THE STUDY OF PROMOTERS IN IONIC REACTIONS

By

Junbin Han
B.S., ShanXi University, Taiyuan, China, 2008

A Dissertation
Submitted to the Faculty of the College of Arts and Sciences of the University of Louisville in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

Department of Chemistry
University of Louisville
Louisville, Kentucky

May 2014
SYNTHESIS OF N-HETEROCYCLES THROUGH CYCLIZATION-TRIGGERED TANDEM ADDITIONS TO ALKynes AND THE STUDY OF PROMOTERS IN IONIC REACTION

By

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A Dissertation Approved on

April 15, 2014

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ACKNOWLEDGEMENTS

First of all, I would like to express my deepest gratitude to my advisor, Dr. Gerald (GB) Hammond for his excellent guidance, patience, and caring. No matter what happened, He always stood beside me supporting me every step I went through. I also would like to thank Dr. Bo Xu for his talented guidance of my research and his great practical perspective that transcended textbooks.

I would like to acknowledge the computational studies support provided by Professor Robert J. Paton (Oxford University, England). In addition, I would also like to thank the following faculty members for reading this thesis and participating in my defense committee: Dr. F. Luzzio, Dr. M. Maurer, Dr. J. Liu, and Dr. J, Du. Many thanks to Dr. Neal Stolowich who offered me numerous help tips on how to run NMR experiments. Dr. William Richmond has been very helpful in solving many problems on our HPLC, and GC-MS apparatus.

I am also privileged to work with so many kind and talented people in the lab. I am grateful to the past and present group members of the Hammond research group over the years: Dr. Leping Liu, Dr. Weibo Wang, Dr. Zhuang Jin, Manish Kumar, Deepika Malhotra, Otome Elisha, Shengzong Liang, Zhichao Lu, Rene Ebule, Naoto Shimizu, Andrew Flach, Tony Montgomery, and Mallory Durham. It is really a big international family. I very much enjoyed time we spent brainstorming about research and discussion
about many small but important things about life in the lab with our knowledgeable
advisors, Dr. Gerald (GB) Hammond and Dr. Bo Xu.

I am thankful to various funding agencies: the National Institutes of Health for supporting
me with a graduate fellowship, the National Science Foundation, and the University of
Louisville for a Sponsored Research Tuition Award (School of Interdisciplinary and
Graduate Studies).

I am grateful to my parents. They were always supporting me and encouraging me with
their best wishes. Last but not least, I would like to thank my wife Xuan Wang and my
lovely daughter Olivia Han. They have brought me great joy and peace beyond words
and knowledge. All amazing things happened at Louisville. Best wishes to Louisville.
Our research mainly focused on three parts related to the rapid construction of N-heterocycles and the search for ionic reaction promoters. First, N-heterocycles of different ring sizes and with different substitution patterns constitute extremely important structure classes (e.g., alkaloids) in the search for bioactivity. A contemporary challenge in organic synthesis is the mapping of new chemical spaces through tandem or cascade reactions in an atom economical fashion. Our strategy to access these biologically important heterocycles is through a cyclization-triggered tandem addition to alkynes catalyzed by readily available alkynophilic coinage metals like copper. In this manner, a variety of functional groups could be introduced to the ring system through a carbon-carbon forming reaction. Second, in chemistry, a promoter is defined as a substance added to a catalyst to improve its performance in a chemical reaction. Promoters interact with active components of catalysts and thereby alter their chemical effect on the catalyzed substance. In our studies, we found $\text{KCTf}_3$ is an ideal promoter that is readily available and able to tolerate harsh reaction conditions. When $\text{KCTf}_3$ is added to reaction system, a reshuffling of ions occurs and a $\text{CTf}_3^-$ reactive cationic species will be
generated in situ, which improves the efficiency of a reaction. Third, silver-mediated halogen abstraction is the most preferred method to generate cationic gold from a gold catalyst precursor. However, the use of silver activators is problematic because of its high cost, generation of unwanted side reactions and Au-Ag intermediates. We found that a gold phthalimide complex (L-Au-Ph) could be easily synthesized, and upon contact with either a Brønsted acid or a Lewis acid it generates an active gold phthalimide complex that not only avoid problems caused by silver promoters but also yields an efficient and highly reactive gold catalyst for the most popular types of gold-catalyzed reactions, including X-H (X = O, N, C) additions to C-C unsaturated compounds (alkyne/allene/alkene), and cycloisomerizations.
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CHAPTER 1
SYNTHESIS OF N-HETEROCYCLES
THROUGH CYCLIZATION-TRIGGERED TANDEM ADDITIONS

1.1 Introduction

Chemical synthesis plays a major role in medicine, agricultural and material research. Unhindered access to diverse classes of biologically active lead compounds is an essential part of drug discovery. In the search for bioactivity, N-heterocycles of different ring sizes and different substitution patterns are among the most important structural classes in medicinal chemistry.\textsuperscript{1-5} A large percentage of drugs in the market contain one or more N-heterocycles (Figure 1). Based on an analysis of the top 200 brand-name drugs in the market in 2007, 108 out of these top 200 drugs contain at least one N-heterocycle, among them, 5-, 6-, and 7-membered rings are the most common ring sizes; within this subgroup the bridged N-heterocycles and cyclic amino acids are prevalent (Figure 1). Although the synthesis of N-heterocycles has been around for over a century and a variety of well-established methods are available, there are still unmet needs to carry concise and efficient synthesis of structurally more complex N-heterocycles, especially when larger amounts of material are needed for extensive biological studies or clinic trials.\textsuperscript{6} The need to map new chemical spaces through tandem or cascade reactions in an
atom economical fashion inspired us to develop a strategy to access biologically important heterocycles of different ring sizes (e.g., 5-7), with different substitution patterns (e.g., cyclic amino acids) through the use of alkynophilic coinage metals capable of catalyzing tandem additions/cyclization of alkynes. This tandem chemistry may enable us to rapidly generate biologically important N-heterocycles like 5-7 membered rings and cyclic amino-acids, with a facility unmatched by previous methods.

Figure 1. Analysis of the top 200 selling brand-name drugs by retail dollars in 2007 (Based on the data compiled by Prof. Njardarson-University of Arizona).

http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster
The addition of nucleophiles to an *in situ* generated imine/enamine/iminium is a successful strategy in organic synthesis. One example is the copper catalyzed alkynylation of an *in situ* generated imine from an aldehyde and an aromatic primary amine (Scheme 1, a). Another common example is the use of an *in situ* generated imine in a Mannich type reaction (Scheme 1, b). Although these tandem reactions are very efficient for building acyclic (linear) products, they are hard pressed to generate ring systems, because it is difficult to make the corresponding starting material--there is simply no general method to install an amino group next to an aldehyde or ketone without extensive protection/deprotection steps.

Scheme 1. Addition of terminal alkynes to imines and Mannich reaction.

One the other hand, the transition metal catalyzed intramolecular amination of alkene/allene/alkyne is a well-established method to generate N-heterocycles, but this approach does not permit introduction of new functionalities to the heterocycle for further
manipulation. We proposed a versatile strategy to generate N-heterocycles in a tandem manner: first, an intramolecular hydroamination of amino-alkyne 1 to generate an enamine/imine/iminium *in situ*, which can react with a functionalized carbon nucleophile to give double addition products in one pot. In this way, we not only accomplish the construction of N-heterocycles, but we also introduce a new functional group on the ring system through a carbon-carbon bond forming reaction, an important prerequisite if one wants to pursue further transformation towards complex ring systems. An additional advantage is that the alkyne functionality is easy to introduce and is chemically inert to commonly used reactions conditions (e.g. acid or base).

![Scheme 2. Cyclization-triggered tandem addition.](image)

Depending on the substitution pattern of the starting material and of the catalyst used, the transition metal catalyzed hydroamination of alkynes can yield an enamine or imine (*in the case of primary amines*).\(^6,10,11\) The reported methodologies have focused mostly on hydroamination using primary amines.\(^6,10,11\) The addition of a terminal alkyne to an activated enamine is the methodology of choice for the synthesis of racemic or chiral
propargyl amines.\textsuperscript{12-14} And the two processes can be catalyzed by the same metal catalyst (e.g., copper), so we proposed that the two processes be conducted in tandem: when a secondary amine attacks an intramolecularly tethered alkyne, the resulting activated enamine intermediate becomes a new electrophilic precursor capable of reacting with a second nucleophile, such as a terminal alkyne, to give a new addition product (Scheme 2-a). This tandem amination/alkynylation sequence will introduce an additional alkyne to the N-heterocycle, which can undergo further transformations (e.g., cycloisomerization). In this manner, various rings system can be obtained (Scheme 2-a). Moreover, a terminal alkyne is not the only nucleophile of choice. When we use an allylsilane as a nucleophile, we introduce an additional alkene to the system, which can undergo further transformations like metathesis (Scheme 2-b, middle). And when a nucleophile like TMS-CN is used, hydrolysis of the resulting intermediate will provide facile access to the very important cyclic \(\alpha\)-amino-acids (see Figure 1 for examples of commercial drugs). As other types of nucleophiles are considered, more highly diversified ring systems can be expected (Scheme 2-d and e). Because the second addition was triggered by the first addition (intramolecular amination), we decided to name this a cyclization-triggered addition strategy.

Literature reports on tandem addition of two different nucleophiles to an alkyne in one pot are rare. Li and coworkers reported the tandem addition of an amine and alkyne to unsaturated esters through a proposed iminium intermediate (Scheme 3-a).\textsuperscript{15} Che and coworkers have reported a gold(I) catalyzed tandem synthesis of pyrrolo[1,2-a]quinolines (Scheme 3-b);\textsuperscript{16,17} but their reaction requires aromatic amines tethered to terminal alkynes, and it can only work for the synthesis of methyl substituted 5-membered rings. The gold
catalyzed one-pot synthesis of 1,2-dihydroquinoline derivatives from amines, internal alkynes, and terminal alkynes have also been reported by Bertrand and co-workers.\textsuperscript{18} We envisioned a broader scope for our tandem hydroamination/alkynylation process, namely, the amination of inactive alkynes (terminal or internal) in the presence of a single metal catalyst operating on both, the hydroamination and alkynylation steps. Our strategy is much more general and powerful because: i) synthetically more useful aliphatic amines or other functionalized amines can be used; ii) the alkyne tethered to the amine does not need to be activated (there is no need to attach an ester or other electron-withdrawing group) and can be terminal or internal; iii) the nucleophile used in the second addition is not limited to terminal alkynes; iv) different rings sizes (e.g., 5-, 6- and 7-membered rings) can be accessed.

\begin{center}
\includegraphics[width=\textwidth]{Scheme3.png}
\end{center}

Scheme 3. Double additions of amine and terminal alkyne to alkynes.

\section*{1.2. Tandem amination/alkynylation}

Our first application of cyclization-triggered tandem additions strategy was tandem amination/alkynylation. When a secondary amine attacks an electrophilically activated alkyne, the resulting activated enamine intermediate then becomes a new electrophilic
precursor capable of reacting with a second nucleophile, such as a terminal alkyne, to give a new addition product. This essentially corresponds to a double addition to a triple bond. If the first step is an intramolecular cyclization using an aminoalkyne (Scheme 4), then the second step adds a second alkynyl group (C≡C-R³), which can then interact with R¹ or R² and spur further transformations (e.g., cycloisomerization).

![Scheme 4. Cyclization-triggered alkynylation.](image)

1.2.1. **Screening of conditions**

The reaction of aminoalkyne **1-1a**—readily prepared from an alkyne alcohol by a tosylation/amination sequence—with phenylacetylene **1-2a** was used as model (Table 1). Among the various coinage metal catalysts screened, copper was the best, and Cu(I) was better than Cu(II) (Table 1, entries 1-5). Copper’s excellent performance may be due to its higher tolerance toward basic amines and the fact that it is a superior catalyst for alkynylation (Sonogashira-type reactions). Under microwave conditions, this reaction is very fast and gives excellent yields, but conventional heating also works very well if longer reaction times are employed (Table 1, entry 8). This reaction was initially conducted in dioxane, however, toluene or acetonitrile also give excellent results (Table 1, entries 9 and 10). At first, we used a large excess of terminal alkyne **1-2a** to avert a potential competition between the two terminal alkynes, but, to our surprise, even when
the number of equivalents of 1-2a was reduced from 4.0 to 1.5, the reaction still furnished 1-3a in excellent yields (Table 1, entry 11). Larger scale did not reduce the yield of product (Table 1, entry 12).

Table 1. Screening of conditions for tandem amination/alkynylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>1b/ equiv</th>
<th>solvent</th>
<th>temp/time</th>
<th>yield%</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>AuCl</td>
<td>4</td>
<td>dioxane</td>
<td>MW(^a)/100°C/0.5h</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)(_2)</td>
<td>4</td>
<td>dioxane</td>
<td>MW/100°C/0.5h</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>PdCl(_2)</td>
<td>4</td>
<td>dioxane</td>
<td>MW/100°C/0.5h</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>AgNO(_3)</td>
<td>4</td>
<td>dioxane</td>
<td>MW/100°C/0.5h</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>Cul</td>
<td>4</td>
<td>dioxane</td>
<td>MW/100°C/0.5h</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>CuBr</td>
<td>4</td>
<td>dioxane</td>
<td>MW100°C/0.5h</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>CuBr</td>
<td>4</td>
<td>dioxane</td>
<td>MW/60°C/0.5h</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>CuBr</td>
<td>4</td>
<td>dioxane</td>
<td>Heat 100°C/12h</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>CuBr</td>
<td>4</td>
<td>Toluene</td>
<td>MW100°C/0.5h</td>
<td>98</td>
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<tr>
<td>10</td>
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<tr>
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<tr>
<td>12(^c)</td>
<td>CuBr</td>
<td>1.5</td>
<td>dioxane</td>
<td>MW100°C/0.5h</td>
<td>99</td>
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\(^a\) The reactions were conducted in 0.25 mmol scale. \(^b\) MV = microwave. \(^c\) The reactions were conducted in 3 mmol scale.

### 1.2.2. Scope of this tandem amination/alkynylation reaction

The scope of this tandem amination/alkynylation reaction is outlined in Table 2. The reaction worked extremely well in all cases giving near quantitative chemical yields of five-, six-, and seven-membered rings. Complete regioselectivity was observed. When a N-methyliminodiacetic acid (MIDA) boronate\(^{19}\) alkyne 1-2f was used, the terminal alkyne product 1-3k was obtained (Table 2, entry 11); this may be due to cleavage of MIDA boronate during the reaction. When a chiral aminoalkyne was used (1-1g), a small
chiral induction was observed \((dr = 1:1.3, \text{Table 2, entry 12})\), probably because the existing chiral center is relatively far away from the newly generated chiral center. The sterically encumbered TMS-substituted aminoalkyne \textbf{1-1h} didn’t give the desired product \((\text{Table 2, entry 13})\). And the reaction of proline derivative \textbf{1-1i} gave a fused ring product \((\text{Table 2, entry 14})\). The regioselectivity obeyed Baldwin’s rules.\(^{20}\) The cyclization of 3-yn-amine \textbf{1b} and \textbf{1-1a} gave five-membered ring products through \textit{5-endo-dig} and \textit{5-exo-dig} processes. And the reactions of 5-yn-amine \((\text{e.g., } \textbf{1-1c})\) and 6-yn-amine \((\text{e.g., } \textbf{1-1e})\) give six-membered and seven-membered rings, through \textit{6-exo-dig} and \textit{7-exo-dig} processes, respectively.

Attempts to form 3- or 4-membered rings under similar conditions, using \textbf{1j}, were unsuccessful \((\text{eq 1})\). Surprisingly, the reaction of 7-yn-amine \textbf{1-1k} led to the intermolecular hydroamination/alkynylation product \textbf{1-4a} in good yield through a double addition to phenyl acetylene rather than the corresponding eight-membered ring \((\text{eq 2})\).

Taking this as cue for a possible intermolecular variant, we reacted an unfunctionalized alkyne \textbf{1-1l} with a simple secondary amine, using similar conditions \((\text{eq 3})\). This reaction gave the desired product \textbf{1-4b}, albeit in lower chemical yield. We have not yet conducted optimization studies for this intermolecular version.

The cycloisomerization of \(1_1n\)-enynes and \(1_1n\)-diynes is currently a highly competitive field in organic synthetic chemistry.\(^{21}\) Our newly found method provides direct entry to functionalized \(1_1n\)-enynes, as showcased by the synthesis of \(1_6\)-enyne \((3e)\) in high yield in a single step \((\text{Table 2, entry 5})\). Our reaction is also capable of furnishing fused ring systems, if a cyclic secondary amine is present \((\text{Table 2, entry 14})\).
Table 2. Scope of tandem amination/alkynylation reaction.\textsuperscript{a}

\[
\begin{array}{ccc}
\text{entry} & \textbf{1-1} & \textbf{1-2} & \textbf{1-3} \text{(yield \%)} \\
1 & \text{Bn}^+ \text{H}^+ \text{NH}_2 \text{C} \equiv \text{C} \equiv \text{C} & \text{Ph} \equiv \text{C} \equiv \text{H} & \textbf{1-3a}, 99 \\
2 & \text{\textbf{1-1a}} & \text{\textbf{1-2a}} & \text{\textbf{1-3b}, 99} \\
3 & \text{\textbf{1-1b}} & \text{\textbf{1-2a}} & \text{\textbf{1-3c}, 98} \\
4 & \text{\textbf{1-1c}} & \text{\textbf{1-2a}} & \text{\textbf{1-3d}, 95} \\
5 & \text{\textbf{1-1d}} & \text{\textbf{1-2a}} & \text{\textbf{1-3e}, 98} \\
6 & \text{\textbf{1-1e}} & \text{\textbf{1-2a}} & \text{\textbf{1-3f}, 90} \\
7 & \text{\textbf{1-1a}} & \text{\textbf{1-2b}} & \text{\textbf{1-3g}, 95} \\
8 & \text{\textbf{1-1a}} & \text{\textbf{1-2c}} & \text{\textbf{1-3h}, 99} \\
9 & \text{\textbf{1-1a}} & \text{\textbf{1-2d}} & \text{\textbf{1-3i}, 99} \\
10 & \text{\textbf{1-1a}} & \text{\textbf{1-2e}} & \text{\textbf{1-3j}, 95} \\
11 & \text{\textbf{1-1a}} & \text{\textbf{1-2f}} & \text{\textbf{1-3k}, 89} \\
\end{array}
\]
1.2.3. Experimental

$^1$H, $^{13}$C, $^{19}$F and $^{31}$P NMR spectra were recorded at 500, 126, 470 and 162 MHz respectively, using CDCl$_3$ as a solvent. The chemical shifts are reported in $\delta$ (ppm) values relative to ($\delta$ 7.26 ppm for $^1$H NMR, $\delta$ 77.0 ppm for $^{13}$C NMR and CFCl$_3$ $\delta$ 0.00 ppm for $^{19}$F NMR), multiplicities are indicated by s(singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, $J$, are reported in Hertz (Hz). All air and or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMSO) were chemically dried using a commercial solvent purification system. All other reagents and
solvents were employed without further purification. The products were purified using a commercial flash chromatography system or a regular glass column. TLC was developed on Merck silica gel 60 F<sub>254</sub> aluminum sheets. Elemental analysis was performed at Atlantic Microlabs Inc., Norcross, Georgia 30091. The microwave reactor (CEM, model Discovery) was used in microwave condition. HRMS (High Resolution Mass Spectrometry) obtained at the CREAM Mass Spectrometry Facility, University of Louisville.

**General procedure for the preparation of aminoalkyne 1-1.**<sup>22</sup>

N-Benzyl-4-pentyn-1-amine (1a). 4-pentyn-1-ol (25 mmol, 2.5 g) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> 100 mL, and the solution was cooled down to -10 °C, then methanesulfonyl chloride (2.15 mL, 28 mmol) and triethylamine (5.5 mL, 40 mmol) are introduced by syringe successively. The mixture is stirred for 30 min at -10°C, then it is poured onto ice-water (100 mL) during stirring. The organic layer is washed successively with 1 M hydrochloric acid solution (15 mL), saturated aqueous sodium bicarbonate solution (15 ml), and brine (15 mL). The organic layer is dried over magnesium sulfate, filtered, and concentrated to give crude 4-hexyn-1-yl methanesulfonate, which was used directly in the next step. Dimethyl sulfoxide (20 mL) and benzylamine (5.4 g, 50 mmol) are added to the above mentioned crude product. The resulting solution is heated in an oil bath at 47-53°C for 5 hr and then the reaction mixture is allowed to cool to room temperature. The reaction solution is poured into a separatory funnel containing 100 mL of aqueous 1% sodium hydroxide solution and the resulting mixture is extracted with ether (3×100 mL). The combined ether extracts are washed with brine (50 mL), dried
over magnesium sulfate, and concentrated in a rotary evaporator under vacuum. The residue is purified by flash chromatography (1:1 hexane-ether containing 1% triethylamine as the eluent) to give a colorless liquid 1-1a (3.6 g, 75%, 2 steps).

**General procedure for preparation of 1-3.**

![Chemical structure of 1-1a](image)

1-benzyl-2-methyl-2-(phenylethynyl)pyrrolidine (1-3a).

N-Benzyl-4-pentyn-1-amine 1a (43 mg, 0.25 mmol), 1.0 mmol of phenylacetylene (102 mg, 1.0 mmol) and dioxane (1 mL) was added to a microwave tube reactor, and CuBr (1.8 mg, 5% equiv) is added while the mixture is stirred. After all the starting materials are dissolved, the microwave reactor is flushed with argon. Then the reaction mixture is heated to 100ºC under microwave irradiation for 0.5 hr. The resulting reaction solution is directly concentrated in a rotary evaporator and purified by flash chromatography (20:1 hexane:ether containing 0.5% Et3N ) to give a yellow liquid 1-3a (68 mg, 99%).

1-benzyl-2-methyl-2-(phenylethynyl)pyrrolidine (1-3a): IR(neat): 2971, 2804, 1489, 1140, 755, 692 cm\(^{-1}\); \(^1\)HNMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.56 (s, 3H), 1.70 - 1.99 (m, 3H), 2.25 (t, \(J = 8.5\) Hz, 1H), 2.52 (q, \(J = 7.5\) Hz, 1H), 2.95 (td, \(J = 9\) Hz, 2.5 Hz, 1H), 3.41 (d, \(J = 13.5\) Hz, 1H), 4.04 (d, \(J = 13.5\) Hz, 1H), 7.20-7.40 (m, 5H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 20.7, 26.2, 40.7, 51.9, 55.0, 60.6, 85.0, 91.0, 123.7, 127.0, 128.0, 128.4, 129.1, 132.1, 140.2; GC/MS (EI) \(m/z\): 275; Anal. Calcd. for C\(_{20}\)H\(_{21}\)N: C, 87.23; H, 7.69. Found: C, 86.96; H, 7.82.
1-benzyl-2-butyl-2-(phenylethynyl)pyrrolidine (1-3b): IR(near): 2935, 2804, 1597, 1490, 1453, 1137, 755, 692 cm⁻¹; ¹HNMR (500 MHz, CDCl₃): 1.00 (t, J = 7.5 Hz, 3 H), 1.40 - 1.84 (m, 6 H), 1.74 - 2.01 (m, 3 H), 2.20 (t, J = 8.5 Hz, 1 H), 2.52 (q, J = 8.0 Hz, 1 H), 2.96 (td, J = 8.0 Hz, 2 Hz, 1 H), 3.39 (d, J = 13.5 Hz, 1 H), 4.08 (d, J = 13.5 Hz, 1 H), 7.22 - 7.55 (m, 10 H); δ ¹³C NMR (125 MHz, CDCl₃): 14.4, 20.9, 23.5, 27.6, 38.1, 39.2, 51.9, 55.0, 64.3, 85.5, 91.1, 124.0, 126.9, 127.9, 128.43, 128.49, 129.0, 132.0, 140.6; GC/MS (EI) m/z: 317, 261; Anal. Calcd. for C₂₃H₂₇N: C, 87.02; H, 8.57. Found: C, 87.07; H, 8.61.

1-benzyl-2-pentyl-2-(phenylethynyl)piperidine (1-3c): IR(near): 2932, 2858, 2819, 1490, 1444, 737, 691; ¹HNMR (500 MHz, CDCl₃): 0.96 (t, J = 7 Hz, 3 H), 1.30 - 1.83 (m, 10 H), 1.86 - 2.03 (m, 3 H), 2.17 - 2.24 (m, 1 H), 2.51 - 2.54 (m, 1 H), 2.96 (td, J = 9.0 Hz, 3.0 Hz, 1 H), 3.40 (d, J = 13.5 Hz, 1 H), 4.10 (d, J = 13.5 Hz, 1 H), 7.23 - 7.55 (m, 10 H); ¹³C NMR (125 MHz, CDCl₃): 14.4, 20.9, 22.9, 25.4, 30.1, 32.1, 38.1, 39.5, 51.9, 55.0, 64.3, 85.5, 91.0, 124.0, 126.9, 127.9, 128.4, 128.5, 129.1, 132.0, 140.7; GC/MS (EI) m/z: 345, 313, 260, 241, 175; Anal. Calcd. for C₂₅H₃₁N: C, 86.90; H, 9.04. Found: C, 86.64; H, 9.13.
1-benzyl-2-methyl-2-(phenylethynyl)piperidine (1-3d): $^1$HNMR (500 MHz, CDCl$_3$): 1.42 - 1.52 (m, 2 H), 1.57 (s, 3 H), 1.62-1.79 (m, 3 H), 1.90 (d, $J = 9.6$ Hz, 2 H), 2.38 (td, $J = 9$ Hz, 2 Hz, 1 H), 2.62 (d, $J = 12$ Hz, 1 H), 3.19 (d, $J = 13.5$ Hz, 1 H), 4.17 (d, $J = 13.5$ Hz, 1 H), 7.22 - 7.56 (m, 10 H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 22.4, 26.4, 29.3, 40.7, 49.1, 55.8, 55.9, 86.0, 90.7, 123.9, 126.7, 127.9, 123.3, 128.4, 128.9, 132.0, 140.9; GC/MS (EI) m/z: 290, 275, 268, 264, 261.

![1-3d](image)

1-allyl-2-pentyl-2-(phenylethynyl)piperidine (1-3e): IR(neat): 2932, 2858, 2808, 1489, 916, 755, 690; $^1$HNMR (500 MHz, CDCl$_3$): 0.91 (t, $J = 7$ Hz, 3 H), 1.30 - 1.52 (m, 8 H), 1.58 - 1.68 (m, 1 H), 1.78 - 1.94 (m, 4 H), 2.12 - 2.20 (m, 1 H), 2.46-2.50 (m, 1 H), 2.93 (dd, $J = 13.5$ Hz, 8Hz, 1 H), 3.15 (td, $J = 9.0$ Hz, 2.0 Hz, 1 H ), 3.49 (dd, $J = 13.5$ Hz, 5 Hz, 1 H), 5.11(d, $J = 10$ Hz, 1 H), 5.25 (dd, $J = 17$ Hz, 1Hz, 1 H), 5.91 - 6.00 (m, 1 H), 7.29-7.49 (m, 5 H); $^{13}$C NMR (125 MHz, CDCl$_3$): 14.3, 20.7, 22.8, 25.5, 30.0, 32.04, 32.05, 38.2, 39.4, 51.9, 53.8, 85.7, 90.5, 116.6, 123.8, 127.9, 128.4, 131.9, 137.2; GC/MS (EI) m/z: 296, 211, 136, 70, 41; Anal. Calcd. for C$_{21}$H$_{29}$N: C, 85.37; H, 9.89. Found: C, 85.12; H, 10.08.

![1-3e](image)

1-benzyl-2-methyl-2-(phenylethynyl)azepane (3f): IR(neat): 3430, 2970, 1489, 1140, 754, 691, 538; $^1$HNMR (500 MHz, CDCl$_3$): $\delta$ 1.40-1.54 (m, 3 H), 1.54-1.57 (s, 3 H),
1.61-1.67 (m, 1 H), 1.78-1.89 (m, 2 H), 1.98 - 2.05 (m, 1 H), 2.09-2.15 (m, 1 H), 2.52 (q, $J = 14.5$ Hz, 9.5 Hz, 1 H), 2.81(dd, $J = 14.5$ Hz, 9.5 Hz, 1 H), 3.73 (d, $J = 14.5$ Hz, 1 H), 3.98 (d, $J = 14.5$ Hz, 1 H), 7.26-7.51 (m, 10 H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 22.7, 27.2, 29.6, 31.1, 43.5, 48.5, 57.4, 58.1, 82.5, 94.7, 124.1, 126.7, 127.8, 128.25, 128.26, 128.9, 142.0; GC/MS (EI) m/z: 303, 261, 212, 156, 110, 92; Anal. Calcd. for C$_{22}$H$_{25}$N: C, 87.08; H, 8.30. Found: C, 87.01; H, 8.19.

1-benzyl-2-(hex-1-yn-1-yl)-2-methylpyrrolidine (1-3g): IR(neat): 2966, 2805, 1455, 1240, 1143, 736, 698; $^1$HNMR (500 MHz, CDCl$_3$): $\delta$ 0.96 (t, $J = 7.5$ Hz, 3 H), 1.42 (s, 3 H), 1.44 - 1.86 (m, 7 H), 2.04 - 2.11 (m, 1 H), 2.27 (t, $J = 7.5$ Hz, 2 H), 2.49 (dd, $J = 13$ Hz, 8 Hz, 1 H), 2.85 (td, $J = 7.5$ Hz, 2 Hz, 1 H), 3.28 (d, $J = 13$ Hz, 1 H), 3.90 (d, $J = 13$ Hz, 1 H), 7.21-7.40 (m, 5 H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 13.8, 18.5, 20.6, 22.1, 26.5, 31.6, 40.9, 51.7, 54.9, 60.0, 81.2, 84.6, 126.8, 128.3, 129.0, 140.7; GC/MS (EI) m/z: 347, 257, 241, 195, 169, 121; Anal. Calcd. for C$_{18}$H$_{25}$N: C, 84.65; H, 9.87. Found: C, 84.43; H, 9.98.

1-benzyl-2-methyl-2-((triethylsilyl)ethynyl)pyrrolidine (1-3h): IR(neat): 2955, 2152, 1456, 1234, 1017, 860, 733; $^1$HNMR (500 MHz, CDCl$_3$): $\delta$ 0.65 (q, $J = 7.5$ Hz, 6 H),
1.06 (t, J = 7.5 Hz, 9 H), 1.46 (s, 3 H), 1.69 - 1.88 (m, 3 H), 2.12 - 2.18 (m, 1 H), 2.40 - 2.43 (m, 1 H), 2.89 (td, J = 9 Hz, 3 Hz, 1 H), 3.32 (d, J = 13.5 Hz, 1 H), 3.93 (d, J = 13.5 Hz, 1 H), 7.22 - 7.39 (m, 5 H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 4.9, 7.8, 20.6, 26.2, 40.8, 51.7, 55.0, 60.6, 85.2, 108.9, 126.9, 128.3, 129.0, 140.5; GC/MS (EI) m/z: 300, 271, 213, 209, 189; Anal. Calcd. for C$_{20}$H$_{31}$NSi: C, 76.61; H, 9.97. Found: C, 76.72; H, 10.10.

1-benzyl-2-(5-chloropent-1-yn-1-yl)-2-methylpyrrolidine (1-3i): IR(neat): 2969, 2804, 1454, 1143, 737, 699; $^1$HNMR (500 MHz, CDCl$_3$): δ 1.43(s, 3 H), 1.68 - 1.86 (m, 3 H), 1.96-2.12(m, 3 H), 2.40 (dd, J =13 Hz, 8 Hz, 1 H), 2.47 (t, J = 6.5 Hz, 2 H), 2.87 (td, J = 9 Hz, 3 Hz, 1 H), 3.26 (d, J = 13 Hz, 1 H), 3.72 (t, J = 6.5 Hz, 2 H), 3.91 (d, J = 13 Hz, 1 H), 7.22 - 7.39 (m, 5 H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 16.4, 20.6, 26.4, 32.1, 40.9, 43.9, 51.7, 54.9, 59.9, 82.4, 82.5, 126.9, 128.4, 129.0, 140.5; GC/MS (EI) m/z: 275, 258, 197, 165, 132, 93; Anal. Calcd. for C$_{17}$H$_{22}$NCl: C, 74.03; H, 8.04. Found: C, 73.88; H, 8.22.

1-benzyl-2-ethynyl-2-methylpyrrolidine (1-3k): IR(neat): 3296, 2972, 2807, 1455, 1363, 1143, 699, 639; $^1$HNMR (500 MHz, CDCl$_3$): δ 1.47 (s, 3 H), 1.7-1.9 (m, 3 H), 2.12-2.2 (m, 1 H), 2.37 (s, 1 H), 2.40 (dd, J = 13 Hz, 8Hz, 1 H), 2.88 (td, J = 9 Hz, 3 Hz, 1 H), 3.30 (d, J = 13 Hz, 1 H), 3.93 (d, J = 13 Hz, 1 H), 7.22-7.39 (m, 5 H); $^{13}$C NMR
(125 MHz, CDCl₃): δ 20.5, 26.1, 40.6, 51.6, 54.7, 59.8, 72.0, 85.3, 126.9, 128.4, 128.9, 140.3; GC/MS (EI) m/z: 199, 115, 91, 54. Anal. Calcd. for C₁₄H₁₇N: C, 84.37; H, 8.60. Found: C, 84.72; H, 8.60.

2-methyl-1-((S)-1-phenylethyl)-2-(phenylethynyl)pyrrolidine (1-3l) was obtained as a mixture of two diastereoisomers in ratio of 1:1.3. IR(neat): 2970, 2817, 1489, 1453, 1141, 755, 701; ¹H NMR (500 MHz, CDCl₃): major isomer: δ 1.02 (s, 3 H), 1.52 (t, J = 6 Hz, 3 H), 1.66 - 1.96 (m, 2 H), 1.97 - 2.04 (m, 1 H), 2.23 - 2.31 (m, 1 H), 2.85 (q, J = 8 Hz, 1 H), 3.18 (td, J = 9 Hz, 3 Hz, 1 H), 4.03 (q, J = 6.5 Hz, 1 H), 7.20-7.59 (m, 10 H); (EI) m/z: 290, 242, 182, 141, 105; Calcd. for C₂₁H₂₃NCl: C, 87.15; H, 8.01. Found: C, 86.91; H, 8.10.

(8aS)-4-methyl-4-(phenylethynyl)hexahydro-1H-pyrrolo[2,1-c][1,4]oxazine (1-3n) was obtained as a mixture of two diastereoisomers in ratio of 1:1.3. ¹H NMR (500 MHz, CDCl₃): major isomer: δ 1.34-1.36 (m, 1 H), 1.37 (s, 3 H), 1.72-1.84 (m, 3 H), 2.50 -2.55 (m, 1 H), 2.70-2.73 (m, 1 H), 3.09 (td, J = 9, 2.5 Hz, 1 H), 3.25-3.32 (m, 2 H), 3.85 (d, J = 10.5 Hz, 1 H), 4.06 (dd, J = 10.5, 2.5 Hz, 1 H), 7.28-7.32 (m, 3 H), 7.46-7.48(m, 2 H); ¹³C NMR (125 MHz, CDCl₃): δ 20.1, 23.7, 25.8, 46.6, 57.0, 72.3, 75.5, 86.0, 88.1, 127.9, 128.1, 129.0, 131.9.
**N-benzyl-N-(1,4-diphenylbut-3-yn-2-yl)oct-7-yn-1-amine (1-4a):** $^1$HNMR (500 MHz, CDCl$_3$): $\delta$ 1.10-1.33 (m, 3 H), 1.34-1.46 (m, 4 H), 1.85 (t, $J = 3.5$ Hz, 1 H), 2.07 (td, $J = 9$ Hz, 3 Hz, 2 H), 2.41 - 2.60 (m, 2 H), 2.94 (d, $J = 7.5$ Hz, 1 H), 2.43 (d, $J = 14.5$ Hz, 1 H), 3.80 (t, $J = 7.2$ Hz, 1 H), 3.87 (d, $J = 14.5$ Hz, 1 H), 7.18-7.45 (m, 15 H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 18.5, 26.9, 28.1, 28.7, 28.8, 40.8, 51.0, 55.4, 55.7, 68.3, 84.9, 85.9, 88.0, 123.7, 126.4, 126.9, 128.0, 128.2, 128.3, 128.4, 128.9, 129.7, 131.9, 139.0, 140.2; GC/MS (EI) m/z: 408, 384, 356, 317, 274, 226, 198;

$^1$H and $^{13}$C NMR spectra of compound 1-3a
1.3. Tandem amination/cyanation

In Section 1.2, we described the synthesis of functionalized five-, six-, and seven-membered N-heterocycles, via a Cu(I)-catalyzed, one-pot, tandem hydroamination/alkynylation, a process we called cyclization-triggered addition. In this section, we wanted to investigate if this protocol could be extended to the tandem addition of two different nucleophiles to an alkyne, beginning with an intramolecular hydroamination of aminoalkyne 1-1 and ending with the addition of a second nucleophile to the in situ generated enamine or imine. Indeed, our one-pot cyclization-triggered addition furnished α-CN substituted N-heterocycles in very good to excellent yields.
1.3.1. Screening of conditions for tandem amination/cyanation

To begin screening for optimized reaction conditions, we used the reaction of aminoalkyne 1-1a and TMS-CN as our initial model because the reported synthesis of α-cyano-N-heterocycles—oxidative cyanation of a cyclic tertiary amine—often suffers from limited scope and lack of regioselectivity. Using 5% CuBr as catalyst, our tandem reaction gives 30% of the desired product 1-5a with excellent regioselectivity (Table 3, entry 1). When the reaction is carried out at higher temperature under microwave conditions, the yield of 1-5a is excellent (Table 3, entry 2). Gold catalyst also works well in this reaction (Table 3, entry 3). Under microwave conditions, the Cu(I)-catalyzed reaction is very fast (30 min), but conventional heating also works very well if longer reaction times are employed (Table 3, entry 4). Increasing the scale of this reaction does not reduce the yield of product.

Table 3. Screening for the best conditions for a tandem amination/cyanation.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>temp, time</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr</td>
<td>dioxane</td>
<td>rt, 12 h</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>CuBr</td>
<td>dioxane</td>
<td>mw(a), 100 °C, 0.5 h</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>IPrAuCl/AgOTf</td>
<td>dioxane</td>
<td>mw(a), 100 °C, 0.5 h</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>CuBr</td>
<td>dioxane</td>
<td>100 °C, 12 h</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>CuBr</td>
<td>toluene</td>
<td>mw(a), 100 °C, 0.5 h</td>
<td>90</td>
</tr>
<tr>
<td>6(b)</td>
<td>CuBr</td>
<td>dioxane</td>
<td>mw(a), 100 °C, 0.5 h</td>
<td>82</td>
</tr>
</tbody>
</table>

\(a\) mw = microwave; \(b\) using 10 equiv of water; IPrAuCl = Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I).
With optimized conditions in hand, we turned our attention to less basic amines (Table 4). The aromatic amine tethered alkyne $1\text{-}5\text{m}$ gave mostly the hydration product (Table 4, entry 1). We then decided to use a gold catalyst, (iPrAuCl/AgOTf), capable of strong alkyne activation and with good thermal stability; this catalyst gave the desired product in excellent yield (Table 4, entry 2). We obtained similar results using the amide tethered alkyne $1\text{-}5\text{n}$ (Table 4, entries 3 and 4).

Table 4. Screening for the best conditions for a tandem amination/cyanation using less basic aminoalkynes.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>1-1</th>
<th>catalyst</th>
<th>Temp</th>
<th>time</th>
<th>yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-1m</td>
<td>CuBr</td>
<td>mw, 100 °C, 40 min</td>
<td>0$^a$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1-1m</td>
<td>IPrAuCl/AgOTf</td>
<td>mw, 100 °C, 40 min</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1-1n</td>
<td>CuBr</td>
<td>mw, 100 °C, 40 min</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1-1n</td>
<td>IPrAuCl/AgOTf</td>
<td>mw, 100 °C, 40 min</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ was isolated as major product (80%)

1.3.2. **Scope of the tandem amination/cyanation sequence**

The scope of the tandem amination/cyanation sequence is outlined in Table 5.

Table 5. Scope of tandem amination/cyanation process.
<table>
<thead>
<tr>
<th>entry</th>
<th>1-1</th>
<th>catalyst</th>
<th>1-5 (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1-1a.png" alt="Structure1" /></td>
<td>CuBr</td>
<td><img src="1-5a.png" alt="Structure5a" />, 95</td>
</tr>
<tr>
<td>2</td>
<td><img src="1-1m.png" alt="Structure1" /></td>
<td>iPr-AuCl/AgOTf</td>
<td><img src="1-5m.png" alt="Structure5m" />, 81</td>
</tr>
<tr>
<td>3</td>
<td><img src="1-1n.png" alt="Structure1" /></td>
<td>iPr-AuCl/AgOTf</td>
<td><img src="1-5n.png" alt="Structure5n" />, 99</td>
</tr>
<tr>
<td>4</td>
<td><img src="1-1d.png" alt="Structure1" /></td>
<td>CuBr</td>
<td><img src="1-5d.png" alt="Structure5d" />, 96</td>
</tr>
<tr>
<td>5</td>
<td><img src="1-1o.png" alt="Structure1" /></td>
<td>CuBr</td>
<td><img src="1-5o.png" alt="Structure5o" />, 92</td>
</tr>
<tr>
<td>6</td>
<td><img src="1-1b.png" alt="Structure1" /></td>
<td>CuBr</td>
<td><img src="1-5b.png" alt="Structure5b" />, 95</td>
</tr>
<tr>
<td>7</td>
<td><img src="1-1c.png" alt="Structure1" /></td>
<td>CuBr</td>
<td><img src="1-5c.png" alt="Structure5c" />, 95</td>
</tr>
<tr>
<td>8</td>
<td><img src="1-1i.png" alt="Structure1" /></td>
<td>CuBr</td>
<td><img src="1-5i.png" alt="Structure5i" />, 81&lt;br&gt;dr = 8:1</td>
</tr>
<tr>
<td>9</td>
<td><img src="1-1p.png" alt="Structure1" /></td>
<td>iPr-AuCl/AgOTf</td>
<td><img src="1-5p.png" alt="Structure5p" />, 80</td>
</tr>
<tr>
<td>10</td>
<td><img src="1-1f.png" alt="Structure1" /></td>
<td>CuBr</td>
<td><img src="1-5f.png" alt="Structure5f" />, 15</td>
</tr>
<tr>
<td>11</td>
<td><img src="1-1g.png" alt="Structure1" /></td>
<td>CuBr</td>
<td><img src="5g.png" alt="Structure5g" />, 95&lt;br&gt;dr = 1:2</td>
</tr>
<tr>
<td>12</td>
<td><img src="1-1e.png" alt="Structure1" /></td>
<td>CuBr</td>
<td><img src="1-5e.png" alt="Structure5e" />, 80</td>
</tr>
<tr>
<td>13</td>
<td><img src="1-1q.png" alt="Structure1" /></td>
<td>iPr-AuCl/AgOTf</td>
<td><img src="1-5q.png" alt="Structure5q" />, 66</td>
</tr>
</tbody>
</table>
This reaction worked extremely well in all cases giving near-quantitative chemical yields of five-, and six-membered rings. Complete regioselectivity was observed in all cases.

The regioselectivity obeyed Baldwin’s rules,9 that is, cyclization of 4-yn-amine 1-1a and 3-yn-amine 1-1m gave five-membered ring products through 5-endo-dig and 5-exo-dig processes whereas the reaction of 5-yn-amine (e.g., 1-1c) produced a six-membered ring through a 6-exo-dig process, and the reaction of 6-yn-amine (e.g., 1-1f) furnished a seven-membered ring through a 7-exo-dig process. When a chiral aminoalkyne was used (1-1g), a moderate chiral induction was observed (dr = 1:6, Table 5, entry 8).

1.3.3. Experimental

General procedure for preparation of 1-5

1-Benzyl-2-methylpyrrolidine-2-carbonitrile (1-5a). N-Benzyl-4-pentyn-1-amine 1a (43 mg, 0.25 mmol), trimethylsilyl cyanide (99 mg, 1.0 mmol), dioxane (1 mL) and water (4.5 mg, 1.0 equiv) were charged into a microwave tube reactor, and CuBr (1.8 mg, 5% equiv) was added to the mixture under stirring. After all the starting materials were dissolved, the microwave reactor was flushed with argon. Then the reaction mixture was heated to 100°C under microwave irradiation for 0.5 h. The resulting reaction mixture was directly concentrated in a rotary evaporator and purified by silica gel flash chromatography (4:1 hexane:ether) to give a yellow liquid 1-5a (48 mg, 95%). IR (neat): 2978, 2943, 2810, 2216, 1455, 1369, 1159, 740, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 1.42 (s, 3 H), 1.62-1.81 (m, 3 H), 2.21-2.39 (m, 2 H), 2.90 (td, J = 8.4 Hz, 3.2 Hz, 1 H),
3.22 (d, J = 13.2 Hz, 1 H), 3.88 (d, J = 13.2 Hz, 1 H), 7.11-7.22 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): 19.9, 23.7, 38.9, 51.6, 54.5, 61.4, 120.0, 127.2, 128.4, 128.5, 138.5; ESI-HRMS (ESI+): m/z calcd. for C$_{13}$H$_{16}$N$_2$(M$^+$-CN) 174.1282, found 174.1277.

**Procedure for deuterium experiment on 1-5a**

1-Benzyl-2-methylpyrrolidine-2-carbonitrile (1-5a), N-benzyl-4-pentyn-1-amine 1a (43 mg, 0.25 mmol), trimethylsilyl cyanide (99 mg, 1.0 mmol), dioxane (1 mL) and deuterium water (9.0 mg, 2.0 equiv) were charged into a microwave tube reactor, and CuBr (1.8 mg, 5% equiv) was added to the mixture under stirring. After all the starting materials were dissolved, the microwave reactor was flushed with argon. Then the reaction mixture was heated to 100°C under microwave irradiation for 0.5 h. Then we compare the deuterium experiment $^1$H NMR spectra with original spectra, using benzyl proton as standard (chemical shift at 3.88). The deuterium substitution was found on the ring carbon as well as on the exocyclic carbon. The deuterium content was calculated by integration of the $^1$H NMR. For a chemical shift of 1.42 corresponding to the methyl group, the original integration is 3 for 3 $^1$H. After the deuteration experiment, the integration decreased to 1.36, which meant that 55% corresponded to deuterium ($^2$H). The remaining 45% corresponded to $^1$H.

1-benzyl-2-methylpyrrolidine-2-carbonitrile (1-5a).

IR (neat): 2978, 2943, 2810, 2216, 1455, 1369, 1159, 740, 700 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): 1.42 (s, 3 H), 1.62-1.81 (m, 3 H), 2.21-2.39 (m, 2 H), 2.90 (td, J = 8.4 Hz, 3.2 Hz, 1 H), 3.22 (d, J = 13.2 Hz, 1 H), 3.88 (d, J = 13.2 Hz, 1 H), 7.11-7.22 (m, 5 H); $^{13}$C
NMR (100 MHz, CDCl₃): 19.9, 23.7, 38.9, 51.6, 54.5, 61.4, 120.0, 127.2, 128.4, 128.5, 138.5; HRMS (ESI+): m/z calcd. for C₁₃H₁₆N₂(M⁻-CN) 174.1282, found 174.1277.

1-benzyl-2-methylpyrrolidine-2-carbonitrile (1-5m).

IR (neat): 2957, 2870, 2223, 1709, 1600, 1342, 1190, 996, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.83 (t, J = 7.2 Hz, 3 H), 1.18-1.32 (m, 3 H), 1.39-1.60 (m, 2 H), 1.94-2.16 (m, 3 H), 2.22-2.31 (m, 1 H), 2.47-2.54 (m, 1 H), 3.33-3.40 (m, 1 H), 3.50 (q, J = 14.8 Hz, 7.2 Hz, 1 H), 6.75-6.85 (m, 3 H), 7.17-7.25 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 13.8, 22.5, 22.8, 26.5, 35.6, 39.9, 50.7, 60.8, 115.2, 118.5, 121.3, 129.0, 144.5; HRMS (ESI+): m/z calcd. for C₁₃H₁₆N₂(M⁻-CN) 202.1596, found 202.1588.

1-benzyl-2-methyl-6-oxopiperidine-2-carbonitrile (1-5n).

IR (neat): 2919, 1652, 1393, 1289, 731, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.50 (s, 3 H), 1.77-2.15 (m, 3 H), 2.28-2.33 (m, 1 H), 2.45-2.51 (m, 1 H), 2.59-2.69 (m, 1 H), 4.27 (d, J = 16 Hz, 1 H), 5.26 (d, J=16Hz, 1 H), 7.19-7.29 (m, 5 H); ¹³C NMR (100 MHz, CDCl₃): δ 18.1, 27.8, 32.0, 36.8, 47.8, 57.4, 120.5, 126.9, 127.2, 128.6, 138.0, 170.1; HRMS (ESI+): m/z calcd. for C₁₄H₁₆N₂O(M⁻-CN) 202.1232, found 202.1155.

1-benzyl-2-methylpiperidine-2-carbonitrile (1-5d)

IR (neat): 2942, 2805, 1451, 1377, 1124, 737, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.45 (s, 3 H), 1.42-1.61 (m, 3 H), 1.80 (d, J = 10 Hz, 1 H), 2.04-2.11(m, 1 H), 2.60 (d, J
12.4 Hz, 1 H), 3.00 (d, \( J = 13.6 \) Hz, 1 H), 3.99 (d, \( J = 13.6 \) Hz, 1 H), 7.10-7.19 (m, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 22.0, 25.2, 26.8, 38.5, 49.4, 55.8, 57.9, 119.4, 127.0, 128.3, 128.4, 138.8; HRMS (ESI+): m/z calcd. for C\(_{14}\)H\(_{18}\)N\(_2\)(M\(^{+}\)-CN) 188.1439, found 188.1433.

1-benzylpyrrolidin-2-carbonitrile (1-5o)

IR (neat): 2906, 2870, 1494, 1453, 1125, 744, 700 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 1.50 (s, 1 H), 1.80-1.96 (m, 2 H), 2.01-2.14 (m, 2 H), 2.52 (dd, \( J = 16.8 \) Hz, 8.8 Hz, 1 H), 2.87 (td, \( J = 9.2 \) Hz, 4 Hz, 1 H), 3.60 (d, \( J = 13.2 \) Hz, 1 H), 3.85 (d, \( J = 12.8 \) Hz, 1 H), 7.16-7.28 (m, 5 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 21.8, 29.5, 51.2, 53.2, 56.5, 118.0, 127.5, 128.5, 128.8, 137.6; HRMS (ESI+): m/z calcd. for C\(_{12}\)H\(_{14}\)N\(_2\)(M\(^{+}\)-CN) 160.1126, found 160.1120.

1-benzyl-2-butylpyrrolidin-2-carbonitrile (1-5b).

IR (neat): 2957, 2871, 1690, 1454, 734, 700 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 0.87 (t, \( J = 7.2 \) Hz, 7 H), 1.26-1.56 (m, 3 H), 1.61-1.95 (m, 4 H), 2.16-2.26 (m, 1 H), 2.33 (q, \( J = 9.2 \) Hz, 1 H), 2.91 (t, \( J = 8.8 \) Hz, 1 H), 3.26 (d, \( J = 13.2 \) Hz, 1 H), 3.97 (d, \( J = 12.8 \) Hz, 1 H), 7.25 - 7.58 (m, 5 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 13.9, 20.1, 22.8, 26.7, 36.2, 36.5, 51.6, 54.5, 65.8, 119.9, 127.1, 128.3, 128.5, 138.6; HRMS (ESI+): m/z calcd. for C\(_{16}\)H\(_{22}\)N\(_2\)(M\(^{+}\)-CN) 216.1752, found 216.1745.

1-benzyl-2-pentylpiperidin-2-carbonitrile (1-5c).
IR (neat): 2929, 2859, 1690, 1455, 1363, 1145, 737, 700 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.92 (t, $J=6$ Hz, 3 H), 1.28-1.60 (m, 7 H), 1.75-2.04 (m, 4 H), 2.26-2.33 (m, 1 H), 2.42 (dd, $J=18$ Hz, 9.2 Hz, 1 H), 2.94 (td, $J=8.4$ Hz, 1.2 Hz, 1 H), 3.35 (d, $J=12.8$ Hz, 1 H), 4.06 (d, $J=12.8$ Hz, 1 H), 7.22-7.39 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 14.0, 20.2, 22.5, 24.5, 29.4, 31.6, 36.2, 36.8, 51.7, 54.6, 119.9, 127.2, 128.4, 128.5, 138.6; HRMS (ESI+): m/z calcd. for C$_{18}$H$_{26}$N$_2$ (M$^+$-CN) 244.2065, found 244.2060.

4-methylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-4-carbonitrile (1-5i)

IR (neat): 2900, 2830, 1730, 1600, 1423, 1210, 925, 730 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$), major isomer: $\delta$ 1.30 (s, 3 H), 1.52-1.79 (m, 4 H), 2.31 (dd, $J=16.8$ Hz, 8 Hz, 1 H), 2.45-2.49 (m, 1 H), 3.02-3.17 (m, 3 H), 3.81 (d, $J=11.6$ Hz, 1 H) 3.97 (dd, $J=10.8$ Hz, 3.2 Hz, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$): $^{13}$C NMR (100 MHz, CDCl$_3$), major isomer: $\delta$ 20.0, 21.0, 25.7, 47.3, 57.8, 58.0, 72.0, 73.2, 118.1; HRMS (ESI+): m/z calcd. for C$_9$H$_{14}$N$_2$O (M$^+$-CN) 140.1075, found 140.1071.

2-pentyl-1-phenylpiperidine-2-carbonitrile (1-5p)

IR (neat): 2956, 2859, 1705, 1342, 1191, 750, 695 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$0.79 (t, $J=6.4$ Hz, 3 H), 1.16-1.36 (m, 7 H), 1.42-1.59 (m, 2 H), 1.94-2.17 (m, 3 H), 2.21-2.28 (m, 1 H), 2.47-2.53 (m, 1 H), 3.33-3.38 (m, 1 H), 3.46-3.52 (m, 1 H), 6.76 (t,
$J$=7.2Hz, 1 H), 6.80-6.84 (m, 2 H), 7.17-7.23 (m, 2 H); $^1$C NMR (100 MHz, CDCl$_3$): 14.0, 22.5, 22.8, 24.4, 29.0, 31.5, 35.8, 39.9, 50.7, 60.8, 115.2, 118.5, 121.3, 129.0, 144.5; HRMS (ESI$^+$): m/z calcd for C$_{17}$H$_{24}$N$_2$(M$^+$-CN) 230.1909, found 230.1903.

1-isopropyl-2-methylpyrrolidine-2-carbonitrile (1-5g).

IR (neat): 2942, 2805, 1451, 1377, 1124, 737, 699cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$), major isomer: $\delta$ 0.95 (s, 3 H), 1.40 (d, $J$ = 6.4 Hz, 3 H), 2.28-2.33 (m, 1 H), 2.45-2.51 (m, 1H), 2.59-2.69 (m, 1 H), 4.27 (d, $J$ = 16 Hz, 1 H), 5.26 (d, $J$ = 16 Hz, 1 H), 7.19-7.29 (m, 5 H); $^1$C NMR (100 MHz, CDCl$_3$): $\delta$ 18.1, 27.8, 32.0, 36.8, 47.8, 57.4, 120.5, 126.9, 127.2, 128.6, 138.0, 170.1; HRMS (ESI$^+$) (ESI$^+$): m/z calcd. for C$_{14}$H$_{18}$N$_2$(M$^+$- CN) 188.1439, found 188.1436.

1-allyl-2-pentylpiperidine-2-carbonitrile (1-5e).

IR (neat): 2955, 2859, 1643, 1452, 1161, 993, 921cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.82 (t, $J$=6Hz, 3 H), 1.18-1.50 (m, 1 H), 1.72-1.86 (m,1 H), 2.28-2.35 (m, 1 H), 2.28-2.34 (m, 1 H), 2.80 (dd, $J$ = 13.2 Hz, 8 Hz, 1 H), 3.13 (t, $J$ = 7.6 Hz, 1 H), 3.39 (dd, $J$ = 13.2 Hz, 4Hz, 1 H), 5.06 (d, $J$ = 10.4 Hz, 1 H), 5.20 (d, $J$ = 16.8 Hz, 1 H), 5.72-5.82 (m, 1 H); $^1$C NMR (100 MHz, CDCl$_3$): $\delta$ 14.0, 20.0, 22.5, 24.6, 29.3, 31.6, 36.3, 36.8, 51.7, 53.3, 65.8, 117.3, 119.7, 135.3; HRMS (ESI$^+$): m/z calcd. for C$_{14}$H$_{24}$N$_2$(M$^+$- CN) 194.1909, found 194.1903.
Deuterium experiments $^1$H NMR spectra for compound 1-5a

$^1$H and $^{13}$C NMR spectra of compound 1-5d
1.4. Tandem amination/trifluomethylation

1.4.1. Screening of conditions for tandem amination/trifluomethylation

Encouraged by the success of the tandem amination/cyanation sequence, we turned our attention to the synthesis of trifluoromethylated N-heterocycles, a medicinally important class of compounds\textsuperscript{23-25} whose synthesis usually requires multisteps.\textsuperscript{10-11} Simply by reacting our in situ generated enamine intermediate with a nucleophilic CF\textsubscript{3} source, our protocol would lead to a one-step synthesis of a CF\textsubscript{3}-containing N-heterocycle. We used the reaction of aminoalkyne 1-1b and TMS-CF\textsubscript{3} to optimize reaction conditions. Using 5% CuBr as catalyst, we observed none of the desired product 1-6b (Table 6, entry 1); this result is reasonable if one realizes that TMS-CF\textsubscript{3} is a rather inert reagent unless a suitable
activator is present (i.e., a fluoride source to cleave the TMS group). Although CsF was not successful (Table 6, entry 2), either copper or gold catalysts, in combination with AgF, produced very good yields of 1-6b (Table 6, entries 3 and 4). CuF₂ also furnished the desired product, albeit in low yield (Table 6, entry 5). Because both gold and copper worked equally well, we suspected that the real catalyst was AgF. Indeed, we found this to be the case (Table 6, entry 8). The optimized loading of AgF was found to be 1.5 equiv (Table 6, entry 9). Higher temperatures have a deleterious effect on the yield of 6 (Table 6, entry 11), and the reaction proceeded well even at room temperature, although longer times were needed (Table 6, entry 12).

Table 6. Screening of condition for tandem amination/trifluoromethylation/ sequence.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>temp °C</th>
<th>time</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuBr (5%)</td>
<td>100</td>
<td>40 min</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CuBr (5%)/CsF (1.0 equiv)</td>
<td>100</td>
<td>40 min</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>IPrAuCl, AgF (1.0 equiv)</td>
<td>100</td>
<td>40 min</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>CuBr(5%)/AgF(2.0 equiv)</td>
<td>100</td>
<td>40 min</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>CuF₂ (2.0 equiv)</td>
<td>100</td>
<td>40 min</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>AgF (2.0 equiv)</td>
<td>100</td>
<td>40 min</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>AgF (0.2 equiv)</td>
<td>100</td>
<td>40 min</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>AgF (1.0 equiv)</td>
<td>100</td>
<td>40 min</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>AgF (1.5 equiv)</td>
<td>100</td>
<td>40 min</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>AgF (4.0 equiv)</td>
<td>100</td>
<td>40 min</td>
<td>82</td>
</tr>
<tr>
<td>11</td>
<td>AgF (1.5 equiv)</td>
<td>120</td>
<td>40 min</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>AgF (1.5 equiv)</td>
<td>rt</td>
<td>6 h</td>
<td>88</td>
</tr>
</tbody>
</table>

mw = microwave; iPrAuCl = Chloro[1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene]gold(I).
1.4.2. **Scope of tandem amination / trifluoromethylation**

The scope of our tandem amination / trifluoromethylation reaction is outlined in Table 7. The reaction worked extremely well in all cases giving near quantitative chemical yields of five-, and six-membered rings.

Table 7. Tandem amination / trifluoromethylation process.

<table>
<thead>
<tr>
<th>entry</th>
<th>1-1</th>
<th>1-6 (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>1-6a, 92%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Image" /></td>
<td>1-6m, 90%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Image" /></td>
<td>1-6d, 88%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Image" /></td>
<td>1-6b, 91%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Image" /></td>
<td>1-6c, 92%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Image" /></td>
<td>1-6p, 89%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Image" /></td>
<td>1-6g, 90%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Image" /></td>
<td>1-6e, 87%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Image" /></td>
<td>1-6r, 95%</td>
</tr>
</tbody>
</table>
Complete regioselectivity was observed and its regioselectivity also obeyed Baldwin’s rules. When a chiral aminoalkyne was used (1-1g), a moderate chiral induction was observed ($dr = 77:23$, Table 7, entry 7). It should be noted that AgF worked equally well with basic aliphatic aminoalkynes and less basic aromatic aminoalkynes.

In order to determine the nucleophilic intermediate in the tandem amination/trifluoromethylation process, we monitored this reaction by $^{19}$F NMR and $^1$H NMR under similar conditions to those used in Table 7 (but using CD$_3$CN as solvent because of its better dissolving properties toward the silver salt). Five minutes into the reaction we observed a peak ascribed to CF$_3$Ag in $^{19}$F NMR ($\delta$ -25.5, d, $J_{2F-Ag} = 94$ Hz), together with a signal corresponding to CF$_3$H in $^{19}$F NMR ($\delta$ -79.9, d, $J_{2F-H} = 79$ Hz) and $^1$H NMR ($\delta$ 6.70, d, $J_{2F-H} = 79$ Hz). The formation of CF$_3$H can be explained by protodemetalation of the CF$_3$Ag intermediate. Thus, it is highly likely that CF$_3$Ag is the real nucleophilic species in the reaction.$^{12}$

We conducted deuterium experiments to explore further the mechanism of this tandem process (Scheme 5). For both, tandem amination/cyanation and tandem amination/trifluoromethylation reactions, deuterium substitution was found on the ring carbon as well as on the exocyclic carbon. These results indicate that the proposed enamine intermediate probably undergoes additional transformations like retrohydroamination or tautomerization before the second nucleophilic attack takes place.
Scheme 5. Deuterium experiments on amination/cyanation and
amination/trifluoromethylation reactions

In order to verify the above enamine formation mechanism, we investigated the reaction of 1-1p in the absence of a second nucleophile (Scheme 6). Without a second nucleophile, the reaction of 1-1p produces a relatively complex mixture; its NMR spectrum signaled the presence of enamine intermediates and other by-products. We tentatively assigned the structure of the enamine intermediates as 1-7 and 1-8. Silica gel flash chromatography of this reaction mixture gave products 1-9 and 1-10.

Scheme 6. Reaction of 1p in the absence of a second attacking nucleophile
Because 1-9 and 1-10 are not detected in the reaction mixture prior to silica gel chromatography, their formation can only be explained by invoking hydration of the corresponding enamines during chromatography. This experiment not only confirms the role of enamine as intermediate, but also underscores the importance of having a second attacking nucleophile (i.e., the tandem sequence) for a clean reaction to take place. Furthermore, the isolation of 1-9 implies that the hydroamination is indeed reversible. Although enamine is generally considered as nucleophile, in the presence of suitable catalyst like copper, it can function as electrophile. 13

1.4.3. Experimental

General procedure for preparation of 1-6.

1-Benzyl-2-methyl-2-(trifluoromethyl)pyrrolidine (1-1a). N-Benzyl-4-pentyn-1-amine 1a (43 mg, 0.25 mmol), trifluoromethyltrimethyl silane (71 mg, 0.5 mmol), dioxane (1 mL) and water (4.5 mg, 1.0 equiv) were charged into a microwave tube reactor, and AgF (48 mg, 1.5 equiv) was added to the mixture under stirring. After all the starting materials were dissolved, the microwave reactor was flushed with argon. Then the reaction mixture was heated to 100°C under microwave irradiation for 40 min. The resulting reaction mixture was directly concentrated in a rotary evaporator and purified by flash chromatography (20:1 hexane:ether) to give a yellow liquid 1-6a (56 mg, 92%). IR(neat): 2946, 2843, 1460, 1470, 1144, 763, 690 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 1.07 (s, 3 H), 1.28-1.38 (m, 3 H), 1.98-2.12 (m, 3 H), 2.23-2.32 (m, 3 H), 2.58 (t, J = 6.4 Hz, 1 H), 3.35 (d, J = 13.6 Hz, 1 H), 3.71 (d, J = 13.6 Hz, 1 H), 6.98-7.05 (m, 5 H); 13C NMR (100
37 MHz, CDCl\textsubscript{3}): \( \delta \) 17.6, 22.3, 35.7, 51.9, 53.4, 67.5 (q, \( J = 23.2 \) Hz), 126.7, 128.4 (q, \( J = 285 \) Hz), 128.0, 128.2, 140.3; \( ^{19} \)F NMR (370 MHz, CDCl\textsubscript{3}): major isomer: \( \delta \) -77.87; HRMS (ESI\textsuperscript{+}): m/z calcd. for C\textsubscript{13}H\textsubscript{16}F\textsubscript{3}N (M\textsuperscript{+} - H) 242.1157, found 242.1153.

1-benzyl-2-methyl-2-(trifluoromethyl)pyrrolidine (1-6a).

![](image)

IR (neat): 2946, 2843, 1460, 1144, 763, 690 cm\textsuperscript{-1}; \( ^{1} \)H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 1.07 (s, 3 H), 1.28-1.38 (m, 3 H), 1.98-2.12 (m, 3 H), 2.23-2.32 (m, 3 H), 2.58 (t, \( J = 6.4 \) Hz, 1 H), 3.35 (d, \( J = 13.6 \) Hz, 1 H), 3.71 (d, \( J = 13.6 \) Hz, 1 H), 6.98-7.05 (m, 5 H); \( ^{13} \)C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta \) 17.6, 22.3, 35.7, 35.7 (d, \( J = 1.5 \) Hz), 51.9, 53.4, 67.5 (q, \( J = 23.2 \) Hz), 126.7, 128.4 (q, \( J = 285 \) Hz), 128.0, 128.2, 140.3; \( ^{19} \)F NMR (370 MHz, CDCl\textsubscript{3}): major isomer: \( \delta \) -77.87; HRMS (ESI\textsuperscript{+}): m/z calcd. for C\textsubscript{13}H\textsubscript{16}F\textsubscript{3}N (M\textsuperscript{+} - H) 242.1157, found 242.1153.

2-butyl-1-phenyl-2-(trifluoromethyl)pyrrolidine (1-6m).

![](image)

IR (neat): 2960, 2874, 1720, 1601, 1504, 1329, 1151, 751, 694 cm\textsuperscript{-1}; \( ^{1} \)H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 0.82 (t, \( J = 6.8 \) Hz, 3 H), 1.06-1.32 (m, 4 H), 1.73-1.84 (m, 1 H), 1.84-1.96 (m, 1 H), 1.98-2.15 (m, 2 H), 2.23-2.39 (m, 2 H), 3.42-3.55 (m, 2 H), 6.79 (t, \( J = 7.6 \) Hz, 1 H), 6.96 (d, \( J = 8.4 \) Hz, 1 H), 7.22 (t, \( J = 8 \) Hz, 1 H); \( ^{13} \)C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta \) 13.8, 22.1, 22.7, 24.4, 31.1, 34.8 (d, \( J = 6.4 \) Hz), 68.9 (q, \( J = 24.8 \) Hz), 116.0 (q, \( J = 2.4 \) Hz), 128.1 (q, \( J = 288.9 \) Hz), 128.7, 146.1; \( ^{19} \)F NMR (370 MHz, CDCl\textsubscript{3}): major isomer: \( \delta \) -73.20; HRMS (ESI\textsuperscript{+}): m/z calcd. for C\textsubscript{15}H\textsubscript{20}F\textsubscript{3}N (M\textsuperscript{+} - H) 270.1470, found 270.1465.
1-benzyl-2-methyl-2-(trifluoromethyl)piperidine (1-6d)

IR (neat): 2943, 2853, 2857, 1454, 1369, 1253, 1139, 725, 697 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.28 (s, 3 H), 1.35-1.59 (m, 5 H), 1.89-1.98 (m, 1 H), 2.26-2.45 (m, 1 H), 2.55-2.64 (m, 1 H), 3.48 (d, \(J = 14.8\) Hz, 1 H), 3.99 (d, \(J = 14.8\) Hz, 1 H), 7.14-7.27 (m, 5 H);

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 20.5 25.7 (d, \(J = 6\) Hz), 32.8, 46.5, 54.2, 59.1 (q, \(J = 20.9\) Hz), 126.6, 127.8, 128.2, 129.4 (q, \(J = 295.1\) Hz), 140.9; \(^{19}\)F NMR (370 MHz, CDCl\(_3\)): major isomer: \(\delta\) -67.82; HRMS (ESI\(^+\)): m/z calcd. for C\(_{14}\)H\(_{18}\)F\(_3\)N (M\(^+\) - H) 256.1313, found 256.1310.

1-benzyl-2-butyl-2-(trifluoromethyl)pyrrolidine (1-6b).

IR (neat): 2958, 2874,1455, 1372, 1286, 1143, 731, 698 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.80 (t, \(J = 6.4\) Hz, 3 H), 1.18-1.36 (m, 4 H), 1.50-1.63 (m, 4 H), 1.75-1.80 (m, 1 H), 1.90-1.96 (m, 1 H), 2.58 (t, \(J = 6.4\) Hz, 1 H), 3.64 (d, \(J = 14.4\) Hz, 1 H), 3.78 (d, \(J =13.6\)Hz, 1 H), 7.04-7.18 (m, 5 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 14.1 (q, \(J = 21.7\) Hz), 22.2, 23.3, 25.5, 30.8, 31.2, 51.5, 52.1 (t, \(J = 11\) Hz), 67.5 (q, \(J = 23.2\) Hz), 126.7 (d, \(J = 43.4\) Hz), 127.9 (d, \(J = 27.9\) Hz), 128.3 (d, \(J = 29.4\) Hz), 129.0 (q, \(J = 290\) Hz), 140.4; \(^{19}\)F NMR (370 MHz, CDCl\(_3\)): major isomer: \(\delta\) -73.95; HRMS (ESI\(^+\)): m/z calcd. for C\(_{16}\)H\(_{22}\)F\(_3\)N (M\(^+\)-H) 284.1626, found 284.1622.

1-benzyl-2-pentyl-2-(trifluoromethyl)piperidine (1-6c)

IR (neat): 2955, 2932, 2857, 1453, 1360, 740, 698 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.91 (t, \(J = 6\) Hz, 3 H), 1.33-1.56 (m, 8 H), 1.64-1.83 (m, 4 H), 1.88-1.98 (m, 1 H), 2.06-2.15 (m, 1 H), 2.74 (t, \(J = 6.8\) Hz, 2 H), 3.81 (d, \(J = 13.6\) Hz, 1 H), 3.94 (d, \(J = 13.6\) Hz, 1 H), 7.22-7.32 (m, 5 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 14.0, 22.2, 22.6, 23.3, 30.0, 31.1, 31.2, 31.8, 51.5, 52.1 (d, \(J = 1.6\) Hz), 67.6 (q, \(J = 23.2\) Hz), 126.7, 127.9, 128.2, 129.0 (q, \(J = 290.5\) Hz), 140.4; \(^{19}\)F NMR (370 MHz, CDCl\(_3\)), major isomer: \(\delta\) -73.95; HRMS (ESI\(^+\)): m/z calcd for C\(_{18}\)H\(_{26}\)F\(_3\)N (M\(^+\)-H): 312.1939, found 312.1934.

2-pentyl-1-phenyl-2-(trifluoromethyl)piperidine (1-6p).

IR (neat): 2957, 2930, 1720, 1560, 1504, 1330, 1152, 751, 695 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.83 (t, \(J = 6.8\) Hz, 3 H), 1.06-1.30 (m, 8 H), 1.73-1.83 (m, 1 H), 1.94-2.13 (m, 2 H), 2.23-2.38 (m, 2 H), 3.39-3.53 (m, 2 H), 6.82 (t, \(J = 7.6\) Hz, 1 H), 6.95 (d, \(J = 8.4\) Hz, 2 H), 7.22 (t, \(J = 6.8\) Hz, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 13.9, 22.1, 22.2, 22.5, 29.3, 31.4, 31.5, 34.7 (d, \(J = 1.5\) Hz), 52.3, 68.9 (q, \(J = 25.6\) Hz), 116.0 (t, \(J = 2.3\) Hz), 118.6, 128.1 (q, \(J = 288.9\) Hz), 128.7, 146.1; \(^{19}\)F NMR (370 MHz, CDCl\(_3\)), major isomer: \(\delta\) -73.20; HRMS (ESI\(^+\)): m/z calcd for C\(_{15}\)H\(_{20}\)F\(_3\)N (M\(^+\)-H) 298.1783, found 298.1778.

2-methyl-1-((R)-1-phenylethyl)-2-(trifluoromethyl)pyrrolidine (1-6g).
IR (neat): 2981, 2361, 1700, 1456, 1383, 1166, 699 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.23 (s, 3 H), 1.40 (d, \(J = 6.4\) Hz, 3 H), 1.52-1.80 (m, 2 H), 1.79-1.90 (m, 2 H), 2.20-2.29 (m, 2 H), 2.68-2.74 (m, 1 H), 3.10-3.14 (m, 1 H), 3.84-3.87 (m, 1 H), 7.09-7.38 (m, 5 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 19.8, 23.5, 38.7, 51.5, 54.4, 61.3, 119.9, 125.2, 127.1, 128.3 (q, \(J = 290\) Hz), 128.9, 138.4; \(^{19}\)F NMR (370 MHz, CDCl\(_3\)): major isomer: \(\delta\) -74.33; HRMS (ESI+): m/z calcd. for C\(_{14}\)H\(_{24}\)F\(_3\)N (M\(^{+}\) - H) 256.1313, found 256.1310.

1-allyl-2-pentyl-2-(trifluoromethyl)piperidine (1-6e)

IR (neat): 2957, 2858, 1457, 1144, 918, 699 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.752 (t, \(J = 6\) Hz, 3 H), 1.11-1.22 (m, 6 H), 1.42-1.50 (m, 2 H), 1.52-1.74 (m, 3 H), 1.84-1.92 (m, 1 H), 2.64-2.72 (m, 1 H), 2.72-2.80 (m, 1 H), 3.07-3.27 (m, 2 H), 4.90 (d, \(J = 18\) Hz, 1 H), 5.07 (dd, \(J = 17.2\) Hz, 1.6 Hz), 5.59-5.70 (m, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 14.0, 22.1, 22.6, 23.0, 29.8, 30.8, 31.2, 31.7, 50.7, 51.6, 67.2 (q, \(J = 23.1\) Hz), 115.4, 129.0 (q, \(J = 290.9\) Hz), 137.3; \(^{19}\)F NMR (370 MHz, CDCl\(_3\)), major isomer: \(\delta\) -74.13; HRMS (ESI+): m/z calcd. for C\(_{14}\)H\(_{24}\)F\(_3\)N (M\(^{+}\) + H): 264.1939, found 264.1935.

2-methyl-1-phenyl-2-(trifluoromethyl)pyrrolidine (1-6n).

IR (neat): 2984, 2922, 2851, 1601, 1504, 1319, 1154, 751, 695 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.24 (s, 3 H), 1.55-1.60 (m, 2 H), 1.73-1.86 (m, 1 H), 2.19-2.28 (m, 1 H), 3.14-3.28 (m, 2 H), 6.58 (t, \(J = 7.6\) Hz, 1 H), 6.73 (d, \(J = 8.4\) Hz, 1 H), 6.93-6.99 (m, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 20.1, 22.1 (d, \(J = 1.6\) Hz), 38.7 (d, \(J = 1.5\) Hz), 51.7, 65.8 (q,
$J = 27.1$ Hz), 117.3 (q, $J = 3.1$ Hz), 127.8 (q, $J = 286.6$ Hz), 128.6, 145.6; $^{19}$F NMR (370 MHz, CDCl$_3$): major isomer: δ -74.69; HRMS (ESI+): m/z calcd. for C$_{12}$H$_{14}$F$_3$N (M$^+$-H) 228.1000, found 228.0996.

$^1$H and $^{13}$C NMR spectra of compound 1-6a
1.5. **Tandem amination/phosphorylation**

1.5.1. **Background**

α-Aminophosphonates and their corresponding α-aminophosphonic acids have received much attention in organic and medicinal chemistry because they are structural analogues of the corresponding α-amino acids and transition state mimics of peptide hydrolysis.²⁶⁻²⁹ Moreover, α-aminophosphonates have broad applications due to their biological activity²⁹⁻³³ such as antibacterial,³⁴,³⁵ anti-cancer,³⁶ antiviral, and as enzyme inhibitors.³⁷,³⁸ We have successful used our strategy for tandem amination/alkynylation, amination/cyanation, and amination/trifluoromethylation.³⁹,⁴⁰ An advantage of our approach is that all of these processes take place in one pot and one batch, without protection/deprotection steps. In our following research, we continue to explore application of this strategy to synthesize important α-aminophosphonates.
Despite their importance, most literature syntheses of cyclic α-aminophosphonates have significant limitations. For example, the most common method to make α-aminophosphonates—the Kabachnik-Fields reaction (the three-component coupling of a carbonyl, an amine and a hydrophosphoryl compound)\textsuperscript{41-46}—is effective to construct acyclic (linear) products, but much less so in the generation of ring systems, because of the difficulty in preparing the corresponding starting material without extensive protection and de-protection steps (Scheme 7a).\textsuperscript{47} Another method to make α-aminophosphonates is the oxidative addition of a dialkyl phosphite to a cyclic amine. In 2009, Li’s group reported such synthesis using oxygen as an oxidant (Scheme 7b),\textsuperscript{48} but this method suffers from a narrow substrate scope (a benzylic proton must be present). The third method is the decarboxylative-coupling of natural α-amino acids and phosphites (Scheme 7c).\textsuperscript{49} However, this method relies on natural cyclic amino acids as starting materials, and the pool of natural cyclic amino acids (e.g., L-proline) is shallow. This problem is magnified when cyclic amino acids with ring sizes that natural amino acids lack—such as a six-membered—are needed. Consequently, their syntheses require more steps. Similar to our strategy, Doye’s group reported the synthesis of α-aminophosphonates through early transition metal titanium catalyzed hydroamination followed by addition of dialkylphosphite.\textsuperscript{50} Because Doye’s method only works for primary amine, and our methodology mainly uses secondary amines, our method is a good complement to Doye’s method.
The keystone of our strategy—transforming an enamine into a good electrophile—runs contrary to the ingrained teachings on enamine nucleophilicity. Although a handful of reports on the reaction of enamine with nucleophiles exist,\textsuperscript{12,13,51} they pale in comparison to the overwhelming number of reports on enamine used as nucleophiles. Not only the use of enamines as electrophiles uncommon in organic synthesis, even the mechanism of enamine activation is poorly understood; for example, unlikely interactions in the Cu-catalyzed reaction of enamines have been proposed previously (Scheme 8a).\textsuperscript{12,13,15} While enamines are known to be good nucleophiles, they can also be made to act as a good electrophile. It is instructive to consider the oxygen analog as a model of comparison: enol ethers are normally good nucleophiles, but if they are activated by, say a Brønsted acid, then they become good electrophiles. One notable example of this transformation is the tetrahydropyranyl (THP) protection of alcohols (Scheme 8b). In theory, an enamine can also be protonated to generate an iminium intermediate (Scheme 8c). Most mechanistic studies have shown preferential attack at N by proton followed by rearrangement to the more stable C-protonated iminium form,\textsuperscript{52} which can then act as electrophile. As it happens, in the case of electron rich enamines (e.g., R = alkyl), both,
the starting material and the product, are rather basic (i.e., alkyl amines), and therefore, they combine to neutralize the acidity of the acid catalyst, so this method often does not work except for enamines with electron-withdrawing groups.

Scheme 8. Activation of enamine – converting enamine to an electrophile.

One solution to this problem consists in using a late transition metal Lewis acid, which normally has a relative higher affinity for the electron-rich double bond. The electrophilic activation of this double bond facilitates nucleophilic attack (Scheme 8d). DFT calculations\(^{53}\) predict the \(\eta_2\)-bound Cu:enamine \(\sigma\)-complex to be more stable (by 2.2 kcal/mol) than the corresponding \(\sigma\)-complex, while Cu:enamine coordination is also stronger than to an alkynyl group (Scheme 4). Unsymmetrical coordination of Cu(I) to the enamine \(\pi\)-bond leads to shortening of the C-N bond and increased positive charge at the \(\alpha\)-carbon: calculated Mulliken charges show the enamine transfers 0.32 units of charge to CuBr with a build up at C\(\alpha\) by 0.13. We posit that in the presence of a suitable
catalyst, even an electron rich enamine can act as an electrophile. Specifically, our strategy could deliver N-heterocycles through a transition metal-activated enamine that acts as electrophile. The same metal catalyzes both, the generation of the enamine \textit{in situ}—by intramolecular amination of an alkyne—and its reaction with a nucleophile.

It should be noted that cyclic enamines (where the nitrogen is part of the ring) are not trivial to prepare. Whereas acyclic enamines can be easily made by the reaction of an aldehyde or ketone with a secondary amine, the equivalent approach to synthesize a cyclic enamine (e.g., I in Scheme 7) would require placing an amino group and an aldehyde (or ketone) in the same molecule, a task that would add extra protection/deprotection steps. An additional experimental difficulty of working with enamines, especially electron-rich enamines (e.g., N,N-dialkyl/arylenamines), is that they are sensitive to moisture and hydrolyze with relative ease. This trait makes them difficult to isolate and purify. But our tandem chemistry overcomes this problem by using an \textit{in situ} generated enamine, which reacts with another nucleophile simultaneously. Our method involves a tandem addition of two different nucleophiles to an alkyne. Literature reports on tandem addition of two different nucleophiles to an alkyne in one pot are not common.
1.5.2. Optimization of the reaction condition

In a preliminary attempt, reaction of aminoalkyne 1-1m and diethyl phosphite 1-11a in the presence of 5 mol % CuBr in 1, 4-dioxane at room temperature for 6 hours gave the desired product 1-12a in 76% yield (Table 8, entry 1). In addition, pyrrolidine 1-13a was isolated in 20% yield (Table 8, entry 1). Water strongly affected the ratio of 1-12a and 1-13a. Two equivalents of water in dioxane depressed the formation of 1-12a (58% yield) and increased the yield of 13a (Table 8, entry 2). Most of starting material was converted to pyrrolidine 1-13a in the presence of 20 mol % formic acid. The best choice of solvent was toluene, which provided 1-13a in better yield (Table 8, entry 4). Further optimization revealed that the yield of 1-13a could be improved to 92% yield by adding 3 Å molecular sieves (Table 8, entry 5). Higher temperature led to faster reaction, but the yield was reduced slightly (Table 8, entry 6). And this reaction could not be catalyzed by strong Brønsted acid (Table 8, entry 7). With optimized conditions in hand, we examined the scope of this reaction (Table 9).

Table 8. Optimization of the reaction condition for 1-12a

![Table 8 Diagram]
Various aminoalkynes were used in the reaction. Both, benzyl amines and aromatic amines, were tolerated. The aromatic amine 1-1t with a methoxy group in the para position produced 1-12t in good yield (Table 9, entry 9). The reaction of substrate 1-1u, with an electron-withdrawing chloro substituent on the aromatic ring, did not take place, and most of the starting material was recovered (Table 9, entry 10). Complete regioselectivity was observed in all cases. The regioselectivity obeyed Baldwin’s rules. That is, cyclization of 3-yn-amine 1-1m and 4-yn-amine 1-1r gave five-membered ring products through 5-endo-dig and 5-exo-dig mechanisms whereas the reaction of 5-yn-amine (e.g., 1-1d) produced a six-membered ring through a 6-exo-dig pathway. When chiral aminoalkyne 1-1g was used, a moderate chiral induction was observed (dr = 1:1.1, Table 9, entry 11). Dimethyl and dibenzyl phosphites could also be employed using our reaction conditions (Table 9, entries 12-13). Both of them gave excellent yields of products.
The proposed mechanism of enamine activation is shown in Scheme 10. The aminoalkyne 1-1 is first activated by coordination to the Lewis acidic copper center. Nucleophilic attack of the lone electron pair of nitrogen atom generates the enamine 1-15 through intermediate 1-14. This enamine intermediate 1-15 can form a complex 1-16 with CuBr. Then the nucleophile (diethyl phosphite in our case)--activated by base (amine starting material or product)--reacts with the activated enamine intermediate to give the final product. Alternatively, the enamine intermediate 1-15 can react with CuBr and the nucleophile first to generate an iminium intermediate and a Nu-Cu species. Addition of Nu-Cu to the iminium intermediate furnishes final product. This mechanism is based on the classic role of iminium species (Scheme 8). At this time, it is difficult to verify which of the two possible mechanisms prevail. The iminium mechanism (mechanism A) involves generation of two relative energetic species: a Nu-Cu species and an iminium species (Scheme 10), so we prefer the more concerted mechanism B.

Scheme 10. Proposed mechanisms (Nu-H = dialkyl phosphite)
Table 9. Scope of the tandem amination/ phosphorylation.

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Note: Condition: 5 mol% CuBr, 1-1 (0.15 mmol), 1-11 (0.3 mmol), 3A MS, toluene, rt, 6h. Isolated yield. The isolated product was contaminated with a small amount of dibenzyolphosphate.
In summary, a one-pot cyclization triggered addition strategy has been successfully used to synthesize cyclic α-aminophosphonates in good to excellent yields. Both five and six membered ring can be generated under mild conditions.

1.5.4. Experimental

Diethyl (2-butyl-1-phenylpyrrolidin-2-yl)phosphonate (1-12m). Typical Procedure.

N-(oct-3-yn-1-yl) aniline 1a (30 mg, 0.15 mmol), diethyl phosphite (41 mg, 0.3 mmol), toluene (1 mL) were charged into a small vial, and CuBr (1.1 mg, 5% equiv) was added to the mixture under stirring. Then the reaction mixture was stirred at room temperature for 6 h. The resulting reaction mixture was directly concentrated in a rotary evaporator and purified by silica gel flash chromatography (3:1 hexane: ethyl acetate) to give a yellow liquid 1-12m (48 mg, 92%).

\[^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3): \delta = 0.73 (t, J = 7.6 \text{ Hz, 3 H}), 0.83-0.96(m, 1 \text{ H}), 1.12-1.34 (m, 9 \text{ H}), 1.76-1.93 (m, 2 \text{ H}), 1.98-2.15 (m, 2 \text{ H}), 2.23-2.37 (m, 1 \text{ H}), 2.51-2.62, 3.31-3.42 (m, 2 \text{ H}), 3.88-4.09 (m, 4 \text{ H}), 6.63-6.76 (m, 1\text{ H}), 7.16-7.22 (m, 4 \text{ H}); \[^{13}\text{C} \text{ NMR} (100 \text{ MHz, CDCl}_3): \delta = 13.8, 16.5(d, J = 3.9 \text{ Hz}), 16.5 (d, J = 3.1 \text{ Hz}), 22.7 (d, J = 1.6 \text{ Hz}), 22.7, 24.4 (d, J = 10.1 \text{ Hz}), 32.0 (d, J = 10.9 \text{ Hz}), 35.7, 51.8 (d, J = 3.1 \text{ Hz}), 61.4 (d, J = 7.8 \text{ Hz}), 62.7(d, J = 7 \text{ Hz}), 66.2 (d, J = 154 \text{ Hz}), 155.5, 117.4, 128.4, 146.4; \[^{31}\text{P} \text{ NMR} (162 \text{ MHz, CDCl}_3) \delta = 28.77. \text{ESI-HRMS (ESI+): m/z calcd. for C}_{18}\text{H}_{30}\text{NO}_3\text{P (M}^+ + \text{ H)} 340.2042, \text{found 340.2047.}}

Diethyl (1-benzyl-2-butylpyrrolidin-2-yl)phosphonate (1-12b)

Yield: 50 mg (94%); yellow oil. \[^1\text{H} \text{NMR} (700 \text{ MHz, CDCl}_3): \delta = 0.91 (t, J = 7 \text{ Hz, 3 H}), 1.21-1.37 (m, 10 \text{ H}), 1.40-1.48 (m, 2 \text{ H}), 1.62-1.69 (m,1 \text{ H}), 1.61-1.72 (m, 1 \text{ H}), 1.73-
1.82 (m, 3 H), 1.83-1.94 (m, 1 H), 2.22-2.28 (m, 1 H), 2.65-2.74 (m, 2 H), 3.94 (d, J = 1.4 Hz, 2 H), 4.06-4.17 (m, 4 H), 7.14-7.31 (m, 5 H); 13C NMR (100 MHz, CDCl3): δ = 14.2, 16.7 (t, J = 8.9 Hz, 2C), 22.7 (d, J = 3 Hz), 23.4, 25.7 (d, J = 8.9 Hz), 31.9, 32.6 (d, J = 11.9 Hz), 51.5 (d, J = 3.7 Hz), 53.4, 61.1 (d, J = 7.4 Hz), 62.1 (d, J = 8.2 Hz), 65.2 (d, J = 143.7 Hz); 31P NMR (162 MHZ, CDCl3): δ = 30.51. ESI-HRMS (ESI+): m/z calcd. for C19H32NO3P (M+ + H) 354.2193, found 354.2197.

Diethyl (2-methyl-1-phenylpyrrolidin-2-yl)phosphonate (1-12r).
Yield: 41 mg (93%); Yellow oil. 1H NMR (400 MHz, CDCl3): δ = 1.23 (t, J = 7.2 Hz, 1 H), 1.30 (t, J = 7.2 Hz, 1 H), 1.56 (d, 14.4Hz, 1 H), 1.78-1.96 (m, 2 H), 2.09-2.21 (m, 1 H), 2.66-2.76 (m, 1 H), 3.34-3.41 (m, 1 H), 3.43-3.49 (m, 1 H), 3.95-4.13 (m, 4 H), 6.72-6.78 (m, 1 H), 7.20-7.23 (m, 4 H); 13C NMR (100 MHz, CDCl3): δ = 16.5, 16.5, 21.5 (d, J = 10.9 Hz), 22.6 (d, J = 1.6 Hz), 40.4, 51.0 (d, J = 11.0 Hz), 63.6 (d, J = 7.8 Hz), 62.8 (d, J = 6.9Hz), 62.9 (d, J = 158.8 Hz), 116.1 (d, J = 1.6 Hz), 117.6, 128.4, 146.0 (d, J = 1.5 Hz); 31P NMR (162 MHZ, CDCl3) δ = 28.41. ESI-HRMS (ESI+): m/z calcd. for C15H24NO3P (M+ + H) 298.1567, found 298.1572.

Diethyl (1-benzyl-2-methylpyrrolidin-2-yl)phosphonate (1-12a).
Yield: 41 mg (88%); yellow oil. 1H NMR (400 MHz, CDCl3): δ = 1.26 (td, J = 7.2, 3.2 Hz, 6 H), 1.32 (d, J = 15.2 Hz, 3 H), 1.52-1.73 (m, 4 H), 2.31-2.48 (m, 2 H), 2.72-2.79 (m, 1 H), 3.55 (d, J = 13.2 Hz, 1 H), 4.03-4.19 (m, 4 H), 7.18-7.29 (m, 5 H); 13C NMR (100 MHz, CDCl3): δ = 16.6(d, J = 5.4 Hz), 16.7 (d, J = 5.4 Hz), 18.8 (d, J = 10.9 Hz), 22.6 (d, J = 4.7 Hz), 36.7, 51.5 (d, J = 10.1 Hz), 54.2, 61.3 (d, J = 7.8 Hz), 62.7 (d, J = 7.7 Hz), 64.1 (d, J = 143.2 Hz), 126.6, 128.1, 128.5, 140.8; 31P NMR (162 MHZ, CDCl3) δ = 28.77. ESI-HRMS (ESI+): m/z calcd. for C16H26NO3P (M+ + H) 312.1723, found 312.1724.
Diethyl (1-benzylpyrrolidin-2-yl)phosphonate (1-12o).
Yield: 30 mg (67%); yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.27$ (td, $J = 7.0$, 3.5 Hz, 6 H), 1.52-1.74 (m, 2 H), 1.85-1.78 (m, 1 H), 2.12-2.19 (m, 1 H), 2.83-2.89 (m, 1 H), 2.92 (dd, $J = 10$, 6 Hz, 1 H), 3.34 (d, $J = 13.2$ Hz, 1 H), 4.07-4.20 (m, 4 H), 4.36 (d, $J = 13.2$ Hz, 1 H), 7.11-7.30 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.6$ (d, $J = 5.4$ Hz), 16.6 (d, $J = 5.4$ Hz), 24.4 (d, $J = 5.4$ Hz), 27.0 (d, 9.2 Hz), 54.3 (d, $J = 15.5$ Hz), 58.6, 60.2 (d, $J = 2.3$ Hz), 61.3, 61.8 (d, $J = 7.7$ Hz), 62.6 (d, $J = 7$ Hz), 126.8, 128.0, 128.8, 139.4; $^{31}$P NMR (162 MHz, CDCl$_3$): $\delta = 27.13$. ESI-HRMS (ESI+): m/z calcd. for C$_{15}$H$_{24}$NO$_3$P (M$^+$ + H) 298.1567, found 298.1572.

Diethyl (1-benzyl-2-methylpiperidin-2-yl)phosphonate (1-12d).
Yield: 41 mg (83%); yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.33$ (t, $J = 7.2$ Hz, 6 H), 1.39 (d, $J = 14.4$ Hz, 3 H), 1.76-1.54 (m, 2 H), 1.68-1.71 (m, 1 H), 2.05-2.13 (m, 1 H), 2.39-2.45 (m, 1 H), 2.77-2.89 (m, 1 H), 3.73 (dd, $J = 14.4$, 2.8 Hz, 1 H), 4.02 (d, $J = 14.8$ Hz, 1 H), 4.09-4.20 (m, 1 H), 7.04-7.04 (m, 1 H), 7.21 (m, $J = 7.6$ Hz, 2 H), 7.22-7.31 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.7$ (t, $J = 6.1$ Hz, 2 C), 21.0 (d, $J = 3.8$ Hz, 21.8 (d, $J = 6.6$ Hz), 26.0, 35.7 (d, $J = 3$ Hz), 46.9 (d, $J = 3.8$ Hz), 55.6, 58.2 (d, $J = 130.6$ Hz), 60.9 (d, $J = 8.3$ Hz), 61.6 (d, $J = 7.6$ Hz), 126.4, 128.0, 128.0, 141.2; $^{31}$P NMR (162 MHZ, CDCl$_3$): $\delta = 31.77$. ESI-HRMS (ESI+): m/z calcd. for C$_{15}$H$_{28}$NO$_3$P (M$^+$ + H) 326.1880, found 326.1886.

Diethyl (1-benzyl-2-pentylpiperidin-2-yl)phosphonate (1-12c).
Yield: 49 mg (86%); yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.83$ (t, $J = 6$ Hz, 3 H), 1.12-1.33 (m, 14 H), 1.52-2.08 (m, 3 H), 2.16-2.28 (m, 1 H), 2.58-2.72 (m, 2 H), 3.89 (s, 2 H), 3.92-4.18 (m, 4 H), 7.18-7.28 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 14.1$, 16.6 (t, $J = 5.2$ Hz, 2 C), 22.5, 22.7 (d, $J = 3.8$ Hz), 23.5 (d, $J = 9.7$ Hz), 30.0, 31.9, 32.9 (d, $J =$
11.9 Hz), 51.5 9d, \( J = 3.7 \text{Hz} \), 53.4, 61.1 (d, \( J = 8.2 \text{Hz} \)), 62.1 (d, \( J = 7.4 \text{Hz} \)), 65.2 (d, \( J = 143.6 \text{Hz} \)), 126.5, 128.1, 128.3, 140.9; \(^{31}\text{P} \) NMR (162 MHz, CDCl\(_3\)) \( \delta = 28.80 \). ESI-HRMS (ESI+): m/z calcd. for \( \text{C}_{21}\text{H}_{36}\text{NO}_3\text{P} \) (M\(^{+} \)+ H) 382.2506.

**Diethyl (2-pentyl-1-phenylpiperidin-2-yl)phosphonate (1-12s).**

Yield: 49 mg (89%); yellow oil. \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.72 \) (t, \( J = 6.8 \text{Hz} \), 3 H), 0.77-0.92 (m, 1 H), 0.96-1.22 (m, 7 H), 1.14 (t, \( J = 6.8 \text{Hz} \), 3 H), 1.22 (t, \( J = 7.2 \text{Hz} \), 3 H), 1.72-1.88 (m, 2 H), 1.92-2.11 (m, 2 H), 2.18-2.30 (m, 1 H), 2.46-2.58 (m, 1 H), 3.27-3.39 (m, 2 H), 3.80-4.05 (m, 4 H), 6.58-6.69 (m, 1 H), 7.06-7.16 (m, 4 H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta = 13.9, 16.5 \) (t, \( J = 3.8 \text{Hz} \), 2C), 22.2 (d, \( J = 9.8 \text{Hz} \)), 22.4, 22.7, 29.3, 31.5, 32.3 (d, \( J = 10.6 \text{Hz} \)), 35.6, 51.8, 61.5 (d, \( J = 7.6 \text{Hz} \)), 62.8, 6.8 Hz), 66.2 (d, \( J = 154.1 \text{Hz} \)); \(^{31}\text{P} \) NMR (162 MHz, CDCl\(_3\)) \( \delta = 28.80 \). ESI-HRMS (ESI+): m/z calcd. for \( \text{C}_{20}\text{H}_{34}\text{NO}_3\text{P} \) (M\(^{+} \)+ H) 368.2349, found 368.2346.

**Diethyl (1-(4-methoxyphenyl)-2-pentylpiperidin-2-yl)phosphonate (1-12t).**

Yield: 54 mg (91%); yellow oil. \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta = 0.77 \) (t, \( J = 7.2 \text{Hz} \), 3 H), 0.87-1.01 (m, 1 H), 1.03-1.22 (m, 7 H), 1.19 (t, \( J = 7.2 \text{Hz} \), 3 H), 1.26 (t, \( J = 7.2 \text{Hz} \), 3 H), 1.68-1.89 (m, 2 H), 1.95-2.01 (m, 2 H), 2.01-2.13 (m, 1 H), 2.46-2.57 (m, 1 H), 3.28-3.36 (m, 2 H), 3.73 (s, 3 H), 3.88-4.09 (m, 4 H), 6.78 (d, \( J = 8.8 \text{Hz} \), 2 H), 7.17 (d, \( J = 9.2 \text{Hz} \), 2 H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta = 13.9, 16.5 \) (t, \( J = 5.3 \text{Hz} \), 2C), 22.2 (d, \( J = 10.6 \text{Hz} \)), 22.4, 22.9, 29.3, 31.5, 32.4 (d, \( J = 10.7 \text{Hz} \)), 35.2, 52.1(d, \( J = 3 \text{Hz} \)), 55.6, 61.3 (d, \( J = 7.6 \text{Hz} \)), 62.7 (d, \( J = 7.6 \text{Hz} \)), 66.1 (d, \( J = 154.8 \text{Hz} \)), 113.9, 117.4, 140.6, 152.2. \(^{31}\text{P} \) NMR (162 MHz, CDCl\(_3\)) \( \delta = 28.98 \), ESI-HRMS (ESI+): m/z calcd. for \( \text{C}_{21}\text{H}_{36}\text{NO}_4\text{P} \) (M\(^{+} \)+ H) 398.2455, found 398.2458.
Diethyl (2-methyl-1-((R)-1-phenylethyl)pyrrolidin-2-yl)phosphonate (1-12g).
Yield: 43 mg (88%); yellow oil. The spectrum contains mixture of diastereoisomers. The ratio is 48:52, which is based on $^{31}$P NMR. $^{31}$P NMR (162 MHZ, CDCl$_3$) δ = 28.40, 30.72. ESI-HRMS (ESI+): m/z calcd. for C$_{17}$H$_{28}$NO$_3$P (M$^+$ + H) 326.1880, found 326.1882.

Dimethyl (1-benzyl-2-methylpyrrolidin-2-yl)phosphonate (1-12v).
Yield: 39 mg (91%); Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): δ = 1.38 (d, J = 16 Hz, 1 H), 1.67-1.75 (m, 3 H), 2.40-2.56 (m, 2H), 2.77-2.85 (m, 1 H), 3.58 (d, J = 12.8 Hz, 1 H), 3.78 (d, J = 10 Hz, 1 H), 3.85 (d, J = 9.6 Hz, 1 H), 4.21 (d, J = 12.8 Hz, 1 H), 7.18-7.39 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 18.6 (d, J = 10.9 Hz), 22.6 (d, J = 5.4 Hz), 36.8, 51.5 (d, J = 10 Hz), 53.2 (d, J = 7.7 Hz), 54.0 (d, J = 7.7 Hz), 54.2, 62.1(d, J = 161.1 Hz), 126.6, 128.1, 128.5, 140.5. $^{31}$P NMR (162 MHZ, CDCl$_3$) δ = 31.24. ESI-HRMS (ESI+): m/z calcd. for C$_{14}$H$_{22}$NO$_3$P (M$^+$ + H) 284.1410, found 284.1412.

Dibenzyl (1-benzyl-2-methylpyrrolidin-2-yl)phosphonate (1-12w)
Yield: 61 mg (91%); Yellow oil. (The spectrum contaminated with dibenzyl phosphite) $^1$H NMR (400 MHz, CDCl$_3$): δ = 1.42 (d, J = 15.6 Hz), 1.58-1.79 (m, 3 H), 2.42-2.58 (m, 2 H), 2.78-2.86 (m, 1 H), 3.63 (d, J = 12.8 Hz, 1 H), 4.25 (d, J = 13.2 Hz, 1 H), 4.86-5.15 (m, 4 H), 7.16-7.38 (m, 15 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 18.6 (d, J = 11.6 Hz), 22.6 (d, J = 4.7 Hz), 36.8, 51.6 (d, J = 9.3 Hz), 54.3, 62.2 (d, J = 159.5 Hz), 66.8 (d, J = 7.7 Hz), 68.4 (d, J = 7.7 Hz), 126.6, 127.8, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 128.5, 128.6, 132.7, 133.5, 140.5. $^{31}$P NMR (162 MHZ, CDCl$_3$) δ = 31.24. ESI-HRMS (ESI+): m/z calcd. for C$_{26}$H$_{30}$NO$_3$P (M$^+$ + H) 436.2036, found 436.2037.
2-butyl-1-phenylpyrrolidine (1-13a)

Yellow oil; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.85$ (t, $J = 7.2$ Hz, 1 H), 1.24-1.37 (m, 5 H), 1.62-1.68 (m, 1 H), 1.73-1.78 (m, 1 H), 1.83-1.99 (m, 3 H), 3.06 (dd, $J = 16$ Hz, 9.2 Hz, 1 H), 3.33 (t, $J = 6.8$ Hz, 1 H), 3.55 (t, $J = 6$ Hz, 1 H), 6.48 (d, $J = 8.4$ Hz, 2 H), 6.56 (t, $J = 6.8$ Hz, 1 H), 7.11-7.18 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 14.2$, 22.8, 23.5, 28.9, 30.3, 32.8, 48.2, 58.6, 111.7, 115.1, 129.1, 147.3. ESI-HRMS (ESI+): m/z calcd. for C$_{14}$H$_{21}$N (M$^+$ + H) 204.1747, found 204.1750.

$^1$H and $^{13}$C NMR spectra of compound 1-12d
1.6. **Tandem Amination/Cyanation/Alkylation**

In our earlier work (Scheme 11a), the starting material used was a secondary amine-tethered alkyne, which cyclized via an enamine intermediate. When we started out with a primary amine-tethered alkyne, such as 1-18a, the tandem amination/cyanation sequence, using our previous conditions,\(^{40}\) gave only 46% of the desired product 1-20a (Table 10, entry 1). The major byproduct of this reaction was imine 1-21a. Increasing the amount of trimethylsilyl cyanide and changing the temperature did not improve the yield significantly (Table 10, entries 2-5). We also found that 1-20a was unstable toward silica gel chromatography. We explained this result by invoking a thermodynamic equilibrium between 1-20a and 1-21a that prevented its complete conversion to 1-20a.
Scheme 11. Synthesis of N-heterocycles via cyclization triggered tandem reactions.

Table 10. Using a primary amine-tethered alkyne 1-18a as starting material.

<table>
<thead>
<tr>
<th>entry</th>
<th>TMS-CN</th>
<th>condition</th>
<th>time</th>
<th>20a&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 equiv</td>
<td>mw / 100°C</td>
<td>30 min</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>4 equiv</td>
<td>mw / 100°C</td>
<td>60 min</td>
<td>42%</td>
</tr>
<tr>
<td>3</td>
<td>2 equiv</td>
<td>mw / 100°C</td>
<td>30 min</td>
<td>32%</td>
</tr>
<tr>
<td>4</td>
<td>8 equiv</td>
<td>100°C</td>
<td>20 h</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>8 equiv</td>
<td>rt</td>
<td>20 h</td>
<td>50%</td>
</tr>
</tbody>
</table>

<sup>a</sup> <sup>1</sup>H-NMR yield.

1.6.1. Optimization of the reaction condition

We speculated that if the nitrogen in 1-18a could be further substituted, the resulting tertiary amine would be rendered more stable. This strategy succeeded using
chloroacetonitrile 1-22a as the alkylating reagent (Table 11, entry 1). And we also found that acetonitrile was a better solvent for this transformation (Table 11, entry 2). Reducing the amount of 1-22a slightly increased the yield (Table 11, entry 3) and conventional heating also worked well (Table 11, entry 4) though longer reaction times were needed. Under the same optimized conditions however, the reaction of the internal alkyne-tethered amine 1-18c was sluggish (Table 11, entry 5), probably because the imine intermediate was less reactive. We solved this problem by adding a Lewis acid co-catalyst – Sc(OTf)$_3$, which is known to activate imines toward nucleophilic attack.$^{55}$

1.6.2. Scope and mechanism of tandem Amination/Cyanation/Alkylation

Table 11. Optimization of the tandem amination/cyanation sequence using a primary amine

<table>
<thead>
<tr>
<th>entry</th>
<th>1-18</th>
<th>1-21</th>
<th>1-22a</th>
<th>co-catalyst</th>
<th>solvent</th>
<th>condition</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-18a</td>
<td>4 equiv</td>
<td>4 equiv</td>
<td>-</td>
<td>dioxane</td>
<td>mw /100°C / 30 min</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>1-18a</td>
<td>4 equiv</td>
<td>4 equiv</td>
<td>-</td>
<td>acetonitrile</td>
<td>mw /100°C / 30 min</td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td>1-18a</td>
<td>4 equiv</td>
<td>2 equiv</td>
<td>-</td>
<td>acetonitrile</td>
<td>mw / 90°C / 30 min</td>
<td>93%</td>
</tr>
<tr>
<td>4</td>
<td>1-18a</td>
<td>4 equiv</td>
<td>2 equiv</td>
<td>-</td>
<td>acetonitrile</td>
<td>100°C / 12h</td>
<td>85%</td>
</tr>
<tr>
<td>5</td>
<td>1-18c</td>
<td>4 equiv</td>
<td>2 equiv</td>
<td>-</td>
<td>acetonitrile</td>
<td>mw /100°C / 30 min</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>1-18c</td>
<td>4 equiv</td>
<td>2 equiv</td>
<td>Sc(OTf)$_3$</td>
<td>acetonitrile</td>
<td>100°C / 12h</td>
<td>85%</td>
</tr>
</tbody>
</table>

The reaction scope of our new three-component tandem reaction is tabulated in Table 12. A variety of alkylation reagents were compatible with our tandem reaction sequence (Table 12, entries 1-5). In general, the use of Sc(OTf)$_3$ as co-catalyst was helpful if the reaction was sluggish$^{55}$ (Table 12, entries 3, 5, 9).
Table 12. Scope of three-component tandem amination/cyanation/alkylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>1-18</th>
<th>R₈Cl (1-22)</th>
<th>condition</th>
<th>1-23 isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-18a</td>
<td>Cl-CN</td>
<td>A</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>1-18a</td>
<td>Cl-CONH₂</td>
<td>A</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>1-18a</td>
<td>Cl-C₆H₄</td>
<td>A</td>
<td>79</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>1-18a</td>
<td>Cl-Cl</td>
<td>A</td>
<td>99</td>
</tr>
<tr>
<td>5ᶜ</td>
<td>1-18a</td>
<td>-C₆H₁₁</td>
<td>B</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>1-18b</td>
<td>Cl-CN</td>
<td>B</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>1-18b</td>
<td>Cl-C₆H₄</td>
<td>B</td>
<td>89</td>
</tr>
<tr>
<td>8ᵇ</td>
<td>1-18b</td>
<td>Cl-Cl</td>
<td>B</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>1-18c</td>
<td>Cl-CN</td>
<td>B</td>
<td>81</td>
</tr>
</tbody>
</table>
Our proposed mechanism for the formation of 1-23 is shown in Scheme 12. The alkylation step could occur in the beginning (pathway A) or in the last step of the reaction (pathway B).

![Scheme 12. Proposed mechanism for the formation of 1-23d.](image)

We favored pathway B because, as shown in Scheme 13, 1-18a is known to cyclize to imine 1-21a easily in the presence of a copper catalyst, and the isolated 1-20a is prone to react with TMS-CN.

![Scheme 13. Mechanistic investigation for the formation of 1-23](image)

When the starting material was a mixture of 1-20a and 1-21a, we obtained the final product 1-23d in good yield, using the same standard reaction conditions (Scheme 13).
1.6.3. Experimental

General procedure for synthesis of 1-(Cyanomethyl)-2-methyl-4,4-diphenylpyrrolidine-2-carbonitrile (1-23).

Amino alkyne 1-18a (43 mg, 0.25 mmol), trimethylsilyl cyanide (99 mg, 1.0 mmol), dioxane (1 mL) and water (4.5 mg, 1.0 equiv) were charged into a microwave tube reactor, and CuBr (1.8 mg, 5% equiv) was added to the mixture under stirring. After all the starting materials were dissolved, the microwave tube reactor was flushed with argon. Then the reaction mixture was heated to 100°C under microwave irradiation for 0.5 h. The resulting reaction mixture was directly concentrated in a rotary evaporator and purified by silica gel flash chromatography (4:1 hexane:ether) to give a yellow liquid 1-23a (48 mg, 95%).

1-(Cyanomethyl)-2-methyl-4,4-diphenylpyrrolidine-2-carbonitrile (1-23a). Yellow oil (70.1 mg, 93% yield); IR (neat): 3457, 3027, 2970, 2810, 2215, 1739, 1446, 1366, 1217, 734, 695 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.56 (s, 3 H), 2.69 (d, \(J = 11.2\) Hz, 1 H), 3.35 (d, \(J = 7.6\) Hz, 1 H), 3.44 (d, \(J = 11.2\) Hz, 1 H), 3.55 (d, \(J = 13.6\) Hz, 1 H), 3.79 (d, \(J = 13.6\) Hz, 1 H), 4.12 (d, \(J = 7.6\) Hz, 1 H), 7.17-7.41 (m, 10 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 24.5, 37.3, 51.7, 52.4, 60.6, 64.4, 115.7, 119.2, 126.5, 126.6, 126.9, 127.0, 128.6, 128.7, 145.3, 150.0; ESI-HRMS (ESI+): m/z calcd. for C\(_{25}\)H\(_{24}\)N\(_2\) (M\(^+\) - CN) 326.1908, found 326.1906.

2-(2-Cyano-2-methyl-4,4-diphenylpyrrolidin-1-yl)acetamide (1-23b). Brown solid (73.5 mg, 92% yield). IR (neat): 3446, 3210, 3170, 2960, 2920, 2875, 2234, 1747, 1679, 1648, 1451, 1218, 1114, 705 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.57 (s, 3 H), 2.94 (d, \(J = 14.4\) Hz, 1 H), 3.18 (d, \(J = 16.8\) Hz, 1 H), 3.24 (d, \(J = 14.4\) Hz, 1 H), 3.37 (d, \(J = 10\) Hz, 1 H), 7.17-7.41 (m, 10 H); ESI-HRMS (ESI+): m/z calcd. for C\(_{25}\)H\(_{24}\)N\(_2\) (M\(^+\) - CN) 326.1908, found 326.1906.
Hz, 1 H), 3.45 (d, J = 17.2 Hz, 1 H), 3.83 (d, J = 10 Hz, 1 H), 5.98 (s, 1 H), 6.24 (d, 1 H),
7.14-7.32 (m, 10 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 24.4, 51.1, 52.5, 52.6, 60.8, 64.6,
120.4, 126.4, 126.7, 126.8, 126.8, 128.7, 145.8, 147.4, 172.6. ESI-HRMS (ESI+): m/z calcd. for C$_{20}$H$_{21}$N$_3$O (M$^+$ - CN) 293.1654, found 293.1652.

1-Benzyl-2-methyl-4,4-diphenylpyrrolidine-2-carbonitrile (1-23c). Yellow oil (66.8
mg, 79% yield). IR (neat): 3061, 3033, 2832, 2222, 1714, 1597, 1495, 1448, 1210, 1145,
1038, 907, 758, 698 cm$^{-1}$. Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.60 (s, 3 H), 2.54
(d, J = 14 Hz, 1 H), 3.02 (d, J = 10.8 Hz, 1 H), 3.43 (d, J = 14 Hz, 1 H), 3.49 (d, J = 13.2
Hz, 1 H), 3.71 (d, J = 10 Hz, 1 H), 4.10 (d, J = 13.6 Hz, 1 H), 7.11-7.39 (m, 15 H); ESI-
HRMS (ESI+): m/z calcd. for C$_{20}$H$_{19}$N$_3$ (M$^+$ - CN) 275.1548, found 275.1553.

1-(2-Chloroethyl)-2-methyl-4,4-diphenylpyrrolidine-2-carbonitrile (1-23d). Yellow oil (80.4mg, 99% yield). IR (neat): 3024, 2988, 2768, 2107, 1685, 1395, 1039, 785 cm$^{-1}$.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.44 (s, 3 H), 2.46 (d, J = 14 Hz, 2 H), 2.73-2.88 (m, 1
H), 3.02-3.11 (m, 2 H), 3.31 (d, J = 13.6 Hz, 1 H), 3.59-3.64 (m, 2 H), 3.95 (d, J = 10 Hz,
1 H), 7.05-7.38 (m, 10 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 24.8, 42.5, 51.5, 51.8, 52.5,
61.8, 64.9, 120.3, 126.1, 126.6, 126.9, 127.3, 128.2, 128.6, 145.9, 149.7. ESI-HRMS
(ESI+): m/z calcd. for C$_{20}$H$_{19}$ClN$_2$ (M$^+$ - CN) 298.1362, found 298.1359.

1-(Cyanomethyl)-2,4-dimethyl-4-phenylpyrrolidine-2-carbonitrile (1-23f). Yellow oil
(54.4mg, 91% yield). 1-23f was obtained as a mixture of two diastereoisomers in ratio of
(1:1). IR (neat): 3047, 2963, 2879, 2119, 1704, 1602, 1495, 1448, 1257, 1029, 907, 763,
735 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.54 (s, 3 H), 1.56 (s, 3 H), 2.34 (d, J = 13.6
Hz, 1 H), 2.55 (d, J = 13.6 Hz, 1 H), 2.93 (d, J = 9.2 Hz, 1 H), 3.50 (d, J = 16.8 Hz, 1 H),
3.67 (d, $J = 9.6$ Hz, 1 H), 3.74 (d, $J = 16.8$ Hz, 1 H), 7.16-7.28 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 23.9, 28.5, 37.2, 42.5, 55.3, 60.6, 66.5, 117.6, 119.4, 125.2, 126.4, 128.6, 144.3. ESI-HRMS (ESI+): m/z calcd. for C$_{15}$H$_{17}$N$_3$ (M$^+$ - CN) 213.1392, found 213.1389.

1-Benzyl-2,4-dimethyl-4-phenylpyrrolidine-2-carbonitrile (1-23g). Yellow oil (64.6 mg, 89% yield). IR (neat): 3061, 2972, 2800, 2154, 1606, 1499, 1443, 1373, 1127, 1033, 762, 698, 549 cm$^{-1}$. 1-23g was obtained as a mixture of two diastereoisomers in ratio of (1:1). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.50 (s, 3 H), 1.61 (s, 3 H), 2.16 ($J = 13.6$ Hz, 1 H), 2.55 (d, $J = 13.2$ Hz, 1 H), 2.84 (d, $J = 9.6$ Hz, 1 H), 3.02 (d, $J = 9.6$ Hz, 1 H), 3.49 (d, $J = 13.6$ Hz, 1 H), 4.09 (d, $J = 13.2$ Hz, 1 H), 7.31-7.43 (m, 5 H). ESI-HRMS (ESI+): m/z calcd. for C$_{20}$H$_{22}$N$_2$ (M$^+$ - CN) 264.1572, found 264.1569.

1-(2-Chloroethyl)-2,4-dimethyl-4-phenylpyrrolidine-2-carbonitrile (1-23h). Yellow oil (61.1 mg, 93% yield). IR (neat): 3033, 2983, 2835, 2100, 1665, 1443, 1373, 1273, 1225, 1033, 762, 736, 570 cm$^{-1}$. 1-23h was obtained as a mixture of two diastereoisomers in ratio of (1:1). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.51 (s, 3 H), 1.57 (s, 3 H), 2.09 (d, $J = 14.0$ Hz, 1 H), 2.47 (d, $J = 14.0$ Hz, 1 H), 2.74 (d, $J = 9.6$ Hz, 1 H), 2.79-2.84 (m, 1 H), 3.07-3.18 (m, 1 H), 3.26 (d, $J = 7.2$ Hz, 1 H), 3.57-3.66 (m, 2 H), 7.21-7.47 (m, 5 H). ESI-HRMS (ESI+): m/z calcd. for C$_{15}$H$_{19}$ClN$_2$ (M$^+$ - CN) 236.1206, found 236.1201.

1-(Cyanomethyl)-2-ethyl-4,4-diphenylpyrrolidine-2-carbonitrile (1-23i). Yellow oil (63.8 mg, 81% yield). IR (neat): 3069, 2963, 2874, 2229, 1681, 1446.94, 1220, 1145, 987, 725, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.93 (t, $J = 6$ Hz, 3H), 1.26-1.55 (m, 2H), 2.64 (d, $J = 14$ Hz, 1H), 3.26 (d, $J = 10.4$ Hz, 1H), 3.32 (d, $J = 13.6$ Hz, 1H), 3.49
(d, J = 17.6 Hz, 1 H), 3.76 (d, J = 16.8 Hz, 1 H), 4.13 (d, J = 10 Hz, 1 H), 7.13-7.33 (m, 10 H); $^1^3$C NMR (100 MHz, CDCl$_3$): $\delta$ 14.0, 18.1, 37.5, 39.3, 50.2, 51.6, 64.4, 65.2, 115.7, 118.6, 126.4, 126.6, 126.8, 127.0, 128.5, 128.7, 145.3, 148.1. ESI-HRMS (ESI+): m/z calcd. for C$_{21}$H$_{21}$N$_3$ (M$^+$ - CN) 289.1705, found 289.1711.

$^1$H and $^13$C NMR spectra of compound 1-23b
1.7. Tandem Amination/Oxidation

We then turned our attention to the tandem amination/oxidation sequence. Knölker and coworkers have reported a silver(I)-promoted oxidative cyclization of homopropargylamines to yield pyrroles, but their method has only limited scope (only 2 substrates reported). Because we had already reported that hydroamination was a reversible process and the migration of the triple bond was plausible, we were confident that homopropargylamines were not the only starting materials that could be employed in our protocol. Thus, we chose 5-yn-amine 1-1c, where the N atom is separated from the alkyne carbon by a 4-carbon chain. Even though the most favored cyclization path for 1c is the 6-exo-dig pathway, we did not observe the formation of a six-membered ring, rather, the pyrrole product 24c was obtained in the presence of catalytic amounts of AgF (Table 13, entry 1), albeit the yield was very low (6%). A stoichiometric amount of silver was needed to increase the yield (Tale 13, entry 2). The reaction was cleaner if it was
conducted at room temperature (Table 13, entry 3). We also investigated the effect of
different silver salts. Silver acetate exhibited the highest activity while other silver salts,
such as silver nitrate, only generated trace amounts of product (Table 13, entries 3, 9 and
10). A screening of various solvents demonstrated that DCM was the most appropriate
for the reaction (Table 13, entry 5). In general, 2 equivalent of silver acetate and longer
reaction times gave better yields (Table 13, entries 7-8). Our attempt to reduce the
amount of silver salt by using a catalytic amount of silver acetate in combination with an
oxidant was unsuccessful (Table 13, entry 13).

Table 13. Optimization of pyrrole 1-1c via tandem amination / oxidation.

<table>
<thead>
<tr>
<th>entry</th>
<th>[Ag]</th>
<th>solvent</th>
<th>condition</th>
<th>1-24c&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgF (0.1 equiv)</td>
<td>dioxane</td>
<td>90°C / 12 h</td>
<td>6%</td>
</tr>
<tr>
<td>2</td>
<td>AgF (1.0 equiv)</td>
<td>dioxane</td>
<td>90°C / 12 h</td>
<td>22%</td>
</tr>
<tr>
<td>3</td>
<td>AgF (1.0 equiv)</td>
<td>dioxane</td>
<td>rt / 12 h</td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td>AgOAc (1.0 equiv)</td>
<td>dioxane</td>
<td>rt / 24 h</td>
<td>40%</td>
</tr>
<tr>
<td>5</td>
<td>AgOAc (1.0 equiv)</td>
<td>DCM</td>
<td>rt / 24 h</td>
<td>52%</td>
</tr>
<tr>
<td>6</td>
<td>AgOAc (1.0 equiv)</td>
<td>DCM</td>
<td>rt / 24 h</td>
<td>66%</td>
</tr>
<tr>
<td>7</td>
<td>AgOAc (2.0 equiv)</td>
<td>DCM</td>
<td>rt / 24 h</td>
<td>62%</td>
</tr>
<tr>
<td>8</td>
<td>AgOAc (2.0 equiv)</td>
<td>DCM</td>
<td>rt / 40 h</td>
<td>81% (74%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>AgNO&lt;sub&gt;3&lt;/sub&gt; (2.0 equiv)</td>
<td>DCM</td>
<td>rt / 24 h</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>AgCO&lt;sub&gt;3&lt;/sub&gt; (2.0 equiv)</td>
<td>DCM</td>
<td>rt / 24 h</td>
<td>no rxn</td>
</tr>
<tr>
<td>11</td>
<td>CuBr (0.1 equiv)</td>
<td>DCM</td>
<td>rt / 24 h</td>
<td>complex</td>
</tr>
<tr>
<td>12</td>
<td>CuBr (1.0 equiv)</td>
<td>DCM</td>
<td>rt / 24 h</td>
<td>complex</td>
</tr>
<tr>
<td>13</td>
<td>AgOAc (0.1 equiv)/DDQ (1.1 equiv)</td>
<td>DCM</td>
<td>rt / 40 h</td>
<td>trace</td>
</tr>
</tbody>
</table>

<sup>a</sup> NMR yield; <sup>b</sup> isolated yield.
1.7.1. **Scope and mechanism of tandem amination and oxidation**

The scope of our pyrrole synthesis is depicted in Table 14. This reaction worked well for both aliphatic and aromatic amines tethered to the alkyne starting material when the carbon chain link between the amine and alkyne moieties is between 2-4 carbons. Typically, a silver fluoride salt furnished better yields when the starting material was a substituted aniline.

Table 14. Reaction scope for synthesis of pyrrole 1-24 via tandem amination/oxidation.\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>1-1</th>
<th>1-24</th>
<th>yield(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>74%</td>
</tr>
<tr>
<td>2(^b)</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>71%</td>
</tr>
<tr>
<td>3(^b)</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>62%</td>
</tr>
<tr>
<td>4(^b)</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td>80%</td>
</tr>
<tr>
<td>6(^b)</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
<td>73%</td>
</tr>
</tbody>
</table>

\(^a\) Reaction condition: amino alkyne (0.25mmol), silver acetate (0.375 mmol), DCM (1 mL), rt, 40 h;  
\(^b\) silver fluoride (0.375 mmol) was used; \(^c\) isolated yields.
A reasonable mechanism for the formation of pyrrole 1-24\textsubscript{a} is illustrated in Scheme 14. Hydroamination of 5-yn-amine 1-1\textsubscript{c} produces a six-membered enamine 1-25 through a 6-\textit{exo-dig} pathway.\textsuperscript{40} Migration of the double bond in enamine 1-25 yields 1-26 and hydroamination in the presence of a metal catalyst is reversible,\textsuperscript{40} therefore upon retro-hydroamination, 1-26 delivers alkyne 1-27, which undergoes a second round of the hydroamination-migration protocol (i.e., 1-27 to 1-29). Oxidation or dehydrogenation of 1-29 with the silver oxidant furnishes the final pyrrole product 1-24\textsubscript{a}.\textsuperscript{56}

\begin{center}
\begin{tikzpicture}
  \begin{scope}
    \node at (0,0) {\textbf{Scheme 14. Proposed mechanism for formation of 1-24.}};
    \node at (0,-2) {1.7.2. \textbf{Experimental}};
    \end{scope}
\end{tikzpicture}
\end{center}

Amino alkyne 1-1\textsubscript{c} (61 mg, 0.25 mmol) and silver acetate (63 mg, 0.375 mmol) and DCM (1 mL) were added to a glass vial. The mixture was stirred for 40 h at room temperature and was concentrated immediately after in a rotary evaporator and purified by silica gel flash chromatography (5:1 hexane:ether) to give a yellow liquid 1-24\textsubscript{c} (45 mg, 74%).

\textbf{1-Benzyl-2-hexyl-1H-pyrrole (1-24\textsubscript{c})}. Yellow oil (44.6 mg, 74\% yield). IR (neat): 2930, 2851, 1700, 1658, 1518, 1248, 1033, 837, 698 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}):
δ 0.78 (t, $J = 7.2$ Hz, 3 H), 1.05-1.28 (m, 6 H), 1.41-1.53 (m, 2 H), 2.36 (d, $J = 8.0$ Hz, 2 H), 4.95 (s, 2 H), 5.88 (s, 1 H), 6.05 (t, $J = 2.4$ Hz, 1 H), 6.53, 6.86-6.96 (m, 2 H), 7.11-7.27 (m, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 14.1, 22.6, 26.2, 28.8, 29.1, 31.6, 50.2, 105.8, 107.0, 120.7, 126.3, 127.3, 128.6, 133.7, 138.6. ESI-HRMS (ESI+): m/z calcd. for C$_{17}$H$_{23}$N (M$^+$ + H) 242.1903, found 242.1905.

**2-Hexyl-1-phenyl-1H-pyrrole (1-24s).** Yellow oil (40.4 mg, 71% yield). IR (neat): 2963, 2930, 2860, 1709, 1667, 1457, 1294, 1168, 1075, 1033, 693 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 0.83 (t, $J = 6.8$ Hz, 3 H), 1.14-1.30 (m, 6 H), 1.44-1.55 (m, 2 H), 2.51 (t, $J = 8$ Hz, 2 H), 6.05 (s, 1 H), 6.20 (s, 1 H), 6.73 (d, $J = 1.2$ Hz, 1 H), 7.18-7.43 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 14.0, 22.5, 26.7, 29.0, 29.1, 31.5, 106.6, 107.8, 121.4, 126.1, 127.0, 129.0, 134.3, 140.5. ESI-HRMS (ESI+): m/z calcd. for C$_{16}$H$_{21}$N (M$^+$ + H) 228.1747, found 228.1745.

**2-Hexyl-1-(4-methoxyphenyl)-1H-pyrrole (1-24t).** Yellow oil (39.3 mg, 62% yield). IR (neat): 2963, 2930, 2857, 1615, 1514, 1463, 1302, 1247, 1040, 838, 709 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 0.768 (t, $J = 6.6$ Hz, 3 H), 1.12-1.23 (m, 6 H), 1.33-1.47 (m, 2 H), 2.39 (t, $J = 7.6$ Hz, 2 H), 3.77 (d, $J = 1.2$ Hz, 3 H), 5.95 (s, 1 H), 6.11 (s, 1 H), 6.61 (d, $J = 1.2$ Hz, 1 H), 6.84-6.88 (m, 2 H), 7.10-7.18 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 14.0, 22.5, 26.6, 29.0, 29.1, 31.6, 55.5, 106.1, 107.4, 114.1, 121.6, 127.4, 133.8, 134.6, 158.5. ESI-HRMS (ESI+): m/z calcd. for C$_{17}$H$_{23}$NO (M$^+$ + H) 258.1852, found 228.1855.

**1-Benzyl-2-butyl-1H-pyrrole (1-24b).** Yellow oil (46.3 mg, 80% yield). IR (neat): 2961, 2924, 2855, 1698, 1603, 1497, 1322, 1078, 755, 695 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 0.884 (t, $J = 7.6$ Hz, 3 H), 1.24-1.40 (m, 2 H), 1.49-1.61 (m, 2 H), 2.50 (t, $J = 8$ Hz,
2H), 5.04 (s, 2 H), 5.97 (s, 1 H), 6.14 (t, J = 2.4 Hz, 1 H), 6.62 (s, 1 H), 7.00 (m, 2 H), 7.22-7.36 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 13.9, 22.5, 25.9, 31.0, 50.2, 105.8, 107.0, 120.7, 126.3, 127.3, 128.7, 133.7, 138.6. ESI-HRMS (ESI+): m/z calcd. for C₁₅H₁₉N (M⁺ + H) 214.1590, found 213.1591.

¹H and ¹³C NMR spectra of compound 1-24b
1.8. Summary and future direction

In conclusion, we have successfully developed a cyclization triggered addition strategy. In this way, we not only accomplished the construction of N-heterocycles with different ring sizes, but we also introduced a new functional group on the ring system through a carbon-carbon forming reaction. Our work is significant because this tandem chemistry is expected to provide fast entries to complex N-heterocycles. Unlike many literature syntheses, it uses unprotected free amines as starting materials without seeking any kind of protecting groups and with good atom-economy. The broader implications of this reaction include an asymmetrical version, and its application to natural product synthesis.
2.1 Background

Chemical synthesis plays a vital role in pharmaceuticals, materials, agrochemicals and many other related fields. Among the repertoire of catalysts used in chemical synthesis, cationic metal Lewis acids are one of the most common catalyst systems through electrophilic activation of organic substrates.\(^\text{57}\)

Among the commonly used cationic metal catalysts, their counterions can be OTf\(^-\), ClO\(_4^-\), BF\(_4^-\) and other weakly coordinating anions. Metal triflates (M\(^+\)OTf\(^-\)) are by far the most common used because they are relative stable and usually are cheaper and easier to procure. Triflates of most metals (e.g., Ag, Yb, In, Ga, Sc) are commercially available.

Figure 2. Better than OTf\(^-\) and NTf\(_2^-\).
Recently, cationic metal salts containing trilimidate (NTf$_2^-$) have appeared as a unique class of catalysts that display outstanding $\sigma$- and $\pi$-Lewis acid character.\textsuperscript{58} Consequently, these metal trilimidates often outperform their triflate analogues in catalysis.\textsuperscript{58} In 2010, Dalla and Dunach published a review article in *Angew. Chem.* titled ‘Metal Trilimidates: Better than Metal Triflates as Catalysts in Organic Synthesis…’.\textsuperscript{58} Despite intensive investigations, there is no concrete rationnle to explain benefits of trilimidates, chemists usually explain their higher performance to its more delocalized charge, higher steric hindrance and reduced nucleophilicity compared to triflate.\textsuperscript{58}

In the periodic table, N to in the left side of O, C is to the left side of N. If NTf$_2^-$ is better than OTf$^-$ and this trend continues, CTf$_3^-$ will be even better than NTf$_2^-$ (Figure 2). CTf$_3^-$ will have even more delocalized negative charge, bigger size, increased stability and reduced nucleophilicity. Indeed, CTf$_3^-$ based cationic metals (e.g., Yb(CTf$_3$)$_3$) have shown good reactivity in reactions like nitration of aromatics.\textsuperscript{59} Even though CTf$_3^-$ based cationic metal catalysts have potential to outperformance NTf$_2^-$ and OTf$^-$ based catalysts, chemists rarely use them. The obvious reason is the lack of commercial availability and the fact that they are troublesome to make.\textsuperscript{59} We propose that the laborious preparation of a catalyst containing CTf$_3^-$ or even other ideal counterions for the purposes of enhancing the reactivity is unnecessary; instead the same effect can be achieved *in situ* by simply using a commercial catalyst contain common counterion (e.g., OTf$^-$), and adding to it the alkali salt of a CTf$_3^-$ (e.g., K$^+$CTf$_3^-$). When a salt like KCTf$_3$ is added to reaction system, a reshuffling of ions will occur, a CTf$_3^-$ based reactive cationic species will be generated *in situ* and in so doing it will improve the efficiency of a reaction.
2.2. Selection of reaction promoters

In chemistry, a promoter is defined as a substance added to a catalyst to improve its performance in a chemical reaction. Promoters interact with active components of catalysts and thereby alter their chemical effect on the catalyzed substance. Therefore, we can call compounds like KCTf$_3$ a reaction promoter. We are now pleased to report the discovery of K$^+$CTf$_3^-$, a promoter capable of improving most cationic metal catalyzed reactions.

Potential reaction promoters are not limited to KCTf$_3$. In theory, any salts containing counter anions which have a good track record for good reactivity can be used. An ideal promoter should be readily available and be able to tolerate harsh reaction conditions. For example, salts of [PF$_6$]$^-$ or [BPh$_4$]$^-$, although ubiquitous, cannot be considered ideal because they undergo facile fluoride abstraction or hydrolysis by adventitious water/acid, respectively. The number of commercially available salts that meet our requirements of coordinating ability, stability and availability are less than a handful, namely, LiNTf$_2$, NaBARF (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), Li$^+$[Al((CF$_3$)$_3$C-O)]$_4$ and KCTf$_3$. All the corresponding counterions in these promoters have shown good reactivity in metal catalyzed reactions.

To investigate the feasibility of our reshuffling tactic we chose gold catalyzed reactions as a testing ground. We screened the commercially available salts listed above to gauge their potential as reaction promoters in the gold-catalyzed intermolecular hydroamination of alkynes (Figure 3). Most of the salts screened enhanced the kinetics of the reaction,
but KCTf₃ clearly gave the best result. The reaction inhibition observed with Li⁺[Al[(CF₃)₃C-O)]₄⁻⁻ could be explained by the instability of the aluminum anion under the reaction conditions.

Figure 3. Effect of promoters on hydroamination reaction

Figure 4. Effect of promoters in the rearrangement of allenyl ester.
We proceeded to investigate further the most promising reaction promoters, this time using another gold(I)-catalyzed reaction: the isomerization of an allenyl carbinol ester (Figure 3), a reaction known to experience significant catalyst decay over time. Again, KCTf$_3$ gave the best result. We found that LiNTf$_2$ slowed down the reaction in the beginning but could maintain its reactivity effect with time, probably due to the stabilizing effect of NTf$_2^{-}$. NaBARF enhanced the rate of the reaction significantly but only in the beginning. We attributed the time leveling effect of NaBARF to catalyst deactivation under the reaction conditions.

### 2.3. General ionic reaction promoter

We expanded the study of our reaction promoters to other gold catalyzed reactions without modifying the original reaction conditions reported in the literature (Scheme 15). Because the kinetics of the reactions in Scheme 15 are approximately pseudo-zero order, the relative rate of each reaction is a good parameter to evaluate the efficiency of the catalyst/promoter system. We measured the initial rate, first in the presence, and then in the absence, of a reaction promoter for each of the reactions tested. Again, KCTf$_3$ accelerated significantly and consistently all the gold catalyzed reactions tested. For example, in X-H (X = O, N) additions to alkyne/alkene (Scheme 15, a-b), KCTf$_3$ increased the reaction rate 3.5 and 11 fold. In the cycloisomerization of 1,6-enynes (Scheme 15, c-d) KCTf$_3$ increased the reaction rate up to 33 fold. NaBARF performed marginally better than KCTf$_3$ in only one case (Scheme 15b), but inhibited the other reactions (Scheme 15a and Scheme 15c).
With this string of successes in gold catalysis, we turned our focus to other representative ionic reactions, specifically Lewis acid catalyzed reactions (Scheme 16). Again, we found that KCTf$_3$ increased significantly the rate of Lewis acid catalyzed reactions. For example, the Friedel-Crafts acylation (Scheme 16a) is one of the most important methods to prepare acylated aromatics.\textsuperscript{55} KCTf$_3$ showed a one-hundred fold increase in the Yb(OTf)$_3$ catalyzed acylation of anisole (Scheme 16a).\textsuperscript{84} Notably, in the Sc(OTf)$_3$ catalyzed allylation of aromatic aldehydes\textsuperscript{85} (Hosomi-Sakurai Reaction) (Scheme 16b), the addition of KCTf$_3$ (1.6\%) led to a 95\% yield of product after only 3 h (Scheme 16b). KCTf$_3$ performed remarkably well in the Yb(OTf)$_3$ catalyzed ring-opening of methylenecyclopropanes (Scheme 16c)\textsuperscript{86} and in a Prins-type cyclization, catalyzed by Sc(OTf)$_3$ (Scheme 16d).\textsuperscript{87}

We then expanded the range of ionic reactions in our study to encompass those catalyzed by other transition metals such as silver and rhodium.\textsuperscript{88} Again, as shown in Scheme 17 a-b, KCTf$_3$ accelerated both reactions. In recent years, visible light photoredox catalysis
using transition metal complexes has attracted much attention. In our hands, the Ru catalyzed visible light photoredox reaction shown in Scheme c gave only trace amounts of product, but when we added 10% KCTF$_3$ to this reaction we noticed a substantial improvement (65% yield after 3h).

Scheme 16. Effect of reaction promoter in various classical Lewis acid catalyzed reactions.

Scheme 17. Effect of reaction promoter in silver, rhodium and ruthenium catalyzed ionic reactions.
We deemed KCTf$_3$ a quasi-universal promoter because it enhanced, in consistent and significant manner, the reaction rates and the chemical yields of a wide spectrum of ionic reactions, ranging from traditional Lewis acid catalysis to transition metal catalysis to organocatalysis and even visible-light-photocatalysis. We attribute its all-around success to the fact that CTf$_3^-$ is relatively large (larger than NTf$_2^-$) and weakly coordinating, and it does not have labile metal-fluorine or metal-carbon bonds. In addition, CTf$_3^-$ is a carbon-based soft anion; this feature further enables ion reshuffling because most transition metal catalysts have a relatively soft metal center. KCTf$_3$ is also a neutral salt, that is, it will not interfere with acidic or basic species in the reaction system.

In a small number of the reactions studied, explicitly those shown in Scheme 17a and Scheme 15d, the acceleration effect of KCTf$_3$ was only marginally better than the control. This means that our promoter will not be highly effective in every reaction. First, we believe that the effectiveness of a promoter highly depends on the existing state of ionic species in the reaction system. The majority of organic reactions are conducted in solvents of relatively low dielectric constant (e.g., dichloromethane, toluene, THF), where ionic species like cationic metals or their related complex exist as ion pairs. For example, cationic gold catalysts (e.g., LAu$^+$BF$_4^-$) appear to exist as ion pairs in commonly used low dielectric constant solvents like DCM or chloroform, according to recent studies by Macchioni and coworkers. In these cases, counterions are close to the reactive metal center and therefore have a strong influence on the reaction rate, therefore, a reaction promoter may play a big role. Most of our reaction examples belong to this category. On the other hand, in reactions conducted in high dielectric constant solvents (e.g., water, methanol or acetone), the majority of ionic species will exist as
dissociated ions\textsuperscript{91,92}. In these cases, counterions will be far away from the reaction center and therefore will have a minimum influence on the reaction rate. In these cases, a reaction promoter will not be very useful. The reaction shown in Scheme 17a was conducted in acetone ($\varepsilon = 20.7$), which has much larger dielectric constant than the solvent used in other reactions (e.g., chloroform, $\varepsilon = 4.8$ or dioxane, $\varepsilon = 2.3$). Another example of this solvent effect was shown in eq 5, this reaction is similar to the reaction in Scheme 16c, except it was conducted in EtOH ($\varepsilon = 24.5$) instead of AcOH ($\varepsilon = 6.2$). Clearly, the effect of the promoter was significantly reduced when EtOH was used as solvent.

We also believe that the effectiveness of a promoter depends on the rate-determining step. If the counterion is not involved in the turnover limiting step of a reaction, we expect the beneficial effect of KCTf$_3$ will not be significant.

2.4. Summary and future direction

In summary, we have found a mechanism-independent approach to improve the kinetics of a vast gamut of cationic metal catalyzed reactions using one simple ionic promoter. Our approach is practical because a commercially available promoter can improve many metal catalyzed reactions without modifying their original reaction conditions. Further implications and applications of ionic promoters include applications to other ionic transformations and exploratory work on asymmetric reactions that are ionic in nature. We will try to develop a practical rule for the use of promoters in synthesis.
2.5. Experimental

General

$^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded at 400, 100 and 162 MHz respectively, using CDCl$_3$ as a solvent. The chemical shifts are reported in δ (ppm) values relative to CHCl$_3$ (δ 7.26 ppm for $^1$H NMR, δ 77.0 ppm for $^{13}$C NMR and CFCl$_3$ δ 0.00 ppm for $^{19}$F NMR), multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), m (multiplet) and br (broad). Coupling constants, $J$, are reported in Hertz. All air and/or moisture sensitive reactions were carried out under argon atmosphere. Solvents (tetrahydrofuran, ether, dichloromethane and DMF) were chemically dried using a commercial solvent purification system. All other reagents and solvents were employed without further purification. The products were purified using a CombiFlash system or a regular glass column. TLC was developed on Merck silica gel 60 F254 aluminum sheets. KCTf$_3$ was purchased from Synquest Labs. All other chemicals like metal catalysts and ligands were purchased from Aldrich, Alfa Aesar or Strem.

General procedure for kinetic measurements

Monitoring of reactions using in situ NMR spectroscopy

When $^1$H NMR was used to monitor the progress of a reaction, a solution of tetramethylsilane in CDCl$_3$ (sealed in a capillary tube) was used as external standard for NMR integration. In some cases, 1,3,5-tri-tert-butylbenzene (internal standard) was used. The reactions were monitored with $^1$H NMR (single pulse or 1 scan for fast reactions, 8 scans for slow reactions). Some NMR measurements were conducted using NMR experiment array (a series of spectra measured at predetermined time intervals over a period of time by adjusting the pre-acquisition delay). NMR experiment array gives
better precision for both concentration (via integrations) and reaction time, because each measurement is conducted at almost identical shimming and temperature conditions. The concentrations of substrate and product were determined by relative integration to the t-butyl peak in the standard (tetramethylsilane or 1,3,5-tri-tert-butylbenzene).

**Monitoring of reactions using GC-MS.**

The model reaction was conducted in the presence of internal standard (hexadecane or acetophenone). For analysis, 1-5 mL of sample was taken from the reaction mixture and was diluted with a suitable solvent (e.g., hexane or ethyl acetate). The diluted solution was injected into a GC-MS using an autosampler. Each GC reading is the average of three runs. Typically three reactions under the same conditions were conducted in parallel.

**Synthesis of starting materials**

**Synthesis of gold complexes (L-AuCl).** All gold complexes (L-AuCl) were synthesized using a slightly modified version of a literature method. These complexes were prepared via the following general procedure:

Sodium tetrachloroaurate(III) dihydrate (1 mmol) was dissolved in water, and the orange solution was cooled in ice. To this solution, 2,2’-thiodiethanol (3 mmol) was slowly added (ca. 45 min) with stirring. A solution of the phosphine ligand (1 mmol) in EtOH (if the ligand could not be dissolved, more EtOH was used) was added dropwise to yield a white solid. The solid was filtered off, washed with water followed by EtOH, and ultimately dried in vacuum.

**Preparation of cationic gold (L-Au^+OTf^-) stock solution.** Standard stock solutions of cationic gold catalyst were made by weighing the L-Au(I)Cl complex into a vial and adding corresponding deuterated solvent, then 1.2 equiv of AgOTf was added, the vial
was sonicated for 3-5 min at 5-10 °C, then the vial was centrifuged and the clear solution was transferred to a clean glass vial with a screw cap. The solution was kept in freezer (-20°C) until it was used.

**Effects of promoter in various ionic reactions.**
All the following reactions were monitored using the general procedure for kinetic measurement.

**General procedure for the gold catalyzed hydroamination of aniline with phenylacetylene.**
0.1 mL of a standard cationic gold solution in CDCl$_3$ (0.05 M) and 0.35 mL CDCl$_3$ were introduced into a NMR tube, and then aniline (0.1 mmol, 9.3 mg), phenylacetylene (10.8 mmol, 1.103g), additive (0.015 mmol), were introduced in its solid state. The reaction was kept at room temperature and was monitored by $^1$H NMR. Each data point corresponded to 8 scans.

**General procedure for the gold catalyzed rearrangement of allenyl ester.**
0.2 mL of a standard cationic gold solution in CDCl$_3$ (0.01 M) and 0.3 mL CDCl$_3$ were introduced into a NMR tube, and then allenyl ester (0.05mmol, 12.5 mg) and additive ($4\times10^{-3}$ mmol), were introduced in its liquid and solid state, respectively. The reaction was kept at room temperature and was monitored by $^1$H NMR. Each data point corresponded to 8 scans.

**Gold catalyzed cyclization of propargyl amide**
Following the general procedure for kinetic experiments using *in situ* NMR spectroscopy, 0.15 mL of a standard cationic gold solution in CDCl$_3$ (0.01 M) and 0.35 mL CDCl$_3$ were introduced into a NMR tube, and then propargyl amide (16 mg, 0.1 mmol) and the internal standard were introduced in its solid state. The reaction was kept at room temperature and was monitored $^1$H NMR. Each data point corresponded to 1 scan.
Gold catalyzed hydroamination of alkene

A standard solution of starting material (aminoalkene) was prepared by dissolving aminoalkene (0.5 mmol) and n-hexadecane (internal standard) in dioxane (2.5 mL). For each reaction, DalPhos-AuCl (2 mol%), AgOTf (2 mol%) and different promoters were added to a corresponding reactor containing 0.5 mL standard solution. All reactions were stirred and heated to 100°C. The progress of reaction was monitored by GC/MS.
Gold catalyzed intramolecular cycloisomerization of enyne

\[
\text{MeOOC} \quad \text{COOMe} \quad \xrightarrow{2\% \text{ PPh}_{3}\text{Au}^{+}\text{OTf}^{-}} \quad \text{MeOOC} \quad \text{COOMe}
\]

\[
\text{CDCl}_{3}, \text{rt} \quad \text{promotor (4\%)}
\]

Gold catalyzed intramolecular cycloisomerization of enyne

\[
\text{R} \quad \text{COOEt} \quad \xrightarrow{\text{PPh}_{3}\text{Au}^{+}\text{OTf}^{-} (4\%) \ \text{CDCl}_{3}, \text{rt} \ \text{promotor (8\%)} } \quad \text{R} \quad \text{CH}_{3} \quad \text{COOEt}
\]
Friedel-Crafts acylation

\[
\text{OMe} \quad \overset{5\% \text{ Yb(OTf)}_3, \text{Ac}_2\text{O (3 equiv)}}{\text{dioxane, 40}^\circ\text{C, promotor (10\%)}} \quad \text{AcO} \quad \text{OMe}
\]

A standard solution of starting material was prepared by dissolving anisole (1.4 mmol), Yb(OTf)$_3$ (5 mol%) and n-hexadecane (internal standard) in 3.5 mL dioxane. Different promoters (10 mmol%) and acetic anhydride (0.6 mmol) were added into the corresponding reactors containing 0.5 mL standard solution. All reactions was stirred and carried out at 40°C. The progress of reaction was monitored by GC/MS.
**Hosomi-Sakurai reaction**

![Chemical reaction diagram](image)

A standard solution of starting material was prepared by dissolving 4-chlorobenzaldehyde (0.4 mmol), allyltrimethylsilane (0.8 mmol) and n-hexadecane (internal standard) in dioxane. Different promoters and Sc(OTf)_3 (0.4 mol%) were added to the corresponding reactors containing 1 mL standard solution. All reactions were conducted at room temperature. The progress of reaction was monitored by GC/MS.

**Lewis acid-catalyzed ring-opening**

![Chemical reaction diagram](image)

A standard solution was prepared by dissolving methylenecyclopropane (0.4 mmol), Yb(OTf)_3 (0.4 mol%) and n-hexadecane (internal standard) in 4 mL acetic acid. Different promoters (0.8 mmol%) were added into the corresponding reactors containing 1 mL standard solution. The reactions were stirred and conducted at room temperature. The progress of reaction was monitored by GC/MS.

**Silver catalyzed cyclization of propargyl amide**

![Graph](image)
Rhodium catalyzed hydroamination of alkene

A standard solution of starting material was prepared by dissolving aminoalkene (0.5 mmol) and n-hexadecane (internal standard for GC) in dioxane (2.5 mL). [Rh(COD)$_2$]BF$_4$ (2.5 mol%), DavePhos (3 mol%) and different promoters were added into the corresponding reactors containing 0.5 mL standard solution. All reactions were stirred and heated to 70°C. The progress of reaction was monitored by GC/MS.
Organo iminium catalysis

A standard solution was prepared by dissolving cinnamaldehyde (2 mmol), organocatalyst (10 mmol%) and n-hexadecane (internal standard) into 6 mL dioxane. Cyclopentadiene and different promoters (20 mmol%) were added into the corresponding reactors containing 1.5 mL standard solution. The reactions were stirred at room temperature.

Visible-light photocatalysis

A standard solution was prepared by dissolving benzoyl peroxide (2 mmol) and anisole (1 mmol) in 4 mL dioxane. Photoredox catalyst Ru(bpy)$_3$Cl$_2$ (2 mmol%), sodium bicarbonate (0.75 mmol), and different promoters (4 mmol%) were added into the
corresponding reactor containing 1 mL standard solution. The reactions were stirred at room temperature and were illuminated with a 26-W household bulb. The reaction was monitored by GC/MS.
CHAPTER 3
BRØNSTED ACID- OR LEWIS ACID-ASSISTED ACTIVATION OF AN IMIDOGOLD PRECATALYST

3.1. Background

Cationic gold catalysis is a landmark addition to the field of organic synthesis.\textsuperscript{70-75} Silver-mediated halogen abstraction is the most preferred method to generate cationic gold from a gold catalyst precursor (e.g., L-Au-Cl) due to the mild conditions needed and the relative availability of silver activators (AgX, X= OTf, SbF\textsubscript{6}, NTf\textsubscript{2} etc.). However, the use of silver activators is not without problems. First, some of the preferred silver activators are either relatively expensive (e.g., AgNTf\textsubscript{2}), commercially unavailable, or troublesome to prepare (e.g., Ag[B(C\textsubscript{6}F\textsubscript{5})\textsubscript{4}]). Second, the presence of silver may cause side reactions.\textsuperscript{96} Indeed, recent reports have revealed that the silver mediated halogen abstraction is not as simple a process as initially thought (Figure 5). Possibly because of the high affinity of silver towards gold and halogen, various Au-Ag intermediates (A,\textsuperscript{97} B,\textsuperscript{98} C\textsuperscript{99}) are formed during the halogen abstraction step. These intermediates have been isolated and identified (Figure 5). The presence of silver could also have an additional deleterious effect: the formation of a dinuclear gold-silver resting state (i.e., intermediate D in Figure 5).\textsuperscript{100}
There are alternative ways to generate cationic gold. For example, Teles and others reported the protonolysis of \( \text{Ph}_3\text{PAu-CH}_3 \), which they used in the hydration and amination of alkynes with good turnover numbers (Scheme 18a). Nolan and coworkers reported a Brønsted acid activation of NHC-Au-OH that generated cationic \([\text{NHC-Au}]^+\) or \([\text{Au-O-Au}]^+\) species (Scheme 18b). Bertrand and coworkers generated cationic gold taking advantage of the high affinity of silica towards chloride (Scheme 18c). Recently, Lafolle and Gandon reported the use of \( \text{Cu(OTf)}_2 \) to activate L-AuCl.

![Diagram of various Au-Ag intermediates](image)

Figure 5. Various Au-Ag Intermediates formed in the generation of cationic gold.

![Scheme 18](image)

Scheme 18. Typical non-silver based cationic gold generation methods.
The aforementioned non-silver activation methods have limitations. First of all, gold precatalysts like L-Au-CH₃ and L-Au-OH have only been synthesized successfully for a limited set of ligands.¹⁰²,¹⁰⁷-¹¹⁰ This limitation is a constraint in gold catalysis because different gold-catalyzed reactions usually require different ligands for optimal efficiency.⁶⁷ Second, for each of the activation methods reported, only a limited set of gold-catalyzed reactions has been tested.¹⁰¹ Third, the relative reactivity of the non-silver based system *viz a viz* the equivalent silver based system has not been aptly compared.

### 3.2. Synthesis and activation of L-Au-Pht

In our continuing effort to improve the efficiency of gold catalysis, we found that a gold phthalimide complex (**L-Au-Pht**) can be easily synthesized from L-Au-Cl and potassium phthalimide for a diversity of ligands (Scheme 19).¹¹¹,¹¹² **L-Au-Pht** in itself is not an active gold catalyst (or a good Lewis acid) because the bond between gold and phthalimide is strong. Nonetheless, we thought that the reactivity or Lewis acidity of **L-Au-Pht** could be greatly increased by applying the concept of combined acids catalysis—Brønsted acid assisted Lewis acid (BLA) and Lewis acid assisted Lewis acid (LLA)—proposed by Yamamoto and coworkers¹¹³ (Scheme 20, top). In this manner, the reactivity of the L-Au-Pht/acid system could be fine-tuned by simply choosing one of the many readily available Brønsted acids and Lewis acids found in the literature—each of which has its own acid strength and counterion. We are now pleased to report the success of this novel and silver-free approach to generate cationic gold.
Our new gold catalyst system not only has shown superior reactivity in all major types of
gold-catalyzed reactions but also is devoid of the drawbacks of silver-gold interactions.
$^{31}$P NMR is a good indicator of the electronic properties of gold complexes, which in turn
is a good correlation of catalytic reactivity. Smaller $^{31}$P NMR chemical shifts indicate
more electron positive gold centers (Scheme 20, bottom). Treatment of Ph$_3$PAu-Pht with
TfOH does generate a cationic gold species system similar to the commonly used
Ph$_3$PAu-OTf (Scheme 20, bottom).

We used the hydroamination of alkynes$^{11,114}$ as a model system to evaluate the response
of our imido gold precatalyst to Brønsted acids, and found that acid strength correlated
with performance. This procedure was superior to the traditional silver halide removal
protocol (Figure 6).
To compare a large number of acid activators in a quantitative fashion, we measured the initial reaction rate for each activator at a given concentration (Table 15). We found that weak acids like benzoic acid did not promote this reaction, but stronger acids were more effective (\(\text{HCTf}_3 > \text{HNTf}_2 > \text{TfOH}\)). In general, a \(\text{Ph}_3\text{PAu-Pht/acid}\) combination showed better reactivity than the standard \(\text{Ph}_3\text{PAu-Pht/AgX}\) system. Most Lewis acids also worked well. The counterions of Brønsted acids or Lewis acids played an important role (rate: \(\text{CTf}_3 > \text{NTf}_2 > \text{TfO}^- > \text{BF}_4^-\)). We also evaluated other gold catalyst precursors (\(\text{Ph}_3\text{PAuCl}, \text{Ph}_3\text{PAu-Sac}, \text{Ph}_3\text{Pau-OAc}\), Table 15, entries 8, 9, 10) and found them less effective (not to mention the fact that the synthesis of \(\text{Ph}_3\text{PAu-Sac}\) and \(\text{Ph}_3\text{Pau-OAc}\) required the corresponding silver salts). The data in Table 15 also demonstrates that we have many more options to choose from compared to silver activators. For example, if a strong Brønsted acid cannot be tolerated in a reaction system, then we can replace it with...
a milder acid, such as Yb(OTf)$_3$ (Table 15, entry 13, its aqueous solution is close to neutral), or AgCTf$_3$ (Table 15, entry 18).

Table 15. Relative rate of intermolecular hydroamination.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph$_3$PAuCl/AgOTf (0.2%)</td>
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</tr>
<tr>
<td>2</td>
<td>Ph$_3$P-Au-Pht/no acid</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Ph$_3$P-Au-Pht/PhCOOH (0.2%)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ph$_3$P-Au-Pht/HBF$_4$ (0.2%)</td>
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</tr>
<tr>
<td>5</td>
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</tr>
<tr>
<td>6</td>
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<tr>
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</tr>
<tr>
<td>8</td>
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</tr>
<tr>
<td>9</td>
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</tr>
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<tr>
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</tr>
<tr>
<td>17</td>
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</tr>
<tr>
<td>18</td>
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</tr>
<tr>
<td>19</td>
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</tr>
</tbody>
</table>

When we switched to an electron-richer ligand (JohnPhos), using the same conditions, the reaction was completed in only 15 min.
We also investigated the influence of the concentration of acid activator on the rate of hydroamination. We found a linear relationship between these two parameters (Figure 7).

![Relative rate of hydroamination vs. concentration of HCTf₃](image)

Figure 7. Relative rate of hydroamination vs. concentration of HCTf₃ (related rates are based on rate of reaction using 0.1% acid).

This data suggest that the rate-determining stage of hydroamination is actually the protodeauration step, which is consistent with our earlier studies.⁶⁷

A polymer-based strong acid (Nafion), and a strong acid cation-exchange resin (Dowex 50WX8) did not activate L-Au-Pht in the hydroamination reaction (e.g., see table 15, entry 19). These results suggested that protodeauration is an intermolecular process because there was no acid present in the solution phase under the reaction conditions, and the polymer-attached acid cannot help in the protodeauration step because of steric constraints (Scheme 21).

![Scheme 21. Effect of polymer-based acid activation on hydroamination.](image)
3.3. Scope of gold phthalimide and acid approach

To assess the generality of our approach, we screened other common gold-catalyzed reactions and compared our results with standard silver-based methods. We began by investigating the most common type of gold-catalyzed reaction, namely the X-H (X = O, N, C) addition to C-C unsaturated compounds (alkyne/allene/alkene) (Scheme 22). First, we examined the addition of X-H to alkenes and allenes, which in general is more challenging than the addition to alkynes. Indeed, the addition of a basic alkyl amine to an alkene (Scheme 22a) is a very demanding reaction in gold catalysis not only because the basic amine binds strongly to cationic gold but also because the basic amine may inhibit protodeauration by quenching any acid present in the system. Hartwig and co-workers have used cationic rhodium complexes (2.5% loading) of a biaryldialkylphosphine (DavePhos) to catalyze this reaction. Not surprisingly, a commonly used gold catalytic system, PPh$_3$PAu/AgOTf, gives very low conversion (5%) even at high catalyst loading (Scheme 22a). Instead, our Ph$_3$P-Au-Pht/HCTf$_3$ system gives very good yields under the same conditions (Scheme 22a) using a much lower loading (0.5%), and a simple Ph$_3$P ligand. Our L-Au-Pht/acid system also showed good reactivity in the intermolecular hydroamination of allene (Scheme 22b) whereas the silver-based system is less efficient. Lafolle and Gandon reported the use of Cu(OTf)$_2$ to activate L-AuCl directly in the intramolecular C-H addition of alkene (Scheme 22c); our L-Au-Pht/ HCTf$_3$ also worked well in this reaction.

Next, we turned our attention to the X-H addition to alkynes and chose the hydration of alkynes, a typical gold-catalyzed reaction. Ph$_3$PAuCl/AgOTf was not efficient at relatively low temperature and catalyst loading, but our Ph$_3$P-Au-Pht/HCTf$_3$ performed
nicely (Scheme 22d). Nolan and coworkers\textsuperscript{118} have reported a high turnover number in the [(NHC)Au\textsuperscript{I}]-catalyzed alkyne hydration, albeit high temperatures were needed to complete this reaction. We found that the IPr-Au-Cl/AgSbF\textsubscript{6} system was slow at lower temperature (60\textdegree C), but our IPr-Au-Pht/HCTf\textsubscript{3} system was capable of completing the reaction in less than 45 min (Scheme 22b). A similar outcome took place in the gold-catalyzed cyclization of homopropargylic diols (Scheme 22e).\textsuperscript{119,120} For example, Ph\textsubscript{3}PAuCl/AgOTf was able to complete the reaction in less than 0.5h using a relatively high loading (2%), but at low loading (0.1%) only trace amounts of product were observed after 5h. In contrast, our Ph\textsubscript{3}P-Au-Pht/HCTf\textsubscript{3} furnished the product in high yield after only 1 h, under the same conditions. Furthermore, our L-Au-Pht/HCTf\textsubscript{3} system worked well in the C-H addition to alkynes (Scheme 22f),\textsuperscript{121} whereas the silver-based system only gave trace amounts of product under the same conditions.

Having obtained positive results in the X-H (X = O, N, C) addition to C-C unsaturated compounds, we proceeded to examine a wider range of gold-catalyzed reactions (Scheme 23). In the gold-catalyzed cycloisomerization of 1,6-enyne, the silver-based system catalyzed a fast conversion to product using a relatively high loading (2%), but at a lower loading (0.2%), the reaction was sluggish (Scheme 23a). However, our Ph\textsubscript{3}P-Au-Pht/HCTf\textsubscript{3} system was very efficient even at 0.02% catalyst loading. A similar result occurred during the cycloisomerization of propargyl amide: the Ph\textsubscript{3}PAuCl/AgOTf system was very slow at low catalyst loadings whereas our Ph\textsubscript{3}P-Au-Pht/HCTf\textsubscript{3} system was able to finish the reaction in less than 3 h with the same gold catalyst loading.
Ph₃PAuCl (5%) / AgOTf (10%) / 6h
Ph₃P-Au-Pht (5%) / HCTf₃ (10%) / 5h 95%
Ph₃P-Au-Pht (0.5%) / HCTf₃ (1%) / 12h 95%

Ph₃PAuCl (5%) / AgOTf (10%) / 19h trace
Ph₃P-AuNTf₂ (5%) / 19h 45%
Ph₃P-Au-Pht (5%) / HCTf₃ (10%) / 19h 59%

SegPhos(Au-Cl)₂ (5%) / Cu(OTf)₂ (10%) 110°C / 24h 96%
Johnphos-Au-Pht (2.5%) / HCTf₃ (5%) 100°C / 5h 96%

n-C₆H₁₃-H
Ph₃PAuCl (1%) / AgOTf (2%) / rt / 19h 0%
Ph₃P-Au-Pht (1%) / HCTf₃ (2%) / rt / 19h 82%
IPrAuCl (0.1%) / AgSbF₅ (0.2%) / 45min / 65°C 10%
IPr-Au-Pht (0.1%) / HCTf₃ (0.2%) / 45 min / 65°C 100%

Ph₃PAuCl (0.1%) / AgOTf (0.2%) / 5h trace
Ph₃P-Au-Pht (0.1%) / HCTf₃ (0.2%) / 1h 94%

Ph₃PAuCl (5%) / AgOTf (5%) / rt / 17h trace
Ph₃P-Au-Pht (2.5%) / HCTf₃ (5%) / rt / 17h 52%
JohnPhos-Au-Pht (2.5%) / HCTf₃ (5%) / 65°C / 45 h 92%
Scheme 22. Addition of X-H (X=O,N,C) to alkyne/allene/alkene.

We also tested the carbene transfer reaction recently reported by Zhang and coworkers (Scheme 23c),\textsuperscript{122} in this reaction the authors used L-Au-NTf\textsubscript{2} (5\% loading, L = Ph\textsubscript{3}P or BrettPhos, prepared from L-Au-Cl and AgNTf\textsubscript{2}). Our system worked equally well but needed only a 10-fold lower catalyst loading (0.5\%). In our study, the only reaction in which our silver-free method and the conventional silver-based method worked equally well at low loading and relative low temperature was in the cycloisomerization of allenone (Scheme 23d), first reported by Hashmi and coworkers.\textsuperscript{123-125}
In the above examples, the activation of \textbf{L-Au-Pht} needed relatively strong acids but, in some reactions, the starting material or the product may not withstand the presence of strong Brønsted acids or Lewis acids. An added feature of our approach is that it allows us to either reduce the amount of acid activator or use a weaker acid instead. This flexibility is another advantage of our method as there are a large number of commercially available Brønsted acids or Lewis acids to choose from. For example, the addition of a carboxylic acid to an alkyne could produce a useful intermediate—a functionalized vinyl acetate (Scheme 24a)\textsuperscript{126}—but a silver-based cationic gold generation protocol produces a mixture of double bond migration products and the hydrolysis by-product, 2-octanone (Scheme 24a). Using our silver-free method to generate cationic gold, the weak carboxylic acid in the starting material is able to activate the \textbf{L-Au-Pht} pre-catalyst. In this manner, we obtained the vinyl ester exclusively, without any double bond migration. The same approach was used successfully in the intramolecular version of the reaction (Scheme 24b), leaving the terminal double bond untouched.

Although in most of the aforementioned reactions we used 2 equiv (vs. gold catalyst) of acid activator, we can reduce the amount of acid activator further (e.g., 0.9 equiv vs gold) and foster even milder conditions. For example, in the gold(I)-catalyzed isomerization of allenyl carbinol ester to 1,3-butadien-2-ol ester,\textsuperscript{68} the resulting product is hydrolyzed by the trace water present in the system when 2 equiv (vs. gold catalyst) of acid activator was used. But we can overcome this problem by simply using less than 1 equiv of acid activator or by choosing a milder Lewis acid (Scheme 24c).
3.4. Summary and future direction

In summary, the Brønsted acid- or Lewis acid-activation of imido gold precatalyst (L-Au-Pht) is a superior way to generate cationic gold, compared to a silver-based activator. Our silver-free system led to higher reactivity and, in most cases, higher turnover number in a large variety of gold-catalyzed reactions. Since large number of chiral Brønsted acids and Lewis acids are available, our method may be even applicable in asymmetrical synthesis, through the combination of L-Au-Pht and chiral Brønsted- or Lewis acids.
3.5. Experimental

Synthesis of starting materials


\[
\begin{align*}
\text{L-Au-Cl} & \quad \text{acetone} \\
\text{K-N} & \quad \text{L-Au-Pht} \\
\text{O-N} & \quad + \text{KCl}
\end{align*}
\]

A mixture of Ph\textsubscript{3}PAuCl (0.1 mmol, 49 mg) and potassium phthalimide (0.15 mmol, 27 mg) was dissolved in acetone (1 mL). The suspension was stirred at 45°C for 3 h. Then the reaction mixture was filtered and washed with small amount of acetone. Then most of the acetone in the filtrate was evaporated under vacuum and the residue was further washed by water. The white solid obtained was dried under vacuum to give gold(I) phthalimide complex in quantitatively yield.

General procedure for Synthesis of L-Au-Sac.

\[
\begin{align*}
\text{L-Au-Cl} & \quad \text{sodium saccharin} \\
\text{AgOTf} & \quad \text{L-Au-Sac} \\
\text{acetone} & \quad + \text{AgCl}
\end{align*}
\]

A mixture of Ph\textsubscript{3}PAuCl (0.1 mmol, 49 mg), silver triflate (0.15 mmol, 38mg) and saccharin sodium salt (0.15 mmol, 31 mg) was dissolved in acetone (1 mL). The suspension was stirred at 45°C for 3 h. Then the reaction mixture was filtered and washed with small amount of acetone. Then most of the acetone in the filtrate was evaporated under vacuum and the residue was further washed by water. The white solid obtained was dried under vacuum to give gold(I) saccharin complex.
**Ph$_3$P-Au-Pht.** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40-7.76 (m, 19 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.4, 136.2 (d, $J = 4$ Hz), 134.3 (d, $J = 15$ Hz), 132.5, 131.8 (d, $J = 8$ Hz), 129.2 (d, $J = 12$ Hz), 128.6, 121.9; $^{31}$P NMR (162 MHz, CDCl$_3$): $\delta$ 32.69. ESI-HRMS (ESI+): m/z calcd. for C$_{26}$H$_{20}$AuNO$_2$P (M$^+$ + H) 606.0897, found 606.0895.

**Johnphos-Au-Pht.** $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.88 (t, $J = 8$ Hz, 1H), 7.62-7.68 (m, 2H), 7.53-7.57 (m, 2H), 7.44-7.50 (m, 2 H), 7.24-7.29 (m, 3 H), 7.11-7.16 (m, 2 H), 6.85 (t, $J = 8$ Hz, 1 H), 1.45 (d, $J = 16$ Hz, 18 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 177.9, 150.2 (d, $J = 6$ Hz), 142.4 (d, $J = 6$ Hz), 136.7 (d, $J = 3$ Hz), 133.6 (d, $J = 3$ Hz), 133.0 (d, $J = 6$ Hz), 132.0, 130.4 (d, $J = 2$ Hz), 128.9, 128.5, 127.0, 126.6 (d, $J = 6$ Hz), 126.0 (d, $J = 45$ Hz), 121.4, 37.8 (d, $J = 25$ Hz, 2 C), 30.9 (d, $J = 6$ Hz, 6 C); $^{31}$P NMR (162 MHz, CDCl$_3$): $\delta$ 58.18. ESI-HRMS (ESI+): m/z calcd. for C$_{28}$H$_{32}$AuNO$_2$P (M$^+$ + H ) 642.1830, found 642.1833.
**IPr-Au-Pht**. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.43-7.54 (m, 4 H), 7.35-7.43 (m, 2 H), 7.24-7.33 (m, 4 H), 7.17-7.23 (m, 2 H), 2.6 (m, 4 H), 1.43 (d, $J = 8$ Hz, 12 H), 1.24 (d, $J = 8$ Hz, 12 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.1, 177.3, 145.7, 136.3, 133.9, 131.7, 130.6, 124.2, 123.0, 121.3, 28.9, 24.4, 24.1. ESI-HRMS (ESI+): m/z calcd. for C$_{35}$H$_{41}$AuN$_3$O$_2$ (M + H) 732.2864, found 732.2862.

**DalPhos-Au-Pht**. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.77-7.84 (m, 1 H), 7.68-7.74 (m, 1 H), 7.52-7.62 (m, 4 H), 7.29-7.36 (m, 1 H), 7.23-7.26 (m, 1 H), 4.39 (t, $J = 12$ Hz, 2 H), 3.77 (d, $J = 12$ Hz, 2 H), 3.01 (t, $J = 8$ Hz, 2 H), 2.72 (d, $J = 8$ Hz, 2 H), 2.13-2.34 (m, 12 H), 1.97-2.04 (m, 6 H), 1.63-1.77 (m, 12 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.6, 159.3 (d, $J = 7$ Hz), 136.6, 135.4, 132.5, 132.1, 126.9 (d, $J = 5$ Hz), 124.9 (d, $J = 6$ Hz), 122.8 (d, $J = 46$ Hz), 121.7, 66.7, 54.6, 42.3 (d, $J = 2$ Hz), 36.4, 28.6 (d, $J = 9$ Hz); $^{31}$P NMR (162 MHz, CDCl$_3$): $\delta$ 51.32. ESI-HRMS (ESI+): m/z calcd. for C$_{38}$H$_{47}$AuN$_2$O$_3$P (M$^+$ + H$^+$) 807.2984, found 807.2991.
Ph₃P-Au-Sac. ¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, J = 8 Hz, 1 H), 7.85 (d, J = 8 Hz, 1 H), 7.65-7.76 (m, 2 H), 7.44-7.63 (m, 15 H); ¹³C NMR (100 MHz, CDCl₃): δ 166.2, 141.9, 134.3 (d, J = 14 Hz), 133.2 (d, J = 11 Hz), 132.1, 131.6, 129.4 (d, J = 12 Hz), 128.2 (d, J = 63 Hz), 124.4, 120.5; ³¹P NMR (162 MHz, CDCl₃): δ 32.35. ESI-HRMS (ESI+): m/z calcd. for C₂₅H₂₀AuNO₃PS (M⁺ + H) 642.0562, found 642.0564.

JohnPhos-Au-Sac. ¹H NMR (400 MHz, CDCl₃): δ 7.83-7.91 (m, 2 H), 7.76-7.80 9 (m, 1 H), 7.61-7.70 (m, 2 H), 7.46-7.55 (m, 2 H), 7.40-7.46 (m, 2 H), 7.29-7.34 (m, 1 H), 7.10-7.19 (m, 3 H), 1.45 (d, J = 16 Hz, 18 H); ¹³C NMR (100 MHz, CDCl₃): δ 165.4, 150.3 (d, J = 13 Hz), 142.3, 141.7 (d, J = 6 Hz), 133.4 (d, J = 3 Hz), 133.0 (d, J = 7 Hz), 132.7, 132.1, 130.6 (d, J = 2 Hz), 129.2, 128.7, 127.7, 126.7 (d, J = 7 Hz), 125.0 (d, J = 47 Hz), 123.9, 120.2, 38.1 (d, J = 26 Hz, 2 C), 31.0 (d, J = 6 Hz, 6 C); ³¹P NMR (162 MHz, CDCl₃): δ 57.92. ESI-HRMS (ESI+): m/z calcd. for C₂₇H₃₂AuNO₃PS (M⁺ + H) 678.1501, found 678.1503.

**General procedures for model reactions**
**General Procedure for the Gold-Catalyzed Hydroamination of Aniline with Phenylacetylene.** To a mixture of aniline (9 mmol, 0.838 g), phenylacetylene (10.8 mmol, 1.103 g), and activator (0.2%, 0.018 mmol) was added L-Au-Pht (0.1%, 0.009 mmol), and resultant mixture was stirred at 55 °C. An aliquot (ca. 3 μL) from reaction mixture was dissolved in CDCl₃ (0.5 mL) and was analyzed by ¹H-NMR to monitor the progress of the reaction. Because at the initial period of reaction (< 20% conversion), the kinetic curve appeared to be linear, we used linear least squares fit of the data to determine relative initial reaction rate.

![Graph showing the reaction progress over time](image)

Ph₃PAu-Pht/HCTf₃

Ph₃PAu-Pht/HNTf₂

Ph₃PAu-Pht/HOTf

Ph₃PAuCl/AgOTf

![Diagram showing the reaction](image)

Ph₃PAuCl (5%) / AgOTf (10%) / 6h  5%

Ph₃P-Au-Pht (5%)/ HCTf₃ (10%) / 6h  89%
General Procedure for the Gold-Catalyzed Intramolecular Hydroamination of Aminoalkene. To a stirred solution of aminoalkene (0.25 mmol, 63 mg) in 0.2 mL d$_8$-toluene, acid activator (10 mol%, 0.025 mmol) and Ph$_3$P-Au-Pht (5%, 0.0125 mmol) were added. The reaction mixture was stirred at 80 °C and the progress of reaction was monitored by $^1$H NMR.

![Chemical structure](image1)

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<th>Catalyst</th>
<th>Reaction Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph$_3$PAuCl (5%) / AgOTf (10%)</td>
<td>19h</td>
<td>trace</td>
</tr>
<tr>
<td>Ph$_3$PAuNTf$_2$ / 19h</td>
<td></td>
<td>45%</td>
</tr>
<tr>
<td>Ph$_3$P-Au-Pht (5%) / HCTf$_3$ (10%)</td>
<td>19h</td>
<td>59%</td>
</tr>
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</table>

General Procedure for the Gold-Catalyzed hydroamination of Carbazate to Allene. Allene (0.04 mmol, 10 mg), Methyl carbazate (0.04 mmol, 3.7mg) and Ph$_3$PAuNTf$_2$ (5 mol%, 1.5mg) were added into NMR tube with 0.5 mL CDCl$_3$ as solvent. The reactions were conducted at 40 °C and the progress of reaction was monitored by $^1$H NMR.

![Chemical structure](image2)

<table>
<thead>
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<th>Catalyst</th>
<th>Reaction Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>SegPhos(Au-Cl)$_2$ (5%) / Cu(OTf)$_2$ (10%)</td>
<td>110°C / 24h</td>
<td>96%</td>
</tr>
<tr>
<td>Johnphos-Au-Pht (2.5%) / HCTf$_3$ (5%)</td>
<td>100°C / 5h</td>
<td>96%</td>
</tr>
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</table>

General Procedure for the Gold-Catalyzed hydroalkylation of olefin. To a stirred solution of ene-β-ketoamide (0.25 mmol, 67.8 mg) in 0.5 mL d$_8$-toluene, 70% HCTf$_3$ (7.4 mg, 1.25 × 10$^{-2}$ mmol) and Johnphos-Au-Pht (4.1 mg, 6.25 × 10$^{-3}$ mmol) were added, the reaction was conducted at 100 °C and monitored by $^1$H NMR.
General Procedure for the Gold-Catalyzed Hydration. To a stirred solution of 1-octyne (2 mmol, 220 mg) and acid activator (2%, 0.04 mmol) in a mixed solvent (MeOH / water = 4:1) was added L-Au-Pht (1%, 0.02 mmol). The reaction mixture was stirred at room temperature and monitored by $^1$H NMR.

General Procedure for the Gold-Catalyzed Cycloisomerization of 2-Alkynyl-1,5-diols. Standard stock solution (0.01 M) of L-Au-Pht were made by weighing the gold complex into a vial using CDCl$_3$ as solvent. Standard stock solutions (0.02 M) of AgOTf and HCTf$_3$ were also prepared using acetone as solvent. The model reaction was conducted in a NMR tube. 10 µL (10$^{-4}$ mmol) of AgOTf or HCTf$_3$ stock solution were added to a NMR tube and the solvent was removed by vacuum. Then diol (0.1 mmol, 22.4 mg) in 0.4 mL CDCl$_3$, and corresponding L-Au-Pht stock solution (10 µL) were
added to the NMR tube. The reactions were conducted at room temperature and monitored by $^1$H NMR.

**General Procedure for the Gold-Catalyzed Nakamura Reaction.** Acetyl acetone (0.2 mmol, 20 mg), phenylacetylene (0.4 mmol, 40.9 mg), 70% HCTf$_3$ (0.01 mmol, 5.9 mg) and L-Au-Pht ($5 \times 10^{-3}$ mmol) were added into a NMR tube with 0.5 mL CDCl$_3$ as solvent. The reactions were conducted at room temperature and monitored by $^1$H NMR.

**General Procedure for the Gold-Catalyzed Cycloisomerization of 1,6-enyne.** Standard stock solutions (0.01 M) of catalyst were made by weighing the gold complex into a vial and adding CDCl$_3$ as solvent. AgOTf and HCTf$_3$ were also made solutions (0.02 M) in acetone. The model reaction was conducted in a NMR tube. 40 µL ($10^{-4}$ mmol) of AgOTf and HCTf$_3$ solution were added to different NMR tubes and solvent was removed by high vacuum. 1,6-enyne (0.1 mmol, 21.0 mg) in 0.4 mL CDCl$_3$ and
corresponding L-Au-Pht solutions (20 μL) were added to NMR tube. The reactions were conducted at room temperature and monitored by 1H NMR.

General Procedure for the Gold-Catalyzed cycloisomerization of propargyl amide. Standard stock solutions (0.01 M) of L-Au-Pht were made by weighing the gold complex into a vial and adding CDCl₃ as solvent. AgOTf and HCTf₃ were also made solutions (0.05 M) in acetone. The model reaction was conducted in a NMR tube. 40 μL (10⁻⁴ mmol) of AgOTf and HCTf₃ solution were added to different NMR tubes and solvent was removed by high vacuum. Propargyl amide (0.1 mmol, 15.9mg) in 0.35 mL CDCl₃ and corresponding L-Au-Pht solutions (1×10⁻³ mmol, 0.1 mL) were added to NMR tube. The reactions were conducted at room temperature and monitored by 1H NMR.

General Procedure for the Gold-Catalyzed carbene transfer reaction. 1-octyne (0.3 mmol, 33.6 mg), 8-Methylquinoline N-oxide (0.39 mmol, 62.1mg), 70% HCTf₃ (3× 10⁻³ mmol, 1.8 mg) and JohnPhos-Au-Pht (1.5 × 10⁻³ mmol, 0.9 mg) were added into a small
vial with 0.5 mL acetonitrile as solvent. The reactions were conducted at 60°C and monitored by $^1$H NMR.

![Chemical Structure](image)

\[ \text{Ph}_3\text{PAuCl} (0.02\%) / \text{AgOTf} (0.04\%) / 0.5\text{h} \quad 95\% \\
\text{Ph}_3\text{P-Au-Pht} (0.02\%) / \text{HCTf}_3 (0.04\%) / 0.5\text{h} \quad 95\% \]

**General Procedure for the Gold-Catalyzed cycloisomerization of allenone.** Standard stock solution (0.001 M) of L-Au-Pht were made by weighing the gold complex into a vial and adding CDCl$_3$ as solvent. AgOTf and HCTf$_3$ were also made solutions (0.002 M) in acetone. The model reaction was conducted in a NMR tube. 10 μL ($2 \times 10^{-5}$ mmol) of AgOTf and HCTf$_3$ solution were added to different NMR tubes and solvent was removed by high vacuum. Allenyl ester (0.05 mmol, 11.7 mg) in 0.4 mL CDCl$_3$ and corresponding L-Au-Pht solutions ($1 \times 10^{-5}$ mmol, 10 μL) were added to NMR tube. The reactions were conducted at room temperature and monitored by $^1$H NMR.

![Chemical Structure](image)

\[ \text{JohnPhos-Au-CI/AgOTf} (1\%) / 12\text{h} \quad 3\% \quad + \quad \text{mixtures of Z/E isomers of double bonds migrated products and hydrolyzed ketone} \]

\[ \text{Johnphos-Au-Pht} (1\%) / 18\text{h} \quad 96\% \quad \text{(single product)} \]

\[ \text{Johnphos-Au-Pht} (0.2\%) / 48\text{h} \quad 92\% \quad \text{(single product)} \]

**General Procedure for the Gold-Catalyzed addition of carbonic acid to alkyne.** 1-octyne (1.2 mmol, 132.2 mg), benzoic acid (1 mmol, 122.1 mg), and JohnPhos-Au-Pht
(0.01 mmol, 6.4mg) were added into a small vial with 0.5 mL d8-toluene as solvent. The reactions were conducted at 60°C monitored by 1H NMR.

General Procedure for the Gold-Catalyzed intramolecular addition of carbonic acid to alkyne. 4-Pentynoic acid (0.45mmol, 44.1mg) and Ph3P-Au-Pht (9 × 10^{-4} mmol, 90 µL) were added into NMR tube with 0.5 mL CDCl3 as solvent. The reactions were conducted at room temperature and monitored by 1H NMR.

General Procedure for the Gold-Catalyzed isomerization of allenyl carbinol ester to 1,3-butadien-2-ol esters. Standard stock solutions (0.01 M) of L-Au-Pht were made by weighing the gold complex into a vial and adding CDCl3 as solvent. HCTf3 was also made solutions (0.05 M) in acetone. The model reaction was conducted in a NMR tube. 30 µL of HCTf3 solution (1.5 × 10^{-5} mmol, 4.4 mg) was added to NMR tubes and solvent was removed by high vacuum. Allenyl ester (0.05 mmol, 12.5 mg) in 0.4 mL CDCl3 and corresponding L-Au-Pht solution (1×10^{-3} mmol, 100 µL) were added to NMR tube. The reactions were conducted at room temperature and monitored by 1H NMR.

NMR spectra for gold complexes
REFERENCES


(28) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. Stereoselective Synthesis of β-Oxygenated α-Hydroxyphosphonates by Lewis Acid-Mediated Stereoselective

(29) Basle, O.; Li, C.-J. Copper-catalyzed aerobic phosphonation of sp3 C-H bonds. Chemical Communications (Cambridge, United Kingdom) 2009, 4124-4126.


(44) Bhagat, S.; Chakraborti, A. K. An Extremely Efficient Three-Component Reaction of Aldehydes/Ketones, Amines, and Phosphites (Kabachnik–Fields Reaction) for


(53) DFT optimizations were performed with Gaussian 09, Revision C.01, Frisch, M. J. et al. Wallingford CT, 2009. Full computational details and references are provided in the Supporting Information.


(60) www.britannica.com/EBchecked/topic/478746/promoter


(64) Ivanova, S. M.; Nolan, B. G.; Kobayashi, Y.; Miller, S. M.; Anderson, O. P.; Strauss, S. H. Relative Lewis Basicities of Six \(\text{Al(ORF)}_4^-\) Superweak Anions and the Structures of \(\text{LiAl(OCH(CF}_3)_2}4^-\) and \(1\text{-Et-3-Me-1,3-C}_3\text{H}_3\text{N}_2\text{}[\text{Li(ORF)}_2][\text{Li(ORF)}_2]\). *Chem. Eur. J.* 2001, 7, 503-510.


(116) AgCTf3 is available from Sigma-Aldrich (catalog No. L511854).


APPENDIX

LIST OF ABBREVIATIONS

CI: Chemical Ionization
DCM: Dichloromethane
DIBALH: Diisobutylaluminium hydride
DME: 1,2-Dimethoxyethane
DMSO: Dimethylsulfonyl Oxide
DNBA: 2,4-Dinitrobenzoic acid
dr: diastereomeric ratio
ee: Enantiomeric excess
EI: Electrospray Ionization
EPR: Electron paramagnetic resonance
EtOAc: Ethyl Acetate
GC: Gas Liquid Chromatography
h: Hour
HMPA: Hexamethylphosphoramide
HOAc: Acetic acid
HOMO: Highest occupied molecular orbital
HPLC: High performance liquid chromatography
HRMS: High resolution mass spectroscopy
Hz: Hertz
IR: infrared
LDA: Lithium diisopropylamide
LUMO: Lowest unoccupied molecular orbital
M: Molar
m: meta
mg: milligram
min: minute
mL: milliliter
mmol: millimole
MsOH: Methanesulfonic acid
mT: millitorr
NaHMDS: Sodium-Hexamethyldisilazane
NBO: Natural bond orbital
NBS: N-Bromosuccinimide
NCS: N-Chlorosuccinimide
NMR: Nuclear magnetic resonance spectroscopy
o: ortho
p: para
ppm: Parts per million
PTSA: p-Toluene sulfonic acid
TBS: tert-Butyldimethylsilyl
tert: tertiary
TES: Triethylsilyl
TIPS: Triisopropylsilyl
TMS: Trimethylsilyl
TfOH: Trifluoromethanesulfonic acid
THF: Tetrahydrofuran
TLC: Thin layer chromatography

Gaussian 03, Revision C.02 at the HF/6-311++g level of theory. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V.
Title: Highly Efficient Cu(I)-Catalyzed Synthesis of N-Heterocycles through a Cyclization-Triggered Addition of Alkynes

Author: Junbin Han, Bo Xu, and Gerald B. Hammond

Publication: Journal of the American Chemical Society

Publisher: American Chemical Society

Date: Jan 1, 2010

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CURRICULUM VITAE

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Education
08/2004 - 05/2008 ShanXi University, Taiyuan, China Applied Chemistry B.S.
Advisor: Professor Zhao Zhang
08/2008 - Present University of Louisville. Louisville, KY Organic Chemistry PhD
Advisor: Professor Gerald B. Hammond, Endowed Chair in Organic Chemistry

Research experience and Publication

1. “Improved, Highly Efficient, and Green Synthesis of Bromofluorenones and Nitrofluorenones in Water”

2. “Sustainable Recycling of Benzoic Acid Production Waste: Green and Highly Efficient Methods To Separate and Recover High Value-Added Conjugated Aromatic Compounds from Industrial Residues”

3. N-heterocycles through cyclization-triggered tandem additions. We developed a strategy to access biologically important N-heterocycles of different ring sizes (e.g., 5-7) and different substitution patterns (e.g., cyclic amino acids)

4. “Highly Efficient Cu(I)-Catalyzed Synthesis of N-Heterocycles through a Cyclization-Triggered Addition of Alkynes”

5. “Synthesis of α-CN and α-CF3 N-Heterocycles through Tandem Nucleophilic Additions”

6. “Synthetic Evolutions in the Nucleophilic Addition to Alkynes.”

6. “Synthesis of Cyclic α-Aminophosphonates through Copper-Catalyzed Enamine Activation”


7. “Synthesis of Substituted Pyrrolidines and Pyrroles via Tandem Amination/Cyanation/Alkylation or Amination/Oxidation Sequences”


Explore counter ion and additive effect on reaction rate and yield. We find a mechanism independent approach to improve kinetic of ionic chemical reactions in general through use of simple ionic additives. (Physical organic chemistry, kinetic of ionic organic reactions). We also explored other factor of counter ion that could influence the reactivity of catalytic system, such as hydrogen bonding.

8. “Broadly Applicable Reaction Promoter for Cationic Metal Catalysis”


9. Han, J.; Xu, B.; Hammond, G. B. (Manuscript to be submitted)

We found a novel strong Brønsted acid. Compare with previous applied strong acids, the new generation have much higher reactivity toward carbon-carbon bond forming reactions, such as hosomi-sakurai reaction. We also explored other applications of this novel strong Brønsted acid. We developed a silver-free gold(I) catalytic system, which can be activated by the Brønsted acid Lewis acid during reaction. This system showed higher activity than tradition used combination of gold catalysts and silver salts (AgOTf anf AgNTf$_2$). We also applied this strategy to other cationic transition metal catalyzed reactions.

10. Brønsted Acids or Lewis Acids Assisted Activation of Imido-Gold Precatalyst


We developed a novel silver reagent AgCTf$_3$, which greatly increased the activity of many reactions. AgCTf$_3$ is now sold by Sigma-Aldrich (Silver tris(trifluoromethanesulfonyl) methide, catalog no. L511854).


**Patents**


Presentation in National Conferences


Award

- 2013-2014 Sponsored Research Tuition Award, School of Interdisciplinary and Graduate Studies, University of Louisville

Skills

- 8 year experience in synthesis, additive and counter ions effect on catalytic system, methodology, reaction kinetic measurement, fluorine compound, glove box for air-sensitive experiments, recycling technique for industrial residue and reagent development with several papers in major academic journals as the first author.
- Solid understanding and hands-on experience with all modern analytical equipment such as HPLC, GC-MS, LC-MS, IR, UV-Vis, NMR, FT-ICRMS.
- Excellent communication and organization skills.
- Great ability to function well within multidisciplinary teams