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

Junbin Han
University of Louisville

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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

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

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A Dissertation Approved on

April 15, 2014

by the following Dissertation Committee:

_____
Dr. Gerald B. Hammond
Dissertation Director

_____
Dr. Frederick A. Luzzio

_____
Dr. Muriel C. Maurer

_____
Dr. Jinjun Liu

_____
Dr. Jian Du‑Caines

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ABSTRACT

SYNTHESIS OF N-HETEROCYCLES THROUGH CYCLIZATION-TRIGGERED
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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 $KCTf_3$ is an ideal promoter that is readily available and able to tolerate harsh reaction conditions. When $KCTf_3$ is added to reaction system, a reshuffling of ions occurs and a 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-Pht**) 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.[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.[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.
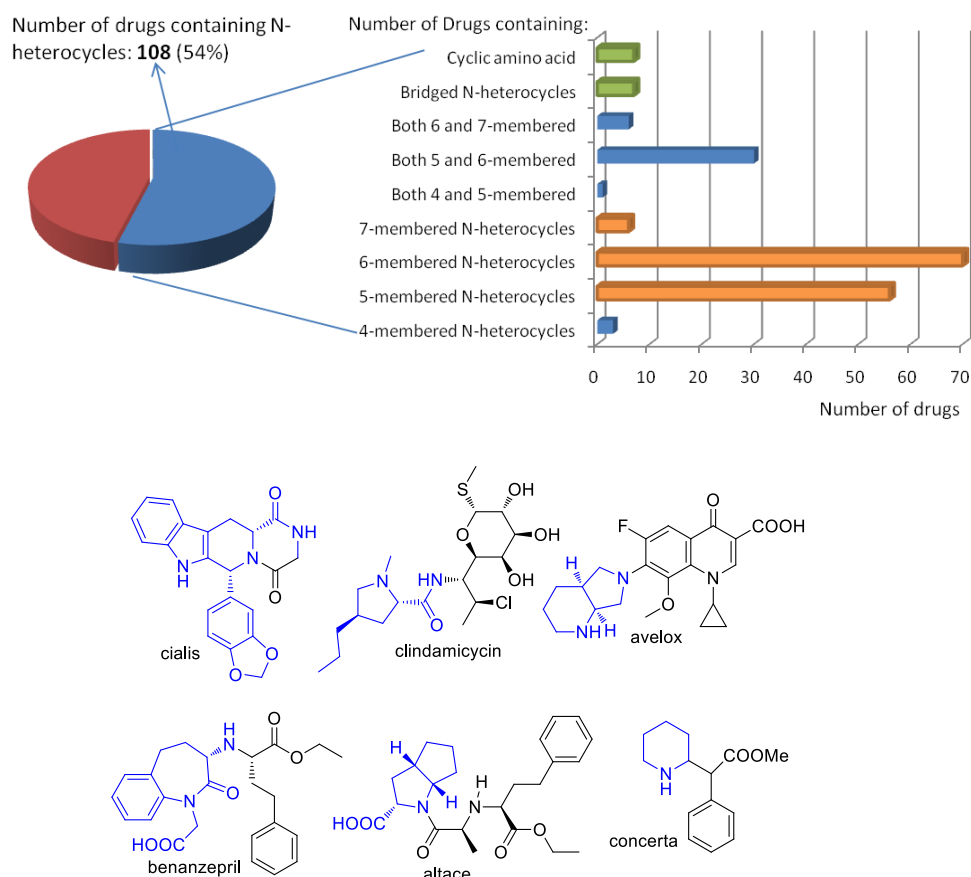
Figure 1. Analysis of the top 200 selling brand-name drugs by retail dollars in 2007 (Based on the data compiled by Prof. Njardarson-University of Arizona).

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).[7] Another common example is the use of an *in situ* generated imine in a Mannich type reaction (Scheme 1, b).[8] 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.[9]
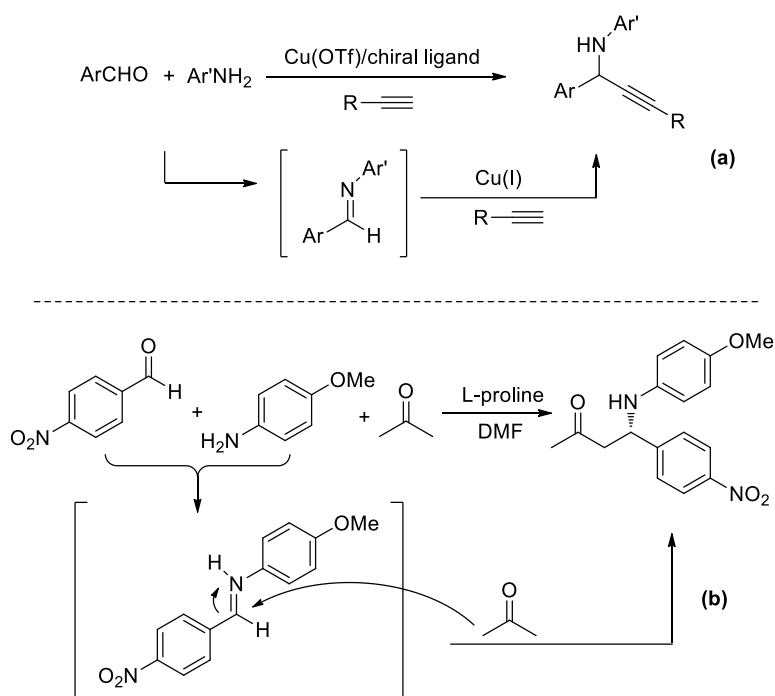
Scheme 1. Addition of terminal alkynes to imines and Mannich reaction.

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).
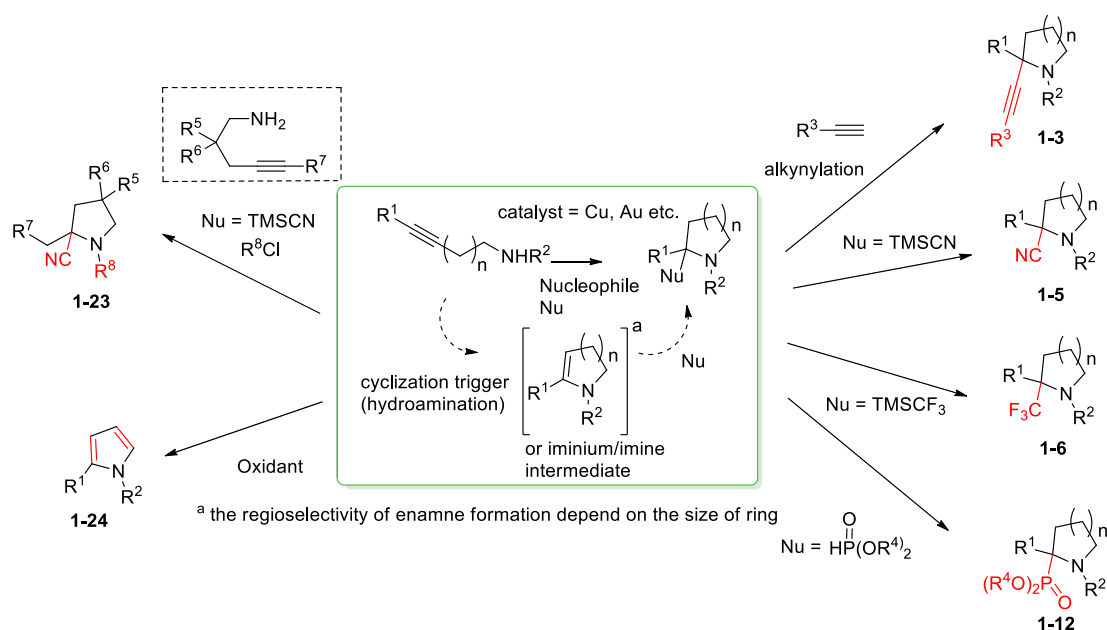
Scheme 2. Cyclization-triggered tandem addition.

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.[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 α-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).[15] Che and coworkers have reported a gold(I) catalyzed tandem synthesis of pyrrolo[1,2-a]quinolines (Scheme 3-b);[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.[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.
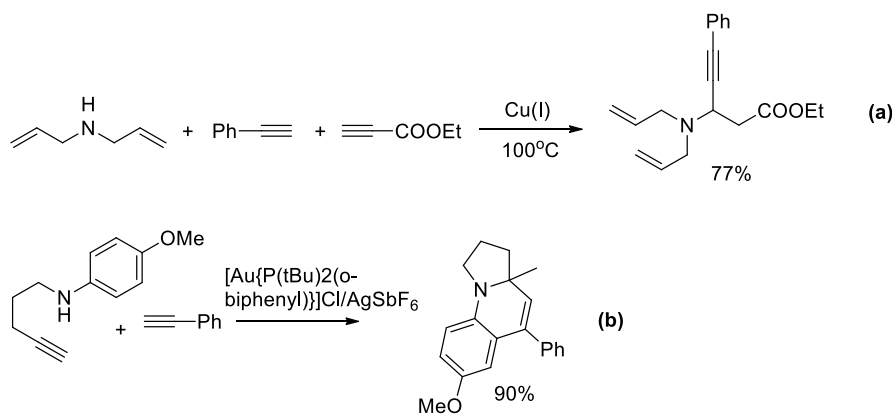
Scheme 3. Double additions of amine and terminal alkyne to alkynes.

1.2. Tandem amination/alkynylations

Our first application of cyclization-triggered tandem additions strategy was tandem amination/alknylations. 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-R^3), which can then interact with R^1 or R^2 and spur further transformations (e.g., cycloisomerization).
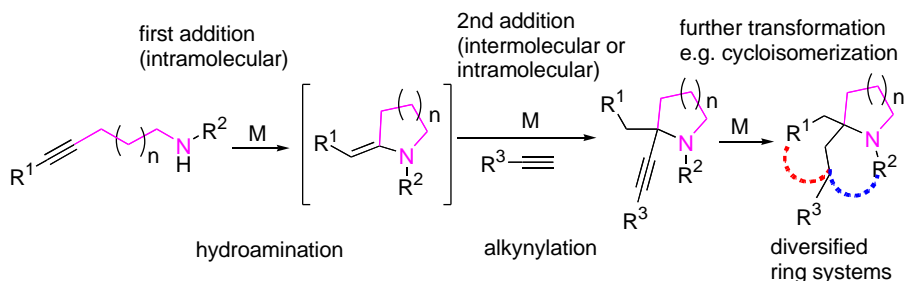
Scheme 4. Cyclization-triggered alkynylation.

1.2.1. Screening of conditions

The reaction of aminoalkyne **1-1a**—readily prepared from an alkynyl 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/alkynlation.

entry[a]	catalyst	1b/ equiv	solvent	temp/time	yield%
1	AuCl	4	dioxane	MW[b]/100°C/0.5h	15
2	Cu(OTf)$_2$	4	dioxane	MW/100°C/0.5h	50
3	PdCl$_2$	4	dioxane	MW/100°C/0.5h	15
4	AgNO$_3$	4	dioxane	MW/100°C/0.5h	42
5	CuI	4	dioxane	MW/100°C/0.5h	95
6	CuBr	4	dioxane	MW100°C/0.5h	99
7	CuBr	4	dioxane	MW/60°C/0.5h	65
8	CuBr	4	dioxane	Heat 100°C/12h	99
9	CuBr	4	Toluene	MW100°C/0.5h	98
10	CuBr	4	CH$_3$CN	MW100°C/0.5h	98
11	CuBr	1.5	dioxane	MW100°C/0.5h	99
12[c]	CuBr	1.5	dioxane	MW100°C/0.5h	99

[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

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chiral induction was observed (*dr* = 1:1.3, 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 **1-1h** didn't give the desired product (Table 2, entry 13). And the reaction of proline derivative **1-1i** gave a fused ring product (Table 2, entry 14). The regioselectivity obeyed Baldwin's rules.[20] The cyclization of 3-yn-amine 1b and **1-1a** gave five-membered ring products through *5-endo-dig* and *5-exo-dig* processes. And the reactions of 5-yn-amine (e.g., **1-1c**) and 6-yn-amine (e.g., **1-1e**) give six-membered and seven-membered rings, through *6-exo-dig* and *7-exo-dig* processes, respectively.

Attempts to form 3- or 4-membered rings under similar conditions, using 1j, were unsuccessful (eq 1). Surprisingly, the reaction of 7-yn-amine 1-1k led to the intermolecular hydroamination/alkynylation product **1-4a** in good yield through a double addition to phenyl acetylene rather than the corresponding eight-membered ring (eq 2). Taking this as cue for a possible intermolecular variant, we reacted an unfunctionalized alkyne **1-1l** with a simple secondary amine, using similar conditions (eq 3). This reaction gave the desired product **1-4b**, albeit in lower chemical yield. We have not yet conducted optimization studies for this intermolecular version.

The cycloisomerization of 1,*n*-enynes and 1,*n*-diynes is currently a highly competitive field in organic synthetic chemistry.[21] Our newly found method provides direct entry to functionalized 1,*n*-enynes, as showcased by the synthesis of 1,6-enyne (3e) in high yield in a single step (Table 2, entry 5). Our reaction is also capable of furnishing fused ring systems, if a cyclic secondary amine is present (Table 2, entry 14).

Table 2. Scope of tandem amination/alkynylation reaction.[a]

entry	1-1	1-2	1-3 (yield %)
1	1-1a	1-2a	1-3a, 99
2	1-1b	1-2a	1-3b, 99
3	1-1c	1-2a	1-3c, 98
4	1-1d	1-2a	1-3d, 95
5	1-1e	1-2a	1-3e, 98
6	1-1f	1-2a	1-3f, 90
7	1-1a	1-2b	1-3g, 95
8	1-1a	1-2c	1-3h, 99
9	1-1a	1-2d	1-3i, 99
10	1-1a	1-2e	1-3j, 95
11	1-1a	1-2f	1-3k, 89

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| 12 | **1-1g** (Ph-CH(CH₃)-NH-CH₂CH₂-C≡C-H) | **1-2a** | **1-3l**, 99 (dr = 1:1.3) |

Entry 12: **1-1g**, **1-2a**, **1-3l**, 99 (*dr* = 1:1.3)

Entry 13: **1-1h**, **1-2a**, **1-3m**, 0

Entry 14: **1-1i**, **1-2a**, **1-3n**, 85 (*dr* = 1:7.8)
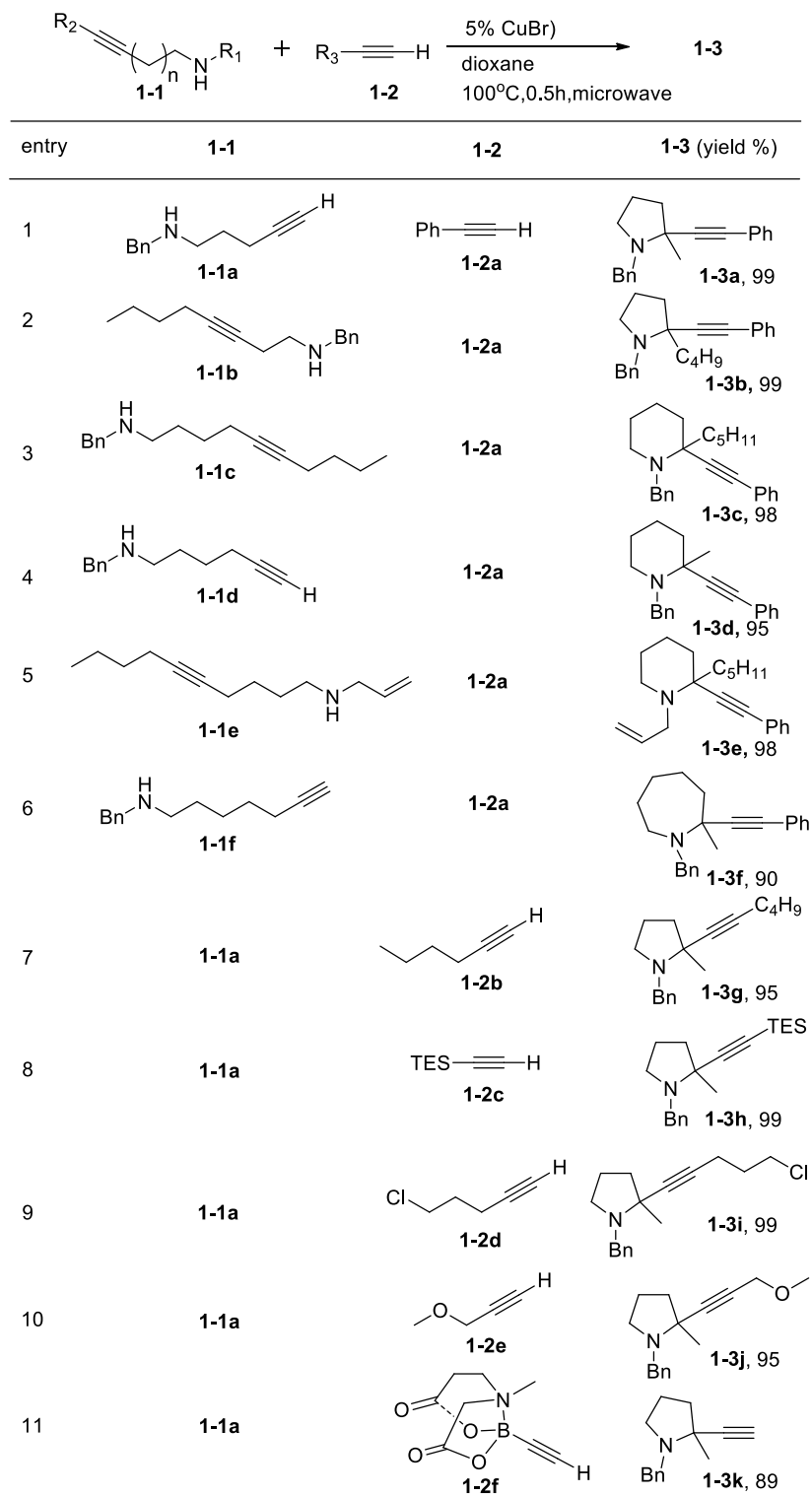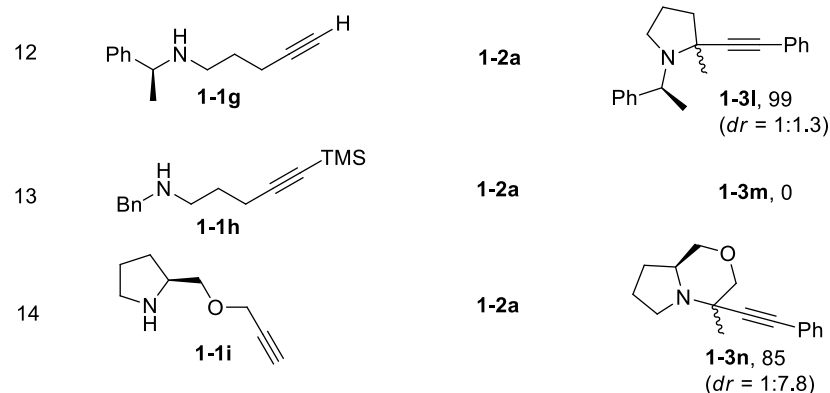
ª **1** (0.5 mmol), **2** (2.0 mmol), 1 mL dioxane.

Ph-N(H)-CH₂-C≡C-CH₃ **1-1j** + **1-2a** → CuBr 5%, microwave, 100 °C/0.5h → complex reaction **eq 1**

1-1k + **1-2a** → CuBr 5%, microwave, 100 °C/0.5h → **1-4a**, 61% **eq 2**

n-C₆H₁₃—≡—H **1-1l** + Et₂NH → CuBr 5%, microwave, 100 °C/0.5h, dioxane → **1-4b**, 25% **eq 3**
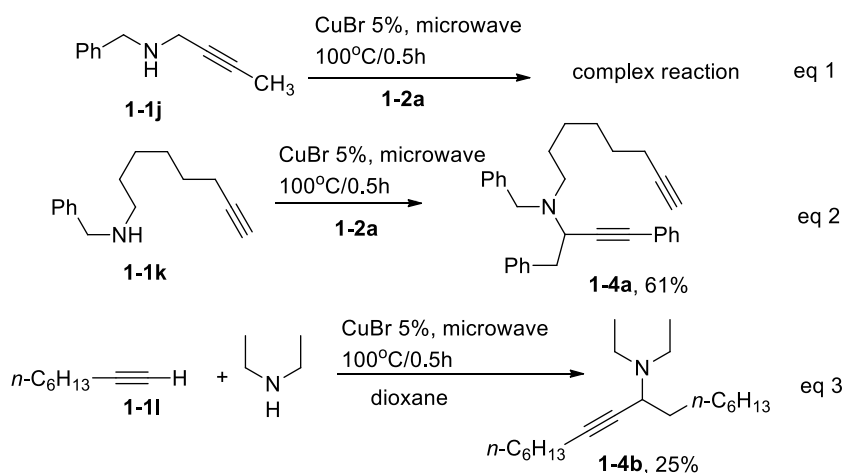
1.2.3. Experimental

¹H, ¹³C, ¹⁹F and ³¹P NMR spectra were recorded at 500, 126, 470 and 162 MHz respectively, using CDCl₃ as a solvent. The chemical shifts are reported in δ (ppm) values relative to (δ 7.26 ppm for ¹H NMR, δ 77.0 ppm for ¹³C NMR and CFCl₃ δ 0.00 ppm for ¹⁹F 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_{254} 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.[22]
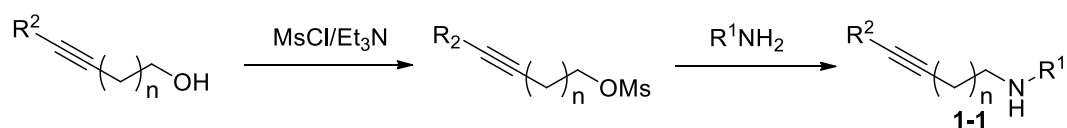
N-Benzyl-4-pentyn-1-amine (1a). 4-pentyn-1-ol (25 mmol, 2.5 g) was dissolved in CH_2Cl_2 100 mL, and the solution was cooled down to -10 °C, then methanesulfonyl chloride (2.15 mL, 28 mmol) and triethylamine (5.5 mL, 40 mmol) are introduced by syringe successively. The mixture is stirred for 30 min at -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 (15ml), 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

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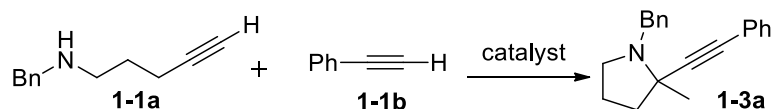
1-benzyl-2-methyl-2-(phenylethynyl)pyrrolidine (1-3a).

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, CDCl₃): δ 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, CDCl₃): δ 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 C₂₀H₂₁N: C, 87.23; H, 7.69. Found: C, 86.96; H, 7.82.
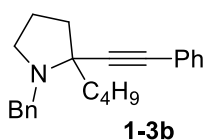
1-benzyl-2-butyl-2-(phenylethynyl)pyrrolidine (1-3b): IR(neat): 2935, 2804, 1597, 1490, 1453, 1137, 755, 692 cm-1; ^{1}HNMR (500 MHz, CDCl$_3$): 1.00(t, J = 7.5 Hz, 3 H), 1.40 - 1.84 (m, 6 H), 1.74 - 2.01 (m, 3 H), 2.20 (t, J = 8.5 Hz, 1 H), 2.52 (q, J = 8.0 Hz, 1 H), 2.96 (td, J = 8.0 Hz, 2 Hz, 1 H), 3.39 (d, J = 13.5Hz, 1 H), 4.08 (d, J = 13.5 Hz, 1 H), 7.22 - 7.55 (m, 10 H); δ ^{13}C NMR (125 MHz, CDCl$_3$): 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 C$_{23}$H$_{27}$N: C, 87.02; H, 8.57. Found: C, 87.07; H, 8.61.

1-3c
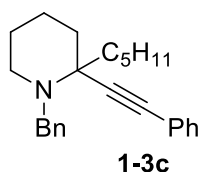
1-benzyl-2-pentyl-2-(phenylethynyl)piperidine (1-3c): IR(neat): 2932, 2858, 2819, 1490, 1444, 737, 691; ^{1}HNMR (500 MHz, CDCl$_3$): 0.96 (t, J = 7 Hz, 3 H), 1.30 - 1.83 (m, 10 H), 1.86 - 2.03 (m, 3 H), 2.17 - 2.24 (m, 1 H), 2.51 - 2.54 (m, 1 H), 2.96 (td, J = 9.0 Hz, 3.0 Hz, 1 H), 3.40 (d, J = 13.5 Hz, 1 H), 4.10 (d, J = 13.5 Hz, 1 H), 7.23 - 7.55 (m, 10H); ^{13}C NMR (125 MHz, CDCl$_3$): 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 C$_{25}$H$_{31}$N: C, 86.90; H, 9.04. Found: C, 86.64; H, 9.13.

1-3d
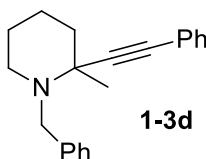
1-benzyl-2-methyl-2-(phenylethynyl)piperidine (1-3d): ^{1}HNMR (500 MHz, CDCl$_3$): 1.42 - 1.52 (m, 2 H), 1.57 (s, 3 H), 1.62-1.79 (m, 3 H), 1.90 (d, J = 9.6 Hz, 2 H), 2.38 (td, J = 9 Hz, 2 Hz, 1 H), 2.62 (d, J = 12 Hz, 1 H), 3.19 (d, J = 13.5 Hz, 1 H), 4.17 (d, J = 13.5 Hz, 1 H), 7.22 - 7.56 (m, 10 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 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.

1-3e
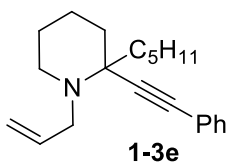
1-allyl-2-pentyl-2-(phenylethynyl)piperidine (1-3e): IR(neat): 2932, 2858, 2808, 1489, 916, 755, 690; 1HNMR (500 MHz, CDCl3): 0.91 (t, J = 7 Hz, 3 H), 1.30 - 1.52 (m, 8 H), 1.58 - 1.68 (m, 1 H), 1.78 - 1.94 (m, 4 H), 2.12 - 2.20 (m, 1 H), 2.46-2.50 (m, 1 H), 2.93 (dd, J = 13.5 Hz, 8Hz, 1 H), 3.15 (td, 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); 13C 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.

1-3f
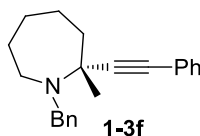
1-benzyl-2-methyl-2-(phenylethynyl)azepane (3f): IR(neat): 3430, 2970, 1489, 1140, 754, 691, 538; ^{1}HNMR (500 MHz, CDCl$_3$): δ 1.40-1.54 (m, 3 H), 1.54-1.57 (s, 3 H),

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, 9.5Hz, 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$_3$): δ 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.
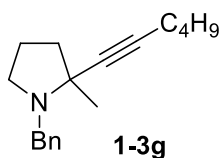
1-benzyl-2-(hex-1-yn-1-yl)-2-methylpyrrolidine (1-3g): IR(neat): 2966, 2805, 1455, 1240, 1143, 736, 698; ^{1}HNMR (500 MHz, CDCl$_3$): δ 0.96 (t, J = 7.5 Hz, 3 H), 1.42 (s, 3 H), 1.44 - 1.86 (m, 7 H), 2.04 - 2.11 (m, 1 H), 2.27 (t, J = 7.5 Hz, 2 H), 2.49 (dd, J = 13 Hz, 8 Hz, 1 H), 2.85 (td, J = 7.5 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$_3$): δ 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.
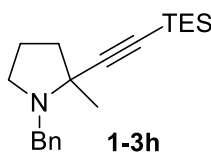
1-benzyl-2-methyl-2-((triethylsilyl)ethynyl)pyrrolidine (1-3h): IR(neat): 2955, 2152, 1456, 1234, 1017, 860, 733; ^{1}HNMR (500 MHz, CDCl$_3$): δ 0.65 (q, J = 7.5 Hz, 6 H),

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.
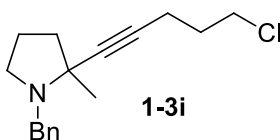
1-benzyl-2-(5-chloropent-1-yn-1-yl)-2-methylpyrrolidine (1-3i): IR(neat): 2969, 2804,

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.
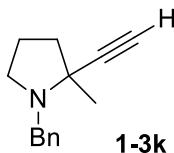
1-benzyl-2-ethynyl-2-methylpyrrolidine (1-3k): IR(neat): 3296, 2972, 2807, 1455,

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, CDCl$_3$): 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 C$_{14}$H$_{17}$N: C,84.37; H, 8.60. Found: C, 84.72; H, 8.60.
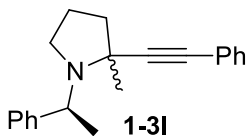
2-methyl-1-((S)-1-phenylethyl)-2-(phenylethynyl)pyrrolidine (1-3l) was obtained as a mixture of two diastereoisomers in ratio of 1:1.3. IR(neat): 2970, 2817, 1489, 1453, 1141, 755, 701; ^{1}HNMR (500 MHz, CDCl$_3$): major isomer: δ 1.02 (s, 3 H), 1.52 (t, *J* = 6 Hz, 3 H), 1.66 - 1.96 (m, 2 H), 1.97 - 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 C$_{21}$H$_{23}$NCl: C, 87.15; H, 8.01. Found: C, 86.91; H, 8.10.
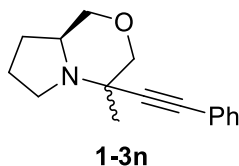
(8aS)-4-methyl-4-(phenylethynyl)hexahydro-1H-pyrrolo[2,1-c][1,4]oxazine **(1-3n)** was obtained as a mixture of two diastereoisomers in ratio of 1:1.3. ^{1}HNMR (500 MHz, CDCl$_3$): major isomer: δ 1.34-1.36 (m, 1 H), 1.37 (s, 3 H), 1.72-1.84 (m, 3 H), 2.50 -2.55 (m, 1 H), 2.70-2.73 (m, 1 H), 3.09 (td, *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); ^{13}C NMR (125 MHz, CDCl$_3$): 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.

1-4a
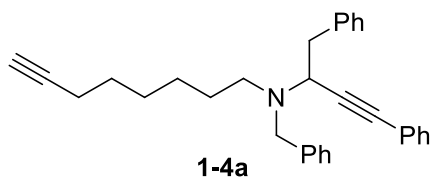
N-benzyl-N-(1,4-diphenylbut-3-yn-2-yl)oct-7-yn-1-amine (1-4a): ^{1}HNMR (500 MHz, CDCl$_3$): δ 1.10-1.33 (m, 3 H), 1.34-1.46 (m, 4 H), 1.85 (t, J = 3.5 Hz, 1 H), 2.07 (td, J = 9 Hz, 3 Hz, 2 H), 2.41 - 2.60 (m, 2 H), 2.94 (d, J = 7.5 Hz, 1 H), 2.43 (d, J = 14.5 Hz, 1 H), 3.80 (t, J = 7.2 Hz, 1 H), 3.87 (d, J = 14.5 Hz, 1 H), 7.18-7.45 (m, 15 H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 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

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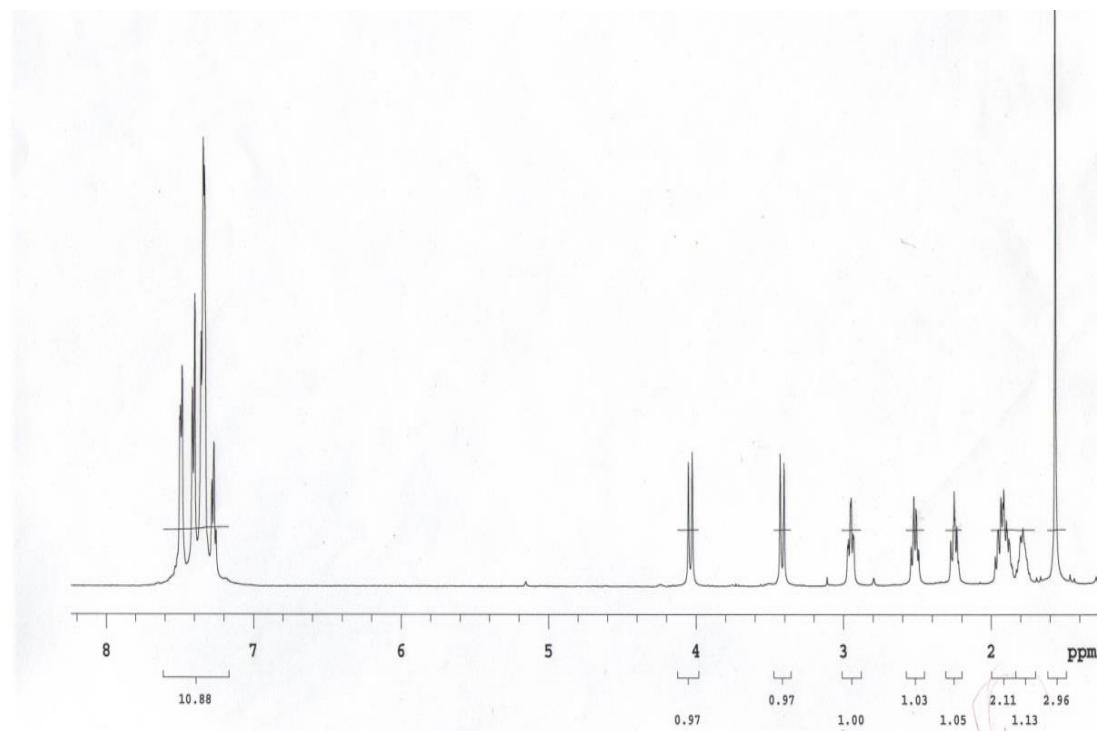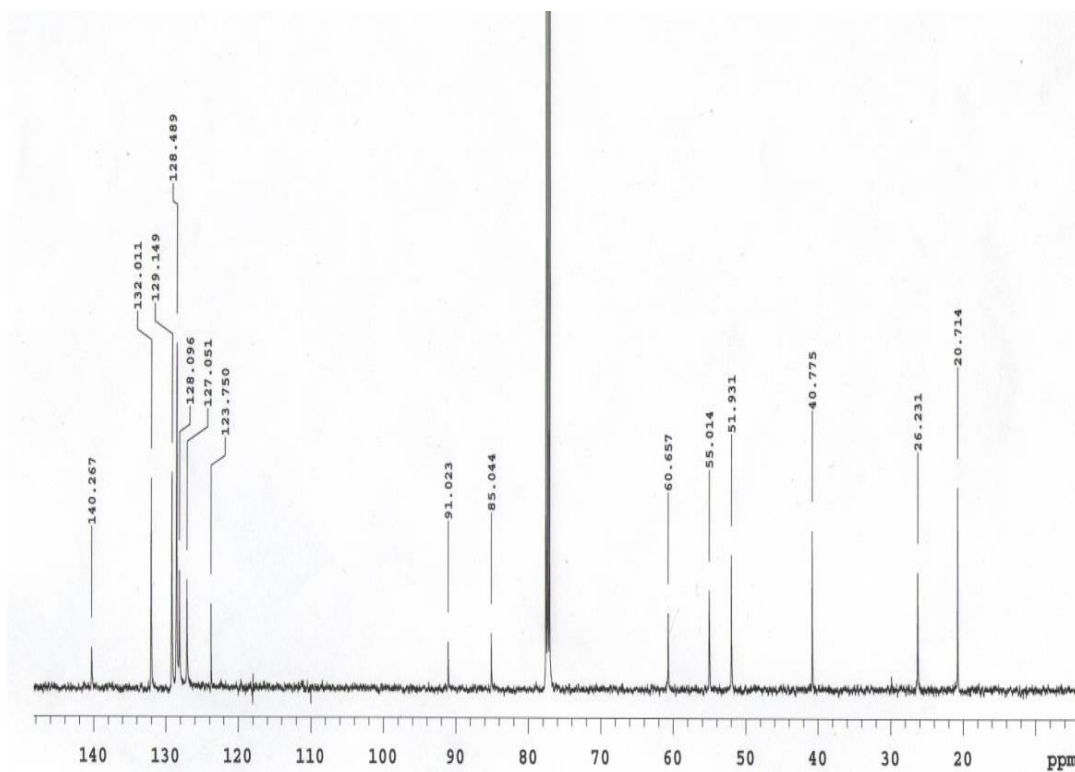
1.3. Tandem amination/cyanation

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/cynation

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[8]--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.
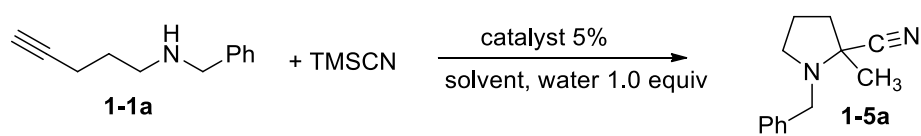
entry	catalyst	solvent	temp, time	yield %
1	CuBr	dioxane	rt, 12 h	30
2	CuBr	dioxane	mw[a], 100 °C, 0.5 h	95
3	IPrAuCl/ AgOTf	dioxane	mw[a], 100 °C, 0.5 h	90
4	CuBr	dioxane	100 °C, 12 h	92
5	CuBr	toluene	mw[a], 100 °C, 0.5 h	90
6[b]	CuBr	dioxane	mw[a], 100 °C, 0.5 h	82

[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 **1-5m** 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 **1-5n** (Table 4, entries 3 and 4).

Table 4. Screening for the best conditions for a tandem amination/cyanation using less basic aminoalkynes.
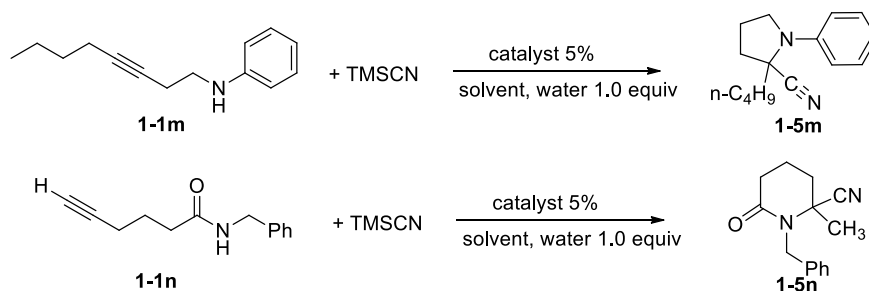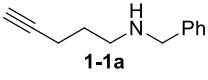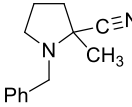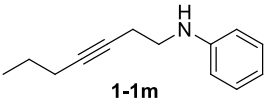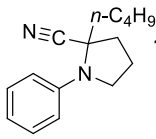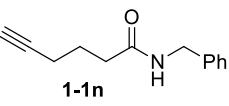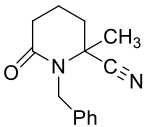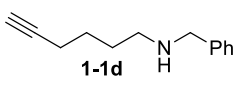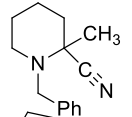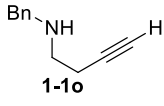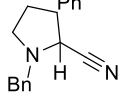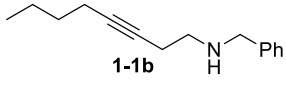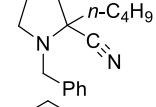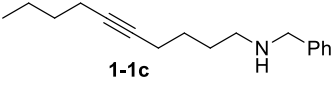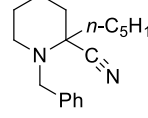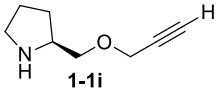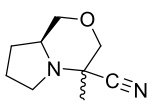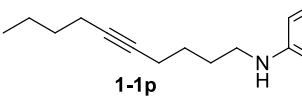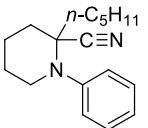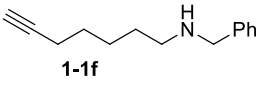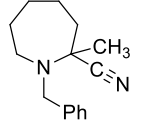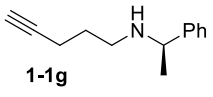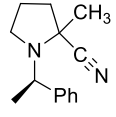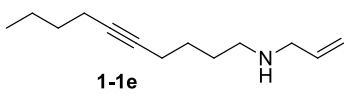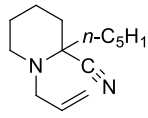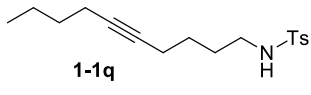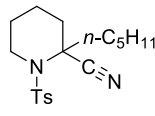
entry	1-1	catalyst	Temp	time	yield%
1	**1-1m**	CuBr	mw, 100 ºC, 40 min		0ª
2	**1-1m**	IPrAuCl/AgOTf	mw, 100 ºC, 40 min		81
3	**1-1n**	CuBr	mw, 100 ºC, 40 min		0
4	**1-1n**	IPrAuCl/AgOTf	mw, 100 ºC, 40 min		99

a   was isolated as major product (80%)
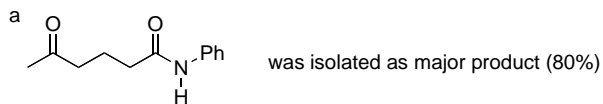
1.3.2.   Scope of the tandem amination/cyanation sequence

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

Table 5. Scope of tandem amination/cyanation process.

$$\text{1-1} + \text{TMS-CN (4 equiv)} \xrightarrow[\text{100 °C, 0.5 h, microwave}]{\text{5% catalyst, 1.0 equiv water, dioxane}} \text{1-5}$$

entry	1-1	catalyst	1-5 (yield %)[a]
1	1-1a	CuBr	1-5a, 95
2	1-1m	iPr-AuCl/AgOTf	1-5m, 81
3	1-1n	iPr-AuCl/AgOTf	1-5n, 99
4	1-1d	CuBr	1-5d, 96
5	1-1o	CuBr	1-5o, 92
6	1-1b	CuBr	1-5b, 95
7	1-1c	CuBr	1-5c, 95
8	1-1i	CuBr	1-5i, 81 dr = 6:1
9	1-1p	iPr-AuCl/AgOTf	1-5p, 80
10	1-1f	CuBr	1-5f, 15
11	1-1g	CuBr	5g, 95 dr = 1:2
12	1-1e	CuBr	1-5e, 80
13	1-1q	iPr-Au/AgOTf	1-5q, 66

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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
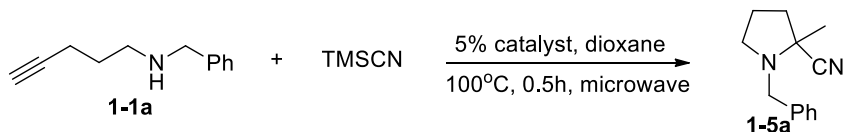
1-1a

5% catalyst, dioxane
100°C, 0.5h, microwave

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 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, 700cm-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, 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).
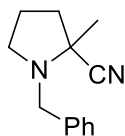
IR (neat): 2978, 2943, 2810, 2216, 1455, 1369, 1159, 740, 700cm-1; ^{1}H NMR (400 MHz,

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, CDCl$_3$): 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 C$_{13}$H$_{16}$N$_2$(M$^+$-CN) 174.1282, found 174.1277.

1-benzyl-2-methylpyrrolidine-2-carbonitrile (1-5m).
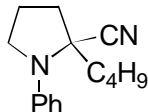
IR (neat): 2957, 2870, 2223, 1709, 1600, 1342, 1190, 996, 749 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.83 (t, J = 7.2 Hz, 3 H), 1.18-1.32 (m, 3 H), 1.39-1.60 (m, 2 H), 1.94-2.16 (m, 3 H), 2.22-2.31 (m, 1 H), 2.47-2.54 (m, 1 H), 3.33-3.40 (m, 1 H), 3.50 (q, J = 14.8 Hz, 7.2 Hz, 1 H), 6.75-6.85 (m, 3 H), 7.17-7.25 (m, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$): d 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 C$_{13}$H$_{16}$N$_2$ (M$^+$-CN) 202.1596, found 202.1588.

1-benzyl-2-methyl-6-oxopiperidine-2-carbonitrile (1-5n).
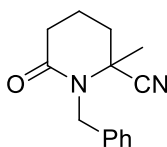
IR (neat): 2919, 1652, 1393, 1289, 731, 699cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.50 (s, 3 H), 1.77-2.15 (m, 3 H), 2.28-2.33 (m, 1 H), 2.45-2.51 (m, 1 H), 2.59-2.69 (m, 1 H), 4.27 (d, J = 16 Hz, 1 H), 5.26 (d, J=16Hz, 1 H), 7.19-7.29 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$): d 18.1, 27.8, 32.0, 36.8, 47.8, 57.4, 120.5, 126.9, 127.2, 128.6, 138.0, 170.1; HRMS (ESI+): m/z calcd. for C$_{14}$H$_{16}$N$_2$O(M$^+$- CN) 202.1232, found 202.1155.

1-benzyl-2-methylpiperidine-2-carbonitrile (1-5d)
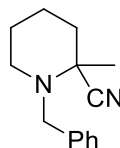
IR (neat): 2942, 2805, 1451, 1377, 1124, 737, 699 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.45 (s, 3 H), 1.42-1.61 (m, 3 H), 1.80 (d, J = 10 Hz, 1 H), 2.04-2.11(m, 1 H), 2.60 (d, J

= 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$_3$): δ 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-benzylpyrrolidine-2-carbonitrile (1-5o)
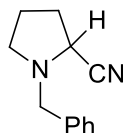
IR (neat):2906, 2 870, 1494, 1453, 1125, 744, 700 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ

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$_3$): δ 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-butylpyrrolidine-2-carbonitrile (1-5b).
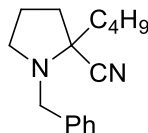
IR (neat):2957, 2871, 1690, 1454, 734, 700 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.87 (t,

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$_3$): δ 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-pentylpiperidine-2-carbonitrile (1-5c).
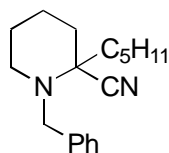
IR (neat):2929, 2859, 1690, 1455, 1363, 1145, 737, 700cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.92 (t, J=6Hz, 3 H), 1.28-1.60 (m, 7H), 1.75-2.04 (m, 4 H), 2.26-2.33 (m, 1 H), 2.42 (dd, J = 18 Hz, 9.2Hz, 1 H), 2.94 (td, J = 8.4 Hz, 1.2Hz, 1 H), 3.35 (d, J = 12.8 Hz, 1 H), 4.06 (d, J = 12.8 Hz, 1 H), 7.22-7.39 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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)
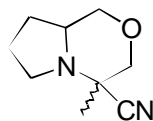
IR (neat): 2900, 2830, 1730, 1600, 1423, 1210, 925, 730 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$), major isomer: δ 1.30 (s, 3H), 1.52-1.79 (m, 4 H), 2.31 (dd, J = 16.8 Hz, 8 Hz, 1 H), 2.45-2.49 (m, 1 H), 3.02-3.17 (m, 3 H), 3.81 (d, J = 11.6 Hz, 1 H) 3.97 (dd, J = 10.8 Hz, 3.2 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$): ^{13}C NMR (100 MHz, CDCl$_3$), major isomer: δ 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)
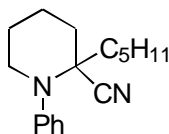
IR (neat): 2956, 2859, 1705, 1342, 1191, 750, 695cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ0.79 (t, J=6.4Hz, 3 H), 1.16-1.36 (m, 7 H), 1.42-1.59 (m, 2 H),1.94-2.17 (m, 3 H), 2.21-2.28 (m, 1 H), 2.47-2.53 (m, 1 H), 3.33-3.38 (m, 1 H), 3.46-3.52 (m, 1 H), 6.76 (t,

J=7.2Hz, 1 H), 6.80-6.84 (m, 2 H), 7.17-7.23 (m, 2 H); ^{13}C NMR (100 MHz, CDCl₃):

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).
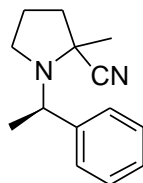
IR (neat): 2942, 2805, 1451, 1377, 1124, 737, 699cm^{-1}; ^{1}H NMR (400 MHz, CDCl₃),

major isomer: δ 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); ^{13}C 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+) (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).
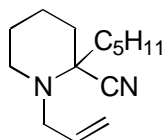
IR (neat): 2955, 2859, 1643, 1452, 1161, 993, 921cm^{-1}; ^{1}H NMR (400 MHz, CDCl₃): δ

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); ^{13}C NMR (100 MHz, CDCl₃): δ 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.

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Deuterium experiments ^{1}H NMR spectra for compound 1-5a

^{1}H and ^{13}C NMR spectra of compound 1-5d

Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Operator: JunbinH
File: Carbon_01
VNMRS-400 "ulnmr400"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
64 repetitions
OBSERVE C13, 100.5222010 MHz
DECOUPLE H1, 399.7718181 MHz
Power 40 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 16 min, 41 sec

138.610 128.476 128.349 127.136 119.867 77.304 76.992 76.672 65.793 54.513 51.633 36.491 36.215 26.684 22.822 20.121 13.915

220 200 180 160 140 120 100 80 60 40 20 0 ppm

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[23-25] whose synthesis usually requires multisteps.[10-11] Simply by reacting our *in situ* generated enamine intermediate with a nucleophilic CF_3 source, our protocol would lead to a one-step synthesis of a CF_3-containing N-heterocycle. We used the reaction of aminoalkyne **1-1b** and TMS-CF_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_3 is a rather inert reagent unless a suitable

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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). CuF_2 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.
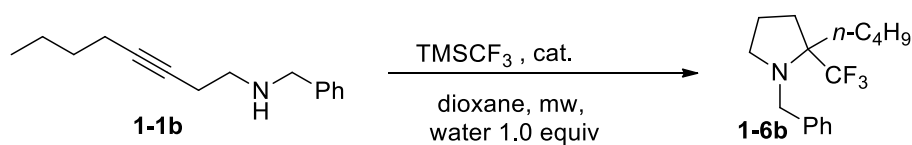
entry[a]	catalyst	temp °C	time	yield %
1	CuBr (5%)	100	40 min	0
2	CuBr (5%)/CsF (1.0 equiv)	100	40 min	0
3	IPrAuCl, AgF (1.0 equiv)	100	40 min	80
4	CuBr(5%)/AgF(2.0 equiv)	100	40 min	82
5	CuF₂ (2.0 equiv)	100	40 min	15
6	AgF (2.0 equiv)	100	40 min	90
7	AgF (0.2 equiv)	100	40 min	40
8	AgF (1.0 equiv)	100	40 min	70
9	AgF (1.5 equiv)	100	40 min	91
10	AgF (4.0 equiv)	100	40 min	82
11	AgF (1.5 equiv)	120	40 min	82
12	AgF (1.5 equiv)	rt	6 h	88
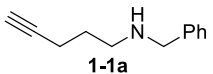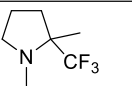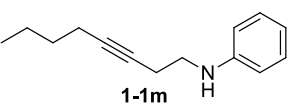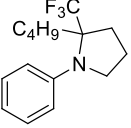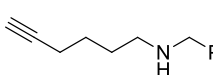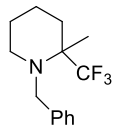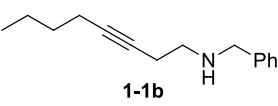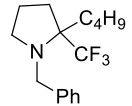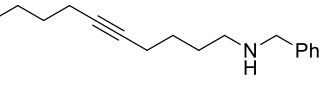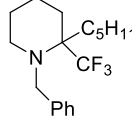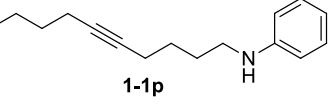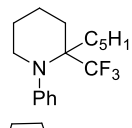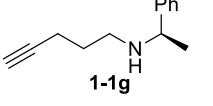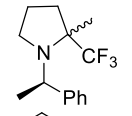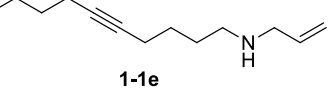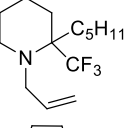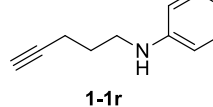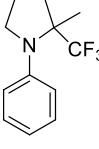
mw = microwave; iPrAuCl = Chloro[1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene]gold(I).

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.

$$1\text{-}1 \quad + \quad TMSCF_3 \quad \xrightarrow[\text{dioxane, 40 min, mw,100 }^{o}\text{C}]{\text{1.5 equiv AgF, H}_2\text{O 1 equiv}} \quad 1\text{-}6$$

entry	1-1	1-6 (yield %)
1	1-1a	1-6a, 92%
2	1-1m	1-6m, 90%
3	1-1d	1-6d, 88%
4	1-1b	1-6b, 91%
5	1-1c	1-6c, 92%
6	1-1p	1-6p, 89%
7	1-1g	1-6g, 90% dr = 77:23
8	1-1e	1-6e, 87%
9	1-1r	1-6r, 95%

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_3CN as solvent because of its better dissolving properties toward the silver salt). Five minutes into the reaction we observed a peak ascribed to CF_3Ag in ^{19}F NMR (δ -25.5, d, $J^2_{F\text{-}Ag}$ = 94 Hz),[12] together with a signal corresponding to CF_3H in ^{19}F NMR (δ -79.9, d, $J^2_{F\text{-}H}$ = 79 Hz) and ^{1}H NMR (δ 6.70, d, $J^2_{F\text{-}H}$ = 79 Hz). The formation of CF_3H can be explained by protodemetalation of the CF_3Ag intermediate. Thus, it is highly likely that CF_3Ag 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.
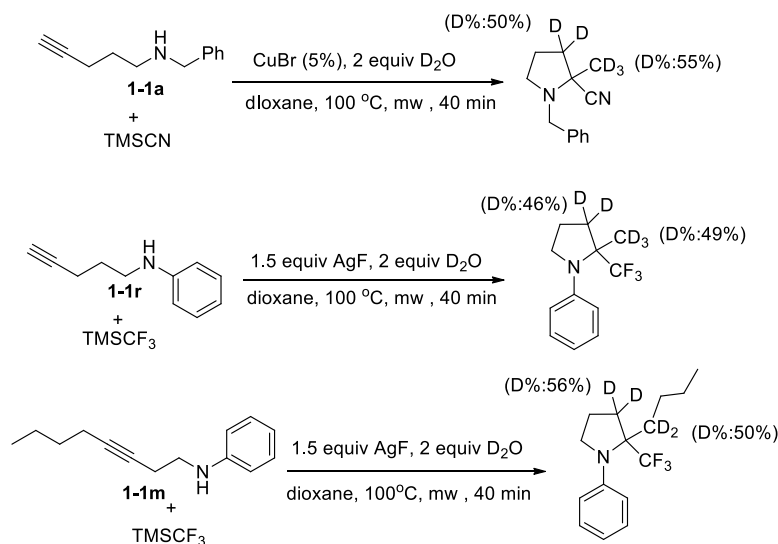
Scheme 5. Deuterium experiments on amination/cyanation and

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**.
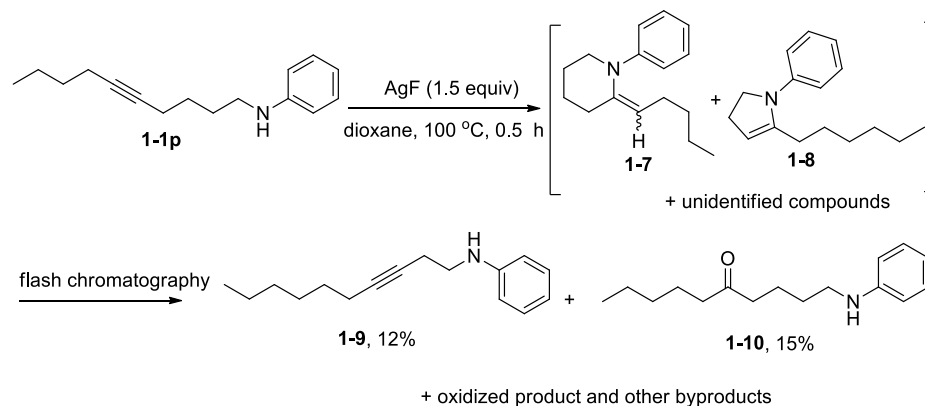
Scheme 6. Reaction of 1p in the absence of a second attacking nucleophile

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.
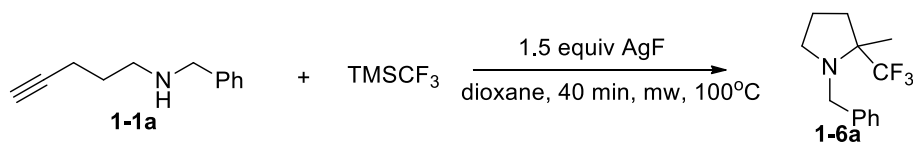
1-Benzyl-2-methyl-2-(trifluoromethyl)pyrrolidine (**1-1a**). N-Benzyl-4-pentyn-1-amine 1a (43 mg, 0.25 mmol), trifluoromethyltrimethyl silane (71 mg, 0.5 mmol), dioxane (1 mL) and water (4.5 mg, 1.0 equiv) were charged into a microwave tube reactor, and AgF (48 mg, 1.5 equiv) was added to the mixture 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, 690cm^{-1}; 1H NMR (400 MHz, CDCl$_3$): 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); ^{13}C NMR (100

MHz, CDCl$_3$): δ 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$_3$): major isomer: δ -77.87; HRMS (ESI+): m/z calcd. for C$_{13}$H$_{16}$F$_3$N (M$^+$- H) 242.1157, found 242.1153.

1-benzyl-2-methyl-2-(trifluoromethyl)pyrrolidine (1-6a).
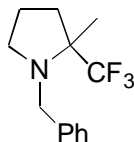
IR (neat): 2946, 2843, 1460, 1470, 1144, 763, 690 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.07 (s, 3 H), 1.28-1.38 (m, 3 H). 1.98-2.12 (m, 3 H), 2.23-2.32 (m, 3 H), 2.58 (t, J = 6.4 Hz, 1 H), 3.35 (d, J = 13.6 Hz, 1 H), 3.71 (d, J = 13.6 Hz, 1 H), 6.98-7.05 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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$_3$): major isomer: δ -77.87; HRMS (ESI+): m/z calcd. for C$_{13}$H$_{16}$F$_3$N (M$^+$-H) 242.1157, found 242.1153.

2-butyl-1-phenyl-2-(trifluoromethyl)pyrrolidine (1-6m).
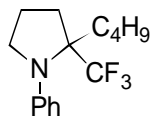
IR (neat): 2960, 2874, 1720, 1601, 1504, 1329, 1151, 751, 694 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.82 (t, J = 6.8 Hz, 3 H), 1.06-1.32 (m, 4 H), 1.73-1.84 (m, 1 H), 1.84-1.96 (m, 1H), 1.98-2.15 (m, 2 H), 2.23-2.39 (m, 2 H), 3.42-3.55 (m, 2 H), 6.79 (t, J=7.6Hz, 1 H), 6.96 (d, J=8.4Hz, 1 H), 7.22 (t, J = 8 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.8, 22.1, 22.7, 24.4, 31.1, 34.8 (d, J=6.4Hz), 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$_3$): major isomer: δ -73.20; HRMS (ESI+): m/z calcd. for C$_{15}$H$_{20}$F$_3$N (M$^+$- H)270.1470, found 270.1465.

1-benzyl-2-methyl-2-(trifluoromethyl)piperidine (1-6d)
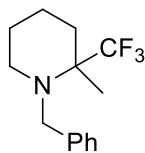
IR (neat): 2943, 2853, 2857, 1454, 1369, 1253, 1139, 725, 697 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.28 (s, 3 H), 1.35-1.59 (m, 5 H), 1.89-1.98 (m, 1 H), 2.26-2.45 (m, 1 H), 2.55-2.64 (m, 1 H), 3.48 (d, J = 14.8 Hz, 1 H), 3.99 (d, J = 14.8 Hz, 1 H), 7.14-7.27 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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: δ -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).
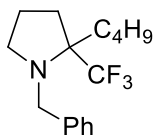
IR (neat): 2958, 2874,1455, 1372, 1286, 1143, 731, 698 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.80 (t, J= 6.4Hz, 3 H), 1.18- 1.36 (m, 4 H), 1.50-1.63 (m, 4 H), 1.75-1.80 (m, 1 H), 1.90-1.96 (m, 1 H), 2.58 (t, J = 6.4 Hz, 1 H), 3.64 (d, J = 14.4 Hz, 1 H), 3.78 (d, J=13.6Hz, 1 H), 7.04-7.18 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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: δ -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)
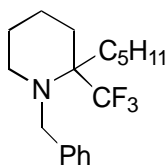
IR (neat): 2955, 2932, 2857, 1453, 1360, 1142, 740, 698 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.91 (t, J = 6 Hz, 3 H), 1.33-1.56 (m, 8 H), 1.64-1.83 (m, 4 H), 1.88-1.98 (m, 1 H), 2.06-2.15 (m, 1 H), 2.74 (t, J = 6.8 Hz, 2 H), 3.81 (d, J=13.6Hz, 1 H), 3.94 (d, J = 13.6 Hz, 1 H), 7.22-7.32 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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: δ -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).
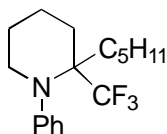
IR (neat): 2957, 2930, 1720, 1560, 1504, 1330, 1152, 751, 695 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.83(t, J = 6.8 Hz, 3 H), 1.06-1.30 (m, 8 H), 1.73-1.83 (m, 1 H), 1.94-2.13 (m, 2 H), 2.23-2.38 (m, 2 H), 3.39-3.53 (m, 2 H), 6.82 (t, J = 7.6 Hz, 1 H), 6.95 (d, J = 8.4 Hz, 2 H), 7.22 (t, J = 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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: δ -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).
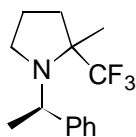
IR (neat): 2981, 2361, 1700, 1456, 1383, 1166, 699cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.23 (s, 3 H), 1.40 (d, J = 6.4 Hz, 3 H), 1.52-1.80 (m, 2 H), 1.79-1.90 (m, 2 H), 2.20-2.29 (m, 2 H), 2.68-2.74 (m, 1 H), 3.10-3.14 (m, 1 H), 3.84-3.87 (m,1 H), 7.09-7.38 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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: δ -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)
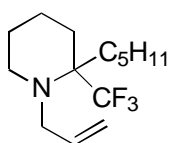
IR (neat): 2957, 2858, 1457, 1144, 918, 699 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.752 (t, J = 6 Hz, 3 H), 1.11-1.22 (m, 6 H), 1.42-1.50 (m, 2 H), 1.52-1.74 (m, 3 H), 1.84-1.92 (m,1 H), 2.64-2.72 (m, 1 H), 2.72-2.80 (m, 1 H), 3.07-3.27 (m, 2 H), 4.90 (d, J = 18 Hz, 1 H), 5.07 (dd, J = 17.2 Hz, 1.6 Hz), 5.59-5.70 (m, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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: δ -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).
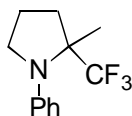
IR (neat): 2984, 2922, 2851, 1601, 1504, 1319, 1154, 751, 695 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.24 (s, 3 H), 1.55-1.60 (m, 2 H), 1.73-1.86 (m, 1 H), 2.19-2.28 (m, 1 H), 3.14-3.28 (m, 2 H), 6.58 (t, J = 7.6 Hz, 1 H), 6.73 (d, J = 8.4 Hz, 1 H), 6.93-6.99 (m, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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
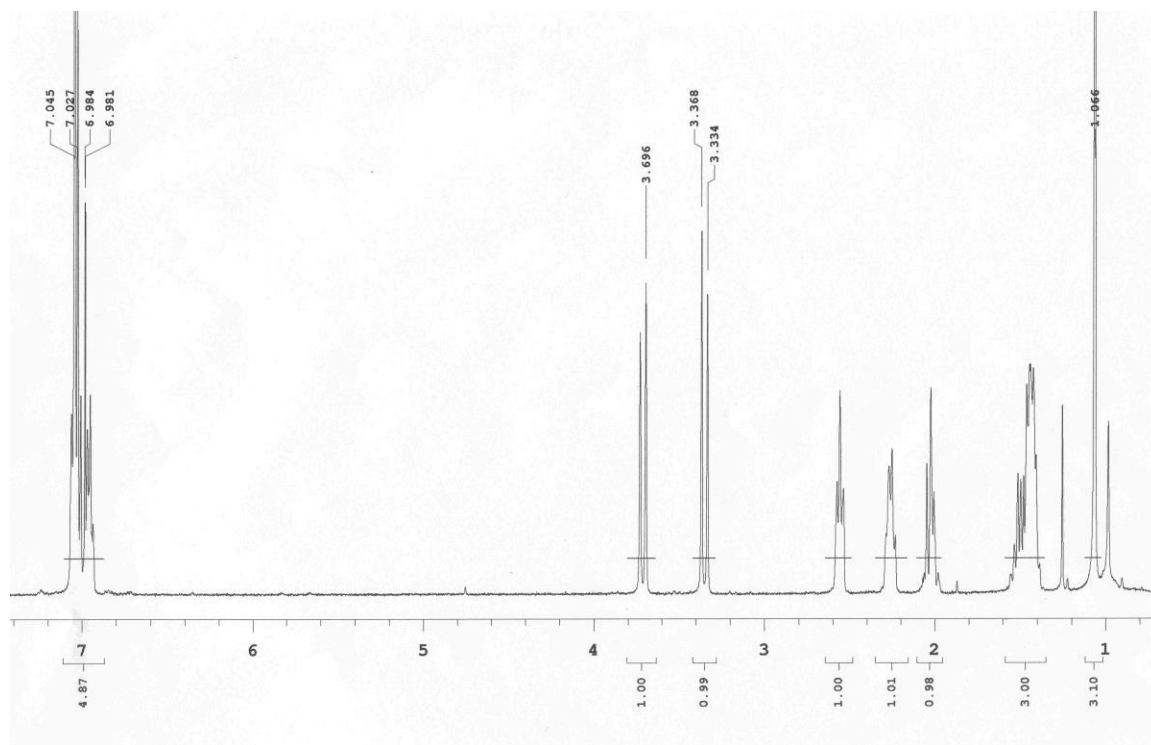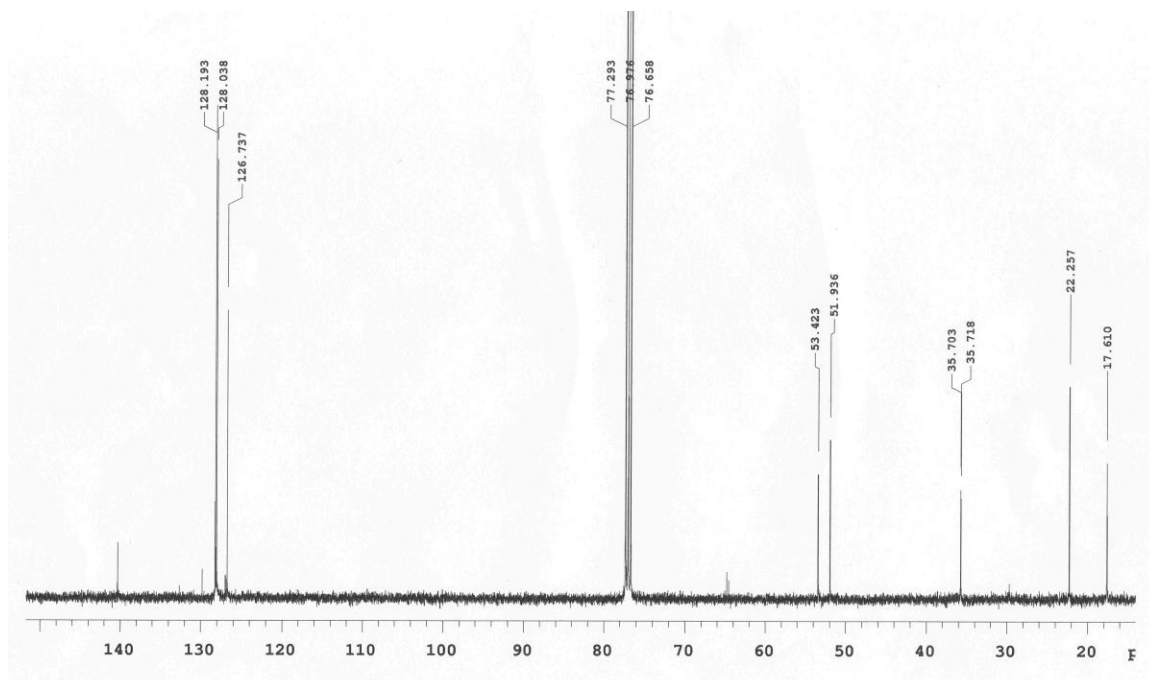
1.5. Tandem amination/phosphorylation

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 activity[29-33] 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)[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).[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),[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).[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.[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.
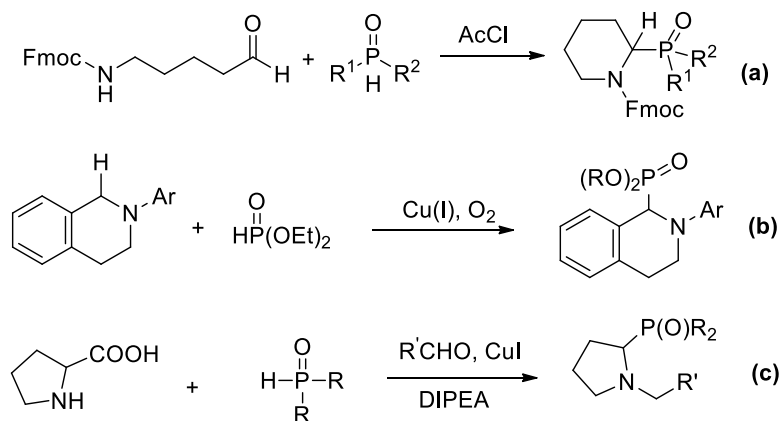
Scheme 7. Literature synthesis of cyclic α-amino phosphonates derivatives.

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,[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).[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,[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.
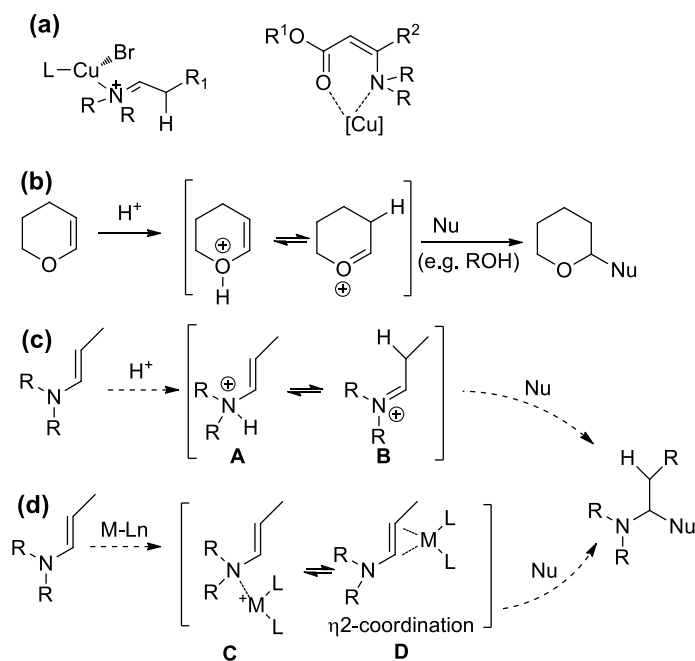
Scheme 8. Activation of enamine – converting enamine to an electrophile.

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 η2–bound Cu:enamine σ–complex to be more stable (by 2.2 kcal/mol) than the corresponding σ–complex, while Cu:enamine coordination is also stronger than to an alkynyl group (Scheme 4). Unsymmetrical coordination of Cu(I) to the enamine π-bond leads to shortening of the C-N bond and increased positive charge at the α-carbon: calculated Mulliken charges show the enamine transfers 0.32 units of charge to CuBr with a build up at Cα 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 *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.[9] 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.[54] This trait makes them difficult to isolate and purify. But our tandem chemistry overcomes this problem by using an *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.[16-18]

Cu:enamine π-complex
G_{rel} 0.0

N bound σ-complex
G_{rel} 2.2
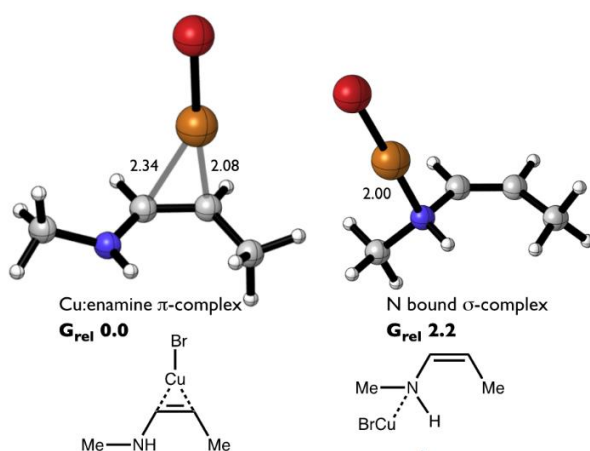
Scheme 9. CuBr coordination to enamine and alkyne (B3LYP-D3/6-311+G(d,p) with

LANL2DZ ECPs for Cu/Br. Relative free energy at 298K in kcal/mol, calculation was

conducted by Dr. Robert S. Paton at University of Oxford)

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**[a]
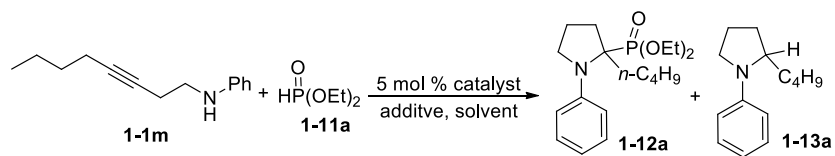
entry	catalyst	additive	solvent	temp/time	yield[b] **1-12a** (**1-13a**)%
1	CuBr	none	dioxane	rt, 6h	76(21)
2	CuBr	H_2O (2 equiv)	dioxane	rt, 6h	58(37)
3	CuBr	HCOOH	dioxane	rt, 6h	12(63)
4	CuBr	none	toluene	rt, 6h	86
5	CuBr	3A MS	toluene	rt, 6h	92
6	CuBr	3A MS	toluene	microwave, 100°C, 0.5h	88

[a] Reaction condition: amino alkyne **1-1m** (0.15 mmol), diethyl phosphite **1-11a** (0.3 mmol) with 5 mol % CuBr in 1mL solvent.[b] Isolated yields.

1.5.3. Scope of the tandem amination/ phosphorylation
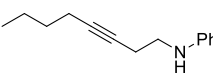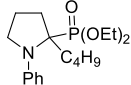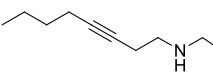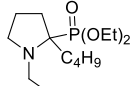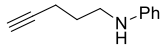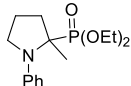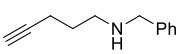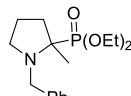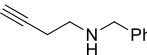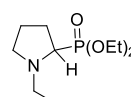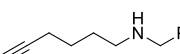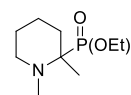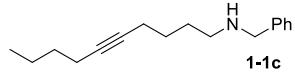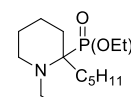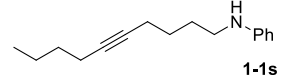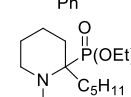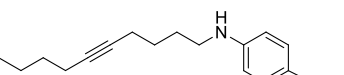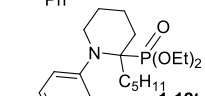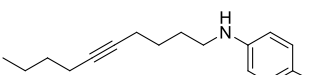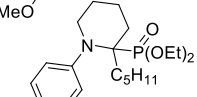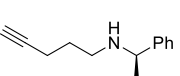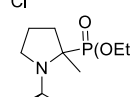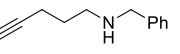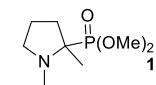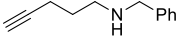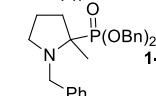
Various aminoalkynes were used in the reaction. Both, benzyl amines and aromatic amines, were tolerated. The aromatic amine **1-1t** with a methoxy group in the *para* position produced **1-12t** in good yield (Table 9, entry 9). The reaction of substrate **1-1u**, with an electron-withdrawing chloro 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. [20] 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.
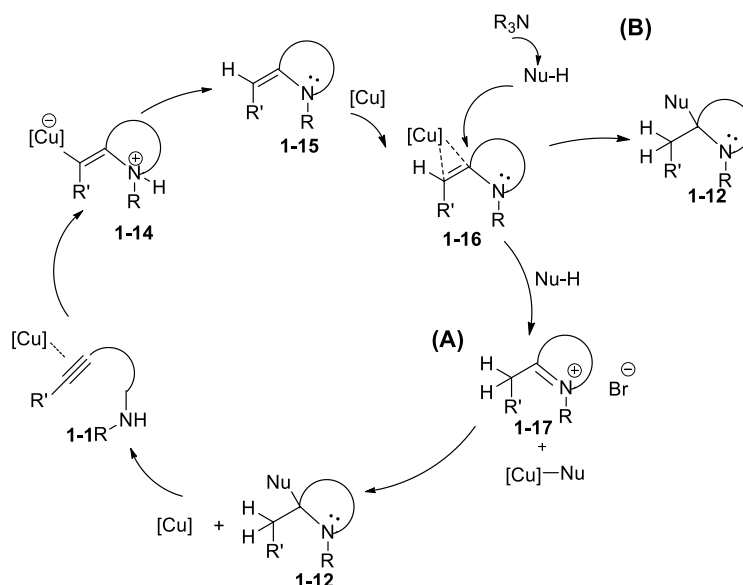
Scheme 10. Proposed mechanisms (Nu-H =dialkyl phosphite)

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Table 9. Scope of the tandem amination/ phosphorylation.

entry	**1-1**	**1-11**	**1-12**, yield
1	**1-1m**	**1-11a**	**1-12m** 92%
2	**1-1b**	**1-11a**	**1-12b** 94%
3	**1-1r**	**1-11a**	**1-12r** 93%
4	**1-1a**	**1-11a**	**1-12a** 88%
5	**1-1o**	**1-11a**	**1-12o** 67%
6	**1-1d**	**1-11a**	**1-12d** 83%
7	**1-1c**	**1-11a**	**1-12c** 86%
8	**1-1s**	**1-11a**	**1-12s** 89%
9	**1-1t**	**1-11a**	**1-12t** 91%
10	**1-1u**	**1-11a**	**1-12u** 0
11	**1-1g**	**1-11a**	**1-12g** 88% dr= 1:1.1
12	**1-1a**	**1-11b**	**1-12v** 91%
13	**1-1a**	**1-11c**	**1-12w** 94%

[a] Condition: 5mol% CuBr, 1-1 (0.15 mmol), 1-11 (0.3 mmol), 3A MS, toluene, rt, 6h. [b] Isolated yield. [c]The isolated product was contaminated with a small amount of dibenzylphosphite.

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

Diethyl (1-benzyl-2-butylpyrrolidin-2-yl)phosphonate (1-12b)
Yield: 50 mg (94%); yellow oil. ^{1}H NMR (700 MHz, CDCl$_3$): δ = 0.91 (t, J = 7 Hz, 3 H), 1.21-1.37 (m, 10 H), 1.40-1.48 (m, 2 H), 1.62-1.69 (m,1 H), 1.61-1.72 (m, 1 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); ^{13}C NMR (100 MHz, CDCl$_3$): 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); ^{31}P NMR (162 MHZ, CDCl$_3$): δ = 30.51. ESI-HRMS (ESI+): m/z calcd. for C$_{19}$H$_{32}$NO$_3$P (M$^+$ + H) 354.2193, found 354.2197.

Diethyl (2-methyl-1-phenylpyrrolidin-2-yl)phosphonate (1-12r).

Yield: 41 mg (93%); Yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): 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); ^{13}C NMR (100 MHz, CDCl$_3$): 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); ^{31}P NMR (162 MHz, CDCl$_3$) δ = 28.41. 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-methylpyrrolidin-2-yl)phosphonate (1-12a).

Yield: 41 mg (88%); yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): 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); ^{13}C NMR (100 MHz, CDCl$_3$): 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; ^{31}P NMR (162 MHZ, CDCl$_3$) δ = 28.77. ESI-HRMS (ESI+): m/z calcd. for C$_{16}$H$_{26}$NO$_3$P (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$_3$): δ = 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, 6Hz, 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, 1H), 7.11-7.30 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 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 = 15.5Hz), 58.6, 60.2 (d, J = 2.3Hz), 61.3, 61.8 (d, J = 7.7 Hz), 62.6 (d, J = 7Hz), 126.8, 128.0, 128.8, 139.4; ^{31}P NMR (162 MHZ, CDCl$_3$) δ = 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$_3$): δ = 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$_3$): δ = 16.7 (t, J = 6.1 Hz, 2C), 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$_3$): δ = 31.77. ESI-HRMS (ESI+): m/z calcd. for C$_{17}$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$_3$): δ = 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, 5H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.1, 16.6 (t, J = 5.2 Hz, 2C), 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 = 3.7Hz), 53.4, 61.1 (d, J = 8.2 Hz), 62.1 (d, J = 7.4 Hz), 65.2 (d, J =143.6 Hz), 126.5, 128.1, 128.3, 140.9; ^{31}P NMR (162 MHZ, CDCl$_3$) δ = 28.80. ESI-HRMS (ESI+): m/z calcd. for C$_{21}$H$_{36}$NO$_3$P (M$^+$ + H) 382.2506.

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

Yield: 49 mg (89%); yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.72 (t, J = 6.8 Hz, 3 H), 0.77-0.92 (m, 1 H), 0.96-1.22 (m, 7 H), 1.14 (t, J = 6.8 Hz, 3 H), 1.22 (t, J = 7.2 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}C NMR (100 MHz, CDCl$_3$): δ =13.9, 16.5 (t, J = 3.8 Hz, 2C), 22.2 (d, J = 9.8 Hz), 22.4, 22.7, 29.3, 31.5, 32.3 (d, J = 10.6 Hz), 35.6, 51.8, 61.5 (d, J = 7.6 Hz), 62.8, 6.8 Hz), 66.2 (d, J = 154.1 Hz); ^{31}P NMR (162 MHZ, CDCl$_3$): δ = 28.80. ESI-HRMS (ESI+): m/z calcd. for C$_{20}$H$_{34}$NO$_3$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}H NMR (400 MHz, CDCl$_3$): δ = 0.77 (t, J = 7.2 Hz, 3 H), 0.87-1.01 (m, 1 H), 1.03-1.22 (m, 7 H), 1.19 (t, J = 7.2 Hz, 3 H), 1.26 (t, J = 7.2 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 Hz, 2 H), 7.17 (d, J = 9.2 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 13.9, 16.5 (t, J = 5.3 Hz, 2C), 22.2 (d, J = 10.6Hz), 22.4, 22.9, 29.3, 31.5, 32.4 (d, J = 10.7 Hz), 35.2, 52.1(d, J = 3 Hz), 55.6, 61.3 (d, J = 7.6 Hz), 62.7 (d, J = 7.6 Hz), 66.1 (d, J = 154.8 Hz), 113.9, 117.4, 140.6, 152.2. ^{31}P NMR (162 MHZ, CDCl$_3$) δ = 28.98, ESI-HRMS (ESI+): m/z calcd. for C$_{21}$H$_{36}$NO$_4$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, 7.7 Hz), 126.6, 127.8, 127.8, 127.9, 128.0, 128.1, 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$_3$): δ = 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$_3$): δ = 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

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Spectrum labels (ppm): 141.267, 128.028, 128.006, 126.389, 77.336, 77.017, 76.698, 61.661, 61.585, 60.924, 60.641, 58.875, 57.569, 55.580, 46.927, 46.869, 35.699, 35.669, 28.006, 21.816, 21.747, 20.835, 20.897, 16.745, 16.692, 16.691

```
PULSE SEQUENCE          OBSERVE  C13, 100.5062403   DATA PROCESSING
Relax. delay 1.000 sec  DECOUPLE  H1, 399.7083433    Line broadening 2.0 Hz
Pulse 45.0 degrees      Power 44 dB                  FT size 65536
Acq. time 1.311 sec     continuously on              Total time 38 minutes
Width 25000.0 Hz        WALTZ-16 modulated
1000 repetitions
```

```
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
Sample #39, Operator: Junb
File: CARBON_001
VNMRS-400  "ulnmr400"
```

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**.
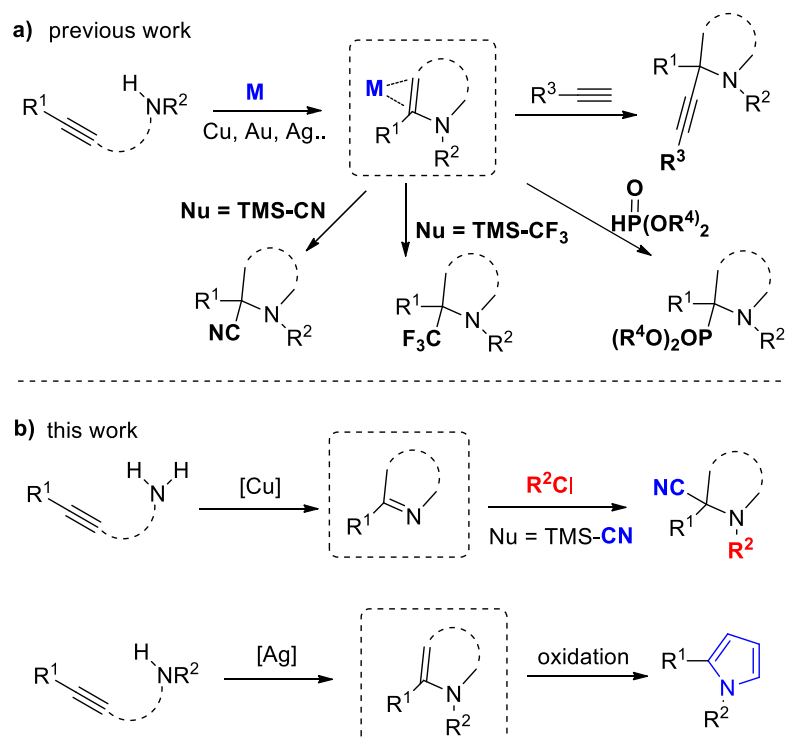
Scheme 11. Synthesis of N-heterocycles *via* cyclization triggered tandem reactions.

Table 10. Using a primary amine-tethered alkyne **1-18a** as starting material.
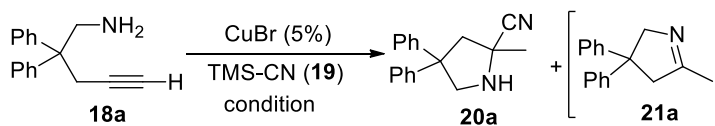
entry	TMS-CN	condition	time	20a[a]
1	4 equiv	mw / 100°C	30 min	46%
2	4 equiv	mw / 100°C	60 min	42%
3	2 equiv	mw / 100°C	30 min	32%
4	8 equiv	100°C	20 h	50%
5	8 equiv	rt	20 h	50%

[a] ^{1}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

entry	1-18	1-21	1-22a	co-catalyst	solvent	condition	yield 23
1	**1-18a**	4 equiv	4 equiv	-	dioxane	mw /100°C / 30 min	80%
2	**1-18a**	4 equiv	4 equiv	-	acetonitrile	mw /100°C / 30 min	87%
3	**1-18a**	4 equiv	2 equiv	-	acetonitrile	mw / 90°C / 30 min	93%
4	**1-18a**	4 equiv	2 equiv	-	acetonitrile	100°C / 12h	85%
5	**1-18c**	4 equiv	2 equiv	-	acetonitrile	mw /100°C / 30 min	trace
6	**1-18c**	4 equiv	2 equiv	Sc(OTf)$_3$	acetonitrile	100°C / 12h	85 %

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.

$$\text{1-18} + R^8Cl \;(\text{1-22}) \xrightarrow[\text{CH}_3\text{CN, mw, 90}^\circ\text{C, 40 min}]{\text{CuBr (5\%), TMSCN (4 equiv)}} \text{1-23}$$

entry	1-18	R^8Cl (1-22)	condition[a]	1-23 isolated yield (%)
1	1-18a	Cl–CN (chloroacetonitrile)	A	1-23a 93
2	1-18a	Cl–CH$_2$C(O)NH$_2$	A	1-23b 92
3	1-18a	Cl–CH$_2$Ph (benzyl chloride)	A	1-23c 79
4[b]	1-18a	Cl–CH$_2$CH$_2$–Cl	A	1-23d 99
5[c]	1-18a	Cl(CH$_2$)$_5$	B	1-23e 42
6	1-18b	Cl–CN	B	1-23f 91
7	1-18b	Cl–CH$_2$Ph	B	1-23g 89
8[b]	1-18b	Cl–CH$_2$CH$_2$–Cl	B	1-23h 93
9	1-18c	Cl–CN	B	1-23i 81

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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).
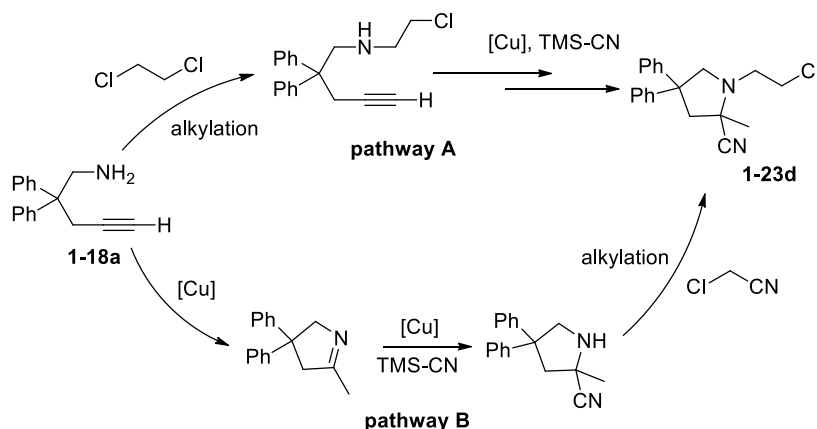
Scheme 12. Proposed mechanism for the formation of **1-23d**.

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.
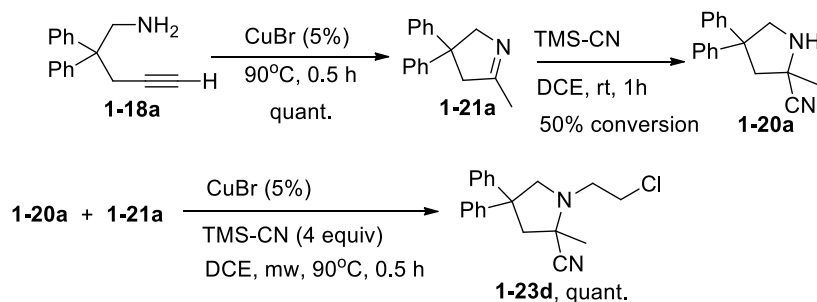
Scheme 13. Mechanistic investigation for the formation of **1-23**

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$_3$): δ 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$_3$): δ 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$_3$): δ 1.57 (s, 3H), 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), 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$_3$): δ 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$_3$): δ 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$_3$): δ 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$_3$): δ 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$_{21}$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$_3$): δ 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$_3$): δ 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$_3$): δ 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, 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$_3$): δ 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$_3$): δ 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); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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, 1285, 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
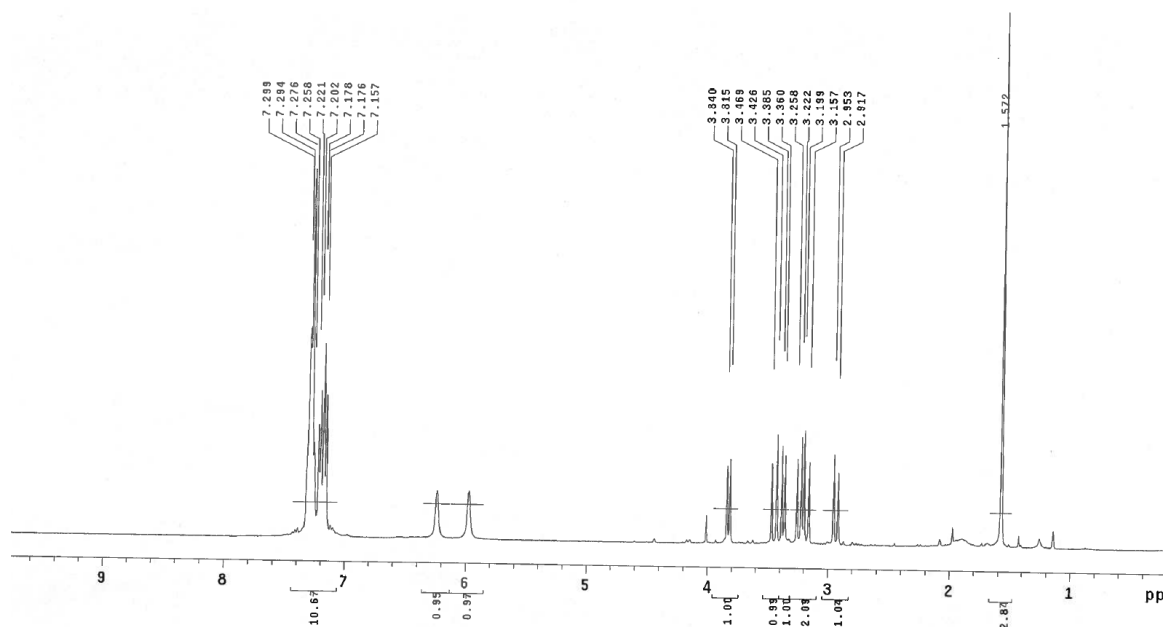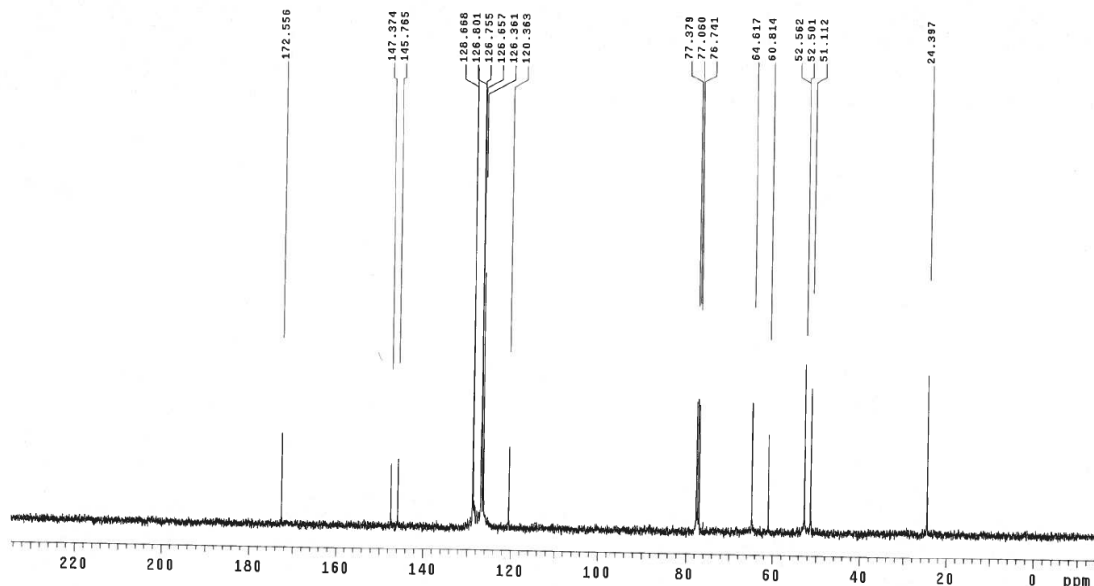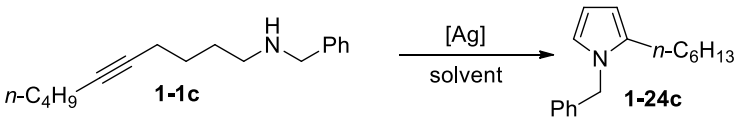
1.7. Tandem Amination/Oxidation

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).[56] Because we had already reported that hydroamination was a reversible process and the migration of the triple bond was plausible,[40] 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,[40] 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.
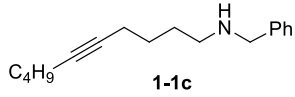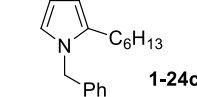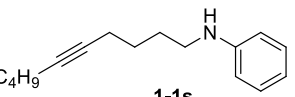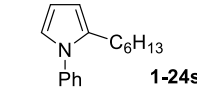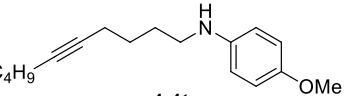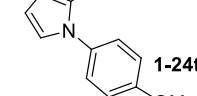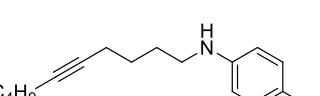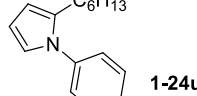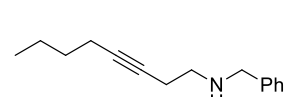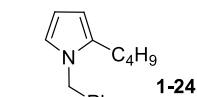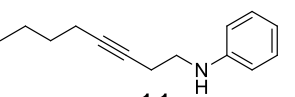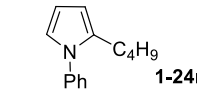
entry	[Ag]	solvent	condition	1-24c[a]
1	AgF (0.1 equiv)	dioxane	90°C / 12 h	6%
2	AgF (1.0 equiv)	dioxane	90°C / 12 h	22%
3	AgF (1.0 equiv)	dioxane	rt / 12 h	31%
4	AgOAc (1.0 equiv)	dioxane	rt / 24 h	40%
5	AgOAc (1.0 equiv)	DCM	rt / 24 h	52%
6	AgOAc (1.5 equiv)	DCM	rt / 24 h	66%
7	AgOAc (2.0 equiv)	DCM	rt / 24 h	62%
8	**AgOAc (2.0 equiv)**	**DCM**	**rt / 40 h**	**81% (74%[b])**
9	AgNO$_3$ (2.0 equiv)	DCM	rt / 24 h	trace
10	AgCO$_3$ (2.0 equiv)	DCM	rt / 24 h	no rxn
11	CuBr (0.1 equiv)	DCM	rt / 24 h	complex
12	CuBr (1.0 equiv)	DCM	rt / 24 h	complex
13	AgOAc (0.1 equiv)/ DDQ (1.1 equiv)	DCM	rt / 40 h	trace

[a] NMR yield; [b] 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]

entry	1-1	1-24	yield[c]
1	1-1c	1-24c	74%
2[b]	1-1s	1-24s	71%
3[b]	1-1t	1-24t	62%
4[b]	1-1u	1-24u	0%
5	1-1b	1-24b	80%
6[b]	1-1m	1-24m	73%

[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 **1-24a** is illustrated in Scheme 14. Hydroamination of 5-yn-amine **1-1c** produces a six-membered enamine **1-25** through a *6-exo-dig* pathway.[40] Migration of the double bond in enamine **1-25** yields **1-26** and hydroamination in the presence of a metal catalyst is reversible,[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 **1-24a**.[56]
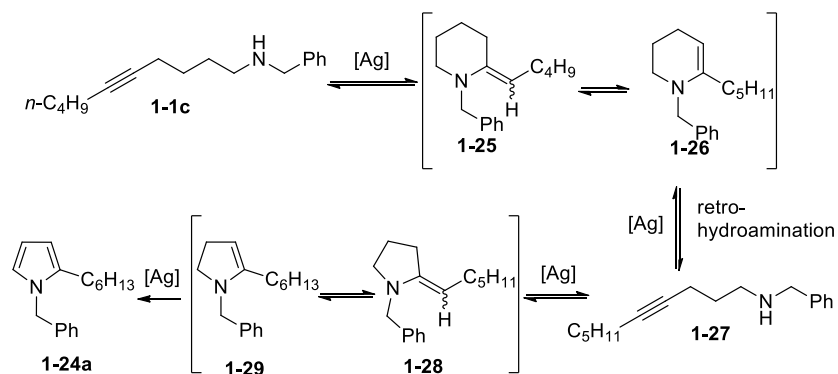
Scheme 14. Proposed mechanism for formation of **1-24**.

1.7.2.   Experimental

Amino alkyne **1-1c** (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 **1-24c** (45 mg, 74%).

1-Benzyl-2-hexyl-1H-pyrrole (**1-24c**). Yellow oil (44.6 mg, 74% yield). IR (neat): 2930, 2851, 1700, 1658, 1518, 1248, 1033, 837, 698 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$):

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 (40.4mg, 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): 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 = 1.2Hz, 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); ^{13}C NMR (100 MHz, CDCl$_3$): 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

C$_{15}$H$_{19}$N (M$^+$ + H) 214.1590, found 213.1591.

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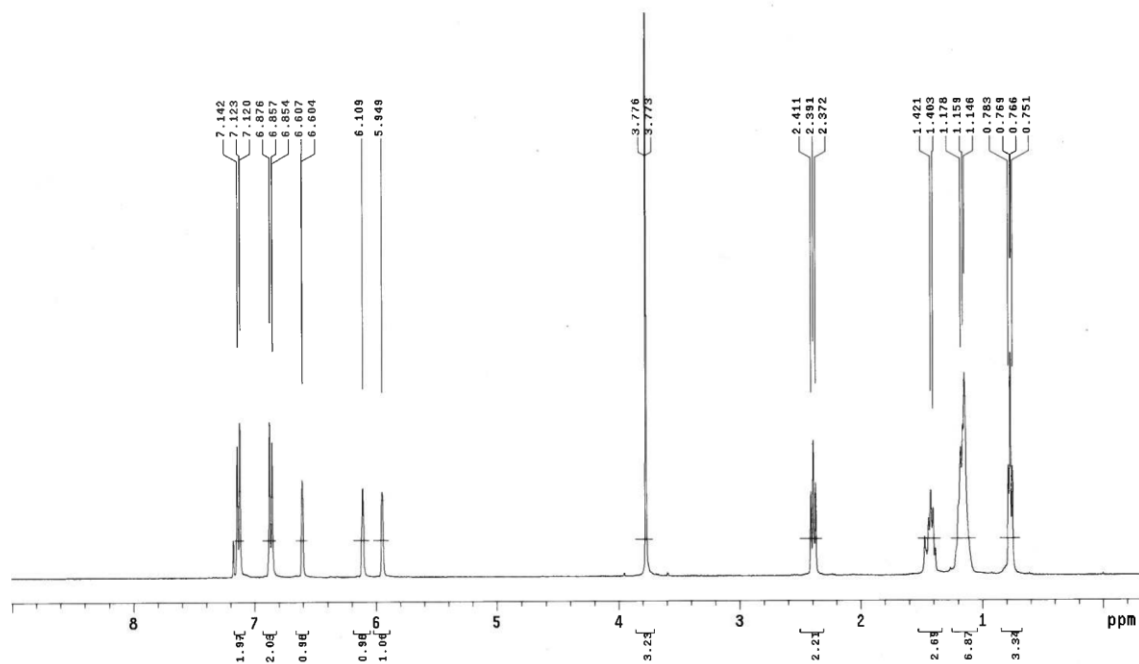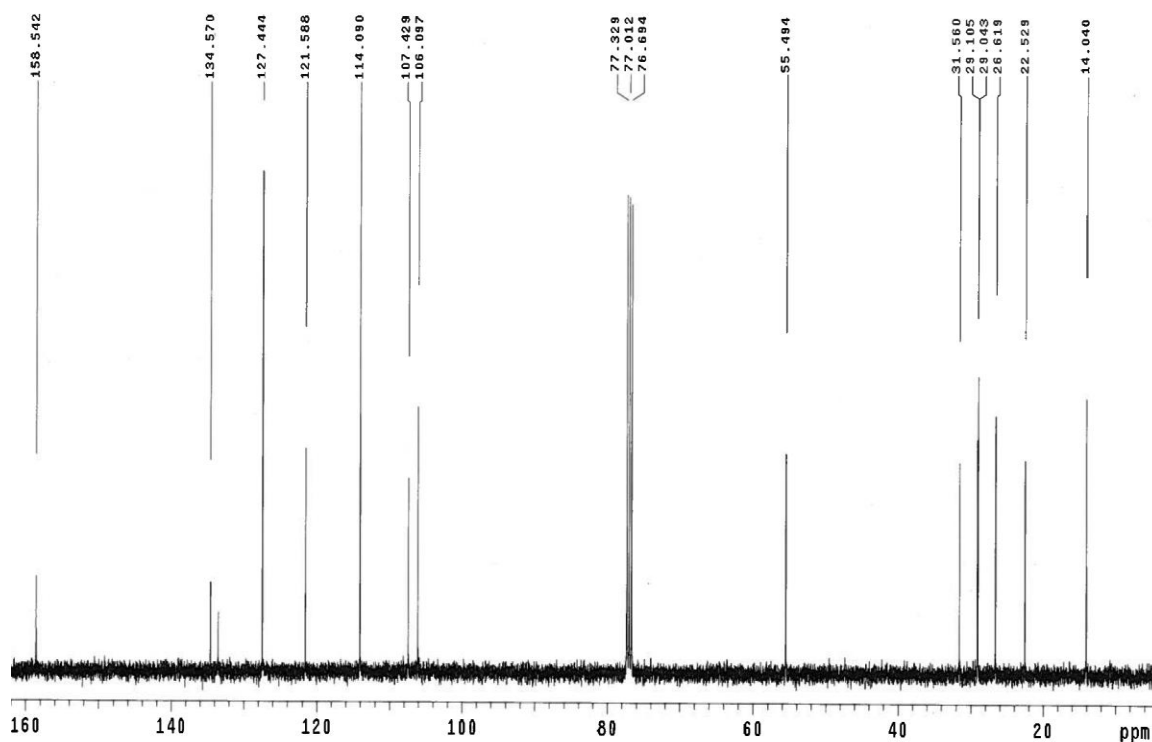
1.8. Summary and future direction

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

CHAPTER 2

BROADLY APPLICABLE REACTION PROMOTER FOR CATIONIC METAL CATALYSIS

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.[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.
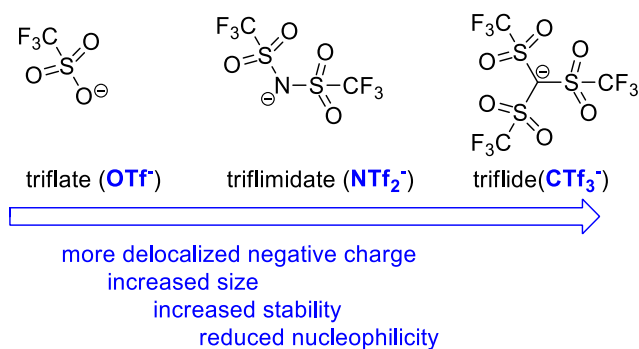
Figure 2. Better than OTf^- and NTf_2^-.

Recently, cationic metal salts containing triflimidate (NTf_2^-) have appeared as a unique class of catalysts that display outstanding σ- and π-Lewis acid character.[58] Consequently, these metal triflimidates often outperform their triflate analogues in catalysis.[58] In 2010, Dalla and Dunach published a review article in *Angew. Chem.* titled 'Metal Triflimidates: Better than Metal Triflates as Catalysts in Organic Synthesis…".[58] Despite intensive investigations, there is no concrete rationnle to explain benefits of triflimidates, chemists usually explain their higher performance to its more delocalized charge, higher steric hindrance and reduced nucleophilicity compared to triflate.[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 **O**Tf 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.[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.[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.[60] 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 a have 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),[61,62] $Li^+[Al[(CF_3)_3C-O)]_4]^-$,[63,64] and $KCTf_3$. All the corresponding counterions in these promoters have shown good reactivity in metal catalyzed reactions.[65,66]

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).[67] Most of the salts screened enhanced the kinetics of the reaction,

but KCTf$_3$ clearly gave the best result. The reaction inhibition observed with Li$^+$[Al[(CF$_3$)$_3$C-O)]$_4$]$^{-63,64}$ could be explained by the instability of the aluminum anion under the reaction conditions.
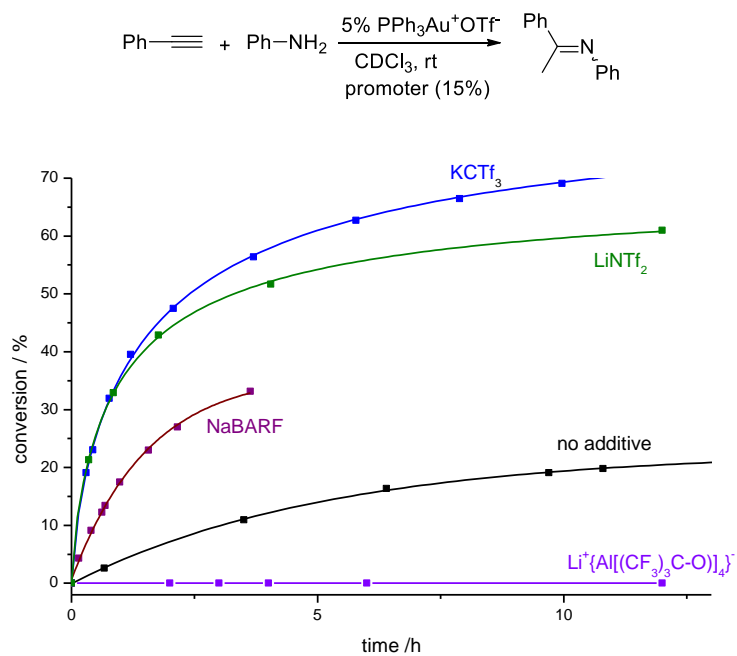
Figure 3. Effect of promoters on hydroamination reaction
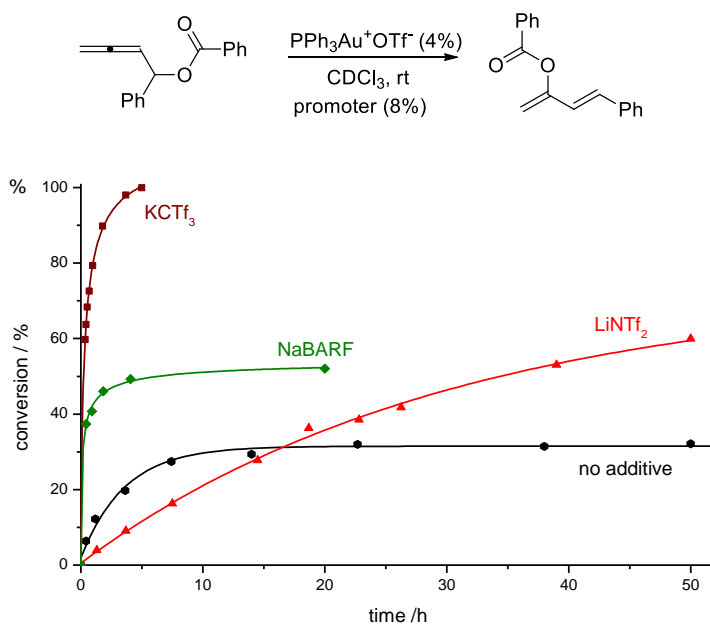
Figure 4. Effect of promoters in the rearrangement of allenyl ester.

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),[68] a reaction known to experience significant catalyst decay over time.[67] 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$_2^-$.[58,69] 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),[70-80] KCTf$_3$ increased the reaction rate 3.5 and 11 fold. In the cycloisomerization of 1,6-enynes (Scheme 15, c-d)[81-83] 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).

a) 1.5% PPh$_3$Au$^+$OTf$^-$, CDCl$_3$, rt, promoter (3%)

	rel. rate
no promoter	1.0
KCTf$_3$	11.4
NaBARF	0

b) DalPhos-Au$^+$OTf$^-$ (2%), dioxane, 100 °C, promoter (4 %)

	rel. rate
no promoter	1.0
KCTf$_3$	3.5
NaBARF	4.3

c) 2% PPh$_3$Au$^+$OTf$^-$, CDCl$_3$, rt, promoter (4 %)

	rel. rate
no promoter	1.0
KCTf$_3$	33.0
NaBARF	0

d) R = n-C$_6$H$_{13}$; PPh$_3$Au$^+$OTf$^-$ (4%), CDCl$_3$, rt, promoter (8%)

	rel. rate
no promoter	1.0
KCTf$_3$	1.8
NaBARF	1.0
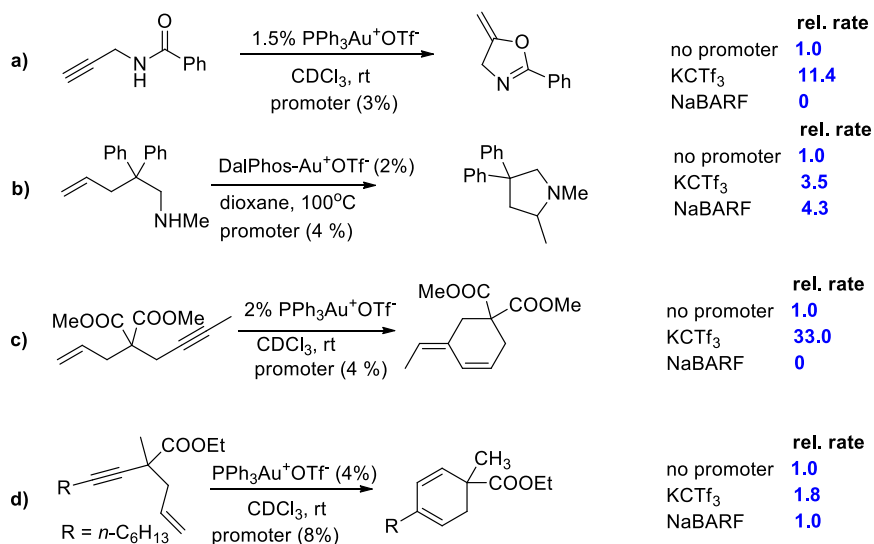
Scheme 15. Effect of reaction promoter in cationic gold catalyzed reactions.

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.[55] KCTf$_3$ showed a one-hundred fold increase in the Yb(OTf)$_3$ catalyzed acylation of anisole (Scheme 16a).[84] Notably, in the Sc(OTf)$_3$ catalyzed allylation of aromatic aldehydes[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)[86] and in a Prins-type cyclization, catalyzed by Sc(OTf)$_3$ (Scheme 16d).[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.[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.[89] In our hands, the Ru catalyzed visible light photoredox reaction shown in Scheme c[90] 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).
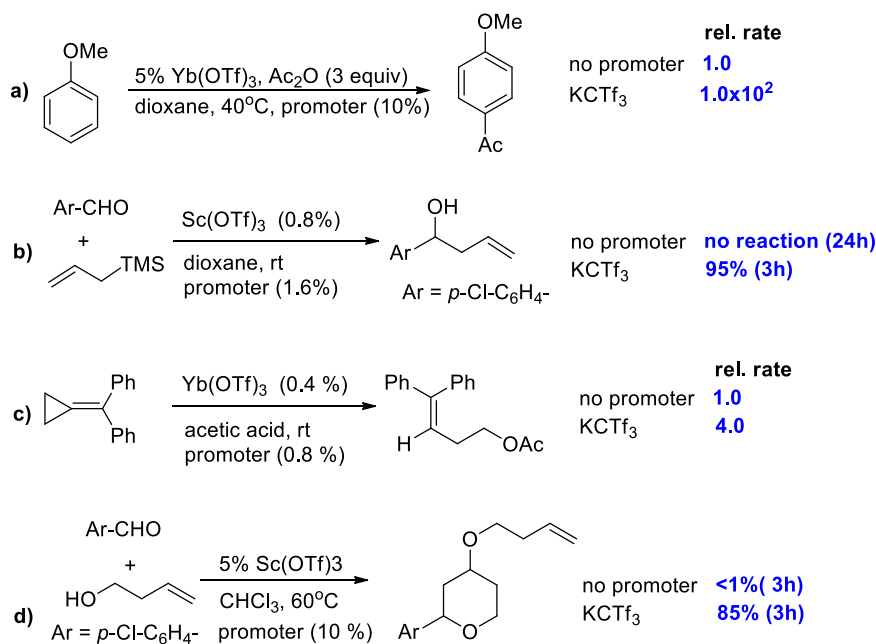
Scheme 16. Effect of reaction promoter in various classical Lewis acid catalyzed reactions.
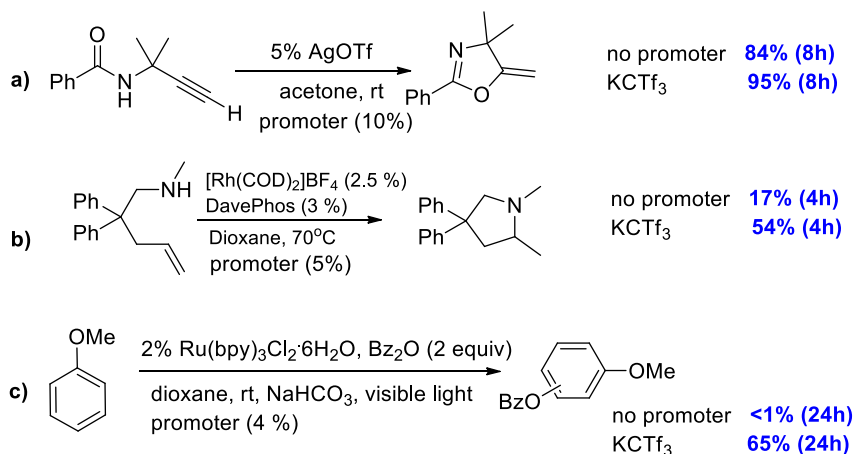
Scheme 17. Effect of reaction promoter in silver, rhodium and ruthenium catalyzed ionic

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,[59] 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.[91,92] 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.[93,94] 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.[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.
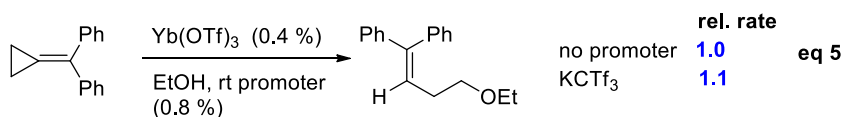
2.4. Summary and future direction

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.[95] 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 ^1H 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 (4×10^{-3} mmol), were introduced in its liquid and solid state, respectively. The reaction was kept at room temperature and was monitored by ^1H 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 ^1H NMR. Each data point corresponded to 1 scan.
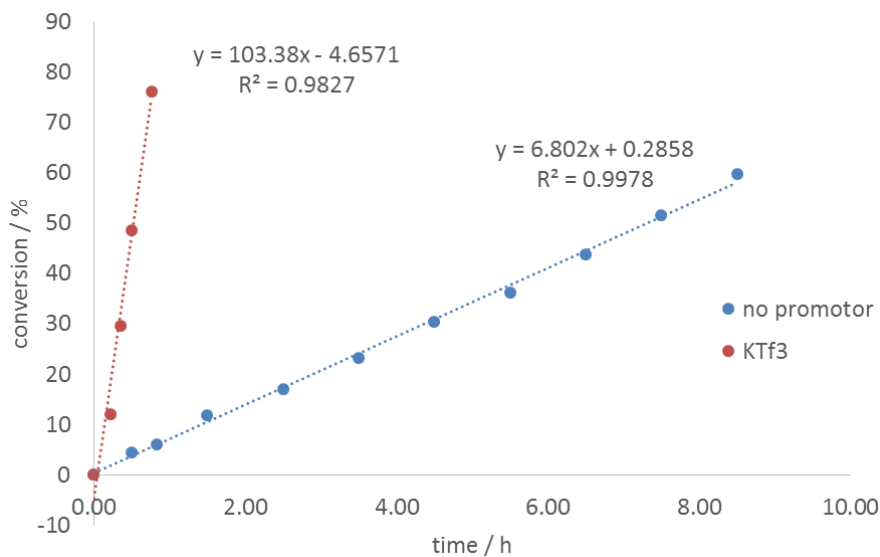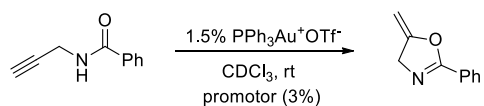
Gold catalyzed hydroamination of alkene
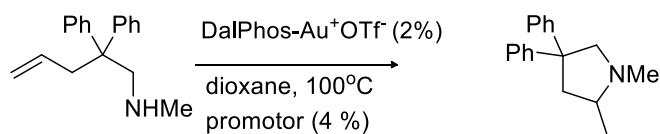
A standard solution of starting material (aminoalkene) was prepared by dissolving aminoalkene (0.5 mmol) and n-hexadecane (internal standard) in dioxane (2.5 mL). For each reaction, DalPhos-AuCl (2 mol%), AgOTf (2 mol%) and different promoters were added to a corresponding reactor containing 0.5 mL standard solution. All reactions were stirred and heated to 100°C. The progress of reaction was monitored by GC/MS.
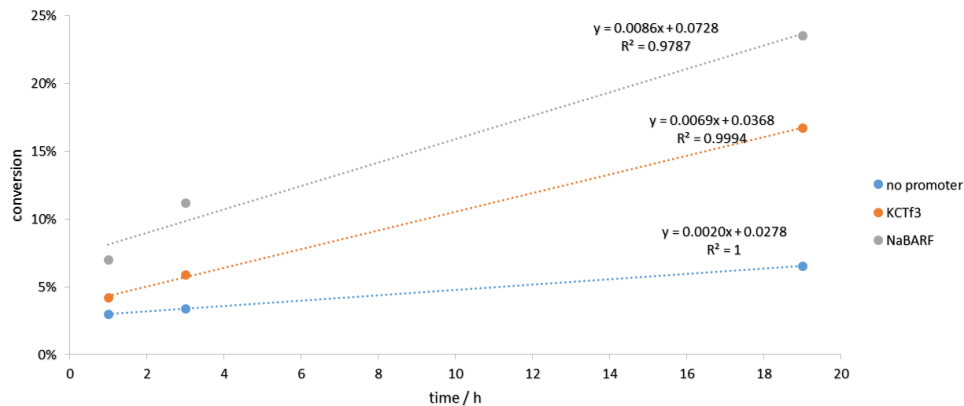
$y = 0.0086x + 0.0728$
$R^2 = 0.9787$

$y = 0.0069x + 0.0368$
$R^2 = 0.9994$

$y = 0.0020x + 0.0278$
$R^2 = 1$

conversion

time / h

- no promoter
- KCTf3
- NaBARF

Gold catalyzed intramolecular cycloisomerization of enyne

MeOOC COOMe → 2% PPh$_3$Au$^+$OTf$^-$ / CDCl$_3$, rt / promotor (4 %) → MeOOC COOMe

$y = 133.09x + 3.8838$
$R^2 = 0.9936$

$y = 1.9134x + 1.0347$
$R^2 = 0.9309$

conversion / %

time / h

- KCTf3
- no promotor

Gold catalyzed intramolecular cycloisomerization of enyne

R COOEt → PPh$_3$Au$^+$OTf$^-$ (4%) / CDCl$_3$, rt / promotor (8%) → R CH$_3$ COOEt

R = n-C$_6$H$_{13}$

$y = 8.9505x + 0.205$
$R^2 = 0.9897$

$y = 4.9501x + 2.0221$
$R^2 = 0.9862$
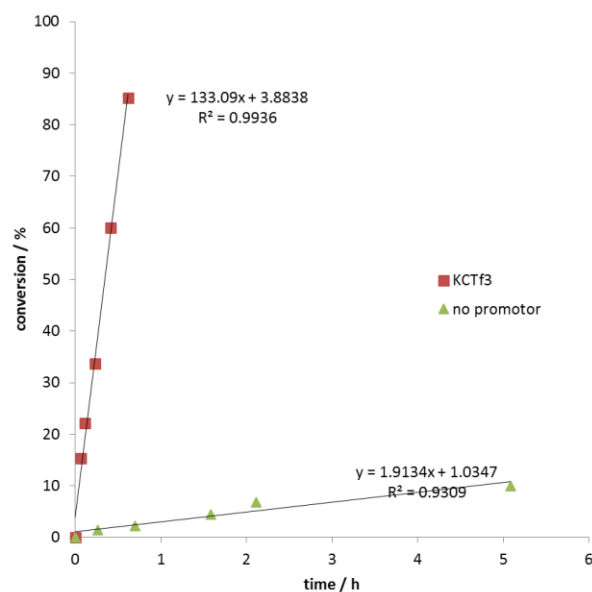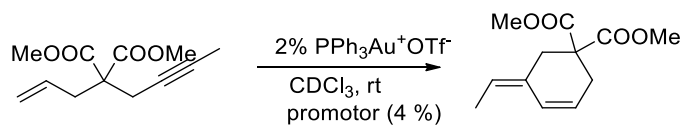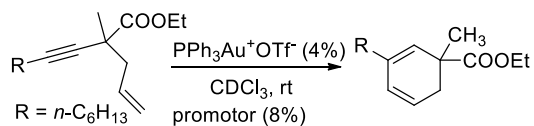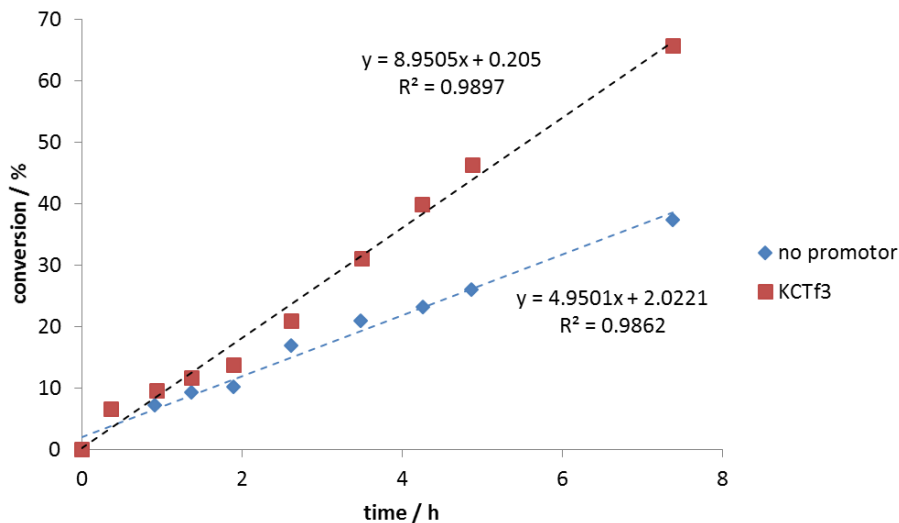
Friedel-Crafts acylation
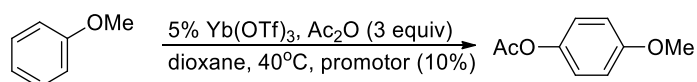
A standard solution of starting material was prepared by dissolving anisole (1.4 mmol), Yb(OTf)$_3$ (5 mol%) and n-hexadecane (internal standard) in 3.5 mL dioxane. Different promoters (10 mmol%) and acetic anhydride (0.6 mmol) were added into the corresponding reactors containing 0.5 mL standard solution. All reactions was stirred and carried out at 40°C. The progress of reaction was monitored by GC/MS.
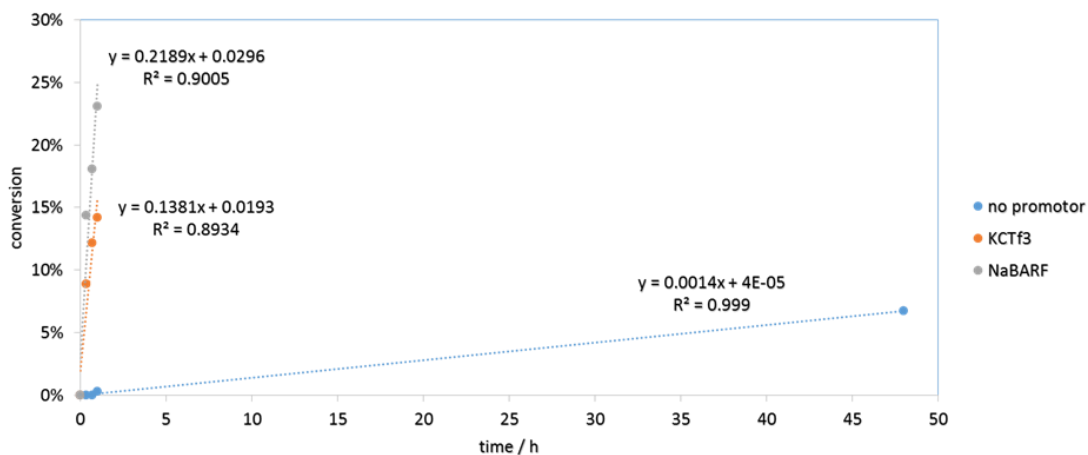
$y = 0.2189x + 0.0296$
$R^2 = 0.9005$

$y = 0.1381x + 0.0193$
$R^2 = 0.8934$

$y = 0.0014x + 4E-05$
$R^2 = 0.999$

Hosomi-Sakurai reaction

Ar-CHO
+
⟍⟍TMS

Sc(OTf)$_3$ (0.4 %)
───────────────→
dioxane, rt
promotor (0.8 %)

Ar⟍⟍⟍⟍
OH

Ar = p-Cl-C$_6$H$_4$-
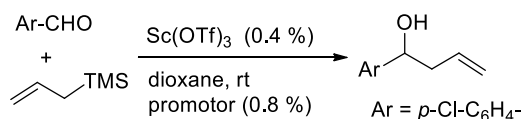
A standard solution of starting material was prepared by dissolving 4-chlorobenzaldehyde (0.4 mmol), allyltrimethylsilane (0.8 mmol) and n-hexadecane (internal standard) in dioxane. Different promoters and Sc(OTf)$_3$ (0.4 mol%) were added to the corresponding reactors containing 1 mL standard solution. All reactions were conducted at room temperature. The progress of reaction was monitored by GC/MS.

Lewis acid-catalyzed ring-opening

◁═⟨Ph, Ph⟩

Yb(OTf)$_3$ (0.4 %)
───────────────→
acetic acid, rt
promotor (0.8 %)

Ph⟍Ph
H⟍⟍OAc
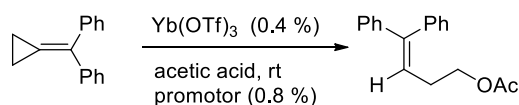
A standard solution was prepared by dissolving methylenecyclopropane (0.4 mmol), Yb(OTf)$_3$ (0.4 mol%) and n-hexadecane (internal standard) in 4 mL acetic acid. Different promoters (0.8 mmol%) were added into the corresponding reactors containing 1 mL standard solution. The reactions were stirred and conducted at room temperature. The progress of reaction was monitored by GC/MS.
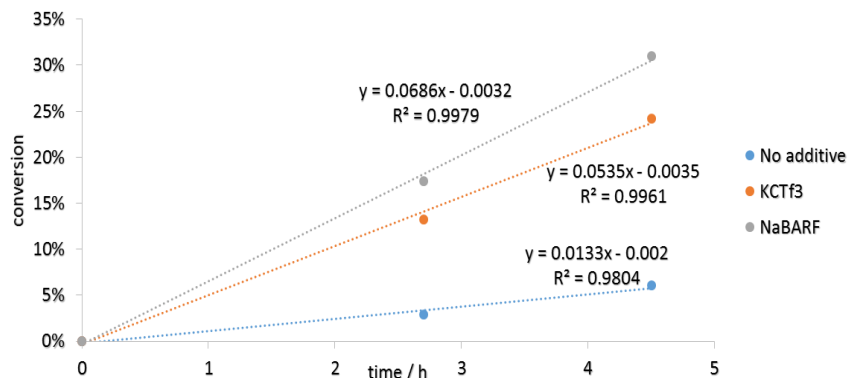
Silver catalyzed cyclization of propargyl amide
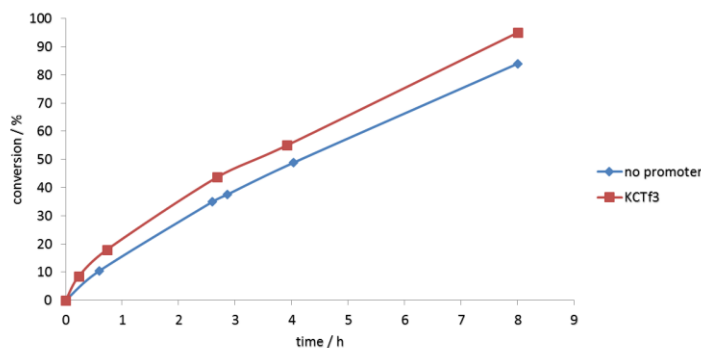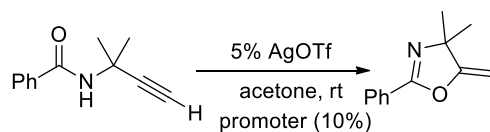
Rhodium catalyzed hydroamination of alkene
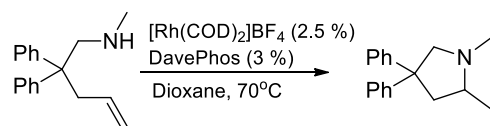
A standard solution of starting material was prepared by dissolving aminoalkene (0.5 mmol) and n-hexadecane (internal standard for GC) in dioxane (2.5 mL). [Rh(COD)$_2$]BF$_4$ (2.5 mol%), DavePhos (3 mol%) and different promoters were added into the corresponding reactors containing 0.5 mL standard solution. All reactions were stirred and heated to 70°C. The progress of reaction was monitored by GC/MS.
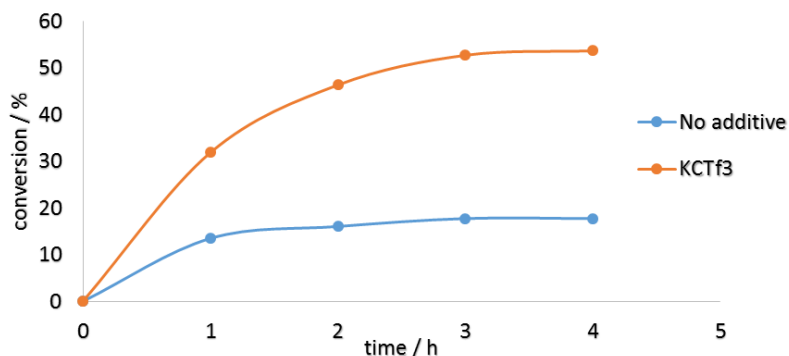
Organo iminium catalysis
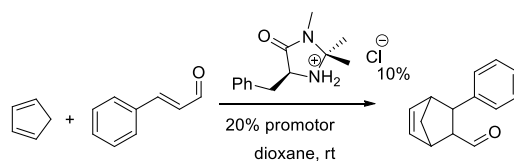
A standard solution was prepared by dissolving cinnamaldehyde (2 mmol), organocatalyst (10 mmol%) and n-hexadecane (internal standard) into 6 mL dioxane. Cyclopentadiene and different promoters (20 mmol%) were added into the corresponding reactors containing 1.5 mL standard solution. The reactions were stirred at room temperature.
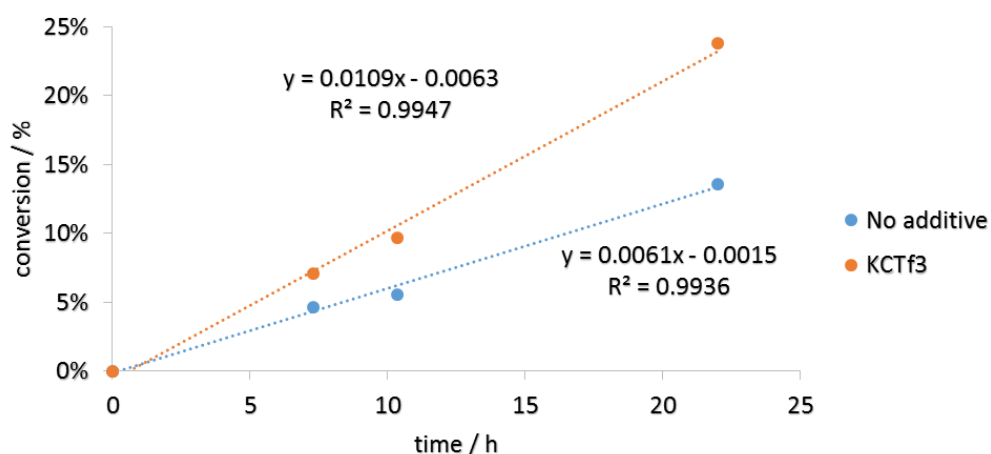
Visible-light photocatalysis
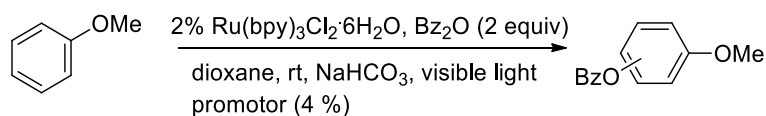
A standard solution was prepared by dissolving benzoyl peroxide (2 mmol) and anisole (1 mmol) in 4 mL dioxane. Photoredox catalyst $Ru(bpy)_3Cl_2$ (2 mmol%), sodium bicarbonate (0.75 mmol), and different promotors (4 mmol%) were added into the

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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.[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_6^-, NTf_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., $AgNTf_2$[69]), commercially unavailable, or troublesome to prepare (e.g., $Ag[B(C_6F_5)_4]$[80]). Second, the presence of silver may cause side reactions.[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**,[97] **B**,[98] **C**[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).[100]

There are alternative ways to generate cationic gold.[101] For example, Teles and others[11,102] reported the protonolysis of $Ph_3PAu-CH_3$, 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 $[NHC-Au]^+$ or $[Au-O-Au]^+$ species (Scheme 18b).[103,104] Bertrand and coworkers generated cationic gold taking advantage of the high affinity of silica towards chloride (Scheme 18c).[105] Recently, Lafolle and Gandon reported the use of $Cu(OTf)_2$ to activate L-AuCl.[106]
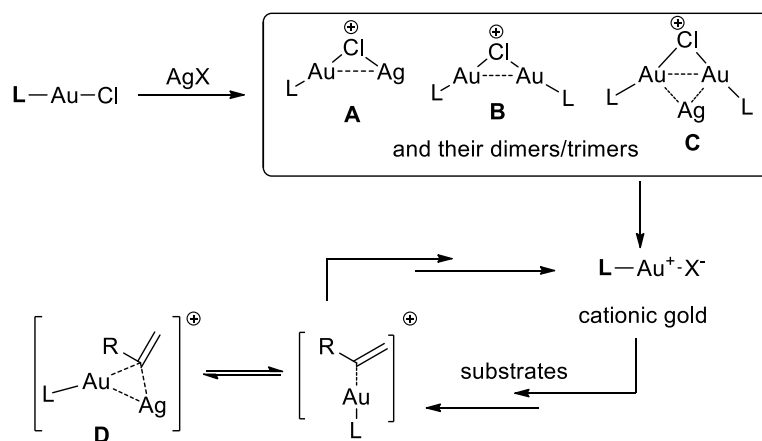
Figure 5. Various Au-Ag Intermediates formed in the generation of cationic gold.
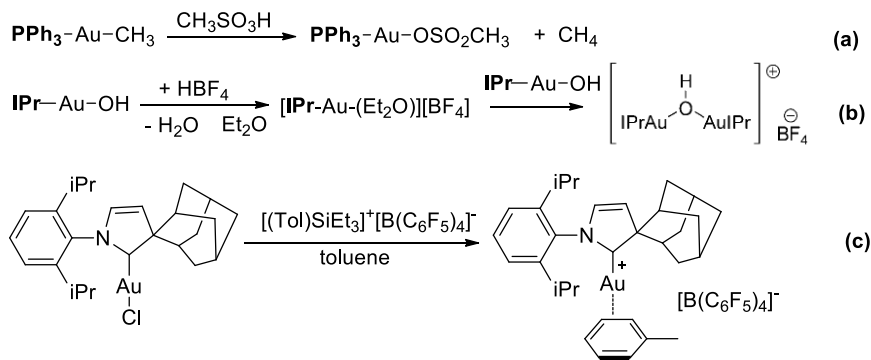
Scheme 18. Typical non-silver based cationic gold generation methods.

The aforementioned non-silver activation methods have limitations. First of all, gold precatalysts like L-Au-CH$_3$ 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 coworkers[113] (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.

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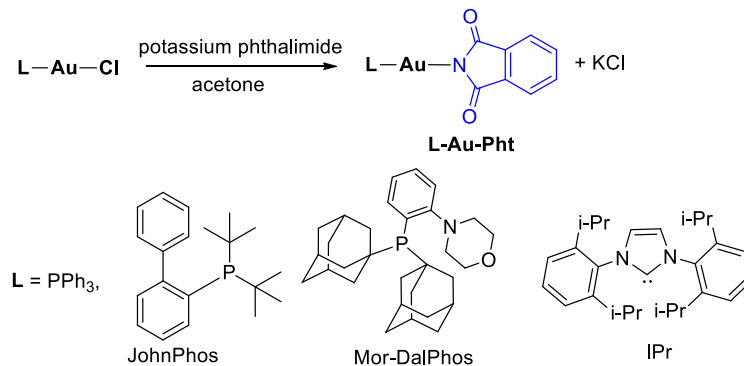
Scheme 19. Synthesis and activation of L-Au-Pht.

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).
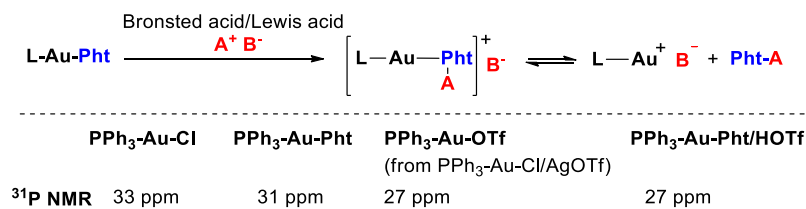
Scheme 20. Brønsted acid- or Lewis acid-activation of L-Au-Pht.

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).

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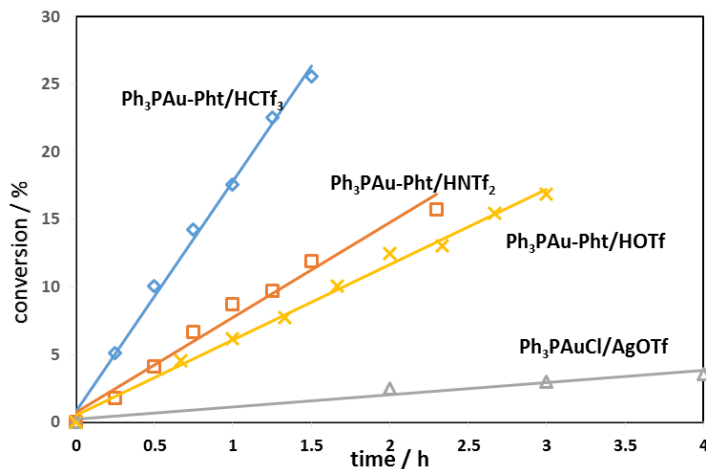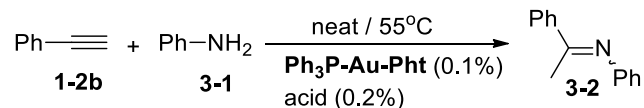
Figure 6. Effects of acid promoter on the rate of hydroamination.

To compare a large number of acid activators in 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 (HCTf$_3$>HNTf$_2$>TfOH).[115] In general, a Ph$_3$PAu-Pht/acid combination showed better reactivity than the standard Ph$_3$PAu-Pht/AgX system. Most Lewis acids also worked well. The counterions of Brønsted acids or Lewis acids played an important role (rate: CTf$_3^-$>NTf$_2^-$>TfO$^-$>BF$_4^-$). We also evaluated other gold catalyst precursors (Ph$_3$PAuCl, Ph$_3$PAu-Sac, Ph$_3$Pau-OAc, Table 15, entries 8, 9, 10) and found them less effective (not to mention the fact that the synthesis of Ph$_3$PAu-Sac and Ph$_3$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).[116]

Table 15. Relative rate of intermolecular hydroamination.

entry	catalyst	relative rate
1	**Ph$_3$PAuCl** / AgOTf (0.2%)	**1.0**
2	**Ph$_3$P-Au-Pht** / no acid	**0**
3	**Ph$_3$P-Au-Pht** / PhCOOH (0.2%)	**0**
4	**Ph$_3$P-Au-Pht** / HBF$_4$ (0.2%)	**2.4**
5	**Ph$_3$P-Au-Pht** / TfOH (0.2%)	**6.3**
6	**Ph$_3$P-Au-Pht** / HNTf$_2$ (0.2%)	**7.4**
7	**Ph$_3$P-Au-Pht** / HCTf$_3$ (0.2%)	**19.1**
8	**Ph$_3$P-Au-Cl** / HCTf$_3$ (0.2%)	**3.3**
9	**Ph$_3$P-Au-OAc** / HCTf$_3$ (0.2%)	**11.8**
10	**Ph$_3$P-Au-Sac** / HCTf$_3$ (0.2%)	**18.6**
11	**Ph$_3$P-Au-Pht** / Sc(OTf)$_3$ (0.2%)	**2.6**
12	**Ph$_3$P-Au-Pht** / In(OTf)$_3$ (0.2%)	**2.5**
13	**Ph$_3$P-Au-Pht** / Yb(OTf)$_3$ (0.2%)	**2.5**
14	**Ph$_3$P-Au-Pht** / Cu(OTf)$_2$ (0.2%)	2.1
15	**Ph$_3$P-Au-Pht** / In(CTf$_3$)$_3$ (0.2%)	**28.4**
16	**Ph$_3$P-Au-Pht** / Yb(CTf$_3$)$_3$ (0.2%)	**27.2**
17	**Ph$_3$P-Au-Pht** / AgOTf (0.2%)	**0.5**
18	**Ph$_3$P-Au-Pht** / Ag(CTf)$_3$ (0.2%)	**6.4**
19	**Ph$_3$P-Au-Pht** / Nafion	**0**
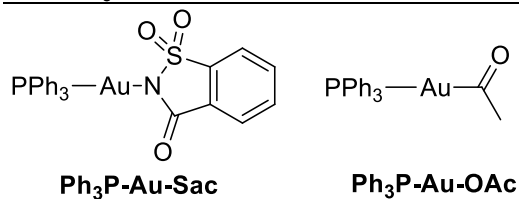
When we switched to an electron-richer ligand (JohnPhos), using the same conditions, the reaction was completed in only 15 min.

97
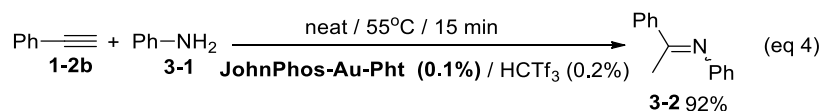
We also investigated the influence of the concentration of acid activator on the rate of hydroamination. We found a linear relationship between these two parameters (Figure 7).
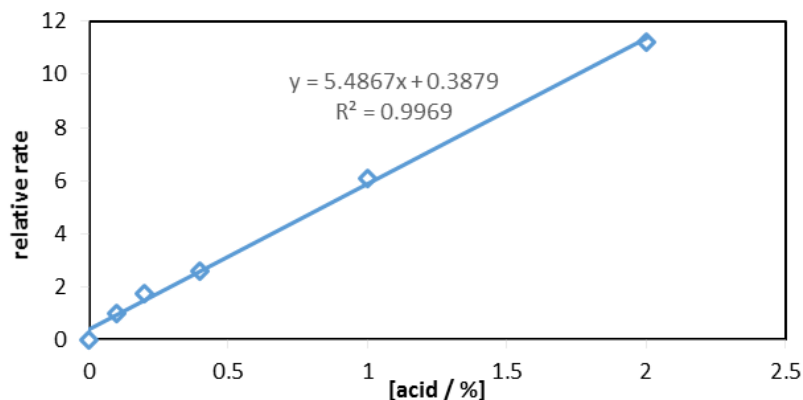
Figure 7. Relative rate of hydroamination vs. concentration of HCTf$_3$ (related rates are based on rate of reaction using 0.1% acid).

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).
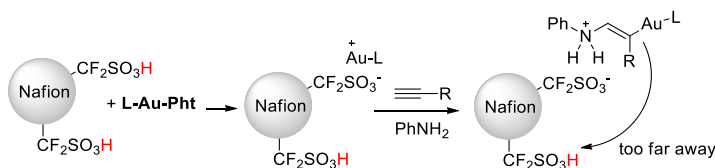
Scheme 21. Effect of polymer-based acid activation on hydroamination.

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[80] 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.[15] 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[117] (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[106] (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[118] have reported a high turnover number in the [(NHC)Au^I]-catalyzed alkyne hydration, albeit high temperatures were needed to complete this reaction. We found that the IPr-Au-Cl/AgSbF$_6$ system was slow at lower temperature (60^0C), but our IPr-Au-Pht/HCTf$_3$ 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).[119,120] For example, Ph$_3$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$_3$P-Au-Pht/HCTf$_3$ furnished the product in high yield after only 1 h, under the same conditions. Furthermore, our L-Au-Pht/HCTf$_3$ system worked well in the C-H addition to alkynes (Scheme 22f),[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$_3$P-Au-Pht/HCTf$_3$ system was very efficient even at 0.02% catalyst loading. A similar result occurred during the cycloisomerization of propargyl amide: the Ph$_3$PAuCl/AgOTf system was very slow at low catalyst loadings whereas our Ph$_3$P-Au-Pht/HCTf$_3$ system was able to finish the reaction in less than 3 h with the same gold catalyst loading.

(a)
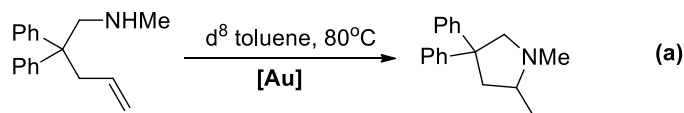
Ph₃PAuCl (5%) **/** AgOTf (10%) **/** 6h   5%
Ph₃P-Au-Pht (5%)/ HCTf₃ (10%) / 5h   95%
Ph₃P-Au-Pht (0.5%)/ HCTf₃ (1%) / 12h   95%

(b)
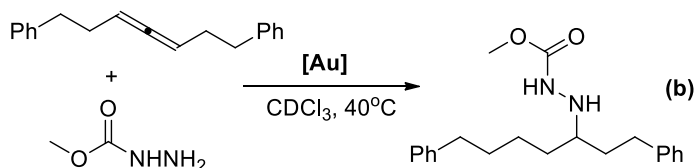
Ph₃PAuCl (5%) **/** AgOTf (10%) **/** 19h   trace
Ph₃PAuNTf₂ (5%) **/** 19h   45%
Ph₃P-Au-Pht (5%)/ HCTf₃ (10%) / 19h   59%
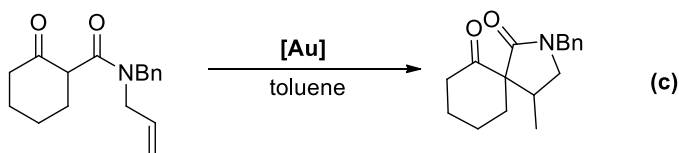
(c)

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

(d)
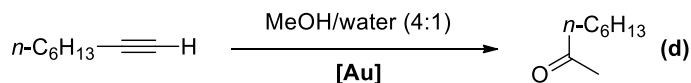
Ph₃PAuCl (1%) **/** AgOTf (2%) **/** rt /19h   0%
Ph₃P-Au-Pht (1%)/ HCTf₃ (2%) / rt / 19h   82%

IPrAuCl (0.1%) **/** AgSbF₆ (0.2%) / 45min / 65 °C   **10**%
IPr-Au-Pht (0.1%)/ HCTf₃ (0.2%) / 45 min / 65 °C   100%
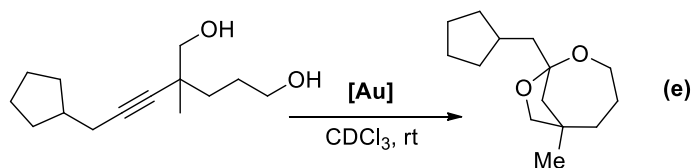
(e)

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

(f)
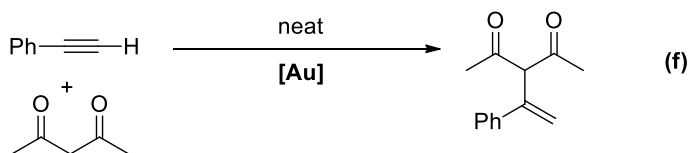
Ph₃PAuCl (5%) **/** AgOTf (5%) **/** rt **/** 17h   trace
Ph₃P-Au-Pht (2.5%)/ HCTf₃ (5%) / rt / 17h   52%
JohnPhos-Au-Pht (2.5%)/ HCTf₃ (5%) / 65°C /45 h   92%

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);[122] in this reaction the authors used L-Au-NTf$_2$ (5% loading, L = Ph$_3$P or BrettPhos, prepared from L-Au-Cl and AgNTf$_2$). 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.[123-125]
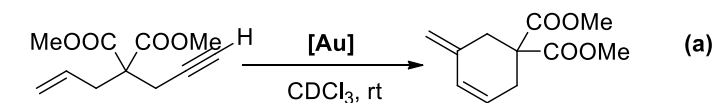
Ph$_3$PAuCl (0.2%) / AgOTf (0.4%) / 1.5h   0% (no reaction)
Ph$_3$P-Au-Pht (0.02%)/ HCTf$_3$ (0.04%) / 1.5h   71%
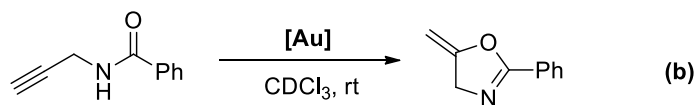
Ph$_3$PAuCl (1%) / AgOTf (2%) / 2.5h   5%
Ph$_3$P-Au-Pht (1%)/ HCTf$_3$ (2%) / 2.5h   92%
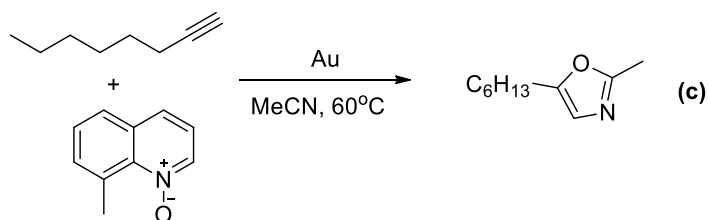
Ph$_3$P-Au-NTf$_2$ or BrettoPhos-AuNTf$_2$ (5%) / 3 h   92-99%
JohnPhos-Au-Pht (0.5%)/ HCTf$_3$ (1%) / 3 h   95%
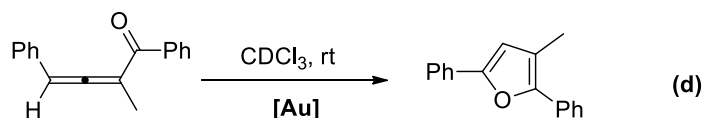
Ph$_3$PAuCl (0.02%) / AgOTf (0.04%) / 0.5h   95%
Ph$_3$P-Au-Pht (0.02%)/ HCTf$_3$ (0.04%) / 0.5h   95%

Scheme 23. Other examples of gold-catalyzed reactions.

In the above examples, the activation of **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)[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 **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,[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).
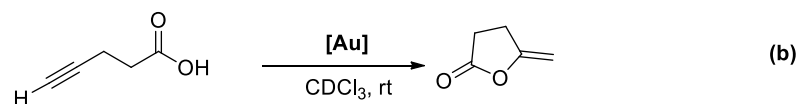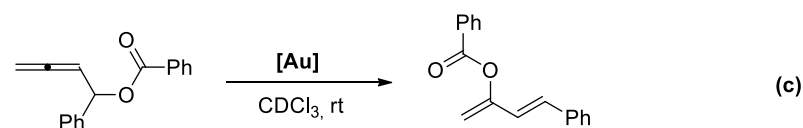
Scheme 24. Gold catalyzed reaction which need milder conditions.

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

General procedure for Synthesis of Gold(I) Phthalimide Complex (L-Au-Pht).
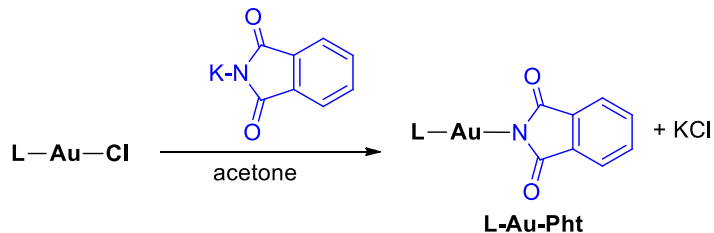
A mixture of Ph$_3$PAuCl (0.1 mmol, 49 mg) and potassium phthalimide (0.15 mmol, 27 mg) was dissolved in acetone (1 mL). The suspension was stirred at 45°C for 3 h. Then the reaction mixture was filtered and washed with small amount of acetone. Then most of the acetone in the filtrate was evaporated 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.
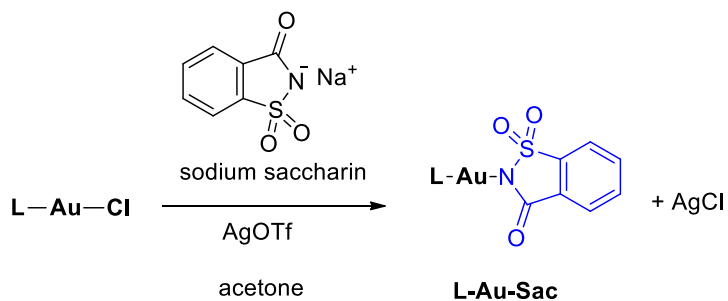
A mixture of Ph$_3$PAuCl (0.1 mmol, 49 mg), silver triflate (0.15 mmol, 38mg) and saccharin sodium salt (0.15 mmol, 31 mg) was dissolved in acetone (1 mL). The suspension was stirred at 45°C for 3 h. Then the reaction mixture was filtered and washed with small amount of acetone. Then most of the acetone 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.
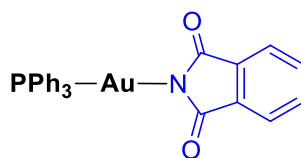
Ph₃PAu-Pht

Ph₃P-Au-Pht. ^{1}H NMR (400 MHz, CDCl₃): δ 7.40-7.76 (m, 19 H); ^{13}C NMR (100 MHz, CDCl₃): δ 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, CDCl₃): δ 32.69. ESI-HRMS (ESI+): m/z calcd. for C₂₆H₂₀AuNO₂P (M⁺ + H) 606.0897, found 606.0895.
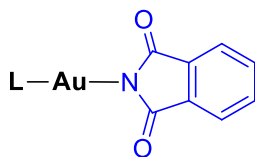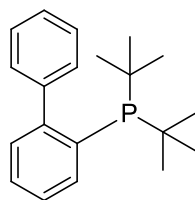
JohnPhos-Au-Pht   L = JohnPhos

Johnphos-Au-Pht. ^{1}H NMR (400 MHz, CDCl₃): δ 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, CDCl₃): δ 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, CDCl₃): δ 58.18. ESI-HRMS (ESI+): m/z calcd. for C₂₈H₃₂AuNO₂P (M⁺ + H) 642.1830, found 642.1833.

IPr-Au-Pht

L = IPr
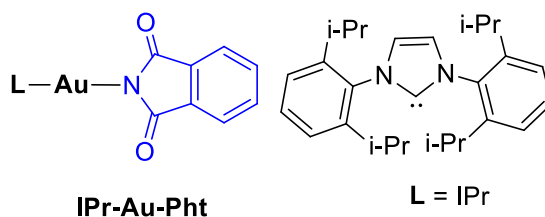
IPr-Au-Pht. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.43-7.54 (m, 4 H), 7.35-7.43 (m, 2 H), 7.24-7.33 (m, 4 H), 7.17-7.23 (m, 2 H), 2.6 (m, 4 H), 1.43 (d, J = 8 Hz, 12 H), 1.24 (d, J = 8 Hz, 12 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 178.1, 177.3, 145.7, 136.3, 133.9, 131.7, 130.6, 124.2, 123.0, 121.3, 28.9, 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.

Mor-DalPhos-Au-Pht

L = Mor-DalPhos
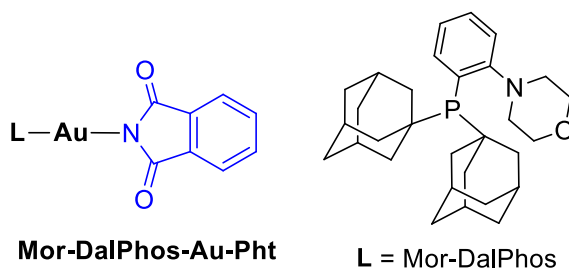
DalPhos-Au-Pht. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.77-7.84 (m, 1 H), 7.68-7.74 (m, 1 H), 7.52-7.62 (m, 4 H), 7.29-7.36 (m, 1 H), 7.23-7.26 (m, 1 H), 4.39 (t, J = 12 Hz, 2 H), 3.77 (d, J = 12 Hz, 2 H), 3.01 (t, J = 8 Hz, 2 H), 2.72 (d, J = 8 Hz, 2 H), 2.13-2.34 (m, 12 H), 1.97-2.04 (m, 6 H), 1.63-1.77 (m, 12 H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 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$_3$): δ 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.
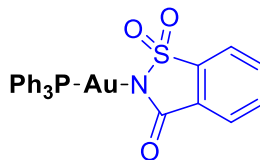
Ph₃P-Au-Sac

Ph3P-Au-Sac. ^{1}H NMR (400 MHz, CDCl$_3$): 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); ^{13}C NMR (100 MHz, CDCl$_3$): 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; ^{31}P NMR (162 MHz, CDCl$_3$): δ 32.35. ESI-HRMS (ESI+): m/z calcd. for C$_{25}$H$_{20}$AuNO$_3$PS (M$^+$ + H) 642.0562, found 642.0564.
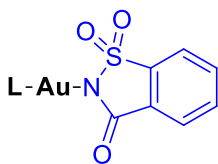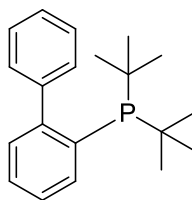
JohnPhos-Au-Sac   L = JohnPhos

JohnPhos-Au-Sac. ^{1}H NMR (400 MHz, CDCl$_3$): 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); ^{13}C NMR (100 MHz, CDCl$_3$): 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); ^{31}P NMR (162 MHz, CDCl$_3$): δ 57.92. ESI-HRMS (ESI+): m/z calcd. for C$_{27}$H$_{32}$AuNO$_3$PS (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, 1.103g), 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 CDCl$_3$ (0.5 mL) and was analyzed by ^{1}H-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.
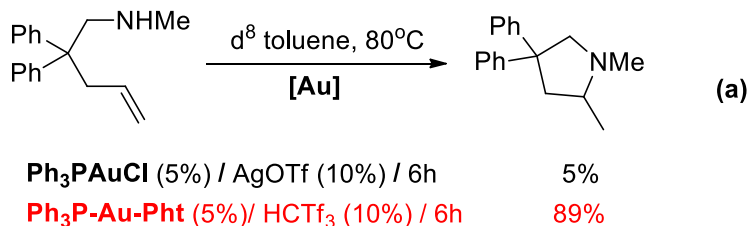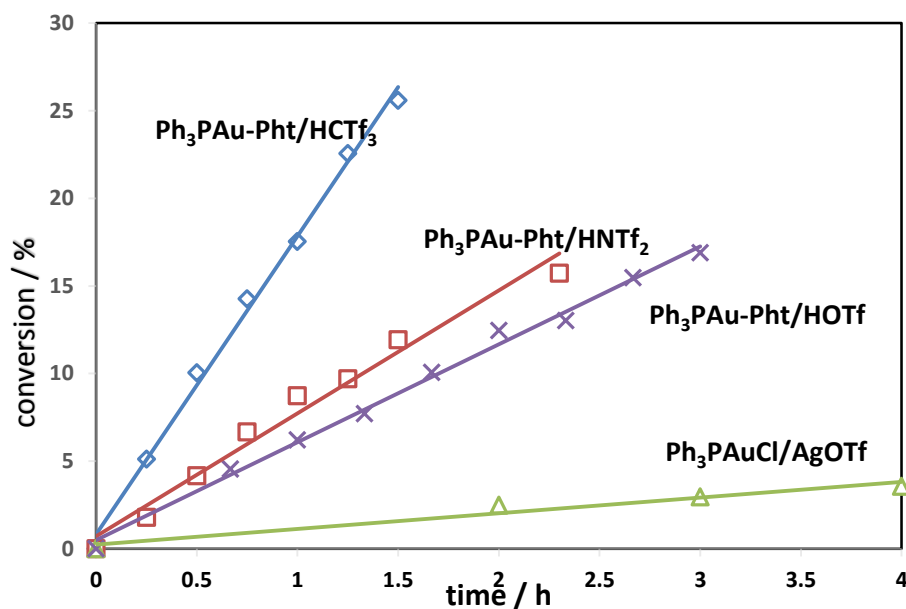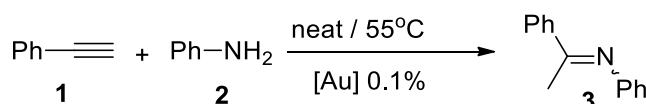
General Procedure for the Gold-Catalyzed Intramolecular Hydroamination of Aminoalkene. To a stirred solution of aminoalkene (0.25 mmol, 63 mg) in 0.2 mL d^8-toluene, acid activator (10 mol%, 0.025 mmol) and **Ph₃P-Au-Pht** (5%, 0.0125 mmol) were added. The reaction mixture was stirred at 80 °C and the progress of reaction was monitored by ^{1}H NMR.

Ph₃PAuCl (5%) **/** AgOTf (10%) **/** 19h   trace
Ph₃PAuNTf2 / 19h   45%
Ph₃P-Au-Pht (5%)/ HCTf₃ (10%) / 19h   59%
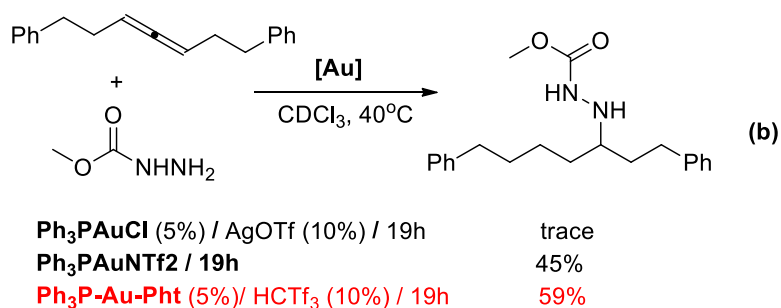
General Procedure for the Gold-Catalyzed hydroamination of Carbazate to Allene.

Allene (0.04 mmol, 10 mg), Methyl carbazate (0.04 mmol, 3.7mg) and Ph₃PAuNTf₂ (5 mol%, 1.5mg) were added into NMR tube with 0.5 mL CDCl₃ as solvent. The reactions were conducted at 40 °C and the progress of reaction was monitored by ^{1}H NMR.

SegPhos(Au-Cl)₂ (5%) /Cu(OTf)₂ (10%)   110°C / 24h   96%
Johnphos-Au-Pht (2.5%) / HCTf₃(5%)   100°C / 5h   96%
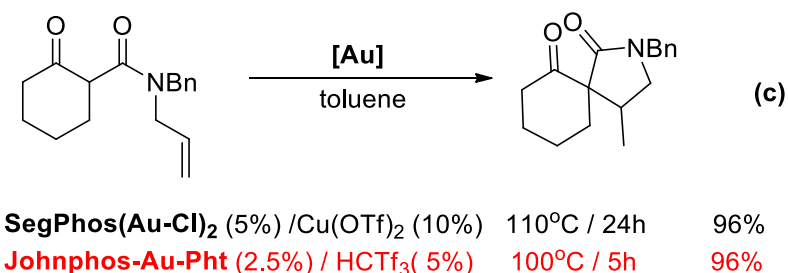
General Procedure for the Gold-Catalyzed hydroalkylation of olefin. To a stirred solution of ene-β-ketoamide (0.25 mmol, 67.8 mg) in 0.5 mL d^8-toluene, 70% HCTf₃ (7.4 mg, 1.25 × 10^{-2} mmol) and **Johnphos-Au-Pht** (4.1 mg, 6.25 × 10^{-3} mmol) were added, The reaction was conducted at 100 °C and monitored by ^{1}H NMR.

(d)

$n\text{-}C_6H_{13}$———H → (MeOH/water (4:1), [Au]) product: methyl ketone (2-octanone), $n\text{-}C_6H_{13}$

Ph₃PAuCl (1%) **/** AgOTf (2%) **/ rt** /19h   0%
Ph₃P-Au-Pht (1%)/ HCTf₃ (2%) / rt / 19h   82%

IPrAuCl (0.1%) **/** AgSbF₆ (0.2%) **/** 4h / 65 °C   83%
IPr-Au-Pht (0.1%)/ HCTf₃ (0.2%) / 45 min / 65 °C   100%
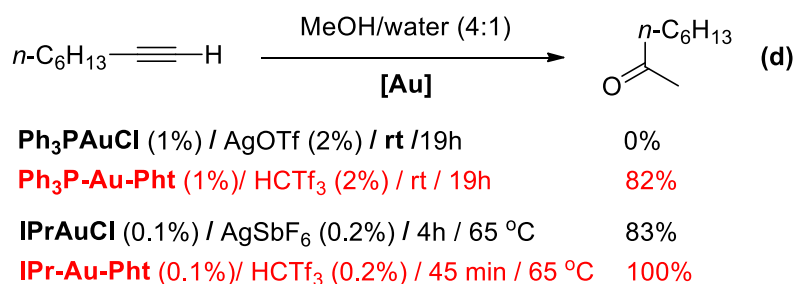
General Procedure for the Gold-Catalyzed Hydration. To a stirred solution of 1-octyne (2 mmol, 220 mg) and acid activator (2%, 0.04 mmol) in a mixed solvent (MeOH / water = 4:1) was added L-Au-Pht (1%, 0.02mmol). The reaction mixture was stirred at room temperature and monitored by ^{1}H NMR.

(e)

[diol substrate] → ([Au], CDCl₃, rt) → [bicyclic product, Me]

Ph₃PAuCl (0.1%) **/** AgOTf (0.2%) **/** 5h   trace
Ph₃P-Au-Pht (0.1%)/ HCTf₃ (0.2%) / 1h   94%
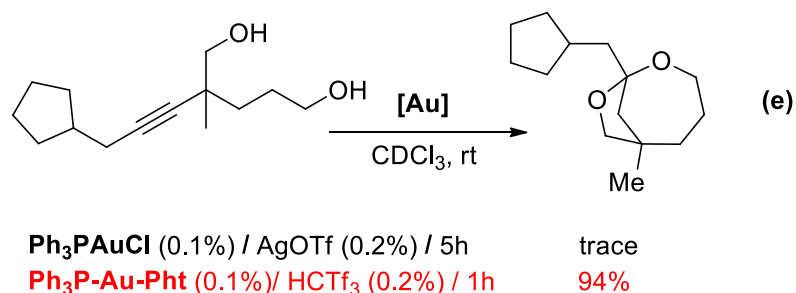
General Procedure for the Gold-Catalyzed Cycloisomerization of 2-Alkynyl-1,5-diols. Standard stock solution (0.01 M) of L-Au-Pht were made by weighing the gold complex into a vial using CDCl₃ as solvent. Standard stock solutions (0.02 M) of AgOTf and HCTf₃ were also prepared using acetone as solvent. The model reaction was conducted in a NMR tube. 10 μL (10^{-4} mmol) of AgOTf or HCTf₃ stock solution were added to a NMR tube and the solvent was removed by vacuum. Then diol (0.1 mmol, 22.4mg) in 0.4 mL CDCl₃, 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.

Ph—≡—H

O   O

neat
[Au]

O   O

Ph

(f)
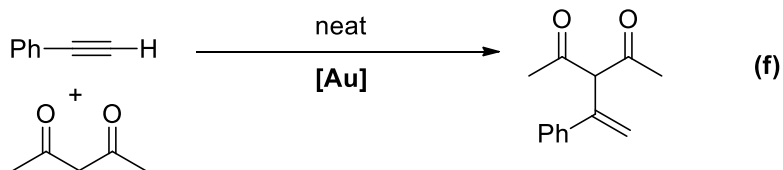
Ph₃PAuCl (5%) **/** AgOTf (5%) **/** rt **/** 17h   trace
Ph₃P-Au-Pht (2.5%)/ HCTf₃ (5%) / rt / 17h   52%
JohnPhos-Au-Pht (2.5%)/ HCTf₃ (5%) / rt/45 h   92%

General Procedure for the Gold-Catalyzed Nakamura Reaction. Acetyl acetone (0.2 mmol, 20 mg), phenylacetylene (0.4 mmol, 40.9 mg), 70% HCTf₃ (0.01mmol, 5.9 mg) and L-Au-Pht (5 × 10^{-3} mmol) were added into a NMR tube with 0.5 mL CDCl₃ as solvent. The reactions were conducted at room temperature and monitored by ^{1}H NMR.

MeOOC COOMe H

[Au]

CDCl₃, rt

COOMe
COOMe

(a)
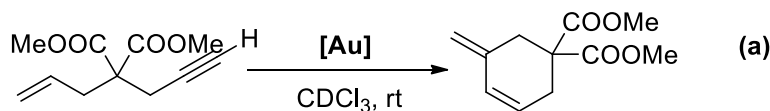
Ph₃PAuCl (0.2%) **/** AgOTf (0.4%) **/** 1.5h   0% (no reaction)
Ph₃P-Au-Pht (0.02%)/ HCTf₃ (0.04%) / 1.5h   71%

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 CDCl₃ as solvent. AgOTf and HCTf₃ 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 HCTf₃ 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 CDCl₃ and

corresponding L-Au-Pht solutions (20 µL) were added to NMR tube. The reactions were

conducted at room temperature and monitored by ^{1}H NMR.

(b)
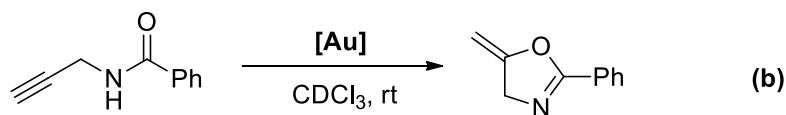
Ph$_3$PAuCl (1%) / AgOTf (2%) / 2.5h   5%
Ph$_3$P-Au-Pht (1%)/ HCTf$_3$ (2%) / 2.5h   92%

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 CDCl$_3$ as solvent. AgOTf and HCTf$_3$ 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 HCTf$_3$ 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 CDCl$_3$

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 ^{1}H NMR.

(c)
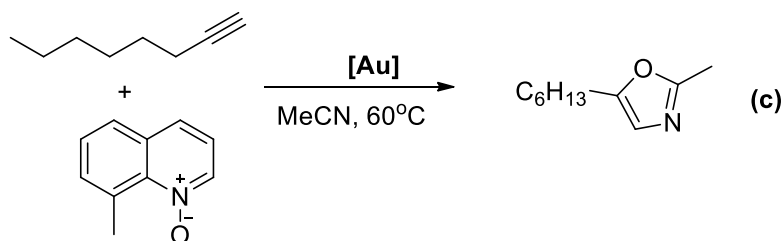
Ph$_3$P-Au-NTf$_2$ or BrettoPhos-AuNTf$_2$ (5%) / 3 h   92-99%
JohnPhos-Au-Pht (0.5%)/ HCTf$_3$ (1%) / 3 h   95%

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% HCTf$_3$ (3×10^{-3}

mmol, 1.8 mg) and JohnPhos-Au-Pht (1.5×10^{-3} mmol, 0.9 mg) were added into a small

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vial with 0.5 mL acetonitrile as solvent. The reactions were conducted at 60°C and monitored by ^{1}H NMR.

(d)
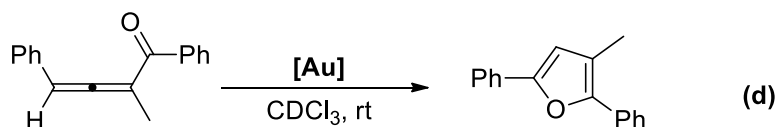
Ph₃PAuCl (0.02%) **/** AgOTf (0.04%) **/** 0.5h   95%

Ph₃P-Au-Pht (0.02%)/ HCTf₃ (0.04%) / 0.5h   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 CDCl₃ as solvent. AgOTf and HCTf₃ were also made solutions (0.002 M) in acetone. The model reaction was conducted in a NMR tube. 10 µL (2 × 10⁻⁵ mmol) of AgOTf and HCTf₃ 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 CDCl₃ and corresponding L-Au-Pht solutions (1×10⁻⁵ mmol, 10 µL) were added to NMR tube. The reactions were conducted at room temperature and monitored by ^{1}H NMR.

(a)
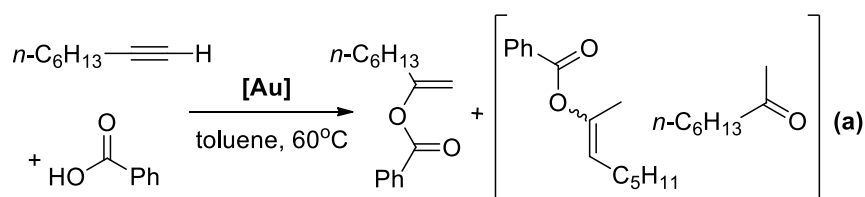
JohnPhos-Au-Cl/AgOTf (1%) / 12h   3% + mixtures of Z/E isomers of
                                                                                double bonds migrated products
                                                                                and hydrolyzed ketone

Johnphos-Au-Pht (1%) /18h   96% (single product)
**Johnphos-Au-Pht** (0.2%) /48h   92% (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 d^8-toluene as solvent. The reactions were conducted at 60°C monitored by ^{1}H NMR.

(b)

Ph$_3$P-Au-Pht (0.2%)/ 1h   95% (single product)
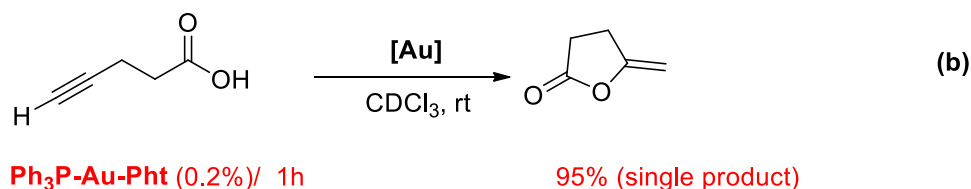
General Procedure for the Gold-Catalyzed intramolecular addition of carbonic acid to alkyne. 4-Pentynoic acid (0.45mmol, 44.1mg) and Ph$_3$P-Au-Pht (9×10^{-4} mmol, 90 µL) were added into NMR tube with 0.5 mL CDCl$_3$ as solvent. The reactions were conducted at room temperature and monitored by ^{1}H NMR.


(c)

JohnPhos-AuCl (2%) **/** AgOTf (4%) **/** 2h   25%
JohnPhos-Au-Pht (2%)/ HCTf$_3$ (1.5%) / 2 h   82%
JohnPhos-Au-Pht (2%)/ AgCTf$_3$ (4%) / 2 h   85%
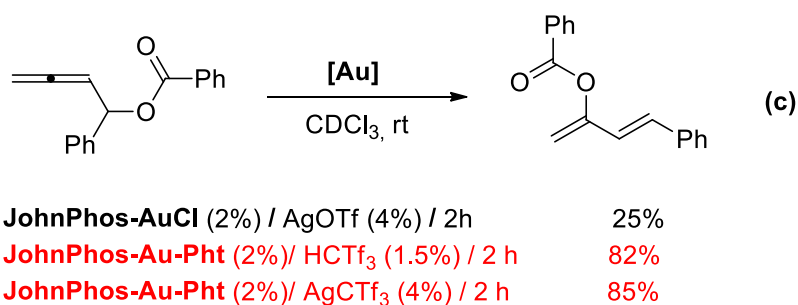
General Procedure for the Gold-Catalyzed isomerization of allenyl carbinol ester to 1,3-butadien-2-ol esters. Standard stock solutions (0.01 M) of L-Au-Pht were made by weighing the gold complex into a vial and adding CDCl$_3$ as solvent. HCTf$_3$ was also made solutions (0.05 M) in acetone. The model reaction was conducted in a NMR tube. 30 µL of HCTf$_3$ 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 CDCl$_3$ 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 ^{1}H NMR.

NMR spectra for gold complexes

JohnPhos-Au-Pht

JohnPhos-Au-Pht
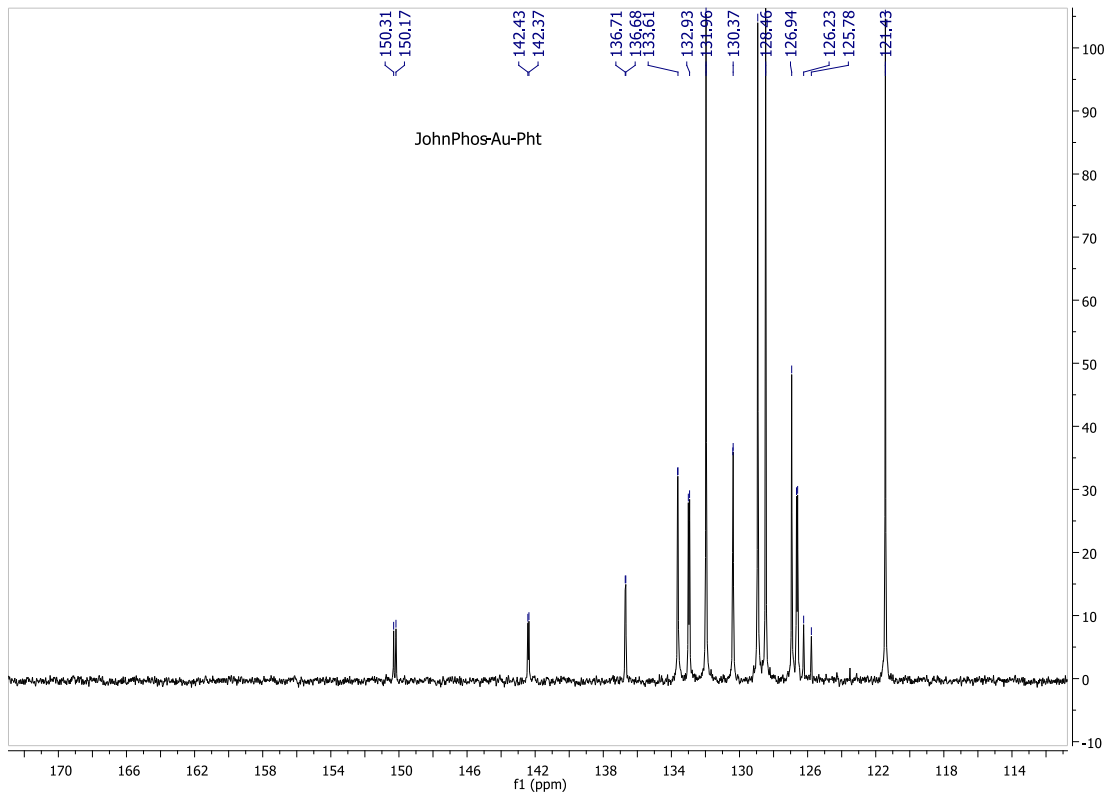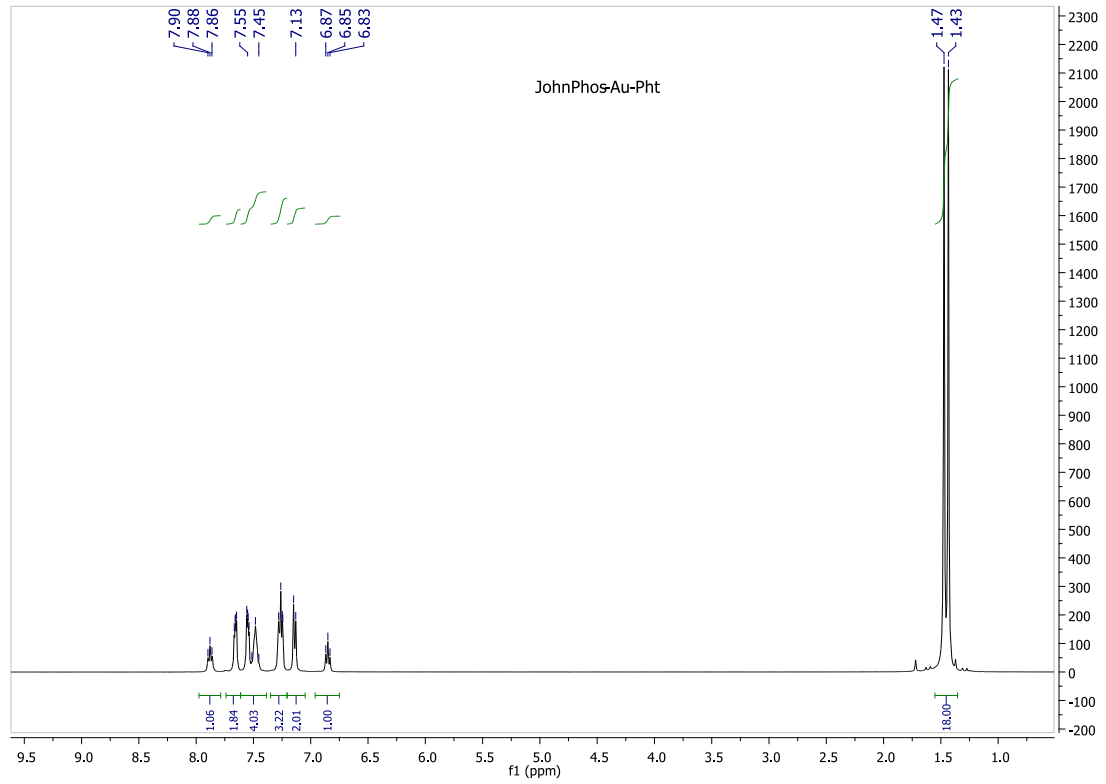
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APPENDIX

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.

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CURRICULUM VITAE

Junbin Han

PhD candidate   Chemistry Department, University of Louisville

Phone: 502-468-8648   2320 South Brook Street, Louisville, Kentucky 40292

Email: jbhan001@exchange.louisville.edu

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

+ Separating and recovering high value-added products from benzoic acid industrial residue and further functionalization and polymerization (OLED) of corresponding molecules.

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

   Zhang, X.; **Han, J.-B**.; Li, P.-F.; Ji, X.; Zhang, Z. *Synth. Commun.* **2009**, *39*, 3804.

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"

   Zhang, X.; Qiao, P.; Ji, X.; **Han, J**.; Liu, L.; Weeks, B. L.; Yao, Q.; Zhang, Z. *ACS*

   Sustainable Chemistry & Engineering **2013**.

+ 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)

3. "Highly Efficient Cu(I)-Catalyzed Synthesis of N-Heterocycles through a Cyclization-Triggered Addition of Alkynes"

   Han, J.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.* **2009**, *132*, 916.

4. "Synthesis of α-CN and α-CF3 N-Heterocycles through Tandem Nucleophilic Additions"

   Han, J.; Xu, B.; Hammond, G. B. *Org. Lett*. **2011**, *13*, 3450.

5. "Synthetic Evolutions in the Nucleophilic Addition to Alkynes."

B. Xu, W. Wang, L. Liu, **J. Han**, Z. Jin and G. B. Hammond *J. Organomet. Chem.* **2011,** *696*, 269-276

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

    Han, J.; Paton, R. S.; Xu, B.; Hammond, G. B. *Synthesis* **2013**, *45*, 463.

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

    Han, J.; Xu, B.; Hammond, G. B. *J. Org. Chem* **2014**, (Manuscript submitted)

➕ 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"

    Han, J.; Wang, W.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.* **2014.** Manuscript submitted

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
    Han, J.; Lu, Z.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.***2014.** Manuscript submitted.

➕ 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**).

11. **Han, J**.; Xu, B.; Hammond, G. B. (in preparation).

Patents

1. Zhang, Z; Zhang, Xi; Qing, L; **Han, J**. Synthesis of 2-Nitrofluorenone. 2008. China. CN101245018. Filed C07C205/45 (2006.01). Issued August 20, 2008

2. Zhang, Z; Zhang, Xi**; Han, J**; Feng Y; Ji, X. Synthesis of 2, 4, 7- Trinitro-9-fluorenone. 2008. China. CN101302165. Field C07C205/45(2006.01). Issued November 12, 2008

3. Zhang, Z; Zhang, Xi; **Han, J**; Ji, X; Zhang, P. Synthesis 2-Bromo-7-nitro-9-fluorenone. 2009. China. CN101514161. Field C07C205/45(2006.01). Issued August 26, 2009

4. Zhang, Z; Zhang, Xi; **Han, J**; Ji, X; Shanshan, Jiang. Synthesis 2, 7-Dibromo-4-nitro-9-fluorenone. 2009. China. CN101214060. Field C07C205/45(2006.01). Issued August 26, 2009

Presentation in National Conferences

"Size enhanced reactivity: Theory of ionic transition state expansion", 246th American Chemical Society National Meeting & Exposition, September 9, 2013, Indianapolis, IN (Oral presentation) **Han, J**.; Xu, B.; Hammond, G. B. (Abstract: ORGN191).

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

➢ Microsoft Office, SciFinder, Beilstein Crossfire, Reaxys, ChemOffice, OriginLab, EndNote.