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Bis(amidate)bis(amido) Titanium Complex: A Regioselective Intermolecular Alkyne Hydroamination Catalyst

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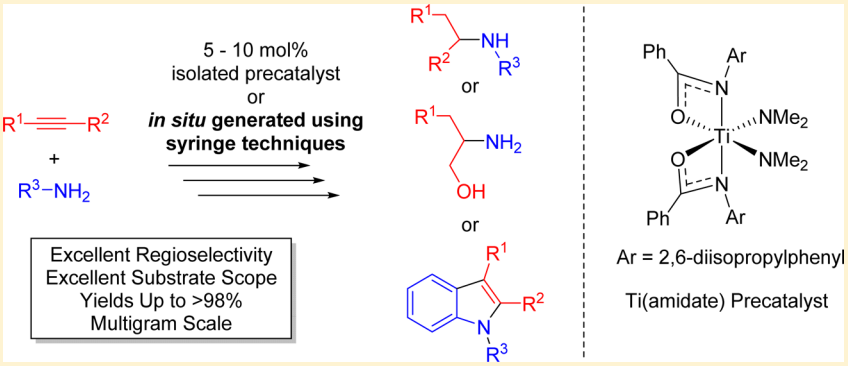
Supporting Information



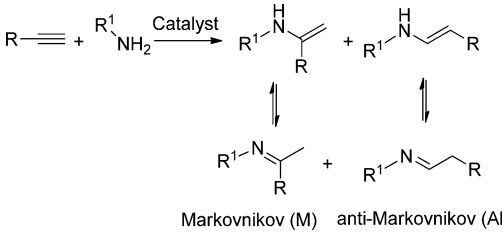
ABSTRACT: An efficient and selective bis(amidate)bis(amido) titanium precatalyst for the anti-Markovnikov hydroamination of alkynes is reported. Hydroamination of terminal and internal alkynes with primary alkylamines, arylamines, and hydrazines is promoted by 5−10 mol % of Ti catalyst. Various functional groups are tolerated including esters, protected alcohols, and imines. The in situ generated complex shows comparable catalytic activity, demonstrating its synthetic versatility for benchtop application. Applications of this catalyst for the synthesis of amino alcohols and a one-pot procedure for indole synthesis are described. A mechanistic proposal that invokes turnover-limiting protonolysis is presented to rationalize the observed regioselectivities.

INTRODUCTION

Nitrogen-containing organic molecules are ubiquitous in pharmaceuticals and agrochemicals, making the efficient construction of C−N bonds of considerable interest. In this regard, the catalytic addition of an N−H bond across an unsaturated C−C bond, known as hydroamination, is an often targeted 100% atom economic C−N bond forming reaction.[1−7] For intermolecular versions of this reaction the starting materials employed (amines, alkenes, and alkynes) are inexpensive and commercially available and do not require the installation of activating or protecting groups. Because of the electron-rich nature of both the amine and alkene/alkyne, this reaction is particularly kinetically challenging and demands catalytic conditions to realize this desirable transformation.[1,6,7] Numerous catalysts based on elements from across the periodic table have been reported to induce hydroamination.[8−55] Notably, early transition metal systems, especially those based on group 4 metals, have also been extensively reported.[1,3,5,47−53,56−78] The main advantages of using such group 4 complexes are improved cost effectiveness and low toxicity in comparison to late-transition metals. They also show improved robustness and functional group tolerance when compared to lanthanide- and alkaline-earth metal-based systems.[1,2,6,14−42,79]

While the intermolecular hydroamination of alkenes affords secondary and tertiary amines directly, the development of catalytic systems able to effect such transformations has proved challenging.[2,16,18−20,24,39,44,59,76,77] The analogous reaction of amines with alkynes is well established,[2,6,7,60,74,75,80] and notably group 4 metals have been used to great advantage to address this synthetic challenge.[1,3,5,60−68,73,77,80−87] The products of this reaction are reactive imine and enamine species (Scheme 1), which are useful synthetic intermediates that can be used for subsequent transformations in "one-pot" procedures.[3,4,9,11,26,47,66,88−102] Commercially available $Ti(NMe_2)_4$ is catalytically active for hydroamination; however, there are significant substrate scope limitations.[86,103] Additionally, when

Scheme 1. Intermolecular Hydroamination of Alkynes



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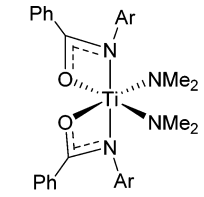
terminal alkyne substrates are used with $Ti(NMe_2)_4$, mixtures of the Markovnikov (M) and anti-Markovnikov (AM) regioisomers are produced (Scheme 1).[86] Recent contributions exploiting the π-acidity of gold have realized efficient terminal alkyne hydroamination to access the Markovnikov product selectively,[97,104−106] while group 4 metal systems have been reported to prefer the anti-Markovnikov products with select substrate combinations.[2,3,5,56,63,66,82,83]

Group 4 hydroamination catalysts with cyclopentadienyl-type (Cp) ligands have been used for alkyne hydroamination.[1] Notably, Ind_2TiMe_2 described by Doye and co-workers[67] has been reported as one of the most general alkyne hydroamination catalysts to give impressive reactivity in the reaction of a variety of aryl and alkylamines with terminal and internal alkynes with good substrate-controlled regioselectivity. For example, the hydroamination of terminal alkylalkynes with alkylamines yields anti-Markovnikov products preferentially while arylamines afford the Markovnikov products. This catalyst can even be used with known challenging amine substrates, such as benzylamine or other nonsterically demanding primary amines; however, slow addition of amine is required.

Noncyclopentadienyl based titanium complexes have also been shown to be efficient hydroamination catalysts. For example, building upon the original work of Rothwell and co-workers,[107] the Beller group[64,82] described a series of in situ generated catalysts using various aryloxide ligands, whereby the regioselectivity was influenced by the choice of ligand. These systems were able to achieve hydroamination with less sterically demanding alkylamines without the need of slow addition; however, no one aryloxide ligand provided good reactivity *and* regioselectivity over a broad range of substrates. Furthermore, while alkylamine substrates afforded anti-Markovnikov products preferentially in most cases, arylamines once again gave the Markovnikov products in excess.

Our group has previously reported a bis(amidate)bis(amido) titanium complex (**1**) for intermolecular terminal alkyne hydroamination (Figure 1).[66] Complex **1** is easily synthesized



Ar = 2,6-diisopropylphenyl

1

Figure 1. Bis(amidate)bis(amido)titanium precatalyst **1**.

from inexpensive and commercially available starting materials in two synthetic steps on a multigram scale. Precatalyst **1** displays outstanding selectivity for the anti-Markovnikov product and more impressively, it can be used with all primary amine substrates, even benzylamine and allylamine, without any modification in synthetic protocol. Furthermore, good functional group tolerance has been established. For example, protected alcohols, ethers, and esters can all be incorporated into substrates that are suitable for hydroamination with precatalyst **1**. Most importantly, we show here that the commercially available[108] bis(amidate)bis(amido) titanium complex **1** is a broadly useful precatalyst for regioselective alkyne hydroamination.

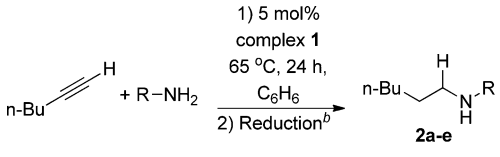
Herein, we show that complex **1** can be used with both terminal and internal alkynes with good to excellent regioselectivity in all cases. Furthermore, we show that complex **1** can be used with a range of reaction conditions to realize the hydroamination of terminal and internal alkynes with aryl and alkyl primary amines and even hydrazines. To facilitate versatile benchtop use, complex **1** can be prepared in situ using simple syringe techniques, with no reduction in catalytic efficiency. The synthetic utility of precatalyst **1** is further illustrated in the efficient synthesis of amino alcohols and indoles. Finally, the observed results can be rationalized using a [2 + 2] cycloaddition mechanistic proposal with a turnover-limiting associative protonolysis step.[5]

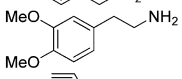
RESULTS AND DISCUSSION

Terminal Alkyne Hydroamination with Alkyl Amines.

Precatalyst **1** can be used for the regioselective hydroamination of the least sterically demanding 1-hexyne with a variety of alkylamines to give the anti-Markovnikov product selectively (Table 1). Here, we show that even minimal steric bulk and

Table 1. Hydroamination of 1-Hexyne and Alkylamines by Complex 1[a]



Entry	Amine	Yield(%)[c]
1		88 (**2a**)
2		88 (**2b**)
3		88 (**2c**)
4		78 (**2d**)
5		70 (**2e**)

[a]Conditions: 1-hexyne (1 equiv), amine (1 equiv), complex **1** (0.05 equiv), 65 °C, nitrogen atmosphere. [b]For reduction conditions, see Experimental Section. [c]Isolated yields.

some functional groups can be incorporated into the amine cosubstrates without sacrificing regioselectivity. These syntheses were performed using equimolar quantities of amine and alkyne with 5 mol % of **1** in benzene at 65 °C for 24 h to produce either the aldimine product or an aldimine−enamine mixture. The resulting mixture was then quantitatively reduced to the secondary amine product with stoichiometric reducing reagents to facilitate isolation and purification. These conditions were chosen for consistency and could be further optimized for select substrate combinations. For example, **2b** and **2c** required only 12 h to go to completion, as noted by monitoring the reaction by ^1H NMR spectroscopy. Thus, the results in Table 1 show that product decomposition with extended reaction times is not problematic. In all cases, spectroscopic monitoring of these reactions showed only the formation of the anti-Markovnikov hydroamination product and no Markovnikov intermediates could be detected. Furthermore, various nonprotic solvents can be tolerated with these reaction conditions; however, coordinating solvents such as diethyl ether demand longer reaction times. This is proposed

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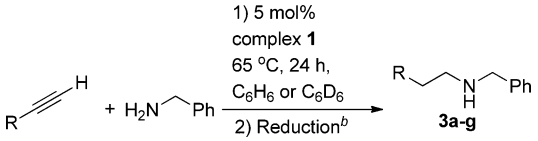
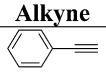
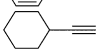
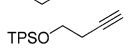
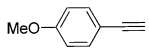
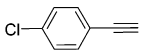
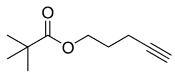
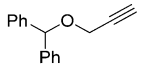
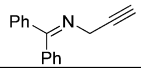
to be due to the fact that such solvents reversibly coordinate reactive sites at the metal center, thereby slowing catalysis.

As shown in Table 1, good yields of the secondary amine products can be obtained in all cases. *tert*-Butylamine is a commonly used substrate for regioselective alkyne hydroamination as the favorable steric bulk of the amine often translates to higher yields and better anti-Markovnikov selectivity.[67,81,82] Here, we observe the anti-Markovnikov product not only for *tert*-butylamine, but also for other amines including benzylamine with no need to modify reaction conditions. Also, to the best of our knowledge, precatalyst **1** is the only complex reported to promote hydroamination with allylamine.[89,90,102] The alkene provides a useful handle for further synthetic elaboration of the amine product. Catechol derivatives, such as 3,4-dimethoxyphenethylamine are known to coordinate to Lewis acidic metal centers;[109,110] however, this is not problematic with **1** and illustrates the functional group tolerance of this system.

Next, the alkyne substrate scope was explored, and the challenging substrate, benzylamine, was selected for this investigation. As shown in Table 2, an extensive array of

Table 2. Hydroamination of Benzylamine and Terminal Alkynes Catalyzed By Complex 1[a]



Entry	Alkyne	Yield (%)[c]
1		87 (**3a**)
2		87 (**3b**)
3		95[d] (**3c**)
4		70 (**3d**)
5		76[e] (**3e**)
6		83 (**3f**)
7		93 (**3g**)
8		80[e] (**3h**)
9		89[f] (**3i**)
10		79[f,g] (**3j**)

[a]Conditions: terminal alkyne (1 equiv), benzylamine (1.2 equiv), complex **1** (0.05 equiv), 65 °C, nitrogen atmosphere. [b]For reduction conditions, see Experimental Section. [c]Isolated yields. [d]Reaction time 120 h. [e]Isolated as the aldehyde after hydrolysis using SiO_2. [f]10 mol % of **1** at rt. [g]Isolated as the *N*-benzhydryl-*N*-benzyl diamine.

alkynes react regioselectively with benzylamine to give the anti-Markovnikov product. Phenylacetylene is known to form the anti-Markovnikov product in group 4 hydroamination catalysis.[61,64,65,86] Indeed this was also the case for **1** as the desired regioisomer was obtained in excellent yield (entry 1), using a similar protocol to that described above. Because of the fact that benzylamine is a known challenging substrate, a slight excess of amine (1.2 equiv) was used. Not surprisingly, increasing the steric demands of the substituent of the terminal alkyne does not affect regioselectivity (entries 2 and 3). These results show that precatalyst **1** can accommodate steric bulk on both the amine and alkyne partners, although sluggish reactivity was observed with *t*-butyl substituted alkyne (entry 3). Most importantly, a broad range of functionalized terminal alkynes undergo hydroamination to give only the anti-Markovnikov amine products **3d–j** in good to excellent yields (72–93%, Table 2, entries 4–10) after reduction of the imine/enamine intermediates. However, when 4-bromophenylacetylene was reacted with benzylamine in the presence of complex **1** a complex mixture of products resulted, under either standard reaction conditions or with reduced reaction temperatures. Gratifyingly, challenging protected propargyl alcohols and protected propargyl amines can be used as substrates. In these cases, higher catalyst loadings (10 mol %) and reduced reaction temperatures (room temperature) result in good yields of these desirable functionalized small molecules.[111]

Terminal Alkyne Hydroamination with Aryl Amines. The hydroamination of terminal alkyl alkynes with aromatic amines is also of interest, and as described earlier, these substrates typically give the Markovnikov product preferentially.[1,64,67,71,81,82] Using the general protocol described above (5 mol % **1**, 65 °C) with aniline as a substrate resulted in complex product mixtures, as observed by ^{1}H NMR spectroscopy. Specifically, when phenylacetylene and aniline were reacted at 65 °C for 24 h, multiple products were observed. Column chromatography of the crude reaction mixture resulted in the isolation of known tetrahydroisoquinoline **5a** in modest yield.[112] However, reduction of the crude reaction mixture afforded **5b** along with the anticipated anti-Markovnikov hydroamination product (Scheme 2). These observations can be rationalized by the formation of a common intermediate **4**, which is the direct precursor to the reduced product **5b**. Intermediate **4** can be obtained from an in situ intermolecular reaction between the two tautomers of the hydroamination product (Scheme 2). Thus we propose that **5a** is formed spontaneously through a proton-catalyzed intramolecular electrophilic aromatic substitution of **4** upon exposure to silica gel during purification by column chromatography.[112,113]

Aniline is known to be a highly reactive substrate in hydroamination and can be used at ambient temperature with some catalyst systems.[65] In order to reduce the unwanted side reactivity described above, a variety of arylamines and terminal alkynes were reacted at room temperature (Table 3). Subsequent reduction generally afforded the corresponding secondary amine product in moderate to high yields (62–83%). Good regioselectivity for the anti-Markovnikov product was observed when aniline and *para*-methoxyaniline were reacted with phenylacetylene (Table 3, entries 1 and 2). Similar good regioselectivity was observed when sterically bulky alkylalkynes were reacted with *para*-methoxyaniline (Table 3, entry 3 and 4); however, reaction with *t*-butyl acetylene was still sluggish, requiring a reaction temperature of 110 °C to reach full conversion within 24 h. When this particular reaction was monitored by ^{1}H NMR spectroscopy it was observed that 72 h at room temperature was required to realize conversions greater than 80%. When the protected propargyl alcohol was used as a substrate, similar outstanding regioselectivities were observed (entries 5 and 6). However, when a linear alkylalkyne such as 1-hexyne was used, selectivity was diminished, although the anti-Markovnikov product remains the major regioisomer (Table 3, entries 7 and 8). To the best of our knowledge, complex **1** is the only system reported for consistently accessing the anti-Markovnikov product as the major product with aryl amines.

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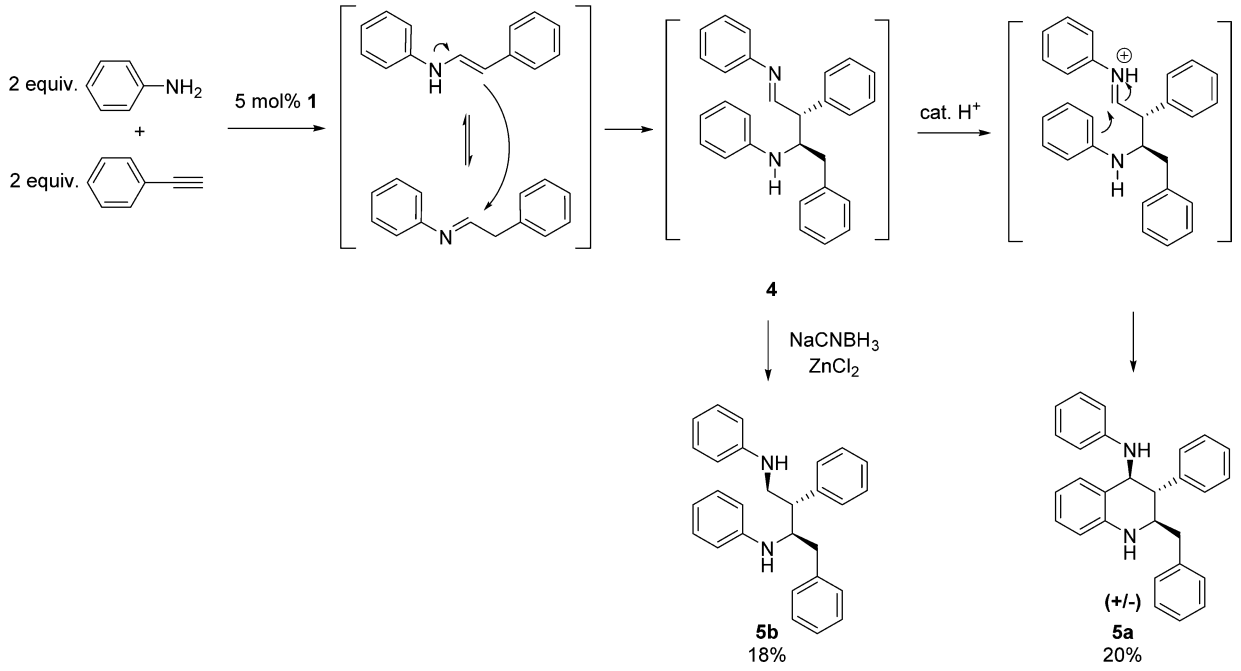
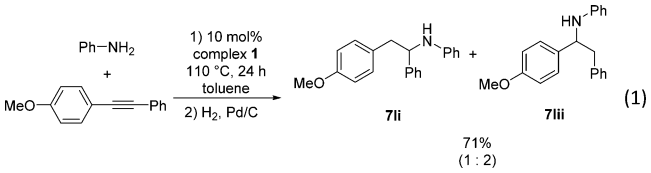
Scheme 2. Spontaneous Formation of Tetrahydroisoquinoline from Hydroamination of Phenylacetylene with Aniline



Bulky 2,6-dimethylaniline can be used for hydroamination, although higher reaction temperatures were required, presumably because of the increased steric demand of this starting material. Notably, exclusive anti-Markovnikov selectivity was achieved with this bulky substrate with electronically biased phenylacetylene (Table 3, entry 9). However, only the Markovnikov product was observed when 1-hexyne and protected propargyl alcohol were used with this bulky substrate (Table 3, entries 10 and 11). This complete change in regioselectivity is proposed to result from a turnover-limiting associative protonolysis step during the catalytic cycle (vide infra).

Internal Alkyne Hydroamination with Aryl and Alkyl Amines. Internal alkynes have also been examined as substrates for hydroamination with complex **1** (Table 4). Such substrates are more challenging for this sterically bulky catalyst. Thus, arylamines were investigated first, because of their increased reactivity. These more challenging hydroamination reactions require 10 mol % catalyst loading and elevated temperatures of 110 °C. While these temperatures are higher than those presented previously in this work, this temperature is consistent with other state-of-the-art literature protocols.[1,7,67]

The hydroamination/reduction sequence of symmetric and unsymmetric internal alkynes with aniline, *para*-methoxyaniline and even pentafluoroaniline afford **7a–f** in high yields (Table 4, entries 1–6, 8). Symmetric alkynes are consistently observed to be more challenging substrates because of a lack of bond polarization,[61,77,84,114] but are still tolerated by **1**. The imine–enamine mixture from the reaction of aniline and diphenylacetylene required the use of H_2 and Pd/C to quantitatively reduce the mixture. Similar to other related catalysts, the use of an unsymmetric alkyne, 1-phenyl-1-propyne, only gave the anti-Markovnikov isomer.[63,67] However, excellent regioselectivity is not limited to alkynes with electronic bias. A dialkyl substituted alkyne with a bulkier isopropyl group incorporated on one side and methyl on the other (Table 4, entry 7) resulted in only one isolable product. This result suggests that steric factors effectively control the regioselectivity achieved with complex **1**. Furthermore, regioselective reactivity is not limited to arylamines, as even benzylamine can be used for the regioselective hydroamination of internal alkynes. Here with these less reactive amines, elevated temperatures and longer reaction times were required when nonpolar diphenylacetylene was used (Table 4, entries 9–11). The reaction of a sterically symmetric but electronically unsymmetric diarylacetylene, (4-methoxyphenyl)phenylacetylene, with aniline under these reaction conditions was successful, but loss of regioselectivity was observed (eq 1). Upon reduction using H_2 and Pd/C, an



inseparable mixture of regioisomers was isolated in a 1:2 ratio (determined by quantitative ^{13}C NMR spectroscopy) favoring the product where the aniline addition occurred closer to the more electron-rich arene. The observed regioselectivity suggests that although steric factors dominate the control of regioselectivity with complex **1**, some electronic factors can also influence this control.

In Situ Catalyst Preparation. While complex **1** displays a promising scope of reactivity, including functional group tolerance, the air and moisture sensitivity of this crystalline material limits the use of this commercially available precatalyst[108] and it is preferably stored and handled using a glovebox. However, the facile synthesis of complex **1** from the addition of 2 equiv of the easily prepared amide proligand to a solution of commercially available $Ti(NMe_2)_4$ in toluene[66] illustrates that this catalyst system could be easily assembled in situ using simple syringe techniques.

Table 5 shows the comparison of the in situ prepared complex **1** in a variety of reactions on NMR tube scale. As is shown in Table 5, we were delighted to observe that the use of in situ generated complex was comparable to the use of isolated complex **1** in all

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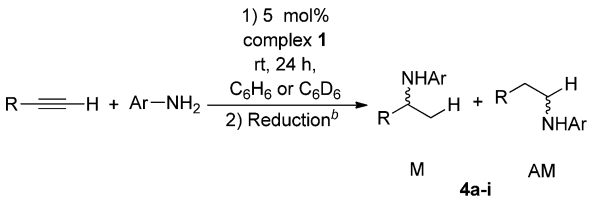
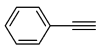
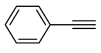
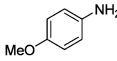
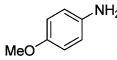
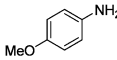
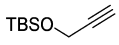
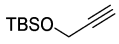
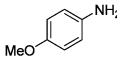
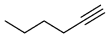
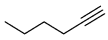
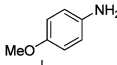
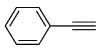
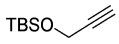
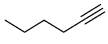
Table 3. Hydroamination of Terminal Alkynes and Arylamines Catalyzed By Complex 1[a]



Entry	Alkyne	Arylamine	Yield (%) (AM:M)[c]
1			83 (>49:1) (**6a**)
2			76 (>49:1) (**6b**)
3			80 (>49:1) (**6c**)
4			87 (>49:1)[d] (**6d**)
5			80 (>49:1)[e] (**6e**)
6			75 (>49:1)[e] (**6f**)
7			62 (1.6:1)[f] (**6g**)
8			77 (2.3:1)[f] (**6h**)
9			62 (>49:1)[g] (**6i**)
10			23 (1:>49)[g] (**6j**)
11			72 (1:>49)[g] (**6k**)

[a]Conditions: terminal alkyne (1 equiv), arylamine (1.2 equiv), complex **1** (0.05 equiv), rt, nitrogen atmosphere. [b]For reduction conditions, see Experimental Section. [c]Isolated yields. [d]Reaction temperature 110 °C. [e]10 mol % **1**. [f]Combined yield of both isomers. [g]Reaction temperature 65 °C.

cases (entries 1−3). The modestly reduced yields reported here are due to the small scale of the reaction and not a loss in catalytic activity. Most importantly, the scope of reactivity, as well as the excellent regioselectivity for the anti-Markovnikov product was preserved when the in situ precatalyst was used (entries 4 and 5). Using this method of precatalyst generation, the use of a glovebox can be completely avoided.

When developing catalysts for application in synthesis, one must develop systems that are amenable to scale-up. Scheme 3 shows that these simple syringe techniques under an inert atmosphere can be used in a representative hydroamination reaction of phenylacetylene with benzylamine on multigram scale. On this scale column chromatography can be avoided. Thus, after reduction with $NaBH_4$ and isolation of the free amine using a back extraction protocol, product **3a** was obtained in 77% yield (3.01 g) (Scheme 2). This example demonstrates the practicality and versatility of this easy to use and broadly applicable catalytic system for the synthesis of secondary amines from alkynes and primary amines.

Scheme 3. Precatalyst 1 Prepared In Situ for Multigram, Column-Free Synthesis and Isolation of 3a

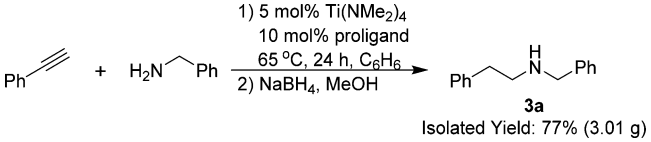
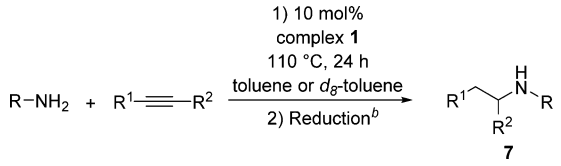


Table 4. Hydroamination of Internal Alkynes by Complex 1[a]



Entry	R	R^1	R^2	Yield (%)[c]
1	Ph	Ph	Me	>98 (**7a**)
2		Et	Et	>98 (**7b**)
3		Ph	Ph	98[d] (**7c**)
4	PMP[e]	Ph	Me	>98 (**7d**)
5		Et	Et	>98 (**7e**)
6		Ph	Ph	>98 (**7f**)
7		*i*Pr	Me	76 (**7g**)
8	C_6F_5	Ph	Me	91 (**7h**)
9	Bn	Ph	Me	78 (**7i**)
10		Et	Et	74 (**7j**)
11		Ph	Ph	65[f] (**7k**)

[a]Conditions: internal alkyne (1 equiv), amine (1.2 equiv), complex **1** (0.1 equiv), 110 °C, nitrogen atmosphere. [b]For reduction conditions, see Experimental Section. [c]Isolated yield. [d]Reduction with H_2 and Pd/C. [e]PMP = *para*-methoxyphenyl. [f]Required 130 °C for 48 h.

Applications of Hydroamination Precatalyst 1 in Synthesis. Precatalyst **1** has been shown to be useful in one-pot syntheses of tetrahydroisoquinolines using first hydroamination and a subsequent modified Pictet−Spengler cyclization.[47] Furthermore, α-cyanoamines, diamines, imidazolidinones, α-amino acids and their derivatives can be synthesized in a one-pot procedure featuring hydroamination with precatalyst **1** in a modified Strecker reaction.[88,89] In this report, we show that the extended scope of reactivity of **1** can be used to give an advantage in the synthesis of free α-amino alcohols and indoles.

Aminoalcohol Synthesis. The electron-rich arylamine *para*-methoxyaniline is a valuable substrate as it can serve to prepare primary amines. Thus, by combining the reactivity of protected propargyl alcohols with *para*-methoxyaniline, precursors to aminoalcohols can be prepared. For example, the hydroamination of a TBS-protected 3-phenyl-2-propyn-1-ol with *para*-methoxyaniline can be performed at 110 °C for 24 h, and the reduced product of this reaction can then undergo mild oxidative cleavage using periodic acid.[115] This resulted in the simulataneous deprotection of the PMP and silyl groups, affording the corresponding free amino alcohol as a racemic mixture (**8**) in 38% isolated yield (Scheme 4).

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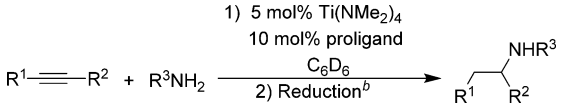
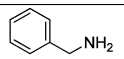
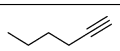
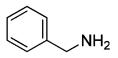
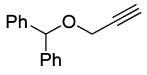
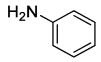
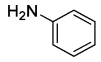
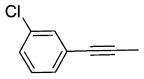
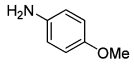
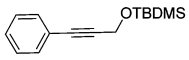
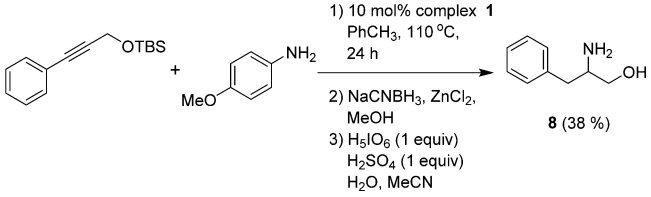
Table 5. Comparison of Crystalline Precatalyst 1 and In Situ Generated Complex 1[a]



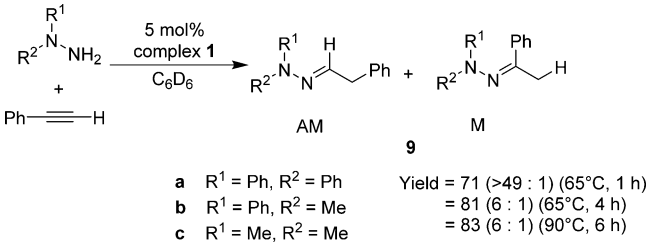
Entry	Amines	Alkyne	Temp. (°C)	Yield[c] (%) (Precatalyst 1)
1			65	79 (88)
2			Rt	72 (89)[d]
3			Rt	86 (83)
4			110	93
5			110	58

[a]Conditions: alkyne (1 equiv), amine (1.2 equiv), 5 mol % of $Ti(NMe_2)_4$ (0.05 equiv), 10 mol % of ligand (0.1 equiv), nitrogen atmosphere. [b]For reduction conditions, see Experimental Section. [c]Isolated yields of the anti-Markovnikov product. [d]10 mol % of $Ti(NMe_2)_4$ and 20 mol % of proligand at rt.

Scheme 4. Synthesis of Amino Acid Through Hydroamination/Oxidative Deprotection



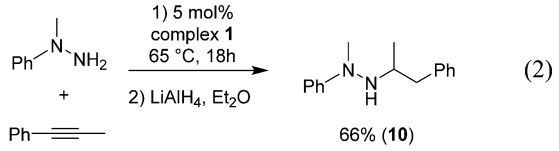
Scheme 5. Hydrohydrazination Using Complex 1



Hydrohydrazination and Indole Synthesis. Hydrazines are similar to primary amines; however, not all catalysts that induce hydroamination are able to mediate efficient reactivity for hydrohydrazination.[84] This is due to the different reactivity imparted by the two adjacent nitrogen atoms in the hydrazine substrates. The most efficient hydrohydrazination catalyst reported to date, a titanium-imido complex, is able to perform this reaction with terminal alkynes at room temperature.[116] Hydrohydrazination products are of interest because of their potential usefulness as reactive intermediates. For example, hydrazones are key intermediates in the Fischer indole synthesis.[117]

The functional group tolerance of **1** suggested that this catalyst may also be useful for hydrohydrazination. In initial experiments, the reaction of 1,1-diphenylhydrazine with phenylacetylene in the presence of 5 mol % of complex **1** at 65 °C for 1 h successfully afforded the anti-Markovnikov product (**9a**) in good yield and with excellent selectivity (Scheme 5). The less reactive mixed arylalkyl, 1-methyl-1-phenylhydrazine, and the alkylalkyl, 1,1-dimethylhydrazine, were also viable substrates, where **9b** and **9c** were obtained in good yields; however, a reduction in regioselectivity was observed. Furthermore, both substrates required longer reaction times, and **9c** also required elevated temperature.

Furthermore, hydrohydrazination is not limited to terminal alkynes. For example, 1-methyl-1-phenylhydrazine can be reacted with and 1-phenyl-1-propyne using modified conditions to give **10** regioselectively in 66% yield (eq 2).



(2)

The hydrazone products of the hydrohydrazination reaction have been previously reported to undergo a Lewis acid catalyzed Fischer indole synthesis to afford substituted indoles.[84,92] Here, using a one-pot synthesis, the crude mixture from the hydrohydrazination reaction is subjected to zinc dichloride at 100 °C (Scheme 6). 1-Methyl-1-phenylhydrazine was reacted with 1-phenyl-1-propyne or phenylacetylene in the one-pot sequential hydrohydrazination/Fischer indole synthesis, which results in the formation of **11a** and **11b** in good yields with excellent regioselectivity. Using 1,1-diphenylhydrazine, **11c** was afforded with excellent regioselectivity albeit in lower yields, which is proposed to be due to premature cleavage of the N−N bond in the hydrazone intermediate. Indole formation using 1-methyl-1-phenylhydrazine and TBS protected propargyl alcohol was also successful by applying this

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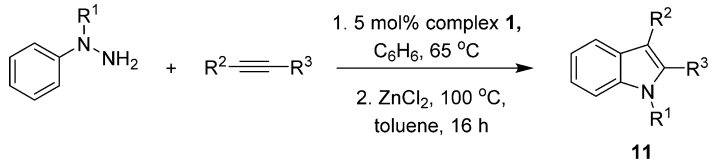
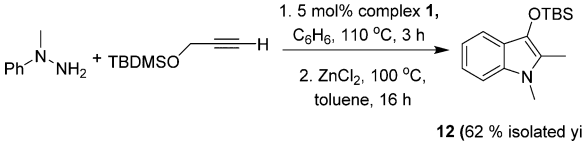
Scheme 6. Sequential Hydroamination/Fischer Indole Synthesis



a R^1 = Me, R^2 = Ph, R^3 = Me Yield = 66 (18 h)
b R^1 = Me, R^2 = Ph, R^3 = H = 72 (4 h)
c R^1 = Ph, R^2 = Ph, R^3 = H = 33 (1 h)

one-pot method (eq 3). However, as Markovnikov selectivity was observed for the hydrohydrazination reaction using these



(3)

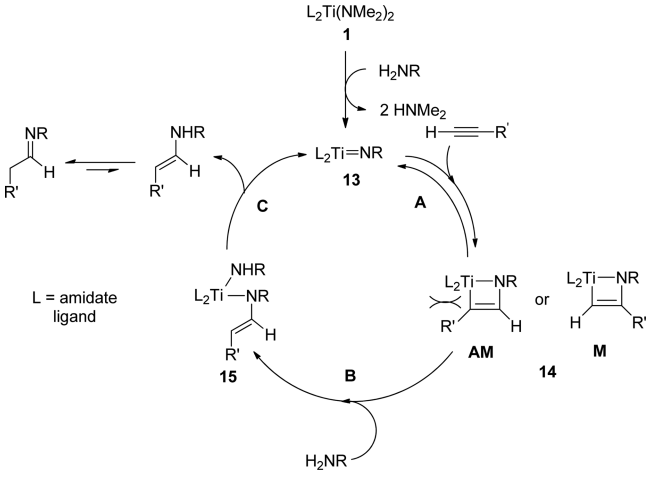
12 (62 % isolated yield)

substrates, 3-((*tert*-butyldimethylsilyl)oxy)-1,2-dimethyl-1*H*-indole (**12**) was afforded. The observed reactivity and regioselectivity for the sequential hydroamination/Fischer indole synthesis using complex **1** is similar to other reported group 4 catalysts.[84,92,118]

These examples of using **1** in synthesis highlight the flexibility of this precatalyst. The functional group tolerance can be used to give an advantage in preparing aminoalcohols and substituted indoles. Most importantly, hydroamination is a powerful, atom-economic method for generating reactive aldimine, ketamine, and hydrazones as reactive intermediates that do not need to be isolated before using in further transformations. Thus precatalyst **1** is easily incorporated into one-pot synthetic protocols.

Mechanistic Proposal. Detailed mechanistic studies with group 4 metal complexes for alkyne hydroamination have been reported by several groups.[5,58] In the case of titanium, the most widely accepted mechanism involves a catalytically active imido-titanium complex **13** (Scheme 7). Computational calculations by

Scheme 7. General Mechanism of Bisamido Group 4 Catalyzed Hydroamination



Bergmen and Straub suggested that [2 + 2] cycloaddition of **13** (step A) could be the turnover-limiting step; however, the authors also discuss the possibility of a turnover-limiting protonolysis step that would proceed by an associative mechanism.[59] Kinetic studies by Doye and co-workers suggested that the protonation of the azacyclobutene **14** (step B) is slow compared to the reversible formation of **14**.[5]

In our previous investigations, we demonstrated that an imidotitanium variant of **1** showed catalytic activity comparable to that of complex **1**.[47] Furthermore, complex **1** cannot catalyze hydroamination with secondary amine substrates.[47] These results suggest that our system follows the same mechanistic pathway as these other group 4 catalysts. Efforts to probe this catalytic system using computational methods have been complicated by multiple equilibria that must be considered because of the known hemilability of the amidate ligands.[119] However, by using kinetic isotope effect experiments, the hydroamination reaction with deuterium-enriched *t*-butylamine (>95% *d* incorporation by integration of the ^{1}H NMR spectrum) was undertaken, and a primary kinetic isotope effect of 3.40 ± 0.15 has been observed.[120] This observation suggests that hydroamination with complex **1** cannot invoke a turnover-limiting [2 + 2] cycloaddition, and instead, the protonolysis of the metallacyclic intermediate would be turnover limiting. Analogous to this proposal, detailed kinetic investigations of alkene hydroamination with a zirconium analogue of **1** is also consistent with a protonolysis event being turnover limiting.[76] With a rapid and reversible [2 + 2] cycloaddition and a turnover-limiting protonolysis step, as previously presented by Doye, the Curtin−Hammett principle applies for determining regioselectivity in the reaction of alkyne hydroamination.

Presuming protonolysis proceeds via an associative mechanism, we attribute the excellent substrate scope and anti-Markovnikov selectivity, even when arylamines are used, to the flexible steric environment provided by the amidate ligand, which can accommodate the more sterically demanding anti-Markovnikov metallacyclic intermediate. However, when excessively sterically hindered amines are used, such as 2,6-dimethylaniline, Markovnikov selectivity is observed. This change in regioselectivity would put the bulky substituent of the alkyne away from the sterically demanding coordinated 2,6-dimethylaniline in the proposed transition state for the turnover-limiting associative protonolysis step (**14** to **15**).

■ CONCLUSIONS

Bis(amidate)bis(amido) titanium complex **1** is an effective, selective, easy to use, and overall general hydroamination precatalyst. We have demonstrated that complex **1** can be used to catalyze the hydroamination of a wide variety of alkynes (terminal alkyl, aryl, and internal alkynes) with various primary amines (alkylamines, arylamines, as well as hydrazines). In addition, complex **1** also tolerates a wide range of functional groups such as alkenes, esters, ethers, protected alcohols, and imines. The products of these reactions are isolated in good to excellent yields with the anti-Markovnikov isomer being formed

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preferentially in most cases. Most impressively, excellent reactivity and regioselectivity is observed, even in cases where challenging nonbulky alkylamine, including allylamine, substrates are used. Furthermore, an in situ preparation of complex **1** is presented, including an example of a multigram scale reaction. This facile approach for generating the catalyst enhances its versatility and convenience without the need of a glovebox.

The favorable reactivity and selectivity of **1** have been used to give an advantage in synthetic routes to access an amino alcohol and indoles, further demonstrating the usefulness of complex **1**. The broad substrate scope and regioselectivity disclosed here can be rationalized by a mechanistic proposal involving a rapid and reversible cycloaddition and turnover-limiting protonolysis step, which is supported by an observed primary kinetic isotope effect on the N−H bond of the amine substrate. These observations and mechanistic proposals point toward the importance of hemilabile, small-bite-angle amidate ligands in designing catalytic systems with flexible coordination spheres for enhanced reactivity.

EXPERIMENTAL SECTION

General Methods. Synthesis of the metal complexes and subsequent reactions involving these precatalysts were performed under an inert atmosphere of nitrogen using standard Schlenk line or glovebox techniques. Diethylether was distilled from sodium/benzophenone under inert atmosphere. Benzene was purified and dried by passage through a column of activated alumina and sparged with nitrogen. Benzene-d_6 was degassed via three cycles of freeze−pump−thaw and stored over activated 4 Å molecular sieves in the glovebox. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on 300 or 400 MHz spectrometers with chemical shifts given relative to the residual solvent. All substrates were distilled from either 4 Å molecular sieves or CaH_2 and stored over molecular sieves before use. The amide proligand and titanium precatalyst were prepared according to literature procedures.[47,66] Unless otherwise stated, all reagents were purchased from commercial sources. The following substrates were prepared by using literature procedures: triisopropylsilyloxy-3-butyne,[121] 4-pentynyl-1-*tert*-butanoate,[122] prop-2-ynyloxydiphenylmethane,[123] *N*-(diphenylmethylene)-2-propyne-1-amine,[66] (*tert*-butyldimethylsilyloxy)-1-propyne,[124] (4-methoxyphenyl)phenylacetylene,[125] [3-[[*tert*-butyldimethylsilanyloxy]-1-propyn-1-yl]-benzene,[126] 1-chloro-3-prop-1-ynyl-benzene,[127] *N*,*N*-d2-*tert*-butylamine.[79] The following products synthesized by using **1** were described in previous report: *N*-benzylhexylamine[66] (**2a**), *N*-isopropylhexylamine[66] (**2b**), *N*-*tert*-butylhexylamine[66] (**2c**), *N*-(phenylmethyl)-2-phenylethylamine[47] (**3a**), *N*-benzyl(2-cyclohexyl)ethylamine)[66] (**3b**), *N*-benzyl(3,3-dimethyl)-butylamine[66] (**3c**), 4-triphenylsiloxybutanal[66] (**3e**), *N*-(benzyl)-[2-(4′-methoxy)phenyl]ethylamine[47] (**3f**), *N*-(benzyl)-[2-(4′-chloro)phenyl]-ethylamine[47] (**3g**), 5′-oxopentyl-2′2′-dimethylpropanoate[47] (**3h**).

General Methods for Hydroamination with 1. *Method A.* A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with a solution of **1** (0.05 equiv) dissolved in anhydrous benzene (∼2 mL), the alkyne (1 equiv), and the amine (1 equiv). The Schlenk tube was then sealed and stirred at 65 °C for 24 h. After cooling the reaction mixture to room temperature, the resulting hydroamination products were directly subjected to a reduction method listed below. Removal of solvent by rotary evaporation and purification by column chromatography afforded the purified amine products.

Method B. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with a solution **1** (0.1 equiv) dissolved in anhydrous toluene (∼2 mL), the alkyne (1 equiv), and the amine (1.2 equiv). The Schlenk tube was sealed and stirred at 110 °C for 24 h. After allowing the reaction mixture to cool to room temperature, the resultant hydroamination products were directly subjected to a reduction method listed below. Removal of solvent by rotary evaporation and purification by column chromatography afforded the purified amine products.

Method C. A J. Young NMR tube was charged with a solution of **1** (0.05 equiv) dissolved in anhydrous benzene-d_6 (∼1 mL), the alkyne (1 equiv), and the amine (1.2 equiv). The J. Young NMR tube was sealed and kept at ambient temperature for 24 h. The progress of the reaction was monitored by ^{1}H NMR spectroscopy. The resultant hydroamination products were transferred to a 10 mL vial equipped with a magnetic stir bar and subjected to a reduction method listed below. Removal of solvent by rotary evaporation and purification by column chromatography afforded the purified amine products.

Method D. A standard solution of $Ti(NMe_2)_4$ (0.035 M, 0.05 equiv) in benzene-d_6 was added to *N*-(2,6-diisopropylphenyl)-benzamide (0.10 equiv) suspended in 0.100 mL of benzene-d_6 in a 1 dram vial. The vial was gently shaken until all the solid completely dissolved (<5 min), after which the alkyne (1 equiv) and the amine (1.2 equiv) were added. The mixture was quantitatively transferred into a J. Young NMR tube by rinsing the vial twice with 0.05 mL of C_6D_6. The NMR tube was sealed and maintained at the specified reaction temperature for 24 h. The progress of the reaction was monitored by ^{1}H NMR spectroscopy. The resulting hydroamination products were transferred to a 10 mL vial equipped with a magnetic stir bar and subjected to a reduction method listed below. Removal of solvent by rotary evaporation and purification by column chromatography afforded the purified amine products.

General Methods for Reductions. *Method I: Lithium Aluminum Hydride.* The resultant mixture from the hydroamination reaction was diluted with anhydrous diethylether (∼10 mL). LAH (1.4 equiv) was added, and the reaction mixture was stirred for 24 h at room temperature. Saturated NH_4Cl (0.1 mL) was added to quench the reaction, and the mixture was filtered on a Buchner funnel. The solid residual was washed with 3 portions of diethylether (∼5 mL). The organic filtrates were combined.

Method II: Sodium Borohydride. The resultant mixture from the hydroamination reaction was diluted with MeOH (∼10 mL). $NaBH_4$ (1.2 equiv) was added, and the reaction mixture was stirred for 24 h at room temperature. After removal of the solvent by rotary evaporation, saturated Na_2CO_3 (10 mL) and DCM (10 mL) were added to the residue. The aqueous layer was extracted with DCM (3 × 25 mL), and the combined organic layers were dried over Na_2SO_4 and filtered.

Method III: Sodium Cyanoborohydride. A modified literature procedure was used.[64] The resultant mixture from the hydroamination reaction was diluted with MeOH (∼10 mL). $NaCNBH_3$ (2 equiv) and $ZnCl_2$ (1 equiv) were added, and the reaction mixture was stirred for 24 h at room temperature. The mixture was filtered, and the solid residual was washed with DCM (∼15 mL). Saturated Na_2CO_3 (7 mL) was added to the filtrate. After extraction with DCM (6 × 30 mL), the organic layer was dried over $MgSO_4$ or Na_2SO_4 and filtered.

Synthesis and Characterization of Compounds. *N-(3,4-Dimethoxyphenethyl)hexan-1-amine[128] (**2d**).* This compound was prepared from 3,4-dimethoxyphenethylamine (0.045 mL, 0.6 mmol) and 1-hexyne (0.022 g, 0.5 mmol) following hydroamination Method A and reduced using Method I. Isolated as a colorless oil (0.059 g, 78%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (3H, m), 1.23−1.30 (6H, m), 1.43−1.47 (2H, m), 2.60 (2H, t, J = 7.2 Hz), 2.73−2.77 (2H, m), 2.82−2.87 (2H, m), 3.85 (3H, s), 3.86 (3H, s), 6.73−6.81 (3H, m).

*N-Allylhexan-1-amine (**2e**).* This compound was prepared from allylamine (0.055 g, 1 mmol) and 1-hexyne (0.086 g, 1 mmol) following hydroamination Method A and reduced using Method II. Isolation of this compound was done by back extraction. Following removal of solvent from the crude mixture of Method II, 2 mL of EtOAc and 2 mL of 1 M $HCl_{(aq)}$ were added to the residual. The organic layer was extracted with 1 M $HCl_{(aq)}$ (3 × 2 mL). The combined aqueous layer was washed with EtOAc (10 mL), basified with 3 M $NaOH_{(aq)}$ and extracted with EtOAc (4 × 10 mL). The combined organic layer was dried over Na_2SO_4 and filtered, and solvent was removed by rotary evaporation, which afforded the product as a colorless oil (0.095 g, 70%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (3H, t, J = 6.8 Hz), 1.23−1.31 (7H, m), 1.45−1.52 (2H, m), 2.60 (2H, t, J = 7.1 Hz), 3.24 (2H, d, J = 6.1 Hz), 5.06−5.19 (2H, m), 5.86−5.95 (1H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 14.0, 22.6, 27.0, 30.0, 31.7, 49.3, 52.4, 115.9, 136.7; MS (ESI) m/z 142 ([M + H]$^+$); HRMS (ESI-TOF) m/z Calcd for $C_9H_{20}N$ ([M + H]$^+$), 142.1596, found 142.1596.

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*N-[2-(Cyclohexen-1-yl)ethyl]-phenylmethanamine (**3d**).* This compound was prepared from benzylamine (0.055 mL, 0.6 mmol) and 1-ethynyl-1-cyclohexene (0.060 g, 0.5 mmol) following Method C and reduced using Method II. Isolated as a yellow oil (0.075 g, 70%). An analytically pure sample was obtained by a bulb-to-bulb distillation after column chromatography: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49–1.60 (5H, m), 1.84 (2H, s), 1.95 (2H, s), 2.11–2.14 (2H, m), 2.66 (2H s), 3.76 (2H, s), 5.43 (1H, s), 7.20–7.28 (5H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 22.6, 23.1, 25.4, 28.3, 38.4, 47.1, 54.0, 122.9, 127.0, 128.2, 128.5, 135.6, 140.7; MS (ESI) m/z 216 ([M + H]$^+$). Anal. Calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.44; H, 9.78; N, 6.19.

*N-(Phenylmethyl)-O-(diphenylmethyl)-3-oxopropyl-1-amine (**3i**).* This compound was prepared from benzylamine (0.055 mL, 0.6 mmol) and prop-2-ynyloxydiphenylmethane (0.109 g, 0.5 mmol) following Method C and reduced using Method II. Isolated as a yellow oil (0.147 g, 89%). This compound was also prepared from benzylamine (0.066 mL, 0.6 mmol) and prop-2-ynyloxydiphenylmethane (0.107 g, 0.5 mmol) following Method D (reacted at room temperature) and reduced using Method II. Isolated as a yellow oil (0.119 g, 72%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.86 (2H, quintet, J = 6.4 Hz), 2.67 (2H, t, J = 6.4 Hz), 3.33 (1H, br s), 3.48 (2H, d, J = 6.4 Hz), 3.75 (2H, s), 5.25 (1H, s), 7.16–7.29 (15H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 29.4, 46.5, 53.5, 67.3, 83.6, 126.5, 127.1, 127.3, 126.8, 128.3, 128.4, 138.9, 142.2; MS (ESI) m/z 332 ([M + H]$^+$). HRMS (ESI-TOF) m/z Calcd for $C_{23}H_{26}NO$ ([M + H]$^+$), 332.2007, found 332.2014.

*N-(Diphenylmethyl)-N′-(phenylmethyl)-propyl-1,3-diamine (**3j**).* This compound was prepared from benzylamine (0.052 mL, 0.5 mmol) and *N*-(diphenylmethylene)-2-propyne-1-amine (0.087 g, 0.4 mmol) following Method C and reduced using Method II except 3 equiv of $NaBH_4$ was used. Isolated as a colorless oil (0.100 g, 79%). An analytically pure sample was obtained by a bulb-to-bulb distillation after column chromatography: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71 (4H, m), 2.63 (2H, t, J = 6.3 Hz), 2.70 (2H, t, J = 6.3 Hz), 3.75 (2H, s), 4.77 (1H, s), 7.15–7.36 (15H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 30.2, 46.8, 48.1, 54.1, 67.7, 126.8, 126.7, 127.2, 128.1, 128.3, 128.4, 140.4, 144.2; MS (ESI) m/z 331 ([M + H]$^+$). Anal. Calcd for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48. Found: C, 83.67; H, 8.01; N, 8.54.

*Synthesis of (±)-(2-Benzyl-3-phenyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine[112] (**5a**).* A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with a solution **1** (0.074 g, 0.1 mmol), phenylacetylene (0.202 g, 2.0 mmol), and aniline (0.223 g, 2.4 mmol) dissolved in anhydrous benzene (~3–4 mL). The Schlenk tube would then be sealed and maintained at 65 °C for 24 h. After cooling the reaction mixture to room temperature, CH_2Cl_2 was added to quench the reaction. After workup and removal of solvent by rotary evaporation, the desired product was separated using column chromatography. The pure product was obtained as a white foamy solid in 20% yield (0.077 g): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.48 (1H, dd, J = 10.7, 13.6 Hz), 2.78 (1H, dd, J = 2.4, 13.0 Hz), 3.14 (1H, t, J = 9.7 Hz), 3.87–3.93 (1H, m), 3.93 (2H, br s), 4.80 (1H, d, J = 9.8 Hz), 6.35–6.45 (3H, m), 6.60–6.70 (2H, m), 7.05–7.15 (3H, m), 7.2–7.5 (11H, m).

*Synthesis of 2,4-N1,N3-Tetraphenyl-butane-1,3-diamine (**5b**).* A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with a solution **1** (0.035 g, 0.05 mmol), phenylacetylene (0.102 g, 1.0 mmol), and aniline (0.112 g, 1.2 mmol) dissolved in anhydrous benzene (~3–4 mL). The Schlenk tube would then be sealed and maintained at 80 °C for 4 h. After cooling the reaction mixture to room temperature, MeOH (~10 mL). $NaCNBH_3$ (2 equiv) and $ZnCl_2$ (1 equiv) were added, and the reaction mixture was stirred for 24 h at room temperature. The mixture was filtered, and the solid residual was washed with DCM (~15 mL). Sat. Na_2CO_3 (7 mL) were added to the filtrate. After extraction with DCM (6 × 30 mL), the organic layer was dried over $MgSO_4$ or Na_2SO_4. Following filtration and removal of solvent by rotary evaporation, the pure product was obtained as an oil in 18% yield (0.071 g): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.48 (1H, dd, J = 7.2, 14.0 Hz), 2.47 (1H, dd, J = 4.4, 14.0 Hz), 3.08–3.14 (1H, m), 3.39 (1H, dd, J = 8.8, 12.0 Hz), 3.60 (2H, br s), 3.74 (1H, dd, J = 4.8, 12.4 Hz), 4.10–4.16 (1H, m), 6.50 (2H, d, J = 8.4 Hz), 6.61 (2H, d, J = 8.0 Hz), 6.65–6.73 (2H, m), 7.00–7.50 (14H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 38.6, 47.9, 50.1, 57.7, 114.2, 114.6, 118.5, 118.6, 127.3, 128.3, 129.2, 129.9, 129.9, 130.2, 130.5, 130.5, 139.0, 141.3, 148.5, 149.0; HRMS (ESI-TOF) Calcd for $C_{28}H_{28}N_2Na$ [M + Na$^+$] 415.2150, found 415.2146.

*Phenethyl(phenyl)amine[129] (**6a**).* This compound was prepared from aniline (0.112 g, 1.2 mmol) and phenylacetylene (0.102 g, 1.0 mmol) following Method A except reacted at room temperature and reduced using Method III. Isolated as a yellow oil (0.163 g, 83%). This compound was also prepared from aniline (0.109 mL, 1.2 mmol) and phenylacetylene (0.109 mL, 1.0 mmol) following Method D (reacted at room temperature) and reduced using Method III. Isolated as a yellow oil (0.170 g, 86%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.01 (2H, t, J = 7.0 Hz), 3.49 (2H, t, J = 7.0 Hz), 4.13 (1H, br s), 6.72 (2H, d, J = 8.9 Hz), 6.83 (1H, t, J = 7.3 Hz), 7.26–7.44 (7H, m).

*(4-Methoxy-phenyl)-phenethyl-amine (**6b**).* This compound was prepared from *para*-methoxyaniline (0.148 g, 1.2 mmol) and phenylacetylene (0.102 g, 1.0 mmol) following Method C and reduced using Method III. Isolated as a yellow oil (0.172 g, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.96 (2H, t, J = 7.0 Hz), 3.41 (2H, t, J = 7.0 Hz), 3.47 (1H, br s), 3.80 (3H, s), 6.62 (2H, d, J = 8.9 Hz), 6.85 (2H, d, J = 8.9 Hz), 7.26–7.40 (5H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 35.8, 46.2, 56.0, 114.5, 115.1, 126.6, 128.8, 129.0, 139.6, 142.5, 152.4; MS (EI) m/z 227 (M$^+$). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.06; H, 7.42; N, 6.37.

*N-(2-(Cyclohex-1-en-1-yl)ethyl)-4-methoxyaniline (**6c**).* This compound was prepared from *para*-methoxyaniline (0.074 g, 1.2 mmol) and1-ethynylcyclohexene (0.053 g, 1.0 mmol) following Method C and reduced using Method III. Isolated as a yellow oil (0.093 g, 80%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.56–1.68 (4H, m), 1.96 (2H, br m), 2.03 (2H, br m), 2.27 (2H, t, J = 6.8 Hz), 3.14 (2H, t, J = 6.8 Hz), 3.67 (1H, br s), 3.76 (3H, s), 5.54 (1H, s), 6.60 (2H, d, J = 79.2 Hz), 6.80 (2H, t, J = 8.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 23.4, 23.9, 26.3, 28.9, 38.8, 43.5, 56.8, 115.2, 114.3, 115.9, 124.5, 136.0, 143.8, 153.0; MS (EI) m/z 231 (M$^+$). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.12; H, 9.11; N, 5.81.

*N-(3,3-Dimethylbutyl)-4-methoxyaniline (**6d**).* This compound was prepared from *para*-methoxyaniline (0.074 g, 1.2 mmol) and *t*-butyl acetylene (0.041 g, 1.0 mmol) following Method C and reduced using Method III. Isolated as a yellow oil (0.090 g, 87%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (9H, s), 1.52 (2H, m), 3.08 (2H, m), 3.23 (1H, br s), 3.76 (3H, s), 6.59 (2H, d, J = 9.1 Hz), 6.80 (2H, d, J = 9.1 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 30.6, 30.9, 42.3, 44.7, 56.8, 115.1, 115.9, 144.0, 153.0; MS (EI) m/z 207 (M$^+$). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.38; H, 10.33; N, 6.76.

*[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-phenylamine (**6e**).* This compound was prepared from aniline (0.056 g, 0.6 mmol) and (*tert*-butyldimethylsilyloxy)-1-propyne (0.093 g, 1.5 mmol) following Method C except with 10 mol % of **1** and reduced using Method III. Isolated as a yellow oil (0.106 g, 80%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.11 (6H, s), 0.96 (9H, s), 1.84–1.90 (2H, m), 3.26 (2H, t, J = 6.5 Hz), 3.80 (2H, t, J = 5.8 Hz), 6.62–6.73 (2H, m), 7.18–7.22 (2H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 5.4, 18.3, 25.9, 32.0, 41.9, 61.9, 112.6, 116.9, 129.2, 148.6; MS (EI) m/z 226 (M$^+$). HRMS (EI-EB) m/z Calcd for $C_{15}H_{28}NOSi$ (M$^+$), 266.1940, found 266.1926.

*[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-(4-methoxy-phenyl)-amine (**6f**).* This compound was prepared from *para*-methoxyaniline (0.074 g, 0.6 mmol) and (*tert*-butyldimethylsilyloxy)-1-propyne (0.085 g, 0.5 mmol) following Method A except reacted at room temperature with 10 mol % of **1** (0.05 mmol) and reduced using Method III. Isolated as a yellow oil (0.111 g, 75%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.10 (6H, s), 0.95 (9H, s), 1.80–1.88 (2H, m), 3.21 (2H, t, J = 6.5 Hz), 3.77 (3H, s), 3.78 (2H, t, J = 5.7 Hz), 6.59 (2H, d, J = 9.0 Hz), 6.80 (2H, d, J = 9.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ −5.2, 26.1, 32.3, 43.0, 56.0, 57.9, 62.1, 114.1, 115.1, 143.1, 152.1; MS (EI) m/z 295 (M$^+$). Anal. Calcd for $C_{16}H_{29}NO_2Si$: C, 65.03; H, 9.89; N, 4.74. Found: C, 65.24; H, 9.77; N, 5.06.

*N-Phenyl-(1-methyl-pentyl)-amine and n-Hexylaniline[130] (**6g**).* These compounds were prepared from aniline (0.112 g, 1.2 mmol)

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and 1-hexyne (0.082 g, 1.0 mmol) following Method A except reacted at room temperature and reduced using Method III. A combined yield of 62% (0.115 g) was obtained for the mixture of regioisomers (1.6:1, AM:M) as an oil, which were inseparable by chromatography. The ^{1}H for the mixture have been provided: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (6H, t, J = 7.2 Hz, AM and M), 1.26 (2H, d, J = 6.4 Hz, M), 1.36−1.54 (11H, m, AM and M), 1.62−1.72 (4H, m, AM and M), 3.17 (2H, t, J = 7.1 Hz, AM), 3.50−3.57 (1H, m, M), 3.62 (1H, br s, M), 6.64−6.72 (4H, m, AM and M), 6.77−6.79 (2H, m, AM and M), 7.22−7.27 (4H, m, AM and M).

(4-Methoxy-phenyl)-(1-methyl-pentyl)-amine and Hexyl-(4-methoxy-phenyl)-amine ***(6h)***. These compounds were prepared from *para*-methoxyaniline (0.148 g, 1.2 mmol) and 1-hexyne (0.082 g, 1.0 mmol) following Method A except reacted at room temperature and reduced using Method III. A combined yield of 77% (0.160 g) was obtained for the mixture of regioisomers (2.3:1, AM:M) as an oil, which were inseparable by chromatography. The ^{1}H and ^{13}C NMR spectra as well as the elemental analysis for the mixture have been provided: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (6H, t, J = 7.2 Hz, AM and M), 1.17 (2H, d, J = 6.4 Hz, M), 1.30−1.40 (11H, m, AM and M), 1.60−1.61 (4H, m, AM and M), 3.07 (2H, t, J = 7.1 Hz, AM), 3.22 (1H, br s, M), 3.30−3.50 (1H, m, M), 3.76 (6H, s, AM and M), 6.57 (4H, d, J = 9 Hz, AM and M), 6.79 (4H, d, J = 9 Hz, AM and M); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 15.0, 15.1, 21.8, 23.7, 23.8, 27.9, 29.4, 30.7, 32.7, 38.0, 46.1, 50.5, 56.8, 115.0, 115.7, 116.0, 116.0, 143.1, 144.0, 152.8, 153.0; HRMS Calcd for $C_{13}H_{21}NO$ [M^+] 207.1623, found 207.16242. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.44; H, 10.09; N, 6.61.

N-(2,6-Dimethylphenyl)-benzeneethanamine[114] ***(6i)***. This compound was prepared from 2,6-dimethylaniline (0.133 g, 1.1 mmol) and phenylacetylene (0.102 g, 1.0 mmol) following Method A and reduced using Method I. Isolated as a colorless oil (0.140 g, 62%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (6H, s), 2.97 (2H, t, J = 6.9 Hz), 3.13 (1H, br s), 3.36 (2H, t, J = 6.9 Hz), 6.87−7.42 (8H, m).

[2-(tert-Butyl-dimethyl-silanyloxy)-1-methylethyl]-(2,6-dimethyl-phenyl)-amine ***(6j)***. This compound was prepared from 2,6-dimethylaniline (0.074 mL, 0.6 mmol) and (*tert*-butyldimethyl-silyloxy)-1-propyne (0.084 g, 0.5 mmol) following Method C and reduced using Method II. Isolated as a yellow oil (0.042 g, 23%). An analytically pure sample was obtained by a bulb-to-bulb distillation after column chromatography: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (6H, s), 0.95 (9H, s), 1.14 (3H, t, J = 6.4 Hz), 2.29 (6H, s), 3.33 (1H, m), 3.56 (2H, br m), 3.65 (1H, m), 6.80 (1H, t, J = 7.3 Hz,), 6.98 (2H, d, J = 7.0 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ −5.2, −5.1, 18.4, 18.7, 19.1, 26.2, 53.8, 66.7, 121.5, 129.0, 129.6, 145.4; MS (ESI) m/z 294 ([M + H]$^+$). Anal. Calcd for $C_{17}H_{31}NOSi$: C, 69.56; H, 10.65; N, 4.77. Found: C, 69.41; H, 10.55; N, 4.90.

N-(Hexan-2-yl)-2,6-dimethylaniline[5] ***(6k)***. This compound was prepared from 2,6-dimethylaniline (0.133 g, 1.1 mmol) and 1-hexyne (0.082 g, 1.0 mmol) following Method A and reduced using Method I. Isolated as a colorless oil (0.147 g, 72%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (3H, t, J = 7.1 Hz), 1.13 (3H, d, J = 6.3 Hz), 1.13−1.47 (5H, m), 1.64 (1H, m), 2.34 (6H, s), 2.88 (1H, br s), 3.32−3.37 (1H, m), 6.84−7.06 (3H, m).

N-(1-Phenylpropan-2-yl)-aniline[131] ***(7a)***. This compound was prepared from aniline (0.058 g, 0.6 mmol) and 1-phenyl-1-propyne (0.056 g, 0.5 mmol) following Method B and reduced using Method III. Isolated as a colorless oil (0.107g, >98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (3H, d, J = 6.4 Hz), 2.77 (1H, dd, J = 7.2, 13.2 Hz), 3.02 (1H, dd, J = 4.8, 13.2 Hz), 3.60 (1H, s), 3.83−3.88 (1H, m), 6.70−6.80 (3H, m), 7.25−7.40 (7H, m).

N-(Hexan-3-yl)aniline ***(7b)***. This compound was prepared from aniline (0.055 mL, 0.6 mmol) and 3-hexyne (0.057 mL, 0.5 mmol) following Method C except at 110 °C in toluene-d_8 and reduced using Method II. Isolated as a colorless oil (0.086 g, >98%). An analytically pure sample was obtained by a bulb-to-bulb distillation after column chromatography: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (6H, t, J = 7.5 Hz), 1.40−1.68 (6H, m), 3.36 (1H, quintet, J = 5.8 Hz), 3.45 (1H, br s), 6.63 (2H, dd, J = 1.0, 8.5 Hz), 6.70 (1H, tt, J = 1.0, 7.2 Hz), 7.18−7.18 (2H, m) ; ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 10.0, 14.2, 19.1, 27.3, 36.7, 53.8, 112.8, 116.4, 129.2, 148.2; MS (EI) m/z 178 ([M + H]$^+$). Anal. Calcd for $C_{12}H_{19}N$: C, 81.30; H, 10.80; N, 7.90. Found: C, 81.36; H, 10.80; N, 7.90.

N-(1,2-Diphenylethyl)benzeneamine[60,132] ***(7c)***. This compound was prepared from aniline (0.112 g, 1.2 mmol) and diphenylacetylene (0.107 g, 1.0 mmol) following Method B and reduced using a literature procedure.[57] To a round-bottom flask, Pd/C (53 mg, 10 mol % of Pd, 0.05 mmol of Pd, 5 mol %) and dry THF was added and stirred under an H_2 atmosphere for 30 min. The volatile components of the crude hydroamination reaction mixture was removed in vacuo, dissolved in dry THF, and added to the Pd/C suspension. The resulting mixture was stirred under 1 atm of H_2 for 72 h. Filtration over Celite, removal of solvent in vacuo and purification by column chromatography afforded the pure product. Isolated as a colorless oil (0.269 g, 98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.02 (1H, dd, J = 8.4, 14.0 Hz), 3.15 (1H, dd, J = 5.8, 14.0 Hz), 4.13 (1H, br s), 4.58−4.62 (1H, m), 6.47 (2H, d, J = 7.8 Hz), 6.62−6.65 (1H, m), 7.04−7.08 (2H, m), 7.13 (2H, d, J = 6.7 Hz), 7.23−7.35 (8H, m).

4-Methoxy-N-(1-phenylpropan-2-yl)-aniline[131] ***(7d)***. This compound was prepared from *para*-methoxyaniline (0.074 g, 0.6 mmol) and 1-phenyl-1-propyne (0.058 g, 0.5 mmol) following Method B and reduced with Method III. Isolated as a colorless oil (0.123 g, >98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (3H, d, J = 6.0 Hz), 2.71 (1H, dd, J = 7.2, 13.2 Hz), 2.97 (1H, dd, J = 4.8, 13.2 Hz), 3.30 (1H, br s), 3.71−3.75 (1H, m), 3.79 (3H, s), 6.63−6.67 (2H, m), 6.82−6.87 (2H, m), 7.21−7.36 (5H, m).

(1-Ethyl-butyl)-(4-methoxy-phenyl)-amine ***(7e)***. This compound was prepared from *para*-methoxyaniline (0.074 g, 0.6 mmol) and 3-hexyne (0.041 g, 0.5 mmol) following Method C except at 110 °C in toluene-d_8 and reduced using Method III. Isolated as a colorless oil (0.107 g, >98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (6H, t, J = 7.2 Hz), 1.40−1.62 (6H, m), 3.15 (1H, br s), 3.19−3.24 (1H, m), 3.76 (3H, s), 6.56 (2H, d, J = 9.0 Hz), 6.77 (2H, d, J = 9.0 Hz) ; ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 11.0, 15.3, 20.2, 28.2, 37.7, 55.9, 56.9, 115.3, 116.0, 143.6, 152.6; MS (EI) m/z 207 (M^+). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32 ; H, 10.21; N, 6.76. Found: C, 75.26; H, 10.10; N, 7.16.

(1,2-Diphenyl-ethyl)-(4-methoxy-phenyl)-amine ***(7f)***. This compound was prepared from *para*-methoxyaniline (0.074 g, 0.6 mmol) and (phenylethynyl)benzene (0.089 g, 0.5 mmol) following Method C except at 110 °C in toluene-d_8 and reduced using Method III. Isolated as a colorless oil (0.151 g, >98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.06 (1H, dd, J = 8.2, 13.9 Hz), 3.18 (1H, dd, J = 5.6, 13.8 Hz), 3.72 (3H, s), 3.90 (1H, br s), 4.56−4.60 (1H, m), 6.50 (2H, d, J = 9 Hz), 6.71 (2H, d, J = 9 Hz), 7.17−7.39 (10H, m) ; ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 45.4, 55.9, 60.3, 114.9, 115.1, 126.7, 126.9, 127.2, 128.7, 128.7, 129.4, 138.0, 141.7, 143.9, 152.3; MS (EI) m/z 303 (M^+). Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.12; H, 6.93; N, 4.72.

(4-Methoxy-phenyl)-(4-methylpentanyl)-amine ***(7g)***. This compound was prepared from *para*-methoxyaniline (0.074 g, 0.6 mmol) and 4-methylpent-2-yne (0.042 g, 0.5 mmol) following Method B and reduced using Method III. Isolated as a yellow oil (0.081 g, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (3H, d, J = 6.6 Hz), 0.96 (3H, d, J = 6.6 Hz), 1.15 (3H, d, J = 6.2 Hz), 1.44−1.54 (1H, m), 1.71−1.85 (1H, m), 3.03 (1H, br s), 3.41−3.52 (1H, m), 3.76 (3H, s), 6.57 (2H, d, J = 9.0 Hz), 6.79 (2H, d, J = 12.8 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 21.2, 22.7, 23.2, 25.3, 47.1, 47.7, 56.0, 114.7, 115.1, 142.1, 155.2; MS (EI) m/z 207 (M^+). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.38; H, 10.18; N, 6.51.

(1,2-Diphenyl-ethyl)-(4-methoxy-phenyl)-amine ***(7h)***. This compound was prepared from pentafluoroaniline (0.110 g, 0.6 mmol) and 1-phenyl-1-propyne (0.058 g, 0.5 mmol) following Method B and reduced using Method I. Isolated as a colorless oil (0.137 g, 91%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (3H, d, J = 6.7 Hz), 2.70 (1H, dd, J = 7.0, 13.4 Hz), 2.89 (1H, dd, J = 5.7, 13.7 Hz), 3.34−3.37 (1H, m), 3.95−4.03 (1H, m), 7.16−7.32 (5H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 21.2, 44.1, 52.3, 126.6, 128.4, 129 (^{13}C NMR signals for the fluorinated arene was not observed); ^{19}F NMR ($CFCl_3$, 282 MHz) δ −171.9, −164.8, −159.1; MS (ESI) m/z 300 ([M − H]$^-$); HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{11}NF_5$ ([M − H]$^-$), 300.0806, found 300.0812.

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N-(1-Methyl-2-phenylethyl)-N-benzylamine[73] ***(7i)***. This compound was prepared from benzylamine (0.066 mL, 0.6 mmol) and 1-phenyl-1-propyne (0.063 mL, 0.5 mmol) following Method C except at 110 °C in toluene-d_8 and reduced using Method III. Isolated as a colorless oil (0.151 g, 78%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (3H, d, J = 6.4 Hz), 1.45 (1H, br s), 2.66 (1H, dd, J = 6.6, 13.3 Hz), 2.79 (1H, dd, J = 6.8, 13.3 Hz), 2.96 (1H, sextet, J = 6.4 Hz), 3.75 (1H, d, J = 13.3 Hz), 3.87 (1H, d, J = 13.3 Hz), 7.17−7.34 (10H, m).

N-Benzyl-3-hexylamine[32] ***(7j)***. This compound was prepared from benzylamine (0.066 mL, 0.6 mmol) and 3-hexyne (0.041 g, 0.5 mmol) following Method B and reduced using Method III. Isolated as a colorless oil (0.070 g, 74%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81−0.87 (6H, m), 1.25−1.46 (7H, m), 2.44 (1H, quintet, J = 5.8 Hz), 3.69 (2H, d, J = 2.0 Hz), 7.14−7.29 (5H, m).

N-(1,2-Diphenyl-ethyl)-N-benzylamine[133] ***(7k)***. This compound was prepared from benzylamine (0.0066 mL, 0.6 mmol) and (phenylethynyl)benzene (0.092 g, 0.5 mmol) following Method B except in anhyd toluene at 130 °C for 48 h and reduced using Method III. Isolated as a yellow oil (0.094 g, 65%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.88−3.00 (2H, m), 3.47 (1H, d, J = 13.7 Hz), 3.67 (2H, d, J = 13.7 Hz), 3.90 (1H, dd, J = 5.5, 8.5 Hz), 7.11−7.38 (15H, m).

N-(2-(4-Methoxyphenyl)-1-phenylethylbenzenamine ***(7li)*** *and N-(1-(4-Methoxyphenyl)-2-phenylethylbenzenamine*[134] ***(7lii)***. These compounds were prepared from aniline (0.056 g, 0.6 mmol) and (4-methoxyphenyl)phenylacetylene (0.104 g, 1.0 mmol) following Method B and reduced using a literature procedure.[57] To a round-bottom flask, Pd/C (27 mg, 10 mol % of Pd, 0.025 mmol of Pd, 5 mol %) and dry THF were added and stirred under an H_2 atmosphere for 30 min. The volatile components of the crude hydroamination reaction mixture were removed in vacuo, dissolved in dry THF, and added to the Pd/C suspension. The resulting mixture was stirred under 1 atm of H_2 for 72 h. Filtration over Celite, removal of solvent in vacuo and purification by column chromatography afforded the pure product. A combined yield of 71% (0.105 g) was obtained for the mixture of regioisomers (1:2, i:ii) as a pale yellow oil, which were inseparable by chromatography. The ^{1}H and ^{13}C NMR spectra for the mixture have been provided: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.00−3.21 (2H, m, i and ii), 3.85 (3H, s, i and ii), 4.18 (1H, br s, i and ii), 4.61−4.65 (1H, m, i and ii), 6.55 (2H, d, J = 8.1 Hz, i and ii), 6.69−6.74 (1H, m, i and ii), 6.87−6.94 (2H, m, i and ii), 7.09−7.20 (4H, m, i and ii), 7.28−7.40 (5H, m, i and ii); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 44.2, 45.1 (ii), 55.1 (i and ii), 58.5 (ii), 59.2, 113.6, 113.9, 117.3, 117.3, 126.4, 126.6, 126.9, 127.4, 128.4, 128.4, 128.9, 129.2, 129.5, 130.1, 135.3, 137.7, 143.4, 147.3, 158.3, 158.5; MS (ESI) m/z 304 ([M + H]$^+$); HRMS Calcd for $C_{21}H_{22}NO$ [M + H]$^+$ 304.1701, found 304.1699.

[2-(3-Chloro-phenyl)-1-methyl-ethyl]-phenyl-amine (Table 5, Entry 4). This compound was prepared from aniline (0.056 g, 1.2 mmol) and 1-chloro-3-(propyn-1-yl)-benzene (0.075 g, 1.0 mmol) following Method D (reacted at 110 °C) and reduced using Method III. Isolated as an oil (0.115 g, 93%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (3H, d, J = 6.4 Hz), 2.70 (1H, dd, 7.2, 13.0 Hz), 2.93 (1H, dd, J = 4.8, 13 Hz), 3.52 (1H, br s), 3.74−3.84 (1H, m), 6.64 (2H, d, J = 8.0 Hz), 6.76 (1H, t, J = 7.2 Hz), 7.08−7.27 (6H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 20.3, 42.0, 49.3, 113.5, 117.5, 126.6, 127.8, 129.6, 129.7, 134.2, 140.8, 147.1; MS (EI) m/z 245 (M$^+$). Anal. Calcd for $C_{15}H_{16}ClN$: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.62; H, 6.79; N, 5.79.

[1-Benzyl-2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(4-methoxy-phenyl)-amine (Table 5, Entry 5). This compound was prepared from *p*-methoxyaniline (0.074 g, 0.6 mmol) and [3-[[*tert*-butyldimethylsilanyloxy]-1-propyn-1-yl]-benzene (0.123 g, 0.5 mmol) following Method D (reacted at 110 °C) and reduced using Method III. Isolated as an oil (0.107 g, 58%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (3H, s), 0.10 (3H, s), 1.00 (9H, s), 2.90−2.95 (2H, m), 3.56−3.62 (2H, m), 3.60 (1H, s), 3.71−3.73 (1H, m), 3.79 (3H, s), 6.65 (2H, d, J = 9.0 Hz), 6.82 (2H, d, J = 9.0 Hz), 7.22−7.36 (5H, m); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ −5.2, 18.5, 26.1, 37.0, 55.9, 56.9, 62.6, 115.1, 115.5, 126.3, 128.5, 129.6, 139.2, 141.5, 152.4; MS (EI) m/z 371 (M$^+$). Anal. Calcd for $C_{22}H_{33}NO_2Si$: C, 71.11; H, 8.95; N, 3.77. Found: C, 71.26; H, 8.84; N, 3.63.

Synthesis of 2-Amino-3-phenylpropan-1-ol[135] **(8).** A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with a solution **1** (0.035 g, 0.05 mmol) dissolved in anhydrous benzene (~1−2 mL), *p*-methoxyaniline (0.074 g, 0.6 mmol) and [3-[[*tert*-butyldimethylsilanyloxy]-1-propyn-1-yl]-benzene (0.123 g, 0.5 mmol). The Schlenk tube was then sealed and heated at 65 °C for 24 h. After cooling the reaction mixture to room temperature, the mixture was diluted with MeOH (~10 mL) and $NaCNBH_3$ (2 equiv), and $ZnCl_2$ (1 equiv) was added. The reaction mixture was then stirred for 24 h at room temperature. The mixture was filtered, and the solid residual was washed with DCM (~15 mL). Sat. Na_2CO_3 (7 mL) was added to the filtrate. After extraction with DCM (6 × 30 mL), the organic layer was dried over $MgSO_4$. Removal of solvent with rotary evaporation and isolation using column chromatography afforded [1-benzyl-2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-(4-methoxy-phenyl)-amine (0.123 g, 66%). This amine (0.131 g, 1.0 mmol) was dissolved in MeCN/H_2O (20 mL, 1:1) and 1 M aqueous H_2SO_4 (1.0 mmol) and H_5IO_6 (0.080 g, 1.0 mmol) was added. The reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was washed with DCM (3 × 50 mL) and purified by column chromatography. The product was obtained as an oil in 57% yield (0.030 g): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (3H, s), 2.54 (1H, dd, J = 8.6, 13.5 Hz), 2.80 (1H, dd, J = 5.3, 13.5 Hz), 3.10−3.20 (1H, m), 3.39 (1H, dd, J = 7.2, 10.7 Hz), 3.64 (1H, dd, J = 2.8, 10.7 Hz), 7.18−7.33 (5H, m).

General Method for Hydrohydrazination with 1. A J. Young NMR tube was charged with a solution of **1** (0.05 equiv) dissolved in anhydrous benzene-d_6 (~0.3 mL), the alkyne (1 equiv), and the amine (1.2 equiv). The J. Young NMR tube was then sealed and heated at 65 °C. The progress of the reaction was monitored by ^{1}H NMR spectroscopy until full conversion was observed. The reaction mixture was cooled to room temperature and diluted with hexanes (10 mL). The precipitate was filtered off, and the solvents were removed by rotary evaporation. The crude product was purified by column chromatography to afford the products as a mixture of regioisomers.

1,1-Diphenyl-2-(2-phenylethylidene)hydrazine[136] ***(9a)***. This compound was prepared from 1,1-diphenylhydrazine (0.23 g, 1.2 mmol) and phenylacetlyene (0.10 g, 1.0 mmol) following the general method for hydrohydrazination described above. The product was obtained as an oil in 71% yield (0.203 g): ^{1}H NMR (C_6D_6, 400 MHz) δ 3.70 (2H, d, J = 7.6 Hz), 6.67 (1H, t, J = 7.6 Hz), 7.14−7.43 (15H, m).

1-Methyl-1-phenyl-2-(2-phenylethylidene)hydrazine[136] ***(9b AM)***. This compound was prepared from 1-methyl-1-phenylhydrazine (0.29 g, 2.4 mmol) and phenylacetylene (0.20 g, 2.0 mmol) following the general method for hydrohydrazination described above. The product was obtained as an oil in 69% yield (0.311 g). This compound was also prepared following general method D using 1-methyl-1-phenylhydrazine (0.29 g, 2.4 mmol) and phenylacetylene (0.20 g, 2.0 mmol): ^{1}H NMR (C_6D_6, 400 MHz) δ 2.56 (3H, s), 3.57 (2H, d, J = 5.7 Hz), 6.45 (1H, t, J = 5.4 Hz), 6.86 (1H, t, J = 7.2 Hz), 7.07 (1H, m), 7.15 (4H, m), 7.24 (2H, m), 7.32 (2H, dd, J = 8.7, 1.3 Hz).

1-Methyl-1-phenyl-2-(1-phenylethylidene)hydrazine[137] ***(9b M)***. This compound was from 1-methyl-1-phenylhydrazine (0.29 g, 2.4 mmol) and phenylacetylene (0.20 g, 2.0 mmol) following the general method for hydrohydrazination described above. The product was obtained as an oil in 12% yield (0.054 g). This compound was also prepared following general method D using 1-methyl-1-phenylhydrazine (0.29 g, 2.4 mmol) and phenylacetlyene (0.20 g, 2.0 mmol): ^{1}H NMR (C_6D_6, 400 MHz) δ 1.95 (3H, s), 2.89 (3H, s), 6.89 (1H, t, J = 7.2 Hz), 7.04 (2H, m), 7.17 (3H, m), 7.22 (2H, m), 7.88 (2H, m).

1,1-Dimethyl-2-(1-phenylethylidene)hydrazine[84] ***(9c AM)***. This compound was from 1,1-dimethylhydrazine (0.14 g, 2.4 mmol) and phenylacetylene (0.20 g, 2.0 mmol) following the general method for hydrohydrazination described above. The product was obtained as an oil in 71% yield (0.230 g): ^{1}H NMR (C_6D_6, 300 MHz) δ 2.76 (6H, s), 3.57 (2H, d, J = 5.7 Hz), 6.69 (1H, t, J = 5.8 Hz), 7.22−7.33 (5H, m).

(E)-1,1-Dimethyl-2-(1-phenylethylidene)hydrazine[84] ***(9c M)***. This compound was from 1,1-dimethylhydrazine (0.14 g, 2.4 mmol) and phenylacetylene (0.20 g, 2.0 mmol) following the general method for hydrohydrazination described above. The product was obtained as an oil in 12% yield (0.038 g): ^{1}H NMR (C_6D_6, 400 MHz) δ 2.35 (3H, s), 2.60 (6H, s), 7.35−7.36 (5H, m).

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1-Methyl-1-phenyl-2-(1-phenylpropan-2-yl)hydrazine[136] ***(10)***. This compound was from 1-methyl-1-phenylhydrazine (0.25 g, 2.1 mmol) and 1-phenyl-1-propyne (0.20 g, 1.72 mmol) following the general method for hydrohydrazination described above. Product obtained after reduction with LAH and isolation by column chromatography. The product was obtained as an oil in 66% yield (0.273 g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (3H, d, J = 6.1 Hz), 2.68−2.75 (1H, m), 2.81−2.89 (1H, m), 3.03 (3H, s), 3.35−3.43 (2H, m), 6.80 (1H, t, J = 7.2 Hz), 6.96 (2H, d, J = 7.9 Hz), 7.26−7.39 (7H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 19.3, 40.0, 42.2, 54.5, 113.2, 118.0, 126.5, 128.6, 129.0, 129.5, 139.5, 152.4; MS (ESI) m/z 241 ($[M + H]^+$); HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{21}N_2$ ([M + H]+), 241.1705, found 241.1705.

General Method for Sequential Hydrohydrazination/Fischer Indole Synthesis. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with a solution **1** (0.05 equiv) in anhydrous benzene (~0.5 mL), the alkyne (1 equiv), and the hydrazine (1.2 equiv) dissolved. The Schlenk tube was then sealed and heated to 65 °C for 1−18 h. $ZnCl_2$ (3 equiv) and toluene (15 mL) were added. The reaction mixture was heated at 100 °C for 16 h. The reaction was quenched with diethylether (30 mL), and the mixture was filtered through a plug of silica gel. The solvents were removed by rotary evaporation, and the crude product was purified by column chromatography to afford the indole product.

1,2-Dimethyl-3-phenylindole[84] ***(11a)***. This compound was prepared from 1-methyl-1-phenylhydrazine (0.25 g, 2.0 mmol) and 1-phenyl-1-propyne (0.20 g, 1.7 mmol) following the general method for indole synthesis described above. The product was obtained as a solid in 66% yield (0.248 g): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (3H, s), 2.92 (3H, s), 7.13 (1H, d, J = 7.9 Hz), 7.22−7.34 (4H, m), 7.43 (2H, t, J = 7.6 Hz), 7.63 (2H, d, J = 8.2 Hz), 7.94 (1H, d, J = 7.7 Hz).

1-Methyl-3-phenylindole[84] ***(11b)***. This compound was prepared from 1-methyl-1-phenylhydrazine (0.29 g, 2.4 mmol) and phenylacetlyene (0.2 g, 2 mmol) following the general method for indole synthesis described above. The product was obtained as a solid in 72% yield (0.298 g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87 (3H, s), 7.24−7.32 (5H, m), 7.49 (2H, t, J = 7.6 Hz), 7.71 (2H, m), 8.01 (1H, d, J = 7.9 Hz).

1,3-Diphenylindole[51] ***(11c)***. This compound was prepared from 1,1-diphenylhydrazine (0.09 g, 0.5 mmol) and 1-phenyl-1-propyne (0.05 g, 0.5 mmol) following the general method for indole synthesis described above. The product was obtained as a solid in 33% yield (0.044 g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92−7.12 (6H, m), 7.19−7.23 (2H, m), 7.24−7.29 (1H, m), 7.32−7.36 (2H, m), 7.47−7.49 (1H, m), 7.70−7.72 (2H, m), 8.05−8.07 (1H, m).

3-((tert-Butyldimethylsilyl)oxy)-1,2-dimethyl-1H-indole[138] ***(12)***. This compound was prepared from 1-methyl-1-phenylhydrazine (0.17 g, 1.4 mmol) and (*tert*-butyldimethylsilyloxy)-1-propyne (0.20 g, 1.2 mmol) following the general method for indole synthesis described above. The product was obtained as a solid in 62% yield (0.205 g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.13 (6H, s), 1.07 (9H, s), 2.29 (3H, s), 3.59 (3H, s), 7.01 (1H, m), 7.09 (1H, m), 7.13 (1H, d, J = 8.2 Hz), 7.46 (1H, d, J = 7.8 Hz).

***N*-(Phenylmethyl)-2-phenylethylamine (3a).**[47] A 500 mL Schlenk flask equipped with a stir bar was charged with the amide proligand (0.06 g, 0.002 mol) and suspended in 25 mL of anhydrous benzene. To this suspension, $Ti(NMe_2)_4$ (0.06 g, 0.002 mol) was added, and the solution was allowed to stir at room temperature for 5 min. Phenylacetylene (2.2 mL, 0.02 mol) and benzylamine (2.2 mL, 0.02 mol) were then added, and the mixture was heated to 65 °C and allowed to stir for 24 h. After cooling the solution to room temperature, MeOH (20 mL) and $NaBH_4$ (2.26g, 0.06 mol) were then added, and mixture was stirred at room temperature for 24 h. After removal of solvent by rotary evaporation, 1 M $HCl_{(aq)}$ (60 mL) and EtOAc (60 mL) was added to the residual. The organic layer was extracted with 1 M $HCl_{(aq)}$ (2 × 60 mL). The combined aqueous layer was washed with EtOAc (60 mL), basified with 3 M $NaOH_{(aq)}$ and extracted with EtOAc (4 × 100 mL). The combined organic layer was dried over Na_2SO_4 and filtered, and solvent was removed by rotary evaporation. The resulting brown suspension was diluted with EtOAc and filtered through a pad of Celite. The product was obtained as a yellow oil in 77% yield (3.01g): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (1H, s), 2.89−2.99 (4H, m), 3.86 (2H, s), 7.24−7.40 (10H, m).

Details of Kinetics Experiments. *1-Decyne with t-Butylamine Using 1 as Precatalyst.* These reactions were carried out on an NMR tube scale and monitored at 303.0 ± 0.2 K on a Bruker AV400 spectrometer with 5 mm BBI-Z probe (inverse coil geometry, broadband Z-gradient tuning). One equivalent of alkyne (0.532 mmol), 1 equiv of *t*-butylamine (0.532 mmol), 1 equiv of 1,3,5-trimethoxybenzene (0.532 mmol, internal standard), and 5 mol % of precatalyst **1** (0.0266 mmol) were dissolved in C_6D_6 (500 mg). Data points were collected every 5 or 10 min. Each run was repeated at least once to estimate the error of k_{obs} or ν. The runs were averaged, and the percent error was estimated from $(k_{obs(max)} - k_{obs(min)})/k_{obs(average)}$. This percent error was used to calculate absolute error. In all cases, the percent error of rate constants was below 10%. The ratios of k_{obs} or ν were taken using the average values. The error on the ratios was estimated using the following formula:

$$a = A(b/B + c/C)$$

where $A = B/C$, and a, b, c are the errors on A, B, C, respectively.

The methylene peak used in the above experiments (δ 1.99, m, 2H, $—CH_2—C{\equiv}CH$) to monitor the concentration of 1-decyne was found to be obscured by the corresponding product resonance. Therefore, the acquisition time was set to a longer interval (~5 s), and integration of the alkyne proton peak (δ 1.84, 1H, t, $—CH_2—C{\equiv}CH$) referenced to internal standard was used to determine the number of moles of 1-decyne. The concentration was determined using the moles of 1-decyne and the volume of C_6D_6. [1-Decyne] was plotted directly against time in minutes to give a linear correlation, which was used to estimate the rate of reaction (see Figure S1, Supporting Information). Slopes and R^2 values were determined using the trendline routine in Microsoft Excel.

$$\nu_{(run1)} = 7.65 \times 10^{-3}\ \text{mol L}^{-1}\ \text{min}^{-1}$$

$$\nu_{(run2)} = 7.52 \times 10^{-3}\ \text{mol L}^{-1}\ \text{min}^{-1}$$

$$\nu_{(average)} = 7.59 \pm 0.07 \times 10^{-3}\ \text{mol L}^{-1}\ \text{min}^{-1}$$

R^2 = 0.9884 (both runs plotted in same series).

1-Decyne with N,N-d$_2$-t-Butylamine Using 1 as Precatalyst. Details identical to above.

$$\nu_{(run1)} = 2.31 \times 10^{-3}\ \text{mol L}^{-1}\ \text{min}^{-1}$$

$$\nu_{(run2)} = 2.15 \times 10^{-3}\ \text{mol L}^{-1}\ \text{min}^{-1}$$

$$\nu_{(average)} = 2.23 \pm 0.08 \times 10^{-3}\ \text{mol L}^{-1}\ \text{min}^{-1}$$

R^2 = 0.9915 (both runs plotted in same series).

■ ASSOCIATED CONTENT

Supporting Information

Plot of kinetic data and figures giving ^{1}H and ^{13}C NMR spectra for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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