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An Easy-To-Use, Regioselective, and Robust Bis(amidate) Titanium Hydroamination Precatalyst: Mechanistic and Synthetic Investigations toward the Preparation of Tetrahydroisoquinolines and Benzoquinolizine Alkaloids

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Abstract: Amidate-supported titanium amido complexes are efficient and regioselective precatalysts for intermolecular hydroamination of terminal alkynes with primary amines. The synthesis and characterization of the first bis(amidate)-supported titanium-imido complex is reported. Its role as the active catalytic species is suggested in the course of product distribution studies using deuterated substrates. The bis(amidate)-supported precatalysts exhibit good functional-group tolerance, even performing hydroaminations in the presence of ester and amide groups. This functional-group tolerance was exploited in the synthesis of a variety of 1-substituted tetrahydroisoquinoline alkaloids and a one-pot hydroaminative procedure for the high yielding preparation of the benzo[*a*]quinolizine skeleton.

Keywords: alkynes · homogeneous catalysis · hydroamination · isoquinoline · titanium

Introduction

Nitrogen-containing organic molecules are a vast and important class of compounds, which contain many biologically-active natural products and synthetic pharmaceuticals. Recent developments in the preparation of such compounds involve the metal-catalyzed addition of amines to carbon–carbon multiple bonds, known as hydroamination.[1] The selective hydroamination of alkenes, which forms substituted amines directly, remains a significant challenge;[2] however, the analogous reaction with alkynes to form enamines and imines is now a viable option for the synthesis of increasingly complex molecules.[3]

Early systems reported for the intermolecular hydroamination of alkynes relied on mercury and thallium salts as precatalysts, the toxicity of which has limited wider applications.[4] Since then, catalytic systems based on late transition metals, f-block organometallics,[5] and s-block bases[6] have been developed. Unfortunately, many of these systems suffer from high cost, or severe air and moisture sensitivity. A practical alternative to these is the less expensive Group 4 metals, titanium and zirconium. Many research groups, including those of Bergman,[7] Odom,[8] Beller,[9] Doye,[10] Livinghouse,[11] Richeson,[12] and our own,[13] have demonstrated the viability of Group 4 systems, particularly zirconocene and titanocene-based organometallics and titanium amido complexes prepared from $Ti(NMe_2)_4$.

Two key challenges facing such catalysts are functional-group tolerance and high regioselectivity, both of which are crucial for practical synthetic application. Because of the oxophilicity of the titanium metal centre, and the electron-deficient nature of the catalytic intermediates, careful ligand design is needed to generate complexes that will tolerate diverse substrates. In addition, the regioselective intermolecular hydroamination of terminal alkynes remains nontrivial: for the majority of Group 4 catalytic systems reported to date, the use of *tert*-butylamine is a requirement for exclusively anti-Markovnikov addition.[8a–c,9a,d,12,14]

Tetrakis(dialkylamido)titanium complexes have been shown to be catalytically viable; however, limited substrate scope and low regioselectivity preclude their use as general precatalysts.[8b,13c] In an effort to address the challenges listed above, our group has focused on augmenting commercially available $Ti(NR_2)_4$ species with an easily modified ligand set. As previously reported, we have employed organic amides as versatile proligands for titanium and zirconium

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amido complexes, and have demonstrated the efficiency of these complexes in both intra- and intermolecular hydroamination reactions.[13a,b] The highly modular nature of these ligands results in a tunable series of precatalysts with varying steric and electronic properties. The electron-withdrawing amidate ligands render the metal center very electropositive, resulting in comparatively higher activity in hydroamination reactions than the more electron-rich Cp-based systems. As well, unlike related amidinate and guanidinate ligands, amidates contain a mixed N,O chelating motif. These ligands can form strong Ti–O bonds between the ligand and metal, leading to robust complexes.

Screening experiments determined that electron-withdrawing or sterically demanding ligands enhance catalytic activity in hydroamination reactions.[13a] As well, those ligands with significant steric bulk also increase regioselectivity for the anti-Markovnikov isomer.[13b] The most active and selective precatalyst (**1**) from these screens contains the bulky 2,6-diisopropylphenyl substituent on the nitrogen of the amidate ligands (Figure 1). Preliminary results indicated that complex **1** displays unique selectivity for the anti-Markovnikov product of intermolecular hydroaminations with terminal alkyl alkynes, even when employing nonbulky amino-substrates, such as benzylamine. As well, alkynes substituted with heteroatoms containing functional groups are easily tolerated.[13b]

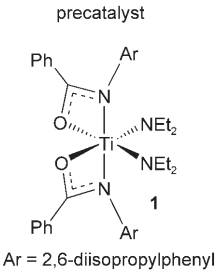
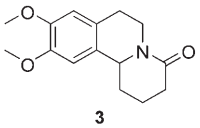


Figure 1. Bis(amidate)bis-(amido)titanium precatalyst **1**.

Herein, we report investigations into the reactivity and selectivity of titanium-amidate complex **1** for intermolecular alkyne hydroamination. We have prepared and fully characterized the first amidate-supported titanium-imido species (**2**), and discuss the structure and reactivity of this new complex. Isotopic labeling experiments have been carried out to probe the mechanism of this reaction. We have also examined the scope of reactivity of this complex, and have identified significant functional-group tolerance. We have taken advantage of this catalytic activity and functional-group tolerance for the development of a one-pot procedure for the synthesis of the isoquinoline framework, including an efficient route to the benzo[*a*]quinolizine ring system **3**. This framework is a precursor to several naturally occurring alkaloids.[15]



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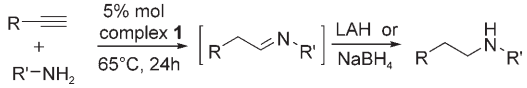
Results and Discussion

Preliminary results: Encouraged by our success with Group 4 amidate complexes as precatalysts for the intramolecular hydroamination of aminoalkynes,[13a] we sought to develop a Group 4 amidate-based system to affect intermolecular alkyne hydroamination with efficiency, selectivity, and wide-ranging substrate scope. Due to the limited number of catalytic systems capable of carrying out regioselective hydroaminations between terminal alkynes and alkylamines,[16] we chose these substrates as our primary focus.

Our initial experiments revealed that complex **1** displays significantly enhanced reactivity and regioselectivity relative to titanium-amidate complexes with other, less-bulky substituents, as well as other Group 4 systems reported in the literature.[7–12] In fact, previous reports of alkyne hydroamination have indicated that the steric nature of the amine substrate is critical in determining regioselectivity, with more bulky amines typically being required to induce anti-Markovnikov selectivity.[8a–c,9a,d,12,14] For reactions catalyzed by **1**, however, no Markovnikov product is observed by ^{1}H NMR spectroscopy, even when employing challenging amine substrates, such as benzylamine. This high regioselectivity for a hydroamination catalyst is unique to titanium-amidate complex **1**.

The hydroamination of selected alkynes with alkylamines is shown in Table 1. A mixture of the alkyne, amine, and 5 mol% of **1** were heated to 65°C in benzene for 24 h to complete the hydroamination; the imine formed was then directly reduced with lithium aluminum hydride or sodium borohydride to give the corresponding secondary amines in good to excellent yield. Among the effectively transformed substrates are alkylalkynes of varied steric bulk and arylalkynes-substituted with both electron-donating and -withdrawing groups. It should be emphasized that, unless other-

Table 1. Hydroamination of alkynes and alkylamines catalyzed by complex **1**.

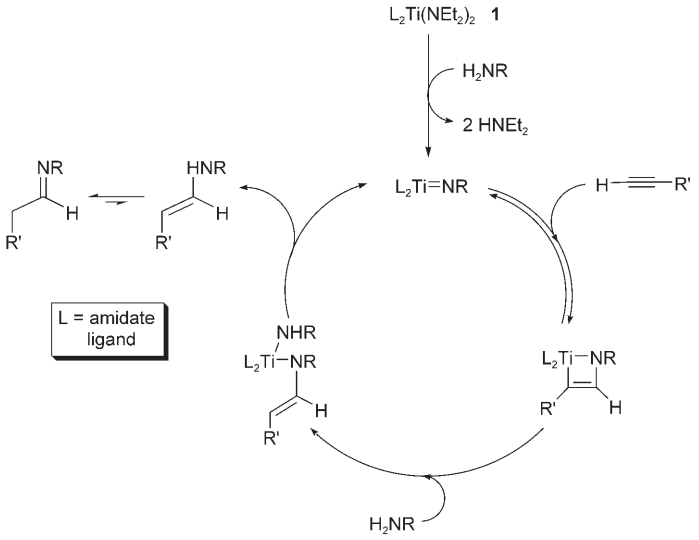


Entry	Alkyne	Amine	Yield [%]
1		$BnNH_2$	88
2		$iPrNH_2$	88
3		$tBuNH_2$	82
4		$BnNH_2$	87
5		$iPrNH_2$	89
6		$tBuNH_2$	72[a]
7		$BnNH_2$	95[b]
8		$iPrNH_2$	82[b,c]
9		$BnNH_2$	87
10		$iPrNH_2$	86
11		$tBuNH_2$	74
12		$BnNH_2$	83
13		$iPrNH_2$	78
14	MeO	$tBuNH_2$	79
15		$BnNH_2$	93
16		$iPrNH_2$	68
17	Cl	$tBuNH_2$	91

[a] Reaction time 72 h. [b] Reaction time 120 h. [c] Yield determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

wise noted, the times and temperatures employed do not reflect optimized reaction conditions and were chosen for consistency. The isolated yields shown in Table 1 demonstrate the efficiency of this reaction. Interestingly, *tert*-butylamine is slightly less reactive than other less bulky amine substrates, possibly due to unfavorable steric interactions with the large 2,6-diisopropylphenyl groups on the amidate ligands.

Mechanistic investigations: After gathering promising preliminary data on the hydroamination activity of precatalyst **1**, we endeavored to probe the operative mechanism of our catalytic system. Attempted hydroamination reactions between secondary amines and alkynes were unsuccessful, supporting the hypothesis that a titanium-imido complex is the active catalytic species. Bergman and Doye have carried out elegant rate law determinations to fully elucidate the reaction mechanism for a related group-4-mediated alkyne hydroamination that proceeds via metal-imido species.[10c,17] Furthermore, Livinghouse,[11] Beller,[9] Odom,[8] and Richeson[12] have implicated imido complexes as the catalytically active species in their respective Group 4 systems. Due to the aforementioned substrate scope limitations in our case, we also propose a catalytic cycle consistent with the generally accepted imido-based mechanism that was initially established in the Bergman laboratories (Scheme 1).[17]

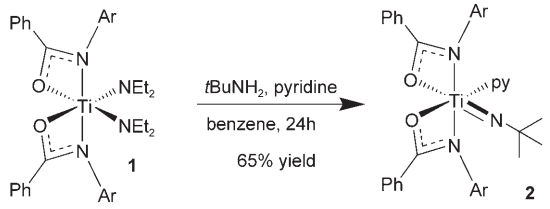


Scheme 1. Proposed simplified catalytic cycle.

The X-ray crystallographic analysis of precatalyst **1** has been communicated.[13b] The solid-state C_2-symmetric structure exhibits bonding consistent with the geometric isomer shown in Figure 1. The two amido ligands are in a *cis* arrangement, with a Ti–N distance of 1.899 Å, indicative of Ti–N multiple-bond character and each amido ligand being a formal 4 electron donor to the d^0 metal center. This is further corroborated by the sum of the bond angles about each amido nitrogen (360°). Furthermore, the 2,6-diisopropylphenyl substituents are oriented *trans* to one another, placing the majority of the steric bulk close to the two reactive ligands, resulting in a favorable environment for sterically imposed selectivity during hydroamination. However, ^{1}H NMR spectroscopic evidence reveals a degree of ligand fluxionality in solution;[18] therefore, catalytic intermediates could exhibit alternative coordination geometries, thereby impacting reactivity and selectivity.

Because we propose an imido complex as the active catalytic species, an investigation into the structure and reactivity of amidate-supported titanium-imido complexes was undertaken. In particular, reactivity changes upon transformation to the imido, such as coordination geometry isomerism,[19] ligand dissociation,[7a] or transamidation[20] have precedence and could affect catalytic activity. In addition, a direct comparison of the reactivity of bis(amido) precatalyst **1** and an imido catalyst would give an indication of the importance of an "induction period" to form the catalytically active species.[10c]

Bis(amidate)titanium-imido complex **2** was prepared by treating precatalyst **1** with one equivalent of *tert*-butylamine [Eq. (1)]. The resulting 14-electron imido-species was stabilized by the addition of pyridine as a neutral donor to generate a stable 16-electron complex, which was isolated as a yellow microcrystalline solid. Recrystallization from a hexanes/benzene mixture gave **2** in 65% yield. This is the first structural analysis of an amidate-supported titanium-imido complex.



Ar = 2,6-diisopropylphenyl

X-ray-quality crystals were obtained and the crystallographic analysis confirms the structure as a monomeric, C_1-symmetric pseudo-octahedral titanium-imido complex (Figure 2, Tables 2 and 3). The coordination geometry of the amidate ligands is the same as in the structure of **1**. This demonstrates that, in the solid state, a *trans* orientation of the amidate nitrogens is the preferred conformation due to the bulky *N*-substituents. This contrasts with a similar zirconium-imido complex utilizing the same amidate ligands, which is observed to change coordination geometries from pseudo-octahedral to distorted pentagonal pyramidal upon transformation to the imido.[19] The Ti–N3 bond length of 1.711 Å is consistent with other reported titanium-imido complexes,[21] and suggests a formal Ti–N triple bond. The nearly linear geometry of the imido nitrogen (Ti-N3-C39 angle of 172.3°) is also consistent with a strong degree of sp character of the imido ligand. Because of the pseudo-octahedral geometry of the imido complex, a significant *trans* influence can be observed between the strongly donating

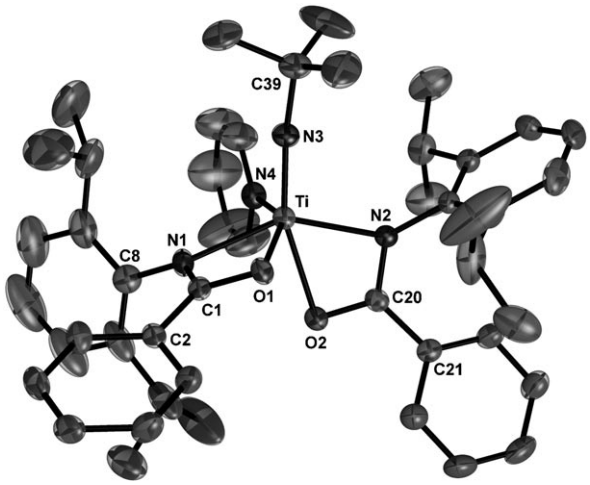


Figure 2. ORTEP diagram of bis(amidate)titanium-imido-pyridine complex **2** (ellipsoids plotted at 50% probability).

Table 3. Crystal data and summary of data collection and refinement for **2**.

formula	$C_{47}H_{58}N_4O_2Ti$
F_w	758.57
crystal size [mm]	$0.15\times0.10\times0.05$
color, habit	yellow, plate
crystal system	primitive
lattice type	monoclinic
space group	$P2_1/n$
a [Å]	10.6407(8)
b [Å]	16.785(1)
c [Å]	24.495(2)
α [°]	90.0
β [°]	92.639(3)
γ [°]	90.0
V [Å^3]	4370.3(6)
Z	4
ρ_{calcd} [g cm^{-3}]	1.153
radiation	$Mo_{K\alpha}$ ($\lambda=0.71073$ Å)
$F(000)$	1624.00
μ ($Mo_{K\alpha}$) [cm^{-1}]	2.36
$2\theta_{max}$ [°]	50.2
total no. of reflns	76836
no. of unique reflns	7693 ($R_{int}=0.087$)
no. of reflns with $I=2\sigma(I)$	4301
no. of variables	465
R_1 (F^2, all data)	0.098
wR_2 (F^2, all data)	0.142
R_1 (F, $I=2\sigma(I)$)	0.053
wR_2	0.125
goodness of fit	1.05

Table 2. Selected bond lengths [Å] and angles [°] for **2**.

Bond lengths [Å]		Bond angles [°]			
Ti–O1	2.097(2)	Ti-N3-C39	172.3(2)	N2-Ti-N3	101.81(9)
Ti–O2	2.262(2)	N1-Ti-O1	61.77(8)	N2-Ti-N4	98.81(8)
Ti–N1	2.181(2)	N1-Ti-O2	86.29(7)	N3-Ti-O1	99.70(9)
Ti–N2	2.096(2)	N1-Ti-N2	145.88(8)	N3-Ti-O2	162.21(9)
Ti–N3	1.711(2)	N1-Ti-N3	111.03(9)	N3-Ti-N4	97.01(10)
Ti–N4	2.201(2)	N1-Ti-N4	86.40(8)	N4-Ti-O1	147.64(8)
N1–C1	1.307(3)	N2-Ti-O1	104.58(8)	N4-Ti-O2	87.77(8)
O1–C1	1.299(3)	N2-Ti-O2	60.46(7)		
N2–C20	1.332(3)				
O2–C20	1.275(3)				

imido nitrogen and the corresponding *trans* oxygen of the amidate ligand:[22] the Ti–O distances differ by more than 0.165 Å (Ti–O1: 2.0969 Å; Ti–O2: 2.2620 Å). In addition, there is less delocalization between the N2-C20-O2 atoms than the amidate ligand in which the oxygen is *trans* to the pyridine nitrogen (N1–C1: 1.307 Å; O1–C1: 1.299 Å; N2–C20: 1.332 Å; O2–C20: 1.275 Å). This is indicative of an unsymmetric binding motif for the N2-C20-O2 amidate, in which the negative charge is more localized on the nitrogen and the oxygen is acting primarily as a neutral carbonyl donor.

Diagnostic signals in the NMR spectra of this complex reveal the formation of the pyridine-stabilized imido. A resonance at $\delta=68.25$ ppm in the ^{13}C NMR spectrum is diagnostic for the quaternary carbon atom of the *tert*-butyl imido substituent.[21a,c] Furthermore, a doublet at $\delta=9.23$ ppm could be observed in the ^1H NMR spectrum corresponding to the *ortho* protons of one equivalent of coordinated pyridine. Two multiplets corresponding to the methine protons of the isopropyl groups are observed at $\delta=3.66$ and 4.41 ppm, which is consistent with two nonequivalent ligand environments at room temperature. However, variable temperature NMR spectroscopic experiments showed that these two signals coalesce at 75 °C. This solution-phase behavior is consistent with a labile pyridine ligand that renders the imido complex C_2 symmetric on the NMR time scale. Here, the high yielding preparation, isolation, and full characterization of the titanium-imido complex **2** demonstrates the viability of the bis(amidate)bis(amido) complex **1** as a useful precursor to the imido intermediate proposed as the catalytically active species.

To further probe the role of the imido-species as the catalytically active complex, the product formation from a series of experiments using both deutero- and protio-1-decyne (**4**) and *tert*-butylamine (**5**) were carefully monitored. The hydroamination between the two protio substrates **4** and **5** with precatalyst **1** proceeds to completion after 24 h at 65 °C. Subsequent reduction with lithium aluminum hydride gives only the anti-Markovnikov product in 91% isolated yield. Running this same reaction in an NMR tube for 6 h at room temperature results in 75% conversion to the enamine product **6** [Eq. (2)]. Only a trace of aldimine product is observable at this stage of the reaction. The coupling constant between the olefinic protons (C_β–H: m, $\delta=4.54$ ppm; C_α–H: t, $\delta=5.94$ ppm) is 12.8 Hz, which suggests the *E* double

bond isomer, consistent with the [2+2] cycloaddition mechanism proposed above.

The relative reactivity of both precatalyst **1** and titanium-imido **2** was assessed by comparing product formation in two side-by-side reactions, using identical reaction conditions. J. Young NMR tubes with one equivalent of alkyne **4**, 10 equivalents of amine **5**, 5 mol% of either precatalyst **1** or **2**, and one equivalent of 1,3,5-trimethoxybenzene (as internal standard) were prepared and the reaction progress at 325.0 K was monitored by using ^{1}H NMR spectroscopy. This experiment showed that both **1** and **2** are equally active for intermolecular hydroamination reactions, with each showing 50% product formation in approximately 50 minutes. This suggests that, in contrast to previously reported titanocene-based systems, there is no significant "induction period" to form the catalytically active imido species from this precatalyst.[10c] It also supports that both **1** and **2** mediate the reaction via a common catalytically active species.

While this experiment shows that both **1** and **2** are catalytically active for the selected intermolecular hydroamination reaction, there is a possibility that reversible C–H activation of the alkyne to give a terminally bound titanium-alkynyl species could be a nonproductive side reaction, as has been observed for Cp*$_2$Ti=NPh.[23] Isotopic labeling experiments shed further light on this potentially competing reaction. In a room temperature reaction between 1-[D]-1-decyne (**7**) and **5**, the enamine product **8** is observed [Eq. (3)]. The disappearance of the diagnostic triplet at $\delta = 5.94$ ppm in the ^{1}H NMR spectrum of this reaction confirms that the linear enamine product **8** is the major product. The multiplet at $\delta = 4.54$ ppm corresponding to C_β–*H* has simplified to a broadened triplet, indicative of minimal coupling to the adjacent deuterium. A small signal, constituting less than 5% of the generated product, is visible at $\delta = 5.94$ ppm, and corresponds to the nondeuterated enamine **6**. This is likely due to a small amount of exchange between the basic amine and the slightly acidic deuterium on the alkyne [Eq. (4)].[24] The clean conversion of deuterated alkyne to deuterated linear enamine product **8** is consistent with a [2+2]-cycloaddition mechanism with no significant competing C–H activation of the terminal alkyne.

These product distribution investigations for the bis(amidate) titanium-catalyzed system are consistent with the general mechanistic proposals for Group 4 catalytic reactions that invoke imido species as key intermediates. Ongoing investigations include kinetic investigations to carefully probe the detailed mechanism of the catalytic cycle proposed here.

The bis(amido)-complex **1** and the imido-complex **2** are both air and moisture sensitive. However, they display excellent thermal stability in the solid state, such that under inert atmosphere, both **1** and **2** can be stored indefinitely. Furthermore, super-heating of [D$_8$]toluene solutions (140 °C, for up to four days) of **1** and **2**, respectively, results in no observable decomposition by ^{1}H NMR spectroscopy.

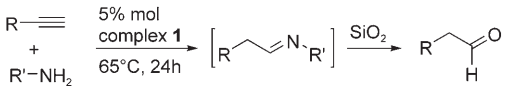
The preparation and use of **1** as a precatalyst for practical synthetic applications was also shown to be viable, as the crude product from the protonolysis reaction between Ti(NR$_2$)$_4$ and two equivalents of the amide proligand is as catalytically active as the purified complex. The entire reaction scheme, including catalyst preparation, hydroamination, and hydrolysis or reduction can be performed in the same flask. Furthermore, the in situ preparation of the precatalyst is easily accomplished by using standard syringe techniques and the subsequent hydroamination reactions are equally successful, as long as noncoordinating solvents are used. This bench-top protocol suggests that precatalyst **1** could be exploited for more demanding syntheses and, consequently, substrate scope investigations were undertaken.

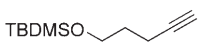
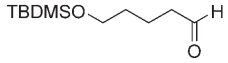
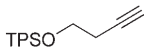
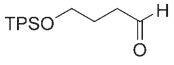
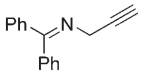
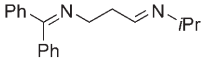
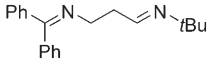
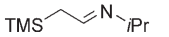
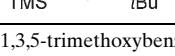
Functional-group tolerance: To fully investigate the scope of reactivity of precatalyst **1**, and to determine its usefulness for practical synthetic applications, we have endeavored to expand the applicability of alkyne hydroamination to include a variety of challenging substrates, including those with carbonyl groups and relatively acidic protons.

As previously reported, **1** can tolerate a variety of heteroatom-substituted alkynes in hydroamination reactions with no appreciable drop in yield or regioselectivity.[13b] Some examples of reactions carried out using common organic protecting groups are shown in Table 4. The reactions were carried out for 24 h at 65 °C in benzene, after which time the intermediate imines were hydrolyzed over silica gel and purified. In the case of the sensitive imine products in entries 5–8, yields are based on ^{1}H NMR integrations relative to an internal standard (1,3,5-trimethoxybenzene). Only anti-Markovnikov regioisomers were observed. In addition, there were no signs of imine metathesis with the use of the bulky diphenyl protecting group for entries 5 and 6,[25] as well as no signs of trimethylsilyl-group migration to the nitrogen atom in entries 7 and 8.[26]

In addition to silyl-ether protected alcohols, imine-protected primary amines, and TMS-protected alkynes, we have determined that carboxylic acid derivatives can be tolerated by our catalytic system. The results of hydroamination studies on

Table 4. Hydroamination of protected alkynes catalyzed by complex **1**.



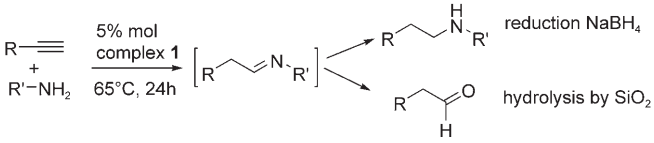
Entry	Alkyne	Amine	Product	Yield [%]
1		$BnNH_2$		76
2		$iPrNH_2$		94
3		$BnNH_2$		76
4		$iPrNH_2$		92
5		$iPrNH_2$		92[a]
6		$tBuNH_2$		99[a]
7		$iPrNH_2$		90[a]
8		$tBuNH_2$		78[a]

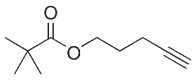
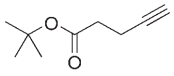
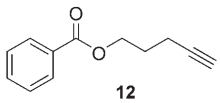
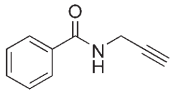
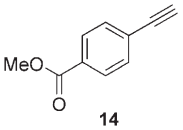
[a] Yield of intermediate aldimine determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

ester and amide-containing substrates are summarized in Table 5. Again, only anti-Markovikov selectivity was observed. It should be noted that less bulky carboxylic acid derivatives **12**, **13**, and **14** (entries 7–13) were unreactive toward benzylamine; however, *tert*-butyl-substituted esters **10** and **11** reacted cleanly with all alkyl amines (entries 1–6). Thus, these ester-functionalized substrates can be elaborated to reveal either an alcohol or carbonyl moiety in subsequent steps. The usage of either bulky *tert*-butyl esters (entries 1–6) or electronically saturated benzoate esters (entries 7–9) is required when employing alkylalkyne substrates, as methyl and ethyl ester-containing alkynes cause catalyst decomposition. However, a less bulky ester incorporated into an aromatic alkyne is an effective substrate for amines (entries 12 and 13).

Amazingly, the propargylic phenyl amide **13** (entries 10 and 11) was a highly effective substrate for bulkier amines, despite the presence of an acidic proton and its structural similarities to the auxiliary ligand motif. This reaction was observed to proceed to completion by ^1H NMR spectroscopy in less than 2 h at 65 °C. Indeed, this result demonstrates the remarkable stability of the amidate-supported catalytic intermediates, especially considering that precatalyst **1** is prepared by protonolysis of amides not unlike **13**. Furthermore, no ligand substitution or transamidation[20] were observed in the NMR spectra of this reaction and isolated yields for the desired products are very good (Table 5).

Table 5. Hydroamination of carboxylic acid derivatives catalyzed by complex **1**.



Entry	Alkyne	Amine	Isolated Yield [%]
1		$BnNH_2$	80[a]
2		$iPrNH_2$	90[a]
3	**10**	$tBuNH_2$	95[a]
4		$BnNH_2$	80[b]
5		$iPrNH_2$	85[b]
6	**11**	$tBuNH_2$	74[b]
7		$BnNH_2$	nr[c]
8		$iPrNH_2$	86[a]
9	**12**	$tBuNH_2$	70[a]
10		$iPrNH_2$	77[b]
11		$tBuNH_2$	80[b]
12	**13**	$iPrNH_2$	70[b]
13		$tBuNH_2$	91[b]
	14		

[a] Isolated yield after hydrolysis. [b] Isolated yield after imine reduction with $NaBH_4$ reduction. [c] nr = no reaction.

Precatalyst **1** is currently, to the best of our knowledge, the only early transition-metal-based hydroamination catalytic system that retains activity in the presence of carbonyl containing substrates. Coupled with the aforementioned tolerance of silyl-ethers and imines, hydroamination with **1** has the potential to be a powerful method for the practical synthesis of a wide variety of nitrogen-containing molecules. To this end, we have explored the potential application of this catalyst as an alternative route for the synthesis of tetrahydroisoquinolines (THIQs).

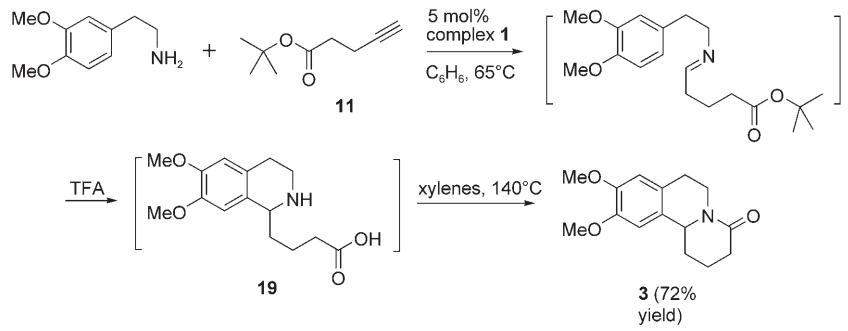
Applications to isoquinoline synthesis: Due to the favorable reactivity, selectivity, and functional-group tolerance of precatalyst **1**, it is well suited among Group 4 hydroamination catalysts to be used for challenging synthetic applications. Key among these applications is the construction of nitrogen-containing heterocycles. Hydroamination has been used as a key step in the syntheses of this broad class of molecules, including the preparation of indolines,[27] indoles,[28] indolizidines,[27,29] pyrroles,[29,30] pyrrolizidines,[27] and quinolines.[31]

1-Substituted-THIQs are compounds of great interest due to their biological and pharmacological properties. For instance, 1-methyl- and 1-phenyl-THIQ are involved in the treatment of Parkinsons's and other nervous system diseases.[32] The synthesis of this class of compounds has received much attention, and there are a myriad of protocols for the construction of the ring system, including the Pictet–Spengler cyclization, the Bischler–Napieralski cyclization, the

Pomeranz–Fristch reaction, and many other extensions of these classic methods.[33] Doye and co-workers have recently reported an enantioselective synthesis of two naturally occurring THIQs by using intramolecular alkyne hydroamination followed by asymmetric imine reduction as the key steps.[34] In addition, 3-methyl and 3,4-dimethyl-THIQs have been prepared by using *n*BuLi-catalyzed intramolecular hydroamination of alkenes.[35] Previously, we reported the construction of 1-subsituted-THIQs by using intermolecular alkyne hydroamination from commercially available starting materials.[13b] Our approach avoids sensitive aldehyde-containing precursors and the synthesis of complex intramolecular substrates. We have now extended this method to be a general, one-step protocol for the synthesis of these compounds.

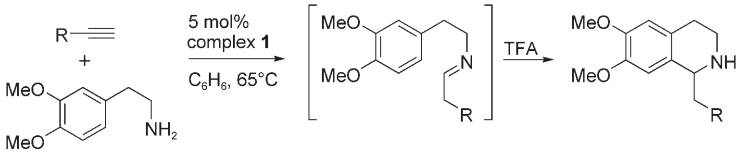
The results in Table 6 summarize the efficiency and scope of this procedure. The reaction involves an intermolecular hydroamination, catalyzed by **1**, between commercially available 3,4-dimethoxyphenethylamine and a variety of alkynes, followed by trifluoroacetic acid-catalyzed cyclization of the imine. Alkylalkynes are very effective substrates for this reaction, giving good to excellent yields of the cyclized product. The product in entry 4 (**18**), formed in 79% isolated yield, is an advanced synthetic precursor to (±)-homolaudanosine, which only requires N methylation to complete the synthesis.

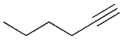
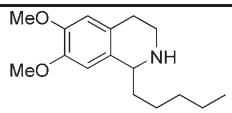
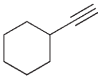
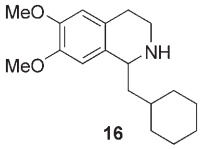
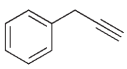
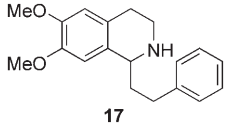
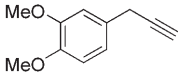
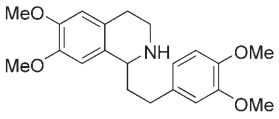
To exploit the functional-group tolerance of precatalyst **1**, the synthesis of yet more complex structures was undertaken. As a demonstration of the potential utility of this catalyst, this method was extended to the construction of the tricyclic benzo[*a*]quinolizine framework. First, the ester starting material **11** was easily prepared from an enolate and propargyl bromide. Then, by combining the ester-group tolerance of precatalyst **1** with the general protocol outlined above, we prepared **3** in one pot in 72% overall yield from starting alkyne **11** (Scheme 2). The flexibility in this synthetic approach and the overall efficiency of the sequential reaction compares favorably with previous reports of the synthesis of **3**.[36] Simultaneous cyclization and deprotection of the carboxylic acid group by using TFA gives δ-amino acid **19**, which was then further cyclized by refluxing in xylenes. This technique is highly atom efficient, with only *tert*-butanol and water being eliminated in the course of the reaction, avoids the preparation of elaborate synthetic precursors, and retains the carbonyl group as a synthetic handle for further elaboration. In addition, given the high degree of steric and functional-group tolerance exhibited by precatalyst **1**, it is conceivable that more highly functionalized starting materials could be used to incorporate additional functionalities into the framework.



Scheme 2. One-pot synthesis of tricyclic benzo[*a*]quinolizine framework **3**.

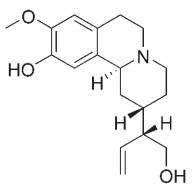
Table 6. The synthesis of 1-substituted THIQs.



Entry	Alkyne	Product	Isolated Yield [%]
1		 **15**	95
2		 **16**	72
3		 **17**	85
4		 **18**	79

Conclusion

Titanium-amidate complex **1** is an active and selective precatalyst for the hydroamination of terminal alkynes with a wide variety of amine substrates. This precatalyst provides



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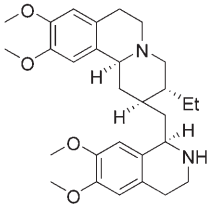

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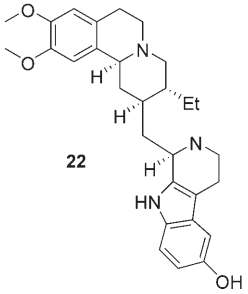

22

the anti-Markovnikov regioselective product in high yields with challenging alkyl amine substrates, regardless of the steric bulk in either the amine or the alkyne starting materials. Due to the stability afforded by the amidate ligand set, complex **1** exhibits notable functional-group tolerance for an early metal system, which allows the incorporation of protected alcohols, amines, and carboxylic acid derivatives in the hydroamination substrates. This favorable reactivity profile permits the application of this precatalyst in sequential one-pot reactions and has been exploited to carry out the synthesis of isoquinoline-type alkaloids and also to prepare the benzo[*a*]quinolizine scaffold **3**. These complex ring structures are easily assembled by using this method and provide an illustration of the potential application of precatalyst **1** for the total synthesis of complex alkaloid natural products.

Experimental Section

General: All reactions were performed under an atmosphere of nitrogen by using standard Schlenk line and glovebox techniques unless otherwise stated. THF and diethyl ether were distilled from sodium/benzophenone under inert atmosphere. Hexanes and toluene were purified by passage through a column of activated alumina and degassed with nitrogen. [D_6]Benzene and [D_8]toluene were degassed and dried over molecular sieves prior to use in NMR spectroscopic experiments. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker 300 or 400 MHz Avance spectrometer at ambient temperature; chemical shifts are given relative to residual protio solvent. IR samples were prepared as Nujol mulls on NaCl disks or KBr pellets and recorded on a BOMEM Michelson Series MB-100 FTIR spectrophotometer. Mass spectra were recorded on a Kratos MS-50 spectrometer by using an electron impact (70 eV) source. Elemental analyses and single-crystal X-ray structure determinations were performed at the Department of Chemistry, University of British Columbia.

Tetrakis(diethylamido)titanium was purchased from Strem and used as received. The following alkyne substrates were purchased from commercial sources, distilled from 4 Å molecular sieves and stored over molecular sieves before use: 1-hexyne, cyclohexylethyne, 3,3-dimethylbutyne, phenylacetylene, 4′-methoxyphenylacetylene, 4-chlorophenylacetylene, 1-decyne, trimethylsilylacetylene, and 3-phenylpropyne. The following amine substrates were purchased from commercial sources, distilled from CaH_2 and stored over molecular sieves before use: benzylamine, isopropylamine, *tert*-butylamine, and 3,4-dimethoxyphenethylamine. The precatalyst bis(diethylamido)bis{*N*-[2,6-bis(1-methylethyl)phenyl]benzamidate}titanium (**1**),[13b] was prepared as described in the literature. The deuterated substrate 1-[D]-1-decyne (**7**),[37] was prepared as described in the literature. The following alkyne substrates were prepared by using literature procedures and then dried by using the protocol described above: 1-(*tert*-butyldimethylsilyloxy)-4-pentyne,[38] 1-triisopropylsilyloxy-3-butyne,[39] *N*-(diphenylmethylene)-2-propyn-1-amine,[13b] 4-pentynyl-1-*tert*-butanoate (**10**),[40] *tert*-butyl-4-pentynoate (**11**),[41] 4-pentynyl-1-benzoate (**12**),[42] *N*-2-propynylbenzamide (**13**),[43]and 4-ethynylbenzoic acid methyl ester (**14**).[44] The following hydroamination products have been previously reported: *N*-benzylhexylamine,[13b] *N*-isopropylhexylamine,[13b] *N*-(*tert*-butyl)hexylamine,[13b] *N*-benzyl(2-cyclohexyl)ethylamine,[13b] *N*-isopropyl(2-cyclohexyl)-ethylamine,[13b] *N*-*tert*-butyl(2-cyclohexyl)ethylamine,[13b] *N*-benzyl(3,3-dimethyl)butylamine,[13b] *N*-isopropyl(3,3-dimethyl)butylamine[13b] *N*-(benzyl)-2-phenylethylamine,[45] *N*-isopropyl-2-phenylethylamine,[46] *N*-*tert*-butyl-2-phenylethylamine,[47] *N*-isopropyl-(2-(4′-methoxy)phenyl) ethylamine,[48] 4-triphenylsiloxybutanal,[13b] 5-(*tert*-butyldimethylsiloxy)-pentanal,[13b] *tert*-butyl-5-(*N*-benzyl)aminopentanoate,[49] and 6,7-dimethoxy-1-pentyl-1,2,3,4-tetrahydroisoquinoline (**15**).[13b] Several products could be compared with previous literature reports and are appropriately cited. In cases for which the full characterization did not include high-field NMR spectroscopic data, these data are provided here.

Bis[*N*-2′,6′-diisopropylphenyl(phenyl)amidate](*tert*-butylimido)-(pyridino)titanium (2): A 25 mL Schlenk tube was charged with **1** (100 mg, 0.133 mmol), anhydrous benzene (5 mL), and *tert*-butylamine (1.2 equiv, 0.16 mmol, 12 mg). The reaction was stirred for 24 h at room temperature. Anhydrous pyridine (1.2 equiv, 0.16 mmol, 13 mg) was then added to the pale-red solution and stirring was continued for 6 h. The solvent was removed in vacuo and the crude product was redissolved in anhydrous hexanes. Filtration through Celite and recrystallization from hexanes/benzene afforded **2** in 65% yield. ^{1}H NMR ([D_6]benzene, 300 MHz): $\delta = 0.83$ (6H, brd, $J = 9.0$ Hz; $CH(CH_3)_2$), 1.09 (9H, s; N–C-(CH_3)$_3$), 1.21 (6H, brd, $J = 6.2$ Hz; $CH(CH_3)_2$), 1.27 (12H, brd, $J = 6.6$ Hz; $CH(CH_3)_2$), 3.63–3.67 (2H, m; $CH(CH_3)_2$), 4.38–4.42 (2H, m; $CH(CH_3)_2$), 6.41–7.17 (12H, m; Ar–*H*), 7.80–7.86 ppm (7H, m; Ar–*H*, Py–*H*), 9.23 (2H, brd; Py–H_{ortho}); MS (EI): *m*/*z*: 679 [*M*−Py]$^+$, 664 [*M*−Py−Me]$^+$; elemental analysis calcd for $C_{47}H_{58}N_4O_2Ti$: C 74.42, H 7.65, N 7.38; found: C 74.23, H 7.81, N 7.16.

General procedure for hydroamination reactions catalyzed by complex 1

Example procedure: reaction between phenylacetylene and benzylamine:[13b] A 10 mL Schlenk tube was charged with **1** (20 mg, 0.026 mmol), phenylacetylene (20 equiv, 55 mg, 0.52 mmol), benzylamine (20 equiv, 56 mg, 0.52 mmol), and approximately 3 mL of anhydrous benzene. The reaction was stirred at 65 °C for 24 h. The reaction was cooled to room temperature and diluted with 10 mL MeOH. $NaBH_4$ (24 mg, 0.62 mmol) was added and the reaction mixture was stirred for 24 h at room temperature. After removal of the solvent in vacuo, saturated $NaCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added to the residue. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and purification by flash chromatography (diethyl ether/Et_3N 50:1) afforded pure *N*-(phenylmethyl)-2-phenylethanimine (87%) as an oil.

***N*-(Benzyl)-[2-(4′-methoxy)phenyl]ethylamine**: 4′-Methoxyphenylacetylene (35 mg, 0.27 mmol), benzylamine (29 mg, 0.27 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $LiAlH_4$ (15 mg, 0.40 mmol) gave the desired product (53 mg, 83% yield). ^{1}H NMR ([D_3]chloroform, 300 MHz): $\delta = 1.78$ (1H, brs; NH), 2.78 (2H, t, $J = 5.2$ Hz; $PhCH_2CH_2NH$), 2.86 (2H, t, $J = 5.2$ Hz; $PhCH_2CH_2NH$), 3.77 (3H, s; OCH_3), 3.79 (2H, s; $NHCH_2Ph$), 6.80 (2H, d, $J = 8.6$ Hz; Ar–*H*), 7.09 (2H, d, $J = 8.6$ Hz; Ar–*H*), 7.20–7.31 ppm (5H, m; Ar–H); ^{13}C NMR ([D_3]chloroform, 75 MHz): $\delta = 35.4$, 50.7, 53.8, 55.2, 113.9, 126.9, 128.1, 128.4, 129.6, 132.0, 140.2, 158.0 ppm; MS (EI): *m*/*z*: 241 [*M*]$^+$, 240 [*M*−H]$^+$, 91 ($PhCH_2^+$); IR (NaCl/neat): 3384 (vw; NH), 1583 (s), 1246 (m), 736 cm^{-1} (m); HRMS *m*/*z*: calcd for $C_{16}H_{19}NO$: 241.14666 [*M*]$^+$; found: 241.14633.

***N*-*tert*-Butyl-[2-(4′-methoxy)phenyl]ethylamine**: 4′-Methoxyphenylacetylene (35 mg, 0.27 mmol), *tert*-butylamine (39 mg, 0.53 mmol), and preca-

talyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $LiAlH_4$ (15 mg, 0.40 mmol) gave the desired product (44 mg, 79% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta = 1.05$ (9H, s; C(CH_3)$_3$), 2.67–2.80 (4H, m; PhCH_2CH_2NH), 3.76 (3H, s; OCH_3), 6.82 (2H, d, $J = 8.6$ Hz; Ar–*H*), 7.10 ppm (2H, d, $J = 8.6$ Hz; Ar–*H*); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): $\delta = 29.0$, 36.2, 44.2, 50.2, 55.2, 113.8, 129.5, 132.2, 158.0 ppm; MS (EI): *m*/*z*: 207 $[M]^+$, 206 $[M-H]^+$, 192 $[M-CH_3]^+$; IR (NaCl/neat): 3414 (vw; NH), 3030 (w), 1514 (s), 821 cm^{-1} (w); HRMS *m*/*z*: calcd for $C_{13}H_{21}NO$: 207.16231 $[M]^+$; found: 207.16241.

***N*-(Benzyl)-[2-(4′-chloro)phenyl]ethylamine**: 4′-Chlorophenylacetylene (37 mg, 0.27 mmol), benzylamine (29 mg, 0.27 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $LiAlH_4$ (15 mg, 0.40 mmol) gave the desired product (62 mg, 93% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta =$ 1.78 (1H, brs; N*H*), 2.77–2.91 (4H, m; PhCH_2CH_2NH), 3.80 (2H, s; NHCH_2Ph), 7.13 (2H, d, $J = 8.4$ Hz; Ar–*H*), 7.23–7.35 ppm (7H, m; Ar–H); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): $\delta = 35.7$, 50.3, 53.8, 127.0, 128.1, 128.4, 128.5, 130.0, 131.9, 138.5, 140.1 ppm; MS(EI): *m*/*z*: 245 $[M]^+$, 244 $[M-H]^+$, 91 (PhCH_2^+); IR (NaCl/neat): 3383 (vw; NH), 1493 (s), 1359 (m), 713 cm^{-1} (m); HRMS *m*/*z*: calcd for $C_{15}H_{16}N^{35}Cl$: 245.09713 $[M]^+$; found: 245.09699.

***N*-Isopropyl-[2-(4′-chloro)phenyl]ethylamine**: 4′-Chlorophenylacetylene (37 mg, 0.27 mmol), isopropylamine (32 mg, 0.53 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $LiAlH_4$ (15 mg, 0.40 mmol) gave the desired product (36 mg, 68% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta =$ 1.03 (6H, d, $J = 6.3$ Hz; CH(CH_3)$_2$), 1.40 (1H, brs; NH), 2.75–2.84 (5H, m; PhCH_2CH_2NH, CH(CH_3)$_2$), 7.13 (2H, d, $J = 8.3$ Hz; Ar–*H*), 7.25 ppm (2H, d, $J = 8.3$ Hz; Ar–*H*); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): $\delta = 22.9$, 35.9, 48.6, 128.5, 130.0, 131.9, 138.6 ppm; MS (EI): *m*/*z*: 197 $[M]^+$, 196 $[M-H]^+$, 182 $[M-CH_3]^+$; IR (NaCl/neat): 3425 (vw, NH), 1643 (m), 623 cm^{-1} (m); HRMS *m*/*z*: calcd for $C_{11}H_{16}N^{35}Cl$: 197.09713 $[M]^+$; found: 197.09671.

***N*-*tert*-Butyl-[2-(4′-chloro)phenyl]ethylamine**: 4′-Chlorophenylacetylene (37 mg, 0.27 mmol), *tert*-butylamine (39 mg, 0.53 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $LiAlH_4$ (15 mg, 0.40 mmol) gave the desired product (52 mg, 91% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta =$ 1.07 (9H, s; C(CH_3)$_3$), 2.71–2.82 (4H, m; PhCH_2CH_2NH), 7.14 (2H, d, $J = 8.3$ Hz; Ar–*H*), 7.25 ppm (2H, d, $J = 8.3$ Hz; Ar–*H*); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): $\delta = 28.9$, 36.5, 43.9, 50.4, 128.5, 130.0, 131.9, 138.7 ppm; MS (EI): *m*/*z* 211 $[M]^+$, 210 $[M-H]^+$, 196 $[M-CH_3]^+$; IR (NaCl/neat): 3425 (vw, NH), 2964 (m), 1493 (m), 810 cm^{-1} (m); HRMS *m*/*z*: calcd for $C_{12}H_{18}N^{35}Cl$: 211.11278 $[M]^+$; found: 211.11394.

5-Oxopentyl-2′,2′-dimethylpropanoate:[50] Alkyne **10** (45 mg, 0.27 mmol), benzylamine (29 mg, 0.27 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent hydrolysis gave the desired product (40 mg, 80% yield). With alkyne **10** (45 mg, 0.27 mmol) and isopropylamine (31 mg, 0.53 mmol), the product was obtained (45 mg, 90% yield). With alkyne **10** (45 mg, 0.27 mmol) and *tert*-butylamine (39 mg, 0.53 mmol), the product was obtained (48 mg, 95% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta = 1.77$–1.81 (4H, m; C$H_2\times$ 2), 2.48–2.53 (2H, m; CH_2CHO), 4.31 (3H, t, $J = 6.0$ Hz; CH_2O), 7.39–7.50 (3H, m; Ar–*H*), 7.99–8.02 (2H, m; Ar–*H*), 9.77 ppm (1H, t, $J =$ 1.3 Hz; C*H*O); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): 18.6, 28.1, 43.3, 64.3, 128.3, 129.5, 130.2, 132.9, 166.5, 201.8 ppm; MS (EI): *m*/*z*: 207 $[M]^+$, 105 ($C_6H_5CO^+$); IR (NaCl/neat): 2939 (w), 1716 (s, CO), 1276 (s), 675 cm^{-1} (m).

***tert*-Butyl-5-(*N*-isopropyl)aminopentanoate**: Alkyne **11** (41 mg, 0.27 mmol), isopropylamine (32 mg, 0.53 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $NaBH_4$ (15 mg, 0.40 mmol) gave the desired product (48 mg, 85% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta = 1.02$ (6H, d, $J = 6.2$ Hz; C$H_3\times$2), 1.41 (9H, s; C$H_3\times$3), 1.44–1.62 (4H, m; NHCH_2CH_2CH_2CH$_2$CO), 2.20 (2H, t, $J = 6.9$ Hz; CH_2CO), 2.57 (2H, t, $J = 7.0$ Hz; NHCH_2), 2.76 ppm (1H, m; CH(CH_3)$_2$); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): 22.9, 28.1, 29.8, 35.4, 47.1, 48.7, 80.1, 173.0 ppm; MS (EI): *m*/*z* 215 $[M]^+$, 158 $[M-t\mathrm{Bu}]^+$; IR (NaCl/neat): 3305 (vw, NH), 1730 (s, CO), 712 cm^{-1} (m).

***tert*-Butyl-5-(*N*-*tert*-butyl)aminopentanoate**: Alkyne **11** (41 mg, 0.27 mmol), *tert*-butylamine (39 mg, 0.53 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $NaBH_4$ (15 mg, 0.40 mmol) gave the desired product (45 mg, 74% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta = 1.07$ (9H, s; C$H_3\times$3), 1.41 (9H, s; C$H_3\times$3), 1.50–1.64 (4H, m; NHCH_2CH_2CH_2CH$_2$CO), 1.76 (1H, brs; N*H*), 2.20 (2H, t, $J = 7.1$ Hz; CH_2CO), 2.52 ppm (2H, t, $J = 7.2$ Hz; NHCH_2); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): 23.0, 28.1, 28.9, 30.37, 35.37, 42.1, 50.4, 80.1, 173.1 ppm; MS (EI): *m*/*z* 229 $[M]^+$, 214 $[M-\mathrm{Me}]^+$; IR (NaCl/neat): 3423 (vw, NH), 1735 (s, CO), 750 cm^{-1} (m); HRMS *m*/*z*: calcd for $C_{13}H_{27}NO_2$: 229.20418 $[M]^+$; found: 229.20412.

5-Oxopentylbenzoate:[51] Alkyne **12** (37 mg, 0.27 mmol), isopropylamine (32 mg, 0.27 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent hydrolysis gave the desired product (48 mg, 86% yield). With alkyne **12** (37 mg, 0.27 mmol) and *tert*-butylamine (39 mg, 0.53 mmol), the product was obtained (39 mg, 70% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta = 1.77$–1.81 (4H, m; C$H_2\times$2), 2.48–2.53 (2H, m; CH_2CHO), 4.31 (3H, t, $J = 6.0$ Hz; CH_2O), 7.39–7.50 (3H, m; Ar–*H*), 7.99–8.02 (2H, m; Ar–*H*), 9.77 ppm (1H, t, $J = 1.3$ Hz; C*H*O); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): 18.6, 28.1, 43.3, 64.3, 128.3, 129.5, 130.2, 132.9, 166.5, 201.8 ppm; MS (EI): *m*/*z*: 207 $[M]^+$, 105 ($C_6H_5CO^+$); IR (NaCl/neat): 2939 (w), 1716 (s, CO), 1276 (s), 675 cm^{-1} (m).

***N*-(3-Isopropylamino)propylbenzamide**: Alkyne **13** (43 mg, 0.27 mmol), isopropylamine (31 mg, 0.53 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $NaBH_4$ (12 mg, 0.42 mmol) gave the desired product (45 mg, 77% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta = 1.05$ (6H, d; $J =$ 6.2 Hz; C$H_3\times$2), 1.69–1.74 (3H, m; CH_2, NH), 2.74–2.80 (3H, m; CH_2, CH(CH_3)$_2$), 3.51–3.54 (2H, m; CH_2NHCO), 7.37–7.44 (3H, m; Ar–H), 7.77–7.80 (2H, m; Ar–H), 8.60 ppm (1H, brs; NH); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): 22.9, 28.6, 40.4, 46.5, 48.9, 126.9, 128.3, 131.1, 134.8, 167.1; MS (EI): *m*/*z*: 209 $[M+\mathrm{H}]^+$, 193 $[M-\mathrm{Me}]^+$; IR (NaCl/neat): 3421 (vw, NH), 1635 (s, CO), 713 cm^{-1} (m).

***N*-(3-*tert*-Butylamino)propylbenzamide**: Alkyne **13** (43 mg, 0.27 mmol), *tert*-butylamine (39 mg, 0.53 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $NaBH_4$ (12 mg, 0.32 mmol) gave the desired product (50 mg, 80% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta = 1.08$ (3H, s; C$H_3\times$ 3), 1.57 (1H, brs; NH), 1.67–1.75 (2H, m; CH_2), 2.76 (2H, t, $J = 5.5$ Hz; CH_2), 3.51–3.56 (2H, m; CH_2), 7.34–7.44 (3H, m; Ar–H), 7.78–7.80 (2H, m; Ar–H), 8.61 ppm (1H, brs; NH); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): $\delta = 28.8$, 40.8, 42.0, 50.6, 126.9, 128.3, 131.0, 134.8, 167.0 ppm (quaternary carbon atom not observed); MS (EI): *m*/*z*: 235 $[M+\mathrm{H}]^+$, 219 $[M-\mathrm{Me}]^+$; IR (NaCl/neat): 3283 (w, NH), 1637 (s, CO), 707 cm^{-1} (m).

Methyl-4-[2-(isopropylamino)ethyl]benzoate: Alkyne **14** (43 mg, 0.27 mmol), isopropylamine (31 mg, 0.53 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $NaBH_4$ (12 mg, 0.42 mmol) gave the desired product (42 mg, 70% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta = 1.03$ (6H, d, $J = 6.2$ Hz; CH(CH_3)$_2$), 1.67 (1H, brs; N*H*), 2.86–2.90 (5H, m; C$H_2\times$2, CH(CH_3)$_2$), 3.88 (3H, s; OCH_3), 7.25 (2H, d, $J = 6.3$ Hz; Ar–H), 7.94 ppm (2H, d, $J = 6.3$ Hz; Ar–H); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): $\delta = 22.8$, 36.5, 48.3, 48.6, 60.8, 128.6, 128.7, 129.8, 145.4, 166.6 ppm; MS (EI): *m*/*z*: 221 $[M]^+$, 220 $[M-H]^+$, 206 $[M-CH_3]^+$; IR (NaCl/neat): 3429 (vw, NH), 1682 (s, CO), 1311 (m), 744 cm^{-1} (w); HRMS: *m*/*z*: calcd for $C_{13}H_{19}NO_2$: 221.14158 $[M]^+$; found: 221.14083.

Methyl-4-[2-(*tert*-butylamino)ethyl]benzoate: Alkyne **14** (43 mg, 0.27 mmol), *tert*-butylamine (39 mg, 0.53 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described above. Subsequent reduction with $NaBH_4$ (12 mg, 0.32 mmol) gave the desired product (58 mg, 91% yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): $\delta = 1.04$ (9H, s; C(CH_3)$_3$), 2.80 (4H, brs; C$H_2\times$2), 3.87 (3H, s; OCH_3), 7.25 (2H, d, $J = 6.3$ Hz; Ar–H), 7.92 (2H, d, $J = 6.3$ Hz; Ar–H); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): $\delta = 28.9$, 37.2, 43.6, 50.3, 52.0, 128.1, 128.7,

129.7, 145.8, 166.1 ppm; MS (EI): m/z: 235 $[M]^+$, 234 $[M-H]^+$, 220 $[M-CH_3]^+$; IR (NaCl/neat): 3416 (vw, NH), 1720 (s, CO), 1278 (s), 744 cm^{-1} (m); HRMS: m/z: calcd for $C_{14}H_{21}NO_2$: 235.15723 $[M]^+$; found: 235.15728.

General procedure for the synthesis of THIQs (Table 6)

Example procedure: (±)-6,7-dimethoxy-1-pentyl-1,2,3,4-tetrahydroisoquinoline (15):[13b] A 25 mL Schlenk tube was charged with **1** (30 mg, 0.040 mmol), 3,4-dimethoxyphenethylamine (20 equiv, 145 mg, 0.80 mmol), 1-hexyne (20 equiv, 66 mg, 0.80 mmol), and approximately 2 mL of anhydrous benzene. The reaction was stirred for 24 h at 65 °C. The mixture was then cooled to room temperature and trifluoroacetic acid (4 mL) was added. The reaction was refluxed for 12 h. After cooling, saturated $NaHCO_3$ (100 mL) was added. The aqueous phase was extracted with ether (3×75 mL) and dried over $MgSO_4$. Removal of the solvent in vacuo followed by purification by flash chromatography (CH_2Cl_2/MeOH 50:1) afforded pure **15** (200 mg, 95 % yield) as an oil.

3-(3,4-Dimethoxyphenyl)propyne: Magnesium turnings (211 mg, 8.68 mmol) were suspended in anhydrous THF (5 mL). The reaction was heated to 55 °C, after which five drops of 1,2-dibromoethane were added. A solution of 4-bromoveratrole (1.13 mL, 1.71 g, 7.86 mmol) in anhydrous THF (10 mL) was added to the suspension while maintaining the reaction temperature at 60–65 °C. The reaction was vigorously stirred until the magnesium was consumed. The solution was then transferred via cannula to another flask containing methoxylallene (500 mg, 7.25 mmol) and CuI (280 mg, 1.37 mmol) and stirred for a further 30 min. The reaction was quenched by the addition of saturated NH_4Cl (50 mL) and NaCN (200 mg). The aqueous phase was extracted with diethyl ether (3×50 mL) and the combined organic extracts were dried over $MgSO_4$. Removal of the solvent in vacuo and purification by flash chromatography afforded 3-(3,4-dimethoxyphenyl)propyne (55 %) to give a pale yellow solid. This synthetic intermediate was then used in the preparation of THIQ **18**. ^{1}H NMR ([D$_3$]chloroform 400 MHz): δ = 2.17 (t, 1H, J = 2.7 Hz; −C≡C*H*), 3.54 (d, 2H, J = 2.7 Hz; −C*H*$_2$−), 3.85 (s, 3H; −OC*H*$_3$), 3.87 (s, 3H; −OC*H*$_3$), 6.80 ppm (m, 1H; Ar−*H*), 6.86 (m, 2H; Ar−*H*); ^{13}C NMR ([D$_3$]chloroform 400 MHz): δ = 23.6 (−*C*H$_2$−), 55.1, 55.2 (−O*C*H$_3$×2), 70.1 (−C≡*C*H), 81.8 (−*C*≡CH), 110.7, 110.8, 119.3 (C$_{Ar}$–H×3), 128.0, 147.3, 148.5 ppm (quat. C$_{Ar}$); MS (EI): m/z: 176 $[M]^+$, 161 $[M-CH_3]^+$.

(±)-6,7-Dimethoxy-1-(cyclohexyl)methyl-1,2,3,4-tetrahydroisoquinoline (16):[48] Cyclohexylethyne (29 mg, 0.27 mmol), 3,4-dimethoxyphenethylamine (48 mg, 0.27 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described for THIQ's to give 56 mg of product (72 % yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): δ = 0.93–1.96 (13H, m; cyclohexylmethyl), 2.03 (1H, brs; NH), 2.68–3.23 (4H, m; C$_3$,C$_4$–C*H*$_2$×2), 3.82 (3H, s; C*H*$_3$O), 3.83 (3H, s; C*H*$_3$O), 3.97 (1H, dd, J = 8.6 Hz, 3.0 Hz; C$_1$–C*H*), 6.54 ppm (2H, s; Ar−*H*); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): δ = 26.5, 26.7, 27.0, 29.5, 32.7, 34.6, 35.0, 40.8, 45.0, 52.7, 56.1, 56.3, 109.7, 112.1, 127.1, 147.5, 147.6 ppm (one of the aromatic quaternary carbon atoms is not observed); MS (EI): m/z: 289 $[M]^+$, 192; IR (NaCl/neat): 2920 (m), 1512 cm^{-1} (m).

(±)-6,7-Dimethoxy-1-[2-(phenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (17):[52] 3-Phenylpropyne (93 mg, 0.80 mmol), 3,4-dimethoxyphenethylamine (145 mg, 0.80 mmol), and precatalyst **1** (10 mg, 0.0133) were used in the general procedure described for THIQ's to give the 202 mg of product (85 % yield). ^{1}H NMR ([D$_3$]chloroform, 400 MHz): δ = 1.94 (1H, brs; N*H*), 1.95–2.15 (2H, m; C*H*$_2$Ph), 2.69–2.73 (6H, m; C$_3$,C$_4$–CH$_2$×2, C*H*$_2$CH$_2$Ph), 3.80 (3H, s; CH$_3$O), 3.83 (3H, s; CH$_3$O), 3.96 (1H, m; C$_1$–CH), 6.54 (1H, s; Ar−H), 6.55 (1H, s; Ar−H), 7.17–7.29 ppm (5H, m; Ph−H); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): δ = 29.1, 32.1, 32.2, 40.9, 54.9, 55.9, 56.2, 109.1, 112.9, 125.8, 127.0, 128.4, 128.4, 142.2, 147.2, 147.3 ppm; IR (NaCl/neat): 2937 (w), 1512 cm^{-1} (m).

(±)-6,7-Dimethoxy-1-[2-(3,4-dimethoxylphenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline 18):[53] 3-(3,4-Dimethoxyphenyl)propyne (93 mg, 0.80 mmol), 3,4-dimethoxyphenethylamine (145 mg, 0.80 mmol), and precatalyst **1** (10 mg, 0.0133) were in the general procedure described for THIQ's to give the 202 mg of product (85 % yield). ^{1}H NMR ([D$_3$]chloroform, 300 MHz): δ = 2.08–2.14 (2H, m; CH$_2$), 2.08–2.14 (2H, m; C$_3$,C$_4$–CH$_2$×2), 3.78 (3H, s; CH$_3$O), 3.79 (3H, s; CH$_3$O), 3.84 (3H, s; CH$_3$O), 4.10 (1H, m; C$_1$–CH), 6.57 (1H, s; Ar−H), 6.59 (1H, s; Ar−H), 6.84 (2H, d, J = 14.5 Hz; Ar−H), 7.15 ppm (2H, d, J = 14.5 Hz; Ar−H); ^{13}C NMR ([D$_3$]chloroform, 75 MHz): δ = 27.9, 31.6, 37.8, 40.5, 54.8, 55.7, 55.8, 55.8, 55.9, 109.1, 111.2, 111.6, 111.7, 120.0, 126.1, 128.6, 134.2, 147.2, 147.5, 147.7, 148.8 ppm; MS (EI): m/z: 358 $[M+H]^+$, 357 $[M]^+$, 342 $[M-CH_3]^+$; IR (NaCl/neat): 2849 (s), 1446 cm^{-1} (m).

1,2,3,6,7-Hexahydro-9,10-dimethoxy-4*H*-benzo[*a*]quinolizin-4-one (3):[15] A 25 mL Schlenk tube was charged with **1** (30 mg, 0.040 mmol), 3,4-dimethoxylphenethylamine **4** (20 equiv, 145 mg, 0.80 mmol), *tert*-butyl-5-pentynoate (20 equiv, 124 mg, 0.80 mmol), and approximately 5 mL benzene. The reaction was stirred for 24 h at 65 °C. After cooling the mixture to room temperature, trifluoroacetic acid (5 mL) was added and the reaction mixture was refluxed for 12 h. The solvent was then replaced with xylenes (15 mL) and the reaction refluxed for another 24 h. After cooling, NaOH (1 N, 15 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over $MgSO_4$. Removal of the solvent in vacuo and purification by flash chromatography (CH_2Cl_2/MeOH 100:1) afforded pure **3** (151 mg, 72 %) as an oil. ^{1}H NMR ([D$_3$]chloroform, 400 MHz): δ = 1.62–1.91 (4H, m; C$_1$,C$_2$–CH$_2$), 2.33–2.89 (5H, m; C$_3$,C$_7$–CH$_2$, C$_{6\alpha}$–CH), 3.83 (6H, s; CH$_3$O×2), 4.57 (1H, dd, J = 10.7, 4.5 Hz; C$_{11b}$–CH), 4.83 (1H, ddd, J = 12.0, 4.3, 2.0 Hz; C$_{6\beta}$–CH), 6.59 (1H, s; Ar−H), 6.64 ppm (1H, s; Ar−H); ^{13}C NMR ([D$_3$]chloroform, 100 MHz): δ = 19.5, 28.4, 30.9, 32.1, 39.6, 55.8, 56.0, 56.6, 108.2, 111.5, 127.2, 129.1, 147.6, 147.7, 169.2 ppm; MS (ESI): m/z: 262 $[M+H]^+$.

1-[D]-1-Decyne:[37] This compound was prepared by using an analogous procedure to that reported previously. A 94 % deuterium incorporation was established by ^{1}H NMR spectroscopy.[37]

CCDC-606 054 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif/

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