Ti-Catalyzed 1,2-Diamination of Alkynes using 1,1-Disubstituted Hydrazines

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Supporting Information Placeholder.

ABSTRACT: Ti-catalyzed alkyne diamination and Ti-catalyzed alkyne hydrohydrazination proceed through a common *N*-aminoazatitanacyclobutene intermediate. Previously, these reactions have existed as processes catalyzed by distinct catalysts, where there are many reports (and catalysts) for hydrohydrazination, and only a single example (and catalyst) for diamination. Here, we demonstrate that a diamidoamine Ti catalyst, (NNN)Ti(=NNR$_2$) (**1,** (NNN)H$_2$ = N-methyl-N',N"-bis(trimethylsilyl)diethylenetriamine; R = alkyl, aryl), is capable of catalyzing both diamination and hydrohydrazination, where the selectivity is dictated by simple changes to the reaction conditions, capitalizing on the fact that there are entropic differences at the selectivity branch point between diamination (unimolecular) and hydrohydrazination (bimolecular). This discovery leads to an expanded substrate scope for alkyne diamination, and an understanding of how structure-activity relationships can impact the relative rates (selectivity) of diamination and hydrohydrazination. More broadly, these results suggest that this strategy may be more generally applied to Ti hydrohydrazination catalysts to uncover new catalysts capable of alkyne diamination with 1,1-disubstituted hydrazines.

INTRODUCTION

1,2-diamines are important structural motifs found in pharmaceuticals,[1,2,3] natural products,[4,5] and agrochemicals.[6,7] They may also be employed as ligands for metal complexes, perhaps most famously for Noyori-type asymmetric hydrogenation catalysts.[8,9]

Diamination, the direct installation of two nitrogen atoms across carbon-carbon multiple bonds, is a potentially convenient and straightforward route to the synthesis of 1,2-diamines.[10] After the first report of alkene diamination in 2005,[11,12] several examples have expanded the utility of the transformation.[13,14] Compared to alkenes, alkyne diamination is relatively under-developed. After the seminal report from the Muniz group on intramolecular alkyne diamination[15] with tethered sulfonamides catalyzed by Pd(OAc)$_2$, sporadic studies on both intra- and inter-molecular alkyne diamination have been reported.[16,17,18,19,20] Existing methods mostly rely on late transition metals like Pd or Cu, and operate on bespoke alkyne substrates that are prepared by multi-step synthesis. Many reagents for diamination also require multistep synthesis. For example, diaziridinones[14] have gained considerable attention in olefin diamination and are prepared from urea derivatives, which can be challenging when preparing unsymmetrical derivatives.[21]

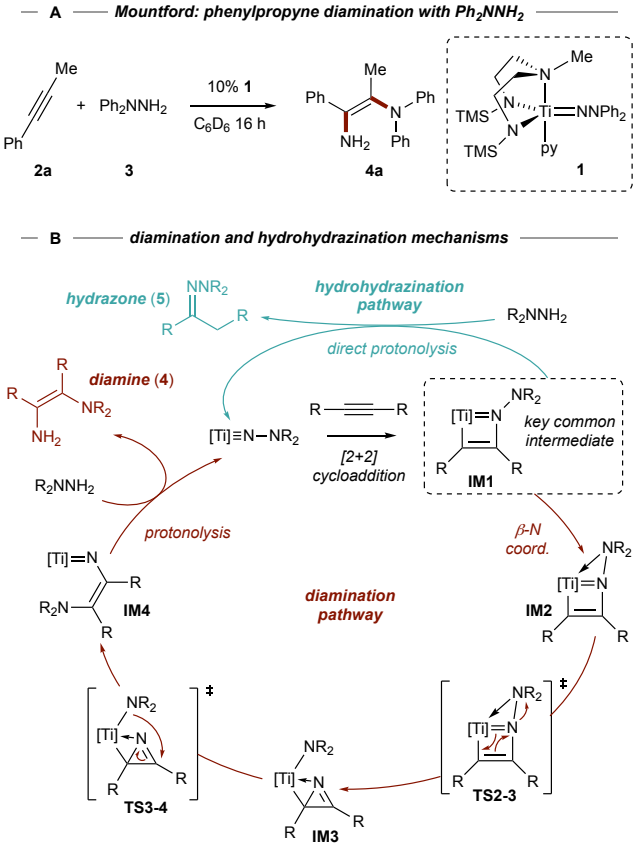

Figure 1. (A) Previous report of alkyne diamination of 1-phenyl-1-propyne (**2a**) with 1,1-diphenylhydrazine (**3**). (B) The proposed mechanisms of diamination and hydrohydrazination share a common [2+2] cycloadduct intermediate, **IM1**.

Titanium is an earth abundant and non-toxic metal, which makes it an attractive catalyst candidate.[22,23,24] In 2007, Mountford and co-workers reported the diamination of phenylpropyne with 1,1-diphenylhydrazine catalyzed by a titanium diphenylhydrazido(2-) complex (**1**) (Figure 1A).[25]

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This transformation is proposed to occur through the initial [2+2] cycloaddition between the Ti hydrazido(2-) Ti=N and the alkyne to form a *N*-aminoazatitanacyclobutene cycloadduct **IM1** (Figure 1B, maroon pathway).[26] **IM1** equilibrates with the key intermediate **IM2** in which the N_β is bent to coordinate to the metal. From **IM2**, it is proposed that irreversible unimolecular N_α-N_β bond cleavage is triggered by the attack of Ti-C bond on N_α to first form azirine **IM3** via **TS2-3**, followed by amide insertion to form the vinyl imido product **IM4**. Finally, protonolysis of **IM4** by hydrazine releases the 1,2-diamine while regenerating the Ti hydrazido(2-). This catalytic reaction is wholly unique: it has only been reported for 1 substrate (phenylpropyne), 1 hydrazine (1,1-diphenylhydrazine), and 1 catalyst (**1**).[25] In fact, even slight changes to the ligand in the Mountford NNN catalyst **1** (*e.g.* using N-^{i}Pr substitution on the ligand framework instead of N-TMS) changes the reactivity from alkyne diamination to hydrohydrazination.[27]

The diamination report from the Mountford group is all the more remarkable when put in the context of the reactivity of other Ti hydrazido complexes. Many other Ti hydrazido complexes have instead been shown to catalyze alkyne hydrohydrazination reactions,[28,29,30,31] in which the N-H bond of a hydrazine is added across the triple bond. The established reaction mechanism[22,32,33] suggests the involvement of the same intermediate azatitanacyclobutene **IM1**, which undergoes hydrazinolysis to generate a hydrazone (Figure 1B, teal pathway). This bimolecular protonolysis step is often considered as the rate determining step of the reaction.

Given that diamination and hydrohydrazination are proposed to proceed through the same intermediate (**IM1**), we hypothesized that the two catalytic reactions could exist in competition with each other, wherein changes to the catalytic conditions could impact the $\Delta\Delta G^{\ddagger}$ between the two pathways and provide access to either diamination or hydrohydrazination products with the same catalyst. Herein, we report a more general strategy for the Ti-catalyzed 1,2-diamination of alkynes using 1,1-disubstituted hydrazines, building off the seminal work from the Mountford group.[25] By tuning the reaction concentration and temperature, the product selectivity can be altered between diamine and hydrazone. This expanded study further allows for the incorporation of electronically varied substrates, which sheds additional light on the key steps related to the product selectivity of this catalytic reaction.

RESULTS AND DISCUSSION

We chose as a model the reaction of 1-phenyl-1-propyne **(2a)** and 1-methyl-1-phenylhydrazine **(3a)** catalyzed by **1**. Interestingly, while the previous study using 1,1-diphenylhydrazine resulted in complete diamination,[25] reaction of 1-methyl-1-phenylhydrazine results in similar amounts of diamine **(4aa)** (37%) and hydrazone **(5aa)** (29%), (Figure 2) produced from the competition of alkyne diamination and hydrohydrazination, respectively.

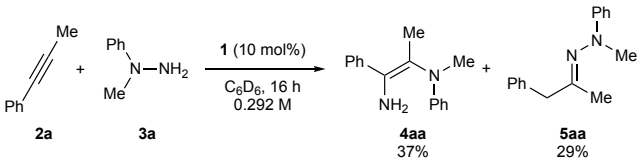

Figure 2. Model reaction of phenylpropyne (**2a**) with $PhMeNNH_2$ (**3a**) catalyzed by **1**.

We hypothesized that hydrazine concentration would have a drastic impact on selectivity given that the proposed N_α-N_β bond cleavage of **IM2** in alkyne diamination is a unimolecular step, while conversely the protonolysis of **IM1** in hydrohydrazination is a bimolecular step (Figure 1B). In fact, an orderly trend of product ratios with concentration was observed when the reaction concentration was tuned from 3.86 M to 0.03 M at room temperature (Figure 3). At high concentration (3.86 M), hydrazone **5aa** was observed *exclusively* in the reaction mixture. Decreasing the concentration from 3.8 M to 0.52 M produced 28% hydrazone **5aa** with 19% diamine **4aa** with a **4aa** : **5aa** ratio of 0.6. When the concentration was further decreased to 0.29 M, diamine **4aa** was formed as the major product (37%) along with significant amount of hydrazone **5aa** (29%) in the reaction mixture. Finally, further dilution (0.03 M) provided 48% diamine **4aa** with a **4aa** : **5aa** ratio of 11:1 at room temperature. Under these low concentration conditions, excellent diamination selectivies can typically be achieved at moderate yield and high conversion; unfortunately, mass balance remains an issue in these reactions.

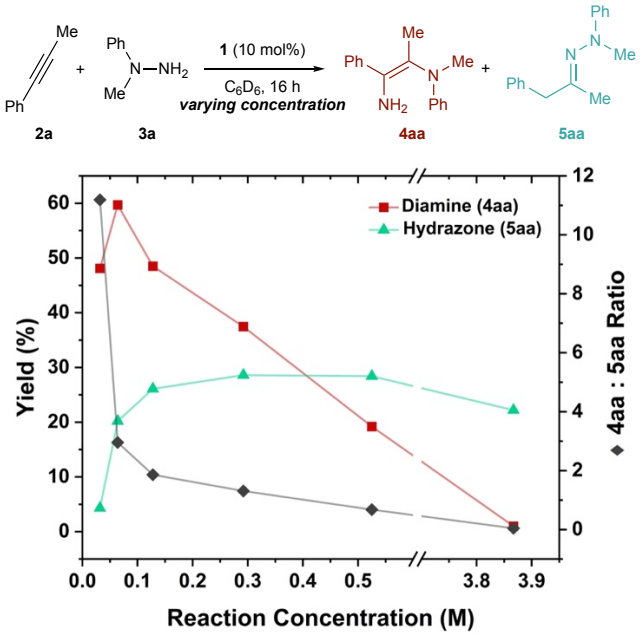

Figure 3. Effect of concentration on the product distribution and ratio of diamine vs hydrazone at room temperature

Temperature should also play an important role in the reaction, as the bimolecular reactions are entropically disfavored at high temperature. Indeed, even only at a slightly higher temperature (33 °C vs r.t.), 67% diamination

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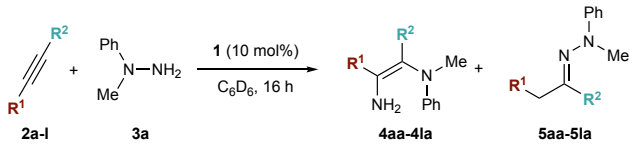
is observed with >20:1 selectivity at low concentration (0.032 M). However, higher reaction temperatures resulted in decomposition to several unidentified products, and thus temperature was not further explored as a variable. With these influences in mind, we have explored the ability of a variety of alkynes and 1,1-disubstituted hydrazines undergo diamination catalyzed by **1** under optimized conditions of 0.032 M concentration at 33 °C. In all catalytic reactions below, some amount of unidentified catalyst decomposition product was observed.

Next, the ability of other alkynes to undergo diamination by **3a** was examined (Table 1). In addition to 1-Phenyl-1-propyne **(2a)**, various differently-substituted phenylpropyne derivatives (**2b**-**2f**) underwent successful diamination. Electron-rich derivatives 1-(4-methylphenyl)-1-propyne **(2b)** and 1-(4-methoxylphenyl)-1-propyne **(2c)** produced the corresponding 1,2-diamines **(4ba, 4ca)** in moderate to good yield with excellent selectivity. Although 1-(4-fluorophenyl)-1-propyne **(2d)** (σ_p^F = 0.06)[34] produced 51% diamine **(4da)** with >20:1 selectivity, the more electron deficient 1-(4-chlorophenyl)-1-propyne **(2e)** (σ_p^{Cl} = 0.23) gave the corresponding 1,2-diamine **(4ea)** in 43% yield along with 11% hydrazone **(5ea)**. Following this trend, the more electron-deficient alkyne (σ_p^{CF3} = 0.54), 1-(4-trifluoromethylphenyl)-1-propyne **(2f)** resulted in even poorer selectivity for diamination, rendering 15% diamine **(4fa)** in addition to 34% hydrazone **(5fa)** in the reaction mixture. Since the key selectivity-determining step toward diamination involves intramolecular nucleophilic attack of the Ti-C_α on the N_α atom of the azatitanacyclobutene **IM2** (Figure 4, **TS2-3**),[26] a lower nucleophilicity of Ti-C_α should disfavor diamination while not impacting hydrohydrazination. The presence of an electron-withdrawing functionality (*e.g.* *p*-Cl *p*-CF_3) on the aromatic ring should decrease the nucleophilicity of Ti-C_α, which thus accounts for the poorer diamination selectivity in reactions with **2e** and **2f**. Diamination was also successful with other internal alkynes such as 1-phenyl-1-butyne **(2g)** and diphenylacetylene **(2h)**, although these reactions were slower. Diphenylacetylene in particular underwent reaction much more slowly and also decomposed, subsequently leading to lower reaction yields under the optimized reaction times.

Table 1. Scope of the reaction of 1-methyl-1-phenylhydrazine (**3a**) with varying alkynes.[a]



2a-l 3a 4aa-4la 5aa-5la (or enamine)

alkyne	% conv.	% yield 4	% yield 5	4:5
Ph—≡—Me **2a**	100	67	3	> 20
(*p*-Me)C_6H_4—≡—Me **2b**	62	34	4	8.5
(*p*-OMe)C_6H_4—≡—Me **2c**	87	51	2	> 20
(*p*-F)C_6H_4—≡—Me **2d**	68	51	2	> 20
(*p*-Cl)C_6H_4—≡—Me **2e**	81	43	11	3.9
(*p*-CF_3)C_6H_4—≡—Me **2f**	51	15	34	0.44
Ph—≡—Et **2g**	57	43	n.d.	> 20
Ph—≡—Ph **2h**	64	17[b]	2	8
^{n}Bu—≡—H **2i**	100	0	100	0
(*p*-Me)C_6H_4—≡—H **2j**	72	*intractable mixture*		
^{t}Bu—≡—H **2k**	0	*no reaction*		
Et—≡—Et **2l**	0	*no reaction*		

[a]Conditions: 2.5 μmol (10 mol%) **1**, 0.030 mmol (1.2 equiv.) alkyne, 0.025 mmol (1 equiv.) hydrazine, 0.8 mL C_6D_6, 33 ˚C, 16 h. ^{1}H NMR yields vs. Ph_3CH standard. [b]72 h.

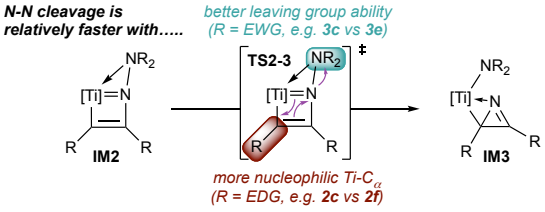


Figure 4. Schematic demonstrating electronic factors that lower the barrier for N-N cleavage and rearrangement from **IM2** to **IM3**.

Terminal alkynes did not undergo successful diamination with **3a**. 4-ethynyltoluene **(2j)** gave an intractable reaction mixture under the optimized conditions, while 1-hexyne **(2i)** underwent exclusive hydrohydrazination to quantitatively produce hydrazone **(5ia)** with Markovnikov selectivity. The preference for hydrohydrazination with 1-hexyne can likely be rationalized in the context of the N-N cleavage step (*c.f.* Figure 4, **TS2-3**): the lack of an electron donor group on Ti-C_α renders it less nucleophilic and reduces the propensity of the C-N coupling and N-N cleavage, and the overall lack of steric encumbrance at Ti may further promote bimolecular hydrazinolysis of **IM2** to form **5ia**.

Unfortunately, the bulky aliphatic terminal alkyne, *tert*-butylacetylene **(2k)** and internal aliphatic alkyne 3-hexyne **(2l)** did not show any alkyne conversion under the reaction conditions. Likely, the first [2+2] cycloaddition step is kinetically inaccessible at room temperature[35] or the intermediate is unstable[25] for these alkynes.

Next, the scope of hydrazines capable of undergoing 1,2-diamination of phenylpropyne was explored (Table 2). Various *para*-substituents on the phenyl ring **(3b-g)** were

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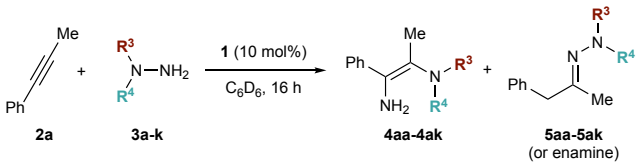
well tolerated. Both 1-methyl-1-(4-methylphenyl)hydrazine **(3b)**, 1-methyl-1-(4-methoxylphenyl)hydrazine **(3c)** (σ_p^{OMe} = -0.27) gave good to moderate diamine yields **(4ab, 4ac)** with similar selectivity. 1-methyl-1-(4-fluorophenyl)hydrazine **(3d)** provided 58% diamine **(4ad)**, while the more electon-deficient -chloro **(3e)** (σ_p^{Cl} = 0.23) and -bromo **(3f)** (σ_p^{Br} = 0.23) substituents performed exceptionally well under the optimized conditions, giving >70% yield **(4ae, 4af)** with excellent selectivity. Similarly, 1-methyl-1-(4-trifluoromethoxyphenyl)hydrazine **(3g)** (σ_p^{OCF3} = 0.35) also worked well under the reaction conditions to provide 37% diamine **(4ag)** with 100% selectivity. A trend can be observed that diamination selectivity is higher for electron-poor hydrazines **(3e, 3f, 3g)** compared to electron-rich ones **(3c)**. This trend can be rationalized by the better leaving group capability of the '-NR_2' functionality of the azatitanacyclobutene **IM2**, where electron-deficient groups can undergo more facile nucleophilic attack leading to faster diamination (Figure 4, **TS2-3**).

Table 2. Scope of the reaction of 1-phenyl-1-propyne (**2a**) with varying 1,1-disubstituted hydrazines.[a]



hydrazine	% conv.	% yield 4	% yield 5	4:5
3a Ph, Me, $N-NH_2$	100	67	3	> 20
3b (*p*-Me)C_6H_4, Me, $N-NH_2$	74	60	8	7.5
3c (*p*-OMe)C_6H_4, Me, $N-NH_2$	49	32	4	8
3d (*p*-F)C_6H_4, Me, $N-NH_2$	85	58	2	> 20
3e (*p*-Cl)C_6H_4, Me, $N-NH_2$	94	73	2	> 20
3f (*p*-Br)C_6H_4, Me, $N-NH_2$	95	70	2	> 20
3g (*p*-OCF_3)C_6H_4, Me, $N-NH_2$	40	37	n.d.	>20
3h Ph, Et, $N-NH_2$	36	25[b]	4	6
3i $N-NH_2$	50[c]	n.d.	28	0
3j Me, Me, $N-NH_2$	0	*no reaction*		
3k (*p*-OMe)C_6H_4, (*p*-OMe)C_6H_4, $N-NH_2$	100[d]	80	n.d.	>20

[a]Conditions: 2.5 µmol (10 mol%) **1**, 0.030 mmol (1.2 equiv.) alkyne, 0.025 mmol (1 equiv.) hydrazine, 0.8 mL C_6D_6, 33 ˚C, 16 h. ^{1}H NMR yields vs. Ph_3CH standard. [b]72 h. [c]0.21 M conc. [d]0.13 M conc.

Diamination appears to be dramatically influenced by the steric bulk of the 1,1-disubstituted hydrazines: the reaction of 1-ethyl-1-phenylhydrazine **(3h)** provided only 25% diamine **(4ah)** with a drastically slower reaction rate and overall conversion than **3a** (>72 h). Additionally, no conversion was observed with 1,1-dimethylhydrazine **(3j)**. One probable reason for this nonreactivity could be the instability/nucleophilicity of the potential (NNN)Ti($NNMe_2$) intermediate, which can dimerize quickly to shut down any reactivity.[28,36,37,38] Reactions with 1-aminopiperidine **(3i)** did not occur at low concentration, while at high concentration, only hydrazones **(5ai)** were formed. Finally, the reaction of 1,1-Bis(4-methoxyphenyl)hydrazine (**3k**), resulted in excellent yield of **4ak** with 100% selectivity. **3k** is a promising substrate because the PMP groups could in principle be oxidatively deprotected to the free amine.

CONCLUSION

In conclusion, we have demonstrated a general strategy to produce 1,2-diamines from alkynes and 1,1-disubstituted hydrazines catalyzed by **1**, capitalizing on the effect of concentration and temperature on the relative rates of two competing reactions (hydrohydrazination and diamination) from a common [2+2] cycloadduct (**IM1**). Here, entropically more favored unimolecular diamination can be promoted under highly dilute conditions and slightly elevated temperatures, under which conditions competing bimolecular hydrohydrazination reaction is disfavored.

Expansion of the substrate scope of diamination further allows for an examination of how electronic effects impact the relative propensities for diamination and hydrohydrazination. In the reactions catalyzed by **1**, hydrazines with better N_β leaving groups (*e.g.* electron-poor) and electron-rich arylacetylenes (better nucleophiles) resulted in higher selectivity toward diamination over hydrohydrazination.

Although **1** was initially reported as a diamination catalyst,[25] our studies indicate that it can also act as a hydrohydrazination catalyst under higher concentration conditions. Based on this switch of reactivity by simple concentration changes, we speculate that all Ti-hydrazido complexes may be capable of this dual diamination/hydrohydrazination reactivity, where different catalyst structures likely exist along a spectrum of propensities for the two reactions. This raises the possibility that already- reported hydrohydrazination catalysts may be able to convert to diamination catalysts under lower concentration or higher temperature conditions—assuming that the catalysts are active enough to operate at ultra-low concentrations, or stable enough to

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survive much higher temperature conditions. We are currently exploring such possibilities in our labs.

ASSOCIATED CONTENT

Supporting Information.
Full experimental details (.pdf)

The Supporting Information is available free of charge on the ACS Publications website.

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