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Ti-Catalyzed Multicomponent Oxidative Carboamination of Alkynes with Alkenes and Diazenes

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Supporting Information

ABSTRACT: The inter- or intramolecular oxidative carboamination of alkynes catalyzed by $[py_2TiCl_2NPh]_2$ is reported. These multicomponent reactions couple alkenes, alkynes and diazenes to form either *α*,*β*-unsaturated imines or *α*-(iminomethyl)cyclopropanes via a Ti^{II}/Ti^{IV} redox cycle. Each of these products is formed from a common azatitanacyclohexene intermediate that undergoes either *β*-H elimination or *α*,*γ*-coupling, wherein the selectivity is under substrate control.

Simple intermolecular alkyne carboamination reactions can potentially provide convenient access points to a range of important functional groups and reactive intermediates such as *α*,*β*-unsaturated imines, *α*-functionalized imines, or *α*-functionalized cyclopropanes.[1] Although analogous alkyne hydrofunctionalization reactions[2] have been heavily studied, the current methods for alkyne carboamination are limited to coupling of diaryl aldimines and alkynes using early transition metals,[3] through intramolecular reactions catalyzed by late transition metals,[4] or through multistep processes catalyzed by Cu and Rh.[5] Similarly, alkene carboamination[6] has seen considerable advances recently, but these methods are still mainly limited to intramolecular cyclization reactions. Accessing practical, intermolecular multicomponent carboamination catalysis remains a significant challenge.

Recently, we reported a multicomponent, $py_3TiCl_2(NPh)$-catalyzed formal [2+2+1] reaction of alkynes and diazenes for the oxidative synthesis of penta- and trisubstituted pyrroles (Figure 1).[7] In our preliminary studies of the mechanism, we found that an alkyne initially undergoes [2+2] cycloaddition with a Ti imido to generate an azatitanacyclobutene intermediate, ***I***, which then undergoes insertion of a second alkyne to generate an azatitanacyclohexadiene, ***II***. This species then reductively eliminates pyrrole, and the resulting Ti^{II} fragment is reoxidized to a Ti^{IV} imido by azobenzene. We anticipate that this new mode of Ti^{II}/Ti^{IV} redox reactivity has the potential to open up vast new classes of Ti-catalyzed reactions.

Given that the mechanisms of each alkyne coupling step in the [2+2+1] pyrrole synthesis are different, we postulated that it should be possible to decouple the reacting partners and design multicomponent coupling reactions of different unsaturated substrates. Encouragingly, Odom,[8] Livinghouse[9] and Mindiola[3c−e] have recently demonstrated that isocyanides, nitriles and imines can intercept analogous [2+2] imide+alkyne

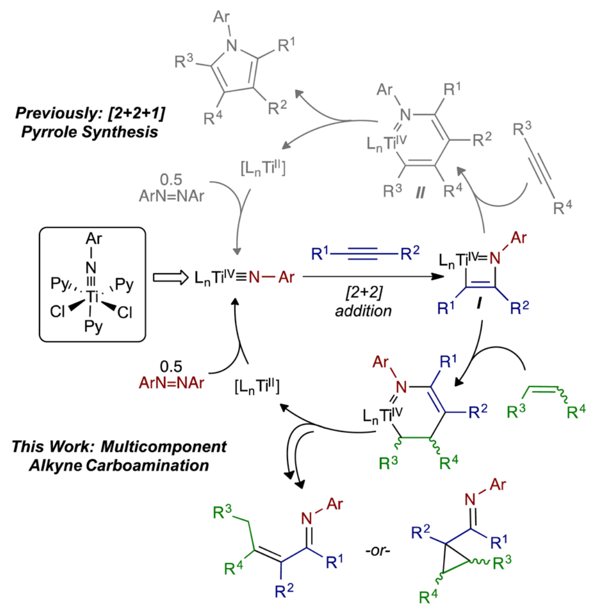

Figure 1. Overview of Ti-catalyzed nitrene transfer reactions.

azatitanacyclobutene intermediates in hydroamination-like reactions.

Our initial target of this strategy was the multicomponent coupling of an alkyne and an alkene with azobenzene. Alkenes were chosen as the third reacting partner because they readily undergo 1,2- and 2,1-insertion reactions, but typically do not undergo intermolecular [2+2] reactions with Ti imidos,[10] thus limiting the potential for unwanted alkene homocoupling. Herein, we report our initial results on the intra- and intermolecular oxidative multicomponent coupling of alkynes, alkenes and diazenes, which yields formal alkyne carboamination products: either *α*,*β*-unsaturated imines or *α*-functionalized cyclopropanes.

We initially focused on the $[py_2TiCl_2(NPh)]_2$-catalyzed reaction of tethered enynes with azobenzene, envisioning that the intramolecular reactions would be less likely to suffer from competitive pyrrole formation or alkyne trimerization (Table 1). Reaction of 2.2 equiv undec-1-en-6-yne (**1a**) with 5 mol % $[py_2TiCl_2(NPh)]_2$ in the presence of 1 equiv azobenzene at 115 °C gave the *α*,*β*-unsaturated imine 1-(2-methylcyclopent-1-en-

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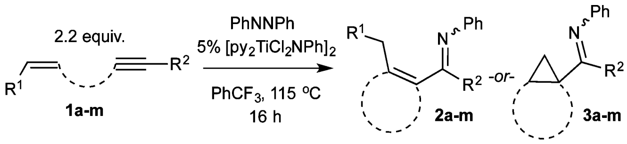
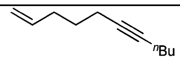
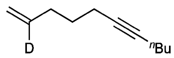
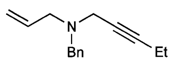
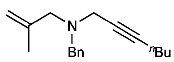
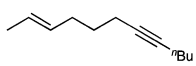
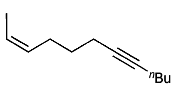
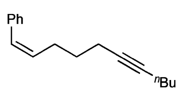
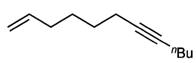
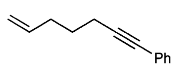
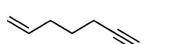
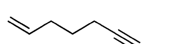
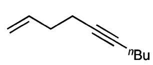
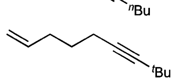
Table 1. Scope of Multicomponent Carboamination of Tethered Enynes with PhNNPh[a]



	Substrate	% Isolated Yield[b] (2:3)	^{1}H NMR % Yield (2:3)
1a		50 (>99:1)	92 (85:15)
1b		86 (44:56)	92 (53:47)
1c		37 (>99:1)	-[d]
1d		13 (1: >99)[e]	29 (1: >99)
1e		60 (>99:1)	91 (>99:1)
1f		69 (>99:1)	86 (>99:1)
1g		50 (>99:1)	-[d]
1h		54 (49:51)	-[d]
1i		57 (5:95)[f]	-[d]
1j	 Ar = p-CF$_3$Ph	36 (1:>99)[g]	-[d]
1k	 Ar = p-MeOPh	37 (1:>99)[h]	-[d]
1l		0	n.d.
1m		0	n.d.

[a]Loading of [py$_2$TiCl$_2$NPh]$_2$ and reaction yields with respect to PhNNPh. [b]Isolated as the ketone product after hydrolysis. See SI for details. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Could not be determined due to peak overlap in the ^{1}H NMR spectrum. [e]Isolated as the retro-ene product **3d′** (Figure 3). [f]As a mixture of **2i**, **3i** and **4i** (Figure 5). [g]As **4j**. [h]As a mixture of **3k** and **4k**.

1-yl)-*N*-phenylpentan-1-imine (**2a**) in 50% isolated yield (Figure 2).[7]

This product likely forms through the expected azatitanacyclohexene intermediate ***III***, but instead of C−N reductive coupling to form a dihydropyrrole, the metallacycle collapses via *β*-H elimination to give ***IV***, followed by subsequent N−H reductive elimination to ***V*** and dienamine isomerization (Figure 2). Alternately, direct *β*-H abstraction by the amide from intermediate ***III*** could also form ***V***.[11] Unlike in the previously reported pyrrole synthesis, it is likely that the sp^3-hybridized *α*-C is less prone to C−N reductive elimination due to poor orbital overlap,[12] which allows for the *β*-H elimination pathway to kinetically outcompete direct C−N elimination.

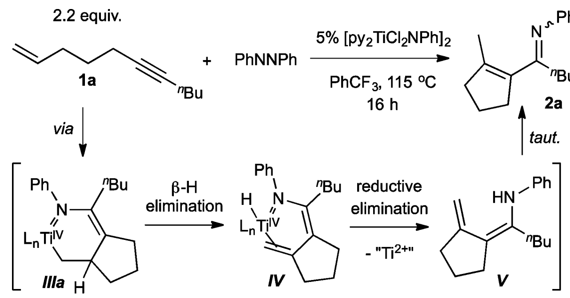


Figure 2. Tethered enynes yield *α*,*β*-unsaturated imines upon catalysis with PhNNPh.

In an attempt to shut down *β*-H elimination, we next examined substrates that upon metalation would lack a *β*-H to eliminate. Treatment of *N*-benzyl-*N*-(2-methylallyl)hept-2-yn-1-amine (**1d**) under catalytic conditions gave 1-(1-benzyl-5-methylenepiperidin-3-yl)pentan-1-one (**3d′**) in low yield upon acidic workup. This product arises from isomerization via retro-ene ring opening of a *cis*-cyclopropane (**3d**), which is generated via catalysis (Figure 3).

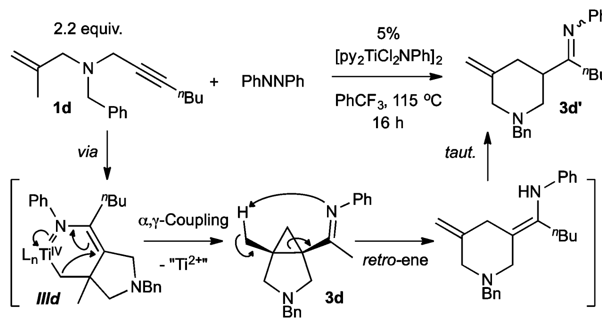


Figure 3. Internally substituted alkenes yield *α*-(iminomethyl)-cyclopropanes upon catalysis with PhNNPh as *β*-H elimination/abstraction is shut down.

Remarkably, by shutting down the *β*-H elimination process, the azatitanacyclohexene ***IIId*** collapses via attack of the *α*-C on the *γ*-C,[13] resulting in reductive elimination of an *α*-imino functionalized cyclopropane. In fact, this cyclopropanation can also be observed when using the deuterated analogue **1b**: because *β*-D elimination (which must occur in **1b**) is typically slower than *β*-H elimination (in **1a**), there should be a larger k_{rel} for forming the cyclopropane **3** versus the *α*,*β*-unsaturated imine **2** in the reaction of **1b**. This is reflected in the ^{1}H NMR product ratios, where **1a** forms an 85:15 ratio of **2a**:**3a**, whereas at similar overall conversion **1b** forms a larger percentage of **3b**, 50:50 **2b**:**3b**.

The overall preliminary mechanistic manifold of these carboaminations is presented in Figure 4. Azatitanacyclohexenes (***III***) are prone to metallacycle collapse via competitive *α*,*γ*-coupling (***VI***) or *β*-H elimination/abstraction (***IV***). These pathways are kinetically accessible because the *α*- and *β*-carbons are sp^3-hybridized, making direct C−N reductive coupling

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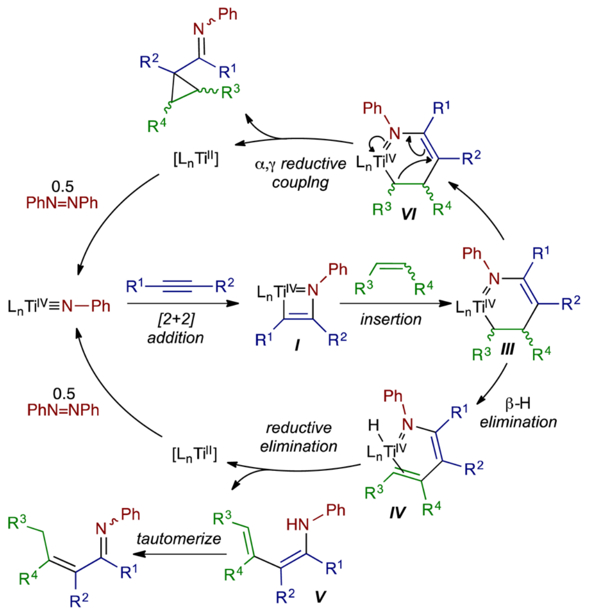


Figure 4. Proposed mechanism for Ti-catalyzed alkyne carboamina-tions.

more challenging while opening up alternative reductive cleavage pathways through the increased flexibility of the metallacycle. This is characteristic of all of the multicomponent reactions reported herein.

To probe the scope of carboamination and selectivity for β-H elimination vs α,γ-coupling, we examined catalysis with several more tethered enynes (Table 1). In most cases, isolated yields of the reactions were moderate due to the difficulty in separating the product isomers, but ^{1}H NMR analysis of the crude mixtures generally indicated that the reactions proceeded to total conversion. Terminal and internal alkenes were competent for catalysis, and there was little difference in utilizing *E* or *Z* alkenes **1e** and **1f**. Only internal alkynes are currently compatible because their more-reactive terminal counterparts undergo [2+2+1] pyrrole synthesis and alkyne trimerization too rapidly.[7]

Interestingly, simply changing from a propyl linker (**1a**) to a butyl linker (**1h**) erodes selectivity for the α,β-unsaturated imine **2h** from 85:15 to 50:50, indicating that there is a subtle steric balance between β-H elimination and α,γ-coupling. Shorter tethers (**1l**), as expected, do not undergo reaction and bulky substituents on the alkyne (**1m**), which enforce the wrong [2+2] regiochemistry necessary for alkene insertion, also do not react productively.

Aryl-substituted alkynes heavily favor α,γ-coupling due to increased electrophilicity of the γ-C caused by the aryl substituent (**1i**−**1k**). Furthermore, the resulting electrophilic bicyclo[3.1.0]hexane arylimines (**3i**−**3k**) undergo further reactivity in situ: titanium Lewis acid-catalyzed carbocation rearrangement yields the fused 1-arylbicyclo[4.1.0]heptan-2-imines **4i**−**4k** (Figure 5).

Next, intermolecular heterocouplings between internal alkynes and terminal unactivated alkenes were attempted (Table 2). Terminal alkenes compete effectively with alkynes for the second insertion into the azametallacyclobutene intermediate. Even at a 1:1 ratio of 1-octene:3-hexyne, moderate yields of the α,γ-unsaturated imine product were obtained, with the remaining mass balance undergoing competitive [2+2+1] pyrrole formation. The yield of the α,γ-unsaturated product **6b** could be increased from 31% to 61% by doubling the concentration of 1-octene. In all cases, terminal alkenes react via 2,1-insertion, indicating that this step is likely under steric control where the alkene substituent orients preferentially toward an uncrowded Ti center rather than a 2° carbon substituent.

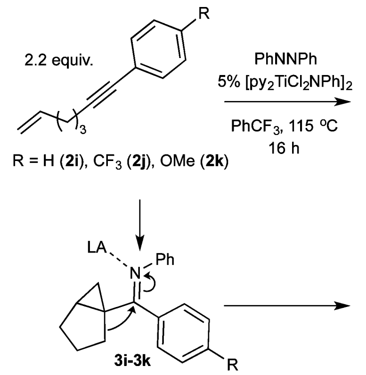
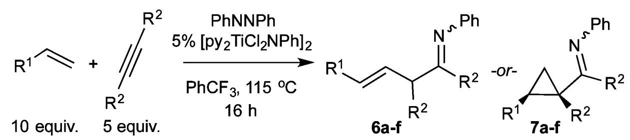
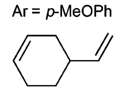


Figure 5. Phenyl-substituted alkynes yield bicyclo[3.1.0]hexane imines that can undergo Lewis acid-catalyzed carbocation rearrangement.

Table 2. Intermolecular Multicomponent Carboamination of Alkynes and Alkenes with PhNNPh[a]



	Alkene	R^2	% Isolated Yield (**6**:**7**)[b]	^{1}H NMR % Yield (**6**:**7**)[c]
5a	Hex^n (1-octene)	Me	54 (40:60)	n.d.
5b	Hex^n (1-octene)	Et	61 (>99:1)	n.d.
5c	Ar (allyl), Ar = *p*-MeOPh	Me	42 (9:91)	63 (15:85)[d]
5d	Ar (allyl), Ar = *p*-MeOPh	Et	51 (>99:1)	70 (71:29)[e]
5e[f]		Et	40 (>99:1)	n.d.
5f	^{t}Bu (vinyl)	Et	0	n.d.

[a]Loading of $[py_2TiCl_2NPh]_2$ and reaction yields with respect to PhNNPh. [b]Isolated as the ketone product after hydrolysis. See SI for details. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]96:4 ratio of *cis*:*trans* cyclopropane product. [e]74:26 ratio of *cis*:*trans* cyclopropane product. [f]Reaction run in neat alkene.

As was the case in the intramolecular multicomponent couplings, subtle structural changes in intermolecular hetero-couplings also lead to dramatic shifts in selectivity between β-H elimination/abstraction and α,γ-coupling products. This selectivity shift is apparent in the reaction of 4-allylanisole with internal alkynes: reaction with 3-hexyne gives a 71:29 ratio of **6d**:**7d**, whereas reaction with 2-butyne inverts the selectivity and yields a 15:85 ratio of **6c**:**7c** by ^{1}H NMR analysis. The *cis*:*trans* selectivity of the cyclopropanes also varies heavily between the 3-hexyne product **7d** (74:26) and 2-butyne product **7c** (96:4), which has similarly been observed in Kulinkovich-type cyclopropanation reactions.[14]

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In addition to unsubstituted linear terminal alkenes, terminal alkenes bearing 2° groups are also competent for catalysis. 4-Vinylcyclohex-1-ene undergoes reaction to give low yields of the product with exclusive reactivity at the terminal alkene. Bulkier alkenes, such as 3,3-dimethylbut-1-ene, fail to react.

In conclusion, we have demonstrated the first examples of a three-component oxidative alkyne carboamination, generating either α,β-unsaturated imines or α-functionalized cyclopropanes. Preliminary mechanistic studies indicate that these Ti-catalyzed reactions proceed through a common azametallacyclohexene intermediate. Somewhat remarkably, both intra- and intermolecular reactions proceed in moderate to good yields and selectivities despite the large potential for the occurrence of undesired competitive processes such as alkyne homocoupling. We are currently examining new catalyst classes to further understand and increase control over the rate and selectivity of these unique transformations, as well as further pursuing new Ti redox catalytic reactions promoted by diazene oxidants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09939.

Full experimental procedures, characterization data and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Sandhu, J. S.; Sain, B. *Heterocycles* **1987**, *26*, 777. (b) Amslinger, S. *ChemMedChem* **2010**, *5*, 351−356. (c) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051−3060. (d) Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969−2984. (e) Okajima, T. *Nucl. Acids Symp. Series* **2007**, *51*, 215−216. (f) Kumar, A. K. *Int. J. Pharm. Pharm. Sci.* **2013**, *5*, 467−472.

(2) For a review of hydroamination, see: Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795−3892.

(3) (a) Ruck, R. T.; Zuckerman, R. L.; Krska, S. W.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 5372−5374. (b) Ruck, R. T.; Bergman, R. G. *Organometallics* **2004**, *23*, 2231−2233. (c) Basuli, F.; Aneetha, H.; Huffman, J. C.; Mindiola, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 17992−17993. (d) Aneetha, H.; Basuli, F.; Bollinger, J.; Huffman, J. C.; Mindiola, D. J. *Organometallics* **2006**, *25*, 2402−2404. (e) Basuli, F.; Wicker, B.; Huffman, J. C.; Mindiola, D. J. *J. Organomet. Chem.* **2011**, *696*, 235−243. For a review on titanium carboamination, see: (f) Mindiola, D. J. *Comments Inorg. Chem.* **2008**, *29*, 73−92.

(4) (a) Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058−6059. (b) Yoshino, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, *131*, 7494−7495. (c) Maizuru, N.; Inami, T.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 1206−1209. (d) Zavesky, B. P.; Babij, N. R.; Wolfe, J. P. *Org. Lett.* **2014**, *16*, 4952−4955. (e) Patil, N. T.; Kavthe, R. D.; Yamamoto, Y. *Adv. Heterocycl. Chem.* **2010**, *101*, 75−95. (f) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153−1160.

(5) Rh-catalyzed alkyne carboaminations are two-step reactions involving Cu-catalyzed alkyne/azide cycloaddition followed by Rh-catalyzed iminovinylidene formation: Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972−14974.

(6) Piou, T.; Rovis, T. *Nature* **2015**, *527*, 86−90.

(7) Gilbert, Z. W.; Hue, R. J.; Tonks, I. A. *Nat. Chem.* **2016**, *8*, 63−68.

(8) Odom, A. L.; McDaniel, T. J. *Acc. Chem. Res.* **2015**, *48*, 2822−2833.

(9) McGrane, L. P.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459−5460.

(10) Only ethylene has been observed: Polse, J. L.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 13405−13414.

(11) Agapie, T.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2007**, *129*, 14281−14295.

(12) (a) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205−9219. (b) Low, J. J.; Goddard, W. A. *Organometallics* **1986**, *5*, 609−622.

(13) Suzuki, K.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 8729−8730.

(14) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789−2834.

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