ABSTRACT: The inter- or intramolecular oxidative carboamination of alkynes catalyzed by [py₂TiCl₂(NPh)]₂ is reported. These multicomponent reactions couple alkynes, 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. Although analogous alkyne hydrofunctionalization reactions have been heavily studied, the current methods for alkyne carboamination are limited to coupling of diarylaldimines and alkynes using early transition metals, through intramolecular reactions catalyzed by late transition metals, or through multistep processes catalyzed by Cu and Rh. Similarly, alkene carboamination 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, py₃TiCl₃(NPh)-catalyzed formal [2+2+1] reaction of alkynes and diazenes for the oxidative synthesis of penta- and trisubstituted pyrroles (Figure 1). 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.

We initially focused on the [py₂TiCl₂(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 % [py₂TiCl₂(NPh)]₂ in the presence of 1 equiv azobenzene at 115 °C gave the α,β-unsaturated imine 1-(2-methylcyclopent-1-en-...
As a mixture of \( \text{3k} \) and \( \text{4k} \) (Figure 5). \( ^g \) As a mixture of \( \text{3l} \) and \( \text{4l} \). \( ^h \) As a mixture of \( \text{3m} \) and \( \text{4m} \).

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

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

The overall preliminary mechanistic manifold of these carboaminations is presented in Figure 4. Azatitanacyclohexenes (III) are prone to metallacycle collapse via competitive \( \alpha \),\( \gamma \)-coupling (VI) or \( \beta \)-H elimination/abstraction (IV). These pathways are kinetically accessible because the \( \alpha \) - and \( \beta \)-carbons are sp\(^3\)-hybridized, making direct C–N reductive coupling to V and dienamine isomerization (Figure 2). Alternately, direct \( \beta \)-H abstraction by the amide from intermediate \( \text{III} \) could also form V.\(^11\) Unlike in the previously reported pyrrole synthesis, it is likely that the sp\(^3\)-hybridized \( \alpha \)-C is less prone to C–N reductive elimination due to poor orbital overlap,\(^12\) which allows for the \( \beta \)-H elimination pathway to kinetically outcompete direct C–N elimination.

In an attempt to shut down \( \beta \)-H elimination, we next examined substrates that upon metalation would lack a \( \beta \)-H to eliminate. Treatment of \( \text{N-benzyl-N-(2-methylallyl)hept-2-yn-1-amine (1d)} \) under catalytic conditions gave 1-(1-benzyl-5-methyleneepiperidin-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).

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 \( \beta \)-H elimination to give IV, followed by subsequent N–H reductive elimination to V and dienamine isomerization (Figure 2). Alternately, direct \( \beta \)-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 \( \alpha \)-C is less prone to C–N reductive elimination due to poor orbital overlap,\(^12\) which allows for the \( \beta \)-H elimination pathway to kinetically outcompete direct C–N elimination.

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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 1H 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 alkenes 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 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. As was the case in the intramolecular multicomponent couplings, subtle structural changes in intermolecular heterocouplings 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 1H 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
In addition to unsubstituted linear terminal alkenes, terminal alkenes bearing $\alpha$-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 alkylene carboamination, generating either $\alpha,\beta$-unsaturated imines or $\alpha$-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 alkyl 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.

**REFERENCES**


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