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Oxidative Nitrene Transfer from Azides to Alkynes via Ti(II)/Ti(IV) Redox Catalysis: Formal [2+2+1] Synthesis of Pyrroles

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Catalytic oxidative nitrene transfer from azides with the early transition metals is rare, and has not been observed without the support of redox noninnocent spectator ligands. Here, we report the formal [2+2+1] coupling of azides and alkynes *via* Ti^{II}/Ti^{IV} redox catalysis from simple Ti halide imido precatalysts. These reactions yield polysubstituted N-alkyl pyrroles, including N-benzyl protected pyrroles and rare examples of very electron rich pentaalkyl pyrroles. Mechanistic analysis reveals that [2+2+1] reactions with bulky azides have different mechanistic features from previously-reported reactions using azobenzene as a nitrene source.

Nitrene transfer reactions are powerful tools for functional group installation in organic chemistry. For example, transition metal-catalyzed nitrene transfer, particularly with late transition metals, has been used frequently in alkene aziridinations¹ and C-H functionalizations.² Due to the thermodynamic stability of the d⁰ configuration, early transition metal-mediated nitrene transfers are rare³ and predominately stoichiometric. Recently, major successes has been achieved in employing redox noninnocent (RNI) ligands to stabilize the early transition metals in their d⁰ state, allowing the metal to act as a conduit for electron transfers that are ligand-centered. Both the Heyduk^{4b, 5} and Wolczanski⁶ groups have developed catalytic reactions with RNI ligand scaffolds and organic azides to allow for facile nitrene that could be used in small transfer molecule synthesis/functionalization (Figure 1).

Recently, we reported the Ti-catalyzed formal [2+2+1] multicomponent coupling of alkynes and aryl diazenes for the synthesis of penta- and trisubstituted pyrroles, which at the time was the first example of catalytic nitrene transfer from Ti.⁷ In the absence of ancillary RNI ligands, we hypothesize that the

success of this reaction is predicated on the ability of Ti to backbond into the substrates and/or the products, either of which can act as a π -acceptor to mask the Ti^{II} species. Inspired by the successes of Wolczanski and Heyduk in RNI-promoted catalytic oxidative nitrene transfer from azides with group 4 metals, we sought to investigate the use of azides in [2+2+1] pyrrole synthesis in the absence of an engineered RNI ligand.



Figure 1. Nitrene transfer reactions catalyzed by early transition metal/redox noninnnocent ligand systems.

Although organic azides are well-known to undergo Huisgen cycloadditions with alkynes to form triazoles—either thermally⁸ or with myriad metal catalysts⁹—we hypothesized that Ti^{II} intermediates generated in the reaction would be sufficiently reactive to reduce the azide and turn over the catalytic cycle at rates competitive with this potential background reaction. Further, organic azides offer several advantages over diazenes. For example, alkyl azides—unlike alkyl diazenes—are typically stable above 130 °C and thus could allow access to N-alkyl pyrroles, allowing for installation of N-protecting groups on the

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pyrrole.¹⁰ This would also give access to pentaalkyl pyrroles, which are extremely rare structures due to their oxidative instability and difficulty of synthesis.¹¹ Additionally, many diazenes are made from azides,^{5b, 12} so direct use of azides could streamline precursor synthesis. A wide variety of organic azides are also easily accessed through simple substitution chemistry, providing a more straightforward method for synthesizing complex N-substituted pyrroles.¹³ Herein, we report that organic azides are competent reaction partners for Ti-catalyzed formal [2+2+1] pyrrole synthesis and related oxidative multicomponent alkyne aminations. These reactions provide access to N-alkyl functionalized products, in contrast to previously-described methods which were limited to N-arylated products.^{7d}



Figure 2. Top: initial reaction attempts of 1a and 2a catalyzed by $py_3TiCl_2(N'Bu)$ were marred by azide decomposition.

Initial coupling attempts of *p*-tolyl azide (**1a**) with 3-hexyne (**2a**) catalyzed by 10% py₃TiCl₂(N^{*t*}Bu) in C₆D₅Br at 115 °C yielded 16% of the desired pyrrole product, 2,3,4,5-tetraethyl-N-(*p*-tolyl) pyrrole (**3aa**). However, this reaction is marred by significant side-product formation: 4,5-diethyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole, (**6a**), N-(*p*-tolyl)hexan-3-imine, (**7a**), and 4,4'-azotoluene (**8a**). All of the sideproducts in this reaction can be ascribed to thermal azide decomposition—**6a** from the uncatalyzed [3+2] Huisgen condensation of **1a** with **2a**; **7a** from the Ti-catalyzed hydroamination of **2a** with aniline, which is formed during azide decomposition to the free nitrene; and **8a** from thermal azide coupling.¹⁴



Attempts to improve the selectivity and yield of this reaction through reaction optimization only marginally improved catalysis, and as a result *alkyl* azides were explored. Alkyl azides are significantly more thermally robust than aryl azides and undergo [3+2] addition more slowly, and are thus less likely to undergo competitive decomposition under catalytic conditions. Reaction of adamantyl azide (**1b**) with **2a** catalyzed by 10% py₃TiCl₂(N'Bu) in C₆D₅Br at 115 °C resulted in low conversion, presumably due to inhibition of alkyne binding by azide (eq 1). By moving to a more Lewis acidic catalyst (THF) $\pi_1^{(1)}$ (Mtoh), which more indiscriminately binds ligards, the desired pyfrote product **3ba** was formed in 80% yield with no detectable azide decomposition side-products (eq 2).

Kinetic analysis of the $(THF)_3TiI_2(Ntol)$ -catalyzed reaction of **1b** with **2a** through variable time normalization analysis¹⁵ yields the rate law in Figure 3 (top). Assuming a mechanistic manifold similar to [2+2+1] pyrrole formation with azobenzene as the nitrene source^{7a, 7d} the 2nd order dependence of 3-hexyne indicates that 2nd insertion of **2a** into the azatitanacyclobutene intermediate **II** is the rate-determining step of catalysis.



Figure 3. Comparison of the mechanisms of pyrrole formation with azide or azobenzene reveal different mechanisms of reoxidation.

However, the remainder of rate law for 1b is different from the azobenzene reaction (Figure 3, top). With 1b, the reaction is 1st order [Ti], in contrast to 0.5 order [Ti] in azobenzene reactions. This indicates that Ti dimerization is not kinetically relevant, unlike in azobenzene reactions where an on-cycle dimer is required for catalyst reoxidation to occur. This also indicates that the Ti=NAd group is sterically bulky enough to avoid offcycle dimerization, which is often kinetically relevant in Ti imido-catalyzed reactions.¹⁶ The zero-order dependence on 1b indicates that Ti^{II} oxidation is fast compared to alkyne insertion, and that sterically-encumbered 1b doesn't inhibit catalysis through competitive binding to Ti, where PhNNPh does. In contrast, substituting 1b for n-decN₃ (1c) gives a reaction that is 0.5 order [Ti], as well as -0.5 order [decN₃]. This observation further indicates that steric bulk prevents dimerization and azide inhibition in reactions with 1b.

Next, the scope of internal alkynes was investigated (Table 1). Simple internal alkyl alkynes 3-hexyne (2a) and 2-butyne (2b) give high yields; however, diphenylacetylene (2c) yields no product. In these with excess alkyne, trimerization of the

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remaining alkyne can occur after productive catalysis is complete. By shortening reaction times to 2h (Entry 2), lower but satisfactory yields can still be obtained in the absence of trimerized byproducts. 1-phenyl-1-propyne (2d) gives a 1.6 : 1 mixture of regioisomeric pyrroles **3bd** and **4bd** in high yield. This is in contrast to the reaction of 2d with PhNNPh, which yields all three possible pyrrole regioisomers in a statistical distribution:^{7d} with **1b**, the stereoelectronic effect¹⁷ of the N-adl group prevents [2+2] cycloaddition with the aryl of **2d** oriented toward NAd, which is required for the formation of **5d**. **Table 1.** Internal alkyne scope.

		, ∕ ^{R³} 10% (THF) ₃ Til₂(Ntol)			
	R ¹ N ₃ +	CeDeBr	115 °C	R-	H ^o
	F	R ²	,	≺ B3	R ²
	1 2		3 (+ isomers for 3d)		
En-	Azide	Alkyne	Alkyne	t	% Yield
try			equiv.	(h)	(NMR)
1 ^b	Ad	Et-Et	5	16	(80)
	1b	2a			
2^{c}	Ad	Et-Et	5	2	23 (59)
	1b	2a			
3 ^b	Ad	MeMe	5	16	(94)
	1b	2b			
4^{b}	Ad	Ph-Ph	5	16	trace
	1b	2c			
5 ^b	Ad	PhMe	5	16	$(70)^{d}$
	1b	2d			
6 ^{ce}	<i>n</i> -dec	Et-Et	3	6	(37)
	1c	2a			
7 ^{cf}	<i>n</i> -dec	Et-Et	3	6	(35)
	1c	2a			
8 ^c	n-dec	Et-Et	3	6	(42)
	1c	2a			
9°	n-dec	Et-Et	5	2	48 (64)
	1c	2a			
10°	Bn	Et-Et	5	2	59 (62)
	1d	2a			
11 ^c	tol	Et-Et	5	2	(30)
	1 a	2a			
12 ^g	tol	Et-Et	8	3	(52)
	1 a	2a			
13 ^c	PhSCH ₂	Et-Et	5	2	0
	1e	2a			
14 ^c	Ph ₃ C	Et-Et	5	2	0
	1f	2a			

^aNMR yield calculated with respect to **1** with Ph₃CH internal standard. ^bConditions: 0.2 mmol **1b**, 1.0 mmol **2**, 10 mol % (THF)₃TiI₂(Ntol) 115°C, 0.5 mL C₆D₅Br, average of 2 runs. ^cConditions: 0.1 mmol **1**, **2a**, 10 mol % (THF)₃TiI₂(Ntol), 115°C, 2 h, 0.5 mL C₆D₅Br, average of 2-3 runs. ^d1.6 : 1.0 : 0 ratio of **3bd : 4bd : 5bd** ^cConducted at 80 ^cC. ^fConducted at 100 ^cC. ^gConditions: 0.1 mmol **1a**, 0.8 mmol **2**, 10 mol % (THF)₃I₂Ti(Ntol), 115°C, 0.5 mL C₆D₅Br.

In the pursuit of accessing N-protected pyrroles, we sought to expand the azide scope in the system. Primary alkyl azides such as n-decyl azide (1c) are challenging because of the tendency for primary metal-imidos to dimerize.^{16c} They are also better nucleophiles, which could hinder leadaly sis^C through coordination to Ti, akin to hydroamination reactions with primary alkyl amines.¹⁸ Nonetheless, *n*-decyl azide (**1c**) gives moderate yield of pentaalkyl pyrroles (Table 1 entries 6-9).

In reactions of 1c, small amounts of 1-iododecane are formed along with the 3ca. This likely forms through $S_N 2$ of N_3 of by iodide, forming a titanium azido complex. Reaction of TMSN₃ with Ti halide catalysts similarly yields TMS-halides and unreactive Ti azido species. Given this observation, we suspected that the lower yields of 1c were a result of catalyst death; indeed, when additional 1c was added at the end of the reaction, no additional product formed. However, reducing the concentration, decreasing the reaction time, and using excess 2aresults better yields with respect to 1c (entry 9).

Benzyl azide (1d) gives good yields in the coupling with 2a (entry 10)—potentially allowing access to NH pyrroles through hydrogenolysis of the resulting benzyl protecting group. Aryl azides still perform poorly even at high alkyne and catalyst loading due to their propensity to undergo uncatalyzed [3 + 2] cycloadditions and thermal decomposition (entries 11 and 12).

(THF)₃TiI₂(Ntol) rapidly cyclotrimerizes terminal alkynes,¹⁹ which bind faster and stronger to Ti than internal alkynes. Accordingly, we returned to the less-active py₃TiCl₂(N'Bu) for [2+2+1] of azides with terminal alkynes (Table 2). At a 2:1 alkyne : azide stoichiometry, simple alkyl (2e) and aryl (2f) acetylenes give moderate yields of pyrroles along with small amounts (typically < 20% yield) of trimerization. In contrast, reactions with azobenzene as the nitrene source require significant excesses of azobenzene (1:4 alkyne: azobenzene) to suppress trimerization. This indicates that azides are significantly better at intercepting Ti^{II} intermediate IV than post-rate-determining-step azobenzene, imparting chemoselectivity for pyrrole formation over alkyne trimerization (Figure 3).

Terminal alkynes could potentially give 3 regioisomeric trisubstituted pyrroles 3, 4 and 5. In all cases, the size of the adamantyl group completely impedes the formation of the 2,5disubstituted pyrroles 5. Reaction of *p*-tolylacetylene (2f, entry 2) shows a 1 : 1 mixture of **3bf : 4bf**, a contrast to the product distribution observed using azobenzene as the nitrene source, which yields 3:4 in a 4:1 with phenylacetylene.¹ This further demonstrates that bulky alkyl imidos bias the reaction toward trisubstituted products where the substituents are pointed away from N such as 4. With a bulky alkyne substrate such as tbutylacetylene (1g), no reaction was observed with 1b. With less bulky p-tolyl azide (1a), pyrrole formation can be observed in low yield, albeit with significant nitrene decomposition products (vide supra). Similarly, bulky (trimethylsilyl)acetylene (2h) gives low pyrrole yields, as [3+2] cycloaddition and cyclotrimerization better compete with the productive reaction.

In summary, simple Ti catalysts are capable of affecting oxidative nitrene transfer reactions with azides and alkynes to generate pyrroles. This reaction is only the 2nd example of Ti-catalyzed nitrene transfer from an azide, and a rare example of 2-electron group 4 redox catalysis. Unlike previous examples of group 4-catalyzed oxidative nitrene transfer from azides, this

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reaction does not require ancillary redox noninnocent ligands and instead relies on "classical" redox noninnocence through π backbonding into the substrates and products, albeit at the cost of potentially higher reaction temperatures.

Table 2. Terminal alkyne scope.^a



^aConditions : 0.2 mmol **1** (1 equiv.), 0.42 mmol **2** (2.1 equiv.), 10 mol % py₃TiCl₂(N'Bu), 115 °C, 6 h, 0.5 ml C6D5Br, average of 2 runs ^bProduct ratio determined by quantitative GC-FID. ^c0.21 mmol **2i**.

This protocol allows access to N-alkylpyrrole derivatives, in complement to previously-reported Ti-catalyzed [2+2+1] pyrrole syntheses with diazenes, which were limited to N-aryl pyrroles. There are several examples of highly substituted N-alkyl pyrroles with important bioactivity, such as atorvastatin.²⁰ These azide reactions also have contrasting mechanistic features to the diazene reactions: for example, azide reactions can effectively outcompete alkyne cyclotrimerization, even with highly reactive terminal alkynes. Furthermore, azide reactions do not require a dimeric species to undergo reoxidation, changing the rate dependence of catalyst concentration when compared to diazene reactions. The mechanistic insight herein provides a platform for the further development of Ti-catalyzed oxidative amination reactions into practical methods.

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