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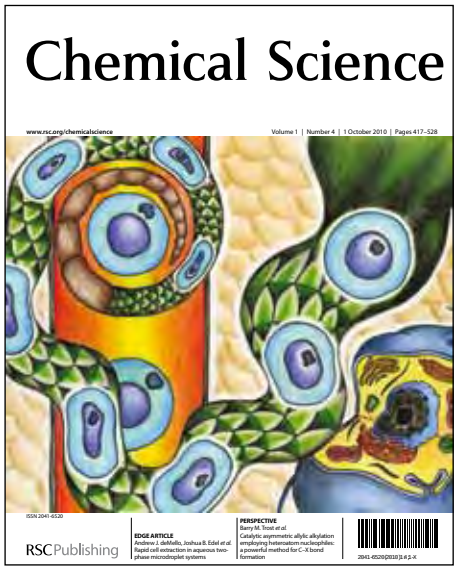

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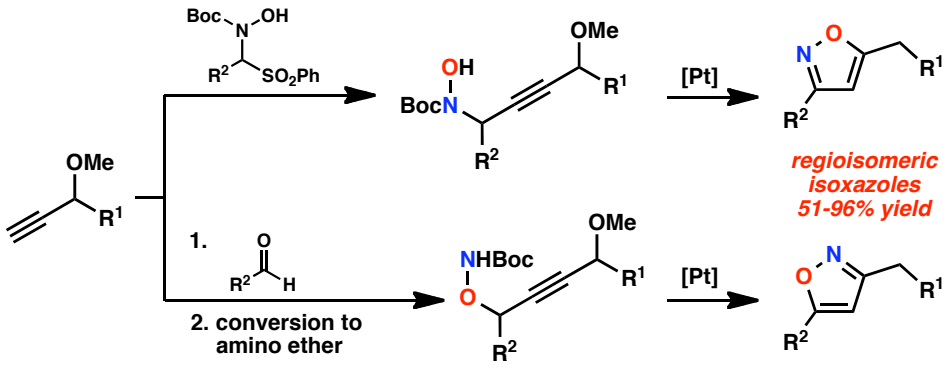
Platinum-Catalyzed Cyclizations via Carbene Intermediates: Syntheses of Complementary Positional Isomers of Isoxazoles

Paul Allegretti and Eric M. Ferreira*

A novel synthesis of regioisomeric isoxazoles is described. Via an interesting Pt-carbene intermediate, substrates featuring oxygen- or nitrogen-based nucleophiles can be cyclized to form differentially substituted isoxazoles.



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ARTICLE TYPE

Platinum-Catalyzed Cyclizations via Carbene Intermediates: Syntheses of Complementary Positional Isomers of Isoxazoles

Paul A. Allegretti and Eric M. Ferreira*[a]

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A novel synthesis of regioisomeric isoxazoles is described. Using catalytic platinum, both propargylic *N*-hydroxycarbamates and *N*-alkoxycarbonyl amino ethers can be cyclized to form differentially substituted isoxazoles. Reaction conditions are developed that address specific aspects of the catalytic manifold. A unique mechanism involving a Pt-carbene intermediate is proposed, and deuterium labeling studies corroborate this hypothesis. This regiocomplementary approach to isoxazoles is highlighted in the syntheses of antirhinovirus analogues, illustrating the relevance of this science to medicinal chemistry.

The prevalence of the heterocyclic structure in pharmaceutical and materials chemistry is well established. Among heterocycles, isoxazoles continue to prove highly valuable to interests both synthetic[1] and medicinal.[2] Their importance necessitates convenient synthetic methods to access their core structures. There are several accepted methods for isoxazole synthesis,[3] notably the [3+2] cycloaddition of nitrile oxides with C–C multiple bonds[4,5] or the combination of hydroxylamine with various three-carbon components;[6] each, however, has its respective limitations (decreased regioselectivity, substrate specificity, forcing conditions, etc.). More recent developments have been aimed at addressing some of these drawbacks.[7] One such strategy is the metal-catalyzed intramolecular cyclization of a heteroatom nucleophile onto an unsaturation unit.[8] An attractive attribute within this approach would be the ability to produce regioisomeric isoxazoles from a common advanced intermediate. Herein we report the platinum-catalyzed synthesis of complementary 3,5-disubstituted isoxazoles from easily accessed propargylic *N*-hydroxycarbamates and propargylic carbamoyl ethers.

Recently, we described the Pt-catalyzed synthesis of furans from homopropargylic alcohols, proposing a unique generation of a carbene intermediate (Figure 1, **A**→**C**).[9-11] We anticipated that we could expand upon this reaction manifold to form alternative heterocyclic compounds from the appropriate precursors. Isoxazole syntheses via alkyne activation processes have seen relatively limited exploration.[8] With regard to this heterocyclic structure, substrates bearing an N–O bond with either nitrogen- or oxygen-based nucleophiles could be implemented in this context. This approach presents unique challenges, however. Specifically, the substrates must be easily accessible and competent reactants under the catalytic conditions, and the additional nitrogen substituent (R^3) must be cleavable, ideally in the same reaction process. If these challenges could be overcome, then this method would serve as an attractive and convenient protocol for the syntheses of isoxazoles, with potential for access to regiocomplementarity.

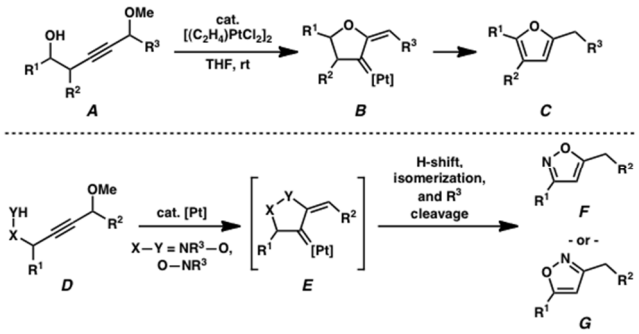
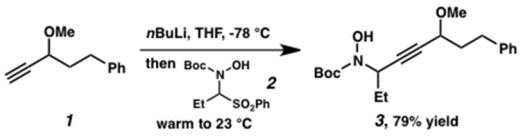


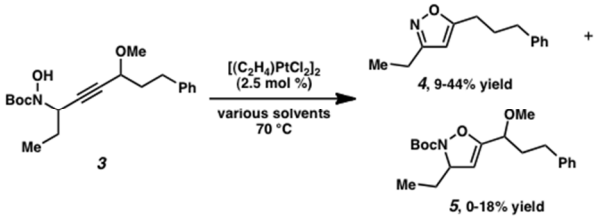
Figure 1. Development of Pt-catalyzed isoxazole formations.

First, we needed an efficient synthetic route to precursors containing the requisite N–O connectivity. Although the additions of alkyne nucleophiles into nitrones has been described,[12] the *N*-hydroxylamine products generally featured alkyl groups bound to nitrogen. We were concerned the presence of a Lewis basic nitrogen would impede the proposed reaction or that the alkyl groups (e.g., benzyl) would not easily cleave.[13,14] An isolated report from Denis, however, described the use of *N*-Boc nitrone surrogates as electrophiles in alkynylations by generating the nitrone species in situ from corresponding (phenylsulfonyl)alkyl-*N*-hydroxycarbamates, and this method appeared ideal for the syntheses of the targeted substrates.[15] Using terminal alkyne **1**, addition into the in situ generated nitrone from hydroxycarbamate **2** proved effective, and the resulting *N*-hydroxycarbamate (**3**) was produced in good yield overall (Scheme 1).



Scheme 1

With hydroxycarbamate **3** in hand, we evaluated conditions to induce cyclization (Scheme 2). The original conditions we had developed in the furan chemistry ($[(C_2H_4)PtCl_2]_2$, THF, 23 °C) displayed minimal reactivity, and even at elevated temperatures in various solvents, the desired isoxazole (**4**) was produced in low yield. Variation of catalyst species resulted in only marginal changes to the reaction profile.[16] Conspicuously, in most of the $PtCl_2$/olefin catalyst systems, the corresponding isoxazoline (**5**) was observed in measurable quantities, a product arising from simple intramolecular addition of the hydroxyl group across the alkyne.[17]



Scheme 2

We saw the formation of isoxazoline **5** as a clue toward explaining the problematic reactivity. In our experiences with the aforementioned furan chemistry, the corresponding dihydrofuran (e.g., **7**, Figure 2) was seldom observed.[18] A proton transfer event to the methyl ether was believed to be required for the generation of the productive carbene intermediate. With compound **3**, we hypothesized that a potential hydrogen bonding interaction between the cyclic oxonium and the carbamate carbonyl was inhibiting proton transfer. Protodemetalation of intermediate **8** therefore intervenes, leading to competitve formation of isoxazoline **5**.[19]

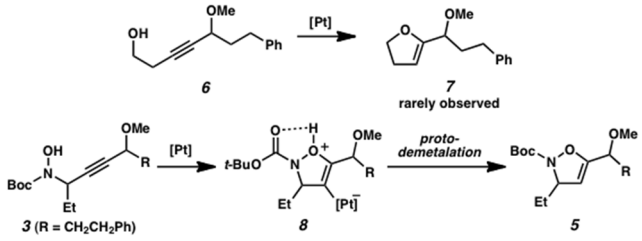
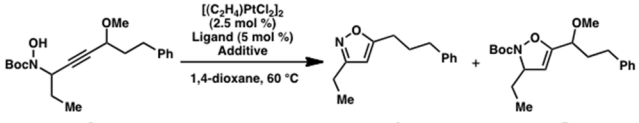


Figure 2. Isoxazoline formation related to proton transfer event.

From this hypothesis, we reasoned that an acidic additive should facilitate ether ionization. Indeed, addition of AcOH to the reaction mixture provided a noticeable improvement (Table 1, entry 1). Our observation that olefin ligands could influence reactivity in the furan chemistry then prompted us to examine the addition of L-type monodentate ligands, and PPh_3 did improve the overall reaction (entry 2). A range of acids were then evaluated in the reaction, and TFA was found to be the optimal acid for cleanly affording isoxazole **4** while minimizing the isoxazoline byproduct. Bases substantially inhibited the reaction (entry 7). Phosphorus ligands were also screened. Systems utilizing alkylphosphines were prohibitively slow, likely due to the more electron rich metal center being less capable of activating the alkyne for nucleophilic attack. Triarylphosphines and phosphites were both quite effective (entries 8, 12), but $P(OPh)_3$ provided the most consistent behavior[20] and we therefore settled on that catalyst system.

Table 1. Ligand and acid effects on isoxazole formation.



entry	ligand (5 mol %)	additive (equiv)	time (h)	yield *4* (%)[a]	yield *5* (%)[a]
1	--	AcOH (10)	32	39	11
2	PPh_3	AcOH (10)	21	48	14
3	PPh_3	$(NH_4)HCO_2$ (10)	70	0	0
4	PPh_3	H_3PO_4 (10)	70	76	11
5	PPh_3	TFA (10)	17	81	1
6	PPh_3	TsOH (2)	17	0	0
7	PPh_3	Na_2CO_3 (1)	60	6	1
8	PPh_3	TFA (5)	17	96	1
9	PCy_3	TFA (5)	70	57	3
10	$P(n\text{-}Bu)_3$	TFA (5)	70	49	4
11	$P(t\text{-}Bu)_2(o\text{-biphenyl})$	TFA (5)	70	47	2
12	$P(OPh)_3$	TFA (5)	17	96	2

[a] GC yield (determined using 4,4'-bis(*t*butyl)biphenyl as internal standard).

Having established the optimized cyclization conditions, a number of isoxazoles were synthesized using this method (Figure 3). An array of 3,5-disubstituted isoxazoles can be accessed from their corresponding *N*-hydroxycarbamates[21] in good overall yield. Particularly noteworthy is isoxazole **13**, which features a separate Boc carbamate. The stability of this functional group highlights the process of how the Boc group on the isoxazole nitrogen is removed; delocalization of the nitrogen lone pair in a putative enamide intermediate likely facilitates selective ionization and cleavage.[22]

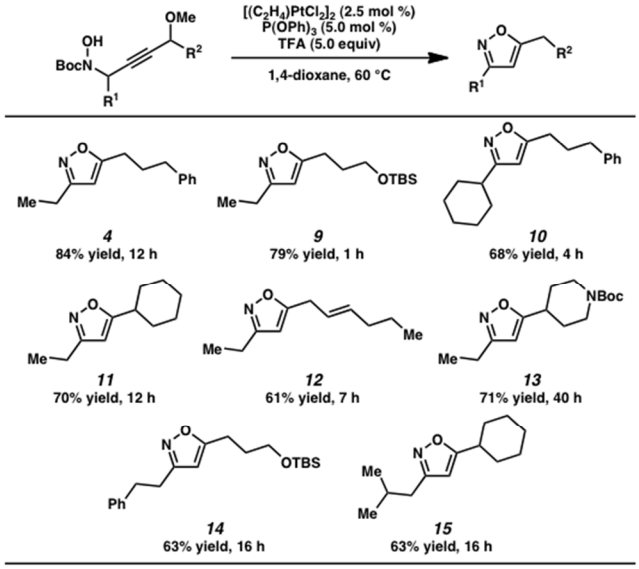


Figure 3. Pt-catalyzed synthesis of isoxazoles from propargylic *N*-hydroxycarbamates.

Given the success of the isoxazole syntheses from the propargylic *N*-hydroxy-*N*-alkoxycarbonylamines, we speculated that we could access the regioisomeric isoxazole by reversing the positions of the nitrogen and oxygen atoms. Illustrated in Figure 4, a nitrogen-based nucleophile would attack the activated alkyne, and leaving group extrusion followed by a 1,2-shift would lead to an analogous enamide intermediate. Again, cleavage of the carbamate and aromatization would afford the isoxazole.

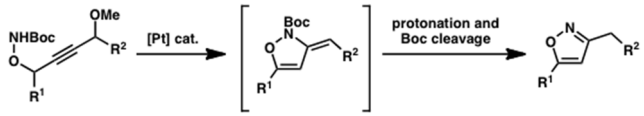
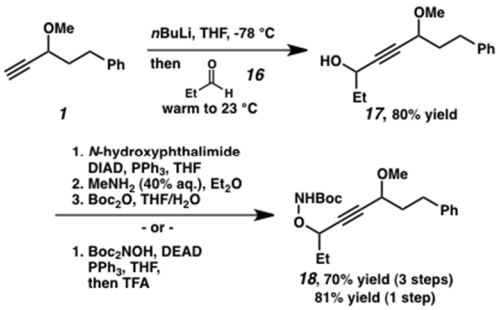


Figure 4. Regioisomeric isoxazole formation using nitrogen-based nucleophiles.

The syntheses of these substrates can be accomplished by two straightforward methods. Addition of alkyne **1** into propionaldehyde affords propargylic alcohol **17** (Scheme 3). From this compound, a Mitsunobu reaction using *N*-hydroxyphthalimide[23] followed by aminolysis and Boc installation affords the carbamoyl ether (**18**). Alternatively, a one-pot Mitsunobu reaction using Boc_2NOH and cleavage of one of the two butoxycarbonyl groups afforded the identical substrate in comparable yield.



Scheme 3

We were delighted to discover that under the aforementioned catalytic platinum conditions the amino ethers cyclized to form the regioisomeric isoxazoles (Figure 5). A number of these isoxazole products (**19**-**24**) are the direct complements of the heterocycles formed from the *N*-hydroxycarbamates (Figure 4, **4**, **9**-**13**), each pair originating from the same propargylic ether starting material. These reactions proceeded more efficiently than the ones utilizing the oxygen-nucleophile counterparts; the yields were uniformly higher and the reaction times were shorter.[24] As before, a variety of 3,5-disubstituted isoxazoles were accessed in generally excellent yields, also showing notable functional group compatibility, tolerating carbamates (**24**), carboxylic acids (**30**), thioethers (**31**), and sulfoxides (**32**).

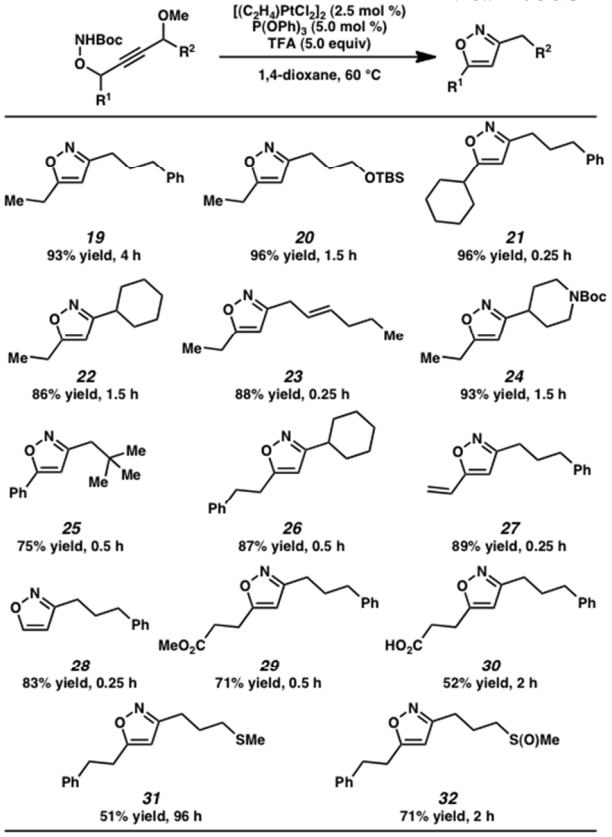
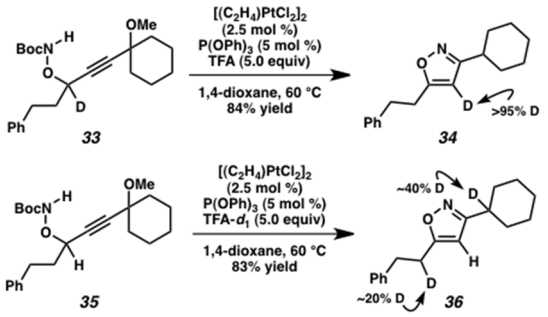


Figure 5. Pt-catalyzed synthesis of isoxazoles from propargylic *N*-Boc amino ethers.

Toward further understanding the mechanism of this process, we started by considering our work in furan formation (see above, Scheme 1). Based on our observations in that chemistry, we proposed that a formal [1,2] hydrogen shift onto the platinum carbene (**B**) was a pivotal step, leading to an enol that subsequently isomerized to the aromatic furan. We believed that a related mechanistic pathway was operative here, where an enol ether or enamide intermediate protonates at the exocyclic position, and loss of the Boc group generates the isoxazole product. Deuterium labeling studies proved consistent with this mechanistic proposal (Scheme 4). Compound **33**, bearing a deuterium at the propargylic site that is presumably involved in the [1,2]-shift, was subjected to the standard catalytic cyclization conditions with protic TFA. Indeed, deuterium-labeled isoxazole **34** was produced with essentially complete incorporation. Conversely, when the analogous protic substrate (**35**) was subjected to the same conditions using TFA-d_1, deuterium atoms were incorporated at two different positions in measurable amounts.[25]



Scheme 4

Figure 6 illustrates our rationale for the production of isoxazole **36**. Incorporation at the methine position is readily explained via the intermediacy of enamine **37**; protonation by TFA-d_1 and Boc cleavage produces the isoxazole.[26] Although the secondary incorporation at the homobenzylic position appears unusual, it can be rationalized by a stepwise migratory process leading to enamine **43**. The hydride migrates to the electron-deficient carbene of intermediate **40**, affording oxocarbenium **41**. If this species is sufficiently long lived prior to demetalation, deuterium can exchange α to the oxocarbenium, ultimately producing deuterated isoxazole **44**.

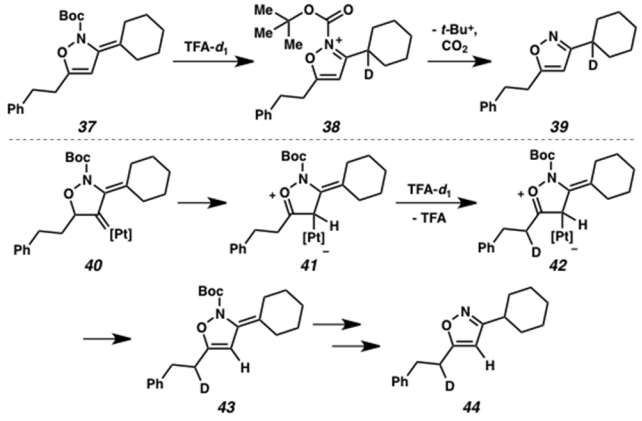
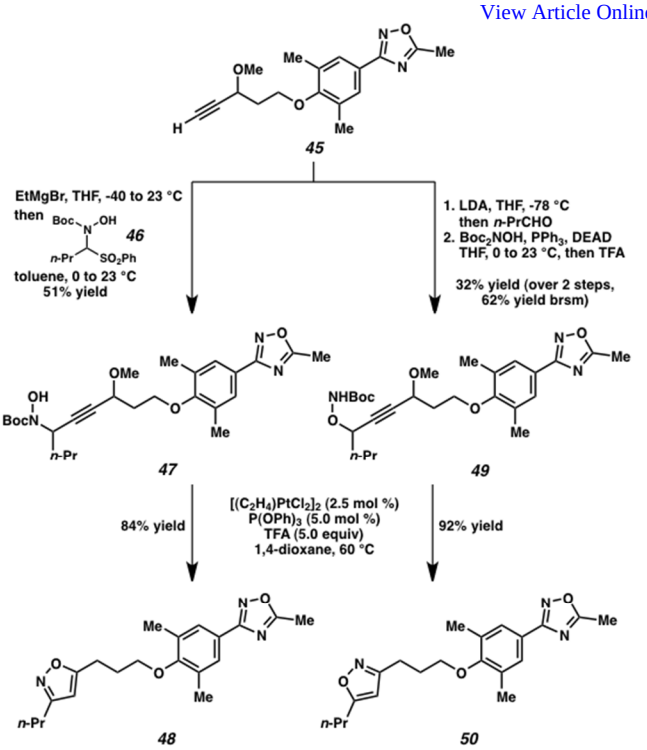


Figure 6. Mechanistic rationale for deuterium incorporation in **36**.

We believe the development of this methodology for complementary isoxazole syntheses will have particularly useful implications in medicinal chemistry. A demonstration of this utility is depicted in Scheme 7. Isoxazole **48** has been previously evaluated for its promising antirhinovirus activity.[27] One key facet demonstrated in studies on this family of compounds was that the positioning of the nitrogen and oxygen atoms in the isoxazole heterocycle was highly relevant to its activity.[28,29] Propargylic ether **45** can serve as a direct and convenient branchpoint for the formation of regioisomeric isoxazoles, simply by using the appropriate nitrone or aldehyde electrophiles. Both isoxazoles are easily formed, with the Pt-catalyzed cyclizations proceeding in excellent yields. One could also envision simple molecular diversification via the introduction of alternative nitrones and aldehydes. We anticipate the convenience of this heterocycle synthesis will render this a highly enabling tool for medicinal chemists.



Scheme 7

To summarize, we have developed the platinum-catalyzed cyclizations of both propargylic *N*-hydroxylamines and propargylic aminoethers to form regioisomeric isoxazoles. Initial reactivity insights allowed the formulation of new catalytic condtions, and the transformations proceed in good to excellent yields overall. Importantly, both regioisomeric isoxazoles can be readily accessed using the same propargylic ether starting material. By simply selecting the appropriate electrophile in the acetylide addition (either nitrone or aldehyde), the connectivity of the downstream isoxazole can be established. This accessibility is highlighted in the direct syntheses of medicinally-relevant isoxazoles **48** and **50**. Deuterium labeling experiments further support our mechanistic hypothesis of a unique platinum carbene intermediate and offer insights toward its reactivity. The continued exploration of new transformations utilizing this method of carbene generation, as well as further developments in this area of catalysis, will be reported in due course.

Acknowledgment

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, compound characterization data, and spectra. See DOI: 10.1039/b000000x/

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The hydroalkoxylation product was observed in two cases: 1) When gold catalysts were employed, consistent with the notion that gold is less effective at electron donation to generate the carbene species in our proposed mechanism, regardless of a proton transfer event; 2) At very low temperatures (-60 °C), the hydroalkoxylation product could be observed in small quantities under platinum conditions. At slightly higher temperatures (-40 °C), the product was never observed.

Isoxazoline **5** does not convert to the corresponding isoxazole product when subjected to the reaction conditions.

With PPh_3, we observed yield variations in up to 5%. This variation did not occur with $P(OPh)_3$.

The *N*-hydroxycarbamate substrates were each synthesized from the appropriate alkyne and nitrone precursors. See the Supporting Information for experimental details.

(*a*) Susbtrates based on other *N*-alkoxycarbonyl groups, such as methyl and allyl, could also be cyclized to form the same isoxazoles. The unsubstituted (NH) hydroxylamine afforded trace product. The *t*-butoxycarbonyl group was found to be the optimal substituent for this transformation. See the Supporting Information for details. (*b*) In Wada's related oxidative iodocyclization (ref 7d), he found that an *N*-isopropyloxycarbonyl group provided the highest yields of isoxazoles.

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The higher reactivity of these substrates relative to the *N*-hydroxycarbamates could be attributed to the nature of the heteroatom nucleophile. Differential conformational preferences arising from allylic strain effects of the carbamate functional group may also play a role in the relative reactivity.

As a control, isoxazole **26** was exposed to the reaction conditions using TFA-d_1. After 24 h no deuterium incorporation was observed.

The nitrogen-bound proton accounts for a source of hydrogen atoms, and consequently incomplete incorporation of deuterium.

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For an additional medicinal chemistry study demonstrating the importance of nitrogen and oxygen positioning, see, A. D White, C. F. Purchase, II, J. A. Picard, M. K. Anderson, S. B. Mueller, T. M. A. Bocan, R. F. Bousley, K. L. Hamelehle, B. R. Krause, P. Lee, R. L. Stanfield and J. F. Reindel, *J. Med. Chem*. **1996**, *39*, 3908-3919.