Transition Metal Mediated Nitrene C-H Insertion

Reported by Grant T. Rice March 10, 2008

Introduction

Owing to the ubiquity of nitrogen containing natural products and pharmacophores intense efforts have been made in the advancement of C-N bond forming methodologies. Recently, metal mediated nitrene insertions have opened many new reliable retrons in total synthesis. Many well developed intramolecular systems for C-H amination have been elucidated while exciting new diastereoselective intermolecular methodologies have shown promising developments. Ultimately the strengths of C-H amination have been demonstrated by Du Bois and co-workers in their total synthesis of (+)-Saxitoxin.

Seminal Porphyrin Inspired Metal Nitrene C-H Insertions

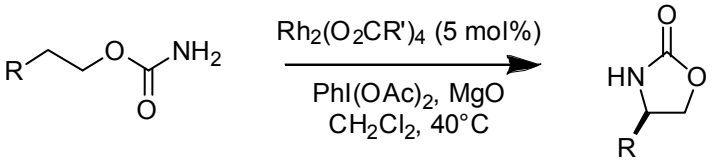
As far back as the mid 1960's the idea of nitrene formation followed by C-H activation to form carbon nitrogen bonds was being investigated.[1] It was not until 1982, however, that Breslow and co-workers were able to demonstrate the first metal mediated nitrene insertion. Using Mn(III) and Fe(III) porphyrins Breslow was able to translate what was known for P-450 oxidations into a working system for aminations.[2] Subsequently, Breslow went on to demonstrate that using $Rh_2(OAc)_4$ as a catalyst and $PhI(OAc)_2$ as an oxidant high yielding amination reactions can be exhibited.[3] In 1983 Motherwell and co-workers demonstrated that a system using iron chloride and chloramine-T formed a ferrous nitrene species that would selectively monoaminate the tertiary C-H bonds of adamantane. Similarly to Breslow, Motherwell also noted that the proposed oxenoid intermediate in P-450 oxidations was an inspiration for a metal nitrenoid species.[4] In 1988 Mansuy and co-workers made another great advancement in this field by displaying chemoselectivity for allylic aminations in the reaction of a manganese porphyrin nitrenoid with a simple alkene.[5] Although the method was not synthetically useful it demonstrated the possibility for a highly chemoselective C-H amination reaction.

Current Metal Nitrene C-H Insertion Methodologies

Stemming from the pioneering breakthroughs by the aforementioned groups, the field of nitrene insertions has matured into synthetically useful and reliable methodologies. By recognizing the strengths of the C-H insertion system developed by Breslow, Du Bois and co-workers have developed multiple methodologies using similar catalytic conditions to Breslow's examples. Circumventing the need for

excess hydrocarbon, Du Bois used a carbamate tether to affect the formation of oxazolidinones via metal

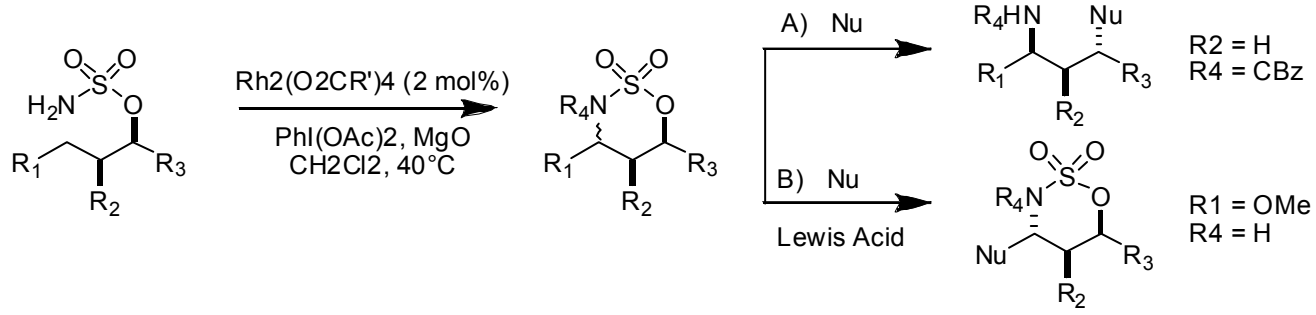
Scheme 1: Oxazolidinone Formation Via Rhodium Catalyzed C-H Amidation



nitrene insertion.[6] This tether allowed for a significant decrease in catalyst loadings, and more importantly, synthetically useful yields based upon one equivalent of starting carbamate (Scheme 1).

Du Bois has further extended this methodology by simply changing the carbamate tether to a sulfamate ester. Due to the longer S-O and S-N bonds, similar conditions to those for oxazolidinone formation result in the formation of oxathiazinanes.[7] Interestingly, conditions have been developed by Du Bois to allow for rapid derivatization. For example, the simple addition of a nucleophile to the oxathiazinane results in an S_N2 displacement of the oxygen in high yields (Scheme 2.A). By starting with a methyl ether alpha to the C-H functionalization site subsequent addition of a Lewis Acid and nucleophile to the corresponding aminal results in the in situ formation of an imine followed by a highly selective nucleophillic addition (Scheme 2.B).[8]

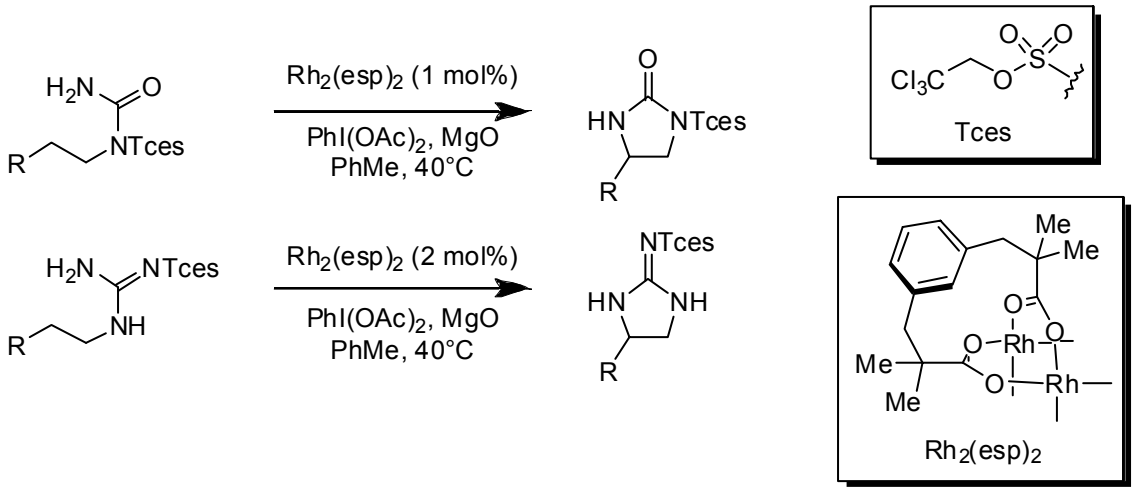
Scheme 2: Oxathiazinane Formation Followed By Nucleophilic Derivitization



Du Bois and co-workers have also developed a set of conditions for the formation of urea and guanidine derivatives.[9] Mechanistic insights including radical clock experiments and Hammett analyses into rhodium mediated nitrene insertions allowed Du Bois to develop $Rh_2(esp)_2$ which shows increased catalyst stability as well as reactivity.[10] Due to the reactivity of the urea and guanidine precursors with $PhI(OAc)_2$ the Tces protecting group was also shown to be necessary for the desired amination reactions. Using these conditions both functionalizations are able to occur with a similar substrate scope to the oxazolidinone methodology (Scheme 3).

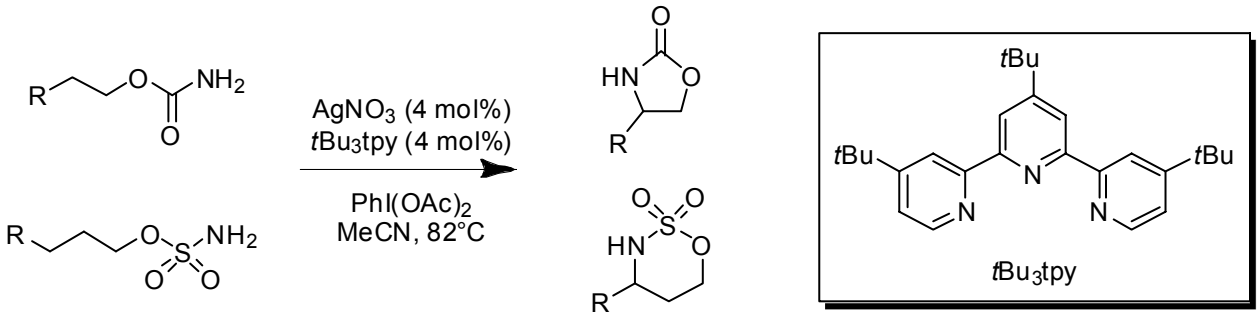
In a similar system to Du Bois' carbamate and sulfamate ester methodologies, He and co-workers have demonstrated that using very affordable silver nitrate and tBu$_3$tpy ligand as a catalyst, oxazolidinone and oxathiazinane functionalizations takes place via a silver nitrene species (Scheme 4).[11]

Scheme 3: Urea and Guanidine Formation



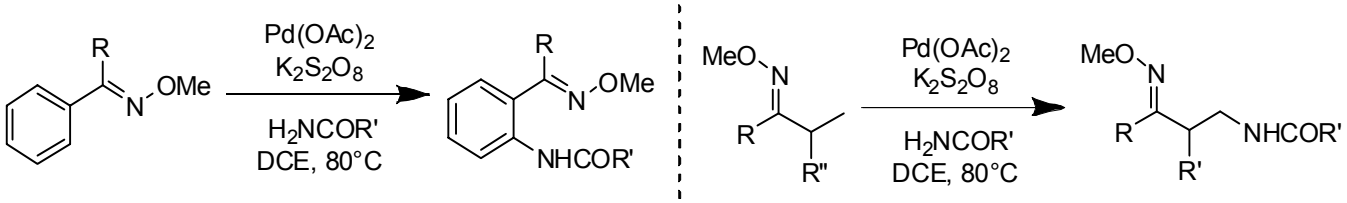
This methodology displays similar substrate scope and yields to Du Bois' methodology, however, this system has yet to be as fully developed.

Scheme 4: Silver Nitrene C-H Amidation



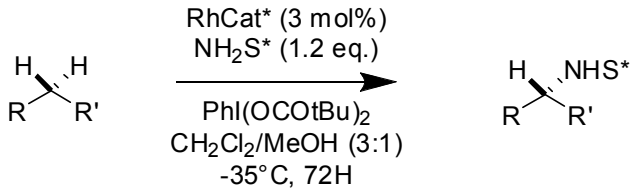
Using a much different approach, Che and co-workers have developed a "palladium catalyzed cascade C-H activation/Nitrene insertion".[12] This methodology allows for the functionalization of unactivated aromatic C-H bonds as well as primary aliphatic C-H bonds in high yields (Scheme 5). Although the scope of this methodology is currently limited to simple aryl substrates and rigid aliphatic substrates, similar methodologies have previously shown poor reactivities towards metal mediated nitrene functionalization on 1° and aromatic C-H bonds.

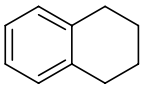
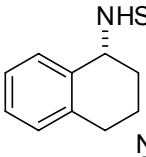
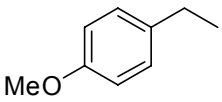
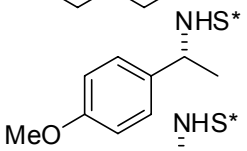
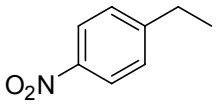
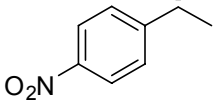
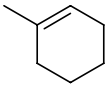
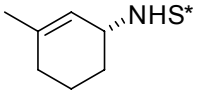
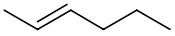
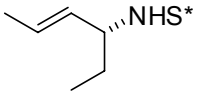
Scheme 5: Palladium Catalyzed Cascade C-H Activation/Nitrene Insertion

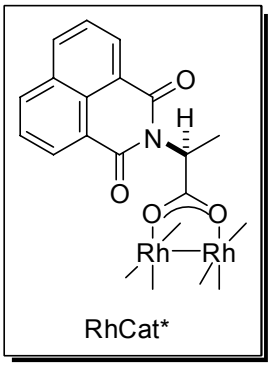


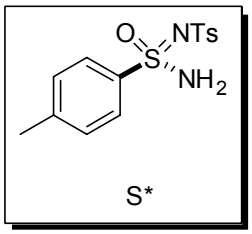
Recently Dauban and co-workers have demonstrated an intermolecular diastereoselective nitrene insertion *en route* to enantioenriched aliphatic amines.[13] Using a chiral rhodium catalyst as well as a chiral sulfonimidamide, Dauban was able to effect benzylic functionalization in high yields and diastereomeric ratios. Furthermore, using simple alkene substrates, Dauban has demonstrated allylic amination in high yields with previously low dr's (Table 1).

Table 1: Diastereoselective C-H Amidation Via Rhodium Nitrene



Entry	Substrate	Product	Yield	dr
1			86	99:1
2			92	99:1
3			82	93.5:6.5
4			90	95:5
5			66	80:20



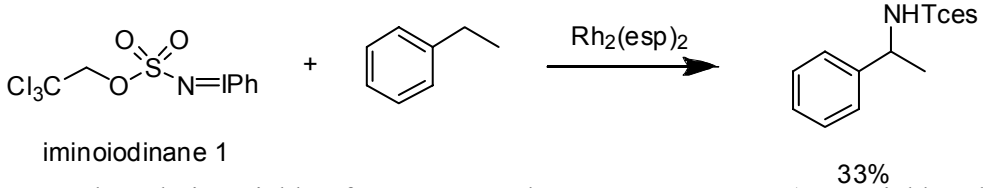


Mechanistic Insights Into Intermolecular Nitrene Insertions

Mechanistically, asymmetric intermolecular nitrene methodology poses many interesting questions. Du Bois and co-workers have performed extensive mechanistic studies detailing the origin of

reactivity as well as the possibility for asymmetric induction on a system similar to Dauban and co-workers.[14] Based on previous studies, Du Bois has produced convincing data that suggests the intramolecular system is going through a concerted asynchronous transition state.[15] It is hypothesized that for an intermolecular system to exhibit enantioselectivity it would also be necessary to go through a similar transition state. Concurrently to Dauban and co-workers, Du Bois has developed an intermolecular C-H amination reaction. It is postulated that the first step in this mechanism is the formation of an iminoiodinane species. Experiments show that as a preformed species iminoiodinane 1 is a competent species for functionalization (Scheme 6).

Scheme 6: Iminoiodinane as a Reactive Species

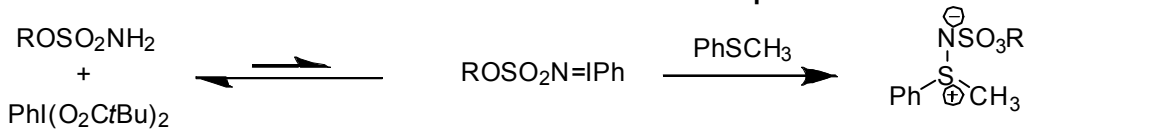


iminoiodinane 1

33%

Based upon the relative yields of $TcesNH_2$ and $tBuCH_2OSO_2NH_2$ (72% yield and 47% yield on model systems respectively), it is believed that iminoiodinane formation is an equilibrium process that favors the reactants. It is known that PhSMe reacts with iminoiodinanes to form sulfilimines. To test for *in situ* formation of iminoiodinane species PhSMe was added to both iterations of iminoiodinane precursors resulting in the corresponding sulfilimines (Scheme 7).

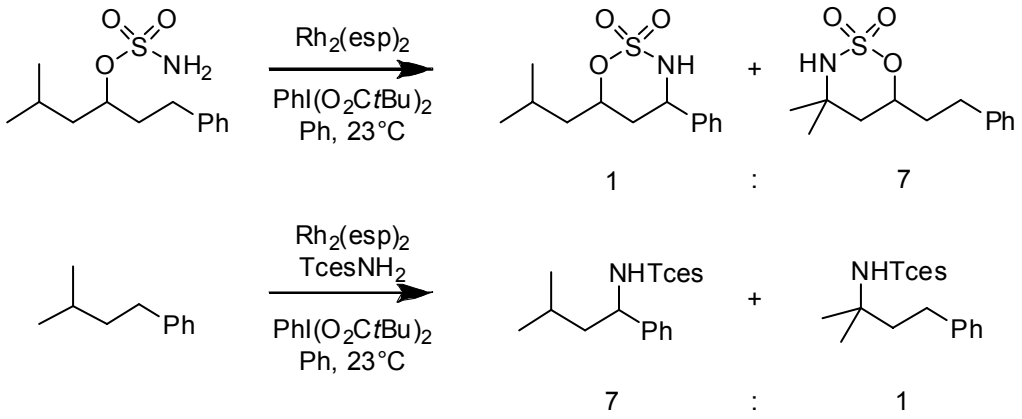
Scheme 7: Sulfilimine Formation as Evidence for Iminoiodinane Equilibrium



R = CH_2CCl_3 - 27% yield
R = CH_2tBu - 6% yield

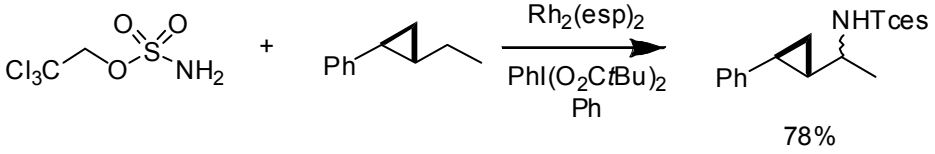
At this point, competition studies were conducted yielding interesting results. When compared to the intramolecular system the intermolecular system exhibited reversed selectivities, preferring benzylic C-H insertion over 3° C-H insertion (Scheme 8).

Scheme 8: Relative Selectivities for Intra and Intermolecular Amidation Reactions



This result suggested that similar mechanistic studies for the intermolecular system may reveal new insights into the differences between inter and intramolecular functionalization. To differentiate between a C-H abstraction, radical rebound mechanism a radical trap reaction was conducted resulting in no product formation indicative of a radical pathway (Scheme 9).

Scheme 9: Test for Evidence of Radical Mediated Mechanism

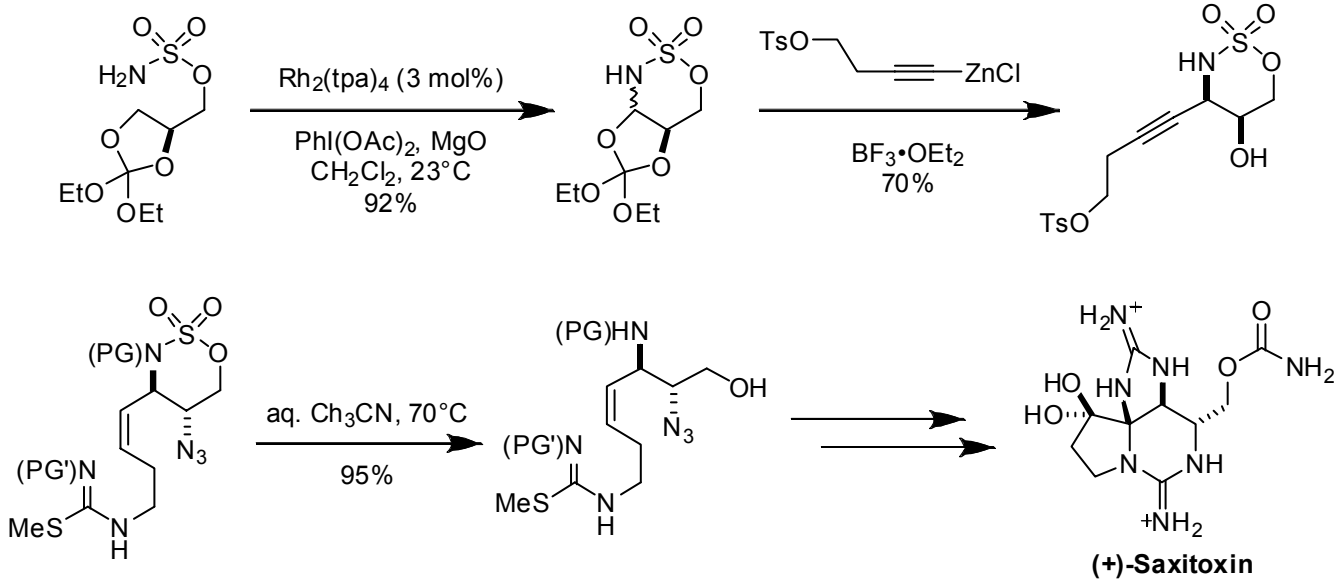


A Hammett analysis of 4-substituted ethyl benzene gave a ρ value of -0.73 for the functionalization. This positive charge build-up in the transition state indicates that this reaction is indeed going through an asynchronous process. Furthermore, stabilization of the transition state via electron donating groups is consistent with the trends exhibited by both the intra and intermolecular systems. Upon combining these mechanistic data, it seems likely that although the inter and intramolecular systems have different selectivities, the intermolecular system still proceeds through a concerted asynchronous transition state. Du Bois postulates that the selectivity difference between the intra and intermolecular aminations is due in part to a kinetic steric barrier, however a full explanation has not been elucidated at this time.

Total Synthesis of (+)-Saxitoxin

In recent years Du Bois and co-workers have displayed the great strengths in C-H amination via metal nitrenes through various synthetic endeavors. The total synthesis of (+)-Saxitoxin, a poison found

Scheme 10: Rh Nitrene Functionalization, Lewis Acid Promoted Nuclephillic Addition and Sulfamate Ester Deprotection En Route to (+)-Saxitoxin



in red tide, by the Du Bois group is a stunning example of the synthetic utility of their groups developed nitrene methodology. Although two very elegant racemic syntheses of the molecule had been demonstrated in 1976 and 1984 by Kishi and co-workers (17 steps, 0.24% yield) and Jacobi and co-workers (14 steps, 0.51% yield) respectively, an asymmetric synthesis of this highly complex natural product had yet to be established.[16, 17] By not only developing methodology for oxathiazinane formation, but also developing a highly diastereoselective Lewis acid promoted nucleophillic addition and a highly efficient deprotection method the total synthesis became easily accessible.[18] Ultimately, Du Bois was able to synthesize (+)-Saxitoxin in 19 steps and 1.6% overall yield (Scheme 10).

Conclusion

Metal mediated nitrene chemistry is certainly valuable to organic synthesis. The power of intramolecular C-H amination is displayed quite elegantly in the total synthesis of (+)-Saxitoxin by Du Bois and co-workers. Currently, methodological efforts are being focused on asymmetric intermolecular C-H amination reactions. Dauban and co-workers have demonstrated that simple aliphatic molecules can be enantioenriched through diastereoselective aminations. Although the intermolecular variants of C-H amination are not as well developed as their intramolecular counterparts, the field remains promising for eventual success.

References

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