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REVIEW

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Rhodium-Catalyzed C−H Amination. An Enabling Method for Chemical Synthesis

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ABSTRACT: Reaction methods for selective C−H amination are finding ever-increasing utility for the preparation of nitrogen-derived fine chemicals. This brief account highlights the remarkable versatility of dirhodium-based catalysts for promoting oxidation of aliphatic C−H centers in both intra- and intermolecular reaction processes.

1. INTRODUCTION

In the past decade, a wave of new reaction technologies has been unveiled that make possible the selective modification of aliphatic and arene C−H bonds.[1,2] The availability of such methods begets an addendum to the *Logic of Chemical Synthesis*, as the C−H bond may now be considered a synthon for other functional groups.[3] Our lab has been engaged in this problem area for some time now, focusing primarily on the development of selective reactions for the oxidation of aliphatic C−H bonds to generate alcohol and amine products.[4] As amines and amine derivatives are ubiquitous in designed molecules and natural products, the problem of C−H amination has large application potential and has been a particularly fruitful area of research (Figure 1). This highlight provides an overview of our studies to elucidate both intra- and intermolecular processes for C−H bond amination. We are by no means the only research group interested in this problem area, and while this review is meant to be a personal account, acknowledgement to others' work will be made where relevant.[5] The general subject of C−H to C−N bond conversion has been reviewed in a number of comprehensive treatises to which interested readers are referred.[6]

2. INITIAL DISCOVERIES

The literature is replete with chemical oxidants that have the thermodynamic capacity to react with aliphatic C−H bonds of all types. For example, the enthalpic energy for the reaction between a simple hydrocarbon such as cyclohexane and cyclohexylazide to generate dicyclohexylamine and dinitrogen is estimated to be ≤−40 kcal/mol.[7] Despite such a favorable thermodynamic driving force, this transformation does not occur at any measurable rate under normal reaction conditions. Accordingly, the problem of C−H oxidation is, in its essence, a problem of kinetics, underscored by the challenge to identify catalyst systems that reduce the activation barrier for the C−H oxidation event while maintaining some ability to discriminate between C−H bonds in different steric and electronic environments. The countless examples of selective diazoalkane (i.e., carbenoid) C−H insertion processes with dimeric rhodium(II) tetracarboxylate and tetraamidate complexes are exceptional in this regard.[8] As originally noted by Breslow and, later, elaborated by Müller, these same catalysts can perform analogous C−H amination

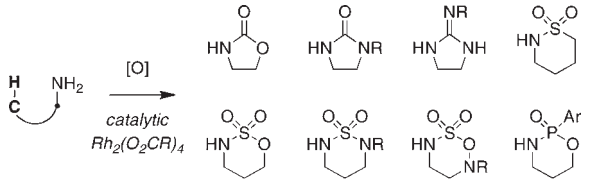

Figure 1. Heterocycle synthesis through intramolecular C−H amination.

reactions using hypervalent iminoiodinanes as nitrenoid precursors (Figure 2).[9,10] These collective works marked the starting point for our investigations.

A select few hypervalent iminoiodinane reagents, the most notable of which is TsN═IPh, have enjoyed great utility as electrophilic N-atom donors, particularly for the generation of aziridine products from alkenes. Preparation of iminoiodinanes, however, has been limited to a small subset of sulfonamide derivatives, thus restricting the ability to expand further the use of this class of iodine(III) oxidants.[11] Both Che and we realized that in situ preparation of an iminoiodinane species might be possible by simply mixing an amide starting material with $PhI(OAc)_2$, PhI═O, or a related iodine(III) reagent.[12,13] This idea has proven successful and has enabled the application of carbamate, urea, guanidine, alkylsulfonamide, sulfamate, sulfamide, and phosphoramide starting materials in electrophilic N-atom transfer reactions (Figure 1). To our knowledge, the equivalent iminoiodinanes have not been described for any of these materials, save for a single trichloroethylsulfamate derivative.

Initial discoveries from our lab highlighted the value of carbamate and sulfamate ester derivatives as substrates for intramolecular C−H amination reactions (Figure 3).[14] Commercial $Rh_2(OAc)_4$ or $Rh_2(oct)_4$ proved generally effective for many of these reactions, and that remains true today (catalyst loading typically range from 2−5 mol %, TONs ∼20−50). Reactions of carbamates occasionally call for application of the Ikegami/Hashimoto $Rh_2(O_2CCPh_3)_4$, a complex easily generated from $Rh_2(OAc)_4$.[15] Despite efforts to optimize further the carbamate insertion reaction, this substrate type has been the most limited. Reactions of secondary alcohol-derived carbamates

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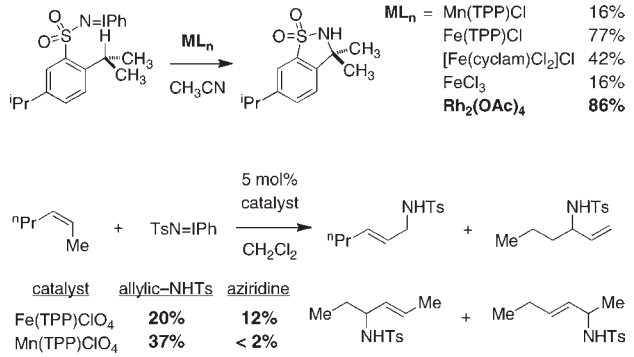

Figure 2. Early examples of C−H amination using iminoiodinane reagents.

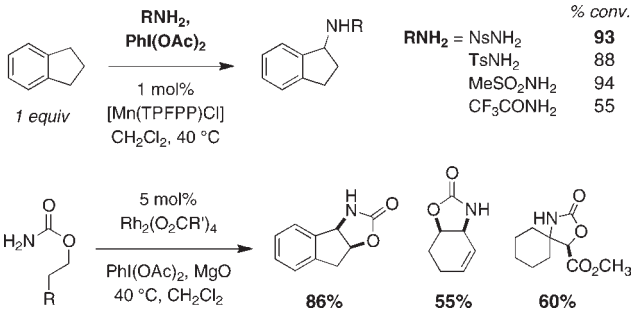

Figure 3. Nitrenoid C−H insertion through in situ iodoimine formation.

generally yield ketone products rather than the desired oxazolidinones.[14,16] Oxidation of tertiary, benzylic, and allylic C−H bonds can afford oxazolidinone products in modest to high yields; by contrast, amination of secondary methylene centers has always been difficult. A report by He describes the application of a Ag(I)·terpyridine catalyst (thought to be dimeric) for intramolecular carbamate C−H insertion reactions.[17] The performance of this catalyst system is as good as, and in some cases exceeds, that of any dimeric rhodium catalyst tested in our hands.

Current limitations of the carbamate process notwithstanding, a number of examples demonstrate the utility of carbamate activation and intramolecular C−H insertion for oxazolidinone synthesis. Oxidation of stereogenic tertiary C−H centers occurs with complete retention of stereochemistry (as measured by GC), thus making accessible optically pure tetrasubstituted amine derivatives. Reactions are generally tolerant of common functional groups (acetals, silyl ethers, esters, secondary and tertiary amides) and oxazolidinone formation is strongly favored over the larger six-membered ring. Indeed, we have only noted the formation of larger heterocyclic ring products in one or two rare instances.

Cyclization reactions with sulfamate esters are nicely complementary to those of carbamate esters, the former class of substrates showing a strong predilection towards the six-membered ring [1,2,3]-oxathiazinane-2,2-dioxide (Figure 4).[18] These cyclic sulfamate heterocycles have added value as electrophilic azetidine equivalents and can be made to react with a number of common nucleophiles to generate 1,3-difunctionalized amine derivatives.[19]

3. METHOD DEVELOPMENT

We have found sulfamate esters to be optimal substrates for both intra- and intermolecular (vide infra) C−H amination

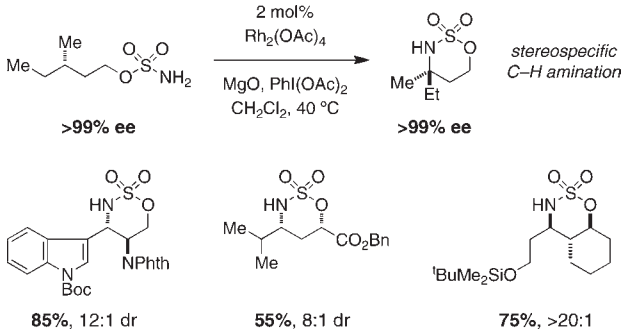

Figure 4. Stereospecific and stereoselective C−H amination with sulfamate ester substrates.

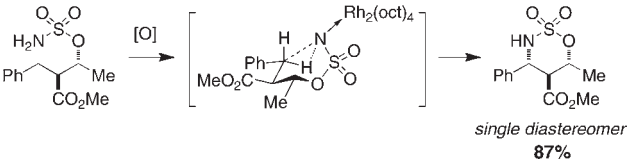

Figure 5. Diastereoselective Rh-catalyzed C−H insertion through a putative chairlike transition structure.

reactions.[18] Most of our mechanistic insights have come from studies with this family of reagents, as will be highlighted in the subsequent section. The strong bias for six-membered ring formation can sometimes be overridden by appropriate substrate design to form both five- and seven-membered ring products, although in competition, the larger seven-membered ring is generally preferred. A report by Che indicates that a Ru(II)-porphyrin catalyst will engage phenethyl alcohol-derived sulfamates to give the five-membered heterocycles in modest to high yields.[20] In our hands, dirhodium catalysts have typically underperformed with these same phenylethyl alcohol substrates. Six- and, in some cases, seven-membered ring formation can be highly diastereoselective using either chiral secondary alcohol- or branched primary alcohol-derived substrates. A transition-state model that has proven highly predictive for these diastereoselective transformations posits a chairlike arrangement in the stereochemical-defining C−H insertion event (Figure 5).[21]

Sulfamate esters and alkylsulfonamides have been examined as substrates in reactions with optically active Rh, Ru, and Cu catalysts for enantioselective C−H amination reactions. Examples of intermolecular C−H amination with simple hydrocarbons such as indane and tetralin are many and are reported to give high enantiomeric product ratios using catalysts derived from chiral α-amino acids.[22] It is worth noting here the impressive achievements of Dauban and Dodd, who have described an outstanding process for diastereoselective intermolecular C−H amination of benzylic hydrocarbons (Figure 6).[23] The combination of an optically active dirhodium tetracarboxylate catalyst and a chiral sulfonimidamide nitrogen source efficiently produces benzylic and allylic amination products with exceptional levels of diastereoinduction.

Recent reports describe, for the first time, asymmetric intramolecular oxidations with 3-arylpropanol sulfamates. Such transformations are exacted using a Ru(II)-pybox precatalyst or a tetralactamate-based rhodium dimer (Figure 7).[24,25] While the substrate scope is not extensive with either of these catalyst systems, product enantiomeric excesses can exceed 90%.

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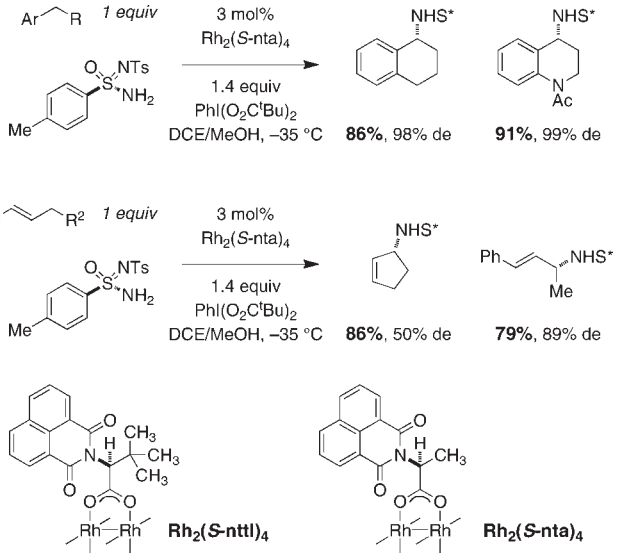

Figure 6. Highly selective intermolecular C−H amination reactions, as described by Dauban and Dodd; DCE = 1,2-dichloroethane.

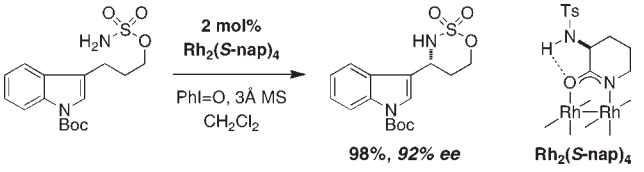

Figure 7. Chiral tetra-lactamate dirhodium catalyst for enantioselective C−H amination with arylpropyl-derived sulfamates.

The advent of a strapped carboxylate dirhodium catalyst, $Rh_2(esp)_2$, marks an important advance for C−H amination chemistry.[26] This particular catalyst is unmatched in performance by other, more common tetracarboxylate systems (i.e., $Rh_2(oct)_4$, $Rh_2(O_2CCPh_3)_4$). Intramolecular sulfamate ester insertion reactions can be effected in high yield with catalyst loadings as low as 0.1 mol % (Figure 8). In addition, C−H amination reactions with sulfamide (Figure 9), urea, and guanidine substrates are efficiently promoted using $Rh_2(esp)_2$.[27,28] Other dirhodium complexes markedly under-perform with these types of starting materials.

Extensive mechanistic studies have been conducted to determine the factors that influence catalyst stability and turnover numbers in sulfamate C−H amination reactions.[29] It appears that $Rh_2(esp)_2$ does not suffer, in the way that other dirhodium catalysts do, from rapid carboxylate ligand exchange under the reaction conditions. Nuclear magnetic resonance experiments with ^{13}C-labeled $Rh_2(OAc)_4$ have shown that [^{13}C]AcOH is produced within 60 s of initiating an amination reaction. Control experiments indicate that the hypervalent iodine oxidant, $PhI(OAc)_2$, reacts with $Rh_2(OAc)_4$ to induce carboxylate exchange; the analogous reaction is not observed with $Rh_2(esp)_2$.[30] We speculate that carboxylate metathesis somehow renders the catalyst susceptible to oxidative decomposition through a pathway(s) that is still undetermined at this time.

We have gained additional insight into the differential performance of $Rh_2(esp)_4$ by following changes in the reaction solution color and by identifying a one-electron-oxidized form of the

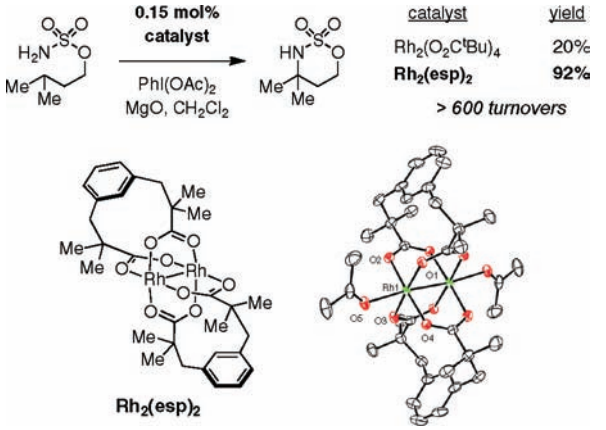

Figure 8. Optimal catalyst performance with a strapped carboxylate ligand design.

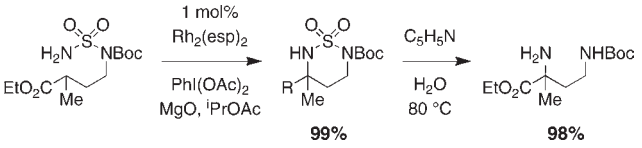

Figure 9. $Rh_2(esp)_2$-catalyzed intramolecular C−H amination to prepare 1,3-diamines.

catalyst, $[Rh_2(esp)_2]^+$.[30] Generation of this bright-red species appears to be correlated with the ability of the substrate to rapidly intercept the putative nitrenoid oxidant. That is to say, if the nitrenoid does not react quickly with the substrate C−H bond, the mixed-valent $[Rh_2(esp)_2]^+$ is formed. Fortuitously, certain carboxylic acids, including $^tBuCO_2H$—the byproduct of using $PhI(O_2C^tBu)_2$ as a terminal oxidant—are capable of reducing $[Rh_2(esp)_2]^+$ back to the neutral, bright-green Rh(II)/(II) dimer. We believe that a principal reason for the success of $Rh_2(esp)_2$ in amination reactions is the stability of its one-electron-oxidized form. Other tetracarboxylate rhodium dimers appear to quickly decompose when oxidized to the Rh(II)/(III) level, as evidenced by the fast bleaching of the solution color to a pale yellow. Under the reaction conditions, the stability of $[Rh_2(esp)_2]^+$ is such that it can re-enter the catalytic cycle as opposed to simply decomposing to inactive Rh(III) species. We have found that the addition of different carboxylic additives to the reaction medium can improve overall turnover numbers and product yields, a result that we ascribe to the ability of certain carboxylic acids to reduce rapidly the Rh(II)/(III) dimer.[30,31]

Catalyst development and mechanistic studies have enabled us to advance an effective method for *inter*molecular C−H amination (Figure 10).[32] This process utilizes $Rh_2(esp)_2$, $PhI(O_2C^tBu)_2$ as oxidant, and $Cl_3CCH_2OSO_2NH_2$ ($TcesNH_2$) as the nitrogen source. Slow addition of oxidant to a solution of catalyst, oxidant, and *one equivalent* of substrate can result in moderate to high isolated yields of benzylic amine products. In general, benzylic hydrocarbons display optimal performance as substrates for this reaction. This finding is somewhat surprising, given earlier mechanistic data that show tertiary C−H bonds to be slightly more reactive (~2−3 times) than benzylic C−H centers.[18,32a] Investigations are ongoing to determine the origin of these reactivity/selectivity differences and to improve further this intermolecular oxidation method with the ultimate goal of

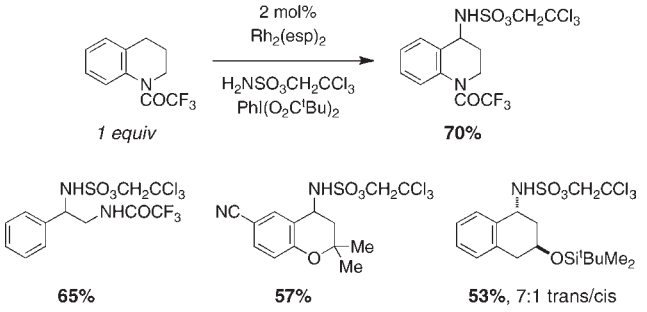

Figure 10. Intermolecular benzylic C−H amination promoted efficiently by $Rh_2(esp)_2$.

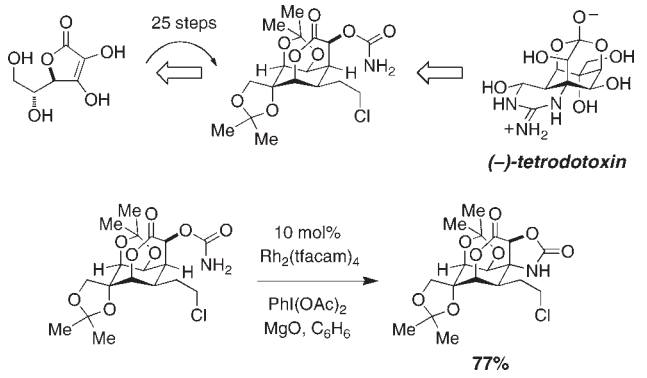

Figure 11. Carbamate C−H insertion highlighted in the synthesis of the *fugu* toxin.

identifying conditions that allow for the high-yielding, selective and stereospecific modification of tertiary C−H bonds.

4. APPLICATIONS IN SYNTHESIS

Natural products synthesis provides an optimal forum for demonstrating the potential of C−H amination technologies to transform the practice of small-molecule assembly. De novo synthesis of the toxin synonymous with the Japanese *fugu*, (−)-tetrodotoxin, is exemplary in this regard (Figure 11).[33] The application of a selective carbamate insertion reaction at step 25 in the synthetic sequence occurs in high yield and with exquisite selectivity for the bridgehead tertiary C−H bond. The compatibility of the insertion reaction with common functional groups is a general feature of this method and related reactions with other nitrogen derivatives (i.e., sulfamates, sulfonamides, sulfamides, guanidines, ureas). The application of carbamate C−H amination has also found utility in the preparation of amino acid derivatives and amino sugars.[34]

Sulfamate ester C−H insertion has been used to synthesize β-amino and diamino acids, the latter of which is embedded in the structure of the manzacidins (Figure 12).[35] Stereospecific tertiary C−H amination offers a direct method for crafting the stereogenic tetrasubstituted amine moiety common to this small family of natural products. The synthesis of such structural elements is one of the signature features of the Rh-catalyzed amination process.

Ethereal C−H bonds are competent substrates for metal-mediated C−H amination. The heightened reactivity of such centers vis-à-vis benzylic and secondary C−H bonds can be exploited for the purpose of biasing the positional selectivity of

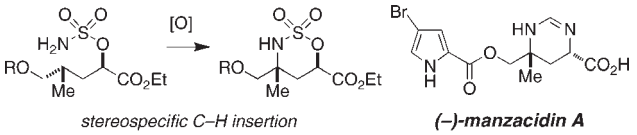

Figure 12. Sulfamate ester oxidation en route to complex amino acids.

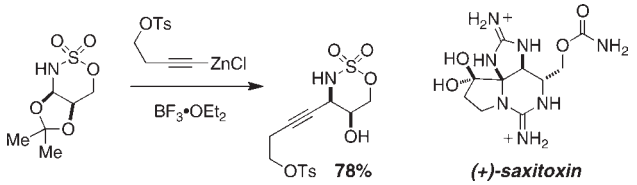

Figure 13. Unique N,O-acetal electrophiles derived from sulfamate ester C−H amination.

the oxidation event in substrates of increasing complexity.[36] The corresponding N,O-acetals have value as latent electrophiles to which a number of different nucleophiles may be added under Lewis acid catalysis. We have used this technology in a first-generation synthesis of the paralytic shellfish poison, (+)-saxitoxin (Figure 13).[37] Others have found application of the ethereal C−H bond amination for the purpose of modifying sugar derivatives.[38]

5. CONCLUSION

The past decade has witnessed a large upsurge in methods development aimed at the general problem of selective C−H functionalization. Through the invention of intramolecular reaction processes involving carbamate and sulfamate esters, and later sulfamides, sulfonamides, hydroxylamine sulfamates, guanidines, and ureas, C−H amination is beginning to take root as a mainstream technology for heterocycle and amine assembly. These discoveries have inspired collateral efforts to develop intermolecular amination reactions and to demonstrate the strategic value of such methods in complex chemical synthesis. Such advances notwithstanding, controlling chemoselectivity through reagent design in substrates possessing multiple C−H bond-types and other reactive functional groups (e.g., alkenes) remains a grand challenge for tomorrow's research.

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