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Published on Web 01/03/2007

Catalytic Intermolecular Amination of C−H Bonds: Method Development and Mechanistic Insights

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Abstract: Reaction methodology for intermolecular C−H amination of benzylic and 3° C−H bonds is described. This process uses the starting alkane as the limiting reagent, gives optically pure tetrasubstituted amines through stereospecific insertion into enantiomeric 3° centers, displays high chemoselectivity for benzylic oxidation, and enables the facile preparation of isotopically enriched ^{15}N-labeled compounds. Access to substituted amines, amino alcohols, and diamines is thereby made possible in a single transformation. Important information relevant to understanding the initial steps in the catalytic cycle, reaction chemoselectivity, the nature of the active oxidant, and pathways for catalyst inactivation has been gained through mechanistic analysis; these studies are also presented.

Introduction

The invention of efficient and selective chemical methods for C−H bond oxidation poses a formidable challenge in reaction design. While versatile protocols for both C−H amination and hydroxylation have become available in recent years, the vast majority of such processes are directed by attendant functional groups through covalent or noncovalent attachments.[1,2] The power of these methods notwithstanding, high yielding, chemoselective intermolecular oxidation of C−H centers remains a most alluring problem of great potential reward.[3] This report documents a catalytic intermolecular oxidation method made possible through the advent of $Rh_2(esp)_2$ (Figure 1).[4−6] Combining this unique dimeric Rh tetracarboxylate with an appropriate nitrogen source and an inexpensive terminal oxidant provides ready access to value-added amine derivatives. Importantly, the intermediate Rh-nitrene shows discriminate reactivity, oxidizing preferentially benzylic C−H groups over all others. Reactions are typically conducted *using limiting amounts of the starting alkane*, a second distinguishing feature of this process. Consequently, select mono- and diamines, amino alcohols, and amino esters are afforded in a single step.

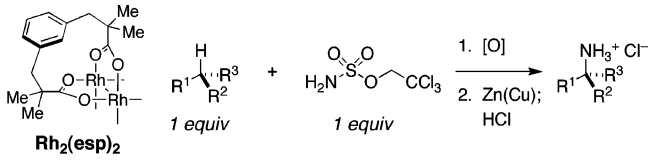


Figure 1. Amine synthesis through intermolecular C−H amination.

Results and Discussion

Reaction Optimization. Early studies to define favorable reaction conditions for promoting effective intermolecular amination of C−H bonds focused on the choice of amide nitrogen source. The availability and stability of sulfamate esters make them particularly attractive reagents for such a process.[7] In model reactions performed with 2 mol % $Rh_2(esp)_2$, 1 equiv of ethylbenzene as substrate, and an iodine(III) oxidant, sulfamate esters derived from aliphatic alcohols (Table 1, entries 1, 2) proved superior to all other sulfonamides and amides tested. In addition, we determined soon after initiating these studies that slow addition of oxidant (∼3 h) was beneficial for effecting high product yield.[8] To perform the reaction in this manner,

(1) (a) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley−VCH: Weinheim, 2005; pp 379−416. (b) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422−6425. (c) Lebel, H.; Leogane, O.; Huard, K.; Lectard, S. *Pure Appl. Chem.* **2006**, *78*, 363−375. (d) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657−669. (e) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919. (f) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586.

(2) For some recent examples, see: (a) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am Chem. Soc.* **2006**, *128*, 9032−9033. (b) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420−7424. (c) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543. (d) Wong, M.-K.; Chung, N.-W.; He, L.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 158−162. (e) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149−8150.

(3) For representative examples of intermolecular C−H amination, see: (a) Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1019−1026. (b) Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078−12079. (c) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561−9564. (d) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507−4510. (e) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233−2236. (f) Yang, J.; Weinberg, R.; Breslow, R. *Chem. Commun.* **2000**, 531−532.

(4) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378−15379.

(5) A recent report by Müller, Dauban, and Dodd demonstrates highly efficient and diastereoselective, intermolecular C−H amination reactions under $Rh_2((S)\text{-nttl})_2$ catalysis using limiting amounts of the starting hydrocarbon, see: Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641−4644.

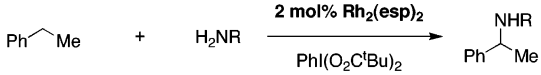
(6) While this manuscript was in submission, Reddy and Davies reported enantioselective intermolecular C−H insertion reactions using a dirhodium catalyst derived from adamantyl *S*-glycine, see: Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013−5016.

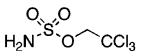
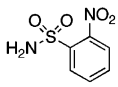
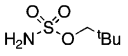
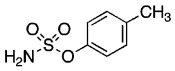
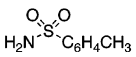
(7) Du Bois, J. *Chemtracts: Org. Chem.* **2005**, *18*, 1−13.

(8) A 1-hour dropwise addition reduced product yields by ∼15%.

10.1021/ja0650450 CCC: $37.00

Table 1. Varying the Influence of the Nitrene Precursor on C−H Insertion



Entry	H_2NR	Yield[a,b]	Entry	H_2NR	Yield[a,b]
1		72	5		29
2		47	6	$H_2NSO_2CH_3$	20
3		20	7	$H_2NSO_2CF_3$	35
4		< 5	8	H_2NCOCF_3	< 5

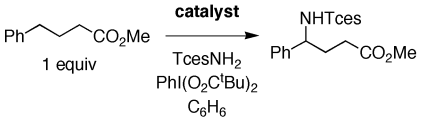
[a] $Rh_2(esp)_2 = Rh_2(\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate$)_2$. [b] Reactions performed with 1 equiv of ethylbenzene and H_2NR, 2 equiv of $PhI(O_2C^tBu)_2$, and 2 mol % catalyst in C_6H_6 at 23 °C. Oxidant was added dropwise as a C_6H_6 solution over 3 h.

$PhI(O_2C^tBu)_2$ was prepared as a surrogate to $PhI(OAc)_2$.[9] The former is now commercially available, stable to prolonged storage, and, unlike $PhI(OAc)_2$, dissolves easily in nonpolar solvents such as C_6H_6, thus enabling a timed delivery of the oxidant solution. Following this protocol, we were surprised to discover that the electron-deficient trichloroethylsulfamate ($TcesNH_2$, entry 1) afforded a significantly higher product yield than the neopentyl analogue (entry 2).[10] Although we do not, at this time, have a definitive explanation for this difference, subsequent competition studies have revealed a 5-fold enhanced rate for the insertion reaction with $TcesNH_2$ in comparison to its isosteric counterpart.

Intermolecular C−H insertion may be accelerated further by employing C_6H_6 as solvent. In comparison to CH_2Cl_2, C−H amination in C_6H_6 is markedly faster (~2.5 times).[11] Although individual rate analyses were not performed for other solvents, those tested, which include EtOAc, toluene, C_6H_5Cl, and $C_6H_5CF_3$, gave suboptimal results with respect to product yield.[12]

While $TcesNH_2$, dropwise addition of $PhI(O_2C^tBu)_2$, and C_6H_6 as solvent are all essential components of the optimized process, the choice of catalyst is of foremost consequence. Reactions executed with other tetracarboxylate Rh dimers fail to match the performance demonstrated by $Rh_2(esp)_2$ (Table 2).[13] The robustness of this complex under the reaction conditions has been ascribed to the strapped dicarboxylate design, which seemingly disfavors ligand dissociation from the dirhodium core.[4] It is interesting to note, however, that $Rh_2(S\text{-biTISP})_2$ is ineffective at promoting C−H amination in this model reaction.[14,15] This complex is assembled from two benzene-linked diproline units and is extraordinarily effective at catalyzing carbene C−H insertion and alkene cyclopropanation. The reasons for the inability of $Rh_2(S\text{-biTIPS})_2$ to effect C−H amination, particularly in view of the results with $Rh_2(esp)_2$, are unclear at this time.

Table 2. Comparison of $Rh_2(esp)_2$ to Other Rodium Catalysts



catalyst	%conv.[a]
$Rh_2(O_2C^tBu)_4$	< 5
$Rh_2(O_2CCPh_3)_4$	10
$Rh_2(NHCOCF_3)_4$	35
$Rh_2(S\text{-TCPTAD})_4$	15
$Rh_2(S\text{-biTISP})_2$	0
$Rh_2(esp)_2$	**75 (70)**[b]

[a] Product conversion estimated by integration of the ^1H NMR spectrum of the unpurified reaction mixture. [b] Isolated yield in parentheses.

Delineating the Substrate Scope. Conditions formulated for the reaction of ethylbenzene with $TcesNH_2$ enable oxidation of a number of functionalized starting materials (Table 3). Substrates possessing benzylic C−H bonds are especially effective, giving disparate amine, diamine, amino alcohol, and amino ester products in yields ranging from 50% to 74% (entries 1−8). Importantly, these yields are cited for reactions performed with limiting amounts of the alkane. The efficiency of this method using a single equivalent of starting material is noteworthy, as most other reported C−H oxidation reactions of this type rely on excess (5 or more equiv) substrate to effect high product conversion.[16]

Oxidation reactions conducted with starting hydrocarbons having two inequivalent benzylic sites (entries 5−8) show preferential reactivity at the more sterically accessible and/or more electron-rich carbon center. An example with 6-methoxytetralin (entry 5), for which steric effects do not serve as a controlling element, gives a 7:1 mixture of C1/C4 amide products.[17] The electronic bias observed in this reaction is consistent with the reactivity of an electrophilic oxidant.[7]

Substrates possessing 3° C−H centers can be functionalized to generate tetrasubstituted carbamine derivatives. Despite the higher intrinsic reactivity of 3° C−H bonds vis-à-vis benzylic centers (vide infra), product yields with 3°-derived starting materials are surprisingly reduced. Steric effects between the substrate and dirhodium catalyst likely influence the rate at which the reactive oxidant is trapped. Presumably, if the putative nitrenoid is not intercepted quickly, deleterious side reactions ensue, which result in catalyst decomposition. This rationale forms the basis for our current mechanistic model and explains why intermolecular insertion is most effective for substrates having a number of sterically accessible reactive sites. Other data bolster this conclusion, including the reaction of *cis*-1,4-

(9) Prepared from $PhI(OAc)_2$ in a single step; see Supporting Information for details. Stang, P. J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* **1988**, *110*, 3272−3278.

(10) $TcesNH_2$ was first employed for alkene aziridination reactions, see: Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672−13673.

(11) Reaction rates in C_6H_6 and CH_2Cl_2 were measured in intramolecular C−H amination experiments, the details of which will appear in a forthcoming article: Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J., manuscript in preparation.

(12) Following a recent publication by Müller, Dauban, and Dodd (see ref 5), we have conducted reactions in 3:1 CH_2Cl_2/MeOH at 23 °C and at reduced temperatures (−40 → 20 °C). Under these conditions with $Rh_2(esp)_2$ as the catalyst and $TcesNH_2$ as the nitrogen source, reaction yields are greatly diminished (<10%) from those reported in Tables 1−3.

(13) $Rh_2(S\text{-TCPTAD})_4$ is the dirhodium tetracarboxylate complex derived from *N*-tetrachlorophthalimidoyl-protected *S*-adamantylglycine. This catalyst has been recently reported to promote efficient asymmetric intermolecular C−H amination of benzylic substrates (5 equiv) using $NsNH_2$ and $PhI(OAc)_2$, see ref 6.

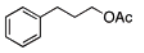
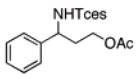
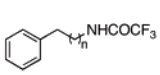
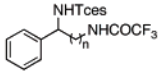
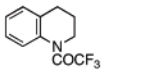
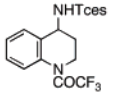
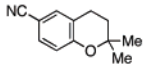
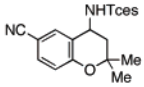
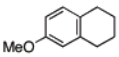
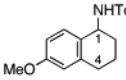
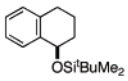
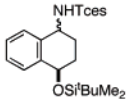
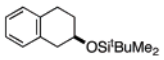
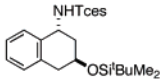
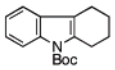
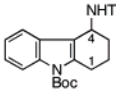
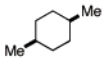
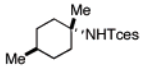
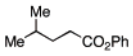
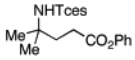
(14) $Rh_2(S\text{-biTISP})_2$ = bis-{1,3-[*N*,*N*′-di(2,4,6-triisopropylbenzenesulfonyl)-(2*S*,2′*S*),(5*R*,5′*R*)-prolinate]benzene} dirhodium. Davies has reported the design and reactivity of this bridging prolinate complex. For leading references, see: (a) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 2117−2120. (b) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2003**, *5*, 1403−1406.

(15) Rather surprisingly, the efficiency of this catalyst for promoting intramolecular C−H amination is also greatly reduced from that of $Rh_2(esp)_2$.

(16) Reports by Che and Müller, Dauban, and Dodd also describe amination reactions using limiting amounts of substrate, see refs 3e and 5, respectively.

(17) Isolable amounts (15−20%) of the C1/C4-diaminated products are also generated.

Table 3. Intermolecular C−H Amination Catalyzed by $Rh_2(esp)_2$

Entry	Substrate	Product[a]	Yield[b]
1			74
2			n = 1 65 2 70
3			70
4			57
5			51[c]
6			60[d]
7			53[e]
8			50[f]
9			46[g]
10			25 (70)[h]
11	 99.9% ee	 99.9% ee	10 (27)[h,i]
12			38 (95)[h]

[a] Tces = $SO_3CH_2CCl_3$. [b] All reactions were performed at 23 °C in C_6H_6 with 2 mol % $Rh_2(esp)_2$, 1 equiv of substrate and $H_2NSO_3CH_2CCl_3$, and 2 equiv of $PhI(O_2C^tBu)_2$. [c] 7:1 mixture of C1/C4 isomers in addition to ~15% of C1,C4-diaminated product. [d] Cis/trans = 1:1. [e] Cis/trans = 7:1. [f] 8:1 mixture of C4/C1 isomers in addition to ~20% of C1,C4-diaminated products. [g] Obtained as a single diastereomer. [h] Yield in parentheses is based on 5 equiv of substrate. [i] Optical purity was determined by HPLC.

dimethylcyclohexane, which gives a 46% yield of oxidized product (entry 9) due to the availability of two 3° C−H bonds. In addition, improved reaction performance is always noted when more than 1 equiv of substrate is used (entries 10−12). Although efficient intermolecular amination of stoichiometric quantities of 3° C−H substrates remains a primary challenge, reactions with meso or chiral agents (entries 9 and 11, respectively) demonstrate unequivocally that oxidation is stereospecific. This property is a hallmark of Rh-mediated nitrene insertion and makes optically pure tetrasubstituted amines directly available from enantiomeric starting materials.[7]

As a final note, intermolecular C−H amination presents a convenient and direct method for the preparation of ^{15}N-labeled materials. We have developed a protocol, easily conducted on a multigram scale, for the synthesis of $Cl_3CCH_2OSO_2{}^{15}NH_2$. Oxidation reactions performed with this ^{15}N source furnish isotopically enriched amine-derivatives. As with all of the Tces-amine protected compounds, cleavage of the trichloroethoxysulfonyl group is possible to give the free base after workup (Figure 2).[18]

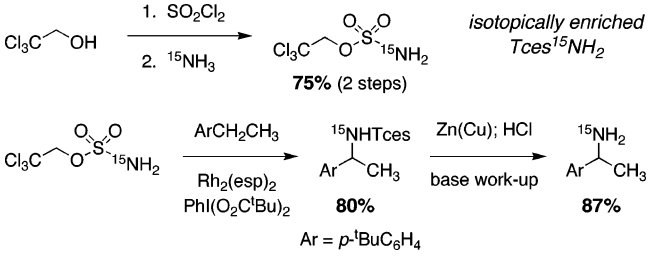
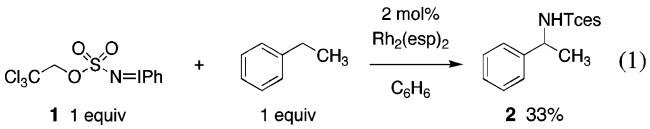


Figure 2. Direct method for preparing ^{15}N-labeled amines.

Exploring the Reaction Mechanism: The Initial Steps. Efforts to develop improved catalysts and protocols for C−H amination are tied intimately to a deeper understanding of the mechanistic details of the oxidation reaction. The intriguing reactivity differences between $TcesNH_2$ and $^tBuCH_2OSO_2NH_2$ have given clues relevant for deducing the first steps in the reaction cycle. Our original hypothesis posited that Rh-nitrene formation would occur through the intermediacy of an iminoiodinane species (i.e., $ROSO_2N{=}IPh$).[19] Control experiments have demonstrated that TcesN=IPh **1** does indeed react with 2 mol % $Rh_2(esp)_2$ and ethylbenzene to give 33% of the amine product (eq 1).[20] Although the yield for this reaction is substantially lower than that recorded in entry 1 of Table 1, this finding establishes iminoiodinane **1** as a chemically competent intermediate on the reaction cycle. Moreover, when $TcesNH_2$ and $PhI(O_2C^tBu)_2$ are combined in C_6D_6 in the absence of catalyst, a small amount (≤10%) of a new product, assigned as TcesN=IPh **1**, is generated.[21]



By contrast, no sign of iminoiodinane formation is observed (within the limits of ^1H NMR detection) when the same experiment is conducted with $^tBuCH_2OSO_2NH_2$ and oxidant. Collectively, these data suggested to us that the condensation reaction between sulfamate and oxidant is an equilibrium process that largely favors the starting materials.

To validate the reversible nature of the reaction between sulfamate and $PhI(O_2C^tBu)_2$, we sought a reagent that would react exclusively with $ROSO_2N{=}IPh$. Thioanisole, PhSMe, was identified in this context and is oxidized solely to the sulfilimine in the absence of any added catalyst. Accordingly, treatment of either $TcesNH_2$ or $^tBuCH_2OSO_2NH_2$ with oxidant and PhSMe in C_6D_6 for >100 h produced sulfilimines **3** and **4** in 85% and 65%, respectively (Figure 3). Although both reactions are slow, competition experiments and initial rate data establish that sulfilimine **3** is generated 5 times faster than **4**, thus mirroring the differences in C−H insertion reactivity for the two sulfamate

(18) See Supporting Information for details.
(19) Iminoiodinanes of the general form $RSO_2N{=}IPh$ have found extensive use as nitrene equivalents, particularly for metal-catalyzed alkene aziridination reactions, see ref 1.
(20) TcesN=IPh was prepared from $TcesNH_2$ and $PhI(OAc)_2$ using KOH, see: Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610−3619.
(21) Assignment is based on comparison of the NMR spectrum to that of authentic TcesN=IPh.

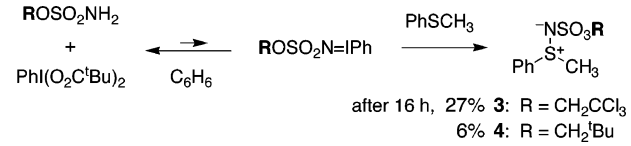


Figure 3. Sulfilimine formation gives evidence for equilibrium reaction between sulfamate and oxidant.

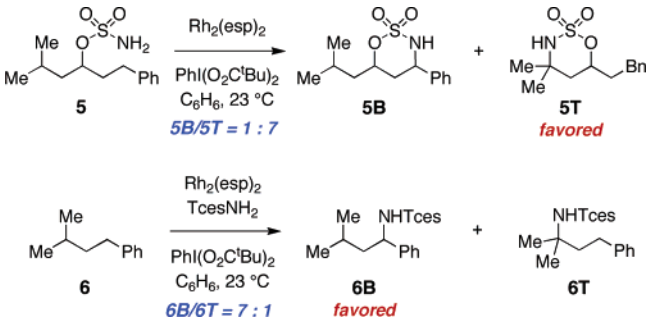


Figure 4. Disparate chemoselectivity in intra- and intermolecular reactions.

esters. While these data corroborate the proposed equilibrium reaction for $ROSO_2N{=}IPh$ formation, the stepwise details for this condensation process are still open to debate and remain subject to investigation in our lab.[22]

Exploring the Reaction Mechanism: A Rh-Nitrene Oxidant. Studies to assess the differential reactivities of disparate C−H bonds have been conducted through a series of intramolecular competition experiments.[7,11] Substrates such as **5**, when treated with $PhI(OAc)_2$ and 2 mol % $Rh_2(esp)_2$, cyclize to give a mixture of two possible products (Figure 4). The ratio of these compounds (not corrected for statistical factors) provides a relative assessment of the influence of substituents on C−H bond activity. As seen with sulfamate **5** and $Rh_2(esp)_2$, 3° C−H bond insertion is favored over benzylic oxidation.[23] Rather surprisingly, however, when an analogous, intermolecular experiment was performed, the ratio of benzylic to 3° C−H amination was reversed. One inference that is drawn from such opposing results posits that the nature of the oxidizing species is different for the two types of reaction processes. For intramolecular C−H oxidation, data from our lab strongly implicate a Rh-bound nitrene as the active oxidant, which inserts into a C−H bond through a concerted asynchronous transition state.[7] Given the striking divergence in the aforementioned results, we were compelled to conduct related mechanistic studies in the intermolecular manifold.

Although stereospecific C−H insertion on optically active 3° substrates (entries 9 and 11, Table 3) is consistent with a singlet nitrene or nitrenoid reacting through a concerted oxidation event, this result alone does not discount a C−H abstraction/fast radical rebound pathway.[24] To differentiate between these two mechanistic scenarios, C−H amination was performed with

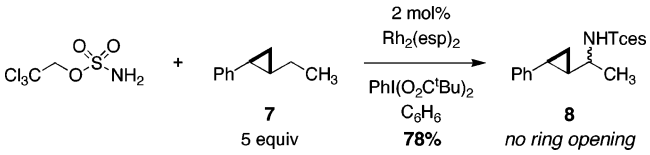


Figure 5. Cyclopropyl clock substrate shows no ring-opening.

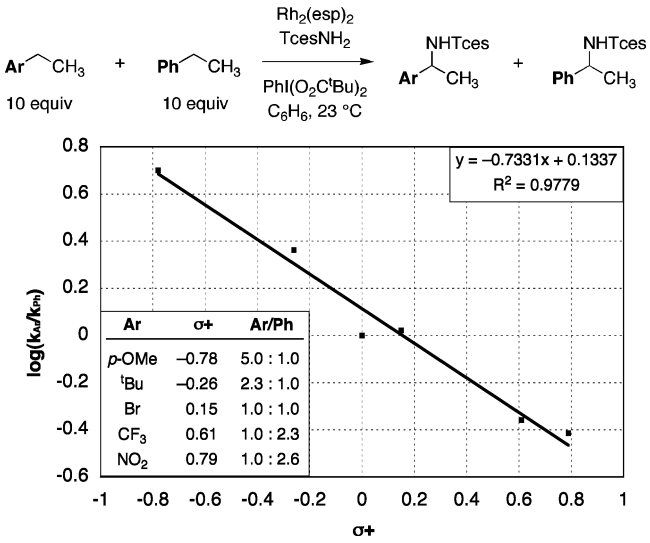


Figure 6. Hammett analysis through competition experiments with *p*-substituted ethylbenzene substrates.

a radical clock substrate **7** (Figure 5).[25] This same cyclopropane derivative has been employed to establish the concerted nature of the dioxirane-mediated C−H hydroxylation reaction.[26] In our hands, high yields (78%) of insertion product were obtained using 5 equiv of **7** with no indication of cyclopropane fragmentation having occurred. A related phenyl-substituted cyclopropane substrate was tested in the intramolecular reaction and also affords none of the ring cleavage products.[7,11] If a C−H abstraction/radical rebound mechanism was operative, the lifetime of the putative radical would have to be exceedingly short (ca. 200 fs).[26]

The electronic nature of the transition state for intermolecular C−H amination was further assessed by way of Hammett analysis. Competition experiments performed using a series of 4-substituted ethylbenzene derivatives confirmed a small, but discernible preference for oxidation of electron-rich arene substrates (Figure 6). Plotting these data as $\log(k_{Ar}/k_{Ph})$ versus σ^+ yielded a ρ-value of -0.73 ($R^2 = 0.98$).[27] Correlation with σ^+ and the small, negative ρ-value indicate that cationic charge stabilization (δ^+) in the transition state at the oxidizing carbon center is due in part to resonance contribution. The Hammett results, in combination with the outcome of the cyclopropane clock experiment, give compelling evidence for a concerted asynchronous transition state model for the Rh-mediated nitrene

(22) Currently, we speculate that $ROSO_2N{=}IPh$ formation proceeds through a dissociative (S_N1-like) mechanism involving $[PhI(O_2C^tBu)]^+$ generation. Exchange reactions conducted in C_6D_6 using equimolar amounts of $PhI(OAc)_2$ and $PhI(O_2C^tBu)_2$ give rise within minutes to $PhI(OAc)(O_2C^tBu)$. Such data are consistent with carboxylate dissociation and iodonium ion formation. Details of these experiments will be reported shortly.

(23) Our observed trends in C−H bond reactivity parallel those observed for Rh-catalyzed diazoalkane insertion reactions. For leading references, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley and Sons, Ltd.: New York, 1998. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861−2903. Also see: Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063−3070.

(24) For general discussions on mechanisms of C−H hydroxylation, see: (a) Groves, J. T. *J. Inorg. Biochem.* **2006**, *100*, 434−447. (b) Newcomb, M.; Toy, P. H. *Acc. Chem. Res.* **2000**, *33*, 449−455.

(25) The rate constant for fragmentation of the cyclopropylcarbinyl radical formed from **7** has been measured at $k = 7 \times 10^{10}$ s^{-1}, see: Choi, S.-Y.; Toy, P. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 8609−8613.

(26) Simakov, P. A.; Choi, S.-Y.; Newcomb, M. *Tetrahedron Lett.* **1998**, *39*, 8187−8190.

(27) Plotting these data versus σ_p gives an R^2 of 0.87. See Supporting Information for additional details.

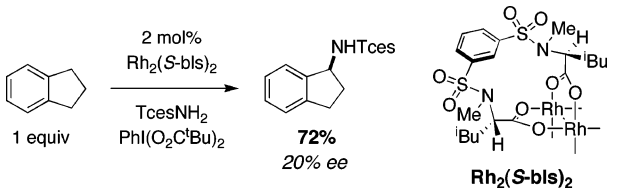


Figure 7. Chiral catalyst leads to modest enantioselectivity.

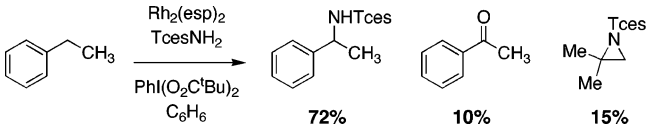


Figure 8. Side products isolated from intermolecular C−H amination.

insertion reaction.[28] Such a mechanism is in keeping with the trends in C−H bond reactivity noted for intramolecular oxidation, which follow a qualitative rate scale of 3° > α-ethereal ≥ benzylic > 2° ≫ 1°.[7] In addition, the −0.73 ρ-value is similar to the value measured in our labs for intramolecular C−H amination ($\rho = -0.55$),[11,29] and for both intra- and intermolecular Rh-catalyzed carbene insertion ($\rho = -0.78$ and -1.27, respectively).[30,31] Taken together, these data argue strongly in favor of a common nitrene-like oxidant for both intra- and intermolecular amination reactions. In addition, they intimate certain parallels between Rh-catalyzed nitrene and carbene C−H functionalization.

Reactions with optically active dinuclear catalysts offer a most convenient method for determining if the metal and nitrene oxidant are associated in the C−N bond-forming event. Following our work to develop strapped dicarboxylate complexes such as $Rh_2(esp)_2$, we have engineered and tested chiral variants of similar design.[32] Although product enantiomeric ratios have been modest to date, the observation that asymmetric Rh dimers such as Rh_2(*S*-bls)$_2$ can afford some degree of stereoinduction gives strong circumstantial support for a metal-bound nitrene (i.e., nitrenoid) as the active oxidant in our reaction (Figure 7).[33] Future efforts are aimed at developing new chiral complexes that lead to improved levels of product enantio-control. The modularity of the bis-sulfonamide ligand is well suited for this purpose.

The collective body of experimental data has led us to conclude that intra- and intermolecular C−H amination reactions are mechanistically analogous, both processes following through a Rh-nitrene intermediate that inserts directly into the C−H bond. How then does one explain the disparate trends in chemoselectivity between these two reaction manifolds (see Figure 4)? For intermolecular C−H amination, we conclude that selectivity manifests as a function of the rate in which the active oxidant is trapped by the substrate versus the rate at which said oxidant decomposes through nonproductive pathways (vide infra). Benzylic starting materials containing two equally reactive C−H bonds can intercept the nitrene faster than a substrate bearing only a single 3° site. This explanation alone, however, is incomplete, and other factors must be at play to account for the magnitude of the selectivity differences between intra- and intermolecular experiments. At this time, we have little appreciation for the manner in which a substrate must orient to undergo productive reaction with the Rh-nitrene. The approach of the substrate is influenced by the ligand architecture on the catalyst, and perhaps such steric effects, which would necessarily slow the rate of the insertion event, are exacerbated for 3° C−H centers. Clearly, more studies are needed to achieve a greater understanding of the mechanistic subtleties that control efficiency and selectivity in the intermolecular C−H amination reaction. These issues aside, it is of note that intermolecular C−H insertion with diazoalkanes and Rh catalysts is highly successful on benzylic substrates, but generally fails for 3° C−H derivatives.[23]

Side Reactions and Catalyst Arrest. The asymmetric induction observed with Rh_2(*S*-bls)$_2$ together with the stereospecific nature of the amination event, cyclopropyl clock experiments, and Hammett studies implicate a Rh-nitrene as the active oxidant in both intra- and intermolecular insertion reactions.[7] Rapid trapping of this reactive intermediate is thought to be essential for high catalyst turnover and efficient product formation. Thus, we wish to understand in detail alternative pathways by which the nitrenoid species reacts and through which catalyst decomposition occurs. Analytical studies on the intermolecular insertion reaction have identified a small number of byproducts whose formation suggests a secondary, radical-based pathway may initiate when C−H insertion is slow. Specifically, the production of dimethylaziridine (Figure 8), generated in modest yields in most of our intermolecular amination reactions, is explained through radical decarboxylation of $^tBuCO_2H$ to afford isobutylene, which itself is then oxidized. In addition to the Tces-aziridine, acetophenone has also been isolated. Formation of the ketone is not the result of overoxidation of the benzylic Tces-amine, as control experiments have shown. Importantly, these types of side products have never been characterized in Rh-catalyzed intramolecular insertion reactions, nor are they observed to form when excess substrate is employed for intermolecular oxidation. Products from C−H abstraction, thus, seem to appear only when the intermediate metallo-nitrene is not intercepted rapidly by the substrate.

Additional efforts to identity and quantify all products from amination reactions with moderately effective substrates have given us cause to examine the fate of the sulfamate ester. In such cases, mass balance of $TcesNH_2$ from spent reaction mixtures does not account for all of the material employed. Speculating that an *N*-centered radical might be, in part, responsible for triggering pathways that lead to the formation of products such as dimethylaziridine and acetophenone, we assumed that fragmentation of such a species would also occur to liberate trichloroethoxy radical. To test this hypothesis, the cyclopropyl-derived sulfamate ester **9** was prepared and subjected to the intermolecular amination conditions (Figure 9). Alkoxyl radicals such as **13** are known to ring-open to give unsaturated carbonyl products (e.g., cinnamaldehyde **11**). Reaction of **9** in the presence of ethylbenzene, while affording 20%

(28) Our findings are in accord with prior work by Müller's lab, for which a ρ-value of −0.90 (vs σ^+) was recorded in experiments with PhI=NNs as oxidant, see: (a) Müller, P.; Baud, C.; Nägeli, I. *J. Phys. Org. Chem.* **1998**, *11*, 597−601. (b) Nägeli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta* **1997**, *80*, 1087−1105.
(29) For consistency, all ρ-values have been calculated against σ^+-constants.
(30) Wang, J.; Chen, B.; Bao, J. *J. Org. Chem.* **1998**, *63*, 1853−1862.
(31) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165−4169.
(32) Preparation of and reactions with this catalyst will be described in a future manuscript, see: Kim, M.; Du Bois, J., manuscript in preparation.
(33) For other examples of asymmetric C−H amination under Rh-catalysis, see: (a) Fruit, C.; Müller, P. *Helv. Chim. Acta* **2004**, *87*, 1607−1615. (b) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 5917−5920. Also, see ref 3c.

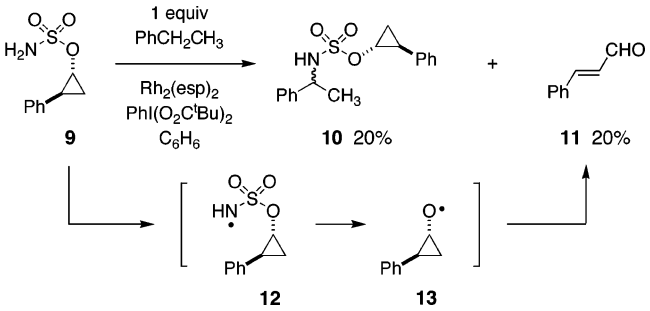


Figure 9. Cyclopropanol-derived sulfamate gives mechanistic clues.

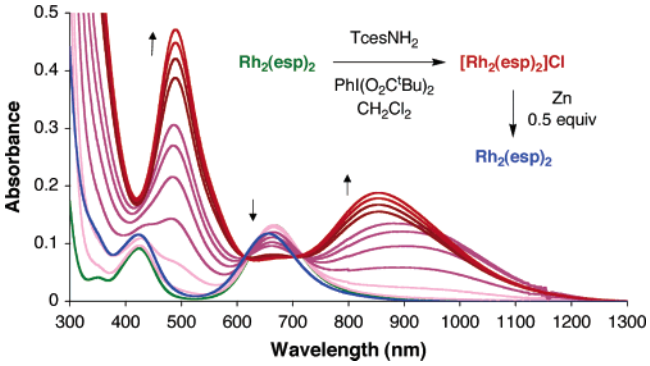


Figure 10. (−) UV/vis spectrum for $Rh_2(esp)_2$; (−) mixed-valent $[Rh_2(esp)_2]Cl$ formed via one-electron oxidation with $TcesNH_2$ and oxidant; (−) reaction of oxidized species with Zn returns $Rh_2(esp)_2$.

of the benzylic amine **10**, also gave equivalent amounts of aldehyde **11**.[34,35] Presently, we do not appreciate the steps that would lead to formation of an *N*-sulfamoyl radical such as **12**. At a minimum, however, this finding offers some explanation for the incomplete recovery of sulfamate in reactions that do not proceed well.

As a final point in this discussion, it is interesting to consider the consequence to the rhodium catalyst in the event that an *N*-sulfamoyl radical is produced. One indication that the catalyst is changing form is suggested by the color of the reaction solution. In either C_6H_6 or CH_2Cl_2, an immediate change from the deep green of the Rh^{2+}/Rh^{2+} dimer to a bright red is noted upon addition of $PhI(O_2C^tBu)_2$ to a solution of $Rh_2(esp)_2$ and $TcesNH_2$.[36] The UV/vis spectrum for this red species is quite similar to that previously recorded for the mixed-valent Rh^{2+}/Rh^{3+} tetraacetate (λ_{max} = 850 nm (ϵ = 406 M^{-1} cm^{-1}), 489 nm (ϵ = 1012 M^{-1} cm^{-1})) (Figure 10).[37] In addition, we have demonstrated that the green Rh^{2+}/Rh^{2+} complex is restored upon addition of 1 equiv of a one-electron reducing agent such as Cp_2Fe or 0.5 equiv of powdered Zn. When these experiments are conducted in CH_2Cl_2, spectral shifts from the UV/vis data, in addition to HRMS analysis of the red product, indicate that Cl^- is coordinated axially to the Rh^{2+}/Rh^{3+} complex. This adduct, $Rh_2(esp)_2Cl$, is stable for prolonged periods even at ambient temperature, but is completely inactive as a catalyst for C−H amination. Such findings offer incontrovertible evidence that CH_2Cl_2 oxidation occurs (likely through C−H abstraction) as a side reaction and explain why C_6H_6 is the preferred solvent for the intermolecular process. In C_6H_6, no solvent oxidation takes place;[38] without a strong axial ligand to stabilize the higher Rh^{2+}/Rh^{3+} state, it appears that an oxidized Rh species is either catalytically active for C−H amination or the red complex is somehow reduced back to $Rh_2(esp)_2$. The latter scenario possibly occurs through a disproportionation reaction between two mixed-valent dimers, thereby reducing the total concentration of active catalyst over time.[39]

To summarize, our data indicate that C−H amination follows through a concerted asynchronous two-electron oxidation pathway. The inability to intercept rapidly the Rh-nitrene oxidant leads to deleterious side reactions involving the production of free radical species and a mixed-valent form of the $Rh_2(esp)_2$ catalyst. The activity and/or fate of the red $[Rh_2(esp)_2]^+$ adduct in C_6H_6 remains unknown at this time. Knowledge of how it is formed, its stability in C_6H_6, and its pathway(s) for decomposition is essential for improving the performance of our intermolecular amination method. Studies to gain such information are in progress.

Conclusions

$Rh_2(esp)_2$-catalyzed intermolecular C−H amination serves as a uniquely effective method for amine synthesis from benzylic and 3° substrates. Distinctive elements of this process include the use of limiting amounts of starting material, stereospecific modification of 3° sites, chemoselectivity toward benzylic C−H centers, the ready availability of both $TcesNH_2$ and $Tces^{15}NH_2$, and the facility of removing the Tces group to afford the corresponding amine. Continued efforts to explore the mechanistic underpinnings of this novel transformation should give way to additional methodological advances.

Experimental Procedures

General Experimental Procedures. All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of nitrogen. Organic solutions were concentrated under reduced pressure (~15 Torr) by rotary evaporation. Freshly purified solvents were employed unless otherwise noted. Dichloromethane, benzene, and toluene were dried by passage through activated alumina columns under 12 psi of N_2. Preparation of $Rh_2(esp)_2$ followed a modified version of a previously published protocol.[4,40]

General Procedure for Intermolecular C−H Amination. A flask containing $TcesNH_2$ (137 mg, 0.60 mmol) in 0.6 mL of C_6H_6 was charged with $Rh_2(esp)_2$ (9 mg, 12 μmol, 0.02 equiv) and substrate (0.60 mmol). To this bright green mixture was added 1.4 mL of a 0.83 M C_6H_6 solution of $PhI(O_2C^tBu)_2$ (1.2 mmol, 2.0 equiv) via syringe pump over 3 h. During the addition of $PhI(O_2C^tBu)_2$, a change in the reaction color to brown or red was generally observed. Following the transfer of oxidant, the solution was stirred at 23 °C for 1−2 h. Dichloromethane (5 mL) and 2 mL of a saturated aqueous solution of thiourea were then added, and the orange biphasic mixture was stirred vigorously for 30 min.[41] The contents were transferred to a separatory funnel, and

(34) The reaction of **9** with 5 equiv of $PhCH_2CH_3$ yields 55% of the benzylic amine **10** and <10% of **11**.
(35) For ring-opening of a cyclopropylalkoxy radical, see: DePuy, C. H.; Dappen, G. M.; Hausser, J. W. *J. Am. Chem. Soc.* **1961**, *83*, 3156−3157.
(36) In general, the solution color changes from green to red for all reactions as the dropwise addition of oxidant nears completion. When an excess of substrate is employed, the green color persists throughout the reaction course.
(37) Wilson, C. R.; Taube, H. *Inorg. Chem.* **1975**, *14*, 2276−2279.
(38) Gas chromatography and HPLC analysis of spent reaction mixtures have never revealed products of benzene amination/aziridination.
(39) Disporportion of tetracarboxylate Rh^{2+}/Rh^{3+} complexes has been described, see ref 37 and: Kadish, K. M.; Das, K.; Howard, R.; Dennis, A.; Bear, J. L. *Bioelectrochem. Bioenerg.* **1978**, *5*, 741−753.
(40) $Rh_2(esp)_2$ is readily prepared on scale (40 g) and is available from Aldrich Chemical Co.
(41) Thiourea is used to decomplex any remaining $Rh_2(esp)_2$ catalyst, thereby facilitating product purification.

the organic phase was collected. The aqueous layer was extracted with 2×10 mL of CH_2Cl_2. The combined organic extracts were washed with 2×10 mL of a 0.1 M pH 7 Na_2HPO_4/NaH_2PO_4 buffer, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the isolated material by chromatography on silica gel (conditions given in the Supporting Information) afforded the desired product.

Acknowledgment. We are grateful to Professors John Brauman and Dan Stack for their valuable insights, and we thank Professor Huw Davies for graciously providing samples of both Rh_2(*S*-biTIPS)$_2$ and Rh_2(*S*-TCPTAD)$_4$ catalysts. K.W.F. is the recipient of both National Science Foundation and Amgen fellowships. The National Science Foundation, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck, and Pfizer are acknowledged for their generous support of this work.

Supporting Information Available: Analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0650450