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Selective Intermolecular Amination of C–H Bonds at Tertiary Carbon Centers**

Prof. Jennifer L. Roizen,

Department of Chemistry, Duke University, 3236 French Science Center, 124 Science Drive, Durham, NC 27708-0346 (USA)

David N. Zalatan, and

Department of Chemistry, Stanford University, CA 94305-5080 (USA), jdubois@stanford.edu

Prof. J. Du Bois

Department of Chemistry, Stanford University, CA 94305-5080 (USA)

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The preparation of tetrasubstituted amine derivatives through intermolecular amination of tertiary C–H bonds remains an outstanding challenge in methods development given the allure of such a technology for streamlining synthesis (Figure 1).^[1,2] While there exist a small number of reports in which this reaction has been demonstrated, almost all examples require superstoichiometric amounts of substrate.^[3] Owing to recent insights gained through mechanistic studies, we now report a general method for the selective amination of tertiary C–H centers.^[4] The reaction is operationally simple, tolerant of most common functional groups, and delivers a protected amine that is easily liberated. The influence of different nitrogen sources on product selectivity is also highlighted along with mechanistic studies that implicate steric effects as a principal determinant of site selectivity.

We have recently provided evidence that the dirhodium tetracarboxylate catalyst, $[\text{Rh}_2(\text{esp})_2]$,^[5] when subjected to C–H amination reaction conditions, undergoes competitive one-electron oxidation to a red, mixed-valent $\text{Rh}^{2+}/\text{Rh}^{3+}$ dimer.^[4,6] Fortuitously, this species is reduced under the reaction conditions by $t\text{BuCO}_2\text{H}$, a byproduct of the hypervalent iodine oxidant used to drive the amination event.^[4a] Our understanding of this process has resulted in a modification of the reaction conditions to include $\text{PhMe}_2\text{CCO}_2\text{H}$, a carboxylic acid additive that serves as an effective reducing agent and offers improved catalyst turnover

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Correspondence to: J. Du Bois.

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numbers in intermolecular amination reactions of benzylic substrates.^[4a,7] Application of these conditions to the oxidation of isoamyl-benzoate **1** (1.0 equiv), however, furnishes only a small amount of the desired amine **2** (Figure 2).

Careful analysis of the oxidation of **1** has revealed that the nitrogen source, 2,2,2-trichloroethoxysulfonamide (TcesNH₂), is largely consumed in spite of the poor yield of **2**.^[8] The low mass recovery of TcesNH₂ suggests that oxidation of the methylene center of the alkoxysulfonamide may be occurring. For this reason, we have examined alternative sulfonamide derivatives, including aryl- and phenolic-based reagents. Results from reactions performed with [Rh₂(esp)₂] (1mol%), PhI(OAc)₂, and PhMe₂CCO₂H (0.5 equiv) demonstrate enhanced catalyst turnover numbers (TONs) when aryloxysulfonamide reagents are employed (Figure 2).^[9] Of these, the sulfamate prepared from 2,6-difluorophenol, DfsNH₂, has proven optimal. Empirical studies reveal that the inclusion of both MgO and 5 Å molecular sieves further improves catalyst TONs, as does an initial substrate concentration of 1.0 M.^[10–12] The reaction mixture appears as a green slurry from which product **2** can be isolated in 57% yield (12 h).^[13,14]

A collection of disparate substrates possessing tertiary C–H bonds and assorted functional groups can be oxidized smoothly using DfsNH₂ as the nitrogen source (Table 1). As a general rule, the mass balance of this reaction is primarily accounted for by unreacted starting material and the reported product. The amination reaction is responsive to the proximity of electron-withdrawing groups to the site of oxidation; product yields generally improve as the distance between the C–H bond to be oxidized and polar substituents increases (Table 1, entries 1,2).^[4b,15] Both electronic and steric elements can be exploited to influence positional selectivity in molecules containing multiple tertiary C–H centers. Oxidation of the acylated natural product cycloheximide is exemplary in this regard, as only a single product isomer is generated despite the presence of four tertiary C–H bonds (Table 1, entry 3). Other examples include the menthol derivative shown in entry 4 for which reaction occurs exclusively at the C–H bond of the cyclohexyl tertiary carbon center. The direct preparation of substituted diamino acids and 1,5-diamines in a single step from common starting materials is also of particular note (Table 1, entries 5,6).

Oxidation of a bridged bicyclic substrate (Table 1, entry 7) furnishes the product of secondary methylene oxidation in 62% yield and as a single stereoisomer. Selectivity for amination of the *exo*-C–H bond can be rationalized on the basis of both steric and stereoelectronic effects. The inability to functionalize the bridgehead C–H bond is unsurprising, since Rh-catalyzed electrophilic amination processes generally disfavor reactions of C–H bonds that are rich in s-orbital character.^[17] By contrast, bridgehead C–H bonds in unstrained bicyclic systems, such as those found in adamantane, smoothly engage in this reaction. In the example shown in entry 8, the product is a masked form of memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist that is used clinically for the treatment of late-stage Alzheimer's disease.^[3d,18]

C–H amination products derived from DfsNH₂ may be free based in refluxing aqueous CH₃CN; no additional additives are required to effect this transformation. Selective cleavage of the aryloxysulfonamide occurs without incident to benzoate, pivaloate, and arenesulfonyl

functional groups (Figure 3). The product amines are isolated as trifluoroacetate salts after purification by reverse-phase HPLC.

Comparative amination studies conducted with DfsNH₂ and TcesNH₂ indicate that the choice of the nitrogen source can influence reaction selectivity. We have noted previously that oxidation of isoamylbenzene **7** with TcesNH₂ affords a 1:8 product ratio favoring benzylic sulfonamide **8B** (Table 2, entry 1). Under the same reaction conditions, the sulfamate ester derived from neopentyl alcohol generates a 1:4 product ratio of **8T** and **8B** (Table 2, entry 2). Conversely, reaction of **7** and DfsNH₂ furnishes a 1.5:1 mixture of **8T** and **8B**, slightly favoring the product of tertiary C–H amination (Table 2, entry 3). Other sulfamate derivatives (Table 2, entries 4,5), which are competent for intermolecular tertiary C–H oxidation (see Figure 2), give results similar to DfsNH₂ (i.e., ca. 1:1 **8T/8B**).

We wish to understand whether the observed, albeit small, variations in product selectivity (i.e., **8T** versus **8B**) manifest as a result of 1) steric interactions between the nitrogen source, catalyst, and substrate, or 2) a change in mechanism between stepwise or concerted asynchronous C–H oxidation. When using either DfsNH₂ or TcesNH₂ as the nitrogen source,^[4b] stereospecific insertion into an optically active tertiary substrate is noted (Figure 4). Such a finding is consistent with C–H functionalization occurring through a concerted asynchronous nitrenoid insertion event or a stepwise C–H abstraction/radical rebound pathway involving a short-lived radical pair. The plausibility of the latter pathway for [Rh₂(esp)₂]-catalyzed intermolecular C–H amination with TcesNH₂ is supported by recent density functional theory calculations by Bach and co-workers,^[19] and by desorption electrospray ionization mass spectrometry (DESI-MS) experiments from Perry et al.^[20] DESI-MS studies have identified two dirhodium nitrene species that differ in oxidation state (i.e., Rh²⁺/Rh²⁺ versus Rh²⁺/Rh³⁺), at least one of which is capable of H-atom abstraction from C–H bonds (e.g., CH₂Cl₂, C–H bond dissociation energy (BDE) = 97 kcalmol^{−1}).^[21]

To further query the properties of TcesNH₂ and DfsNH₂, a comparative kinetic isotope measurement has been conducted with monodeuterated ethyl benzene and dideuterioadamantane (Figure 5). These data establish that KIEs for both sulfamate agents are equivalent within error, irrespective of the nature of the C–H bond undergoing oxidation (i.e., benzylic or tertiary). The magnitudes of the recorded KIEs are surprisingly large (5.2–6.9, ¹³CNMR analysis) and are suggestive of a transition structure for intermolecular C–H amination in which extensive C–H bond breaking has occurred.^[22] Ruthenium- and copper-catalyzed nitrene-insertion reactions displaying similar primary KIE values are generally believed to follow a stepwise rather than concerted asynchronous course.^[3c,23,24] A measured KIE of 2.6 ± 0.2 has been determined for an analogous Rh₂(OAc)₄-catalyzed intramolecular amination event,^[25] for which a large body of experimental and theoretical evidence supports a concerted nitrenoid C–H insertion event.

Amination reactions using a cyclopropane clock, *cis*-**11**, have been performed in an attempt to identify a short-lived radical intermediate on the pathway to product (Figure 6). The rate constant for ring opening of *trans*-**11** has been measured at 7 × 10¹⁰ s^{−1}, which is appropriate for detection of radicals having picosecond lifetimes.^[26] In the amination event with *cis*-**11**, generation of 1–4 % of *trans*-cyclopropane **12** gives evidence for the

intermediacy of a cyclopropylcarbiny radical, which undergoes subsequent reversible cyclopropane ring opening. The identical outcomes for TcesNH₂ and DfsNH₂ in this, the KIE, and stereospecificity experiments lead us to conclude that steric effects between the nitrenoid complex and substrate principally govern product selectivity (see Table 2). While it appears that the cyclopropane clock results are consistent with a stepwise process for intermolecular C–H amination,^[19] DESI-MS^[20] and UV/Vis spectroscopic data^[4a,6] are commensurate with the presence of more than one dirhodium complex following initiation of the reaction. Thus, it is possible that different catalyst species present in solution at disparate concentrations promote C–H amination through mechanistically distinct pathways.

We have developed an effective process for generating tetrasubstituted amine derivatives through selective, intermolecular tertiary C–H bond amination. The optimized reaction is performed with limiting amounts of substrate, 1 mol % of commercially available [Rh₂(esp)₂], and inexpensive PhI(OAc)₂ as the terminal oxidant. The identification of aryloxysulfonamides, in particular DfsNH₂, as functional nitrogen sources has been an instrumental find. Competition studies with substrates possessing disparate C–H bond types reveal variations in product selectivity, which derive solely from the choice of sulfamate ester. Future studies are aimed at providing a unified mechanistic model for Rh-catalyzed C–H amination that explains these data and that guides our efforts to further advance such technologies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Synthesis of tetrasubstituted amine derivatives through intermolecular, Rh-catalyzed tertiary C–H bond amination. TcesNH₂ = 2,2,2-trichloroethoxysulfonamide; esp = $\alpha,\alpha,\alpha,\alpha'$ -tetramethyl-1,3-benzenedipropionate.

Figure 2.
Influence of sulfonamide on reaction efficiency.

Figure 3.
Hot aqueous CH_3CN effects amine deprotection.

Figure 4.
Enantiospecific insertion into a C–H bond at a tertiary carbon center.

Figure 5.

Primary KIE values for intermolecular C–H amination, as determined by ¹³C NMR integration. Values in parentheses are obtained by HRMS; see the Supporting information for details.

Figure 6.

Cis-trans isomerization implicates transient cyclopropyl-car-biny radical formation.

Table 1

A generalized procedure for tertiary C–H bond amination with a limiting amount of alkane substrate.^[a]

$ \begin{array}{c} \text{H} \\ \\ \text{R}^1-\text{C}-\text{R}^2-\text{R}^3 \\ \xrightarrow[\text{MgO, 5 \AA MS, } i\text{PrOAc}]{\begin{array}{c} 1 \text{ mol\% } [\text{Rh}_2(\text{esp})_2] \\ 1.2 \text{ equiv DfsNH}_2 \\ \text{PhI}(\text{OAc})_2, \text{PhMe}_2\text{CCO}_2\text{H} \end{array}} \\ \text{R}^1-\text{C}(\text{NHDfs})-\text{R}^2-\text{R}^3 \end{array} $			
Entry	Substrate	Product	Yield [%] ^b
1			70
2			45
3			57
4			68
5			50
6			63
7			62
8			50

^[a] Reactions performed in *i*PrOAc with 1.0 equiv of substrate, 1.2 equiv of DfsNH₂, 2.0 equiv of PhI(OAc)₂ and MgO, 0.5 equiv of PhMe₂CCO₂H, 5 Å MS, and 1 mol% of [Rh₂(esp)₂].^[16]

^[b] Yields are based on isolated material following chromatography on silica gel. Bbs = *p*-bromobenzene-sulfonyl.

Table 2

influence of sulfamate ester on product selectivity.

Entry	ROSO_2NH_2	8T	8B
1	$\text{Cl}_3\text{CCH}_2\text{OSO}_2\text{NH}_2$	1	8
2	$\text{Me}_3\text{CCH}_2\text{OSO}_2\text{NH}_2$	1	4
3	$2,6\text{-F}_2\text{C}_6\text{H}_3\text{OSO}_2\text{NH}_2$	1.5	1
4	$(\text{CF}_3)_2\text{CHOSO}_2\text{NH}_2$	1	1
5	$p\text{tBuC}_6\text{H}_4\text{OSO}_2\text{NH}_2$	1	1