Catalytic Allylic Amination versus Allylic Oxidation: A Mechanistic Dichotomy

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Allylic oxidation of hydrocarbon substrates is the foundation of many industrial and fine-chemical production processes. Direct allylic oxidation of cycloalkenes (C_{5-8}) has been widely discussed in the chemical literature. However, certain mechanistic details related to the presence of allylic free radicals have yet to be fully resolved. The corresponding copper-catalyzed allylic amination reaction has not been previously achieved. We report the first examples of this class of amination reaction using saccharin and bis-*p*-toluenesulfonamide as nitrogen sources and t-BuOOH and PhI(saccharinate)$_2$ as oxidants. Kinetic studies on stoichiometric model reactions demonstrate that the oxidant is not involved in the RDS of the transformation, and studies with 3,3,6,6-tetradeuteriocyclohexene conclusively show a mechanistic dichotomy between the catalytic oxidation and amination reactions. Both oxidative processes involve η^1-allyl intermediates, and regiochemical results are a consequence of discrete copper complexes. A mechanistic rationale involving allylic transpositions explains this mechanism dichotomy.

Introduction

The development of mild conditions for the selective functionalization of hydrocarbons remains an important agenda for the chemistry community.[1] Processes ranging from fine chemical synthesis to industrial-scale modification of chemical feedstock would benefit from this developmental work. Realizing a mild catalytic method for the amination of hydrocarbons would be a significant contribution in this area. Several methods have been introduced to affect allylic amination by way of C−H activation. Stoichiometric reagents such as sulfur or selenium imino compounds[2] (RN = X = NR, X = S, Se) or molybdenum oxaziridine[3] are each capable of converting simple alkenes into allylic amines. More recently, complexes of the VIIIb family of elements (Fe, Mo, and Ru) have all been identified as catalysts for the conversion of alkenes into N-aryl allylic amines.[4−8] Initial reports of these catalyses used iodanes (PhI=NTs)[9] and aryl hydroxylamines[10] as nitrogen sources. However, modern catalytic variants use aromatic nitro or nitroso compounds[4,5,8,11] as the amine precursor. Despite advances in this field, the reaction conditions necessary for these transformations are quite severe.

In this paper, we report two mild copper-mediated allylic amination reactions that occur between room temperature and 50 °C. Building on the knowledge base of the Kharasch Sosnovsky allylic oxidation reaction,[12−14] we found that inexpensive copper salts serve as efficient activator/catalyst for amination and that saccharin is a suitable nitrogen source. In addition to profiling cycloalkenes and other imido and sulfonamide reagents, we demonstrate intimate mechanistic details of both amination reactions through the use of 3,3,6,6-tetradeuteriocyclohexene. Experiments reported herein also provide new unambiguous details for the catalyzed allylic oxidation that resolves long-standing controversies regarding the nature of the allylic reaction inter-

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(1) Jones, W. D. *Acc. Chem. Res.* **2003**, *36*, 140−146. Fekl, U.; Goldberg, K. I. *Adv. Inorg. Chem.* **2003**, *54*, 259−320. Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507−514. Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633−639.

(2) Bruncko, M.; Khuong, T.-A. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 454−456. Katz, T. J.; Shi, S. *J. Org. Chem.* **1994**, *59*, 8297−8298. Kresze, G.; Braxmeier, H.; Muensterer, H. *Org. Synth.* **1987**, *65*, 159−165. Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *J. Am. Chem. Soc.* **1976**, *98*, 269−271.

(3) Liebeskind, L. S.; Sharpless, K. B.; Wilson, R. D.; Ibers, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 7061−7063. Moeller, E. R.; Joergensen, K. A. *J. Am. Chem. Soc.* **1993**, *115*, 11814−11822.

(4) Johannsen, M.; Jorgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5979−5982.

(5) Srivastava, R. S.; Nicholas, K. M. *J. Org. Chem.* **1994**, *59*, 5365−5371.

(6) Malkov, A. V.; Baxendale, I. R.; Bella, M.; Langer, V.; Fawcett, J.; Russell, D. R.; Mansfield, D. J.; Valko, M.; Kocovsky, P. *Organometallics* **2001**, *20*, 673−690.

(7) Cenini, S.; Ragaini, F.; Tollari, S.; Paone, D. *J. Am. Chem. Soc.* **1996**, *118*, 11964−11965. Stultz, L. K.; Huynh, M. H. V.; Binstead, R. A.; Curry, M.; Meyer, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 5984−5996.

(8) Ragaini, F.; Cenini, S.; Tollari, S.; Tummolillo, G.; Beltrami, R. *Organometallics* **1999**, *18*, 928−942. Ragaini, F.; Cenini, S.; Turra, F.; Caselli, A. *Tetrahedron* **2004**, *60*, 4989−4994.

(9) Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* **1988**, *29*, 1927−1930.

(10) Ho, C.-M.; Lau, T.-C. *New J. Chem.* **2000**, *24*, 859−863.

(11) Srivastava, R. S.; Khan, M. A.; Nicholas, K. M. *J. Am. Chem. Soc.* **1996**, *118*, 3311−3312. Srivastava, R. S. *Tetrahedron Lett.* **2003**, *44*, 3271−3274.

(12) Andrus, M. B.; Zhou, Z. *J. Am. Chem. Soc.* **2002**, *124*, 8806−8807. Andrus, M. B.; Sekhar, B. B. V. S. *J. Heterocycl. Chem.* **2001**, *38*, 1265−1271. Andrus, M. B.; Asgari, D. *Tetrahedron* **2000**, *56*, 5775−5780. Clark, J. S.; Tolhurst, K. F.; Taylor, M.; Swallow, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1167−1170. DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1996**, *37*, 2633−2636.

(13) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845−866.

(14) Andrus, M. B.; Chen, X. *Tetrahedron* **1997**, *53*, 16229−16240.

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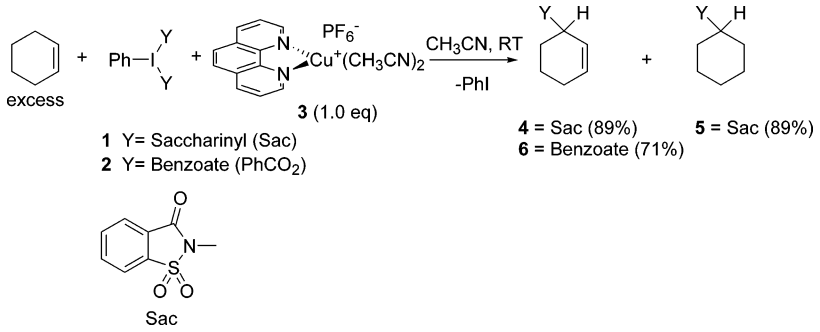
Scheme 1. Copper-Mediated Allylic Amination and Allylic Oxidation with Hypervalent Iodine Oxidant



mediate. Results from the copper-mediated amination and oxidation reactions are contrasted.

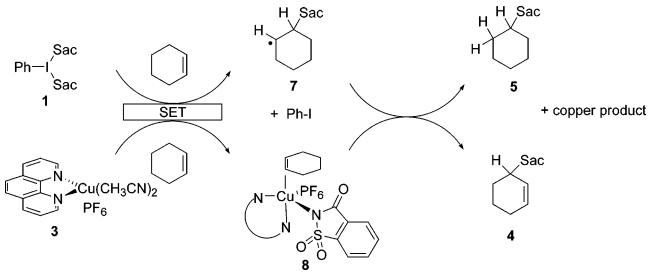
Results and Discussion

To affect allylic amination of cycloalkenes, two different oxidative conditions mediated by copper-phenanthroline complexes were investigated. Slow infusion of solid (disaccharinyliodo)benzene (**1**)[15,16] into a solution containing cyclohexene and (Phen)Cu(CH_3CN)$_2^+PF_6^-$ (**3**) gave both 3-saccharinylcyclohexene (**4**) and saccharinylcyclohexane (**5**) in high yield. The yields of both **4** and **5** (~89% relative to saccharin units) are consistent with the reaction stoichiometry since the hypervalent iodine reagent provides two equivalents of the saccharin moiety. Chromatographic methods demonstrated that adducts **4** and **5** formed in nearly equal quantities in the reaction, suggesting that a carbon-based radical may be responsible for the requisite C−H bond scission. Compound **4** possessed a diagnostic allylic spin system in the ^{1}H NMR consisting of two alkene resonances (6.09 (m) and 5.96 (dd)) and one allylic hydrogen at 4.98. Adduct **5**, on the other hand, had one characteristic proton signal at δ 4.16 ppm associated with a secondary CH−N structure. Under no circumstances could the copper complex be made catalytic. Substoichiometric amounts of (Phen)$CuPF_6$ always led to yields of **4** and **5** commensurate with the quantity of complex used.

Similarly, the infusion of benzoate derivative[17] **2** into a cyclohexene/(Phen)$CuPF_6$ mixture gave the cyclohexenyl ester in 71% yield. In this reaction, however, neither saturated ester nor benzoic acid was found as a complementary product. The absence of benzoic acid is not surprising since the benzoate ion forms strong complexes with copper(II) ion,[18] but the absence of the saturated ester is significant since it indicates that the oxidation reaction does not use any type of carbon-based intermediate as an oxidant of the cycloalkene.

Pairing observations from the amination and oxidation reactions, it is reasonable to conclude that the (Phen)Cu(CH_3CN)$_2^+PF_6^-$ complex appears to serve several roles in these allylic oxidations. First, complex **3** readily oxidizes in the presence of both hypervalent iodine reagents. In each case, the original dark brown

Scheme 2. Single-Electron Activation of Hypervalent Iodine 1



complex color changes to either green or blue suspensions, respectively, as **1** or **2** is infused. Addition of **1** or **2** in one portion to the reaction mixture results in a negligible yield of **4** and **5**. We propose that solvated (Phen)$CuPF_6$ facilitates decomposition of **1** or **2** by a single-electron-transfer mechanism. In the case of reagent **1**, decomposition produces low concentrations of saccharin radical and the oxidized copper(II) complex (**8**) (see Scheme 2). Strong stabilization of the saccharin radical makes it a weak hydrogen atom abstractor. This radical accomplishes its appointed task by coupling with cyclohexene to generate a carbon-based radical (**7**). This new radical is capable of C−H bond cleavage with production of *N*-cyclohexylsaccharin. Later experiments conclusively demonstrate the presence of η^2-cyclohexene copper(III) complex (**8**) as a key reaction intermediate. A SET mechanism also rationalizes the production of cyclohexenylbenzoate when reagent **2** is utilized.[19] Copper(I)-mediated decomposition of **2** would yield a benzoate radical and a copper(II) species similar to **8**. The benzoate radical is apparently competent for hydrogen abstraction, yielding benzoic acid and the analogous benzoate-copper(III) complex. A secondary methesis reaction with (Phen)$CuPF_6$ consumes the benzoic acid, thus removing it from the organic phase. Infrared analysis of the filtered copper residue shows a carbonyl band at 1720 cm^{-1}, which is consistent with a benzoate-copper complex.[20]

Despite success in functionalizing the allylic site in cyclohexene with I(III) reagents, no conditions rendered the copper complex catalytic. This limitation prompted us to examine other oxidative conditions. Review of the Kharasch Sosnovsky reaction literature revealed salient issues associated with the typical carboxylic acid/peroxide/

(15) Papadopoulou, M.; Varvoglis, A. *J. Chem. Res. Synth.* **1983**, 66−67.

(16) Papadopoulou, M.; Varvoglis, A. *J. Chem. Res., Synth.* **1984**, 166−167.

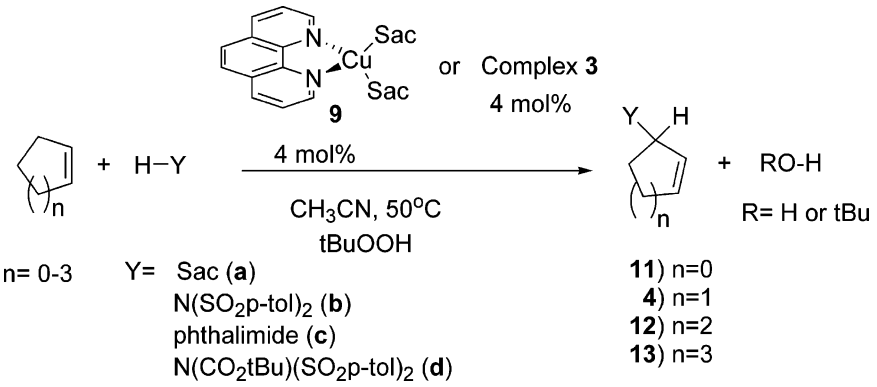
(17) Stang, P. J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* **1988**, *110*, 3272−3278.

(18) May, W. R.; Jones, M. M. *J. Inorg. Nucl. Chem.* **1962**, *24*, 511−517. Borel, M. M.; Busnot, A.; Busnot, F.; Leclaire, A. *Thermochem. Acta* **1981**, *43*, 149−160.

(19) Cohen, T.; Lewin, A. H. *J. Am. Chem. Soc.* **1966**, *88*, 4521−4522.

(20) Rehorek, D.; Trumpa, H.; Franzen, R.; Thomas, P. *Zeit. Anorgan. Allg. Chem.* **1973**, 402, 58−66. Tian, L.; Long, X.-Y. *Jiegou Huaxue* **2000**, *19*, 363−367.

Table 1. Reaction Profile for the Copper(I)-Catalyzed Allylic Amination Reaction



H−Y	pK_a[24]	cyclopentene	cyclohexene	cycloheptene	cyclooctene
a	14.6	72[a]	80	60	10
b	12.0	trace[b]	35	trace[b]	0
c		0	0	0	0
d	15.9	trace	trace	trace	0

[a] Yields are for reactions heated to 50 °C for 8 h, and yields are reported relative to the oxidative equivalence of t-BuOOH. Cycloalkenes are present in 10-fold excess relative to oxidant. [b] GC-MS data show a small peak in the chromatograph that has the expected molecular ion (M^+, *m/z*) for the adduct of H−Y and cycloalkene.

copper catalyst mixture. First, carboxylic acids can be used as reagents in allylic oxidations.[21] Second, a range of peroxide and peracids serve as oxidants in these reactions.[13,14,22,23] Third, a copper(I)−copper(III) redox couple is generally accepted as the basis of catalytic turnover. And finally, the involvement of the alkene substrate in the mechanism is not clearly established. Literature reviews as late as 2002 still speculated that solution phase allylic radicals were involved as reaction intermediates.[13]

From these leads we anticipated that imides, *N*-acylsulfonamides, or bis-sulfonamides could be surrogates for the carboxylic acid component in the Kharasch Sosnovsky reaction. pK_a values for these imides and sulfonamides span the range of carboxylic acids (CH_3CN solvent) and extend systematically into the more basic regime; equally important, the same nitrogen species are not easily oxidized by peroxides. These considerations led to a simple, efficient amination reaction that uses either complex **3** or (Phen)$CuSac_2$ (**9**) as catalyst and t-BuOOH as oxidant. In a typical experiment, mixtures of complex **3** or **9** (4 mol %), excess cyclohexene, and saccharin (Sac-H, 25 equiv) dissolve in acetonitrile and are heated to 50 °C, at which point 70% t-$BuOOH_{(aq)}$ (25 equiv) is added in one portion. After 8 h, compound **4** is isolated in 80% yield. The same reaction and same reaction efficiency can be achieved when the copper(I) complex (Phen)CuSac (**10**, 4 mol %) is employed. We surveyed the reaction profile in terms of amine derivatives and cycloalkenes, and these results are summarized in Table 1.

Saccharin is the most widely applicable amine derivative in this catalysis. It is the only reagent that reacts with all four cycloalkenes, and in comparison to bis-*p*-toluenesulfonamide it gives a substantially higher yield. The efficiency with which saccharin functionalized each cycloalkene mirrors the results for the analogous *tert*-butyl perbenzoate allylic oxidation.[25] Ground state conformations of cyclopentene and cyclohexene position allylic hydrogens nearly coplanar with orbitals in the alkene, thus maximizing orbital overlap as the C−H is broken. More flexible cycloalkenes ($n = 2$ and 3) relax this restrictive arrangement, lose stabilizing interactions, and make these cycloalkenes less reactive. Second, the acidity of the H−N bond is not a critical factor in the success of this catalysis. Data in Table 1 show that the most acidic amine derivative, bis-*p*-toluenesulfonamide, is not a particularly effective reagent in this catalysis. Only the most reactive cycloalkene reacts with this bis-sulfonamide. A more compelling rational for saccharin's success is its specific assembly of functional groups at the nitrogen center. Further, the fused cyclic structure of saccharin constrains the conformational mobility and renders the nitrogen more accessible for catalysis.

The balanced equation for this catalysis utilizes a Fenton-type reaction to reoxidize the copper center.[26] As such, water and *tert*-butyl alcohol are reported as byproducts. However, saccharin itself appears capable of reoxidizing copper(I) by a coupled hydrogen reduction mechanism (see Scheme 3). Heating a mixture of complex **10**, formed in situ from $CuSac(CH_3CN)_3$ and phenanthroline, with excess saccharin under inert conditions brings about a chemical change as noted by

(21) Brunel, J.-M.; Legrand, O.; Buono, G. *C. R. Acad. Sci.* **1999**, *2*, 19−23. Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567−3571. Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831−1834. Kawasaki, K.-I.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337−6350. Rispens, M. T.; Zondervan, C.; Feringa, B. L. *Tetrahedron: Asym.* **1995**, *6*, 661−664. Lee, W. S.; Kwong, H. L.; Chan, H. L.; Choi, W. W.; Ng, L. Y. *Tetrahedron: Asym.* **2001**, *12*, 1007−1013. Rothenberg, G.; Feldberg, L.; Wiener, H.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2429−2434. Sekar, G.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961−2967. Zondervan, C.; Feringa, B. L. *Tetrahedron: Asym.* **1996**, *7*, 1895−1898.

(22) Le Bras, J.; Muzart, J. *J. Mol. Catal. A: Chem.* **2002**, *185*, 113−117.

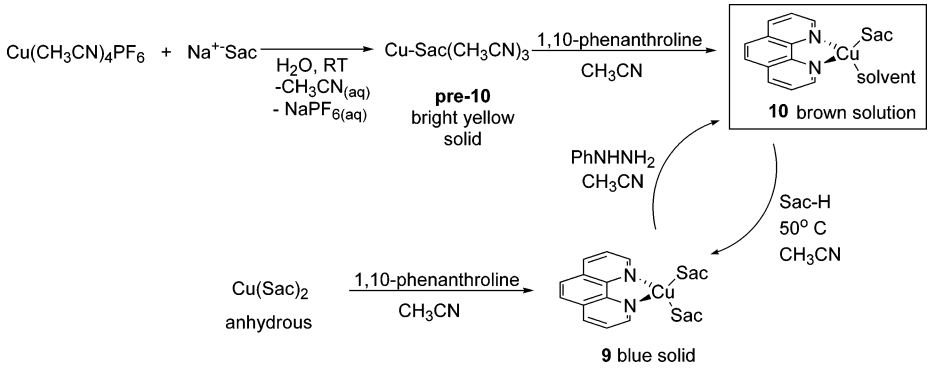
(23) Beckwith, A. L. J.; Zavitsas, A. A. *J. Am. Chem. Soc.* **1986**, *108*, 8230−8234.

(24) Leito, I.; Kaljurand, I.; Koppel, I. A.; Yagupolskii, L. M.; Vlasov, V. M. *J. Org. Chem.* **1998**, *63*, 7868−7874.

(25) Kawasaki, K.; Shigenobu, T.; Katsuki, T. *Synlett.* **1995**, 1245−6. Rawlinson, D. J.; Sosnovsky, G. *Synthesis* **1972**, 1−28.

(26) Van Dyke, B. R.; Clopton, D. A.; Saltman, P. *Inorg. Chim. Acta* **1996**, *242*, 57−61. Sawyer, D. T.; Sobkowiak, A.; Matsushita, T. *Acc. Chem. Res.* **1996**, *29*, 409−416.

Scheme 3



a distinct color change from a soluble dark brown complex to a sky-blue precipitate. The original brown solution can be regenerated by adding phenylhydrazine (0.5 equiv). By comparison a similar sky-blue complex **9** can be precipitated from a mixture of $Cu(Sac)_2$ and phenanthroline. Solid samples from both preparative routes were studied by electron spin resonance spectroscopy at 298 K. The spectra obtained for both were very similar qualitatively, and *g*-values agreed closely. A simple interpretation is that these spectra arise from magnetically dilute copper(II) species. The appearance and position of the signals in both ESR spectra imply an axially symmetric electronic environment for copper(II). Thus in each spectrum the strong feature centered at 3350 G in the sample from $CuSac(CH_3CN)_3$ and at 3370 G in sample from $Cu(Sac)_2$ may be assigned to a perpendicular *g*-value of 2.08 and 2.07, respectively. The weaker feature at approximately 3120 G and at 3140 G for each respective spectrum can be ascribed to parallel *g*-values of 2.23 and 2.22. The close qualitative and quantitative match suggests that the copper(II) molecule is the same in both experiments. It is difficult to unequivocally rule out Fenton chemistry here, but these experiments suggest a reasonable redox alternative.

Mechanistic Studies

Emerging from extensive work by Walling,[27] Kochi,[28] and Beckwith and Zavitsas[23] on the mechanism of the Kharasch Sosnovsky reaction is a process that includes homolysis of the peroxide O−O bond, formation of Cu(II) carboxylate complex and alkoxy radical, and allylic C−H cleavage brought about by the reactive alkoxy radical. The oxidative process by which the carboxylate ligand is transferred to the putative allylic radical is still controversial; however, Beckwith's proposed coupling of Cu(II) carboxylate with allylic radical followed by allylic carboxylate transfer best accommodates the regio- and stereochemical data.[29] Although no accurate kinetic data for each of these steps are known, it is agreed that the first two steps are exceedingly fast. Therefore, peroxide is not involved in the rate-determining step.[14]

We tested for peroxide effects in our allylic amination reaction and found that indeed the reaction rates were independent of t-BuOOH concentration. On the basis of the observation that complex **9** serves as a stoichiometric reagent in the amination reaction, a series of reaction mixtures consisting of excess cyclohexene (>10 equiv) and **9** in acetonitrile were heated to 50 °C and then either 1.0, 2.0, or 4.0 equiv of t-BuOOH relative to **9** was added. Shown in Figure 1 are the initial pre-equilibrium rate curves for the production of **4** over the first 10% of the reaction. Each curve is the composite of three trials with the only variant being the concentration of t-BuOOH. As expected, under pseudo-first-order kinetics the formation of compound **4** increased directly with the concentration of complex **9**.

The curvatures in the pseudo-first-order kinetic data strongly suggest that a η^2-alkene-copper intermediate is present under pre-equilibrium conditions. To test this hypothesis, we conducted deuterium labeling studies to test for migration of the π-bond during amination. We reasoned that 3,3,6,6-tetradeuteriocyclohexene would delineate the fate of the alkene moiety. Shown in Figure 2 are two alternatives for the deuterium-labeled alkene. One possibility involves oxidation at one of the CD_2 groups with delivery of the heteroatom to that carbon. This would retain the original position of the alkene ($\mathbf{4_r}$) and two alkene proton resonances would be observed (δ 6.09 (m) and 5.96 (dd)). Alternatively, π-bond migration with delivery of the heteroatom at an sp^2 hybrid carbon in the original alkene ($\mathbf{4_m}$) would result in one alkene and one allylic proton signal (δ 5.96 (dd)) and 4.98 (m)). This strategy also resolves whether unbound allylic radicals exist in this reaction class, since an unbound radical would scramble the deuterium label equally in the alkene and allylic site. Tetradeuteriocyclohexene was prepared by the method of Wolfe,[30] and the distilled alkene was subjected to amination conditions using both $PhI(Sac)_2$ and Sac-H/t-BuOOH oxidative conditions. Shown in Figure 3 are the ^1H NMR spectra for both the catalytic amination product and the amination material formed with $PhI(Sac)_2$. These data, regardless of synthetic method, are unassailable in the fact that all steps in the allylic amination reaction occur while bound to the copper center. In the case of catalytic amination with saccharin (H−Sac), approximately 89% of C−N bond formation occurs at one of the original allylic carbons ($\mathbf{4_r}$). Conversely, the stoichiometric variation with $PhI(Sac)_2$ gives ~88% C−N bond formation at one of the original alkene carbon sites. Because solvent effects are notable in the Kharasch Sosnovsky

(27) Walling, C.; Zavitsas, A. A. *J. Am. Chem. Soc.* **1963**, *85*, 2084−2090.
(28) Kochi, J. K. *J. Am. Chem. Soc.* **1962**, *84*, 3271−3277.
(29) Andrus, M. B.; Argade, A. B.; Chen, X.; Pamment, M. G. *Tetrahedron Lett.* **1995**, *36*, 2945−2948.
(30) Wolfe, S.; Campbell, P. G. C. *Can. J. Chem.* **1965**, *43*, 1184−1198.

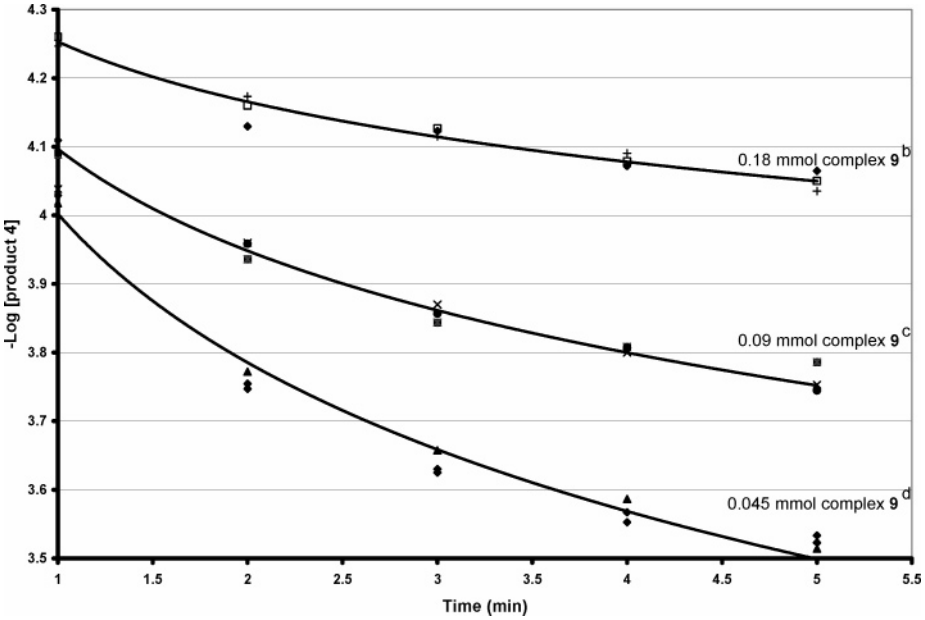


Figure 1. Pre-equilibrium rate curves for the production of amine **4**. (a) Production of amine **4** measured by gas chromatography using anthracene as an internal standard. (b) Composite data of three trials using 0.18, 0.36, and 0.72 mmol of t-BuOOH, respectively. (c) Composite data of three trials using 0.09, 0.18, and 0.36 mmol of t-BuOOH, respectively. (d) Composite data of three trials using 0.05, 0.10, and 0.20 mmol of t-BuOOH, respectively.

reaction, the hypervalent iodine reaction was repeated in both CH_3CN and CH_2Cl_2, but the results were nearly identical.

Deuterium labeling results in the allylic amination reaction prompted us to conduct analogous labeling experiments for the traditional Kharasch Sosnovsky oxidation reaction. Although 3,3,6,6-tetradeuteriocyclohexene has been used in the palladium allylic oxidation reaction,[31] it had never been used to follow up the copper-catalyzed allylic oxidation. In a related vein, Bäckvall[32] used partially labeled 1,2-dideuteriocyclohexene to demonstrate the existence of a (η^3-allyl)-palladium intermediate in the quinone-based palladium-catalyzed oxidation. It is important to note at this juncture that (η^3-allyl)copper intermediates are an alternative way of scrambling the deuterium label, although from a bonding perspective, the η^3-allyl is unlikely since it involves a 21-electron copper intermediate. Figure 4 compiles the ^{1}H NMR spectra for both the *tert*-butyl perbenzoate catalysis and the $PhI(O_2CPh)_2$ stoichiometric oxidation. Both methods gave nearly identical distributions of deutereium label, with the alkene migration product dominating, 57%:43%. Note that this ratio is not 50:50. Again, as with the allylic amination, solution phase free allylic radicals or η^3-allyl systems are not operative in the mechanism; however, a mechanism does scramble the deuterium label but at a slower rate than product formation.

Considering the deuterium labeling results from both the amination and oxidation reactions, several fundamental conclusions are evident. First, C−H abstractions from cyclohexene must occur on a copper-alkene complex. Scheme 3 suggests pre-equilibrium coordination of the alkene establishes and maintains the regiochemistry of the deuterium atoms prior to C−N or C−O bond

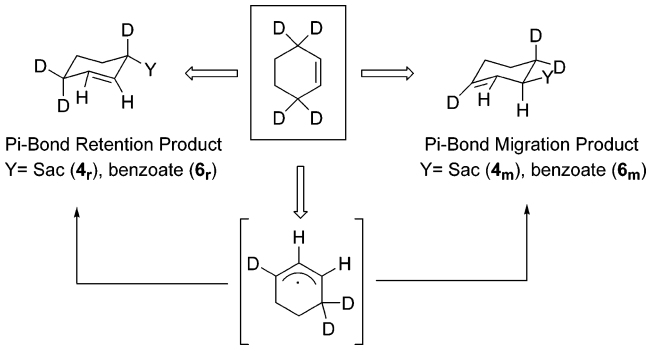


Figure 2. Deuterium labeling consequences from 3,3,6,6-tetradeuteriocyclohexene.

formation. Complex **11** is a 19-electron system assuming an associative mechanism. Nineteen-electron catalysts and reaction intermediates are documented in the literature, and each are susceptible to one-electron oxidation.[33,34] A similar oxidative process would bring about an 18-electron d^8-Cu(III) intermediate similar to complex **12**. Once **12** forms, a six-electron pericyclic rearrangement transfers either saccharin or benzoate to an allylic carbon, giving a new η^2-complex, **13-retention**. The descriptor retention is added in this case because the location of the original π-bond is retained in the final product. Dissociation of the alkene complex yields $\mathbf{4_r}$ and copper(I) complex **10**, which serves as a precatalyst.

Implicit in the catalytic scheme are two additional equilibration processes. First, complex **12** can experience homolysis of the Cu−C bond, leading to the original

(31) Wolfe, S.; Campbell, P. G. C. *J. Am. Chem. Soc.* **1971**, *93*, 1497−1499.

(32) Grennberg, H.; Simon, V.; Bäckvall, J. E. *Chem. Commun.* **1994**, 265−266.

(33) Hamon, J. R.; Astruc, D.; Michaud, P. *J. Am. Chem. Soc.* **1981**, *103*, 758−66. Rigaut, S.; Delville, M.-H.; Losada, J.; Astruc, D. *Inorg. Chim. Acta* **2002**, *334*, 225−242. Rigaut, S.; Delville, M.-H.; Astruc, D. *J. Am. Chem. Soc.* **1997**, *119*, 11132−11133. Astruc, D. *Acc. Chem. Res.* **1986**, *19*, 377−383.

(34) Piper, T. S.; Karipides, A. G. *Inorg. Chem.* **1965**, *4*, 923−924. Sorrell, T. N.; Allen, W. E.; White, P. S. *Inorg. Chem.* **1995**, *34*, 952−960. Clezy, P. S.; Liepa, A. J. *Aust. J. Chem.* **1971**, *24*, 1027−1040.

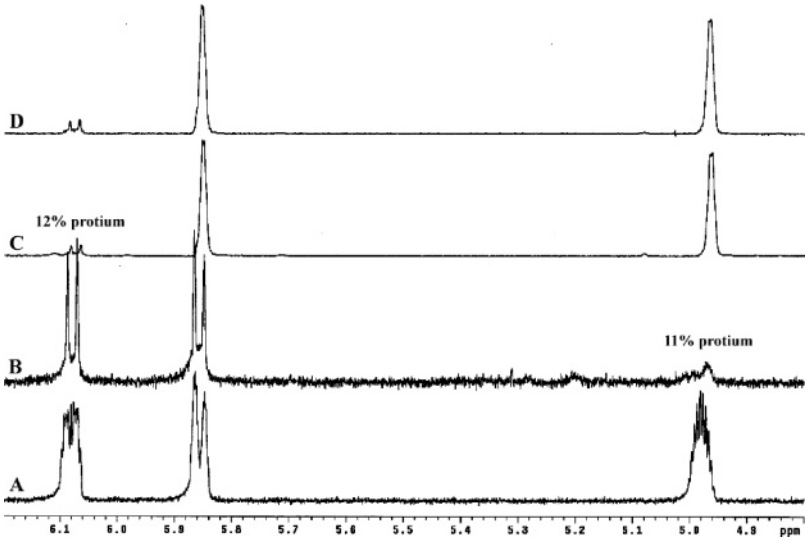


Figure 3. Proton NMR spectra for the amination of 3,3,6,6-tetradeuteriocyclohexene. (A) Allylic spin system for **4** prepared with cyclohexene. (B) Catalytic amination with Sac−H and t-BuOOH prepared with tetradeuteriocyclohexene. (C) Amination of tetradeuteriocyclohexene using $PhI(Sac)_2$ in acetonitrile. (D) Amination of tetradeuteriocyclohexene using $PhI(Sac)_2$ in dichloromethane.

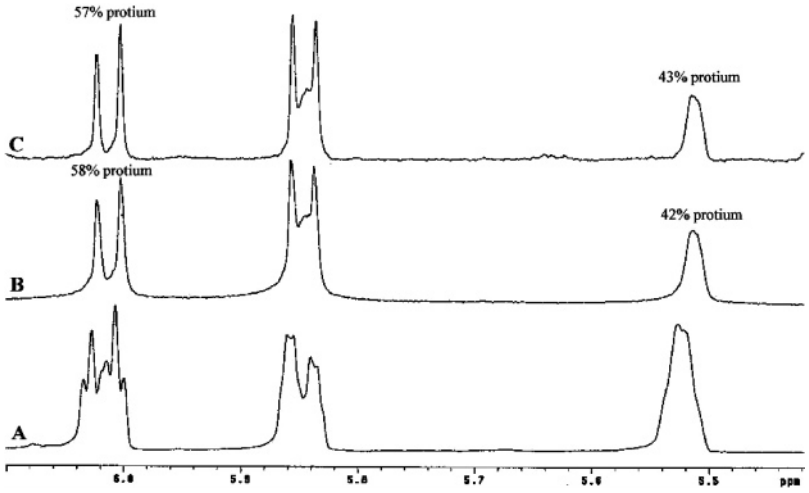


Figure 4. Proton NMR spectra for the allylic oxidation of 3,3,6,6-tetradeuteriocyclohexene. (A) Allylic spin system for **6** prepared with cyclohexene. (B) Catalytic oxidation with $PhCO_3$t-Bu using tetradeuteriocyclohexene. (C) Oxidation of tetradeuteriocyclohexene using $PhI(O_2CPh)_2$ in acetonitrile.

catalyst and cyclohexenyl radical. Radical−copper(II) recombination with the opposite regiochemistry scrambles the deuterium label and yields equal amounts of $\mathbf{4_r}$ and $\mathbf{4_m}$. Homolysis−recombination must be slow relative to C−N bond formation since only a small amount (12%) of π-bond migration is observed. However, a similar scrambling manifold in the allylic oxidation must be competitive with C−O bond formation since a larger percentage of π-bond migration is observed. The homolysis−recombination mechanism is preferable to a $\eta^1-\eta^3-\eta^1$ isomerization, which invokes a dubious 21-electron copper intermediate.

A second equilibration process involving O−N tautomerization rationalizes the results for the hypervalent iodine oxidations. Recall that $PhI(saccharinyl)_2$ and $PhI(O_2CPh)_2$ gave opposite regioisomeric products in their respective catalytic oxidations. Oxidation gave consistent results regardless of oxidative method, while the two amination methods gave opposite regioisomers. In the former case, only the Cu−O benzoate tautomer is possible as a reactive intermediate. Therefore, both oxidants provided the same product distribution. Saccharin, on the other hand, has both Cu−O and Cu−N tautomers accessible. Figure 5 shows the exclusive mechanistic course for the Cu−O isomer. A similar six-electron rearrangement involving the Cu−N intermediate produces the O-cyclohexenyl adduct **15**. Computational and experimental work by Cristiano shows that the O-allylic to N-allylic transposition of saccharin is favored by $\Delta H = -4.1$ kcal.[35] Implications for deuterium labeling are such that allylic transposition yields the $\mathbf{4_m}$ isomer since the π-bond migrates during the [3,3]-rearrangement. We demonstrated the feasibility of this reorganization by synthesizing **15** through the condensation of 3-cyclohexenol and 3-chloro-1,2-benzisothiazole-1,1-dioxide in pyridine. At room temperature, **15** formed as determined by gas chromatography. Upon

(35) Araujo, N. C. P.; Barroca, P. M. M.; Bickley, J. F.; Brigas, A. F.; Cristiano, M. L. S.; Johnstone, R. A. W.; Loureiro, R. M. S.; Pena, P. C. A. *J. Chem. Soc., Perkin Trans.* **2002**, 1213−1219. Cristiano, M. L. S.; Brigas, A. F.; Johnstone, R. A. W.; Loureiro, R. M. S.; Pena, P. C. A. *J. Chem. Res. Synop.* **1999**, 704−705.

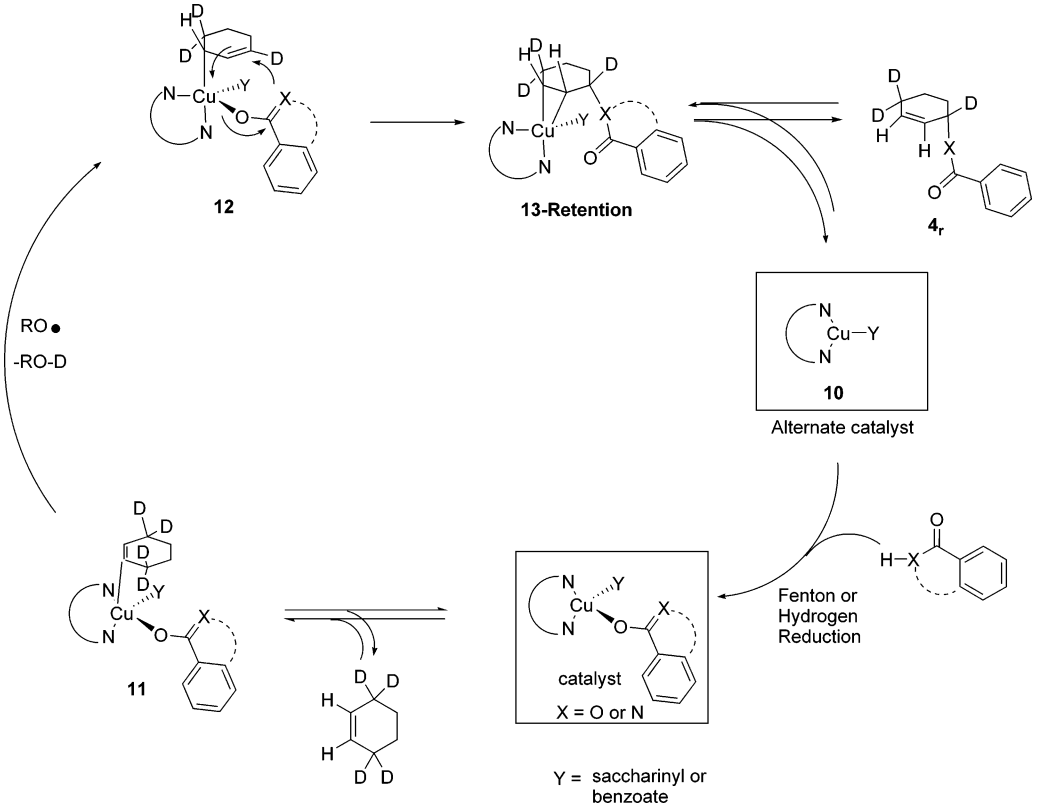
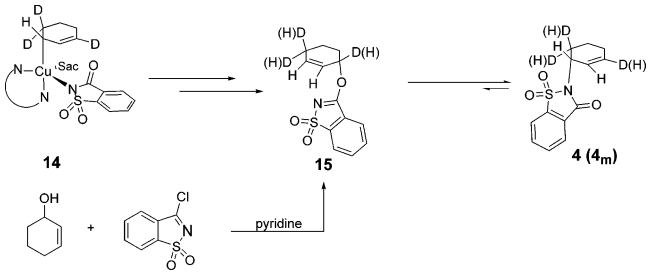


Figure 5. Proposed catalytic scheme resulting in the formation of $\mathbf{4_r}$.

Scheme 4. O- to N-Allylic Transposition with Alkene Migration



heating to 50 °C for 2 h, the chromatographic band for **15** decreased and compound **4** became the major product.

Our choice of a concerted [3,3]-allylic C−O or C−N bond formation from **12** or **14** is not the only possible mechanism however. The allylic transposition model has been invoked commonly to explain enantioselective ester formation in the Kharasch Sosnovsky reaction. An alternative mechanism involves direct reductive elimination from intermediate **12** or **14**. A reductive elimination mechanism would reverse the deuterium labeling results. For instance, **12** would yield $\mathbf{4_m}$ after sequential C−O bond formation and allylic isomerization, while **14** would provide $\mathbf{4_r}$. Our experiments cannot differentiate between these pathways; however, experimental evidence and density functional calculations on d^{10}-metals demonstrate that the bond strength of the M−O tautomer should be approximately 10 kcal mol^{-1} stronger than a comparative M−N bond.[36] This energy difference manifests itself in larger activation energies for reductive elimination of the C_{sp3}−O product than for C_{sp3}−N.[37] Under all of our reaction conditions, this activation energy difference should give a highly selective C_{sp3}−N ($\mathbf{4_m}$) product ratio. Our data do not conform to this situation; therefore, the reductive elimination pathway does not appear to be competitive with a concerted [3,3]-allylic rearrangement.

Conclusions

Results from this work demonstrate that a simple and convenient copper-mediated amination reaction can be developed. The major limitation appears to be a practical nitrogen source with an appropriate ensemble of electron-withdrawing groups. These electron-withdrawing groups both protect the nitrogen from oxidation and also provide a facility to shuttle the nitrogen onto the carbon substrate through one or a series of allylic rearrangements. Product distribution in both reactions reveals that the allylic C−N bond in the amine product forms faster than the related allylic C−O bond in the ester product. Deuterium is scrambling only to the extent of 11−12% in the amination reaction, while scrambling in the oxidation reaction occurs to the extent of 43%. Intramolecular isomerization of the Cu(III)-cyclohexenyl intermediate has been suggested as a key step in the asymmetric Kharasch Sosnovsky reaction, and results from this work definitively show the likelihood of this process. Finally, 3,3,6,6-tetradeuteriocyclohexene provided definitive proof that all steps of the allylic C−H activation and subsequent functionalization (either C−N or C−O tautomers) must occur while bound to the copper center. This critical observation provides

(36) Åkermark, B.; Almemark, M.; Jutand, A. *Acta Chem. Scand. Ser. B* **1982**, *B36*, 451−457. MacGregor, S. A.; Neave, G. W.; Smith, C. *Faraday Discuss.* **2003**, *124*, 111−127.

(37) Bryndza, H. E.; Fong, L. K.; Paciello, R. A.; Tam, W.; Bercaw, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1444−1456.

both opportunities and challenges for further developmental work.

Experimental Section

General Considerations. All reactions were conducted under an inert atmosphere of nitrogen or argon, and all glassware was oven-dried before use. Anhydrous solvents were dried over sodium ketyl where applicable or distilled from P_2O_5 before use. Compounds **1**,[15] **3**,[38] and **9**[39] were prepared according to literature procedures, as were 3,3,6,6-tetradeuteriocyclohexene[30] and 3-chloro-1,2-benzisothiazole-1,1-dioxide.[40] All other chemicals were obtained from Sigma/Aldrich Chemical Co. or Acros Chemical Company and were used without further purification. Proton and carbon NMR were measured on a Varian Unity Plus 300 MHz, a Varian Inova 500 MHz, or a Varian Inova 600 MHz spectrometer, and the chemical shifts are relative to residual solvent resonances. X-band ESR spectra were obtained on solid state samples in quartz tubes and employing a Bruker EMX 10 ESR spectrometer. Microwave frequencies were near 9.73 GHz, and the power level was 0.100 mW. Spectra were scanned four times and averaged to yield a composite spectrum in each case. Infrared data were collected on a PE Paragon 1600 spectrometer. Kinetic data were collected on a Hewlett-Packard series II 5980 gas chromatograph equipped with a 30 m HP 1 column. Kinetic samples contained anthracene as an internal standard and were normalized.

Preparation of 4 and 5. The copper complex $Cu(CH_3CN)_4PF_6$ (0.130 g, 0.35 mmol) and phenanthroline (63 mg, 0.35 mmol)[41] were both weighed into a 25 mL three-neck round-bottom flask. The flask was equipped with a condenser and solid addition tube filled with $PhI(Sac)_2$ (0.202 g, 0.35 mmol, 98% iodometric purity). The vessel was flushed with N_2 for 0.3 h. Dry acetonitrile (6 mL) and cyclohexene (1 mL) were added by syringe, and a deep brown solution formed after 0.5 h of stirring at RT. The solid $PhI(Sac)_2$ was added in about 12 portions over 1.0 h. After the addition was completed the mixture was stirred at RT for 3.0 h, at which point a bright blue suspension remained. The resulting suspension was concentrated *in vacuo*, resuspended in DCM, and then filtered through a 2 cm plug of silica gel in a 15 mL fritted filter. The silica was washed with additional DCM (100 mL). After being concentrated, the reaction mixture was separated by flash chromatography (silica gel, 3:1 hexane/ethyl acetate) and gave **4** (82 mg, 89%, $R_f = 0.35$) and **5** (83 mg, 89%, $R_f = 0.38$). Both **4** and **5** were isolated as white solids. Compound **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (m, 1H), 7.83 (m, 3H), 6.09 (m, 1H), 5.86 (dd, $J = 6.2$, 0.8 Hz, 1H), 4.98 (m, 1H), 2.30 (m, 2H), 2.15 (m, 2H), 1.99 (m, 1H), 1.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 138.0, 134.6, 134.1 132.7, 127.2, 124.9, 124.1, 120.6, 51.1, 27.2, 24.3, 21.1; IR (KBr) 3093, 2914, 1723, 1595, 1462 cm^{-1}; HRMS (FAB$^+$, *m/z*) calcd for $C_{13}H_{14}NO_3S$ ($M + H^+$) 264.0694, found 264.0667. Compound **5**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (m, 1H), 7.84 (m, 3H), 4.16 (m, 1H), 2.17 (m, 2H), 2.08 (m, 2H), 1.91 (m, 2H), 1.71 (m, 1H), 1.38 (m, 2H), 1.29 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.6, 137.7, 134.5, 134.1, 127.4, 124.9, 120.6, 54.9, 30.3, 26.1, 25.0; IR (KBr) 1722, 1460 cm^{-1}; HRMS (FAB$^+$, *m/z*) calcd for $C_{13}H_{16}NO_3S$ ($M + H^+$) 266.0857, found 266.0849.

Similarly, the production of **4-d$_3$** and **5-d$_5$** was completed through the use of 3,3,6,6-tetradeuteriocyclohexene. Compound **4-d$_3$**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (m, 1H), 7.83 (m, 3H), 6.09 (m, 1H), 5.86 (dd, $J = 6.2$, 0.8 Hz, 1H), 4.98 (m, 1H), 2.30 (m, 2H), 2.15 (m, 2H), 1.99 (m, 1H), 1.77 (m, 1H); (FAB$^+$, *m/z*) calcd for $C_{13}H_{10}D_3NO_3S$ ($M + H^+$) 266.0821, found 266.0669. Compound **5-d$_5$**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (m, 1H), 7.87 (m, 1H), 7.83 (m, 2H), 4.14 (d, $J = 12.2$ Hz, 1H), 2.17 (m, 2H), 2.08 (m, 2H), 1.91 (m, 2H), 1.71 (m, 1H), 1.38 (m, 2H), 1.29 (m, 1H); HRMS (FAB$^+$, *m/z*) calcd for $C_{13}H_{11}D_5NO_3S$ ($M + H^+$) 270.1086, found 270.1078.

Preparation of Copper(I) Saccharin pre-10. Freshly prepared $Cu(CH_3CN)_4PF_6$ (3.001 g, 8.0 mmol) and sodium saccharinate·H_2O (2.136 g 0.96 mmol) were weighed into a 100 mL Schlenk flask. A septum was placed on the sidearm, and the flask was attached to a reversible filter frit. The vessel was evacuated and flushed with nitrogen three times. Distilled water (50 mL) was sparged with nitrogen gas for 0.5 h, and then 25 mL of the water was removed by syringe and added into the Schlenk flask. Initially the mixture was dissolved, and then a bright yellow precipitate collected. After 2.0 h of stirring at RT the apparatus was inverted and the yellow solid was filtered at partial vacuum. The entire vessel was backfilled with nitrogen, and a 10 mL water rinse was added to the original flask. This water was pulled through the collected solid. An additional water wash (10 mL) was conducted, and the lemon-colored solid was dried at high vacuum for 14 h. The powder was dried further in a vacuum-drying pistol with refluxing xylene. The dry solid is stable in air for approximately one month. A noticeable green tint is observed at that time. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.89 (m, 1H), 7.79 (m, 3H), 3.35 (br s, 2 H), 2.06 (s, 2H, free CH_3CN); IR (Nujol) 1611, 1581, 1299 cm^{-1}; HRMS (FAB$^+$, *m/z*) calcd for $C_{13}H_{13}CuN_4O_3S$ ($M + H^+$) 369.0083, found 369.0086.

General Experimental for the Catalytic Addition of Saccharin to Cycloalkenes. Into a 15 mL two-neck pear-shaped flask were added dry $Cu(Sac)_2$ (**9**) (39 mg, 0.091 mmol), 1,10-phenanthroline (17 mg, 0.091 mmol), and saccharin (H−Sac) (412 mg, 2.25 mmol). The flask was equipped with a condenser, sealed with a septum, and then flushed with N_2 for 0.2 h. The solids dissolved in anhydrous CH_3CN (2.2 mL), and the resulting solution was stirred at 50 °C for 0.7 h. To the ink-blue solution were added cycloalkene (1 mL, approximately 10 mmol depending cycloalkene used) and 70% t-BuOOH (0.31 mL, 2.25 mmol). The mixture was stirred at 50 °C under N_2 for 14 h. The reaction mixture was transferred into a round-bottom flask and concentrated *in vacuo* to remove acetonitrile and water, then the copper residue was removed from the mixture by dissolution in DCM (5 mL) and filtration through a 2 cm plug of silica gel in a 15 mL fritted filter. The product was eluted from the silica by rinsing with additional DCM (100 mL). In no case did the crude reaction mixture show evidence for a saturated product similar to **5**. Flash chromatography (silica, 3:1 hexane/ethyl acetate) gave the desired addition product. Each allylic amination product recrystallized smoothly from a minimum amount of 95% ethanol.

***N*-(2-Cyclopentenyl)saccharin (11a).** Through the general procedure above, cyclopentene was converted into 402 mg (72%) of **11a** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (m, 1H), 7.84 (m, 3H), 6.25 (m, 1H), 5.95 (dd, $J = 4.5$, 2.4 Hz, 1H), 5.40 (m, 1H), 2.79 (m, 1H), 2.43 (m, 2H), 2.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 138.2, 138.2, 138.1, 134.6, 138.1, 126.1, 124.9, 120.6, 59.6, 31.8, 29.1; IR (KBr) 3097, 2977, 2944, 1727, 1594, 1459 cm^{-1}; HRMS (FAB$^+$, *m/z*) calcd for $C_{12}H_{12}NO_3S$ ($M + H^+$) 250.0538, found 250.0522.

***N*-(2-Cycloheptenyl)saccharin (12a).** Through the general procedure above, cycloheptene was converted into 374 mg (60%) of **12a** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, $J = 6.9$ Hz, 1H), 7.86 (m, 3H), 5.94 (m, 2H), 4.96 (d, $J = 11.4$ Hz, 1H), 2.39 (m, 2H), 2.16 (m, 1H), 2.07 (m, 2H), 1.80 (m, 1H), 1.66 (m, 1H), 1.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 137.7, 134.6, 134.2, 132.7, 131.3, 127.4, 125.0, 120.7, 55.1, 32.4, 28.6, 28.4, 26.1; IR (KBr) 3090, 3024, 2928,

(38) Kubas, G. J. *Inorg. Synth.* **1990**, *28*, 68−70.
(39) Icbudak, H.; Olmez, H.; Yesilel, O. Z.; Arslan, F.; Naumov, P.; Jovanovski, G.; Ibrahim, A. R.; Usman, A.; Fun, H.-K.; Chantrapromma, S.; Ng, S. W. *J. Mol. Struct.* **2003**, *657*, 255−270.
(40) Differding, E.; Lang, R. W. *Helv. Chim. Acta* **1989**, *72*, 1248−1252.
(41) The dimeric copper(I) complex $[(Phen)CuI]_2$ facilitates the same reaction.

2856, 1729, 1612, 1550 cm^{-1}; HRMS (FAB^+, *m/z*) calcd for $C_{14}H_{16}NO_3S$ ($M + H^+$) 278.0851, found 278.0826.

***N*-(2-Cyclooctenyl)saccharin (13a).** Through the general procedure above, *cis*-cyclooctene was converted into 65 mg (10%) of **13a** as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, $J = 7.4$, 1.1 Hz, 1H), 7.72 (m, 3H), 6.07 (m, 1H), 5.81 (m, 1H), 5.67 (m, 1H), 2.21 (m, 4H), 1.8−1.56 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 143.5, 133.9, 133.3, 131.5, 128.3, 127.5, 123.3, 121.8, 81.1, 34.5, 28.6, 26.4, 25.7, 23.1; IR (KBr) 3035, 2943, 2863, 1719, 1594 cm^{-1}; HRMS (FAB^+, *m/z*) calcd for $C_{14}H_{16}NO_3S$ ($M + H^+$) 278.0851, found 278.0826.

***N*-(2-Cyclohexenyl)-di-*p*-toluenesulfonimide (4b).** Through the general procedure above, cyclohexene and bis-*p*-toluenesulfamide (739 mg, 2.25 mmol) was converted into 319 mg (35%) of **4b** as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, $J = 9.4$ Hz, 4H), 7.34 (d, $J = 9.4$ Hz, 4H), 5.73 (m, 1H), 5.39 (d, $J = 10.4$ Hz 1H), 4.80 (m, 1H), 2.45 (s, 6H), 2.43 (m, 1H), 2.10 (m, 1H), 1.96 (m, 1H), 1.85 (m, 2H), 1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 129.5, 128.2, 127.1, 60.5, 28.4, 23.9, 22.8, 21.6; IR (KBr) 3031, 2937 1595, 1493, 1168 cm^{-1}; HRMS (FAB^+, *m/z*) calcd for $C_{20}H_{23}NO_4S_2$ ($M + H^+$) 406.1147, found 406.1120.

Preparation of 4 from 3-Chloro-1,2-benzisothiazole-1,1-dioxide and 2-Cyclohexen-1-ol. Solid 3-chloro-1,2-benzisothiazole-1,1-dioxide (100 mg, 0.50 mmol) was weighed into a 10 mL two-neck pear-shaped flask, and the flask was equipped with a condenser and sealed with a septum. The vessel was purged with N_2 for 0.2 h, and 2-cyclohexenol (0.5 mL, 5.0 mmol) and pyridine (0.5 mL) were added by syringe. The mixture was heated to 50 °C for 14 h. The mixture was diluted with ethyl acetate (40 mL) and extracted twice with 0.1 M HCl (10 mL) and then with saturated brine (10 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated. A sample (2 mg) of the residue was diluted with DCM, and a gas chromatogram was obtained. The major band (>98% of signal) showed a molecular ion at 199 *m/z* ($M^+ - SO_2$). The sample was spiked with an authentic sample of **4**, and the chromatogram showed the same band and molecular ion pattern.

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