Solvent effects on the chemo- and site-selectivity of transition metal-catalyzed heterogeneous nitrene transfer reactions: Alternatives to chlorinated solvents.

Robert M. Ward,¹ Yun Hu,¹ Noah P. Tu² and Jennifer M. Schomaker¹,*

¹Department of Chemistry, University of Wisconsin, 1101 University Avenue, Madison, WI 53706

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Abstract

Transition metal-catalyzed, non-enzymatic nitrene transfer (NT) reactions that selectively transform C–H and C=C bonds to new C–N bonds represent a powerful strategy to streamline the preparation of valuable amine building blocks. Our group has been engaged in the development of silver-catalyzed NT reactions, where the nature of the ligand can be used to tune the chemo-, site- and enantioselectivity of the amination event in a predictable manner. However, the majority of solvents employed for these reactions are environmentally unfriendly and typically include dichloromethane, chloroform, 1,2-dichloroethane and benzene. In addition, the need for PhIO as the oxidant in our system gives heterogenous mixtures that have limited reaction throughput to date. In this work, a high-throughput experimentation (HTE) protocol for heterogeneous NT reaction mixtures is coupled with the American Chemical Society Pharmaceutical Roundtable (ACSPR) solvent tool to identify suitable replacements for chlorinated solvents and to better understand how the solvent affects chemo- and site-selectivity in NT. Silver catalysts were compared and contrasted other popular catalysts for NT using our HTE protocol, including dinuclear Rh and Fe/Mn
phthalocyanine catalysts, to highlight key differences between these systems. Several unexpected solvents were identified that gave both high conversions and selectivities in diverse NT reactions, providing alternatives to traditional chlorinated solvents. We hope these insights will encourage the community to: (1) consider more diverse solvent selections when developing new synthetic methods, (2) employ solvent tools to identify favorable solvent characteristics/parameters and (3) consider SHE impacts in reaction design.

Introduction

The prevalence of the carbon-nitrogen (C–N) bond in drugs, biomolecules and agrochemicals has stimulated the development of many strategies to introduce nitrogen into simple building blocks in an efficient manner. Transition-metal-catalyzed, non-enzymatic nitrene transfer (NT) is one approach to convert strong C–H bonds to new C–N bonds; however, catalysts must be capable of selecting for reaction at one specific C–H bond among many other possibilities. To address this challenge, our group has developed a suite of silver catalysts for the chemo-, site- and enantioselective additions of metal-supported nitrenes to alkenes, allenes and diverse C–H bonds (Scheme 1). The key design principle for tunability centers on finding the right combinations of silver(I) salts and sp² nitrogen-containing ligands to enforce diverse coordination environments at the metal nitrene with a predictable impact on the reaction selectivity. In this regard, silver catalysis differs from most first-row transition metal chemocatalysts (Fe, Mn, Co)[3-5] supported by simple porphyrins, phthalocyanines and salen ligands, as well as precious metals (Rh, Ru)[6,7] ligated to bridging carboxylate or similar ligands to furnish a ‘paddlewheel’ geometry around the metal center. These latter catalysts, with the exception of tailored porphyrin ligands designed by the Zhang group,[8] tend to favor only one type of C–H bond for amination. Thus, it can be challenging to tune the chemo- and site-selectivity of the NT by changes to the ligands supporting these metals. In contrast, we have shown that simple N-dentate ligands for silver(I) salts enable predictable and tunable chemo-[2f,g] site-[2h,c,e] and stereoselective transformations (Scheme 1).
One of the drawbacks of silver-catalyzed NT has been the perceived need to utilize chlorinated solvents to achieve high conversion, yield and selectivity. A handful of other solvents have been employed in NTs catalyzed by Rh, Fe and Mn complexes, including acetonitrile (MeCN), benzene (PhH) and isopropyl acetate (iPrOAc); however, the impact of different solvents on the solution-state structure of the silver complex and on potential non-covalent interactions (NCIs) that drive selectivity in the NT is unexplored.

Another issue with many NT transfer protocols is their heterogeneous nature, which makes small-scale screening by NMR or other spectroscopic techniques untenable. We have addressed these challenges by: 1) developing a convenient high-throughput experimentation (HTE) platform for rapid screening of heterogeneous mixtures of solvents, metals, ligands, oxidants and additives for NT that can be translated to other C–H functionalizations, 2) identifying alternative solvents for NT to replace chlorinated ones, 3) contrasting the behavior of silver against other conventional catalysts (Rh, Fe, Mn) for NT to better

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**Scheme 1.** Selected examples of tunable, chemo-, site- and enantioselective silver-catalyzed NT reactions.
understand the unique features of each catalyst system, and 4) improving our understanding of the role that solvent plays in dictating chemo- and site-selectivity in NT to aid in predictive catalyst design moving forward.

Solvent screenings in academic settings are typically narrow and rely heavily on familiar solvents, including tetrahydrofuran (THF), Et₂O, CH₂Cl₂, toluene (PhMe), dimethylformamide (DMF) and MeCN. While these solvents often prove successful, several are considered problematic with respect to safety, health and environment (SHE) and are not appealing in an industrial setting. From a sustainability viewpoint, solvents comprise the majority of the non-aqueous chemical waste from a reaction and better alternatives significantly reduce environmental impact. The American Chemical Society Pharmaceutical Roundtable (ACSPR) tool provides an array of potential replacements for problematic solvents; other solvent selection guides are available from companies that include GSK, Pfizer and Sanofi. These resources provide insights into solvent choice, including comparisons between diverse solvents in terms of SHE impacts.

In this paper, we report a HTE platform for heterogeneous catalysis based on ChemBeads technology that reveals surprising replacements for chlorinated solvents that are well-suited for a variety of transition metal-catalyzed NT reactions. As solvent effects have not been well-studied in NT, this works sheds insight into key differences between Ag and traditional metals (Rh, Fe, Mn) employed for NT that help to rationalize the unusual tunability and selectivity observed with Ag. We hope these insights will encourage the community to (1) consider more diverse solvent selections when developing new synthetic methods, (2) use solvent tools to identify favorable solvent characteristics/parameters and (3) consider the overall SHE impact of the solvent in reaction design.

**Results and discussion**

*Rationale for initial solvent choices.* While CH₂Cl₂ is an excellent solvent for Ag-catalyzed NT due to its high functional group compatibility, relative inertness to reactive intermediates and its ability to dissolve most organic compounds, health and environmental concerns necessitate the use of alternatives outside
the academic laboratory. To address this issue, non-traditional solvents were explored in NT reactions catalyzed by Ag and selected transition metals (Rh, Mn, Fe).

Previous work from our group suggested that the tunable chemo- and site-selectivity displayed by silver-catalyzed NT (Scheme 1) is due to a number of factors that can be manipulated for predictable catalyst design. These factors include: 1) how steric pressure around the putative silver nitrene impacts the trajectory of approach of a functional group (either an alkene or a C–H bond) to the reactive species, 2) whether NCIs are present between the substrate and catalyst in the selectivity-determining transition state (TS), and 3) the sensitivity of bond dissociation enthalpies (BDEs) to the identity of the nitrene precursor and catalyst. To assess the impact of solvent on these factors, the ACS solvent tool was used as a guide, where multivariate Principal Component Analysis (PCA) reduces a large number of potentially correlated parameters describing solvent features to a small number of descriptors. Two PCA descriptors that informed choices for initial solvent studies included polarity (PC1) and the ability to accept a H-atom from a donor (PC2), our experience in Ag-catalyzed NT was used to further narrow down solvent choices to those most likely to be tolerated under the reaction conditions. Solvents chosen for initial investigations were roughly divided into five classes: 1) aromatic solvents bearing π-withdrawing (PhNO₂), σ-withdrawing (PhCF₃), σ-donating (PhH, p-xylene), and π-donating (PhMe) groups, 2) alkyl ethers with activated 3° (trimethoxymethane (TMM), TAME) and 2° C–H bonds (dioxane, THF) to test if intermolecular amination competes with the intramolecular process, 3) carbonyl-bearing solvents (acetone, MIBK, EtOAc, iPrOAc, dimethyl carbonate (DMC)) to ascertain if Lewis basic groups coordinate to Ag as L- or L₂-type ligands to deliver different selectivities, 4) alcohols (2-propanol (IPA), tert-amyl alcohol, H₂O, hexafluoroisopropanol (HFIP)) to test the impact of solvent coordination to the catalyst or reaction with the PhIO, and 5) conventional NT solvents (CH₂Cl₂, DCE, MeCN, PivCN) and hexane as controls. For the sake of simplicity, the solvents and catalysts employed in this study are shown in Figure 1.

General process for high-throughput experimentation (HTE). One barrier to extensive solvent screening is the need for large quantities of valuable metals and ligands. HTE is an efficient way to generate large data sets on much smaller scales than traditional reactions. However, in the case of Ag-catalyzed NT, the poor
solubility of silver triflate and other silver salts in many organic solvents presents a challenge, as does the need to use sparingly soluble PhIO as the oxidant. Attempts to run HTE using reagent slurries showed poor shelf life and inconsistent results; thus, we sought a solid delivery vehicle to dispense sub-milligram amounts of required reagents in a reasonably reproducible manner. ChemBeads technology developed by

![ChemBeads Technology](image)

**Figure 1.** Solvents and catalysts employed in this study.

AbbVie appeared ideal for our needs. With the help of AbbVie, a variety of silver salts were successfully loaded onto ChemBeads. Molecular sieves (MS) were loaded into 96-well plates using a 50 mg ChemBead scoop, while the substrates and solvents were dispersed using a multi-channel pipetter (see Schemes S1-S7 in the Supporting Information for experimental details). The HTE reactions were conducted using three different procedures to assess ease of the experimental set-up and the reproducibility offered by each procedure. **Procedure A** was carried out on a 0.01 mmol scale and is described in detail in Sections III-VI in the Supporting Information. This process was validated with control experiments using **Procedures B-C** (see the SI), then applied to an initial screen of 24 solvents. Analysis was carried out using 1-chloro-2,4-dinitrobenzene as the internal standard (IS); yields are reported as the ratio of product and starting material.
Studies of chemoselective NT using carbamate precursors. Metal-supported nitrenes react with π-bonds to form aziridines; thus, chemoselectivity in systems bearing both alkenes and allylic C–H bonds can be problematic. Challenges in achieving catalyst control over chemoselectivity in the amination of homoallylic carbamates inspired our efforts in Ag-catalyzed NT (Scheme 1A). Tunable chemoselectivity was reported in CH$_2$Cl$_2$, where the preference for aziridination or C–H insertion depended on the Ag:ligand ratios. Bicyclic aziridine formation dominated at lower loadings of 1,10-phenanthroline (phen) as the ligand (1:1.25 AgOTf:phen). At higher ligand loadings (1:3 AgOTf:phen), the selectivity was reversed to give C–H amination as the major product. Previous experiments showed that coordinating counteranions in the Ag salt increased the amount of C–H insertion; thus, we were curious if coordinating solvents would have a similar effect or whether tunable chemoselectivity would be maintained across diverse solvents.

Both the (Z)-1 and (E)-2 isomers of a homoallylic carbamate were treated with 10 mol % AgOTf and either 10 mol % or 40 mol % phen (Scheme 2, Figure S3 in the SI for the full list of solvents). Scheme 2A show the total conversion of the homoallylic carbamates (Z)-1 or (E)-2 to products cis-1a, cis-1b, trans-2a and/or trans-2b, while the heat map in Scheme 2B shows the preference for formation of the bicyclic aziridine (BA) or the allylic amine (CH). Interestingly, several solvents gave little-to-no conversion using a 1:1 ratio of AgOTf:phen, including xylene, trimethoxymethane (TMM), tert-amyl alcohol, DMC, PrOAc, TAME, 1,4-dioxane, PhMe, H$_2$O, MeCN, EtOAc, IPA, THF, HFIP and hexane. In some cases, this may be due to the poor solubility of the reagents in non-polar solvents, while in other cases, the solvent may bind to the Lewis acidic silver catalyst and shut down reactivity. Solvents that gave no conversion using a 1:4 ratio of AgOTf:phen include xylene, PhMe, MIBK, TMOA, tert-amyl alcohol, DMC, PrOAc, TAME, PivCN, DMSO, dioxane, PhMe, H$_2$O, MeCN, EtOAc, IPA, THF, HFIP and hexane. Again, this may be due to solubility issues; five solvents (PhNO$_2$, PhCF$_3$, acetone, CH$_2$Cl$_2$ and DCE) gave product using a 1:4 ratio of AgOTf:phen, while nine showed reactivity at lower loadings of phen.
When a 1:1 ratio of AgOTf:phen was employed (Scheme 2A), both CH₂Cl₂ and DCE performed in agreement with our previously reported work,²f giving good yields and good-to-excellent chemoselectivity (Scheme 2B) for BA over CH. For CH₂Cl₂ and DCE, the chemoselectivity was lower using (Z)-1 as compared to (E)-1. PhNO₂ (and to a lesser extent, PhCF₃) gave promising yields and chemoselectivity for

Scheme 2. Impact of solvent on chemoselective NT using (E)- and (Z)-alkenes and Ag or Rh catalysts. Reaction conversions were determined via ¹H-NMR using 1-chloro-2,4-dinitrobenzene as the internal standard. Site-selectivity was determined for reactions with >10% conversion and was not determined (ND) if the conversion was <10%. If no desired product was observed, the results are labeled not available (NA).

the aziridine (BA:CH 6.7:1 to 20:1). Interestingly, anisole gave promising conversion in the NT, but much lower chemoselectivity for the aziridines (2.6:1-3:1). This may be due to anisole engaging in weak
interactions with the Ag to effectively increase the steric environment around the metal nitrene, ultimately favoring C–H insertion. Acetone gave more C–H amination, especially with (Z)-I; other carbonyl-containing solvents (see Tables S1 and S3 in the SI for details) gave either low conversion or no observable products. These results suggest that coordinating solvents increase the steric environment around the Ag center and either change the chemoselectivity or shut down reactivity. Finally, although MeCN gave no reaction at low ligand loadings, the more sterically congested PivCN gave ~20% conversion to the aziridines with excellent 20:1 chemoselectivity.

When a 1:4 ratio of AgOTf:phen was employed (Scheme 2A), CH₂Cl₂ performed as reported in our previous work,²f giving excellent chemoselectivity for C–H amination over aziridination. PhNO₂ and PhCF₃ also showed chemoselectivity for C–H amination, albeit with lower conversion. Thus, aromatic solvents bearing electron-withdrawing groups may be viable alternatives to chlorinated solvents for both aziridination and C–H amination with additional optimization, while PivCN is a promising alternative for aziridination. However, use of chlorinated solvents is justified when tunable chemoselectivity is desired by altering the Ag:phen ratios.

The reaction of (Z)-I with Rh₂(OAc)₄ (Scheme 2A) showed conversion with a much broader range of solvents compared to Ag-based catalysts; however, the ratio of BA:CH cis-1a:cis-1b was much lower, ranging from ~1.3:1 to 3.2:1. More importantly, Rh catalysis does not facilitate tunable chemoselectivity.

Studies of site-selective C–H amination using sulfamates as nitrene precursors.

Comparison of solvent and catalyst in the cyclization of homobenzyl sulfamates. The 1,3-aminoalcohol moiety is common in pharmaceuticals and bioactive natural products. Intramolecular amination via NT of sulfamates provides a streamlined approach to these motifs, as they prefer to form 6- over 5-member rings, due to a more favorable 7-member TS dictated by the longer oxygen-sulfur bonds in a sulfamate compared to the oxygen-carbon bonds in the analogous carbamates.²b Indeed, sulfamate 3 formed only 6-member ring 4 over the 5-member heterocycle 5, irrespective of the catalyst (Ag, Rh or Fe) or the solvent (Scheme 3).
Paradine, White-Clark and [FePc]SbF₆ catalysts revealed differences dependent on the catalyst and solvent. We were pleased to find that NT reactions of 3 to 4 catalyzed by (tpa)AgOTf were effective in non-chlorinated solvents, including PhOMe, DMC, iPrOAc and PivCN (Scheme 3, Condition A). While PhMe, MIBK, tert-amyl alcohol and PhNO₂ gave lower conversions, the mass balances were good; extended reaction times may render these as potential alternatives to chlorinated solvents. In general, [Ag(Py₅Me₂)OTf]₂ gave lower conversions than (tpa)AgOTf, although MIBK, TAA and PhNO₂ gave higher yields (Scheme 3, Condition B).

In comparison to the silver catalysts, Rh₂(OAc)₄ displayed higher yields across the range of tested solvents (Scheme 3, Conditions C-D), although this is offset by the significantly higher cost of Rh compared to Ag. The soluble oxidant PhI(OAc)₂ (PIDA) generally gave higher conversion as compared to PhIO, but yields were comparable or higher using PhIO in iPrOAc, DMC, PhCF₃, TAA and PivCN.

Conversions of 3 to 4 were lower using phthalocyanine-supported [Fe] and [Mn] complexes (typically used in PhH or chlorinated solvents), as compared to Rh₂(OAc)₄, although extended reaction times may prove beneficial (Scheme 3, Conditions E-G). These catalysts tolerated PhOMe, PhCF₃, DMC, iPrOAc and

![Scheme 3](image)

Scheme 3. Performance of various catalysts and solvents in the benzylic C–H amination of 3 represented here as % yield in the table. The reaction conditions for each catalyst system can be found in Tables S6-S12 in the Supporting Info. Solvents are listed by order of the $E^TN$ polarity scale values. Solvents without $E^TN$ values are denoted as not available (n/a).
PivCN as suitable replacements for PhH or DCE. The White-Paradine catalyst performed better than [FePc]SbF₆ or the White-Clark catalyst.

In summary, all three types of catalyst systems (Ag, Rh, Fe/Mn) tolerated a greater diversity of solvents than we anticipated. Despite the flammability of DMC and iPrOAc, the GSK solvent selection guide does recommend them as suitable alternatives for chlorinated solvents.¹¹

**Amination of 3º C(sp³)–H vs. 2º benzylic C–H bonds using sulfamate nitrene precursors.** In situations with two competing reactive γ C–H bonds, achieving good site-selectivity can be challenging. For example, an electrophilic metallonitrene intermediate must select between the electron-rich 3º C(sp³)–H and the weaker benzylic C–H bond of 6 (Scheme 4) to furnish 3-amino-1-propanols 7 and 8.²ᵇ,c,d It should be pointed out that the solvent may also engage with the counteranion of the catalyst, potentially increasing the electrophilicity of the reactive intermediate. The ability of Ag to bind simple sp² N-dentate ligands and form sterically diverse coordination geometries was used to tune the site-selectivity between amination at either the benzylic or the 3º alkyl C(sp³)–H bond to give 7 and 8, respectively. Excess tert-butylbipyridine (‘Bubpy) favored the formation of 8, while switching to a tpa ligand in PhCF₃ favored formation of 7. Experimental and computational studies suggested that non-covalent interactions (NCIs) in the TS using Ag(tpa)OTf biased selectivity in favor of 7,²ᵇ,d as the aromatic ring of 6 can participate in a π–π stacking or Ag–π interactions with a pyridine on the bound ligand.

**Scheme 4.** Impact of catalyst on the site-selectivity of Ag-catalyzed C–H amination between competing benzylic and 3º alkyl C(sp³)–H bonds.
The possibility of a π-π interaction between the pyridine arm of the tpa ligand and the aromatic group of the substrate was supported by a small initial solvent screen of aprotic solvents using a similar sulfamate 9 (Scheme 5A). This study showed that more lipophilic solvents (as determined by the $E_{TN}$ polarity scale values) gave greater selectivity for amination of the benzylic C–H bond to furnish 10. To further test the impact of solvent on the ratio of benzylic:tertiary (B:T) C–H bond amination (10:11), a set of 24 solvents was examined with three different ligands, tpa, (o-Me)$_3$tpa and 2 equivalents tert-butylbipyridine (‘Bubpy) (Scheme 5). The HTE data using tpa as the ligand agreed well with previous results in the same solvents. All the screened solvents gave conversion to products >60% except for TAME and HFIP. The B:T 10:11 ratio tracked reasonably well with $E_{TN}$ in hexane and aromatic solvents, with p-xylene ($E_{TN}$ 0.074) providing the highest B:T ratio at 7.5:1, which drops to 2.7:1 in p-nitrobenzene ($E_{TN}$ 0.324).

Ethereal solvents gave moderate B:T selectivity, tracking reasonably well with $E_{TN}$ within this solvent class. Interestingly, ketones and esters (acetone, MIBK, EtOAc, iPrOAc, DMC) were all suitable solvents in terms of conversion and yield but showed little difference in the B:T 10:11 ratios, varying from 4.6:1 with DMC to 3.4:1 with EtOAc. Protic solvents (IPA, TAA, H$_2$O, HFIP) varied in terms of their success in NT. The B:T 10:11 ratio in H$_2$O agreed with previous work (HTE 3.1:1; literature 2.7:1), but much to our surprise, tert-amyl alcohol (TAA, $E_{TN}$ 0.32) gave a much higher B:T 10:11 ratio of 7.3:1 vs. PhNO$_2$ ($E_{TN}$ 0.324, B:T 2.7:1). Benchmarking TAA using our standard protocol on a 0.1 mmol scale still showed a marked preference for benzylic C–H amination (B:T = 5.3:1), indicating factors in addition to polarity play a role in controlling the site-selectivity. One possibility is that the TAA may react or engage with the PhIO to form a new active oxidant that leads to a higher preference for benzylic C–H amination. A more likely hypothesis to rationalize the high selectivity for benzylic C–H amination observed in TAA is that the alcohol itself may serve as a ligand for Ag, where the steric bulk of the alcohol may minimize the competing formation of the dimer. Finally, conventional solvents for NT (CH$_2$Cl$_2$, DCE, MeCN, PivCN) were included as controls. All of these solvents gave good conversions and yields using (tpa)AgOTf as the catalyst, with B:T ratios ranging from 1.9:1 to 3:1, again correlating reasonably well with $E_{TN}$ values.
Scheme 5. A) Solvent effects on the site-selective amination of a 3º C(sp³)–H vs. a 2º benzylic C–H bond. B) Site-selective amination of a 3º C(sp³)–H vs. a 2º benzylic C–H bond with a panel of 24 solvents and two ligands, tpa and (o-Me)₃tpa. If no desired product was observed, the results are labeled not available (NA). Solvents are listed by order of the $E^{I}_{N}$ polarity scale values. Solvents without $E^{I}_{N}$ values are denoted as not available (n/a).
The fluxionality of Ag complexes in solution can lead to monomer-dimer equilibria that may be impacted by the solvent identity; this is something that should be borne in mind when choosing an Ag/solvent combination for NT. In addition, the relative solubilities of monomeric vs. dimeric catalytic species may differ, resulting in unexpected site-selectivity in the NT. To explore this further, reaction of 9 was carried out with AgOTf supported by an (o-Me)tpa ligand, which shows significantly more dimer formation in CD$_2$Cl$_2$ by VT-NMR, as compared to (tpa)AgOTf (although dimer is still present using tpa). In general, the (o-Me)tpa ligand gave similar or slightly lower conversion to products than tpa (Scheme 5A). A lower and narrower range of B:T ratios ($0.7:1 - 2.6:1$, Scheme 5B) was also noted compared to tpa ($1.9:1 - 7.5:1$). This suggests that either the solvent has little impact on the monomer:dimer ratio with this catalyst system or that the additional Me group on the pyridine arms of the ligand leads to a decreased tendency to engage in effective π-π interactions that favor benzylic C–H amination; these hypotheses would need to be explored computationally.

Finally, a (Bubpy)$_2$AgOTf catalyst has been reported to select for 3º C(sp$^3$)–H bonds over benzylic ones in the amination of 9. In general, (Bubpy)$_2$AgOTf gave lower conversion than (tpa)AgOTf or [Ag(Py$_5$Me$_2$)OTf]$_2$. However, PhMe, PrOAc, MIBK, TAA, PhNO$_2$ and PivCN all gave ~60% conversion of 9. Of these solvents, only PhMe (3:1) MIBK (3.5:1) and PivCN (11:1) favored 3º C(sp$^3$)–H amination; there appears to be no correlation between site-selectivity and $E^\text{T}_N$. Other solvents showing lower conversion of 9, but high site-selectivity in favor of T, include hexane, PhCF$_3$, CH$_2$Cl$_2$, DCE, EtOAc, DMC and MeCN. Solvents with poor site-selectivity include xylene, TAME, dioxane, PhOMe, TAA, PhNO$_2$ and IPA. While we did not examine the monomer:dimer equilibrium by VT-NMR and DOSY, it is likely solvent impacts whether the monomeric or dimer Ag complex functions as the major catalytic species in solution and leads to the observed differences in site-selectivity. The important message from these studies is that not only does the ligand identity determine the tunability of the NT, but the solvent plays a key role. In summary, Scheme 5 shows that the best conditions for benzylic C–H amination at rt use (tpa)AgOTf in TAA, while the best unoptimized conditions for T amination employ (o-Me)$_2$tpaAgOTf.
in PivCN. In cases where it is desirable to use the same solvent to achieve tunable site-selective NT by changing only the ligand identity, DMC and PhCF₃ give results superior to chlorinated solvents.

The minimal response of the B:T 10:11 selectivity using the dimeric Ag catalyst supported by (o-Me)₃tpa prompted us to compare its behavior to that of Rh₂(OAc)₄ (Scheme 5, cat 4), which forms a highly electrophilic metal-supported nitrene that favors amination at e-rich 3° C(sp³)–H bonds. Differences in response to solvent identity between silver catalysts and Rh₂(OAc)₄ were explored using a 12 solvent screen. Reaction of 9 in CH₂Cl₂ with Rh₂(OAc)₄ gives a 1.5:1 T:B 11:10 ratio, but all solvents tested proved compatible with the reaction conditions and gave full conversion of 9. The observed T:B 11:10 ratios were slightly higher than the value in CH₂Cl₂ and ranged from 2.0 – 2.7:1. However, the similar ratios suggested that the solvent has little impact on site-selectivity, in marked contrast to the primarily monomeric (tpa)AgOTf, but similar to the dimeric complex formed from AgOTf and (o-Me)₃tpa.

White and coworkers found that [Fe] and [Mn] phthalocyanine-supported complexes for C–H amination display excellent selectivity for activated C–H bonds, including benzylic ones. Sulfamate 9 was reported to give the best selectivity with [FePc]SbF₆ (14:1 B:T 10:11) in a mixture of PhH/MeCN, while the White-Paradine catalyst gave modest selectivity (3:1 B:T 11:10). A set of 12 solvents were tested with [FePc]SbF₆ and the White-Paradine (WP)/White-Clark (WC) catalysts (Scheme 5, cat 5-7). All solvents gave conversion to products, with the exception of TMM, which may poison the [Fe] and [Mn] catalysts. In agreement with literature precedent, [FePc]SbF₆ provided superior selectivity for benzylic amination to 10 as compared to the WP catalyst (for solvents with Pdt/IS ratios > 0.20, selectivity is represented by 20:1). MIBK and TAA provided lower selectivity for benzylic C–H amination than the other solvents tested. Selectivity using the WC catalyst appeared more sensitive to the nature of the solvent as compared to either the [FePc]SbF₆ or WP catalysts, perhaps due to the increased Lewis acidity of the former. As expected, none of these catalysts preferred 11 over 10 in any tested solvent.

Studies of site-selective C–H amination using carbamates as nitrene precursors.

Formation of 5- vs. 6-membered rings via C–H amination of carbamates. The challenge in directly comparing the reactivity of sulfamate 3 (Scheme 3) vs. carbamate 12 (Scheme 6) in NT is that 12 can form
either 13 through amination of a benzylic C–H bond or 14 by reaction at the unactivated 2º C–H bond, depending on the catalyst. The reactivities and site-selectivities of NT with Ag(dmBOX)ClO₄, [Ag(Py₅Me₂)ClO₄]₂ and Rh₂(OAc)₄ were compared in diverse solvents (Scheme 6). Ag(dmBOX)ClO₄ gave excellent selectivity for 13 in all solvents except TAME and iPrOAc. MIBK and PhOMe gave results comparable to CH₂Cl₂ and DCE and are potential replacements for chlorinated solvents.

The dimeric [Ag(Py₅Me₂)ClO₄]₂ complex favors formation of the 5-member ring 14 over 13 in CH₂Cl₂, even when the latter C–H bond is weaker, as is the case in 12. Conversion was lower as compared to the less sterically congested Ag(dmBOX)ClO₄, but extended reaction times could mitigate this issue. MIBK, PhOMe and DCE showed the highest conversions, while site-selectivity favoring the 5-member ring 14

Scheme 6. Site-selectivity with dissimilar C–H bonds: formation of 5-MR 13 vs. 5-MR 14 carbamates using a 12 solvent screen with Ag(dmBOX)ClO₄, [Ag(Py₅Me₂)ClO₄]₂ and Rh₂(OAc)₄. If no desired product was observed, the results are labeled not available (NA).
was highest in DCE (4.5:1) and PhCF₃ (3:1). Finally, Rh₂(OAc)₄ gave poorer conversion as compared to Ag(dmBOX)ClO₄, with a slight preference for formation of 14 across multiple solvents.

Tunable, chemocatalyzed site-selective amination between competing similar C–H bonds to furnish 1,2- or 1,3-aminoalcohols is difficult, especially when the bonds are unactivated. Despite this, we recently reported two new Ag catalysts capable of tuning for formation of either a 5- or 6-member ring in aminations of C–H bonds with similar steric environments and bond dissociation enthalpies (BDE). Notably, BOX ligands that favor the 6-member ring have been employed to great effect in enantioselective aminations of propargylic and benzylic C–H bonds. Solvent screening of with Ag(dmBOX)ClO₄ (Scheme 7) gave only recovered in alcoholic solvents (94 – 100%). With the exception of PhMe, non-polar solvents (Eₜ < 0.198) gave no products by ¹H NMR; in contrast, electron-deficient aromatic (PhCF₃, PhNO₂) and chlorinated solvents (DCE, CH₂Cl₂) gave complete conversion of 15. Electron-rich arenes (PhOME) gave lower yields than electron-poor ones, possibly due to Ag-π(solvent) interactions that increase steric hindrance and/or reduce the electrophilicity of the silver nitrene; coordination of Ag to the ether oxygen is another possibility. Ketones gave slightly better conversion compared to esters; interestingly, PivCN gave full conversion, but MeCN gave no reaction; presumably, steric pressure from the ℜ-butyl group of PivCN hinders coordination of the solvent to the Ag center. Formation of the 6-member ring 16 was favored in all cases over 17, although the selectivity was moderate (1.6 – 4 16:17). The best combination of yield and ratios of 16:17 were noted with PhCF₃ (98%, 3.8:1), CH₂Cl₂ (95%, 3:1), PhNO₂ (72%, 4:1), DCE (98%, 3.5:1) and PivCN (98%, 3:1). Solvents with sterically accessible oxygen lone pairs gave lower selectivities, supporting the hypothesis that a less hindered coordination environment around Ag, coupled with the potential for binding of the Lewis basic carbonyl of the carbamate to the Ag center, helps to favor formation of the larger ring.

Preferred formation of the 5-member ring using [Ag(Py₅Me₂)ClO₄]₂ was previously reported in aminations of unactivated 3º, 2º and even 1º C–H bonds. Examining the effect of solvent on the ratio of 16:17 showed a similar trend in reactivity as compared to Ag(dmBOX)ClO₄. With the exception of HFIP, polar protic solvents and non-polar solvents (Eₜ < 0.198) gave no product formation. Esters and DMC
Scheme 7. Site-selectivity with similar C–H bonds: formation of 6- or 5-member cyclic carbamates from unactivated C–H bonds in a 12 solvent screen with Ag(dmBOX)ClO₄, Ag(Py₅Me₂)ClO₄, and Rh₂(OAc)₄. If no desired product was observed, the results are labeled not available (NA).
gave poor conversion, presumably due to oxygen coordinating to the Ag of the dimeric complex. In agreement with results using dmBOX as the ligand, electron-deficient (PhCF₃, PhNO₂) and chlorinated solvents (DCE, CH₂Cl₂) provided the highest NMR yields with full conversion of 15. All solvents promoting effective NT gave >20:1 ratio of 17:16, suggesting the steric pressure exerted by [Ag(Py₅Me₂)ClO₄]₂ compared to Ag(dmBOX)ClO₄ favors a 6-member TS to exclusively favor 17.

Finally, employing the same 12-solvent set used with Rh₂(OAc)₄ gave low conversions of 15, favoring formation of 17:16 in >20:1 ratio. Thus, in reactions of carbamate-based nitrene precursors, the less expensive [Py₅Me₂AgClO₄]₂ catalyst is superior to Rh₂(OAc)₄. Overall, several alternatives to chlorinated solvents were identified that give good yields and tunable site-selective NT reactions.

**Conclusion**

Extensive solvent screens using HTE approaches can be used to provide more sustainable conditions for NT reactions, as well as insights into functional group tolerance, non-covalent interactions, and other factors that affect catalysis. In this study, different carbamate and sulfamate nitrene precursors were examined with a range of Ag, Rh, Fe and Mn catalysts in an array of solvents to assess the conversion, yield, and/or chemo- and site-selectivity of the reaction. Key to the success of these studies was the implementation of a HTE platform able to tolerate the heterogenous reaction conditions of these oxidation C‒H functionalization reactions. Sulfamates were the most tolerant of a diverse range of solvents. Polar solvents with coordinating lone pairs (H₂O, tert-amyl alcohol), as well as solvents with low dielectric constants (hexane), were viable using (tpa)AgOTf as the catalyst. The hypothesis that non-polar solvents maximize π-π stacking or Ag-π interactions between the (tpa)AgOTf catalyst and the aryl group of the substrate to favor benzylic C‒H bond amination was insufficient to explain the trends in site-selectivity using t-amyl alcohol and hexane. Further experimentation is necessary to assess whether solvent-dependent solubility or a change in the solution state of the active catalyst are operate and impact site-selectivity. Benchmarking other common NT catalysts with a broader range of solvents revealed that more environmentally sustainable solvents (DMC, iPrOAc, PhOMe) are compatible with NT conditions. Moreover, catalysts thought to promote concerted NT processes (Rh) appeared more tolerant of diverse solvents than those thought to proceed...
through triplet nitrene intermediates (Ag, Fe, Mn). However, the Lewis acidity of the metal may also play a major role in dictating the sensitivity to solvent.

In general, carbamates were more sensitive to the solvent identity, providing either decreased or no conversion to products in non-polar and polar protic solvents. Computational studies of Ag-catalyzed NT involving carbamate precursors suggest that coordination between the Ag and the carbamate carbonyl oxygen is important; this key interaction may be more easily disrupted by solvent identity than in sulfamates. Finally, reactions involving tunable site-selective NT between two competing C–H bonds were more tolerant of solvent changes than reactions focused on tunable chemoselectivity between an alkene and an allylic C–H bond. Overall, these solvent studies provided additional insight into the role of solvent in transformations involving highly reactive metal-supported nitrenes and provide several greener alternatives to the chlorinated solvents and benzene typically used for NT. Thus, performing broader solvent screens can be beneficial to SHE considerations in the development of new methods, can justify why certain solvents must be used and serve as mechanistic probes to shed additional insights into factors that determine reactivity and selectivity.

AUTHOR INFORMATION

Corresponding Author

*schomakerj@chem.wisc.edu

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Supporting Information. Experimental procedures, computational details, and characterization data for all new compounds are available in the Supporting Information.

The following files are available free of charge: Supplementary Information (PDF)

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ABBREVIATIONS

\( dr \), diastereomeric ratio; \( ee \), enantiomeric excess; INT, intermediate; NCI, non-covalent interaction; DFT (density functional theory)

REFERENCES


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