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

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Abstract

Transition metal-catalyzed, non-enzymatic nitrene transfer (NT) reactions to selectively transform C–H and C=C bonds to new C–N bonds are a powerful strategy to streamline the preparation of valuable amine building blocks. However, many catalysts for these reactions use environmentally unfriendly solvents that include dichloromethane, chloroform, 1,2-dichloroethane and benzene. We developed a high-throughput experimentation (HTE) protocol for heterogeneous NT reaction mixtures to enable rapid screening of a broad range of solvents for this chemistry. Coupled with the American Chemical Society Pharmaceutical Roundtable (ACSPR) solvent tool, we identified several attractive replacements for chlorinated solvents. Selected catalysts for NT were compared and contrasted using our HTE protocol, including silver supported by *N*-dentate ligands, dinuclear Rh complexes and Fe/Mn phthalocyanine catalysts.

Introduction

The prevalence of the carbon-nitrogen (C–N) bond in drugs, biomolecules and agrochemicals has stimulated new strategies to introduce nitrogen into 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;[1] however, useful catalysts must show good selectivity. Our group has developed a suite of silver catalysts for chemo-, site- and enantioselective additions of metal-supported nitrenes to alkenes, allenes and diverse C–H bonds.[2] Interestingly, the ligand identity can tune the chemo- and site-selectivity of the NT event, a situation unique compared to most first-row transition metal chemocatalysts (Fe, Mn, Co)[3-5] and precious metal (Rh, Ru)[6,7] catalysts ligated by bridging carboxylates. Such catalysts, with the exception of tailored porphyrin ligands for Co designed by the Zhang group,[8] tend to show selectivity only for specific types of C–H bonds and modifying the supporting ligands to tune selectivity is challenging. In contrast, simple N-dentate ligands on Ag(I) salts enable controlled chemo-,[2f,g] site-[2b,c,e] and stereoselective[2h,i] transformations, where the right combinations of silver(I) salts and sp^2 nitrogen-containing ligands enforce diverse coordination environments at the metal nitrene that predictably impact reaction selectivity.

A drawback of Ag-catalyzed NT is the perceived need to use chlorinated solvents. Non-chlorinated solvents have certainly been employed in NT reactions catalyzed by diverse metals (acetonitrile, pivalonitrile, benzene, isopropyl acetate, $PhCF_3$);[6i,9] however, the impact of solvent on the solution-state structure of Ag complexes and non-covalent interactions (NCIs) that may drive selectivity is largely unknown. Solvent screening in academic settings typically include only a few standard solvents, many of which are problematic with respect to safety, health and environment.[10] The American Chemical Society Pharmaceutical Roundtable (ACSPR) tool[11] and solvent selection guides from GSK[12], Pfizer,[13] Sanofi[14] and others[15] offers appealing alternatives, but exploring diverse solvents using a traditional approach is onerous. In this work, we implemented a high-throughput experimentation (HTE) platform for heterogeneous NT reactions based on ChemBeads technology for rapid screening of solvents, metals (Ag, Fe, Mn, Rh), ligands and oxidants. Our goals were to identify replacements for chlorinated solvents and obtain insights into the influence that the solvent might have on the tunability and selectivity observed with Ag and other common catalysts for NT.

Experimental design

Rationale for initial solvent choices. While CH_2Cl_2 is an excellent solvent for Ag-catalyzed NT, health[16] and environmental concerns[17] necessitate alternatives outside the academic laboratory. Previous studies in CH_2Cl_2 suggest that the tunable chemo- and site-selectivity displayed in Ag-catalyzed NT is due to:[2] 1) steric pressure around the nitrene impacting the trajectory of approach of a functional group (e.g. alkene or C–H bond) to the reactive species, 2) NCIs present between the substrate and catalyst, and 3) the sensitivity of bond dissociation enthalpies to the nitrene precursor and catalyst.[2] To assess solvent impact on these factors, multivariate Principal Component Analysis (PCA) in the ACS solvent tool was used to reduce a large number of potentially correlated parameters describing solvent features to two main descriptors. These PCA descriptors were polarity (PC1) and the ability to accept a H-atom from a donor (PC2).[11] A representative range of solvents (24) were chosen from amongst 272 entries in the database for initial investigations and divided into five classes (abbreviations are given in Figure 1): 1) aromatic solvents bearing π-withdrawing ($PhNO_2$), σ-withdrawing ($PhCF_3$), σ-donating (PhH, *p*-xylene), and π-donating (PhOMe) groups, 2) alkyl ethers (trimethoxymethane, *t*-amylmethylether, dioxane, THF) to test for possible intermolecular amination, 3) carbonyl-bearing solvents (acetone, methyl-*iso*-butyl ketone, EtOAc, ^{i}PrOAc, dimethyl carbonate) to ascertain if Lewis basic groups coordinate to Ag as L- or L2-type ligands and influence selectivity, 4) alcohols (^{i}PrOH, *tert*-amyl alcohol, hexafluoroisopropanol (HFIP)) and H_2O to test whether these solvents coordinate to the catalyst or react with PhIO, and 5) typical NT solvents (CH_2Cl_2, $(CH_2)_2Cl_2$ (DCE), MeCN, PivCN) and hexane as controls.

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 generates large data sets on much smaller scales than traditional reactions.[18] However, the poor solubility of AgOTf and other metal salts in many organic solvents presents a challenge. 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 reproducible manner. ChemBeads technology was ideal for our needs and with the help of AbbVie, Ag and other metal salts used in this study were successfully loaded onto ChemBeads.[19]

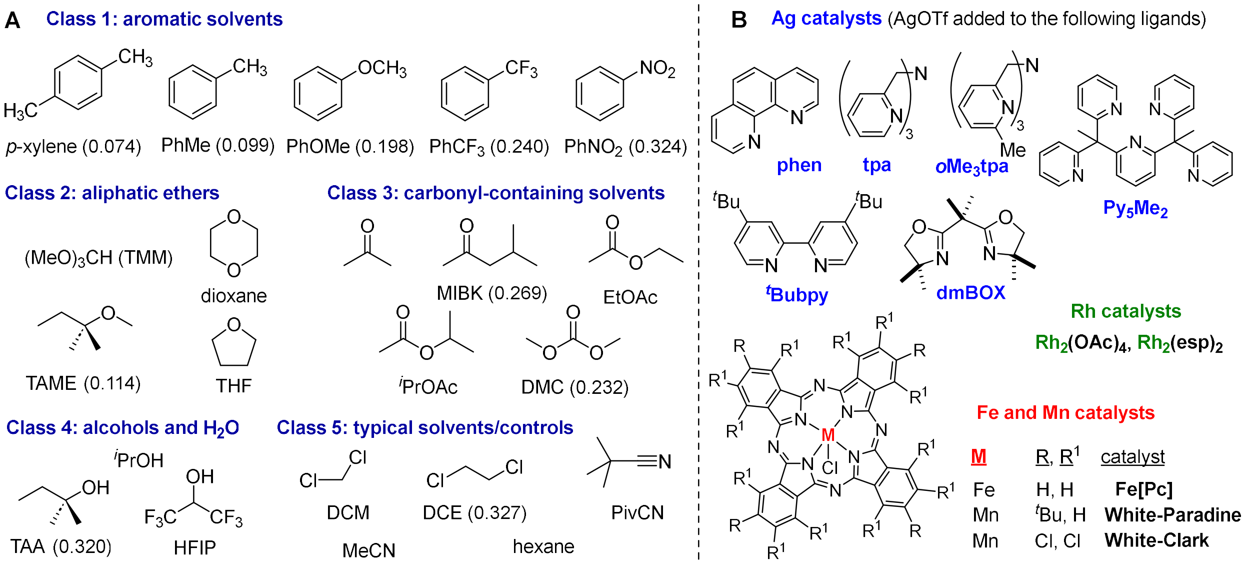


Figure 1. Solvents and catalysts employed in this study.

HTE reactions were carried out on a 0.01 mmol scale. ChemBeads coated with either the catalyst or the precursor metal salt were added to a 96-well plate, followed by addition of a stock solution of ligand in a suitable solvent dispersed using a multi-channel pipetter. The contents were mixed and the solvent evaporated in a dry box. A stock solution of substrate in DCE was added and the mixture dried overnight in a dry box purged with N_2. A portion of 4 Å MS was added using a 50 mg ChemBead scoop, followed by addition of PhIO or suitable oxidant using a 5 mg scoop, then addition of the solvent. Selected HTE studies were validated with control experiments run on at least a 10x scale using conventional glassware and/or vials equipped with a stir bar. Once HTE results were validated by scale-up, conditions were applied to a broader screen of solvents. Analysis was carried out using 1-chloro-2,4-dinitrobenzene as the internal standard (IS) and yields reported as the ratio of (product + starting material)/IS (Sections III-VI in the Supporting Information contain additional details).

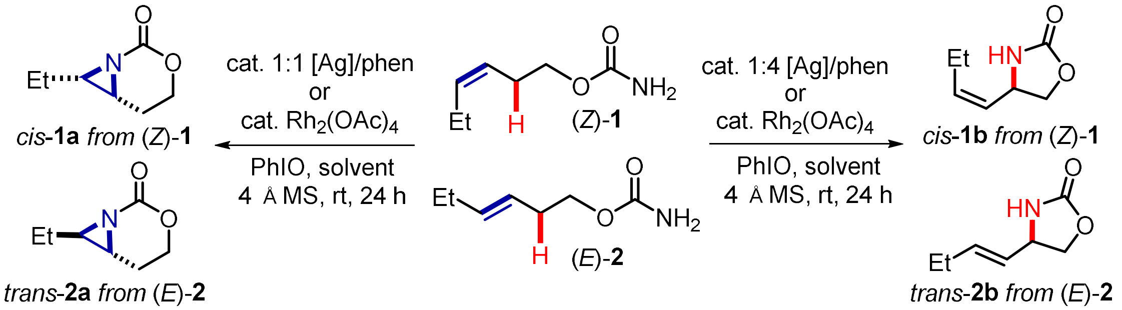
Results and discussion

Studies of chemoselective NT using carbamate precursors. Carbamates containing both alkenes and allylic C–H bonds often give poor chemoselectivity with Rh catalysts.[20] We found selectivity for aziridination vs. C–H insertion is tunable using Ag-catalyzed NT in CH_2Cl_2, depending on the Ag:ligand ratios (Scheme 1).[2c,g] Bicyclic aziridines (BA) *cis*-**1a** and *trans*-**2a** dominate at low 1,10-phenanthroline (phen) (1:1.25 AgOTf:phen) loadings, but higher ligand loadings (1:3 AgOTf:phen) reverse the selectivity to favor C–H amination (CH) *cis*-**1b** and *trans*-**2b**. We were curious as to the solvent impact on chemoselectivity and whether green alternatives for CH_2Cl_2 could be identified that maintain the tunable selectivity.[2f,g] (*Z*)-**1** and (*E*)-**2** were treated with 10 mol % AgOTf and either 10 mol % or 40 mol % phen (Scheme 1, Figure S3 in the SI for a full solvent list). Scheme 1A shows the total conversion of (*Z*)-**1** or (*E*)-**2** to products *cis*-**1a**, *cis*-**1b**, *trans*-**2a** and/or *trans*-**2b**, while the heat map in Scheme 1B shows the preference for BA or CH. Several solvents showed little-to-no conversion with 1:1 AgOTf:phen, due to poor reagent solubility, coordination of polar solvents to the Ag catalyst or reaction of the nitrene with the solvent; however, seven solvents ($PhNO_2$, $PhCF_3$, PhOMe, DCE, PivCN, acetone, CH_2Cl_2) gave moderate-to-excellent conversions of both (*Z*)-**1** or (*E*)-**2**. When a 1:4 ratio of AgOTf:phen was used, five solvents ($PhNO_2$, $PhCF_3$, acetone, CH_2Cl_2, DCE), showed good conversion to *cis*-**1b** and *trans*-**2b**.

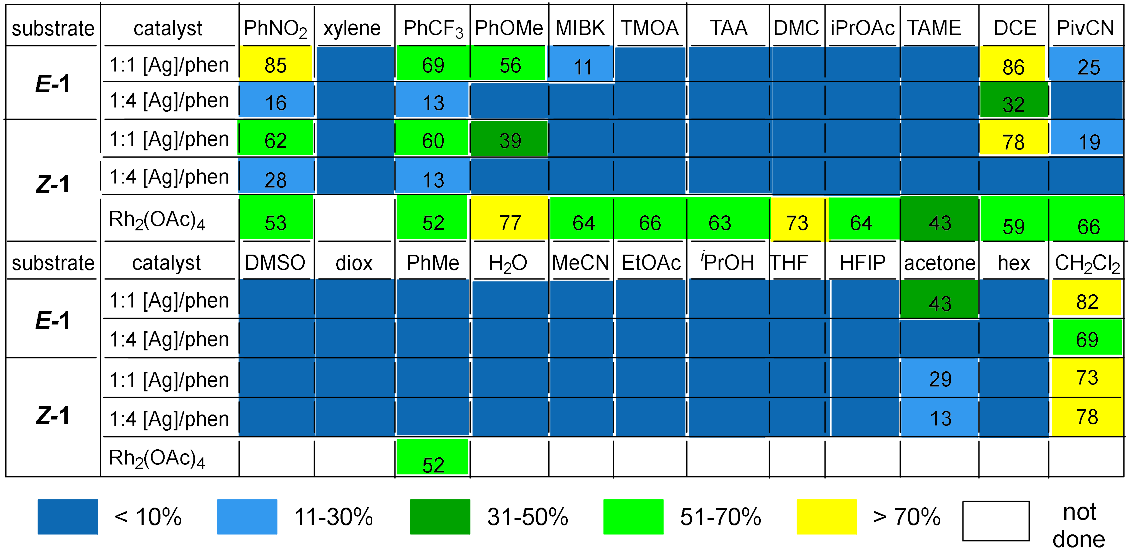
In terms of chemoselectivity (Scheme 1B), reactions in CH_2Cl_2 and DCE at a 1:1 ratio of AgOTf:phen agreed with previous results[2f] in favor of the BAs *cis*-**1a** and *trans*-**2a**. $PhNO_2$ (and to a lesser extent, $PhCF_3$) also gave good selectivity for aziridine (BA:CH 6.7:1 to 20:1). While PhOMe gave promising conversion, the lower chemoselectivity (BA:CH 2.6:1 to 3:1) is likely due to interactions of the e-rich PhOMe with Ag that increase bulk around the Ag nitrene to favor C–H insertion. Acetone gave more C–H amination (CH) to *cis*-**1b** and *trans*-**2b** and other carbonyl- and nitrile-containing solvents (Tables S1, S3 in the SI) gave poor results due to binding of the Lewis basic groups to Ag.

A 1:4 ratio of AgOTf:phen (Scheme 1A) gave high ratios of CH:BA in CH_2Cl_2.[2f] $PhNO_2$ and $PhCF_3$ also preferred C–H amination in low conversion, but did show tunability for BA vs CH, depending on the Ag/ligand ratio. While PivCN can be used in aziridination, chlorinated solvents are justified when tunable chemoselectivity is desired by altering the Ag:phen ratios.

Reaction of (*Z*)-**1** with $Rh_2(OAc)_4$ (Scheme 1A) gave good conversions across a broad range of solvents, with BA:C–H *cis*-**1a**:*cis*-**1b** ratios ranging from ~1.3:1 to 3.2:1. However, Rh catalysis does not facilitate tunable chemoselectivity.



A: Reaction yield (%) heatmap of combined products

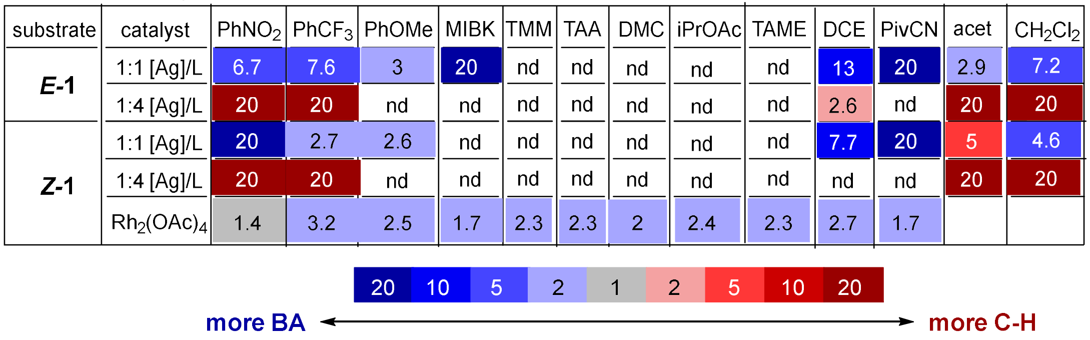


substrate	catalyst	$PhNO_2$	xylene	$PhCF_3$	PhOMe	MIBK	TMOA	TAA	DMC	iPrOAc	TAME	DCE	PivCN
***E*-1**	1:1 [Ag]/phen	85	🟦	69	56	11	🟦	🟦	🟦	🟦	🟦	86	25
	1:4 [Ag]/phen	16	🟦	13	🟦	🟦	🟦	🟦	🟦	🟦	🟦	32	🟦
***Z*-1**	1:1 [Ag]/phen	62	🟦	60	39	🟦	🟦	🟦	🟦	🟦	🟦	78	19
	1:4 [Ag]/phen	28	🟦	13	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦
	$Rh_2(OAc)_4$	53		52	77	64	66	63	73	64	43	59	66

substrate	catalyst	DMSO	diox	PhMe	H_2O	MeCN	EtOAc	^{i}PrOH	THF	HFIP	acetone	hex	CH_2Cl_2
***E*-1**	1:1 [Ag]/phen	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	43	🟦	82
	1:4 [Ag]/phen	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	69
***Z*-1**	1:1 [Ag]/phen	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	29	🟦	73
	1:4 [Ag]/phen	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦	13	🟦	78
	$Rh_2(OAc)_4$			52									

🟦 < 10% 🟦 11-30% 🟩 31-50% 🟩 51-70% 🟨 > 70% ⬜ not done

B: Chemoselectivity heatmap



substrate	catalyst	$PhNO_2$	$PhCF_3$	PhOMe	MIBK	TMM	TAA	DMC	iPrOAc	TAME	DCE	PivCN	acet	CH_2Cl_2
***E*-1**	1:1 [Ag]/L	6.7	7.6	3	20	nd	nd	nd	nd	nd	13	20	2.9	7.2
	1:4 [Ag]/L	20	20	nd	nd	nd	nd	nd	nd	nd	2.6	nd	20	20
***Z*-1**	1:1 [Ag]/L	20	2.7	2.6	nd	nd	nd	nd	nd	nd	7.7	20	5	4.6
	1:4 [Ag]/L	20	20	nd	nd	nd	nd	nd	nd	nd	nd	nd	20	20
	$Rh_2(OAc)_4$	1.4	3.2	2.5	1.7	2.3	2.3	2	2.4	2.3	2.7	1.7		

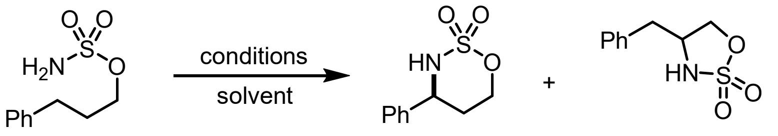
20 10 5 2 1 2 5 10 20

more BA ← → **more C-H**

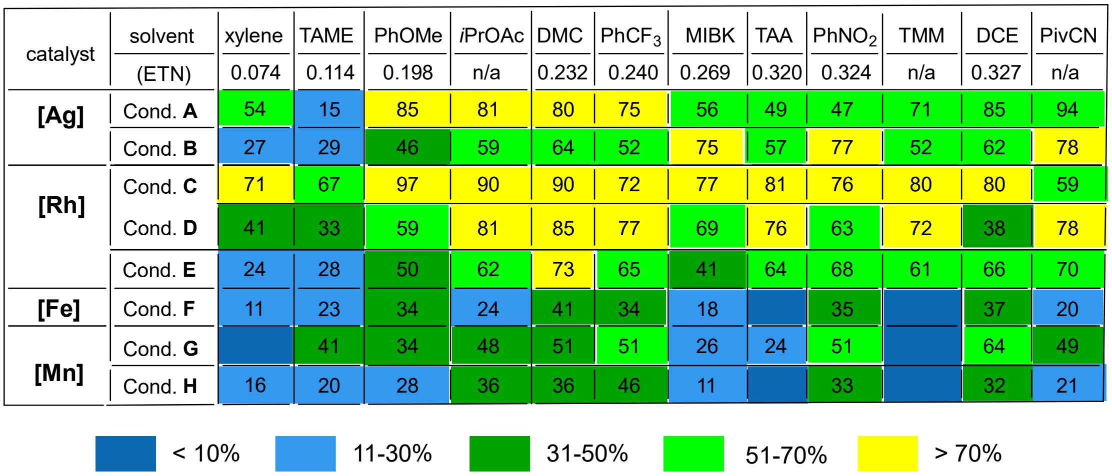
Scheme 1. Impact of solvent on chemoselective NT using (*E*)- and (*Z*)-alkenes and Ag or Rh catalysts. Conversions were determined via ^{1}H-NMR with 1-chloro-2,4-dinitrobenzene as an internal standard. Site-selectivity was determined for >10% conversion and was not determined (nd) if the conversion was <10%.

Site-selective C–H amination using bis-homobenzylic sulfamates as nitrene precursors. The 1,3-aminoalcohol moiety is common in pharmaceuticals and bioactive natural products. Intramolecular amination of sulfamates via NT favors the formation of 6- over 5-member rings, due to a more favorable 7-member transition state dictated by the longer O–S bonds in sulfamates compared to the O–C bonds in the analogous carbamates.[2b] Indeed, sulfamate **3** (Scheme 2) formed only **4**, irrespective of the catalyst (Ag, Rh or Fe) or solvent. Comparing the efficiency of NT using (tpa)AgOTf (tpa, tris(2-pyridylmethyl)amine), $[Ag(Py_5Me_2)OTf]_2$ (Py_5Me_2, 2,6-bis(1,1-bis(2-pyridyl)ethyl)pyridine), $Rh_2(OAc)_4$, $Rh_2(esp)_2$, White-Paradine, White-Clark and $[FePc]SbF_6$ catalysts revealed solvent-dependent differences. The (tpa)AgOTf-catalyzed NT of **3** to **4** was effective in non-chlorinated solvents, including PhOMe, dimethyl carbonate, ^{i}PrOAc and PivCN (Scheme 2, Condition A). PhMe, MIBK, *tert*-amyl alcohol and $PhNO_2$ gave lower conversions, but are also potential alternatives to chlorinated solvents.[11] In general, $[Ag(Py_5Me_2)OTf]_2$ gave lower conversion than (tpa)AgOTf, although methyl-*iso*-butyl ketone, *tert*-amyl alcohol and $PhNO_2$ gave higher yields (Scheme 2, Condition B). In comparison to Ag catalysts, $Rh_2(OAc)_4$ and $Rh_2(esp)_2$ displayed better yields across the range of tested solvents (Scheme 2, Conditions C-E), although Ag is less expensive.

Conversion of **3** to **4** were lower with phthalocyanine-supported [Fe] and [Mn] complexes (typically used



3 **4** **5 (not observed)**



catalyst	solvent (ETN)	xylene 0.074	TAME 0.114	PhOMe 0.198	*i*PrOAc n/a	DMC 0.232	PhCF$_3$ 0.240	MIBK 0.269	TAA 0.320	PhNO$_2$ 0.324	TMM n/a	DCE 0.327	PivCN n/a
[Ag]	Cond. **A**	54	15	85	81	80	75	56	49	47	71	85	94
	Cond. **B**	27	29	46	59	64	52	75	57	77	52	62	78
[Rh]	Cond. **C**	71	67	97	90	90	72	77	81	76	80	80	59
	Cond. **D**	41	33	59	81	85	77	69	76	63	72	38	78
	Cond. **E**	24	28	50	62	73	65	41	64	68	61	66	70
[Fe]	Cond. **F**	11	23	34	24	41	34	18	🟦	35	🟦	37	20
[Mn]	Cond. **G**	🟦	41	34	48	51	51	26	24	51	🟦	64	49
	Cond. **H**	16	20	28	36	36	46	11	🟦	33	🟦	32	21

🟦 < 10% 🟦 11-30% 🟩 31-50% 🟩 51-70% 🟨 > 70%

Cond. A: cat = AgOTf, L = tpa, PhIO; **Cond. B**: cat = AgOTf, L = Py$_5$Me$_2$, PhIO; **Cond. C**: cat = Rh$_2$(OAc)$_4$, PIDA; **Cond. D**: cat = Rh$_2$(OAc)$_4$, PhIO; **Cond. E**: cat = Rh$_2$(esp)$_2$, PIDA; **Cond. F**: cat = [FePc]Cl, PhIO; **Cond. G**: cat = White-Paradine, PhIO; **Cond. H**: cat = White-Clark, PhIO.

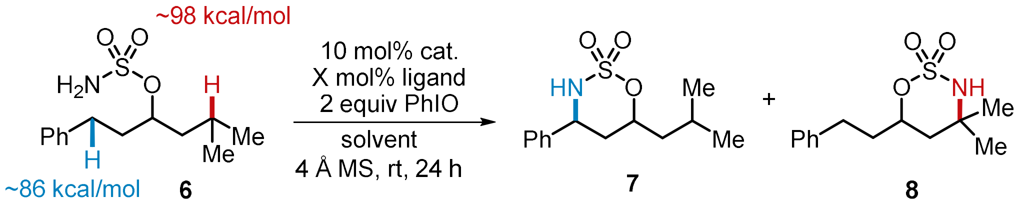
Scheme 2. Performance of various catalysts and solvents in benzylic C–H amination of **3** (% yield). Reaction conditions for each catalyst system are in Tables S6-S12 in the Supporting Info. Solvents are listed in order of E^{T}_{N} polarity scale values. Solvents without E^{T}_{N} values are denoted as not available (n/a).

in PhH or solvent mixtures) compared to Rh and Ag complexes (Scheme 2, Conditions F-H). However, PhOMe, PhCF$_3$, dimethyl carbonate, ^{i}PrOAc and PivCN were suitable replacements for PhH or (CH$_2$)$_2$Cl$_2$, with the White-Paradine catalyst superior to the [FePc]SbF$_6$ or the White-Clark catalyst overall. Gratifyingly, all three catalyst systems (Ag, Rh, Fe/Mn) tolerate a greater diversity of solvents than anticipated, with dimethyl carbonate and ^{i}PrOAc recommended by the GSK solvent selection guide as the most suitable alternatives for chlorinated solvents.[12]

Amination of 3° C(sp^3)–H vs. 2° benzylic C–H bonds with sulfamate nitrene precursors. Achieving good site-selectivity between two competing γ C–H bonds, such as an electron-rich 3° C(sp^3)–H and a weaker benzylic C–H bond in **6** (Scheme 3) to furnish 3-amino-1-propanols **7** and **8**, is challenging.[2b-e] We first wanted to determine solvent scope with eight different catalysts, then ascertain the impact of catalyst and solvent on the site-selectivity to furnish **7** and **8** (Schemes 3-4).

Of the Ag-based catalysts, Ag(tpa)OTf was the most tolerant of solvent identity, giving good-to-excellent yields. Non-chlorinated alternatives include aliphatic and aromatic hydrocarbons, ethers, esters, dimethyl carbonate, ketones, alcohols and nitriles; even water could be employed. The other two silver catalysts, Ag(*o*-Me_3tpa)OTf and Ag(*t*Bubpy)$_2$OTf, showed a narrower range of useful solvents, but again, several non-chlorinated options were identified. Dinuclear Rh(II) complexes $Rh_2(OAc)_4$ and $Rh_2(esp)_2$ showed the best yields and solvent scope of the tested catalysts, with [FePc]SbF_6 and Mn-based catalysts showing lesser solvent tolerance compared to Rh and Ag catalysts.

Of greater interest was the impact of solvent and catalyst on the site-selectivity of the C–H insertion reaction. Ag binds simple sp^2 *N*-dentate ligands to yield diverse coordination geometries that enable flexible site-selective amination of either type of C–H bond of **6** to give **7** and **8**, respectively. As shown in Scheme 4, Ag(tpa)OTf favors **7**, while (^{t}Bubpy)$_2$AgOTf strongly prefers **8** in certain solvents. Computational studies suggested that non-covalent interactions in the Ag(tpa)OTf nitrene transition state bias selectivity towards **7**,[2b,d] where the aromatic ring of **6** participates in a π-π stacking or Ag-π interactions with a pyridine on the bound ligand. All solvents preferred **7** in varying ratios of **7**:**8** using this catalyst; HTE data agreed with results from larger scale reactions performed in typical glassware (see Section XIII in the Supporting



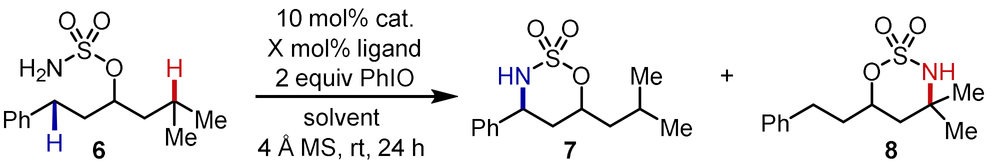
catalyst	hexane	xylene	PhMe	TAME	dioxane	PhOMe	*i*PrOAc	EtOAc	DMC	$PhCF_3$	MIBK
Ag(tpa)OTf	75	85	99	28	75	84	95	74	90	79	81
Ag(*o*-Me_3tpa)OTf	39	54	90	20	99	78	83	76	71	77	54
Ag(*t*Bubpy)$_2$OTf	48	45	57	31	51	68	79		48	37	58
$Rh_2(OAc)_4$			84	86		99	99		95	79	86
$Rh_2(esp)_2$	88	78	86	71	86	80	78	81	77	78	80
[FePc]SbF_6			37	43		39	44		41	35	25
White-Paradine			🟦	40		41	30		32	22	37
White-Clark			32	35		41	27		30	26	20

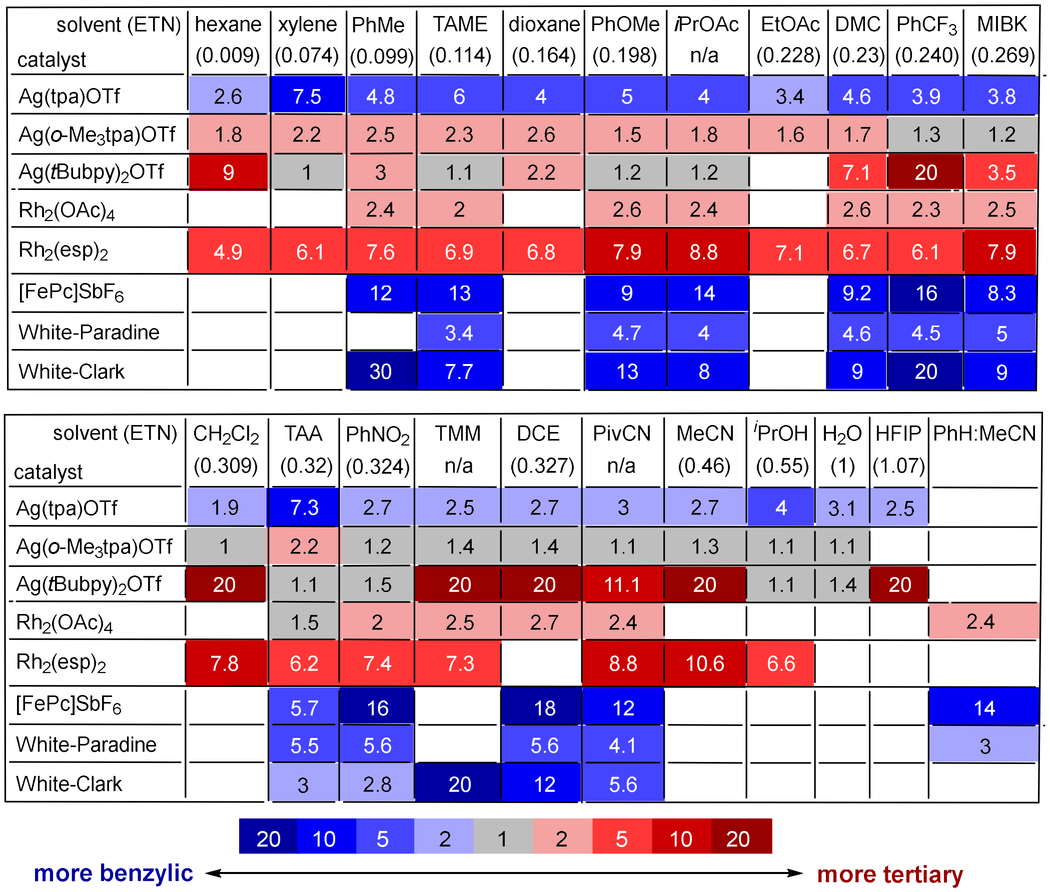
catalyst	CH_2Cl_2	TAA	$PhNO_2$	TMM	DCE	PivCN	MeCN	^{i}PrOH	H_2O	HFIP	PhH:MeCN
Ag(tpa)OTf	64	83	81	88	99	85	74	70	61	28	
Ag(*o*-Me_3tpa)OTf	78	70	69	36	91	45	29	60	70	🟦	
Ag(*t*Bubpy)$_2$OTf	50	58	69	20	50	51	35	47	24	13	
$Rh_2(OAc)_4$		89	64	93	91	87					
$Rh_2(esp)_2$	79	79	84	99		98	81	99			
[FePc]SbF_6		20	34	🟦	38	39					51
White-Paradine		26	33	🟦	33	31					59
White-Clark		12	23	12	25	33					

🟦 < 10% 🟦 11-30% 🟩 31-50% 🟩 51-70% 🟨 > 70% ☐ not done

Scheme 3. Solvent effects on total yield in the site-selective amination of a 3° C(sp^3)–H vs. a 2° benzylic C–H bond.

Information). The **7**:**8** ratio tracked with E^T_N in hexane and aromatic solvents, with *p*-xylene (E^T_N 0.074) providing the highest **7**:**8** ratio at 7.5:1, dropping to 2.7:1 in *p*-$PhNO_2$ (E^T_N 0.324). Ethers gave moderate selectivity for **7**, while ketones and esters showed little difference in the benzylic:tertiary (B:T) **7**:**8** ratios, varying from 4.6:1 with dimethyl carbonate to 3.4:1 with EtOAc. Protic solvents gave varied results. The B:T **7**:**8** ratio in H_2O agreed with previous results (HTE 3.1:1; literature 2.7:1),[21] but to our surprise, *tert*-amyl alcohol (E^T_N 0.32) gave a higher B:T **7**:**8** ratio of 7.3:1 vs. $PhNO_2$ (B:T 2.7:1), which has a similar E^T_N value of 0.324. Benchmarking *tert*-amyl alcohol on a 0.1 mmol scale gave similar results (B:T = 5.3:1), indicating that polarity is not the only factor that controls site-selectivity. The alcohol can serve as a ligand





solvent (ETN) catalyst	hexane (0.009)	xylene (0.074)	PhMe (0.099)	TAME (0.114)	dioxane (0.164)	PhOMe (0.198)	*i*PrOAc n/a	EtOAc (0.228)	DMC (0.23)	PhCF$_3$ (0.240)	MIBK (0.269)
Ag(tpa)OTf	2.6	7.5	4.8	6	4	5	4	3.4	4.6	3.9	3.8
Ag(*o*-Me$_3$tpa)OTf	1.8	2.2	2.5	2.3	2.6	1.5	1.8	1.6	1.7	1.3	1.2
Ag(*t*Bubpy)$_2$OTf	9	1	3	1.1	2.2	1.2	1.2		7.1	20	3.5
Rh$_2$(OAc)$_4$			2.4	2		2.6	2.4		2.6	2.3	2.5
Rh$_2$(esp)$_2$	4.9	6.1	7.6	6.9	6.8	7.9	8.8	7.1	6.7	6.1	7.9
[FePc]SbF$_6$			12	13		9	14		9.2	16	8.3
White-Paradine				3.4		4.7	4		4.6	4.5	5
White-Clark			30	7.7		13	8		9	20	9

solvent (ETN) catalyst	CH$_2$Cl$_2$ (0.309)	TAA (0.32)	PhNO$_2$ (0.324)	TMM n/a	DCE (0.327)	PivCN n/a	MeCN (0.46)	^{i}PrOH (0.55)	H$_2$O (1)	HFIP (1.07)	PhH:MeCN
Ag(tpa)OTf	1.9	7.3	2.7	2.5	2.7	3	2.7	4	3.1	2.5	
Ag(*o*-Me$_3$tpa)OTf	1	2.2	1.2	1.4	1.4	1.1	1.3	1.1	1.1		
Ag(*t*Bubpy)$_2$OTf	20	1.1	1.5	20	20	11.1	20	1.1	1.4	20	
Rh$_2$(OAc)$_4$		1.5	2	2.5	2.7	2.4					2.4
Rh$_2$(esp)$_2$	7.8	6.2	7.4	7.3		8.8	10.6	6.6			
[FePc]SbF$_6$		5.7	16		18	12					14
White-Paradine		5.5	5.6		5.6	4.1					3
White-Clark		3	2.8	20	12	5.6					

Scheme 4. Site-selective amination of a 3° C(sp^3)–H vs. a 2° benzylic C–H bond using 22 solvents and 8 different catalysts. Solvents are listed in order of E^{T}_{N} polarity scale values. Solvents without E^{T}_{N} values are denoted as not available (n/a).

for Ag, where its bulk minimizes competing formation of dimeric Ag species in solution that favor amination of the 3° C–H bond to give **8**. This occurs to a lesser extent with ^{i}PrOH, while HFIP is too electron-poor to function as an effective ligand. Control solvents for NT (CH$_2$Cl$_2$, DCE, MeCN, PivCN) using (tpa)AgOTf gave B:T ratios from 1.9:1 to 3:1, again correlating reasonably well with E^{T}_{N} values.

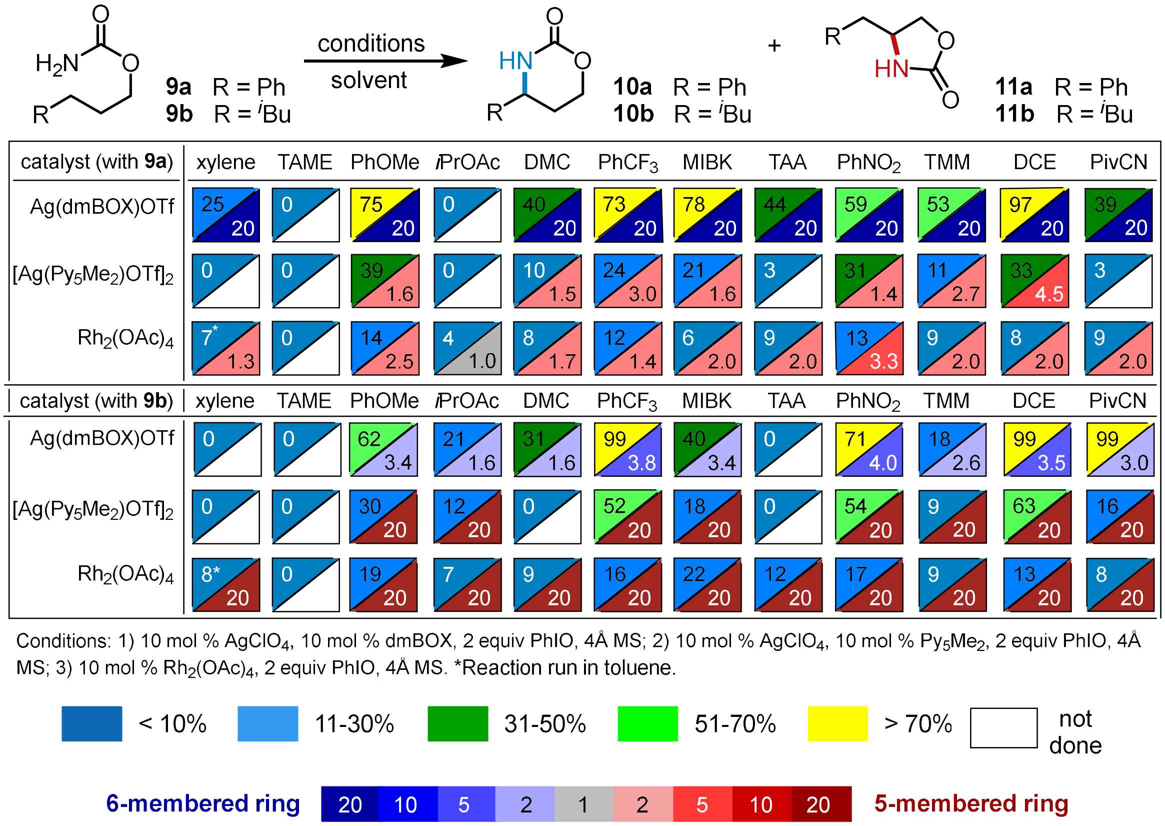
In contrast to Ag(tpa)OTf, Ag(^{t}Bubpy)$_2$OTf selects for the 3° C(sp^3)–H bond of **6** in chlorinated solvents to give **8**.[2b-] This catalyst shows a strong solvent dependence, where the majority of aromatic, ether, ester and alcohol-containing solvents gave poor selectivity. PivCN, MeCN and dimethyl carbonate all strongly favor **8** and are promising alternatives to chlorinated solvents.

The case of AgOTf supported by (*o*-Me_3)tpa is an interesting one, as the fluxionality of Ag complexes in solution can yield solvent-dependent monomer-dimer equilibria.[22] Ag(*o*-Me_3tpa)OTf shows significantly more dimer formation in CD_2Cl_2 by VT-NMR compared to Ag(tpa)OTf and Ag(^{t}Bubpy)$_2$OTf. While similar conversion to Ag(tpa)OTf is noted, Ag(*o*-Me_3tpa)OTf displays a narrow range of B:T **7**:**8** ratios (0.7:1 – 2.6:1) compared to the two other Ag catalysts and less sensitivity to solvent effects. Overall, the best Ag conditions for benzylic C–H amination to **7** at rt use (tpa)AgOTf in *t*-amyl alcohol, while the best conditions for amination to **8** use [Ag(*o*-Me-tpa)OTf]$_2$ in PivCN. When it is desirable to use the same solvent in tunable site-selective NT by changing only the ligand identity, both dimethyl carbonate and $PhCF_3$ are superior to chlorinated solvents.

The minimal response of the **7**:**8** ratio with [Ag(*o*-Me-tpa)OTf]$_2$ prompted us to compare it to dimeric $Rh_2(OAc)_4$ and $Rh_2(esp)_2$ catalysts.[2c] Reaction of **6** in CH_2Cl_2 with $Rh_2(OAc)_4$ gave a 1.5:1 T:B **8**:**7** ratio and all solvents gave full conversion of **6**. Observed T:B **8**:**7** ratios ranged from 2.0 – 2.7:1; these ratios were higher with $Rh_2(esp)_2$, but showed similar trends, highlighting the minimal impact of solvent on site-selective NT catalyzed by dinuclear Rh complexes, behavior similar to dimeric [Ag(*o*-Me_3tpa)OTf]$_2$.

[Fe] and [Mn] phthalocyanine-supported complexes show excellent selectivity for amination of benzylic C–H bonds.[4a,b] Sulfamate **6** was reported to give the best selectivity with [FePc]SbF_6 (14:1 B:T **7**:**8**) in a mixture of PhH/MeCN, while the White-Paradine catalyst gave modest selectivity (3:1 B:T **7**:**8**).[4a] A set of 12 solvents were tested with [FePc]SbF_6, White-Paradine (WP) and White-Clark (WC) catalysts (Scheme 4). All solvents gave products with the exception of TMM. In agreement with literature, [FePc]SbF_6 gave superior selectivity for benzylic amination to **7** as compared to the WP catalyst (for solvents with Pdt/IS ratios > 0.20, selectivity is represented by 20:1). Selectivity using the WC catalyst appeared more sensitive to solvent compared to [FePc]SbF_6 or THE WP catalysts, perhaps due to the increased Lewis acidity of the former. As expected, none of these catalysts preferred **8** over **7** in any solvent.

Formation of 5- vs. 6-member rings via C–H amination of carbamates. The challenge in directly comparing the reactivity of sulfamate **3** (Scheme 2) to carbamate **9a** (Scheme 5, top) is that **9a** can form either **10a** or **11a**, depending on the catalyst. The same is true for **9b**, although the challenge is to differentiate between two similar methylene C(sp^3)–H bonds (Scheme 5, bottom). Reactivity and site-selectivity with Ag(dmBOX)ClO_4, [Ag(Py_5Me_2)ClO_4]$_2$ and $Rh_2(OAc)_4$ were compared in diverse solvents for both **9a-b**. For **9a**, Ag(dmBOX)ClO_4 preferred **10a**, with PhOMe, $PhCF_3$ and MIBK serving as good replacements for chlorinated solvents. In contrast, [Ag(Py_5Me_2)ClO_4]$_2$ preferred **11a** over **10a**;[2e] although $(CH_2)_2Cl_2$ was the best solvent, PhOMe and $PhCF_3$ were reasonable alternatives. $Rh_2(OAc)_4$ showed a slight preference for **11a** across multiple solvents.



9a R = Ph
9b R = ^{i}Bu
10a R = Ph
10b R = ^{i}Bu
11a R = Ph
11b R = ^{i}Bu

catalyst (with **9a**)	xylene	TAME	PhOMe	*i*PrOAc	DMC	$PhCF_3$	MIBK	TAA	$PhNO_2$	TMM	DCE	PivCN
Ag(dmBOX)OTf	25 20	0	75 20	0	40 20	73 20	78 20	44 20	59 20	53 20	97 20	39 20
[Ag(Py_5Me_2)OTf]$_2$	0	0	39 1.6	0	10 1.5	24 3.0	21 1.6	3	31 1.4	11 2.7	33 4.5	3
$Rh_2(OAc)_4$	7* 1.3	0	14 2.5	4 1.0	8 1.7	12 1.4	6 2.0	9 2.0	13 3.3	9 2.0	8 2.0	9 2.0

catalyst (with **9b**)	xylene	TAME	PhOMe	*i*PrOAc	DMC	$PhCF_3$	MIBK	TAA	$PhNO_2$	TMM	DCE	PivCN
Ag(dmBOX)OTf	0	0	62 3.4	21 1.6	31 1.6	99 3.8	40 3.4	0	71 4.0	18 2.6	99 3.5	99 3.0
[Ag(Py_5Me_2)OTf]$_2$	0	0	30 20	12 20	0	52 20	18 20	0	54 20	9 20	63 20	16 20
$Rh_2(OAc)_4$	8* 20	0	19 20	7 20	9 20	16 20	22 20	12 20	17 20	9 20	13 20	8 20

Conditions: 1) 10 mol % $AgClO_4$, 10 mol % dmBOX, 2 equiv PhIO, 4Å MS; 2) 10 mol % $AgClO_4$, 10 mol % Py_5Me_2, 2 equiv PhIO, 4Å MS; 3) 10 mol % $Rh_2(OAc)_4$, 2 equiv PhIO, 4Å MS. *Reaction run in toluene.

< 10%	11-30%	31-50%	51-70%	> 70%	☐ not done

6-membered ring 20 10 5 2 1 2 5 10 20 **5-membered ring**

Scheme 5. Site-selectivity with dissimilar (**9a**) and similar (**9b**) C–H bonds: formation of 6-MR **10a-b** vs. 5-MR **11a-b** carbamates with Ag(dmBOX)ClO_4, [Ag(Py_5Me_2)ClO_4]$_2$ and $Rh_2(OAc)_4$.

The impact of solvent and catalyst on site-selectivity in the reaction of **9b** was also explored (Scheme 5, bottom). The best combinations of yield and **10b**:**11b** ratios were noted with PhOMe (62%, 3.4:1), $PhCF_3$

(99%, 3.8:1), $PhNO_2$ (71%, 4:1), DCE (99%, 3.5:1) and PivCN (99%, 3:1). Formation of **11b** using $[Ag(Py_5Me_2)ClO_4]_2$ showed similar solvent trends to $Ag(dmBOX)ClO_4$. $PhCF_3$ (52%, 1:20), $PhNO_2$ (54%, 1:20) and DCE (63%, 1:20); surprisingly, PivCN gave low conversion. Finally, $Rh_2(OAc)_4$ gave low conversions of **9b**, favoring **11b**:**10b** in >20:1 ratio, highlighting the benefits of less expensive $[Py_5Me_2AgClO_4]_2$ compared to $Rh_2(OAc)_4$ using carbamates as nitrene precursors.

Conclusion

An HTE approach to rapidly screen heterogeneous nitrene transfer reactions catalyzed by Ag, Rh, Fe and Mn catalysts revealed alternatives to chlorinated solvents that give high yields and selectivities, while shedding insight into how reaction outcomes are impacted by the nature of the substrate, solvent and catalyst. General findings include: 1) sulfamates are more tolerant of diverse solvents as compared to carbamates, due to the need to coordinate the carbonyl group of the latter to the metal to promote good reactivity, 2) Rh catalysts tolerate a broader range of solvents than Ag, Fe and Mn complexes, but selectivity in the presence of multiple reactive sites is lower, and 3) the most promising replacements for chlorinated solvents include $PhNO_2$, $PhCF_3$, dimethyl carbonate, ^{i}PrOAc, PhOMe and PivCN.

Tunable chemoselective aziridination vs. C–H amination of carbamates by varying Ag:ligand ratios performed best in CH_2Cl_2, but $PhNO_2$ and $PhCF_3$ are potential substitutes. Solvents with lone pairs or electron density that engage with Ag should be avoided, as they disrupt the coordination environment and give poor chemoselectivity. $Rh_2(OAc)_4$ gave poor chemoselectivity and no tunability in the NT.

Amination of bis-homobenzylic sulfamates gave only the six-membered heterocycle, irrespective of the catalyst (Ag, Rh, Fe or Mn). Solvents giving good results with all tested catalysts include PhOMe, ^{i}PrOAc, dimethyl carbonate, $PhCF_3$, $PhNO_2$ and PivCN; these are good substitutes for CH_2Cl_2 and DCE. The analogous bis-homoallylic carbamates gave mixtures of 5- and 6-member rings, depending on the catalyst; however, moderately tunable, catalyst-controlled NT was observed in $PhCF_3$ or $PhNO_2$ using Ag catalysts. $Ag(dmBOX)ClO_4$ preferred to form the 6-membered ring using PhOMe, dimethyl carbonate, MIBK, *t*-amyl alcohol and trimethoxymethane, all suitable replacements for chlorinated solvents. Carbamates were more sensitive to solvent identity, providing decreased or no conversion in polar protic solvents, due to the disruption of key coordination between the Ag and the carbamate carbonyl oxygen.

Interestingly, the site-selectivity of amination in sulfamates bearing competing benzylic and 3° alkyl C(sp^3)–H bonds responded differently to solvent effects depending on the catalyst. A (tpa)AgOTf catalyst favored benzylic amination in all tested solvents, with selectivity ranging from 1.9:1 in CH_2Cl_2 to 7.5:1 in xylene. Surprisingly, many solvents could replace CH_2Cl_2, delivering both high yield and selectivity for the benzylic amine product. Selectivity was reversed using Ag(^{t}Bubpy)$_2$OTf, ranging from 1:1 to 20:1 depending on solvent. With this catalyst, hexane, dimethyl carbonate, ^{i}PrOAc and PivCN can replace chlorinated solvents. Selectivity using [(*o*-Me$_3$tpa)AgOTf]$_2$ and $Rh_2(OAc)_4$ as catalysts was low; $Rh_2(esp)_2$ showed higher selectivity for amination of tertiary C–H bond, but all three catalysts showed little response to solvent. Fe- and Mn-based catalysts were selective for benzylic C–H bond amination. Overall, this study highlights the benefits of using HTE, ChemBead technologies and a range of solvent selection tools to explore a broader range of solvents than is typical in academic labs. These insights enable a better understanding of how yields and selectivities in NT reactions respond to substrate, catalyst and solvent identity to provide attractive alternatives to environmentally unfriendly or unsustainable solvents.

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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: Supporting Information (PDF)

The authors have cited additional references within the Supporting Information.[1-4]

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ABBREVIATIONS

dr, diastereomeric ratio; *ee*, enantiomeric excess; INT, intermediate; NCI, non-covalent interaction

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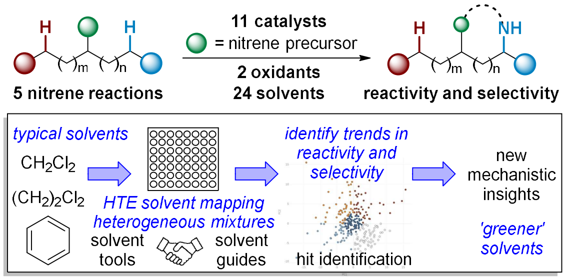
Table of Contents Graphic



A high-throughput experimentation protocol for heterogeneous nitrene transfer (NT) reactions was used to identify replacements for chlorinated solvents. Selected catalysts for NT, including silver supported by *N*-dentate ligands, dinuclear Rh complexes and Fe/Mn phthalocyanine catalysts, were compared and contrasted using our HTE protocol in terms of both yields and selectivity.