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Investigation of transition metal-catalyzed nitrene transfer reactions in water

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ABSTRACT

Transition metal-catalyzed nitrene transfer is a powerful method for incorporating new C—N bonds into relatively unfunctionalized scaffolds. In this communication, we report the first examples of site- and chemoselective C—H bond amination reactions in aqueous media. The unexpected ability to employ water as the solvent in these reactions is advantageous in that it eliminates toxic solvent use and enables reactions to be run at increased concentrations with lower oxidant loadings. Using water as the reaction medium has potential to expand the scope of nitrene transfer to encompass a variety of biomolecules and highly polar substrates, as well as enable pH control over the site-selectivity of C—H bond amination.

1. Introduction

The development of selective carbon–nitrogen (C—N) bond-forming reactions is of great interest, as amines are present in a multitude of bioactive natural products and pharmaceuticals. While there are several synthetic methods available to introduce C—N bonds into organic substrates, transition metal-catalyzed nitrene transfer reactions are appealing for the direct amination of C—H bonds. An important challenge in nitrene transfer catalysis is to identify strategies that enable selective reaction at a desired site in the presence of multiple reactive C—H bonds. A variety of transition metal catalysts, including ones based on Rh, Ru, Fe, Mn, Cu, Ir, Co and Ag, have been studied with the goal of achieving predictable catalyst control over the C—N bond forming event.[1] In our own research program, we have successfully utilized the unique ability of Ag to adopt diverse coordination geometries in solution to control nitrene transfer selectivity, based on simple changes to the reaction conditions. For example, we have developed tunable, chemoselective nitrene transfer protocols where the Ag:ligand ratio determines the selectivity between aziridination and C—H insertion in homoallylic and homoallenic carbamates (Scheme 1, top).[2] Additionally, site-selective C—H insertion of Ag-supported nitrenes derived from sulfamates have been developed where the selectivity is dictated and tuned by the identity of the ligand (Scheme 1, middle).[3]

In the context of transition metal-catalyzed nitrene transfer, general experimental protocols typically involve the use of anhydrous organic solvents, including isopropyl acetate, dichloromethane, chloroform or acetonitrile. Water has long been thought to be detrimental to nitrene transfer reactions, as there is potential to limit the formation of a critical imidoiodinane intermediate **A** (Scheme 1, bottom), change the catalyst geometry by serving as a ligand for the metal, promote catalyst death, or destroy the electrophilic metal nitrene **B**. For these reasons, molecular sieves or other desiccants are typically used; however, the impact of water on nitrene transfer has never been explicitly studied. Since Breslow's example of a successful Diels-Alder reaction in water, there have been efforts directed towards identifying other useful organic reactions that take place in water or 'on water'.[4] In some cases, these reactions employ more environmentally benign conditions and display increased reactivity and/or selectivity.[5,6] In light of these developments, we were curious whether our Ag-catalyzed nitrene transfer reactions might tolerate the presence of water and enable the utilization of highly polar substrates, eliminate the use of chlorinated solvents, decrease the current high loadings of PhIO oxidant and perhaps lead to improved chemo- and site-selectivities. In this manuscript, we divulge our investigations into how various metal-catalyzed C—H aminations are affected by the inclusion of water.

2. Results and discussion

Initial experiments focused on tunable chemoselectivity using carbamates as the nitrene precursors (Table 1). In our previous

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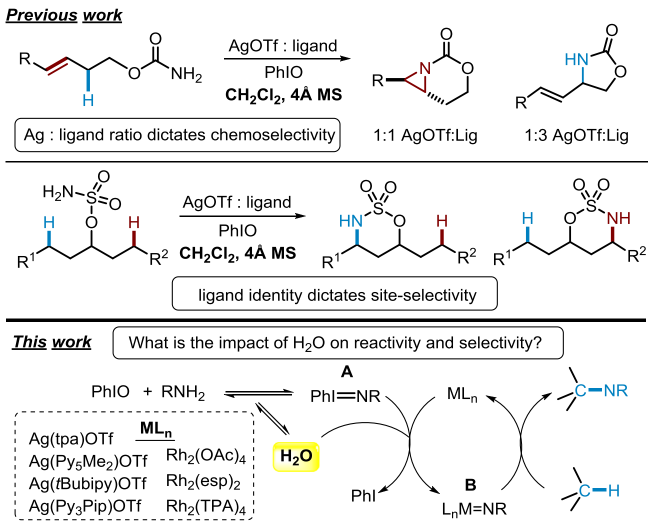
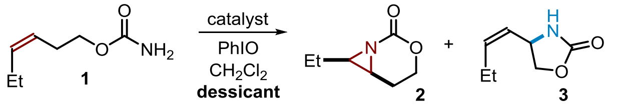


Scheme 1. Ag-catalyzed nitrene transfer.

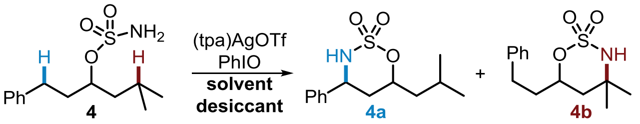
Table 1
Effect of water on carbamate nitrene transfer reagents.



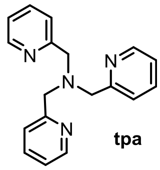
entry	catalyst[a,b]	dessicant	A : I	2	3	total yield[c]
1	1:1.25 AgOTf:phen	4 Å MS	15.7 : 1	67%	4%	71%
2	1:3 AgOTf:phen	4 Å MS	0 : 100	0%	93%	93%
3	1:1.25 AgOTf:phen	none	4.2 : 1	21%	5%	26% (70%)
4	1:3 AgOTf:phen	none	0 : 100	0%	3%	3% (93%)

[a] Aziridination: 20 mol % AgOTf, 25 mol % phen, 2 equiv PhIO, CH_2Cl_2.
[b] C-H insertion: 10 mol % AgOTf, 30 mol % phen, 3.5 equiv PhIO, CH_2Cl_2.
[c] Recovered starting material **1** in parentheses.

Table 2
Water tolerance of sulfamate nitrene transfer reagents.



entry	solvent[a]	desiccant	4a : 4b	total yield[b]
1	CH_2Cl_2	4 Å MS	2.4 : 1	84%[c]
2	CH_2Cl_2	none	3 : 1	100%
3[d]	CH_2Cl_2 + H_2O	none	2.9 : 1	94%
4	H_2O	none	2.7 : 1	66%
5[e]	H_2O	none	2.9 : 1	73%



tpa

[a] In CH_2Cl_2: 10 mol % AgOTf, 12.5 mol % tpa, 3.5 equiv PhIO, rt, 30 min.
[b] NMR yields using a mesitylene internal standard. [c] Isolated yield. [d] 50 µL H_2O added. [e] Heated to 40 °C.

work, a 1:1.25 ratio of AgOTf to 1,10-phenanthroline (phen) as the ligand furnished selective aziridination to **2** (entry 1), whereas employing a 1:3 ratio of AgOTf:phen resulted in the selective formation of the C—H insertion product **3** (entry 2).[2] As expected, the exclusion of molecular sieves resulted in little product formation and recovery of the majority of the starting material **1** (entries 3–4). Although only minimal conversion was seen, it was interesting to note that the selectivity was similar to reactions run with molecular sieves. This observation suggests that water does not occupy a coordination site on the silver catalyst and has little effect on the coordination geometry of the purported silver nitrene. Rather, the difficulty of oxidizing carbamates to the key iminoiodinane intermediate **A** (Scheme 1, bottom) likely gives rise to an equilibrium that favours the starting materials over **A** when water is not sequestered. The sensitivity of carbamate-derived iminoiodinanes to water prompted us to examine other nitrene precursors.

Next, we investigated the effect of water on **4**, a sulfamate-derived nitrene precursor, where C—H insertion can occur at either a benzylic or tertiary alkyl C—H site (Table 2); Pérez has reported a single example of Cu-catalyzed styrene aziridination using PhI=NTs in water.[7] Our previous work showed that a tris(2-pyridyl-methyl)amine (tpa) ligand favors benzylic insertion to furnish **5** (entry 1).[1j,3] Interestingly, when the desiccant was excluded, there was essentially no impact on yield or selectivity (entry 2). This observation was encouraging, as it suggested that water is not as detrimental to C—H amination as had previously been thought. Even with the addition of water (entry 3), the reaction still proceeded smoothly with no change in the **4a**:**4b** ratio, indicating the geometry of the silver catalyst is likely not changing in the presence of water. When the nitrene transfer reaction of **4** was run in water as the solvent, full conversion to products **4a** and **4b** was noted, albeit in slightly lower yield compared to dichloromethane (entry 4), presumably due to the lower solubility of **4** in water. Heating the reaction to 40 °C increased the yield of **4a-b** to 73%, with the remainder of the mass balance made up of starting material (entry 5). Heating the reaction also has the advantage of dissolving the polymeric PhIO oxidant, which is insoluble in dichloromethane; this enables a simpler workup procedure that does not require a filtration step. Instead, extraction with either diethyl ether or ethyl acetate can be utilized, a greener alternative to the standard dichloromethane solvent. A control reaction in Et_2O resulted only in recovered **4**, indicating that the chemistry is happening in the aqueous medium and not during the extraction process. Heating these reactions resulted in an essentially biphasic mixture, suggesting the possibility that the chemistry may be happening 'on-water'.[8] Organic reactions occurring at the organic-liquid water interface have the same economic and environmental benefits as those happening in solution, but on-water reactions allow for the use of substrates that are not soluble in aqueous systems. Overall, these results indicate that water does not hinder reactivity in Ag-catalyzed C—H bond amination reactions using sulfamates as the nitrogen source. This surprising result stimulated our curiosity as to whether other reported transition metal catalysts exhibit similar activity in water.

Table 3 describes results using **4** in the presence of a variety of other reported transition metal catalyst systems.[1,9–12] Dinuclear Rh catalysts, including the popular Rh$_2$esp$_2$ (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate), all favored tertiary C(sp^3)-H insertion to furnish **4b** (entries 1–3), mimicking the selectivity and activity observed in organic solvents.[9] The preference for **4b** increased as the size of the carboxylate bridging ligand increased from OAc to esp to TPA (triphenylacetate). Catalysts based on Ru, Fe, and Mn (entries 4–6) gave no product formation (entries 4–6).[10–12] Additional Ag(I) catalysts developed in our group, including (^{t}BuBipy)$_2$AgOTf, [(Py$_5$Me$_2$)AgOTf]$_2$, and [α-Me-(*anti*)-Py$_3$PipAg]OTf were subjected to the same reaction conditions as (tpa)AgOTf (entries 7–9).[13–16] (^{t}BuBipy)$_2$AgOTf in water resulted in lower mass balance than reactions run in dichloromethane, perhaps due to the increased fluxionality of this complex, as compared to other Ag catalysts; the site-selectivity slightly favored **4b** (entry 7). Both [(Py$_5$Me$_2$)AgOTf]$_2$ and [α-Me-(*anti*)-Py$_3$PipAg]OTf delivered results similar to those observed for (tpa)AgOTf. These results show that by utilizing complementary Rh and Ag catalysts, tunable site-selective C—H amination can be achieved using water as the reaction medium.

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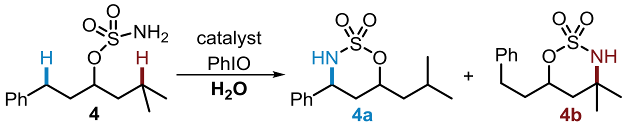
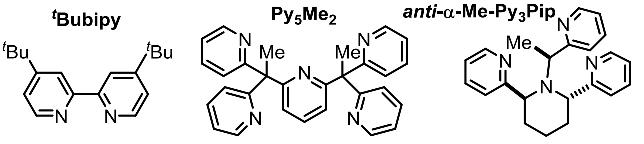
Table 3
Catalyst activity in aqueous solvent.



entry	catalyst[a-c]	4a : 4b	total yield[d]
1	Rh_2esp_2	1 : 6.5	90%
2	$Rh_2(TPA)_4$	1 : 25	79%
3	$Rh_2(OAc)_4$	1 : 1.5	60% (20%)
4	$[Ru_2(hp)_4Cl]$	---	0% (66%)
5	$[FePc]Cl + AgSbF_6$	---	0% (70%)
6	$[Mn(^tBuPc)]Cl + AgSbF_6$	---	0% (54%)
7	$(^tBubipy)_2AgOTf$	1 : 1.8	45%
8	$[(Py_5Me_2)AgOTf]_2$	3.1 : 1	70%
9	[α-Me-(anti)-Py_3PipAg]OTf	2.6 : 1	83%

[a] 10 mol % AgOTf, 12.5 mol % ligand, 3.5 equiv PhIO, H_2O. [b] 2 mol % Rh cat., 2 equiv PhIO, H_2O. [c] See the SI for conditions for entries 4-6. [d] NMR yields based on mesitylene as internal standard, recovered starting material **4** in parentheses.

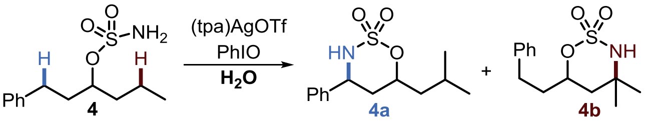


Following initial catalyst screening, further optimization was carried out to determine if water enabled the use of less solvent, less oxidant and lower catalyst loadings, as compared to standard conditions (Table 4). The oxidant could be lowered to 2 equiv from the standard 3.5 equiv, but cutting the PhIO to 1 equiv resulted in incomplete conversion, even with longer reaction times (entries 1–3). The stronger PhIO oxidant (entry 4) gave superior results to both $PhI(OAc)_2$ and $PhI(OPiv)_2$ (entries 5–6). Solvent concentration did not have a significant effect on selectivity or reactivity (compare entry 2 vs. 4, 7–8). However, the substitution of water for dichloromethane did allow reactions to be run at higher concentrations (0.4 M vs. 0.05 M). For ease of reaction setup, a 0.2 M concentration was preferred for studies of catalyst loading (entries 9–11). When the amount of (tpa)AgOTf was decreased to 5 mol% (entry 9), incomplete conversion was observed in the standard 30 min reaction time. This was easily corrected by running the reaction overnight (entry 8), enabling the catalyst loading to be further decreased to 2 mol% (entry 11), provided isolated (tpa)AgOTf is utilized to ensure the proper Ag:ligand stoichiometry. Furthermore, Ag-nitrene catalysis tolerated a variety of electrolytes in buffered solutions at a range of acidic and basic pH values (entries 12–14).

With optimized conditions in hand, other sulfamates were briefly investigated and the site-selectivities of the C—H amination compared to previous results in dichloromethane (Table 5). Another substrate **5**, displaying both benzylic C—H and tertiary C—H insertion sites, behaved similarly using (tpa)AgOTf in water as compared to dichloromethane, favoring benzylic insertion to **5a**. The nonpolar substrate **6**, featuring two very similar tertiary C—H bonds, resulted in minimal selectivity to favor insertion at the isopropyl C—H bond **6b**. The preferred insertion into the allylic C—H bond of **7** in water matched the previous results in dichloromethane; **8**–**13** were similarly well-behaved. Overall, these results indicate that although there is a slight sensitivity of (tpa)AgOTf to water, overall, the reactions are surprisingly similar to those carried out in organic solvents.

Intermolecular nitrene transfer presents a greater challenge as compared to intramolecular reactions. However, water proved to be an effective solvent for the intermolecular amination of

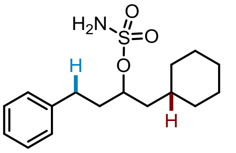
Table 4
Reaction optimization.



entry	equiv PhIO	conc.	mol % cat.[a]	4a : 4b	total yield[b]
1	3.5	0.05 M	10%	2.7 : 1	73%
2	2	0.05 M	10%	2.8 : 1	83%
3	1	0.05 M	10%	2.8 : 1	62% (20%)
4	**2**	**0.1 M**	**10%**	**2.9 : 1**	**80%**
5	2 $PhI(OAc)_2$	0.1 M	10%	2.9 : 1	54%
6	2 $PhI(OPiv)_2$	0.1 M	10%	2.7 : 1	51%
7	2	0.2 M	10%	3.4 : 1	82%
8	2	0.4 M	10%	3.2 : 1	80%
9	2	0.2 M	5%	2.6 : 1	65% (8%)
10[c]	2	0.2 M	5%	3.0 : 1	80%
11[c]	2	0.2 M	2%	3.0 : 1	79%
12[d]	2	0.1 M	10%	2.9 : 1	52%
13[e]	2	0.1 M	10%	2.7 : 1	77%
14[f]	2	0.1 M	10%	3.2 : 1	75%

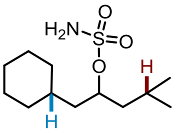
[a] Standard conditions: 10 mol % AgOTf, 12.5 mol % tpa, 3.5 equiv PhIO, 0.05 M H_2O, 40°C, 30 min. [b] NMR yields based on mesitylene as internal standard, recovered **4** in parentheses. [c] The reaction was run overnight. [d] pH 2.8 Na_2HPO_4:citric acid hydrate buffer. [e] pH 5.0 NaOAc:HOAc buffer. [f] pH 9.5 Na_2CO_3:$NaHCO_3$ buffer.

Table 5
Examples of intramolecular amination in water.



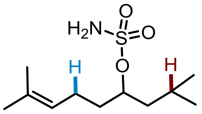
5

CH_2Cl_2: 73% 5a 20% 5b
H_2O[a]: 66% 18%



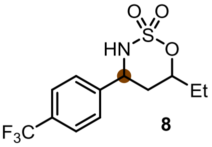
6

CH_2Cl_2: 36% 6a 50% 6b
H_2O: 32% 35%



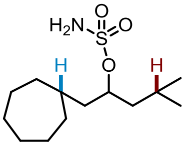
7

CH_2Cl_2: 74% 7a 8% 7b
H_2O: 58% 10%



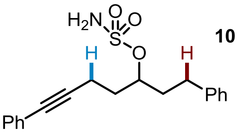
8

H_2O: 62%



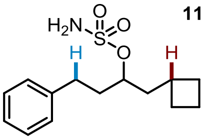
9

CH_2Cl_2: 69% 9a 29% 9b
H_2O: 62% 31%



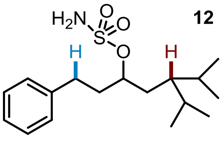
10

$CHCl_3$: 41%[a] 10a 27% 10b
H_2O: 36%[b] 25%



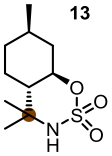
11

CH_2Cl_2: 64% 11a 21% 11b
H_2O: 51% 14%



12

CH_2Cl_2: 63% 12a 0% 12b
H_2O: 72% 8%



13

H_2O: 87%

Conditions: 10 mol % AgOTf, 12.5 mol % tpa, 2 equiv PhIO, 0.1 M H_2O, 40 °C. [a]*dr* = 6.5:1 *syn*:*anti* [b]*dr* = 7.0:1 *syn*:*anti*

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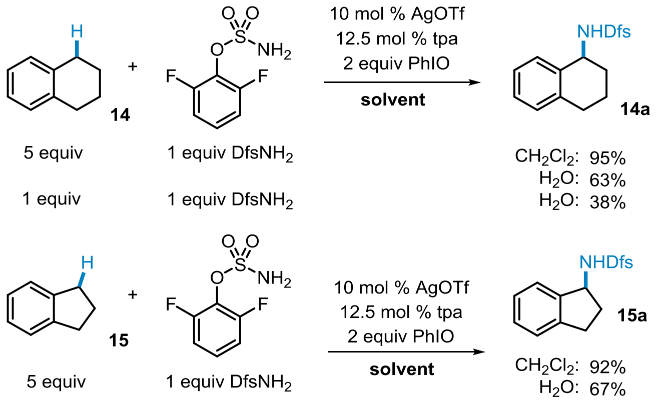

Scheme 2. Intermolecular C—H amination in water.

1,2,3,4-tetrahydronapthalene **14** and indane **15** using thesulfamate nitrene precursor $DfsNH_2$. The C—H insertion products **14a-15a** were furnished in moderate yields (Scheme 2). While an excess of the substrate **14** resulted in improved yields, product **14a** was still noted using only an equimolar amount of **14** and $DfsNH_2$. While modest, these results nonetheless showcase the first examples of intermolecular, silver-catalyzed C—H insertion in water.

3. Concluding remarks

An exploration of the effect of water on metal-catalyzed nitrene transfer showed that the long-held perception that this chemistry is sensitive to water is not always true. Both Ag and Rh catalysts give high yields of amine products, provided sulfamates are used as the nitrogen source. A decrease in the required amount of solvent, oxidant, and catalyst was tolerated with Ag catalysts; these conditions were general for sulfamate precursors. While the chemistry in water mimics intramolecular reactions in organic solvents more closely, intermolecular nitrene transfer was also reported for the first time. This study paves the way for applications of transition metal-catalyzed nitrene transfer reactions to highly polar biomolecules[17] and the development of strategies that utilize simple changes in aqueous pH to tune the site-selectivity of C—H amination events.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmc.2018.04.002.

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