Calix[4]pyrrole as a Promoter of the CuCl-Catalyzed Reaction of Styrene and Chloramine-T

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Summary: Calix[4]pyrrole, an easy-to-prepare anion receptor, acts to promote the cuprous chloride-catalyzed aziridination of styrene by the nitrene source chloramine-T in acetonitrile. The mechanism of action is believed to involve incipient anion-receptor interactions involving the calix[4]pyrrole NH protons and the chlorine atom of the CuCl, rather than direct bonding to, and activation of, the chloramine-T. Consistent with this supposition were the findings that (1) the use of calix[4]pyrrole, in combination with CuCl, did promote enhanced reactivity when PhI═NTs was used as the nitrene source and (2) the presence of calix[4]pyrrole had no effect on the reaction when CuI was used as a catalyst. Decreased yields were also seen with $CuCl_2$, and no appreciable aziridination product was observed when the calix[4]pyrrole was replaced by an appropriately chosen dipyrromethane control compound. On the other hand, the enhancement effect provided by calix[4]pyrrole proved relatively insensitive to the presence of trace quantities of water.

Introduction

Anion recognition has emerged as an important subdiscipline within the rapidly expanding area of supramolecular chemistry. While a large number of elegant anion receptors have been reported in recent years, many of which have proved useful as sensors, carriers, and extractants,[1] little focus within the field has been devoted to the development of functional systems, namely, those that exploit anion-receptor interactions to modulate or promote chemical reactivity. Although, a stoichiometric system capable of activating dichloromethane was recently described by Smith and co-workers[2] and the use of anion recognition to enhance phosphate ester hydrolysis was reported by Král et al. in 2006,[3] we are currently unaware of any examples where a simple anion receptor[4] is used to promote a bond-forming reaction.[5] In principle, the ability to polarize a bond through partial or complete complexation of an incipient anionic leaving group could serve to promote reactivity in transformations where weakening or rupture of an anion−substrate bond is critical to reactivity.[6] As a first demonstration of this potentially broad principle, we report here the use of calix[4]pyrrole **1** to promote the CuCl-catalyzed aziridination of styrene using chloramine-T as the nitrene source.

Copper-catalyzed nitrene transfer to olefins as a route to aziridines has attracted considerable interest in recent years.[7] The most commonly employed nitrene source is the iminoiodinane PhI═NTs; unfortunately, this compound is not commercially available, and its preparation suffers from variable yields.[8] Furthermore, PhI═NTs is hydrolytically unstable, and when it acts as a nitrene source, a byproduct of the reaction is iodobenzene. In contrast, chloramine-T (as the mono- or trihydrate, $TsNClNa\cdot(H_2O)_n$; $n = 1$ or 3) is an inexpensive, commercially available source of nitrene that produces nontoxic and readily separable sodium chloride as a byproduct.[9] Thus, efforts have been made in recent years to exploit chloramine-T as an alternative to PhI═NTs. In 1998, Komatsu and co-workers reported the aziridination of olefins using chloramine-T as nitrene source and copper(I) triflate as a catalyst.[10] A drawback

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(4) As defined for the purposes of this paper, an anion receptor is a synthetic system that achieves recognition through a combination of non-metal-based electrostatic interactions and hydrogen bonds. After submission of the manuscript an interesting report appeared wherein the authors used a thiourea receptor to catalyze an asymmetric Pictet−Spengler-type ring closure (Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405.

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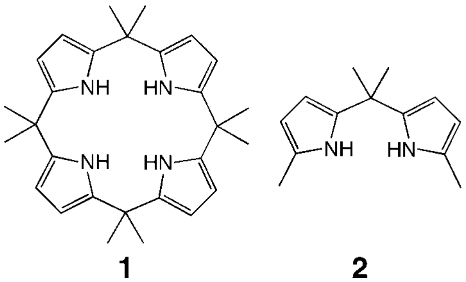
Chart 1. Calix[4]pyrrole and Dipyrromethane Control Compound



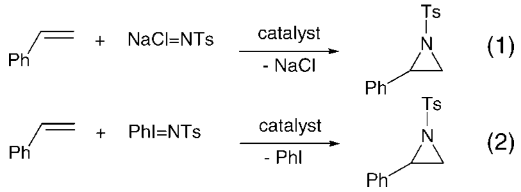
1 **2**

of this procedure was that the commercially available hydrate form of chloramine-T had to be dehydrated prior to reaction, an operation for which an explosion hazard was reported.[11] The same year, Taylor and co-workers reported the aziridination of olefins using chloramine-T trihydrate in conjunction with 5 mol % CuOTf and 6 mol % of an *N*-alkylimine ligand derived from pyridine-2-carboxaldehyde.[12] Another elegant use of chloramine-T trihydrate was reported by Xia and co-workers, who demonstrated aziridinations in aqueous media using CuI and tetra(*n*-butyl)ammonium bromide as a phase-transfer catalyst.[13] Recently, Pedro J. Pérez (no relation to the present author) and co-workers reported improved yields for the reaction of olefins with chloramine-T using 5 mol % of various copper(I) tris(pyrazolyl) borate complexes as the catalyst.[14] On the other hand, Vedernikov and co-workers have recently reported that very simple copper systems, such as combinations of $CuCl_2$ and pyridine ligands, are good catalysts for olefin aziridinations using PhI=NTs as the nitrene source.[11,15]

Chloramine-T displays a very low solubility in moderately polar organic solvents. Sharpless and co-workers pointed out the possibility that phenyltrimethylammonium tribromide could act as a phase-transfer catalyst by enhancing the solubility of chloramine-T in acetonitrile, in addition to serving as a source of positive bromine species for olefin aziridination.[16] Lewis acids not able to engage in redox transformations have also been found to catalyze reactions of chloramine-T, including styrene aziridination; presumably, this takes place via coordination of the chloride to the Lewis acid center, a process that results in activation of the N−Cl bond.[17,18]

We were attracted by the idea of using noncovalent interactions for the activation of chloramine-T in conjunction with a simple copper source as catalyst for nitrene transfer. In particular, we have studied the effect of calix[4]pyrrole (Chart 1)[19] on the activity of cuprous chloride-mediated reaction of chloramine-T with styrene (see eq 1 in Scheme 1). Calix[4]pyrrole **1** is an inexpensive anion receptor that is potentially amenable to kilogram-scale production. Our results are summarized in Table 1.[20]

Scheme 1. Reactions of Interest in the Present Study



No aziridine was detected by ^{1}H NMR spectroscopy when a mixture of chloramine-T and a 5-fold excess of styrene was stirred overnight, either in dichloromethane (entry 1) or in acetonitrile (entry 2). The addition of 2% CuCl (entry 3), $CuCl_2 \cdot 2H_2O$ (entry 4), or CuOTf (entry 5) did not catalyze the reaction. Likewise, calix[4]pyrrole **1** alone was also found to be ineffective (entry 6). However, when a mixture of CuCl (2%) and calix[4]pyrrole (2%) was added to the reaction mixture in acetonitrile, a 32% yield (NMR-based) of 1-tosyl-2-phenylaziridine was found after 5 h. The yield increased to 41% when the reaction time was increased to 15 h (entry 7). Analogous reactions were conducted in Oviedo and in Austin with concordant results being obtained. Interestingly, the presence of small amounts of water did not have a significant effect on the reaction; thus, the yield of the aziridine was the same within error when chloramine-T$\cdot 3H_2O$ was used instead of chloramine-

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[18] (a) Similar effects have been seen with bromamine-T and iron(III) porphyrins; see: Vyas, R; Gao, G.-Y.; Harden, J. D.; Zhang, P *Org. Lett.* **2004**, *6*, 1907–1910. (b) Gao, G.-Y.; Harden, J. D.; Zhang, P. *Org. Lett.* **2005**, *7*, 3191–3193. More complex chemistry is seen in the case of Mn(V) corrole-promoted ArI=NTs aziridinations; see: Zdilla, M. J.; Abu-Omar, M. M. *J. Am. Chem. Soc.* **2006**, *128*, 16971–16979.

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[20] Two general procedures were used. Procedure A: For benchtop work, a Schlenk flask was loaded with CuCl (2 mg, 0.020 mmol), calix[4]pyrrole (9 mg, 0.020 mmol), hexamethylbenzene (9 mg, 0.055 mmol), and a PTFE-coated stirbar in a drybox. The flask was stoppered with a rubber septum, taken out of the box, and attached to a vacuum-nitrogen line, and acetonitrile (20 mL) was injected. Styrene (580 μL) was injected via microsyringe. Under a stream of N_2, chloramine-T was added in one portion. Immediately, the mixture underwent several color changes, finally becoming green. After the desired time, a 1 mL aliquot of the solution was filtered through a 2 cm column of diatomaceous earth packed with dichloromethane, with 20 mL of dichloromethane being used to complete the elution. The filtrate solution was vacuum-dried, and the residue was dissolved in 0.5 mL of $CDCl_3$ and analyzed by ^{1}H NMR, spectroscopy, integrating the signals of the aziridine product [^{1}H NMR ($CDCl_3$): 7.75 (s, 1H), 7.73 (s, 1H), 7.20–7.08 (m, 7H), 3.65 (dd(7.2, 4.5), 1H), 2.85 (d(7.2), 1H), 2.31 (s, 3H), 2.26(d(4.5), 1H)][21] against the 2.24 ppm singlet of hexamethylbenzene. Procedure B: For drybox work, a round bottom flask was charged with CuCl (60 mg, 0.600 mmol), calix[4]pyrrole (270 mg, 0.120 mmol), and a PTFE-coated stirbar. Following addition of styrene (5.8 mL, 50.0 mmol) and acetonitrile (160 mL), the resulting reaction mixture was rapidly stirred. Chloramine-T (2.8 g, 10.0 mmol) was then added in one portion with continued stirring. The flask was then sealed with a rubber septum, and reaction progress was monitored using TLC (1:4 EtOAc/hexanes, R_f = 0.37). After 15 h, the solvent was evaporated, leaving a residue, which was redissolved in CH_2Cl_2. Remaining insoluble material was removed by filtration through alumina. Purification using column chromatography (silica gel, 1:4 EtOAc/hexanes as eluent) afforded 1.3 g (49% yield) of the aziridine product as a white crystalline solid. Spectroscopic data were consistent with the product obtained from procedure A.

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Table 1. Aziridination of Styrene under Various Conditions[a]

entry	solvent	catalyst (mol %)	yield (%)[b]
1	CH_2Cl_2		
2	MeCN		
3	MeCN	CuCl (2%)	
4	MeCN	$CuCl_2 \cdot 2H_2O$ (2%)	
5	MeCN	$[Cu(OTf)]_2 \cdot C_6H_6$ complex (2%)	
6	MeCN	calix[4]pyrrole **1** (2%)	
7	MeCN	CuCl (2%), calix[4]pyrrole **1** (2%)	41 (32)[c]
8	MeCN	CuCl (2%), calix[4]pyrrole **1** (2%)[d]	41 (32)[c]
9	MeCN	CuCl (2%), calix[4]pyrrole **1** (2%)[e]	41 (32)[c]
10	MeCN	CuCl (2%), dipyrromethane **2** (2%)	
11	CH_2Cl_2	CuCl (2%), calix[4]pyrrole **1** (2%)	
12	MeCN	CuI (4%)	54
13	MeCN	CuI (4%), calix[4]pyrrole **1** (4%)	53
14	CH_2Cl_2	CuCl (2%)[f]	36[c]
15	CH_2Cl_2	CuCl (2%), calix[4]pyrrole **1** (2%)[f]	51[c]
16	MeCN	$CuCl_2 \cdot 2H_2O$ (2%), calix[4]pyrrole **1** (2%)	33 (11)[c]
17	MeCN	CuCl (2%), calix[4]pyrrole **1** (4%)	45 (32)[c]
18	MeCN	CuCl (2%), calix[4]pyrrole **1** (4%)	60[g]
19	MeCN	CuCl (7%), calix[4]pyrrole **1** (14%)	74[g]
20	MeCN	CuCl (7%), calix[4]pyrrole **1** (14%)	49[gh]
21	MeCN	CuCl (2%), N,N'-dibutylurea (2%)	8[i]
22	MeCN	CuCl (2%), N,N'-dibutylthiourea (2%)	7[i]

[a] Reactions were run according to procedure A of ref 20, unless otherwise indicated. [b] Yields were based on chloramine-T·H_2O and calculated using ^{1}H NMR spectroscopic analysis (integration relative to an internal standard). [c] Yields after 15 h; values in parentheses (where provided) are yields after 5 h. [d] Chloramine-T·$3H_2O$ was used instead of chloramine-T·H_2O. [e] Molecular sieves (4 Å) were added and chloramine-T·H_2O was previously dried in vacuo for 24 h prior to use. [f] PhI=NTs was used instead of chloramine-T·H_2O; molecular sieves (4 Å) were added to the reaction mixture. [g] Procedure B of ref 20 was used. [h] Isolated yield. [i] Yield after 48 h.

T·H_2O (entry 8) or when the reaction was conducted over activated 4 Å molecular sieves using chloramine-T·H_2O that was previously dried in vacuo for 24 h (entry 9). Taken in concert, these observations lead us to propose that the calix[4]pyrrole, present in substoichiometric concentrations, is acting to promote the copper-catalyzed aziridination of styrene under these conditions.

Consistent with this hypothesis is the finding that under identical reaction conditions no appreciable quantity of the aziridine product is produced when calix[4]pyrrole **1** is replaced with dipyrromethane **2**[22] (entry 10). The use of acetonitrile was found to be necessary, since no aziridine could be detected when dichloromethane was used as the solvent (entry 11). Acetonitrile is generally considered the solvent of choice for Cu-catalyzed aziridination reactions, and its superior performance can be attributed to a combination of its relatively high polarity (making it a good solvent for chloramine-T) and its high affinity for Cu.

The finding that both CuCl and **1** are needed for catalytic activity leads us to suggest that calix[4]pyrrole, an excellent host for chloride in polar aprotic media,[19c] interacts with one of the incipient chloride anions present in the system. Thus, one of the possible roles of calix[4]pyrrole would be to activate the Cu−Cl bond toward the formation of the postulated nitrene intermediate. As an instance of a similar behavior, the activity of complexes containing a Cu−Cl fragment has been recently found to be increased in the presence of NaBAr$^f_4$, presumably as the result of anion exchange.[11] As a matter of fact, we have found that the N−H signal of calix[4]pyrrole was shifted from 7.48 to 9.98 upon addition of an equimolar amount of CuCl in CD_3CN, a finding fully consistent with the presence of a strong hydrogen bond interaction. Additional support was obtained through control studies involving the use of CuI in lieu of CuCl. In accord with literature precedent,[13] the use of CuI afforded aziridine in 54% yield (entry 12). However, the addition of calix[4]pyrrole to a CuI-promoted reaction afforded no significant increase in yield (53%; entry 13). This is consistent with calix[4]pyrrole, which has no appreciable affinity for iodide anion,[19b] serving to promote the reaction through interaction with the copper chloride.[19d]

As a complement to the above studies, we explored the effect of calix[4]pyrrole on the CuCl-catalyzed reaction of styrene with PhI=NTs (see eq 2, Scheme 1). Vedernikov and co-workers reported that when acetonitrile is used as the solvent and $CuCl_2$ (5 mol %) as the catalyst, the yield of the reaction is 94%.[11] This high yield reflects the fact that PhI=NTs is a more reactive nitrene source than chloramine-T. Thus, in order to gauge the effect, if any, calix[4]pyrrole might have on PhI=NTs-based aziridinations, the reaction was studied in dichloromethane, a less effective solvent for promoting the reaction. In dry dichloromethane and with the reaction run over molecular sieves to avoid an significant lowering of yield due to PhI=NTs hydrolysis, the calix[4]pyrrole-free CuCl-catalyzed reaction afforded 36% of the aziridine in 5 h (entry 14). However, when a combination of CuCl and **1** was used as the catalyst, the yield increased to 51% in 5 h (entry 15). Since PhI=NTs is not a source of an anion with which the calixpyrrole could establish a strong interaction, we propose that the yield enhancement observed with calixpyrrole must be due to the activation of CuCl as a result of a bond-polarizing chloride···calixpyrrole hydrogen bonding interaction.

A different possible role for the calix[4]pyrrole would be to form a supramolecular adduct with chloramine-T via N−H···Cl hydrogen bonds. This, in turn, could serve to (a) activate the N−Cl bond of chloramine-T, as was proposed to occur when a high oxidation iron corrole complex was used to catalyze the aziridination reaction,[17] or (b) enhance the solubility of chloramine-T.[16] However, in contrast to what was observed in the case of CuCl, no discernible changes in chemical shifts could be seen when calixpyrrole **1** was mixed with chloramine-T. We thus ascribe the enhanced activity seen with **1** to activation of the CuCl bond via interaction with the calix[4]pyrrole NH protons. Such a conclusion is fully consistent with the finding by Arndtsen and co-workers that the nature of the chiral counteranion, X^-, has a dramatic effect on the CuX-catalyzed aziridination of styrene by PhI=NTs.[24]

Significantly lower yields per unit time are seen when $CuCl_2 \cdot 2H_2O$ is used as catalyst instead of CuCl. In fact, the use of 2 mol % of **1** in conjunction with 2 mol % of $CuCl_2 \cdot 2H_2O$ produced yields of the aziridine of only 11% and 33% after 5 and 15 h, respectively (entry 16). This lower level of activity (compared with CuCl) may reflect the presence of two chloride atoms per copper center in $CuCl_2 \cdot 2H_2O$ and,

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(22) 1,9-Bisformyl-5,5-dimethyldipyrromethane[23] (1.5 g, 6.5 mmol) and KOH (2.60 g, 46.3 mmol) in ethylene glycol (40 mL) and hydrazine hydrate (1.80 g, 56.3 mmol) were heated at reflux for 2 h. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (50 mL) and water (50 mL), and the aqueous layer was extracted with additional CH_2Cl_2 (50 mL). The organic layers were combined and dried (Na_2SO_4), and the CH_2Cl_2 was removed under vacuum to afford an off-white powder (1.05 g, 80%): ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3H), 2.17 (s, 3H), 5.75–5.78 (m, 1H), 5.92–5.94 (m, 1H), 7.48 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 13.0, 29.2, 35.2, 103.5, 105.2, 126.9, 137.9; HRMS (CI+) calcd 202.1470, obsd 202.1473 ($C_{13}H_{18}N_2$).

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hence, a reduced anion-receptor interaction on a per chloride atom basis.[25]

Increasing the amount of calix[4]pyrrole **1** to 4 mol % increased the yield of the aziridine slightly. Specifically, using 2 mol % of CuCl in combination with a 4 mol % of **1** increased the yield to 32% after 5 h and to 45% after 15 h (entry 17). This finding is consistent with the above hypothesis, namely, that the presence of excess calix[4]pyrrole favors formation of a species featuring an incipient calixpyrrole···Cl interaction. Importantly, the proposed chloride-anion specific activation effect would also be expected even if less commonly accepted mechanisms, such as ones where the Cu(I) cation acts as a Lewis acid to promote the addition of Cl^- and $[CuNTs]^+$ across the carbon−carbon double bond followed by chloride displacement by the bound TsN, rather than direct nitrene transfer, are responsible for the observed aziridination.

Another method found to increase yield of aziridine product was to perform the reaction in an inert atmosphere drybox (60% yield, entry 18). Under these conditions (which presumably preclude formation of less active Cu(II) species) and using increased concentrations of calix[4]pyrrole and CuCl (7% and 14%, respectively) gave rise to high yields of product (74% yield, entry 19). Using these near-optimized conditions, the aziridination reaction was performed on a gram scale, which afforded the aziridine product in 49% isolated yield (entry 20).

In summary, we have demonstrated that the presence of calix[4]pyrrole exerts a significant effect on the copper chloride-catalyzed reaction of styrene with chloramine-T. This finding serves to illustrate what could be a general new approach to reaction enhancement, namely, one wherein an anion receptor serves to activate an incipient anion-cleavage event. Interestingly, however, we have found that neither *N*,*N*′-dibutylurea nor *N*,N′-dibutylthiourea, both putative anion receptors under the reaction conditions, is effective in promoting the CuCl-catalyzed aziridination reaction of styrene (entries 21 and 22). Thus, it appears that judicious selection of the reaction chemistry, as well as the anion receptor, is likely to prove important if the present results are to be generalized.

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