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Chlorosulfonamide Salts Are Superior Electrophilic Chlorine Precursors for the Organocatalytic Asymmetric Chlorocyclization of Unsaturated Amides

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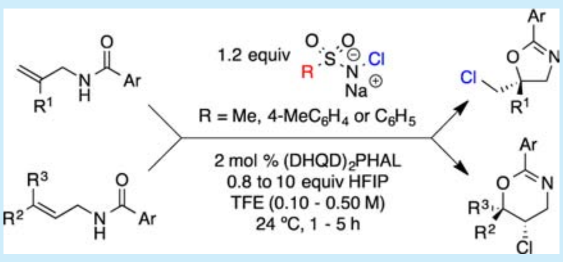
S *Supporting Information*

ABSTRACT: Chloramine-T·3H_2O and other chlorosulfonamide salts can serve as readily available, stable, and inexpensive precursors of electrophilic chlorine in the organocatalytic asymmetric chlorofunctionalization of olefins. In conjunction with commercially available organocatalysts, they can be utilized in the asymmetric chlorocyclization of unsaturated amides to yield products with unprecedented levels of stereoselectivity even at ambient temperatures and high concentrations.



Catalytic asymmetric halofunctionalization of olefins has witnessed an explosive growth in recent years.[1] While preliminary reports focused on asymmetric halolactonization reactions, recent studies have significantly improved the scope of these reactions to include haloetherifications,[2] haloaminations,[3] dihalogenations,[4] haloamidations, and even intermolecular trapping of chiral halonium ions[5] with various nucleophiles. Not surprisingly, numerous modes of intermolecular interactions have been exploited to achieve this elusive goal. These include chiral Lewis base catalysis, H-bonding catalysis, ion-pairing phenomena, and, more recently, phase transfer catalysis.[6] These studies have led to a wealth of information regarding the reactivity of halonium ions and their modes of decomposition and, consequently, to the development of novel reactions. These transformations serve as a facile means to access a variety of chiral heterocyclic products.

Although highly enantioselective variants of many transformations have appeared in recent years, these initial forays in reaction discovery were largely driven by the desire to understand and address the challenges associated with enantioselective alkene halogenation reactions. From a practical standpoint, the use of readily available, stable, and cheap reagents on preparatory scales with no compromise on the stereoselectivity of the reaction is highly desirable. If realized, these measures will bring alkene halogenation reactions at par with some of the well-established asymmetric alkene functionalization reactions such as epoxidations, aziridinations, and dihydroxylations.

In 2011, our laboratory reported the organocatalytic asymmetric chlorocyclization of unsaturated amides mediated by 1,3-dichloro-5,5-diphenyl hydantoin (DCDPH) in the presence of 1−2 mol % of the commercially available $DHQD_2PHAL$ catalyst.[7] During optimization studies we had noted that the identity of both the solvent and the electrophilic chlorenium source had a pronounced effect on the enantioselectivity of the reaction. DCDPH (synthesized in one step from the corresponding hydantoin)[8] emerged as the best candidate after evaluating numerous chlorenium sources. The reactions were rapid (typical reaction time was around 1 h). Nonetheless, cryogenic temperatures (−30 °C) and relatively high dilutions (0.04 M) were still required to obtain the best results. Moreover, modification of the benzamide moiety was paramount to obtaining the highest enantioselectivity (the optimal group for a given olefin substituent being established by a trial and error approach). We hoped to improve upon some of these limitations. Of specific interest were the discovery of an inexpensive, stable, and commercially available chlorenium source and the development of reaction conditions that are amenable to preparatory scale applications to improve the generality and usefulness of this transformation. Preliminary studies had revealed that chloramine-T·3H_2O results in the formation of the desired oxazoline product in trace quantities, but with an appreciable level of stereoinduction in the presence of $(DHQD)_2PHAL$ as the chiral catalyst in $CHCl_3$ (<10% yield; 43% *ee* after 8 h; entry 1, Table 1). The low yield is perhaps not surprising since chloroamine-T·H_2O is not known to act as an electrophilic chlorine source in aprotic solvents. In fact, there is ample precedence for the use of chloramine-T to generate metallo-nitrenes under anhydrous conditions in aprotic solvents.[9] Subsequent to this discovery, we were able to demonstrate that CF_3CH_2OH was the optimal solvent for this reaction in the presence of DCDPH as the terminal chlorenium source. We decided to reevaluate chloramine-T·3H_2O as the chlorenium precursor in this reaction under the assumption that the use of CF_3CH_2OH as the protic

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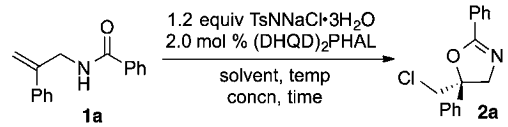
Table 1. Evaluation of Chlorosulfonamide Salts As Chlorenium Precursors for the Asymmetric Chlorocyclization of 1a



entry	solvent	temp	concn	time	additive	conv[a]	ee[b]
1	$CHCl_3$	−40 °C	0.04 M	8 h	none	<10%	43%
2	TFE	−40 °C	0.04 M	8 h	none	15%	93%
3[c]	TFE	24 °C	0.10 M	24 h	none	60%	93%
4	HFIP	24 °C	0.10 M	15 min	none	>95%	60%
5	TFE	24 °C	0.10 M	1 h	0.5 equiv of AcOH	88%	84%
6	TFE	24 °C	0.10 M	1 h	0.5 equiv of CF_3CO_2H	79%	82%
7	TFE	24 °C	0.10 M	1 h	0.5 equiv of pTSA	83%	77%
8	TFE	24 °C	0.10 M	1 h	0.5 equiv of $PhB(OH)_2$	86%	84%
9	TFE	24 °C	0.10 M	1 h	1.0 equiv of Li_2CO_3	66%	88%
10	TFE	24 °C	0.10 M	1 h	1.0 equiv of Cs_2CO_3	47%	87%
11	TFE	24 °C	0.10 M	1 h	1.0 equiv of K_3PO_4	50%	86%
12	TFE	24 °C	0.10 M	1 h	1.0 equiv of NaOAc	69%	88%
13	TFE	24 °C	0.10 M	3 h	1.0 equiv of HFIP	>95%	90%
14	**TFE**	24 °C	0.10 M	**20 min**	**10.0 equiv of HFIP**	**95%**	**92%**
15[e]	TFE	24 °C	0.10 M	20 min	10.0 equiv of HFIP	95%	89%
16[f]	TFE	24 °C	0.10 M	90 min	10.0 equiv of HFIP	90%	89%

[a]Determined by ^1H NMR using MTBE as external standard. [b]Determined by chiral HPLC. [c]2.0 equiv of $TsNNaCl·3H_2O$ was used. [e]$PhSO_2NNaCl$ was used. [f]$CH_3SO_2NNaCl·xH_2O$ was used. TFE = 2,2,2-trifluoroethanol; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; pTSA = *p*-Toluenesulfonic acid.

solvent in lieu of $CHCl_3$ should accelerate the reaction with chloramine-T·$3H_2O$. Additionally, recent studies from our group have shown that catalyst protonation by fluorinated alcohols enables better substrate−catalyst interactions via H-bonding interactions.[10] Furthermore, there was negligible background reaction with chloramine-T·$3H_2O$ even at ambient temperatures (<5% conversion in 20 min, the optimized reaction time scale).

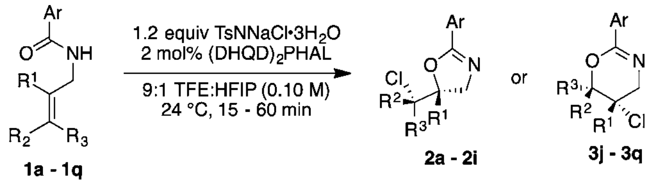
Employing 1.2 equiv of chloramine-T·$3H_2O$ in CF_3CH_2OH in the presence of 2 mol % of $(DHQD)_2PHAL$ gave significant improvements in both the conversion and enantioselectivity of this transformation. The desired oxazoline was isolated in 93% *ee* at 15% conversion of the olefin into product (entry 2, Table 1). It must be highlighted that this was the highest stereoinduction obtained for this particular substrate to date. Emboldened by the negligible background reaction even at ambient temperatures, the reaction was run using 2.0 equiv of chloramine-T·$3H_2O$ at 24 °C. To our delight, the conversion improved to 60% with no loss in enantioselectivity although a long reaction time (24 h) was still required (entry 3, Table 1). A further increase in reaction times did not improve conversions. Marginal improvements in conversions were realized by using a large excess of chloramine-T·$3H_2O$ (up to 20 equiv) or a much higher catalyst loading (up to 30 mol %; see Table S5 in the SI). However, these measures were deemed excessive for the improvement garnered from these changes. On running the reaction in hexafluoroisopropanol (HFIP) as the solvent (see entry 4 in Table 1), the reaction was complete in <15 min! Nonetheless, the enantioselectivity of the reaction was significantly lower (60% *ee*). Under the premise that additives might lead to faster reaction rates without compromising the enantioselectivity, numerous protic and basic additives were evaluated (see Tables S1 and S2 in the SI for other results). Indeed, significant improvements in conversion were seen in the presence of 0.50 equiv of numerous protic additives (compare conversions in entries 5−8 with entry 3 in Table 1). But disappointingly, there was a noticeable decrease in the enantioselectivity in every instance. Inorganic bases led to a smaller, yet measurable decrease in the enantioselectivity while not improving the conversions significantly (entries 9−12 in Table 1).

The dramatic rate acceleration prompted us to evaluate HFIP as an additive for this reaction. Indeed, in the presence of 1.0 equiv of HFIP as an additive, the reaction was virtually complete in 3 h to give the product in 90% *ee* (entry 13 in Table 1). The reaction times could be decreased to 20 min if the reactions were run in the presence of 10 equiv of HFIP to give the product in 92% *ee* (entry 14, Table 1). A more elaborate list of protic additives can be found in the SI. Preliminary results indicate no direct correlation between the pK_a of the additive and the conversions/*ee*'s of the reaction.[11]

A similar level of stereoinduction was obtained with chloramine-B and chloramine-M as the chlorenium precursors (both chloramine salts returned the product in 89% *ee*, entries 15 and 16, Table 1). It warrants emphasis that numerous other commercially available chlorenium sources were aslo evaluated in this study (NCS, NCP, TCCA, *t*-BuOCl, etc.; see Table S3 in the SI); nonetheless, the isolated yields and/or enantioselectivity were consistently higher with *N*-chlorosulfonamide salts.

This new protocol is more general with regards to substrate scope and gave comparable yields and enantioselectivities for all substrates evaluated in our previous study.[7] As seen in Table 2, all 1,1-disubstituted olefin substrates furnished the corresponding chiral oxazoline heterocycles in good to excellent yields and enantioselectivity. Comparison of entries 1−5 in Table 2 indicates a narrow distribution of enantioselectivity as a function of the benzamide group (i.e., the C2 substituent of the product) if chloramine-T·$3H_2O$ is used (92 → 99% *ee*) as opposed to DCDPH (83 → 98% *ee*). Entries 6−8 indicate that, for a given nucleophile (i.e., 4-bromobenzamide motif), the enantioselectivities are consistently about 5−6% *ee* higher with various alkene substituents using the new protocol. Likewise, *trans*-disubstituted and trisubstituted alkene substrates also

Table 2. Substrate Scope Evaluation with Chloramine-T·3H_2O/(DHQD)$_2$PHAL and Comparison to DCDPH/(DHQD)$_2$PHAL System



entry	R^1	R^2, R^3	Ar	product	yield[a]/ *ee*[b] (TsNNaCl)	yield[a]/ *ee*[b] (DCDPH)
1	C_6H_5	H, H	C_6H_5	**2a**	85%, 92% *ee*	96%, 90% *ee*
2	C_6H_5	H, H	4-Br-C_6H_4	**2b**	87%, 97% *ee*	93%, 98% *ee*
3	C_6H_5	H, H	4-CH_3-C_6H_4	**2c**	92%, 92% *ee*	90%, 83% *ee*
4	C_6H_5	H, H	2-F-C_6H_4	**2d**	87%, 99% *ee*	86%, 88% *ee*
5	C_6H_5	H, H	3-Pyr	**2e**	85%, >99% *ee*	84%, 92% *ee*
6	4-Br-C_6H_4	H, H	4-Br-C_6H_4	**2f**	87%, 90% *ee*	89%, 84% *ee*
7	4-Cl-C_6H_4	H, H	4-Br-C_6H_4	**2g**	88%, 92% *ee*	94%, 87% *ee*
8[c]	3-OMe-C_6H_4	H, H	4-Br-C_6H_4	**2h**	86%, 92% *ee*	72%, 93% *ee*
9	4-Cl-C_6H_4	H, H	3,5-NO_2-4-CH_3-C_6H_2	**2i**	90%, 87% *ee*	87%, 88% *ee*
10	H	C_6H_5, H	4-OCH_3-C_6H_4	**3j**	93%, >99% *ee*	93%, >99% *ee*
11	H	4-CF_3-C_6H_4, H	4-Br-C_6H_4	**3k**	90%, 97% *ee*	94%, 95% *ee*
12	H	4-Br-C_6H_4, H	4-Br-C_6H_4	**3l**	83%, 91% *ee*	85%, 93% *ee*
13	H	4-F-C_6H_4, H	4-Br-C_6H_4	**3m**	93%, 82% *ee*	99%, 95% *ee*
14	H	2-Me-C_6H_4, H	4-Br-C_6H_4	**3n**	95%, 91% *ee*	99%, 87% *ee*
15	H	C_6H_5, C_6H_5	4-Br-C_6H_4	**3o**	84%, 92% *ee*	92%, 86% *ee*
16	H	C_6H_5, CH_3	4-Br-C_6H_4	**3p**	64%, 92% *ee*	52%, 91% *ee*
17	H	4-CH_3-C_6H_4, H	4-Br-C_6H_4	**3q**	86%, 40% *ee*	73%, 37% *ee*

[a]Isolated yields after chromatographic purification. [b]Determined by chiral HPLC. [c]15% of the mass balance was the ring chlorinated product with DCDPH.

furnished the corresponding dihydrooxazine heterocycles in yields and enantioselectivites that were comparable to those utilizing the first generation conditions (see entries 10−17 in Table 2).[7]

Chloramine salts have found widespread use in alkene functionalization reactions such as aziridinations, amino hydroxylations, and epoxidations—transformations that exploit the *nucleophilicity* of the chloramine salts.[12] Nonetheless, their use as electrophilic chlorinating reagents is much less common and is practically unknown in the context of enantioselective chlorinations. Chloramine-T·3H_2O is known to disproportionate into an equilibrium mixture of *N*-chlorotoluenesulfonamide (TsNHCl), dichloramine-T ($TsNCl_2$), and toluene sulfonamide ($TsNH_2$) in aqueous solutions.[13] The $TsNCl_2$ thus generated has been invoked in electrophilic aromatic chlorination reactions.[14]

Control experiments that employed only 0.5 equiv of $TsNCl_2$ gave >98% conversion into product and 80% *ee* indicating that the primary byproduct in reactions that employ $TsNCl_2$ (presumably TsNHCl) is also a potent chlorenium precursor in this chemistry. The lower enantioselectivity is likely attributable to the higher background reaction with $TsNCl_2$ (employing 1.1 equiv of $TsNCl_2$ with 20 mol % of catalyst leads to 87% *ee*; see SI). Given these results, we postulate that TsNHCl formed by the protonation of chloramine-T·3H_2O under reaction conditions is the active chlorenium source. Whether or not TsNHCl itself is the chlorenium source or it rapidly disproportionates into $TsNCl_2$, prior to transfer of Cl^+ to the olefin, is the subject of current investigations. Attempts to synthesize and isolate pure *N*-chlorotoluenesulfonamide have been unsuccessful thus far.[15]

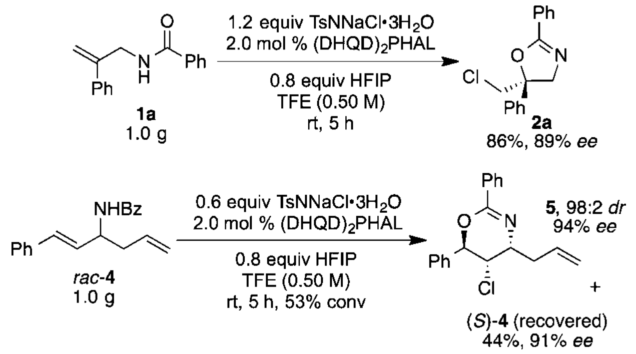
We were also cognizant that chloramine salts have a tendency to undergo photocatalyzed decomposition to furnish chlorine radicals even at ambient temperatures.[16] Reactions run in the dark or in the presence of stoichiometric quantities of radical scavengers (1.0 equiv of butylated hydroxytoluene) showed no noticeable deviations from results obtained otherwise (see Table S4 in the SI) indicating that it is unlikely that chlorine radicals are involved in this reaction.

The role of the HFIP additive in accelerating the reaction remains speculative at this stage. The higher acidity with respect to CF_3CH_2OH might lead to a more rapid protonation of chloramine-T·3H_2O leading to faster reactions (pK_a of HFIP is 9.3, pK_a of TFE is 12.5). Similar rate accelerations with other protic additives, and the lack thereof, with inorganic base additives seem to further bolster the protonation hypothesis.

Finally, we sought to explore whether this protocol was amenable to preparatory scale reactions. Gram-scale reaction of **1a** was conveniently run at ambient temperatures at 0.5 M initial concentration of the substrate by employing 2 mol % of the catalyst (Scheme 1). The HFIP additive loading could be reduced to 0.80 equiv at the expense of longer reaction times (5 h). The isolated yields and enantioselectivity were comparable to the microscale reactions. Our recently disclosed kinetic resolution reaction could also be run on gram scale using this protocol (see the transformation of *rac*-**4** to **5**) with comparable levels of stereoinduction as our previously optimized reaction conditions.[10]

In conclusion, the discovery of chloramine-T·3H_2O as a chlorenium ion precursor has led to the development of a practical and more robust protocol for catalytic asymmetric chlorocyclization of unsaturated amides. Reactions can now be run at ambient temperatures at significantly higher concentrations in open reaction vessels.

Scheme 1. Gram Scale Chlorocyclizations Using Chloramine-T·3H_2O/(DHQD)$_2$PHAL



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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