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Ritter-enabled catalytic asymmetric chloroamidation of olefins†

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Intermolecular asymmetric haloamination reactions are challenging due to the inherently high halenium affinity (HalA) of the nitrogen atom, which often leads to *N*-halogenated products as a kinetic trap. To circumvent this issue, acetonitrile, possessing a low HalA, was used as the nucleophile in the catalytic asymmetric Ritter-type chloroamidation of allyl-amides. This method is compatible with *Z* and *E* alkenes with both alkyl and aromatic substitution. Mild acidic workup reveals the 1,2-chloroamide products with enantiomeric excess greater than 95% for many examples. We also report the successful use of the sulfonamide chlorenium reagent dichloramine-T in this chlorenium-initiated catalytic asymmetric Ritter-type reaction. Facile modifications lead to chiral imidazoline, guanidine, and orthogonally protected 1,2,3 chiral tri-amines.

Introduction

The last decade has witnessed dramatic progress in the asymmetric halofunctionalization of olefins as a relatively new addition to the field of asymmetric catalysis.[1] To reach this point, catalytic events have had to outcompete a number of intrinsic difficulties associated with halonium ions, including olefin-to-olefin halenium transfer and equilibrium of the putative cyclic haliranium to the open β-halocarbenium ion.[2] Overcoming these challenges has enabled the construction of carbon–halogen bonds, as well as the vicinal formation of carbon–halogen,[3] carbon–carbon,[4] carbon–oxygen[5] and carbon–nitrogen[6] bonds greatly increasing the molecular and stereochemical complexity in a single step transformation.

The importance of the catalytic asymmetric halofunctionalization chemistry is reflected by the large number of reports on intramolecular halocyclizations,[4,5h–aa,6k–aa] along with a growing list of intermolecular halofunctionalizations.[3,5a–g,6a–j] Early investigations focused on the more accessible intramolecular cases, although recent reports demonstrate that the entropically challenged intermolecular events have also succumbed to excellent strategies in delivering products in high yield and enantioexcess. Nonetheless, intermolecular asymmetric haloamination and haloamidation reactions have not seen the same level of progress, especially with organocatalysts with unactivated olefins.[6a–j] An important challenge in the development of such reactions can be attributed to the high halenium affinity (HalA) of the nitrogen atom as compared to other nucleophiles, which leads to the direct halogenation of the nitrogen atom as opposed to the target functionality, such as the olefin (see Fig. 1b, HalA (Cl) values).[2a] This is especially detrimental in asymmetric halogenations, as the transfer of the halenium to the nitrogen atom would shunt the path of the halogen through the catalyst, which is necessary to achieve enantiofacial selectivity. As a result, haloamination reactions differ from the successful catalytic asymmetric haloetherifications/esterifications since alcohols and other oxygen nucleophiles have a lower HalA than the corresponding nitrogen nucleophiles. There are a few elegant examples of intermolecular asymmetric catalytic solutions to circumvent the high halonium affinity of nitrogen in the literature (Fig. 1a). These solutions have required either, (1) the use of a "pro-nucleophile", *i.e.*, the halenium addition to the olefin revealing a more nucleophilic nitrogen atom (see the work of Masson, Zhou, and Burns),[6c,e,f,h] or (2) the addition of a nitrogen nucleophile to an α,β-unsaturated system that subsequently captures a halenium ion (Feng and coworkers).[6a,b,d,g,i,j]

In our approach, we envisioned the use of a nitrogen atom with attenuated HalA in the same range calculated for oxygen nucleophiles. Presumably, this would circumvent the ability for the nitrogen atom to participate prematurely in abstraction of the halenium from its donor. A cursory look at HalA (Cl) values led to the nitrile functionality as a potential candidate (see Fig. 1b).[2a] We imagined the use of an alkyl nitrile would lead to a halenium-induced Ritter reaction, effectively introducing a nitrogen atom. Previous reports have shown nitriles as nucleophilic participants in different halenium induced Ritter-type reactions, although not in an asymmetric fashion.[7] The

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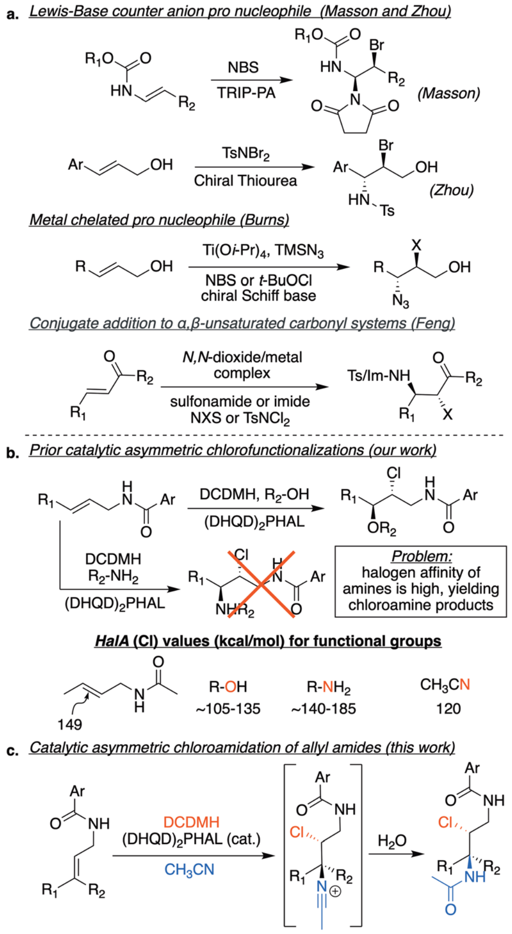


Fig. 1 (a) Prior art in catalytic asymmetric haloamination (or equivalent functionality) of olefins; (b) generalized example of catalytic asymmetric chlorofunctionalizations. Initial attempts using this strategy failed to deliver the chloroamination product. HalA (Cl) values suggest the need for a nucleophilically tempered nitrogen source. The HalA (Cl) of nitrile is close to the HalA (Cl) of alcohols, which have successfully succumbed to haloetherifications; (c) putative strategy for the Ritter-mediated chloroamidation reaction.

closest related example is from Pasquato and coworkers that employed acetonitrile to open a pre-formed enantiopure thiiranium ion, resulting in the corresponding acetamide.[8] In fact, we had also observed what we presumed to be a Ritter side product previously, while developing an effective strategy towards catalytic asymmetric dihalogenation. During our optimizations, we had observed that although acetonitrile was capable of delivering the desired dihalogenated product, albeit not as the optimum solvent system, the Ritter side product was evident.[3e] This observation laid the foundation for the development of this reaction as a route for haloamidation of olefins in an asymmetric fashion.

Utilizing nitriles as the nucleophilic partners in chloroamidations, we demonstrate the use of cinchona alkaloid dimer catalysts, along with a variety of chlorenium sources, in an efficient methodology to deliver products in high yields and enantioselectivity. Furthermore, we show that the immediate product of the Ritter-type reaction is the trapping of the putative nitrilium cation with the donor of the chlorenium, and in fact, when dichloramine-T is used, the sulfonylamidine product is stable for isolation. Vicinal chloramines[9] and in particular enantioenriched vicinal chloroamides are useful in downstream synthesis of chiral aziridine, oxazoline, and amino alcohol moieties.[10] To expand on this chemistry, we employ vicinal chloroamidines to synthesize enantioenriched imidazoline, guanidine, and orthogonally protected 1,2,3 chiral tri-amines.

Results and discussion

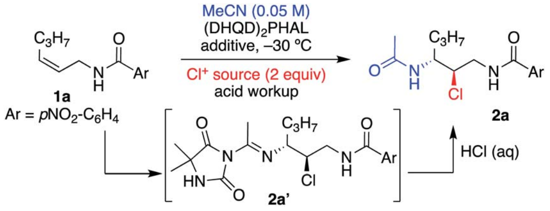
Our prior success in using the cinchona alkaloid dimers in the catalytic asymmetric intra- and intermolecular halofunctionalization of allyl amides prompted the following investigation for developing a process for haloamidations.[3e,5e,11] Cognizant of the issues with using amine or amide nucleophiles, namely, their elevated reactivity towards abstracting haleniums from their respective sources, we opted to use nitriles, possessing an attenuated affinity for halenium ions.

Ritter-type exploratory investigations

The study was initiated with substrate **1a**, which had previously shown excellent results in delivering enantioenriched 1,2-chloroethers.[5e] Early exploration of the reaction with acetonitrile, catalytic $(DHQD)_2PHAL$, and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) revealed the presence of Ritter-type products. Nonetheless, unlike the product of a classical Ritter-reaction that yields the corresponding amide by trapping of the nitrilium ion intermediate with water,[7g,j,12] the observed product was the result of the hydantoin anion trap of the nitrilium ion intermediate as indicated by the mass spectrum of the crude product (see **2a′**, Table 1, as well as Tables S2 and S3† for NMR evidence). Mild acid workup hydrolyzed the amidine product **2a′** to provide the α-chloroamide **2a**. Interestingly, without the presence of $(DHQD)_2PHAL$, the nitrilium ion is trapped by water, as indicated by direct amide formation that yields **2a**. The control over product formation suggests that the catalyst is not innocent in the addition of the hydantoin ion to the nitrilium ion. This divergent pathway hints towards an associative complex between $(DHQD)_2PHAL$ and DCDMH.[5j] We also discovered that polarization of the olefin, resulting from the inductive electron withdrawing nature of the amide, albeit not large, is sufficient in dictating the regiochemistry in the Ritter type mechanism for **1a** in both catalyzed and non-catalyzed reactions (see Table S4,† entries 1 and 2 for uncatalyzed *vs.* catalyzed regiochemical outcomes).

Table 1 illustrates the optimization of the reaction under various conditions with the *Z* aliphatic substrate **1a**. The reaction provides **2a** in 68% yield (96% ee), however, requiring 72 h to reach completion (entry 1, Table 1). In our previously reported studies on asymmetric halofunctionalization reactions,[3e,11a,b,13] we had observed an increased performance, both in terms of rate of reaction and yield of products, when a fluorinated alcohol additive was employed. Presumably, the acidic nature of the alcohol, and its attenuated nucleophilicity, are good combinations that lead to rate acceleration without

Table 1 Summary of optimization studies for chloroamidation



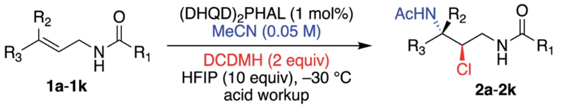
Entry	Additive (equiv.)	Cl$^+$ source	Cat. (mol%)	Time (h)	Yield[a] (%)	ee[b] (%)
1	None	DCDMH	10	72	68	96
2	HFIP (2)	DCDMH	10	0.5	71	99
3	HFIP (10)	DCDMH	10	0.5	78	99
4[c]	HFIP (10)	DCDMH	10	0.5	78	98
5[c]	HFIP (10)	NCS	10	96	70	98
6	HFIP (10)	TCCA	10	0.5	42	98
7[d]	HFIP (10)	DiCh-T	10	0.5	12	99
8	HFIP (10)	DCDMH	1	0.5	76	99
9[e]	HFIP (10)	DCDMH	1	9	67	99
10	TFE (10)	DCDMH	1	5	67	96
11	PhCO$_2$H (10)	DCDMH	1	2	29	97
12[f]	HFIP (10)	DCDMH	1	4	53	99

[a] NMR yield on a 0.05 mmol scale. [b] Enantiomeric excess determined by chiral HPLC. [c] Reaction completed at room temperature. [d] Major product was the incorporation of the *p*-tolyl sulfonamide from DiCh-T (see **3a** for structure). [e] 0.6 equiv. of DCDMH was used. [f] Reaction completed in dichloromethane (0.10 M) with 10 equiv. of acetonitrile.

nucleophilic participation in the reaction.[14] There is also evidence that protonation of cinchona alkaloid dimeric catalysts could lead to altered conformations.[15] An early screening of solvents showed that the addition of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP, entries 2 and 3, Table 1) improved the enantiomeric excess of **2a**, while tremendously increasing the rate of the reaction.

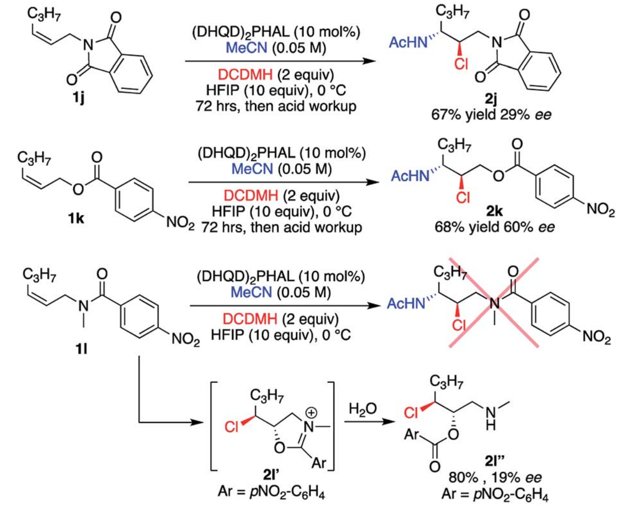
DCDMH proved to be the optimal chlorenium source as the less active NCS (entry 5) was sluggish and gave slightly lower ee, while the more active chlorenium TCCA (entry 6) gave a lower yield. Use of dichloramine-T returned the product in high ee, although in low yields. Interestingly, the mass balance was identified as the *p*-tolyl sulfonylamidine product **3a** (addition of the *p*-tolyl sulfonamide to the Ritter intermediate, yielding a stable product, *vide infra*). Lowering the catalyst loading (entry 8) led to a negligible change in reaction proficiency, and thus 1 mol% (DHQD)$_2$PHAL was chosen as standard for ensuing reactions. Less reactive substrates required increased catalyst loading to achieve optimal proficiency (see Table S1† for experiments and discussion). Varying the equivalents of

Table 2 Optimized amide functionality



Entry	Pdt	Time (h)	R$_1$	R$_2$	R$_3$	Yield[a] (%)	dr	ee[b] (%)
1	**2a**	0.5	pNO$_2$-C$_6$H$_4$	C$_3$H$_7$	H	90	>20 : 1	99
2	**2b**	2	Ph	C$_3$H$_7$	H	81	>20 : 1	98
3[c]	**2c**	0.5	pMeO-C$_6$H$_4$	C$_3$H$_7$	H	89	>20 : 1	99
4	**2d**	0.5	pF-C$_6$H$_4$	C$_3$H$_7$	H	85	>20 : 1	99
5	**2e**	0.5	pt-Bu-C$_6$H$_4$	C$_3$H$_7$	H	79	>20 : 1	99
6	**2f**	0.5	pBr-C$_6$H$_4$	C$_3$H$_7$	H	91	>20 : 1	99
7	**2g**	18	Me	C$_3$H$_7$	H	58	>20 : 1	94
8	**2h**	5	pNO$_2$-C$_6$H$_4$	H	C$_3$H$_7$	81	>20 : 1	97
9[c]	**2i**	5	pBr-C$_6$H$_4$	H	C$_3$H$_7$	59	>20 : 1	95

[a] Isolated yield on a 0.1 mmol scale. [b] Enantiomeric excess determined by chiral HPLC. [c] Absolute stereochemical determination was verified by X-ray crystal analysis (see ESI).



Scheme 1 Alternative functional handles.

DCDMH had no effect on the enantiopurity of the final product, although the yield suffered slightly with lower amounts (entry 9). A quick screen of acidic additives (entries 10 and 11) proved HFIP's superiority and was thus maintained as part of the standard reaction condition. Decreasing nucleophile equivalents (entry 12) provided slightly lower yield and longer reaction times but retained high enantioselectivity for **1a**.

Next, we examined the nature of the amide on the performance of the reaction (Table 2). Comparing to the standard substrate **1a**, electronic perturbations to the aryl of the amide group did not alter the course or results of the reactions, delivering products **2b**–**2f** in good yields and high enantioselectivity (entries 1–6, Table 2). The acetamide substrate **1g**, though sluggish, provided the chloroamidation product **2g** with good enantiocontrol (94% ee). Nonetheless, the results were inferior in terms of yield, enantiopurity of product, and time to completion of the reaction in comparison to arylamide substrates **1a**–**1f**. Interestingly, the *E* aliphatic substrate **1h** was nonreactive without HFIP, but reacted under the standard condition to yield product **2h** in good yield and high enantioselectivity (entry 8, Table 2).

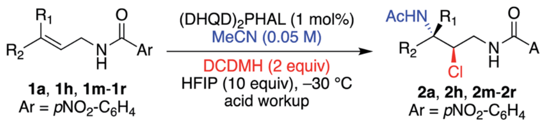
A note regarding the absolute stereochemistry of the molecules reported in this manuscript: products **2c** and **2i** were crystalline, and their 3-dimensional structures were solved, revealing the stereochemistry of the (DHQD)$_2$PHAL catalyzed reaction. The absolute stereochemistry of other molecules in this report are by analogy to these two structures.[16]

The requirement for a secondary amide substrate was briefly examined with the analogous imide **1j**, ester **1k**, and *N*-methylated tertiary amide **1l** (Scheme 1). Substrates **1j** and **1k** yielded their respective chloroamide products **2j** and **2k**, respectively, albeit with less enantiocontrol than the aryl amide substrates, while requiring a higher catalyst loading (10 mol%). The anticipated chloroamide product was not observed upon treatment of **1l** under slightly modified conditions (10 mol% catalyst instead of 1 mol%, and 0 °C instead of −30 °C), but instead chloroester **2l″** was isolated in good yield. As depicted in Scheme 1, **2l″** is presumably obtained from the hydrolysis of the presumed intermediate **2l′**. Taken together, these results not only indicate the need for a hydrogen bonding element supplied by the 2° amide, but also the amide confirmation presumably plays a significant role in the success of these asymmetric catalytic reactions.

Exploring the substrate scope of the Ritter-type asymmetric chloroamidation reaction

Table 3 illustrates the results of the substrate scope for *E* and *Z* aliphatic allyl-amides. In all cases, the minor diastereomer was not observed. *Z*-Olefins (entries 1–5) reacted smoothly to yield

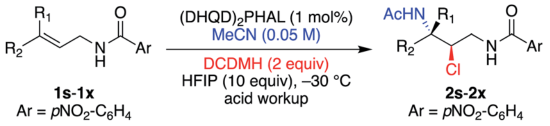
Table 3 Aliphatic allyl-amide substrate scope



Entry	Pdt	Time (h)	R$_1$	R$_2$	Yield[a] (%)	dr	ee[b] (%)
1	**2a**	0.5	C_3H_7	H	90 (83)[c]	>20 : 1	99
2	**2m**	0.5	C_6H_{13}	H	79	>20 : 1	99
3	**2n**	0.5	C_2H_5	H	73	>20 : 1	99
4	**2o**	5	TBDPSOC$_2$H$_4$	H	62	>20 : 1	99
5[d]	**2p**	72	BnOCH$_2$	H	23 (69)[e]	>20 : 1	99[f]
6	**2h**	5	H	C_3H_7	81	>20 : 1	96
7	**2q**	6	H	C_6H_{13}	83	>20 : 1	94
8	**2r**	6	Me	Me	79	na	99
9[g]	*ent*-**2a**	0.5	C_3H_7	H	87	>20 : 1	99
10[g]	*ent*-**2h**	5	H	C_3H_7	87	>20 : 1	97

[a] Isolated yields on a 0.1 mmol scale. [b] Enantioselectivity determined by chiral HPLC. [c] Isolated yields on a 1.0 mmol scale. [d] 15 mol% (DHQD)$_2$PHAL was added over the course of the reaction (3 days), maintaining the temperature at 0 °C. [e] Combined yield of the acetamide product and the α-chlorinated acetamide product (see ESI). [f] Both acetamide and α-chlorinated acetamide were obtained with 99% ee (see ESI). [g] Reaction performed with quasi-enantiomeric (DHQ)$_2$PHAL.

Table 4 Aryl allyl-amide substrate scope



Entry	Pdt[a]	R_1	R_2	Yield[b] (%)	dr[c]	ee major[d] (%)	ee minor[d] (%)
1	**2s**	Ph	H	95	65 : 35	99	99
2	**2t**	pCl-C_6H_4	H	92	66 : 34	97	98
3	**2u**	pMe-C_6H_4	H	78	50 : 50	99/99	99/99
4[e]	**2v**	$p$$CF_3$-$C_6H_4$	H	12 (76)[f]	>20 : 1	89[g]	na
5	**2w**	H	Ph	53	74 : 26	99	93
6	**2x**	Me	Ph	57	61 : 39	99	97
7[h]	*ent*-**2s**	Ph	H	84	63 : 37	99	99
8[h]	*ent*-**2w**	H	Ph	66	70 : 30	92	99

[a] Time of completion for products **2s**, **2u**, **2x**, and *ent*-**2s** was 1 h, while **2w** and *ent*-**2w** required 10 h, with **2v** the most sluggish, necessitating 120 h. [b] Isolated yield on a 0.1 mmol scale. [c] Diastereomeric ratio determined by NMR. [d] Enantiomeric excess determined by chiral HPLC. [e] 15 mol% $(DHQD)_2PHAL$ was added over the course of the reaction (3 days), maintaining the temperature at 23 °C. [f] Combined yield of acetamide product and α-chlorinated acetamide product (see ESI). [g] The α-chlorinated acetamide product had enantiomeric excess of 87% (see ESI). [h] Reaction performed with quasi-enantiomeric $(DHQ)_2PHAL$.

the corresponding chloroamide products in high yields, enantioselectivities (99% ee for all examples), and regioselectivities. This was true of the less electronically biased examples **1o** and **1p**, which often result in lower performance due to inductive changes in polarity, leading to regioisomeric products.[3a,e] The extended reaction time required for **1p** led to the over-chlorinated product **2p′** (resulting from the α-chlorination of the acetamide moiety) in ∼2 : 1 ratio (**2p′** : **2p**).

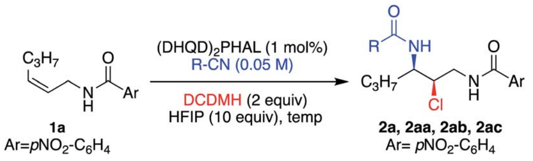
The same success was observed for the corresponding *E*-isomeric substrates, providing the chloroamide products with slightly less enantiocontrol (≥94% ee) and excellent yields (entries 6 and 7). The tri-substituted allyl amide **1r** was also not problematic, providing the product **2r** in high yield as well as high ee (entry 8). The quasi-enantiomeric $(DHQ)_2PHAL$ catalyst gave comparable results for the *Z* and *E* isomeric substrates **1a** and **1h**, yielding *ent*-**2a** and *ent*-**2h**, in 99% ee and 97% ee, respectively (entries 9 and 10).

Aryl substituted allyl amide substrates proved more problematic, leading to diastereomeric products, presumably as a result of carbocationic stabilization afforded by the aromatic group (Table 4).[3e,5e,11b] As expected, the more electron rich systems, having the ability to stabilize the benzylic carbocation, resulted in lower selectivity (entries 1–3), while the electron deficient $p$$CF_3$-Ph substituent restored the high diastereomeric selectivity observed with the alkyl systems (entry 4).[11b,17] Similar to **1p**, the extended reaction time required for full conversion of **1v** to the product led to α-chlorination of the acetamide functionality as the major product (∼5 : 1 **2v′** : **2v**). Nonetheless, while the chloroamidation of electron rich aryls led to low drs, each diastereomer was isolated in high enantiomeric excess, suggesting the olefinic face selectivity during the chlorination is preserved.

Efforts to improve diastereoselectivity, such as employing a less polar co-solvent, decreasing equivalents of HFIP, and increasing catalyst loading were unfruitful. Neither the *E*-substituted alkene **1w**, nor the trisubstituted alkene **1x** were immune to the observed diminished diastereoselectivity, although in both cases high enantioselectivity of their products were maintained (entries 5 and 6). The reduced yield for product **2w** was attributed to competing intramolecular halocyclization, not observed with *Z* alkenes. The quasi-enantiomeric $(DHQ)_2PHAL$ provided *ent*-**2s** and *ent*-**2w** with similar efficiencies in all categories.

The next variable examined was the nitrile nucleophile, yielding different amide products (Table 5). Reactions of **1a** proceeded smoothly with propionitrile (entry 2), benzonitrile (entry 3), and the bulky pivalonitrile (entry 4). Although the latter two reactions required slightly higher temperatures to accommodate the higher melting points of their respective nitrile solvents, there were no significant observed erosion in

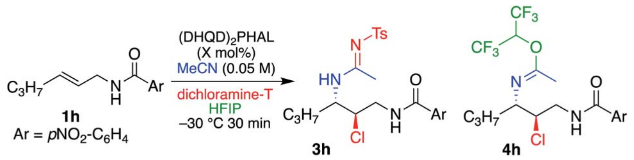
Table 5 Use of different nitriles in the chloroamidation chemistry



Entry	Pdt	R	Temp	Yield[a] (%)	dr[b]	ee major[c] (%)
1	**2a**	Me	−30 °C	90	>20 : 1	99
2	**2aa**	Et	−30 °C	88	>20 : 1	99
3	**2ab**	Ph	0 °C	87	>20 : 1	98
4	**2ac**	*t*-Bu	23 °C	86	>20 : 1	98

[a] Isolated yield on a 0.1 mmol scale. [b] Diastereomeric ratio determined by NMR. [c] Enantiomeric excess determined by chiral HPLC.

Table 6 Optimization of dichloramine-T chloroamidinations



Entry	Catalyst (mol%)	DiCh-T (equiv.)	HFIP (equiv.)	Yield **3h**[a] (%)	**3h** : **4h**[b]	ee[c] (%) **3h**
1	1	2.00	10	43	5.4 : 1	94
2	1	2.00	20	39	2.6 : 1	94
3	1	2.00	0	45	na	62
4	1	3.00	10	49	16 : 1	92
5	1	1.25	10	50	2.6 : 1	95
6	5	2.00	10	56	>20 : 1	96

[a] NMR yield on a 0.05 mmol scale. [b] Ratios are obtained from NMR of crude reaction mixture. [c] Enantiomeric excess determined by chiral HPLC.

enantioselectivities. The versatility in choosing different nitrile nucleophiles enables the assembly of more complex amide structures.

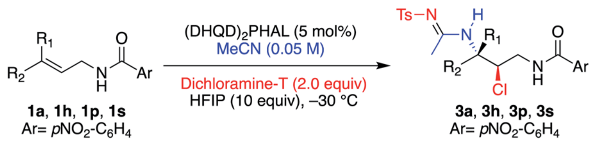
Asymmetric sulfonylamidine products *via* trapping of the Ritter intermediate

As described above, the use of dichloramine-T as the chlorenium source led to low yields of the chloroamide product (see Table 1, entry 7), although reaction conversion was high. Analysis of the reaction products led to the identification of the corresponding chlorosulfonylamidine (see **3a**, Table 7), which results from the capture of the nitrilium ion intermediate with the sulfonylamide generated upon transfer of the halogen. While the amidine products from addition of the hydantoin to the Ritter intermediate were observed before (see structure **2a**′ in Table 1), they were not stable to isolation. Interestingly, the sulfonyl functionality lends stability to the structure, so much so that it does not hydrolyze with aqueous acid treatment.

A quick screen led to a slight modification from conditions used in the Ritter-type reactions with DCDMH (Table 6). Standard conditions used with DCDMH led to a 5.4 : 1 **3h** : **4h** ratio (entry 1). Not surprisingly, increasing equivalents of HFIP worsened the selectivity (entry 2). As illustrated in entry 3, however, omission of HFIP to eliminate the side product **4h** reduces the enantioselectivity of **3h**, similar to reactions that employed DCDMH as the chlorenium source. Interestingly, increased equivalents of dichloramine-T greatly enhanced the product ratio (16 : 1, **3h** : **4h**), while maintaining high ee (entry 4). Further verification of the latter was the observed diminution of the same ratio (2.6 : 1) when 1.25 equivalents of dichloramine-T was employed (entry 5). Alternatively, increase in the amount of catalyst (from 1 mol% to 5 mol%), without increasing dichloramine-T (2 equivalents), led to the same high product ratio (entry 6). It is likely that **4h** originates from the trap of the nitrilium intermediate, as incubation of **3h** in neat HFIP over a prolonged period did not return any **4h.**

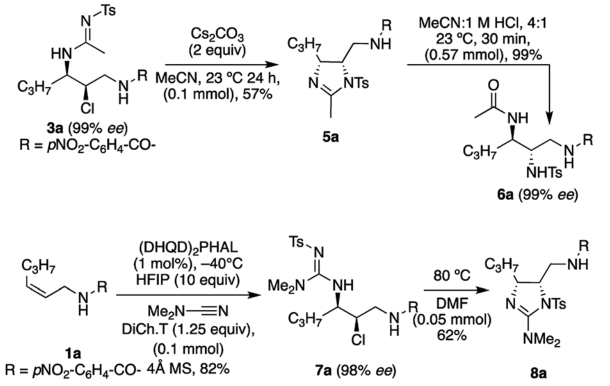
Table 7 lists a short survey of substrates that highlights a similar level of efficiency for the dichloramine-T mediated reaction that yield the chlorosulfonylamidines as compared to the chloroamides obtained with DCDMH. *Z* and *E* aliphatic allyl amides **1a** and **1h** are converted to their corresponding products **3a** and **3h** in good yields and high enantiomeric excess (99%

Table 7 Scope with dichloramine-T mediated chloroamidinations



Entry	Prd[a]	R_1	R_2	Yield[b] (%)	dr[c]	ee major[d] (%)	ee minor[d] (%)
1	**3a**	C_3H_7	H	71	>20 : 1	99	na
2	**3h**	H	C_3H_7	65	>20 : 1	95	na
3	**3p**	$BnOCH_2$	H	65	>20 : 1	96	na
4	**3s**	Ph	H	54[e]	61 : 39	99	97

[a] Time for completion for products **3a** and **3h** was 30 min, while **3s** required 2 h, with **3p** the most sluggish, necessitating 24 h. [b] Isolated yield on a 0.1 mmol scale. [c] Diastereomeric ratio determined by NMR. [d] Enantiomeric excess determined by chiral HPLC. [e] NMR yield on a 0.05 mmol scale.



Scheme 2 Chemical elaborations of chlorosulfonylamidines.

and 95%, respectively). The benzyl protected allylic alcohol **1p** also returned product **3p** with no observable evidence for regioisomeric products in high enantiomeric excess (entry 3). As detailed above, the aryl substituted olefin **1s** was more problematic, leading to diastereomeric products, although with high ee for each isomer.

Reactions of chlorosulfonylamidines

The utility of the sulfonylamide product **3a** was demonstrated *via* its cyclization to form the imidazoline **5a** (Scheme 2).[7d,h] This product was then easily hydrolyzed to the chiral tri-amine **6a** upon treatment with dilute HCl, yielding the orthogonally protected triamine product with two contiguous chiral centers. This could be of synthetic value, as there are few known methods to deliver chiral triamines,[18] in addition, this allows for orthogonal protection. Also illustrated in Scheme 2, is the conversion of **1a** to **7a**, using dimethylcyanamide as the nucleophile, en route to the cyclic guanidine **8a**.[7e] The enantioselectivity obtained in the asymmetric transformation is maintained in subsequent reaction for both sequences described above.

Conclusions

In summary, we describe the catalytic asymmetric chloroamidation of allylic-amides *via* a chlorenium induced Ritter-type reaction. This is achieved through the use of a nucleophilically tempered source, a nitrile, that circumvents the high halonium affinity of most sp^3 nitrogen atoms. The methodology was successful in producing a broad range of chloroamides in good yields and high enantioselectivity. Interestingly, the use of two different chlorenium sources, although both deliver products with high ee, proceed through intermediates that exhibit different chemical stabilities. Presumably, the intermediates are produced by the trapping of the nitrilium with either the residual hydantoin or chloramine-T, after having the chlorenium transferred. The hydantoin-trapped molecule is not as stable to isolation, and is readily hydrolyzed to the corresponding amide. The chloramine-T trapped product, on the other hand, is stable, isolable, and can be manipulated to yield new categories of products.

Conflicts of interest

The authors declare no conflict of interest.

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16 The absolute stereochemistry of **2c** and **2i** were established by single crystal X-ray diffraction (their corresponding Cambridge Structural Database deposition numbers are provided following each compound name). These are: **2c** (1864170) and **2i** (1909607). A note regarding the absolute stereochemistries reported here as compared to our previous work for the catalytic asymmetric dihalogenation of olefins (see ref. 3*e*); we had observed the Ritter product as a side-product of the dihalogenation reaction when acetonitrile was used as a solvent. Although the relative stereochemistry reported in this manuscript is the same as the one reproted previously, our crystallographic analysis of products obtained here show the opposite olefin facial selectivity. The stereochemistry shown for the Ritter product in the dihalogenation study (ref. 3*e*) was based on the absolute stereochemistry of the dihalogenation products, which we now realize is different as compared to the Ritter medicated halofunctionalization. The source of this change in olefin facial selectivity is currently under scrutiny through mechanistic investigations.

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