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COMMUNICATION

Cooperativity within the catalyst: alkoxyamide as a catalyst for bromocyclization, and bromination of (*hetero*)aromatics

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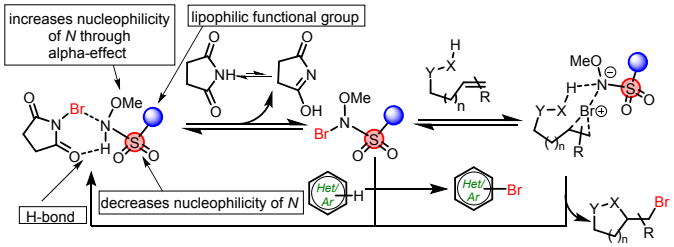
Alkoxyamide has been reported as a catalyst for the activation of the *N*-bromosuccinimide to perform bromocyclization and bromination of a wide range of substrates in a lipophilic solvent, where a adequate suppression of the background reactions were observed. The key feature of the active site is the alkoxy group attached to the sulfonamide moiety, which facilitates acceptance as well as delivery of bromonium species from the bromine source to substrates.

The discovery of new activation mode by involving simple functional group has given a new dimension to organic synthesis. The need of electrophilic bromine for bromocyclization[2,3] or aromatic bromination[4] to achieve promising brominated compounds has stimulated the discovery and development of new catalysts that activate the brominating agent as well as the substrate.[1–4] Considering stability and handiness, *N*-bromoamides are found to be a more viable source of electrophilic bromine over the highly reactive molecular bromine which could often yield unwanted byproducts via bromine free-radical generation.[5] However, sufficient and controlled amount of electrophilic bromine for successful bromination requires overcoming low reactivity of *N*-bromoamides using a catalyst and good solubility of both reagent and catalyst in the reaction solvent.[6] In addition, for the alkene activation through halocyclization/ halofunctionalization, it is challenging to obtain a high degree of enantioselectivity by suppressing a significant amount of the background reaction that arises due to olefin-to-olefin transfer of bromenium ions in the haliranium ion intermediates.[1d] The activation of NXS reagents controlled by a catalyst is still demanding.

Although, the use of a lipophilic solvent is more practical as the byproduct amide (succinimide) can be easily filtered out, the reagents and catalysts are hardly soluble in such solvent. In this line, Yeung and coworkers[7] realized that a solid-liquid phase transfer[8] approach is required for success of the reaction employing a proper catalytic system. Recently, Jiao *et al.*[4h] and Miura *et al.*[4i] respectively reported the activation of NXS reagent using DMSO and triptycenyl-sulfide (Trip-SMe) as catalyst for electrophilic aromatic halogenations. We hypothesized that an easily accessible structure, alkoxyamide could be a logical choice as a catalyst because the nucleophilicity of the *N*-atom can be tuned by introducing different substituents on *N*-atom (Scheme 1).



Scheme 1 Working hypothesis of the alkoxyamide catalysis

Thus in alkoxyamide, while alkoxy-group increases the electron density on the *N*-atom through α-effect, facilitating the ready capture of bromine electrophile, the SO_2 group decreases the electron density on *N*-atom facilitating release of bromonium ion to the substrate. Hence, both groups work in concert for the electrophilic bromine transfer to unactivated alkenes or (*hetero*)aromatic ring via *N*-bromosulfonamide formation resulting in effective phase transfer catalysis for the bromocyclization, and bromination of (*hetero*)aromatics. To the best of our knowledge, the use of alkoxyamide in the catalytic activation of NXS has not been reported so far.

In search of a versatile catalytic system, and looking into the utility of a lipophilic solvent, we have developed alkoxyamide-catalysis which worked with a broad range of substrates. The ready synthesis from commercially available reagents, high stability, reusability, easy handling, and applicability to several key chemical transformation makes this new organocatalyst attractive.

We started our investigation by simply subjecting **2a** to 5 mol % of the alkoxyamide **1a** in heptane[9] with NBS as the brominating source which gave 70% of the bromocyclized product **3a** (Table 1, entry 2). As expected, reaction conducted in the absence of any catalyst (entry 1) was very sluggish. A

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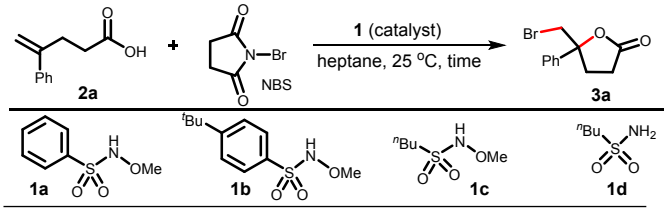
para-tert-butyl substituent on the phenyl ring increased the solubility of the catalyst **1b** to some extent, and the product **3a** was obtained in 90% yield in 3h (entry 4). We envisioned that changing the phenyl moiety to an alkyl group might further increase the solubility of the catalyst, and were delighted to find that 10 mol % of **1c** drove the reaction to completion in just 1 h (entry 5). Further decrease in the catalyst loading to 2.5 mol % could still result in 90% yield in 5.5 h (entry 7).

Here, **1c** acts as a phase-transfer catalyst (PTC) that facilitates the migration of the reactant from one phase to another phase where reaction occurs. The catalyst facilitates the bromine capture (from NBS) and brings the activated species in the liquid phase (so a solid-liquid phase transfer), where the reaction occurs. An interesting question arises concerning the alpha effect of the methoxy group on nitrogen which led us to use 5 mol % of **1d** and obtained trace yield of **3a** (entry 8) which gives a conclusive evidence that the presence of alkoxy group is essential for the catalyst system and adventitious **1d** is not the catalyst for this reaction.[10]

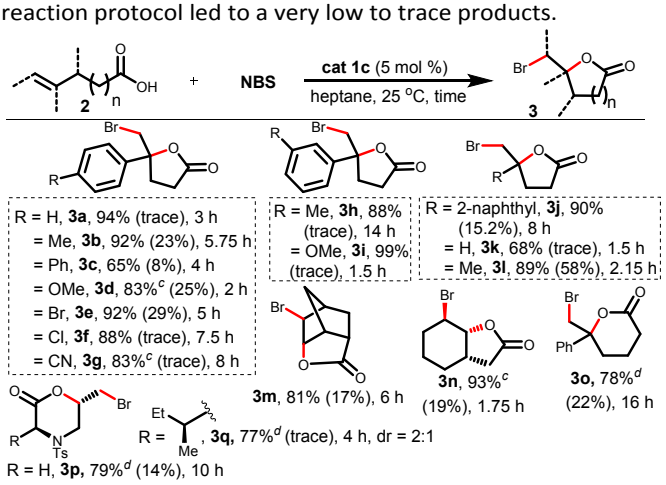
Table 1 Optimization of the reaction conditions[a]



Entry	Cat.	Cat. (mol %)	Time (h)	Yield (%)[b]
1	none	0	3	trace
2	**1a**	5	3	70
3	**1a**	10	2	74
4	**1b**	10	3	90
5	**1c**	10	1	95
6	**1c**	5	2	94
7	**1c**	2.5	5.5	90
8	**1d**	5	3	trace

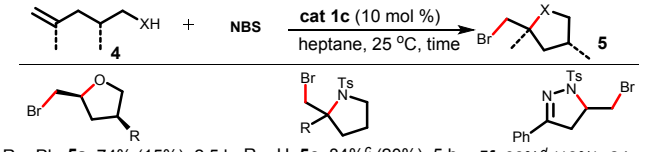
[a]Acid **2a** (0.5 mmol) and NBS (0.55 mmol) in 5 mL heptane. [b]Isolated yields. NBS = *N*-bromosuccinimide.

In order to evaluate the scope and thus the generality of our catalyst, several alkenoic acids (**3a-3q**) equipped with different substituents were subjected to the optimized reaction conditions (**Scheme 2**). The reaction conditions displayed broad scope with respect to the R groups, and various lactone compounds were accessible in high yields. We investigated the effect of the *para* substituents (**3a-3g**) on the phenyl ring and found that apart from the *para*-phenyl substituent **3c**, the yields did not vary much. Likewise, in the case of *meta*-methyl and methoxy substitutions, reactions underwent smoothly to furnish **3h** and **3i** in 88% to a near about quantitative yield. This is in stark contrast to the background reactions in absence of catalyst **1c**, which gave *γ*-lactones only in trace amount. Replacing the phenyl group with a naphthyl moiety also gave similar result. The absence of a methyl group at the 4-position in **2k** will substantially decrease the electron-density at the double bond and consequently suppress the stability of the intermediate, which is reflected in the decreased yield of **3k** as compared to the 4-methyl derivative **3l**. The substrates **3m** and **3n** are also amenable to this protocol. Although, the syntheses of six-membered lactones were a little sluggish in the beginning, increasing the catalyst loading could furnish the *δ*-lactones **3o-3q** in good yields. As expected, eliminating the catalyst from the reaction protocol led to a very low to trace products.



Scheme 2 Scope of the bromolactonization.[a,b] [a]Reactions conducted with olefenic acid **2** (0.5 mmol) and NBS (0.55 mmol) in 5 mL heptane. [b]Isolated yields, in the parenthesis yields of the background reaction are provided. [c]10 mol % and [d]20 mol % of the catalyst was used.

Subsequent to these exploratory studies, we found that **1c** could also be employed as an effective catalyst for the selective formation of substituted cis tetrahydrofurans (**5a-5b**), pyrrolidines (**5c-5e**) and 3,4-dihydropyrazole **5f** in excellent yields. Moreover, catalyst-free conditions gave trivial yields.



Scheme 3 Scope of cyclic ether and amines.[a,b] [a]**4** (0.5 mmol) and NBS (0.55 mmol) in 5 mL heptane. [b]Isolated yields, in the parenthesis yields of the background reactions are provided. [c]10 mol % and [d]20 mol % of the catalyst were used.

At the time of our investigations, the versatility of the catalyst in cyclizations inspired us to ascertain whether **1c** might catalyse other bromomocyclizations. Dearomative bromocyclization[3] of the tryptamine derivative **6a** was first examined using **1c** in 5 mol % catalyst loading with NBS in heptane. To our delight, the reaction proceeded with good conversion and excellent diastereoselectivity (**7a**). Interestingly, increasing the electron density of the indole ring by introducing a methyl group in **6b** led to a highly accelerated reaction profile.

Owing to its excellent catalytic activity for the synthesis of hexahydropyrroloindolines (HPIs) (**7a** and**7b**), we pursued bromocyclizations further and found tryptophan derivative **6c** showed excellent catalytic acceleration to furnish **7c** in 78% yield, while the reaction did not progress without the catalyst.

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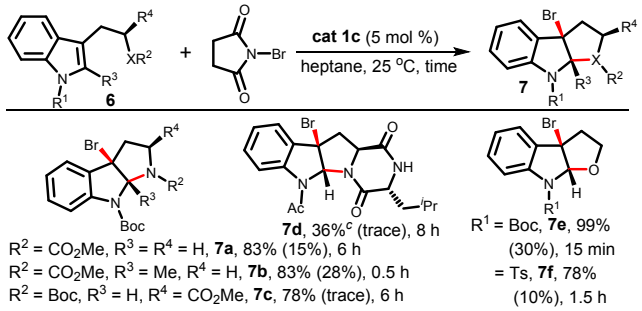
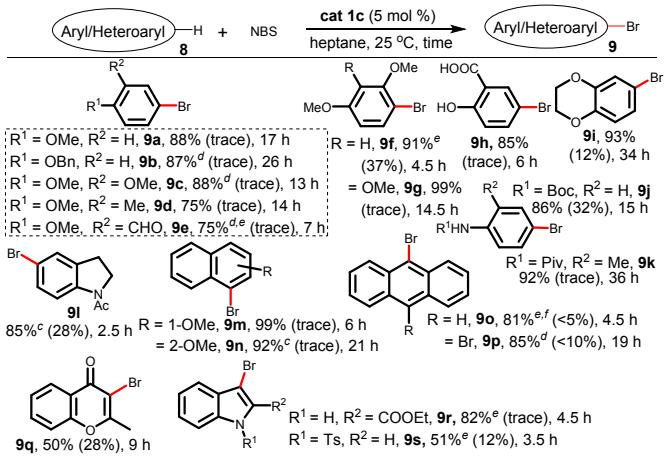
Tryptophol derivatives bearing carbamate or sulfonyl protecting groups on nitrogen atom were excellent substrates for the bromocyclization to provide the corresponding tetrahydrofuroindolines (TFIs) (**7e** and **7f**) in excellent yields (78–99%). The diastereomerically pure **7d** synthesized by this method was previously employed for the total synthesis of alkaloids (–)-protubunine A and B.[3e]



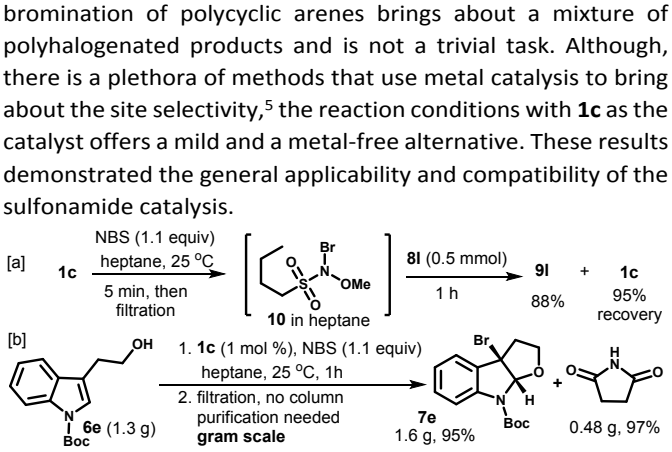
Scheme 4 Scope of the dearomative bromocyclization of tryptamines and tryptophols.[a,b] [a] (0.25 mmol) of **6** and NBS (0.28 mmol) in 2.5 mL heptane. [b]Isolated yields, in the parenthesis yields of the background reactions are provided. [c]Over two steps, bromocyclization followed by Boc deprotection using TFA.

After successfully demonstrating the excellent performance of the alkoxyamide **1c** in catalyzing the bromocyclizations, we sought to explore the flexibility of this catalytic bromocyclization protocol for the bromination of aromatic and *hetero*-aromatic compounds (**Scheme 5**). In this process, the substrates **8a-8s** were subjected to the standard **1c**-catalyzed bromination conditions. Numerous substrates showed unmatched reactivity in the presence of **1c** as compared to the corresponding background reactions under identical conditions. Thus, substituted benzenes (**8a**-**8g**), phenol **8h**, substituted dioxane **8i**, anilines **8j** and **8k**, indoline **8l**, chromene **8q** and indoles **8r-8s**, could all be cleanly brominated. Moreover, site selective monobromination of naphthalenes **8m** and **8n** were smoothly achieved. Notably for substrates having multiple potential reaction sites **8o** and **8p**, a high degree of regioselectivity was observed, producing a single isomer. We observed for the substrates having multiple reaction sites, mono bromination occurs selectively at the site governed by electronic and steric factors.



Scheme 5 Scope of the (*hetero*)aromatic bromination.[a,b] [a]**9** (0.5 mmol) and NBS (0.55 mmol) in 5 mL heptane. [b]Isolated yields, in the parenthesis yields of the background reactions are provided. [c]10 mol % and [d]20 mol % of the catalyst was used. [e]At 60 °C. [f]8% of **9p** also formed.

It may be noted that conventional protocols for the mono-bromination of polycyclic arenes brings about a mixture of polyhalogenated products and is not a trivial task. Although, there is a plethora of methods that use metal catalysis to bring about the site selectivity,[5] the reaction conditions with **1c** as the catalyst offers a mild and a metal-free alternative. These results demonstrated the general applicability and compatibility of the sulfonamide catalysis.



Scheme 6 Bromocyclization using stoichiometric amount of **10** and gram-scale reaction.

As alluded to above, the electrophilic bromofunctionalization likely involves accessing the nitrogen site for the bromine capture and transfer to the substrate. Realization of such results led us to perform a series of control experiments. Addition of one equivalent of NBS to **1c** (**Scheme 6a**) generated a less stable intermediate in 5 min which we speculated to be the *N*-bromo intermediate **10**. This was supported by ^{1}H NMR analysis in $CDCl_3$ where the N-H peak of **1c** cat. 7.05 ppm disappeared. It was found out that the species **10** is not air stable and it decomposes rapidly without the presence of a solvent. Interestingly, the Br in **10** appeared to be a highly electrophilic bromine source which when added to **8l** furnished **9l** in 88% yield and **1c** was recovered in 95% yield. As stoichiometric promoter, the recovered **1c** was again subjected to arene bromination, in the second cycle 92% of **1c** and 80% of **9l** and in the third cycle 88% of **1c** and 81% of **9l** were isolated. We could recover an overall 77% of catalyst **1c** (confirmed by ^{1}H and ^{13}C NMR analysis) after three recovery cycles indicating the robustness and stability of the catalyst **1c** under oxidative conditions.[10]

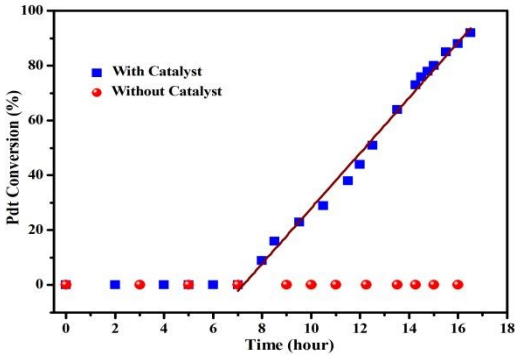


Figure 1 Effect of catalyst on the reaction profile: catalyzed vs uncatalyzed reaction of anisole bromination.

As a further test of scalability and the ease of purification process of this method, we performed a gram-scale reaction involving *N*-boc-tryptophol in the presence of 1 mol % of **1c** with

1.1 equiv of NBS in heptane (**Scheme 6b**). Upon completion, the insoluble succinimide was filtered off and the filtrate was concentrated to give tetrahydrofuroindoline **7e** in 95% yield with >95% purity based on the ^{1}H NMR study. Pure succinimide (confirmed by ^{1}H NMR) was recovered in 97% yield.

Figure 1 shows the progress in product conversion from **8a** to **9a** with respect to time for a catalyzed vs an un-catalyzed reaction. In the presence of catalyst, the reaction proceeds slowly at the beginning (also known as the induction period) followed by acceleration at the later stage. The reaction follows a zero-order kinetics after the initial induction period. The graph describes how the presence of catalyst is important for the reaction to take place.

In summary, we have designed a new phase-transfer catalyst, the alkoxy-amide which has been used effectively for bromocyclizations and brominations. The sulfonyl and alkoxy groups act cooperatively for the capture and release of electrophilic bromonium ion from brominating agent to substrates. The reaction uses a green solvent, mild and operationally simple procedure. The protocol also provides easy isolation of the bromine carrier succinimide by simple filtration. Finally, the role of the catalyst is also supported by NMR experiments. Further application of this alkoxyamide catalysis for the synthesis of enantioenriched compounds are underway.

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Conflicts of interest

There are no conflicts to declare.

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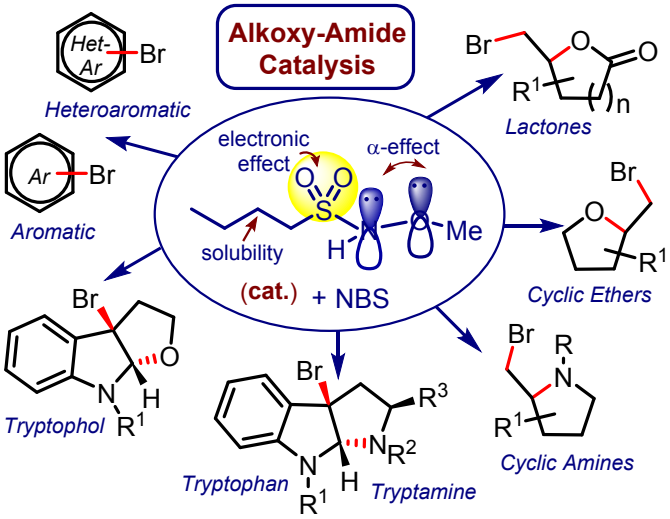

Key Features of this Catalyst

- air-stable and cost effective
- recyclable & easy purification
- regioselective

Method

- blank vs catalytic reaction for all
- mechanistic studies
- 50 examples, upto 99% yield