Spectroscopic and Computational Study of Organocatalytic Umpolung of Bromocations: An Accelerated Stereoselective Dibromination Protocol

Jeetendra Panda,[a] Jigyansa Sahoo,[a] Juhi Dutta,[b,c] Himansu Sekhar Biswal,[b,c] Gokarneswar Sahoo[a,*]

[a]Organocatalysis and Synthesis Laboratory, Department of Chemistry, National Institute of Technology Rourkela, India, 769008

[b]School of Chemical Sciences, National Institute of Science Education and Research (NISER), PO- Bhimpur-Padanpur, Via-Jatni, District- Khurda, PIN - 752050, Bhubaneswar, India

[c]Homi Bhabha National Institute, Training School Complex, Anushakti Nagar, Mumbai 400094, India.

*Corresponding author, email: sahoog@nitrkl.ac.in

This paper is dedicated to Prof. Elias J. Corey and Prof. Dieter Seebach

Abstract: Herein, the reversal of polarity of cationic bromine, organocatalytically, is presented. NBS, a proven bromocation source was converted to a superior bromoanion reagent by H/Br exchange with a secondary amine, substantiated with spectroscopic and computational evidences. The concept has further been used in a successful accelerated organocatalyzed dibromination of olefins, in a non-hazardous, commercially viable process with a wide substrate scope. The reactivity of key entities has been observed through NMR kinetics and reaction acceleration using 10 mol% of catalyst loading accounts for its major success. The nucleophilicity of the bromoanion was found to be superior in comparison to other nucleophiles such as MeOH, H_2O etc. and the protocol dominates over competing allylic bromination reaction.

Introduction:

Since the discovery of "Umpolung" by Wittig in 1951,[1] the technique has been used strategically for several functional groups to bring reversal of bond polarity, and hence the same functional group has been reacted as two entities with inverse electron demand.[2] Later in 1965, Corey and Seebach[3] elaborated the concept and generalised the approach and since then researchers have eyed the possibility of umpolung, in case there is a demand, with the latest example of NHC (N-heterocyclic carbene) organocatalysis defining a complete branch of enamine catalysis.[4] The umpolung at C-atom is well known,[5] but at other atoms, it is still rare.

Halogens possess considerable significance in synthetic chemistry as synthetic intermediates for substitution reactions, cross-coupling reactions and their presence in the molecules could stimulate biological activity.[6] Halogens being more electronegative, umpolung at the bromine centre is mainly studied for the conversion of bromides to the corresponding bromocation by using oxidants, e.g. MBr/oxone (M=Na, K),[7] KBr/HIO_3,[8] HBr/H_2O_2[9] etc. However, the reversal of polarity from bromocation to bromide species has not been documented. Nevertheless, there are unintended reports of such reactions.[10] The bromocation species is mainly catered from a less polar N-Br bond with a small difference in electronegativity (EN_N 3.04, EN_{Br} 2.96) and N being connected to electron withdrawing functionalities such as carbonyl groups in N-bromosuccinimide, haloisocyanuric acid[11] etc.; sulfonyl group in N-bromo-N-benzylbenzenesulphonamide;[10c] carbonyl and sulfonyl groups in N-bromosaccharin.[12] In 1969, Takemura *et al.*[10c] reported the Hoffmann decomposition of N-bromoamines or even N-bromoammonium salts releasing the Bromide species. The release of bromide species from the reaction of NBS with a primary amine and tertiary amine has been noticed by Gong *et al.*[10b] and Huber *et al.*[10a] respectively. Herein we present experimental and computational evidence

of the “umpolung” of cationic Br species achieved organocatalytically and implemented in an accelerated dibromination of inactivated olefins.

Result & Discussion: Owing to the close electronegativity of N and Br atoms, the polarity of N-Br bond depends upon the subsequent functionalities attached to N. NBS with two carbonyl groups attached to a N-atom, is a proven source of bromocation for many reactions.[13] Conceptually removing the carbonyl groups from NBS, would be an interesting reagent with flow of electron towards bromine because of alkyl substituents at N, in an inverse direction than NBS. With an objective to evaluate the nature of Br in **3e**, interestingly the compound **3e** (N-bromopyrrolidine) could easily be obtained in-situ by H/Br exchange with an organocatalyst.

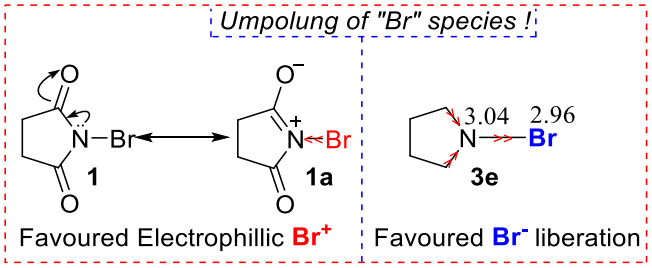


Figure 1: NBS as the bromocation source and “Umpolung” of bromine from *$Br^{\oplus}$ to $Br^{\ominus}$*

Fast exchange of H/Br between NBS and secondary amines-Analytical evidence:
Upon reaction of secondary amines with NBS (**1)**, a quick exchange of the H/Br was observed. The exchanged species N-bromoamine (**3)** and succinimide (**4,** NHS) were characterised by both ^{1}H NMR and HRMS study (Figure 2). The exact mass of N-bromopyrrolidine (**3e**) was not observed, probably because of the low sensitivity of the spectrometer towards low-molecular weight compounds. Nevertheless, the exact mass of corresponding N-bromoamines **3h** and **3i** was observed in a 1:1 isotopic (M:M+2) ratio. Consistently through computational results, the fast H/Br exchange was found to occur with K_{eq} of 7.6 x 10^{6} with a ΔG of -39.27 kJ/mol towards the N-bromopyrrolidine. While benzylamine-a primary amine reacted and disintegrated spontaneously with NBS to unidentified species, the tertiary amines (DABCO, DBU etc.) remained in complexation with Br of NBS as evident from the downfield shifting of the corresponding peaks of the amines in ^{1}H NMR.

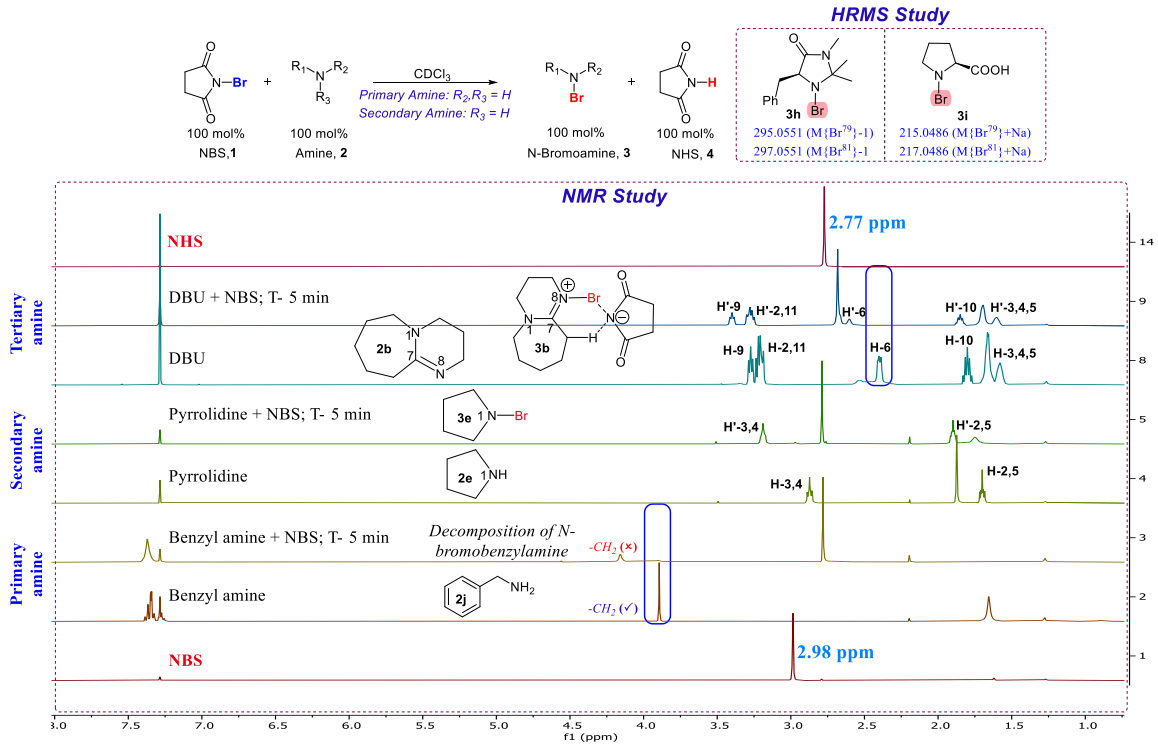
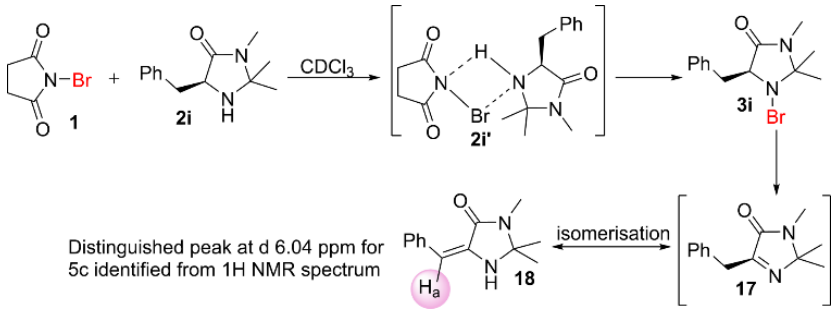


Figure 2: Interaction of NBS with amines: Evidences from NMR and HRMS

Umpolung of Bromocation-Analytical Study:

The N-bromoamine species of pyrrolidine was not characterised completely as it started degrading to different fragments. However, interestingly various intermediates of the reaction of NBS with Macmillan's catalyst (**2i)** starting from complexation, then exchange and subsequent release of bromide ion via elimination pathway could be characterised by ^{1}H NMR spectroscopy. The NMR study showed two singlets at δ 2.765 and 2.771 ppm because of initial complexation, which further separated upon complete exchange of NBS and the amine. Additionally, the continuous enhancement of the singlet at δ 6.04 ppm contributes to the formation of olefin **18** through elimination from intermediate **3i**, followed by isomerisation.



Scheme 1. Exchange of NBS and Macmillan catalyst; NMR evidence towards the release of Br⊖

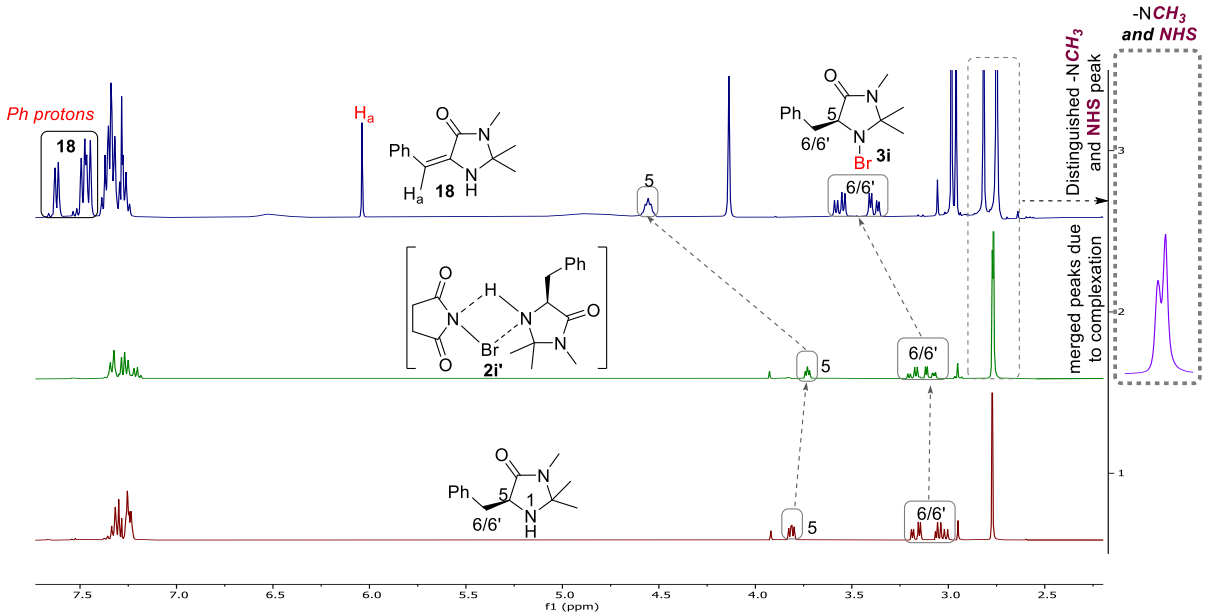


Figure 3. NMR evidence of interaction of NBS and Macmillan's catalyst

Umpolung of Bromocation-Computational study:

The molecular electrostatic potential (MESP) surfaces of N-halosuccinimides and N-halopyrrolidines showed the positive potential values along the N-X bond (X= Cl, Br, I; Figure *4*4). The ESP value ascends from NCS to NIS, which is obvious indicating the increasing cationic character from Cl to I. However, the ESP values along the N-X bond of the N-halopyrrolidines are relatively less positive than those of N-halosuccinimides, which suggested the nucleophilic character of the halogens in N-halopyrrolidines. The nucleophilic character of halogens increases from I to Cl. Thereby, the computational study confirms the anionic properties of N-halopyrrolidine, which is a resultant of exchange between N-halosuccimides and pyrrolidine.

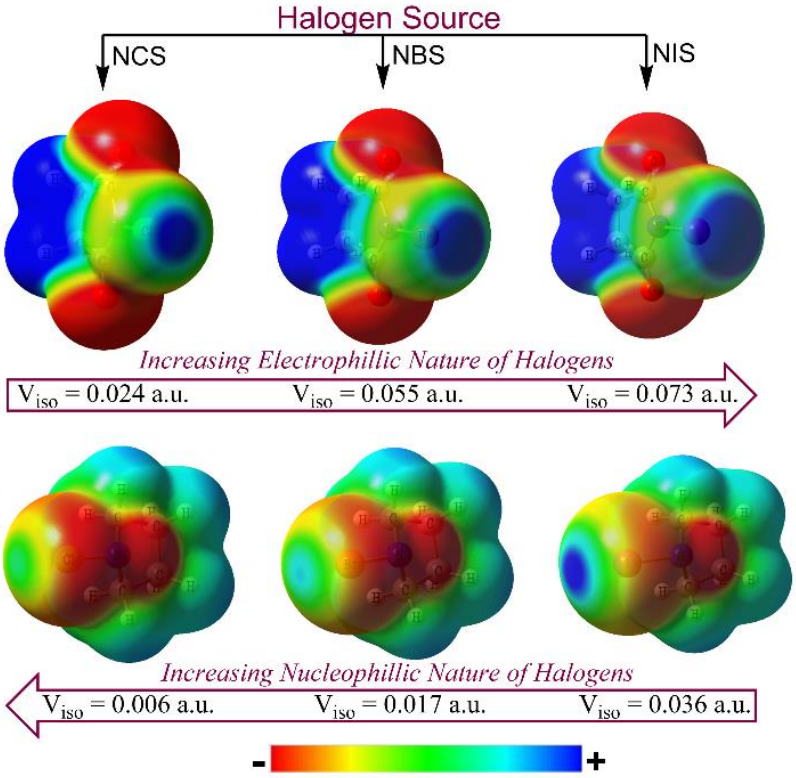


Figure 4. The molecular electrostatic potential surfaces of N-halosuccinimides (top) and N-halopyrrolidine (bottom) at iso=0.001 a.u.

We also carried out computational calculations to affirm the sources of bromocation (Br^+) and bromoanion (Br^-) synthons. We calculated the free energy changes (ΔG) for the dissociations of NBS and NBP, giving rise to Br^+ and Br^- ions (Figure 5). The positive values for ΔG are due to the fact that NBS and NBP are more stable than their dissociated ions. Hence, the less positive ΔG-value hints the most spontaneous process. After comparing the ΔG-values for NBS as Br^+ (ΔG = 802.95 kJ/mol) and Br^- (ΔG = 5972.84 kJ/mol) ions source, this could be concluded that NBS is a good Br^+ ion source than Br^- ion source, whereas NBP is a good source of the Br^- ion (ΔG = 253.87 kJ/mol) than that of Br^+ ion (ΔG = 1020.53 kJ/mol). Again, NBS is better in producing Br^+ ion than NBP, while NBP is better in producing Br^- ion than NBS. Therefore, it can be inferred that NBS is the superior source for the Br^+ synthon and NBP is the superior source for the Br^- synthon.

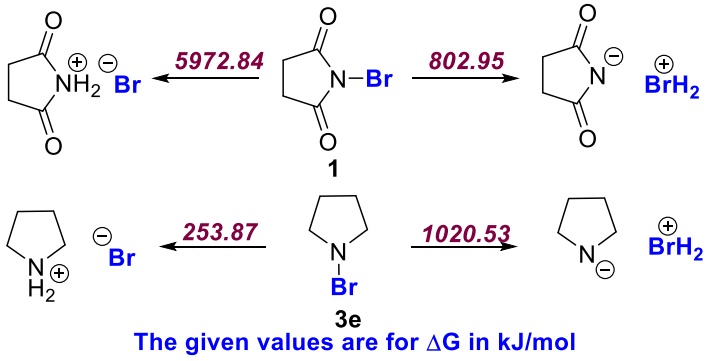
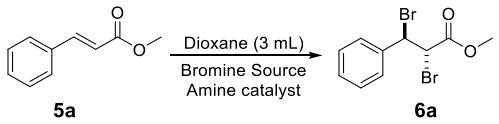


Figure 5. The ΔG-value for each of the dissociations of NBS and NBP.

Umpolung of Bromocation: Experimental Evidence

Experimentally the reversal of polarity of the bromo-cation species was evidenced from several controlled experiments. Acceleration of the dibromination reaction with the addition of 50 mol% of pyrrolidine (**2e**) (Table 1, Entries 1 Vs 2) certainly suggests the superiority of NBP (**3e)** as a bromide source than NBS, and even comparable to HBr (Table 1, Entry 3). The deceleration of dibromination using molecular bromine in presence of pyrrolidine (**2e)** again confirmed NBP (**3e**) as a poor bromo-cation source as Br_2 (100 mol%) would react with pyrrolidine (100 mol%) to form NBP (100 mol%) and HBr (100 mol%).

Table 1.Initial screening for the dibromination of methyl (*E*)-cinnamate



5a **6a**

Entry	Br source (mol%)	Pyrrolidine (mol%)	Time (h)	Conversion (%)
1	NBS (200)	-	158	84
2	NBS (200)	200	24	12
3	**NBS (300)**	**50**	**19**	**100**
4	NBS (100) HBr[a] (100)	-	17	83
5	Br_2 (100)	-	79	66
6	Br_2 (100)	100	78	18

a- 47% aq. HBr solution

Reaction profile for the reactivity of bromine reagents:

A sequential controlled reaction was studied in NMR spectrometer to understand the role of various bromine reagents towards di-bromination of methyl (*E*)-cinnamate (**5a**), where both cationic and anionic Br species are needed. As observed in Figure 1, an instant formation of N-bromopyrrolidine (**3e)** was observed (Step-1) after the addition of an equimolar mixture of NBS (**1)** and pyrrolidine (**2e**), which did not react with the freshly added methyl (*E*)-cinnamate (**5a**) for up to 2 h (step-2). In the next step, the addition of additional 100 mol% NBS (**1**) quickly led to the formation of dibromo compound **6a** up to 42% conversion in 5 h and the subsequent addition of NBS (100 mol%) (step-4) escalated the conversion to 72% in 10 h. Exchanged NHS (**4**, ~300 mol%) was seen in while the pyrrolidine ring disintegrated to multiple unidentified compounds.[24] This experiment was in agreement with the computational calculations, assisting that NBS is a superior source of Bromo-cation and NBP is a superior source of Bromo-anion synthons.

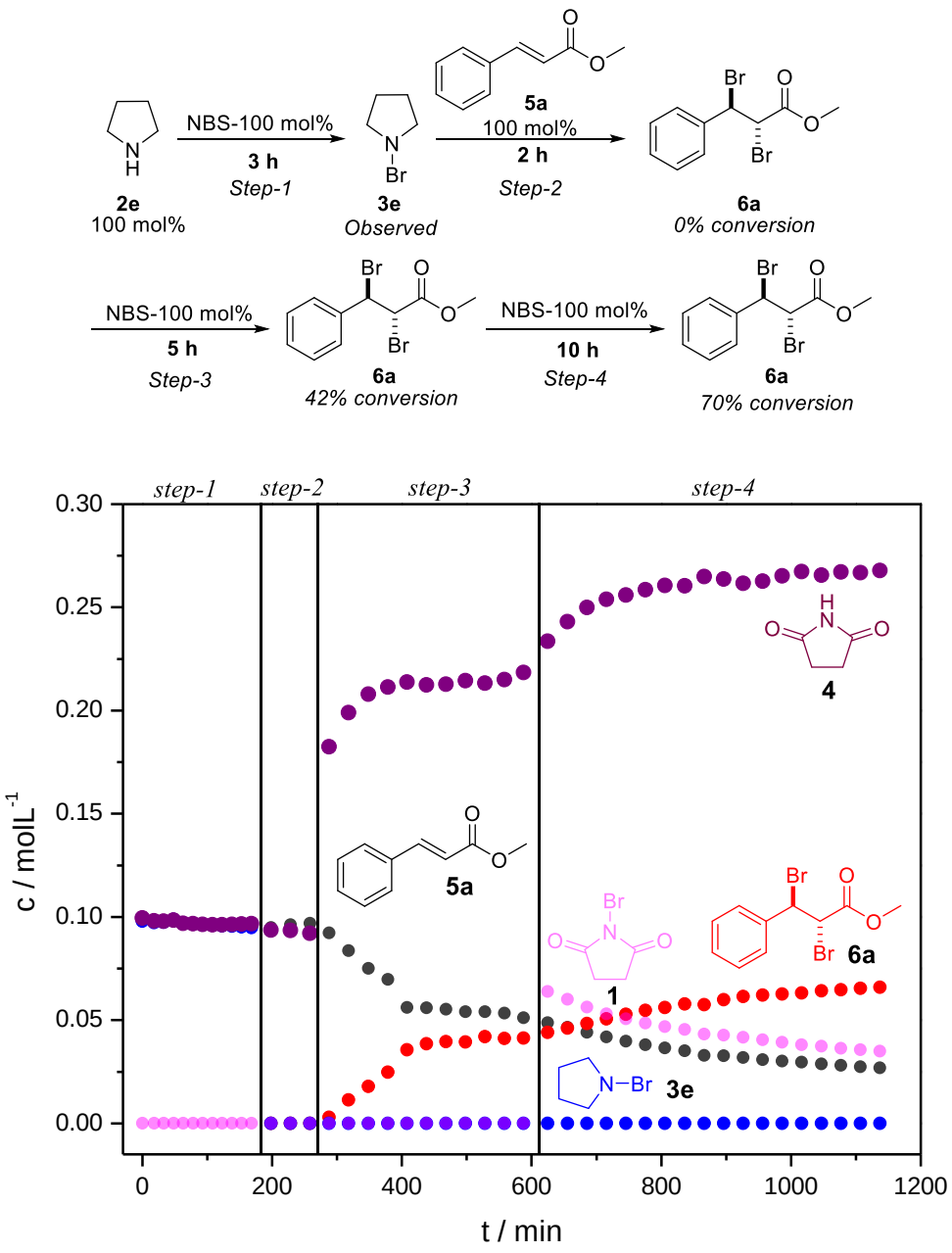


Figure 6. On-line reaction monitoring of a controlled reaction for dibromination of methyl (*E*)-cinnamate by NMR

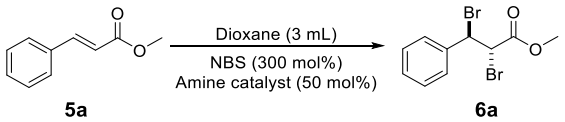
Accelerated organocatalytic dibromination of olefins:

Dibromination of olefins is a highly reported pivotal transformation in organic synthesis leading to bioactive bromocompounds,[14] paving a way for further derivatisation at the reactive C-Br bond.[15] This transformation is primarily attained by the use of molecular bromine,[16] NBS/MBr mixture,[17] tribromides,[18] molecular Br_2/R_4NBr,[19] poly(vinylpyrrolidine)-bromine complex[20] and also by in-situ reversal of polarity of a bromide reagent to a bromo-cation species using an oxidant.[8,9] It is obvious from the above protocols that the set of reagents must provide bromocation and bromoanion synthons. However, the dibromination process via organocatalysis is scant. In 2010, Cordova and co-workers[21] reported a dibromination for electron rich olefins using NBS, Pyrrolidine and NHS. The protocol involves higher temperature and the report remains silent on the role of the reagents. In 2012, Barbas III and co-workers[22] reported an organocatalytic dibromination reaction through the in-situ generation

of molecular bromine from dibromohydrantoin and a thiourea catalyst following a radical pathway. After confirming the organocatalytic in-situ reversal of polarity of bromocation and thereby generating a reaction medium with a bromocation source (NBS) with timely creation of a rich bromoanion source (NBP), the protocol was executed and optimised for the dibromination of electron deficient olefins.

Secondary amines **2e-2i** were found to be optimal catalysts (**Table *1***Table 2, Entries 6-10), while tertiary amines **2a-2d** except for DMAP (Table 2, Entry 4), did not seem to accelerate the reaction. Primary amine **2j** was found to react with NBS (**1**) instantly to some unidentified compound, rendering the dibromination reaction unsuccessful. Among secondary amines pyrrolidine (**2e**) and piperidine (**2f**) showed excellent conversion.

Table 2. Screening of different amines



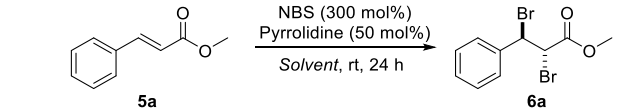
5a **6a**

Entry	Amine	Time (h)	Conversion (%)	dr (*anti*:*syn*)
1	-	**22**	**39**	96:4
2	DABCO (**2a**)	24	0	nd
3	DBU (**2b**)	24	56	100:0
4	DMAP (**2c**)	24	**93**	100:0
5	Triethylamine[10a] (**2d**)	48	34	97:3
6	**Pyrrolidine** (**2e**)	**19**	**100**	98:2
7	Piperidine (**2f**)	24	100	86:14
8	Diethylamine (**2g**)	24	100	92:08
9	L-Proline (**2h**)	24	100	97:3
10	McMillan Catalyst (**2i**)	24	100	90:10
11	Benzyl amine (**2j**)	39	0	62:38
12	Allyl amine (**2k**)	60	28	70:30

Screening of solvents revealed that most of the organic solvents irrespective of their polarity, except DMSO tolerated the protocol with dioxane as the optimum solvent (100% conversion in 19 h). The solvents contaminated with moisture resulted in bromohydrin (**7a**) as the dominant product (

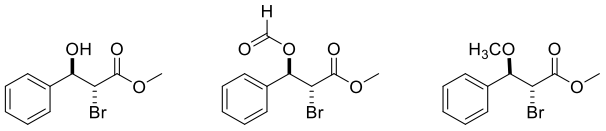
Table **3**, Entries 3, 11, 12), while the nucleophilic solvents such as DMF and MeOH resulted in co-halogenated products **7b**[12] and **7c**[23] respectively. Controlled experiments to compare the nucleophilicity of N-bromopyrrolidine with nucleophilic solvents such as MeOH and H_2O in stoichiometric amount (Table 3, Entries 10 and 11), were performed, resulting the dibromo product **6** exclusively, which shows the supremacy of N-bromopyrrolidine as the preferred nucleophile. However, the co-nucleophile as a solvent undoubtedly dominated the co-halogenated product.

Table 3. Screening of solvents



5a 6a

Other Co-halogentated products:



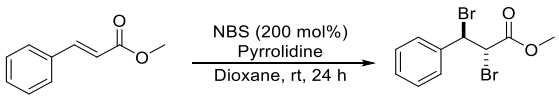
7a 7b 7c

Entry	Solvent	Conversion[a] (%)	Product ratio (6:7)	dr[b] (6) (*anti*:*syn*)
1	Hexane	84	100:0	98:2
2	Toluene	89	100:0	94:6
3	Et_2O	79	100:0	100:0
4	CH_2Cl_2	94	100:0	99:1
5	THF	93	34:59[c]	98:2
6	$CHCl_3$	100	100:0	100
7	EtOAc	97	81:16[d]	97:3
9	Dioxane (dry)	100[e]	100:0	99:1
10	Dioxane + MeOH[f]	86	100:0	100:0
11	Dioxane + H_2O[g]	66	100:0	96:4
12	MeOH	100	0:100	nd
13	Acetone	85	20:65[h]	95:5
14	CH_3CN	100	100:0	92:8
15	DMF	79	17:63[i]	100
16	DMSO	40	70:30	92:8

a: The conversion is presented as the consumption of **5a**; **b**: dr was found from the ^{1}H NMR of the crude reaction mixture by integration of the α-proton; **c**: The by-product **7a** was obtained in 59% conversion; **d**: The by-product **7a** was obtained in 16% conversion; **e**: The reaction was complete in 19 h; **f**: 100 mol% MeOH was used, Reaction time = 41 h; **g**: H_2O was used in stoichiometric amount; **h**: The by-product **7a** was obtained in 65% conversion; **i**: The by-products **7a**:**7b** were obtained in 7:56 conversion ratio respectively.

It was interesting to find that the reaction was highly efficient with only 10 mol% of the organocatalyst. An increase in the equivalence of pyrrolidine (**2e**) diminished the conversion suggesting the fact that 10 mol% pyrrolidine (**2e**) was sufficient to provide 100 mol% of bromide species via several fragmentation processes (Refer SI for the probable fragmentation pathways of N-bromopyrrolidine), which was evident from the disappearing of the ring protons of pyrrolidine in ^{1}H NMR. An equimolar or higher quantity of pyrrolidine (**2e**) to that of NBS (**1**) completely quenched the reaction, again confirming the quick formation of NBP (**3e**) (Table 4, Entries 6-9).

Table 4. Catalytic behaviour of pyrrolidine

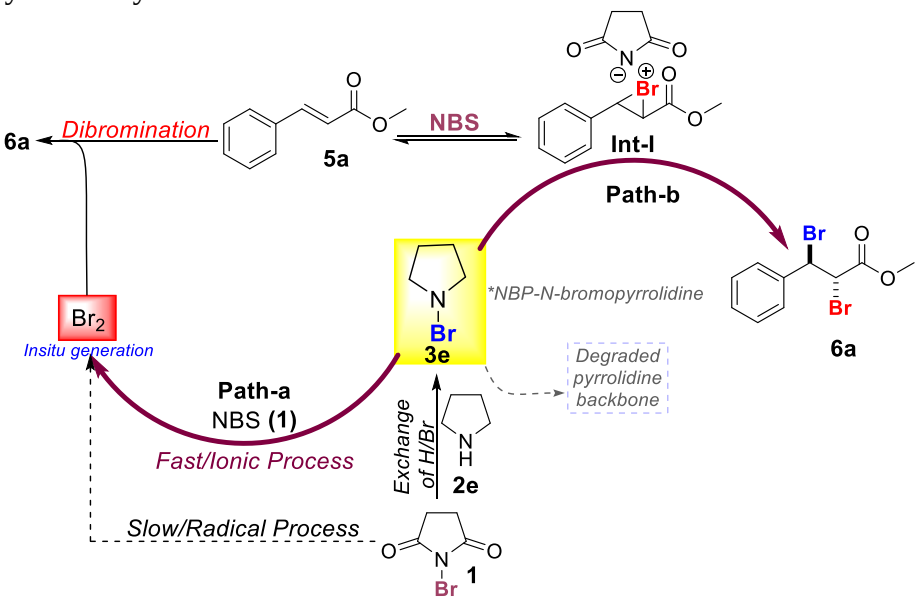


5a 6a

Entry	Pyrrolidine (mol%)	Conversion (%)
1	0	39
2	5	23

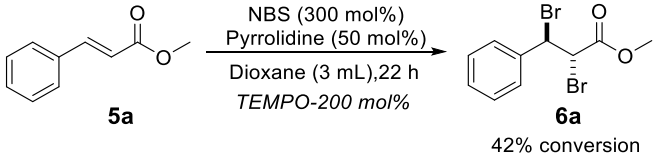
3	10	73
4	25	58
5	50	51
6	100	30
7	200	12
8	300	0
9	400	0
10	500	0

The experimental, spectroscopic and computational findings, affirms that the initial fast exchange of H/Br between NBS and secondary amine results in the formation of **3e** with reversal of polarity of the "Br" atom from a cation to an anion species (step-1). Subsequently the bromide species from N-bromoamine **3e** could react in two ways towards the dibromination reaction of olefins; a) The reaction of N-bromoamine **3e** with NBS to release molecular bromine in a faster rate as opposed to NBS alone, b) The bromide ion from N-bromoamine **3e** reacts with bromonium ion (**Int-I)** generated from the reaction of the olefin with NBS. It was not possible to find the preferability between these pathways. However, NBP certainly accelerated both pathways by providing the bromide ion in comparison to NBS. The release of molecular bromine (path-a) was evident from the colour intensification of the reaction mixture from straw yellow to yellow-ochre.



Scheme 2. Proposed mechanism for the amine catalysed dibromination

The success of the reaction in presence of TEMPO might vouch against the radical pathway for the dibromination reaction.

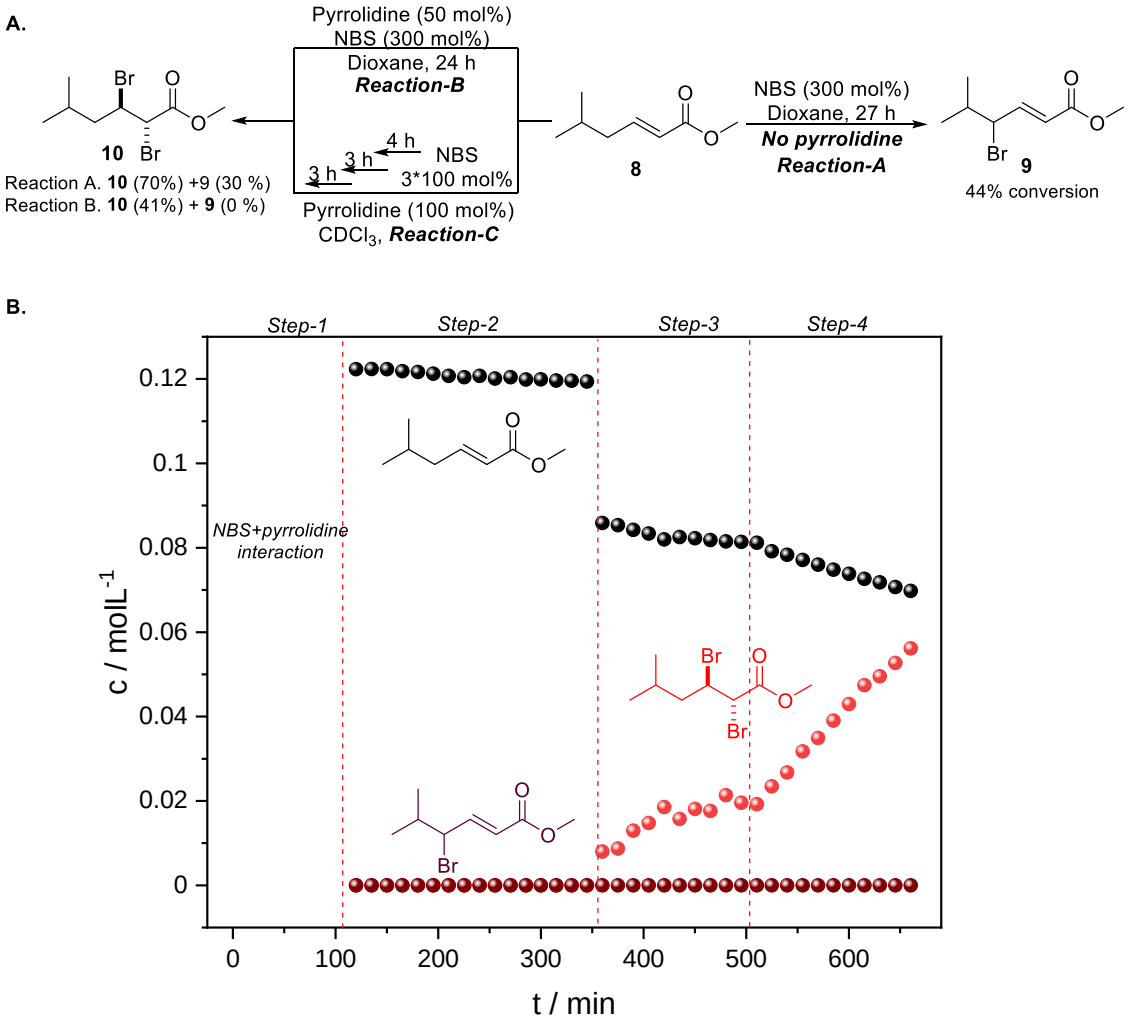


Scheme 3. Evidence in support of ionic mechanism

Allylic bromination Vs Dibromination:

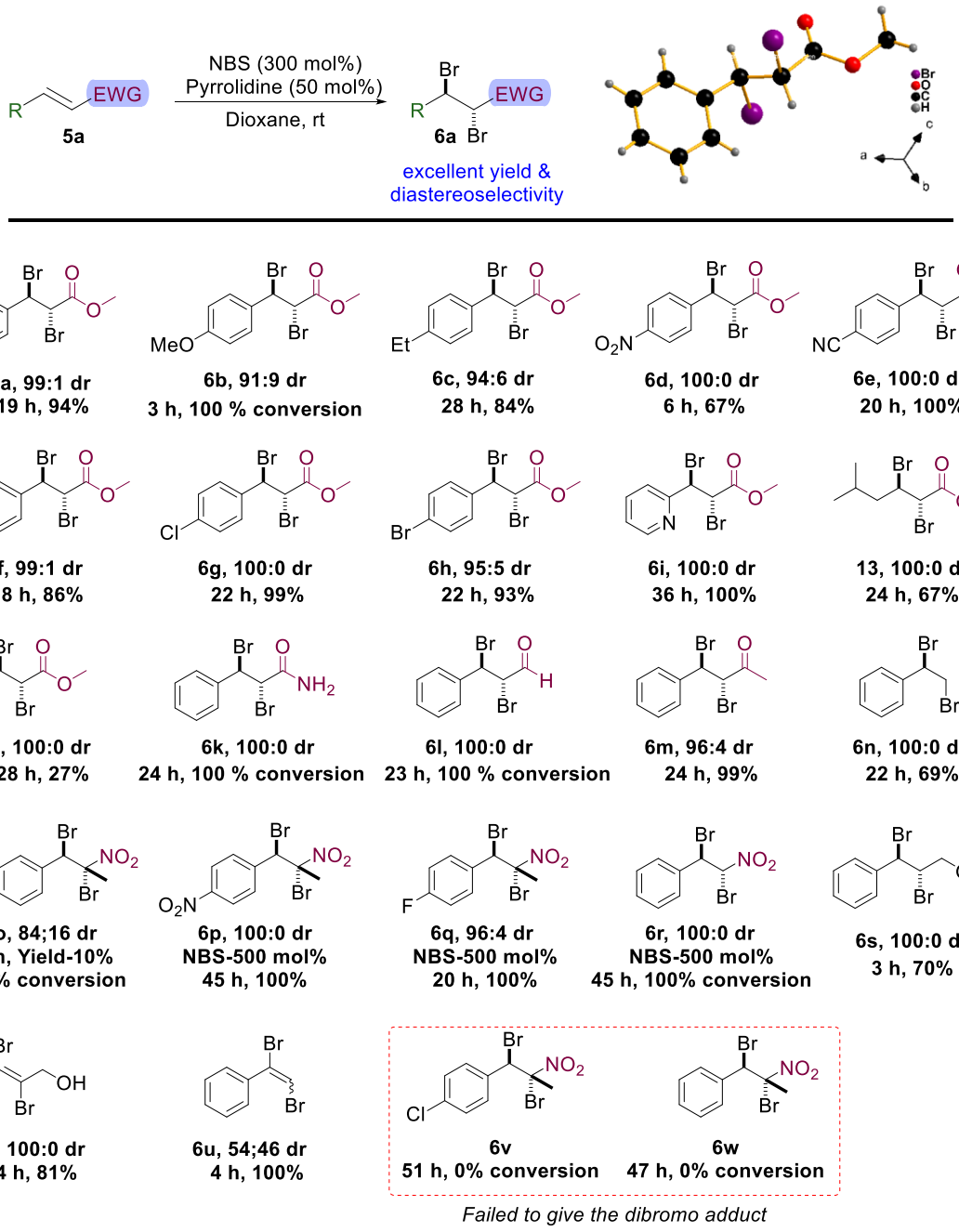
The protocol was examined for an olefin having allylic H for the competing allylic bromination and dibromination transformations. Without the organocatalyst the reaction resulted in only the allylic brominated product **9**,[25] but with the addition of the pyrrolidine, the dibromo product

dominated over the allylic brominated product in 7:3 ratio. The selectivity could be optimised to the dibromo product **10** only, in a sequential NBS addition procedure.



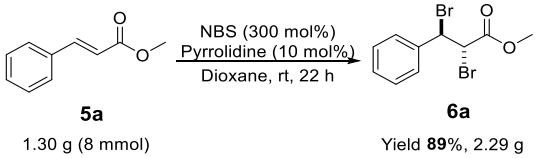
Scheme 4. Allylic bromination Vs. Dibrmination in presence of allylic hydrogen; Reaction **A** and **B** were performed on bench and reaction **C** was performed in NMR tube with $CDCl_3$ as solvent

The protocol led to successful dibromination of olefins of varying diversity such as β-aryl/alkyl-*α*,*β*-unsaturated enoates/enamide/enal/enone, styrenes, nitrostyrenes, allylic alcohols, alkynes etc. in good to excellent yields and diastereoselectivities. Shorter reaction times for the substrates with EWG such as NO_2 and F (**6d** and **6f** respectively), might indicate the opening of the bromonium intermediate **Int-I** as the rate determining step. The nucleophilic attack at the *β*-carbon of the bromonium ion was proved from the bromohydroxylated product **7** by ^{1}H-^{13}C HMBC NMR spectroscopy (See SI for more details). Similarly, the *p*-OMe group can attribute shorter reaction time for product **7b**, owing to the assisted opening of the bromonium ion, which is also evident from the relatively poor diastereomeric ratio (91:9). Almost all olefins attempted, except[26] **5v** and **5w** were compatible in resulting the dibromo products as observed from the ^{1}H NMR of the crude reaction mixture. Only in few cases, the dibromo product was found to be sensitive to column chromatographic purification leading to further decomposed products (Details are included in SI).



Scheme 5. Substrate scope for dibromination

To show the industrial utility, a gram scale dibromination reaction of methyl cinnamate **7** was carried out in presence of only 10 mol% pyrrolidine (**2e**). The diastereospecific dibromo product **6a** was obtained with excellent yield (89 %). Consequently, this protocol can serve as a superior alternative to the conventional procedure using molecular bromine whilst dealing with its highly toxic vapours owing to it high volatility.



Scheme 6. Gram scale synthesis of brominated product with 10 mol% of organocatalyst

Conclusion

Herein the concept of "umpolung" of cationic bromine with experimental and computational evidence, is presented for the first time. There have been few reports on reactions[10] regarding the observed polarity inversion of Br^+ species, but not, conceptualised with the intent of investigation. The reversal of polarity was achieved tactically and catalytically by employing simple organocatalysts along with successful implementation in enhancing the rate of dibromination reaction of olefins. Furthermore, the above protocol can be extended to the asymmetric dibromination reaction[27] employing chiral organocatalysts, which is underway in our laboratory.

References

1. G. Wittig, P. Davis and G. Koenig, *Chem. Ber.*, 1951, **84**, 627–632.
2. E. J. Corey, *Pure Appl. Chem.*, 1967, **14**, 19–38.
3. Popularisation of umpolung by Seebach; (a) First used by Seebach at a lecture, given in the University of Hamburg, July 7th, 1972. (b) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*,1965, **4**, 1075–1077; (c) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 1077–1078.
4. A review article describing organocatalytic umpolung; X. Bugaut and F. Glorius, *Chem. Soc. Rev.*, 2012, **41**, 3511.
5. Few reports about umpolung at C-atom; (a) J. Schreiber, M. Pesaro, W. Leimgruber and A. Eschenmoser, *Helv. Chim. Acta*, 1958, **41**, 2103–2108. (b) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, 1971, 93,5286–5287. (c) B.-T. Gröbel and D. Seebach, *Synthesis*, 1977, 357–402; (d) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 239–258.
6. Reports on Biological activities of Halogenated molecules; (a) R. Wilcken, M. O. Zimmermann, A. Lange, A. C. Joerger and F. M. Boeckler, J. Med. Chem., 2013, 56, 1363-1388. (b) M. R. Scholfield, PhD thesis, Colorado State University, Fall 2016.
7. (a) K. Moriyama, Y. Izumiasawa and H. Tago, *J. Org. Chem.* 2011, **76**, 7249–7255. (b) R. K. Dieter, L. E. Nice and S. E. Vela, *Tetrahedron Lett.* 1996, **37**, 2377-2380.
8. A. Khazaei, M. A. Zolfigol, E. Kolvari, N. Koukabi, H. Soltani and L. S. Bayani, *Synthetic Communications*, 2010, **40**, 2954–2962.
9. A. Podgoršek, S. Stavber, M. Zupan and J. Iskra, *Tetrahedron*, 2009, **65**, 4429–4439.
10. Unintended reports on umpolung of cationic bromine to anionic bromine; (a) T. Huber, D. Kaiser, J. Rickmeier and T. Magauer, *J. Org. Chem.*, 2015, **80**, 2281–2294. (b) L. Gong, L.-J. Xing, T. Xu, X. -P. Zhu, W. Zhou, N. Kang and B. Wang, *Org. Biomol. Chem.*, 2014, **12**, 6557-6560. (c) S. Takemura, H. Terauchi, Y. Kamiya and Y. Ueno, *Chem. Pharm. Bull.*, 1969, **17**, 525-527.
11. Reports suggesting use of haloisouranic acid as a cationic bromine source; (a) L. S. de Almeida, P. M. Esteves and M. C. S. de Mattos, *Synthesis*, 2006, 0221-0223. (b) L. S. de Almeida, P. M. Esteves and M. C. S. de Mattos, *Synlett*, 2006, **10**, 1515-1518. (c) L. S. de Almeida, P. M. Esteves and M. C. S. de Mattos, *Synlett*, 2007, **11**, 1687-1690.
12. A. V. A. de Souza, G. F. Mendonça, R. B. Bernini and M. C. S. de Mattos, *J. Braz. Chem. Soc.*, 2007, **18**, 1575-1579.
13. Reports suggesting use of NBS as a cationic bromine source; (a) I. Saikia, A. J. Borah and P. Phukan, *Chem. Rev.*, 2016, **116**, 6837−7042. (b) X. Huang, M. Seid and J. W. Keillor, *J. Org. Chem.*, 1997**, 62**, 7495-7496. (c) P. K. Prasad, R. N. Reddi and A. Sudalai, *Org. Lett.*, 2016, **18**, 500−503. (d) S. M. Ahmad, D. C. Braddock, G. Cansell and S. A.

Hermitage, *Tetrahedron Letters*, 2007, **48**, 915–918. (e) S. M. Ahmad, D. C. Braddock, G. Cansell, S. A. Hermitage, J. M. Redmond and A. J. P. White, *Tetrahedron Letters*, 2007, **48**, 915–918.

14. Natural products having Br as significant element; (a) D. J. Faulkner, *Nat. Prod. Rep*., 1988, **5**, 613–663. (b) D. J. Faulkner, *Nat. Prod. Rep*., 1992, **9**, 323–364. (c) A. Butler and J. V. Walker, *Chem. Rev*., 1993, **93**, 1937–1944.
15. For synthetic application of C-Br bond check Scheme-2 of this literature; Z. Qi, W. Li, Y. Nu, E. Benassi and B. Qian, *Org. Lett*., 2021, **23**, 2399−2404.
16. (a) M. J. Dagani, H. J. Barda, T. J. Benya and D. C. Sanders, Bromine Compounds, in Ullmann's Encyclopedia of Industrial Chemistry (electronic ed.); Wiley-VCH: Weinheim, 2000.
17. (a) L. –X. Shao and M. Shi, *Synlett*, 2006, **8**, 1269-1271. (b) S. Adimurthy, S. Ghosh, P. U. Patoliya, G. Ramachandraiah, M. Agrawal, M. R. Gandhi, S. C. Upadhyay, P. K. Ghosh and B. C. Ranu, *Green Chem*., 2008, **10**, 232–237.
18. V. Kavala, S. Naik and B. K. Patel, *J. Org. Chem.*, 2005, **70**, 4267-4271.
19. M. Eissen and D. Lenoir, *Chem. Eur. J*., 2008, **14**, 9830 –9841.
20. M. M. Lakouraj, M. Tajbakhsh and M. Mokhtary, *J. Chem. Res*., 2005, **8**, 481-483.
21. M, Zhua, S. Lin, G. –L. Zhao, J. Sun, A. Córdova, *Tetrahedron Lett*., 2010, **51**, 2708-2712.
22. G. H. –Torres, B. Tan and C. F. Barbas III, *Org. Lett*., 2012, **14**, 1858-1861.
23. P. Phukan, P. Chakraborty and D. kataki, *J. Org. Chem.*, 2006, 71, 7533-7537.
24. For decomposed products of pyrrolidine; Z. Wang, A. Lucassen, L. Zhang, J. Yang, K. K. –Höinghaus and F. Qei, *Proceedings of the Combustion Institute*, 2011, **33**, 415–423.
25. V. Singh, S. Chaudhary, V. Sapehiyia, I. kaur, G. L. Kad and J. Singh, *Indian J. Chem*., 2004, **43B**, 1950-1953.
26. Product for the two substrates **7w** and **7x** were not obtained and the reason is currently under study in our laboratory.
27. For chiral Br source; K. Liu, H. –J. Jiang, N. Li, H. Li, J. Wang, Z. –Z. Zhang and J. Yu, *J. Org. Chem*. 2018, **83**, 6815−6823.