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COMMUNICATION

Intramolecular iron(II)-catalyzed aminobromination of allyl *N*-tosyloxycarbamates†

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Allyl *N*-tosyloxycarbamates are found to be catalytically transformed into β-brominated oxazolidinones with $FeBr_2$/*n*-Bu_4NBr in *t*-BuOH.

The aminohalogenation of carbon–carbon double bonds underlies one of the major entries for the functionalization of organic molecules.[1,2] We recently discovered that a cyclopentenyl azidoformate underwent a radical aminobromination reaction with substoichiometric $FeBr_2$ (0.5 equiv.) in the presence of Bu_4NBr (1 equiv.) to furnish the corresponding β-brominated oxazolidinone.[3,4] Whereas this method offered access to the halogenated oxazolidinone, safety precautions were required to handle the potentially hazardous azides. Therefore, the development of a safe azidoformate surrogate is a necessity for the further growth of aminobromination chemistry. The present study demonstrates the potential of allyl *N*-tosyloxycarbamates as they can be converted into brominated oxazolidinones with only catalytic $FeBr_2$ in the presence of Bu_4NBr.

Our idea stems from the belief that heteroatom–heteroatom single bonds are readily cleavable *via* a single-electron transfer process mediated by reducing agents to produce highly reactive free radicals.[5] Therefore, it was envisioned that allyl *N*-tosyloxycarbamates bearing an activated (tosylated) oxygen–nitrogen single bond would react with $FeBr_2$ to possibly afford amidyl radicals *via* reductive extrusion of tosylate, thereby serving as azidoformate surrogates.[6]

The relevance of the hypothesis was initially examined with known cinnamyl substrate **1** (Table 1).[6a] Similar to our previously established protocols for the cyclization of a cyclopentenyl azidoformate, carbamate **1** was first treated with $FeBr_2$/Bu_4NBr in EtOH (entry 1). Under this condition, bromo oxazolidinones **4a/4b** were produced as an inseparable mixture in 21% yield. It should be noted that, contrary to our hypothesis, solvent adducts **5a/5b** were produced, implying the intervention of an aziridine intermediate. Such aziridine species was found to be isolable in another experiment (*vide infra*), albeit in only a minute quantity. Therefore, both radical and aziridination pathways may be involved in this reaction. Nevertheless, the diastereofacial selectivity favoring *syn* bromide **4a** over *anti* **4b** suggested that aminobromination mainly took place in a *syn* fashion, in harmony with an iron-coordinated radical halogen transfer mechanism.[3a–d,4]

Then, effort was made to improve the chemical yield of the cyclized products. In this context, it was assumed that the low production of oxazolidinones **4a/4b** possibly originated from the solvation of the iron(II) catalyst with EtOH, which may retard the cyclization.[7] Thus *i*-PrOH, a slightly bulky solvent that less likely undergoes coordination to iron(II), was next evaluated for its utility (entry 2). As we expected, use of the bulkier solvent led to an increase in the yield of bromides **4a/4b** (69%). The improvement of the yield by solvent switching indicates that the bulkiness of the solvent affects the efficiency of the iron(II)-catalyzed aminobromination reaction. This successful result prompted us to further examine the reaction in *t*-BuOH, which eventually culminated in the significant production of bromides **4a/4b** (84%) with a diastereomeric ratio of 4 : 1 favoring the *syn*-isomer (entry 3).

To clarify the roles of the iron(II) catalyst and the additive, aminobromination was evaluated with either $FeBr_2$ or Bu_4NBr alone (entries 4 and 5). It was revealed that $FeBr_2$ alone could afford cyclized compounds **4a/4b** whereas Bu_4NBr alone could not do so. This distinct outcome reflects the pivotal role of the iron species in promoting reactions and the necessity of the bromide salt as a co-reagent for the regeneration of the iron(II) catalyst. Further evaluation of substrates revealed the superiority of *N*-tosylate **1** to azidoformate **2** in the present iron(II) catalysis (entry 6). Thus, the aminobromination of azidoformate **2** with $FeBr_2$ (0.1 equiv.)/Bu_4NBr (1.2 equiv.) provided cyclized products **4a/4b** in only 19% yield along with a significant amount of unreacted formate **2** (69%). The poor reaction of azidoformate **2** with 0.1 equiv. of $FeBr_2$ is consistent with our previous observation that the satisfactory conversion of an allylic azidoformate required a substoichiometric quantity of the iron(II) catalyst (*ca.* 0.5 equiv.).[4] We assume that the difference in the reactivities of the substrates at a low $FeBr_2$ load partially originates from the different modes by which Lewis acidic iron(II) species interacts with each substrate. The leaving ability of the polar group on the nitrogen atom was also found to affect the reactivity: carbamate **3** possessing a hydroxyl group was found to be much less

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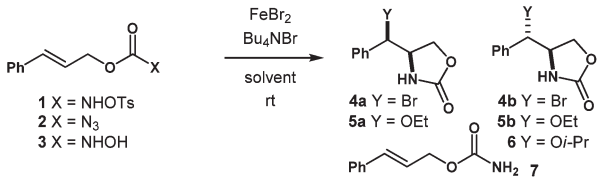
†Electronic supplementary information (ESI) available: Experimental protocols, spectroscopic and analytical data, and copies of ^1H and ^{13}C NMR. See DOI: 10.1039/c2ob07190h

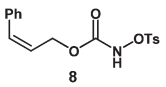
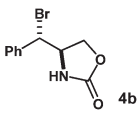
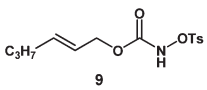
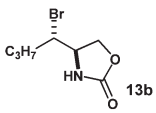
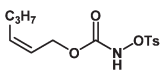
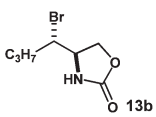
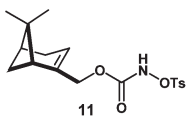
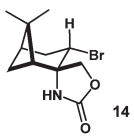
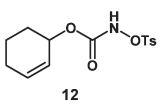
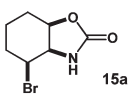
Table 1 Aminobromination of carbamates **1**, **2**, and **3**



Entry	Substrate	$FeBr_2/Bu_4NBr$ (equiv.)	Solvent	Time (h)	Yield (%) (*syn* **4a** : *anti* **4b**)[ab]	**5** or **6**	**7**
1	**1**	0.1/1.2	EtOH	17	21 (1.5 : 1)[c]	**5a/5b** (15)[g]	16
2	**1**	0.1/1.2	*i*-PrOH	14	69 (3.3 : 1)	**6** (9)	14
3	**1**	0.1/1.2	*t*-BuOH	4	84 (4 : 1)	—	5
4	**1**	1.0/0	*t*-BuOH	1	61 (1.1 : 1)	—	21
5	**1**	0/1.0	*t*-BuOH	17	no[d]	—	32
6	**2**	0.1/1.2	*t*-BuOH	22	19 (5 : 1)[e]	—	2
7	**3**	0.1/1.2	*t*-BuOH	22	no[f]	—	0

[a] Stereochemistry was determined by comparison with those of the authentic material. [b] Diastereomeric ratio was determined by ^1H NMR analysis. [c] 47% of unreacted **1** was recovered. [d] 16% of unreacted **1** was recovered. [e] 69% of unreacted **1** was recovered. [f] Unreacted **3** was recovered quantitatively. [g] Stereochemistry of the major isomer has yet to be determined.

Table 2 Aminobromination of *N*-tosyloxyallyl carbamates

Entry	Substrate	Time (h)	Bromide (major)	Yield (%)	dr[c]
1[a]	 **8**	1	 **4b**	88	1.5 : 1
2[b]	 **9**	5	 **13b**	87	1.5 : 1
3[a]	 **10**	1	 **13b**	87	1.9 : 1
4[a]	 **11**	3	 **14**	85[d]	(2*S*,3*S*) only
5[a]	 **12**	4	 **15a**	95	3.8 : 1

[a] The reaction was carried out using $FeBr_2$ (0.2 equiv.) and Bu_4NBr (1.2 equiv.) in *t*-BuOH at room temperature. [b] 0.1 equiv. of $FeBr_2$ was used. [c] Determined by ^1H NMR analysis. [d] Aziridine **16** (4%) was also formed.

reactive than tosylate **1** and azide **2**, and essentially gave no products (entry 7). This also implies that the direct activation of the hydroxyl group with the iron(II) catalyst may not be operative.

Next, the cyclizations of allylic substrates **8**, **9**, **10**, **11**, and **12** were examined under similar conditions (0.1 or 0.2 equiv. $FeBr_2$/1.2 equiv. Bu_4NBr) (Table 2). (*Z*)-Cinnamyl carbamate **8** was transformed into *anti*-bromo oxazolidinone **4b** as the major stereoisomer albeit with somewhat low stereoselectivity (entry 1).[8,9] Contrary to our expectations, (*E*)-olefin **9** and (*Z*)-olefin **10**, both possessing an aliphatic substituent but with opposite olefinic geometry, reacted with $FeBr_2$ in the presence of Bu_4NBr to provide bromide **13b** with the same diastereofacial preference as the major product (entries 2 and 3). Whereas the stereochemical outcome of the reactions of (*Z*)-series **8** and **10** was in good agreement with those predicted on the basis of *syn*-halogen transfer mechanisms, the origin of the unexpected *anti*-selectivity observed for substrate **9** is unclear at present. In contrast to the acyclic substrates, rigid bicyclic substrate **11** allowed

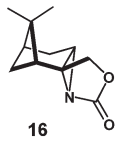


Fig. 1 Minor product generated by aminobromination of **11**

complete stereocontrol in transferring a bromine atom. Compound **14** was obtained in 85% yield as a single isomer having *syn*-arrangement with respect to the vicinal nitrogen and bromine atoms. Interestingly, aziridine **16** (4%) was found to be produced in this case (Fig. 1).

In this context, it could be assumed that the moderate *syn* : *anti* diastereoselectivities obtained for the acyclic substrates were attributable to the formation of the diastereomers through the bromination of the corresponding aziridines. To elucidate the extent of involvement of the non-radical pathway, the aminobromination of substrate **12** that bears an internal double bond was investigated (entry 5). The reaction of **12** was found to provide **15a** (75%) along with diastereomer **15b** (20%) that was likely to be produced by the brominative opening of an aziridine, suggesting again that the radical pathway was predominant. Taking these observations into account, we are currently postulating that the loss of the *syn*/*anti* specificity mainly stems from the flexibility of the radical intermediates, and that the aziridination–bromination is partially involved.

In conclusion, we have demonstrated that allyl *N*-tosyloxycarbamates serve as an allyl azidoformate surrogate for aminohalogenation. Further investigation of the reaction mechanisms and the application of the present method to the synthesis of nitrogen-containing molecules is currently being pursued in our laboratory.

Acknowledgements

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Notes and references

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2 For selected papers on intermolecular aminohalogenation reactions, see: (*a*) S.-J. Zhi, H. Sun, G. Zhang, G. Li and Y. Pan, *Org. Biomol. Chem.*, 2010, **8**, 628; (*b*) Z. Chen, J. Wei, W. Li, Y. Wang, P. Zhao and X. Shi, *Chin. J. Chem.*, 2011, **29**, 1689; (*c*) Z.-G. Chen, Y. Wang, J.-F. Wei, P.-F. Zhao and X.-Y. Shi, *J. Org. Chem.*, 2010, **75**, 2085; (*d*) X.-L. Wu and G.-W. Wang, *Tetrahedron*, 2009, **65**, 8802; (*e*) A. Sliwinska and A. Zwierzak, *Tetrahedron*, 2003, **59**, 5927; (*f*) V. V. Thakur, S. Kumar and A. Sudalai, *Org. Lett.*, 2003, **5**, 861; (*g*) Z. Wang, Y. Zhang, H. Fu, Y. Jiang and Y. Zhao, *Synlett*, 2008, 2667; (*h*) Z.-G. Chen, P.-F. Zhao and Y. Wang, *Eur. J. Org. Chem.*, 2011, 5887; (*i*) X. Huang and W.-J. Fu, *Synthesis*, 2006, 1016; (*j*) A. J. Catino, J. M. Nichols, R. E. Forslund and M. P. Doyle, *Org. Lett.*, 2005, **7**, 2787; (*k*) X. Qi, S.-H. Lee, J. Y. Kwon, Y. Kim, S.-J. Kim, Y.-S. Lee and J. Yoon, *J. Org. Chem.*, 2003, **68**, 9140; (*l*) S. Minakata, Y. Yoneda, Y. Oderaotoshi and M. Komatsu, *Org. Lett.*, 2006, **8**, 967.

3 For selected instances of intramolecular aminohalogenation reactions, see: (*a*) T. Bach, B. Schlummer and K. Harms, *Chem. Commun.*, 2000, 287; (*b*) T. Bach, B. Schlummer and K. Harms, *Chem.–Eur. J.*, 2001, **7**, 2581; (*c*) H. Danielec, J. Klugge, B. Schlummer and T. Bach, *Synthesis*, 2006, 551; (*d*) D. G. Churchill and C. M. Rojas, *Tetrahedron Lett.*, 2002, **43**, 7225; (*e*) S. C. Bergmeier and D. M. Stanchina, *J. Org. Chem.*, 1997, **62**, 4449; (*f*) M. R. Manzoni, T. P. Zabawa, D. Kasi and S. R. Chemler, *Organometallics*, 2004, **23**, 5618; (*g*) S. D. R. Christie, A. D. Warrington and C. J. Lunniss, *Synthesis*, 2009, 146; (*h*) K. Muñiz, C. H. Hövelmann and J. Streuff, *J. Am. Chem. Soc.*, 2008, **130**, 763.

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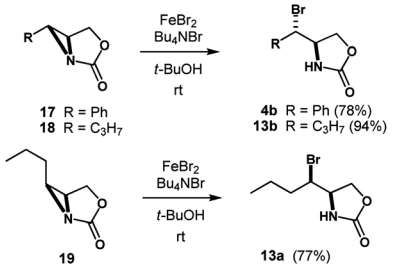
5 Peroxides are known to react with Fe(II) to produce oxyradical species. This process is known as the Fenton reaction: C. Walling, *Acc. Chem. Res.*, 1975, **8**, 125.

6 For examples of utility of *N*-tosyloxycarbamates and related compounds in organic synthesis, see: (*a*) H. Lebel, K. Huard and S. Lectard, *J. Am. Chem. Soc.*, 2005, **127**, 14198; (*b*) T. J. Donohoe, M. J. Chughtai, D. J. Klauber, D. Griffin and A. D. Campbell, *J. Am. Chem. Soc.*, 2006, **128**, 2514; (*c*) H. Lebel and K. Huard, *Org. Lett.*, 2007, **9**, 639; (*d*) H. Lebel, S. Lectard and M. Parmentier, *Org. Lett.*, 2007, **9**, 4797; (*e*) R. Liu, S. R. Herron and S. A. Fleming, *J. Org. Chem.*, 2007, **72**, 5587; (*f*) K. Huard and H. Lebel, *Chem.–Eur. J.*, 2008, **14**, 6222.

7 For instance, $FeBr_2$ has been shown to form a stable tetrahydrate complex with water, see: K. Waizumi, H. Masuda and H. Ohtaki, *Inorg. Chim. Acta*, 1992, **192**, 173. It is thus likely that iron(II) complexes are solvated in the reaction mixture.

8 Authentic bromides **4b**, **13a**, and **13b** were prepared by the stereospecific S_N2 opening of aziridines. Thus, the bromination of aziridines **17–19** with $FeBr_2$/Bu_4NBr afforded the corresponding bromides. However, since an aziridine derived from (*Z*)-cinnamyl substrate was unobtainable due to its significant instability, bromination could not be conducted. The stereochemistry of bromide **14** was unambiguously confirmed by nOe experiments. The structure of compound **15a** was established by coupling constant analysis of the ^1H NMR spectrum.



9 Typical experimental procedures (entry 3, Table 1): *n*-Bu_4NBr (109 mg, 0.34 mmol) and $FeBr_2$ (6.2 mg, 0.028 mmol) were added to a stirred solution of *N*-tosyloxycarbamate **1** (98.0 mg, 0.28 mmol) in *t*-BuOH (5 mL) at room temperature . After sonicating for 3 min, the mixture was stirred at room temperature for a further 4 h. The mixture was transferred to a separatory funnel where it was partitioned between H_2O and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (EtOAc/n-hexane 2 : 5 to 2 : 3) to give *N*-tosyloxycarbamate **1** (3.7 mg, 4%) as a colorless solid, more polar carbamate **7** (2.6 mg, 5%) as a colorless solid, and the most polar inseparable mixture of bromides **4a** and **4b** (60.4 mg, 84%, dr = 4 : 1) as a colorless solid. The diastereomeric ratio of bromides **4a** and **4b** was determined by ^1H NMR analysis of the mixture. The spectroscopic data of carbamate **7** were identical to those reported in the literature. *syn*-Bromide **4a**: colorless needles of mp 113–114 °C (EtOAc/*n*-hexane); IR (neat) ν 3262, 1755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5H), 6.01 (brs, 1H), 4.88 (d, 1H, J = 9.8 Hz), 4.49 (m, 1H), 4.24 (t, 1H, J = 9.2 Hz), 3.94 (dd, 1H, J = 9.8, 5.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 136.4, 129.7, 129.3, 127.9, 67.3, 58.7, 56.7; MS *m*/*z*: 256 $[M + H]^+$, 154 (100%); HRMS (FAB) calcd for $C_{10}H_{11}{}^{79}BrNO_2$ $[M + H]^+$: 255.9973, found: 255.9977. *anti*-Bromide **4b**: colorless needles of mp 171–173 °C (EtOAc/n-hexane); IR (neat) ν 3219, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.34 (m, 5H), 4.96 (brs, 1H), 4.76 (m, 1H), 4.66 (ddd, 1H, J = 11.0, 7.3, 2.7 Hz), 4.51–4.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 137.0, 129.7, 129.4, 128.0, 69.5, 58.0, 54.4; MS *m*/*z*: 256 $[M + H]^+$, 154 (100%); HRMS (FAB) calcd for $C_{10}H_{11}{}^{79}BrNO_2$ $[M + H]^+$: 255.9973, found: 255.9969.