(+)-Tartaric Acid-Catalyzed High Regio- and Stereoselective Aminobromination of Olefins

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(+)-Tartaric acid-catalyzed aminobromination of *α,β*-unsaturated ketones, *α,β*-unsaturated esters and simple olefins utilizing $TsNH_2$/NBS as the nitrogen/halogen sources at room temperature without protection of inert gases achieved good yields (up to 92% yield) of vicinal haloamino products with excellent regio- and stereoselectivity, even just 10% of (+)-tartaric acid was used as catalyst. The regio- and stereochemistry was unambiguously confirmed by X-ray structural analysis of products **2b** and **12c**. The electron-rich and deficient olefins show significant differences in activity to the aminobromination reaction and give the opposite regioselectivities. The 21 cases have been investigated which indicated that our protocol has the advantage of a large scope of olefins. Additionally, tartaric acid as catalyst has the advantage of avoiding any hazardous metals retained in products.

Keywords tartaric acid, aminobromination, regioselectivity, alkenes

Introduction

Aminohalogenations for installing vicinal haloamino moieties of multiply functionalized olefins have become an interesting topic in organic synthesis and medicinal chemistry because the products, the vicinal haloamines, are important building blocks which can readily be converted into numerous derivatives.[1-9]

In the past three decades, G. Li and others have developed many approaches to catalytic aminohalogenation of olefins with the aid of different nitrogen/halogen sources and catalysts. The common nitrogen/halogen sources included 4-$TsNCl_2$, 4-TsNNaCl,[10,11] 2-NsNNaCl (Ns=2-nitrophenylsulfonyl), 2-$NsNCl_2$/2-NsNHNa,[12,13] and NBS/$TsNH_2$.[14] Different metal complexs and salts, such as dichloro(1,10-phenanthroline)palladium(II),[11] CuI, V_2O_5, $MnSO_4$, Mn(III)-salen,[14] CuOTf,[15-17] $\{(C_3F_7CO_2)_2Rh\}_2$,[18,19] $CuCl_2•2H_2O$,[20] CuCN, $Cu(OAc)_2$, and $SnCl_4/BF_3•OEt_2$,[21] were utilized as catalysts. Very recently, we have reported some novel and highly efficent reaction systems for aminobromination of olefins by use of $TsNH_2$/NBS as the nitrogen/halogen sources in the presence of elemental copper powders,[22] aluminium powder,[23] silicon powder[24] and KI[25] as catalysts. This method provides desired products in excellent yields (up to 98% yield) even when just 1% catalyst was used. However, since metal-catalyst is generally limited in pharmaceutical industry, more readily available and nontoxic metal-free catalysts is highly desirable. For this aim, the sulfuric acid-catalyzed aminochlorination of olefins with Chloramine-T was developed by Wang and co-worker,[26] and CO_2-promoted aminohalogenation has also been reported.[27]

In recent years, increasing attention has been paid to organocatalysts due to their great advatages: (i) The organocatalysts are usually commercially available, inexpensive and environmentally friendly. (ii) Reactions catalyzed by organic small moleculars often proceed under an aerobic atmosphere even in wet solvents. (iii) In contrast to metallic Lewis acids, organocatalysts can be recovered and reused. Despite of the developments of organocatalysts in many reactions,[28-39] no report has been found on organocatalyst-promoted aminohalogenation of olefins.

Bearing in mind the advantages of organocatalysts, and considering both Lewis acid and Brønsted acid can catalyze aminohalogenation of electron-deficient olefins, we decided to explore small molecular organic acids as organocatalysts for this reaction. An array of organic acids were investigated and the (+)-tartaric acid was found to be an efficient catalyst for the reaction. Herein, we wish to disclose the outcome of the (+)-tartaric acid-catalyzed regio- and stereoselective aminobromination of olefins in CH_2Cl_2 with $TsNH_2$ and NBS (Scheme 1). To the best of our knowledge, (+)-tartaric acid is the first nontoxic and convenient organocatalyst for aminohalogenation of olefins.

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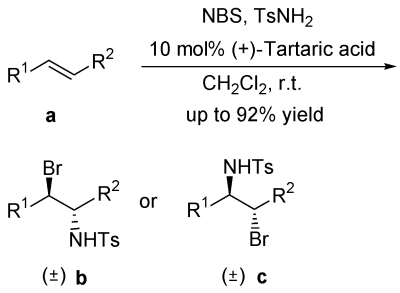
Scheme 1



Results and discussion

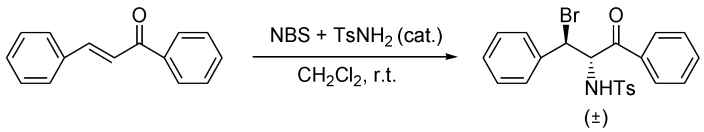
In our initial study, the catalytic activities of various organic acids were examined for the aminobromination of 1,3-diphenylpropen-1-one (the model substrate), with $TsNH_2$ and NBS as nitrogen/halogen source at room temperature without protection of inert gases. The result is summarized in Table 1. Among the monocarboxylic acid, the acetic acid (10 mol% loading) was first employed to perform the reaction in CH_2Cl_2, which afforded desired product only in 36% yield (Table 1, Entry 2). When the amount of catalyst went up from 50 mol% to 100 mol%, the yields were correspondingly increased from 43% to 62% (Entries 3 and 4). The long-chain aliphatic acid also gave unsatisfactory result (46% yield) after stirring at room temperature for 48 h (Entry 5). When stronger trifluoroethanoic acid was used as catalyst (10 mol%), the reaction yield was not improved (Entry 6, 33%) although reaction time was prolonged up to 72 h, which indicates the catalytic activities of organic acids were not related with their acidities. Aromatic acids led to similar results to those of aliphatic monocarboxylic acids (Entries 7—9). Some amino acids have also been investigeted (Entries 10—15, 10 mol% loading, 24 h), none of them afforded good result under the current conditions.

In the ongoing investigation of this reaction, we turned our attention to the dicarboxylic acid, whereas similar disappointing results were observed in most cases (Entries 16—18). To our delight, we found that, in the presence of 10 mol% (±)-tartaric acid, the aminobromination reaction could proceed smoothly to afford the expected product in good yield (Entry 19, 72%). Interestingly, the (+)-tartaric acid (10 mol%) slightly increased this reaction yield from 72% to 76% within 24 h (Entry 20). The reaction time could be shortened as the loading of (+)-tartaric acid was increased from 10 mol% to 100 mol% (Entries 21—22). Unfortunately, the vicinal haloamino product has no optical activity, meaning it is a racemic mixture.

Various solvent systems were also screened for this reaction. The results showed that hexane, toluene, THF, and ethanol were not suitable solvents for this reaction. In contrary, CH_2Cl_2, CH_3CN and some aqueous media such as CH_2Cl_2/H_2O (*V*/*V* 1∶1) system were efficient solvents for this reaction. Best results were observed by the use of CH_2Cl_2 as solvent.

With the optimized condition in hand, the scope of (+)-tartaric acid-catalyzed aminobromination of the olefins was explored. As illustrated in Table 2, the reaction works well for a wide range of olefins. The *α*,*β*-unsaturated ketones (**1a**—**11a)** led to the haloamino products in moderate to good yields with high diastereoselecties (**1b**—**3b**, **4c**—**7c**, **8b**—**11b**) except for **7c**. Notably, the reactivity of the chalcone derivatives depends greatly on the substituents of both benzene rings, especially those on the 4-position of the phenyl

Table 1 Aminobromination of chalcone catalyzed by various organic acids[a]



Entry	Cat./mol%	Time/h	Yield[b]/%	Entry	Cat./mol%	Time/h	Yield[b]/%
1	Non	48	23	12	Aspartic acid (10)	24	38
2	Acetic acid (10)	48	36	13	Histidine (10)	24	16
3	Acetic acid (50)[b]	48	43	14	Lycine (10)	24	21
4	Acetic acid (100)[b]	48	62	15	L-Phenylalanine (10)	24	26
5	Palmitic acid (10)	48	46	16	Succinic acid (10)	48	41
6	Trifluoroethanoic acid (10)	72	33	17	Oxalic acid (10)	48	13
7	Benzonic acid (10)	24	45	18	Citric acid (10)	48	38
8	Salicylic acid (10)	48	22	19	(±)-Tartaric acid (10)	24	72
9	3,5-Dinitrobenzonic acid (10)	48	38	20	(+)-Tartaric acid (10)	24	76
10	*DL*-Threonine(10)	24	22	21	(+)-Tartaric acid (50)	16	75
11	*L*-Alanine(10)	24	15	22	(+)-Tartaric acid (100)	10	76

[a] Unless otherwise specified, all reactions were performed with chalcone (5.0 mmol), $TsNH_2$ (5.0 mmol), NBS (6.0 mmol), acid (0.5 mmol) in CH_2Cl_2 (10.0 mL). [b] Isolated yields by flash column chromatography.

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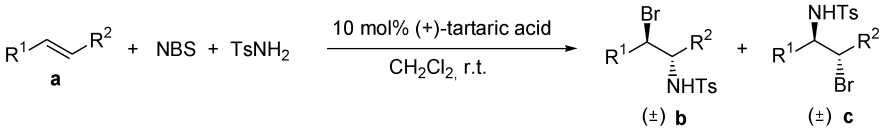
Table 2 (+) Tartaric acid-catalyzed aminobromination of electron-deficient olefins in CH_2Cl_2[a]



Entry	R^1	R^2	Product	*Anti* : *Syn*[b]/%	Time/h	m.p./℃	Yield[c]/%
1a	C_6H_5	C_6H_5CO	**1b**	>95	24	124—126	76
2a	C_6H_5	4'-ClC_6H_4CO	**2b**	>95	48	139—140	66
3a	C_6H_5	4'-$MeOC_6H_4CO$	**3b**	>95	48	159—159.5	60
4a	4-$MeOC_6H_4$	C_6H_5CO	**4c**	>95	0.25	155—156	92
5a	2-Br-4,5-$(MeO)_2C_6H_2$	C_6H_5CO	**5c**	>95	24	152—153	91
6a	3,4,5-$(MeO)_3C_6H_2$	C_6H_5CO	**6c**	>95	48	167—168	68
7a	3-$MeOC_6H_4$	C_6H_5CO	**7c**	—	48	—	Trace
8a	4-FC_6H_4	C_6H_5CO	**8b**	>95	24	150—151	49
9a	4-FC_6H_4	4'-$MeOC_6H_4CO$	**9b**	>95	48	164—165	59
10a	4-FC_6H_4	4'-ClC_6H_4CO	**10b**	>95	48	140—141	67
11a	4-BrC_6H_4	C_6H_5CO	**11b**	>95	48	170—172	61
12a	3,4,5-$(MeO)_3C_6H_2$	MeCO	**12c**	>95	1	177—179	48
13a	4-$MeOC_6H_4$	MeCO	**13c**	>95	1	93—95	75
14a	2-Br-4,5-$(MeO)_2C_6H_2$	MeCO	**14c**	>95	2	88—90	84
15a	4-$MeOC_6H_4$	CH_3OCO	**15c**	>95	1	90—91	79
16a	C_6H_5	C_2H_5OCO	**16b**	>95	48	121—123	62
17a	H	$CH_3(CH_2)_3$	**17b**	>95	24	84—86	45
18a	$CH_2CH_2CH_2CH_2$		**18b**	>95	24	116—117	33
19a	$CH_2CH_2CH_2CH_2CH_2CH_2$		**19b**	>95	6	115—116	70
20a	C_6H_5	C_6H_5	**20b**	>95	24	159—160	31
21a	H	C_6H_5	**21b**	>95	24	168—169	60

[a] Unless otherwise specified, all reactions were performed with olefins (5.0 mmol), $TsNH_2$ (5.0 mmol), NBS (6.0 mmol), (+)-tartaric acid (0.5 mmol) in CH_2Cl_2 (10.0 mL). [b] The ratio of *anti* : *syn* products, >95% means no minor isomer was detected by ^{1}H NMR. [c] Isolated yields by flash column chromatography.

attached directly to the double bond. The chalcones bearing a strong electron-donating group (*e.g.*, OCH_3) on the 4-position of the benzene ring afforded the *trans* isomers as the sole adductive products in nearly quantitative yields (92%, **4c**). The substrates bearing a poor electron-withdrawing group (*e.g.*, F or Br) on the same position gave products in moderate yields (49%—67%, **8b**—**11b**). This approach could be successfully extended to the aromatic enones, leading to the desired products in moderate to good yields (48%—75%, **12c**—**14c**).

α,*β*-Unsaturated esters and simple olefins were also examined in our reaction system. Much to our gratification, the aminobrominated products were obtained easily in both types of substrates. The aminobromination of *α*,*β*-unsaturated esters, methyl 4-methoxycinnamate (**15a**) and ethyl cinnamate (**16a**), afforded the adductive products in 79% (**15c**) and 62% (**16b**) yields, respectivly. For various simple olefins (**17a**—**21a**), the reaction gave the expected products in moderate yields (31%—70%, **17b**—**21b**).

The experimental results revealed that the reactivity of *α*,*β*-unsaturated ketones, *α*,*β*-unsaturated esters and simple olefins catalyzed by (+)-tartaric acid depends remarkably on the electron density of double-bond in the substrates. The higher the electron density is on the carbon-carbon double bond of the substrates due to electron-donating group (for example, CH_3O) being bearded on the 4-position of benzene ring, the higher the reaction activity of substrates is behaved. Such experimental evidences indicate that aminobromination of *α*,*β*-unsaturated carbonyl compound and simple olefins catalyzed by (+)-tartaric acid is an electrophilic addition reaction.

In all cases we examined, the regioselectivities of products have been completely controlled as revealed by their ^{1}H NMR and ^{13}C NMR analysis. The part of the aminobromination of *α*,*β*-unsaturated ketones and *α*,*β*-unsaturated esters catalyzed by (+)-tartaric acid gave the *anti*-*α*-amono-*β*-bromo isomer as the sole products. The identities of compounds (**1b**—**3b**, **8b**—**11b** and **16b**) were confirmed by comparison of their NMR, m.p. and elemental analytic data with the reported ones.[11,13,22-25,27,40-43] X-ray crystallographic study

of 1-(4'-chlorophenyl)-3-phenyl-2-(*p*-toluenesulfon amido)-3-bromopropan-1-one (**2b**, Figure 1) showed clearly that nitrogen atom was attached to the *α*-carbon and bromine atom to the *β*-carbon of *α*,*β*-unsaturated ketones in a *trans* relative stereochemistry.

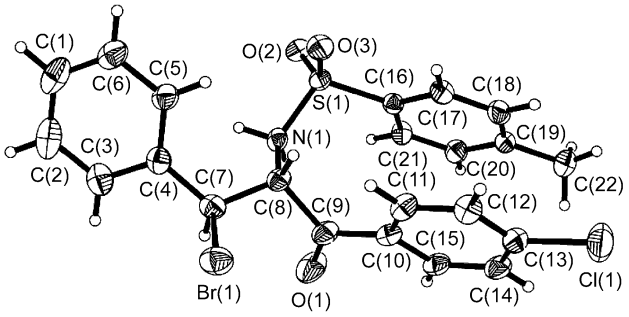


Figure 1 X-ray crystal structure of product **2b**.

A noteworthy feature of the aminobromination process is that the reversal isomers in regioselectivity were observed when the 4-position of benzene ring carried a strong electron-donating group (OCH_3) under our reaction condition. The regioselectivity of these reversal products (**4c**—**7c**, **12c**—**15c**) was confirmed by MS analysis. The prominent fragmented ions, $[ArCHNHTs]^+$ and $[ArCO]^+$ or $[RCO]^+$, were clearly identified. Further supported evidence was X-ray crystallographic analysis of 4-(3,4,5-trimethoxyphenyl)-4-(*p*-toluenesulfonamido)-3-bromobutan-2-one (**12c**, Figure 2), which has been reported previously in literature.[23] The result showed that nitrogen atom was added to *β*-carbon and bromine atom to *α*-carbon of corresponding *α*,*β*-unsaturated ketone.

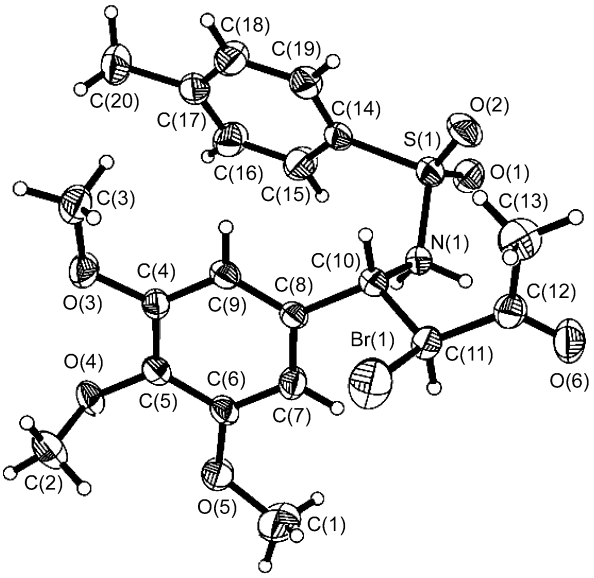


Figure 2 X-ray crystal structure of product **12c** reported in literature 23.

For simple olefins, the styrene gave the *α*-amino-*β*-bromo product (**19b**), which is determined by comparison of its NMR data and m.p. value with literature reported ones.[14,23-25] The regioselectivity of the aminobrominted product of 1-hexene, 1-bromo-2-(*p*-toluenesulfonamido) hexane (**15b**), was confirmed by MS data in which two prominent fragmented ions, $[CH_3(CH_2)_4CHNHTs]^+$ and $[CHNHTsCH_2Br]^+$, were clearly identified.

The electron-rich and deficient olefins give the opposite regioselectivities in our reaction. There was no explanation for these observations although they have been found in a few examples previously reported.[14,26] It seems reasonable to believe there are two possible pathways of the present aminobromination existing during the reaction process: a bromonium intermediate and an aziridinium intermediate formation pathway. For the electron-rich olefins, NBS can produce a positive bromine ion as well as radical.[44-46] Thus, the first step is that the substrate was reacted with NBS to yield a bromonium ion and negative succinimide ion [Figure 3, pathway 1, Eq. (1)] which was previously reported by Sudalai and co-workers.[14] For the second step, the negative *p*-toluenesulfonamide would be produced from negative succinimide reacting with *p*-toluenesulfonamide [pathway 1, Eq. (2)]. At the last step, the S_N2 mechanism of this three-membered ring (bromonium ion) opened by negative *p*-toluenesulfonamide accounts for the excellent *anti*-stereoselectivty. The regioselectivity can be explained by the fact that the *β*-position of the bromonium ion intermediate is loaded by more positive charge than its *α*-position because of the stabilization effect from the phenyl ring.

For the electron-deficient olefins without a 4-OMe, the reaction proceed via the aziridinium intermediate mechanism (Pathway 2) wherein the species of TsN^+Br is formed by the heterolytic cleavage of the N—Br bond from *N*,*N*-dibromo-*p*-toluene sulfonamide ($TsNBr_2$, **2**). The formation of *N*,*N*-dibromo-*p*-toluenesulfonamide from NBS and $TsNH_2$ has been reported in literature.[23] The formation of the aziridinium intermediate from TsN^+X has been demonstrated in the aminohalogenation of olefins with *N*,*N*-dihalo-*p*-toluene sulfonamide.[10,19,47-49] Herein, we believe that the species of TsN^+Br is formed by the heterolytic cleavage of the N—Br bond from *N*,*N*-dibromo-*p*-toluene sulfonamide helped by (+)-tartaric acid in our reaction [pathway 2, Eq. (2)]. Following reaction processes [pathway 2, Eqs. (3) and (4)] are similar to [pathway 1, Eqs. (1) and (3)]. The regioselectivity can be explained by the fact that the *β*-position of the aziridinium ion intermediate is loaded by more positive charge than its *α*-position because of the stabilization effect from the phenyl ring.

Conclusion

We have demonstrated a regio- and stereoselective aminobromination of olefins catalyzed by (+)-tartaric acid in good yields. The reaction catalyzed by organo-

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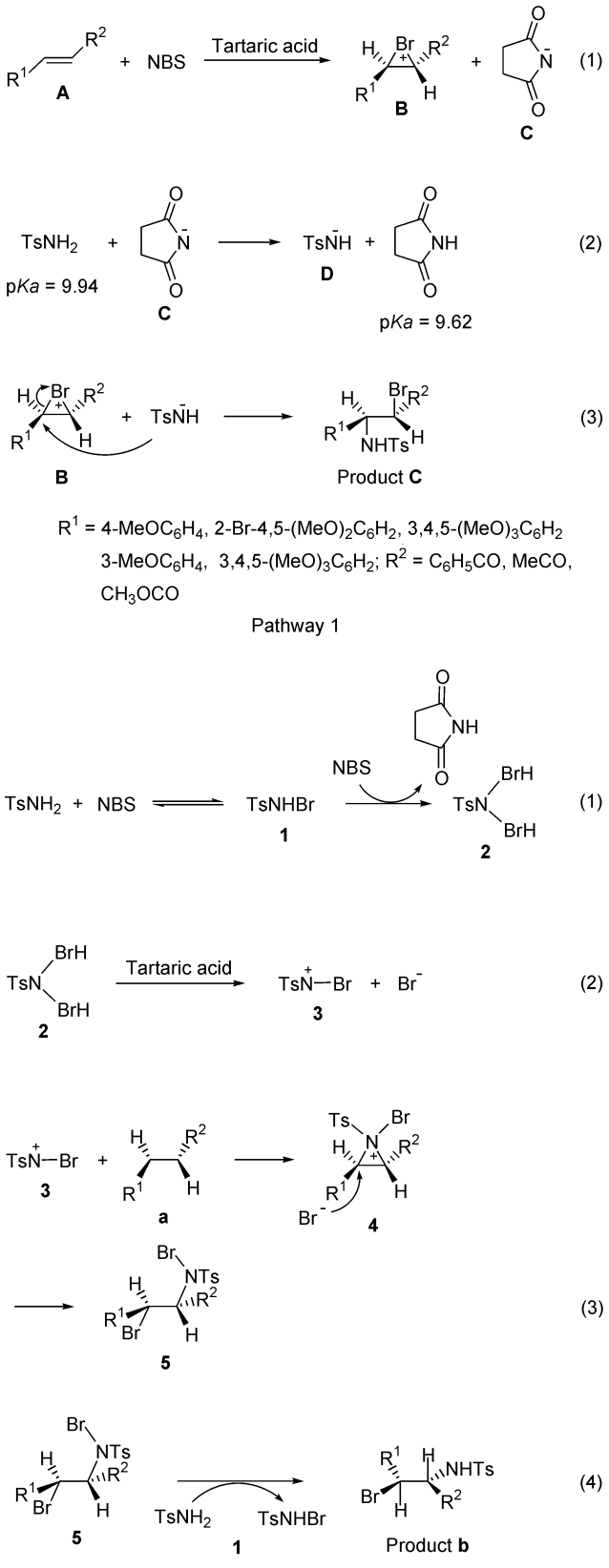

Figure 3 Prossible pathway for the aminobromination process for electron-rich olefins (pathway 1) and electron-deficient olefins (pathway 2)

catalyst provides a novel and convenient protocol to synthesize civinal haloamino derivatives with the combination of $TsNH_2$/NBS as nitrogen/bromine sources at room temperature. The method is successfully applied to a wide range of α,β-unsaturated ketones, α,β-unsaturated esters and simple olefins. Among the α,β-unsaturated carbonly compounds, higher regioselective isomers of α-bromo-β-amino products have been obtained when 4-position of benzene ring bears OCH_3 group. On the contrary, the other α,β-unsaturated carbonyl compounds afforded corresponding α-amino β-bromo isomers.

Experimental

General information

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Reaction progress was monitored by TLC using Merck silica gel 60 F-254 with detection by UV. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.45 MHz) spectra were recorded using $CDCl_3$ as a solvent. Chemical shifts (δ) are relative to TMS as an internal standard. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet), coupling constant J (Hz) and integration. Elemental analysis was carried on an analyzer. Melting point spectrometer is uncorrected. The crystal structure was recorded on an X-ray diffraction spectrometer. Mass data were obtained with a GCMS-QP2010nc Plus mass spectrometer (EI).

General experimental procedure

A mixture of ollifens (5 mmol), (+)-tartaric acid catalyst (10 mol%), $TsNH_2$ (855 mg, 5 mmol) and NBS (1068 mg, 6 mmol) was put into a dried convenience vessel. Then, 10 mL of CH_2Cl_2 was added to the vessel with stirring at room temperature in air. The reaction was monitored by TLC up to desired products with no increase or starting material complete consumed. After completion of the reaction, the reaction mixture was diluted with EtOAc (20 mL) and washed with brine (15 mL×3) and water (15 mL×3). The organic layer was dried by anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product which was purified by column chromatography packed with silica gel using petroleum ether and EtOAc as eluent to afford pure product.

Physical and spectroscopic data, m.p., and element analysis results of all the synthesized compounds are given below.

(±)-3-Bromo-1,3-diphenyl-2-(*p*-toluenesulfonamido) propan-1-one (1b) m.p. 124—126 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.78 (d, J = 7.50 Hz,

2H), 7.59—7.40 (m, 10H), 7.00 (d, J=8.10 Hz, 2H), 5.50 (d, J=3.60 Hz, 1H), 5.12—5.10 (m, 1H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 196.3, 143.6, 136.7, 136.4, 135.2, 134.1 (2), 129.0 (2), 129.5 (2), 128.9 (2), 128.7 (2), 128.6 (2), 127.1 (2), 60.8, 51.7, 21.4. Anal. calcd for $C_{22}H_{20}BrNO_3S$: C 57.64, H 4.37, N 3.06; found C 57.62, H 4.36, N 3.05.

(±)-3-Bromo1-(4'-chlorophenyl)-3-phenyl-2-(*p*-toluene sulfonamido) propan-1-one (2b) m.p. 139—140 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.74 (d, J=8.10 Hz, 2H), 7.44—7.38 (m, 4H), 7.25 (s, 5H), 7.00 (d, J=7.80 Hz, 2H), 5.60 (d, J=9.60 Hz, 1H), 5.44 (dd, J=8.0, 9.0 Hz), 5.07 (d, J=7.50 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 195.6, 143.4, 140.5, 136.3, 133.5, 130.0 (2), 129.2 (2), 128.8 (2), 128.7 (2), 128.4 (2), 128.3 (2), 126.8 (2), 60.0, 51.3, 21.1. Anal. calcd for $C_{22}H_{19}BrClNO_3S$: C 53.57, H 3.86, N 2.84; found C 53.59, H 3.88, N 2.87.

(±)-3-Bromo-1-(4'-methoxyphenyl)-3-phenyl-2-(*p*-toluene sulfonamido) propan-1-one (3b) m.p. 159—159.5 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.78 (d, J=8.40 Hz, 2H), 7.46 (d, J=7.95 Hz, 2H), 7.01 (d, J=7.80 Hz, 2H), 6.90 (d, J=8.40 Hz, 2H), 5.526—5.424 (m, 2H), 5.11 (d, J=6.60 Hz, 1H), 3.89 (s, 3H), 2.265 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 194.5, 164.5, 143.4, 136.8, 136.7, 131.4 (2), 129.4 (2), 129.0 (2), 128.6 (2), 128.1 (2), 127.1 (2), 114.0 (2), 60.4, 55.7, 51.9, 21.4. Anal. calcd for $C_{23}H_{22}BrNO_4S$: C 56.56, H 4.54, N 2.87; found C 56.62, H 4.58, N 2.87.

(±)-2-Bromo-3-(4-methoxyphenyl)-1-phenyl-3-(*p*-toluene sulfonamido) propan-1-one (4c) m.p. 155—156 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.78 (d, J=7.50 Hz, 2H), 7.60—7.53 (m, 2H), 7.42—7.38 (m, 2H), 7.12—7.07 (m, 4H), 6.71—6.64 (m, 3H), 5.40 (d, J=4.20 Hz, 1H), 5.06—5.02 (m, 1H), 3.70 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 193.7, 159.0, 142.6, 137.6, 134.1, 133.9, 128.8(2), 128.5(3), 128.4 (2), 128.3 (2), 126.8 (2), 113.7 (2), 59.9, 54.9, 46.0, 21.1; MS *m/z* (%): 77 (35), 91 (45), 105 (100), 155 (15), 290 (50), 408 (15). Anal. calcd for $C_{23}H_{22}BrNO_4S$: C 56.56, H 4.54, N 2.87; found C 56.60, H 4.58, N 2.87.

(±)-*trans*-2-Bromo-3-(2-bromo-4,5-dimethoxyphenyl)-1-phenyl-3-(*p*-toluenesulfonamido)propan-1-one (5c) m.p. 152—153 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.77—7.53 (m, 5H), 7.40 (dd, J=7.2, 7.3 Hz, 2H), 7.15 (d, J=7.5 Hz, 2H), 6.93 (d, J=8.70 Hz, 2H), 6.86 (s, 1H), 5.58 (d, J=6.00 Hz, 1H), 5.32 (dd, J=4.2, 4.7 Hz, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 193.74, 148.97, 147.96, 142.72, 137.08, 133.90, 133.83, 128.70 (2), 128.36 (2), 128.15 (2), 127.20 (2), 126.67, 114.82, 112.39, 111.72, 59.4, 55.7, 55.4, 42.4, 20.9; MS *m/z* (%): 77 (40), 91 (30), 105 (100), 155 (15), 399 (55), 597 (M^+, 5). Anal. calcd for $C_{24}H_{23}Br_2NO_5S$: C 48.26, H 3.88, N 2.34; found C 48.30, H 3.92, N 2.41.

(±)-*trans*-2-Bromo-1-phenyl-3-(3,4,5-trimethoxyphenyl)-3-(*p*-toluenesulfonamido)propan-1-one (6c) m.p. 167—168 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.79 (d, J=7.80 Hz, 2H), 7.57 (d, J=7.80 Hz, 2H), 7.42—7.37 (m, 2H), 7.09 (d, J=7.8 Hz, 2H), 6.85 (d, J=8.70 Hz, 1H), 6.31 (s, 2H), 5.42 (d, J=4.50 Hz, 1H), 5.08—5.05 (m, 1H), 3.72—3.67 (m, 9H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 193.7, 152.8, 142.7, 137.6, 137.4, 134.1, 134.0, 131.9, 128.8 (2), 128.5 (2), 128.4 (2), 127.0 (2), 126.8 (2), 104.4, 60.7, 60.4, 55.7, 45.6, 21.1; MS *m/z* (%): 65 (5), 77 (25), 91 (25), 105 (100), 155 (5), 195 (30), 350 (80), 549 (M^++1, 5). Anal. calcd for $C_{25}H_{26}BrNO_6S$: C 54.74, H 4.75, N 2.56; found C 54.72, H 4.79, N 2.60.

(±)-3-Bromo-3-(4-fluorophenyl)-1-phenyl-2-(*p*-toluene sulfonamido) propan-1-one (8b) m.p. 150—151 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.79 (d, J=7.50 Hz, 2H), 7.60—7.54 (m, 2H), 7.44—7.39 (m, 2H), 7.19—7.12 (m, 4H), 6.86—6.81 (m, 2H), 6.72 (d, J=8.70 Hz, 1H), 5.39 (d, J=4.80 Hz, 1H), 5.09—5.05 (m, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 193.4, 163.7, 142.9, 137.54, 134.1, 133.9, 132.4, 129.7 (2), 128.9 (2), 128.5 (2), 127.1 (2), 119.1, 116.4, 115.4, 115.1, 59.8, 45.5, 21.1. Anal. calcd for $C_{22}H_{19}BrFNO_3S$: C 55.46, H 3.99, N 2.94; found C 55.48, H 4.01, N 2.93.

(±)-3-Bromo-3-(4-fluorophenyl)-1-(4'-methoxyphenyl)-2-(*p*-toluenesulfonamido)propan-1-one (9b) m.p. 164—165 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.81 (d, J=8.70 Hz, 2H), 7.45 (d, J=7.50 Hz, 2H), 7.29 (d, J=9.9 Hz, 2H), 7.15 (s, 2H), 7.02 (d, J=7.50 Hz, 2H), 6.94—6.85 (m, 2H), 5.46 (d, J=9.30 Hz, 1H), 5.06 (d, J=6.60 Hz, 1H), 3.92 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 194.2, 164.3, 142.8, 136.5, 132.4 (2), 131.1 (2), 130.1 (2), 129.1, 128.9, 127.4, 126.7 (2), 115.3, 115.0, 113.8 (2), 60.1, 55.3, 45.4, 21.0. Anal. calcd for $C_{23}H_{21}BrFNO_4S$: C 54.55, H 4.15, N 2.77; found C 54.58, H 4.16, N 2.79.

(±)-3-Bromo-1-(4-chlorophenyl)-3-(4-fluorophenyl)-2-(tosylamino)-propan-1-one (10b) m.p. 140—141 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.78 (d, J=8.40 Hz, 2H), 7.42—7.39 (m, 2H), 7.11 (d, J=7.82 Hz, 2H), 6.82—7.02 (m, 2H), 5.58 (d, J=6.00 Hz, 1H), 5.43—5.32 (m, 1H), 4.13—4.08 (m, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 195.6, 163.9, 160.7, 143.3, 140.4, 136.2, 133.2, 132.1 (2), 129.9 (2), 128.96 (2), 128.86 (2), 126.5 (2), 115.3, 114.9, 59.7, 49.8, 20.8. Anal. calcd for $C_{22}H_{18}BrClFNO_3S$: C 51.73, H 3.55, N 2.74; found C 51.75, H 3.56, N 2.76.

(±)-3-Bromo-3-(4-bromopheny)-1-phenyl-2-(tosylamino) propan-1-one (11b) m.p. 170—172 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.86 (d, J=7.47 Hz, 2H), 7.65 (s, 1H), 7.52—7.26 (m, 6H), 7.04 (d, J=7.5 Hz, 2H), 5.55—5.44 (m, 2H), 5.01 (d, J=7.05 Hz, 1H), 2.30 (s, 3H); ^{13}CNMR ($CDCl_3$, 75.45 MHz) δ: 196.1, 143.2, 136.2, 135.3, 134.6, 133.8, 131.2 (2), 129.6 (2), 128.9 (2), 128.4 (2), 128.3 (2), 126.5 (2), 122.7, 59.9, 49.8, 20.9. Anal. calcd for $C_{22}H_{19}Br_2NO_3S$: C 49.18, H 3.56, N 2.61; found C 49.21, H 3.54, N 2.65.

(±)-3-Bromo-4-(3,4,5-trimethoxyphenyl)-4-(*p*-toluenesulfonamido)butan-2-one (12c) m.p. 177—179

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℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.49 (d, J= 7.80 Hz, 2H), 7.08 (d, J=7.80 Hz, 2H), 6.58 (d, J= 9.60 Hz, 1H), 6.27 (s, 2H), 4.76 (d, J=9.30 Hz, 1H), 4.51 (d, J=7.50 Hz, 1H), 3.77—3.72 (m, 9H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 201.8, 152.6, 142.8, 137.3, 136.8, 131.1, 128.6 (2), 126.6 (3), 104.1 (2), 60.3, 60.1, 55.5 (2), 53.3, 26.6, 20.9; MS *m*/*z* (%): 65 (10), 91 (35), 195 (40), 350 (100), 406 (10), 487 (M^+ + 1, 13). Anal. calcd for $C_{20}H_{24}BrNO_6S$: C 49.39, H 4.97, N 2.88; found C 49.41, H 4.94, N 2.86.

(±)-3-Bromo-4-(4-methoxyphenyl)-4-(*p*-toluenesulfon amido)butan-2-one (13c) m.p. 93—95 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.50 (d, J= 7.80 Hz, 2H), 7.07 (d, J=7.80 Hz, 4H), 7.68 (d, J= 8.10 Hz, 2H), 6.30 (d, J=9.30 Hz, 1H), 4.80 (d, J= 8.70 Hz 1H), 4.48 (d, J=6.60 Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 201.5, 159.0, 142.5, 136.9, 128.7 (2), 128.4 (2), 128.0, 126.6 (2), 113.4 (2), 59.1, 54.7, 53.6, 27.0, 20.9; MS *m*/*z* (%): 65 (10), 77 (5), 91 (65), 134 (15), 155 (30), 290 (100), 346 (10), 426 (M^+, 2). Anal. calcd for $C_{18}H_{20}BrNO_4S$: C 50.71, H 4.73, N 3.29; found C 50.74, H 4.72, N 3.28.

(±)-3-Bromo-4-(2-bromo-4,5-dimethoxyphenyl)-4-(*p*-toluenesulfonamido)butan-2-one (14c) m.p. 88—90 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.57 (d, J=7.50 Hz, 2H), 7.09 (d, J=7.80 Hz, 2H), 6.85 (s, 1H), 6.65 (s, 1H), 6.57 (d, J=9.00 Hz, 1H), 5.17—5.12 (m, 1H), 4.63 (d, J=5.28 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 201.5, 148.9, 148.0, 142.8, 136.7, 128.7 (2), 126.9, 126.6 (2), 114.8, 112.7, 111.4, 58.9, 55.7, 55.5, 49.6, 27.5, 20.9; MS *m*/*z* (%): 77 (20), 91 (25), 105 (100), 155 (35), 399 (65). Anal. calcd for $C_{19}H_{21}Br_2NO_5S$: C 42.64, H 3.95, N 2.62; found C 42.67, H 3.90, N2.68.

(±)-Methyl 2-bromo-3-(4-methoxyphenyl)-3-(tosylamino) propionate (15c) m.p. 90—91 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.56 (d, J= 7.95 Hz, 2H), 7.25 (d, J=5.52 Hz, 2H), 7.12 (d, J= 7.59 Hz, 2H), 7.02 (d, J=8.37 Hz, 2H), 6.69 (d, J= 8.37 Hz, 2H), 6.19 (d, J=9.15 Hz, 1H), 4.85—4.83 (m, 1H), 4.45 (d, J=5.76 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 168.2, 159.1, 142.6, 137.1 (2), 128.7 (2), 127.7 (2), 126.7 (2), 113.5 (2), 59.1, 54.7, 52.6, 46.3, 20.9. Anal. calcd for $C_{18}H_{20}BrNO_5S$: C 48.88, H 4.56, N 3.17; found C 49.01, H 4.52, N 3.10.

(±)-Ethyl 3-bromo-3-phenyl-2-(tosylamino)propionate (16b) m.p. 121—123 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.63 (d, J=7.8 Hz, 2H), 7.41—7.23 (m, 8H), 5.18—5.12 (m, 2H), 4.48—4.43 (m, 1H), 3.98 (q, J=6.9 Hz, 2H), 2.41 (s, 3H), 1.26 (t, J=6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 168.1, 143.3, 136.1, 135.8, 129.1 (2), 128.5 (2), 128.1, 127.8 (2), 126.9 (2), 61.7, 61.4, 51.4, 20.9, 13.3. Anal. calcd for $C_{18}H_{20}BrNO_4S$: C 50.71, H 4.73, N 3.29; found C 50.75, H 4.74, N 3.30.

1-Bromo-2-(tosylamino)hexane (17b) m.p. 84—86 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.78 (d, J=7.88 Hz, 2H), 7.32 (d, J=7.62 Hz, 2H), 4.70 (s, 1H), 3.41—3.30 (m, 3H), 2.43 (s, 3H), 1.55—0.78 (m, 9H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 143.7, 137.8, 129.8 (2), 127.5 (2), 60.4, 38.2, 32.9, 27.3, 22.1, 21.5, 14.2; MS *m*/*z* (%): 334 (M^+, 8), 240 (50) C_4H_9CH (NHTs). Anal. calcd for $C_{13}H_{20}BrNO_2S$: C 46.71, H 6.03, N 4.19; found C 46.72, H 6.04, N 4.21.

(±)-*trans*-1-Bromo-2-(*p*-toluenesulfonamido)cyclohexane (18b) m.p. 116—117 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.79 (d, J=6.13 Hz, 2H), 7.31 (d, J=7.80 Hz, 2H), 5.34 (s, exchangeable with D_2O, 1H), 3.88 (s, 1H), 3.20 (d, J=3.60 Hz, 1H), 2.43 (s, 3H), 2.25 (s, 2H), 1.80—1.64 (m, 3H), 1.31 (d, J= 6.00 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 143.0, 136.8, 129.1 (2), 126.8 (2), 58.1, 54.5, 35.2, 32.3, 24.7, 22.9, 21.0. Anal. calcd for $C_{13}H_{18}BrNO_2S$: C 46.99, H 5.46, N 4.22; found C 46.96, H 5.48, N 4.21.

(±)-*trans*-1-Bromo-2-(*p*-toluenesulfonamido)cyclooctane (19b) m.p. 115—116 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.77 (d, J=8.10 Hz, 2H), 7.31 (d, J=7.80 Hz, 2H), 4.76 (s, 1H), 4.07—4.02 (m, 1H), 3.45 (s, 1H), 2.44 (s, 3H), 2.30—1.98 (m, 3H), 1.78—1.30 (m, 9H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 143.5, 136.2, 129.5 (2), 127.6 (2), 61.0, 59.6, 32.2, 31.7, 25.7, 25.5, 25.4, 25.0, 21.6. Anal. calcd for $C_{15}H_{22}BrNO_2S$: C 50.00, H 6.15, N 3.89; found C 49.98, H 6.18, N 3.97.

(±)-*trans*-1-Bromo-1,2-diphenyl-2-(*p*-toluenesulfonamido) ethane (20b) m.p. 159—160 ℃ (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 (d, J=7.80 Hz, 2H), 7.26—7.06 (m, 10H), 6.88 (d, J=7.20 Hz, 2H), 5.17 (d, J=2.70 Hz, 1H), 5.1 (s, 1H), 4.8—4.76 (m, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 143.3, 136.8, 136.3, 129.4, 129.3, 129.2, 128.9, 128.7, 128.7, 128.5, 128.4, 128.4, 128.1(2), 127.9, 127.8, 127.2, 127.1, 63.1, 58.4, 21.4. Anal. calcd for $C_{21}H_{20}BrNO_2S$: C 58.61, H 4.68, N 3.25; found C 58.63, H 4.69, N 3.28.

2-Bromo-1-phenyl-1-(*p*-toluenesulfonamido)-ethane (21b) m.p. 168—169 ℃ (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.63 (d, J=7.80 Hz, 2H), 7.34—7.12 (m, 7H), 5.38 (s, exchangeable with D_2O, 1H), 4.57 (d, J=6.21 Hz, 1H), 3.58 (d, J=6.21 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ: 143.1, 137.2, 136.6, 129.0 (2), 128.2 (2), 127.8, 126.7 (2), 126.2 (2), 57.6, 36.1, 21.0. Anal. calcd for $C15_5H_{16}BrNO_2S$: C 50.86, H 4.55, N 3.95; found C 50.82, H 4.57, N 3.96.

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