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Transition Metal-Catalyzed Regio- and Stereoselective Aminobromination of Olefins with $TsNH_2$ and NBS as Nitrogen and Bromine Sources

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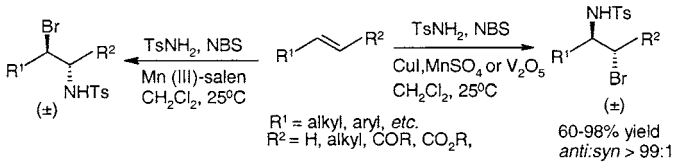
ABSTRACT



A new synthetic procedure for aminohalogenation of olefins has been developed for the preparation of vicinal haloamine derivatives in high yields by using Cu, Mn, or V catalysts with *p*-toluenesulfonamide ($TsNH_2$) and *N*-bromosuccinimide (NBS) as nitrogen and bromine sources, respectively. Unprecedented regio- and stereoselectivity (*anti:syn* > 99:1) toward the aminohalogenation process is shown for olefinic substrates as well as transition metal catalysts.

Transition metal-catalyzed 1,2-functionalization of olefins with amines and halogens (aminohalogenation) represents an important transformation in organic synthesis. These vicinal haloamine derivatives are versatile building blocks in organic and medicinal chemistry.[1] Particularly, the study of highly regioselective and stereoselective aminohalogenation of olefins still remains important and challenging to organic chemists. In the literature, the preparation of vicinal haloamines is achieved by the addition of *N*-halo,[2] *N*,*N*-dihaloarylsulfonamides,[3] *N*-halocarbamates,[4] and *N*,*N*-dihalophosphoramides[5] onto olefins under noncatalytic conditions. A significant limitation with these processes is the poor yield and selectivity in terms of product distribution often obtained under such conditions. Quite recently, Li et al. have reported in a series of papers their significant contributions on aminohalogenation of cinnamic esters catalyzed by various transition metal salts using *N*,*N*′-dichloro-*p*-toluenesulfonamide as the nitrogen as well as chlorine sources.[6]

In our continued efforts to provide new catalytic methods of aziridination,[7] we believed that the reaction between NBS and *p*-toluenesulfonamide in the presence of copper salts would generate metal nitrenes in situ which can then

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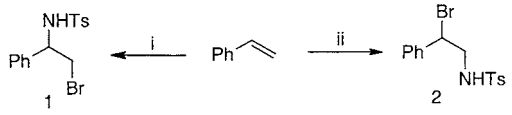
aziridinate olefins. However, the reaction took a different course in furnishing 1,2-bromoamine as the sole product. In this letter, we wish to report, for the first time, a practical process for the regio- and stereospecific aminobromination of various olefins catalyzed by Cu, V, and Mn salts with *p*-toluenesulfonamide ($TsNH_2$) and NBS as amine and bromine sources, respectively.

When styrene was reacted with $TsNH_2$ (1.0 molar equiv) and NBS (1.1 molar equiv) in the presence of catalytic CuI (5 mol %) in CH_2Cl_2, the corresponding aminobrominated product was obtained in high yield with excellent regioselectivity (>99%). Surprisingly, when Mn(III)-salen [*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride] was employed as catalyst, a reversal in regiochemical product was observed without affecting the yield and selectivity (Scheme 1). Simple olefins such as

Scheme 1[a]



[a] Reagents and conditions: (i) styrene (2 mmol), $TsNH_2$ (2 mmol), *N*-bromosuccinimide (2.2 mmol), CuI (5 mol %), CH_2Cl_2, 25 °C; (ii) styrene (2 mmol), $TsNH_2$ (2 mmol), *N*-bromosuccinimide (2.2 mmol), Mn(III)-salen complex (5 mol %), CH_2Cl_2, 25 °C.

styrene and cyclohexene gave very slow reaction with poor regioselectivity and yield in the absence of catalyst.

With this encouraging result, a systematic study was undertaken to screen various metal catalysts for the aminobromination process. Among the various transition metal salts screened, we found that CuI, $MnSO_4$, and V_2O_5 were proven effective in catalyzing the aminobromination of styrene in CH_2Cl_2 as solvent (Table 1). However, other solvents such as $CHCl_3$, benzene, CCl_4, or toluene except alcoholic ones are found to be equally good for the aminobromination process.

A variety of olefins with varied functional groups can be subjected to this reaction. For all of the cases which we examined, the regioselectivity has been completely controlled as revealed by the crude ^1H NMR analysis of the products. Further, the regioselectivity of the product was determined by MS spectroscopy analysis in which two prominent fragmented ions, $[ArCHNHTs]^+$ and $[CHRBr]^+$, were clearly identified. Meanwhile, it is also remarkable to note that exclusive formation of *anti*-isomers has been observed in all the 1,2-disubstituted olefins (Table 2).

However, a noteworthy feature of the aminobromination process is the reversal in regioselectivity observed when

Table 1. Aminobromination of Styrene with $TsNH_2$ and NBS: Effect of Catalysts[a]

sr. no.	catalyst	*t* (h)	product	yield[b] (%)
1	no catalyst	24	1:2 (60:40)	20
2	CuI	2	1	92
3	$CuCl_2 \cdot 2H_2O$	2.5	1	85
4	CuCN	4	1	71
5	$Cu(OAc)_2$	5	1	65
6	$NiCl_2 \cdot 6H_2O$	8	1	58
7	$Ni(OAc)_2 \cdot 4H_2O$	6	1	64
8	$Co(OAc)_2 \cdot 4H_2O$	6	1	65
9	$FeCl_3$	12	1	30
10	$MnSO_4$	2	1	90
11	V_2O_5	2	1	91
12	Mn(III)-salen[c]	1	2	97

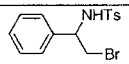
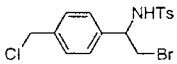
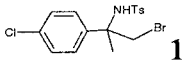
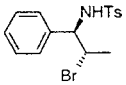
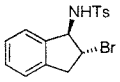
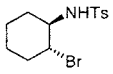
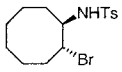
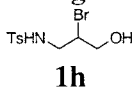
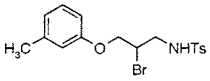
[a] Reaction conditions: styrene (2.0 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), catalyst (5 mol %), CH_2Cl_2 (5 mL), 25 °C. [b] Yields refer to isolated product after column chromatography. [c] *N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride.

Mn(III)-salen was employed as the catalyst under the reaction conditions. The yield and regioselectivity was found to be excellent in all the styrenic substrates studied (Table 3).

α,β-Unsaturated carbonyl compounds represent the most synthetically useful substrate classes for various olefin oxidative reactions. Particularly, the vicinal aminobromination of α,β-unsaturated carbonyl compounds affords functionalized aminobrominated compounds, which can be converted to numerous useful organic molecules by replacing the bromine atom with a series of nucleophiles. Hence, a variety of α,β-unsaturated carbonyl compounds were subjected to aminobromination under the present catalytic conditions, affording products in high yields with excellent control over regio- and diastereoselectivity (Table 4).

(8) General experimental procedure for aminobromination of olefins: To a mixture of olefin (2 mmol), Cu, V, or Mn catalyst (5 mol %), and $TsNH_2$ (0.342 g, 2 mmol) was added slowly via solid addition funnel CH_2Cl_2 (5 mL) and NBS (0.392 g, 2.2 mmol), with stirring at 25 °C. The reaction was monitored by TLC. After completion of the reaction, the solution was diluted with EtOAc (15 mL) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography with silica gel packing, using pet. ether and EtOAc as eluents to afford pure product. (±)-*trans*-3-(4-Chlorophenyl)-3-bromo-2-(*p*-toluenesulfonamido)propiophenone (**3e**): mp 168−170 °C. ^1H NMR ($CDCl_3$): δ 2.31 (s, 3H), 5.00 (d, J = 6.21 Hz, 1H), 5.43−5.52 (m, 1H), 5.66 (d, J = 10.11 Hz, exchangeable with D_2O, 1H), 6.98−7.26 (m, 6H), 7.39−7.50 (m, 5H), 7.87 (d, J = 8.48 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.28, 49.98, 59.65, 126.66, 128.57, 128.98, 129.20, 129.89, 133.97, 134.71, 135.48, 135.63, 137.17, 143.13, 197.05. MS *m*/*z* (% rel intensity): 493 (M^+, 3), 412 (6), 388 (32), 307 (50), 288 (73), 155 (33), 117 (45), 105 (100), 91 (73), 77 (73), 65 (23). (±)-*trans*-Ethyl-3-(4-methoxyphenyl)-3-(*p*-toluenesulfonamido)-2-bromopropionate (**4a**): mp 117−119 °C. ^1H NMR ($CDCl_3$): δ 1.17 (t, J = 6.31 Hz, 3H), 2.34 (s, 3H), 3.74 (s, 3H), 4.11 (q, J = 6.31 Hz, 2H), 4.42 (d, J = 6.25 Hz, 1H), 4.79−4.87 (dd, J = 10.21 and 6.25 Hz, 1H), 6.26 (d, J = 10.21 Hz, exchangeable with D_2O, 1H), 6.67−6.72 (d, J = 9.41 Hz, 2H), 7.00−7.13 (m, 4H), 7.57 (d, J = 9.41 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 13.52, 21.13, 47.19, 54.98, 59.43, 62.26, 113.61, 126.88, 128.17, 128.98, 137.32, 142.80, 159.26, 168.09. MS *m*/*z* (% rel intensity): 455 (M^+, 1), 410 (1), 370 (2), 290 (60), 155 (40), 134 (27), 91 (100), 65 (30).

Table 2. Transition Metal-Catalyzed Aminobromination of Olefins with $TsNH_2$ and NBS[a]

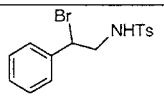
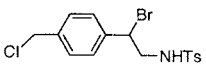
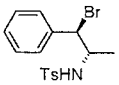
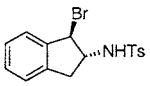
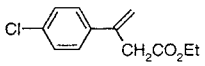
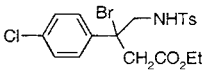
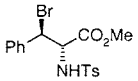
No.	Olefin	t/h	Product	mp (°C) (lit.)[b]	*anti:syn*[c]	Yield (%)[d]		
						CuI	$MnSO_4$	V_2O_5
1.	Styrene	2	 **1a**	168-169 (167)	--	92	90	91
2.	4-Chloromethylstyrene	3	 **1b**	128-130	--	90	88	92
3.	4-Chloro-α-methylstyrene	2	 **1c**	144-146	--	93	82	93
4.	*trans*-β-Methylstyrene	3	 **1d**	134-135	>99:1	92	89	98
5.	Indene	2	 **1e**	169-170	>99:1	89	81	85
6.	Cyclohexene	3	 **1f**	116-117	>99:1	78	66	71
7.	Cyclooctene	3	 **1g**	98-99	>99:1	80	76	85
8.	Allyl alcohol	6	 **1h**	gum	---	75	63	70
9.	3-Methylphenylallyl ether	18	 **1i**	gum	---	76	62	60

[a] Reaction conditions: olefin (2.0 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), catalyst (5 mol %), CH_2Cl_2 (5 mL), 25 °C. [b] Mp values in parentheses refers to mp reported in the literature. [c] Determined by ^1H NMR analysis of crude product. [d] Isolated yield after chromatographic separation.

Interestingly, the amine functionality is generally introduced at the α-position to the carbonyl group except for aromatic substrates with OMe groups (entries 6 and 7). Further, the *trans*-β-bromo-α-amino isomer was formed as the sole product as determined by ^1H NMR analysis of the crude products for all the cases studied. It was further confirmed by converting the vicinal aminobrominated compounds into the corresponding known *trans*-aziridines (J_{trans} = 4.5 Hz). The regiochemistry was assigned on the basis of mass spectroscopy analysis, which showed prominent peaks corresponding to $[ArCHBr]^+$ and $[TsNHCHR]^+$ ion fragments. However, for aromatic substrates with the 4-OMe group, the formation of $[4\text{-}OMe\text{-}C_6H_4\text{-}CH\text{-}NHTs]^+$ and $[Br\text{-}CHCO_2Et]^+$ ion fragments was observed in its mass spectroscopy.

To explain the regio- and stereoselectivity of the aminobromination process, the following experiments were carried out: (i) TsNHBr was isolated and characterized by ^1H NMR, ^{13}C NMR, and MS when $TsNH_2$ was reacted with NBS (in equimolar proportions). (ii) The isolation of *anti*-aminobrominated products obtained in all 1,2-disubstituted olefinic cases studied indicates the formation of the bromonium ion as the most likely reactive intermediate. (iii) When *N*-(*p*-tolylsulfonyl)-2-phenylaziridine was subjected to the reaction conditions (NBS, catalyst, CH_2Cl_2, 25 °C), no aminobrominated product formation was observed, which indicates that aziridine is not the intermediate. (iv) Further when styrene was treated with NBS in the presence of a catalytic amount of CuI in CH_2Cl_2 at 25 °C, a moderate yield (40%) of styrene dibromide was obtained. All the above experiments strongly

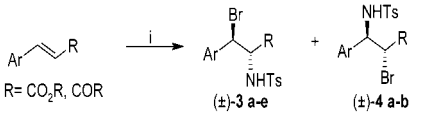
Table 3. Mn(III)-salen-Catalyzed Aminobromination of Olefins with $TsNH_2$ and NBS[a]

No.	Olefin	t/h	Product	mp (°C) (lit.)[b]	*anti:syn*[c]	Yield (%)[d]
1.	Styrene	1	 **2a**	113-114 (111)	-	97
2.	4-Chloromethylstyrene	1.5	 **2b**	111-112	-	95
3.	*trans*-β-Methylstyrene	2	 **2c**	gum	>99:1	97
4.	Indene	2	 **2d**	136-137	>99:1	90
5.		3	 **2e**	gum	-	94
6.	*trans*-Methyl cinnamate	28		136-137	>99:1	65

[a] Reaction conditions: olefin (2.0 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), Mn(III)-salen[*N,N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride] (5 mol %), CH_2Cl_2 (5 mL), 25 °C. [b] Mp values in parentheses refers to mp reported in the literature. [c] Determined by ^1H NMR analysis of crude product. [d] Isolated yield after chromatographic separation.

suggest that the bromonium ion is the most probable intermediate.

Table 4. Transition Metal-Catalyzed Aminobromination of α,β-Unsaturated Carbonyl Compounds with $TsNH_2$ and NBS[a]



(i) Olefin (2 mmol), $TsNH_2$ (2 mmol), *N*-bromosuccinimide (2.2 mmol), catalyst (5 mol%), CH_2Cl_2, 25°C.

no.	Ar	R	*t* (h)	product	*anti*: *syn*[b]	yield[c] (%) CuI	$MnSO_4$	V_2O_5
1	Ph	CO_2Me	24	**3a**	>99:1	75	82	80
2	4-Cl−C_6H_4	CO_2Et	26	**3b**	>99:1	63	78	68
3	Ph	COPh	10	**3c**	>99:1	68	88	87
4	4-Cl-C_6H_4	$COCH_3$	28	**3d**	>99:1	58	60	61
5	4-Cl-C_6H_4	COPh	26	**3e**	>99:1	70	72	70
6	4-MeO-C_6H_4	CO_2Et	20	**4a**	>99:1	75	80	82
7	4-MeO-C_6H_4	COPh	15	**4b**	>99:1	78	88	84

[a] Reaction conditions: olefin (2.0 mmol), $TsNH_2$ (2 mmol), NBS (2.2 mmol), catalyst (5 mol %), CH_2Cl_2 (5 mL), 25 °C. [b] Determined by ^1H NMR analysis of crude product. [c] Isolated yield after chromatographic separation.

In conclusion, we have demonstrated a new catalytic method for the preparation of 1,2-aminobrominated products in preparative yield from a variety of olefins including α,β-unsaturated carbonyl compounds at ambient conditions. The method employs CuI, $MnSO_4$, or V_2O_5 as catalysts and NBS/$TsNH_2$ combination as the bromine and nitrogen sources, respectively. Surprisingly, both catalysts and olefinic substrates have shown unprecedented regio- and stereoselectivity toward the aminobromination process

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Supporting Information Available: ^1H NMR, ^{13}C NMR, mass, IR spectra, and elemental analysis available for all the compounds (**1a**−**i**, **2a**−**e**, **3a**−**e**, and **4a**−**b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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