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Titanium superoxide: a heterogeneous catalyst for *anti*-Markovnikov aminobromination of olefins

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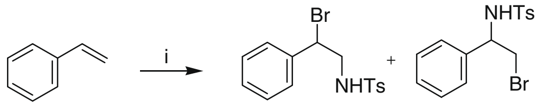
ABSTRACT

A new facile procedure for the aminobromination of olefins in high yields has been described using *p*-toluene sulfonamide (*p*-$TsNH_2$) and *N*-bromosuccinimide (NBS) as nitrogen and bromine sources, respectively, and titanium superoxide as a truly heterogeneous catalyst. The formation of *anti*-Markovnikov product exclusively in all the cases studied possibly proceeding through a free radical reaction pathway is remarkable.

The vicinal haloamine functionality represents a useful structural moiety as well as a versatile building block in organic and medicinal chemistry.[1] In the area of synthetic organic chemistry, these can be readily converted into a variety of useful functional derivatives on replacement of halogen with nucleophiles in both intramolecular and intermolecular fashion.[2] Literature search reveals that vicinal haloaminations are carried out using several catalysts such as V_2O_5,[3] $MnSO_4$,[3] Mn(II) salen,[3] Cu-salts,[4] $InBr_3$,[5] Fe-salt,[6] BF_3,[7] $SnCl_4$,[8] Pd-complex,[9] $PhI(OAc)_2$,[10] *N*-*N*-dihalosulfonamides,[11a] *N*-*N*-dihalocarbamates,[11b–g] *N*-halocarbamates[11h] cyanamide-NBS[11i] as well as by noncatalytic routes which include use of Bronsted acids[12] such as H_2SO_4 or ionic liquid media $[Bmim][BF_4]$.[13] But most of these methods suffer from drawbacks such as lack of product selectivity and use of non-economic, unstable, and toxic metals as catalysts. Hence, a search for readily available non-toxic, inexpensive and reusable catalyst is highly desirable. In this Letter, we report that titanium superoxide[14a] catalyzes aminobromination of olefins, which proceeds regiospecifically in an *anti*-Markovnikov fashion and under truly heterogeneous conditions.

Some time ago, we have reported a new method for the preparation of titanium superoxide, which was found to exist as a remarkably stable radical at ambient conditions.[15] This heterogeneous catalyst has been subsequently found to catalyze the selective oxidation of aromatic primary amines and phenols to the corresponding nitro aromatics and *p*-quinones, respectively.[15] During the course of our study on further application of titanium superoxide in organic synthesis, we have now found that olefins can be regiospecifically aminobrominated using *p*-$TsNH_2$ and NBS as nitrogen and bromine sources under ambient conditions. For instance, when styrene was subjected to bromoamination, the corresponding *anti*-Markovnikov product, **1,** was formed in 81% yield; whereas the commercially available TiO_2, under similar conditions, gave the expected Markovnikov product, **2** in 30% yield (Scheme 1).

Encouraged by this result, it was of interest to screen several other titanium salts such as titanium silicalite (a zeolite), $TiCl_4$, and titanium isopropoxide under similar reaction conditions; the results of which are presented in Table 1. Remarkably, titanium superoxide gave the *anti*-Markovnikov product **1** in 81% yield whereas all other titanium salts furnished the expected Markovnikov product, **2** with low yields. Among several solvents screened, CH_2Cl_2 was found to be more suitable for titanium superoxide-catalyzed aminobromination of olefins. Thus, the optimal condition



	1	2
TiO_2	--	30%
titanium superoxide	81%	--

Scheme 1. Reagents and conditions: Titanium catalyst (10 wt %), *p*-$TsNH_2$ (1.1 equiv), NBS (1 equiv), CH_2Cl_2, 25 °C, 14 h.

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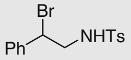
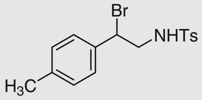
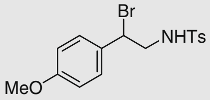
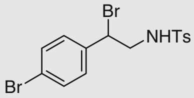
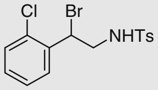
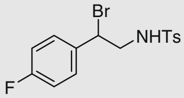
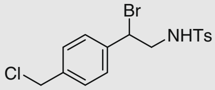
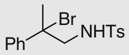
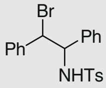
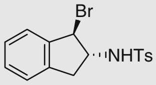
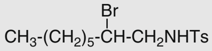
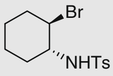
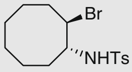
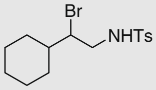
Table 1
Titanium-catalyzed regiospecific aminobromination of styrene[a]

No	Catalyst	Solvent	Yield[b] (%)	
			1	**2**
1	No catalyst	CH_2Cl_2	–	17
2	TiO_2	CH_2Cl_2	–	38
3	Titanium silicalite	CH_2Cl_2	–	23
4	Ti $(OPr^i)_4$	CH_2Cl_2	–	24
5	Titanium superoxide	CH_2Cl_2	81	–
6	Titanium superoxide	$CHCl_3$	61	–
7	Titanium superoxide	EDC	58	–

Reaction conditions: [a]olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), *N*-bromosuccinimide (3 mmol), catalyst (10 wt %), CH_2Cl_2 (20 mL), 25 °C, 14 h.

[b] Isolated yield after chromatographic purification.

Table 2
Titanium superoxide-catalyzed aminobromination of olefins[a]

No	Substrate	Product[b]	Yield[c] (%)	*anti:syn*
1	Styrene		81 (58)[d]	
2	4-Methylstyrene		86	
3	4-Methoxystyrene		67	
4	4-Bromostyrene		69	
5	2-Chlorostyrene		68	
6	4-Fluorostyrene		78	
7	4-Chloromethylstyrene		67	
8	α-Methylstyrene		30	
9	*trans*-Stilbene		61	
10	Indene		80	>99: 1
11	1-Octene	 $CH_3\text{-}(CH_2)_5\text{-}\overset{Br}{CH}\text{-}CH_2NHTs$	66	
12	Cyclohexene		65	>99: 1
13	Cyclooctene		72	>99: 1
14	Vinylcyclohexane		63	

Reaction conditions: [a]olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), *N*-bromosuccinimide (3 mmol), titanium superoxide (10 wt %), CH_2Cl_2 (20 mL), 25 °C, 14 h.

[b] Products were characterized by mp, IR, ^1H and ^{13}C NMR, and elemental analysis.

[c] Isolated yield after chromatographic purification.

[d] Yield in parentheses refers to use of recovered catalyst.

for the aminobromination of olefins turned out to be: olefin (3 mmol), *p*-$TsNH_2$ (3.3 mmol), NBS (3 mmol) and titanium superoxide (10 wt %) in CH_2Cl_2 at ambient conditions.

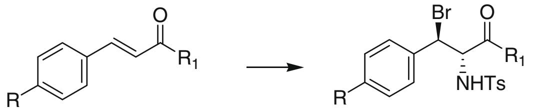
In order to establish its scope, various olefins were subjected to aminobromination; the results of which are presented in Table 2. It is evident that several styrenic substrates including indene underwent the aminobromination regiospecifically to produce the corresponding *anti*-Markovnikov[14b] products. No traces of Markovnikov products were, however, observed in the crude product sample (as confirmed by ^1H and ^{13}C NMR and GC analysis). Interestingly, electron-rich olefins gave relatively higher yields of products as compared to electron-deficient olefins. This may be ascribed to the benzylic radical, which abruptly increases its reactivity, thereby resulting in high yields of the aminobrominated product. Also aliphatic olefins underwent aminobromination smoothly to give 1,2-bromoamines in good yields. After the reaction was complete, solid titanium superoxide was recovered by simple filtration, which on subsequent reuse with styrene as substrate was found to catalyze the aminobromination process with moderate yield (58%). Notably, substrates like indene, cyclohexene, and cyclooctene gave the corresponding aminobrominated products with high *anti*-selectivity > 99:1 (Table 2, entries 10, 12, and 13).

Having established the aminobromination of simple olefins, we turned our attention to α,β-unsaturated carbonyl compounds **3a–c** as substrates and the results are presented in Table 3. For α,β-unsaturated esters or ketones, the reaction was found to be relatively slow and gave poor yields of the expected bromoaminated products **4a–c** (Table 3, entries 1 and 2). However, use of *p*-$TsNBr_2$ resulted in the formation of bromoamino ester **4c** in good yield.

A plausible mechanistic pathway is outlined in Figure 1 to explain the formation of *anti*-Markovnikov product. Firstly, *p*-toluenesulfonamide reacts with NBS to form *p*-TsNH–Br[3] followed by its interaction with titanium superoxide which facilitates the polarization of the NH–Br bond homolytically. Since the catalyst possesses a stable radical, interaction of which with *p*-Ts-NHBr probably generates *p*-$TsNH^{\cdot}$ radical, which in turn adds onto styrene regiospecifically at the homobenzylic position to form benzylic radical. The recombination of this radical with $Br^{\cdot}$ radical leads to *anti*-Markovnikov product. The radical pathway proposed here has been supported by the trapping experiment with TEMPO,[16] which failed to produce the corresponding haloamine. In the case of other titanium salts, the formation of Markovnikov product **2** can be reasoned on the basis of the formation of bromonium ion followed by its preferential opening at the benzylic position with *p*-toluenesulfonamide.

In conclusion, we have described a titanium superoxide-catalyzed regiospecific aminobromination of styrenic and other conjugated olefins to give exclusively *anti*-Markovnikov products in high yields using *p*-$TsNH_2$ and NBS as amine and bromine sources,

Table 3
Titanium superoxide-catalyzed regiospecific aminobromination of α,β-unsaturated carbonyl compounds[a]



3a-c **4a-c**

No	R	R¹	Amine source	Yield[b,c] (%) **4a–c**
a	H	OMe	*p*-$TsNH_2$	20
b	Cl	Ph	*p*-$TsNH_2$	21
c	Cl	Ph	*p*-$TsNBr_2$	68

Reaction conditions: [a]unsaturated ester (3 mmol), *p*-$TsNH_2$ (3.3 mmol), *N*-bromosuccinimide (3 mmol), titanium superoxide (10 wt %), CH_2Cl_2 (20 mL), 25 °C, 18 h.

[b] Products were characterized by mp, IR, ^1H and ^{13}C NMR, and elemental analysis.

[c] Isolated yield after chromatographic purification.

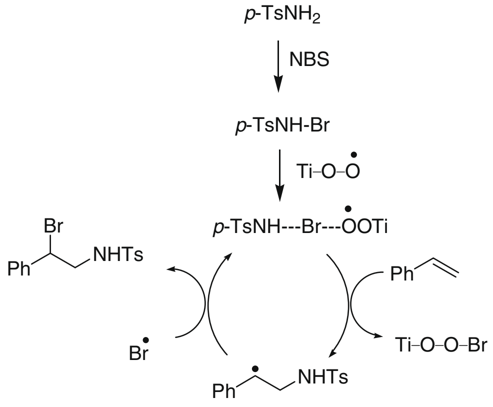


Figure 1. Titanium superoxide catalytic cycle for bromoamination process.

respectively under ambient conditions. The protocol makes use of stable and readily accessible titanium superoxide as solid catalyst for the aminobromination process.

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14. (a) Preparation of titanium superoxide:Aq 50% H_2O_2 (5.98 g, 0.175 mol) was added slowly to a solution of titanium isopropoxide (5.0 g, 0.0175 mol) in anhydrous MeOH (50 ml) over 40 min under N_2 with stirring at room temperature. The yellow precipitate formed was collected by filtration on a sintered funnel, washed with anhydrous methanol, and dried at room temperature. Yield: 3.94 g (98%).(b) Typical experimental procedure for aminobromination of styrene:To a stirred solution of styrene (0.312 g, 3.0 mmol), titanium superoxide (0.030 g, 10 wt %) and *p*-$TsNH_2$ (0.564 g, 3.3 mmol) in 25 mL of dry dichloromethane was added NBS (0.534 g, 3.0 mmol) slowly using a solid addition funnel. The reaction mixture was stirred further at 25 °C for 14 h. When TLC showed the completion of the reaction, the catalyst was filtered off and the filtrate was diluted with water, extracted with CH_2Cl_2 (20×3 mL), and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product, which was purified by column chromatography packed with silica gel using pet ether and EtOAc as eluents to afford the pure bromoaminated product.
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