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p-$MeOC_6H_4N_2^+BF_4^-/TiCl_3$: a novel initiator for halogen atom-transfer radical reactions in aqueous media

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ABSTRACT

With the combination of *p*-methoxybenzene-diazonium tetrafluoroborate with $TiCl_3$ as the initiator, a wide range of halogen atom-transfer radical addition or cyclization reactions could be efficiently implemented in aqueous solution at room temperature.

In the past three decades, we have witnessed significant progress in radical reactions toward organic synthesis.[1] Among various types of radical processes, halogen atom-transfer radical addition (ATRA) reactions, pioneered by Kharasch,[2] further developed by Curran and others,[3] have received considerable attention because of their atom-economic nature and high efficiency.[4] The choice of initiators is crucial to the successful implementation of ATRA transformations. Bis(tributyltin) has been widely used as the initiator for ATRA.[3] However, the high toxicity and difficult separation of the tin-containing residue limit its value in industrial application. Triethylborane, developed by Oshima and co-workers, is the other frequently used initiator, allowing the ATRA to be carried out under very mild conditions in various solvents including water.[5] However, it is highly air sensitive while the initiation requires oxygen whose amount is difficult to control. Other tin-free initiators, including peroxides such as dilauroyl peroxides,[6] water-soluble azo compounds,[7] copper,[8] chromium(II) acetate,[9] bimetallic Rh–Ru complexes,[10] and $Mn_2(CO)_{10}$,[11] are less commonly adopted due to either the harsh conditions required or the lack of generality. It is therefore highly desirable to develop novel tin-free initiators that are safe and widely applicable. We report here that *p*-$MeOC_6H_4N_2^+BF_4^-/TiCl_3$ serves as a powerful initiator, allowing a wide range of ATRA reactions to be performed in aqueous media under mild conditions.

Arenediazonium ions have long been used as the sources for aryl radicals.[12] Upon treatment with a reductant, arenediazonium salts undergo N_2 elimination to give the corresponding aryl radicals, which are able to participate in a number of further transformations, such as H-abstraction or addition to C=C bonds.[13] For example, Heinrich and co-workers nicely introduced the carbodiazenylation of olefins by the three-component condensation of arenediazonium salts, olefins, and alkyl iodides.[13c–f] However, in a few cases, when stoichiometric amounts of diazonium ions were used, the reactions produced primarily the iodine ATRA products between olefins and alkyl iodides.[13c] We were intrigued by this side reaction owing to our interest in ATRA reactions.[14] We wondered (1) if this diazonium salt–reductant combination could be developed into a catalytic system to initiate ATRA reactions and (2) if the initiator could have a wide generality for ATRA. Thus, we first chose *o*-$MeOC_6H_4N_2^+BF_4^-$ (**I-1**) as the aryl radical precursor, and $TiCl_3$ as the reductant to explore this possibility. Ethyl iodoacetate (**1**) and 1-octene (**2a**) were used as the model substrates. The results are summarized in Table 1.

Our initial trial on the addition of **1** to **2a** in CH_2Cl_2 or CH_3CN in the presence of 20 mol % of **I-1** and of 20 mol % of $TiCl_3$ was disappointing (Table 1, entries 1 and 2). However, when the solvent was switched to ethanol, we were delighted to find that the expected product **3a** was observed in 36% yield (Table 1, entry 3). The reaction also proceeded in water, albeit in a lower yield (Table 1, entry 4). These different solvent effects should be attributed to their different abilities to solvate both the organic and inorganic ($TiCl_3$) reagents. With this idea in mind, we tried the mixture of ethanol and water in different ratios. We were pleased to find that, with EtOH/H_2O (4:1, v:v) as the solvent, the yield of **3a** was increased to 76% (Table 1, entry 7). Lowering the amounts of **I-1** and $TiCl_3$ to 10 mol % resulted in only a slight decrease of the product yield (Table 1, entry 9).

We next screened the diazonium salts. Among the four diazonium salts tested (**I-1**–**I-4**), *p*-$MeOC_6H_4N_2^+BF_4^-$ (**I-2**) gave the best result. The ATRA proceeded smoothly at room temperature, and the substrate **1** was all consumed within 2 h. The reaction was clean, and the product **3a** was achieved in 90% isolated yield (Table 1, entry 10). Note that only a trace amount of **3a** could be detected without the presence of the diazonium salts (Table 1, entry 13). With regard to the reductant, $TiCl_3$ was proven to be much superior over other reductants (Table 1, entries 14–17).

With the optimized conditions in hand (Table 1, entry 10), we then examined the generality of this initiation system. As shown

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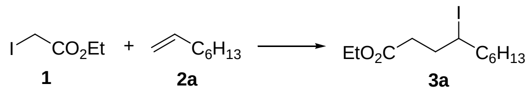
Table 1
Optimization of reaction conditions



$ArN_2^+BF_4^-$:

Ar = *o*-MeO-C_6H_4 (**I-1**), *p*-MeO-C_6H_4 (**I-2**), *p*-COMe-C_6H_4 (**I-3**), Ph (**I-4**)

Entry	Initiator[a] (mol %)	Solvent	Time (h)	Yield[b] (%)
1	**I-1** (20) + $TiCl_3$ (20)	CH_2Cl_2	4	Trace
2	**I-1** (20) + $TiCl_3$ (20)	CH_3CN	4	Trace
3	**I-1** (20) + $TiCl_3$ (20)	EtOH	4	36
4	**I-1** (20) + $TiCl_3$ (20)	H_2O	4	10
5	**I-1** (20) + $TiCl_3$ (20)	EtOH/H_2O(2:3)	4	14
6	**I-1** (20) + $TiCl_3$ (20)	EtOH/H_2O(3:2)	4	46
7	**I-1** (20) + $TiCl_3$ (20)	EtOH/H_2O(4:1)	2	76
8	**I-1** (20) + $TiCl_3$ (20)	EtOH/H_2O(9:1)	3	59
9	**I-1** (10) + $TiCl_3$ (10)	EtOH/H_2O(4:1)	3	64
10	**I-2** (10) + $TiCl_3$ (10)	EtOH/H_2O(4:1)	2	97(90)
11	**I-3** (10) + $TiCl_3$ (10)	EtOH/H_2O(4:1)	3	69(60)
12	**I-4** (10) + $TiCl_3$ (10)	EtOH/H_2O(4:1)	4	74(67)
13	$TiCl_3$ (10)	EtOH/H_2O(4:1)	2	Trace
14	**I-2** (10) + $SnCl_2$ (10)	EtOH/H_2O(4:1)	4	32
15	**I-2** (10) + CuCl (10)	EtOH/H_2O(4:1)	3	6
16	**I-2** (10) + HQ[c] (10)	EtOH/H_2O(4:1)	3	29
17	**I-2** (10) + $FeCl_2$ (10)	EtOH/H_2O(4:1)	4	7

[a] Conditions: **1** (0.5 mmol), **2a** (1.5 mmol), solvent (5 mL), **I**/$TiCl_3$, rt, N_2.
[b] ^1H NMR yield with 4-nitroacetophenone as the internal standard and the isolated yield in parentheses.
[c] HQ: hydroquinone.

in Table 2, the reactions of **1** with various mono-substituted alkenes afforded the expected products in satisfactory yields. A number of functional groups were well tolerated. The reaction of **1** with 1,6-diene **4** via tandem radical processes was also nicely accomplished to give the cyclized product **3j** in 90% isolated yield. These results have clearly demonstrated that **I-2**/$TiCl_3$ is equal to $(Bu_3Sn)_2$ or Et_3B in initiating the above-mentioned ATRA reactions.

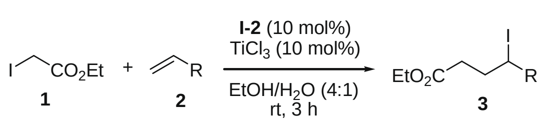
Next, we performed the reactions of various alkyl halides **5** with 1-octene (Table 3). Under the initiation of **I-2**/$TiCl_3$ indicated above, substituted iodoesters **5a** and **5b** smoothly underwent ATRA to 1-octene. Iodoacetonitrile **5c** and even iodoacetic acid **5d** could also be used as the reactants. The initiation system was again suitable for the addition reactions of sulfone **5e** and perfluoroalkyl iodide **5g**.[15] The ATRA to alkynes could also be nicely initiated, as evidenced by the reaction of **5b** with phenylacetylene.[14f] Moreover, bromine ATRA of active bromides, such as **5g** and **5h**, was also successful under the optimized conditions. In all the tested cases, the desired products were achieved in high to excellent yields, illustrating the wide scope of application of **I-2**/$TiCl_3$.

The above investigation dealt with intermolecular ATRA. As an extension, iodine atom-transfer radical cyclization (ATRC) reactions, which provide a synthetically useful entry to heterocycles such as lactones and lactams, could also be conducted with the initiation of **I-2**/$TiCl_3$. As shown in Table 4, a number of substituted *N*-allyliodoacetamides **8** underwent efficient ATRC to give the 5-*exo*-cyclization products **9a**–**f**. The amount of the initiator could be reduced to 5 mol %, when the substrates were more prone to cyclization (Table 4, entries 1 and 5). The 8-*endo*-cyclization reactions[14a] of esters **10** also proceeded under the optimized conditions without any difficulty.

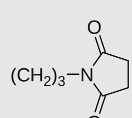
The above results clearly demonstrate the efficiency of **I-2**/$TiCl_3$ in initiating the ATRA and ATRC reactions. With the initiation of **I-2**/$TiCl_3$, the reactions can be performed in the dark under nitrogen atmosphere, while sunlamp irradiation is required for bis(tributyltin) and oxygen is required for triethylborane. Both **I-2** and $TiCl_3$ are readily available and are fairly stable. The speed of initiation can be easily adjusted by the appropriate addition of $TiCl_3$. In addition, aqueous ethanol is used as the solvent, making the **I-2**/$TiCl_3$ protocol of more practical value.

The active species in the **I-2**/$TiCl_3$-chain process are the aryl radicals. Initiation relies on the fact that the aryl radical is generated selectively, and it abstracts an iodine atom from the substrate rather than adding to the C=C bond. This is because the rate constant for the iodine atom abstraction of a phenyl radical from an alkyl iodide is close to the diffusion-controlled limit

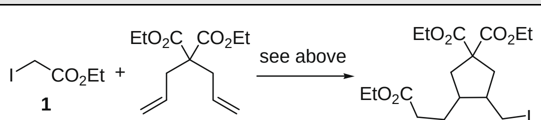
Table 2
I-2/$TiCl_3$-initiated ATRA reactions of **1**



R =
n-C_4H_9 (**3b**, 88%)
n-$C_{10}H_{21}$ (**3c**, 74%)
$(CH_2)_4OH$ (**3d**, 80%)
$(CH_2)_3Br$ (**3e**, 88%)
CH_2OAc (**3f**, 76%)
$(CH_2)_2COCH_3$ (**3g**, 77%)
$(CH_2)_2CO_2Et$ (**3h**, 77%)

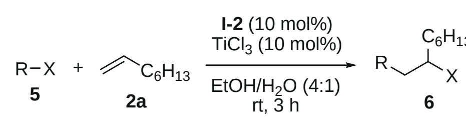


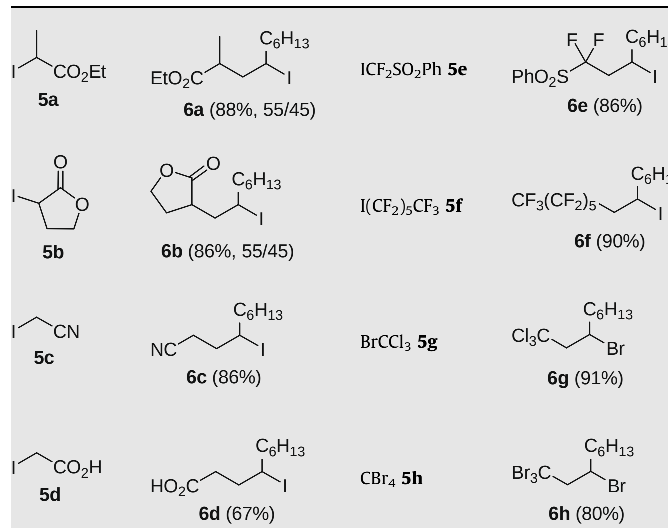
(**3i**, 75%)

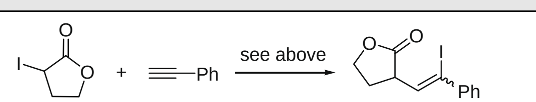


3j (90%)
trans/*cis* = 10:1

Table 3
I-2/$TiCl_3$-initiated ATRA to 1-octene and phenylacetylene

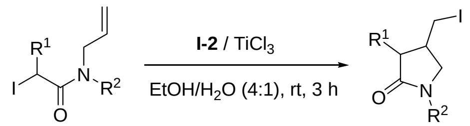






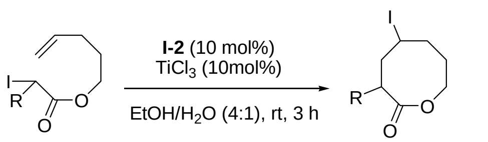
7a (81%, *E*/*Z* = 55/45)

Table 4
I-2/$TiCl_3$-initiated iodine atom-transfer radical cyclization



8 **9**

Entry	R^1	R^2	**I-2**/$TiCl_3$ (mol %)	Product (yield)[a]
1	H	Allyl	5	**9a** (99%)
2	H	Ts	10	**9b** (96%)
3	H	Ms	10	**9c** (86%)
4	H	Me	20	**9d** (40%)
5	Me	Allyl	5	**9e** (96%)[b]
6	Me	Ts	10	**9f** (91%)[c]



10

R = H **11a** (88%)[a]
Me **11b** (90%)[a, d]

[a] Isolated yield based on **8** or **10**.
[b] trans/cis = 78:22.
[c] trans/cis = 84:16.
[d] trans/cis = 17:83.

(>10^9 M^{-1} s^{-1}),[16] which is about 100 times faster than the rate of phenyl radical addition to a monosubstituted alkene (~3×10^7 M^{-1} s^{-1}).[17] More importantly, the rate constant for the iodine atom-transfer from the substrate **1a** to the adduct radical is around 2.7×10^7 M^{-1} s^{-1},[3a,18] at least one order of magnitude higher than that for the trapping of the adduct radical by the diazonium ion **I-2** (estimated to be ~1×10^6 M^{-1} s^{-1}).[19] This allows the iodine atom-transfer chain process to proceed smoothly without the intervention of a termination event. On the other hand, the bromine ATRA of bromoacetates to alkenes is unlikely to happen because bromine atom-transfer to the adduct radical is much slower.[3a,18] This sets one limitation for the application of **I-2**/$TiCl_3$.

In summary, we have demonstrated that *p*-methoxybenzenediazonium tetrafluoroborate in combination with $TiCl_3$ successfully initiates various modes of iodine ATRA in aqueous media under mild conditions, making it a useful complement to the existing initiation systems.

Experimental

Typical procedure for the halogen atom-transfer radical reactions

To the solution of ethyl iodoacetate (**1**, 107 mg, 0.5 mmol) and 1-octene (**2a**, 168 mg, 1.5 mmol) in EtOH (4 mL) and H_2O (1 mL) was added *p*-methoxybenzenediazonium tetrafluoroborate (**I-2**, 7.5 mg, 0.034 mmol) at room temperature under nitrogen atmosphere. Aqueous titanium(III) chloride (30% wt % solution in 2 N hydrochloric acid, 13 μL, 0.034 mmol) was added dropwise under vigorous stirring. After 1 h, additional portions of **I-2** (3.5 mg, 0.016 mmol) and aqueous titanium(III) chloride (7 μL, 0.016 mmol) were added successively. The reaction was monitored by TLC. After the iodoacetate **1** disappeared (1 h), the resulting mixture was extracted with ethyl ether (3 × 20 mL). The combined organic layer was washed with brine, and dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (50:1, v/v) as the eluent to give the product **3a** as a colorless oil (146 mg, 90%).[6]

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