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Oxidative α-Acetoxylation of a β-Oxime Ester with (Diacetoxyiodo)benzene Catalyzed by Sc(III) Salts: A New Approach to Docetaxel Side Chain

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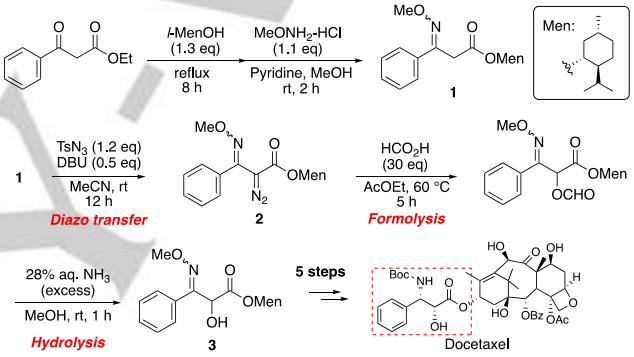
Abstract: Hypervalent iodine(III) compounds emerged as reagents of choice for α-oxidation of various ketones under mild reaction conditions. We report herein a simple method for α-hydroxylation of a β-oxime ester, which involves an oxidative α-acetoxylation using $PhI(OAc)_2$ with a catalytic amount of $Sc(OTf)_3$ or Sc_2O_3-TMSOTf, followed by careful hydrolysis. Scandium(III) salt serves as an excellent reusable catalyst in this system.

Introduction

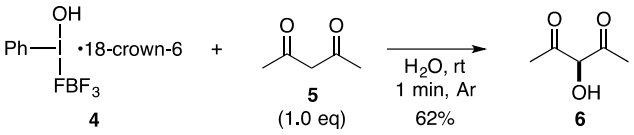
Recently, our group reported an efficient large scale synthesis of docetaxel, a microtubule polymerization inhibitor–type *anti*–cancer agent from bacchatin III,[1] in which a short–path synthesis of C-13 side chain was achieved.[2] In this synthesis, the C–H hydroxylation of β-oxime ester **1** was accomplished through a diazo transfer[3]–formolysis–hydrolysis three-step sequence (Scheme 1). Although, this sequence was highly reliable (all steps were carried out at gram to kg scale, inexpensive/readily available reagents were required, yields of each step were >95%), we were not satisfied with it and further improvement in safety was explored. Thus, the route needed potentially explosive *p*-toluenesulfonyl azide[4] in a diazo transfer step. In addition, potential toxicity and explosive character of the resulting diazo ester **2** prepared in this step cannot be ruled out.[5] It appeared to us that if the multi-step hydroxylation sequence was successfully altered by a safer, chemo-/regioselective, and inexpensive method, the synthesis of docetaxel should be facilitated.

A straightforward α-hydroxylation of carbonyl compound is still a challenging topic in modern organic synthesis.[6] Several methods have been developed for this purpose. For example, oxidation of enol and/or its equivalent with suitable oxidants, such as *m*-CPBA,[7] benzoyl peroxide,[8] oxone,[9] dimethyldioxirane,[10] and I_2/DMSO combinations,[11] *etc.* are now available. In addition, hypervalent λ^3- and λ^5-iodanes function as especially chemo-/regioselective hydroxylating agents toward a wide range of ketones under mild conditions.[12] We report herein an efficient method for α-oxidation of β-oxime ester **1** mediated by hypervalent (diacetoxyiodo)benzene (DIB) (**8**) followed by hydrolysis, leading to the formation of hydroxylated product **3**. In this method, scandium(III) salts were recovered and reused several times without reducing catalyst efficiency. A highly selective 2,2,2-trifluoroethoxide-catalyzed hydrolysis of acetate **9** was also developed.



Scheme 1. Convenient synthesis of α-hydroxy-β-oxime ester **3**.

We have previously reported that hydroxy(phenyl)(tetra-fluoroborato)-λ^3-iodane•18-crown-6 complex **4** served as a versatile and powerful oxidant toward a wide range of functionalities, especially in water.[13] Indeed, this complex **4** readily oxidizes acetylacetone **5** to the corresponding α-hydroxyketone **6** in water (Scheme 2).



Scheme 2. Hydroxylation of β-diketone **5** with **4**.

However, several attempts for direct hydroxylation of β-oxime ester **1** using **4** were found to be unsuccessful, probably because of low tendency of enolization of **1** under neutral to weakly acidic conditions. In fact, no deuterium incorporation was observed when **1** was dissolved either in CD_3OD or CD_3CO_2D at ambient temperature.[14] However, strong acids such as sulfuric acid or metal hydroxide, both of which facilitating the enolization of **1**, were found to be unsuitable since they readily hydrolyzed **1** into corresponding β-keto ester (deamination) and/or carboxylic

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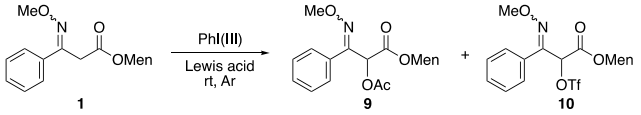
acid (ester hydrolysis). In this context, we surveyed a combination of hypervalent λ^3-iodane and suitable Lewis acid for selective oxidation of **1** (Table 1).

Table 1. Oxidation of β-oxime ester **1** with λ^3-iodanes.



1 **9** **10**

entry	I(III) (eq)	acid (eq)	conditions	yield (%)[a]	
				9	**10**
1	**7** (1.5)	48% HBF_4 (4.5)	MeCN-H_2O (9:1), 1 d	–	–
2	**8** (1.2)	BF_3-Et_2O (1.2)	AcOH, 1 d	90 (78)	–
3	PhI (0.1)[b]	BF_3-Et_2O (1.2)	AcOH, 1 d	70	
4	**8** (1.2)	$MgSO_4$ (1.2)	AcOH, 2 d	20	–
5	**8** (1.2)	$Sc(OTf)_3$ (1.2)	AcOH, 2 h	93	–
6	**8** (1.2)	$Sc(OTf)_3$ (0.05)	AcOH, 6 d	48	22
7	**8** (1.2)	$Yb(OTf)_3$ (0.05)	AcOH, 5 d	37	17
8	**8** (1.2)	$Hf(OTf)_4$ (0.05)	AcOH, 5 d	31	11
9[c]	**8** (1.2)	$Sc(OTf)_3$ (0.05)	AcOH, 13 h	70	15

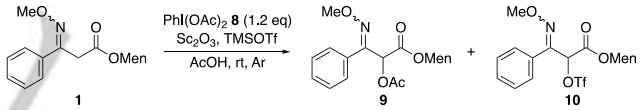
[a] ^{1}H NMR yields. Number in parentheses is isolated yield. [b] *m*-CPBA (1.2 was added. [c] TMSOTf (1.0 eq) was used as co-catalyst.

Initial attempts for iodosylbenzene (**7**)–mediated direct hydroxylation of **1** in the presence of acids were unsuccessful, and resulted in the formation of a complex mixture (Table 1, entry 1). In contrast, Lewis acid-mediated oxidative acetoxylation in acetic acid proceeded smoothly. Thus, exposure of **1** with commercially available **8** and BF_3-Et_2O in acetic acid afforded α-acetoxy-β-oxime ester **9** in high yield (entry 2). A combination of iodobenzene (0.1 eq) and *m*-CPBA (1.2 eq), instead of **8**, also worked well but a slightly decrease in yield was observed (entry 3).[15] Using a weaker Lewis acid, such as $MgSO_4$ provided much lower yield (20%) (entry 4). Interestingly, Group III Lewis acid, $Sc(OTf)_3$, greatly improved the acetoxylation efficiency (entry 5). Since Sc(III) cation still remains "active" after the formation of **9**, the catalyst loading could be reduced to 5 mol%, although reaction time was extended to 6 days (entry 6). In these conditions, the incorporation of triflate ion into the product (formation of **10**) was observed, which might reduce the Lewis acidity of Sc(III) cation. Other Group III and IV metal triflates, such as $Yb(OTf)_3$ and $Hf(OTf)_4$, did not improve the yields of products (entries 7 and 8), (Figure S1). Further improvement in the catalyst efficiency was observed when TMSOTf was added as a co-catalyst since the reaction time could be shortened to *ca.* 1/10 (entry 9).

Although $Sc(OTf)_3$ was found to be a highly effective catalyst, unfortunately it is expensive (*ca.* 2 X 10^4 $/mol).[16] Therefore, we further modified the acetoxylation conditions for practical use. $Sc(OTf)_3$ is generally prepared from Sc_2O_3 and TfOH.[17] Encouraged by this fact, we attempted *in situ* generation of $Sc(OTf)_3$ from much inexpensive Sc_2O_3 and TMSOTf (Table 2) (Figure S2).[18] Exposure of **1** with **8** (1.2 eq), Sc_2O_3 (0.5 mol%), and TMSOTf in AcOH at room temperature resulted in the formation of a mixture of acetate **9** (61%) and triflate **10** (34%) (entry 1), being comparable to the result, in which 5 mol% of $Sc(OTf)_3$ was used (entry 2). The oxidation of **1** proceeded without Sc_2O_3 but the rate of the reaction significantly slowed down (entry 3). Further reduction of the amount of co-catalyst TMSOTf to 0.4 eq did not change the yields of products, since a mixture of **9** (56%) and **10** (39%) was obtained with an acceptable rate (entry 4). It is noted that the both α-acetoxylation and α-triflyloxylation reactions did not show distinct diastereoselectivity under the optimized conditions: thus, a 1:1 mixture of diastereomers of **9** and **10** were obtained in every cases. The optimized reaction conditions found to be quite robust for large-scale application and could be scaled-up to 10 mmol (**1**: 3.3 g) without reduction in yields, even in the air (entries 5 and 6).

Remarkably, the recovered catalyst from optimized reaction conditions was reusable without purification (Scheme 3). Thus, after the completion of the 1st run, excess hexane was added to the reaction mixture in order to extract the desired products, and precipitate Sc(III) salts at the same time. The resulting precipitate was then used for further reactions (2nd and 3rd runs: entries 7 and 8). In these runs, the addition of Sc_2O_3 was not required and only 0.4 eq of TMSOTf was sufficient to maintain high yield of products.[19]

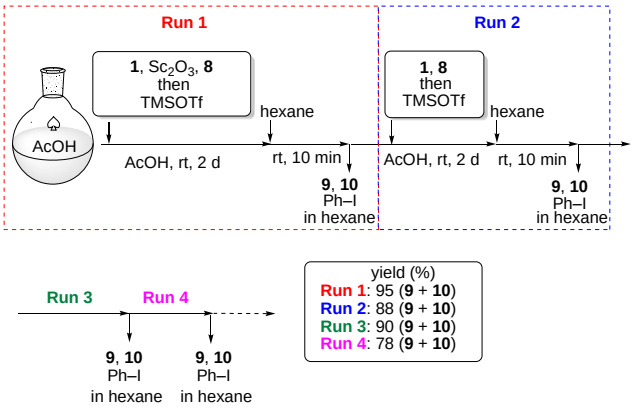
Table 2. Sc_2O_3–TMSOTf catalyzed oxidative acetoxylation of **1**.



1 **9** **10**

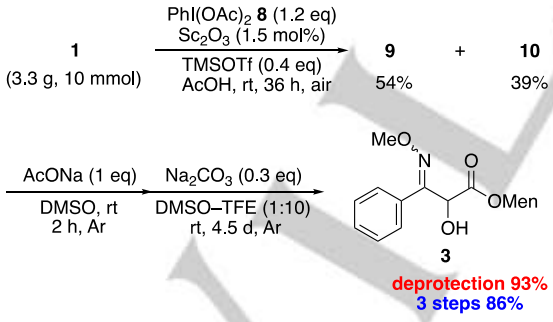
entry	Sc_2O_3 (mol%)	TMSOTf (eq)	Time (h)	yield (%)[a]	
				9	**10**
1	0.5	1.0	11	61	34
2	5[b]	1.0	13	70	30
3	0	1.0	21	58	31
4[c]	1.5	0.4	40	56	39
5[d]	1.5	0.4	40	50	43
6[d,e]	1.5	0.4	48	54	39
7	–[f]	0.4	48	54	34
8	–[f]	0.4	48	52	38

[a] ^{1}H NMR yields. [b] $Sc(OTf)_3$ was used instead of Sc_2O_3. [c] **9** (82%) was isolated after quench with NaOAc. [d] 10 mmol scale. [e] Under air. [f] Solid residue after oxidation was used, instead of Sc_2O_3 (see Scheme 3).



Scheme 3. Reuse of catalyst for oxidation of **1**.

With the optimized conditions in hand, we next surveyed the method for hydrolysis of a mixture of **9** and **10**. After extensive studies on the reaction conditions, a general method for successive acetolysis-hydrolysis was established (Scheme 4). This sequential method was successfully applied to a mixture obtained by oxidation of **1** (same conditions as Table 2, entry 5). Exposure of the mixture with sodium acetate (1 eq) in DMSO resulted in the smooth S_N2 reaction at α-carbon of **10** to afford **9**, which was subjected to the second step directly in one pot. The acyl substitution proceeded with catalytic amount of nucleophile, $CF_3CH_2O^-$. Thus, addition of 2,2,2-trifluoroethanol and Na_2CO_3 (0.3 eq) to the reaction mixture resulted in the clean deprotection of acetyl group to give **3** in high yield (2 steps, 93% yield). Ammonolysis of acetate **9** by aq. NH_3 (28–30%) in methanol also proceeded cleanly (23 h, 97% yield).[2] In contrast, stronger nucheophiles/bases, such as NaOH, LiOH, *i*-PrONa, K_2CO_3/MeOH, and Brønsted acids, did not work well since the formation of many byproducts, such as oxime-/ester hydrolyzed products (*l*-menthol, NH_2OMe, *etc.*), was observed.



Scheme 4. Practical successive acetolysis-hydrolysis of a mixture of **9** and **10** yielding **3**.

One diastereomer exhibiting the *S*-configuration at the hydroxy-α-carbon atom (*S*)-**3** was unambiguously confirmed by X-ray structure analysis (Figure 1).[20,21] In the crystal, (*S*)-**3** adopted (*Z*)-oxime form with *S*-configuration at hydroxy-α-carbon atom.

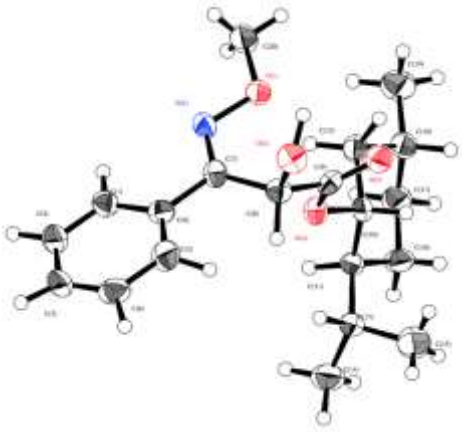
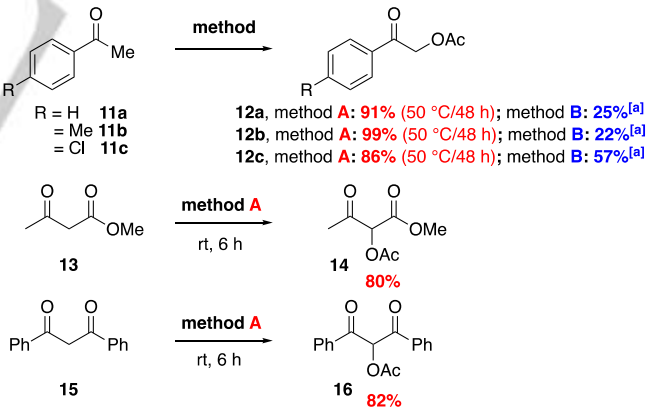


Figure 1. ORTEP drawing of (*S*)-**3**. Thermal ellipsoids drawn at the 50% probability level.

Finally, it is interesting to note that our method can be applied to the α-acetoxylation of acetophenones **11a–c** under mild reaction conditions (Scheme 5). Mizukami and co-workers reported that electron-rich **11a** and **11b** were much less reactive substrates for oxidative acetoxylation.[22] In their conditions, only low yields (<25%) of the corresponding acetoxylated products **12a** and **12b** were obtained even in the presence of an excess amount of sulfuric acid. In contrast, our conditions afforded **12a–c** in high yields. More readily enolizable β-Keto ester **13**, and β-diketone **15** underwent acetoxylation at ambient temperature in high yields under our reaction conditions. In these reactions, no incorporation of triflate, instead of acetate was observed.



Scheme 5. Iodobenzene-catalyzed oxidative acetoxylation of **11**. Method A: **8** (1.2 eq)/$Sc(OTf)_3$ (5 mol%)/AcOH. Method B: **8** (0.8 eq)/H_2SO_4 (1.5 eq)/AcOH-Ac_2O (9:1)/30 °C/6 h. [a] Data taken from reference [22].

Conclusions

In conclusion, we have developed a straightforward route for hydroxylation of β-oxime ester **1**, which constitutes an essential step in short-path synthesis of docetaxel. The DIB–mediated C–H oxidation was found to be effectively catalyzed by a combination of catalytic amount of Sc_2O_3 and TMSOTf. This is,

to the best of our knowledge, the first example of Sc(III)-catalyzed oxidative transformations using DIB **8**. The present method potentially serves as α-hydroxylation of a wide range of carbonyl compounds with acid/base sensitive functionalities. Further studies to optimization of iodoarene-catalyzed acetoxylation are in progress in our laboratory.

Experimental Section

General procedure for oxidative acetoxylation of 1. A typical example (Table 2, entry 4). To a stirred solution of **1** (33 mg, 0.1 mmol), Sc_2O_3 (0.2 mg, 0.0015 mmol), and **8** (38.7 mg, 0.12 mmol) in acetic acid (1.0 mL) was slowly added TMSOTf (7.2 μL, 0.04 mmol) at room temperature under argon and the mixture was stirred for 40 h. The reaction mixture was then added excess hexane and vigorously stirred at room temperature for 10 min. After separation of supernatant from the mixture, the residue was extracted with hexane (1 mL) three times. The residue can be used for further reaction without any treatment. A combined organic layer was concentrated under an aspiratory vacuum to give an oil. ^{1}H NMR analysis (internal standard: *tert*-butyl methyl ether) showed the formation of acetate **9** and triflate **10**, in 56% and 39%, respectively. Because of the labile nature, **10** could not be isolated as a pure form. **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ; 0.55 (d, *J* = 6.9 Hz, 3H for one isomer), 0.68 (d, *J* = 6.9 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H), 0.62–0.71 (m, 1H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.70–0.85 (m, 1H), 0.91–1.1 (m, 1H), 1.21–1.49 (m, 2H), 1.50–1.75 (m, 3H), 1.78–1.88 (m, 1H), 1.98–2.05 (m, 1H), 4.09 (s, 3H for one isomer), 4.10 (s, 3H for another isomer), 4.65–4.80 (m, 3H), 6.66 (s, 3H for one isomer), 6.68 (s, 3H for another isomer), 7.30–7.50 (m, 3H), 7.60–7.67 (m, 2H). ESI-MS (positive) *m/z*: 502 [(M+Na)$^+$]. For isolation of **9**, the residue was added sodium acetate (8.2 mg, 0.1 mmol) in DMSO (1 mL) and stirred at room temperature for 3 h. The mixture was poured into water and extracted with CH_2Cl_2 four times. Combined organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under an aspiratory vacuum to give an oil, which was purified by preparative TLC (hexane/ethyl acetate = 9:1, R_f = 0.4), to give **9** (29.5 mg, 82%) as a colorless oil. Acetate **9** was obtained as a mixture of stereoisomers (*ca*. 1:1 mixture of (*S*)- and (*R*)-isomers at the *α*-position (denoted as (*S*)-**9** and (*R*)-**9**) and oxime *E*/*Z*–mixtures): IR (neat) ν cm^{-1}; 2955, 2869, 1747, 1616, 1445, 1370, 1210, 1046, 700. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 0.44 (d, *J* = 6.9 Hz, 1H for (*R*)-**9**), 0.62–0.71 (m, 1H), 0.68 (d, *J* = 6.9 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.70–0.85 (m, 1H), 0.87 (d, *J* = 7.0 Hz, 3H for (*R*)-**9**), 0.88 (d, *J* = 6.5 Hz, 3H for (*S*)-**9**), 0.91–1.10 (m, 1H), 1.21–1.49 (m, 2H), 1.54–1.67 (m, 3H), 1.81–1.89 (m, 1H for (*R*)-**9**), 1.97–2.03 (m, 1H for (*S*)-**9**), 2.15 (s, 3H for (*S*)-**9**), 2.17 (s, 3H for (*R*)-**9**), 4.04 (s, 3H), 4.65 (td, *J* = 10.9, 4.5 Hz, 1H for (*R*)-**9**), 4.67 (td, *J* = 10.9, 4.5 Hz, 1H for (*S*)-**9**), 6.74 (s, 1H), 7.32–7.40 (m, 3H), 7.60–7.64 (m, 2H for (*S*)-**9**), 7.65–7.69 (m, 2H for (*R*)-**9**). ^{13}C NMR (125 MHz, $CDCl_3$) δ; 20.15, 20.18, 21.21, 21.4, 22.2, 22.4, 23.5, 24.5, 24.6, 25.5, 25.6, 30.7, 31.8, 34.0, 35.0, 46.2, 47.2, 49.6, 62.07, 62.14, 63.2, 63.3, 64.7(2C), 65.86, 65.93, 126.3, 126.5, 126.7, 127.5, 127.7, 127.8, 127.96, 128.0, 128.84, 128.9, 129.1, 130.1, 130.2, 133.0, 133.1, 166.7, 166.9, 169.5. MS *m/z* (relative intensity): 207 (13%, [*M*-(mentylCO$_2$)$^+$]), 165 (11), 138 (8), 134 (27), 103 (40), 83 (100), 77 (13). HRMS (ESI, positive) *m/z* calcd for $C_{22}H_{31}NNaO_5$ [(M+Na)$^+$]: 412.2100; found 412.2091.

Acknowledgements ((optional))

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Keywords: Hypervalent • Iodine • Acetoxylation • Docetaxel • Catalyst reuse

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[18] Sc_2O_3 (4 X 10^3 $/mol, Aldrich), TMSOTf (3 X 10^2 $/mol, TCI America).
[19] Catalyst maintained high activity even after five runs in dichloromethane (Scheme S2).
[20] Slow recrystallization of deprotected product from hexane selectively afforded pure (*S*)-**3** with *S*-configuration at hydroxy-α-carbon atom. See also reference [2].
[21] X-ray data for **3**: $C_{20}H_{29}NO_4$, *M* = 389.49, T = 173 K, orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 9.1946(5) Å, *b* = 12.0882(8) Å, *c* = 17.1926(10) Å, *V* = 1910.9(2) Å^3, *Z* = 4, D_c = 1.208 g cm^{-3}, μ(Mo K$_\alpha$) = 14.819 cm^{-1}. 4363 reflections were collected; 2484 were unique. R = 0.0753, wR_2 = 0.2112. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-1558744.

[22] F. Mizukami, M. Ando, T. Tanaka, J. Imamura, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 335–336.

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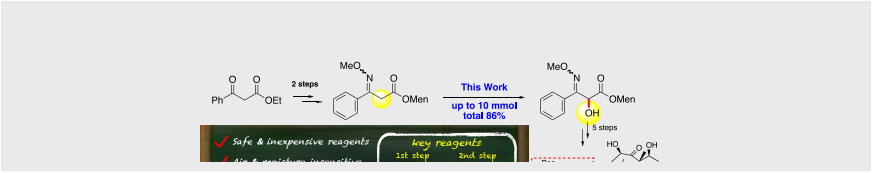

A simple method for α-hydroxylation of a β-oxime ester has been developed, which involves an oxidative α-acetoxylation using $PhI(OAc)_2$ with a catalytic amount of $Sc(OTf)_3$ or Sc_2O_3-TMSOTf, followed by careful hydrolysis. Sc(III) salt found to acts as an excellent reusable catalyst in this system.

*Oxidative acetoxylation

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