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NHC-Catalyzed One-Pot Oxidation and Oxidative Esterification of Allylic Alcohols Using TEMPO: the Effect of Alcohol Additives

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Ye-Won Kang,[a] Hye-Young Jang[a,b]*

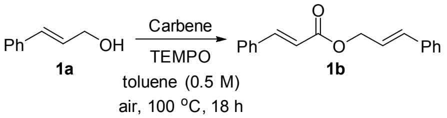
Combination of *N*-heterocyclic carbene (NHC) catalysts and 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was proposed for the synthesis of allylic esters from allylic alcohols. The yield of one-pot conversion of allylic alcohols to esters increased when hexafluoroisopropanol (HFIP) was used. The effect of HFIP in this tandem reaction was investigated by monitoring the reaction using gas chromatographic analysis. Control experiments using oxoammonium showed that the oxidative esterification occurred via a single-electron transfer mechanism.

Powerful and selective radicals such as 2,2,6,6-tetramethylpiperidine-*N*-oxy (TEMPO) and related nitroxides have been used in diverse oxidation reactions.[1-3] For example, the oxidation of alcohols, oxidative bond-forming reactions, and rearrangement reactions occurs by nitroxide radicals. Recently, our research group published *N*-heterocyclic carbene (NHC)-catalyzed oxidative esterification, thioesterification, and amidation of aldehydes using TEMPO, inspired by Studer's carbene-catalyzed TEMPO-ester formation.[4]

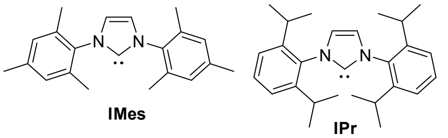
In the previous publication, we reported the one-pot conversion of allylic alcohols to esters with modest yields in the presence of carbene catalysts and 3 equiv of TEMPO.[4b] As an extension of such NHC-catalyzed TEMPO-mediated oxidative reactions, we present herein a one-pot reaction of the oxidation of allylic alcohols and subsequent esterification of aldehydes in the presence of reduced amounts of carbene catalysts and TEMPO.[4b,4c] TEMPO radicals were recycled in the absence of chemical oxidants other than air. The improved results including the higher yields with 1 equiv and less than 1 equiv of TEMPO were explained by gas chromatographic (GC) analysis and control experiments. In addition, although most of the TEMPO-mediated oxidation reactions are known to proceed via two-electron oxidation by oxoammonium,[3] we present that our NHC-catalyzed oxidative reactions using TEMPO undergo single-electron transfer (SET) oxidation.[4-6] Although there are abundant examples of transition-metal-catalyzed oxidation of alcohols to esters, a metal-free carbene-catalyzed one-pot oxidation of alcohols to esters has not been actively reported.[4b,7,8] Therefore, our metal-free TEMPO-mediated conversion of allylic alcohols to esters provides useful synthetic and mechanistic information for further development of TEMPO-mediated oxidative reactions.

The optimization results of one-pot oxidation/oxidative esterification of cinnamyl alcohol **1a** are listed in Table 1. We have previously reported one-pot oxidation/oxidative esterification of allylic alcohols in the presence of 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene (IMes) and TEMPO (entries 1 and 2).[4b] In the absence of alcohol additives, **1a** was converted to **1b** in 45% yield by using IMes (10 mol%) and TEMPO (2 equiv). The yield increased to 59% upon adding 0.2 equiv of ethanol. By changing the alcohol to HFIP, in this study, the yield was increased to 84% (entry 3). Other halogenated ethanol derivatives (CCl_3CH_2OH and CF_3CH_2OH) showed results similar to those obtained using ethanol (entries 4 and 5). The addition of phenol enhanced the yield of **1b**, which was yet lower than that of the reaction with HFIP (entry 6). The reaction with a more acidic phenol derivative, pentafluorophenol, provided **1b** in a lower yield (entry 7). A different carbene catalyst, 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), was tested to obtain **1b** in 69% yield (entry 8). With lower IMes loadings (5 mol%), the yield of **1b** slightly decreased to 78% (entry 9). However, by varying the amount of TEMPO (1 equiv, 0.75 equiv, and 0.5 equiv), it was found that the yield was retained to above 86% upon the addition of 1 equiv and 0.75 equiv of TEMPO but not for 0.5 equiv (entries 10-12). It was also found that in the absence of HFIP the yield was decreased to 12% (entry 13). When HFIP was used as a solvent, the product was not formed. Thus, 0.2 equiv of HFIP was added to the reaction mixture to improve the yield of **1b**.

Table 1. Optimization of one-pot oxidation/oxidative esterification

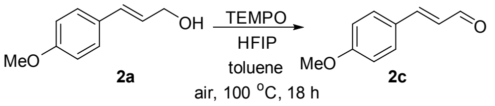


Entry	Catalyst	TEMPO	Additive (equiv)	Yield
1	**IMes** (10 mol%)	2 equiv	--	45%
2	**IMes** (10 mol%)	2 equiv	EtOH (0.2)	59%
3	**IMes** (10 mol%)	2 equiv	HFIP(0.2)	84%
4	**IMes** (10 mol%)	2 equiv	CCl_3CH_2OH (0.2)	58%
5	**IMes** (10 mol%)	2 equiv	CF_3CH_2OH (0.2)	54%
6	**IMes** (10 mol%)	2 equiv	PhOH (0.2)	70%
7	**IMes** (10 mol%)	2 equiv	F_5-PhOH (0.2)	62%
8	**IPr** (10 mol%)	2 equiv	HFIP(0.2)	69%
9	**IMes** (5 mol%)	2 equiv	HFIP(0.2)	78%
10	**IMes** (5 mol%)	1 equiv	HFIP(0.2)	89%
11	**IMes** (5 mol%)	0.75 equiv	HFIP(0.2)	86%
12	**IMes** (5 mol%)	0.5 equiv	HFIP(0.2)	59%
13	**IMes** (5 mol%)	1 equiv	--	12%



In the reaction shown in Table 1, **1a** underwent two-step oxidation, prior to the reaction with another equivalent of **1a**, which acted as an alcohol in the esterification reaction. Theoretically, 2 equiv of TEMPO should be consumed because half of the amount of **1a** underwent alcohol oxidation followed by oxidative esterification of the aldehydes, which required two-electrons in each step. As shown in Table 1, less than 1 equiv of TEMPO appears to be sufficient for the two oxidation processes in the presence of HFIP. To determine the role of HFIP, alcohol oxidation and oxidative esterification were analyzed separately. First, alcohol oxidation was conducted using *p*-OMe-substituted cinnamyl alcohol **2a** in the absence of carbene catalysts (Table 2). Without HFIP, the reaction using 1 equiv of TEMPO afforded **2c** in 66% yield (entry 1). By adding 0.2 equiv of HFIP and 1 equiv of TEMPO, the yield was enhanced to 78% (entry 2). Keeping the amount of HFIP constant and reducing the amount of TEMPO to 0.5 equiv resulted in 34% yield (entry 3). The oxidation of **2a** was slightly improved by HFIP.

Table 2. Oxidation of allylic alcohol **2a**



Entry	TEMPO	HFIP	Yield
1	1 equiv	--	66%
2	1 equiv	0.2 equiv	78%
3	0.5 equiv	0.2 equiv	34%

Next, the effect of HFIP in oxidative esterification was analyzed (Table 3). Under the specified reaction conditions, benzyl alcohol was not oxidized by TEMPO to yield benzaldehyde, implying that in this reaction TEMPO was used only for the oxidative esterification of **1c**. In the absence of HFIP, oxidative esterification product **1d** was formed in 37% yield (entry 1). Upon the addition of HFIP, the yield of 1d increased to 66% (entry 2). Even with only 0.5 equiv of TEMPO, the yield of **1d** was 41%, which was higher than the result of entry 1 (entry 3). A comparison of the results of Tables 2 and 3 showed that the effect of HFIP is probably more critical in the oxidative esterification than in the oxidation of alcohols.

Table 3. . NHC-catalyzed oxidative esterification of aldehyde **1c**

The tandem oxidation/oxidative esterification reactions of **1a** both with and without HFIP were also monitored for 10 h by GC analysis (Figure 1). In the presence of HFIP, alcohol **1a** was converted to ester **1b** (76% conversion at 10 h); Neither aldehyde **1c** nor HFIP-ester[9] was observed during the analysis (Figure 1a). The amount of TEMPO reduced rapidly at the initial stage (2 h) and then remained almost constant for the remainder of analysis. In the absence of HFIP, the amount of **1b** was not greatly increased after 2 h (15% conversion at 10 h). Instead, the amount of cinnamaldehyde was increased. Based on the GC monitoring results, HFIP is assumed to promote the rapid conversion of aldehyde **1c** to ester **1b**, which is consistent with the results of Table 3. Initially, we speculated that the addition of HFIP helped TEMPO recycling, but the concentration of TEMPO was similar in both reactions with and without HFIP.

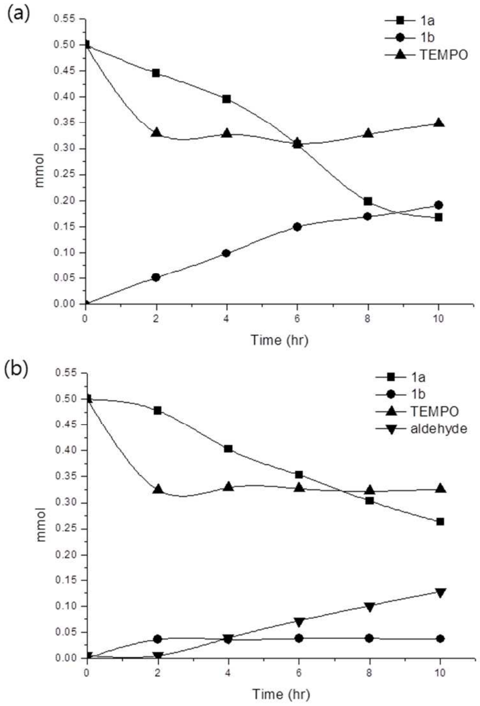
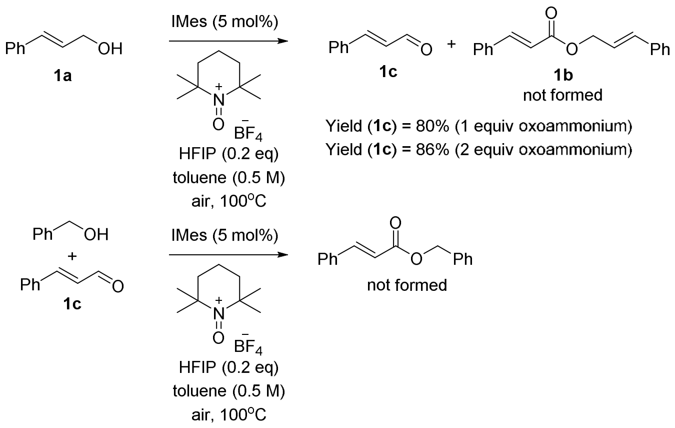


Figure 1. (a) one-pot oxidation/oxidative esterification reaction of **1a** to **1b** in the presence of hexafluoropropanol (HFIP). (b) One-pot oxidation/oxidative esterification reaction of **1a** to **1b** in the absence of HFIP. Reaction conditions: **1a** (0.5 mmol), 2,2,6,6-tetramethylpiperidine-*N*-oxy (TEMPO) (0.5 mmol), IMes (5 mol%), and HFIP (0.1 mmol (a) and 0 mmol (b)) in toluene (0.5 M) at 100 °C.

Next, the tandem oxidation/esterification using independently prepared oxoammonium tetrafluoroborate (BF_4^-) was investigated (Scheme 1). With 1 equiv of oxoammonium, **1a** underwent oxidation to form aldehyde **1c** without forming **1b**. Even with 2 equiv of oxoammonium, **1a** was converted to **1c** without forming **1b**, which indicated that oxoammonium was not an oxidant for this esterification. Furthermore, the reaction of **1c** and benzyl alcohol in the presence of oxoammonium did not afford the benzyl ester. These results show that NHC-catalyzed oxidative esterification is promoted by TEMPO radicals rather than by oxoammonium.

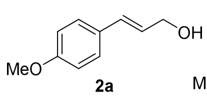
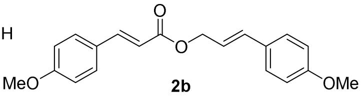
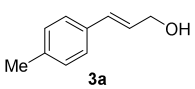
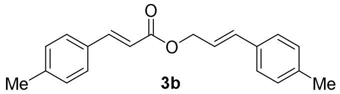
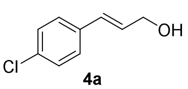
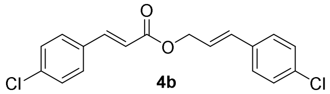
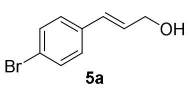
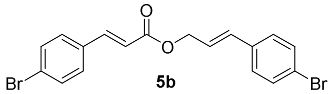
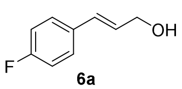
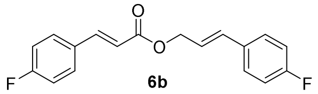
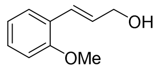
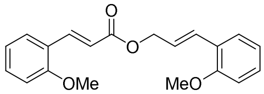
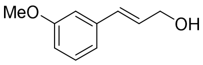
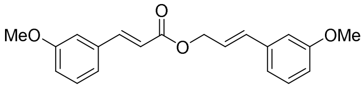
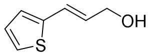
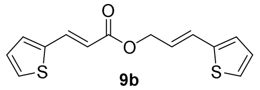
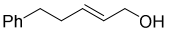
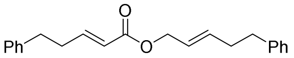
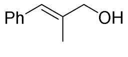
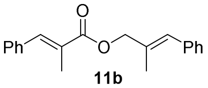


Scheme 1. Oxidation of **1a** and oxidative esterification of **1c** in the presence of oxoammonium

A reaction mechanism supported by the above-mentioned control experiments and GC studies is proposed in Scheme 2. After cinnamaldehyde **1c** was formed by the TEMPO-mediated oxidation of **1a**, **1c** immediately participated in the carbene-catalyzed oxidative esterification. HFIP is presumed to accelerate the rapid adduct formation of **1c** with carbene catalysts, which gives the high yield of esters by lowering the concentration of aldehydes. Intermediates **I** and **II** are oxidized by TEMPO radicals via SET mechanism to afford **III**. As stated in our previous publication,[4b,4c] intermediate **III** did not react with TEMPOH to form TEMPO-esters.[10] Instead, **III** reacted with **1a** to afford **1b**. Reduced TEMPOH was reoxidized by O_2.[11]

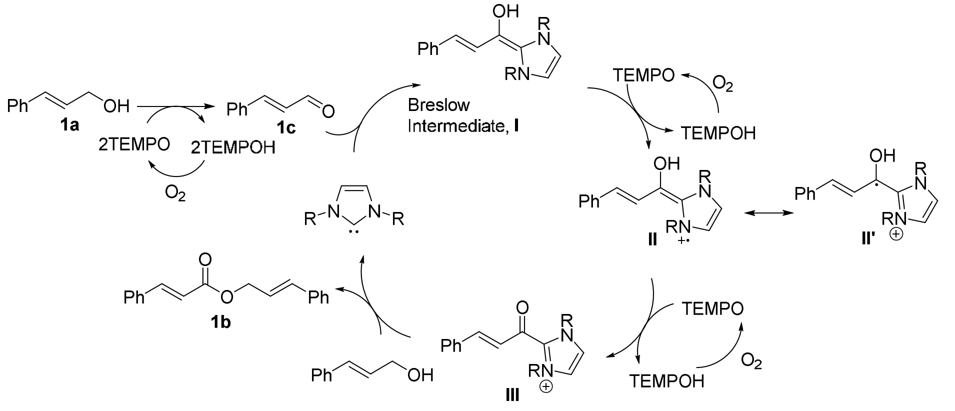
Finally, the substrate scope of this reaction was studied (Table 4). Electron-rich methoxy and methyl-substituted cinnamyl alcohols (**2a** and **3a**) were converted to corresponding esters **2b** and **3b** in 84% and 73% yield, respectively (entries 1 and 2). Halogen (Cl and Br)-substituted cinnamyl alcohols (**4a** and **5a**) also showed similar reactivity to afford **4b** and **5b** in 81% and 80% yield, respectively (entries 3 and 4). Electronegative fluoro-substituted cinnamyl alcohol **6a** was converted to **6b** in a lower yield (58%, entry 5). Electron-deficient NO_2-substituted cinnamyl alcohol was also tested under the optimized conditions. Unfortunately, NO_2-substituted cinnamyl alcohol was converted to NO_2-substituted cinnamaldehyde in 77% yield, and no esterification occurred. In addition to *para*-substituted compounds, *ortho*- and *meta*-substituted compounds **7a** and **8a** were subjected to the reaction conditions, to afford **7b** and **8b** in 58% and 68% yield, respectively (entries 6 and 7). Presumably, the steric effect of the substituent affected the yield of this oxidative esterification. Thiophenyl allylic alcohol **9a** was transformed to **9b** in 63% yield (entry 8). The reaction of aliphatic alcohol **10a** afforded the desired product **10b** in 26% yield (entry 9). The reaction of **11a** showed the steric effect on the olefin of allylic alcohol; the yield of **11b** was 23% which is lower than those of cinnamyl alcohols lacking olefin substitution (entry 10).

Table 4. NHC-catalyzed one-pot oxidation/oxidative esterification

Entry	Reactants	Products	Yield
1	 **2a**	 **2b**	84%
2	 **3a**	 **3b**	73%
3	 **4a**	 **4b**	81%
4	 **5a**	 **5b**	80%
5	 **6a**	 **6b**	58%
6	 **7a**	 **7b**	58%
7	 **8a**	 **8b**	68%
8	 **9a**	 **9b**	63%
9	 **10a**	 **10b**	26%
10	 **11a**	 **11b**	23%

Conclusions

We have presented an efficient one-pot oxidation process using NHC catalysts and TEMPO. In this process, TEMPO radicals function as a recyclable oxidant, based on their loadings and GC data. We have also confirmed that our oxidative esterification process proceeded via SET by TEMPO rather than two-electron transfer by oxoammonium. The role of HFIP is to promote the rapid consumption of aldehydes by adduct formation with carbene catalysts, resulting in high yields of oxidative esterification. The increased concentration of aldehydes is detrimental to carbene-catalyzed oxidative esterification with TEMPO.



Scheme 2. Proposed reaction mechanism

Acknowledgements

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Notes and references

[a]Department of Energy Systems Research, Ajou University, Suwon 443-749, Korea, E-mail:hyjang2@ajou.ac.kr; Fax: +82312191615; Tel: +82 31 219 2555

[b]Korea Carbon Capture & Sequestration R&D Center, Deajeon 305-343, Korea.

† Electronic Supplementary Information (ESI) available: detailed experimental and spectral analysis for new compounds. See DOI: 10.1039/c000000x/

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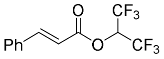

9 HFIP-ester

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