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Transition-Metal-Free Poly(thiazolium) Iodide/1,8-Diazabicyclo[5.4.0]undec-7-ene/Phenazine-Catalyzed Esterification of Aldehydes with Alcohols

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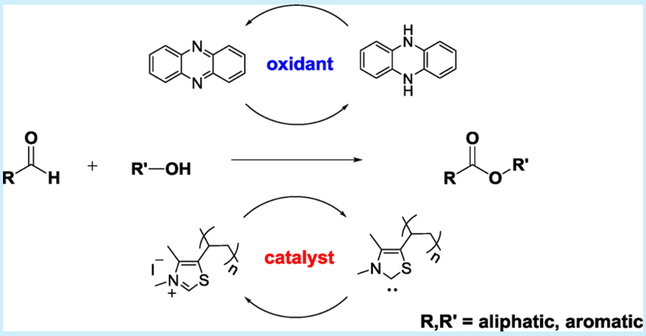
Supporting Information

ABSTRACT: Poly(3,4-dimethyl-5-vinylthiazolium) iodide was used as a polymer precatalyst in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and phenazine for the oxidative esterification of aldehydes with alcohols. Selective functionalization of OH groups was achieved in the presence of NH_2 groups. The poly(thiazolium) iodide/DBU/phenazine system exhibited excellent catalytic activity and could be reused five times without loss of activity.

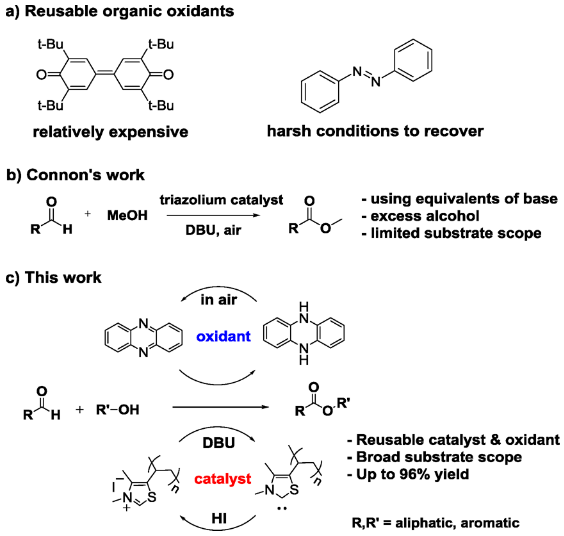


Esters are ubiquitous motifs in natural products and pharmaceuticals. They are also used as building blocks and protecting groups in the synthesis of many biologically active compounds.[1] Thus, the synthesis of esters has garnered considerable attention, and many useful methods have been established.[2] Among them, the direct transformation of aldehydes with alcohols to esters (oxidative esterification) is attractive in terms of atom economy.[3] Extensive efforts have been put forth to identify efficient and practical methods for oxidative esterification, and several viable methods have been reported.[4] Air was used as a clean oxidant in some transition-metal-catalyzed oxidative esterification reactions.[5] Nevertheless, many reported methods involve harsh reaction conditions, have limited substrate scopes, and require transition-metal catalysts that are difficult to prepare. Such requirements restrict the utility of these methods. Thus, metal-free catalysts have garnered considerable interest.

Recently, N-heterocyclic carbene (NHC)-catalyzed redox esterification of aldehydes with alcohols has emerged as a powerful strategy for the formation of esters.[6] Examples of metal-free NHC-catalyzed[7] and NHC transition-metal-catalyzed[5a,b,8] esterifications have been reported. However, the use of stoichiometric amounts of oxidants is required in NHC-catalyzed reactions. Several years ago, Studer et al. had reported an oxidative esterification using 1,3-dimethyltriazolium iodide as a precatalyst in the presence of DBU and 3,3′,5,5′-*tert*-butyldiphenoqinone. However, the catalytic system utilized an expensive quinone as the oxidant although it was readily recovered by oxidation in air (Scheme 1a).[7f]

In 2011, Zeitler et al. also reported an oxidative lactonization using a thiazolium precatalyst with azobenzene as the oxidant, but the oxidant recovery process required harsh conditions and the reaction was only applicable to intramolecular esterification (Scheme 1a).[7h] In 2013, Connon et al. reported an oxidative esterification in the presence of a triazolium precatalyst and excess base (DBU, 110 mol %) in air, albeit with limited substrate scope (Scheme 1b).[6d] Despite these important advances, significant challenges remain for the synthesis of esters under atom-economic, eco-friendly, and mild reaction conditions from readily available materials in the presence of a reusable catalyst.[9,10]

Scheme 1. Examples of Reusable Organic Oxidants and NHC-Catalyzed Esterification Reactions[6d,7f,h]



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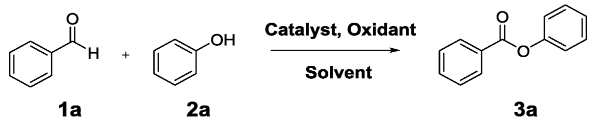
We recently developed highly efficient, recyclable polymer-based organocatalytic systems, such as poly(4-vinylimidazolium) iodide[11] and poly(3,4-dimethyl-5-vinylthiazolium) iodide.[12] These polymeric catalysts were successfully recovered and reused several times without any decrease in performance. As such, we sought to expand the applications of the poly(thiazolium)iodide/base/phenazine system in the esterification of aldehydes with alcohols. Herein, we report a highly efficient method for the oxidative esterification of aldehydes with alcohols, which employs a polymer-based organocatalyst, poly(3,4-dimethyl-5-vinylthiazolium) iodide, as the precatalyst and phenazine as the reusable external oxidant (Scheme 1c). A simple, efficient, ligand-free, transition-metal-free, high-yielding, direct esterification of aldehydes and alcohols in the presence of a reusable poly(thiazolium) precatalyst and DBU was thus developed in this study. To the best of our knowledge, the developed catalytic system facilitates one of the most general and selective oxidative esterification reactions of aldehydes with alcohols currently available.

As a model reaction, we initially examined the reaction of benzaldehyde with phenol (a weak nucleophile) in the presence of the thiazolium polymer precatalyst (5 mol %), phenazine (1.2 equiv), and DBU (10 mol %) in DMSO at room temperature for 18 h (Table 1). The initial reaction conditions were adopted from a previous study.[12a] After the reaction, the expected ester was isolated in 70% yield (entry 1). The amount of catalyst influenced the yield of the reaction (entries 1−3). The yield of the reaction was slightly dependent on the reaction temperature (the yield at 25 °C (entry 2) and 40 °C (entry 4) were 77% and 88%, respectively). The use of oxidants such as phenazine, azobenzene, and benzoquinone afforded the corresponding esters in 88%, 85%, and 8% yields, respectively (entries 4−6). Changing the reaction solvent from DMSO to acetone and DMF gave the corresponding esters in 15% and 78% yields, respectively (entries 7 and 8, respectively). Increasing the amount of phenol led to no noticeable change in the yield (entry 10). However, when 1.2 equiv of the aldehyde was used, the best yield (93%) was observed (entry 11). When the amount of oxidant (phenazine) was decreased to 0.6 equiv, the desired product was obtained in 53% yield (entry 12). No reaction was observed in the absence of a catalyst or phenazine. When a monomer (3,4-dimethyl-5-vinylthiazolium iodide) was used as the precatalyst instead of the polymer precatalyst, the product was isolated in 78% yield (entry 13). The optimum reaction conditions were as follows: 7 mol % of precatalyst, 14 mol % of DBU, 1.2 equiv of phenazine, 1.0 mL of DMSO at 40 °C for 18 h.

Table 1. Screening of Esterification Reaction of Benzaldehyde with Phenol[a]

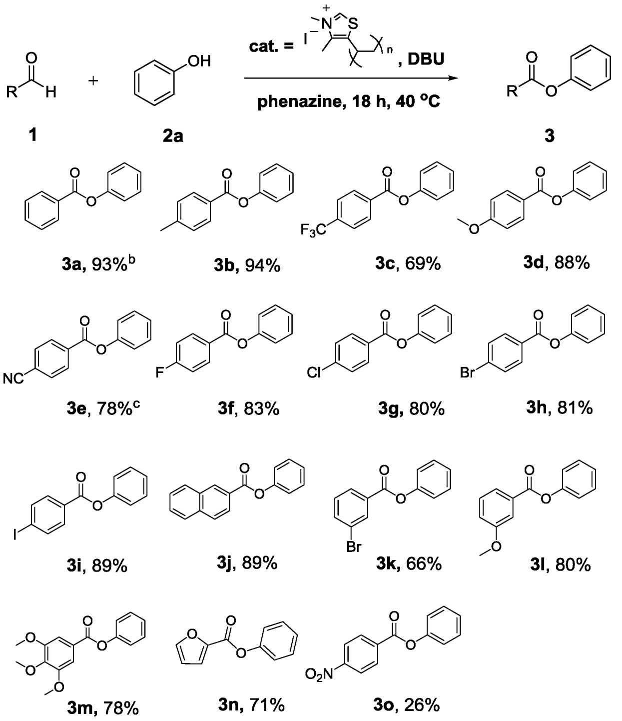


entry	oxidant	solvent[b]	catalyst (mol %)	temp (°C)	yield[c] (%)
1	phenazine	DMSO	5	25	70
2	phenazine	DMSO	7	25	77
3	phenazine	DMSO	10	25	75
4	phenazine	DMSO	7	40	88
5	azobenzene	DMSO	7	40	85
6	benzoquinone	DMSO	7	40	8
7	phenazine	acetone	7	40	15
8	phenazine	DMF	7	40	78
9	phenazine	DMSO	7	60	85
10[d]	phenazine	DMSO	7	40	83
11[e]	phenazine	DMSO	7	40	93
12	phenazine[f]	DMSO	7	40	53
13[g]	phenazine	DMSO	7	40	78

[a] Conditions: benzaldehyde (0.5 mmol), phenol (0.6 mmol), DBU (2 equiv of catalyst), oxidant (0.6 mmol), 18 h, catalyst = poly(3,4-dimethyl-5-vinylthiazolium) iodide. [b] 1 mL used. [c] Isolated yield. [d] Phenol (1 mmol) used. [e] Benzaldehyde (0.6 mmol), phenol (0.5 mmol) used. [f] 0.3 mmol used. [g] 3,4-Dimethyl-5-vinylthiazolium iodide used as a catalyst.

With the optimized reaction conditions in hand, we investigated the activity of the catalyst in the reaction of phenol with a variety of aryl aldehydes (Scheme 2).

Scheme 2. Esterification Reactions of Phenol with Aromatic Aldehydes[a]

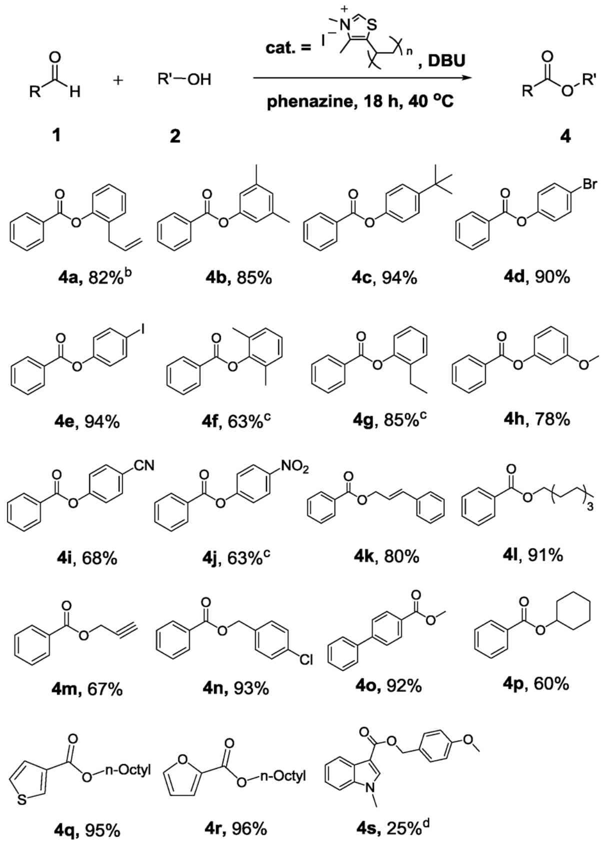


[a] Conditions: aldehyde (0.6 mmol), phenol (0.5 mmol), cat. (7 mol %), DBU (14 mol %), phenazine (0.6 mmol), DMSO (1 mL). [b] Isolated yield. [c] 60 °C.

Benzaldehydes having alkyl, ether, nitrile, or halogen group(s) and 2-naphthaldehyde were converted into the corresponding phenyl esters in good to excellent yields (**3a**−**j**, 69−94%). Benzaldehydes having electron-donating (3-OMe, **3l**) and electron-withdrawing (3-Br, **3k**) groups could be transformed into esters. Notably, 3,4,5-trimethoxy-substituted benzaldehyde (**3m**, 78%) and furan-2-carbaldehyde (**3n**, 71%) were good substrates. However, 4-nitrobenzaldehyde turned out to be a poor substrate (**3o**, 26%).

Next, the esterification of benzaldehyde with various types of alcohols was investigated (Scheme 3). Neither alcohol oxidation nor aldol condensation was observed under the reaction conditions. Various phenols containing alkyl, alkene,

Scheme 3. Esterification of Aromatic Aldehydes with Various Alcohols[a]

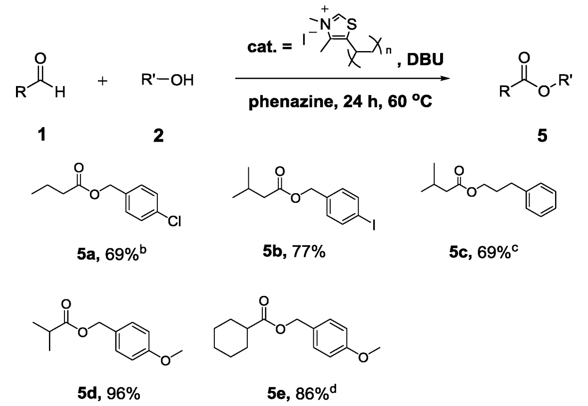


[a]Conditions: aldehyde (0.6 mmol), alcohol (0.5 mmol), cat. (7 mol %), DBU (14 mol %), phenazine (0.6 mmol), DMSO (1 mL). [b]Isolated yield. [c]60 °C. [d]Cat. (11 mol %), DBU (21 mol %), 38 h, 80 °C.

halogen, nitrile, or nitro group(s) afforded high to excellent yields of the corresponding esters (**4a**−**j**). Sterically shielded phenol or phenol bearing a nitro group provided lower yields at 40 °C (**4f**, 48%; **4j**, 29%). In both cases, elevated temperatures (60 °C) were required to drive the reaction to obtain higher yields of 63%. Aliphatic alcohols, such as 3-phenylprop-2-en-1-ol, *n*-octanol, propargyl alcohol, and (4-chlorophenyl)methanol, also worked well for this reaction. Interestingly, double and triple bonds were tolerated in the oxidative esterification (**4k** and **4m**). In the reaction of benzaldehyde with methanol, the expected ester was produced in a high yield. However, during the purification, some of the ester evaporated. Thus, 1,1′-biphenyl-4-carbaldehyde was used instead of benzaldehyde in the reaction with methanol, and the expected product (**4o**) was isolated in 92% yield. A secondary alcohol, cyclohexanol, was also a good substrate (**4p**, 60%). However, a tertiary alcohol, *tert*-butyl alcohol, was unreactive under the reaction conditions. Heteroaromatic aldehydes containing furan or thiophene moieties were good substrates for the esterification with aliphatic alcohols (**4q** and **4r**). However, in the case of indole-3-carboxaldehyde, an *N*-methylated ester, **4s**, was isolated in 25% yield.

Reactions between aliphatic aldehydes and aliphatic alcohols were also examined (Scheme 4). Aliphatic aldehydes, including primary, secondary, and cyclic aldehydes were good substrates and afforded high yields (69−96%) of the corresponding esters.

Scheme 4. Ester Bond Formation with Aliphatic Aldehydes and Alcohols[a]

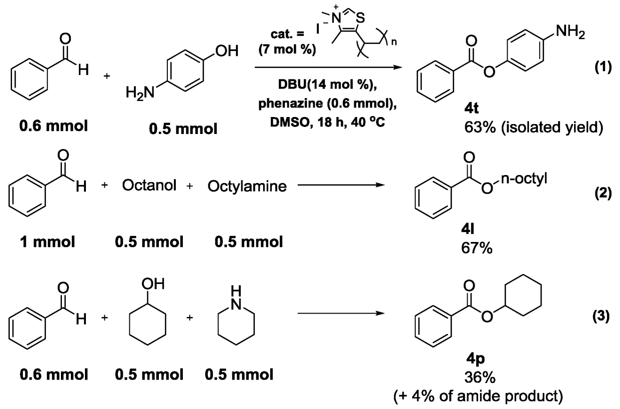


[a]Conditions: aldehyde (2.2 mmol), alcohol (0.5 mmol), cat. (11 mol %), DBU (21 mol %), phenazine (0.6 mmol), 24 h, 60 °C, DMSO (1 mL). [b]Isolated yield. [c]30 h, 80 °C. [d]Aldehyde (0.6 mmol), alcohol (0.5 mmol), cat. (7 mol %), DBU (14 mol %), 18 h, 40 °C.

Relatively higher yields were observed for secondary aldehydes (**5d** and **5e**: 96 and 86%) as compared to primary aldehydes (**5a**−**5c**: 69−77%).

In order to extend the utility of the developed system, the chemical selectivity was examined by studying the reaction of 4-aminophenol with benzaldehyde (Scheme 5, eq 1). An ester was isolated as a major product, and a trace amount of an amide was formed (eq 1). Thus, this method is useful for the selective functionalization of OH groups in the presence of NH$_2$ groups. To determine the selectivity between nucleophiles, a competition experiment between octanol and octylamine with benzaldehyde was carried out (eq 2). The ester (67%) was formed in preference to the amide. A similar experiment with cyclohexanol and piperidine showed a 9:1 preference for the ester (overall yield: 40%) (eq 3).

Scheme 5. Chemoselective Esterification of Benzaldehyde over Amidation



A possible mechanism for the poly(thiazolium)/base/phenazine-catalyzed esterification reaction based on the widely accepted mechanism is depicted in Figure 1.[4b] The benzylic alcohol intermediate is generated upon reaction of the carbene with the aldehyde. Finally, nucleophilic substitution by the alcohol takes place to give the desired esters.

In order to recycle the catalytic system, the catalyst was recovered by addition of hydroiodic acid.[12a] Moreover, we also

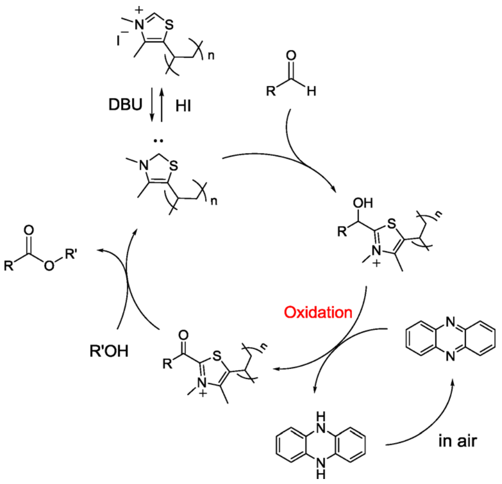


Figure 1. Proposed mechanism for esterification reaction.

recovered phenazine from the reaction mixture to overcome the potential drawback of its stoichiometric use. To our delight, separation of the reduced dihydrophenazine from the product in organic solvents under air afforded the reoxidized, active oxidant phenazine (96–99% in each cycle) (see the Supporting Information). Thus, the recovered catalytic system could be successfully reused without considerable decrease in performance over five cycles (each time, 81–91% yield) (see the SI).

In conclusion, we have developed a novel poly(thiazolium) iodide/DBU-catalyzed oxidative esterification of aldehydes with alcohols. The catalytic system showed high activity with a variety of aromatic and aliphatic aldehydes and alcohols. The methodology described herein has several advantages, including being a metal-free catalytic system, and the recovery and reusability of the organic precatalyst and phenazine oxidant. The polymer precatalyst exhibited higher catalytic activity than the monomeric analog and could be reused five times without a considerable decrease in activity. Thus, the precatalyst has great potential, and further investigations of the applicability of the polymer-based thiazolium system in other reactions are in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01617.

> Experimental procedures, characterization data, and reuse procedures of poly(3,4-dimethyl-5-vinylthiazolium) iodide and phenazine in the reaction of esterification (PDF)

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Notes

The authors declare no competing financial interest.

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